Industria y Comercio

SUPERINTENDENCIA

Organizacion CSA Ltda

PCT

INVENTARIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

1/2

07-98431

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: DERIVADOS DE CUMARINA SUSTITUIDOS CON TIODIAZOL Y SU USO COMO INHIBIDORES DE LA BIOSÍNTESIS DE LEUCOTRIENOS

IPC: A61K 31/5025
A61P 25/20
C07D 487/04

SOLICITANTE: MERCK FROSST CANADA LTD.

DIRECCIÓN: 16711 Trans-canada Highway, Kirkland, Quebec H9H 3L1. Canada

APODERADO: CARLOS R. OLARTE

BOGOTÁ 21 Septiembre 2007

P2007/000150

OlarteRa

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-098431- -00000-0000

Fecha: 2007-09-21 16:36:48 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 563

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL **P2007/000139**

SOLICITUD DE:

1

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

21/10/2007

[X] Capítulo I. [ ] Capítulo II.

2 **SOLICITANTE (71)**

Nombre: ELI-LILLY AND COMPANY

Dirección: Lilly Corporate Center, Indianápolis Indiana 46285 E.U.A.
Nacionalidad o Domicilio: ESTADOUNIDENSE
Lugar de Constitución: ESTADOS UNIDOS DE AMERICA

Teléfono: _____ Fax: _____
E-mail: _____

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

3 **REPRESENTANTE O APODERADO**

Nombre: CARLOS R. OLARTE

Dirección: World Trade Center Torre A, Calle 100 Nº. 8A-37 Piso 10
Teléfono: 601-7700 Fax: 601-7799
E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual _____
Número 79.782.747 Btá
TP 74.295

4 **INVENTOR (ES) (72)**

Nombre: VER PAGINA ADJUNTA

Dirección: VER PAGINA ADJUNTA

Nacionalidad o Domicilio: VER PAGINA ADJUNTA

5 **PCT (86)**

Solicitud Internacional No. PCT/US2006/009942 Fecha Marzo 20, 2006

Publicación Internacional No. WO 2006/102194 Fecha Septiembre 28, 2006

6 Título (54) COMPUESTOS DE IMIDAZOPIRIDAZINA

7 **Clasificación Internacional (51) C07D 487/04, A61P 25/20, A61K 31/5025**

8 **Prioridad**

SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Marzo 21, 2005	60/663.816

9 **Comprobante de pago No. 07- 75.606** **Fecha 18 septiembre 2007**

(10) **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 06-021-173
- [X] Documento de cesión del interventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. ~~79~~.782.747 Btá T.P. 74.295

LISTA DE INVENTORES PCT/US2006/009942

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Nacionalidad: Japonesa

Richard Craig THOMPSON
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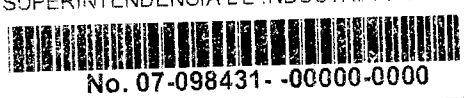
Estados Unidos de América
Nacionalidad: Estadounidense

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-098431- -00000-0000

Fecha: 2007-09-21 16:36:48 Dep. 2020 NUECREACIONI
Tra. 11 PATENTE!YII Eve: 379 FASENACIONALI!
Act. 411 PRESENTACION Folios: 563

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 75,606
FECHA : SEPTIEMBRE 18 DE 2007

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO POPULAR	050-00110-6	68290537	18/09/2007	7,259,000.00

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

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

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

4

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

APOSTILLA EN PODER DE REPRESENTACIÓN DE

ELI LILLY AND COMPANY

Bilingüe inglés- español otorgado en Indianapolis, Indiana, Estados Unidos el 17 de julio de 2003 y firmado por Peter G. Stringer, Director Ejecutivo y Patentes Internacionales de Ely Lilly & Company.

Todd Rokita — Secretario de Estado

Secretario de Estado de Indiana — Estado de Indiana

APOSTILLA

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

1. País: Estados Unidos de América- Este documento Público
2. ha sido firmado por Catherine Michel
3. Quien ejerce funciones de Secretario de la Corte del Circuito en y para el condado Johnson
4. Lleva el sello del Secretario de la Corte del Circuito en y para el estado de Indiana

CERTIFICADO

5. En Indianapolis, Indiana 6. El 22 de julio de 2003
7. Por el Secretario de Estado de Indiana 8. No. A2003- 11279
9. Gran Sello del Estado de Indiana
10. Firma legible de Todd Rokita- Secretario de Estado de Indiana

* Vigente desde el 1 mayo de 2003, todas las apostillas del Secretario de Estado de Indiana tienen el sello impreso electrónicamente.

The Statehouse, Indianapolis, Indiana 46204, (317) 232-6531, fax (317) 233-3283

CERTIFICACION NOTARIAL

Bilingüe inglés- español, el 17 de julio de 2003 el suscrito notario Catherine Michel certifica que Peter G. Stringer, domiciliado en 7620 Castleton Farms, West Drive, Indianapolis, Indiana - 46256 Estados Unidos ejercía funciones de Director Ejecutivo y Patentes Internacionales de Ely Lilly & Company, con sede en Indianapolis, Indiana, Estados Unidos.

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

5

El otorgante fundamenta sus certificaciones en este documento: Delegación de Autoridad concerniente a Ciertas Materias de Patentes, suscrito el 20 de enero de 2003: conforme al poder otorgado al Asesor General de la Compañía por el Comité ejecutivo de la Junta Directiva de Eli Lilly and Company.

Firma del notario público Catherine Michel certifica

Sus funciones vencen el 21 de octubre de 2008 - residente en el condado Johnson

Sello de notario público de Indiana

--

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 28 de julio-2003.

Marlen Neira C

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,

ELI LILLY AND COMPANY

domiciled in

Lilly Corporate Center, Indianapolis, Indiana 46285 US

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,

ELI LILLY AND COMPANY

domiciliado en

Lilly Corporate Center, Indianapolis, Indiana 46285 US

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: 17 July 2003

City,Country/Ciudad,País: Indianapolis, Indiana, United States of America

SECRETARY OF STATE
STATE OF INDIANA

Todd Rokita
Secretary of State

APOSTILLE

(Convention de la Haye du 5 Octobre 1961)

1. **Country: United States of America**

2. **This public document has been signed by** *Catherine Michel*

3. **acting in the capacity of circuit court clerk in & for** *Johnson* **County**

4. **and bears the seal/stamp of circuit court clerk in & for the State of Indiana**

Certified

5. **at Indianapolis, Indiana**

6. **this** *Twenty-second* **day of** *July, 2003*

7. **by Secretary of State of Indiana**

8. **No. A2003-** *11279*

9. **Seal/Stamp:**

10. **Signature:**

Todd Rokita

Indiana Secretary of State

*Effective May 1, 2003 all apostilles from the Indiana Secretary of State will have an electronically printed seal.

The Statehouse, Indianapolis, Indiana 46204, (317) 232-6531, Fax (317) 233-3283

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
FAX: +57-1 638-6201

www.olarteraisbeck.com

Notarial Certification

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

1. That
Peter G. Stringer
of legal age and domiciled in
7620 Castleton Farms, West Drive, Indianapolis, Indiana 46256 US
signed the foregoing document.

2. That the grantor has executed the foregoing document as Executive Director, International Patents
of ELI LILLY AND COMPANY

3. That ELI LILLY AND COMPANY
having its principal place of business located in
Indianapolis, Indiana, United States of America
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):
Delegation of Authority Concerning Certain Patent Matters, executed January 20, 2003; pursuant to the authority granted to the General Counsel of the Company by the executive Committee of the Board of Directors of Eli Lilly and Company

NOTARY PUBLIC (Signature):

NOTARY PUBLIC SEAL INDIANA

Catherine Michel
My Commission Expires October 21, 2008
Resident of Johnson County

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que
mayor de edad y domiciliado
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 legitima.

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):

Secretaria de Estado

Estado de Indiana

APOSTILLA

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

1. País: Estados Unidos de América

2. El presente documento público fue firmado por: Catherine Michel

3. Que actuó en su calidad de Notario Público en y para el condado de Johnson

4. Y lleva el sello del Notario Público en y para el estado de Indiana

Se certifico

5. En Indianápolis, Indiana

6. El 30 de agosto de 2007

7. Por el secretario de Estado, Estado de Indiana.

8. Bajo el Número **A2007-011461**

9. Lleva el Sello del Estado de Indiana.

10. Firmado por Todd Rokita, Secretario de Estado

Todd Rokita

Secretaria Estado de Indiana

MAURICE UR... V.
TRADUCTOR E INTERPRETE O...
INGLES - ESPAÑOL - ESPAÑOL - I...
RFS. MINJUSTICIA 1790 - 19...

10

CERTIFICADO DE CONFORMIDAD

ESTADO DE INDIANA

CONDADO DE MARION

Yo Catherine Michel, un Notario Público debidamente autorizado comisionado en el condado de Johnson, Estado de Indiana, Estados Unidos de América, por medio del presente certifico que el documento adjunto es una fiel copia del documento original y ELI LILLY AND COMPANY.

Firmado el 8 de Agosto de 2007

(Sello)

(Firmado) Catherine Michel

Notario Publico

Cuya comisión vence el 21 de octubre de 2008

Residente del condado de Johnson

MAURICE U...
TRADUCTOR E INTERPRETE
INGLES - ESPAÑOL - ESPAÑOL - IN...
RES. MINJUSTICIA 1790 - 1904

Documento No. P-16354

CESIÓN

Considerando que Yo, inventores o co-inventor de un invento que es objeto de una solicitud de patente ("Solicitud") el cual se denomina Compuestos Farmacéuticos:

COMPUESTOS DE IMIDAZOPIRIDAZINE.

(X) Fue radicada.

(X) En la Oficina de Patentes y Marcas de los Estados Unidos el 21 de MARZO de 2005 con el número serial acordado 60/663816; y considerando que **ELI LILLY AND COMPANY** una corporación organizada y existente bajo las leyes del estado de Indiana, cuya oficina comercial es Lilly Corporate Center, Indianápolis, Indiana 46285, desea adquirir la totalidad del derecho, titulo e interés de todo el invento revelado en dicha Solicitud;

ENTONCES Y POR LO TANTO, en consideración de mi empleo, cualquier acuerdo relacionado con eso u otra consideración buena y valiosa, recibo de la cual se está acusando, yo, por medio del presente documento cedo a Eli Lilly and Company., sus sucesores y beneficiarios (colectivamente "Lilly") la totalidad de mi derecho, título e interés en, y con respecto a la solicitud, incluyendo todos los derechos de prioridad para otros países que se generen a partir de allí, todos los inventos allí revelados y cualquiera y todas las solicitudes de Patente presentes o futuras de tales inventos que pudieran ser radicadas en cualquier país, inclusive, pero no solamente con respecto a continuaciones, continuaciones parciales, divisiones, sustituciones, re- exámenes, re-expediciones, solicitudes internacionales radicadas según el PCT, solicitudes provisionales de Patentes en los Estados Unidos solicitudes

MAURICE URREGO V.
TRADUCTOR E INTERPRETE OFICIAL
INGLES - ESPAÑOL - ESPAÑOL - INGLES
RES. MINJUSTICIA 1700 - 1988

de Patentes provisionales subsiguientes en los Estados Unidos que reclamen algo o la totalidad de este invento, certificados de adición, modelos de utilidades, patentes menores, así como toda la demás propiedad intelectual relacionada con la Solicitud, inclusive, pero no exclusivamente a certificados suplementarios de protección; y a cualquier prórroga de plazo de patente relacionado que pueda otorgarse para Cartas de Patente con respecto a la Solicitud; todo lo anterior para ser llevado a cabo y disfrutado por Lilly para su propio uso y provecho hasta el final del término o términos para los cuales dichas Cartas de Patente y derechos de propiedad intelectual relacionados puedan otorgarse, tan completamente como los mismos hubieran sido llevados a cabo y disfrutados por mí si esta Cesión y venta a Lilly no se hubiera realizado. Por mi mismo y por mis herederos, sucesores y representantes legales, convengo que no se ha hecho o se hará ninguna cesión, venta acuerdo o afectación que pudiera entrar en conflicto con esta cesión.

Además por mi mismo y por mis herederos, sucesores y representantes legales, convengo y acuerdo con Lilly según solicito yo y ellos, sin mayor consideración que será pagada ahora a costa de Lilly: (i) dispondré la ejecución de las solicitudes originales, provisionales sustitutas, de continuación, divisionales, de continuación parcial, re-examinadas o reexpedidas, las especificaciones enmendadas o las declaraciones legitimas o declaraciones juramentadas para dicha solicitud; (ii) comunicare a Lilly cualquier hecho conocido por mi o por ellos con relación a dichos inventos o la historia de los mismos; (iii) dispondré la ejecución de las declaraciones preliminares y el testimonio en cualquier procedimiento de interferencia, procedimientos de descubrimiento de litigio y declaraciones, oposiciones, procedimientos de cancelación, con cursos de prioridad,

procedimientos de uso público, procedimientos de entidad administrativa, litigio y otras acciones procesales y similares; (iv) dispondré a ejecutar y entregar cualquier documento de solicitud, declaraciones juramentadas, declaraciones, cesiones u otros instrumentos; y (v) haré todas las demás acciones que, en opinión razonable del asesor jurídico de Lilly, puedan ser necesarias ó deseables para asegurar el otorgamiento de Cartas de Patente y propiedad intelectual relacionada con Lilly o sus delegados, en los Estados Unidos y en todos los demás países donde Lilly desee tener dichos inventos, o cualquiera de ellos, patentados, con especificaciones y pretensiones de tal forma como sean aprobadas por el asesor jurídico de Lilly y para investir y confirmar a Lilly o sus delegados con el título completo, legal y equitativo para todas las dichas Cartas de Patente y propiedad intelectual relacionada.

En testimonio de lo anterior he ejecutado este documento de cesión en la fecha indicada más adelante.

Fecha: 13 de junio 2005
(Firmado) Elizabeth Aaron Collins,Co-Inventor
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Fecha: 13 de junio 2005
(Firmado) Chafiq Hamdeuchr,Co-Inventor
Domicilio: 14469 Twin Oaks Drive Carmel, IN 46032
Ciudadanía: Español

Fecha: 13 de junio 2005
(Firmado) Erik James Hembre
Domicilio: 1332 North New Jersey

MAURICE URRIGO V.
TRADUCTOR E INTERPRETE OFICIAL
INGLÉS-ESPAÑOL-ESPAÑOL-INGLÉS

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Ciudadanía: Estados Unidos

Fecha: 13 de junio 2005
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Domicilio: 4255 Cobin Court
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Ciudadanía: Estados Unidos

Fecha: 13 de junio 2005
(Firmado)Richard Duane Johnston,Co-Inventor
Domicilio: 3712 Forest Lane
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Ciudadanía: Estados Unidos

Fecha: 13 de junio 2005
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Ciudadanía: Estados Unidos

Fecha: 29 de junio 2005
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Domicilio: 11921 Castlestone rive
Fishers, IN 46038
Ciudadanía: Estados Unidos

Fecha: 13 de junio 2005
(Firmado) Michael John Rupp, Co-Inventor
Domicilio: 10003 schotch Pine Lane
Indianapolis, IN 46256
Ciudadanía: Estados Unidos

Fecha: 13 de junio 2005

MAURICE URREGO V.
TRADUCTOR E INTERPRETE OFICIAL
INGLES/ESPAÑOL - ESPAÑOL - INGLES
RES. MINJUSTICIA 1790 - 1998

15

(Firmado) Takako Takakuma, Co-Inventor

Domicilio: 7653 Germander Lane

Indianapolis, IN 46237

Ciudadanía: Japonés

Fecha: 17 de junio 2005

(Firmado) Richard Craig Thompson, Co-Inventor

Domicilio: 763 North Country Road 900 West

Frankfort, IN 46041

Ciudadanía: Estados Unidos

ESTADOS UNIDOS DE AMERICA
Estado de Indiana
Condado de Marion

Ante mi, un notario público del condado de Marion, Estado de Indiana, compareció personalmente ante mi Elizabeth Aaron Collins, Chafiq Hamdouchi,Erik James Hembre, Philip Arthur Hipskind, Richard Duane Johnston, Heather Janelle Barbosa, Michael John Rupp, Takako Takakuwa, Richard Craig Thompson y quien reconoció haber firmado el documento precedente el 13 de junio de 2005.
(sello)

(firmado: Cheryl A. Karres,)
Notario Público
Residente del condado de Marion
Comisión vence: 10 de mayo de 2007

ESTADOS UNIDOS DE AMERICA

Estado de Indiana
Condado de Marion

Ante mi, un notario público del condado de Marion, Estado de Indiana, compareció personalmente ante mi Jianliana Lu y y quien reconoció haber firmado el documento precedente el 29 de junio de 2005.
(sello)

(firmado: Cheryl A. Karres,)
Notario Público
Residente del condado de Marion
Comisión vence: 10 de mayo de 2007

MAURICE URREGO V.
TRADUCTOR E INTERPRETE OFICIAL
INGLES - ESPAÑOL - ESPAÑOL - INGLES
RES. MIN. JUSTICIA 1790 - 1998

SECRETARY OF STATE
STATE OF INDIANA

Todd Rokita
Secretary of State

APOSTILLE
(Convention de la Haye du 5 Octobre 1961)

1. **Country: United States of America**
2. **This public document has been signed by** *Catherine Michel*
3. **acting in the capacity of notary public in & for** *Johnson* **Country**
4. **and bears the seal/stamp of notary public in & for the State of Indiana**

Certified

5. **at Indianapolis, Indiana**
6. **this** *Thirtieth* **day of** *August, 2007*
7. **by Secretary of State of Indiana**
8. **No. A2007 -** *011461*

9. **Seal/Stamp:**

10. **Signature:**

Todd Rokita
Indiana Secretary of State

*Effective May 1, 2003 all apostilles from the Indiana Secretary of State will have an electronically printed seal.

tdove

CERTIFICATE OF CONFORMITY

STATE OF INDIANA
COUNTY OF MARION

I, Catherine Michel, a Notary Public duly commissioned in the county of Johnson, State of Indiana, United States of America, do hereby certify that the attached document identified as an assignment between inventors and ELI LILLY AND COMPANY, is an exact copy of the original document.

Signed this 8 day of August 2007

NOTARY PUBLIC
Catherine Michel
My Commission Expires
October 21, 2008
Resident of Johnson County

(SEAL)

ASSIGNMENT

WHEREAS I, am an inventor or co-inventor (with the persons listed below) of an invention that is the subject of a patent application ("Application") which is entitled IMIDAZOPYRIDAZINE COMPOUNDS, containing 240 pages, and which:

☐ is being filed:
☒ was filed:

☒ in the United States Patent and Trademark Office
☐ in the United Kingdom Patent Office
☐ in the European Patent Office
☐ in the Spanish Patent Office as a European Application
☐ as an international application under the Patent Cooperation Treaty ("PCT"), with:

☐ United States Patent and Trademark Office acting as Receiving Office, or
☐ International Bureau acting as Receiving Office;
☐

on March 21, 2005 and accorded serial number 60/663816;

and

WHEREAS ELI LILLY AND COMPANY., an Indiana corporation having its principal place of business at Lilly Corporate Center, Indianapolis, Indiana 46285, wishes to acquire the entire interest in all inventions disclosed in such Application;

NOW, THEREFORE, in consideration of my employment, any agreements related thereto, or other good and valuable consideration, the receipt of which is hereby acknowledged, I hereby assign to Eli Lilly and Company, its successors and assigns (collectively "Lilly") my entire right, title and interest in, to and under the Application, including all priority rights for other countries arising therefrom, all inventions therein disclosed, and any and all present or future patent applications to such inventions that may be filed in any country, inclusive of, but not limited to, continuations, continuations-in-part, divisions, substitutions, reexaminations, reissues, international applications filed under the PCT, United States provisional patent applications, subsequent United States provisional patent applications claiming some or all of this invention, certificates of addition, utility models, petty patents, as well as all other intellectual property related to the Application, inclusive of, but not limited to, supplementary protection certificates; and any related patent term extensions which may be granted for Letters Patent with respect to the Application; all of the above to be held and enjoyed by Lilly for its own use and enjoyment to the full end of the term or terms for which such Letters Patent and related intellectual property rights may be granted, as fully and entirely as the same would have been held and enjoyed by me had this Assignment and sale to Lilly not been made.

For myself and for my heirs, successors and legal representatives, I covenant that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this Assignment.

For myself and for my heirs, successors and legal representatives, I further covenant and agree with Lilly that upon request I and they will, without further consideration than that now paid, but at the expense of Lilly: (i) execute original, provisional, substitute, continuation, divisional, continuation-in-part, reexamined, or reissued applications, amended specifications, or rightful declarations or oaths for such application; (ii) communicate to Lilly any facts known to me or them relating to such inventions or the history thereof; (iii) execute preliminary statements and testify in any interference proceedings, litigation discovery proceedings and depositions, oppositions, cancellation proceedings, priority contests, public use proceedings, administrative agency proceedings, litigation and other court actions and the like; (iv) execute and deliver any application papers, affidavits, declarations, assignments, or other instruments; and (v) do all other acts which, in the opinion of counsel for Lilly, may be necessary or desirable to secure the grant of Letters Patent and related intellectual property to Lilly or its nominees, in the United States and in all other countries where Lilly may desire to have such inventions, or any of them, patented, with specifications and claims in such form as shall be approved by counsel for Lilly and to vest and confirm in Lilly or its nominees the full and complete legal and equitable title to all such Letters Patent and related intellectual property.

IN WITNESS WHEREOF I have executed this assignment on the date indicated below.

6-13-05
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UNITED STATES OF AMERICA

STATE OF INDIANA)
) SS:
COUNTY OF MARION)

Before me, a Notary Public for Marion County, State of Indiana, personally appeared Elizabeth Aaron Collins, Chafiq Hamdouchi, Erik James Hembre, Philip Arthur Hipskind, Richard Duane Johnston, Heather Janelle Barbosa, ~~Jianliang Lu,~~ Michael John Rupp, Takako Takakuwa, Richard Craig Thompson and acknowledged the execution of the foregoing instrument this 13th day of June, 2005.

Cheryl A Karres
Notary Public
Commission Expires: ____

Cheryl A. Karres, Notary Public
Resident of Marion County
My Commission Expires:
May 10, 2007

STATE OF INDIANA)
) SS:
COUNTY OF MARION)

Before me, a Notary Public for Marion County, State of Indiana, personally appeared Jianliang Lu, and acknowledged the execution of the foregonig instrument this 29th day of June, 2005.

Cheryl Karres
Notary Public
Commission Expires:

Cheryl A. Karres, Notary Public
Resident of Marion County
My Commission Expires:
May 10, 2007

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

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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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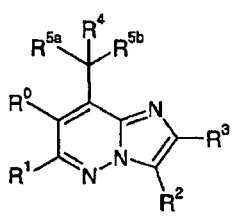
(54) Title: IMIDAZOPYRIDAZINE COMPOUNDS



(I)

(57) Abstract: The present invention relates to novel substituted imidazo[1,2-b]pyridazine compounds of Formula (I): pharmaceutical compositions thereof, and the use such compounds as corticotropin releasing factor 1 (CRF1) receptor antagonists in the treatment of psychiatric disorders and neurological diseases.

WO 2006/102194 A1

IMIDAZOPYRIDAZINE COMPOUNDS

Field of the Invention

This invention relates to novel substituted imidazo[1,2-b]pyridazine compounds, pharmaceutical compositions thereof, and the use of such compounds as corticotropin releasing factor 1 (CRF1) receptor antagonists in the treatment of psychiatric disorders and neurological diseases.

Background of the Invention

Corticotropin releasing factor (CRF) is a 41 amino acid peptide that is the primary physiological regulator of proopiomelanocortin (POMC) derived peptide secretion from the anterior pituitary gland [J. Rivier et al., *Proc. Natl. Acad. Sci* (*USA*) 80:4851 (1983); W. Vale et al., *Science* 213:1394 (1981)]. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in the brain [W. Vale et al., *Rec. Prog. Horm. Res.* 39:245 (1983); G. F. Koob, *Persp. Behav. Med.* 2:39 (1985); E. B. De Souza et al., *J. Neurosci.* 5:3189 (1985)]. There is also evidence that CRF plays a significant role in integrating the response in the immune system to physiological, psychological, and immunological stressors [J. E. Blalock, *Physiological Reviews* 69:1 (1989); J. E. Morley, *Life Sci.* 41:527 (1987)].

There is evidence that CRF has a role in psychiatric disorders and neurological diseases including depression, anxiety-related disorders and feeding disorders. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimer's disease, Parkinson's disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis, as they relate to the dysfunction of CRF neurons in the central nervous system [for a review, see: E. B. De Souze, *Hosp. Practice* 23:59 (1988)]. Furthermore, CRF is known to have a broad extrahypothalmic distribution in the CNS, contributing therein to a wide spectrum of autonomic behavioral and physiological effects [see, e.g., Vale et al., 1983; Koob, 1985; and E. B. De Souze et al., 1985]. For example,

CRF concentrations are significantly increased in the cerebral spinal fluid of patients afflicted with affective disorder or major depression [C. B. Nemeroff et al., *Science* 226:1342 (1984); C. M. Banki et al., *Am. J. Psychiatry* 144:873 (1987); R. D. France et al., *Biol. Psychiatry* 28:86 (1988); M. Arato et al., *Biol. Psychiatry* 25:355 (1989)]. Moreover, excessive levels of CRF are known to produce anxiogenic effects in animal models [see, e.g., Britton et al., 1982; Berridge and Dunn, 1986 and 1987].

The density of CRF receptors is significantly decreased in the frontal cortex of suicide victims, consistent with a hypersecretion of CRF [C. B. Nemeroff et al., *Arch. Gen. Psychiatry* 45:577 (1988)]. In addition, there is a blunted adrenocorticotropin (ACTH) response to CRF (intravenously administered) observed in depressed patients [P.W. Gold et al., *Am. J. Psychiatry* 141:619 (1984); F. Holsboer et al., *Psychoneuroendocrinology* 9:147 (1984); P. W. Gold et al., *New Engl. J. Med.* 314:1129 (1986)]. Preclinical studies in rats and non-human primates provide additional support for the hypothesis that hypersecretion of CRF may be involved in the symptoms seen in human depression [R. M. Sapolsky, *Arch. Gen. Psychiatry* 46:1047 (1989)]. There is also preliminary evidence that tricyclic antidepressants can alter CRF levels and thus modulate the numbers of receptors in the brain [Grigoriadis et al., *Neuropsychopharmacology* 2:53 (1989)].

Neurochemical, endocrine and receptor binding studies have all demonstrated interactions between CRF and benzodiazepine anxiolytics, providing further evidence for the involvement of CRF in these disorders. Chlordiazepoxide attenuates the "anxiogenic" effects of CRF both in the conflict test [K. T. Britton et al., *Psychopharmacology* 86:170 (1985); K.T. Britton et al., *Psychopharmacology* 94:306 (1988)] and in the acoustic startle test [N. R. Swerdlow et al., *Psychopharmacology* 88:147 (1986)] in rats. The benzodiazepine receptor antagonist Ro 15-1788, which was without behavioral activity alone in the operant conflict test, reversed the effects of CRF in a dose-dependent manner while the benzodiazepine inverse agonist FG 7142 enhanced the actions of CRF [K. T. Britton et al., *Psychopharmacology* 94:396 (1988)]. Preliminary studies using the putative CRF receptor antagonist α-helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrates that the antagonist produces "anxiolytic-like" effects that are qualitatively similar to the benzodiazepines [C. W. Berridge and A. J. Dunn, *Horm. Behav.* 21:393 (1987), Brain Research Reviews 15:71 (1990)].

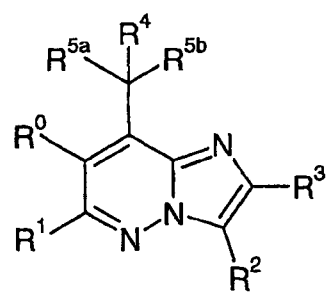
CRF receptor subtypes, CRF1 and CRF2, have been identified and are distributed heterogeneously within the brain [D. T. Chalmers et al., *TIPS* 17:166-72 (1996)] thereby suggesting potential functional diversity [S. C. Heinrichs et al., *Regul. Peptides* 71:15 (1997)]. For example, widely distributed brain CRF1 receptors are strongly implicated in emotionality accompanying exposure to environmental stressors [G. Liebsch et al., *Regul. Peptides* 59: 229-39 (1995); D. W. Schulz, *PNAS* 93: 10477-82 (1996)]. Significantly, CRF1, not CRF2, receptors appear to mediate select anxiogenic like behaviors [Heinrichs et al., 1997]. A more discrete septal/hypothalmic distribution [D. T. Chalmers et al., *J. Neurosci.* 15(10): 6340-50 (1995)] and the availability of alternative endogenous ligands [J. Vaughan et al., *Nature* 378: 287-92 (1995)] suggest an altogether different functional role for the CRF2 receptor [Heinrichs et al., 1997]. For example, a novel CRF-family neuropeptide with preferential affinity for CRF2 relative to CRF1 receptors is reported to suppress appetite without producing the profile of behavioral activation observed with selective CRF1 agonism (H. Tezval et al., *PNAS* 101(25): 9468-9473 (2004)]. In many cases, CRF2 agonism produces similar effects to those reported for CRF1 antagonists or CRF1 gene deletion [S. C. Heinrichs, *Trends in Pharmacological Sciences* 20(8):311-5 (1999)]. While CRF2 agonists have been proposed as antiobesity agents, CRF1 antagonists may be an important treatment for obesity as well [C. Contoreggi et al., *Neuroendocrinology* 80(2):111-23 (2004)].

In view of the above, efficacious and selective antagonists of CRF1 are desired as potentially valuable therapeutic agents for the treatment of psychiatric disorders and neurological diseases. It is thus desirable to discover new CRF1 antagonists.

SUMMARY OF THE INVENTION

The compounds of the present invention include CRF1 receptor antagonists.

One embodiment of the present invention is a compound of Formula I:



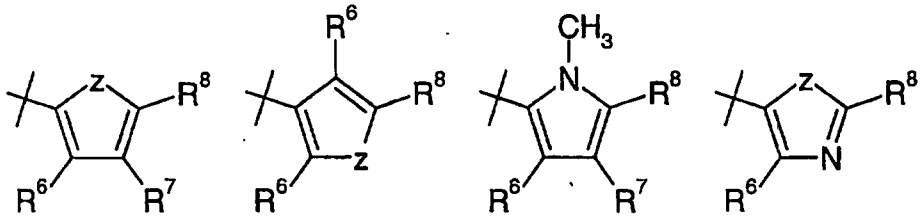
Formula I

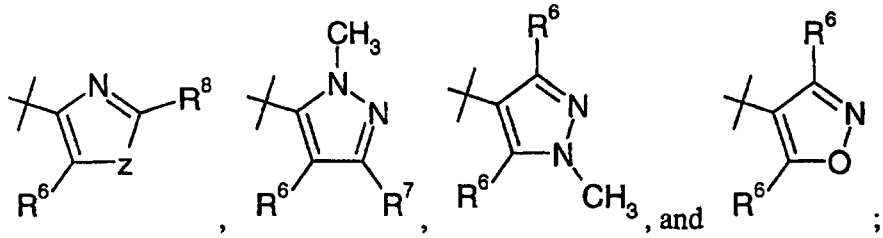
wherein:

R^0 is hydrogen, halo, methyl or ethyl;

R^1 and R^3 are independently methyl, methoxy, or trifluoromethyl;

R^2 is selected from the group consisting of:



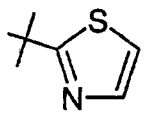


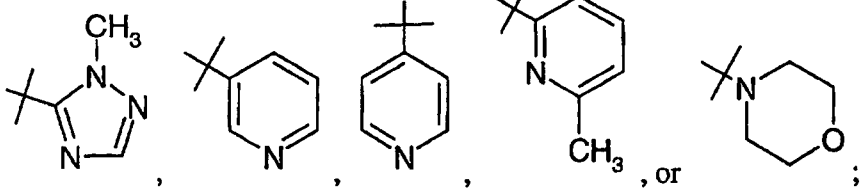
, and ;

R^4 is hydrogen, halo, or hydroxy;

R^{5a} and R^{5b} are independently ethyl or n-propyl;

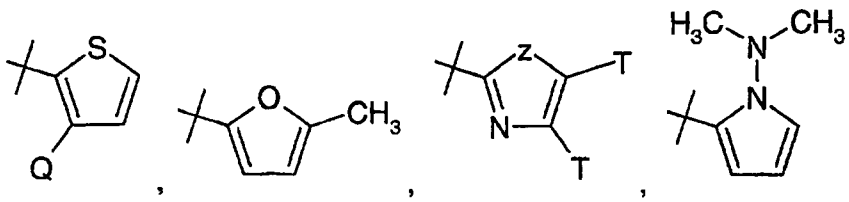
R^6 at each occurrence is independently hydrogen, halo, cyano, $(C_1\text{-}C_4)$alkyl, trifluoromethyl, methoxy, or phenyl;

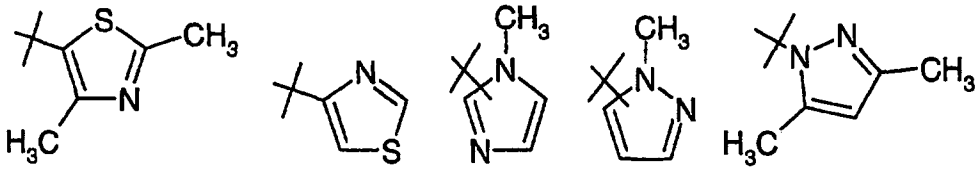
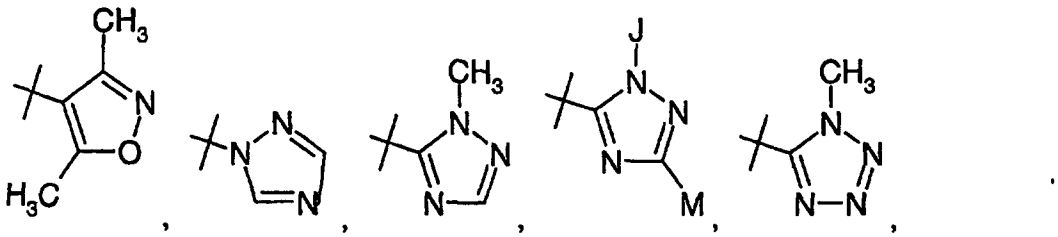
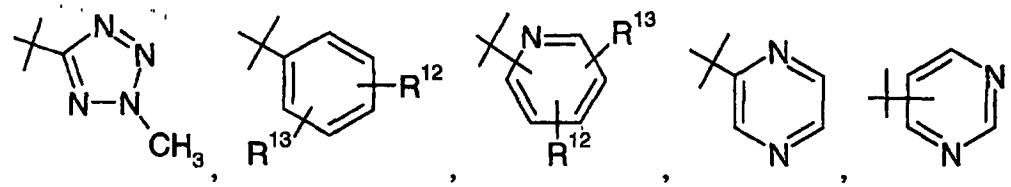
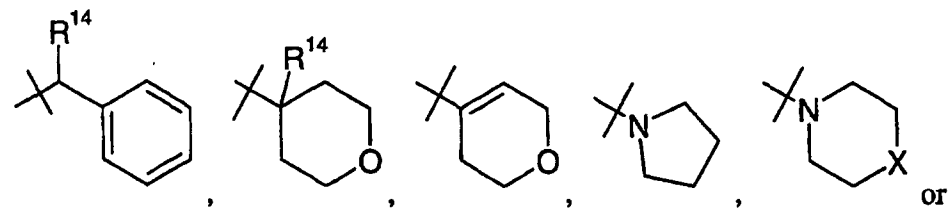
R^7 is hydrogen, halo, methyl, methoxy, dimethylamino,  ,



, or ;

R^8 is selected from the group consisting of hydrogen, halo, cyano, $(C_1\text{-}C_4)$alkyl, R^aR^bN-, carbamyl, $(C_1\text{-}C_2)$alkoxy$(C_1\text{-}C_2)$alkyl, R^{11}-C(O)-,



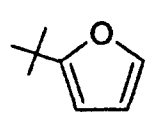
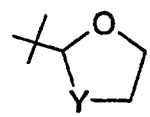

;

R^{11} is methoxy, methylamino, dimethylamino, or phenyl;

R^{12} is hydrogen, halo, methyl, ethyl, trifluoromethyl, methoxy, trifluoromethoxy dimethylamino, acetyl, or methylsulfonyl;

R^{13} is hydrogen, methyl or halo;

R^{14} is hydrogen or hydroxy;

R^{15} is methylthio, cyclopropyl, phenyl,  or  ;

R^a is hydrogen, $(C_1\text{-}C_5)$alkyl, $(C_3\text{-}C_5)$cycloalkyl, methoxy$(C_2\text{-}C_4)$alkyl, acetyl, $(C_1\text{-}C_2)$alkylsulfonyl, (C_3)alkenyl, $R^{15}\text{-}(CH_2)n\text{-}$, or $(C_1\text{-}C_2)$alkyl substituted with cyano, formyl, vinyl, or ethynyl;

R^b is hydrogen or $(C_1\text{-}C_3)$alkyl;

X is $-CH_2-$, -CO-, -O-, -S- or $-SO_2-$;

Y is -CH_2- or -O-;

z is S or O;

n is 1 or 2;

Q is hydrogen or methyl;

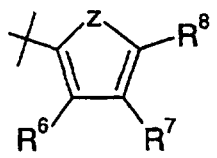
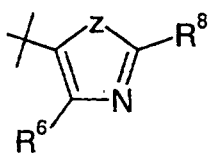
T is hydrogen or methyl;

J is methyl, trifluoroethyl, or tert-butyl; and

M is methyl or halo;

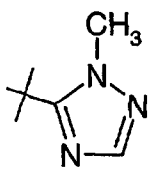
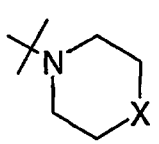
and pharmaceutically acceptable salts thereof.

Another embodiment of the present invention is a compound of Formula I wherein R^0 and R^4 are hydrogen, R^1 and R^3 are methyl, and R^{5a} and R^{5b} are ethyl.

Yet another embodiment of the present invention is a compound of Formula I wherein R^2 is selected from the group consisting of  or  where z is S.

A further embodiment of the present invention is a compound of Formula I wherein R^7 is hydrogen.

Another another embodiment of the present invention is a compound of Formula I wherein R^6 is halo or methyl.

Yet another embodiment of the present invention is a compound of Formula I wherein R^8 is  or  where X is O.

Another embodiment of the present invention is a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

Yet another embodiment of the present invention is a compound of Formula I, for use as a medicament.

A further embodiment of the present invention is use of a compound of Formula I for the manufacture of a medicament for treating anxiety, depression, major depressive disorder, alcohol withdrawal symptoms, or irritable bowel syndrome in a mammal. In another further embodiment, the mammal is a human.

DETAILED DESCRIPTION OF THE INVENTION

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Alkoxy" means an alkyl-O- group, wherein the alkyl group is as herein described. Exemplary alkoxy groups include methoxy, ethoxy, *n*-propoxy, *i*-propoxy, and *n*-butoxy.

"Alkyl" means a saturated aliphatic hydrocarbon group, which may be straight or branched, having 1 to 5 carbon atoms in the chain.

"Alkenyl" means an unsaturated aliphatic hydrocarbon group, which may be straight or branched, having 2 to 4 carbon atoms in the chain.

"Cycloalkyl" means a monocyclic group, having 3 to 5 carbon atoms.

"Halo" means fluoro, chloro, bromo, or iodo.

"Pharmaceutically acceptable salts" refers to the relatively non-toxic, inorganic and organic acid addition salts, and base addition salts, of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds. In particular, acid addition salts can be prepared by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Exemplary acid addition salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactiobionate, sulphamates, malonates, salicylates, propionates, methylene-bis-β-hydroxynaphthoates, gentisates, isethionates, di-p-toluoyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates and quinateslaurylsulphonate salts, and the like. See, for example S.M. Berge, et al.,

"Pharmaceutical Salts," J. Pharm. Sci., 66, 1-19 (1977). Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing. Company, Easton, Pa., 1985, p. 1418.

It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts thereof.

"Therapeutically effective amount" or "effective amount" means the amount of the compound of formula I of the present invention or pharmaceutical composition containing a compound of formula I of the present invention that will elicit the biological or medical response of or desired therapeutic effect on a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

The terms "treatment," "treat," "treating," and the like, are meant to include both slowing or reversing the progression of a disorder. These terms also include alleviating, ameliorating, attenuating, eliminating, or reducing one or more symptoms of a disorder or condition, even if the disorder or condition is not actually eliminated and even if progression of the disorder or condition is not itself slowed or reversed. The term "treatment" and like terms also include preventive (e.g., prophylactic) and palliative treatment. Prevention of the disease is manifested by a prolonging or delaying of the onset of the symptoms of the disease.

The symbol "——" in a molecular structure indicates the position of attachment for that particular substituent.

When any variable occurs more than one time in any constituent or in formula I, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. In choosing compounds of the present invention, one of ordinary skill in the art will recognize that the various substituents, i.e. R^1, R^2, etc., are to be chosen in conformity with well- known principles of chemical structure connectivity.

Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment. For example, an arylcarbonylaminoalkyl substituent is equivalent to aryl-C(O)-NH-alkyl-.

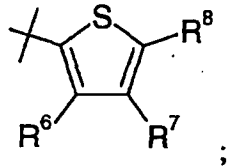
The present invention contemplates specific classes of compounds of Formula I. The following paragraphs describe such specific classes:

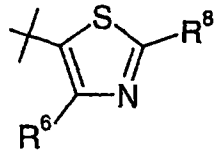
(a) R^0 is hydrogen;

(b) R^1 is methyl;

(c) R^3 is methyl;

(d) R^1 and R^3 are methyl;

(e) R^2 is  ;

(f) R^2 is  ;

(g) R^4 is hydrogen;

(h) R^{5a} is ethyl;

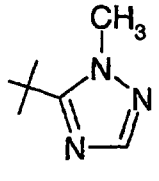
(i) R^{5b} is ethyl;

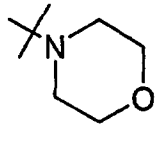
(j) R^{5a} and R^{5b} are ethyl;

(k) R^6 is halo;

(l) R^6 is methyl;

(m) R^7 is hydrogen;

(n) R^8 is  ;

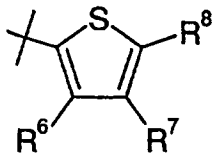
(o) R^8 is  .

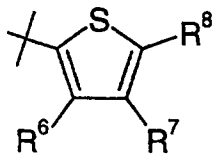
While all the compounds of Formula I are useful CRF1 receptor antagonists, the following paragraphs describe further specific classes:

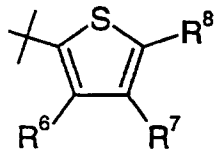
(a) Each of R^1 and R^3 is methyl and each of R^{5a} and R^{5b} is ethyl;

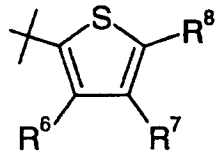
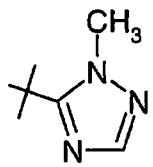
(b) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 is hydrogen;

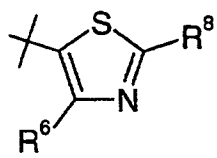
(c) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen;

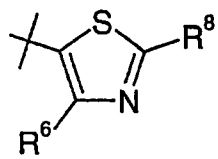
(d) R^2 is  and R^7 is hydrogen;

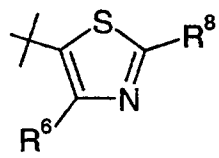
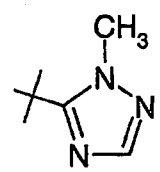
(e) R^2 is  , R^7 is hydrogen, and R^6 is halo;

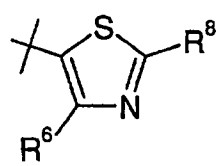
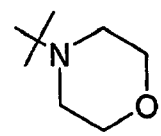
(f) R^2 is  , R^7 is hydrogen, and R^6 is methyl;

(g) R^2 is  , R^7 is hydrogen, and R^6 is halo or methyl, and R^8 is  ;

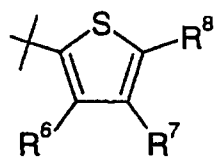
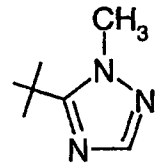
(h) R^2 is  and R^6 is halo;

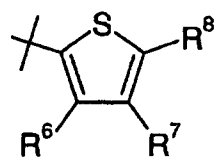
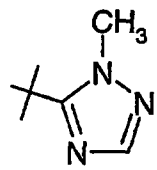
(i) R^2 is  and R^6 is methyl;

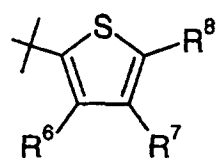
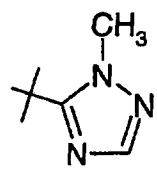
(j) R^2 is  , R^6 is halo or methyl, and R^8 is  ;

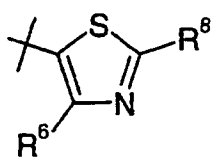
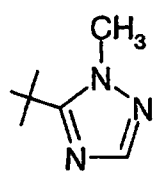
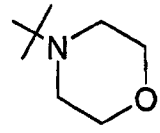
(k) R^2 is  , R^6 is halo or methyl, and R^8 is  .

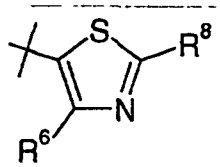
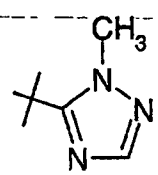
The following paragraphs describe even more specific classes of CRF1 receptor antagonists of the invention:

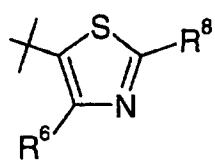
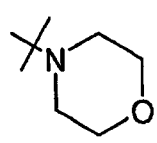
(a) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^7 is hydrogen, and R^6 is halo or methyl, and R^8 is  ;

(b) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^7 is hydrogen, and R^6 is halo, and R^8 is  ;

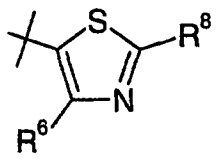
(c) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^7 is hydrogen, and R^6 is methyl, and R^8 is  ;

(d) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^6 is halo or methyl, and R^8 is  or  ;

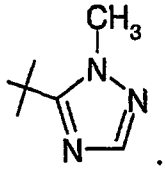
(e) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^6 is halo, and R^8 is  ;

(f) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^6 is halo, and R^8 is  .

(g) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is

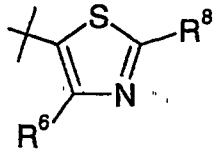


, R^6 is methyl, and R^8 is

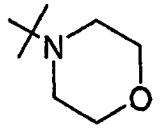


;

(h) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is



, R^6 is methyl, and R^8 is



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Preferably compounds of the invention exhibit a Ki value for CRF1 binding of 1 micromolar or less, more preferably of 500 nanomolar or less. Even more preferably, compounds of the invention exhibit a Ki value for CRF1 binding of 250 nanomolar or less, with 100 nanomolar or less being even further preferred. With even greater preference, compounds of the invention exhibit a Ki value for CRF1 binding of 30 nanomolar or less, while 15 nanomolar or less is even more greatly preferred. Compounds of the invention exhibiting a Ki value for CRF1 binding of 5 nanomolar or less are most preferred.

The present invention also provides a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, diluent, or excipient. A "pharmaceutically acceptable carrier, diluent, or excipient" is a medium generally accepted in the art for the delivery of biologically active agents to mammals, e.g., humans. Such carriers are generally formulated according to a number of factors well within the purview of those of ordinary skill in the art to determine and account for. These include, without limitation: the type and nature of the active agent being formulated; the subject to which the agent-containing composition is to be administered; the intended route of administration of the composition; and the therapeutic indication being targeted. Pharmaceutically acceptable carriers and excipients include both aqueous and non-aqueous liquid media, as well as a variety of solid and semi- solid dosage forms. Such carriers can include a number of different ingredients and additives in addition to the active agent, such additional ingredients being included in the formulation for a variety of reasons, e.g., stabilization of the active agent, well known to those of ordinary skill in the art. Descriptions of suitable

pharmaceutically acceptable carriers, and factors involved in their selection, are found in a variety of readily available sources, e.g., Remington's Pharmaceutical Sciences, 17 th ed., Mack Publishing Company, Easton, Pa., 1985.

These compounds of formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles.

The pharmaceutical compositions containing compounds of general formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Dosage forms suitable for administration generally contain from about 1 mg to about 300 mg of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of about 0.5 to 95% by weight based on the total weight of the composition. Appropriate coatings may be applied to increase palatability or delayed adsorption.

The compounds of formula I are antagonists at the CRF1 receptor and are useful in the treatment of anxiety disorders, depression, major depressive disorder, and stress related disorders. Anxiety disorders are a group of diseases, recognized in the art, that includes phobic disorders, anxiety states, post-traumatic stress disorder and atypical anxiety disorders [The Merck Manual of Diagnosis and Therapy, 16 th edition (1992)]. Emotional stress is often a precipitating factor in anxiety disorders, and such disorders generally respond to medications that lower response to stress. The compounds are also useful in smoking cessation programs. The method of treatment involves administration to a mammal (e.g. a human) an effective amount of a compound of the invention. In particular, therapeutically effective amounts of the compounds of this invention are amounts effective to antagonize, or lower, levels of corticotropin releasing factor (CRF) in a mammal (e.g. a human), thereby alleviating in the mammal's conditions characterized by abnormally high levels of CRF expression.

As such, the present invention provides a method for treating a condition which is treatable by reducing CRF1 receptor stimulation, comprising administering to the mammal (e.g. a human) in need thereof a compound of Formula I, or a pharmaceutically acceptable salt thereof, in an amount effective to antagonize CRF1 receptor stimulation.

The present invention also provides use of a compound of Formula I for the manufacture of a medicament for treating a condition which is treatable by reducing CRF1 receptor stimulation.

The present invention also provides a method of antagonizing CRF1 receptors in a warm-blooded animal, comprising administering to the animal a compound of the invention at amount effective to antagonize CRF1 receptors. The warm-blooded animal is preferably a mammal, and more preferably a human.

The present invention also provides a method of treating a disorder in a warm-blooded animal, which disorder manifests hypersecretion of CRF, or the treatment of which disorder can be effected or facilitated by antagonizing CRF1 receptors, comprising administering to the animal a therapeutically effective amount of a compound of the invention. The warm-blooded animal is preferably a mammal, and more preferably a human.

Compounds of Formula I, or a pharmaceutically acceptable salt thereof, are useful for treating various disorders and conditions in a mammal (e.g. human) including social anxiety disorder; panic disorder; obsessive-compulsive disorder; major depressive disorder; anxiety with co-morbid depressive illness; affective disorder; anxiety; depression; irritable bowel syndrome; post-traumatic stress disorder; supranuclear palsy; immune suppression; gastrointestinal disease; anorexia nervosa, bulimia, or other feeding disorder; drug or alcohol withdrawal symptoms; substance abuse disorder (e.g., nicotine, cocaine, ethanol, opiates, or other drugs); inflammatory disorder; fertility problems; disorders the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF; a disorder selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias; obsessive-compulsive disorder; sleep disorders induced by stress; stress- related illnesses; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, major depressive disorder, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; chronic fatigue syndrome; stress- induced headache; headache; cancer; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, senile

dementia of the Alzheimer's type, and multiinfarct dementia; gastrointestinal diseases such as ulcers, irritable bowel syndrome, Crohn's disease, spastic colon, diarrhea, and post operative ilius and colonic hypersensitivity associated by psychopathological disturbances or stress; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; obesity and the metabolic syndrome; infertility; premature birth; head traumas; spinal cord trauma; ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; cardiovascular and heart related disorders including hypertension, tachycardia and congestive heart failure; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., stress induced fevers, stress induced infections in humans and animals, porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, and dysfunctions induced by confinement in chickens, sheering stress in sheep or human-animal interaction related stress in dogs); muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions (e.g., dependences on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; osteoporosis; psychosocial dwarfism and hypoglycemia.

A compound of this invention can be administered to treat the above disorders or abnormalities by means that produce contact of the active agent with the agent's site of action in the body of a mammal (e.g. human), such as by oral or parenteral administration using appropriate dosage forms. The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals either as individual therapeutic agent or in combination of therapeutic agents. It can be administered alone, but will generally be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The therapeutically effective amounts of the compounds of the invention for treating the diseases or disorders described above in a warm-blooded animal can be determined in a variety of ways known to those of ordinary skill in the art, e.g., by administering various amounts of a particular agent to an animal afflicted with a particular condition and then determining the effect on the animal. Typically,

therapeutically effective amounts of a compound of this invention can be orally administered daily at a dosage of the active ingredient of 0.002 to 200 mg/kg of body weight. Ordinarily, a dose of 0.01 to 10 mg/kg in divided doses one to four times a day, or in sustained release formulation will be effective in obtaining the desired pharmacological effect. It will be understood, however, that the specific dose levels for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease. Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most CNS disorders, a dosage regimen of four-times daily or less is preferred. For the treatment of stress and depression, a dosage regimen of one or two-times daily is particularly preferred.

It will be appreciated that all combinations of specific and preferred embodiments discussed above and the examples discussed below are contemplated as being encompassed by the present invention, provided such combinations do not comprise inconsistent groupings. In addition, all examples described herein are for illustrative purposes, and are not intended to narrow the scope of the invention in any way.

Compounds of the invention can generally be prepared using the synthetic routes illustrated in the Schemes below. Starting materials can be prepared by procedures described in these schemes or by procedures that would be well known to one of ordinary skill in organic chemistry. The variables used in the schemes are as defined below or as in the claims.

The skilled artisan will appreciate that the introduction of certain substituents will create asymmetry in the compounds of Formula I. The present invention contemplates all enantiomers and mixtures of enantiomers and stereoisomers, that is, both the stereomerically pure form (e.g., geometrically pure, enantiomerically pure, or diastereomerically pure) and enantiomeric and stereoisomeric mixtures, including racemates. Enantiomeric and stereoisomeric mixtures can be resolved into their component enantiomers or stereoisomers by well known methods, such as chiral phase gas chromatography, chiral-phase high performance liquid chromatography, or crystallizing the compound as a chiral salt complex. Enantiomers and stereoisomers can

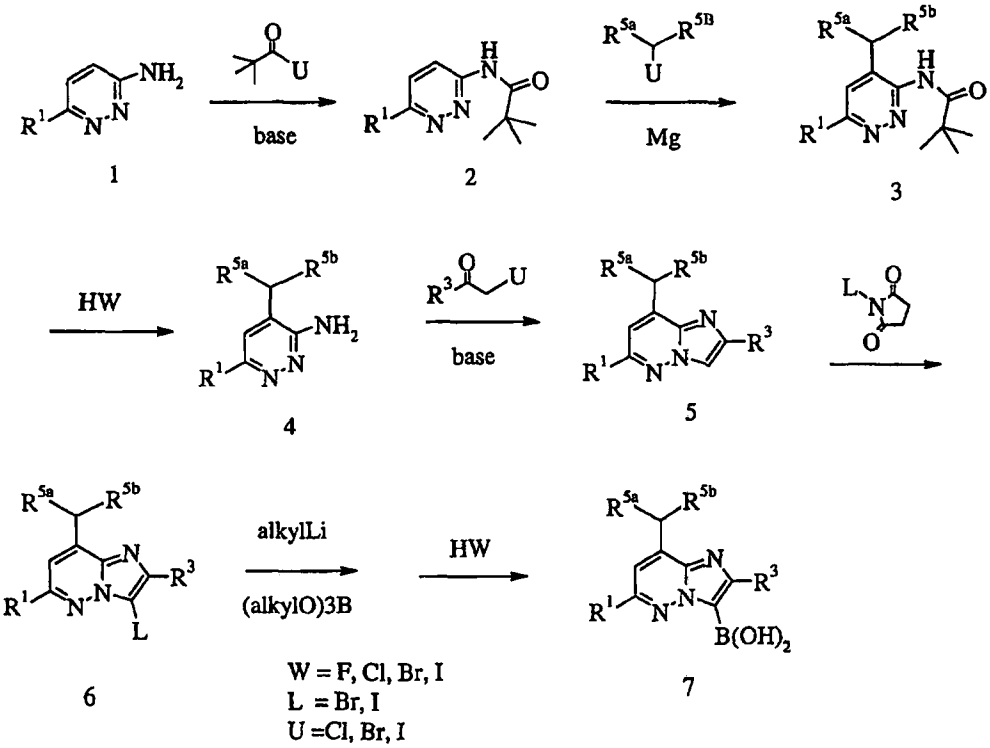
also be obtained from stereomerically- or enantiomerically-pure intermediates, reagents, and catalysts by well known asymmetric synthetic methods.

Pharmaceutically acceptable salts are contemplated to be within the scope of the present invention. The compounds of the present invention are bases and salts of such compounds may be formed with acids, for example, a salt with inorganic acid such as hydrochloric acid or a salt with organic acid such as trifluoroacetic acid.

The compounds of this invention may be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature or exemplified in the experimental procedures. These schemes, therefore, are not limited by the compounds listed nor by any particular substituents employed for illustrative purposes.

Scheme I

Synthesis of Imidazo[1,2-b]pyridazine fragment



R^1, R^3, R^{5a}, and R^{5b} are defined supra.

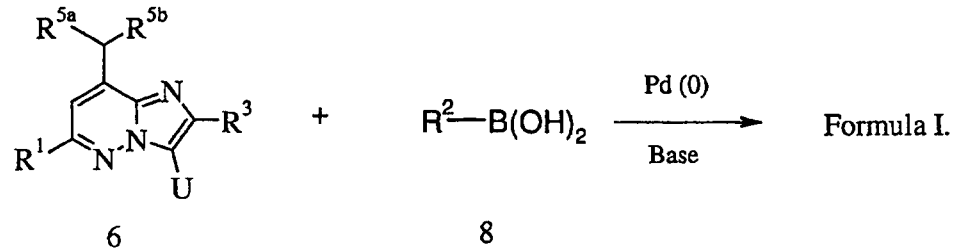
In Scheme I, a substituted 3-amino-pyridazine 1 is acylated with pivaloyl halide and a base, e.g., triethylamine in a polar aprotic solvent, e.g., methylene chloride at from

room temperature to the reflux to give amide 2. Amide 2 is treated with a Grignard reagent in diethylether or THF to give the 4-substituted amide 3. Amide 3 is hydrolyzed with aqueous HCl at from room temperature to 110 °C then neutralized to provide free amine 4. Amine 4 is treated with an alpha-halo ketone and base, e.g., sodium bicarbonate in 95% ethanol at from room temperature to 110 °C to give imidazopyridazine 5. Imidazopyridazine 5 is treated with a halogenating reagent e.g., N-iodo or N-bromosuccinimide in a polar aprotic solvent (e.g., acetonitrile) at from 0 °C to room temperature to give halide 6. Halide 6 undergoes halogen metal exchange with an alkyl lithium reagent, e.g., n-, sec-, or tert- butyllithium in diethylether or THF at from –78 °C to room temperature, followed by treatment with a trialkylborate, e.g., trimethylborate to give an intermediate boronic ester, which is hydrolyzed upon workup with aqueous HCl to provide boronic acid 7.

Scheme II

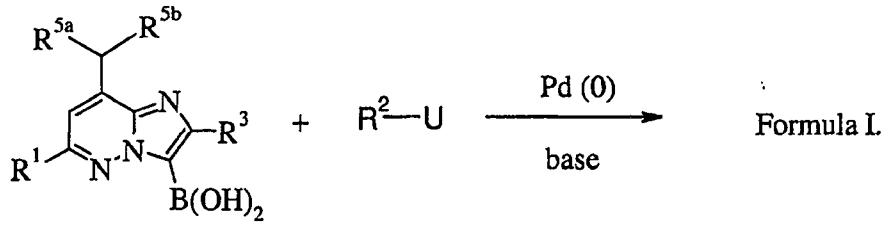
Synthesis of Compounds of Formula I by transition metal catalysis.

Equation 1.



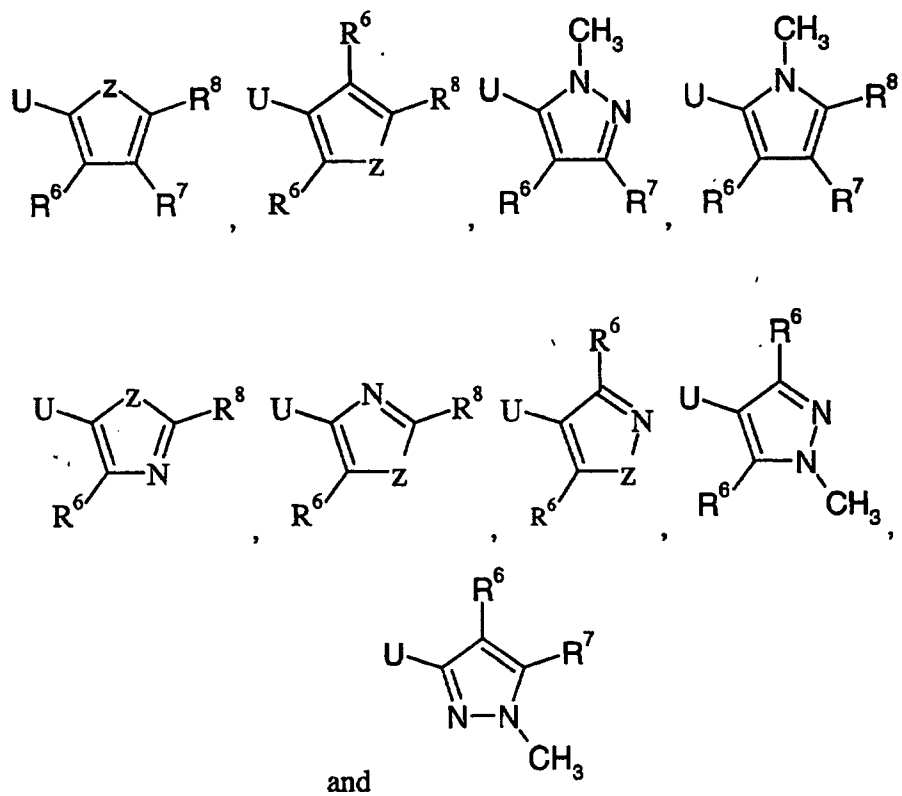
6 8

Equation 2.



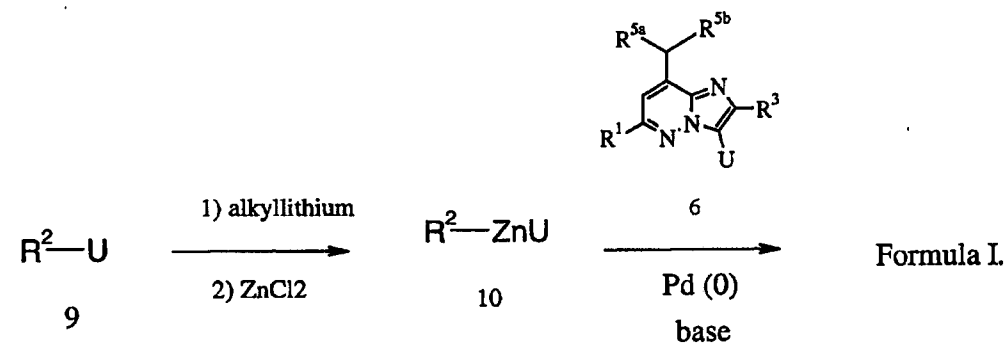
7 9

Where R^2-U is selected from the group consisting of:

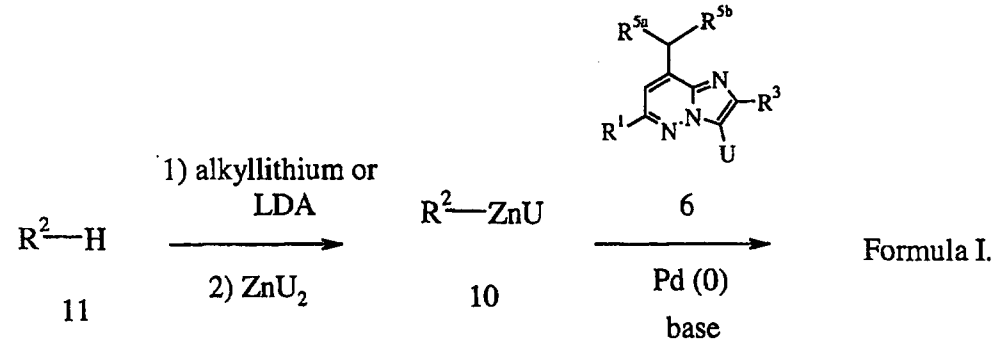


and

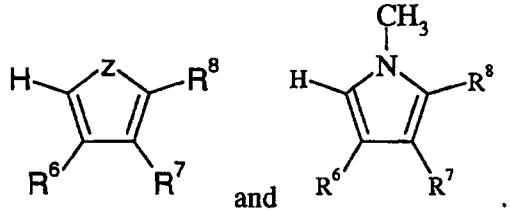
Equation 3.



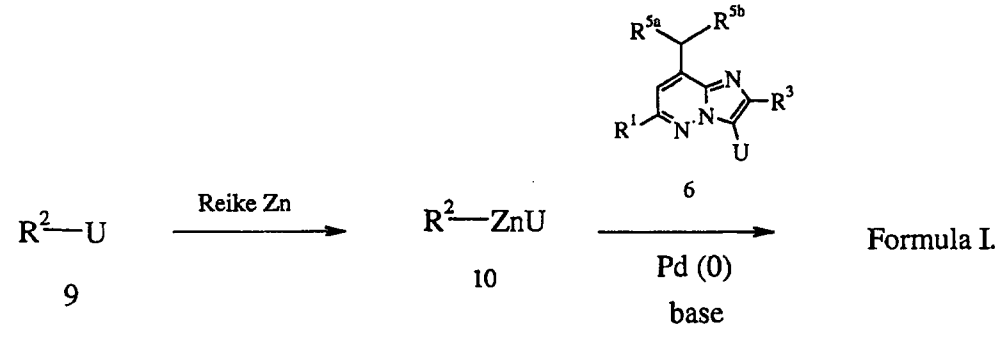
Equation 4.



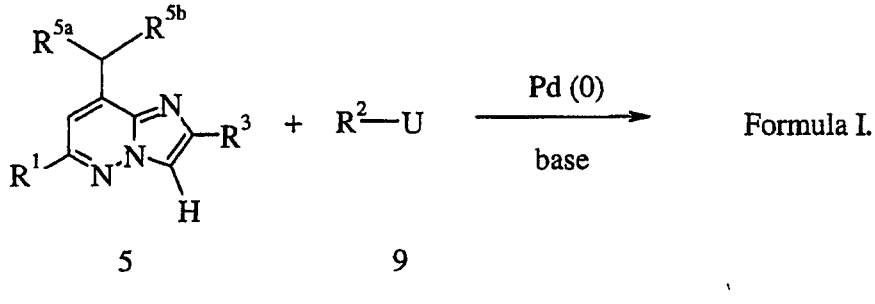
Where R^2-H is selected from the group consisting of:



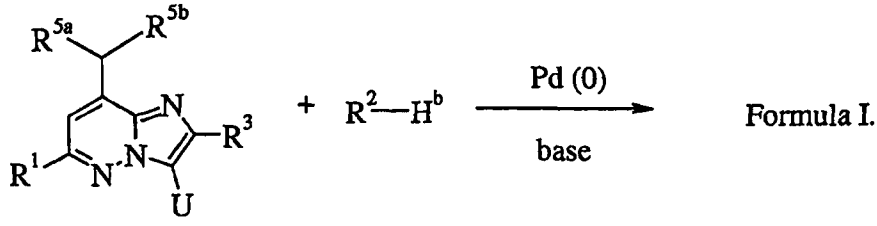
Equation 5.



Equation 6.

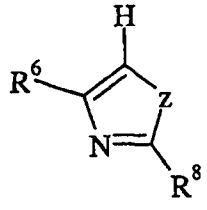


Equation 7.



6 12

Where R^2-H^b is selected from:



R^1, R^2, R^3, R^{5a}, R^{5b} R^6, R^7, R^8, U, and z are defined supra.

In Scheme II equation 1, halide 6 can be used in a coupling reaction with a 5-membered ring heterocyclic boronic acid 8 in the presence of palladium catalysis, e.g., tetrakis-triphenylphosphine palladium (0) in a lower alkanol (methanol or n- or i-propanol)/DME mixture at from 70-120 °C to give compounds of formula I.

Alternately in equation 2, boronic acid 7 can be used in a coupling reaction with a 5 membered ring heterocyclic halide 9 and palladium catalysis, e.g., tetrakis-triphenylphosphine palladium (0) in a lower alkanol (methanol or n- or i-propanol)/DME mixture at from 70-120 °C to give a compound of formula I.

In equation 3, 5-membered ring heterocyclic halides 9 may undergo halogen-lithium exchange with, e.g., n-, sec- or tert-butyl lithium in THF or ether at –65 °C, followed by lithium-zinc exchange with $ZnCl_2$ in either diethylether or THF at temperatures up to room temperature. The *in situ* organozinc reagent 10 may then undergo coupling with halide 6 in the presence of palladium, e.g., $PdCl_2$(dppf) in THF at from 70-120°C to give a compound of formula I.

In equation 4, a 5-membered heterocyclic ring with a ring proton may be lithiated by either an alkyllithium, e.g., n-, sec- or tert-butyl lithium or lithium diisopropyl amide in THF or ether at –65 °C to room temperature followed by lithium-zinc exchange with

anhydrous zinc halide in either diethylether or THF to give an organozinc reagent 10 that is used as in equation 3 above. One skilled in the art will also appreciate that commercially available organozinc reagents 10 can be used directly as an organozinc coupling partner.

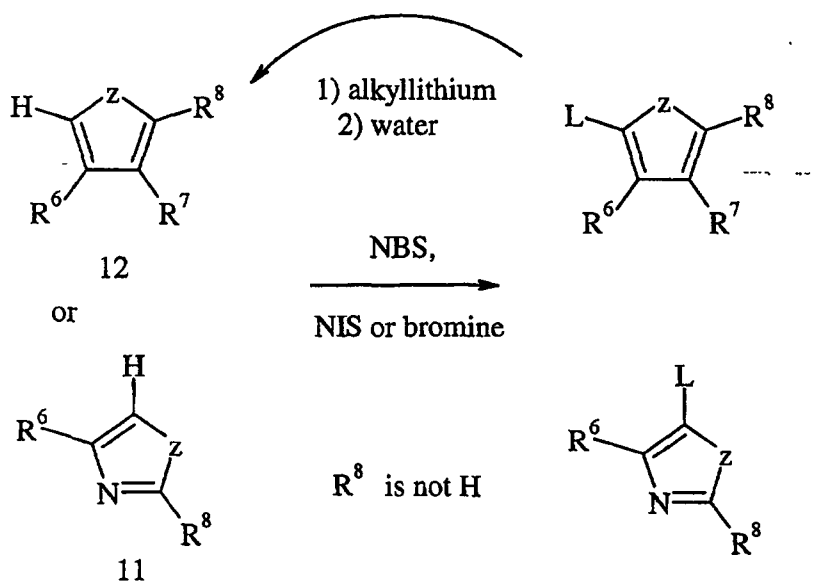
Furthermore from equation 5, it may be advantageous or convenient to use Reike Zn in THF to directly convert a 5-membered ring heterocyclic halide 9 to an organozinc reagent 10 for coupling with a halide 6.

In equation 6, a 5 membered heterocyclic halide 9 can be directly coupled with the imidazo[1,2-b]pyridazine intermediate 5 in the presence of palladium, e.g., $Pd_2(dba)_3$, $PdCl_2$, Palladium acetate/TDBPP, or tetrakis-triphenylphosphine palladium (0) in DMF, THF, or NMP solvent from 70-120°C to give a compound of formula I.

Alternately, from equation 7, the imidazo[1,2-b]pyridazine halide 6 may be directly coupled with a 5 membered heterocycle 11 in the presence of palladium, e.g., $Pd_2(dba)_3$, $PdCl_2$ or Palladium acetate/TDBPP in DMF, THF, or NMP solvent from 70-120 °C to give a compound of formula I.

Scheme III

Synthesis of Substituted 5 Membered Heterocyclic Halides



R^6, R^7, R^8, L, and z are defined supra.

Several 5 membered heterocyclic rings and/or their bromides and/or iodides useful as starting materials for the synthesis of compounds of Formula I are commercially available or may be prepared by methods well know to the skilled artisan. From Scheme III, they may also be prepared by halogenation, e.g., with bromine, NBS or NIS. Furthermore, some of the intermediates 11 and 12 may be prepared by lithium halogen exchange followed by water quench.

Compounds of Formula I as intermediates in the preparation of other compounds of Formula I include the addition of aryllithium reagents (generated by the methods of equations 3 and 4 in Scheme II) to carbonyl compounds, e.g., aldehydes, ketones, esters, and Weinreb amides. The resulting carbinols or carbonyl compounds are further elaborated by halogenation under acidic conditions and by a second aryllithium addition, respectively.

Abbreviations

TBDMSCl or TBDMSiCl – tert-butyl-dimethylsilyl chloride

MS (ES) – Electrospray Mass spectrum

THF – tetrahydrofuran

DMSO – Dimethylsulfoxide

DMF – Dimethylformamide

DCM, CH2Cl2 – dichloromethane

Dioxane – 1,4-dioxane

N2 – nitrogen gas

NIS – N-iodosuccinimide

NBS – N-bromosuccinimide

MeOH - methanol

EtOH – 95% ethanol

RBF, RB – round bottom flask

RBSN – round bottom single neck flask

SiO2 – silica gel

EtOAc, AcOEt – ethylacetate

GFF - glass microfiber filter

HPLC – high pressure liquid chromatography on silica gel

ISCO – ISCO brand low pressure liquid chromatography on silica gel

AcCl – acetyl chloride

LDA – lithium diisopropylamine

KOAc – Potassium Acetate

TBABr – Tetrabutyl ammonium bromide

NMP – N-Methylpyrrolidinone

TDBPP – Tris (2,4-di-*t*-butylphenyl) phosphite.

Pd_2dba_3 – Tris(dibenzylideneacetone)dipalladium

$PdCl_2(dppf)$ – Dichloro(diphenylphosphinoferrocene)palladium

Tetrakis – tetrakis-(triphenylphosphine)-palladium

Dppf - 1,1'-bis(diphenylphosphino)ferrocene)

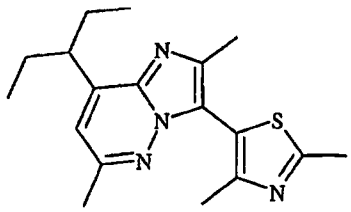
r.t., RT – room temperature

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following examples are provided to describe the invention in further detail. They are intended to illustrate and not to limit the invention in any way whatsoever. Examples 1-255 provide exemplary compounds and illustrate the preparation thereof. Examples A-D illustrate various biological assays that can be used for determining the biological properties of the compounds of the inventions. Those skilled in the art will promptly recognize appropriate variations from the procedures described in the examples.

Example 1.

Preparation of 8-(1-ethyl-propyl)-3-(2,4-dimethyl-5-thiazolyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 6-Methyl-pyridizin-3-ylamine.

3-Chloro-6-methylpyridazine (25.0g, 0.229 moles) is dissolve in 250 mL of NH_4OH and heated to 170 °C in a sealed container for 24 hours. The solvents are evaporated. The residue is triturated in methylene chloride, and a solid is filtered. This trituration procedure is repeated with the filtrate four times. The filtered solids are combined and dried in a vacuum oven overnight to obtain the title compound as an off-white solid 4.32 g (0.040 moles, 20%). ^{1}H-NMR (dmso-d6): δ 7.1 (d, J = 8.9 Hz, 1H); 6.67 (d, J = 8.9 Hz, 1H); 6.04 (s, br, 2H); 2.33 (s, 3H) ppm. ES+ = 110 (100%, M + 1).

B. 2,2-Dimethyl-N-(6-methyl-pyridazine-3-yl)-propionamide.

Method 1: To a dry flask is added 7.12 g (0.065 mole) of 6-methyl-pyridizin-3-ylamine in 170 ml dry methylene chloride. Next, 14.5 ml of triethylamine is added and the reaction is cooled to 0 °C. Pivaloyl chloride (2.7 ml, 1.2 eq) is carefully added, and the reaction mixture is stir 10 minutes, removed from the bath, and stirred 4 hours more. Dichloromethane (200 mL) is added, and the reaction mixture is washed 3 times with saturated aqueous sodium bicarbonate, then brine. The organic layer is dried over sodium sulfate, filtered, and evaporated to an oil. The crude product is purified via silica gel chromatography using a hexane:ethyl acetate gradient giving the title compound as a white solid weighing 1.51 g (7.8 mmoles, 42.7%). ^{1}H-NMR (DMSO-d_6), δ 10.39 (s, 1H); 8.11 (d, J = 9.30 Hz, 1H); 7.51 (d, J = 9.29 Hz, 1H); 2.54 (s, 3H); 1.23 (s, 9H) ppm. ES^+ = 194 (M+1).

Method 2: To a dry pressure tube is added 200 mg (1.56 mol) of 3-chloro-5-methylpyridazine, 190 mg (1.87 mmol) of trimethylacetamide, 14.6 mg (0.023 mmol) of rac-2,2'-bis(diphenylphosphine)-1,1'-binaphthyl , tris(dibenzylideneacetone)-dipalladium (0) , 762.4 mg (2.34 mmol) of cesium carbonate and 1.5 ml dry tetrahydrofuran. The pressure tube is purged with nitrogen and sealed. The reaction is heated to 100 °C overnight. The reaction is then cooled, diluted with dichloromethane, and filtered through celite. Solvents are evaporated and the crude product is purified via silica gel chromatography using a ethyl acetate:hexane gradient to obtain 91 mg (0.47 mmol, 30%) as a white solid.

C. N-[4-(1-Ethyl-propyl)-6-methyl-pyridazin-3-yl]-2,2-dimethyl-propionamide.

Activated magnesium powder (19.2 g, 0.792 moles) is added to a dry 3 L flask fitted with a condensor and a drop funnel. The entire apparatus is heated with a gun dry under vacuum and allowed to cool. Enough ether is added to cover the magnesium. 3-Bromopentane (100 g, 0.662 mmol) is added to the addition funnel in 175 ml of diethyl ether. A 1/3 of the bromopentane solution is added to the magnesium and the reaction mixture is stirred under nitrogen until bubbling occurs. Then, the rest is dripped in at such a rate that the bubbling continues gently. The reaction is stirred for 30 minutes after bubbling ceases. Next, 2,2-dimethyl-*N*-(6-methyl-pyridazine-3-yl)-propionamide (21.3 g, 0.110 mmol) dissolved in 225 ml of dry THF is added dropwise. The reaction mixture is stirred for 1 hour. Saturated sodium tartrate (1 L) is carefully added, and the reaction is stirred for 30 minutes. The reaction mixture is transferred to a larger flask, 2 L of ethyl acetate is added, and the reaction is stirred 1 hour more. The layers are separate and the aqueous layer is extracted several times with ethyl acetate. The organic extracts are combined, and the solvents are evaporated. The residue is taken up in 600 mL of dichloromethane, and iodine (28 g, 0.110 mol) is added. The reaction is stirred for 2 hours. The organic layer is washed once with aqueous solution of sodium sulfite and then with water. The organic layer is dried over sodium sulfate, filtered, and evaporated to red oil. The crude product is purified via silica gel chromatography using a hexanes:ethyl acetate gradient. The product fractions are combined and evaporated. The residue is triturated in ethyl acetate and a light tan solid is filtered to obtain 12.0 g (45.6 mmol, 41 %) of the title compound. ^{1}H-NMR (DMSO-d_6), δ 9.88 (s, 1H); 7.59 (s, 1H); 2.60 (s, 3H); 2.39-2.42 (m, 1H); 1.21-1.37 (m, 2H); 1.38-1.43(m, 2H); 1.23(s, 9H); 0.71 (t, J = 7.49 Hz, 6H) ppm. MS/ES$^+$ = 264.

D. 4-(1-Ethyl-propyl)-6-methyl-pyridazin-3-ylamine.

N-[4-(1-Ethyl-propyl)-6-methyl-pyridazin-3-yl]-2,2-dimethyl-propionamide (12.0 g, 45 mmol) is dissolved in 60 mL of concentrated hydrochloric acid. The reaction mixture is heated to 95 °C in a sealed flask for 2 hours. The reaction is worked up by pouring over ice and extracting with ethyl acetate three times. The organic layer is discarded, and the pH of the aqueous layer is adjusted using 2 N sodium hydroxide. The basic solution is extracted with ethyl acetate five times. The organic extracts are

combined, dried over magnesium sulfate, filtered, and evaporated to obtain 6.68 g (37 mmol, 81%) of the title compound as a brownish oil. ^{1}H-NMR (DMSO-d_6), δ 6.95 (s, 1H); 5.89 (s, br, 2H); 2.52-2.56 (m, 1H); 2.34 (s, 3H); 1.44-1.58 (m, 4H); 0.72 (t, J = 7.04 Hz, 6H) ppm. MS/ES$^+$ = 180 (100%, M+1).

E. 8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

4-(1-Ethyl-propyl)-6-methyl-pyridazin-3-ylamine (850 mg, 4.74 mmol), chloroacetone (0.415 ml, 5.22 mL) and 20 mL of ethanol are heated in the microwave at 110 °C for 35 minutes. Sodium bicarbonate (1.2 g, 14.2 mmol) is added, and the reaction mixture is heated in an oil bath at 100 °C overnight. The solvent is evaporate and the residue is taken up in ethyl acetate and washed three times with brine. The organic layer is dried over sodium sulfate, filtered, and evaporated to a brown oil. The crude product is purified via silica gel chromatography using a hexane:ethyl acetate gradient. The title compound is an oil weighing 3.69 g (17.0 mmol, 84%). ^{1}H-NMR (DMSO-d_6), δ 7.34 (s, 1H); 6.84 (s, 1H); 2.85-3.10 (m, 1H); 2.43 (s, 3H); 2.32 (s, 3H); 1.70-1.80 (m, 4H); 0.712 (t, J = 7.49 Hz, 6H) ppm. MS/ES$^+$ = 219 (100%, M+2).

F. 8-(1-Ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (5.1 g, 0.023 moles) and 50 mL of dry acetonitrile are added to a nitrogen purged flask and are cooled to 0 °C. *NIS* (5.54 g,0.025 moles) in 90 mL of dry acetonitrile is added. The bath is allowed to come to room temperature, and the reaction to stir overnight. The solvents are evaporated. The residue is taken up in ethyl acetate, washed two times with 50% aqueous solution of sodium thiosulfate and with brine. The organic layer is dried over sodium sulfate, filtered, and evaporated to a residue again. The crude product is triturated in a small amount of acetonitrile, and a solid is filter off. The trituration is repeated several times to obtain the title compound as a light tan solid weighing 7.29 g (0.021 moles, 91%). ^{1}H-NMR (DMSO-d_6), δ 6.96 (s, 1H); 3.0-3.3 (m, 1H); 2.51 (s, 3H); 2.35 (s, 3H); 1.71-1.80 (m, 4H); 0.71 (t, J = 7.48 hz, 6H) ppm. MS/ES$^+$ = 344 (100%, M+1).

G. 8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine-3-yl boronic acid.

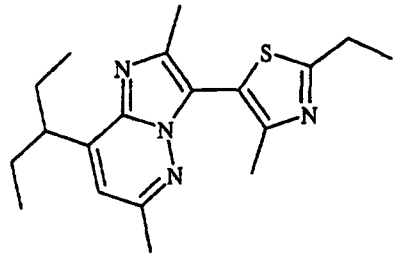
In an oven dried nitrogen purged 3 neck 50mL round bottom flask, 1.00g (2.91 mmol) of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine in 60mL of dry THF is cooled to -78°C. 4.12mL (7.00mmol) of 1.7 M tert-butyllithium in hexanes is added and reaction is stirred at -78 °C for 1 hour. 0.818mL (7.30mmol) of trimethyl borate is added and reaction is followed by MS and TLC (1:1 Hexane:EA) Indication of product is observed by mass spectrum. The reaction is allowed to stir for an additional hour, quenched with 1 N hydrochloric acid, and diluted with ethyl acetate. The organic layer is separated, and the aqueous layer is extracted three times with 100 mL of ethyl acetate. The extracts are combined, dried over $MgSO_4$, filtered, and concentrated. The reaction residue is triturated in hexanes and a solid is filter off. MS, ES^+ = 262.2 (M+1).

H. 8-(1-Ethyl-propyl)-3-(2,4-dimethyl-5-thiazolyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a microwave pressure tube is added 0.340g (1.30mmol) of 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine-3-yl boronic acid, 0.100g (0.521mmol) of 5-bromo-2,4-dimethylthiazole, 0.361g (0.313mmol) of Pd(PPh3)4, 0.650mL (1.30mmol) of 2 M aqueous Na2CO3, and 2mL 7:3:2 DME:H2O:EtOH, and the mixture is heated at 160 °C for 40min. Reaction is checked by MS which indicates product present. The reaction mixture is partitioned between 75mL of ethyl acetate and 75mL of water. The layers are separated and the aqueous is extracted 3X50mL of ethyl acetate, dried (MgSO4), and concentrated under vacuum. The crude mixture is purified by chromatography using hexanes/ethyl acetate as a solvent system. The product containing fractions are combined to obtain 0.100g of the product, 58% yield. MS, ES+ = 329.2 (M+1); ^{1}H-NMR (DMSO-d6) = 6.974 (s, 1H); 3.085-3.052 (m, 1H); 2.665 (s, 3H); 2.438 (s, 3H); 2.290 (s, 3H); 2.147 (s, 3H); 1.849-1.727 (m, 4H); 0.776-0.738 (m, 6H) ppm.

Example 2.

Preparation of 8-(1-ethyl-propyl)-3-(2-ethyl-4-methyl-5- yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 5-Bromo-2-ethyl-4-methylthiazole.

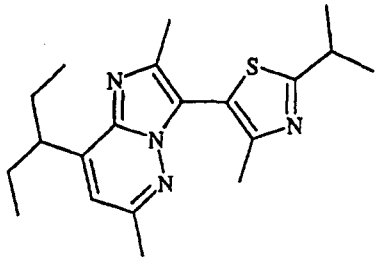
In an oven dried, N_2 purged, 50 mL round bottom flask, 1.00 g (7.86 mmol) of 2-ethyl-4-methylthiazole is reacted with 0.487 mL (9.43 mmol) of bromine in 7mL of acetic acid at room temperature. Reaction is checked by MS after 2 hours. The reaction mixture is partitioned between 50 mL H_2O and 25 mL of CH_2Cl_2. The layers are separated and the aqueous is extracted 3X25mL of CH_2Cl_2. The organics are combined and washed 1X25mL 1N $Na_2S_2O_3$, dried ($MgSO_4$), and concentrated under vacuum to give 1.38g of the title compound, 85% yield. MS, ES+ = 206.0 (M+1); ^{1}H-NMR (DMSO-d6) = 2.940-2.810 (m, 2H); 2.253-2.251 (m, 3H); 1.225-1.222 (m, 3H) ppm.

B. 8-(1-Ethyl-propyl)-3-(2-ethyl-4-methyl-5-thiazolyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure similar to Example 1H, 5-bromo-2-ethyl-4-methylthiazole produces the title product in 27% yield. MS, ES+ = 343.2 (M+1); ^{1}H-NMR (DMSO-d6) = 6.975 (s, 1H); 3.090-3.056 (m, 1H); 3.025-2.968 (m, 2H); 2.439 (s, 3H); 2.291 (s, 3H); 2.155 (s, 3H); 1.835-1.744 (m, 4H); 1.338-1.300 (m, 3H); 0.776-0.740 (m, 6H) ppm.

Example 3.

Preparation of 8-(1-ethyl-propyl)-3-(2-isopropyl-4-methyl-5-thiazolyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 5-Bromo-2-isopropyl-4-methylthiazole.

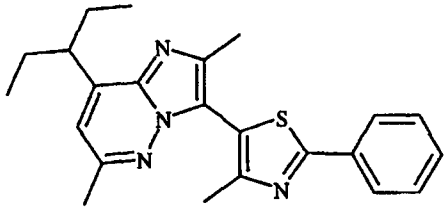
Using a procedure similar to Example 2A, 2-isopropyl-4-methylthiazole produces the title product in 90% yield. MS, ES+ = 220.0 (M+1); ^{1}H-NMR (DMSO-d6) = 3.210-3.175 (m, 1H); 2.257 (s, 3H); 1.264-1.248 (d, 6H) ppm.

B. 8-(1-Ethyl-propyl)-3-(2-isopropyl-4-methyl-5-thiazolyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure similar to Example 1H, 5-bromo-2-isopropyl-4-methylthiazole produces the title product in 29% yield. MS, ES+ = 357.2 (M+1); ^{1}H-NMR (DMSO-d6) = 6.990 (s, 1H); 3.120-3.050 (m, 1H); 2.442 (s, 3H); 2.294 (s, 3H); 2.158 (s, 3H); 1.810-1.750 (m, 4H); 1.362-1.344 (d, 6H); 0.777-0.741 (m, 6H) ppm.

Example 4.

Preparation of 8-(1-ethyl-propyl)-3-(4-methyl-2-phenyl-5-thiazolyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 5-Bromo-4-methy-2-phenylthiazole.

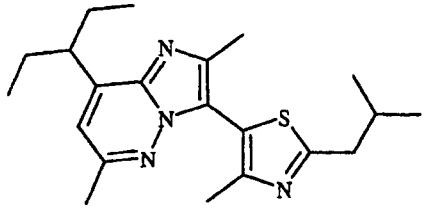
Using a procedure similar to Example 2A, 4-methyl-2-phenylthiazole produces the title product in 90% yield. MS, ES+ = 256.0 (M+1); ^{1}H-NMR (DMSO-d6) = 7.900-7.867 (m, 2H); 7.538-7.512 (m, 3H); 2.407 (s, 3H) ppm.

B. 8-(1-Ethyl-propyl)-3-(4-methyl-2-phenyl-5-thiazolyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure similar to Example 1H, 5-bromo-4-methyl-2-phenylthiazole produces the title product in 24% yield. MS, ES+ = 391.3 (M+1); ^{1}H-NMR (DMSO-d6) = 8.005-7.995 (m, 2H); 7.538-7.534 (m, 3H); 7.010 (s, 1H); 3.185-3.095 (m, 1H); 2.496 (s, 3H); 2.394 (s, 3H); 2.316 (s, 3H); 1.895-1.785 (m, 4H); 0.826-0.788 (m, 6H) ppm.

Example 5.

Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(2-methyl)propyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 5-Bromo-4-methy-2-(2-methyl)propylthiazole.

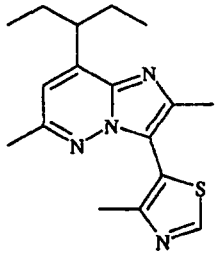
Using a procedure similar to Example 2A, 4-methyl-2-(2-methyl)propylthiazole produces the title product in 96% yield. MS, ES+ = 234.1 (M+1); ^{1}H-NMR (DMSO-d6) = 2.744 (m, 2H); 2.259 (s, 3H); 1.895-2.000 (m, 1H); 0.905-0.888 (m, 6H) ppm.

B. 8-(1-Ethyl-propyl)-3-(4-methyl-2-(2-methyl)propyl-5-thiazolyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure similar to Example 1H, 5-bromo-4-methyl-2-(2-methyl)propylthiazole produces the title product in 7% yield. MS, ES+ = 371.3 (M+1); ^{1}H-NMR (DMSO-d6) = 7.013 (s, 1H); 3.109 (m, 1H); 2.892-2.875 (d, 2H); 2.517 (s, 3H); 2.513 (s, 3H); 2.476 (s, 3H); 2.107-2.073 (m, 1H); 1.868-1.780 (m, 4H); 1.018-1.002 (d, 6H); 0.813-0.775 (m, 6H) ppm.

Example 6.

Preparation of 8-(1-Ethyl-propyl)-3-[4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

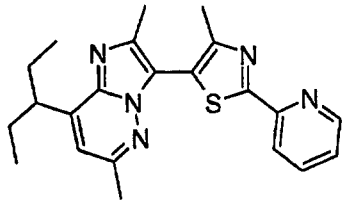


3.00 g of 8-(1-Ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (8.74 mmol), 4.32 g of 4-methyl-2*H*-thiazole (43.6 mmol), 453 mg of triphenylphosphine (1.73 mmol) and 5.85 g of cesium carbonate (18.0 mmol) are placed into the sealed tube with

20 ml of DMF and N2 gas is bubbled in for 40 min. 39 mg of Pd2dba3 (0.43 mmol) is added and the tube is sealed and heated at 130°C overnight. The cooled reaction mixture is filtered and applied onto silica-gel column (Hexane → Hexane : AcOEt = 3: 1) to give 2.12 g of the title compound (77%).^{1}H-NMR (DMSO-d6) δ 9.215 (s, 1H); 6.993 (s, 1H); 3.079 (m, 1H); 2.480 (s, 3H); 2.439 (s, 3H); 2.302 (s, 3H); 1.824-1.751 (m, 4H); 0.780-0.743 (m, 6H) ppm. MS, ES+ = 315.2.

Example 7.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-2-pyridin-2-yl-thiazol-5-yl)-imidazo[1,2-*b*]pyridazine.



A. 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

In an oven dried, N2 purged, 15mL round bottom flask, 0.028 g (0.089 mmol) of 8-(1-ethyl-propyl)-3-[4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine. in 1.5mL of dry CH_2Cl_2 is cooled to 0 C. 0.019 g (0.107 mmol) of NBS is added and reaction is stirred overnight allowing bath to come to room temperature. Reaction mixture is directly purified by chromatography using hexane/ethyl acetate as solvent system. The product containing fractions are combined to obtain 0.012 g, 34% yield. MS, ES+ = 395.1 (M+1); ^{1}H-NMR (DMSO-d6) = 7.070 (s, 1H); 3.10 (m, 1H); 2.49 (s, 3H); 2.36 (s, 3H); 2.25 (s, 3H); 1.85-1.78 (m, 4H); 0.81-0.77 (m, 6H) ppm.

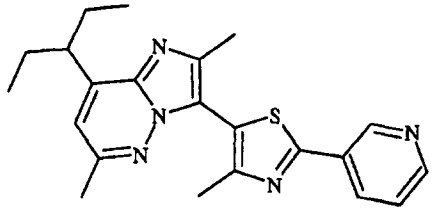
B. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(4-methyl-2-pyridin-2-yl-thiazol-5-yl)-imidazo[1,2-*b*]pyridazine.

A mixture of 3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-*b*]pyridazine (380 mg, 0.96 mmol), 2-pyridinezinc bromide (0.5 M in THF, 2.1 mL, 4 mmol), $Pd(PPh_3)_4$ (30 mg, 0.026 mmol) and THF (3 mL) is heated at 80 °C for 18 hours. Ethyl acetate (20 mL) is added. The organic layer is separated, dried over

magnesium sulfate, filtered, and the solvent removed in vacuo. Purification is performed via silica gel chromatography using a 3:1 mixture of hexanes and ethyl acetate as eluent to produce the title compound 325 mg (86%). ^{1}H-NMR ($CDCl_3$), δ 9.55 (m,1H); 8.10 (m, 1H); 7.73 (m,1H); 7.26 (m,1H); 6.58 (s, 1H); 3.24 (m, 1H); 2.43 (s, 3H); 2.40 (s, 3H); 2.33 (s, 3H); 1.76 (m, 4H); 0.80 (t, 6H) ppm. MS/ES$^+$ = 391 (100%, M+1).

Example 8.

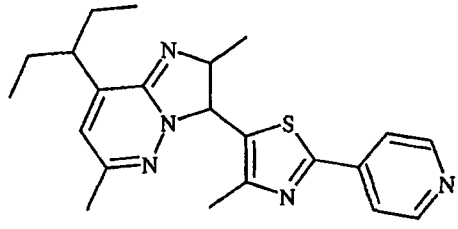
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(3-pyridyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a microwave pressure tube is added 0.070 g (0.178 mmol) of 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine, 0.066g (0.534 mmol) of pyridine-3-boronic acid, 0.103 g (0.089 mmol) of Pd(PPh3)4, 0.267mL (0.534 mmol) of 2 M aqueous Na2CO3, and 1mL 7:3:2 DME:H2O:EtOH, and the mixture is heated at 160 °C for 60 min. The reaction mixture is partitioned between 25mL of ethyl acetate and 25 mL of water. The layers are separated and the aqueous is extracted 3X 25 mL of ethyl acetate, dried (MgSO4), and concentrated under vacuum. The crude mixture is purified by chromatography using hexanes/Ethyl acetate as a solvent system. The product containing fractions are combined to obtain 0.045 g of the product, 64% yield. MS, ES+ = 392.2 (M+1); ^{1}HNMR (DMSO-d6) δ 9.18 (s, 1H); 8.65 (m, 1H); 8.34 (d, 1H); 7.60 (m, 1H); 7.06 (s, 1H); 3.06 (m, 1H); 2.50 (s, 3H); 2.40 (s, 3H); 2.34 (s, 3H); 1.87-1.82 (m, 4H); 0.83-0.79 (m, 6H) ppm.

Example 9.

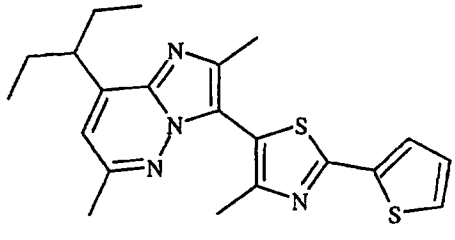
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(4-pyridyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, pyridine-4-boronic acid produces the title compound in 10% yield. MS, ES+ = 392.3 (M+1); ^{1}HNMR (DMSO-d6) = 8.79 (s, 2H); 7.80 (m, 2H); 7.07 (s, 1H); 3.12 (m, 1H); 2.50 (s, 3H); 2.40 (s, 3H); 2.36 (s, 3H); 1.90-1.80 (m, 4H); 0.83-0.79 (m, 6H) ppm.

Example 10.

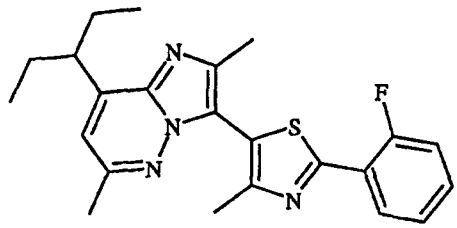
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(thiophene-2-yl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, thiophene-2-boronic acid produces the title compound in 89% yield. MS, ES+ = 397.1 (M+1); ^{1}H-NMR (DMSO-d6) = 7.81-7.79 (d, 1H); 7.78-7.77 (d, 1H); 7.21-7.20 (m, 1H); 7.05 (s, 1H); 3.19-3.15 (m, 1H); 2.50 (s, 3H); 2.39 (s, 3H); 2.27 (s, 3H); 1.85-1.83 (m, 4H); 0.82-0.79 (m, 6H) ppm.

Example 11.

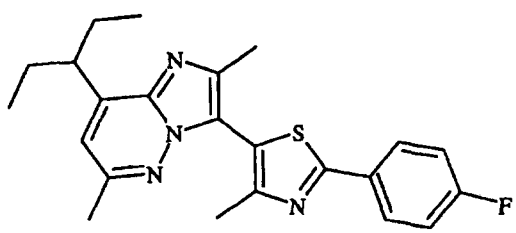
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(2-fluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 2-fluorophenyl boronic acid produces the title compound in 82% yield. MS, ES+ = 409.2 (M+1); ^{1}H-NMR (DMSO-d6) = 8.32-8.28 (m, 1H); 7.60-7.58 (m, 1H); 7.57-7.41 (m, 2H); 7.05 (s, 1H); 3.13-3.12 (m, 1H); 2.49 (s, 3H); 2.40 (s, 3H); 2.35 (s, 3H); 1.91-1.780 (m, 4H); 0.87-0.79 (m, 6H) ppm.

Example 12.

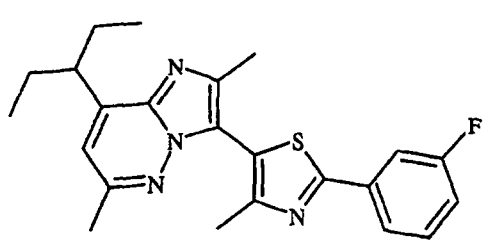
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(4-fluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 4-fluorophenyl boronic acid produces the title compound in 63% yield where the crude mixture is purified by chromatography using 2% methanol in dichloromethane as a solvent system. MS, ES+ = 409.2 (M+1); ^{1}H-NMR (DMSO-d6) = 8.06-8.03 (m, 2H); 7.408-7.36 (m, 2H); 7.05 (s, 1H); 3.14-3.11 (m, 1H); 2.50 (s, 3H); 2.39 (s, 3H); 2.31 (s, 3H); 1.90-1.78 (m, 4H); 0.83-0.79 (m, 6H) ppm.

Example 13.

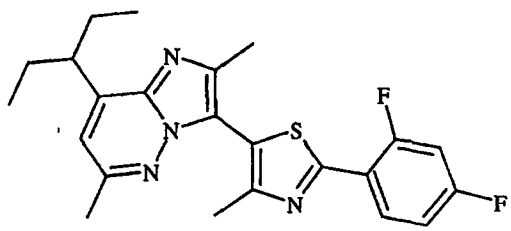
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(3-fluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 3-fluorophenyl boronic acid produces the title compound in 77% yield where the crude mixture is purified by chromatography using 2% methanol in dichloromethane as a solvent system. MS, ES+ = 409.2 (M+1); ^{1}H-NMR (DMSO-d6) = 7.84-7.78 (m, 2H); 7.64-7.57 (m, 2H); 7.41-7.36 (m, 1H); 7.06 (s, 1H); 3.15-3.111 (m, 1H); 2.45 (s, 3H); 2.40(s, 3H); 2.32 (s, 3H); 1.91-1.78 (m, 4H); 0.83-0.79 (m, 6H) ppm.

Example 14

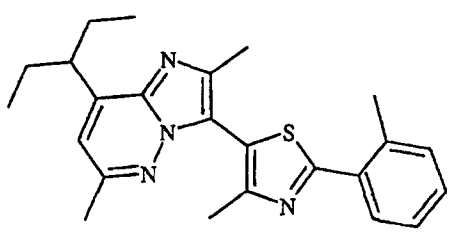
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(2,4-difluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 2,4-difluorophenyl boronic acid produces the title compound in 76% yield. MS, ES+ = 427.2 (M+1); ^{1}H-NMR (DMSO-d6) = 8.370-8.310 (m, 1H); 7.586-7.540 (m, 1H); 7.36-7.32 (m, 1H); 7.054 (s, 1H); 3.14-3.13 (m, 1H); 2.492 (s, 3H); 2.391 (s, 3H); 2.345 (s, 3H); 1.906-1.797 (m, 4H); 0.826-0.788 (m, 6H) ppm.

Example 15.

Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(o-tolyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

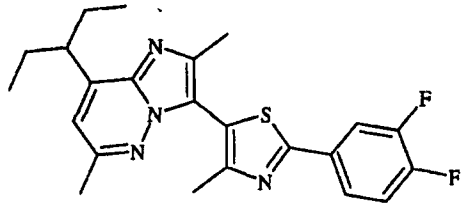


Using a procedure similar to Example 8, o-tolyl boronic acid produces the title compound in 87% yield where the crude mixture is purified by silica gel chromatography using 2% methanol in dichloromethane as a solvent system. MS, ES+ = 405.2 (M+1); ^{1}H-

NMR (DMSO-d6) = 7.857-7.838 (d, 1H); 7.429-7.419 (d, 2H); 7.393-7.352 (m, 1H); 7.049 (s, 1H); 3.145-3.114 (m, 1H); 2.647 (s, 3H); 2.502 (s, 3H); 2.406 (s, 3H); 2.337 (s, 3H); 1.907-1.782 (m, 4H); 0.827-0.791 (m, 6H) ppm.

Example 16.

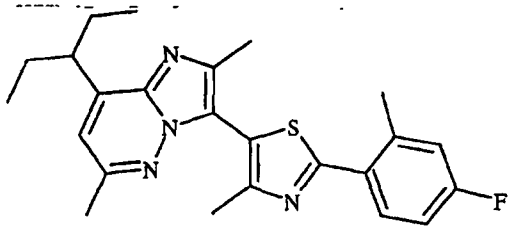
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(3,4-difluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 3,4-difluorophenyl boronic acid produces the title compound in 74% yield where the crude mixture is purified by chromatography using 2% methanol in dichloromethane as a solvent system. MS, ES+ = 427.2 (M+1); ^{1}H-NMR (DMSO-d6) = 8.07-8.02 (m, 1H); 7.849 (s, 1H); 7.66-7.59 (m, 1H); 7.062 (s, 1H); 3.12-3.11 (m, 1H); 2.498 (s, 3H); 2.392 (s, 3H); 2.319 (s, 3H) 1.905-1.779 (m, 4H); 0.826-0.790 (m, 6H) ppm.

Example 17.

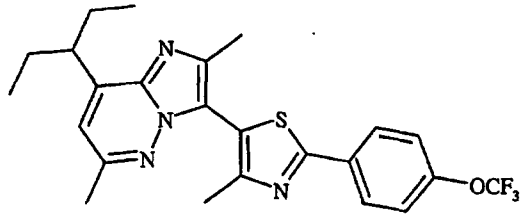
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(4-fluoro-2-methylphenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 4-fluoro-2-methylphenyl boronic acid produces the title compound 0.040g (37% yield). MS, ES+ = 423.2 (M+1); ^{1}H-NMR (DMSO-d6) = 7.918-7.882 (m, 1H); 7.323-7.241 (d, 1H); 7.234-7.192 (m, 1H); 7.049 (s, 1H); 3.142-3.111 (m, 1H); 2.650 (s, 3H); 2.499 (s, 3H); 2.401 (s, 3H); 2.330 (s, 3H); 1.905-1.779 (m, 4H); 0.969-0.788 (m, 6H) ppm.

Example 18.

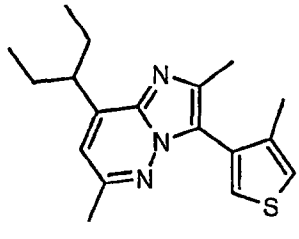
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(4-trifluoromethoxyphenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a microwave pressure tube is added 0.100g (0.254mmol) of 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine, 0.157g (0.762mmol) of 4-(trifluoromethoxy)benzene boronic acid, 0.147g (0.127mmol) of Pd(PPh3)4, 0.381mL (0.762mmol) of 2 M aqueous sodium carbonate, and 2mL Ethanol. The reaction mixture is heated in the microwave at 160°C for up to 1 hour. The reaction mixture is partitioned between 50 mL of ethyl acetate and 50 mL of water. The layers are separated and the aqueous is extracted 3X50mL of ethyl acetate, dried (MgSO4), and concentrated under vacuum. The crude mixture is purified by chromatography using 2% methanol in dichloromethane as a solvent system. The product containing fractions are combined to obtain 0.085g of the product, 70% yield. MS, ES+ = 475.2 (M+1); ^{1}H-NMR (DMSO-d6) = 8.134-8.112 (d, 2H); 7.553-7.532 (d, 2H); 7.059 (s, 1H); 3.142-3.113 (m, 1H); 2.500 (s, 3H); 2.399 (s, 3H); 2.330 (s, 3H); 1.907-1.782 (m, 4H); 0.827-0.791 (m, 6H) ppm.

Example 19.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine.



A. 4,4,5,5-Tetramethyl-2-(4-methyl-thiophen-3-yl)-[1,3,2]dioxaborolane.

To a 250 mL round bottom flask is added 3-bromo-4-methyl-thiophene (5.00 g, 28.24 mmol), bis(pinacolato)diboron (7.89 g, 31.06 mmol) and KOAc (8.32 g, 84.72 mmol) in DMSO (85 mL). The mixture is degassed by bubbling N_2 for 5 min, $PdCl_2(dppf)_2 \bullet CH_2Cl_2$ (1.15 g, 1.42 mmol) is added and the reaction mixture is heated to and stirred at 85 °C overnight. The reaction is cooled to rt, and diluted with EtOAc (400 mL), washed with H_2O (3 x 300 mL); dried with $MgSO_4$, filtered and concentrated. Purification of the crude material by chromatography to give the title compound (3.69 g, 16.5 mmol, 58%). ES-MS (m/z): calcd for $C_{11}H_{17}BO_2S$ (M^+): 224.1; found: 224.9.

B. 4-Methyl 3-thiophene boronic acid.

A solution of 4,4,5,5-tetramethyl-2-(4-methyl-thiophen-3-yl)-[1,3,2]dioxaborolane (3.69 g, 16.47 mmol) in acetone (30 mL) is treated with H_2O (30 mL), followed by $NaIO_4$ (7.05 g, 32.95 mmol). The resulting mixture is stirred at rt overnight. The organic solvent is removed in vacuo. The residue is diluted with H_2O (50 mL), extracted with EtOAc ((2 x 100 mL). The organic extracts are combined, dried with Na_2SO_4, filtered and concentrated. Purification of the crude material by chromatography gives the title compound (0.82 g, 5.78 mmol, 35%). ^1H NMR ($CDCl_3$): δ 1.33 (s, 3H), 2.64-2.66 (m, 2H), 7.00-7.02 (m, 1H), 8.27 (d, J = 3.0 Hz, 1H). ES-MS (m/z): calcd for $C_5H_7BO_2S$ (M-H)$^-$: 141.0; found: 141.1.

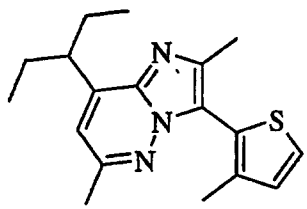
C. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(4-methyl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine.

To a 100 mL round bottom flask containing 4-methyl 3-thiophene boronic acid (0.27 g, 1.91 mmol), and 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.65 g, 1.91 mmol) in 20 mL of a stock solution (DME:H_2O:EtOH = 7:3:2) is added 2 M Na_2CO_3 (1.9 mL). The resulting mixture is degassed by bubbling N_2 for 5 min. Then $Pd(PPh_3)_4$ (0.11 g, 0.096 mmol) is added. The reaction mixture is refluxed overnight. The reaction is diluted with H_2O (20 mL); extracted with EtOAc (3 x 30 mL); dried (Na_2SO_4), filtered and purification of the crude material by chromatography gives the title compound (0.52 g, 1.66 mmol, 87%). ^1H NMR ($CDCl_3$): δ 0.89 (t, J = 7.5 Hz,

6H), 1.75-1.90 (m, 4H), 2.13 (d, J = 0.8 Hz, 3H), 2.44 (s, 3H), 2.49 (s, 3H), 3.30-3.39 (m, 1H), 6.64 (s, 1H), 7.08-7.11 (m, 1H), 7.34 (d, J = 3.1 Hz, 1H). ES-MS (m/z): calcd for $C_{18}H_{23}N_3S$ $(M+H)^+$: 314.5; found: 314.2.

Example 20.

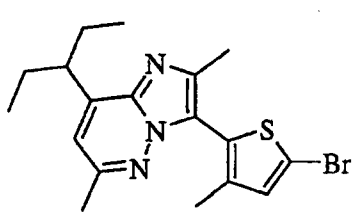
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To mixture of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (12.0 g, 34.96 mmol) and $PdCl_2$(dppf) (1.28 g, 1.75 mmol) is added a 0.5 M solution of 3-methyl-2-thienylzinc bromide in THF (100 mL, 50.0 mmol). The mixture is stirred at 65 °C overnight, diluted with EtOAc (500 mL), washed with 10% citric acid (500 mL), water (400 mL), brine (400 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (10%-20% EtOAc/hexane gradient) furnish the title compound (8.83 g, 28.17 mmol, 81%). ^{1}H NMR ($CDCl_3$), δ 0.92 (t, J = 7.4 Hz, 6H), 1.78-1.95 (m, 4H), 2.18 (s, 3H), 2.50 (s, 3H), 2.54 (s, 3H), 3.33-3.43 (m, 1H), 6.69 (s, 1H), 7.06 (d, J = 4.9 Hz, 1H), 7.46 (d, J = 4.9 Hz, 1H). LC/MS (m/z): calcd. for $C_{18}H_{23}N_3S$ $(M+H)^+$: 314.6; found: 314.2.

Example 21.

Preparation of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

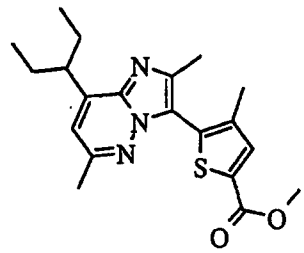


To a solution of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine (8.83 g, 28.17 mmol) and CH_2Cl_2 (90 mL) is added NBS (5.26

g, 29.58 mmol). The solution is stirred at ambient temperature for 2 hours. The solution is washed with water (3 X 75 mL), dried over MgSO4, filtered and concentrated to furnish the title compound (10.5 g, 26.76 mmol, 95%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.3 Hz, 6H), 1.73-1.93 (m, 4H), 2.09 (s, 3H), 2.44 (s, 3H), 2.51 (s, 3H), 3.26-3.36 (m, 1H), 6.68 (s, 1H), 6.98 (d, J = 4.9 Hz, 1H) ppm. LC/MS (m/z): calcd. for $C_{18}H_{22}BrN_3S$ $(M+H)^+$: 392.6; found: 392.1, 394.1.

Example 22.

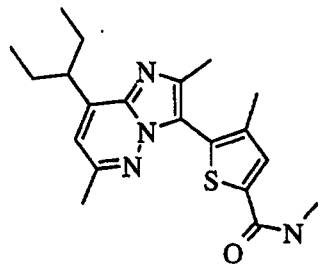
Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid methyl ester.



A solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.00 g, 2.66 mmol) in CH_3OH (12 mL), DMSO (18 mL), Et_3N (2.0 mL) with $Pd(OAc)_2$ (0.12 g, 0.538 mmol), dppf (0.937 g, 1.69 mmol) is reacted at CO atmosphere (100 psi) at 80 °C for 24 h. The reaction mixture is diluted with EtOAc (200 mL), washed with 0.1 M HCl (2 x 50 mL), brine (50 mL); dried with Na_2SO_4; filtered through silica gel and eluted with excess EtOAc. Purification of the crude material by chromatography gives the title compound (0.79 g, 2.12 mmol, 80%). ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J = 7.7 Hz, 6H), 1.75-1.93 (m, 4H), 2.15 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 3.32-3.42 (m, 1H), 3.91 (s, 3H), 6.72 (s, 1H), 7.73 (s, 1H). ES-MS (m/z): calcd for $C_{20}H_{25}N_3O_2S$ $(M+H)^+$: 372.5; found: 372.2.

Example 23.

Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid methylamide.



A. 5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid.

A solution of (1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid methyl ester (0.78 g, 2.10 mmol) in CH_3OH (10 mL) is treated with 5.0 M NaOH (2.1 mL, 10.5 mmol). The resulting reaction mixture is refluxed for 4 h. Organic solvent is removed in vacuo; the aqueous residue is acidified by the addition of 2.0 M HCl to pH 5~6; it is then extracted with EtOAc (3 x 50 mL); dried (Na_2SO_4); filtered and concentration to give the title compound (0.74 g, 2.07 mmol, 98%). ^{1}H NMR (DMSO-d6): δ 0.79 (t, J = 7.6 Hz, 6H), 1.75-1.86 (m, 4H), 2.06 (s, 3H), 2.36 (s, 3H), 2.47 (s, 3H), 3.06-3.14 (m, 1H), 7.01 (s, 1H), 7.68 (s, 1H), 13.1 (bs, 1H). ES-MS (m/z): calcd for $C_{19}H_{23}N_3O_2S$ $(M+H)^+$: 358.5; found: 358.2.

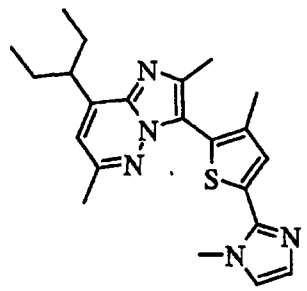
B. 5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid methylamide.

5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid (0.17 g, 0.47 mmol) is reacted with 2.0 M oxalyl chloride in CH_2Cl_2 (3.0 mL) at rt for 1h. The excess reagent and solvent are removed in vacuo. The residue is dissolved in CH_2Cl_2 (3mL), cooled to 0 °C and treated with 2.0 M methyl amine in THF (3 mL). The reaction is stirred at 0 °C for 10 min and rt for 30min. It is diluted with EtOAc (50 mL), washed with H_2O (15 mL0, 0.1 M NaOH (2 x 30 mL); dried (Na_2SO_4); filtered and concentrated. Purification of the crude material by chromatography to give the title compound (0.91g, 0.25 mmol, 53%). ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J = 7.2 Hz, 6H), 1.75-1.91 (m, 4H), 2.14 (s, 3H), 2.47 (s, 3H), 2.52 (s, 3H), 3.02

(d, J = 4.8 Hz, 3H), 3.28-3.36 (m, 1H), 5.90-6.01 (m, 1H), 6.69 (s, 1H), 7.43 (s, 1H). ES-MS (m/z): calcd for $C_{20}H_{26}N_4OS$ $(M+H)^+$: 371.5; found: 371.2.

Example 24.

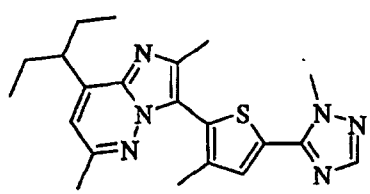
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-imidazol-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo-[*1,2-b*]pyridazine (0.98 g, 2.51 mmol) and 1-methyl-*1H*-imidazole (0.2 mL), $Pd(OAc)_2$ (34 mg, 0.15 mmol), PPh_3 (79 mg, 0.299 mmol), Cs_2CO_3 (1.95 g, 6.0 mmol) in DMF (50 mL) is stirred under N_2 at 130-140°C overnight. The reaction mixture is cooled, diluted with EtOAc (300 mL), washed with H_2O (3 x 100 mL); dried (Na_2SO_4); filtered and concentrated. Purification of the resulting crude material by chromatography yields the title compound (0.51 g, 1.29 mmol, 51%). ^1H NMR ($CDCl_3$): δ 0.89 (t, J = 7.5 Hz, 6H), 1.77-1.92 (m, 4H), 2.17 (s, 3H), 2.51 (s, 3H), 2.54 (s, 3H), 3.30-3.40 (m, 1H), 3.81 (s, 3H), 6.69 (s, 1H), 7.02 (s, 1H), 7.24 (s, 1H), 7.52 (s, 1H). ES-MS (m/z): calcd for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.6; found: 394.3.

Example 25.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.

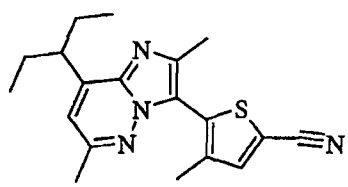


To a –78 °C solution of 1-methyl-1,2,4-triazole (0.15 mL, 2.04 mmol) and THF (3 mL) is added a 1.34 M solution of n-Bu-Li in hexanes (1.60 mL, 2.14 mmol) over 20

minutes, then stirred at –78 °C for 1.5 hours. A 0.5 M solution of $ZnCl_2$ in THF (4.28 mL, 2.14 mmol) is added and the solution warmed to ambient temperature. 3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.019 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) is added and the solution heated at 65 °C overnight diluted with CH_2Cl_2 (30 mL). The organic layer is washed with 10% citric acid (20 mL), water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (20%-60% EtOAc/hexane gradient). The residue is dissolved in Et_2O, treated with Darco®-60 for 15 minutes, dried with Na_2SO_4, and filtered to furnish the title compound (0.24 g, 0.61 mmol, 60%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.4 Hz, 6H), 1.75-1.93 (m, 4H), 2.20 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 3.28-3.37 (m, 1H), 4.14 (s, 3H), 6.69 (s, 1H), 7.45 (s, 1H), 7.87 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{26}N_6S$ $(M+H)^+$: 395.6; found: 395.2.

Example 26.

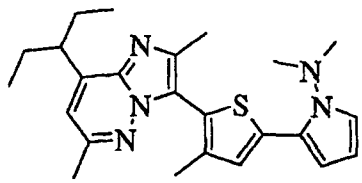
Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carbonitrile.



A solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.28 mmol), DMF (5 mL), and $Zn(CN)_2$ (0.090 g, 0.76 mmol) is degassed with nitrogen for 15 minutes. $Pd(PPh_3)_4$ (0.74 g, 0.064 mmol) and the solution heated at 100 °C overnight. The solution is diluted with EtOAc (50 mL), washed with 2 M NH_4OH (2 X 30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. Purified by ISCO column chromatography (15% - 20% EtOAc/hexane gradient) furnish the title compound (0.39 g, 1.15 mmol, 91%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.15 (s, 3H), 2.46 (s, 3H), 2.51 (s, 3H), 3.26-3.34 (m, 1H), 6.72 (s, 1H), 7.53 (s, 1H). LC/MS (m/z): calcd. for $C_{19}H_{22}N_4S$ $(M+H)^+$: 339.6; found: 339.2.

Example 27.

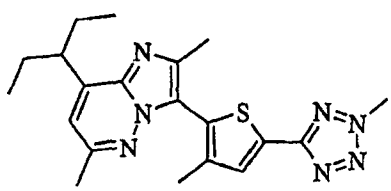
Preparation of (2-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-pyrrol-1-yl)-dimethyl-amine.



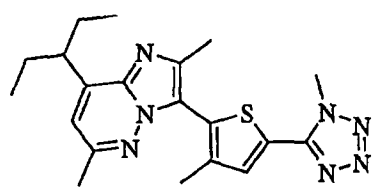
To a 0 °C solution 1-(dimethylamino)-pyrrole (0.24 mL, 2.04 mmol) and THF (4 mL) is added 1.24 M *n*-BuLi (1.73 mL, 2.14 mmol). The solution is warmed to ambient temperature and stirred for two hours. 0.5 M $ZnCl_2$ (4.28 mL, 2.14 mmol) is added and the solution is stirred for one hour. 3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) is added and the solution is heated at 65 °C overnight. The solution is diluted with EtOAc (30 mL), washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (15% -20% EtOAc gradient) furnish the title compound (0.41 g, 0.97 mmol, 95%). ^1H NMR ($CDCl_3$) δ 0.87 (t, *J* = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.11 (s, 3H), 2.51 (s, 6H), 2.83 (s, 6H), 3.29-3.39 (m, 1H), 6.18-6.21 (m, 1H), 6.35 (dd, *J* = 4.0, 1.8 Hz, 1H), 6.65 (s, 1H), 6.98 (dd, *J* = 4.0, 1.8 Hz, 1H), 7.25 (s, 1H). LC/MS (m/z): calcd. for $C_{24}H_{31}N_5S$ $(M+H)^+$: 422.2; found: 422.4.

Example 28 and 29.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(2-methyl-2,5-dihydro-*1H*-tetrazol-5-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine and 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-tetrazol-5-yl)-thiophen-2-yl]-imidazo[1,2 b]pyridazine.



Ex 28.



Ex. 29.

A. 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1H-tetrazol-5-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.

To a solution of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carbonitrile (0.25 g, 0.74 mmol) and DMF (2.5 mL) is added Et_3N•HCl (0.31 g, 2.22 mmol) and NaN_3 (0.14 g, 2.20 mmol). The solution is heated at 100 °C overnight. The solution is diluted with water (20 mL) and extracted with EtOAc (3 X 15 mL), the combined organic layers are washed with 0.1 M HCl (20 mL), water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is recrystalized from acetonitrile furnish the title compound (0.14 g, 0.37 mmol, 50%). ^{1}H NMR ($CDCl_3$), δ 0.81 (t, J = 7.5 Hz, 6H), 1.66-1.87 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 3.26-3.35 (m, 1H), 6.83 (s, 1H), 7.84 (s, 1H). LC/MS (m/z): calcd. for $C_{19}H_{23}N_7S$ $(M+H)^+$: 382.6; found: 382.2.

B. 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(2-methyl-2,5-dihydro-*1H*-tetrazol-5-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine and 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-tetrazol-5-yl)-thiophen-2-yl]-imidazo[1,2 b]pyridazine.

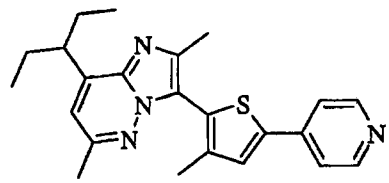
To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1H-tetrazol-5-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine (0.14 g, 0.35 mmol) and THF (3 mL) is added Et_3N (0.1 mL, 0.71 mmol) and MeI (0.024 mL, 0.39 mmol). The solution is stirred overnight, diluted with EtOAc (20 mL), washed with water (15 mL), 0.1 M HCl (15 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%- 40% EtOAc/hexane gradient) furnish Ex. 28 (0.71 g, 0.18 mmol, 51%), and Ex. 29 (0.031 g, 0.078 mmol, 22%).

Ex. 28: ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.4 Hz, 6H), 1.75-1.92 (m, 4H), 2.18 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 3.28-3.38 (m, 1H), 4.38 (s, 3H), 6.68 (s, 1H), 7.71 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{25}N_7S$ $(M+H)^+$: 396.6; found: 396.3.

Ex. 29: ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.4 Hz, 6H), 1.73-1.94 (m, 4H), 2.23 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.28-3.37 (m, 1H), 4.30 (s, 3H), 6.62 (s, 1H), 7.63 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{25}N_7S$ $(M+H)^+$: 396.6; found: 396.3.

Example 30.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-4-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



A. 3-(5-Boronic acid-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a -78 °C solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.20 g, 3.06 mmol) and THF (10 mL) is added 1.30 M *n*-Bu-Li (2.47 mL, 3.21 mmol) drop wise. The solution is stirred at –78 °C for one hour. $B(OMe)_3$ (0.38 mL, 3.65 mmol) is added and the solution is warmed to ambient temperature and stirred for 2 hours. 1 M HCl is added and the solution stirred for 10 minutes extracted with CH_2Cl_2 (2 X 30 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.47 g, 1.32 mmol, 43%). ^1H NMR ($CDCl_3$), δ 0.92 (t, J = 7.5 Hz, 6H), 1.71-1.98 (m, 4H), 2.02 (s, 3H), 2.64 (s, 3H), 2.69 (s, 3H), 3.64-3.83 (m, 1H), 7.06 (d, J = 5.3 Hz, 1H), 7.54 (d, J = 5.3 Hz, 1H), 7.20 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{24}BN_3O_2S$ $(M+H)^+$: 358.4; found: 358.2.

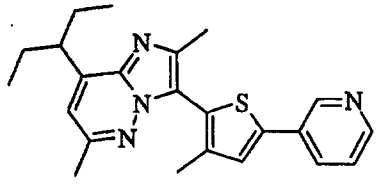
B. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-4-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.

A solution of 3-(5-boronic acid-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.70 mmol), 4-bromopyridine hydrochloride (0.16 g, 0.84 mmol), and 2 M Na_2CO_3 (0.87 mL, 1.75 mmol) and *n*-PrOH (2.5 mL) is degassed with nitrogen for 10 minutes. $Pd(PPh_3)_4$ (0.040 g, 0.035 mmol) is added and the solution heated at 85 °C overnight. The solution is diluted with CH_2Cl_2 (40 mL), washed with 10% Na_2CO_3 (30 mL), water (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-40% EtOAc/hexane gradient) furnish the title compound (0.16 g, 0.41 mmol, 59%). ^1H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.93 (m, 4H), 2.17 (s, 3H), 2.49 (s, 3H), 2.52 (s,

3H), 3.28-3.38 (m, 1H), 6.68 (s, 1H), 7.43 (s, 1H), 7.52 (d, J = 5.5 Hz, 2H), 8.62 (d, J = 5.5 Hz, 2H). LC/MS (m/z): calcd. for $C_{23}H_{26}N_4S$ $(M+H)^+$: 391.2 found: 391.2.

Example 31.

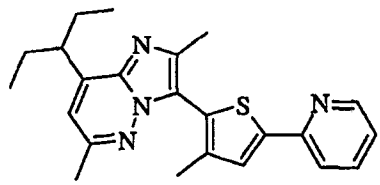
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-3-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To a –78 °C solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.27 mmol), and THF (5 mL) is added 1.34 M *n*-Bu-Li (1.0 mL, 1.34 mmol). The solution is stirred for at -78 °C for 30 minutes and 0.5 M $ZnCl_2$ in THF (2.7 mL, 1.34 mmol) is added and the solution warmed to ambient temperature. After 30 minutes 3-bromopyridine (0.15 mL, 1.53 mmol) and $PdCl_2$(dppf) (0.047 g, 0.064 mmol) is added and the solution heated at 65 °C overnight. The solution is diluted with CH_2Cl_2 (40 mL), washed with 10% citric acid (20 mL), water (20 mL), brine (20 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-40% EtOAc/hexane gradient) concentrated and re-dissolved in Et_2O. The solution is treated with Darco®-60 for 15 minutes, dried over Na_2SO_4, and filtered thru celite® furnish the title compound (0.26 g, 0.67 mmol, 52%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.28-3.38 (m, 1H), 6.68 (s, 1H), 7.26-7.32 (m, 2H), 7.86 (dt, J = 7.9, 1.8 Hz, 1H), 850 (d, J = 3.2 Hz, 1H), 8.89 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{26}N_4S$ $(M+H)^+$: 391.6; found: 391.2.

Example 32.

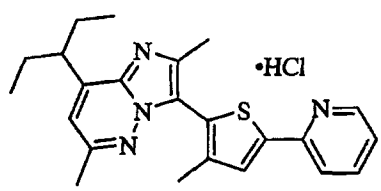
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To a mixture of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.27 mmol) and $PdCl_2$(dppf) (0.047 g, 0.064 mmol) is added a 0.5 M solution of 2-pyridylzinc bromide in THF (5.1 mL, 2.55 mmol). The mixture is stirred at 65 °C overnight, diluted with EtOAc (50 mL), washed with 10% citric acid (50 mL), water (40 mL), brine (40 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-40% EtOAc/hexane gradient) furnish the title compound (0.45 g, 1.15 mmol, 89%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H), 2.52 (s, 6H), 3.30-3.39 (m, 1H), 6.67 (s, 1H), 7.12-7.16 (m, 1H), 7.53 (s, 1H), 7.63-7.71 (m, 2H), 8.57 (dt, J = 1.3, 4.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{23}H_{26}N_4S$ $(M+H)^+$: 391.6; found: 391.2.

Example 33.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine hydrochloride.

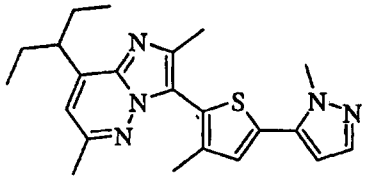


To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine (0.15 g, 38 mmol) and MeOH (2 mL) is added AcCl (0.028 mL, 0.39 mmol). After one hour the solution is concentrated and the residue recrystalized from EtOAc/ hexane furnish the title compound (0.11 g, 0.26 mmol, 69%). ^{1}H NMR ($CDCl_3$), δ 0.97 (t, J = 7.4 Hz, 6H), 1.75-2.03 (m, 4H), 2.17 (s, 3H), 2.66 (s, 3H), 2.77 (s, 3H), 3.86-3.98 (m, 1H), 7.17 (s, 1H), 7.21-7.30 (m, 2H), 7.62 (bs, 1H), 7.67-

7.7.82 (m, 2H), 8.60 (d, J = 4.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{23}H_{26}ClN_5S$ $(M+H)^+$: 428.1; found: 391.2.

Example 34.

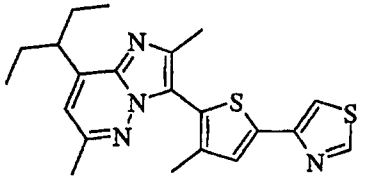
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(2-methyl-2*H*-pyrazol-3-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 25, 1-methylpyrazole (0.17 g, 2.04 mmol), 1.56 M *n*-Bu-Li (1.34 mL, 2.09 mmol), $ZnCl_2$ (4.3 mL, 2.14 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.35 g, 0.89 mmol, 88%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.28-3.38 (m, 1H), 4.05 (s, 3H), 6.42 (d, J = 1.8 Hz, 1H), 6.68 (s, 1H), 7.08 (s, 1H), 7.46 (d, J = 1.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.7; found: 394.2.

Example 35.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-thiazol-4-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.

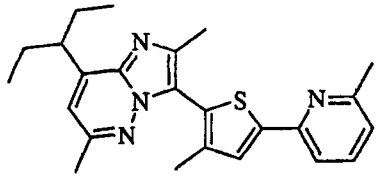


Using a procedure similar to Example 31, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.40 g, 1.02 mmol), 1.34 M *n*-Bu-Li (0.8 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), 4-bromo-thiazole (0.20 mL, 1.22 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.16g, 0.40 mmol, 40%). ^{1}H NMR ($CDCl_3$), δ 0.92 (t, J = 7.4 Hz, 6H), 1.70-1.96 (m, 4H), 2.17 (s, 3H), 2.64 (s, 3H), 2.66 (s, 3H), 3.38-3.48 (m, 1H), 7.16 (d, J = 1.8

Hz, 1H), 7.44 (s, 1H), 7.51 (d, J = 1.8 Hz, 1H), 7.86 (d, J = 1.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}N_4S_2$ $(M+H)^+$: 397.7; found: 397.2.

Example 36.

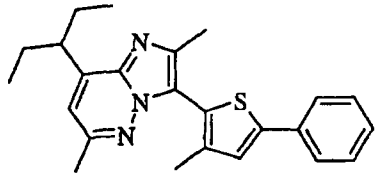
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.60 g, 1.53 mmol) and $PdCl_2$(dppf) (0.056 g, 0.076 mmol) and 0.5 M solution of 6-methyl-2-pyridylzinc bromide in THF (6.0 mL, 3.06 mmol) furnish the title compound (0.29 g, 0.72 mmol, 47%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.73-1.93 (m, 4H), 2.16 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 2.58 (s, 3H), 3.31-3.40 (m, 1H),
6.67 (s, 1H), 7.00 (d, J = 7.9 Hz, 1H), 7.45 (d, J = 7.9 Hz, 1H), 7.52 (s, 1H), 8.56 (t, J = 7.7 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4$ $(M+H)^+$: 405.7; found: 405.2.

Example 37.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-phenyl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.

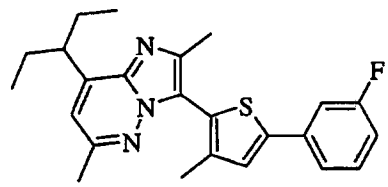


Using a procedure similar to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.27 mmol) and $PdCl_2$(dppf) (0.05 g, 0.069 mmol) and 0.5 M solution of phenylzinc iodide in THF (5.5 mL, 2.76 mmol) furnish the title compound (0.25 g, 0.64 mmol, 50%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.17 (s, 3H), 2.52 (s, 3H), 2.53 (s,

3H), 3.31-3.41 (m, 1H), 6.68 (s, 1H), 7.26 (s, 1H), 7.27-30 (m, 1H), 7.35-7.41 (m, 2H), 7.61-7.66 (m, 2H). LC/MS (m/z): calcd. for $C_{24}H_{27}N_3S$ $(M+H)^+$: 390.3; found: 390.3.

Example 38.

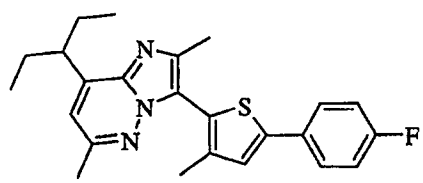
Preparation of 8-(1-ethyl-propyl)-3-[5-(3-fluoro-phenyl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.27 mmol) and $PdCl_2$(dppf) (0.047 g, 0.063 mmol) and 0.5 M solution of 3-flourophenylzinc iodide in THF (5.1 mL, 2.55 mmol) furnish the title compound (0.24 g, 0.59 mmol, 46%). ^1H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.17 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.31-3.39 (m, 1H), 6.69 (s, 1H), 6.94-7.01 (m, 1H), 7.26 (s, 1H), 7.30-7.42 (m, 3H). LC/MS (m/z): calcd. for $C_{24}H_{26}FN_3S$ $(M+H)^+$: 408.7; found: 408.2.

Example 39.

Preparation of 8-(1-ethyl-propyl)-3-[5-(4-fluoro-phenyl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

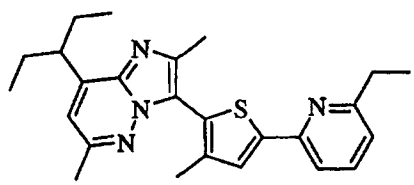


A slurry of 0.05 g/mL of Reike® Zn in THF (0.26 g, 4.01 mmol) and 1-bromo-4-fluoro-benzene (0.29 mL, 2.68 mmol) is heated at a reflux overnight. The solution is filtered under nitrogen. 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.35 g, 0.89 mmol) and $PdCl_2$(dppf) (0.033 g, 0.045 mmol) are added, and the solution is heated at a reflux overnight diluted with EtOAc (30 mL), washed with 10% citric acid (20 mL), water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column

chromatography (10%-15% EtOAc/hexane gradient) furnish the title compound (0.091 g, 0.22 mmol, 25%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.15 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.30-3.38 (m, 1H), 6.68 (s, 1H), 7.08 (d, J = 8.8 Hz, 2H),7.18 (s, 1H), 7.59 (dd, J = 8.5, 5.3 Hz, 2H). LC/MS (m/z): calcd. for $C_{24}H_{26}FN_3S$ $(M+H)^+$: 408.7; found: 408.3.

Example 40.

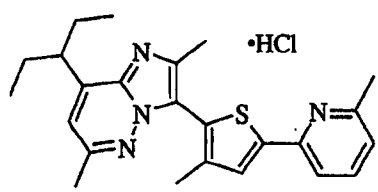
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-ethyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 31, 2-bromo-6-ethyl pyridine (0.26 g, 1.41 mmol), 1.56 M *n*-Bu-Li (0.94 mL, 1.47 mmol), 0.5 M $ZnCl_2$ in THF (3.0 mL, 1.53 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.27 mmol) and $PdCl_2$(dppf) (0.047 g, 0.064 mmol) produce the title compound (0.15 g, 0.36 mmol, 28%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.34 (t, J = 7.5 Hz, 3H), 1.75-1.94 (m, 4H), 2.16 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 2.85 (q, J = 16.2, 7.5 Hz, 2H), 3.31-3.41 (m, 1H), 6.67 (s, 1H), 7.01 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 7.9 Hz, 1H), 7.53 (s, 1H), 8.59 (t, J = 7.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{25}H_{30}N_4S$ $(M+H)^+$: 419.3; found: 419.3.

Example 41.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine hydrochloride.

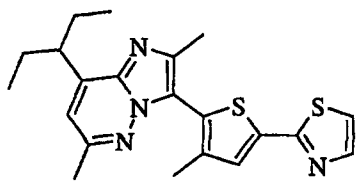


Using a procedure similar to Example 33, 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine (0.55 g, 1.36

mmol), MeOH (6 mL) and AcCl (0.098 mL, 1.36 mmol) furnish the title compound (0.11 g, 0.25 mmol, 42%). ^{1}H NMR ($CDCl_3$), δ 0.96 (t, J = 7.2 Hz, 6H), 1.74-1.89 (m, 2H), 1.89-2.02 (m, 2H), 2.22 (s, 3H), 2.68 (s, 3H), 2.78 (s, 3H), 3.08 (s, 3H), 3.88-3.98 (m, 1H), 7.23 (s, 1H), 7.40 (d, J = 6.9 Hz, 1H), 7.71 (d, J = 4.8 Hz, 1H), 8.06 (s, 1H), 8.82 (s, 1H). LC/MS (m/z): calcd. for $C_{24}H_{29}ClN_4S$ $(M+H)^+$: 441.3; found: 405.2.

Example 42.

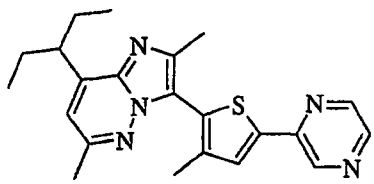
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-thiazol-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.46 g, 1.17 mmol), 0.5 M 2-thiazolylzinc bromide in THF (4.7 mL, 2.35 mmol) and $PdCl_2$(dppf) (0.043 g, 0.059 mmol) furnish the title compound (0.32 g, 0.81 mmol, 70%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.18 (s, 3H), 2.52 (s, 3H), 2.53 (s, 3H), 3.31-3.40 (m, 1H), 7.70 (s, 1H), 7.27 (d, J = 3.6 Hz, 1H), 7.47 (s, 1H), 7.78 (d, J = 3.6 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}N_4S_2$ $(M+H)^+$: 397.7; found: 397.1.

Example 43.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyrazin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.

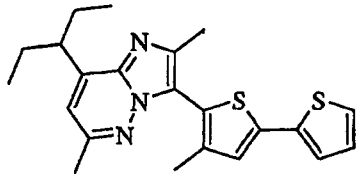


Using a procedure similar to Example 31, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) (example Rupp-2), 2-chloropyrazine (0.11 mL, 1.22 mmol), 1.42 M *n*-Bu-Li (1.52 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), and $PdCl_2$(dppf) (0.037 g, 0.051

mmol) furnish the title compound (0.19 g, 0.49 mmol, 48%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.94 (m, 4H), 2.20 (s, 3H), 2.52 (s, 3H), 2.53 (s, 3H), 3.31-3.40 (m, 1H), 6.69 (s, 1H), 7.63 (s, 1H), 8.40 (d, J = 2.6 Hz, 1H), 8.51 (t, J = 1.9 Hz, 1H), 8.96 (d, J = 0.9 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{25}N_5S$ $(M+H)^+$: 392.3; found: 392.2.

Example 44.

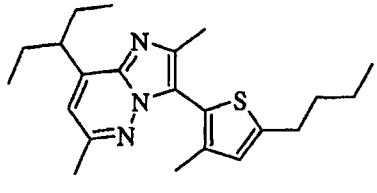
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-[2,2']bithiophenyl-5-yl)-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol), 0.5 M 2-thiophenlyzinc bromide in THF (3.0 mL, 1.53 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol) furnish the title compound (0.25g, 0.63 mmol, 83%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.14 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 3.30-3.39 (m, 1H), 6.68 (s, 1H), 7.02 (dd, J = 5.0, 3.6 Hz, 1H), 7.11 (s, 1H), 7.19 (d, J = 3.6 Hz, 1H), 7.19 (dd, J = 5.0, 1.0 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{25}N_3S_2$ $(M+H)^+$: 396.7; found: 396.2.

Example 45.

Preparation of 3-(5-butyl-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

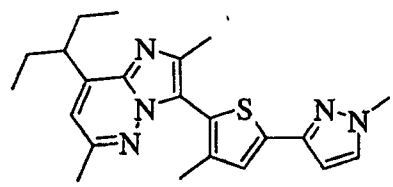


Using a procedure similar to Example 25 from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 0.1.02 mmol), 1.34 M *n*-Bu-Li (1.60 mL, 2.14 mmol), 0.5 M $ZnCl_2$ (4.3 mL, 2.14 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnishes the title compound (0.25g, 0.69 mmol, 68%). ^{1}H NMR

($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 0.97 (t, J = 7.5 Hz, 3H), 1.40-1.51 (m, 2H), 1.67-1.92 (m, 6H), 2.07 (s, 3H), 2.46 (s, 3H), 2.51 (s, 3H), 2.83 (t, J = 8.0 Hz, 2H), 3.30-3.38 (m, 1H), 6.64 (s, 1H), 6.70 (s, 1H) LC/MS (m/z): calcd. for $C_{22}H_{31}N_3S$ $(M+H)^+$: 370.3; found: 370.2.

Example 46.

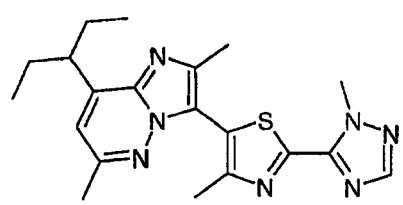
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-pyrazol-3-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure analogous to Example 31, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol), 1.42 M *n*-Bu-Li (0.75 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), 3-bromo-1-methyl-*1H*-pyrazole (Pavlik, J.; Kurzweil, E.; *J. Org. Chem.*, 1991, 56, 22, 6313) (0.20 g, 1.22 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.041g, 0.10 mmol, 10%). ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.94 (m, 4H), 2.15 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 3.31-3.41 (m, 1H), 3.95 (s, 3H), 6.47 (d, J = 2.2 Hz, 1H), 6.67 (s, 1H), 7.25 (s, 1H), 7.36 (d, J = 2.2 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.3; found: 394.2.

Example 47.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[4-methyl-2-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-imidazo[*1,2-b*]pyridazine.

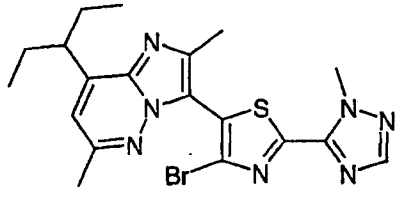


82 mg of 1-Methyl-1,2,4-triazole (0.99 mmol) is dissolved in 2 ml of dry THF and cooled to –78°C and 0.4 ml of n-butyllithium 2.5 M in hexane (0.99 mmol) is added. The reaction mixture is stirred at –78C to room temperature for 10min and cooled to –78°C

again. 1.98 ml of 0.5 M zinc chloride 0.5 M solution in THF (0.99 mmol) is added and stirred at –78C to room temperature for 15 min. 265 mg of 3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.66 mmol) and 27 mg of PdCl2(dppf) (0.033 mmol) are added and the vial is capped with a Teflon cap and heated at 80°C for 2 days. The reaction is cooled to room temperature and quenched with sat. NH4Cl and extracted with CH2Cl2. The separated CH2Cl2 layer is dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane : AcOEt : 2 M NH3 in MeOH=10:2:1) to give 57 mg of the title product. Yield 22%. mass spectrum (m/e):396(M+1). ^{1}H-NMR (CDCl3): δ 7.96 (s, 1H), 6.77 (s, 1H), 4.45 (s, 3H), 3.36 (m, 1H), 2.55 (s, 3H), 2.52 (s, 3H), 2.47 (s, 3H), 1.88 (m, 4H), 0.92 (t, J=7.3Hz, 6H).

Example 48.

Preparation of 3-[4-bromo-2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

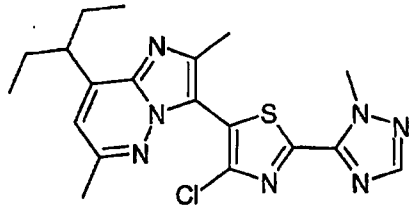


82 mg of 1-methyl-1,2,4-triazole (0.99 mmol) is dissolved in 2 ml of dry THF and cooled to –78°C and 0.4 ml of n-butyllithium 2.5 M in hexane (0.99 mmol) is added. The reaction mixture is stirred at –78°C to room temperature for 10min and cooled to –78°C again. 1.98 ml of 0.5 M zinc chloride 0.5 M solution in THF (0.99 mmol) is added and stirred at –78°C to room temperature for 15min. 152 mg of 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.33 mmol) and 27 mg of PdCl2(dppf) (0.033 mmol) are added and the vial is capped with a Teflon cap and heated at 80°C for 2days. The reaction is cooled to room temperature and quenched with sat. NH4Cl and extracted with CH2Cl2. The separated CH2Cl2 layer is dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:AcOEt:2M NH3 in MeOH=10:2:1) to give 88mg of the title product. Yield 54%.

mass spectrum (m/e):461(M+1). ^{1}H-NMR (CDCl3): 7.98 (s, 1H), 6.77 (s, 1H), 4.44 (s, 3H), 3.35 (m, 1H), 2.59 (s, 3H), 2.55 (s, 3H), 1.88 (m, 4H), 0.92 (t, J=7.5Hz, 6H).

Example 49.

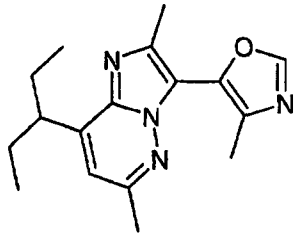
Preparation of 3-[4-chloro-2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



175 mg of 3-[4-Bromo-2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.38 mmol) and 56 mg of copper chloride (0.57 mmol) are placed into 4 ml vial with 3.0 ml of dry DMF and the vial is capped with a Teflon cap. The vial is heated at 130°C overnight. The reaction mixture is applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1 and hexane:AcOEt=8:1) to give 91 mg of crude product. The pure product is recrystalized from Et2O/Hexane. 73 mg (46%). mass spectrum (m/e):416(M+1). ^{1}H-NMR (CDCl3): 7.98 (s, 1H), 6.80 (s, 1H), 4.44 (s, 3H), 3.35 (m, 1H), 2.59 (s, 3H), 1.88 (m, 4H), 0.92 (t, J=7.5Hz, 6H).

Example 50.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-oxazol-5-yl)-imidazo[*1,2-b*]pyridazine.

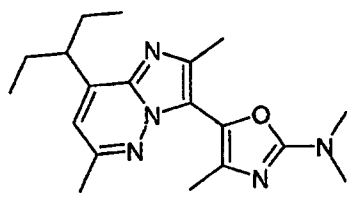


686 mg of 8-(1-Ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.0 mmol), 830 mg of 4-methyl-oxazole. (10 mmol), 105 mg of triphenylphosphine (0.4 mmol) and 1.30 g of cesium carbonate (4.0 mmol) are placed into tube with 10 ml of dry

DMF. N2 gas is bubbled in for 20min and 92 mg of Pd2dba3 (0.1 mmol) is added. The tube is sealed and heated at 130°C overnight. After being cooled to room temperature, water and CHCl2 are added to the mixture. The CHCl2 layer is separated, washed with sat. NaCl , dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:AcOEt=5:1) to give 234 mg of the title product. Yield 39%. mass spectrum (m/e):299(M+1). ^{1}H-NMR (CDCl3): 8.06 (s, 1H), 6.75 (s, 1H), 3.34 (m, 1H), 2.56 (s, 3H), 2.50 (s, 3H), 2.29 (s, 3H), 1.86 (m, 4H), 0.90 (t, J=7.4Hz, 6H).

Example 51.

Preparation of N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-oxazol-2-yl}-dimethylamine.



A. 3-(2-Bromo-4-methyl-oxazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

230 mg of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(4-methyl-oxazol-5-yl)-imidazo[*1,2-b*]pyridazine (0.77 mmol) is dissolved in 20 ml of CH2Cl2 and 178 mg of NBS (1.0 mmol) is added. The reaction mixture is stirred at room temperature overnight. The reaction mixture is washed with sat.-Na2S2O3, sat. NaCl, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1) to give 36 mg of the title compound. Yield 12%. mass spectrum (m/e):378(M+1). ^{1}H-NMR (CDCl3): 6.82 (s, 1H), 3.39 (m, 1H), 2.58 (s, 3H), 2.53 (s, 3H), 2.26 (s, 3H), 1.85 (m, 1H), 0.89 (t, J=7.4Hz, 6H).

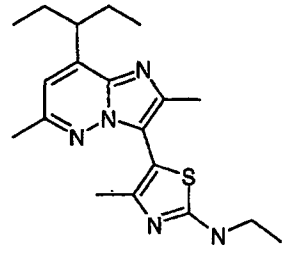
B. N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-oxazol-2-yl}-dimethylamine.

32 mg of 3-(2-Bromo-4-methyl-oxazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.08 mmol) and 78 mg of cesium carbonate (0.24 mmol) are placed into vial with 3 ml of dimethylamine 2.0 M in THF. The vial is capped with a

Teflon cap and heated at 110°C for 3days. The reaction mixture is cooled to room temperature, concentrated, and applied onto a silica-gel chromatography column (Hexane :AcOEt:2M NH3 in MeOH=10:2:1) to give 24 mg of the title product. Yield 89%. mass spectrum (m/e):342(M+1). ^{1}H-NMR (CDCl3): 6.71(s, 1H), 3.34 (m, 1H), 3.13 (s, 6H), 2.56 (s, 3H), 2.49 (s, 3H), 2.14 (s, 3H), 1.84 (m, 4H), 0.89 (t, J=7.5Hz, 6H).

Example 52.

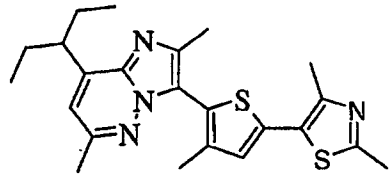
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[(4-methyl-2-ethylamino)-thiazol-5-yl]-imidazo[*1,2-b*]pyridazine.



The title compound is prepared essentially as described in Example 51B. employing 2.0 ml of ethylamine 2.0 M in THF and 182 g of cesium carbonate (0.56 mmol), 78%. mass spectrum (m/e):358 (M+1); 1H-NMR (CDCl3): 6.69(s, 1H), 5.23(br, 1H), 3.38(m, 3H), 2.56(s, 3H), 2.46(s, 3H), 2.17(s, 3H), 1.85(m, 4H), 1.35(t, 3H, J=7.2Hz), 0.90(t, 6H, J=7.2Hz).

Example 53.

Preparation of 3-[5-(2,4-dimethyl-thiazol-5-yl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

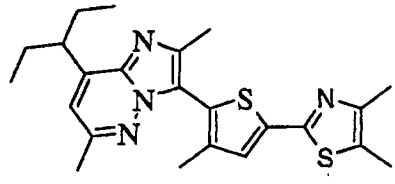


To a –78 °C mixture of 2,4-dimethylthiazole (0.23 g, 2.04 mmol) and THF (3 mL) is added 1.6 M *t*-Bu-Li in hexane (1.30 mL, 2.09 mmol). The mixture is stirred at –78°C for 15 minutes. 0.5 M $ZnCl_2$ in THF (4.3 mL, 2.14 mmol) is added and the solution warmed to ambient temperature. 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-

2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) is added and mixture is stirred at 65 °C overnight, diluted with EtOAc (20 mL), washed with 10% citric acid (15 mL), water (15 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by silica gel chromatography (0%-15% EtOAc/hexane gradient) furnish the title compound (0.21 g, 0.49 mmol, 49%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.14 (s, 3H), 2.49 (s, 3H), 2.52 (s, 3H), 2.57 (s, 3H), 2.66 (s, 3H), 3.28-3.38 (m, 1H), 6.68 (s, 1H), 7.00 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{28}N_4S_2$ $(M+H)^+$: 425.3; found: 425.2.

Example 54.

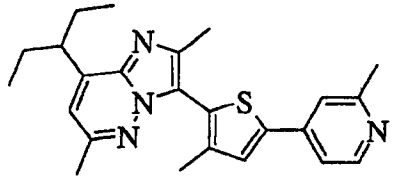
Preparation of 3-[5-(4,5-dimethyl-thiazol-2-yl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 25, from 4,5-dimethylthiazole (0.22 mL, 2.04 mmol), 1.56 M *n*-Bu-Li (1.34 mL, 2.09 mmol), $ZnCl_2$ (4.3 mL, 2.14 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.27 g, 0.64 mmol, 63%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.13 (s, 3H), 2.36 (s, 3H), 2.38 (s, 3H), 2.49 (s, 3H), 2.51(s, 3H), 3.29-3.38 (m, 1H), 6.67 (s, 1H), 7.32 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{28}N_4S_2$ $(M+H)^+$: 425.3; found: 425.2.

Example 55.

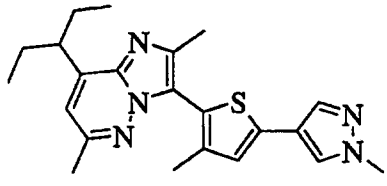
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(2-methyl-pyridin-4-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 31, from 4-bromo-2-methyl pyridine (Fukaya et. el. *Chem. Pharm. Bull.*, 1990, 38, 2446) (0.21 g, 1.22 mmol), 1.56 M *n*-Bu-Li (0.69 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.2 mL, 1.12 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.058 g, 0.14 mmol, 14%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.16 (s, 3H), 2.48 (s, 3H), 2.51 (s, 3H), 2.58 (s, 3H), 3.27-3.37 (m, 1H), 6.68 (s, 1H), 7.29 (d, J = 5.3 Hz, 1H), 7.35 (s, 1H), 7.41 (s, 1H), 8.46 (t, J = 5.3 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.3; found: 405.2.

Example 56.

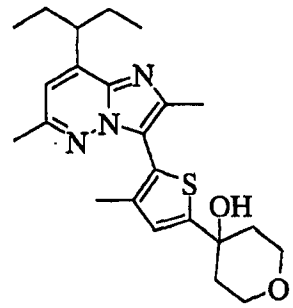
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-pyrazol-4-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure analogous to Example 31, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol), 1.42 M *n*-Bu-Li (0.75 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), 4-bromo-1-methyl-*1H*-pyrazole (0.25 g, 1.53 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnishes the title compound (0.092g, 0.23 mmol, 23%). ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.4 Hz, 6H), 1.73-1.92 (m, 4H), 2.12 (s, 3H), 2.48 (s, 3H), 2.52 (s, 3H), 3.29-3.38 (m, 1H), 3.92 (s, 3H), 6.66 (s, 1H), 6.98 (s, 1H), 7.54 (s, 1H), 7.68 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.3; found: 394.2.

Example 57.

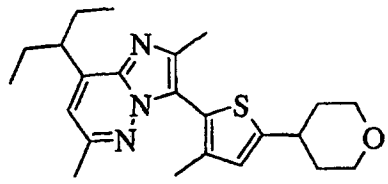
Preparation of 4-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-tetrahydro-pyran-4-ol.



To a -78°C solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.60 g, 1.53 mmol) and THF (10 mL) is added 1.56 M *n*-Bu-Li (1.03 mL, 1.61 mmol). After 30 minutes tetrahydro-pyran-4-one (0.21 mL, 2.29 mmol) is added over 5 minutes. The solution is stirred at –78°C for 2 hours, warmed to ambient temperature, diluted with EtOAc (50 mL), washed with sat. NH_4Cl (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-100% EtOAc/hexane gradient) furnish the title compound (0.38 g, 0.92 mmol, 60%). ^1H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 1.91-2.00 (m, 2H), 2.11 (s, 3H), 2.20-2.30 (m, 2H), 2.46 (s, 3H), 2.51 (s, 3H), 3.30-3.39 (m, 1H), 3.83-3.98 (m, 5H), 6.66 (s, 1H), 6.93 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{31}N_3O_2S$ $(M+H)^+$: 414.3; found: 414.2.

Example 58.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(tetrahydro-pyran-4-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Method A.

To a solution of 4-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-tetrahydro-pyran-4-ol (0.25 g, 0.604 mmol) and CH_2Cl_2

(10 mL) is added TFA (0.79 mL, 10.28 mmol) and Et_3SiH (0.25 mL, 1.57 mmol). The solution is concentrated, dissolved in EtOAc (30 mL), washed with sat. $NaHCO_3$ (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (10%-15% EtOAc/hexane gradient), is dissolved in EtOH (25 mL), 10 % Pd/C (0.07 g, 0.066 mmol) is added and the solution stirred under an atmosphere of H_2. After 2 hours the solution is filtered thru celite® and concentrated. The residue is purified by ISCO column chromatography (30% EtOAc in hexane) furnish the title compound (0.033 g, 0.083 mmol, 14%). ^1H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.95 (m, 4H), 1.97-2.04 (m, 2H), 2.09 (s, 3H), 2.20-2.30 (m, 2H), 2.46 (s, 3H), 2.52 (s, 3H), 3.00-3.11 (m, 1H), 3.30-3.40 (m, 1H), 3.54 (dt, J = 11.8, 2.2 Hz, 2H), 4.08 (dd, J = 11.8, 2.2 Hz, 2H), 6.65 (s, 1H), 6.75 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{31}N_3OS$ $(M+H)^+$: 398.7; found: 398.2.

Method B.

A. 4-(5-Bromo-4-methyl-thiophen-2-yl)-tetrahydro-pyran-4-ol.

To a -78°C solution of 2-bromo-3-methyl-thiophene (2.0 g, 17.75 mmol) and THF (30 mL) is added 2.0 M LDA (9.32 mL, 18.63 mmol). After 30 minutes at –78°C tetrahydro-pyran-4-one (2.3 mL, 23.07 mmol) is added and the solution is warmed to ambient temperature. The solution is washed with sat. NH_4Cl (30 mL). The aqueous phases is extracted with EtOAc. The combined organic layers are dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (30%-100% EtOAc/hexane gradient) furnish the title compound (2.3 g, 8.30 mmol, 47%). ^1H NMR ($CDCl_3$), δ 1.82 (m, 2H), 2.00 (s, 3H), 2.06-2.15 (m, 3H), 2.16 (s, 3H), 3.77-3.84 (m, 2H), 3.87 dt, J = 11.3, 2.2 Hz, 2H), 6.67 (s, 1H). LC/MS (m/z): calcd. for $C_{10}H_{13}BrO_2S$ $(M+H)^+$: 277.0; found: 260.9.

B. 4-(5-Bromo-4-methyl-thiophen-2-yl)-tetrahydro-pyran.

To a solution of 4-(5-bromo-4-methyl-thiophen-2-yl)-tetrahydro-pyran-4-ol (2.3 g, 8.30 mmol) and 1,2-dichloroethane (50 mL) is added ZnI_2 (3.97 g, 12.45 mmol) and sodium cyanoborohydride (3.91, 62.23 mmol). The solution is stirred for 1 hour, filtered

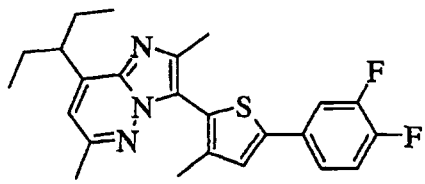
thru celite and concentrated. The residue is purified by ISCO column chromatography (5%-10% EtOAc/hexane gradient) furnish the title compound (1.53 g, 5.86 mmol, 71%). ^{1}H NMR ($CDCl_3$), δ 1.69-1.82 (m, 2H), 1.84-1.92 (m, 2H), 2.14 (s, 3H), 2.84-2.98 (m, 1H), 3.49 (dt, *J* = 11.8, 2.2 Hz, 2H), 4.00-4.07 (m, 2H), 6.51 (s, 1H).

C. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(tetrahydro-pyran-4-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.

Using a procedure similar to Example 25, 4-(5-bromo-4-methyl-thiophen-2-yl)-tetrahydropyran (0.83 g, 3.19 mmol), 1.56 M *n*-Bu-Li (2.04 mL, 3.19 mmol), $ZnCl_2$ (6.4 mL, 3.19 mmol), 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.56 mmol) and $Pd(PPh_3)_4$ (0.092 g, 0.008 mmol) furnish the title compound (0.072 g, 0.18 mmol, 11%). Spectrum identical to that from Method A.

Example 59.

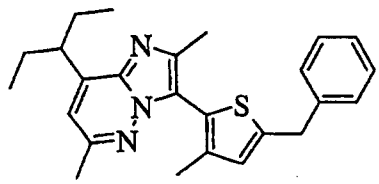
Preparation of 3-[5-(3,4-difluoro-phenyl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.27 mmol) and $PdCl_2$(dppf) (0.047 g, 0.064 mmol) and 0.5 M solution of 3,4-difluorophenylzinc bromide in THF (5.1 mL, 2.55 mmol) are reacted. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) and is chromatographed (50 x 250 C18 Symmetry column, 30-80% water: 0.1 % TFA /ACN: 0.1% TFA gradient) furnish the title compound (0.18 g, 0.42 mmol, 33%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, *J* = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.16 (s, 3H), 2.50 (s, 3H), 2.54 (s, 3H), 3.31-3.40 (m, 1H), 6.69 (s, 1H), 7.13-7.21 (m, 1H), 7.18 (s, 1H), 7.31-7.36 (m, 1H), 7.39-7.46 (m, 1H). LC/MS (m/z): calcd. for $C_{24}H_{25}F_2N_3S$ $(M+H)^+$: 426.3; found: 426.2.

Example 60.

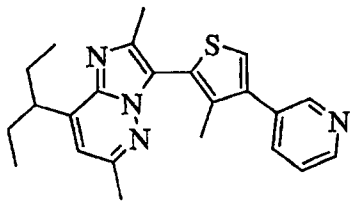
Preparation of 3-(5-benzyl-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.765 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol) and 0.5 M solution of benzylzinc bromide in THF (4.6 mL, 2.29 mmol) are reacted. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) and is chromatographed (50 x 250 C18 Symmetry column, 40-65% water: 0.1 % TFA /ACN: 0.1% TFA gradient) furnish the title compound (0.062 g, 0.15 mmol, 20%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.06 (s, 3H), 2.45 (s, 3H), 2.51 (s, 3H), 3.29-3.39 (m, 1H), 4.16 (s, 2H), 6.65 (s, 1H), 6.68(s, 1H), 7.22-7.29 (m, 1H), 7.31-7.36 (m, 4H). LC/MS (m/z): calcd. for $C_{25}H_{29}N_3S$ $(M+H)^+$: 404.3; found: 404.2.

Example 61.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-4-pyridin-3-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.

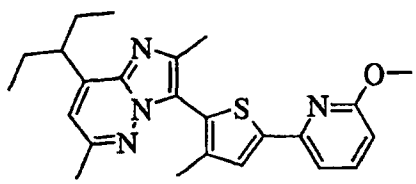


A solution of 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.64 mmol), pyridine-3-boronic acid (0.086 g, 0.70 mmol), 2 M Na_2CO_3 (0.48 mL, 0.96 mmol) and, *n*-PrOH (3 mL), is degassed with nitrogen for 10 minutes. $Pd(OAc)_2$ (2.7 mg, 0.0013 mmol) and PPh_3 (0.010 g, 0.038 mmol) are added and the solution is heated at 90 °C overnight. The solution is diluted with EtOAc (30 mL), washed with 10% Na_2CO_3 (30 mL), water (30 mL), brine (30 mL),

dried over $MgSO_4$, filtered, and concentrated. The residue is purified by ISCO (20-40% EtOAc gradient) furnish the title compound (0.051 g, 0.13 mmol, 20%). ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.09 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.29-3.40 (m, 1H), 6.69 (s, 1H), 7.33-7.43 (m, 1H), 7.47 (s, 1H), 7.80 (d, J = 7.9 Hz, 1H), 8.61 (bs, 1H), 8.78 (bs, 1H). LC/MS (m/z): calcd. for $C_{23}H_{26}N_4S$ $(M+H)^+$: 391.2; found: 391.4.

Example 62.

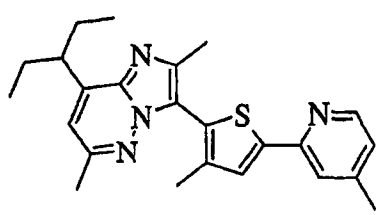
Preparation of 8-(1-ethyl-propyl)-3-[5-(6-methoxy-pyridin-2-yl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.765 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol) and 0.5 M solution of 6-methoxy-2-pyridylzinc bromide in THF (3.0 mL, 1.53 mmol) furnish the title compound (0.12 g, 0.29 mmol, 38%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.15 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 3.98 (s, 3H), 6.61 (d, J = 7.5 Hz, 1H), 6.70(s, 1H), 7.23 (d, J = 7.5 Hz, 1H), 7.52 (s, 1H), 7.56 (d, J = 7.7 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4OS$ $(M+H)^+$: 421.3; found: 421.3.

Example 63.

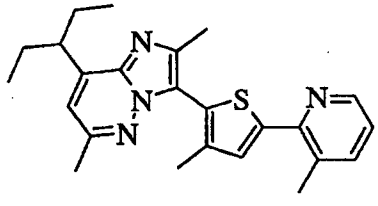
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(4-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.765 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol) and 0.5 M solution of 4-methyl-2-pyridylzinc bromide in THF (3.0 mL, 1.53 mmol) furnish the title compound (0.21 g, 0.52 mmol, 68%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H), 2.40 (s, 3H), 2.52 (s, 6H), 3.30-3.40 (m, 1H), 6.67 (s, 1H), 6.97(d, J = 4.8 Hz, 1H), 7.49 (s, 1H), 7.52 (s, 1H), 8.42 (d, J = 4.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.3; found: 405.3.

Example 64.

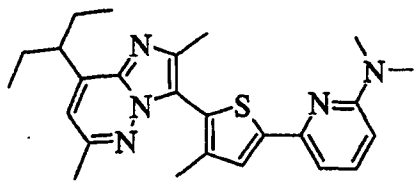
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(3-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine) (0.30 g, 0.765 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol) and 0.5 M solution of 3-methyl-2-pyridylzinc bromide in THF (5.0 mL, 2.50 mmol) furnish the title compound (0.22 g, 0.54 mmol, 71%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 2.63 (s, 3H), 3.29-3.39 (m, 1H), 6.67 (s, 1H), 7.06-7.14 (m, 1H), 7.44 (s, 1H), 7.74 (dd, J = 7.5, 0.9 Hz, 1H), 8.47 (dd, J = 4.9, 0.9 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.3; found: 405.3.

Example 65.

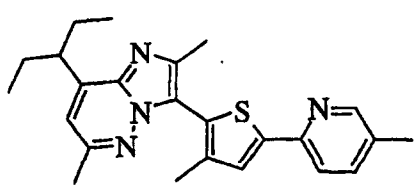
Preparation of (6-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-pyridin-2-yl)-dimethyl-amine.



Using a procedure similar to Example 39, from Rieke® Zn in THF (0.20 g, 3.06 mmol), (6-bromo-pyridin-2-yl)-dimethyl-amine (Newkomw et. el. *J. Org. Chem.*, 1988, 3, 786) (0.41 mL, 2.04 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.35 g, 0.89 mmol), and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.16 g, 0.37 mmol, 36%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.15 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 3.21 (s, 6H), 3.30-3.40 (m, 1H), 6.40 (d, J = 8.4 Hz, 1H), 6.66 (s, 1H), 6.95 (d, J = 7.4 Hz, 1H), 7.45 (dd, J = 8.4, 7.4 Hz, 1H), 7.46 (s, 1H). LC/MS (m/z): calcd. for $C_{25}H_{31}N_5S$ $(M+H)^+$: 434.3; found: 434.3.

Example 66.

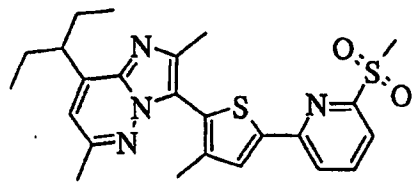
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(5-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.765 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol) and 0.5 M solution of 4-methyl-2-pyridylzinc bromide in THF (3.0 mL, 1.53 mmol) furnish the title compound (0.23 g, 0.57 mmol, 74%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.16 (s, 3H), 2.35 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 3.31-3.41 (m, 1H), 6.67 (s, 1H), 7.48(s, 1H), 7.50 (d, J = 2.2 Hz, 1H), 7.56 (d, J = 7.9 Hz, 1H), 8.39-8.40 (m, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.3; found: 405.3.

Example 67.

Preparation of 8-(1-ethyl-propyl)-3-[5-(6-methanesulfonyl-pyridin-2-yl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 2-Bromo-6-methanesulfonyl-pyridine.

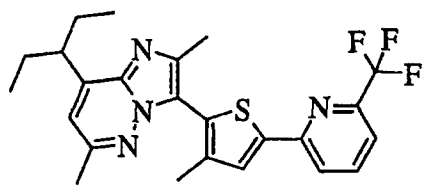
To a solution of 2-bromo-6-methylsulfanyl-pyridine (Testaferri et. el *Tetrahedron*, 1985, 41, 1373) (2.15 g, 10.53 mmol) and CH_2Cl_2 (30 mL) is added 56-87% mCPBA (12 g, 42.15 mmol). The solution is cooled with ice to ambient temperature and the solution is stirred for 2 hour, washed with sat. $Na_2S_2O_3$ (15 mL), sat. $NaHCO_3$ (2 X 15 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by recrystalization from EtOAc /hexane furnish the title compound (1.71 g, 7.24 mmol, 69%). ^1H NMR ($CDCl_3$), δ 3.26 (s, 3H), 7.73 (dd, J = 8.0, 0.9 Hz, 1H), 7.82 (dd, J = 8.0, 7.5 Hz, 1H), 8.05 (dd, J = 7.5, 0.9 Hz, 1H). LC/MS (m/z): calcd. for $C_6H_6BrNO_2S$ $(M+H)^+$: 235.9; found: 235.9.

B. 8-(1-ethyl-propyl)-3-[5-(6-methanesulfonyl-pyridin-2-yl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure similar to Example 25, 2-bromo-6-methanesulfonyl-pyridine (0.29 mL, 1.22 mmol), 1.3 M *n*-Bu-Li (0.82 mL, 1.07 mmol), $ZnCl_2$ (2.14 mL, 1.07 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.13 g, 0.28 mmol, 27%). ^1H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.18 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.30 (s, 3H), 3.30-3.38 (m, 1H), 6.70 (s, 1H), 7.64 (s, 1H), 7.83 (dd, J = 7.6, 0.8 Hz, 1H), 7.89 (dd, J = 7.9, 0.8 Hz, 1H), 7.93 (dd, J = 7.9, 7.6 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4O_2S_2$ $(M+H)^+$: 469.3; found: 469.2.

Example 68.

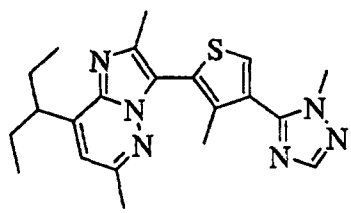
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-trifluoromethyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 25, 2-chloro-6-trifluoromethyl-pyridine (0.29 mL, 1.22 mmol), 1.34 M *n*-Bu-Li (0.80 mL, 1.07 mmol), $ZnCl_2$ (2.14 mL, 1.07 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.20 g, 0.44 mmol, 43%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, *J* = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.18 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.30-3.40 (m, 1H), 6.69 (s, 1H), 7.50 (dd, *J* = 7.5, 0.9 Hz, 1H), 7.65 (s, 1H), 7.78 (d, *J* = 7.9 Hz, 1H), 7.84 (dd, *J* = 7.9, 7.5 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{25}F_3N_4S$ $(M+H)^+$: 459.3; found: 459.2.

Example 69.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-4-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.

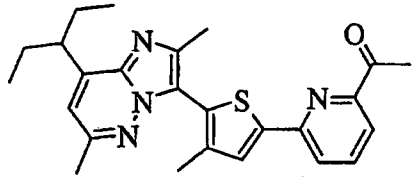


To a slurry of 0.05 g/ mL of Reike® Zn in THF (3.0 mL, 2.29 mmol) is added a solution of 5-bromo-1-methyl-*1H*-[1,2,4]triazole and THF (2 mL). The solution was heated at 65 °C for 1 hour, cooled to ambient temperature and the excess Zn allowed to settle for 1 hour. The solution was transferred to a flask containing 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (example Rupp-152) (0.32 g, 0.70 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat.

NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (50%-100% Et_2O) to furnish the title compound (0.058 g, 0.15 mmol, 19%). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.11 (s, 3H), 2.47 (s, 3H), 2.49 (s, 3H), 3.27-3.37 (m, 1H), 3.97 (s, 3H), 6.68 (s, 1H), 7.64 (s, 1H), 7.99 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{26}N_6S$ $(M+H)^+$: 395.2; found: 395.4.

Example 70.

Preparation of 1-(6-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-pyridin-2-yl)-ethanone.



A. 3-[5-(6-Bromo-pyridin-2-yl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure similar to Example 25, 2,6-dibromo-pyridine (0.91 g, 3.82 mmol), 1.34 M *n*-Bu-Li (1.50 mL, 2.00 mmol), $ZnCl_2$ (4.0 mL, 2.00 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.75 g, 1.92 mmol) and $PdCl_2$(dppf) (0.070 g, 0.096 mmol) furnish the title compound (0.26 g, 0.55 mmol, 29%). ^1H NMR ($CDCl_3$), δ 0.89 (t, J = 7.4 Hz, 6H), 1.74-1.93 (m, 4H), 2.16 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.30-3.39 (m, 1H), 6.68 (s, 1H), 7.31 (dd, J = 7.5, 1.3 Hz, 1H), 7.49-7.57 (m, 2H), 7.58 (s, 1H).

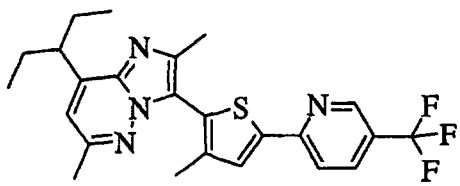
B. 1-(6-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-pyridin-2-yl)-ethanone.

To a –78°C solution of 3-[5-(6-bromo-pyridin-2-yl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine) (0.26 g, 0.55 mmol), and THF (5 mL), is added 1.34 M *n*-Bu-Li (0.43 mL, 0.58 mmol). After 30 minutes *N*-methoxy-*N*-methyl-acetamide (0.065 mL, 0.61 mmol) is added and the solution warmed to ambient

temperature. The solution is diluted with EtOAc (30 mL), washed with sat. NH_4Cl (25 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15-20% EtOAc/hexane gradient) furnish the title compound (0.030 g, 0.069 mmol, 13%). ^1H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.19 (s, 3H), 2.52 (s, 3H), 2.53 (s, 3H), 2.77 (s, 3H), 3.30-3.40 (m, 1H), 6.69 (s, 1H), 7.59 (s, 1H), 7.77-7.85 (m, 2H), 7.87 (dd, J = 6.8, 2.2 Hz, 1H). LC/MS (m/z): calcd. for $C_{25}H_{28}N_4OS$ $(M+H)^+$: 433.3; found: 433.2.

Example 71.

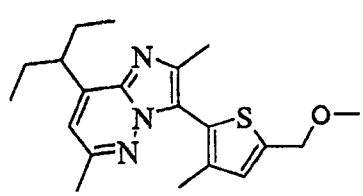
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(5-trifluoromethyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 2-bromo-5-trifluoromethyl-pyridine (2.14 mL, 1.07 mmol), 1.34 M *n*-Bu-Li (0.80 mL, 1.07 mmol), $ZnCl_2$ (2.14 mL, 1.07 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.17 g, 0.37 mmol, 36%). ^1H NMR ($CDCl_3$), δ 0.90 (t, J = 7.3 Hz, 6H), 1.76-1.94 (m, 4H), 2.18 (s, 3H), 2.19 (s, 3H), 2.53 (s, 3H), 3.31-3.40 (m, 1H), 6.70 (s, 1H), 7.63 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.78 (dd, J = 8.4, 2.2 Hz, 1H), 7.79-7.82 (m, 1H). LC/MS (m/z): calcd. for $C_{24}H_{25}F_3N_4S$ $(M+H)^+$: 459.3; found: 459.2.

Example 72.

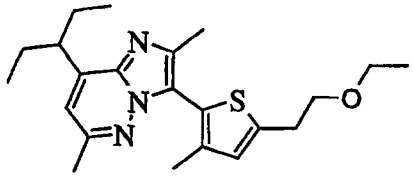
Preparation of 8-(1-ethyl-propyl)-3-(5-methoxymethyl-3-methyl-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a –78°C solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol) and THF (3 mL) is added 1.34 M *n*-Bu-Li (0.50 mL, 0.80 mmol). After 30 minutes iodo-methoxy-methane (0.097 mL, 1.15 mmol) is added and the solution warmed to ambient temperature. After 1 hour the solution is diluted with EtOAc (40 mL) washed with water (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.12 g, 0.34 mmol, 44%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.72-1.90 (m, 4H), 2.09 (s, 3H), 2.45 (s, 3H), 2.49 (s, 3H), 3.28-3.37 (m, 1H), 3.44 (s, 3H), 4.61 (s, 2H), 6.65 (s, 1H), 6.93 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{27}N_3OS$ $(M+H)^+$: 358.3; found: 358.3.

Example 73.

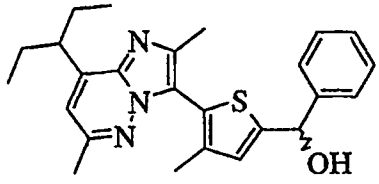
Preparation of 3-[5-(2-ethoxy-ethyl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 72, from of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol), 1.34 M *n*-Bu-Li (0.53 mL, 0.84 mmol), 1-bromo-2-ethoxy-ethane (0.13 mL, 1.15 mmol) and KI (0.013 g, 0.076 mmol) furnish the title compound (0.11 g, 0.29 mmol, 38%). ^{1}H NMR ($CDCl_3$), δ 0.86 (t, J = 7.5 Hz, 6H), 1.23 (t, J = 7.0 Hz, 3H), 1.72-1.90 (m, 4H), 2.06 (s, 3H), 2.45 (s, 3H), 2.49 (s, 3H), 3.09 (t, J = 7.0 Hz, 2H), 3.28-3.37 (m, 1H), 3.55 (q, J = 7.0 Hz, 2H), 3.71 (t, J = 7.0 Hz, 2H), 6.64 (s, 1H), 6.77 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{31}N_3OS$ $(M+H)^+$: 386.3 found: 386.3.

Example 74.

Preparation of {5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-phenyl-methanol.



A. (5-Bromo-4-methyl-thiophen-2-yl)-phenyl-methanol.

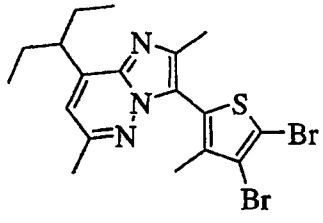
To a –78°C solution of 2-bromo-3-methyl-thiophene (4.7 g, 26.54 mmol) and Et_2O (100 mL) is added 2.0 M LDA (14.6 mL, 29.2 mmol). After 1 hour benzaldehyde (3.0 mL, 29.2 mmol) is added and the solution warmed to ambient temperature and stirred for 2 hour. The solution is washed with sat. NH_4Cl (75 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (3.29 g, 11.62 mmol, 44%). ^1H NMR ($CDCl_3$), δ 2.11 (s, 3H), 3.38-3.46 (m, 1H), 5.90 (s, 1H), 6.54 (s, 1H), 7.30-7.45 (m, 5H). LC/MS (m/z): calcd. for $C_{12}H_{11}BrOS$ $(M+H)^+$: 281.0, 283.0; found: 264.9, 266.9.

B. {5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-phenyl-methanol.

Using a procedure analogous to Example 30C, from 3-(5-boronic acid-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.1.15 mmol), (5-bromo-4-methyl-thiophen-2-yl)-phenyl-methanol (0.33 g, 1.15 mmol), 2 M Na_2CO_3 (0.86 mL, 1.72 mmol) *n*-PrOH (1 mL), $Pd(OAc)_2$ (0.0052 g, 0.023 mmol), and PPh_3 (0.018 , 0.069 mmol). The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) and is chromatographed (50 x 250 C18 Symmetry column, 25-70% water: 0.1 % TFA /ACN: 0.1% TFA gradient) furnish the title compound (0.017 g, 0.041 mmol, 3.5%). ^1H NMR ($CDCl_3$), δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-1.90 (m, 4H), 2.04 (s, 3H), 2.43 (s, 3H), 2.49 (s, 3H), 2.75 (bs, 1H), 3.26-3.38 (m, 1H), 6.05 (s, 1H), 6.65 (s, 1H), 6.76 (s, 1H), 7.30-7.45 (m, 3H), 7.50-7.56 (m, 1H). LC/MS (m/z): calcd. for $C_{25}H_{29}N_3OS$ $(M+H)^+$: 420.3; found: 420.3.

Example 75.

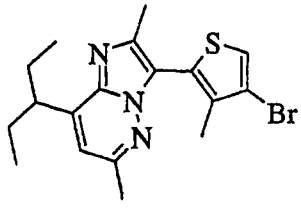
Preparation of 3-(4,5-dibromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (4.00 g, 10.20 mmol) and AcOH (40 mL) is added Br_2 (0.57 mL, 11.21 mmol) and the solution heated at 110 °C overnight. Br_2 (0.57 mL, 11.21 mmol) is added and the solution heated at 110 °C for 2 hours. The solution is poured into 5 M NaOH (200 mL) and ice (200 mL). The slurry is extracted with EtOAc (2 x 150 mL). The combined organic layers are washed with water (200 mL), 20% $NaHSO_3$ (200 mL), sat. $NaHCO_3$ (200 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (5%-15% EtOAc gradient) furnish the title compound (2.66 g, 5.64 mmol, 55%). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-1.91 (m, 4H), 2.12 (s, 3H), 2.43 (s, 3H), 2.50 (s, 3H), 3.25-3.35 (m, 1H), 6.69 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{21}Br_2N_3S$ $(M+H)^+$: 470.0; found: 470.3.

Example 76.

Preparation of 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

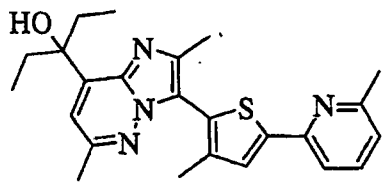


To a –78 °C solution of 3-(4,5-dibromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.22 g, 0.47 mmol) and THF (3 mL) is added 1.6 M *n*-BuLi (0.31 mL, 0.49 mmol). After 20 minutes the solution is quenched with water (1 mL), warmed to ambient temperature, diluted with EtOAc (30 mL), washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified

by ISCO (5%-10% EtOAc gradient) furnish the title compound (0.056 g, 0.14 mmol, 31%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.93 (m, 4H), 2.09 (s, 3H), 2.44 (s, 3H), 2.49 (s, 3H), 3.27-3.36 (m, 1H), 6.68 (s, 1H), 7.44 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{22}BrN_3S$ $(M+H)^+$: 392.2; found: 392.3.

Example 77.

Preparation of 3-{2,6-Dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazin-8-yl}-pentan-3-ol.



A. 2-(5-Bromo-4-methyl-thiophen-2-yl)-6-methyl-pyridine.

To a –78°C solution of 2-bromo-3-methyl-thiophene (2.0 mL, 17.75 mmol) and THF (30 mL) is added 2.0 M LDA (9.76 mL, 19.52 mmol). After 45 minutes 0.5 M $ZnCl_2$ (39.0 mL, 19.50 mmol) is added and the solution stirred for 30 minutes. 2-Bromo-6-methyl-pyridine (2.4 mL, 21.29 mmol) and $Pd(PPh_3)_4$ (0.50 g, 0.44 mmol) is added and the solution is warmed to ambient temperature and stirred for 2 hour. The solution is washed with sat. NH_4Cl (20 mL). The aqueous layer is extracted with CH_2Cl_2 (30 mL). The combined organic layers are washed with sat. NH_4Cl (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue is purified by ISCO column chromatography (10%-20% EtOAc/hexane gradient) furnish the title compound (2.34 g, 8.73 mmol, 49%). ^{1}H NMR ($CDCl_3$), δ 2.21 (s, 3H), 2.54 (s, 3H), 6.99 (d, J = 7.9 Hz, 1H), 7.23 (s, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.53 (dd, J = 7.9, 7.9 Hz, 1H). LC/MS (m/z): calcd. for $C_{11}H_{10}BrNS$ $(M+H)^+$: 267.0, 269.0; found:267.7, 269.5.

B. 2,6-Dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.

000

A solution of 2,6-dimethyl-imidazo[*1,2-b*]pyridazine (below) (0.50 g, 3.39 mmol), 2-(5-bromo-4-methyl-thiophen-2-yl)-6-methyl-pyridine (1.00 g, 3.73 mmol), Cs_2CO_3 (2.32 g, 7.13 mmol) and DMF (5 mL) is de-gassed for 15 minutes with N_2. $Pd_2(dba)_3$ (0.15 g, 0.16 mmol) and PPh_3 (0.17 g, 0.65 mmol) is added and the solution is heated at 130°C overnight. The solution is diluted with CH_2Cl_2 (30 mL) washed with water (2 x 25 mL), brine (25 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (100% EtOAc), followed by recrystalization from acetonitrile / water furnish the title compound (0.45 g, 1.35 mmol, 39%). ^{1}H NMR ($CDCl_3$), δ 2.13 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 2.57 (s, 3H), 6.90 (d, J = 9.2 Hz, 1H), 7.01 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.52 (s, 1H), 7.56 (dd, J = 8.0, 7.5 Hz, 1H), 7.77 (d, J = 9.2 Hz, 1H). LC/MS (m/z): calcd. for $C_{19}H_{18}N_4S$ $(M+H)^+$: 335.1; found: 335.1.

C. 1-{2,6-Dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazin-8-yl}-propan-1-one.

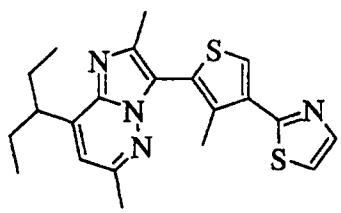
To a –78°C solution of 2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine (0.34 g, 1.02 mmol) and THF (9 mL) is added 2.0 M LDA (0.61 mL, 1.22 mmol). After 3 minutes, *N*-methoxy-*N*-methyl-propionamide (Wolberg et. el. *Chem. Eur. J.*, 2001, 7, 4562) (1.17 g, 1.42 mmol) is added and the solution stirred for 20 minutes, warmed to ambient temperature and stirred for 30 minutes. The solution is diluted with EtOAc (50 mL) washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (0.10 g, 0.26 mmol, 25%). ^{1}H NMR ($CDCl_3$), δ 1.28 (t, J = 7.0 Hz, 3H), 2.13 (s, 3H), 2.54 (s, 3H), 2.58 (s, 6H), 3.59 (q, J = 7.0 Hz, 2H), 7.03 (d, J = 7.5 Hz, 1H), 7.33 (s, 1H), 7.47 (d, J = 7.9 Hz, 1H), 7.55 (bs, 1H), 7.58 (dd, J = 7.9, 7.5 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{22}N_4OS$ $(M+H)^+$: 391.2; found: 391.2.

D. 3-{2,6-Dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazin-8-yl}-pentan-3-ol.

To a –0°C solution of 1-{2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazin-8-yl}-propan-1-one (0.040 g, 0.10 mmol) and Et_2O (5 mL) is added 3.0 M ethyl magnesium bromide (0.68 mL, 2.05 mmol). The solution is warmed to ambient temperature, diluted with EtOAc (30 mL) washed with sat. NH_4Cl (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (0.016 g, 0.038 mmol, 37%). ^1H NMR ($CDCl_3$), δ 0.89 (t, J = 7.4 Hz, 6H), 1.92-2.01 (m, 4H), 2.14 (s, 3H), 2.46 (s, 3H), 2.53 (s, 3H), 3.57 (s, 3H), 6.39 (s, 1H), 6.66 (s, 1H), 7.01 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 7.9 Hz, 1H), 7.52 (s, 1H), 7.57 (dd, J = 7.9, 7.5 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4OS$ $(M+H)^+$: 421.3; found: 421.3.

Example 78.

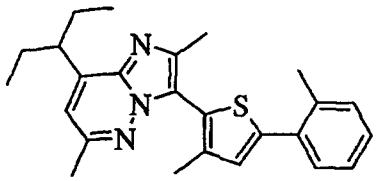
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-4-thiazol-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.25 g, 0.64 mmol) and $PdCl_2$(dppf) (0.023 g, 0.032 mmol) is added a 0.5 M solution of 2-thiazolylzinc bromide (3.82 mL, 1.91 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (25 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (15%-20% EtOAc gradient) furnish the title compound (0.19 g, 0.48 mmol, 76%). ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.92 (m, 4H), 2.36 (s, 3H), 2.47 (s, 3H), 2.50 (, 3H), 3.29-3.39 (m, 1H), 6.69 (s, 1H), 7.33 (d, J = 3.3 Hz, 1H), 7.89 (d, J = 3.3 Hz, 1H), 7.99 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}N_4S_2$ $(M+H)^+$: 397.2; found: 397.3.

Example 79.

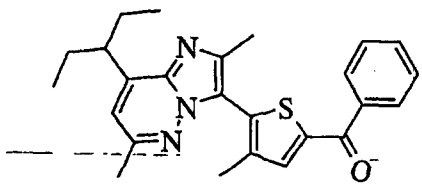
Preparation of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-o-tolyl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



Using the procedure analogous to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.15 g, 0.38 mmol) and $PdCl_2$(dppf) (0.014 g, 0.019 mmol) and 0.5M solution of 2-methylphenylzinc iodide in THF (3 mL, 1.53 mmol) furnish the title compound (0.069 g, 0.17 mmol, 46%). ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.19 (s, 3H), 2.53 (s, 3H), 2.54 (s, 3H), 2.55 (s, 3H), 3.32-3.40 (m, 1H), 6.68 (s, 1H), 7.02 (s, 1H), 7.22-7.30 (m, 3H), 7.48-7.53 (m, 1H). LC/MS (m/z): calcd. for $C_{25}H_{29}N_3S$ $(M+H)^+$: 404.3; found: 404.3.

Example 80.

Preparation of {5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-phenyl-methanone.

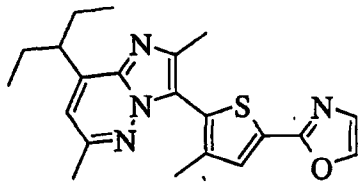


To a -78°C solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol) and THF (5 mL) is added 1.30 M *n*-Bu-Li (0.50 mL, 0.80 mmol). After 30 minutes *N*-methoxy-*N*-methyl-benzamide (0.13 mL, 0.84 mmol) is added, the solution is warmed to ambient temperature, and stirred overnight. The solution is diluted with EtOAc (20 mL), washed with sat. NH_4Cl (15 mL), water (15 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.066 g, 0.16 mmol, 21%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.4 Hz, 6H), 1.74-1.93 (m, 4H), 2.18 (s, 3H), 2.52 (s, 3H), 2.54 (s,

3H), 3.29-3.38 (m, 1H), 6.71 (s, 1H), 7.49-7.54 (m, 2H), 7.56 (s, 1H), 7.57-7.62 (m, 1H), 7.89-7.94 (m, 2H). LC/MS (m/z): calcd. for $C_{25}H_{27}N_3OS$ $(M+H)^+$: 418.2; found: 418.2.

Example 81.

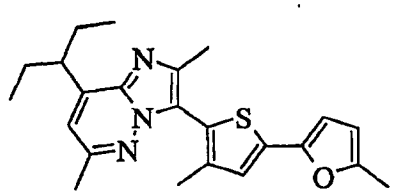
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-oxazol-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To a –78 °C solution of oxazole (0.14 g, 2.04 mmol) and THF (3 mL) is added 1.6 M *t*-Bu-Li in hexane (1.32 mL, 2.14 mmol). The mixture is stirred at –78°C for 15 minutes. 0.5 M $ZnCl_2$ in THF (4.3 mL, 2.14 mmol) is added and the solution warmed to ambient temperature. 3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) is added and mixture is stirred at 65 °C overnight, diluted with EtOAc (30 mL), washed with 10% citric acid (20 mL), water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20% EtOAc/hexane gradient) and is chromatographed (50 x 250 C18 Symmetry column, 20-70% water: 0.1 % TFA /ACN: 0.1% TFA gradient) to furnish the title compound (0.020 g, 0.053 mmol, 5%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H), 2.49 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 6.69 (s, 1H), 7.19 (s, 1H), 7.59 (s, 1H), 7.65 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}N_4OS$ $(M+H)^+$: 381.3; found: 381.1.

Example 82.

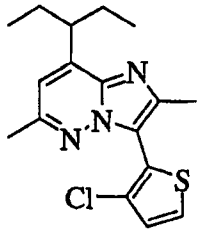
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(5-methyl-furan-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



To a 0°C mixture of 2-methylfuran (0.18 mL, 2.04 mmol) and Et_2O (2 mL) is added 1.6 M *t*-Bu-Li in hexane (1.30 mL, 2.14 mmol). The mixture is heated at a reflux for 30 minutes, cooled to 0°C, and 0.5 M $ZnCl_2$ in THF (4.3 mL, 2.14 mmol) is added and the solution warmed to ambient temperature. 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) is added and mixture is stirred at 65°C overnight, diluted with EtOAc (30 mL), washed with 10% citric acid (15 mL), water (15 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20% EtOAc/hexane gradient) furnish the title compound (0.20 g, 0.51 mmol, 50%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.12 (s, 3H), 2.35 (s, 3H), 2.48 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 6.62 (dd, J = 3.1, 0.9 Hz, 1H), 6.40 (d, J = 3.1 Hz, 1H), 6.66 (s, 1H), 7.12 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{27}N_3OS$ $(M+H)^+$: 394.3; found: 394.2.

Example 83.

Preparation of 3-(3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

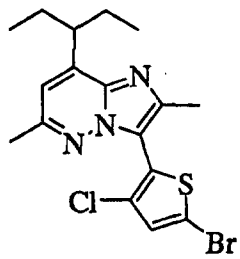


To a flask of 2-bromo-3-chloro-thiophene (Lemaire et. el., *Synth. Commun.*, 1994, 24, 95) (2.53 g, 12.82 mmol) is added 0.05 g/mL Reike® zinc in THF (25 mL, 19.24 mmol). The solution is heated at a reflux for 2 hours. The excess zinc is allowed to settle and the solution transferred to a flask containing 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (example KW1-A03735-193) (2.01 g, 6.41 mmol) and $PdCl_2$(dppf) (0.23 g, 0.32 mmol). The solution is heated at a reflux overnight, quenched with sat. NH_4Cl (25 mL) and extracted with EtOAc (2 X 25 mL). The combined organic layers are dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (2%-15% EtOAc/hexane gradient) furnish the title compound (1.32 g, 6.68 mmol, 62%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m,

4H), 2.48 (s, 3H), 2.49 (s, 3H), 3.37-3.36 (m, 1H), 6.67 (s, 1H), 7.07 (d, J = 5.4 Hz, 1H), 7.48 (d, J = 5.4 Hz, 1H). LC/MS (m/z): calcd. for $C_{17}H_{20}ClN_3S$ $(M+H)^+$: 334.1; found: 334.1.

Example 84.

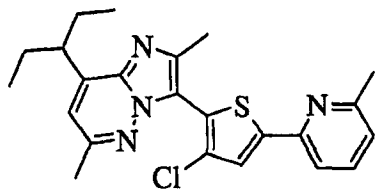
Preparation of 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a solution of 3-(3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine. (1.15 g, 3.44 mmol) and CH_2Cl_2 (12 mL) is added NBS (0.64 g, 3.62 mmol). The solution is stirred at ambient temperature overnight, washed with water (2 x 75 mL), brine (75 mL), dried over Na_2SO_4, filtered and concentrated to furnish the title compound (1.36 g, 3.29 mmol, 96%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.49 (s, 3H), 2.53 (s, 3H), 3.26-3.36 (m, 1H), 6.70 (s, 1H), 7.07 (s, 1H). LC/MS (m/z): calcd. for $C_{17}H_{19}BrClN_3S$ $(M+H)^+$: 412.1; found: 412.0.

Example 85.

Preparation of 3-[3-chloro-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Method A.

To a flask of 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.73 mmol) and $PdCl_2$(dppf) (0.027 g, 0.036 mmol) is added 0.5 M solution of 6-methyl-2-pyridylzinc bromide in THF (2.9 mL, 1.45

mmol). The mixture is stirred at 65 °C overnight, diluted with EtOAc (50 mL), washed with sat. NH_4CL (40 mL), water (40 mL), brine (40 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-40% EtOAc/hexane gradient) furnish the title compound (0.072 g, 0.17 mmol, 23%). ^1H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.58 (s, 3H), 3.30-3.39 (m, 1H), 6.70 (s, 1H), 7.06 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.54 (s, 1H), 7.60 (dd, J = 7.7, 7.5 Hz, 1H). LC/MS (m/z): calcd. for $C_{23}H_{25}ClN_4S$ $(M+H)^+$: 425.2; found: 425.2.

Method B.

A. 2-(4-Chloro-thiophen-2-yl)-6-methyl-pyridine.

To a solution of 2-bromo-4-chloro-thiophene (Gronowitz, Rosén *Chemica Scripta*, 1971, 1, 33) (1.50 g, 7.60 mmol) and 0.5 M solution of 6-methyl-2-pyridylzinc bromide in THF (23.00 mL, 11.39 mmol) is added $Pd(PPh_3)_4$ (0.18 g, 0.15 mmol). The solution is heated at 40°C overnight, diluted with Et_2O (50 mL), washed with sat. NH_4Cl (40 mL), dried over $MgSO_4$, filtered on concentrated. The residue is purified by ISCO column chromatography (5%-20% EtOAc/hexane gradient) furnish the title compound (0.45 g, 2.15 mmol, 28%). ^1H NMR ($CDCl_3$), δ 2.56 (s, 3H), 7.02 (d, 7.7 Hz, 1H), 7.13 (d, J = 0.9 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.39 (d, J = 0.9 Hz, 1H), 7.54 (dd, J = 7.9, 7.7, 1H).

B. 2-(5-bromo-4-chloro-thiophen-2-yl)-6-methyl-pyridine.

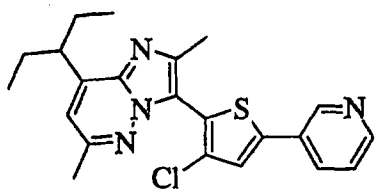
To a 0°C solution of 2-(4-chloro-thiophen-2-yl)-6-methyl-pyridine (example Rupp-96) (0.45 g, 1.45 mmol) and CH_2Cl_2 (10 mL) is added Br_2 (0.15 mL, 2.91 mmol). The solution is warmed to ambient temperature and stirred for 1 hour. The solution is washed with sat. $NaHCO_3$ (10 mL), sat. $Na_2S_2O_3$ (10 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.59 g, 2.04, 95%). ^1H NMR ($CDCl_3$), δ 2.55 (s, 3H), 7.05 (d, 7.9 Hz, 1H), 7.29 (s, 1H), 7.34 (d, J = 7.9 Hz, 1H), 7.58 (dd, J = 7.9, 7.9, 1H). LC/MS (m/z): calcd. for $C_{10}H_7BrClNS$ $(M+H)^+$: 288.0; found: 287.9.

C. 3-[3-Chloro-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

A solution of 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.39 g, 1.78 mmol), 2-(5-bromo-4-chloro-thiophen-2-yl)-6-methyl-pyridine (0.59 g, 2.04 mmol), Cs_2CO_3 (1.23 g, 3.77 mmol), and DMF (5 mL), is de-gassed with N_2 for 15 minutes. PPh_3 (0.089 g, 0.34 mmol) and $Pd_2(dba)_3$ (0.079 g, 0.86 mmol) is added and the solution heated at 110°C for 48 hours. The solution is diluted with EtOAc (30 mL), washed with sat. NH_4Cl (25 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) and is chromatographed (19 x 300 C18 Symmetry column, 20-45% water: 0.1 % TFA /ACN: 0.1% TFA gradient) furnish the title compound (0.078 g, 0.18 mmol, 10%). Spectrum identical to Method A.

Example 86.

Preparation of 3-(3-chloro-5-pyridin-3-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Method A.

A solution of 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.61 mmol), pyridine-3-boronic acid (0.082 g, 0.67 mmol), 2 M Na_2CO_3 (0.45 mL, 0.91 mmol) and, *n*-PrOH (1 mL), is degassed with nitrogen for 10 minutes. $Pd(OAc)_2$ (0.0027 g, 0.0012 mmol) and PPh_3 (0.0095 g, 0.036 mmol) are added and the solution is heated at 88°C overnight. The solution is diluted with EtOAc (15 mL), washed with water (10 mL), sat. $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtered and concentrated. Purified by ISCO column chromatography (15-40% EtOAc/hexane gradient) furnish the title compound (0.095 g, 0.23 mmol, 38%). ^1H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.29-3.38 (m, 1H), 6.71 (s, 1H), 7.32-7.37 (m, 2H), 7.85-7.90 (m, 1H), 8.57 (d, J = 4.0 Hz, 1H), 8.89 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{23}ClN_4S$ $(M+H)^+$: 411.2; found: 411.2.

Method B.

A. 3-(4-Chloro-thiophen-2-yl)-pyridine.

A solution of 2-bromo-4-chloro-thiophene (Gronowitz, Rosén *Chemica Scripta*, 1971, 1, 33) (1.45 g, 7.34 mmol), pyridine-3-boronic acid (0.95 g, 7.71 mmol), 2 M Na_2CO_3 (5.50 mL, 11.01 mmol) and, *n*-PrOH (3 mL), is degassed with N_2 for 10 minutes. $Pd(OAc)_2$ (0.033 g, 0.15 mmol) and PPh_3 (0.12 g, 0.44 mmol) are added and the solution is heated at 85°C for 48 hours, diluted with CH_2Cl_2 (50 mL), washed with 10 % Na_2CO_3 (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (0.74 g, 3.78 mmol, 51%). ^{1}H NMR ($CDCl_3$), δ 7.12-7.13 (m, 1H), 7.20 (d, *J* = 1.4 Hz, 1H), 7.31 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.78-7.82 (m, 1H), 8.55 (d, *J* = 4.9 Hz, 1H), 8.82 (d, *J* = 2.2 Hz, 1H).

B. 3-(5-Bromo-4-chloro-thiophen-2-yl)-pyridine.

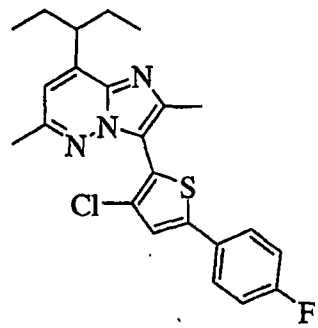
Using a procedure similar to Example 85 Method B. step B, 3-(4-chloro-thiophen-2-yl)-pyridine (0.74 g, 3.78 mmol), and Br_2 (0.39 mL, 7.56 mmol) furnish the title compound (0.99 g, 3.61 mmol, 95%). ^{1}H NMR ($CDCl_3$), δ 7.13 (s, 1H), 7.34 (dd, *J* = 8.1, 4.4 Hz, 1H), 7.74-7.78 (m, 1H), 8.58 (d, *J* = 4.4 Hz, 1H), 8.78 (s, 1H).

C. 3-(3-Chloro-5-pyridin-3-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure similar to Example 85 Method B Step C, from 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 2.30 mmol), 3-(5-bromo-4-chloro-thiophen-2-yl)-pyridine) (0.76 g, 2.76 mmol), Cs_2CO_3 (1.57 g, 4.83 mmol), PPh_3 (0.11 g, 0.44 mmol) and $Pd_2(dba)_3$ (0.10 g, 0.11 mmol). The residue is purified by ISCO column chromatography (15%-30% EtOAc/hexane gradient) furnish the title compound (0.35 g, 0.85 mmol, 37%). Spectrum identical to Method A.

Example 87.

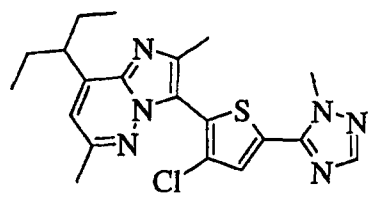
Preparation of 3-[3-chloro-5-(4-fluoro-phenyl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 25, 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.61 mmol), 4-flourophenylboronic acid (0.093 g, 0.67 mmol), 2 M Na_2CO_3 (0.45 mL, 0.91 mmol), *n*-PrOH (2 mL), $Pd(OAc)_2$ (0.0068 g, 0.030 mmol) and PPh_3 (0.016 g, 0.061 mmol) furnish the title compound (0.041 g, 0.096 mmol, 16%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.29-3.38 (m, 1H), 6.70 (s, 1H), 7.07-7.13 (m, 2H), 7.22 (s, 1H), 7.54-7.60 (m, 2H). LC/MS (m/z): calcd. for $C_{23}H_{23}ClFN_3S$ $(M+H)^+$: 428.2; found: 428.1.

Example 88.

Preparation of 3-[3-chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Method A.

To a –78 °C solution of 1-methyl-1,2,4-triazole (0.18 mL, 2.33 mmol) and THF (3 mL) is added a 1.56 M solution of *n*-Bu-Li in hexanes (1.49 mL, 2.33 mmol). The solution is stirred at –78°C for 30 minutes, 0.5 M solution of $ZnCl_2$ in THF (4.70 mL, 2.33 mmol) is added and the solution warmed to ambient temperature. 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.32 g,

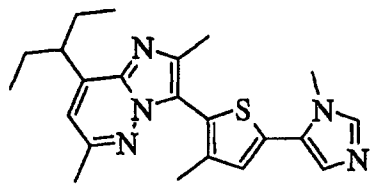
0.78 mmol) and $PdCl_2$(dppf) (0.028 g, 0.039 mmol) is added and the solution heated at 60 °C for 2 days, diluted with EtOAc (50 mL), washed with sat. NH_4Cl (30 mL), water (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-10% EtOAc/hexane gradient) furnish the title compound (0.19 g, 0.46 mmol, 59%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.29-3.37 (m, 1H), 4.16 (s, 3H), 6.73 (s, 1H), 7.48 (s, 1H), 7.90 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{23}ClN_6S$ $(M+H)^+$: 415.2; found: 415.1.

Method B.

A 5-L reaction flask equipped with a cooling bath, air stirrer, gas dispersion tube and thermometer probe is charged with 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-1H-[1,2,4]triazole (162.0 g, 0.745 moles), 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (250.1 g, 0.898 moles), NMP (800 mL), KOAc (366.0 g), TBABr (50.5 g), and additional NMP (700 mL) to form a mixture. While stirring, N_2 is bubbled through the mixture for 1 hour. A mixture of $Pd(OAc)_2$ (8.37 g) and TDBPP (24.56 g) are added in one portion, then heated to 120 °C for 3 hours. The reaction is cooled to 50 °C and transferred to a 12 L flask. The mixture is cooled to 20-25 °C, then added de-ionized H_2O (3.5 L) is added dropwise to precipitate out a sticky solid that gradually solidifies with stirring overnight. The solids are filtered, washed with de-ionized H_2O (2 x 2L), and fried on the filter plate for 30-60 minutes. The crude solids (595 g) are warmed in EtOAc (6.0 L) to 30 °C, then filtered through GFF paper to remove insolubles. The filtrate is dried over Na_2SO_4, treated with Darco (30.0 g), heated to 35 °C, filtered, and concentrated to give brown solids (432 g). The crude solids are eluted through a silica plug (1.0 kg) with CH_2Cl_2 (4.0 L), followed by EtOAc (16.0 L). Similar fractions are combined and concentrated under vacuum to approximately 6.0 L, then treated with Darco overnight with stirring. After filtering off the Darco through GFF paper, the filtrate is concentrated to solids (336 g). The solids are crystallized from EtOAc: heptane (1:2) to afford the title compound as a pale yellow solid (187 g, 60.5%, >98% area-% by reverse phase: Zorbax SB-C8, 4.6 mm x 250 mm, 5 microns, UV = 218 nm, flow rate 1.0 mL/min., oven temp. 25°C, isocratic = 30% water (0.1% TFA) & 70% AcCN.

Example 89.

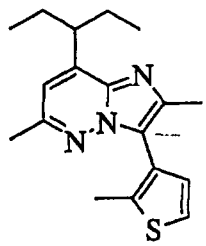
Preparation of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(3-methyl-*3H*-imidazol-4-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using the procedure analogous to Example 31, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol), 1.34M *n*-Bu-Li (0.80 mL, 1.07 mmol), 0.5M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), 5-iodo-1-methyl-*1H*-imidazole (0.24 g, 1.22 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.061g, 0.15 mmol, 15%). ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.4 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 3.24-3.38 (m, 1H), 3.61 (s, 3H), 6.68 (s, 1H), 7.02 (s, 1H), 7.23 (s, 1H), 7.55 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.3; found: 394.2.

Example 90.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine.



A. 4,4,5,5-Tetramethyl-2-(2-methyl-thiophen-3-yl)-[1,3,2]dioxaborolane.

A mixture of 3-bromo-2-methyl-thiophene (Saika et. el. *Chem. Soc. Chem. Communication*, 18, 1994, 2133; Steinkopf et. el.; *Justus Liebigs Ann. Chem.*, 513, 1934, 281; 3.1 g, 17.51 mmol), DMSO (50 mL), 4,4,5,5,4',4',5',5'-Octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl] (4.90g, 19.26 mmol), and KOAc (5.20 g, 52.58 mmol) is de-gassed with N_2 for 15 minutes. $PdCl_2$(dppf) (0.70 g, 0.88 mmol) is added and the solution stirred at ambient temperature overnight, then warmed to 85°C for 3 hours. The solution is diluted with water (200 mL), extracted with EtOAc (2 x 100 mL). The

combined organic layers washed with water (2 x 200 mL), brine (200 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (5%-20% EtOAc/hexane gradient) furnish the title compound (1.52 g, 6.78 mmol, 39%). ^{1}H NMR ($CDCl_3$), δ 1.34 (s, 12H), 2.72 (s, 3H), 7.04 (d, J = 5.0 Hz, 1H), 7.22 (d, 5.0 Hz, 1H).

B. 2-Methyl-thiophene-3-boronic acid.

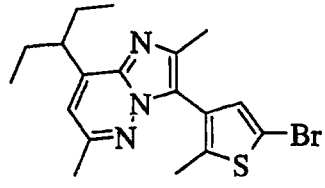
To a solution of 4,4,5,5-tetramethyl-2-(2-methyl-thiophen-3-yl)-[1,3,2]dioxaborolane (1.52 g, 6.78 mmol), acetone (15 mL) and water (15 mL) is added $NaIO_4$ (2.90 g, 13.56 mmol). The solution is stirred at ambient temperature for 24 hours, then heated to a reflux for 24 hours. The solution is concentrated dissolved in EtOAc (1450 mL), washed with water (100 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.75g, 5.49 mmol, 78%). ^{1}H NMR ($CDCl_3$), δ 2.93 (s, 3H), 7.10 (d, J = 5.3 Hz, 1H), 7.51 (d, 5.3 Hz, 1H).

C. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(2-methyl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine.

(1.65 g, 4.80 mmol), 2-methyl-thiophene-3-boronic acid (0.75 g, 5.28 mmol), 2 M Na_2CO_3 (3.60 mL, 7.20 mmol) and *n*-PrOH (20 mL) is degassed with N_2 for 10 minutes. $Pd(OAc)_2$ (0.022 g, 0.096 mmol) PPh_3 (0.076 g, 0.29 mmol) is added and the solution heated at 60°C for 24 hours, then heated at 90°C for 24 hours. The solution is concentrated, diluted in EtOAc (50 mL) washed with 10% Na_2CO_3 (40 mL), water (40 mL), brine (40 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (10%-15% EtOAc/hexane gradient) furnish the title compound (0.78 g, 2.49 mmol, 52%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.74-1.94 (m, 4H), 2.38 (s, 3H), 2.44 (s, 3H), 2.50 (s, 3H), 3.30-3.40 (m, 1H), 6.64 (s, 1H), 7.11 (d, J = 5.3 Hz, 1H), 7.20 (d, J = 5.3 Hz, 1H). LC/MS (m/z): calcd. for $C_{18}H_{23}N_3S$ $(M+H)^+$: 314.2; found: 314.2.

Example 91.

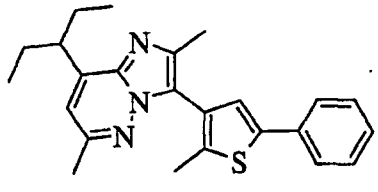
Preparation of 3-(5-bromo-2-methyl-thiophen-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine. (0.76 g, 2.42 mmol) and CH_2Cl_2 (10 mL) is added NBS (0.60 g, 3.37 mmol). The solution is stirred at ambient temperature for 2 hours and concentrated. The solution is dissolved in Et_2O (30 mL) washed with water (3 x 30 mL), brine (30 mL) dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.95 g, 2.42 mmol, >99%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.93 (m, 4H), 2.31 (s, 3H), 2.42 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 6.66 (s, 1H), 7.04 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{22}BrN_3S$ $(M+H)^+$: 392.2; found: 392.1.

Example 92.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-5-phenyl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine.

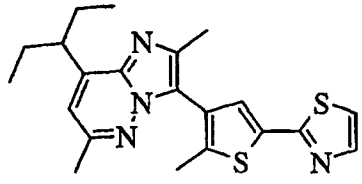


Using a procedure similar to Example 32, from 3-(5-bromo-2-methyl-thiophen-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.51 mmol) and $PdCl_2$(dppf) (0.019 g, 0.025 mmol) and 0.5 M solution of phenylzinc iodide in THF (2.0 mL, 1.02 mmol). The residue is purified by column chromatography (0-10% EtOAc/hexane gradient) and is chromatographed (50 x 250 C18 Symmetry column, 30-70% water: 0.1 % TFA /ACN: 0.1% TFA gradient) furnish the title compound (0.081 g, 0.21 mmol, 41%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.94 (m, 4H), 2.40 (s, 3H), 2.48 (s, 3H), 2.52 (s, 3H), 3.32-3.41 (m, 1H), 6.66 (s, 1H), 7.23-7.30 (m, 1H),

7.32 (s, 1H), 7.34-7.41 (m, 2H), 7.57-7.63 (m, 2H). LC/MS (m/z): calcd. for $C_{24}H_{27}N_3S$ $(M+H)^+$: 390.2; found: 390.2.

Example 93.

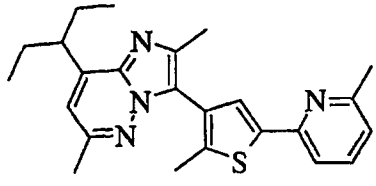
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-5-thiazol-2-yl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 3-(5-bromo-2-methyl-thiophen-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.51 mmol), 0.5 M 2-thiazolylzinc bromide in THF (8.1 mL, 4.05 mmol) and $PdCl_2$(dppf) (0.019 g, 0.025 mmol) furnish the title compound (0.20 g, 0.50 mmol, >99%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.40 (s, 3H), 2.45 (s, 3H), 2.50 (s, 3H), 3.29-3.38 (m, 1H), 6.60 (s, 1H), 7.22 (d, J = 3.2 Hz, 1H), 7.52 (s, 1H), 7.75 (d, J = 3.2 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}N_4S_2$ $(M+H)^+$: 397.1; found: 397.2.

Example 94.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[2-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-3-yl]-imidazo[*1,2-b*]pyridazine.

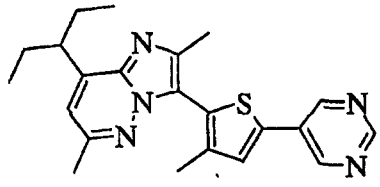


Using a procedure similar to Example 32, from 3-(5-bromo-2-methyl-thiophen-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.24 g, 0.61 mmol) and $PdCl_2$(dppf) (0.022 g, 0.031 mmol) and 0.5 M solution of 6-methyl-2-pyridylzinc bromide in THF (3.7 mL, 1.84 mmol) furnish the title compound (0.086 g, 0.21 mmol, 34%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.39 (s, 3H), 2.46 (s, 3H), 2.51 (s, 3H), 2.57 (s, 3H), 3.31-3.40 (m, 1H), 6.65 (s, 1H), 6.97 (d, J = 7.8 Hz,

1H), 7.41 (d, J = 7.8 Hz, 1H), 7.50-7.56 (m, 2H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4$ $(M+H)^+$: 405.2; found: 405.2.

Example 95.

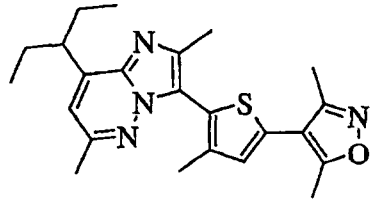
Preparation of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyrimidin-5-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 74B, from of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.51 mmol), 5-pyrimidine boronic acid (0.076 g, 0.61 mmol), 2 M Na_2CO_3 (0.38 mL, 0.76 mmol), $Pd(OAc)_2$ (0.0023 g, 0.011 mmol), PPh_3 (0.0080 g, 0.0031 mmol), and *n*-PrOH (2 mL) is furnished the title compound (0.084 g, 0.21 mmol, 42%). ^{1}H NMR ($CDCl_3$), δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-1.91 (m, 4H), 2.17 (s, 3H), 2.48 (s, 3H), 2.51 (s, 3H), 3.26-3.36 (m, 1H), 6.69 (s, 1H), 7.74 (s, 1H), 8.95 (s, 2H), 9.10 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{25}N_5S$ $(M+H)^+$: 392.3; found: 392.2.

Example 96.

Preparation of 3-[5-(3,5-Dimethyl-isoxazol-4-yl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

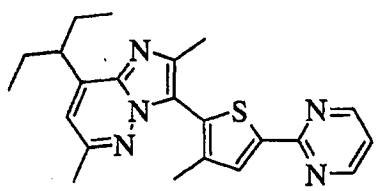


To a flask of 4-iodo-3,5-dimethyl-isoxazole (0.34 g, 1.53 mmol) is added a solution of Rieke® zinc 5g/100 mL in THF (3 mL, 2.29 mmol). The slurry is heated at a reflux for 4 hours, the zinc is allowed to settle and the solution transferred to a flask of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol). The solution is

heated at 50 °C overnight, diluted with EtOAc (20 mL), washed with 0.1 M HCl (15 mL), water (15 mL), brine (15 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-30% EtOAc/hexane gradient) furnish the title compound (0.22 g, 0.54 mmol, 71%). ^{1}H NMR ($CDCl_3$), δ 0.92 (t, J = 7.5 Hz, 6H), 1.78-1.96 (m, 4H), 2.21 (s, 3H), 2.47 (s, 3H), 2.53 (s, 3H), 2.56 (s, 3H), 2.61 (s, 3H), 3.33-3.42 (m, 1H), 6.72 (s, 1H), 6.98 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{28}N_4OS$ $(M+H)^+$: 409.3; found: 409.2.

Example 97.

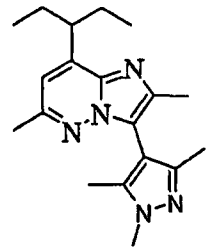
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyrimidin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



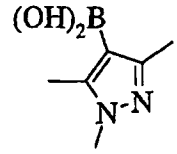
A solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol), 2-tributylstannanyl-pyrimidine (0.34 g, 0.92 mmol) and THF (5 mL) is de-gassed with N_2 for 10 minutes Triphenylarsine (0.047 g, 0.15 mmol) and $Pd_2(dba)_3$ (0.035 g, 0.038 mmol) is added and the solution heated at 55°C for 48 hours and concentrated. The residue is purified by ISCO column chromatography (15%-30% EtOAc/hexane gradient), dissolved in acetonitrile (20 mL), washed with hexane (3 x 20 mL) and concentrated to furnished the title compound (0.097 g, 0.25 mmol, 32%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.4 Hz, 6H), 1.74-1.92 (m, 4H), 2.18 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 3.29-3.38 (m, 1H), 6.67 (s, 1H), 7.08 (t, J = 4.8, 1H), 7.93 (s, 1H), 8.69 (s, 2H). LC/MS (m/z): calcd. for $C_{22}H_{25}N_5S$ $(M+H)^+$: 392.3; found: 392.2.

Example 98.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(1,3,5-trimethyl-*1H*-pyrazol-4-yl)-imidazo[*1,2-b*]pyridazine.



A. 1,3,5-Trimethylpyrazole-4-boronic acid.



To a dry flask is added 300 mg (1.59 mmol) of 4-bromo-1,3,5-trimethyl pyrazole to 4.0 ml THF. The mixture is cooled to -78^0C and 1eq of n-BuLi (1.6 M) is added via syringe. The mixture is stirred 1.5 hrs, and 0.19ml of trimethylborate (1.08 eq) is added. The reaction mixture is stirred 2 hrs, allowing bath to reach -10^0C, then 1.5 ml of 5N HCl is added and stirred 30 minutes longer. The aqueous layer is extracted 3 times with ethyl acetate. The combined organics are dried over MgSO4, filtered, and evaporated to an oil. The oil is dissolved in methanol/methylene chloride and re-evaporated. The residue is triturated with acetone/ethyl acetate then filtered to obtain title compound as a white solid 92.1 mg (37.6%). ^{1}H-NMR (DMSO-d_6): δ5.92 (s); 3.72 (s, 3H); 2.34 (s, 3H); 2.26 (s, 3H) ppm.

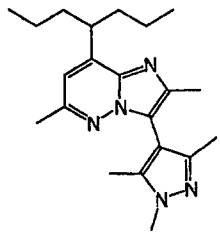
B. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(1,3,5-trimethyl-*1H*-pyrazol-4-yl)-imidazo[*1,2-b*]pyridazine.

3-Iodo-2,6-dimethyl-8-(1-ethyl-propyl)-imidazo[*1,2-b*]pyridazine (200mg, 0.582 mmol), 1,3,5-trimethylpyrazole-4-boronic acid (233mg, 1.53 mmol), Pd(PPh3)4 (13.4mg, 0.01 mmol) are combined in a microwave pressure tube. Then 0.58 ml of 2N Na2CO3 and 3.0ml of dimethoxyethane/H20/ethanol (7:3:2) solution is added. The mixture is microwaved at 155^0C for 20minutes. Water is added and the mixture is extracted four times with ethyl acetate. The combined organics are dried over MgSO4, filtered, then

evaporated to a residue which is chromatographed using hexanes, then 1:1 hexanes: ethyl acetate, then 100% ethyl acetate to give the title compound (6.4%) as a yellow oil. ^{1}H-NMR (DMSO-d_6): δ6.86 (s, 1H); 3.73 (s, 3H); 3.06-3.10 (m, 1H); 2.41 (s, 3H); 2.22 (s, 3H); 2.03 (s, 3H); 1.93 (s, 3H); 1.74-1.83 (m, 4H); 0.77 (t, J = 7.26 Hz, 6H) ppm. MS/ ES+ = 327 (100%, M+2).

Example 99.

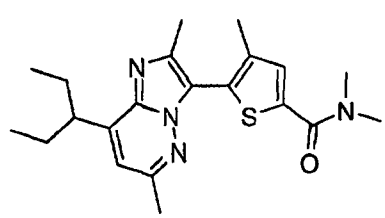
Preparation of 2,6-Dimethyl-8-(1-propyl-butyl)-3-(1,3,5-trimethyl-*1H*-pyrazol-4-yl)-imidazo[*1,2-b*]pyridazine.



3-Iodo-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine (75 mg, 0.20 mmol), 1,3,5-trimethylpyrazole-4-boronic acid (80 mg, 0.52 mmol), 2N Na2CO3 solution (0.22 ml), and 5.0mg (0.0004 mmol) of Pd(PPh3)4 are combined in microwave pressure vessel with 1.5ml of dimethylether/H2O/ethanol (7:3:2) solution. The mixture is microwaved at 140^{0}C for 25 minutes. The mixture is evaporated and chromatographed on silica gel column using hexanes then 3:1 hexane:ethyl acetate, then 1:1 hexane:ethyl acetate to give the title compound (22.8%) as a clear oil. ^{1}H-NMR (DMSO-d_6): δ6.88 (s, 1H); 3.72 (s, 3H); 3.06-3.10 (m, 1H); 2.40 (s, 3H); 2.21 (s, 3H); 2.02 (s, 3H); 1.92 (s, 3H); 1.60-1.76 (m, 4H); 1.08-1.21 (m, 4H); 0.82 (t, J = 7.49 Hz, 6H) ppm. MS/ ES+ = 354 (100%, M+1).

Example 100.

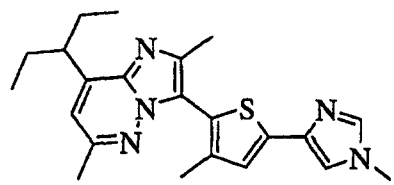
Preparation of 5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid dimethylamide.



Using a procedure analogous to Example 23 B, 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid (151 mg, 0.42 mmol) and 2.0 M dimethylamine (2.0 mL, 4 mmol) give the title compound (161 mg, 0.42 mmol, 100%). 1H NMR (CDCl3): δ 0.89 (t, J = 7.4 Hz, 6H), 1.75-1.94 (m, 4H), 2.14 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.15-3.50 (m, 7H), 6.72 (s, 1H), 7.30 (s, 1H). ES-MS (m/z): calcd for C21H28N4OS (M+H)+: 385.6 found: 385.3.

Example 101.

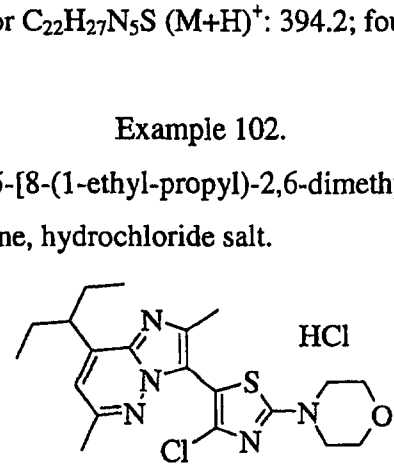
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-Imidazol-3-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 31. from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol), 1.34 M *n*-BuLi (0.80 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), 3-iodo-1-methyl-*1H*-imidazole (0.24 mL, 1.22 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.030g, 0.076 mmol, 8%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, *J* = 7.5 Hz, 6H), 1.74-1.93 (m, 4H), 2.13 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 3.31-3.40 (m, 1H), 3.72 (s, 3H), 6.66 (s, 1H), 7.09 (d, *J* = 1.3 Hz, 1H), 7.19 (s, 1H), 7.86 (d, *J* = 1.3 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.2; found: 394.2.

Example 102.

Preparation of N-{4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine, hydrochloride salt.

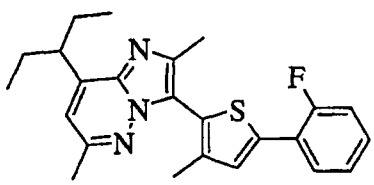


IPA (225.0 mL) is added to compound N-{4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine (18.8 g, 0.0448 mmol,

below) in a 1 L 1-neck round-bottomed flask The starting material slurry is heated to 50 °C on a Buchi bath, at which time a hazy solution resulted. Concentrated (12 M) aqueous HCl (3.73 mL, 0.0448 mmole, 1.0 eq) is added all at once, and the hazy solution is stirred at 50 °C on the Buchi for 10 minutes, then evaporated to a yellow solid under vacuum. After 20 minutes at room temperature under vacuum (weight of 20.9 g), acetone (100 mL) is added and the resulting yellow slurry is stirred at room temperature for 1 hour, then cooled with an ice bath and stirred for an additional 1 hour. The slurry is filtered, rinsed with acetone, and dried overnight under vacuum at 40°C to provide pale yellow-white crystalline solid 19.18 g (94%). ^{1}H NMR (DMSO): δ 7.52 (s, 1H), 3.73 (t, J = 4.6, 4H), 3.49 (t, J = 5.2 Hz, 4H), 3.39 (m, 1H), 2.57 (s, 3H), 2.49 (s, 3H), 1.77 (m, 4H), 0.80 (t, J = 7.4 Hz, 6H).

Example 103.

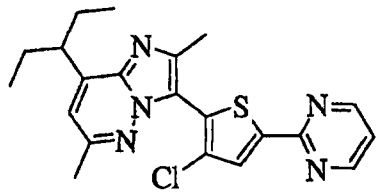
Preparation of 8-(1-ethyl-propyl)-3-[5-(2-fluoro-phenyl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure analogous to Example 30 B, 3-(5-boronic acid-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.18 g, 0.50 mmol), 1-bromo-2-fluoro-benzene (0.072 g, 0.65 mmol), and 2 M Na_2CO_3 (0.38 mL, 0.76 mmol), *n*-PrOH (2 mL), and $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol) furnish the title compound (0.022 g, 0.054 mmol, 11%). ^{1}H NMR ($CDCl_3$), δ 0.93 (t, *J* = 7.4 Hz, 6H), 1.71-1.96 (m, 4H), 2.19 (s, 3H), 2.66 (s, 3H), 2.67 (s, 3H), 3.41-3.50 (m, 1H), 7.15 (s, 1H), 7.15-7.23 (m, 2H), 7.28-7.35 (m, 1H), 7.45 (d, *J* = 1.4 Hz, 1H), 7.66 (dt, *J* = 7.8, 1.6 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{26}FN_3S$ $(M+H)^+$: 408.2; found: 408.2.

Example 104.

Preparation of 3-(3-chloro-5-pyrimidin-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 3-(3-Chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a –78 °C solution of 3-(3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.0 g, 5.97 mmol) and THF (30 mL) is added 1.6 M *n*-BuLi (4.1 mL). After 30 minutes $B(OMe)_3$ (0.74 mL, 6.59 mmol) is added, the solution is warmed to ambient temperature and stirred overnight. 1 M HCl (30 mL) is added and the solution stirred for 20 minutes. The solution is made basic with 5 M NaOH. The organic layer is extracted with 1 M NaOH (30 mL). The combined aqueous layers are made acidic with 5 M HCl, K_3PO_4•3 H_2O is added and the PH adjusted to 5.5 using 1 M NaOH. The combined aqueous layers are extracted with EtOAc (200 mL), washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (2.20 g, 5.82 mmol, 97%). LC/MS (m/z): calcd. for $C_{17}H_{21}BClN_3O_2S$ $(M+H)^+$: 378.7; found: 378.0.

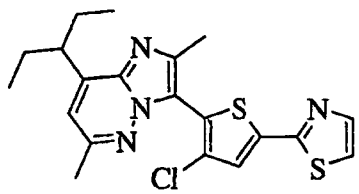
B. 3-(3-Chloro-5-pyrimidin-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

A solution of 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25g, 0.66 mmol), 2-bromo-pyrimidine (0.21 g, 1.32 mmol), 2 M Na_2CO_3 (0.66 mL, 1.32 mmol), and *i*-PrOH (3 mL) are degassed with N_2 for 15 minutes. $Pd(OAc)_2$ (7.4 mg, 0.033 mmol) and PPh_3 (0.026 g, 0.099 mmol) are added and the solution is heated at 90 °C overnight. The solution is diluted with EtOAc (35 mL), washed with 10% Na_2CO_3 (35 mL), brine (35 mL), dried over Na_2SO_4, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (0.077 g, 0.19 mmol, 29%). ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 7.4 Hz, 6H), 1.75-1.93 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H),

3.27-3.40 (m, 1H), 6.71 (s, 1H), 7.16 (t, J = 5.0 Hz, 1H), 8.00 (s, 1H), 8.74 (d, J = 5.0 Hz, 2H). LC/MS (m/z): calcd. for $C_{21}H_{22}ClN_5S$ $(M+H)^+$: 412.1; found: 412.2.

Example 105.

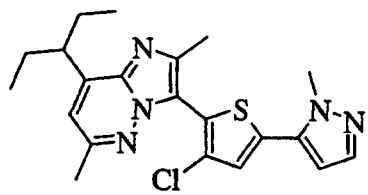
Preparation of 3-(3-chloro-5-thiazol-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 104, 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25g, 0.66 mmol), 2-bromo-pyrimidine (0.21 g, 1.32 mmol), 2 M Na_2CO_3 (0.66 mL, 1.32 mmol) and *i*-PrOH (3 mL), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), and PPh_3 (0.026 g, 0.099 mmol) furnish the title compound (0.099 g, 0.24 mmol, 35%). ^{1}H NMR ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.28-3.38 (m, 1H), 6.71 (s, 1H), 7.33 (t, J = 3.3 Hz, 1H), 7.49 (s, 1H), 7.81 (d, J = 3.3 Hz, 2H). LC/MS (m/z): calcd. for $C_{21}H_{22}ClN_5S$ $(M+H)^+$: 417.1; found: 417.1.

Example 106.

Preparation of 3-[3-chloro-5-(2-methyl-2*H*-pyrazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

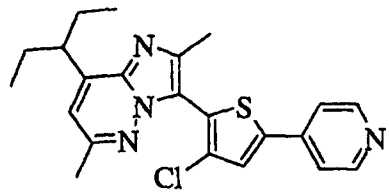


To a –78 °C solution of 1-methyl-1*H*-pyrazole (0.12 g, 1.45 mmol) and THF (4 mL) is added 1.6 M *n*-BuLi (0.91 mL, 1.45 mmol). After 45 minutes 0.5 M $ZnCl_2$ (2.9 mL, 1.45 mmol) is added and the solution is warmed to ambient temperature. After 30 minutes 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (example Rupp-88) (0.30 g, 0.73 mmol) and $PdCl_2$(dppf) (0.027

g, 0.036 mmol) are added and the solution heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-30% EtOAc/hexane gradient) furnish the title compound (0.15 g, 0.36 mmol, 50%). ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.52 (s, 6H), 3.26-3.36 (m, 1H), 4.05 (s, 3H), 6.45 (d, J = 1.9 Hz, 1H), 6.71 (s, 1H), 7.14(s, 1H), 7.49 (d, J = 1.9 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}ClN_5S$ $(M+H)^+$: 414.2; found: 414.2.

Example 107.

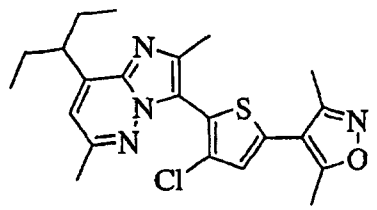
Preparation of 3-(3-chloro-5-pyridin-4-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 104, 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25g, 0.66 mmol), 4-bromo-pyridine hydrochloride (0.26 g, 1.32 mmol), 2 M Na_2CO_3 (1.00 mL, 1.99 mmol), *i*-PrOH (3 mL), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), and PPh_3 (0.026 g, 0.099 mmol) furnish the title compound (0.16 g, 0.59 mmol, 59%). ^1H NMR ($CDCl_3$) δ 0.87 (d, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.27-3.36 (m, 1H), 6.72 (s, 1H), 7.45-7.49 (m, 3H), 8.63 (d, J = 1.3 Hz, 1H), 8.64 (d, J = 1.3 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{23}ClN_4S$ $(M+H)^+$: 411.1; found: 411.1.

Example 108.

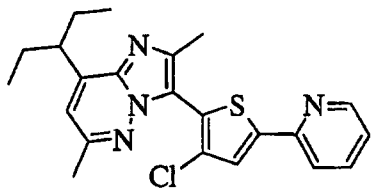
Preparation of 3-[3-chloro-5-(3,5-dimethyl-isoxazol-4-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 104, 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25g, 0.66 mmol), 4-iodo-3,5-dimethyl-isoxazole (0.30 g, 1.32 mmol), 2 M Na_2CO_3 (0.66 mL, 1.32 mmol) and *i*-PrOH (3 mL), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), and PPh_3 (0.026 g, 0.099 mmol) furnish the title compound (0.14 g, 0.50 mmol, 50%). ^{1}H NMR ($CDCl_3$) δ 0.87 (d, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.43 (s, 3H), 2.53 (s, 6H), 2.57 (s, 3H), 3.27-3.38 (m, 1H), 6.71 (s, 1H), 7.01 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{25}ClN_4OS$ $(M+H)^+$: 429.2; found: 429.2.

Example 109.

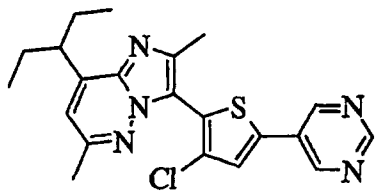
Preparation of 3-(3-chloro-5-pyridin-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.25 g, 0.61 mmol) and $PdCl_2$(dppf) (0.022 g, 0.030 mmol) is added a 0.5 M solution of 2-pyridylzinc bromide (2.40 mL, 1.21 mmol) and the solution heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-40% EtOAc/hexane gradient) followed by recrystallization from CH_3CN furnish the title compound (0.15 g, 0.36 mmol, 60%). ^{1}H NMR ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.73-1.93 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.29-3.38 (m, 1H), 6.70 (s, 1H), 7.17-7.23 (m, 1H), 7.56 (s, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.70-7.76 (m, 1H), 8.59 (d, J = 4.7 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{23}ClN_4S$ $(M+H)^+$: 412.0; found: 412.4.

Example 110.

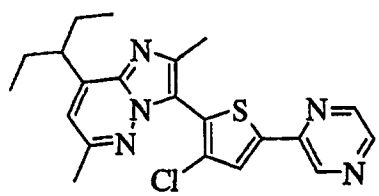
Preparation of 3-(3-chloro-5-pyrimidin-5-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 104, 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25g, 0.66 mmol), 4-bromo-pyrimidine (0.21 g, 1.32 mmol), 2 M Na_2CO_3 (0.66 mL, 1.32 mmol), *i*-PrOH (3 mL), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), and PPh_3 (0.026 g, 0.099 mmol) furnish the title compound (0.053 g, 0.13 mmol, 20%). ^{1}H NMR ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.27-3.37 (m, 1H), 6.73 (s, 1H), 7.40 (s, 1H), 8.97 (s, 2H), 9.18 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{22}ClN_5S$ $(M+H)^+$: 412.1; found: 411.2.

Example 111.

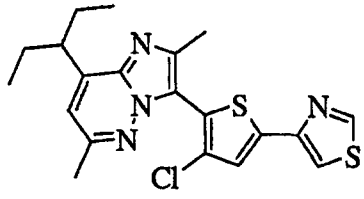
Preparation of 3-(3-chloro-5-pyrazin-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 104, 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.40g, 1.06 mmol), 2-iodo-pyrazine (0.16 g, 1.59 mmol), 2 M Na_2CO_3 (1.06 mL, 2.12 mmol) and *i*-PrOH (5 mL), $Pd(OAc)_2$ (0.012 g, 0.053 mmol), and PPh_3 (0.042 g, 0.16 mmol) furnish the title compound (0.15 g, 0.36 mmol, 34%). ^{1}H NMR ($CDCl_3$) δ 0.87 (d, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.51 (s, 3H), 2.52 (s, 3H), 3.25-3.37 (m, 1H), 6.71 (s, 1H), 7.66 (s, 1H), 8.45 (d, J = 2.6 Hz, 1H), 8.51-8.53 (m, 1H), 8.96 (d, J = 1.0 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{22}ClN_5S$ $(M+H)^+$: 412.1; found: 412.3.

Example 112.

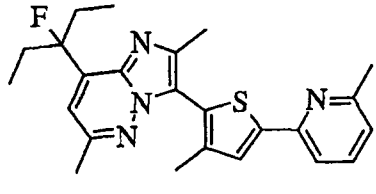
Preparation of 3-(3-chloro-5-thiazol-4-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a 0 °C solution of 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.60 g, 1.45 mmol) and THF (2 mL) is added 0.05 g/mL of Reike® Zn (3.80 mL, 2.91 mmol). The solution is heated at a reflux for 1 hour, and the excess Zn allowed to settle for 1 hour at ambient temperature. The solution is transferred to a flask of 4-bromo-thiazole (Kelly, T. et al. *Tetrahedron Lett.* 1995, 51, 9293) (0.29 g, 1.74 mmol). $PdCl_2$(dppf) (0.027 g, 0.036 mmol) is added and the solution heated at 65 °C overnight, diluted with EtOAc (40 mL), washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) followed by ISCO column chromatography (100% Et_2O) to furnish the title compound (0.098 g, 0.24 mmol, 16%). ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.28-3.38 (m, 1H), 6.70 (s, 1H), 7.45 (s, 1H), 7.49 (d, J = 2.0 Hz, 1H), 8.85 (d, J = 2.0 Hz, 1H). LC/MS (m/z): calcd. for $C_{20}H_{21}ClN_4S_2$ $(M+H)^+$: 417.1; found: 417.3.

Example 113.

Preparation of 8-(1-ethyl-1-fluoro-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.

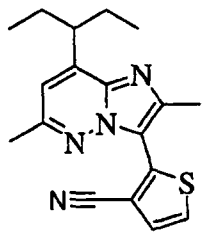


To a –78 °C solution of 3-{2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazin-8-yl}-pentan-3-ol (0.23 g, 0.55 mmol) and CH_2Cl_2 (3 mL) is added a solution of [bis(2-methoxyethyl)amino]sulfur triflouride (0.14 g, 0.60 mmol) and CH_2Cl_2 (2 mL). The solution is warmed to ambient temperature and

stirred overnight. The solution is washed with sat. $NaHCO_3$ (5 mL) and concentrated. The reside is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.13g, 0.31 mmol, 57%). ^1H NMR ($CDCl_3$) δ 0.80 (t, J = 7.5 Hz, 6H), 2.14 (s, 3H), 2.16-2.31 (m, 2H), 2.46 (s, 3H), 2.54 (s, 3H), 2.56 (s, 3H), 2.59-2.70 (m, 2H), 6.98 (s, 1H), 7.00 (d, J = 7.6 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.52 (s, 1H), 7.56 (dd, J = 7.8, 7.6 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{27}FN_4S$ $(M+H)^+$: 423.2; found: 423.4.

Example 114.

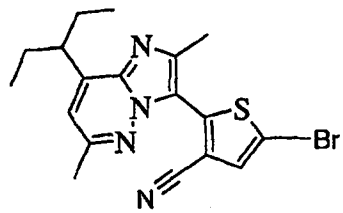
Preparation of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile.



To a solution 0.05 g/mL of Reike® Zn (31 mL, 23.93 mmol) is added 2-bromo-thiophene-3-carbonitrile (Fournari, P. et al. Bull. Soc. Chim. Fr., 1967, 4115) (2.25 g, 11.96 mmol) and THF (5 mL). The solution is heated at a reflux for 2 hours, cooled to ambient temperature and the excess Zn allowed to settle. The solution is transferred via a cannula into a flask of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.5 g, 7.98 mmol) and $PdCl_2$(dppf) (0.29 g, 0.040 mmol). The mixture is heated at 65°C overnight, diluted with EtOAc (75 mL), washed with sat. NH_4Cl (2 x 75 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (10%-20% EtOAc/hexane gradient) furnish the title compound (1.10 g, 3.39 mmol, 42%). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.55 (s, 3H), 2.61 (s, 3H), 3.25-3.34 (m, 1H), 6.75 (s, 1H), 7.35 (d, J = 5.2 Hz, 1H), 7.53 (d, J = 5.2 Hz, 1H). LC/MS (m/z): calcd. for $C_{18}H_{20}N_4S$ $(M+H)^+$: 325.5; found: 325.2.

Example 115.

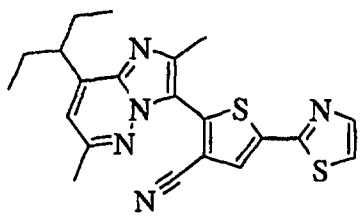
Preparation of 5-bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile.



To a solution of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile (0.83 g, 2.56 mmol) and CH_2Cl_2 (10 mL) is added NBS (0.48 g, 2.69 mmol). The solution is stirred for 1 hour, diluted with Et_2O (100 mL), washed with water (3 x 100 mL), brine (100 mL), dried ($MgSO_4$) filtered and concentrated to furnish the title compound (1.03 g, 2.55 mmol, >99%). ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.56 (s, 3 H), 2.60 (s, 3H), 3.24-3.32 (m, 1H), 6.76 (s, 1H), 7.30 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{19}BrN_4S$ $(M+H)^+$: 404.4; found: 404.1.

Example 116.

Preparation of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-5-thiazol-2-yl-thiophene-3-carbonitrile.

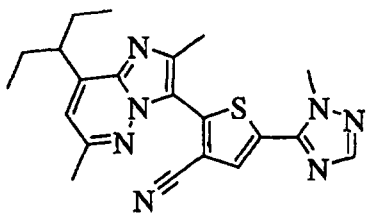


To a flask containing 5-bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile (0.25 g, 0.62 mmol) and $PdCl_2$(dppf) (0.023 g, 0.031 mmol) is added a solution of 0.5 M 2-thiazolylzinc bromide (6.0 mL, 3.10 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 25 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.16 g, 0.39 mmol, 64%). ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.58 (s, 3H), 2.66 (s, 3H), 3.25-3.35 (m, 1H), 6.78 (s, 1H), 7.38 (d, J = 3.5

Hz, 1H), 7.70 (s, 1H), 7.84 (d, J = 3.5 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{21}N_5S_2$ $(M+H)^+$: 408.6; found: 408.1.

Example 117.

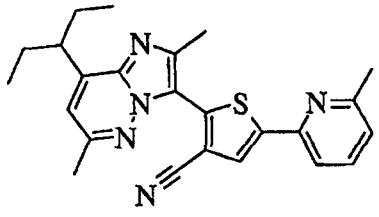
Preparation of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-5-thiazol-2-yl-thiophene-3-carbonitrile.



To a –78 °C solution of 1-methyl-1,2,4-triazole (0.14 mL, 1.86 mmol) and THF (5 mL) is added a 1.6 M solution of *n*-BuLi in hexanes (1.20 mL, 1.86 mmol) after 30 minutes a 0.5 M solution of $ZnCl_2$ in THF (4.70 mL, 2.33 mmol) is added and the solution warmed to ambient temperature and stirred for 30 minute. 5-Bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile (example Rupp-122) (0.25 g, 0.62 mmol) and $PdCl_2$(dppf) (0.023 g, 0.031 mmol) is added and the solution heated at 65 °C overnight, diluted with EtOAc (25 mL), washed with sat. NH_4Cl (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-60% EtOAc/hexane gradient), and is chromatographed (50 x 250 C18 X-Terra RP column, 30-90% 10 mM NH_4HCO_3/water/5 % ACN: ACN gradient). The residue is dissolved in Et_2O (25 mL), washed with sat. $NaHCO_3$ (25 mL), dried over MgSO4, filtered and concentrated to furnish the title compound (0.013 g, 0.032 mmol, 5%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.58 (s, 3 H), 2.67 (s, 3H), 3.26-3.34 (m, 1H), 4.17 (s, 3H), 6.79 (s, 1H), 6.78 (s, 1H), 7.92 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{23}N_7S$ $(M+H)^+$: 406.5; found: 406.2.

Example 118.

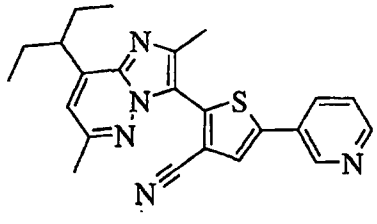
Preparation of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-5-(6-methyl-pyridin-2-yl)-thiophene-3-carbonitrile.



To a flask containing 5-bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile (0.25 g, 0.62 mmol) and $PdCl_2$(dppf) (0.024 g, 0.033 mmol) is added a solution of 0.5 M 6-methyl-2-pyridylzinc bromide in THF (2.50 mL, 1.24 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-25% EtOAc/hexane gradient), furnish the title compound (0.11 g, 0.26 mmol, 39%). ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.76-1.92 (m, 4H), 2.57 (s, 3 H), 2.58 (s, 3H), 2.65 (s, 3H), 3.26-3.35 (m, 1H), 6.75 (s, 1H), 7.09 (d, J = 7.5 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.63 (dd, J = 7.9, 7.5 Hz, 1H), 7.74 (s, 1H). LC/MS (m/z): calcd. for $C_{24}H_{25}N_5S$ $(M+H)^+$: 416.6; found: 416.2.

Example 119.

Preparation of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-5-pyridin-3-yl-thiophene-3-carbonitrile.

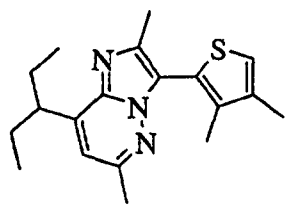


To a –78 °C solution of 3-iodo-pyridine (0.32 g, 1.56 mmol), 0.5 M $ZnCl_2$ in THF (3.20 mL, 1.59 mmol), and THF (2 mL) is added 1.7 M *t*-BuLi (1.85 mL, 3.15 mmol). The solution is warmed to ambient temperature and stirred for 30 minutes. 5-Bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile (0.21 g, 0.52 mmol) and $Pd(PPh_3)_4$ (0.03 g, 0.026 mmol) are added and the solution

heated at 55 °C for 1 hour, cooled to ambient temperature and stirred overnight, diluted with EtOAc (50 mL), washed with sat. NH_4Cl (2 x 40 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-40% EtOAc/hexane gradient), furnish the title compound (0.15 g, 0.37 mmol, 71%). ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.58 (s, 3 H), 2.66 (s, 3H), 3.26-3.35 (m, 1H), 6.78 (s, 1H), 7.34-7.46 (m, 1H), 7.56 (s 1H), 7.91 (d, J = 7.1 Hz, 1H), 8.62 (s, 1H), 8.91 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{23}N_5S$ $(M+H)^+$: 402.6; found: 402.4.

Example 120.

Preparation of 3-(3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 2-Bromo-3,4-dimethyl-thiophene.

To a solution of 3,4-dimethyl-thiophene (2.0 g, 17.82 mmol) (Minato et. al., *Tetrahedron* 1982, 38, 3347) in CH_2Cl_2 (20 mL) is added NBS (3.3 g, 18.72 mmol). The solution is stirred for 1 hour, diluted with Et_2O (100 mL), washed with water (3 x 100 mL), brine (100 mL), dried ($MgSO_4$) filtered and concentrated. The residue is purified by ISCO column chromatography (100% hexane) furnish the title compound (3.0 g, 16.70 mmol). ^1H NMR ($CDCl_3$) δ 2.10 (s, 3H), 2.17 (s, 3H), 6.85 (s, 1H).

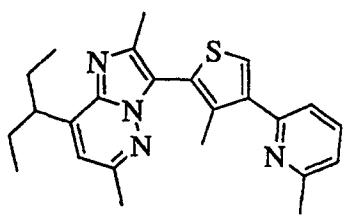
B. 3-(3,4-Dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3,4,3',4'-tetramethyl-[2,2']bithiophenyl-5-yl)-imidazo[*1,2-b*]pyridazine, respectively.

To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.30 g, 10.58 mmol), 2-bromo-3,4-dimethyl-thiophene (3.03 g, 15.88 mmol) and Cs_2CO_3 (7.24 g, 22.23 mmol) and DMF (50 mL) is de-gassed with N_2 for 20 minutes. $Pd_2(dba)_3$ (0.48 g, 0.053 mmol) and PPh_3 (0.56 g, 0.21 mmol) are added and the solution is heated at 120°C overnight. The solution is diluted with EtOAc (200 mL), washed with water (3 x

200 mL), brine (200 mL), dried ($MgSO_4$), filtered and concentrated. The residue is purified by ISCO column chromatography (10% -15% EtOAc/hexane gradient) furnish 2.04 g of a brown oil which is chromatographed (50 x 250 C18 Symmetry column, 30-70% water: 0.1 % TFA /ACN gradient) furnish the title compound (0.41 g, 1.25 mmol, 12%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.94 (m, 4H), 2.00 (s, 3 H), 2.24 (d, J = 1.0 Hz, 3H), 2.45 (s, 3H), 2.50 (s, 3H), 3.29-3.38 (m, 1H), 6.65 (s, 1H), 7.10 (s, 1H). LC/MS (m/z): calcd. for $C_{19}H_{25}N_3S$ $(M+H)^+$: 328.5; found: 328.3.

Example 121.

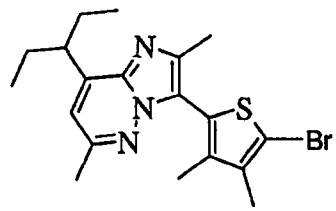
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-4-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (below) (0.25 g, 0.64 mmol) and $PdCl_2$(dppf) (0.023 g, 0.032 mmol) is added a solution of 0.5 M 6-methyl-2-pyridylzinc bromide in THF (2.5 mL, 1.27 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (25 mL), washed with sat. NH_4Cl (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (15%-20% EtOAc gradient) and is chromatographed (50 x 250 C18 Symmetry column, 10-70% water: 0.1 % TFA /ACN: 0.1% TFA gradient). The residue is dissolved in Et_2O (20 mL), washed with sat. $NaHCO_3$ (15 mL) dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.066 g, 1.57 mmol, 31%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.20 (s, 3 H), 2.47 (s, 3H), 2.49 (s, 3H), 2.61 (s, 3H), 3.29-3.38 (m, 1H), 6.66 (s, 1H), 7.09 (d, J = 7.5 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.54 (dd, J = 7.5, 7.8 Hz, 1H), 7.72 (s, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.2; found: 405.3.

Example 122.

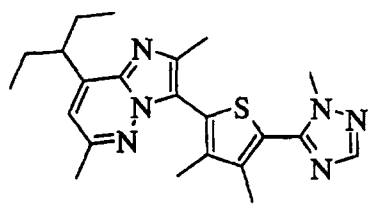
Preparation of 3-(5-bromo-3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a solution of 3-(3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.41 g, 1.25 mmol) and CH_2Cl_2 (30 mL) is added NBS (0.23 g, 1.32 mmol). The solution is stirred for 1 hour, diluted with Et_2O (100 mL), washed with water (3 x 100 mL), brine (100 mL), dried ($MgSO_4$) filtered and concentrated to furnish the title compound (0.41 g, 1.01 mmol, 80%). ^1H NMR ($CDCl_3$) δ 0.86 (t, $J = 7.4$ Hz, 6H), 1.72-1.94 (m, 4H), 2.02 (s, 3 H), 2.18 (s, 3H), 2.43 (s, 3H), 2.49 (s, 3H), 3.27-3.36 (m, 1H), 6.67 (s, 1H). LC/MS (m/z): calcd. for $C_{19}H_{24}BrN_3S$ $(M+H)^+$: 407.4; found: 407.3.

Example 123.

Preparation of 3-[3,4-dimethyl-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

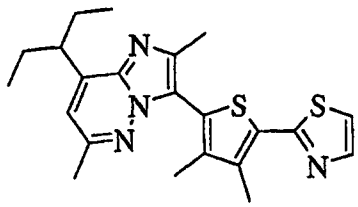


To a –78 °C solution of 1-methyl-1,2,4-triazole (0.056 mL, 0.74 mmol) and THF (2 mL) is added a 1.6 M solution of *n*-BuLi in hexanes (0.46 mL, 0.74 mmol). The solution is warmed to ambient temperature and stirred for 30 minutes. The solution is cooled to 0 °C, a 0.5 M solution of $ZnCl_2$ in THF (4.70 mL, 2.33 mmol) is added and the solution warmed to ambient temperature and stirred for 30 minute. 3-(5-bromo-3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.10 g, 0.25 mmol) and $PdCl_2$(dppf) (0.009 g, 0.012 mmol) is added and the solution heated at 65 °C overnight, diluted with EtOAc (25 mL), washed with sat. NH_4Cl (20 mL), dried

over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-60% EtOAc/hexane gradient), followed by a second purification by ISCO column chromatography (100% Et_2O) furnish the title compound (0.07 g, 0.17 mmol, 70%). ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.06 (s, 3 H), 2.29 (s, 3H), 2.47 (s, 3H), 2.51 (s, 3H), 3.27-3.37 (m, 1H), 3.97 (s, 3H), 6.69 (s, 1H), 8.00 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{28}N_6S$ $(M+H)^+$: 409.6; found: 409.2.

Example 124.

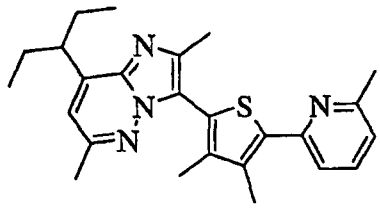
Preparation of 3-(3,4-dimethyl-5-thiazol-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a –78 °C solution of 3-(5-bromo-3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.10 g, 0.25 mmol) and THF (1 mL) is added 1.6 M *n*-BuLi (0.16 mL). The solution is stirred for 45 minutes and 0.5 M $ZnCl_2$ in THF (0.52 mL, 0.26 mmol) is added. The solution is warmed to ambient temperature and stirred for 30 minutes. 2-Bromo-thiazole (0.044 mL, 0.49 mmol), and $PdCl_2$(dppf) (0.009 g, 0.012 mmol) are added and the solution heated at 65 °C overnight, diluted with EtOAc (25 mL), washed with sat. NH_4Cl (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient), furnish the title compound (6.1 mg, 0.015 mmol, 6%). ^1H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.07 (s, 3 H), 2.49 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.29-3.39 (m, 1H), 6.68 (s, 1H), 7.35 (d, J = 3.1 Hz, 1H), 7.86 (d, J = 3.1 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{26}N_4S_2$ $(M+H)^+$: 411.6; found: 411.2.

Example 125.

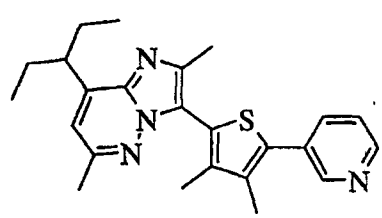
Preparation of 3-[3,4-dimethyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(5-bromo-3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.10 g, 0.25 mmol) and $PdCl_2$(dppf) (9 mg, 0.012 mmol) is added a solution of 0.5 M 6-methyl-2-pyridylzinc bromide in THF (0.98 mL, 0.49 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-30% EtOAc/hexane gradient) furnish the title compound (0.029 g, 0.069 mmol, 29%). ^1H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.72-1.92 (m, 4H), 2.04 (s, 3 H), 2.45 (s, 3H), 2.47 (s, 3H), 2.50 (s, 3H), 2.59 (s, 3H), 3.29-3.38 (m, 1H), 6.66 (s, 1H), 7.04 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 8.0, 7.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{25}H_{30}N_4S$ $(M+H)^+$: 419.6; found: 419.4.

Example 126.

Preparation of 3-[3,4-dimethyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

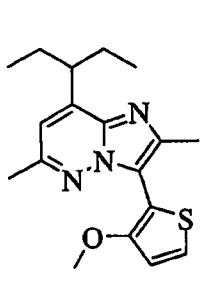


To a –78 °C solution of 3-iodo-pyridine (0.15 g, 0.74 mmol) and 0.5 M $ZnCl_2$ in THF (1.5 mL, 0.75 mmol) is added *t*-BuLi (0.88 mL, 1.49 mmol). The slurry is warmed to ambient temperature and stirred for 30 minutes. 3-(5-bromo-3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.10 g, 0.25 mmol) and $Pd(PPh_3)_4$ (0.014 g, 0.012 mmol) are added and the solution stirred at ambient

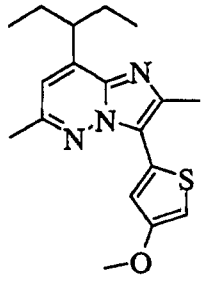
temperature for 2 days, diluted with EtOAc (35 mL), washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (6.1 mg, 0.015 mmol, 6%). ^1H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.07 (s, 3 H), 2.29 (s, 3H), 2.49 (s, 3H), 2.53 (s, 3H), 3.30-3.39 (m, 1H), 6.68 (s, 1H), 7.36 (dd, J = 8.0, 4.5 Hz, 1H), 7.79-7.83 (m 1H), 8.57 (d, J = 4.5 Hz, 1H), 8.79 (d, J = 0.9 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.6; found: 405.2.

Example 127 & 128.

Preparation of 8-(1-ethyl-propyl)-3-(3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and 8-(1-ethyl-propyl)-3-(4-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Ex. 127.



Ex. 128.

To a solution of 3-methoxy-thiophene (2.19 g, 19.14 mmol) in Et_2O (50 mL) is added 1.6 M *n*-BuLi (12.20 mL, 19.46 mmol). The solution is heated at a reflux for 30 minutes and cooled to ambient temperature. As solution of 0.5 M $ZnCl_2$ (38.9 mL, 19.5 mmol) and THF (50 mL) is added and the solution is stirred for 30 minutes. 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.0 g, 6.38 mmol) and $PdCl_2$(dppf) (0.23 g, 0.032 mmol) are added and the solution is heated at 65 °C for 4 hours, diluted with EtOAc (250 mL), washed with sat. NH_4Cl (250 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (10%-25% EtOAc/hexane gradient) furnish the title compounds (1.50 g, 4.55 mmol, 71%) and (0.23 g, 0.70 mmol, 11%), respectively.

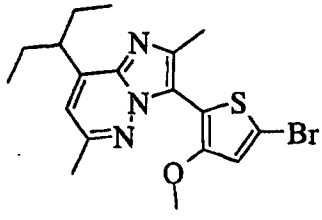
Example 127: ^1H NMR ($CDCl_3$) δ 0.83 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.59 (s, 3H), 2.70 (s, 3H), 3.26-3.35 (m, 1H), 3.86 (s, 3H), 6.32 (d, J = 1.6 Hz, 1H), 6.67 (s, 1H),

7.41 (d, J = 1.6 Hz, 1H). LC/MS (m/z): calcd. for $C_{18}H_{23}N_3OS$ $(M+H)^+$: 330.5; found: 330.3.

Example 128: ^1H NMR ($CDCl_3$) δ 0.84 (t, J = 7.5 Hz, 6H), 1.71-1.88 (m, 4H), 2.47 (s, 3H), 2.49 (s, 3H), 3.26-3.35 (m, 1H), 3.84 (s, 3H), 6.62 (s, 1H), 6.96 (d, J = 5.5 Hz, 1H), 7.39 (d, J = 5.5 Hz, 1H). LC/MS (m/z): calcd. for $C_{18}H_{23}N_3OS$ $(M+H)^+$: 330.5; found: 330.3.

Example 129.

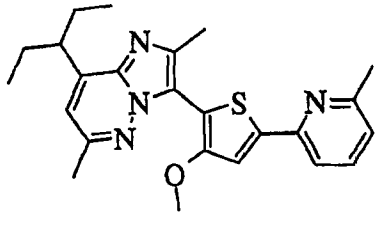
Preparation of 3-(5-bromo-3-methoxy-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a solution of 8-(1-ethyl-propyl)-3-(3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.78 g, 2.37 mmol) and CH_2Cl_2 (10 mL) is added NBS (0.44 g, 2.49 mmol). The solution is stirred for 1 hour, washed with water (3 x 10 mL), concentrated and purified by ISCO column chromatography (5%-15% EtOAc/hexane gradient) to furnish the title compound (0.87 g, 2.13 mmol, 90%). ^1H NMR ($CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.46 (s, 3H), 2.52 (s, 3H), 3.25-3.35 (m, 1H), 3.82 (s, 3H), 6.65 (s, 1H), 6.97 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{22}BrN_3OS$ $(M+H)^+$: 408.1; found: 408.3.

Example 130.

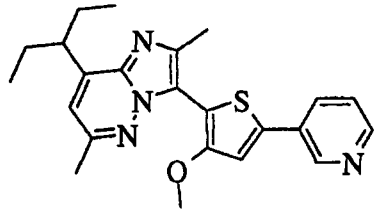
Preparation of 8-(1-ethyl-propyl)-3-[3-methoxy-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(5-bromo-3-methoxy-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.49 mmol) and $PdCl_2$(dppf) (0.018 g, 0.024 mmol) is added a solution of 0.5 M 6-methyl-2-pyridylzinc bromide in THF (3.0 mL, 1.47 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.066 g, 1.57 mmol, 31%). ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.50 (s, 3 H), 2.51 (s, 3H), 2.55 (s, 3H), 3.26-3.37 (m, 1H), 3.90 (s, 3H), 6.63 (s, 1H), 6.99 (d, J = 7.4 Hz, 1H), 7.43 (d, J = 7.7 Hz, 1H), 7.49 (s, 1H), 7.54 (dd, J = 7.4, 7.7 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4OS$ $(M+H)^+$: 421.6; found: 422.4.

Example 131.

Preparation of 8-(1-ethyl-propyl)-3-(3-methoxy-5-pyridin-3-yl-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

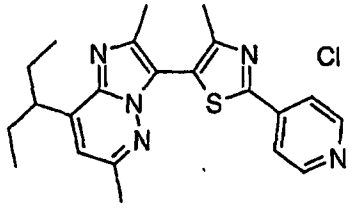


To a –78 °C solution of 3-iodo-pyridine (0.32 g, 1.56 mmol) and 0.5 M $ZnCl_2$ in THF (3.20 mL, 1.59 mmol) is added *t*-BuLi (2.27 mL, 3.85 mmol). The solution is warmed to ambient temperature and stirred for 30 minutes. 3-(5-bromo-3-methoxy-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.26 g, 0.64 mmol) and $Pd(PPh_3)_4$ (0.037 g, 0.032 mmol) are added and the solution heated at 50 °C for 1 hour, cooled to ambient temperature and stirred overnight. The solution is diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-50% EtOAc/hexane gradient), furnish the title compound (0.16 g, 0.39 mmol, 61%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.52 (s, 3 H), 2.55 (s, 3H), 3.28-3.38 (m, 1H), 3.93, (3H), 6.67 (s, 1H), 7.26 (d, J = 3.5 Hz, 1H), 7.31-7.36 (m, 1H), 7.88-

7.92 (m, 1H), 8.55 (d, J = 4.5 Hz, 1H), 8.92 (d, J = 1.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{23}H_{26}N_4OS$ $(M+H)^+$: 407.6; found: 407.4.

Example 132.

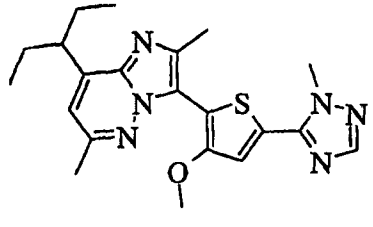
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-2-pyridin-4-yl-thiazol-5-yl)-imidazo[*1,2-b*]pyridazine, hydrochloride salt.



A mixture of 3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (500 mg, 1.27 mmol), 4-pyridineboronic acid (500 mg, 4 mmol), $Pd(PPh_3)_4$ (100 mg, 0.08 mmol), toluene (2 mL), MeOH (1mL), and K_2CO_3 (2 M aqueous solution, 3.5mL) is heated at 100 °C for 18 hours. Ethyl acetate (20mL) is added, and the organic layer is separated, dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification is performed via silica gel chromatography using a 3:1 mixture of hexanes and ethyl acetate to obtain the free amine of the title compound (200 mg, 40%). The purified product is dissolved in ethyl acetate and a freshly prepared solution of hydrogen chloride (0.5 M in ethyl acetate, 2 mL) is added. The solvent is removed in vacuo to give the title compound ^{1}H-NMR ($CDCl_3$), δ 8.2 (m, 2H); 7.05 (m,2H); 6.55 (s, 1H); 3.24 (m, 1H); 2.43 (s, 3H); 2.40 (s, 3H); 2.33 (s, 3H); 1.76 (m, 4H); 0.80 (t, 6H) ppm. MS/ES$^+$ = 391 (100%, M+1).

Example 133.

Preparation of 8-(1-ethyl-propyl)-3-[3-methoxy-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 5-Bromo-1-methyl-1*H*-[1,2,4]triazole.

To a –78 °C solution of 1-methyl-*1H*-[1,2,4]triazole (1.0 mL, 13.20 mmol) and THF (100 mL) is added 1.6 M *n*-BuLi (8.70 mL, 13.86 mmol). After 45 minutes 1,2-dibromo-1,1,2,2-tetrafluoro-ethane (1.76 mL, 14.52 mmol) is added, the solution is warmed to ambient temperature and stirred for 2 hours. The solution is diluted with EtOAc (200 mL), washed with water (150 mL), brine (150 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (1.37 g, 8.46 mmol, 64%). ^1H NMR ($CDCl_3$) δ 3.82 (s, 3H), 7.78 (s, 1H). LC/MS (m/z): calcd. for $C_3H_4BrN_3$ $(M+H)^+$: 162.0; found: 161.9.

B. 8-(1-Ethyl-propyl)-3-(5-iodo-3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a solution of 8-(1-ethyl-propyl)-3-(3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.75 g, 2.28 mmol) and CH_3CN (10 mL) is added NIS (0.54 g, 2.39 mmol). The solution is stirred overnight, concentrated, diluted with EtOAc (30 mL), washed with water (30 mL), sat. NH_4Cl (30 mL), 20% ($NaHSO_3$) (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.91 g, 2.00 mmol, 88%). ^1H NMR ($CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.46 (s, 3H), 2.52 (s, 3H), 3.25-3.35 (m, 1H), 3.83 (s, 3H), 6.64 (s, 1H), 7.12 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{22}IN_3OS$ $(M+H)^+$: 456.4; found: 456.0.

C. 5-Bromo-1-methyl-1*H*-[1,2,4]triazole.

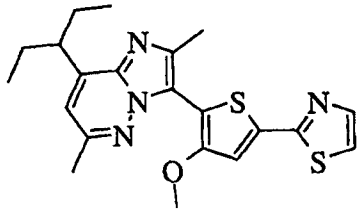
To a –78 °C solution of 1-methyl-1*H*-[1,2,4]triazole (1.0 mL, 13.20 mmol) and THF (100 mL) is added 1.6 M *n*-BuLi (8.70 mL, 13.86 mmol). After 45 minutes 1,2-dibromo-1,1,2,2-tetrafluoro-ethane (1.76 mL, 14.52 mmol) is added, the solution warmed to ambient temperature and stirred for 2 hours. The solution is diluted with EtOAc (200 mL), washed with water (150 mL), brine (150 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (1.37 g, 8.46 mmol, 64%). ^1H NMR ($CDCl_3$) δ 3.82 (s, 3H), 7.78 (s, 1H). LC/MS (m/z): calcd. for $C_3H_4BrN_3$ $(M+H)^+$: 162.0; found: 161.9.

D. 8-(1-Ethyl-propyl)-3-[3-methoxy-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a slurry of 0.05 g/ mL of Reike® Zn in THF (2.8 mL, 2.11 mmol) is added 5-bromo-1-methyl-*1H*-[1,2,4]triazole and THF (2 mL). The solution is heated at 65 °C for 1 hour, cooled to ambient temperature and the excess Zn allowed to settle for 1 hour. The solution is transferred to a flask containing 8-(1-ethyl-propyl)-3-(5-iodo-3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.32 g, 0.70 mmol) and $Pd(PPh_3)_4$ (0.041 g, 0.035 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL) washed with sat. NH_4Cl (30 mL). The aqueous phase is extracted with EtOAc (20 mL). The combined organic layers are dried over $MgSO_4$, filtered and concentrated. The reside is purified by ISCO column chromatography (20%-65% EtOAc/hexane gradient) followed by ISCO column chromatography (100% Et_2O) furnish the title compound (0.19 g, 0.46 mmol, 62%). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.51 (s, 3 H), 2.52 (s, 3H), 3.26-3.37 (m, 1H), 3.92 (s, 3H), 4.15 (s, 3H), 6.67 (s, 1H), 7.48 (s, 1H), 7.89 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{26}N_6OS$ $(M+H)^+$: 411.5; found: 411.3.

Example 134.

Preparation of 8-(1-ethyl-propyl)-3-(3-methoxy-5-thiazol-2-yl-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

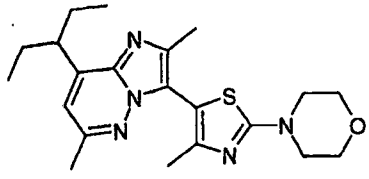


To a flask containing 8-(1-ethyl-propyl)-3-(5-iodo-3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.45 g, 0.99 mmol) and $PdCl_2(dppf)$ (0.057 g, 0.078 mmol) is added a 0.5 M solution of 2-thiazolylzinc bromide (9.9 mL, 4.94 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (50 mL), washed with sat. NH_4Cl (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.29 g, 0.70 mmol, 71%). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-

1.90 (m, 4H), 2.51 (s, 3H), 2.53 (s, 3H), 3.28-3.37 (m, 1H), 3.93 (s, 3H), 6.67 (s, 1H), 7.28 (d, J = 3.3 Hz, 1H), 7.41 (s, 1H), 7.80 (d, J = 3.3 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}N_4OS_2$ $(M+H)^+$: 413.6; found: 414.3.

Example 135.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-2-morpholin-4-yl-thiazol-5-yl)-imidazo[*1,2-b*]pyridazine.



110 mg of 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.28 mmol) and 122 mg of morpholine (1.4 mmol) are dissolved in 3.0 ml of THF and 182 mg of cesium carbonate (0.56 mmol) is added. The mixture is put in 4 ml vial with a Teflon® lined cap and heated at 110°C overnight. The reaction mixture is concentrated and applied to a silica-gel column chromatography column with hexane:EtOAc = 3:1 eluent to give 98 mg of the title compound (88%). mass spectrum (m/e): 400(M+1); ^{1}H-NMR(CDCl3): δ 6.70(s, 1H), 3.87(t, 4H, J=4.8Hz), 3.56(t, 4H, J=4.8Hz), 3.35(m, 1H) 2.56(s, 3H), 2.46(s, 3H), 1.86(m, 4H), 0.90(t, 6H, J=7.6Hz)

The following compounds are prepared essentially as described in Example 135. with 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and the named amine:

Ex	Name	Amine	^{1}H NMR ($CDCl_3$): δ	MS (found) (M+1)
136.	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methylamine	2M Methyl-amine/THF	6.71 (s, 1H), 5.44 (s, NH), 3.35 (m, 1H), 3.06 (s, 3H), 2.57 (s, 3H), 2.47 (s, 3H), 2.19 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.6 Hz, 6H).	344
137.	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-dimethylamine	2M Dimethyl-amine/THF	6.70 (s, 1H), 3.36 (m, 1H), 3.17 (s, 6H), 2.56 (s, 3H), 2.46 (s, 3H), 2.19 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H).	358
138.	N-Ethyl-N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methylamine	N-Methyl-ethylamine	6.70 (s, 1H), 3.59 (q, J = 7.6 Hz, 2H), 3.37 (m, 1H), 3.15 (s, 3H), 2.57 (s, 3H), 2.48 (s, 3H), 2.19 (s, 3H), 1.85 (m, 4H), 1.30 (t, J = 7.5 Hz, 2H), 0.90 (t, J = 7.1 Hz, 6H).	372
139.	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-diethylamine	Diethyl-amine	6.71 (s, 1H), 3.56 (q, J = 7.1 Hz, 4H), 3.35 (m, 1H), 2.56 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 1.30 (t, J = 7.3 Hz, 6H), 0.90 (t, J = 7.3 Hz, 6H).	386

140.	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-(furan-2-ylmethyl)-methylamine	N-Methyl-(furan-2-yl)-methyl-amine	7.44 (s, 1H), 6.69 (s, 1H), 6.38 (s, 2H), 4.72 (s, 2H), 3.36 (m, 1H), 3.14 (s, 3H), 2.57 (s, 3H), 2.48 (s, 3H), 2.20 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.4 Hz, 6H).	424
141.	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-methyl-thiazol-2-yl}thiomorpholine	Thio-morpholine	6.71 (s, 1H), 3.92 (m, 4H), 3.37 (m, 1H), 2.80 (m, 4H), 2.57 (s, 3H), 2.48 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.2 Hz, 6H).	416
142	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(2-methoxy-ethyl)-amine	2-methoxy-ethylamine	6.71 (s, 1H), 5.90 (s, NH), 3.66 (t, J = 5.4 Hz, 2H), 3.56 (t, J = 4.6 Hz, 2H), 3.44 (s, 3H), 3.35 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.2 Hz, 6H).	388
143	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-isopropyl-amine	i-propyl-amine	6.69 (s, 1H), 5.15 (s, NH), 3.74 (m, 1H), 3.35 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.17 (s, 3H), 1.84 (m, 4H), 1.35 (d, J = 5.4 Hz, 6H), 0.90 (t, J = 7.4 Hz, 6H).	372
144.	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-pyrrolidine	Pyrrolidine	6.68 (s, 1H), 3.55 (m, 4H), 3.36(m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.19 (s, 3H), 2.09 (m, 4H), 1.86 (m, 4H), 0.91 (t, J = 7.6 Hz, 6H).	384

145.	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-n-propylamine	n-propyl-amine	6.70 (s, 1H), 5.21 (s, NH), 3.39 (t, J = 7.2 Hz, 2H), 3.29 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.16 (s, 3H), 1.85 (m, 4H), 1.74 (m, 2H), 1.05 (t, J = 7.3 Hz, 3H), 0.90 (t, J = 7.4 Hz, 6H).	372
146	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-benzylamine	Benzyl-amine	7.47-7.23 (m, 5H), 6.70 (s, 1H), 5.52 (s, NH), 6.70 (s, 2H), 3.34 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.19 (s, 3H), 1.85 (m, 4H), 0.91 (t, J = 7.2 Hz, 6H).	420
147	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-(2-methoxy-ethyl)-ethylamine	N-(2-Methoxy-ethyl)-ethylamine		416
148	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(2-methoxy-ethyl)-n-propylamine	N-(2-meth-oxyethyl)-n-propyl-amine	6.69 (s, 1H), 3.72 (m, 4H), 3.47 (t, J = 7.4 Hz, 2H), 3.42 (s, 3H), 3.36 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.16 (s, 3H), 1.87 (m, 6H), 0.99 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.5 Hz, 6H).	430
149	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-piperidine	piperidine	6.68 (s, 1H), 3.53 (t, J = 4.7 Hz, 4H), 3.36 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.86 (m, 4H), 1.71 (m, 6H), 0.90 (t, J = 7.4 Hz,	398

			6H).	
150	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-3-pentylamine	3-amino-pentane	6.70 (s, 1H), 5.24 (s, NH), 3.32 (m, 2H), 2.57 (s, 3H), 2.47 (s, 3H), 1.94 (s, 3H), 1.85 (m, 4H), 1.72 (m, 2H), 1.60 (m, 2H), 1.02 (t, J = 7.5 Hz, 6H), 0.90 (t, J = 7.3 Hz, 6H).	400
151	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-cyclo-propylamine	Cyclo-propylamine	6.70 (s, 1H), 6.51 (s, NH), 3.35 (m, 1H), 2.67 (m, 1H), 2.57(s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 0.91 (t, J = 7.3 Hz, 6H), 0.82 (m, 2H), 0.77 (m, 2H).	370
152	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-allylamine	Allylamine	6.70 (s, 1H), 6.0 (m, 1H), 5.60 (s, NH), 5.38 (dd, J = 1.3, 17.4 Hz, 1H), 5.27 (dd, J = 1.2, 10.3 Hz, 1H), 4.0 (d, J = 5.2 Hz, 2H), 3.45 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.85 (m, 4H), 0.91 (t, J = 6.8 Hz, 6H).	370
153	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-1,2,3,6-tetra-hydro-pyridine	1,2,3,6-tetra-hydro-pyridine	6.70 (s, 1H), 5.96 (m, 1H), 5.81 (m, 1H), 4.02 (t, J = 3.1 Hz, 2H), 3.72 (t, J = 5.5 Hz, 2H), 3.35 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.35 (m, 2H), 2.19 (s, 3H), 1.87 (m,	396

			4H), 0.90 (t, J = 7.4 Hz, 6H).	
154	N-Ethyl-N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-n-propylamine	N-ethyl-n-propyl-amine	6.69 (s, 1H), 3.58 (q, J = 7.1 Hz, 2H), 3.43 (t, J = 7.5 Hz, 2H), 3.36 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.80 (m, 4H), 1.30 (t, J = 6.9 Hz, 3H), 1.04 (t, J = 6.9 Hz, 3H), 0.91 (t, J = 7.5 Hz, 6H).	400
155	N-Methyl-N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-n-propylamine	N-methyl-n-propyl-amine	6.68 (s, 1H), 3.46 (t, J = 8.3 Hz, 2H), 3.35 (m, 1H), 3.16 (s, 3H), 2.56 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.80 (m, 2H), 1.00 (t, J = 7.7 Hz, 3H), 0.91 (t, J = 7.1 Hz, 6H).	386
156	N-Methyl-N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-isopropyl-amine	N-Methyl-2-propyl-amine	6.70 (s, 1H), 4.40 (m, 1H), 3.36 (m, 1H), 2.99 (s, 3H), 2.57 (s, 3H), 2.46 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 1.29 (d, J = 6.4 Hz, 6H), 0.90 (t, J = 7.1 Hz, 6H).	386
157	N-Methyl-N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-2-propyn-1-amine	N-Methyl-2-Propyn-1-amine	6.70 (s, 1H), 4.40 (d, J = 2.5 Hz, 2H), 3.35 (m, 1H), 3.17 (s, 3H), 2.56 (s, 3H), 2.45 (s, 3H), 2.34 (m, 1H), 2.19 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.1 Hz, 6H).	382

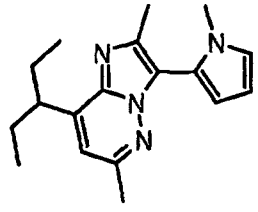
158	N-Methyl-N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-3-amino-propionitrile	N-Methyl-3-amino-propio-nitrile	6.71 (s, 1H), 3.92 (t, J = 6.4 Hz, 2H), 3.37 (m, 1H), 3.25 (s, 3H), 2.9 (t, J = 6.4 Hz, 2H), 2.58 (s, 3H), 2.48 (s, 3H), 2.18 (s, 3H), 1.86 (m, 4H), 0.91 (t, J = 7.4 Hz, 6H).	397
159	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}- cyclopropyl-methylamine	Cyclo-propyl-methyl-amine	6.68 (s, 1H), 5.35 (s, NH), 3.34 (m, 1H), 3.19 (t, J = 6.3 Hz, 2H), 2.56 (s, 3H), 2.45 (s, 3H), 2.16 (s, 3H), 1.86 (m, 4H), 1.19 (m, 1H), 0.91 (t, J = 7.1 Hz, 6H), 0.61 (m, 2H), 0.31 (m, 2H).	384
160	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(2-methylsulfanyl)-ethylamine	2-methyl-sulfanyl-ethylamine	6.72 (s, 1H), 5.58 (s, NH), 3.58 (m, 2H), 3.35 (m, J = 7.3, 14.4, 1H), 2.85 (m, 2H), 2.57 (s, 3H), 2.46 (s, 3H), 2.17 (s, 6H), 1.85 (m, 4H), 0.90 (t, J = 6.7 Hz, 6H).	404
161	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}- N-{[1,3]dioxolan-2-ylmethyl-methylamine	N-{[1,3]di-oxolan-2-yl-methyl}-methyl-amine	6.72 (s, 1H), 5.22 (m, 1H), 4.05 (m, 2H), 3.94 (m, 2H), 3.73 (d, J = 4.5 Hz, 2H), 3.35 (m, J = 6.6, 14.1 Hz, 1H), 3.23 (s, 3H), 2.56 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.84 (m, 4H), 0.91 (t, J = 7.1 Hz, 6H).	430
162	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-	N-Methyl-2-propen-1-yl-amine	6.71 (s, 1H), 5.93 (m, 2H), 5.30 (m, 2H), 4.16 (d, J = 5.9 Hz, 2H), 3.39 (m, 1H),	384

	3-yl]-4-methyl-thiazol-2-yl}- N-Methyl-2-propen-1-yl-amine		3.12 (s, 3H), 2.58 (s, 3H), 2.48 (s, 3H), 2.20 (s, 3H), 1.86 (m, 4H), 0.91 (t, J = 7.5 Hz, 6H).	
163	(R)-N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(tetrahydro-furan-2-ylmethyl)-amine	(R)-(tetrahydro-furan-2-ylmethyl)-amine	6.70 (s, 1H), 5.44 (s, NH), 4.20 (m, 1H), 3.94 (m, 1H), 3.84 (m, 1H), 3.60 (m, 1H), 3.35 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 2.08 (m, 1H), 1.98 (m, 2H), 1.85 (m, 4H), 1.73 (m, 2H), 0.90 (t, J = 7.3 Hz, 6H).	414
164	(S)-N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(tetrahydro-furan-2-ylmethyl)-amine	(S)-(tetrahydro-furan-2-ylmethyl)-amine	6.69 (s, 1H), 5.45 (s, NH), 4.20 (m, 1H), 3.94 (m, 1H), 3.84 (m, 1H), 3.59 (m, 1H), 3.34 (m, 2H), 2.57 (s, 3H), 2.47 (s, 3H), 2.17 (s, 3H), 2.08 (m, 1H), 1.98 (m, 2H), 1.85 (m, 4H), 1.73 (m, 1H), 0.90 (t, J = 7.2 Hz, 6H).	414
165	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-(2-methoxyethyl)-methylamine	N-Methyl-2-methoxy-ethyl-amine	6.70 (s, 1H), 3.74 (t, J = 4.2 Hz, 2H), 3.71 (t, J = 4.1 Hz, 2H), 3.43 (s, 3H), 3.37 (m, 1H), 3.22 (s, 3H), 2.57 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.1 Hz, 6H).	402
166	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-	N-Methyl-benzyl-amine	7.43-7.32 (m, 5H), 6.69 (s, 1H), 4.76 (s, 2H), 3.35 (m, 1H), 3.10 (s, 3H), 2.57(s, 3H), 2.48 (s, 3H), 2.21 (s,	434

	yl}-N-methyl-benzylamine		3H), 1.85 (m, 4H), 0.91 (t, J = 7.3 Hz, 6H).	
167	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-ethyl-benzylamine	N-Ethyl-benzyl-amine	7.41-7.31 (m, 5H), 6.68 (s, 1H), 4.76 (s, 2H), 3.54 (q, J = 7.3, 2H), 3.36 (m, 1H), 2.56(s, 3H), 2.49 (s, 3H), 2.20 (s, 3H), 1.85 (m, 4H), 1.26 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.1 Hz, 6H).	448
168	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(1-methoxy-2-butyl)-amine	1-Methoxy-2-amino-butane		416
169	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-methyl-isobutylamine	N,2-Di-methyl- n-propyl-amine		400
170	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-isobutyl-amine	2-Methyl-n-propyl-amine		386

Example 171.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(1-methyl-^1H-pyrrol-2-yl)-imidazo[*1,2-b*]pyridazine.



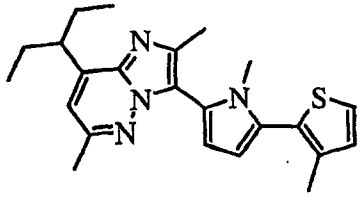
A THF solution (10 mL) of N-methylpyrrole (Aldrich, 800 μL, 9.0 mmol) is cooled to -78 °C under N_2 then treated with *tert*-BuLi (1.7 M in pentane, 5.3 mL, 9.0 mmol). The solution is warmed to room temperature for 30 minutes then cooled to -78 °C and treated with $ZnCl_2$ (Aldrich, 0.5 M in THF, 18 mL, 9.0 mmol). The resulting mixture is warmed to room temperature and treated with a THF slurry (5 mL) containing 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.02 gm, 3.0 mmol) and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 140 mg, 0.17 mmol). The mixture is heated to 60 °C overnight, then poured into sat'd aq NH_4Cl (50 mL) and extracted with diethyl ether (75 mL). The organic extract is ished with aq. brine, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title compound (407.5 mg, 46% yield) as an oil.

ES-MS (m/z): calc'd for $C_{18}H_{24}N_4$: 296.20; found 297.5 $(M+H)^+$

^{1}H NMR (400 mHz, $CDCl_3$): δ 6.86 (s, 1H), 6.65 (s, 1H), 6.32-6.28 (m, 2H), 3.50 (s, 3H), 3.35 (br s, 1H), 2.49 (s, 3H), 2.46 (s, 3H), 1.87-1.75 (m, 4H), 0.87 (t, J = 7.0 Hz, 6H).

Example 172.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[1-methyl-5-(3-methyl-thiophen-2-yl)-^1H-pyrrol-2-yl]- imidazo[*1,2-b*]pyridazine.



A. 3-(5-Bromo-1-methyl-*1H*-pyrrol-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

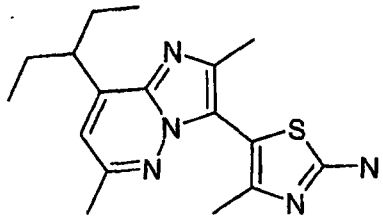
A THF solution (10 mL) of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(1-methyl-*1H*-pyrrol-2-yl)-imidazo[*1,2-b*]pyridazine (414 mg, 1.40 mmol) is cooled to 0 °C and treated with a THF solution of NBS (250 mg, 1.40 mmol). Within 5 min, the reaction mixture is treated with sat Na_2SO_3 (1 mL) then concentrated. The resulting residue is diluted with ethyl acetate (50 mL) and ished with 50% aq sat'd Na_2SO_3 (2x50 mL). The organic extract is dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title compound (374 mg, 71% yield) as a solid. ES-MS (m/z): calc'd for $C_{18}H_{23}BrN_4$: 374.11; found 375 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 6.67 (s, 1H), 6.33 (d, J = 4.0 Hz, 1H), 6.30 (d, J = 4.0 Hz, 1H), 3.40 (s, 3H), 3.36 (br s, 1H), 2.50 (s, 3H), 2.44 (s, 3H), 1.88-1.75 (m, 4H), 0.87 (t, J = 7.3 Hz, 6H).

B. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-[1-methyl-5-(3-methyl-thiophen-2-yl)-*1H*-pyrrol-2-yl]- imidazo[*1,2-b*]pyridazine.

A THF slurry (5 mL) of 3-(5-bromo-1-methyl-*1H*-pyrrol-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (143 mg, 0.38 mmol) and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 19 mg, 0.023 mmol) is treated with 3-methyl-2-thienyl zinc bromide (Aldrich, 0.5 M in THF, 3.8 mL, 1.9 mmol) then heated to 60 °C for 1 hr. The resulting mixture is poured into sat'd NH_4Cl (25 mL) and extracted with diethyl ether (35 mL). The organic extract is washed with aq. NaCl, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 15% ethyl acetate in hexane) to elute the product. The material is purified a second time by flash chromatography using hexane-ethyl acetate gradient (100% hexane to 12% ethyl acetate in hexane) to elute the product. Only the fractions containing pure desired product, as judged by MS analysis, are collected and give the title compound (82.6 mg, 55% yield) as an oil. ES-MS (m/z): calc'd for $C_{23}H_{28}N_4S$: 392.20; found 393.1 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 7.28 (d, J = 5.3 Hz, 1H), 6.96 (d, J = 4.8 Hz, 1H), 6.67 (br s, 1H), 6.39 (d, J = 3.5 Hz, 1H), 6.37 (d, J = 4.0 Hz, 1H), 3.35 (br s, 1H), 3.33, (s, 3H), 2.52 (s, 3H), 2.51 (s, 3H), 2.26 (s, 3H), 1.89-1.76 (m, 4H), 0.87 (t, J = 7.5 Hz, 6H).

Example 173.

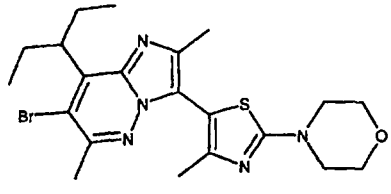
Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-ylamine.



50 mg of 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.13 mmol) and 10 mg of copper (I) oxide are added to 3 ml of 2 M NH3 in MeOH and vial is capped with a Teflon® lined cap, heated at 130°C for overnight. The reaction mixture is concentrated under N2 gas and applied onto a silica-gel chromatography column (Hexane: AcOEt: 2 M NH3 in MeOH = 20:20:1) to give 22 mg of the title compound. Yield 54%: mass spectrum (m/e): 330(M+1); ^{1}H-NMR(CDCl3): 6.72(s,1H), 5.24(br, 2H), 3.40(m, 1H), 2.56(s, 3H), 2.47(s, 3H), 2.18(s, 3H), 1.85(m, 4H), 0.90(t, 6H, J=7.4Hz).

Example 174.

Preparation of N-{5-[7-bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine.



A. 7-Bromo-3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

547 mg of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-thiazol-5-yl)-imidazo[*1,2-b*]pyridazine (1.74 mmol) and 341 mg of NBS (1.92 mmol) are dissolved in 20 ml of CHCl3 and stirred at room temperature overnight. The reaction mixture is washed with sat. $Na_2S_2O_3$, sat. NaCl, dried over Na_2SO_4 and evaporated. The crude materials are

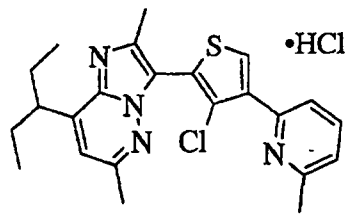
applied onto a silica-gel chromatography column (Hexane:AcOEt=8:1) to give 218 mg of the title compound. Yield 27%. mass spectrum (m/e): 473(M+1); ^{1}H-NMR(CDCl3): 3.44(m, 1H), 2.70(s, 3H), 2.45 (s, 3H), 2.37(s, 3H), 2.03(m, 4H), 0.90(m, 6H).

B. N-{5-[7-bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine.

72 mg of 7-bromo-3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.15 mmol) and 66 mg of morpholine (0.76 mmol) and 97 mg of cesium carbonate (0.3 mmol) are put in 4 ml vial with 3 ml of dry THF. The vial is capped with a Teflon® lined cap and heated at 100°C overnight. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane :AcOEt = 3:1) to give 30 mg of the title compound. Yield 42%.: mass spectrum (m/e): 479(M+1); ^{1}H-NMR(CDCl3): 3.87(t, 4H, J=5.0Hz), 3.55(t, 4H, J=5.0Hz), 3.45(m, 1H), 2.70(s, 3H), 2.44(s, 3H), 2.40(m, 2H), 2.18(s, 3H), 2.01(m, 2H), 0.88(t, 6H, J=7.3Hz).

Example 175.

Preparation of 3-[3-chloro-4-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine, hydrochloride salt.

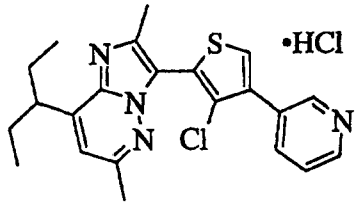


Reike® Zn (0.5 g/ mL solution in THF (1.9 mL,, 1.45 mmol) is added to a flask containing 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.73 mmol). The slurry is heated at 65 °C for 1 hour, placed in a centrifuge for 5 minutes, and the resulting solution is transferred to a flask containing 2-bromo-6-methyl-pyridine (0.12 g, 0.73 mmol) and $PdCl_2$(dppf) (0.018 g, 0.024 mmol). The reaction is heated at 65 °C overnight, diluted with ethyl acetate (20 mL), and washed with a sat. solution of NH_4Cl (15 mL). The organic layer is dried over $MgSO_4$, filtered, and concentrated. The residue is purified by silica gel chromatography using a hexanes and ethyl acetate gradient. The resulting product is dissolved in

dichloromethane (5 mL), treated with a 1 M solution of HCl in EtOH (0.35 mL, 0.35 mmol) and concentrated. The residue is recrystallized from ethyl acetate and hexanes furnish the title compound (0.033 g, 0.072 mmol, 11%). ^{1}H-NMR ($CDCl_3$), δ 0.95 (t, J = 7.3 Hz, 6H), 1.73-2.02 (m, 4H), 2.68 (s, 3H), 2.81 (s, 3H), 3.21 (s, 3H), 3.88-3.98 (m, 1H), 7.25 (s, 1H), 7.65 (d, J = 7.5 Hz, 1H), 8.09 (d, J = 7.5 Hz, 1H), 8.33 (dd, J = 7.5, 7.1 Hz, 1H), 9.26 (s, 1H) ppm. LC/MS (m/z): calcd. for $C_{23}H_{26}Cl_2N_4S$ $(M+H)^+$: 424.2; found: 424.2.

Example 176.

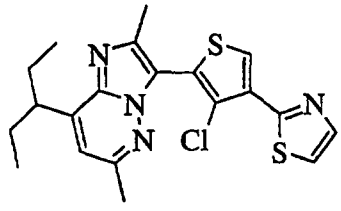
Preparation of 3-(3-chloro-4-pyridin-3-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine, hydrochloride salt.



Using a procedure analogous to Example 175, 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 0.97 mmol), Reike® Zn (0.5 g/ mL solution in THF, 2.5 mL, 1.94 mmol), 3-iodo-pyridine (0.30 g, 1.45 mmol), $PdCl_2$(dppf) (0.035 g, 0.048 mmol), and a 1 M solution of HCl in EtOH (0.61 mL, 0.61 mmol) furnish the title compound (0.076 g, 0.17 mmol, 18%). ^{1}H-NMR ($CDCl_3$), δ 0.95 (t, J = 7.0 Hz, 6H), 1.71-1.88 (m, 2H), 1.88-2.01 (m, 2H), 2.68 (s, 3H), 2.81 (s, 3H), 3.85-3.96 (m, 1H), 5.28 (s, 1H), 7.27 (bs, 1H), 8.09 (bs, 1H), 8.23 (bs, 1H), 8.70 (bs, 1H), 8.89 (bs, 1H), 9.18 (bs, 1H). LC/MS (m/z): calcd. for $C_{22}H_{24}Cl_2N_4S$ $(M+H)^+$: 411.1; found: 411.2.

Example 177.

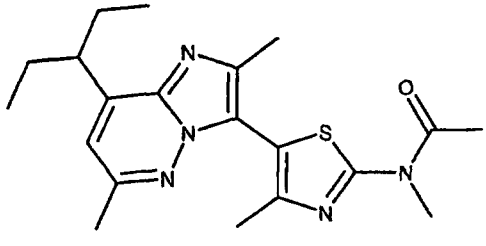
Preparation of 3-(3-chloro-4-thiazol-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure analogous to Example 175, 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.61 mmol), Reike® Zn (0.5 g/ mL solution in THF, 1.6 mL, 1.21 mmol), 2-bromo-thiazole (0.11 mL, 1.21 mmol), and $PdCl_2$(dppf) (0.022 g, 0.030 mmol) furnish the title compound (0.012 g, 0.29 mmol, 6.8%). ^{1}H-NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.94 (m, 4H), 2.52 (s, 6H), 3.27-3.43 (m, 1H), 6.73 (s, 1H), 7.43 (d, J = 3.3 Hz, 1H), 7.94 (d, J = 3.3 Hz, 1H), 8.30 (s,1H) ppm. LC/MS (m/z): calcd. for $C_{20}H_{21}ClN_4S_2$ $(M+H)^+$: 417.1; found: 417.2.

Example 178.

Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-methyl-acetamide.

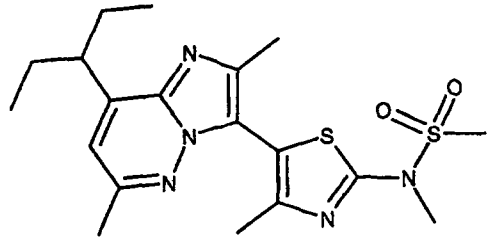


60 mg of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methylamine (0.17 mmol) and 86 mg of triethylamine (0.85 mmol) are dissolved in 3.0 ml of CH_2Cl_2 and 16 mg of acetylchloride (0.2 mmol) is added. The vial is capped with a Teflon® lined cap and shaken at room temperature for 2h. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane :AcOEt = 3:1 and Hexane :AcOEt=2:1) to give 33.8 mg of the title compound. Yield 50%: mass spectrum (m/e): 386(M+1); ^{1}H-NMR(CDCl3): 7.03(s,1H), 3.79(s, 3H),

3.47(m, 1H), 2.54 (s, 3H), 2.47(s, 3H), 2.46(s, 3H), 2.31(s, 3H), 1.86(m, 4H), 0.91(t, 6H, J=7.4Hz).

Example 179.

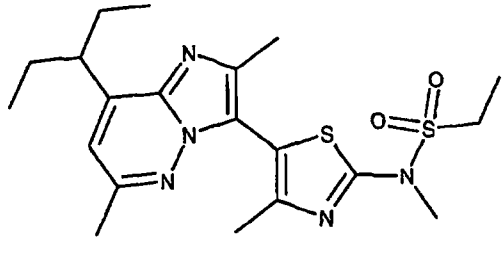
Preparation of N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-methanesulfonyl-methylamine.



60 mg of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methylamine (0.17 mmol) and 86 mg of triethylamine (0.85 mmol) are dissolved in 3.0 ml of CH2Cl2 and 23 mg of methanesulfonyl chloride (0.2 mmol) is added. The vial is capped with a Teflon® lined cap and shaken at room temperature for 2h. The reaction mixture is concentrated and applied to silica-gel chromatography (Hexane :AcOEt = 2:1) to give 53.8 mg of the title compound. Yield 75%. mass spectrum (m/e): 422(M+1); ^{1}HNMR(CDCl3): 6.96(s, 1H), 3.60(s, 3H), 3.34(m, 1H), 3.19(s, 3H), 2.56(s, 3H), 2.48(s, 3H), 2.29(s, 3H), 1.86(m, 4H), 0.90(t, 6H, J=7.4Hz).

Example 180.

Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-ethanesulfonyl-methylamine.

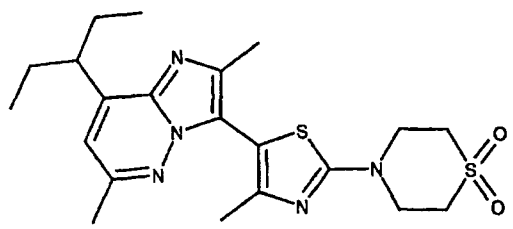


The title compound is prepared by a procedure analogous to Example 178. employing 50 mg of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methylamine (0.15 mmol), 51 mg of triethylamine (0.5 mmol) and 39 mg of ethanesulfonylchloride (0.3 mmol). 48.9 mg, Yield 75%: mass spectrum

(m/e): 436(M+1); ^{1}H-NMR(CDCl3): 6.73(s, 1H), 3.62(s, 3H), 3.42(q, 2H, J=7.4Hz), 3.35(m, 1H), 2.55(s, 3H), 2.48(s, 3H), 2.28(s, 3H), 1.85(m, 4H), 1.46(t, 3H, J=7.4Hz), 0.90(t, 6H, J=7.5Hz).

Example 181.

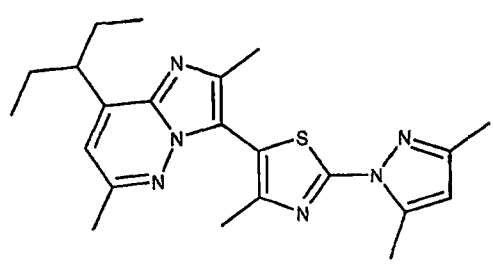
Preparation of 3-[2-(1,1-dioxo-thiomorpholin-4-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



60 mg of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}thiomorpholine(0.14 mmol) is dissolved in 3 ml of CH_2Cl_2 and 62 mg of mCPBA (0.36 mmol) is added. The reaction mixture is stirred at room temperature for 30 min. The reaction mixture is diluted with CH_2Cl_2, washed with sat. NaHCO3 and sat. NaCl. The separated organic layer is dried over Na_2SO_4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:AcOEt:2 M NH3 in MeOH=10:3:1) to give 20.3 mg of the title compound. Yield 33%: mass spectrum (m/e): 448(M+1). ^{1}H-NMR: 6.72 (s, 1H), 4.16 (t, J = 4.7 Hz, 4H), 3.35 (m, 1H), 3.23 (t, J = 5.2 Hz, 4H), 2.57 (s, 3H), 2.48 (s, 3H), 2.19 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.1 Hz, 6H).

Example 182.

Preparation of 3-[2-(3,5-Dimethyl-pyrazol-1-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. {5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-hydrazine.

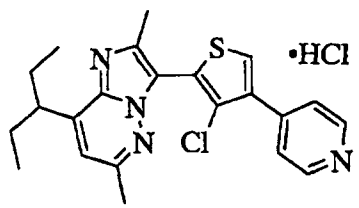
The title compound is prepared essentially as described in Example 135 using hydrazine. MS found (M+1) 345.

B. 3-[2-(3,5-Dimethyl-pyrazol-1-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

28 mg of {5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-hydrazine (0.08 mmol) and 80 mg of 2,4-pentanedione (0.8 mmol) are dissolved in 1.0 ml of AcOH and heated at 100°C for 2 h. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane : AcOEt = 5:1) to give 23 mg of the title compound. Yield 70%: mass spectrum (m/e): 409 (M+1). 6.72 (s, 1H), 6.03 (s, 1H), 3.36 (m, J = 7.1, 14.1 Hz, 1H), 2.75 (s, 3H), 2.55 (s, 3H), 2.50 (s, 3H), 2.32(s, 3H), 2.31(s, 3H), 1.87 (m, 4H), 0.91 (t, J = 7.5 Hz, 6H).

Example 183.

Preparation of 3-(3-chloro-4-pyridin-4-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine, hydrochloride salt.

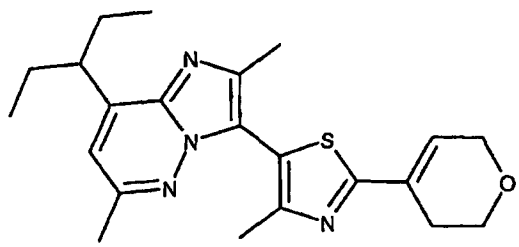


A solution of 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.61 mmol), 4-pyridyl-boronic acid (0.82, 0.67 mmol), a 2 M solution of Na_2CO_3 (0.5 mL, 0.91 mmol), and *n*-PrOH (2.5 mL) are degassed with nitrogen for 10 minutes. $Pd(OAc)_2$ (0.0027 g, 0.012 mmol) and PPh_3 (0.0095 g, 0.036 mmol) are added, and the solution heated at a 90 °C overnight. The solution is diluted with ethyl acetate (40 mL) and washed with a 10 % solution of Na_2CO_3 (30 mL). The organic layer is dried over $MgSO_4$, filtered, and concentrated. The residue is purified by ISCO flash chromatography (20%-30% EtOAc gradient). The resulting product is dissolved in dichloromethane (5 mL), treated with a 1 M solution of HCl in

EtOH (0.35 mL, 0.35 mmol), and concentrated. The residue is recrystallized from acetonitrile and ethyl acetate furnish the title compound (0.15 g, 0.34 mmol, 56%). ^{1}H-NMR ($CDCl_3$), δ 0.95 (t, J = 7.5 Hz, 6H), 1.73-1.88 (m, 2H), 1.89-2.04 (m, 2H), 2.68 (s, 3H), 2.82 (s, 3H), 3.87-3.97 (m, 1H), 7.28 (s, 1H), 8.26-8.34 (m, 3H), 8.95 (d, J = 5.3 Hz, 2H) ppm. LC/MS (m/z): calcd. for $C_{22}H_{24}Cl_2N_4S$ $(M+H)^+$: 411.1; found: 411.2.

Example 184.

Preparation of 3-[2-(3,6-dihydro-*2H*-pyran-4-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 4-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-tetrahydro-pyran-4-ol.

370 mg of 3-(2-Bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.93 mmol) is dissolved in 10 ml of dry THF and cooled to –78°C. 0.6 ml of n-BuLi 2.0 M in hexane (1.2 mmol) is added and stirred at –78°C for 30 min. 141 mg of tetrahydro-*4H*-pyran-4-one (1.41 mmol) is added and stirred at –78°C for 2 h. The reaction mixture is diluted with AcOEt, washed with sat. NH4Cl , dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane : AcOEt : 2 M NH3 in MeOH =10:3:1) to give 152 mg of the title compound. Yield 40%.: mass spectrum (m/e): 415(M+1). ^{1}H NMR ($CDCl_3$): δ 6.74 (s, 1H), 3.99 (t, J = 2.2 Hz, 4H), 3.97 (t, J = 2.2 Hz, 4H), 3.35 (m, 1H), 3.20 (s, OH), 2.56 (s, 3H), 2.48 (s, 3H), 2.36 (s, 3H), 1.88 (m, 4H), 0.91 (t, J = 7.3 Hz, 6H).

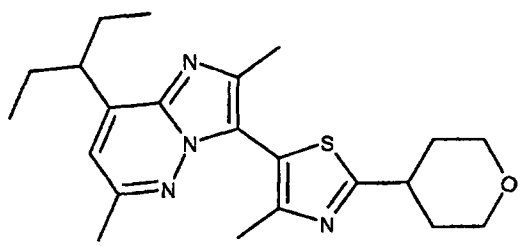
B. 3-[2-(3,6-Dihydro-*2H*-pyran-4-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

150 mg of 4-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-tetrahydro-pyran-4-ol (0.36 mmol) is dissolved in 5 ml of CH2Cl2

and 112 mg of triethylsilane (0.96 mmol) and 717 mg of trifluoroacetic acid (6.3 mmol) are added. The reaction mixture is stirred at room temperature for 1h. The reaction mixture is stirred under reflux for 1 h and cooled down to room temperature. The solvent is removed in *vacuo*. The crude product is applied onto a silica-gel chromatography column (Hexane : AcOEt: 2 M NH3 in MeOH =10:3:1) to give 64 mg of the title compound. Yield 45%. mass spectrum (m/e): 397(M+1). 6.94 (s, 1H), 6.71 (s, 1H), 4.41 (d, J = 2.6 Hz, 2H), 3.98 (t, J = 5.3 Hz, 2H), 3.43 (m, 1H), 2.62(s, 3H), 2.75 (m, 2H), 2.56 (s, 3H), 2.37 (s, 3H), 1.86 (m, 4H), 0.92 (t, J = 8.2 Hz, 6H).

Example 185.

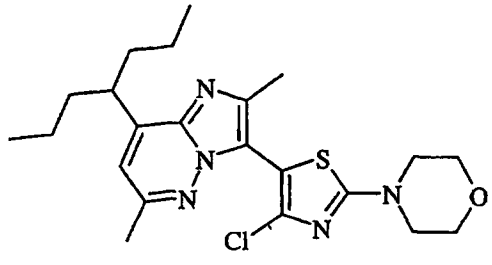
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[4-methyl-2-(tetrahydro-pyran-4-yl)-thiazol-5-yl]-imidazo[*1,2-b*]pyridazine.



Add 3-[2-(3,6-dihydro-2*H*-pyran-4-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (55 mg, 0.14 mmol), 5% palladium on carbon (55 mg) and absolute ethanol (50 ml) to a pressure vessel. Purge the reaction vessel with nitrogen, purge the reaction vessel with hydrogen, pressurize the reaction mixture with hydrogen (415 KPa), seal the vessel, agitate the reaction and heat to 40 °C. Continue the reaction for 18 hours then turn off the heat and allow the reaction mixture to cool to ambient temperature. Vent the excess hydrogen from the vessel and purge the vessel with nitrogen. Filter the reaction mixture to remove the 5% palladium on carbon. The filtrate is concentrated and applied onto a silica-gel chromatography column (Hexane :AcOEt : 2 M NH_3 in MeOH = 10:3:1) to give 12.8 mg of the title compound. Yield 23%. mass spectrum (m/e): 399(M+1). ^{1}H NMR ($CDCl_3$): δ 6.73 (s, 1H), 4.14 (m, 2H), 3.60 (m, 2H), 3.34 (m, 2H), 2.56 (s, 3H), 2.48 (s, 3H), 2.36 (s, 3H), 2.16 (m, 2H), 2.02 (m, 2H), 1.87 (m, 4H), 0.91 (t, J = 7.6 Hz, 6H).

Example 186.

Preparation of 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine.



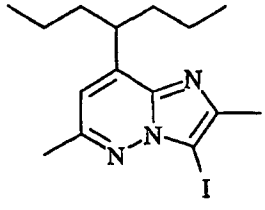
A. 6-Methyl-4-(1-propyl-butyl)-pyridazin-3-ylamine.

6-Methyl-4-(1-propyl-butyl)-pyridazin-3-ylamine can be made using chemistry described in J. Heterocylic Chem. **1991**, *28*, 583. A 250 mL three neck round bottom flask is charged with 3-amino-6-methyl pyridazine (2.5 g, 0.229 moles, 1.0 equiv), water (70 mL), and acetonitrile (50 mL). Concentrated sulfuric acid (3.51 g, 1.91 mL, 0.0344 moles, 1.5 equiv), silver nitrate (3.87 g, 0.0229 moles, 1.0 equiv), and valproic acid (7.21 g, 7.95 mL, 0.050 moles, 2.2 equiv) are added to the reaction mixture. The reaction is heated to 75 °C. As the reaction mixture is heating, a solution of $(NH_4)_2S_2O_8$ (7.85 g, 0.0344 moles, 1.5 equiv) in 40 mL of water is slowly added via an addition funnel over a period of 30 minutes. The reaction mixture is heated at 70-80 °C for two more hours. The reaction mixture is cooled and dichoromethane is added. The reaction is made basic with a 30% aqueous NaOH solution and filtered through a short Celite® plug. The organic layer is separated, and the aqueous layer is extracted two more times with dichoromethane. The combined organic extracts are dried over Na_2SO_4. The solvent is evaporated and the crude material is purified using silica gel chromatography with a 2.0 N solution of NH_3 in MeOH and methylene chloride as eluent. Yield = 0.61 g (13%). MS (APCI): 208 (M+1).

B. 2,6-Dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine.

A 250 mL round bottom flask is charged with 6-methyl-4-(1-propyl-butyl)-pyridazin-3-ylamine (0.611 g, 0.00295 moles, 1 equiv), ethanol 2B (30 mL), and chloroacetone (0.382 g, 0.328 ml, 0.00412 moles, 1.4 equiv). The reaction mixture is heated at 75 °C overnight and then cooled to room temp. $NaHCO_3$ (0.371 g, 0.00442 moles, 1.5 equiv) is slowly added to the reaction mixture that is then heated to 100 °C overnight. The reaction mixture is cooled and the solvent is evaporated. Dichloromethane is added and the reaction mixture is passed through filter paper. The solvent is evaporated to obtain a brown oil which is purified via silica gel chromatography. The material is eluted with a hexanes and ethyl acetate gradient to obtain 0.511 g of the final products. Two peaks are identified in the lc/ms. The mixture is used "as is" in the next reaction. MS (APCI): 246 (M+1).

C. 3-Iodo-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine.



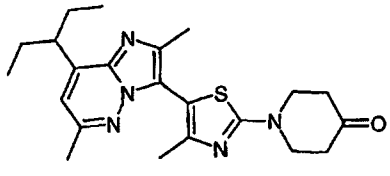
A 50 mL round bottom flask is charged with 2,6-dimethyl-8-(1-propyl-butyl)-imidazo[1,2-*b*]pyridazine (0.51 g, 0.0021 moles) and acetonitrile (3 mL). The reaction mixture is placed on an ice bath and NIS (0.468 g, 0.00208 moles) is added neat. The reaction is stirred overnight and the ice bath melts. The next day, the reaction mixture is partitioned between dichloromethane and a saturated aqueous solution of $NaHCO_3$. The organic layer is collected and the aqueous layer is extracted two more times with dichloromethane. The organic extracts are combined, washed with brine, and dried over Na_2SO_4. The solvent is evaporated and the crude material is purified via silica gel chromatography eluting with hexanes and then a 25:75 mixture of ethyl acetate and hexanes. Yield = 0.435 g (56%). MS (APCI): 372 (M+1).

D. 3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine.

A 15 mL round bottom flask is charged with 3-iodo-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[1,2-*b*]pyridazine (0.200 g, 0.000539 moles), 4-(4-chloro-thiazol-2-yl)-morpholine (0.165 g, 0.000808 moles), Cs_2CO_3 (0.361 g, 0.00108 moles, 2.0 equiv), $Pd(dba)_2$ (0.0092 g, 0.0000161 moles, 0.03 equiv), PPh_3 (0.00847 gram, 0.000323 moles, 0.060 equiv) and DMF (2.0 mL). Nitrogen is bubbled through the reaction mixture for 15 minutes; then, the reaction mixture is heated at 130 °C overnight. The next day, the reaction mixture is partitioned between Et_2O and a saturated solution of NH_4Cl. The aqueous layer is extracted twice more with Et_2O. The organic extracts are combined, washed 2-3 times with H_2O, washed once with brine, and dried over Na_2SO_4. The solvents are evaporated in vacuo and the crude reaction mixture is purified via silica gel chromatography. Yield = 0.1737 g (72%). ^{1}H-NMR ($CDCl_3$), δ 0.87 (t, *J* = 7 Hz, 6H), 1.14- 1.37 (m, 4H), 1.74 (q, *J* = 8 Hz, 4H), 2.54 (s, 3H), 2.50 (s, 3H), 3.48 (m, 1H), 3.53 (t, *J* = 5 Hz, 4H), 3.83 (t, *J* = 5 Hz, 4H), 6.71(br s, 1H) ppm. LC/MS (m/z): calcd. for $C_{22}H_{30}ClN_5OS$ $(M+H)^+$: 448; found: 448.

Example 187.

Preparation of 1-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-piperidin-4-one.



A. 8-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-1,4-dioxa-8-aza-spiro[4.5]decane.

100 mg of 3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.25 mmol), 182 mg of 4-piperidineethylene ketal (1.27 mmol) and 244 mg of Cs2CO3 (0.75 mmol) are put into 4.0 ml vial with 2.0 ml of THF. The vial is capped with a Teflon® lined cap and heated at 110°C for 3 days. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1) to give 116 mg of the title compound. Yield 100%. mass spectrum

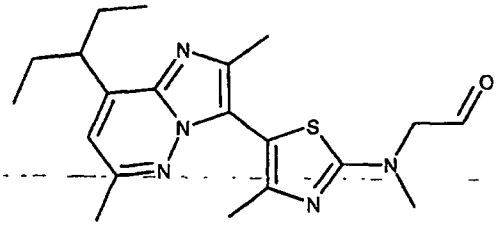
(m/e): 456(M+1). ^{1}H NMR ($CDCl_3$): δ 6.69 (s, 1H), 4.05 (s, 4H), 3.70 (t, J = 6.2 Hz, 4H), 3.35 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.18 (s, 3H), 1.90-1.78 (m, 8H), 0.90 (t, J = 7.2 Hz, 6H).

B. 1-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-piperidin-4-one.

70 mg of 8-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-1,4-dioxa-8-aza-spiro[4.5]decane (0.15 mmol) is dissolved in 10.ml of conc. HCl and stirred at room temperature for 2 h. The reaction mixture is neutralized with sat. NaHCO3, extracted with CH2Cl2, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane :AcOEt=2:1) to give 33.2 mg of the title compound . Yield 52%. mass spectrum (m/e): 412(M+1). ^{1}H NMR ($CDCl_3$): δ 6.70 (s, 1H), 3.94 (t, J = 6.2 Hz, 4H), 3.35 (m, 1H), 2.67 (t, J = 6.5 Hz, 4H), 2.57 (s, 3H), 2.47 (s, 3H), 2.21 (s, 3H), 1.86 (m, 4H), 0.91 (t, J = 7.1 Hz, 6H).

Example 188.

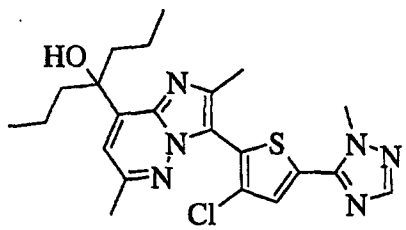
Preparation of ({5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methyl-amino)-acetaldehyde.



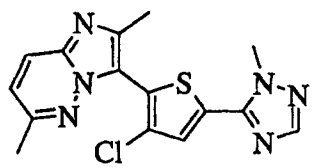
85 mg of N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}- N-{[1,3]dioxolan-2-ylmethyl-methylamine (0.2 mmol) is dissolved in 2 ml of conc. HCl and stirred at 50°C for 30 min. The mixture is cooled to room temperature and neutralized with sat. NaHCO3. The mixture is extracted with CH2Cl2, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (CH2Cl2:MeOH=20:1) to give 73.4 mg of the title compound. Yield 76%. mass spectrum (m/e): 386(M+1). 9.79 (s, 1H), 6.72 (s, 1H), 4.39 (s, 2H), 3.36 (m, 1H), 3.22 (s, 3H), 2.57 (s, 3H), 2.47 (s, 3H), 2.20 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H).

Example 189.

Preparation of 4-{3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-8-yl}-heptan-4-ol.

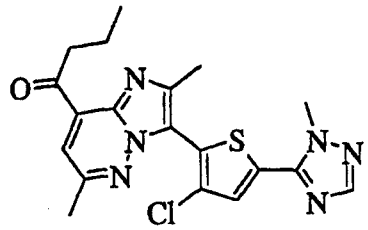


A. 3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A solution of 2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.32 g, 2.17 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-^1H-[1,2,4]triazole (0.72 g, 2.61 mmol), Cs_2CO_3 (1.49 g, 4.57 mmol) and DMF (6 mL) is de-gassed for 15 minutes with N_2. $Pd(OAc)_2$ (0.024 g, 0.11 mmol) and PPh_3 (0.057 g, 0.22 mmol) are added and the solution is heated at 135°C for 4 hours. The solution is diluted with CH_2Cl_2 (50 mL), washed with sat. NH_4Cl (2 x 50 mL), water (50 mL), filtered and concentrated. The residue is purified by ISCO flash chromatography (30%-100% EtOAc gradient) furnish the title compound (0.29 g, 0.84 mmol, 39%). ^1H NMR ($CDCl_3$) δ 2.49 (s, 3H), 2.50 (s, 3H), 4.10 (s, 3H), 6.92 (d, J = 9.2 Hz, 1H), 7.44 (s, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.85 (s, 1H). LC/MS (m/z): calcd. for $C_{15}H_{13}ClN_6S$ $(M+H)^+$: 345.1; found: 345.2.

B. 1-{3-[3-Chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-8-yl}-butan-1-one.



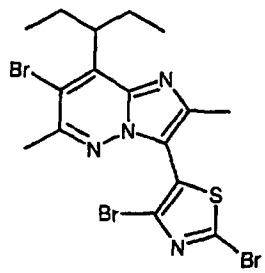
A solution of 3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.58 mmol), *N*-methoxy-*N*-methyl-butylamide (Wolberg, M. et. al. *Chem. Europ. J.* 2001, 7, 4562.) (0.084 g, 0.64 mmol) in THF (3 mL) is cooled to a -78 °C, and a 2.0 M solution of LDA in heptane/ THF/ ethyl benzene (0.58 mL, 1.16 mmol) is added. The solution is warmed to ambient temperature, diluted with dichloromethane (20 mL), and washed with a sat. NH_4Cl solution (15 mL). The organic layer is dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (20%-100% EtOAc gradient) to furnish the title compound (0.11 g, 0.27 mmol, 46%). ^{1}H-NMR ($CDCl_3$), δ 1.04 (t, J = 7.0 Hz, 3H), 1.76-1.86 (m, 2H), 2.56 (s, 3H), 2.59 (s, 3H), 3.51 (t, J = 7.1 Hz, 2H), 4.15 (s, 3H), 7.36 (s, 1H), 7.49 (s, 1H), 7.90 (s, 1H) ppm. LC/MS (m/z): calcd. for $C_{19}H_{19}ClN_6OS$ $(M+H)^+$: 415.1; found: 415.3.

C. 4-{3-[3-Chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-8-yl}-heptan-4-ol.

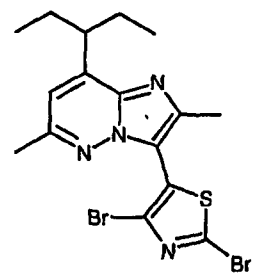
A solution of 1-{3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-8-yl}-butan-1-one (0.15 g, 0.36 mmol) and THF (5 mL) is cooled to 0°C, and a 2.0 M propyl magnesium bromide solution in diethylether (0.22 mL, 0.43 mmol) is added. The reaction is warmed to ambient temperature, diluted with ethyl acetate (30 mL), and washed with a sat. NH_4Cl solution (30 mL). The organic layer is dried over $MgSO_4$, filtered, and concentrated. The residue is purified by ISCO flash chromatography (20%-40% EtOAc gradient) to furnish the title compound (0.016 g, 0.017 mmol, 47%). ^{1}H-NMR ($CDCl_3$), δ 0.90 (t, J = 7.4 Hz, 6H), 1.12-1.29 (m, 2H), 1.37-1.54 (m, 2H), 1.86-2.04 (m, 4H), 2.50 (s, 3H), 2.54 (s, 3H), 4.15 (s, 3H), 6.11 (bs, 1H), 6.73 (s, 1H), 7.48 (s, 1H), 7.90 (s, 1H) ppm. LC/MS (m/z): calcd. for $C_{22}H_{27}ClN_6OS$ $(M+H)^+$: 459.2; found: 459.3.

Example 190, 191, and 192.

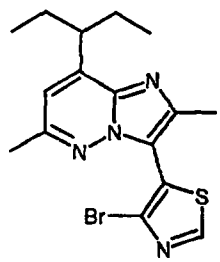
Preparation of 7-bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine; 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine; and 3-(4-bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



190.



191.



192.

A. 8-(1-ethyl-propyl)-2,6-dimethyl-3-thiazol-5-yl-imidazo[*1,2-b*]pyridazine.

2.41 g (7 mmol) of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine, 3.00 g of thiazole (35.2 mmol), 378 mg of triphenylphosphine (1.44 mmol) and 4.71 g of Cs2CO3 (14.5 mmol) are combined with 25 ml of DMF and N2 gas is bubbled in for 30 min. 330 mg of Pd2dba3 (0.36 mmol) is added and the tube is sealed. The reaction tube is heated at 130°C overnight. To the reaction mixture is added water and CH2Cl2, and the CH2Cl2 layer is separated, washed with sat. NaCl and dried over Na2SO4. The solvents are removed *in vauo* and crude product is applied onto a silica-gel chromatography column (Hexane : AcOEt = 3:1) to give 1.48 g of the title compound. Yield 70%. mass spectrum (m/e): 301(M+1); ^{1}H-NMR(CDCl3): 8.93(s, 1H), 8.52(s, 1H), 6.78(s, 1H), 3.35(m, 1H), 2.76(s, 3H), 2.66(s, 3H), 1.86(m, 4H), 0.89(t, 6H, J=7.5Hz).

B. 7-bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine; 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine; and 3-(4-bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

1.05 g (3.5 mmol) of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-thiazol-5-yl-imidazo[*1,2-b*]pyridazine and 1.56 g of NBS (8.75 mmol) are dissolved in 50 ml of CH2Cl2 and stirred at room temperature for 3 days. The reaction mixture is diluted with CH2Cl2 and washed with sat. $Na_2S_2O_3$ and sat. NaCl. The separated organic layer is dried over Na_2SO_4 and evaporated. The reaction mixture is applied onto a silica-gel chromatography column (Hexane : AcOEt = 20:1→8:1) to give three products:

149 mg of 7-bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (9%);

936 mg of 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (58%); and

77 mg of 3-(4-bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (6%).

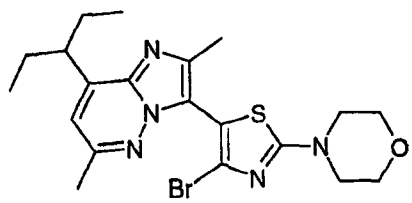
7-Bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine mass spectrum (m/e): 538(M+1); ^{1}H-NMR(CDCl3): 3.45(m, 1H), 2.71(s, 3H), 2.52(s, 3H), 2.38(m, 2H), 2.02(m, 2H), 0.88(t, 6H, J=7.5Hz);

3-(2,4-Dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine mass spectrum (m/e): 459(M+1); ^{1}H-NMR(CDCl3): 6.79(s, 1H), 5.33(m, 1H), 2.57(s, 3H), 2.55(s, 3H), 1.87(m, 4H), 0.90(t, 6H, J=7.5Hz); and

3-(4-Bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine mass spectrum (m/e): 380(M+1); ^{1}H-NMR(CDCl3): 9.01(s, 1H), 6.77(s, 1H), 3.35(m, 1H), 2.55(s, 3H), 2.54(s, 3H), 1.87(m, 4H), 0.91(t, 6H, J=7.5Hz).

Example 193.

Preparation of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



100 mg (0.22 mmol) of 3-(2,4-Dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.22 mmol), 96 mg of morpholine (1.1 mmol) and 215 mg of Cs2CO3(0.66 mmol) are put in a 4 ml vial with dry THF, and the vial is

capped with a Teflon cap. The vial is heated at 120°C for overnight. The reaction mixture is applied onto a silica-gel chromatography column (Hexane :AcOEt :2 M NH3 in MeOH = 9:3:1) to give 72.7 mg of the title compound. Yield 71%. mass spectrum (m/e): 465(M+1); ^{1}H-NMR(CDCl3): 6.73(s, 1H), 3.87(t, 4H, J=5.1Hz), 3.58(t, 4H, J=5.1Hz), 3.35(m, 1H), 2.57(s, 3H), 2.53(s, 3H), 1.86(m, 4H), 0.90(t, 6H, J=7.5Hz).

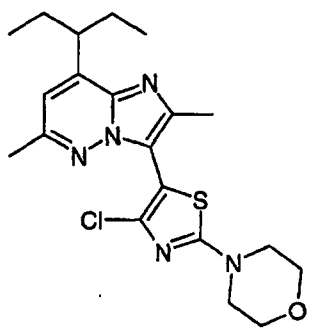
The following compounds are prepared essentially as described in Example 193. Examples 194-197 use 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.22 mmol) and the named amine. Example 198. uses 7-bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and the named amine:

Ex	Name	Amine	^{1}H NMR ($CDCl_3$): δ	MS (found) (M+1)
194	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-methyl-amine	Methyl-amine	6.75 (s, 1H), 5.85 (s, NH), 3.37 (m, 1H), 3.07 (d, J = 5.3 Hz, 3H), 2.59 (s, 3H), 2.55 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.2 Hz, 6H).	409
195	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethylamine	Dimethyl-amine	6.72 (s, 1H), 3.36 (m, 1H), 3.19 (s, 6H), 2.57 (s, 3H), 2.52 (s, 3H), 1.85 (m, 4H), 0.90 (t, 6H, J=7.3Hz)	423
196	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-(2-methoxy-ethyl)-methylamine	N-2-methoxy-ethyl-methyl-amine	6.71 (s, 1H), 3.76 (m, 2H), 3.71 (m, 2H), 3.42 (s, 3H), 3.35 (s, 1H), 3.21 (s, 3H), 2.57(s, 3H), 2.53 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H).	467

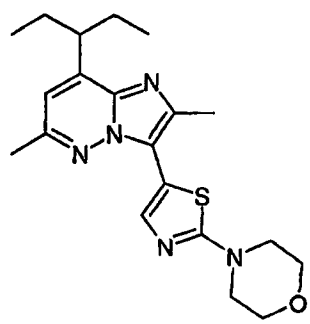
197	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-methyl-i-propyl-amine	N-methyl-i-propyl-amine	6.72 (s, 1H), 4.43 (m, 1H), 3.36 (m, 1H), 3.0 (s, 3H), 2.57 (s, 3H), 2.54 (s, 3H), 1.86 (m, 4H), 1.31 (s, 3H), 1.29 (s, 3H), 0.90 (t, J = 7.4 Hz, 6H).	451
198	N-{5-[7-bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-bromo-thiazol-2-yl}-morpholine	Morpholine	3.87 (t, J = 4.5 Hz, 4H), 3.58 (t, J = 7.8 Hz, 4H), 3.43 (m, 1H), 2.71(s, 3H), 2.50 (s, 3H), 2.38 (m, 2H), 2.01 (m, 2H), 0.88 (t, J = 7.5 Hz, 6H).	544

Example 199 and 200.

Preparation of N-{4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine and N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine.



199.



200.

Method A

40 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and 25 mg of CuCl (0.25 mmol) are put in a 4 ml vial with 2 ml of dry DMF and capped with a Teflon cap. The vial is heated at 120°C overnight. The reaction mixture is filtered, washed with CH2Cl2 and the filtrate is concentrated. The crude product mixture is applied onto a silica-gel chromatography column (Hexane : AcOEt = 2:1 and Hexane : AcOEt = 8:1) to give two products:

4.2 mg of N-{4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine (12%), and

7.2 mg of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine (22%).

N-{4-Chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine mass spectrum (m/e): 420(M+1); ^{1}H-NMR(CDCl3): 6.73(s, 1H), 3.88(t, 4H, J=5.0 Hz), 3.57(t, 4H, J=5.0Hz), 3.35(m, 1H), 2.57(s, 3H), 2.52(s, 3H), 1.85(m, 4H), 0.90(t, 6H, J=7.5Hz.

N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine mass spectrum (m/e): 386(M+1); ^{1}H-NMR(CDCl3): 7.75(s, 1H), 6.70(s, 1H), 3.91(t, 4H, J=5.0Hz), 3.61(t, 4H, J=5.0Hz), 3.34(m, 1H), 2.67(s, 3H), 2.61(s, 3H), 1.85(m, 4H), 0.88(t, 6H, J=7.5Hz).

Method B N-{4-Chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine.

A 20L reactor flask under nitrogen is charged with 2900 ml of dry and degassed DMF then with 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[1,2-b]pyridazine (287 g, 0.836 mol), 2-morpholino-4-chlorothiazole (205.4 g, 1.01 mol, 1.2 equv.), $Pd(OAc)_2$ (3.74 g, 7.91 mmol, 0.01 equiv.), triphenylphosphine (8.77g, 33.1 mmol, 0.04 equiv.), Copper iodide (8 g, 41.59 mmol, 0.05 equiv.) and cesium carbonate (544.9 g, 1.65 mol). The reaction mixture is heated at 120°C. After 16 h at 120°C, 1.87 g of $Pd(OAc)_2$ and 4.38 g of triphenylphosphine more is added. After 1 h, the mixture is cooled, quenched with NH_4Cl solution (4300 mL) and extracted with MTBE (2900 mL), the aqueous phase is extracted twice more with 2000 ml of MTBE. The organic phases are washed with sat NaCl aq (2000 mL), then treated with charcoal 72 g in flask bottle and filtered on Celite®. The filtrate is concentrated under vacuum to afford 373.8 g (79.3%) of the title compound which is 81.4%-area HPLC analysis the rest being solvent and with no detectable Example 200 by-product.

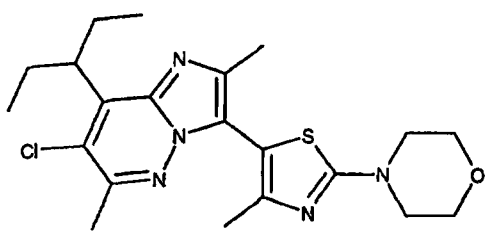
The following title compounds are prepared essentially as described in Examples 199 and 200 Method A:

Example #	Name	Starting material	^{1}H NMR ($CDCl_3$): δ	MS (found) (M+1)
201	N-{4-Chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethylamine	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethylamine	6.72 (s, 1H), 3.36 (m, 1H), 3.19 (s, 6H), 2.57 (s, 3H), 2.51 (s, 3H), 1.84 (m, 4H), 0.90 (t, J = 7.5 Hz, 6H).	378
202	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethyl-amine	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethylamine	7.74 (s, 1H), 6.67 (s, 1H), 3.35 (m, 1H), 2.23 (s, 6H), 2.67(s, 3H), 2.61 (s, 3H), 1.84 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H).	344
203	N-{4-Chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-(2-methoxy-ethyl)-methylamine	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-(2-methoxy-ethyl)-methylamine	6.71 (s, 1H), 3.76 (t, J = 5.3 Hz, 2H), 3.71 (t, J = 5.1 Hz, 2H), 3.42 (s, 3H), 3.36 (m, 1H), 3.20 (s, 3H), 2.58 (s, 3H), 2.52 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.1 Hz, 6H).	423
204	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-(2-methoxy-ethyl)-	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-(2-methoxy-ethyl)-	7.72 (s, 1H), 6.68 (s, 1H), 3.80 (t, J = 5.7 Hz, 2H), 3.72 (t, J = 5.7 Hz, 2H), 3.42 (s, 3H), 3.35 (m, 1H), 3.26 (s, 3H), 2.67 (s, 3H), 2.61 (s, 3H), 1.84	388

	methylamine	methylamine	(m, 4H), 0.88 (t, J = 7.7 Hz, 6H).	
205	N-{4-Chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-methyl-i-propyl-amine	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-methyl-i-propyl-amine	6.71 (s, 1H), 4.48 (m, J = 7.4, 13.2 Hz, 1H), 3.34 (m, J = 7.6, 14.4 Hz, 1H), 3.04 (s, 3H), 2.76 (s, 3H), 2.61 (s, 3H), 1.85 (m, 4H), 1.31 (d, J = 7.1 Hz, 6H), 0.88 (t, J = 7.3 Hz, 6H).	407
206	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-methyl-isopropyl-amine	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-methyl-i-propyl-amine	7.72 (s, 1H), 6.67 (s, 1H), 4.48 (m, 1H), 3.33 (m, 1H), 3.03 (s, 3H), 2.66 (s, 3H), 2.60 (s, 3H), 1.84 (m, 4H), 1.31 (d, J = 6.8, 6H), 0.88 (t, J = 7.2 Hz, 6H).	371

Example 207.

Preparation of N-{5-[7-chloro-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine.

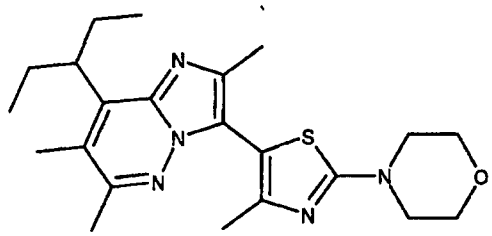


50 mg of N-{5-[7-Bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine (0.1 mmol) is dissolved in 2.0 ml of

dry DMF and 31 mg of CuCl (0.3 mmol) is added. The vial is capped with a Teflon® lined cap and heated at 120°C for overnight. The reaction mixture is applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1) to give 39.2 mg of the title compound. Yield 87%. mass spectrum (m/e): 435(M+1). 3.88 (t, J = 4.8 Hz, 4H), 3.57 (t, J = 5.1 Hz, 4H), 2.64(s, 3H), 2.44 (s, 3H), 2.18 (s, 3H), 2.00 (m, 4H), 0.88 (t, J = 7.4 Hz, 6H).

Example 208.

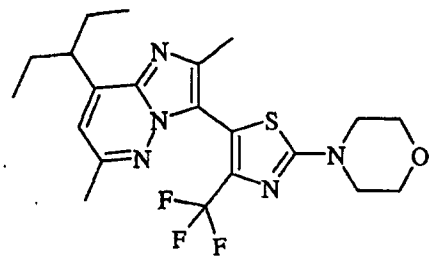
Preparation of N-{5-[7-bromo-8-(1-ethyl-propyl)-2,6,7-trimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine.



50 mg of N-{5-[7-Bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine (0.1 mmol) is dissolved in 4 ml of Et2O and cooled to –78°C. 0.09 ml of n-BuLi 1.6M in hexane (0.15 mmol) is added at –78°C and stirred at –78°C for 20 min. 43 mg of iodomethane (0.3 mmol) is added to the mixture and stirred at –78°C and allowed to come to room temperature overnight. The reaction is quenched with sat. NH4Cl and extracted with Et2O. The separated organic layer is dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane :AcOEt=3:1) to give 29.6 mg of the title compound. Yield 69%. mass spectrum (m/e): 414(M+1). ^{1}H NMR ($CDCl_3$): δ 3.87 (t, J = 4.6 Hz, 4H), 3.56 (t, J = 4.6 Hz, 4H), 3.35 (m, 1H), 2.54 (s, 3H), 2.43 (s, 3H), 2.35 (s, 3H), 2.20 (s, 3H), 2.01 (m, 4H), 0.88 (m, 6H).

Example 209.

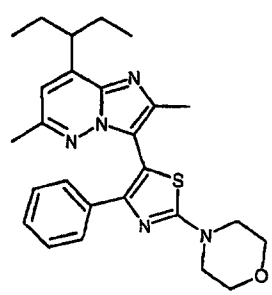
Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-trifluoromethyl-thiazol-2-yl}-morpholine.



170 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.37 mmol) and 100 mg of sodium trifluoroacetate (0.74 mmol) are dissolved in 3 ml of DMF/toluene = 2/1. N2 gas is bubbled into the mixture for 20 min and 141 mg of CuI (0.74 mmol) is added. The vial is sealed and heated in the microwave at 210°C for 30 min. The reaction mixture is applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1 and CH3CN : CH2Cl2 : Hexane = 5 : 45 : 50) to give 64.3 mg of the title compound. Yield 38%. mass spectrum (m/e): 454(M+1). ^{1}H NMR ($CDCl_3$): δ 6.72 (s, 1H), 3.88 (m, 4H), 3.60 (m, 4H), 3.32 (m, 1H), 2.54 (s, 3H), 2.47 (s, 3H), 1.85 (m, 4H), 0.89 (t, J = 7.0 Hz, 6H).

Example 210.

Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-phenyl-thiazol-2-yl}-morpholine.

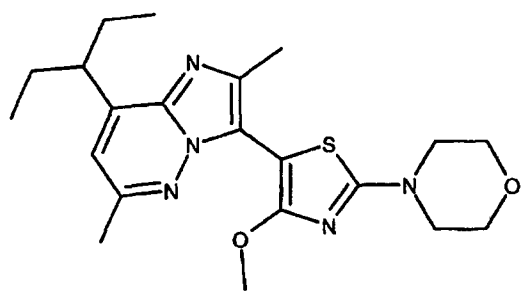


50 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.11 mmol), 40 mg of phenylboronic acid (0.33 mmol) and 0.27 ml of 2 M Na2CO3aq.(0.55 mmol) are put in 2.5 ml of DME / water / EtOH = 7 / 3 / 1. N2 gas is bubbled in the mixture for 20 min and 20 mg of Pd(PPh3)4

(0.017 mmol) is added. The vial is sealed and heated at 160°C for 30 min in Microwave. The reaction mixture are added CH2Cl2 and water and the organic layer is separated, washed with brine, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane : AcOEt = 10:1) to give 27 mg of the title compound. Yield 54% mass spectrum (m/e): 462(M+1). δ 8.29(m, 1H), 7.60(m, 2H), 7.44(m, 1H), 7.22(m, 1H), 6.70 (s, 1H), 3.90 (t, J = 4.6 Hz, 4H), 3.64 (t, J = 5.0 Hz, 4H), 3.36 (m, 1H), 2.52 (s, 3H), 2.09 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.4 Hz, 6H).

Example 211.

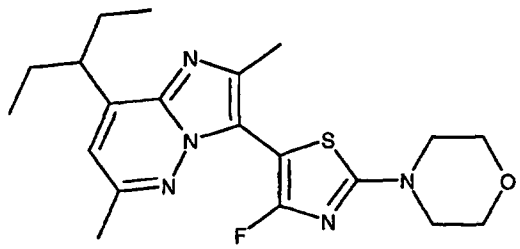
Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methoxy-thiazol-2-yl}-morpholine.



100 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.22 mmol), 24 mg of sodium methoxide (0.44 mmol) and 21 mg of CuI (0.11 mmol) are put into 4 ml vial with MeOH 3 ml and capped with a Teflon® lined cap. The reaction vial is heated at 130°C overnight. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane : THF = 10 : 1) to give 32.8 mg of the title compound. Yield 36%. Mass spectrum (m/e): 416(M+1). ^{1}H NMR ($CDCl_3$): δ 6.64 (s, 1H), 3.96 (s, 3H), 3.86 (t, J = 4.7 Hz, 4H), 3.53 (m, 4H), 3.34 (m, 1H), 2.82 (s, 3H), 2.48 (s, 3H), 1.82 (m, 4H), 0.85 (t, J = 7.4 Hz, 6H).

Example 212.

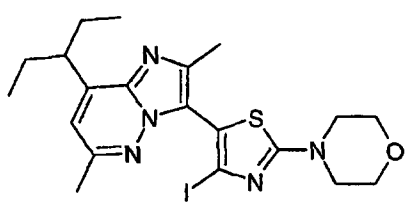
Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-fluoro-thiazol-2-yl}-morpholine.



50 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.11 mmol) is dissolved in 4 ml of diethylether and cooled to –78°C and 0.1 ml of n-BuLi 1.6M in hexane (0.16 mmol) is added at –78°C and stirred at –78°C for 20 min. 104 mg of N-fluorobenzene sulfonimide (0.33 mmol) in 2 ml of toluene is added at –78°C and stirred at room temperature for 1h. sat. NH4Cl is added, and the mixture is extracted with Et2O, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1) to give 4.1 mg of the title compound. Yield 10%. Mass spectrum (m/e): 404 (M+1). 6.71 (s, 1H), 3.87 (t, J = 4.6 Hz, 4H), 3.55 (t, J = 5.0 Hz, 4H), 3.34 (m, 1H), 2.58 (s, 3H), 2.54 (s, 3H), 1.84 (m, 4H), 0.88 (t, J = 7.4 Hz, 6H).

Example 213.

Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-iodo-thiazol-2-yl}-morpholine.

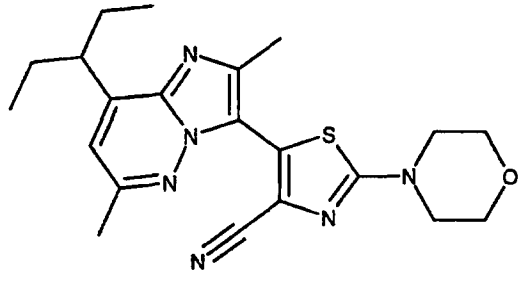


50 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.11 mmol), 30 mg of CF_3CO_2Na (0.22 mmol) and 42 mg of CuI (0.22 mmol) are put into 4 ml vial with DMF / toluene = 2:1. The vial is capped with a Teflon cap and heated at 150°C overnight. The reaction mixture is applied onto a silica-gel chromatography column (Hexane :AcOEt = 5 : 1) to give 54 mg of the

title compound. 96%. Mass spectrum (m/e): 512 (M+1). ^{1}H NMR ($CDCl_3$): δ 6.71 (s, 1H), 3.87 (t, J = 5.4 Hz, 4H), 3.58 (t, J = 5.4 Hz, 4H), 3.36 (m, 1H), 2.57 (s, 3H), 2.53 (s, 3H), 1.85 (m, 4H), 0.91 (t, J = 5.4 Hz, 6H).

Example 214.

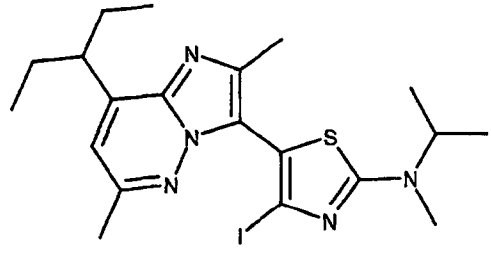
Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-2-morpholin-4-yl-thiazole-4-carbonitrile



50 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.11 mmol), and 30 mg of CuCN (0.33 mmol) are put into 4 ml vial with 2 ml of DMF and the vial is capped with a Teflon cap. The vial is heated at 150°C overnight. The reaction mixture is applied onto a silica-gel chromatography column (Hexane:AcOEt=5:1) to give 12.3 mg of the title compound. Yield 28%. Mass spectrum (m/e): 411(M+1). 6.77 (s, 1H), 3.89 (t, J = 4.8 Hz, 4H), 3.61 (t, J = 5.0 Hz, 4H), 3.32 (m, 1H), 2.62 (s, 3H), 2.59 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.4 Hz, 6H).

Example 215.

Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-iodo-thiazol-2-yl}-N-isopropyl-methylamine.

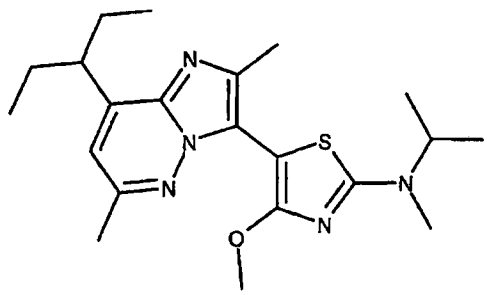


The title compound is prepared essentially as described in Example 213, employing N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-

bromo-thiazol-2-yl}-N-isopropyl-methylamine to give 17.9 mg. Yield 22%: mass spectrum (m/e):498 (M+1). ^{1}H NMR ($CDCl_3$): δ 6.71 (s, 1H), 4.41 (m, 1H), 3.35 (m, 1H), 2.97 (s, 3H), 2.57 (s, 3H), 2.53 (s, 3H), 1.84 (m, 4H), 1.29 (d, J = 5.8 Hz, 6H), 0.90 (t, J = 7.2 Hz, 6H).

Example 216.

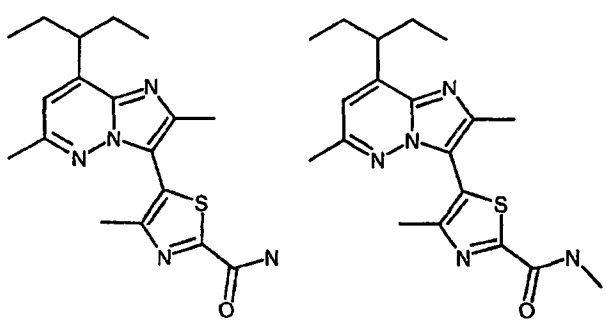
Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methoxy-thiazol-2-yl}-N-isopropyl-methylamine.



The title compound is prepared essentially as described in Example 211, employing N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-bromo-thiazol-2-yl}-N-isopropyl-methylamine to give 52.7. Yield 36%: mass spectrum (m/e):402(M+1). ^{1}H NMR ($CDCl_3$): δ 6.63 (s, 1H), 4.44 (m, 1H), 3.96 (s, 3H), 3.35 (m, 1H), 2.97 (s, 3H), 2.57 (s, 3H), 2.50 (s, 3H), 1.83 (m, 4H), 1.29 (d, J = 6.7 Hz, 6H), 0.88 (t, J = 8 Hz, 6H).

Example 217 and 218.

Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid amide and 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid N-methylamide.



217. 218.

180 mg of 8-(1-Ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.46 mmol) and 124 mg of copper(I) cyanide are put into 4 ml vial with 2 ml of dry DMF. The vial is closed with a Teflon can and heated at 130°C overnight. The crude reaction mixture is applied onto a silica-gel chromatography column (Hexane : AcOEt = 1:1 →1:3) to give

52.1 mg of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid amide (32%) and

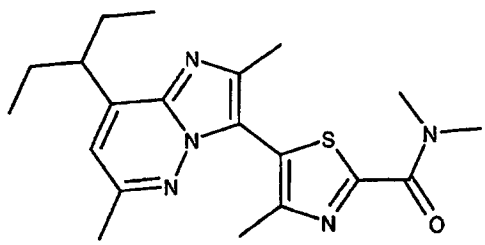
7.6 mg of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid methylamide.

5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid amide: mass spectrum (m/e): 358(M+1) ^{1}H NMR ($CDCl_3$): δ 7.21 (s, NH), 6.76 (s, 1H), 5.59 (s, NH), 3.34 (m, 1H), 2.55 (s, 3H), 2.50 (s, 3H), 2.42 (s, 3H), 1.87 (m, 4H), 0.91 (t, J = 7.2 Hz, 6H). and

5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid methylamide: mass spectrum (m/e): 372(M+1). ^{1}H NMR ($CDCl_3$): 8.77 (s, NH), 6.75 (s, 1H), 4.06 (s, 3H), 3.35 (m, 1H), 2.55 (s, 3H), 2.49 (s, 3H), 2.43 (s, 3H), 1.87 (m, 4H), 0.91 (t, J = 7.6 Hz, 6H).

Example 219.

Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid dimethylamide.

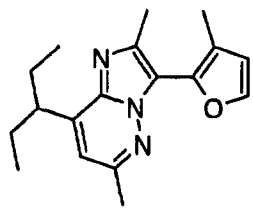


5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid amide (46 mg, 0.13 mmol) and 28 mg of sodium *tert*-Butoxide (0.30 mmol) are put into 4 ml of dry DMSO and stirred at room temperature for 5 min. 141 mg of iodomethane (1.0 mmol) is added and stirred at room temperature for 1 h.

Water is added, and the mixture is extracted with CH_2Cl_2, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane :AcOEt=3:1) to give 22.3 mg of the title compound. Yield 45%: mass spectrum (m/e):386(M+1). 6.75 (s, 1H), 3.70 (s, 3H), 3.35 (m, 1H), 3.21 (s, 3H), 2.55 (s, 3H), 2.50 (s, 3H), 2.41 (s, 3H), 1.86 (m, 4H), 0.91 (t, J = 7.4 Hz, 6H).

Example 220.

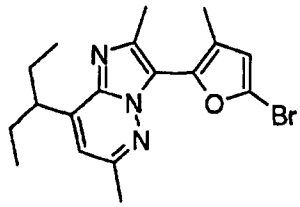
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-furan-2-yl)-imidazo[*1,2-b*]pyridazine.



A THF solution (5 mL) of 3-methylfuran (Acros, 232 mg, 2.83 mmol) is cooled to -78 °C under N_2 then treated with nBuLi (1.6 M in hexane, 1.8 mL, 2.9 mmol). After addition of the nBuLi, the solution is warmed to 0 °C for 15 minutes, then to room temperature for an additional 5 minutes. The reaction mixture is then cooled to -78 °C and treated with $ZnCl_2$ (Aldrich, 0.5 M in THF, 5.8 mL, 2.9 mmol). The resulting mixture is warmed to room temperature and treated with 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (400 mg, 1.17 mmol) and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 95 mg, 0.12 mmol). The mixture is heated to 60 °C for 4 hours, then poured into 1 N HCl (60 mL) and extracted with ethyl acetate (2x60 mL). The combined organic extracts are washed with aq. brine, dried over Na_2SO_4, filtered, and concentrated. The crude residue is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title compound as an oil pyridazine (149 mg, 43% yield). ES-MS (m/z): calc'd for $C_{18}H_{23}N_3O$: 297.2; found 298.5 (M+H); ^{1}H NMR (400 mHz, $CDCl_3$): δ 7.59 (d, J = 1.8 Hz, 1H), 6.71 (s, 1H), 6.47 (d, J = 1.8 Hz, 1H), 3.36 (m, 1H), 2.55 (s, 3H), 2.50 (s, 3H), 2.10 (s, 3H), 1.92-1.79 (m, 4H), 0.90 (t, J = 7.5 Hz, 6H).

Example 221.

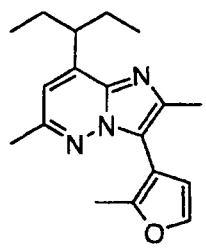
Preparation of 3-(5-bromo-3-methyl-furan-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A CH_2Cl_2 solution (4 mL) of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-furan-2-yl)-imidazo[*1,2-b*]pyridazine (32.4 mg, 0.11 mmol) is cooled to 0 °C under a $CaSO_4$ drying tube and treated with NBS (20.1 mg, 0.11 mmol). After 15 minutes at 0 °C, the mixture is warmed to room temperature. After an additional 10 minutes, the reaction mixture is poured into H_2O (25 mL) and extracted into CH_2Cl_2 (2x25 mL). The combined organic extracts are washed with aq. brine, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 10% ethyl acetate in hexane) to elute the title compound (26.3 mg, 64% yield) as a solid. ES-MS (m/z): calc'd for $C_{18}H_{22}BrN_3O$: 375.1; found 376.2 (M+H); ^1H NMR (400 mHz, $CDCl_3$): δ 6.72 (s, 1H), 6.40 (s, 1H), 3.34 (m, 1H), 2.56 (s, 3H), 2.49 (s, 3H), 2.07 (s, 3H), 1.93-1.77 (m, 4H), 0.89 (t, J = 7.5 Hz, 6H).

Example 222.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-furan-3-yl)-imidazo[*1,2-b*]pyridazine.



A. 3-Bromo-2-methyl furan.

A THF solution (10 mL) of 2,3-dibromofuran (Lancaster, 5.54 gm, 24.5 mmol) under N_2 is treated with $PdCl_2(PPh_3)_2$ (860 mg, 1.2 mmol) and stirred for 10 minutes at

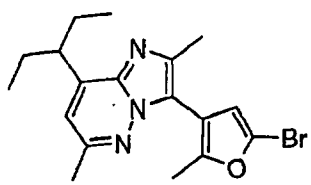
room temperature. The solution is then treated with CH_3ZnCl (Aldrich, 2.0 M in THF, 15 mL, 30 mmol). The resulting mixture is stirred at room temperature overnight then poured into 1 N HCl and extracted into diethyl ether. The organic extract is washed with sat. NaCl, dried over Na_2SO_4, and filtered. The filtrate is then distilled and the product is collected at 120-125 °C to give the title compound as a colorless oil (1.71 gm, 43% yield). ^1H NMR (400 mHz, $CDCl_3$): δ 7.25 (d, J = 1.8 Hz, 1H), 6.34 (d, J = 1.8 Hz, 1H), 2.28 (s, 3H).

B. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(2-methyl-furan-3-yl)-imidazo[*1,2-b*]pyridazine.

A THF solution (10 mL) of 3-bromo-2-methyl furan (prepared as described above) (1.06 gm, 6.58 mmol) is cooled to -78 °C under N_2 then treated with nBuLi (1.6 M in hexane, 4.1 mL, 6.6 mmol). After 10 minutes at -78 °C, the mixture is treated with $ZnCl_2$ (Aldrich, 0.5 M in THF, 13.2 mL, 6.6 mmol). The resulting mixture is warmed to room temperature then treated with 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.13 gm, 3.29 mmol) and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 257 mg, 0.31 mmol). The mixture is heated to 60 °C for 4 hours, then poured into sat. NH_4Cl (50 mL) and extracted with diethyl ether (2x50 mL). The combined organic extracts are washed with sat. NaCl, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title product (685 mg, 70% yield) as an oil. ES-MS (m/z): calc'd for $C_{18}H_{23}N_3O$: 297.2; found 298.2 (M+H); ^1H NMR (400 mHz, $CDCl_3$): δ 7.45 (d, J = 2.0 Hz, 1H), 6.63 (s, 1H), 6.60 (d, J = 2.0 Hz, 1H), 3.35-3.31 (m, 1H), 2.51 (s, 3H), 2.44 (s, 3H), 2.30 (s, 3H), 1.88-1.75 (m, 4H), 0.86 (t, J = 7.5 Hz, 6H).

Example 223.

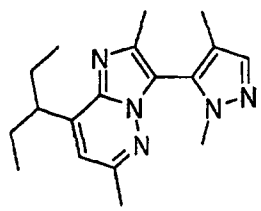
Preparation of 3-(5-bromo-2-methyl-furan-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A CH_2Cl_2 solution (2 mL) of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-furan-3-yl)-imidazo[*1,2-b*]pyridazine (42.3 mg, 0.14 mmol) under a $CaSO_4$ drying tube is treated with N-bromosuccinimide (27.6 mg, 0.16 mg). After 30 minutes the reaction mixture is poured into H_2O (25 mL) and extracted into CH_2Cl_2 (2x25 mL). The combined organic extracts are washed with sat. NaCl, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 12% ethyl acetate in hexane) to elute the title product (36.9 mg, 70% yield) as a white solid. ES-MS (m/z): calc'd for $C_{18}H_{22}BrN_3O$: 375.1; found 376.3 (M+H); ^{1}H NMR (400 mHz, $CDCl_3$): δ 6.67 (s, 1H), 6.50 (s, 1H), 3.33 (m, 1H), 2.53 (s, 3H), 2.44 (s, 3H), 2.29 (s, 3H), 1.90-1.73 (m, 4H), 0.86 (t, J = 7.3 Hz, 6H).

Example 224.

Preparation of 3-(2,4-dimethyl-2*H*-pyrazol-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

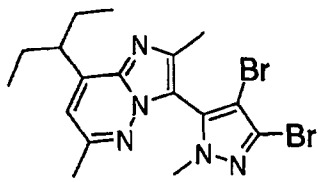


n-BuLi (1.3 ml, 2.09 mmol) is stirred in THF (4 ml), under N_2, and cooled to –72°C. 1,4-dimethyl-*1H*-pyrazole (170 mg, 2.04 mmol, in THF, 1 ml) is added slowly, stirred for 5 min. then allowed to warm to ambient temp. and stirred for 45 min. The mixture is cooled to –72°C and a zinc chloride solution (4.3 ml, 2.14 mmol, 0.5 M in toluene) added, warmed to ambient temp. and treated with 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 40 mg, 0.05 mmol). The mixture is heated to 65°C overnight, cooled to ambient temp., added to water and extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 50 % ethyl acetate in hexane) to elute the product. The title compound is obtained (0.7% yield). ES-MS (m/z): calc'd for $C_{18}H_{25}N_5$: 311.4; found 312.2 $(M+H)^+$. ^{1}H NMR (400 mHz, $CDCl_3$):

δ 7.51 (s, 1H), 6.75 (s, 1H), 3.72 (s, 3H), 3.33 (m, 1H), 2.53 (s, 3H), 2.43 (s, 3H), 2.00 (s, 3H), 1.87 (m, 4H), 0.92 (m, 6H)..

Example 225.

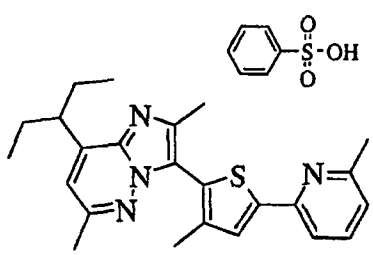
Preparation of 3-(4,5-dibromo-2-methyl-2*H*-pyrazol-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (300 mg, 1.4 mmol), 3,4,5-tribromo-1-methyl-^1H-pyrazole (700 mg, 2.1 mmol) and cesium carbonate (900 mg, 2.8 mmol) are stirred in DMF (5 ml) and degassed by bubbling a stream of nitrogen through the mixture. $PdCl_2(PPh_3)_2$ (14 mg) is added and the mixture heated to 130°C overnight. The mixture is added to water and extracted twice with EtOAc. The combined organic extracts are washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title product (204 mg, 32% yield). ES-MS (m/z): calc'd for $C_{17}H_{21}Br_2N_5$: 455.2; found 455.9 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 6.75 (s, 1H), 3.72 (s, 3H), 3.33 (m, 1H), 2.51 (s, 3H), 2.45 (s, 3H), 1.84 (m, 4H), 0.88 (t, 6H).

Example 226.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine benzenesulfonic acid.

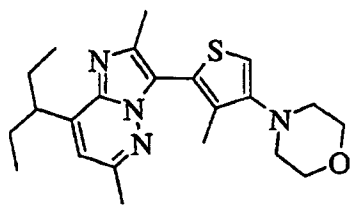


To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine (0.23 g, 0.57 mmol) and MeOH (1

mL) is added a solution of benzenesulfonic acid (0.096 g, 0.57 mmol) and MeOH (1 mL). The solution is concentrated to furnish the title compound (0.32 g, 0.57 mmol, >99%). ^{1}H NMR ($CDCl_3$) δ 0.79 (t, J = 7.0 Hz, 6H), 1.59-1.82 (m, 4H), 2.06 (s, 3H), 2.61 (s, 6H), 2.88 (s, 3H), 3.22-3.32 (m, 1H), 6.79 (bs, 2H), 7.25 (s, 1H), 7.33-7.42 (m, 3H), 7.49 (d, J = 7.9 Hz, 1H), 7.80 (d, J = 7.4 Hz, 2H), 7.92 (dd, J = 7.4, 1.6 Hz, 1H) 8.23 (s, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.2; found: 405.4.

Example 227.

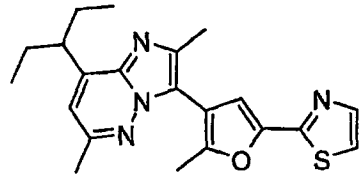
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-4-morpholin-4-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30g, 0.76 mmol), morpholine (0.10 mL, 1.15 mmol), $Pd_2(dba)_3$ (0.035 g, 0.038 mmol), and 2-dicyclohexylphosphino-biphenyl-2'-(N,N-dimethyl-amino)biphenyl (0.018 g, 0.046 mmol) is added 1 M LiHMDS (1.9 mL, 1.91 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (15%-30% EtOAc gradient), dissolved in Et_2O (20 mL) and extracted with 1 M HCl (2 x 30 mL). The aqueous layer is washed with Et_2O (20 mL), made basic with 5 M NaOH (15 mL), extracted with EtOAc (2 x 20 mL), the combined organic layers washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.047 g, 0.12 mmol, 16%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.01 (s, 3H), 2.45 (s, 3H), 2.49 (s, 3H), 2.99-3.05 (m, 4H), 3.28-3.37 (m, 1H), 3.84-3.88 (m, 4H), 6.65 (s, 1H), 6.71 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{30}N_4OS$ $(M+H)^+$: 399.2; found: 399.2.

Example 228.

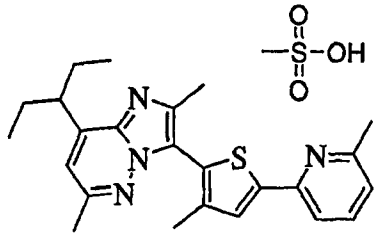
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-5-thiazol-2-yl-furan-3-yl)-imidazo[*1,2-b*]pyridazine.



A THF solution (5 mL) of 2-bromothiazole (Aldrich, freshly distilled, 75.0 μL, 0.84 mmol) is cooled to -78 °C under N_2 then treated with nBuLi (1.6 M in hexane, 0.52 mL, 0.83 mmol). After 15 minutes at -78 °C, the mixture is treated with $ZnCl_2$ (Aldrich, 0.5 M in THF, 1.8 mL, 0.90 mmol). The resulting mixture is warmed to room temperature then treated with a THF slurry (1 mL) containing 3-(5-bromo-2-methyl-furan-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (60.1 mg, 0.16 mmol) and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 22 mg, 0.027 mmol). The mixture is heated overnight at 60 °C, then poured into sat'd NH_4Cl and extracted with diethyl ether. The organic extract is washed with aq. brine, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title compound (45.8 mg, 75% yield) as an oil. ES-MS (m/z): calc'd for $C_{21}H_{24}N_4OS$: 380.17; found 381.1 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 7.83 (d, J = 3.5 Hz, 1H), 7.29 (d, J = 3.1 Hz, 1H), 7.20 (s, 1H), 6.68 (br s, 1H), 3.35 (br s, 1H), 2.53 (s, 3H), 2.49 (s, 3H), 2.40 (s, 3H), 1.90-1.76 (m, 4H), 0.88 (t, J = 7.5 Hz, 6H).

Example 229.

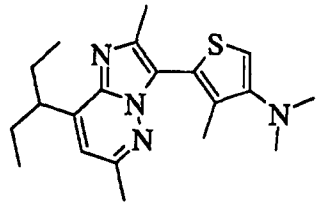
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine; compound with methanesulfonic acid.



To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine (0.55 g, 1.36 mmol) and MeOH (6 mL) is added methane sulfonic acid (0.088 mL, 1.36 mmol). After one hour the solution is concentrated and the solution is treated with Darco-60® for 1 hour, filtered and concentrated to furnish the title compound (0.68 g, 1.36 mmol, >99%). ^{1}H NMR ($CDCl_3$: CD_3OD 95:5) δ 0.85 (t, J = 7.4 Hz, 6H), 1.67-1.91 (m, 4H), 1.96 (s, 3H), 1.97 (s, 3H), 2.20 (s, 3H), 2.61 (s, 3H), 2.90 (s, 3H), 3.17-3.29 (m, 1H), 7.33 (s, 1H), 7.64 (d, J = 7.4 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 8.18 (s, 1H), 8.34 (t, J = 7.9 Hz, 1H), 9.95 (bs, 1H). LC/MS (m/z): calcd. for $C_{25}H_{32}N_4O_2S_2$ $(M+H)^+$: 405.6; found: 405.6.

Example 230.

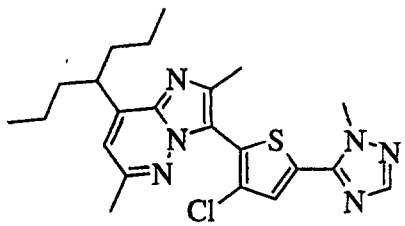
Preparation of {5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-3-yl}-dimethyl-amine.



To a –78 °C solution of dimethyl-(4-methyl-thiophen-3-yl)-amine (0.43 g, 3.06 mmol) and THF (5 mL) is added 1.6 M *n*-BuLi (1.91 mL, 3.06 mmol). The solution is stirred for 1 hour, then 0.5 M $ZnCl_2$ (6.1 mL, 3.06 mmol) is added and the solution warmed to ambient temperature. After 30 minutes 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.70 g, 2.04 mmol) and $PdCl_2$(dppf) (0.075 g, 0.10 mmol) is added and the solution heated at 65 °C overnight. The solution is diluted with EtOAc (35 mL), washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (15% -30% EtOAc gradient) furnish the title compound (0.13 g, 0.36 mmol, 18%). ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-1.90 (m, 4H), 2.03 (s, 3H), 2.45 (s, 3H), 2.50 (s, 3H), 2.77 (s, 6H), 3.28-3.37 (m, 1H), 6.63 (s, 1H), 6.65 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{28}N_4S$ $(M+H)^+$: 357.2; found: 357.2

Example 231.

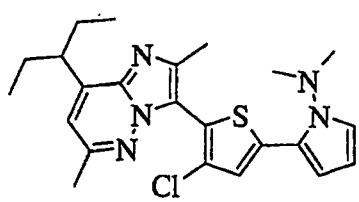
Preparation of 3-[3-chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine.



A slurry of 2,6-dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine (below) (0.30 g, 1.22 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-[1,2,4]triazole (below) (0.41 g, 1.47 mmol), KOAc (0.60 g, 6.11 mmol), TBABr (0.39 g, 1.22 mmol), and NMP (3 mL) is de-gassed with N_2 for 30 minutes. $Pd(OAc)_2$ (0.014 g, 0.061 mmol) and TDBPP (0.040 g, 0.061 mmol) are added and the solution heated at 125 °C for 2.5 hours. The solution is diluted with EtOAc (50 mL), washed with water (3 x 50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (20%-40% EtOAc gradient) furnish the title compound (0.30 g, 0.68 mmol, 56%). ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.4 Hz, 6H), 1.14-1.39 (m, 4H), 1.76 (q, J = 16.3, 7.7 Hz, 4H), 2.51 (s, 3H), 2.52 (s, 3H), 3.41-3.50 (m, 1H), 4.15 (s, 3H), 6.73 (s, 1H), 7.48 (s, 1H), 7.90 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}ClN_6S$ $(M+H)^+$: 443.2; found: 443.3.

Example 232.

Preparation of (2-{4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophen-2-yl}-pyrrol-1-yl)-dimethyl-amine.

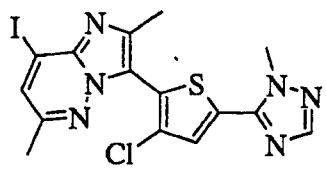


Using a procedure analogous to Example 27, 1-(dimethylamino)-pyrrole (0.20 mL, 1.65 mmol), THF (4 mL), 1.6 M *n*-BuLi (1.10 mL, 1.73 mmol), 0.5 M $ZnCl_2$ (3.46 mL, 1.73 mmol), 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.34 g, 0.82 mmol) and $PdCl_2$(dppf) (0.030 g, 0.041 mmol),

furnish the title compound (0.17 g, 0.38 mmol, 46%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.52 (s, 6H), 2.84 (s, 6H), 3.28-3.39 (m, 1H), 6.21 (dd, J = 4.1, 3.2 Hz, 1H), 6.38 (dd, J = 4.1, 1.8 Hz, 1H), 6.68 (s, 1H), 7.02 (dd, J = 3.2, 1.8 Hz, 1H), 7.29 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{28}ClN_5S$ $(M+H)^+$: 442.2; found: 442.3.

Example 233.

Preparation of 3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 4-Chloro-thiophene-2-carbonitrile.

A 22-L reaction flask is equipped with a cooling bath, air stirrer, gas addition tube, and thermometer probe. The flask is purged with nitrogen, then charged $AlCl_3$ (1025 g, 7.69 moles) and $CHCl_3$(6.6 L, 16.5 vol.). After cooling the mixture to 0-5 °C, it is charged with 2-thiophene carbonitrile (400 g, 3.66 moles) dropwise via an addition funnel over 10-15 minutes while maintaining the temperature at ≤ 10 °C. The mixture is charged with Cl_2 gas (300g, 4.23 moles, 1.16 EQ) subsurface at ≤ 10 °C over 1.25 hours. The progress of the reaction is monitored by GC, wherein the GC sampling method is quenching an aliquot of the reaction mixture into 6N HCl, extracting with EtOAc, drying over Na_2SO_4, filtering, and injecting the filtrate.

When the reaction is deemed complete by GC analysis [the reaction was deemed complete when the ratio of (sm : prod : dichloro) was approximately (1 : 5.8 : 1) by area % GC.], 6N HCl (8.0 L) is added dropwise via addition funnel over 1.5 hours, while maintaining the temperature at ≤ 20 °C [The HCl addition is extremely exothermic and evolves gas]. The reaction is transferred to a separatory funnel and the layers are separated. After extracting the aqueous layer with $CHCl_3$ (4.0 L), the chloroform layers are combined and washed with de-ionized H_2O (6.0L). The organic layer is dried over Na_2SO_4, filtered and concentrated under vacuum to give a pale yellow semi solid 575g, 109.3%). GC (60°C to 280°C temperature gradient) Area-% analysis shows ~68%

product (t_{ret} = 6.5 min) with major impurities being the unreacted starting material (t_{ret} = 5.1 min) and the dichlorinated product (t_{ret} = 7.4 min). GC Method: Column: DB1; $T_{injecyt}$ = 300 °C ; $T_{initial}$ = 60 °C, t = 2.0 min; T_{final} = 280 °C, rate = 18 °C/min.

B. 4-Chloro-2-thiophene carboxamide.

A 12-L reaction flask equipped with a cooling bath, air stirrer, and thermometer probe is charged with KOH (288.6 g, 5.143 moles) and De-ionized H_2O (6.04 L) to form a solution that exotherms to ~31 °C. After allowing the solution to cool to ~28.0 °C, th mixture is charged with 4-chloro-2-thiophene carbonitrile (671.3 g, 4.675 moles)[1] followed by EtOH (675 mL). A gradual exotherm occurs upon the addition of EtOH and continues over 1-1.5 hours to ~38 °C. The reaction is stirred at ambient temperature overnight.

The reaction mixture is filtered under vacuum, washed with de-ionized H_2O and dried to give crude product. The solids are dissolved in EtOAc (10.0 L) treated with Na_2SO_4 and Darco for 1-2 hours; then, filtered and washed with EtOAc. The filtrate is concentrated on the Büchi until solids began to precipitate out at 45 °C at which time the vacuum is released, and the temperature is increased to 60-65 °C to redissolve the solids. With stirring at 60 °C, heptane (3.5 L) is added slowly to precipitate solids. After stirring for 15-20 minutes at 60 °C, the mixture is cooled to 30-40 °C and filtered. The solids are washed with heptane (2 x 0.75 L), and dried to give the title compound (t_{ret} = 9.9 min) as a white solid (235.4 g, 31.2 % 96.4 area % by GC analysis). A second crop is obtained from the filtrate to give 67.8 g, 9.0 %; 94.5% area-% by GC analysis). The Overall yield is 303.2 g, 40.1 %.

C. 4-Chloro-N-dimethylaminomethylene-2-thiophene carboxamide.

A 5-L reaction flask equipped with a heating mantle, air stirrer, Dean-Stark apparatus, and thermometer probe is charged with 4-chloro-2-thiophene carboxamide. (300 g, 1.856 moles) and dimethylformamide dimethylacetal (872 mL) to form a slurry that endotherms 1-2 °C from 22-20 °C. The mixture is heated gradually to 96 °C while collecting the distillate (mostly MeOH). The heating mantle is removed, and the mixture is cooled to $\leq$ 25 °C. De-ionized H_2O (3.0 L) is added via an addition funnel and the

[1] A small amount of solids were undissolved at this point.

temperature is maintained at $\leq$ 35 °C. The reaction mixture is extracted with EtOAc (1 x 3.0 L, 1 x 1.5 L), then combined the organics are washed with de-ionized H_2O (1.5 L). The organic phase is dried over Na_2SO_4, filtered, and concentrated under vacuum to give crude product (400 g).

The crude product is dissolved in EtOAc (320 mL, 0.8 Vol) at 50-60 °C; then, heptane (1700 mL, 4.25 Vol) is added slowly while gradually increasing the temperature to 70 °C. A seed crystal (Lot: PP6-H00086-075-1) is added to the cloudy solution to initiate precipitation. The resulting mixture is stirred to room temperature overnight, then filtered and washed with heptane. The solids are dried to give the title compound (t_{ret} = 13.0 min) as a white solid (329.8 g, 82%; 98.2 % area-% by GC analysis).

D. 5-(4-Chloro-thiophen-2-yl)-1-methyl-^{1}H-[1,2,4]triazole.

A 3-L reaction flask equipped with a cooling bath, air stirrer, and thermometer probe is charged with 4-chloro-N-dimethylaminomethylene-2-thiophene carboxamide. (155 g, 0.715 moles) and HOAc (1500 mL) to form a solution. Using an ice-water cooling bath to maintain the temperature at $\leq$ 30 °C, methylhydrazine (33.2 g, 0.721 moles) is added dropwise via an addition funnel over 15-20 minutes to form a light yellow slurry. Gradually, the reaction is heated to 90 °C and held at 90 °C for 30 minutes. After analysis of the mixture by GC, the reaction is cooled to ~70 °C; then, concentrated to a thick oil/slurry. De-ionized H_2O (1.67 L) is slowly added to precipitate solids; then, the mixture is cooled to < 30 °C, filtered and washed with de-ionized H_2O (1.67 L). The wet solids (125.8 g) are re-dissolved in warm MTBE (1.64 L), dried over Na_2SO_4, filtered and concentrated to dryness giving the title compound as a pale yellow solid (85.8 g, 60.1% 91.9 % area % by GC).

E. 5-(5-Bromo-4-chloro-thiophen-2-yl)-1-methyl-^{1}H-[1,2,4]triazole.

A 3-L reaction flask equipped with a cooling bath, air stirrer, and thermometer probe is charged with 5-(4-Chloro-thiophen-2-yl)-1-methyl-^{1}H-[1,2,4]triazole (105.3 g, 0.527 moles), ACN (1053 mL) and HOAc (105 mL) to form a solution. NBS

(103.2 g, 0.580 moles) is added portion-wise over 30-60 minutes while maintaining the temperature at ≤ 31 °C. After stirring for 1 hour[2], GC analysis indicated reaction completion. The reaction mixture is poured into de-ionized H_2O (2.1 L, 20vol), stirred for 30 minutes, filtered, and washed with de-ionized H_2O (2 x 1 L). The product is dried in a vacuum oven at 45 °C overnight to give the title compound as a pale yellow solid (123.0 g, 83.8 %; 96.6 % area-% by GC).

F. 2,6-Dimethyl-imidazo[1,2-*b*]pyridazine.

A 3 neck 1L round bottom flask is charged with 6-methyl-pyridazin-3-ylamine (20 g, 0.18 moles), ethanol 2B (200 mL), and chloroacetone (23.7 g, 20.4 mL, 0.256 moles, 1.4 equiv). The reaction mixture is heated at 70 °C overnight. NaHCO3 (23.2 g, 0.276 moles, 1.5 equiv) is added portion wise. After most of bubbling subsides, the reaction is heated at 100 °C overnight. The solvents are removed in vacuo and the residue is taken up in dichloromethane and filtered through a filter paper. The solvent is again removed in vacuo. The residue is purified using silica gel chromatography with a hexanes:ethyl acetate gradient to obtain the title compound (15.5 g, 57%). ^{1}H-NMR (DMSO-d6), δ 2.34 (s, 3H), 2.47 (s, 3H), 7.03, (d, J = 10 Hz, 1H), 7.85 (d, J = 10 Hz, 1H), 7.91 (s, 1H) ppm. MS (APCI): 148 (M+1).

G. 3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

A solution of 2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.32 g, 2..17 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-^{1}*H*-[1,2,4]triazole (0.72 g, 2.61 mmol), Cs_2CO_3 (1.49 g, 4.57 mmol) and DMF (6 mL) is de-gassed for 15 minutes with N_2. $Pd(OAc)_2$ (0.024 g, 0.11 mmol) and PPh_3 (0.057 g, 0.22 mmol) are added and the solution is heated at 135°C for 4 hours. The solution is diluted with CH_2Cl_2 (50 mL), washed with sat. NH_4Cl (2 x 50 mL), water (50 mL), filtered and concentrated. The residue is purified by ISCO flash chromatography (30%-100% EtOAc gradient) furnish the title compound (0.29 g, 0.84 mmol, 39%). ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 3H), 2.50 (s, 3H), 4.10 (s, 3H), 6.92 (d, J = 9.2 Hz, 1H), 7.44 (s, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.85 (s, 1H). LC/MS (m/z): calcd. for $C_{15}H_{13}ClN_6S$ $(M+H)^+$: 345.1; found: 345.2.

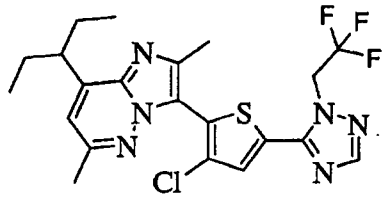
[2] The reaction temperature decreased after 1 hour to 26.7 °C

H. 3-[3-Chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a –78 °C solution of 3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.50 g, 4.35 mmol) and THF (50 mL) is added I_2 (1.21 g, 4.78 mmol). After 10 minutes 2 M LDA (5.44 mL, 10.87 mmol) is added. The solution is stirred for 30 minutes, quenched with water, diluted with EtOAc (100 mL), washed with water (100 mL), sat. $Na_2S_2O_3$ (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (100% EtOAc) furnish the title compound (0.61 g, 1.30 mmol, 30%). ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3H), 2.55 (s, 3H), 4.14 (s, 3H), 7.47 (s, 1H), 7.51 (s, 1H), 7.89 (s, 1H),. LC/MS (m/z): calcd. for $C_{15}H_{12}ClIN_6S$ $(M+H)^+$: 471.0; found: 471.0.

Example 234.

Preparation of 3-{3-chloro-5-[2-(2,2,2-trifluoro-ethyl)-2*H*-[1,2,4]triazol-3-yl]-thiophen-2-yl}-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 5-(4-Chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-^{1}*H*-[1,2,4]triazole.

To a solution of 4-chloro-N-dimethylaminomethylene-2-thiophene carboxamide (1.00 g, 4.62 mmol) and AcOH (1. mL) is added 70 % aqueous 2,2,2-trifluoroethyl-hydrazine (0.79 mL, 4.85 mmol). The solution is heated at 90 °C for 45 minutes, concentrated, dissolved in Et_2O (40 mL), washed with water (30 mL), sat. $NaHCO_3$ (30 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (1.24 g, 4.62 mmol, >99%). ^{1}H NMR ($CDCl_3$) δ 4.88 (q, J = 16.8, 7.8 Hz, 2H), 7.28 (d, J = 0.9 Hz, 1H), 7.31-7.33 (m, 1H), 7.94 (s, 1H). LC/MS (m/z): calcd. for $C_8H_5ClF_3N_3S$ $(M+H)^+$: 268.0; found: 268.0.

B. 5-(5-bromo-4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-^{1}*H*-[1,2,4]triazole.

195

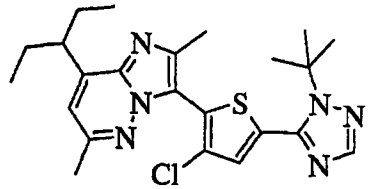
To a solution of 5-(4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-*1H*-[1,2,4]triazole (1.13 g, 4.22 mmol) and AcOH (10 mL) in a sealed tube, is added Br_2 (0.23 mL, 4.43 mmol). The solution is heated at 120 °C for 2 hours, and 140 °C for 5 hours. The solution is concentrated, diluted with Et_2O (150 mL), washed with sat $NaHCO_3$ (75 mL), sat. $Na_2S_2O_3$ (75 mL), brine (75 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (5%-15% EtOAc gradient) furnish the title compound (1.04 g, 3.00 mmol, 71%). ^1H NMR ($CDCl_3$) δ 4.88 (q, J = 16.0, 7.9 Hz, 2H), 7.22 (s, 1H), 7.99 (s, 1H). LC/MS (m/z): calcd. for $C_8H_4BrClF_3N_3S$ $(M+H)^+$: 345.9; found: 346.0.

C. 3-{3-Chloro-5-[2-(2,2,2-trifluoro-ethyl)-*2H*-[1,2,4]triazol-3-yl]-thiophen-2-yl}-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure analogous to Example 231, 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 1.14 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-*1H*-[1,2,4]triazole (0.47 g, 1.37 mmol), KOAc (0.56 g, 5.60 mmol), TBABr (0.37 g, 1.14 mmol), and NMP (3 mL), $Pd(OAc)_2$ (0.013 g, 0.057 mmol) and TDBPP (0.037 g, 0.057 mmol) furnish the title compound (0.43 g, 0.89 mmol, 78%). ^1H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.27-3.36 (m, 1H), 4.98 (q, J = 15.7, 7.9 Hz, 2H), 6.74 (s, 1H), 7.45 (s, 1H), 8.03 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{22}ClF_3N_6S$ $(M+H)^+$: 483.1; found: 483.2.

Example 235.

Preparation of 3-[5-(2-tert-butyl-*2H*-[1,2,4]triazol-3-yl)-3-chloro-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 1-*tert*-Butyl-5-(4-chloro-thiophen-2-yl)-*1H*-[1,2,4]triazole.

Using a procedure analogous to Example 234A, 4-chloro-N-dimethylaminomethylene-2-thiophene carboxamide (5.00 g, 23.07 mmol) and AcOH (50.

mL), *tert*-butylhydrazine hydrochloride (3.16 g, 25.38 mmol) furnish the title compound (0.20 g, 0.83 mmol, 3.6%). ^{1}H NMR ($CDCl_3$) δ 1.63 (s, 9H), 7.07 (d, J = 1.3 Hz, 1H), 7.51 (d, J = 1.3 Hz,1H), 8.08 (s, 1H).

B. 5-(5-Bromo-4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-*1H*-[1,2,4]triazole.

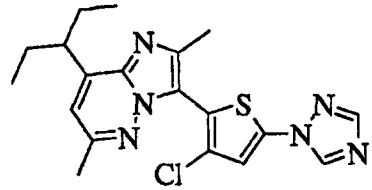
Using a procedure analogous to Example 249B, 1-*tert*-butyl-5-(4-chloro-thiophen-2-yl)-*1H*-[1,2,4]triazole (0.20 g, 0.83 mmol), AcOH (3 mL) and Br_2 (0.051 mL, 0.99 mmol) furnish the title compound (0.27 g, 0.83 mmol, >99%). ^{1}H NMR ($CDCl_3$) δ 1.62 (s, 9H), 7.42 (s, 1H), 8.08 (s, 1H). LC/MS (m/z): calcd. for $C_{10}H_{11}BrClN_3S$ $(M+H)^+$: 320.0; found: 320.0.

C. 3-[5-(2-tert-Butyl-2*H*-[1,2,4]triazol-3-yl)-3-chloro-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure analogous to Example 231, 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.15 g, 0.68 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-*1H*-[1,2,4]triazole (0.20 g, 0.82 mmol), KOAc (0.34 g, 3.42 mmol), TBABr (0.22 g, 0.68 mmol), and NMP (3 mL), $Pd(OAc)_2$ (0.0077 g, 0.034 mmol) and TDBPP (0.022 g, 0.034 mmol) furnish the title compound (0.039 g, 0.085 mmol, 13%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.65 (s, 9H), 1.73-1.91 (m, 4H), 2.51 (s, 6H), 3.26-3.37 (m, 1H), 6.69 (s, 1H), 7.65 (s, 1H), 8.11 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{29}ClN_6S$ $(M+H)^+$: 457.2; found: 457.3.

Example 236.

Preparation of 3-(3-chloro-5-[1,2,4]triazol-1-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 3-(3-Chloro-5-iodo-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

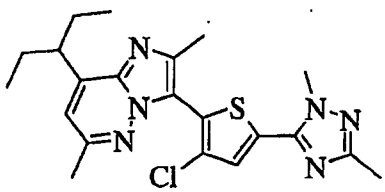
To a solution of 3-(3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine (2 g, 6 mmol) in 10 mL of anhydrous CH_3CN under nitrogen was added portionwise NIS (1.6 g, 7.2 mmol). The reaction mixture is stirred at reflux for 14 hours. After cooling, the solvent is concentrated under vacuum, the residue is disolved in EtOAc and washed with H_2O, 5% solution of sodium bisulfite, H_2O and brine. The organic layer is dried over magnesium sulfate, filtered and concentrated under vacuum. The crude residue is purified by silica gel chromatography using hex/EtOAc 8:2 as eluent mixture, to obtain 2.4 g (90%) of the title compound; mass spectrum 460 (M+1); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.24 (s, 1H), 6.71 (s, 1H), 3.32 (q, 1H, J = 7.2 Hz), 2.52 (s, 3H), 2.49 (s, 3H), 1.84 (q, 4H, J = 7.2 Hz); 0.88 (t, 6H, J = 7.2 Hz) ppm.

B. 3-(3-Chloro-5-[1,2,4]triazol-1-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a solution of 3-(3-chloro-5-iodo-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.65 mmol), *1H*-triazole (0.047 g, 0.69 mmol), CuI (0.0062, 0.033 mmol), Cs_2CO_3 (0.45 g, 1.37 mmol) and DMF (3 mL) is added (*1S, 2S*)-(+)-*N,N'*- dimethylcyclohexane-1,2-diamine (0.014 mL, 0.098 mmol). The solution is heated at 112 °C overnight, diluted with CH_2Cl_2 (10 mL) and filtered thru Celite® and concentrated. The residue is purified by ISCO flash chromatography (30%-40% EtOAc gradient furnish the title compound (0.028 g, 0.070 mmol, 11%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.75-1.92 (m, 4H), 2.51 (s, 3H), 2.52 (s, 3H), 3.26-3.35 (m, 1H), 6.72 (s, 1H), 7.22 (s, 1H), 8.10 (s, 1H), 8.50 (s, 1H). LC/MS (m/z): calcd. for $C_{19}H_{21}ClN_6S$ $(M+H)^+$: 401.1; found: 401.2.

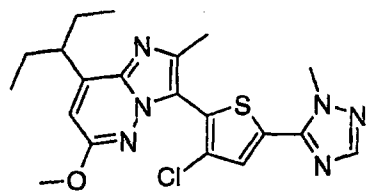
Example 237.

Preparation of 3-[3-chloro-5-(2,5-dimethyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a –78 °C solution of 3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.72 mmol) and THF (5 mL) is added 1.7 M *tert*-BuLi (0.47 mL, 0.80 mmol). After 15 minutes MeI (0.052 mL, 0.83 mmol) is added and the solution warmed to ambient temperature. The solution is diluted with EtOAc (40 mL), washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated. The solution is recrystalized from acetone: hexane furnish the title compound (0.13 g, 0.30 mmol, 42%). ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.36 (s, 3H), 2.51 (s, 6H), 3.27-3.39(m, 1H), 3.40 (s, 3H), 6.72 (s, 1H), 8.02 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{25}ClN_6S$ $(M+H)^+$: 429.2; found: 429.2.

Example 238.Preparation of 3-[3-Chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. N-(6-Methoxy-pyridazin-3-yl)-2,2-dimethyl-propionamide.

3-Chloro-6-methoxy-pyridazine (10.0 g, 69. 18 mmol) is mixed with 2,2-dimethyl-propionamide (8.40 g, 83.01 mmol), BINAP (2.15 g, 3.46 mmol), Cs_2CO_3 (33.8 g, 103.77 mmol) in 1,4-dioxane (150 mL). It is degassed by passing N_2 through for 10 min at rt. $Pd_2(dba)_3$ (3.16 g, 3.46 mmol) is added and the resulting mixture is refluxed overnight. The mixture is cooled to rt, diluted with EtoAc (150 mL); filtered through silica gel; washed with EtOAc (2 x 150 mL). The filtrate is washed with H2O (2 x 300 mL); dried with $MgSO_4$; filtered and concentrated. Purification of the crude material by silica gel chromatography gives the title compound (6.59 g, 31.53 mmol, 46%). 1H NMR (CDCl3): δ. 1.35 (s, 9H), 4.08 (s, 3H), 7.01 (d, J = 9.7 Hz, 1H), 8.41 (d, J = 9.7 Hz, 1H), 8.44 (bs, 1H). ES-MS (m/z): calcd for $C_{10}H_{15}N_3O_2$ $(M+H)^+$: 210.3; found : 210.1.

B. N-[4-(1-Ethyl-propyl)-6-methoxy-pyridazin-3-yl]-2,2-dimethyl-propionamide.

Using a procedure analogous to Example 6a, from N-(6-methoxy-pyridazin-3-yl)-2,2-dimethyl-propionamide (6.09 g, 29.14 mmol) and a Grignard reagent prepared from 3-pentyl bromide (18.1 mL, 160.3 mmol) and Mg (3.84 g, 160.26 mmol) gives the title

compound (5.32 g, 19.08 mmol, 65%). 1H NMR (CDCl3): δ. 0.84 (t, *J* = 7.5 Hz, 6H), 1.36 (s, 9H), 1.50-1.72 (m, 4H), 3.50-3.70 (m, 1H), 4.07 (s, 3H), 6.96 (s, 1H). ES-MS (m/z): calcd for $C_{15}H_{25}N_3O_2$ $(M+H)^+$: 280.4; found : 280.2.

C. 4-(1-Ethyl-propyl)-2-methoxy-6-methyl-pyrrolo[1,2-b]pyridazine.

A solution of N-[4-(1-ethyl-propyl)-6-methoxy-pyridazin-3-yl]-2,2-dimethyl-propionamide (5.32 g, 19.08 mmol) in EtOH (250 mL) is treated with $ZnCl_2$ (26.0 g, 190.8 mmol) and refluxed for 48 h. The reaction is cooled to rt and concentrated. The residue is taken up with EtOAc (250 mL), and H_2O (100 mL). It is washed with H_2O (2 x 100 mL); dried with Na_2SO_4; filtered and concentrated. The residue is then dissolved in EtOAc (80 mL), reacted with chloroacetone (1.6 mL, 20.03 mmoL) at reflux overnight. While it is hot, $NaHCO_3$ (8.10 g) is added and the reaction is refluxed for 1 h. It is cooled to rt and filtered through silica gel washed with EtOAc and concentrated. Purification of the crude material by chromatography gives the title compound (0.48 g, 2.07 mmol, 11%). 1H NMR (CDCl3): δ. 0.84 (t, *J* = 7.5 Hz, 6H), 1.69-1.869 (m, 4H), 2.45 (s, 3H), 3.19-3.30 (m, 1H), 3.94 (s, 3H), 6.39 (s, 1H), 7.49 (s, 1H). ES-MS (m/z): calcd for $C_{14}H_{20}N_2O$ $(M+H)^+$: 233.3; found : 234.1.

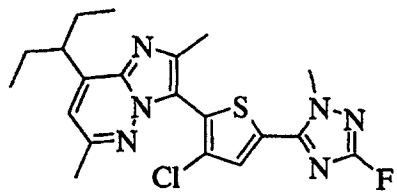
D. 3-[3-Chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

A solution of 4-(1-ethyl-propyl)-2-methoxy-6-methyl-pyrrolo[*1,2-b*]pyridazine (74.8 mg, 0.32 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-^1H-[1,2,4]triazole (107.5 mg, 0.38 mmol), TDBPP (10.4 mg, 0.016 mmol), tetrabutylammonium bromide (103.0 mg, 0.32 mmol), KOAc (158 mg, 1.61 mmol) in NMP (15 mL) is purged with N2 for 5 min. Pd(OAc)2 (3.6 mg, 0.016 mmol) is added and the resulting mixture is stirred at 125 °C for 6 h. The reaction is cooled to rt, and diluted with EtOAc (10 mL); filtered through silica gel; washed with EtOAc (3 x 30 mL). The filtrate is washed with H2O (3 x 30 m); dried with Na2SO4, filtered and concentrated. Purification of the crude material by silica gel chromatography gives the title compound (0.1062 g, 0.2469 mmol, 77%). 1H NMR (CDCl3): δ. 0.89 (t, J = 7.6 Hz, 6H), 1.75-1.90 (m, 4H), 2.52 (s, 3H), 3.22-3.38 (m, 1H), 3.93 (s, 3H), 4.15 (s, 3H), 6.52 (s, 1H), 7.48 (s, 1H), 7.91 (s, 1H). ES-MS (m/z): calcd for $C_{20}H_{23}ClN_6OS$ $(M+H)^+$: 431.9; found: 431.3.

200

Example 239.

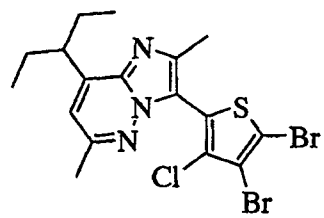
Preparation of 3-[3-chloro-5-(5-fluoro-2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a –78 °C solution of 3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 0.72 mmol) and THF (8 mL) is added 1.7 M *tert*-BuLi (0.47 mL, 0.80 mmol). After 30 minutes the solution is transferred via a cannula into a solution of N-fluorobenzenesulfonamide (0.40 g, 1.25 mmol) and THF. After 30 minutes the solution warmed to ambient temperature. The solution is diluted with EtOAc (40 mL), washed with water (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The solution is purified by ISCO (20%-30% EtOAc gradient) furnish the title compound (0.068 g, 0.16 mmol, 16%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.71-1.93 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.26-3.36 (m, 1H), 4.08 (d J = 2.7 Hz, 3H), 6.75 (s, 1H), 7.97 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{22}ClFN_6S$ $(M+H)^+$: 433.2; found: 433.2.

Example 240.

—Preparation of Preparation of 3-(4,5-dibromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

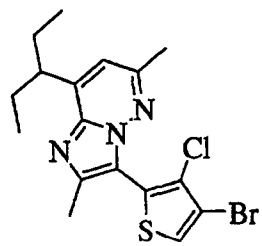


To a solution of 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (5.92 g, 14.34 mmol) and triflouroacetic acid (40 mL) and 98% H_2SO_4 (10 ml) is added NBS (3.83 g, 21.15 mmol). After 10 minutes the solution is poured into ice, and made basic with 5M NaOH. The slurry is extracted with

EtOAc (3 x 100 mL), the combined organic layers washed with water (2 x 400 mL), brine (400 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (6.61 g, 13.44 mmol, 94%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.72-1.92 (m, 4H), 2.47 (s, 3H), 2.52 (s, 3H), 3.25-3.34 (m, 1H), 6.72 (s, 1H). LC/MS (m/z): calcd. for $C_{17}H_{18}Br_2ClN_3S$ $(M+H)^+$: 489.9; found: 490.0.

Example 241.

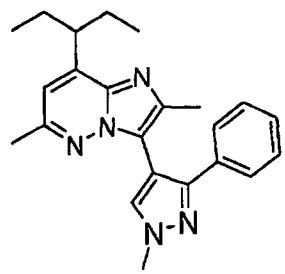
Preparation of 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 76, 3-(4,5-dibromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.83 g, 3.72 mmol), 1.6 M *n*-BuLi (2.56 mL, 4.09 mmol), and THF (30 mL) furnish the title compound (1.05 g, 2.54 mmol, 68%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.48 (s, 3H), 2.51 (s, 3H), 3.27-3.36 (m, 1H), 6.71 (s, 1H), 7.55 (s, 1H). LC/MS (m/z): calcd. for $C_{17}H_{19}BrClN_3S$ $(M+H)^+$: 412.0; found: 412.1.

Example 242.

Preparation of 3-(1-methyl-3-phenyl-*1H*-pyrazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 1-methyl-3-phenyl-*1H*-pyrazole and 1-methyl-5-phenyl-*1H*-pyrazole.

Sodium hydride (60% dispersion in mineral oil, 0.83 g, 20.8 mmol) is suspended in THF (45 ml) and stirred under a nitrogen atmosphere. 3-Phenyl pyrazole (2.5 g, 17.3 mmol dissolved in THF, 15 ml) is added slowly, stirred for 30 minutes then iodomethane (1.3 ml, 20..8 mmol) added and stirred for 3 hrs. The reaction is added to water and extracted twice with ethyl acetate. The combined organic extracts are ished with brine, dried over Na_2SO_4, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 40% ethyl acetate in hexane) to elute the title compound. Obtained is a mixture of 1-methyl-3-phenyl-*1H*-pyrazole and 1-methyl-5-phenyl-*1H*-pyrazole (2.6g, 95% yield).

B. 4-Bromo-1-methyl-3-phenyl-*1H*-pyrazole and 4-bromo-1-methyl-5-phenyl-*1H*-pyrazole.

The mixture of isomers, 1-methyl-3-phenyl-*1H*-pyrazole and 1-methyl-5-phenyl-*1H*-pyrazole (1.0g, 6.3 mmol) and NBS (1.1g, 6.3 mmol) are combined in acetonitrile (25 ml), stirred and heated to 70 °C for 1 hr. The solution is concentrated and the crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 25% ethyl acetate in hexane) to elute 4-bromo-1-methyl-3-phenyl-*1H*-pyrazole (504 mg, 34% yield) and 4-bromo-1-methyl-5-phenyl-*1H*-pyrazole (295 mg, 20% yield), respectively:

^{1}H NMR: (400 mHz, DMSO): δ 8.01 (s, 1H), 7.95 (d, 2H), 7.41 (t, 2H), 7.38 (d, 1H), 3.85 (s, 3H).
^{1}H NMR: (400 mHz, DMSO): δ 7.63 (s, 1H), 7.50 (m, 5H) 3.77 (s, 3H).

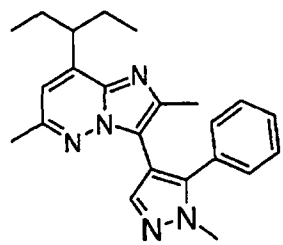
C. 3-(1-Methyl-3-phenyl-*1H*-pyrazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (160 mg, 0.73 mmol), 4-bromo-1-methyl-3-phenyl-*1H*-pyrazole (250 mg, 1.1 mmol) and cesium carbonate (490 mg, 1.50 mmol) are stirred in DMF (5 ml) and degassed by bubbling a stream of nitrogen through the mixture. $PdCl_2(PPh_3)_2$ (15mg) is added and the mixture is heated to 130^{0}C overnight. The mixture is added to water and extracted twice with ethyl acetate. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude

product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 50% ethyl acetate in hexane) to elute the title compound (17.5 mg, 4% yield). ES-MS (m/z): calc'd for $C_{23}H_{27}N_5$: 373.5; found 374.2 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 7.68 (s, 1H), 7.37 (m, 2H), 7.20 (m, 3H), 6.59 (s, 1H), 4.04 (s, 3H), 3.36 (m, 1H), 2.38 (s, 3H), 2.15 (s, 3H), 1.82 (m, 4H), 0.86 (t, 6H).

Example 243.

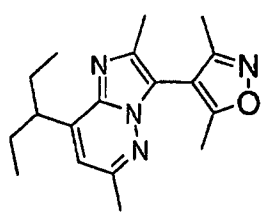
Preparation of 3-(1-methyl-5-phenyl-*1H*-pyrazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using the procedure analogous to Example 242, from 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (160 mg, 0.73 mmol), 4-bromo-1-methyl-5-phenyl-^1H-pyrazole (250 mg, 1.1 mmol), cesium carbonate (490 mg, 1.50 mmol) and $PdCl_2(PPh_3)_2$ (15 mg) in DMF (5 ml) gives the title compound (18 mg, 4% yield). ES-MS (m/z): calc'd for $C_{23}H_{27}N_5$: 373.5; found 374.2 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 7.85 (s, 1H), 7.32 (m, 3H), 7.23 (m, 2H), 6.55 (s, 1H), 3.94 (s, 3H), 3.27 (m, 1H), 2.38 (s, 3H), 2.03 (s, 3H), 1.76 (m, 4H), 0.83 (t, 6H).

Example 244.

Preparation of 3-(3,5-dimethyl isoxazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.,

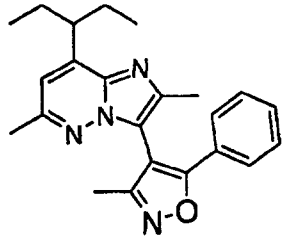


Using the procedure analogous to Example 242, from 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (200 mg, 0.90 mmol), 4-bromo-3,5-dimethyl

isoxazole (Alfa, 320 mg, 1.8 mmol), cesium carbonate (880 mg, 2.70 mmol) and $PdCl_2(PPh_3)_2$ (25mg) in DMF (5 ml), heated at 130 for 4 hrs, then overnight at ambient temperature gives the title compound (65 mg, 23% yield). ES-MS (m/z): calc'd for $C_{18}H_{24}N_4O$: 312.4; found 313.2 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 6.68 (s, 1H), 3.32 (m, 1H), 2.50 (s, 3H), 2.39 (s, 3H), 2.33 (s, 3H), 2.19 (s, 3H), 1.82 (m, 4H), 0.87 (m, 6H).

Example 245.

Preparation of 3-(3-methyl-5-phenyl-isoxazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 4-Bromo-3-methyl-5-phenyl isoxazole.

3-Methyl-5-phenyl isoxazole (Synthesis, **1997**, 439-442) (1.0g, 6.3 mmol) and N-bromosuccinimide (1.2 g, 6.9 mmol) are combined together in acetic acid (30 ml) and heated to reflux with stirring for 2 hrs. The solution is added to water and extracted twice with ethyl acetate. The combined organic extracts are washed with sodium bicarbonate (sat'd) and sat. NaCl then dried over Na_2SO_4, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 10% ethyl acetate in hexane) to elute the title compound (1.5 g, 100% yield). ^1H NMR (400 mHz, $CDCl_3$): δ 8.02 (m, 2H), 7.49 (m, 3H), 6.34, 2.35 (s, 3H).

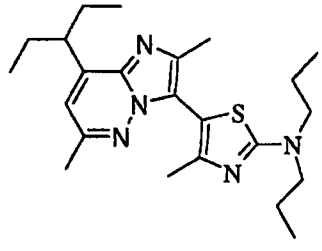
B. 3-(3-Methyl-5-phenyl-isoxazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using the procedure analogous to Example 257, 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (200 mg, 0.90 mmol), 4-bromo-3-methyl-5-phenyl isoxazole (430 mg, 1.8 mmol), cesium carbonate (880 mg, 2.70 mmol) and $PdCl_2(PPh_3)_2$ (25mg) in DMF (5 ml) are combined and heated at 130 °C. for 5 hrs to give the title compound (65

mg, 23% yield). ES-MS (m/z): calc'd for $C_{23}H_{26}N_4O$: 374.5; found 375.1 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 7.50 (d, 2H), 7.31 (m, 3H), 6.69 (s, 1H), 3.39 (m, 1H), 2.48 (s, 3H), 2.20 (s, 6H), 2.33 (s, 3H), 1.84 (m, 4H), 0.88 (m, 6H).

Example 246.

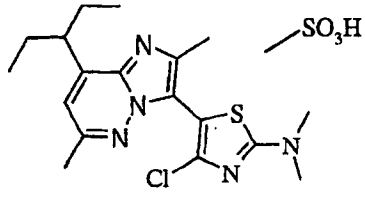
{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-dipropyl-amine.



35 mg of 3-(2-Bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.09mmol) and 45 mg of di-n-propylamine (0.44 mmol) and 57 mg of cesium carbonate(0.18 mmol) are place into 4 ml reaction vial with 3 ml of dry THF and the vial is capped with a Teflon cap. The reaction vial is heated at 100°C for 4h. The reaction mixture is transferred into microwave reaction vessel and sealed. The reaction mixture is heated at 160°C for 30 min by microwave. The mixture is concentrated and applied onto silica-gel chromatography column (Hexane:AcOEt=3:1) to give the title compound. 5.3 mg (14%); mass spectrum(m/e): 414; ^1H-NMR($CDCl_3$):5.59(s, 1H), 3.45(m, 4H), 3.36(m, 1H), 2.57(s, 3H), 2.47(s, 3H), 2.17(s, 3H), 1.80(m, 8H), 0.99(t, 6H, J=7.5Hz), 0.89(t, 6H, J=9.4Hz).

Example 247.

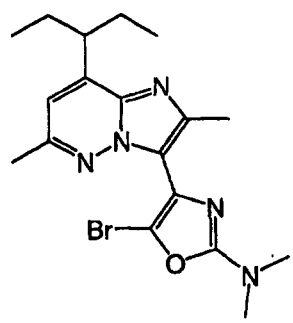
N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-chloro-thiazol-2-yl}-dimethylamine, mesylate salt.



89 mg of N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-chloro-thiazol-2-yl}-dimethylamine (0.236 mmol) is dissolved in 2.0 ml of ethylacetate and 0.236ml of 1M methanesulfonic acid in ethylacetate (0.236 mmol) is added. The solvents are removed under N_2 gas and precipitated crystals are collected, washed with Et2O and dried. 92mg (83%); mass spectrum(m/e): 378(M+1); ^{1}H-NMR($CDCl_3$): 7.30(s, 1H), 3.67(m, 1H), 3.22(s, 6H), 2.93(s, 3H), 2.78(s, 3H), 2.78(s, 3H), 2.71(s, 3H), 1.95(m, 2H), 1.82(m, 2H), 0.96(t, 6H, J=7.3Hz).

Example 248.

Preparation of {5-Bromo-4-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-oxazol-2-yl}-dimethyl-amine.



A. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-oxazol-4-yl-imidazo[*1,2-b*]pyridazine.

500 mg of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.46 mmol) , 622 mg of oxazole (9.0mmol), 79 mg of triphenylphosphine (0.3 mmol) and 989 mg of cesium carbonate (3.03 mmol) are placed into reaction vial with 7 ml of dry DMF. N_2 gas is bubbled into the mixture for 30 min and 67 mg of Pd_2dba_3 (0.07 mmol) is added. The reaction vial is capped with a Teflon cap and stirred at 130°C for 3 days. The reaction mixture is diluted with dichloromethane, washed with sat NaCl, dried over Na_2SO_4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:EtOAc = 3:1) to give the title compound 172 mg (42%); mass spectrum(m/e): 285; ^{1}H-NMR($CDCl_3$): 8.04(s, 1H), 7.97(s, 1H), 6.78(s, 1H), 3.35(m, 1H), 2.80(s, 3H), 2.65(s, 3H), 1.86(m, 4H), 0.88(t, 6H).

B. 3-(2,5-Dibromo-oxazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

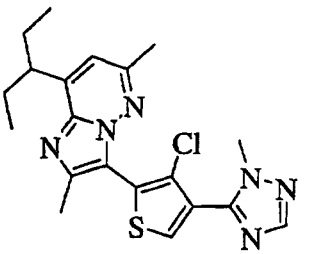
172 mg of 8-(1-ethyl-propyl)-2,6-dimethyl-3-oxazol-4-yl-imidazo[*1,2-b*]pyridazine (0.60 mmol) and 270 mg of NBS (1.51 mmol) are dissolved in 8.0 ml of dichloromethane and stirred at room temperature overnight. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane:EtOAc = 3:1) to give 70 mg of the title compound (26%); mass spectrum(m/e): 442; ^{1}H-NMR($CDCl_3$): 6.82(s, 1H), 3.32(m, 1H), 2.59(s, 3H), 2.54(s, 3H), 1.86(m, 4H), 0.89(t, 6H, J=7.4Hz).

C. {5-Bromo-4-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-oxazol-2-yl}-dimethyl-amine.

67 mg of 3-(2,5-Dibromo-oxazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.15 mmol), 146 mg of cesium carbonate (0.45 mmol) and 3.0 ml of dimethylamine 2.0M in THF (6 mmol) are placed into a 4 ml of reaction vial and the vial is capped with a Teflon cap. The reaction vial is heated at 130°C overnight. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane:AcOE t = 3:1) to give 53 mg of the title compound (87%); mass spectrum(m/e): 406; ^{1}H-NMR($CDCl_3$): 6.72(s, 1H), 3.37(m, 1H), 3.15(s, 6H), 2.58(s, 3H), 2.53(s, 3H), 1.85(m, 4H), 0.90(t, 6H, J=7.2Hz).

Example 249.

Preparation of 3-[3-chloro-4-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

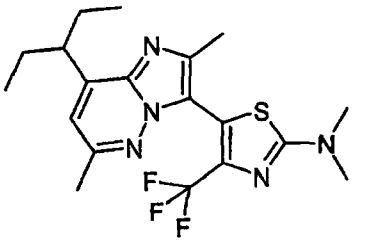


To a flask of 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.49 mmol) is added 0.5 g/ mL Reike® Zn (1.3 mL, 0.97 mmol). The slurry is heated at 65 °C for 1 hour, placed in a centrifuge for 5 minutes, and the solution transferred to a flask containing 5-bromo-1-methyl-*1H*-[1,2,4]triazole (0.12 g, 0.73 mmol) and PdCl2(dppf) (0.018 g, 0.024 mmol). The

solution is heated at 65 °C overnight, diluted with EtOAc (20 mL), washed with sat. NH_4Cl (15 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (20%-50% EtOAc gradient) furnish the title compound (0.018 g, 0.043 mmol, 9%). ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.51 (s, 3H), 2.52 (s, 3H), 3.26-3.37 (m, 1H), 3.95 (s, 3H), 6.72 (s, 1H), 7.82 (s, 1H), 8.01 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{23}ClN_6S$ $(M+H)^+$: 415.2; found: 415.3.

Example 250.

Preparation of {5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-dimethyl-amine.



A. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-thiazol-5-yl-imidazo[*1,2-b*]pyridazine.

Iodoimidazopiridazine (6.75 g, 19.7 mmol), triphenylphosphine (1.03 g, 3.94 mmol), Cs_2CO_3 (12.84 g, 39.4 mmol) and $Pd_2(dba)_3$ (900 mg, 0.98 mmol) are put into a sealed tube with 65 mL of dry DMF and N_2 gas is bubbled into the mixture for 5 minutes. Thiazole (8.36 g, 6.7 mL, 98.4 mmol) is added, and the mixture is heated at 130°C overnight. The mixture is cooled to r.t. and quenched by addition of NH_4Cl saturated solution (200 mL). The mixture is extracted with Et_2O (3 x 100 mL) and the organic layers washed with water (2 x 100 mL) and sat. NaCl (100 mL), dried over $MgSO_4$ and concentrated. The crude product is purified by flash chromatography on silica gel (eluent; hexane:EtOAc= 4:1) to give 3.80 g of the title compound (Yield: 64%). ESIMS: m/z 301 $[M+H]^+$.

B. 3-(2,4-Dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-thiazol-5-yl-imidazo[*1,2-b*]pyridazine. (3.80 g, 12.6 mmol) in CH_3CN (55 mL) at room temperature is added NBS (5.18 g, 29.1 mmol), and the mixture is stirred at room temperature for 3 hours. A white precipitate is formed that is filtered in vacuo, to give 4.86 g of the title compound (Yield: 84%). ESIMS: m/z 459, 461 $[M+H]^+$.

C. 3-(4-Bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a solution of 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (4.86 g, 10.6 mmol) in THF (150 mL) under N_2 atmosphere at –78°C, BuLi (6.63 mL 1.6 M in hexane, 10.6 mmol) is added dropwise for a period of 10 minutes. The mixture is stirred at –78°C for 30 minutes. Water is added, and the mixture is extracted with Et_2O (3 x 100 mL), dried over $MgSO_4$ and concentrated in vacuo. Crude product is purified by flash chromatography on silica gel (eluent hexane:EtOAc 5:1) to give 3.28 g of the title compound (Yield: 82%). ESIMS: m/z 379, 381 $[M+H]^+$..

D. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(4-trifluoromethyl-thiazol-5-yl)-imidazo[*1,2-b*]pyridazine.

To a solution of 3-(4-bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.45 g, 6.5 mmol) in NMP (35 mL) in a sealed tube is added $FSO_2CF_2CO_2Me$ (2.5 g, 1.65 mL, 13 mmol) and CuI (2.48 g, 13 mmol). N_2 gas is bubbled into the mixture for 5 minutes, and the mixture is heated at 120°C for 9 hours. After cooling to room temperature, water (100 mL) and NaCl saturated solution (100 mL) are added to the mixture. The mixture is extracted with Et_2O (5 x 80 mL); washed with water (2 x 100 mL), and dried over $MgSO_4$ and concentrated. The crude product is purified by flash chromatography on silica gel (eluent hexane:EtOAc 5:1) to obtain 960 mg of the title compound (Yield: 40%). ESIMS: m/z 369 $[M+H]^+$.

E. 3-(2-bromo-4-trifluoromethyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

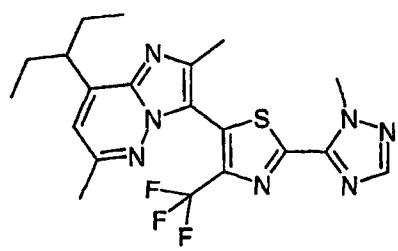
To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-trifluoromethyl-thiazol-5-yl)-imidazo[*1,2-b*]pyridazine (915 mg, 2.48 mmol) in 40 mL of THF under N_2 atmosphere al –78°C, BuLi (1.86 mL 1.6 M in hexane, 2.98 mmol) is slowly added. The mixture is stirred at –78°C for 30 minutes. Then, a solution of CBr_4 (989 mg, 2.98 mmol) in 3 mL of THF is added, and the mixture is stirred at –78°C for 45 minutes. The reaction is quenched by addition of NH_4Cl saturated solution (50 mL), extracted with Et_2O (2 x 50 mL), dried over $MgSO_4$, and concentrated in vacuo. Crude product is purified by flash chromatography on silica gel (eluent CH_2Cl_2) to obtain 685 mg of the title compound (Yield: 62%). ^{1}H NMR ($CDCl_3$): δ0.86 (t, J = 7.5 Hz, 6H), 1.82 (m, 4H), 2.45 (s, 3H), 2.51 (s, 3H), 3.27 (m, 1H), 6.74 (s, 1H). ESIMS: m/z 447, 449 $[M+H]^+$.

F. {5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-dimethyl-amine.

100 mg of 3-(2-Bromo-4-trifluoromethyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.22 mmol) and 218 mg of cesium carbonate (0.66 mmol) are placed in 4 ml reaction vial and 3 ml of dimethylamine 2 M in THF is added. The reaction vial is capped with a Teflon cap and heated at 120°C overnight. The reaction mixture is filtered and concentrated and applied onto a silica-gel chromatography column (Hexane :AcOEt =3:1) to give 85 mg of the title compound. Yield 94%. mass spectrum (m/e) : 412 (M+1).

Example 251.

Preparation of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-[2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-4-trifluoromethyl-thiazol-5-yl]-imidazo[*1,2-b*]pyridazine

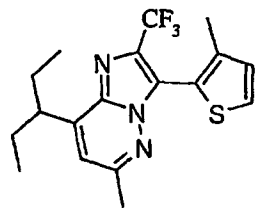


164 mg of 1-Methyl-1,2,4-triazole (1.96 mmol) is dissolved in 2 ml of THF and cooled to –78 °C. 0.8 ml of 2.5M n-butyllithium in hexane (1.96 mmol) is added slowly and stirred at –78 °C, warmed up to room temperature and stirred at r.t. for 15min and

cooled to –78 °C. 3.96 ml of 0.5 M $ZnCl_2$ in THF (1.98 mmol) is added and stirred at room temperature for 15 min. 180 mg of 3-(2-bromo-4-trifluoromethyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and 54 mg of PdCl2(pddf) (0.06 mmol) are added. The vial is capped with a Teflon cap and heated at 80 °C overnight. NH_4Cl aq. is added to quench the reaction and the mixture is extracted by CH_2Cl_2, dried over Na2SO4 and evaporated. The crude product is applied onto silica-gel chromatography column (Hexane :AcOEt=3:1) to give 119 mg of the title compound. Yield 58%. mass spectrum (m/e) : 449(M+1).

Example 252.

Preparation of 8-(1-Ethyl-propyl)-6-methyl-3-(3-methyl-thiophen-2-yl)-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.



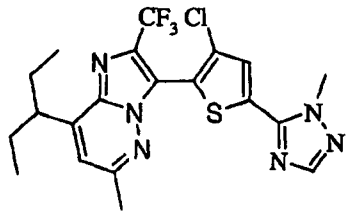
A. 8-(1-Ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.

α-Bromotrifluoroacetone (402 mg, 2.93 mmol) is added to a dry 10 mL microwave reaction tube containing 4-(1-ethyl-propyl)-6-methyl-pyridazin-3-ylamine (500 mg, 2.79 mmol) in EtOH (2.0 mL). The resulting mixture is heated at 110 °C in the microwave for 1 hour. $NaHCO_3$ (246.5 mg, 2.93 mmol) is added, and the reaction is mixed well for 5 minutes. Then, the reaction is heated at 110 °C in the microwave for 1 hour. The solvent is removed via reduced pressure, and the reaction is diluted with ethyl acetate (30 mL). The organic layer is washed with H_2O (3 X 10 mL), and the combined aqueous layers are extracted with ethyl acetate (2 X 20 mL). The combined organic extracts are dried over Na_2SO_4, filtered, and purified by silica gel chromatography to give the title compound (29.5 mg, 0.068 mmol, 9.8 %). ^{1}H-NMR ($CDCl_3$), δ 0.87 (t, J = 7.6 Hz, 6H), 1.86 (m, 4H), 2.60 (s, 3H), 3.30 (m, 1H), 6.80 (s, 1H), 8.14 (s, 1H) ppm. ES-MS (m/z): calcd for $C_{13}H_{16}F_3N_3$ $(M+H)^+$: 271.29; found: 272.2

B. 8-(1-Ethyl-propyl)-6-methyl-3-(3-methyl-thiophen-2-yl)-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.

To a dry 10 ml round bottom flask with reflux condenser containing 8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine (300 mg, 1.11 mmol), 2-bromo-3-methyl-thiophene (216 mg, 1.22 mmol), and Cs_2CO_3 (760 mg, 2.33 mmol) is added NMP (1.7 ml). The mixture is degassed with bubbling N_2 for 15 min and $Pd_2(dba)_3$ (50.8 mg, 0.055 mmol) and PPh_3 (58.2 mg, 0.222 mmol) are added. The reaction mixture is stirred at 130°C overnight. The mixture is cooled to rt, diluted with H_2O; and extracted with EtOAc (3 x 20 ml). The organic layers are dried (Na_2SO_4), filtered and purified by HPLC to give title compound (32 mg, 0.087 mmol, 8%). ^{1}H-NMR ($CDCl_3$), δ 0.93 (t, J = 7.2 Hz, 6H), 1.91 (m, 4H), 2.15 (s, 3H), 2.58 (s, 3H), 3.36 (m, 1H), 6.91 (s, 1H), 7.08 (d, J = 5.3 Hz, 1H), 7.55 (d, J = 5.5 Hz, 1H) ppm. ES-MS (m/z): calcd for $C_{18}H_{20}F_3N_3S$ $(M+H)^+$: 367.44; found: 368.1.

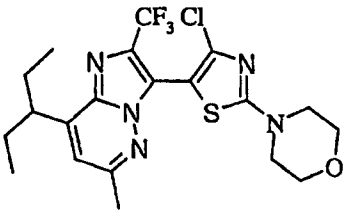
Example 253.Preparation of 3-[3-Chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.



In a dry 25 mL round bottom flask, 8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine (182 mg, 0.671 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-*1H*-[1,2,4]triazole (225 mg, 0.805 mmol), KOAc (330.2 mg, 3.36 mmol), and TBAB (217 mg, 0.671 mmol) are dissolved in NMP (3 mL). The mixture is degassed with bubbling nitrogen for 20 minutes. Then, $Pd(OAc)_2$ (8 mg, 0.034 mmol) and TDBPP (20.4 g, 0.34 moles) are added. The reaction mixture is heated to 125 °C for 3 hours to give the title compound (125 mg, 0.267 mmol, 40%). ^{1}H-NMR ($CDCl_3$), δ 0.88 (t, J = 7.2 Hz, 6H), 1.87 (m, 4H), 2.537 (s, 3H), 3.32 (m, 1H), 4.16 (s, 3H), 6.86 (s, 1H), 7.51 (s, 1H), 7.91 (s, 1H) ppm. ES-MS (m/z): calcd for $C_{20}H_{20}ClF_3N_6S$ $(M+H)^+$: 468.93; found: 469.2.

Example 254.

Preparation of 3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.



A. 8-(1-Ethyl-propyl)-3-iodo-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.

In a dry 25 mL round bottom flask, 8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine (460 mg, 1.70 mmol) are dissolved in dry THF (3.5 mL) and cooled to -78°C. A solution of 2.5 M *n*-butyllithium in hexanes (748 µL, 1.87 mmol) is added dropwise. The reaction mixture is stirred for 20 minutes at -78 °C, then warmed to 0 °C for 15 minutes. A solution of I_2 (453 mg, 1.79 moles) in THF (2.0 mL) is added dropwise. The reaction is stirred for 15 minutes at 0 °C, and then warmed to room temp. The reaction is stirred overnight, and the solvent is removed via reduced pressure. The reaction mixture is redissolved in ethyl acetate (50 mL) and washed with a 1 N solution of $Na_2S_2O_3$ (2 X 20 mL). The aqueous layer is extracted with ethyl acetate (2 X 40 mL). The combined organic extracts are dried with Na_2SO_4, filtered, and purified via silica gel chromatography to give the title compound (595 mg, 1.50 mmol, 88%). ^{1}H-NMR ($CDCl_3$), δ 0.82 (t, J = 8.0 Hz, 6H), 1.83 (m, 4H), 2.64 (s, 3H), 3.27 (m, 1H), 6.82 (s, 1H) ppm. ES$^-$MS (m/z): calcd for $C_{13}H_{15}F_3IN_3$ $(M+H)^+$: 397.18; found: 398.3.

B. 2,4-Dichloro-thiazole.

In a 250 mL round bottom flask, 2.4-thiazolidine dione (12.5 g, 107 mmol) is dissolved in phosphorousoxychloride (70 mL) and pyridine (8.5 mL). The mixture is stirred under reflux for 3 hours and cooled to room temp. The reaction mixture is poured into ice water slowly and extracted with dichloromethane. The combined organic extracts are dried with Na_2SO_4, filtered, and concentrated. The residue is purified via silica gel

chromatography to give title compound (9.18 g, 59.6 mmol, 56%). ^{1}H-NMR ($CDCl_3$), δ 7.01 (s, 1H) ppm.

C. 4-(4-Chloro-thiazol-2-yl)-morpholine.

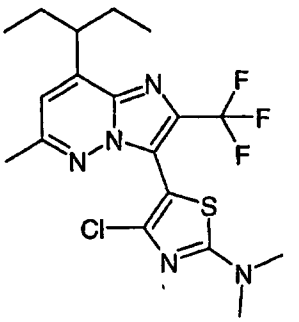
In a 75 mL dry pressure vessel, 2,4-dichloro-thiazole (500 mg, 3.2 mmol) and morpholine (560 μL, 6.4 mmol) are dissolved in dry THF (2.0 mL). Cs_2CO_3 (1.56 g, 4.8 mmol) is added, and the reaction vessel is sealed. The reaction mixture is heated to 110 °C overnight. Solvent is removed via reduced pressure, and the crude reaction mixture is purified via silica gel chromatography to give the title compound (597 mg, 2.92 mmol, 91%). ^{1}H-NMR ($CDCl_3$), δ 3.45 (m, 4H), 3.79 (m, 4H), 6.31 (s, 1H) ppm. ES$^-$MS (m/z): calcd for $C_7H_9ClN_2OS$ $(M+H)^+$: 204.68; found: 205.2.

D. 3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.

In a dry 25 mL round bottom flask, 8-(1-ethyl-propyl)-3-iodo-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine (250 mg, 0.630 mmol), 4-(4-chloro-thiazol-2-yl)-morpholine (194 mg, 0.945 mmol), and Cs_2CO_3 (410 mg, 1.26 mmol) are dissolved in DMF. The mixture is degassed with bubbling nitrogen for 15 minutes. Then, $Pd_2(dba)_3$ (18 mg, 0.032 mmol) and PPh_3 (33 mg, 0.126 mmol) are added. The reaction mixture is heated to 130 °C overnight. The reaction is cooled to room temp., quenched with a solution of NH_4Cl sat? (20 mL), and extracted with Et_2O (3 X 50 mL). The combined organic extracts are washed with brine (30 mL), dried with Na_2SO_4, filtered and concentrated. The residue is purified via reverse phase HPLC with a 30-80% gradient of CH_3CN in 10mM NH_4HCO_3/H_2O/5%CH_3CN (pH 10.0)to give the title compound (11 mg, 0.023 mmol, 4%). ^{1}H-NMR ($CDCl_3$), δ 0.86 (t, J = 7.3 Hz, 6H), 1.84 (m, 4H), 2.55 (s, 3H), 3.31 (m, 1H), 3.54 (dd, J = 5.2, 4H), 3.84 (dd, J = 5.2 Hz, 4H), 6.82 (s, 1H) ppm. ES$^-$MS (m/z): calcd for $C_{20}H_{23}ClF_3N_5OS$ $(M+H)^+$: 473.95; found: 474.2.

Example 255.

Preparation of {4-Chloro-5-[8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethyl-amine.



A. (4-Chloro-thiazol-2-yl)-dimethyl-amine.

Using a procedure analogous to Example 254C, 2,4-dichloro-thiazole (500 mg, 3.2 mmol) and dimethylamine (a 2.0 M solution in THF, 3 mL, 6.4 mmol) are reacted to give the title compound (60 mg, 0.152 mmol, 15%). ^{1}H-NMR ($CDCl_3$), δ 3.09 (s, 6H), 6.22 (s, 1H) ppm. ES-MS (m/z): calcd for $C_5H_7ClN_2S$ $(M+H)^+$: 162.64; found: 163.2.

B. {4-Chloro-5-[8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethyl-amine.

Using a procedure analogous to Example 254D, 8-(1-ethyl-propyl)-3-iodo-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine (250 mg, 0.630 mmol) is coupled with (4-chloro-thiazol-2-yl)-dimethyl-amine (154 mg, 0.945 mmol) to provide desired product. ^{1}H-NMR ($CDCl_3$), δ 0.85 (t, J = 7.4 Hz, 6H), 1.83 (m, 4H), 2.55 (s, 3H), 3.16 (s, 6H), 3.31 (m, 1H), 6.81 (s, 1H) ppm. ES-MS (m/z): calcd for $C_{18}H_{21}ClF_3N_5S$ $(M+H)^+$: 431.91; found: 432.2.

Example A

In Vivo Potency Assessment Using Ex Vivo Binding

To assess in vivo potency, a compound of the present invention is evaluated using ex vivo binding. Using the procedures as provided in D. R. Gehlert *et al.*, *EJP* 509: 145-153 (2005), a compound is administered to a rat via the oral route. The binding of ^{125}I-

sauvagine to the cerebellum is then assessed ex vivo as described in Gehlert *et al.* For example, Example 199 provides an ED_{50} result of 1.3 mg/kg.

Example B

CRF1 Filter Binding Assay

The limitations of plasmid-based human CRF1 expression, in terms of generating a recombinant cell line with sufficient receptor density to develop a binding assay, are overcome by using a Phoenix retroviral expression system licensed from Stanford. The stable HEK-hCRF1 cell line is used to prepare membranes and binding reactions (200 µl) are set up as follows: 50 µl of ^{125}I-sauvagine (0.2 nM final), 50 µl compound and 100 µl CRF1 membrane (25 µg/reaction). The reactions are incubated at room temperature for 2 hours and then terminated by filtration through pre-treated FB Millipore glass fiber filter plates (96 well). The plates are wash twice with ice-cold assay buffer (50 mM tris, 12.5 mM NaCl, 1mM EDTA, 10 mM $MgCl_2$, 0.05% BSA, pH 7.2), air dried over night and counted with 100 µl Microscint 40 in a MicroBeta counter. Non-specific binding (NSB) is determined in the presence of 0.5 µM non-labeled sauvagine. Triplicate determinations are typically run and the median data points plotted by Graph Pad Prism.

Using this assay, the claimed exemplified compounds of the present invention inhibit the binding of ^{125}I-Sauvagine (4 nM) in roller/adherent cells with a Ki (inhibition constant) below 1 µM. For example, Examples 102 and 199 exhibit a Ki of 4.92 ± 0.57 nM and 9.98 ± 0.72 nM, respectively.

Example C

CRF2 Filter Binding Assay

The limitations of plasmid-based human CRF2 expression, in terms of generating a recombinant cell line with sufficient receptor density to develop a binding assay, are overcome by using a Phoenix retroviral expression system licensed from Stanford. The stable HEK-hCRF2 cell line is used to prepare membranes and binding reactions (200 µl) are set up as follows: 50 ul of ^{125}I-sauvagine (0.2 nM final concentration), 50 µl compound and 100 µl CRF2 membrane (25 µg/reaction). The reactions are incubated at room temperature for 2 hours and then terminated by filtration through pre-treated FB Millipore glass fiber filter plates (96 well). The plates are washed twice with ice-cold

assay buffer (50 mM tris, 12.5 mM NaCl, 1mM EDTA, 10 mM $MgCl_2$, 0.05% BSA, pH 7.2), air dried over night and counted with 100 µl Microscint 40 in a MicroBeta counter. Non-specific binding (NSB) is determined in the presence of 0.5 µM non-labeled sauvagine. Alternatively, compounds are evaluated using a Scintillation Proximity assay. This assay is set up as follows: 50ul of ^{125}I-Sauvagine (0.2 nM final concentration), 50 µl compound or non-labelled sauvagine (NSB) and 100 µl containing 250 µg wheat germ agglutinin (WGA) SPA beads and CRF2 membrane (1.5 µg/reaction). Plates are incubated for 4-5 hours at room temperature and then centrifuged at 200 X g for 10 minutes. Bound radioactivity is assessed using a Wallac Trilux scintillation counter. Binding is assessed typically using triplicate determinations and the median data points plotted by Graph Pad Prism. Compounds are initially screened at a fixed concentration and, if sufficient activity is noted, subsequent concentration-response curves are generated.

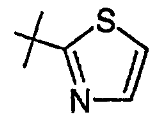
Compounds of the present invention are tested in the CRF2 binding assay and exhibit weak affinity for the CRF2 receptor. For example, Examples 102 and 199 exhibit a percent inhibition at 50 µM of 9.0 ± 2.6 and 16.9 ± 1.9, respectively. These results suggest that the compounds of the present invention are highly selective for the CRF1 receptor.

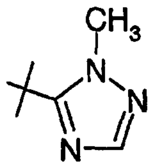
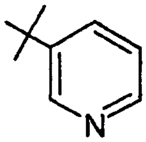
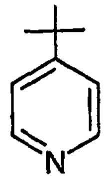
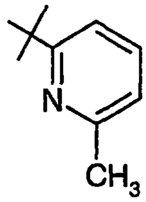
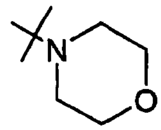
Example D

Bioavailability and Pharmacokinetic Properties

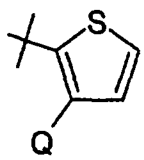
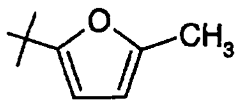
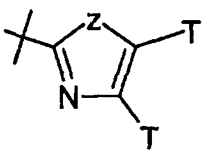
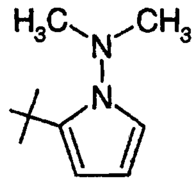
The compounds of Formula I are antagonists of CRF1, and possess surprisingly useful properties related to their pharmacokinetics and bioavailability.

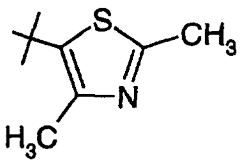
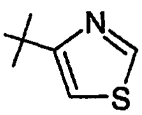
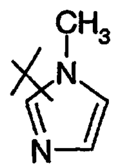
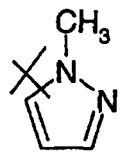
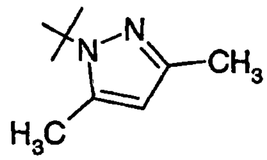
The volume of distribution (Vdist) relates the amount of the drug in the body to the concentration of the drug in the blood or plasma. The volume of distribution refers to the fluid volume that would be required to contain the total amount of the drug in the body at the same concentration as in the blood or plasma: Vdist = amount of drug in the body/ concentration of drug in blood or plasma (Goodman and Gillman's). For a 10 mg dose and a plasma concentration of 10 mg/L, the volume of distribution would be 1 liter. The volume of distribution reflects the extent to which the drug is present in the extravascular tissue. A large volume of distribution reflects the tendency of a compound to bind to the tissue components compared with plasma protein binding. In a clinical

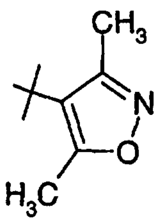
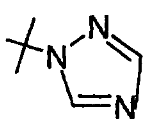
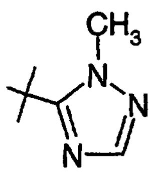
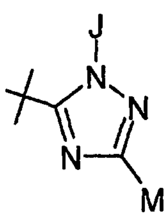
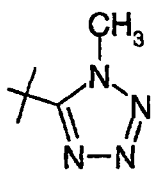
R^7 is hydrogen, halo, methyl, methoxy, dimethylamino,  ,

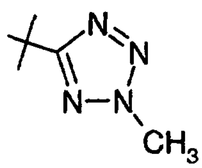
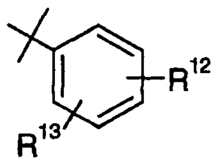
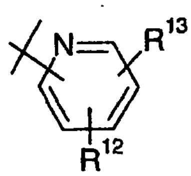
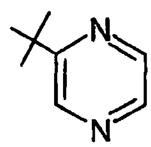
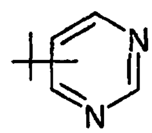
 ,  ,  ,  , or  ;

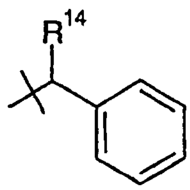
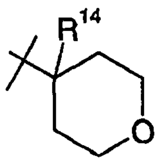
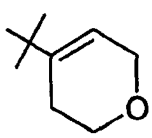
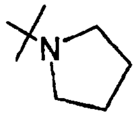
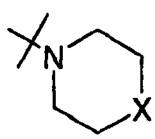
R^8 is selected from the group consisting of hydrogen, halo, cyano, (C_1-C_4)alkyl, R^aR^bN-, carbamyl, (C_1-C_2)alkoxy(C_1-C_2)alkyl, R^{11}-C(O)-,

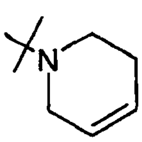
 ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,  or

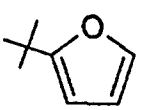
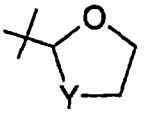
 ;

R^{11} is methoxy, methylamino, dimethylamino, or phenyl;

R^{12} is hydrogen, halo, methyl, ethyl, trifluoromethyl, methoxy, trifluoromethoxy dimethylamino, acetyl, or methylsulfonyl;

R^{13} is hydrogen, methyl or halo;

R^{14} is hydrogen or hydroxy;

R^{15} is methylthio, cyclopropyl, phenyl,  or  ;

R^a is hydrogen, $(C_1\text{-}C_5)$alkyl, $(C_3\text{-}C_5)$cycloalkyl, methoxy$(C_2\text{-}C_4)$alkyl, acetyl, $(C_1\text{-}C_2)$alkylsulfonyl, (C_3)alkenyl, $R^{15}\text{-}(CH_2)n$-, or $(C_1\text{-}C_2)$alkyl substituted with cyano, formyl, vinyl, or ethynyl;

R^b is hydrogen or $(C_1\text{-}C_3)$alkyl;

X is $-CH_2-$, -CO-, -O-, -S- or $-SO_2-$;

Y is $-CH_2-$ or -O-;

z is S or O;

n is 1 or 2;

Q is hydrogen or methyl;

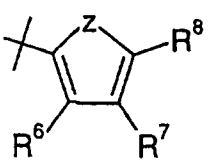
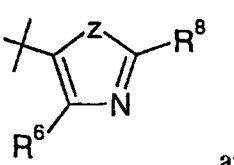
T is hydrogen or methyl;

J is methyl, trifluoroethyl, or tert-butyl; and

M is methyl or halo;

and pharmaceutically acceptable salts thereof.

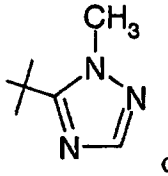
2. The compound of Claim 1 wherein R^0 and R^4 are hydrogen, R^1 and R^3 are methyl, and R^{5a} and R^{5b} are ethyl.

3. The compound according to any one of claims 1 to 2, wherein R^2 is selected from the group consisting of  or  and where z is S.

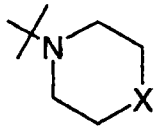
4. The compound according to any one of claims 1 to 3, wherein R^7 is hydrogen.

5. The compound according to any one of claims 1 to 4, wherein R^6 is halo or methyl.

6. The compound according to any one of claims 1 to 5, wherein R^8 is



or



and where X is O.

7. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 6, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

8. A compound according to any one of Claims 1 to 6 for use as a medicament.

9. Use of a compound according to any one of Claims 1 to 6 for the manufacture of a medicament for treating anxiety, depression, major depressive disorder, alcohol withdrawal symptoms, or irritable bowel syndrome in a mammal.

10. Use of a compound according to Claim 9 wherein the mammal is a human.

International application No
PCT/US2006/009942

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/5025 A61P25/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, 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
A	EP 1 364 952 A (EISAI CO., LTD) 26 November 2003 (2003-11-26) examples	1-10
A	WO 97/29109 A (JANSSEN PHARMACEUTICA N.V; NEUROCRINE BIOSCIENCES INC; CHEN, CHEN; WEB) 14 August 1997 (1997-08-14) examples	1-10
A	EP 1 466 527 A (SUMITOMO CHEMICAL TAKEDA AGRO COMPANY, LIMITED) 13 October 2004 (2004-10-13) examples	1-10

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier 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
8 August 2006	16/08/2006

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

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/009942

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MOREAU S ET AL: "Synthesis and anticonvulsant Properties of Triazolo- and Imidazopyridazinyl Carboxamides and Carboxylic Acids" BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol. 6, no. 7, July 1998 (1998-07), pages 983-991, XP002991062 ISSN: 0968-0896 compounds 9,10,11	1-10

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 1364952 A	26-11-2003	WO	02062800 A1	15-08-2002
		US	2004082781 A1	29-04-2004
WO 9729109 A	14-08-1997	AU	713673 B2	09-12-1999
		AU	1599197 A	28-08-1997
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		BR	9707391 A	20-07-1999
		CN	1205009 A	13-01-1999
		CZ	9802445 A3	14-10-1998
		DE	880523 T1	04-07-2002
		EA	980394 A1	29-10-1998
		EE	9800124 A	15-10-1998
		EP	0880523 A1	02-12-1998
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		ID	15905 A	14-08-1997
		JP	3356291 B2	16-12-2002
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		JP	2002121194 A	23-04-2002
		NO	981357 A	03-08-1998
		NZ	330119 A	28-02-2000
		SK	106398 A3	02-12-1998
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EP 1466527 A	13-10-2004	BR	0306810 A	26-10-2004
		CN	1617666 A	18-05-2005
		WO	03061388 A1	31-07-2003
		US	2005032650 A1	10-02-2005

COMPUESTOS DE IMIDAZOPIRIDAZINA

CAMPO DE LA INVENCION

Esta invención se relaciona a compuestos de imidazo[1,2-b]piridazina sustituidos novedosos, composiciones farmacéuticas de éstos, y el uso de los compuestos como antagonistas de receptor de factor de liberación de corticotropina 1 (CRF1) en el tratamiento de trastornos psiquiátricos y enfermedades neurológicas.

ANTECEDENTES DE LA INVENCION

El factor de liberación de corticotropina es un péptido de 41 aminoácidos que es el regulador fisiológico primario de la proopiomelanocortina (POMC) derivada de secreción de péptido de la glándula pituitaria anterior [J. Rivier y colaboradores, *Proc. Natl. Acad. Sci* (*USA*) 80:4851 (1983); W. Vale y colaboradores, *Science* 213:1394 (1981)]. Además de su papel endócrino en la glándula pituitaria, la localización inmunohistoquímica del CRF ha demostrado que la hormona tiene una distribución extrahipotalámica en el sistema nervioso central y produce un amplio espectro de efectos autonómicos, electrofisiológicos y de comportamiento consistentes con un papel de neurotransmisor o neuromodulador en el cerebro [W. Vale y colaboradores, *Rec. Prog. Horm. Res.* 39:245 (1983); G. F. Koob, *Persp. Behav. Med.* 2:39 (1985); E. B. De Souza y

colaboradores, *J. Neurosci.* 5:3189 (1985)]. También existe evidencia de que el CRF juega un papel significante en la integración de la respuesta en el sistema inmune para tensores fisiológicos, psicológicos e inmunológicos [J. E. Blalock, *Physiological Reviews* 69:1 (1989); J. E. Morley, *Life Sci.* 41:527 (1987)].

Existe evidencia de que el CRF tiene un papel en los trastornos psiquiátricos y enfermedades neurológicas que incluyen depresión, trastornos relacionados con la ansiedad y trastornos en la alimentación. Un papel para el CRF también se ha postulado en etiología y patofisiología de la enfermedad de Alzheimer, enfermedad de Parkinson, enfermedad de Huntington, parálisis supranuclear y esclerosis lateral amiotrófica, conforme se relacionan con la disfunción de neuronas de CRF en el sistema nervioso central [para una revisión, ver: E. B. De Souze, *Hosp. Practice* 23:59 (1988)]. Además, el CRF es conocido por tener una distribución extrahipotálmica en el SNC, que contribuye ahí a un amplio espectro del comportamiento autonómico y efectos fisiológicos [ver, por ejemplo, Vale y colaboradores, 1983; Koob, 1985; and E. B. De Souze y colaboradores, 1985]. Por ejemplo, las concentraciones de CRF se incrementan significativamente en el fluido espinal cerebral de pacientes que padecen trastorno afectivo o depresión mayor [C. B. Nemeroff y colaboradores, *Science* 226:1342 (1984); C. M. Banki y colaboradores, *Am. J.*

Psychiatry 144:873 (1987); R. D. France y colaboradores, *Biol. Psychiatry* 28:86 (1988); M. Arato y colaboradores, *Biol. Psychiatry* 25:355 (1989)]. Más aún, los niveles excesivos de CRF se sabe que producen efectos ansiogénicos en modelos animales [ver, por ejemplo, Britton y colaboradores, 1982; Berridge y Dunn, 1986 y 1987].

La densidad de los receptores de CRF se disminuye significativamente en la corteza frontal de víctimas de suicidio, consiste de una hipersecreción de CRF [C. B. Nemeroff y colaboradores, *Arch. Gen. Psychiatry* 45:577 (1988)]. Además, existe una respuesta a la adrenocorticotropina (ACTH) despuntada al CRF (administrado intravenosamente observado en pacientes depresivos [P.W. Gold y colaboradores, *Am. J. Psychiatry* 141:619 (1984); F. Holsboer y colaboradores, *Psychoneuroendocrinology* 9:147 (1984); P. W. Gold y colaboradores, *New Engl. J. Med.* 314:1129 (1986)]. Estudios preclínicos en ratas y primates no humanos proporcionan soporte adicional para la hipótesis de que la hipersecreción del CRF puede ser involucrado en los síntomas vistos en depresión humana [R. M. Sapolsky, *Arch. Gen. Psychiatry* 46:1047 (1989)]. También existe evidencia preliminar de que los antidepresivos tricíclicos pueden alterar niveles de CRF y así modulan los números de receptores en el cerebro [Grigoriadis y colaboradores, *Neuropsychopharmacology* 2:53 (1989)].

Estudios neuroquímicos, endócrinos y de enlazamiento de receptor han demostrado todos interacciones entre el CRF y ansiolíticos de benzodiazepina, que proporcionan además evidencia para el involucramiento de CRF en estos trastornos. El clorodiacepóxido atenúa los efectos "ansiogénicos" de CRF tanto en las pruebas de conflicto [K. T. Britton y colaboradores, *Psychopharmacology* 86:170 (1985); K.T. Britton y colaboradores, *Psychopharmacology* 94:306 (1988)] y en la prueba de sobresalto acústico [N. R. Swerdlow y colaboradores, *Psychopharmacology* 88:147 (1986)] en ratas. El antagonista de receptor de benzodiacepina Ro 15-1788, el cual estuvo sin actividad de comportamiento solo en la prueba de conflicto operante, invirtió los efectos de CRF de una manera dependiente de dosis mientras el agonista inverso de benzodiacepina FG 7142 mejoró las acciones de CRF [K. T. Britton y colaboradores, *Psychopharmacology* 94:396 (1988)]. Estudios preliminares que usan el receptor CRF putativo antagonista de CRF de ovino α-helicoidal (9-41) en una variedad de paradigmas de comportamiento demuestra que el antagonista produce efectos "similares al ansiolítico" que son similares cualitativamente a las benzodiacepinas [C. W. Berridge and A. J. Dunn, *Horm. Behav.* 21:393 (1987), Brain Research Reviews 15:71 (1990)].

Los subtipos de receptor CRF, CRF1 y CRF2, han sido identificados y se distribuyen heterólogamente dentro del

cerebro [D. T. Chalmers y colaboradores, *TIPS* 17:166-72 (1996)] que sugiere de esa manera una diversidad funcional potencial [S. C. Heinrichs y colaboradores, *Regul. Peptides* 71:15 (1997)]. Por ejemplo, los receptores CRF1 de cerebro distribuidos ampliamente están implicados fuertemente en exposición que acompaña emocionalmente a estresantes ambientales [G. Liebsch y colaboradores, *Regul. Peptides* 59: 229-39 (1995); D. W. Schulz, *PNAS* 93: 10477-82 (1996)]. Significativamente, los receptores de CRF1, no CRF2, aparentan mediar para seleccionar ansiogénicos similares a comportamiento [Heinrichs y colaboradores, 1997]. Una distribución septal/hipotálmica más discreta [D. T. Chalmers y colaboradores, *J. Neurosci.* 15(10): 6340-50 (1995)] y la disponibilidad de los ligandos endógenos alternativos [J. Vaughan y colaboradores, *Nature* 378: 287-92 (1995)] sugieren un papel funcional diferente juntos para el receptor CRF2 [Heinrichs y colaboradores, 1997]. Por ejemplo, un neuropéptido de la familia CRF novedosa con afinidad preferencial para CRF2 relativo a receptores CRF1 se reporta para suprimir apetito sin la producción del perfil de activación comportacional observado con agonismo de CRF1 selectivo (H. Tezval y colaboradores, *PNAS* 101(25): 9468-9473 (2004)]. En muchos casos, el agonismo CRF2 produce efectos similares a aquellos reportados para antagonistas CRF1 o eliminación del gen de CRF1 [S. C. Heinrichs, *Trends in*

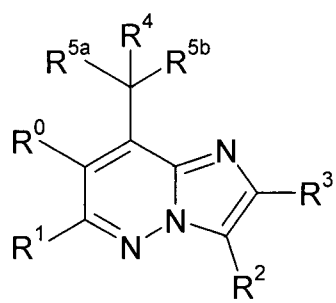
Pharmacological Sciences 20(8):311-5 (1999)]. Mientras que los agonistas se han propuesto como agentes antiobesidad, los antagonistas CRF1 pueden ser además, un tratamiento importante para la obesidad [C. Contoreggi y colaboradores, *Neuroendocrinology* 80(2):111-23 (2004)].

Desde el punto de vista anterior, los antagonistas eficaces y selectivos de CRF1 se desean como agentes terapéuticos de valor potencial para el tratamiento de trastornos psiquiátricos y enfermedades neurológicas. Así es deseable descubrir nuevos antagonistas CRF1.

BREVE DESCRIPCION DE LA INVENCION

Los compuestos de la presente invención incluyen antagonistas del receptor de CRF1.

Una modalidad de la presente invención es un compuesto de la Fórmula I:



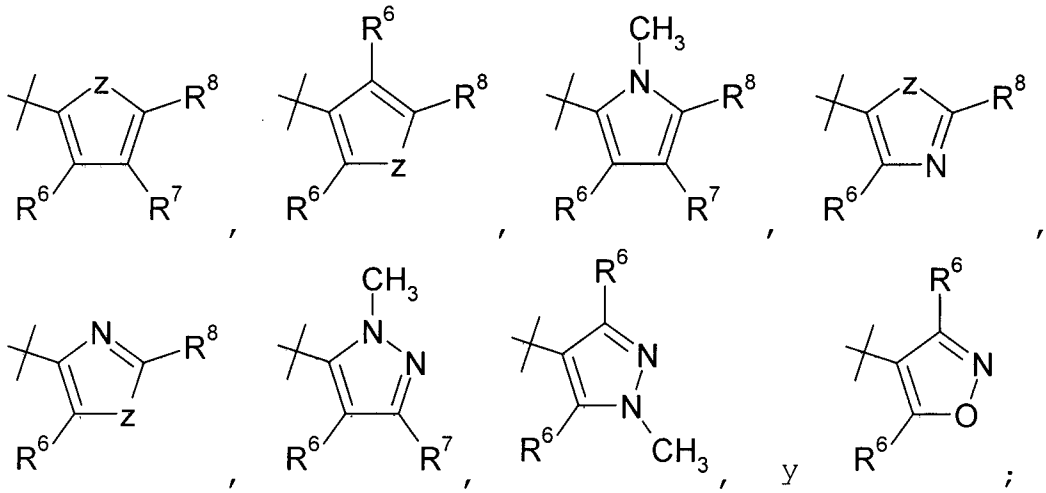
Fórmula I

En donde:

R^0 es hidrógeno, halo, metilo o etilo;

R^1 y R^3 son independientemente metilo, metoxi, o trifluorometilo;

R^2 se selecciona del grupo que consiste de:

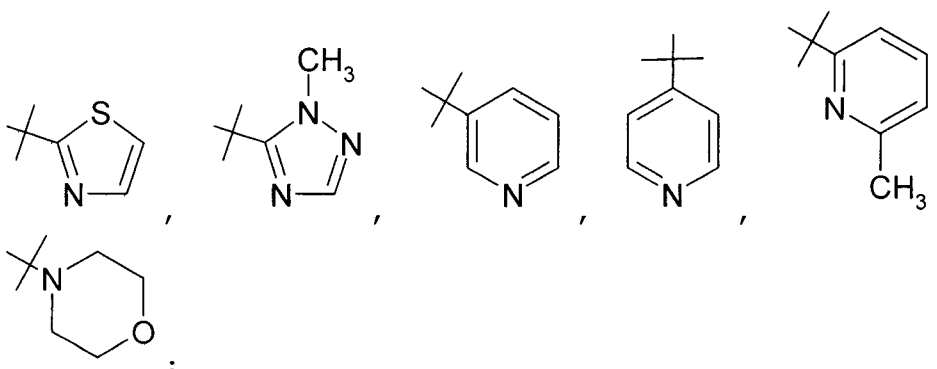


R^4 es hidrógeno, halo, o hidroxi;

R^{5a} y R^{5b} son independientemente etilo o n-propilo;

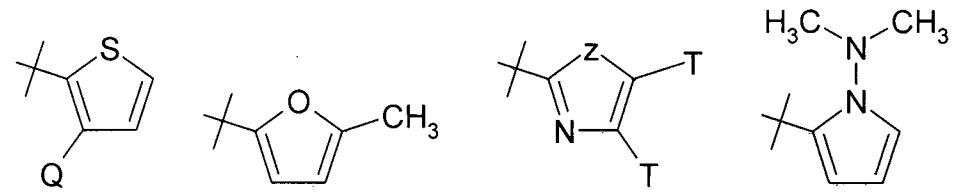
R^6 en cada ocurrencia es independientemente hidrógeno, halo, ciano, alquilo(C_1-C_4), trifluorometilo, metoxi, o fenilo;

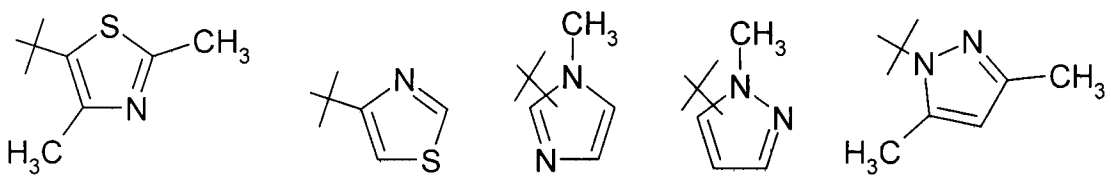
R^7 es hidrógeno, halo, metilo, metoxi, dimetilamino,

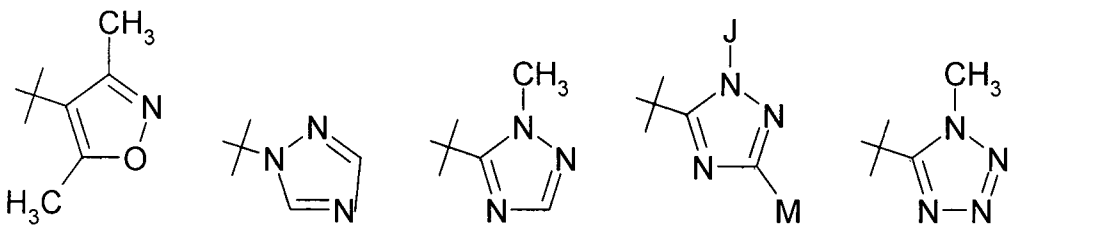


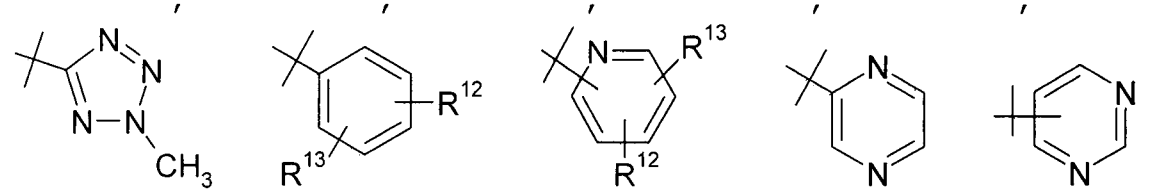
;

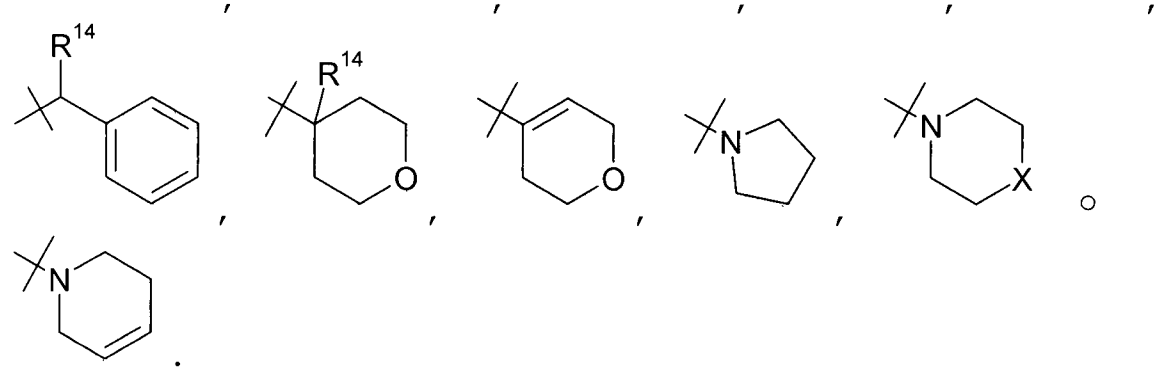
R^8 se selecciona del grupo que consiste de hidrógeno, halo, ciano, alquilo(C_1-C_4), R^aR^bN-, carbamilo, alcoxi(C_1-C_2)alquilo(C_1-C_2), R^{11}-C(O)-,











;

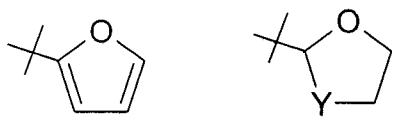
R^{11} es metoxi, metilamino, dimetilamino, o fenilo;

R^{12} es hidrógeno, halo, metilo, etilo, trifluorometilo, metoxi, trifluorometoxi, dimetilamino, acetilo, o metilsulfonilo;

R^{13} es hidrógeno, metilo o halo;

R^{14} es hidrógeno o hidroxi;

R^{15} es metiltio, ciclopropilo, fenilo, fenilo,



o

;

R^a es hidrógeno, alquilo(C_1-C_5), cicloalquilo(C_3-C_5), metoxi(C_2-C_4)alquilo, acetilo, (C_1-C_2)alquilsulfonilo, (C_3)alquenilo, R^{15}-(CH_2)n-, o (C_1-C_2)alquilo sustituido con ciano, formilo, vinilo, o etinilo;

R^b es hidrógeno o alquilo(C_1-C_3);

X es $-CH_2-$, $-CO-$, $-O-$, $-S-$ o $-SO_2-$;

Y es $-CH_2-$ o $-O-$;

Z es S u O;

n es 1 ó 2;

Q es hidrógeno o metilo;

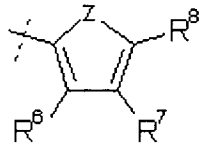
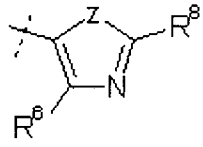
T es hidrógeno o metilo;

J es metilo, trifluoroetilo, o tert-butilo; y

M es metilo o halo;

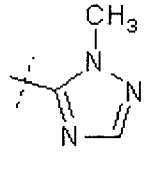
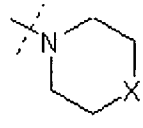
y sales farmacéuticamente aceptables de éstos.

Otra modalidad de la presente invención es un compuesto de la Fórmula I en donde R^0 y R^4 son hidrógeno, R^1 y R^3 son metilo, y R^{5a} y R^{5b} son etilo.

Todavía otra modalidad de la presente invención es un compuesto de la Fórmula I en donde R^2 se selecciona del grupo que consiste de  ó  donde z es S.

Una modalidad más de la presente invención es un compuesto de la Fórmula I en donde R^7 es hidrógeno.

Otra modalidad de la presente invención es un compuesto de la Fórmula I en donde R^6 es halo o metilo.

Todavía otra modalidad de la presente invención es un compuesto de la Fórmula I en donde R^8 es  ó  donde X es O.

Otra modalidad de la presente invención es una composición farmacéutica que comprende un compuesto de la Fórmula I, o una sal farmacéuticamente aceptable de ésta, y un portador, diluyente o excipiente farmacéuticamente aceptable.

Todavía otra modalidad de la presente invención es un compuesto de la Fórmula I, para uso como un medicamento.

Una modalidad más de la presente invención es el uso de un compuesto de la Fórmula I para la fabricación de un medicamento para el tratamiento de ansiedad, depresión, trastorno depresivo mayor, síntomas del retiro de alcohol, o síndrome de intestino irritable en un mamífero. En otra modalidad más, el mamífero es un humano.

DESCRIPCION DETALLADA DE LA INVENCION

Como se usó al inicio, y a través de toda la descripción de la invención, los siguientes términos, a menos que se indique de otra manera, se deben entender que tiene los siguientes significados:

"Alcoxi" significa alquilo-O-grupo, en donde el grupo alquilo es como se describe en la presente. Ejemplarmente los grupos alcoxi incluyen metoxi, etoxi, n-propoxi, i-propoxi, y n-butoxi.

"Alquilo" significa un grupo de hidrocarburo alifático saturado, el cual puede ser lineal o ramificado, que tiene de 1 a 5 átomos de carbono en la cadena.

"Alquenilo" significa un grupo hidrocarburo alifático insaturado, el cual puede ser lineal o ramificado, que tiene de 2 a 4 átomos de carbono en la cadena.

"Cicloalquilo" significa un grupo monocíclico, que tiene de 3 a 5 átomos de carbono.

"Halo" significa flúor, cloro, bromo, o yodo.

"Sales farmacéuticamente aceptables" se refiere a las sales de adición de ácido inorgánico u orgánico relativamente no tóxicas, y sales de adición de base, de compuestos de la presente invención. Estas sales se pueden preparar in situ durante el aislamiento y purificación final de los compuestos. Además, las sales de adición de ácido se pueden preparar mediante reacción separadamente de los compuestos purificados en su forma de base libre con un ácido orgánico o inorgánico apropiado y aislamiento de la sal así formada. Ejemplarmente las sales de adición ácidas incluyen sales de bromohidrato, clorohidrato, sulfato, bisulfato, fosfato, nitrato, acetato, oxalato, valerato, oleato, palmitato, estearato, laurato, borato, benzoato, lactato, fosfato, tosilato, citrato, maleato, fumarato, succinato, tartrato, naftilato, mesilato, glucoheptonato, lactiobionato, sulfamatos, malonatos, salicilatos, propionatos, metilen-bis-β-hidroxinaftoatos, gentisatos, isetionatos, di-p-toluoiltartratos, metanosulfonatos, etanosulfonatos, bencenesulfonatos, p-toluensulfonatos, ciclohexilsulfamatos y quinateslaurilsulfonato, y similares. Ver, por ejemplo, S.M. Berge, y colaboradores, "Pharmaceutical Salts," J. Pharm. Sci., 66, 1-19 (1977). Las listas de sales apropiadas se encuentra en Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing. Company, Easton, Pa., 1985, p. 1418.

Se entenderá que, como se usa en la presente, las referencias para los compuestos de la Fórmula I se pretende que también incluyan las sales farmacéuticamente aceptables de éstas.

"Cantidad terapéuticamente efectiva" o "cantidad efectiva" significa la cantidad del compuesto de la fórmula I de la presente invención o composición farmacéutica que contiene un compuesto de la fórmula I de la presente invención que producirá la respuesta biológica o médica o el efecto terapéutico deseado en un tejido, sistema, animal o humano que está siendo observado por el investigador, veterinario, doctor médico u otro médico.

Los términos "tratamiento", "tratar", "trato", y similares, están significando que incluyen tanto retardo o inversión del progreso de una enfermedad. Estos términos también incluyen alivio, mejoría, atenuación, eliminación, o reducción de uno o más de los síntomas de un trastorno o condición, aún si el trastorno o condición no se elimina en el momento y aún si el progreso del trastorno o condición no se elimina en el momento y aún si el progreso del trastorno o condición no es disminuida o invertida. El término "tratamiento" y los términos similares también incluyen tratamiento preventivo (por ejemplo, profiláctico) y paliativo. La prevención de la enfermedad se manifiesta por

una prolongación o eliminación del comienzo de los síntomas de la enfermedad.

El símbolo "___" en una estructura molecular indica la posición de acoplamiento para aquellos substituyentes particulares.

Cuando cualquier variable ocurre más de una vez en cualquier constituyente o en la fórmula I, su definición en cada ocurrencia es independiente de su definición en toda otra ocurrencia. También, combinaciones de substituyentes y/o variables son permisibles solamente si las combinaciones resultan en compuestos estables. En compuestos de selección de la presente invención, uno de los expertos ordinarios en la técnica reconocerá que los diferentes substituyentes, esto es, R^1, R^2, etc., están para ser seleccionados de conformidad con los principios bien conocidos de conectividad de estructura química.

Bajo la nomenclatura estándar usada en toda esta descripción, la porción Terminal de la cadena lateral diseñada se describe primero, seguida por la funcionalidad adyacente hacia el punto de acoplamiento. Por ejemplo, un substituyente de arilcarbonilaminoalquilo es equivalente a arilo-C(O)-NH-alquilo-.

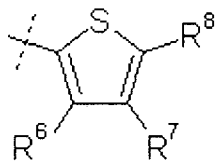
La presente invención contempla clases específicas de compuestos de la Fórmula I. Los siguientes párrafos describen las clases específicas:

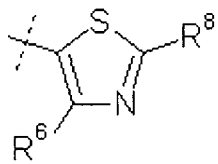
(a) R^0 es hidrógeno;

(b) R^1 es metilo;

(c) R^3 es metilo;

(d) R^1 y R^3 son metilo;

(e) R^2 es  ;

(f) R^2 es  ;

(g) R^4 es hidrógeno;

(h) R^{5a} es etilo;

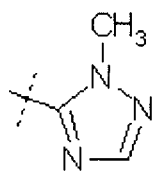
(i) R^{5b} es etilo;

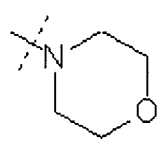
(j) R^{5a} y R^{5b} son etilo;

(k) R^6 es halo;

(l) R^6 es metilo;

(m) R^7 es hidrógeno;

(n) R^8 es  ;

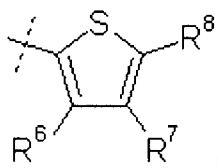
(o) R^8 es  .

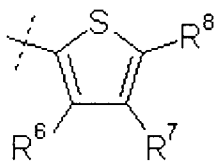
Aunque todos los compuestos de la Fórmula I son antagonistas de receptor CRF1 útiles, los siguientes párrafos describen clases específicas adicionales:

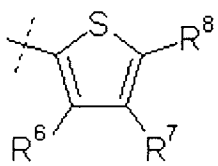
(a) Cada uno de R^1 y R^3 es metilo y cada uno de R^{5a} y R^{5b} es etilo;

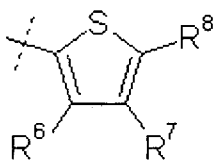
(b) R^1 y R^3 son metilo, R^{5a} y R^{5b} son etilo, y R^0 es hidrógeno;

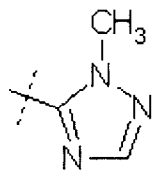
(c) R^1 y R^3 son metilo, R^{5a} y R^{5b} son etilo, y R^0 y R^4 son hidrógeno;

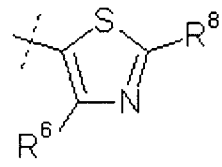
(d) R^2 es  y R^7 es hidrógeno;

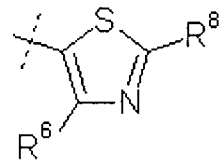
(e) R^2 es  , R^7 es hidrógeno, y R^6 es halo;

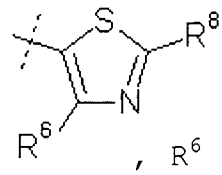
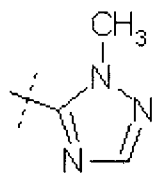
(f) R^2 es  , R^7 es hidrógeno, y R^6 es metilo;

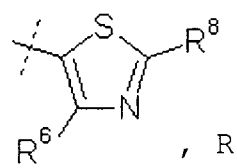
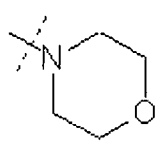
(g) R^2 es  , R^7 es hidrógeno, y R^6 es halo

o metilo, y R^8 es  ;

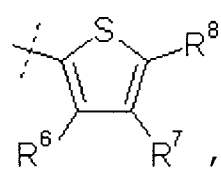
(h) R^2 es  y R^6 es halo;

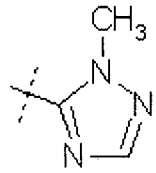
(i) R^2 es  y R^6 es metilo;

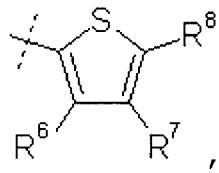
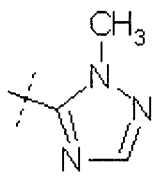
(j) R^2 es  , R^6 es halo o metilo, y R^8 es  ;

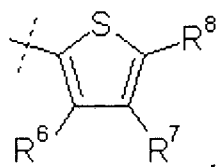
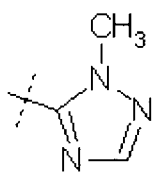
(k) R^2 es  , R^6 es halo o metilo, y R^8 es  .

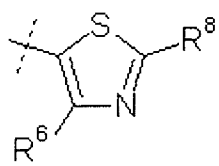
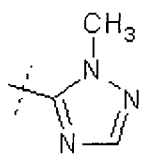
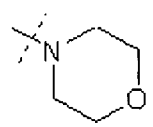
Los siguientes párrafos describen aún más clases específicas de antagonistas de receptor CRF1 de la invención:

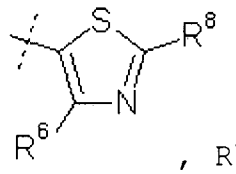
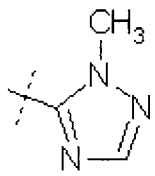
(a) R^1 y R^3 son metilo, R^{5a} y R^{5b} son etilo, y R^0 y R^4 son hidrógeno, R^2 es  , R^7 es hidrógeno, y R^6 es

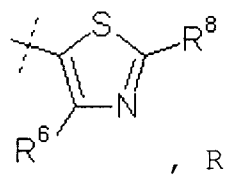
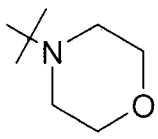
halo o metilo, y R^8 es  ;

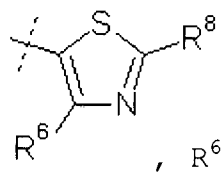
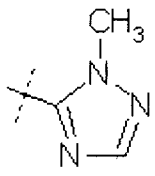
(b) R^1 y R^3 son metilo, R^{5a} y R^{5b} son etilo, y R^0 y R^4 don hidrógeno, R^2 es  , R^7 es hidrógeno, y R^6 es halo, y R^8 es  ;

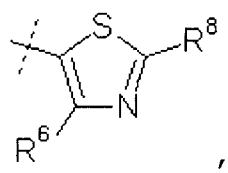
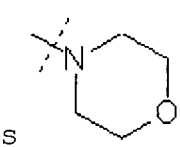
(c) R^1 y R^3 son metilo, R^{5a} y R^{5b} son etilo, y R^0 y R^4 son hidrógeno, R^2 es  , R^7 es hidrógeno, y R^6 es metilo, y R^8 es  ;

(d) R^1 y R^3 son metilo, R^{5a} y R^{5b} son etilo, y R^0 y R^4 son hidrógeno, R^2 es  , R^6 es halo o metilo, y R^8 es  o  ;

(e) R^1 y R^3 son metilo, R^{5a} y R^{5b} son etilo, y R^0 y R^4 son hidrógeno, R^2 es  , R^6 es halo, y R^8 es  ;

(f) R^1 y R^3 son metilo, R^{5a} y R^{5b} son etilo, y R^0 y R^4 son hidrógeno, R^2 es  , R^6 es halo, y R^8 es  .

(g) R^1 y R^3 son metilo, R^{5a} y R^{5b} son etilo, y R^0 y R^4 son hidrógeno, R^2 es  , R^6 es metilo, y R^8 es  ;

(h) R^1 y R^3 son metilo, R^{5a} y R^{5b} son etilo, y R^0 y R^4 son hidrógeno, R^2 es  , R^6 es metilo, y R^8 es  .

Preferiblemente los compuestos de la invención exhiben un valor Ki para CRF1 de enlazamiento de 1 micromolar o menos, más preferiblemente 500 nanomolar o menos. Aún más preferiblemente, los compuestos de la invención exhiben un valor Ki para CRF1 de enlazamiento de 250 nanomolar o menos, con 100 nanomolar o menos de enlazamiento aún más preferido. Aún con mayor preferencia, los compuestos de la invención exhiben un valor Ki para CRF1 de enlazamiento de 30 nanomolar o menos, mientras que 15 nanomolar o menos es aún más grandemente preferido. Los compuestos de la invención exhiben un valor Ki para CRF1 de enlazamiento de 5 nanomolar o menos son los más preferidos.

La presente invención también proporciona una composición farmacéutica que comprende un compuesto de la Fórmula I, o una sal farmacéuticamente aceptable de ésta y un portador, diluyente, o excipiente farmacéuticamente aceptable. Un "portador, diluyente, o excipiente farmacéuticamente aceptable" es un medio generalmente aceptado en la técnica para la administración de agentes biológicamente activos a mamíferos, por ejemplo, humanos. Los portadores generalmente se formulan de acuerdo con un sinnúmero de factores dentro del punto de vista de aquellos de experiencia ordinaria en la técnica para determinar y dar cuenta. Estos incluyen, sin limitación: el tipo y naturaleza del agente activo que se formula; el sujeto al cual será

administrada la composición que contiene el agente; la ruta proyectada de administración de la composición; y la indicación terapéutica a que está dirigida. Los portadores y excipientes farmacéuticamente aceptables incluyen ambos medios líquidos el acuoso y el no acuoso, además de una variedad de formas de dosificación sólida y semisólida. Los portadores pueden incluir un sinnúmero de ingredientes diferentes y aditivos además del agente activo, tales ingredientes adicionales, que se incluyen en la formulación para una variedad de razones, por ejemplo, estabilización del agente activo, son bien conocidos por aquellos de experiencia ordinaria en la técnica. Las descripciones de portadores farmacéuticamente aceptables apropiados, y factores involucrados en su selección, se encuentran en una variedad de fuentes disponibles fácilmente, por ejemplo, Remington's Pharmaceutical Sciences, 17 th ed., Mack Publishing Company, Easton, Pa., 1985.

Estos compuestos de la fórmula I se pueden administrar oralmente, tópicamente, parenteralmente, por inhalación o rocío o rectalmente en formulaciones de unidad de dosis que contienen portadores, adyuvantes y vehículos farmacéuticamente aceptables no tóxicos convencionales.

Las composiciones farmacéuticas que contienen compuestos de fórmula general I pueden estar en una forma apropiada para uso oral, por ejemplo, como tabletas, trociscos, pastillas,

suspensiones acuosas o aceitosas, polvos dispersables o gránulos, emulsiones, cápsulas duras o suaves, o jarabes o elíxires.

Las formas de dosificación apropiadas para administración generalmente contienen desde alrededor de 1 mg hasta alrededor de 300 mg de ingrediente activo por unidad. En estas composiciones farmacéuticas, el ingrediente activo ordinariamente estará presente en una cantidad desde alrededor de 0.5 hasta 95% en peso con base en el peso total de la composición. Los recubrimientos apropiados pueden ser aplicados para incrementar la placidez del sabor o la absorción retardada.

Los compuestos de la fórmula I son antagonistas en el receptor de CRF1 y son útiles en el tratamiento de trastornos de ansiedad, depresión, trastorno depresivo mayor, y trastornos relacionados con la tensión. Los trastornos de ansiedad son un grupo de enfermedades, reconocidas en la técnica, que incluyen trastornos fóbicos, estados de ansiedad, trastornos de estrés postraumático y trastornos de ansiedad atípica [The Merck Manual of Diagnosis and Therapy, 16ª edición (1992)]. El estrés emocional a menudo es un factor de precipitación en trastornos de ansiedad, y tales trastornos generalmente responden a medicamentos que disminuyen la respuesta al estrés. Los compuestos también son útiles en programas de eliminación de tabaquismo. El método

de tratamiento involucra la administración a mamíferos (por ejemplo, un humano) de una cantidad efectiva de un compuesto de la invención. En particular, las cantidades terapéuticamente efectivas de los compuestos de la invención son cantidades efectivas para antagonizar, o disminuir, niveles de factor de liberación de corticotropina (CRF) en un mamífero (por ejemplo, un humano), aliviando de esta manera las condiciones del mamífero caracterizadas por niveles altos de anormalidad de expresión de CRF.

Como tal, la presente invención proporciona un método para tratamiento de una condición la cual es tratable por reducción de estimulación del factor CRF1, que comprende la administración a un mamífero (por ejemplo, humano) en necesidad de éste de un compuesto de la Fórmula I, o una sal farmacéuticamente aceptable de ésta, en una cantidad efectiva para antagonizar la estimulación del receptor CRF1.

La presente invención también proporciona el uso de un compuesto de la Fórmula I para la fabricación de un medicamento para tratar una condición la cual es tratable por reducción de la estimulación del receptor CRF1.

La presente invención también proporciona un método de antagonización de receptores CRF1 en un animal de sangre caliente, que comprende la administración al animal de un compuesto de la invención en cantidad efectiva para antagonizar receptores CRF1. El animal de sangre caliente

preferiblemente es un mamífero, y más preferiblemente un humano.

La presente invención también proporciona un método de tratamiento de un trastorno en un animal de sangre caliente, cuyo trastorno manifiesta hipersecreción de CRF, o el tratamiento del trastorno se puede efectuar o facilitar al antagonizar de receptores CRF1, que comprende la administración al animal de una cantidad terapéuticamente efectiva de un compuesto de la invención. El animal de sangre caliente preferiblemente es un mamífero, y más preferiblemente un humano.

Los compuestos de la Fórmula I, o una sal farmacéuticamente aceptable de éstos, son útiles para el tratamiento de varios trastornos y condiciones en un mamífero (por ejemplo, humano) que incluyen trastorno de ansiedad social; trastorno de pánico; trastorno compulsivo de obesidad; trastorno depresivo mayor; ansiedad con enfermedad depresiva co-mórbida; trastorno afectivo; ansiedad; depresión; síndrome de intestino irritable; trastorno de estrés postraumático; parálisis supranuclear; supresión inmune; enfermedad gastrointestinal; anorexia nerviosa, bulimia; u otros trastornos del apetito; síntomas de abstinencia de drogas o alcohol; trastorno de abuso de sustancias (por ejemplo, nicotina, cocaína, etanol, opiatos, u otros fármacos); trastorno inflamatorio; problemas de

fertilidad; trastornos del tratamiento los cuales se pueden efectuar o facilitar al antagonizar de CRF; que incluyen pero no se limitan a trastornos inducidos o facilitado por CRF; un trastorno seleccionado de trastornos inflamatorios tales como artritis reumatoide y osteoartritis, dolor, asma, psoriasis y alergias; trastorno de ansiedad generalizado; pánico, fobias; trastorno compulsivo obsesivo; trastornos del sueño inducidos por estrés; enfermedades relacionadas con el estrés; percepción del dolor tal como fibromialgia; trastornos del humor tales como depresión, que incluyen depresión mayor, trastorno depresivo mayor, depresión de episodio único, depresión recurrente, depresión inducida por abuso a infante, y depresión postparto; distemia; trastornos bipolares; ciclotímia; síndrome de fatiga; síndrome de fatiga crónica; dolor de cabeza inducido por el estrés; dolor de cabeza; cáncer; infecciones del virus de inmunodeficiencia humano (VIH); enfermedades neurodegenerativas tales como enfermedad de Alzheimer, enfermedad de Parkinson, enfermedad de Huntington, demencia senil del tipo Alzheimer, y demencia multiinfarto; enfermedades gastrointestinales tales como úlceras, síndrome de intestino irritable, enfermedad de Crohn, colon espástico, diarrea, e íleo post operativo e hipersensibilidad colónica asociada por trastornos psicopatológicos y estrés; trastornos del apetito tal como anorexia y bulimia nerviosa; estrés hemorrágico; episodios

psicóticos inducidos por estrés; síndrome de enfermedad eutiróide; síndrome de hormona antidiarréica inapropiada (ADH); obesidad; obesidad y el síndrome metabólico; infertilidad; nacimiento prematuro; traumas en la cabeza; trauma en la médula espinal; daño neuronal isquémico (por ejemplo, isquemia cerebral tal como isquemia hipocampal cerebral); daño neuronal excitotóxico; epilepsia; trastornos cardiovasculares y relacionados con el corazón que incluyen hipertensión, taquicardia y lesión del corazón congestiva; apoplejía; disfunciones inmunes que incluyen disfunciones inmunes inducidas por estrés (por ejemplo, fiebres inducidas por estrés, infecciones inducidas por estrés en humanos y animales, síndrome de estrés porcino, fiebre de transporte de bovino, fibrilación paroxismal equina, y disfunciones inducidas por encierro en pollos, estrés de pastoreo en ovejas o estrés relacionado con interacción en perros; espasmo muscular, incontinencia urinaria; demencia senil del tipo Alzheimer; demencia de infarto múltiple; esclerosis lateral amiotrófica; dependencias y adicciones químicas (por ejemplo, dependencias al alcohol, cocaína, heroína, benzodiacepinas, u otros fármacos); síntomas de abstinencia de droga y alcohol; osteoporosis; infantilismo psicosocial e hipoglucemia.

Un compuesto de esta invención puede ser administrado para tratar los trastornos o anormalidades anteriores por

medios que producen contacto del agente activo con el sitio del agente de acción en el cuerpo de un mamífero (por ejemplo, humano), así como por administración oral o parenteral que usa formas de dosificación apropiadas. Los compuestos se pueden administrar por cualquier medio convencional disponible para uso en conjunto con cualquier farmacéutico ya sea como agente terapéutico o en combinación con agentes terapéuticos. Puede ser administrado solo, pero generalmente será administrado con un portador farmacéutico seleccionado con base en la ruta seleccionada de administración y la práctica farmacéutica estándar.

Las cantidades terapéuticamente efectivas de los compuestos de la invención para tratar las enfermedades o trastornos descritos anteriormente en un animal de sangre caliente se pueden determinar en una variedad de formas conocidas para aquellos de experiencia ordinaria en la técnica, por ejemplo, por administración de varias cantidades de un agente particular a un animal en padecimiento de una condición particular y luego la determinación del efecto en el animal. Comúnmente, las cantidades terapéuticamente efectivas de un compuesto de esta invención pueden ser administradas oralmente diariamente en una dosis del ingrediente activo de 0.002 hasta 200 mg/kg de peso corporal. Ordinariamente, una dosis

de 0.01 hasta 10 mg/kg en dosis divididas de una hasta cuatro veces en un día, o en formulación de liberación sostenida será efectiva en la obtención del efecto farmacológico deseado. Se entenderá, sin embargo, que los niveles de dosificación específicos para cualquier paciente particular dependerán de una variedad de factores que incluyen la actividad del compuesto específico empleado, la edad, peso corporal, salud general, sexo, dieta, tiempo de administración, ruta de administración, y grado de excreción, combinación del fármaco y la severidad de la enfermedad particular. La frecuencia de la dosis también puede varia dependiendo del compuesto usado y la enfermedad particular tratada. Sin embargo, para el tratamiento de la mayoría de los trastornos del SNC, un régimen de dosificación de cuatro veces diarias o menos es preferido. Para el tratamiento de estrés y depresión, un régimen de dosificación de una o más veces al día es particularmente preferido.

Se apreciará que todas las combinaciones de modalidades específicas y preferidas discutidas anteriormente y los ejemplos descritos posteriormente están contemplados como que están abarcados por la presente invención, proporcionadas las combinaciones no comprende agrupamientos inconsistentes. Además, todos los ejemplos descritos en la presente están

para propósitos ilustrativos, y no pretenden reducir el alcance de la invención de ninguna manera.

Los compuestos de la invención generalmente se pueden preparar usando las rutas sintéticas ilustradas en los Esquemas posteriores. Los materiales de arranque se pueden preparar mediante procedimientos descritos en estos esquemas o mediante procedimientos que podrían ser bien conocidos para uno de experiencia ordinaria en química orgánica. Las variables usadas en los esquemas son como se definen a continuación o como en las reivindicaciones.

El técnico experto apreciará que la introducción de ciertos substituyentes creará asimetría en los compuestos de la Fórmula I. La presente invención contempla todos los enantiómeros y mezclas de enantiómeros y estereoisómeros, que están, tanto en la forma pura estereoméricamente (por ejemplo, pura geométricamente, pura enantioméricamente, o pura diastereoméricamente) y mezclas enantioméricas y estereoisoméricas, que incluyen racematos. Las mezclas enantioméricas y estereoisoméricas se pueden resolver en sus componentes enantiómeros o estereoisómeros mediante métodos bien conocidos, tales como cromatografía de gas de fase quiral, cromatografía líquida de alto desempeño de fase quiral, o cristalización del compuestos como un complejo de sal quiral. Los enantiómeros y estereoisómeros

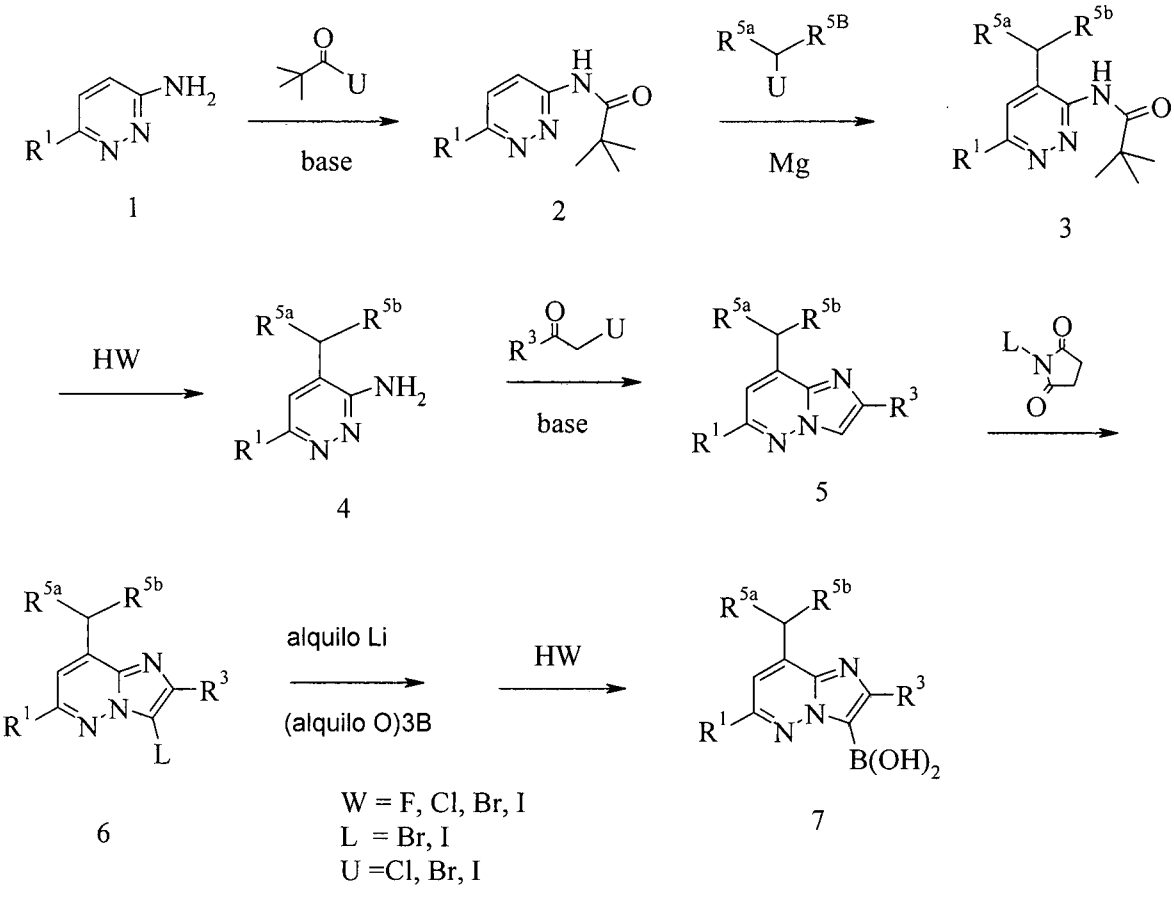
también se pueden obtener de intermedios, reactivos y catalizadores puros estereoméricamente o enantioméricamente mediante métodos sintéticos asimétricos bien conocidos.

Las sales farmacéuticamente aceptables están contempladas para estar dentro del alcance de la presente invención. Los compuestos de la presente invención son bases y sales de los compuestos se pueden formar con ácidos, por ejemplo, una sal con ácido inorgánico tal como ácido hidroclórico o una sal con ácido orgánico tal como ácido trifluoroacético.

Los compuestos de esta invención se pueden preparar mediante el empleo de reacciones como se muestran en los siguientes esquemas, además de otras manipulaciones estándar que son conocidas en la literatura o ejemplificadas en los procedimientos experimentales. Estos esquemas, por lo tanto, no están limitados por los compuestos listados ni por ningún substituyente particular empleado para propósitos ilustrativos.

ESQUEMA DE REACCION I

Síntesis de fragmento de imidazo[1,2-b]piridazina



1 2 3 4 5 6 7

R^1, R^3, R^{5a}, y R^{5b} son definidos supra.

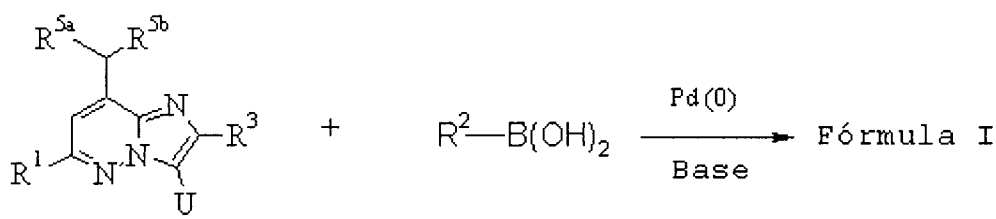
En el Esquema de reacción I, un 3-amino-piridazina 1 sustituido es acilado con haluro de pivaloilo y una base, por ejemplo, trietilamina en un solvente aprótico polar, por ejemplo, cloruro de metileno a temperatura de habitación a reflujo para dar amida 2. La amida 2 se trata con un reactivo Grignard en dietiléter o THF para dar la 4-amida sustituida 3. La amida 3 se hidroliza con HCl acuoso a temperatura desde ambiente hasta 110°C luego se neutraliza para dar la amina 4

libre. La amina 4 se trata con una cetona de alfa-halo y base, por ejemplo, bicarbonato de sodio en etanol al 95% a temperatura desde ambiente hasta 110°C para dar imidazopiridazina 5. La imidazopiridazina 5 se trata con un reactivo de halogenación por ejemplo, N-yodo o N-bromosuccinimida en un solvente aprótico polar (por ejemplo, acetonitrilo) desde 0°C hasta temperatura ambiente para dar el haluro 6. El haluro 6 se somete a intercambio de metal de halógeno con un reactivo de litio de alquilo, por ejemplo, n, sec-, o tert-butillitio en dietiléter o THF desde -78 °C hasta temperatura ambiente, seguido por tratamiento con un trialquilborato, por ejemplo, trimetilborato para dar un éster borónico intermedio, el cual se hidroliza durante el trabajo con HCl acuoso para proporcionar el ácido borónico 7.

Esquema de Reacción II

Síntesis de Compuestos de la Fórmula I mediante catálisis de metal de transición.

Ecuación 1.



6 8

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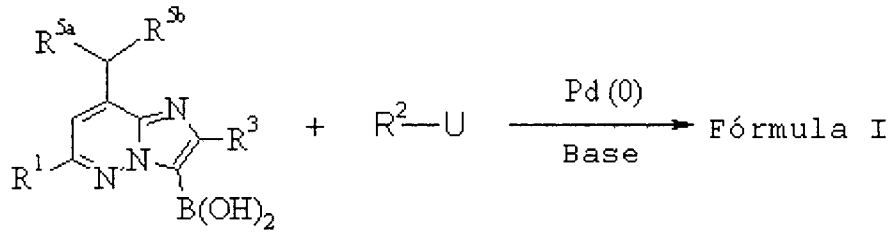
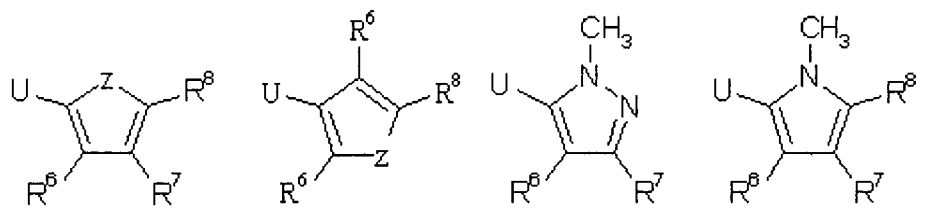
Ecuación 2.

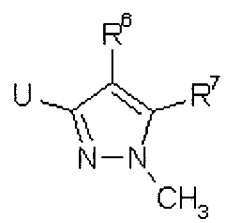


7 9

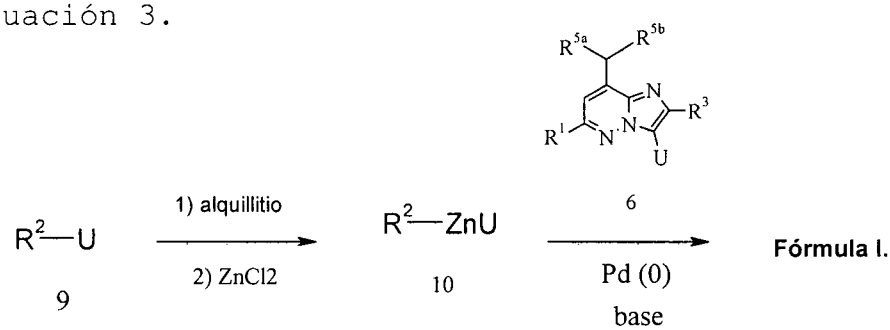
Donde R^2-U se selecciona del grupo que consiste de:



y

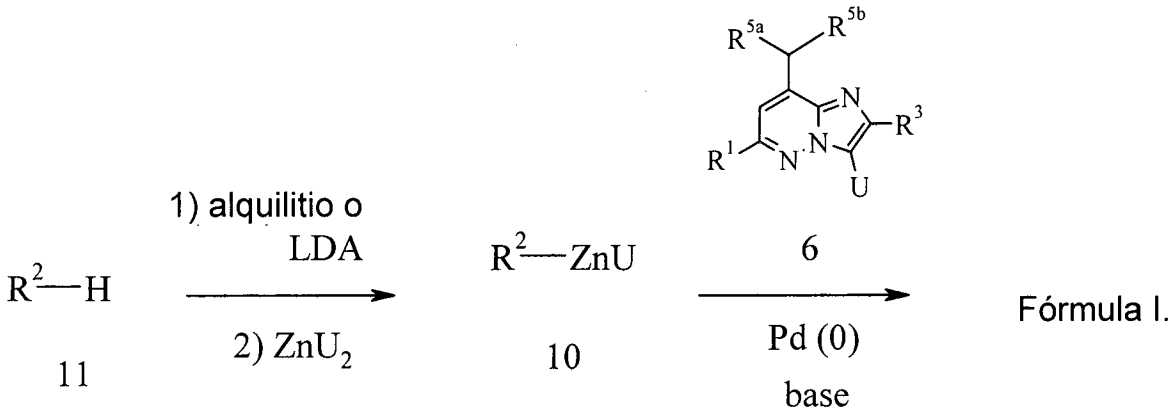


Ecuación 3.

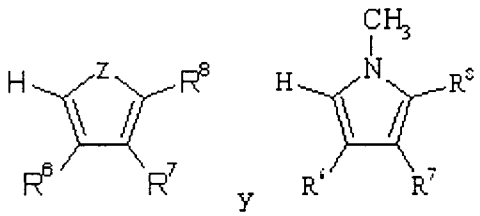


9 10 6

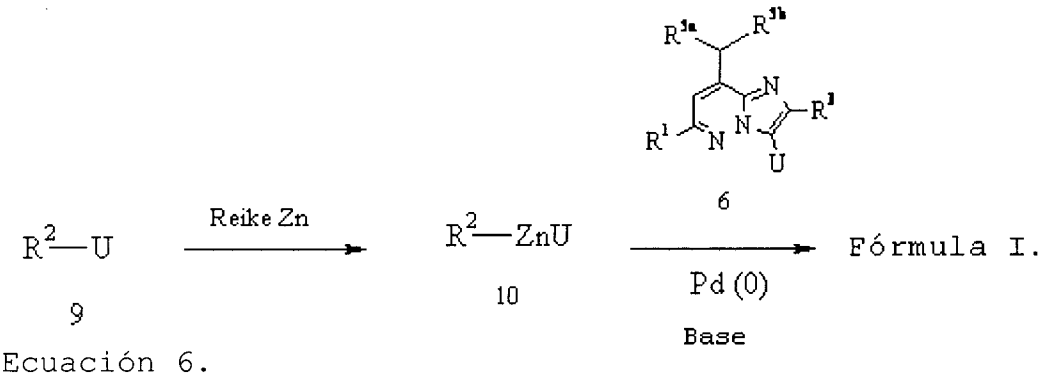
Ecuación 4.



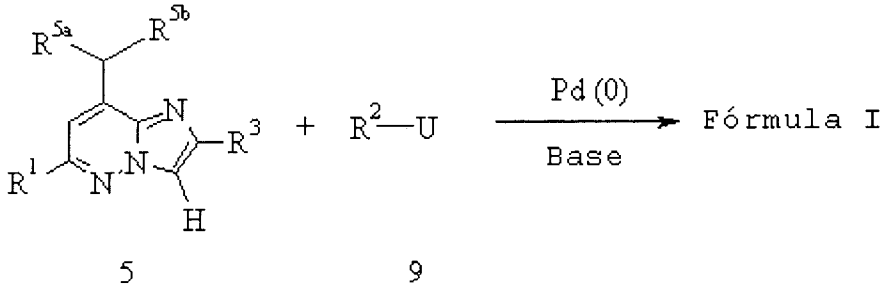
Donde R^2-H se selecciona del grupo que consiste de:



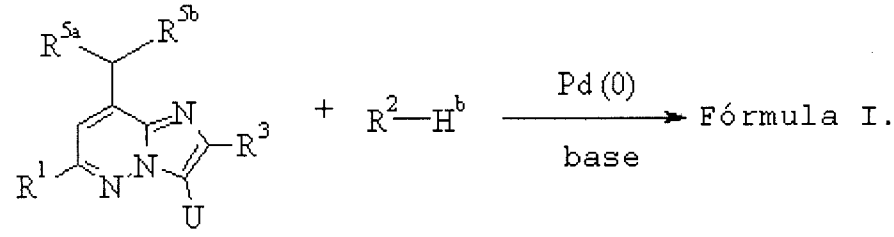
Ecuación 5.



Ecuación 6.

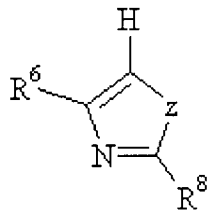


Ecuación 7.



6 12

Donde R^2-H^b se selecciona de:



R^1, R^2, R^3, R^{5a}, R^{5b} R^6, R^7, R^8, U, y z se definen supra.

En el Esquema de reacción II ecuación 1, el haluro 6 se puede usar en una reacción de acoplamiento con un ácido borónico heterocíclico de anillo de 5 miembros 8 en la presencia de catalizador de paladio, por ejemplo, tetrakis-trifenilfosfina de paladio (0) en una mezcla de alcanol(metanol o n- o i-propanol) menor/DME desde 70-120 °C para dar compuestos de la fórmula I.

Alternativamente en la ecuación 2, el ácido borónico 7 se puede usar en una reacción de acoplamiento con un haluro heterocíclico de anillo de 5 miembros 9 y catalizador de paladio, por ejemplo, tetraquis-

trifenilfosfina de paladio (0) en una mezcla de alcanol(metanol o n- o i-propanol)/DME desde 70-120 °C para dar un compuesto de la fórmula I.

En la ecuación 3, los haluros 9 heterocíclicos de anillo de 5 miembros pueden someterse a intercambio de halógeno-litio con, por ejemplo, n-, sec- o Pert-butil litio en THF o éter a -65°C, seguido por intercambio de litio-zinc con $ZnCl_2$ en cualquiera de dietiléter o THF a temperaturas hasta temperatura ambiente. El reactivo de organozinc 10 in situ puede luego someterse a acoplamiento con el haluro 6 en la presencia de paladio, por ejemplo, $PdCl_2$(dppf) en THF desde 70-120°C para dar un compuesto de la fórmula I.

En la ecuación 4, un anillo heterocíclico de 5 miembros con un protón de anillo se pueden litiar mediante ya sea un alquillitio, por ejemplo, n-, sec- o Pert-butil litio o amida de diisopropil litio en THF o éter a -65°C a temperatura ambiente seguido por intercambio de litio-Zinc con haluro de zinc de anhidro en cualquiera de dietiléter o THF para dar un reactivo de organozinc 10 que se usa en la ecuación 3 anterior. Un experto en la técnica también apreciará que los reactivos de organozinc 10 disponibles comercialmente se pueden usar directamente como un compañero de acoplamiento de organozinc.

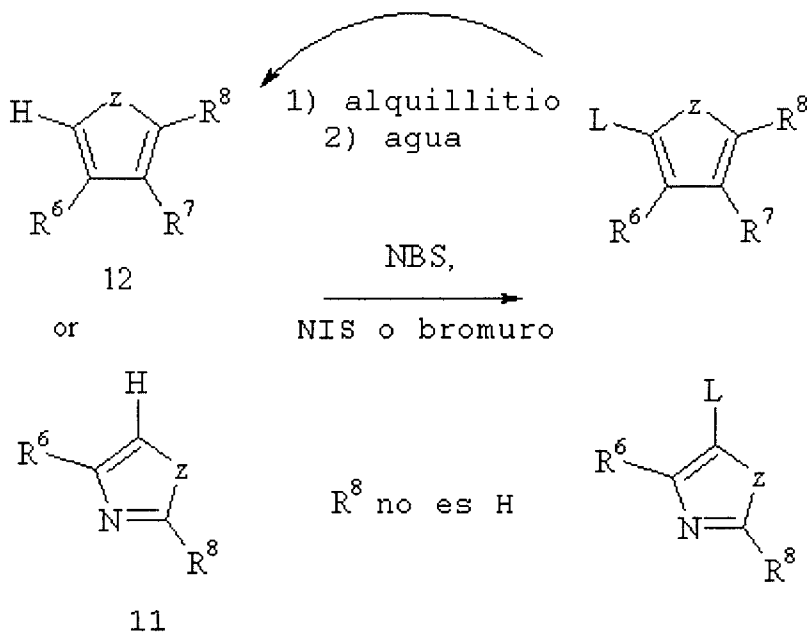
Además de la ecuación 5, puede ser ventajoso o conveniente usar Zn Reike en THF para convertir directamente un halo 9 heterocíclico de 5 miembros a un reactivo de organozinc 10 para acoplamiento con un haluro 6.

En la ecuación 6, un halo heterocíclico 9 de 5 miembros puede ser acoplado directamente con la imidazo[1,2-b]piridazina intermedia 5 en la presencia de paladio, por ejemplo, $Pd_2(dba)_3$, $PdCl_2$, acetato de paladio/TDBPP, o tetraquis-trifenilfosfina de paladio (0) en solvente DMF, THF, o NMP desde 70-120°C para dar un compuesto de la fórmula I.

Alternativamente, de la ecuación 7, el haluro 6 de imidazo[1,2-b]piridazina puede ser acoplado directamente con un heterociclo de 5 miembros 11 en la presencia de paladio, por ejemplo, $Pd_2(dba)_3$, $PdCl_2$, o acetato de paladio/TDBPP en solvente DMF, THF, o NMP desde 70-120°C para dar un compuesto de la fórmula I.

Esquema de Reacción III

Síntesis de Haluros Heterocíclicos de 5 Miembros Sustituidos.



R^6, R^7, R^8, L, y z se definen supra.

Varios anillos heterocíclicos de 5 miembros y/o sus bromuros y/o yoduros útiles como materiales de arranque para la síntesis de compuestos de la Fórmula I están disponibles comercialmente o se pueden preparar por métodos bien conocidos por el técnico experto. Del Esquema III, también se pueden preparar por halogenación, por ejemplo, con bromuro, NBS o NIS. Además, algunos de los intermedios 11 y 12 se pueden

preparar por intercambio de halógeno lítio seguido por apagado con agua.

Los compuestos de la Fórmula I como intermedios en la preparación de otros compuestos de la Fórmula I incluyen la adición de reactivos de arillitio (generados por los métodos de las ecuaciones 3 y 4 en el Esquema II) para compuestos de carbonilo, por ejemplo, aldehídos, cetonas, ésteres, y amidas de Weinreb. Los carbinoles o compuestos de carbonilo que resultan además se elaboran por halogenación bajo condiciones ácidas y mediante una segunda adición de arillitio, respectivamente.

ABREVIATURAS

TBDMSCl o TBDMSiCl - cloruro de tert-butIl-dimetIlsililo

MS (ES) - Espectro de Electrorocío de Masa

THF - tetrahidrofurano

DMSO - Dimetilsulfóxido

DMF - Dimetilformamida

DCM, CH2C12 - diclorometano

Dioxano - 1,4-dioxano

N2 - gas nitrógeno

NIS - N-yodosuccinimida

NBS - N-bromosuccinimida

285

MeOH - metanol

EtOH - 95% etanol

RBF, RB - frasco de fondo redondo

RBSN - frasco de cuello único de fondo redondo

SiO2 - gel de sílice

EtOAc, AcOEt - etilacetato

GFF - filtro de microfibra de cristal

CLAP - Cromatografía líquida de alta presión sobre gel de sílice.

ISCO - cromatografía líquida de baja presión de marca ISCO sobre gel de sílice.

AcCl - cloruro de acetilo

LDA - diisopropilamina de litio

KOAc - Acetato de potasio

TBABr - bromuro de amonio de tetrabutilo

NMP - N-Metilpirrolidinona

TDBPP - Tris (2,4-di-*t*-butilfenil)fosfato.

Pd_2dba_3 - Tris(dibencilideneacetona)dipaladio

$PdCl_2(dppf)$ - Dicloro(difenilfosfinoferrocen)paladio

Tetrakis - tetraquis-(trifenilfosfina)-paladio

Dppf - 1,1'-bis(difenilfosfino)ferroceno)

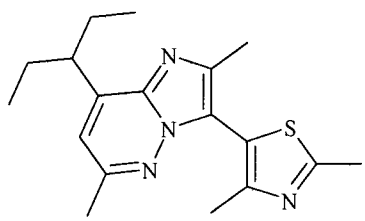
t.a., TA - temperatura ambiente

EJEMPLOS

Sin una elaboración adicional, se cree que alguien experto en la técnica puede, al usar la descripción antecedente, practicar la presente invención a su más amplio grado. Los siguientes ejemplos se proporcionan para describer la invención en mayor detalle. Se pretenden para ilustrar y no limitar la invención de ninguna manera. Los Ejemplos 1-255 proporcionan compuestos ejemplares e ilustran la preparación de los mismos. Los Ejemplos A-D ilustran diversos ensayos biológicos que se pueden usar para determinar las propiedades biológicas de los compuestos de las invenciones. Aquellos expertos en la técnica reconocerán rápidamente las variaciones apropiadas de los procedimientos descritos en los ejemplos.

Ejemplo 1.

Preparación de 8-(1-etil-propil)-3-(2,4-dimetil-5-tiazolil)-2,6-dimetil-imidazo[1,2-b]piridazina.



A. 6-Metil-piridizin-3-ilamina.

La 3-Cloro-6-metilpiridazina (25.0g, 0.229 moles) se disuelve en 250 mL de NH_4OH y se calienta hasta 170°C en un

recipiente sellado durante 24 horas. Los solventes se evaporan. El residuo se tritura en cloruro de metileno, y un sólido se filtra. Este procedimiento de trituración se repite con el producto filtrado cuatro veces. Los sólidos filtrados se combinan y se secan en un horno a vacío durante la noche para obtener el compuesto del título como un sólido blanco apagado 4.32 g (0.040 moles, 20%). ^{1}H-RMN (dmso-d6): δ 7.1 (d, J=8.9 Hz, 1H); 6.67 (d, J=8.9 Hz, 1H); 6.04 (s, br, 2H); 2.33 (s, 3H) ppm. ES+ = 110 (100%, M + 1).

B. 2,2-Dimetil-N-(6-metil-piridazina-3-il)-propionamida.

Método 1: A un matraz seco se agregan 7.12 g (0.065 moles) de 6-metil-piridizin-3-ilamina en 170 ml de cloruro de metileno seco. En seguida, 14.5 ml de trietilamina se agregan y la reacción se enfría hasta 0°C. El cloruro de pivaloilo (2.7 ml, 1.2 eq) se agrega cuidadosamente, y la mezcla de reacción se agita 10 minutos, se remueve del baño, y se agita 4 horas más. El diclorometano (200 mL) se agrega, y la mezcla de reacción se lava 3 veces con bicarbonato de sodio acuoso saturado, luego salmuera. La capa orgánica se seca sobre sulfato de sodio, se filtra, y evapora a un aceite. El producto crudo se purifica por medio de cromatografía en gel de sílice al usar un gradiente de hexano: acetato de etilo dando el compuesto del título como un sólido blanco que pesa 1.51 g (7.8 mmoles, 42.7%). ^{1}H-RMN (DMSO-d6), δ 10.39 (s,

1H); 8.11 (d, J = 9.30 Hz, 1H); 7.51 (d, J = 9.29 Hz, 1H); 2.54 (s, 3H); 1.23 (s, 9H) ppm. ES+ = 194 (M+1).

Método 2: A un tubo seco a presión se agregan 200 mg (1.56 mol) de 3-cloro-5-metilpiridazina, 190 mg (1.87 mmol) de trimetilacetamida, 14.6 mg (0.023 mmol) de rac-2,2'-bis(difenilfosfina)-1,1'-binaftilo, tris (dibencilidenoacetona)-dipaladio (0), 762.4 mg (2.34 mmol) de carbonato de cesio y 1.5 ml de tetrahidrofurano seco. El tubo a presión se purga con nitrógeno y se sella. La reacción se calienta hasta 100°C durante la noche. La reacción luego se enfría, se diluye con diclorometano, y se filtra a través de celite. Los solventes se evaporan y el producto crudo se purifica por medio de cromatografía en gel de sílice al usar un gradiente de acetato de etilo:hexano para obtener 91 mg (0.47 mmol, 30%) como un sólido blanco.

C. N-[4-(1-Etil-propil)-6-metil-piridazin-3-il]-2,2-dimetil-propionamida.

El polvo de magnesio activado (19.2 g, 0.792 moles) se agrega a un matraz seco de 3L acoplado con un condensador y un embudo de goteo. El aparato completo se calienta con una pistola seca bajo vacío y se deja enfriar. Se agrega suficiente éter para cubrir el magnesio. El 3-Bromopentano (100 g, 0.662 mmol) se agrega al embudo de adición en 175 ml de éter dietílico. A 1/3 de la solución de bromopentano se

agrega al magnesio y la mezcla de reacción se agita bajo nitrógeno hasta que sucede del burbujeo. Luego, se gotea el resto a tal velocidad que el burbujeo continúa suavemente. La reacción se agita por 30 minutos después de que se suspendel burbujeo. A continuación, la 2,2-dimetil-N-(6-metil-piridazina-3-il)-propionamida (21.3 g, 0.110 mmol) disuelta en 225 ml de THF seco se agrega gota a gota. La mezcla de reacción se agita durante 1 hora. El tartrato de sodio saturado (1 L) se agrega cuidadosamente, y la reacción se agita por 30 minutos. La mezcla de reacción se transfiere a un matraz más grande, 2 L de acetato de etilo se agrega, y la reacción se agita 1 hora más. Las capas se separan y la capa acuosa se extrae varias veces con acetato de etilo. Los extractos orgánicos se combinan, y los solventes se evaporan. El residuo se toma en 600 mL de diclorometano, y yodo (28 g, 0.110 mol) se agrega. La reacción se agita durante 2 horas. La capa orgánica se lava una vez con solución acuosa de sulfito de sodio y luego con agua. La capa orgánica se seca sobre sulfato de sodio, se filtra, y se evapora a un aceite rojo. El producto crudo se purifica por medio de cromatografía en gel de sílice al usar un gradiente de hexanos:acetato de etilo. Las fracciones de producto se combinan y evaporan. El residuo se tritura en acetato de etilo y un sólido color canela claro se filtra para obtener 12.0 g (45.6 mmol, 41 %) del compuesto del título. ^{1}H-RMN

(DMSO-d_6), δ 9.88 (s, 1H); 7.59 (s, 1H); 2.60 (s, 3H); 2.39-2.42 (m, 1H); 1.21-1.37 (m, 2H); 1.38-1.43(m, 2H); 1.23(s, 9H); 0.71 (t, J = 7.49 Hz, 6H) ppm. MS/ES+ = 264.

D. 4-(1-Etil-propil)-6-metil-piridazin-3-ilamina.

La N-[4-(1-Etil-propil)-6-metil-piridazin-3-il]-2,2-dimetil-propionamida (12.0 g, 45 mmol) se disuelve en 60 mL de ácido clorhídrico concentrado. La mezcla de reacción se calienta hasta 95°C en un matraz sellado durante 2 horas. La reacción se prepara al vaciar sobre hielo y se extrae con acetato de etilo tres veces. La capa orgánica se descarga, y el pH de la capa acuosa se ajusta al usar hidróxido de sodio 2N. La solución básica se extrae con acetato de etilo cinco veces. Los extractos orgánicos se combinan, se secan sobre sulfato de magnesio, se filtran, y evaporan para obtener 6.68 g (37 mmol, 81%) del compuesto del título como un aceite color café. ^{1}H-RMN (DMSO-d6), δ 6.95 (s, 1H); 5.89 (s, br, 2H); 2.52-2.56 (m, 1H); 2.34 (s, 3H); 1.44-1.58 (m, 4H); 0.72 (t, J = 7.04 Hz, 6H) ppm. MS/ES+ = 180 (100%, M+1).

E. 8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

La 4-(1-Etil-propil)-6-metil-piridazin-3-ilamina (850 mg, 4.74 mmol), cloroacetona (0.415 ml, 5.22 mL) y 20 mL de etanol se calientan en el microondas a 110°C por 35 minutos. El bicarbonato de sodio (1.2 g, 14.2 mmol) se agrega, y la

mezcla de reacción se calienta en un baño de aceite a 100°C durante la noche. El solvente se evapora y el residuo se lleva en acetato de etilo y se lava tres veces con salmuera. La capa orgánica se seca sobre sulfato de sodio, se filtra, y se evapora hasta un aceite café. El producto crudo se purifica por medio de cromatografía en gel de sílice al usar un gradiente de acetato de etilo:hexano. El compuesto del título es un aceite que pesa 3.69 g (17.0 mmol, 84%). ^{1}H-RMN (DMSO-d6), δ 7.34 (s, 1H); 6.84 (s, 1H); 2.85-3.10 (m, 1H); 2.43 (s, 3H); 2.32 (s, 3H); 1.70-1.80 (m, 4H); 0.712 (t, J = 7.49 Hz, 6H) ppm. EM/ES+ = 219 (100%, M+2).

F. 8-(1-Etil-propil)-3-yodo-2,6-dimetil-imidazo[1,2-b]piridazina.

La 8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (5.1 g, 0.023 moles) y 50 mL de acetonitrilo seco se agregan a un matraz purgado con nitrógeno y se enfrían hasta 0°C. El NIS (5.54 g, 0.025 moles) en 90 mL de acetonitrilo seco se agrega. El baño se permite que llegue a temperatura ambiente, y la reacción se agita durante la noche. Los solventes se evaporan. El residuo se lleva en acetato de etilo, se lava dos veces con 50% de solución acuosa de tiosulfato de sodio y con salmuera. La capa orgánica se seca sobre sulfato de sodio, se filtra, y evapora de nuevo hasta un residuo. El producto crudo se tritura en

una cantidad pequeña de acetonitrilo, y un sólido se filtra por completo. La trituración se repite varias veces para obtener el compuesto del título como un sólido color canela claro que pesa 7.29 g (0.021 moles, 91%). ^{1}H-RMN (DMSO-d_6), δ 6.96 (s, 1H); 3.0-3.3 (m, 1H); 2.51 (s, 3H); 2.35 (s, 3H); 1.71-1.80 (m, 4H); 0.71 (t, J = 7.48 hz, 6H) ppm. EM/ES+ = 344 (100%, M+1).

G. Ácido 8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina-3-il borónico.

En un matraz de fondo redondo de 50 mL de 3 cuellos purgado con nitrógeno secado al horno, 1.00g (2.91 mmol) de 8-(1-etil-propil)-3-yodo-2,6-dimetil-imidazo[1,2-b]piridazina en 60mL de THF seco se enfría hasta -78°C. 4.12mL (7.00mmol) de tert-butillitio 1.7 M en hexanos se agrega y la reacción se agita a -78°C durante 1 hora. 0.818mL (7.30mmol) de trimetil borato se agrega y se sigue la reacción por EM y CCD (1:1 Hexano:EA). La indicación del producto se observa por el espectro de masas. La reacción se permite agitar por una hora adicional, apagada con ácido clorhídrico 1N, y se diluye con acetato de etilo. La capa orgánica se separa, y la capa acuosa se extrae tres veces con 100 mL de acetato de etilo. Los extractos se combinan, se secan sobre $MgSO_4$, se filtran, y se concentran. El residuo de la reacción se tritura en

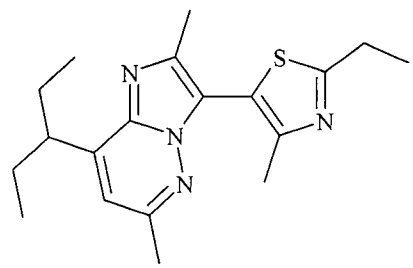
hexanos y se filtra por completo un sólido. EM, ES+ = 262.2 (M+1).

H. 8-(1-Etil-propil)-3-(2,4-dimetil-5-tiazolil)-2,6-dimetil-imidazo[1,2-b]piridazina.

A un tubo de microondas a presión se agrega 0.340g (1.30mmol) de ácido 8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina-3-il borónico, 0.100g (0.521mmol) de 5-bromo-2,4-dimetiltiazol, 0.361g (0.313mmol) de $Pd(PPh_3)_4$, 0.650mL (1.30mmol) de Na_2CO_3 acuoso 2M, y 2mL de 7:3:2 DME:H2O:EtOH, y la mezcla se calienta a 160°C por 40min. La reacción se verifica por EM lo cual indica producto presente. La mezcla de reacción se divide entre 75mL de acetato de etilo y 75mL de agua. Las capas se separan y lo acuoso se extrae 3X50mL de acetato de etilo, se secan ($MgSO_4$), y concentran bajo vacío. La mezcla cruda se purifica por cromatografía al usar hexanos/acetato de etilo como un sistema de solventes. Las fracciones que contienen producto se combinan para obtener 0.100g del producto, 58% de rendimiento. EM, ES+ = 329.2 (M+1); ^{1}H-RMN (DMSO-d6) = 6.974 (s, 1H); 3.085-3.052 (m, 1H); 2.665 (s, 3H); 2.438 (s, 3H); 2.290 (s, 3H); 2.147 (s, 3H); 1.849-1.727 (m, 4H); 0.776-0.738 (m, 6H) ppm.

Ejemplo 2.

Preparación de 8-(1-etil-propil)-3-(2-etil-4-metil-5-il)-2,6-dimetil-imidazo[1,2-b]piridazina.



A. 5-Bromo-2-etil-4-metiltiazol.

En un matraz de fondo redondo de 50 mL, purgado con N_2, secado al horno, 1.00 g (7.86 mmol) de 2-etil-4-metiltiazol reacciona con 0.487 mL (9.43 mmol) de bromo en 7mL de ácido acético a temperatura ambiente. La reacción se verifica por EM después de 2 horas. La mezcla de reacción se divide entre 50 mL de H_2O y 25 mL de CH_2Cl_2. Las capas se separan y el acuoso se extrae 3X25mL de CH_2Cl_2. Los orgánicos se combinan y se lavan 1X25mL 1N $Na_2S_2O_3$, se secan ($MgSO_4$), y se concentran bajo vacío para dar 1.38g del compuesto del título, 85% de rendimiento. EM, ES+ = 206.0 (M+1); 1H-RMN (DMSO-d6) = 2.940-2.810 (m, 2H); 2.253-2.251 (m, 3H); 1.225-1.222 (m, 3H) ppm.

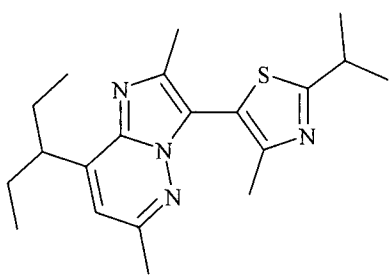
B. 8-(1-Etil-propil)-3-(2-etil-4-metil-5-tiazolil)-2,6-dimetil-imidazo[1,2-b]piridazina.

Al usar un procedimiento similar al Ejemplo 1H, el 5-bromo-2-etil-4-metiltiazol produce el producto del título en

27% de rendimiento. EM, ES+ = 343.2 (M+1); 1H-RMN (DMSO-d6) = 6.975 (s, 1H); 3.090-3.056 (m, 1H); 3.025-2.968 (m, 2H); 2.439 (s, 3H); 2.291 (s, 3H); 2.155 (s, 3H); 1.835-1.744 (m, 4H); 1.338-1.300 (m, 3H); 0.776-0.740 (m, 6H) ppm.

Ejemplo 3.

Preparación de 8-(1-etil-propil)-3-(2-isopropil-4-metil-5-tiazolil)-2,6-dimetil-imidazo[1,2-b]piridazina.



A. 5-Bromo-2-isopropil-4-metiltiazol.

Al usar un procedimiento similar al Ejemplo 2A, el 2-isopropil-4-metiltiazol produce el producto del título en 90% de rendimiento. EM, ES+ = 220.0 (M+1); 1H-RMN (DMSO-d6) = 3.210-3.175 (m, 1H); 2.257 (s, 3H); 1.264-1.248 (d, 6H) ppm.

B. 8-(1-Etil-propil)-3-(2-isopropil-4-metil-5-tiazolil)-2,6-dimetil-imidazo[1,2-b]piridazina.

Al usar un procedimiento similar al Ejemplo 1H, el 5-bromo-2-isopropil-4-metiltiazol produce el producto del título en 29% de rendimiento. EM, ES+ = 357.2 (M+1); 1H-RMN (DMSO-d6) = 6.990 (s, 1H); 3.120-3.050 (m, 1H); 2.442 (s,

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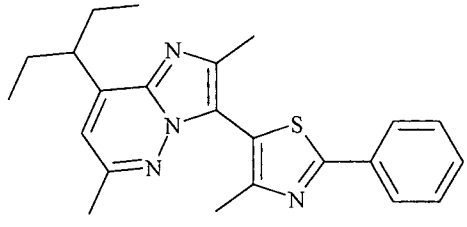
3H); 2.294 (s, 3H); 2.158 (s, 3H); 1.810-1.750 (m, 4H); 1.362-1.344 (d, 6H); 0.777-0.741 (m, 6H) ppm.

Ejemplo 4.

Preparación de 8-(1-etil-propil)-3-(4-metil-2-fenil-5-tiazolil)-2,6-dimetil-imidazo[1,2-b]piridazina.



A. 5-Bromo-4-metil-2-feniltiazol.

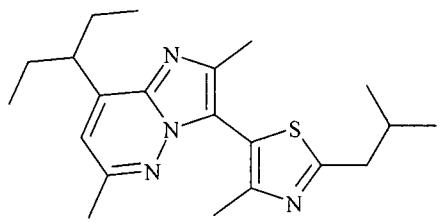
Al usar un procedimiento similar al Ejemplo 2A, el 4-metil-2-feniltiazol produce el producto del título en 90% de rendimiento. EM, ES+ = 256.0 (M+1); 1H-RMN (DMSO-d6) = 7.900-7.867 (m, 2H); 7.538-7.512 (m, 3H); 2.407 (s, 3H) ppm.

B. 8-(1-Etil-propil)-3-(4-metil-2-fenil-5-tiazolil)-2,6-dimetil-imidazo[1,2-b]piridazina.

Al usar un procedimiento similar al Ejemplo 1H, el 5-bromo-4-metil-2-feniltiazol produce el producto del título en 24% de rendimiento. EM, ES+ = 391.3 (M+1); 1H-RMN (DMSO-d6) = 8.005-7.995 (m, 2H); 7.538-7.534 (m, 3H); 7.010 (s, 1H); 3.185-3.095 (m, 1H); 2.496 (s, 3H); 2.394 (s, 3H); 2.316 (s, 3H); 1.895-1.785 (m, 4H); 0.826-0.788 (m, 6H) ppm.

Ejemplo 5.

Preparación de 8-(1-etil-propil)-3-[4-metil-2-(2-metil)propil-5-tiazolil]-2,6-dimetil-imidazo[1,2-b]piridazina.



A. 5-Bromo-4-metil-2-(2-metil)propiltiazol.

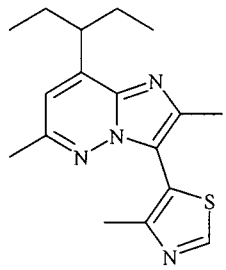
Al usar un procedimiento similar al Ejemplo 2A, el 4-metil-2-(2-metil)propiltiazol produce el producto del título en 96% de rendimiento. EM, ES+ = 234.1 (M+1); 1H-RMN (DMSO-d6) = 2.744 (m, 2H); 2.259 (s, 3H); 1.895-2.000 (m, 1H); 0.905-0.888 (m, 6H) ppm.

B. 8-(1-Etil-propil)-3-(4-metil-2-(2-metil)propil-5-tiazolil)-2,6-dimetil-imidazo[1,2-b]piridazina.

Al usar un procedimiento similar al Ejemplo 1H, el 5-bromo-4-metil-2-(2-metil)propiltiazol produce el producto del título en 7% de rendimiento. EM, ES+ = 371.3 (M+1); 1H-RMN (DMSO-d6) = 7.013 (s, 1H); 3.109 (m, 1H); 2.892-2.875 (d, 2H); 2.517 (s, 3H); 2.513 (s, 3H); 2.476 (s, 3H); 2.107-2.073 (m, 1H); 1.868-1.780 (m, 4H); 1.018-1.002 (d, 6H); 0.813-0.775 (m, 6H) ppm.

Ejemplo 6.

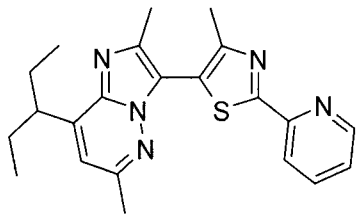
Preparación de 8-(1-Etil-propil)-3-[4-metil-5-tiazolil]-2,6-dimetil-imidazo[1,2-b]piridazina.



3.00 g de 8-(1-Etil-propil)-3-yodo-2,6-dimetil-imidazo[1,2-b]piridazina (8.74 mmol), 4.32 g de 4-metil-2H-tiazol (43.6 mmol), 453 mg de trifenilfosfina (1.73 mmol) y 5.85 g de carbonato de cesio (18.0 mmol) se colocaron en un tubo sellado con 20 ml de DMF y N2 gas se burbujeó durante 40 min. 39 mg de Pd2dba3 (0.43 mmol) se agrega y el tubo se sella y se calienta a 130°C durante la noche. La mezcla de reacción fría se filtra y se aplica en una columna de gel de sílice (Hexano → Hexano : AcOEt = 3: 1) para dar 2.12 g del compuesto del título (77%). ^{1}H-RMN (DMSO-d6) δ 9.215 (s, 1H); 6.993 (s, 1H); 3.079 (m, 1H); 2.480 (s, 3H); 2.439 (s, 3H); 2.302 (s, 3H); 1.824-1.751 (m, 4H); 0.780-0.743 (m, 6H) ppm. EM, ES+ = 315.2.

Ejemplo 7.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(4-metil-2-piridin-2-il-tiazol-5-il)-imidazo[1,2-b]piridazina.



A. 8-(1-etil-propil)-3-[2-bromo-4-metil-5-tiazolil]-2,6-dimetil-imidazo[1,2-b]piridazina.

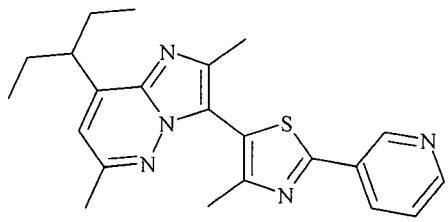
En un matraz de fondo redondo de 15 ml purgado con N2 secado en horno, 0.028 g (0.089 mmol) de 8-(1-etil-propil)-3-[4-metil-5-tiazolil]-2,6-dimetil-imidazo[1,2-b]piridazina. En 1.5mL de CH_2Cl_2 seco se enfría hasta 0°C. 0.019 g (0.107 mmol) de NBS se agrega y la reacción se agita durante la noche permitiendo que el baño llegue a temperatura ambiente. La mezcla de reacción se purifica directamente por cromatografía usando hexano/acetato de etilo como sistema de solvente. Las fracciones que contienen el producto se combinan para obtener 0.012 g, 34% de rendimiento. EM, ES+ = 395.1 (M+1); 1H-RMN (DMSO-d6) = 7.070 (s, 1H); 3.10 (m, 1H); 2.49 (s, 3H); 2.36 (s, 3H); 2.25 (s, 3H); 1.85-1.78 (m, 4H); 0.81-0.77 (m, 6H) ppm.

B. 8-(1-Etil-propil)-2,6-dimetil-3-(4-metil-2-piridin-2-il-tiazol-5-il)-imidazo[1,2-b]piridazina.

Una mezcla de 3-(2-bromo-4-metil-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (380 mg, 0.96 mmol), bromuro de 2-piridinazinc (0.5 M en THF, 2.1 mL, 4 mmol), $Pd(PPh_3)_4$ (30 mg, 0.026 mmol) y THF (3 mL) se calienta a 80°C durante 18 horas. El acetato de etilo (20 mL) se agrega. La capa orgánica se separa, se seca sobre sulfato de magnesio, se filtra, y el solvente se remueve in vacuo. La purificación se llevo a cabo por medio de cromatografía en gel de sílice usando una mezcla 3:1 de hexanos y acetato de etilo como eluyente para producir el compuesto del título 325 mg (86%). ^{1}H-RMN ($CDCl_3$), δ 9.55 (m,1H); 8.10 (m, 1H); 7.73 (m,1H); 7.26 (m,1H); 6.58 (s, 1H); 3.24 (m, 1H); 2.43 (s, 3H); 2.40 (s, 3H); 2.33 (s, 3H); 1.76 (m, 4H); 0.80 (t, 6H) ppm. EM/ES+ = 391 (100%, M+1).

Ejemplo 8.

Preparación de 8-(1-etil-propil)-3-[4-metil-2-(3-piridil)-5-tiazolil]-2,6-dimetil-imidazo[1,2-b]piridazina.

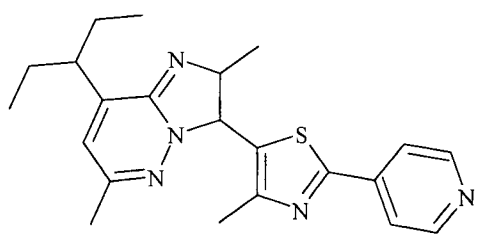


A un tubo de microondas a presión se agrega 0.070 g (0.178 mmol) de 8-(1-etil-propil)-3-[2-bromo-4-metil-5-tiazolil]-2,6-dimetil-imidazo[1,2-b]piridazina, 0.066g (0.534

mmol) de ácido piridina-3-borónico, 0.103 g (0.089 mmol) de Pd(PPh3)4, 0.267mL (0.534 mmol) de Na2CO3 acuoso 2M, y 1mL 7:3:2 DME:H2O:EtOH, y la mezcla se calienta a 160°C durante 60 min. La mezcla de reacción se divide entre 25mL de acetato de etilo y 25 mL de agua. Las capas se separan y el acuoso se extrae 3X 25 mL de acetato de etilo, se seca (MgSO4), y se concentra bajo vacío. La mezcla cruda se purifica por cromatografía usando hexanos/acetato de etilo como un sistema de solvente. Las fracciones que contienen producto se combinan para obtener 0.045 g del producto, 64% de rendimiento. EM, ES+ = 392.2 (M+1); ^{1}HRMN (DMSO-d6) δ 9.18 (s, 1H); 8.65 (m, 1H); 8.34 (d, 1H); 7.60 (m, 1H); 7.06 (s, 1H); 3.06 (m, 1H); 2.50 (s, 3H); 2.40 (s, 3H); 2.34 (s, 3H); 1.87-1.82 (m, 4H); 0.83-0.79 (m, 6H) ppm.

Ejemplo 9.

Preparación de 8-(1-etil-propil)-3-[4-metil-2-(4-piridil)-5-tiazolil]-2,6-dimetil-imidazo[1,2-b]piridazina.

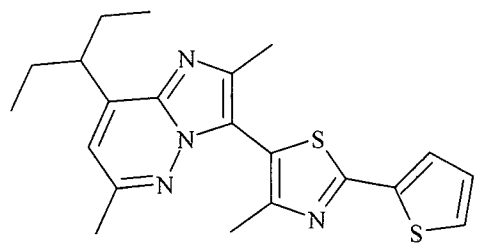


Al usar un procedimiento similar al Ejemplo 8, el ácido piridina-4-borónico produce el compuesto del título en 10% de rendimiento. EM, ES+ = 392.3 (M+1); 1HRMN (DMSO-d6) = 8.79 (s,

2H); 7.80 (m, 2H); 7.07 (s, 1H); 3.12 (m, 1H); 2.50 (s, 3H); 2.40 (s, 3H); 2.36 (s, 3H); 1.90-1.80 (m, 4H); 0.83-0.79 (m, 6H) ppm.

Ejemplo 10.

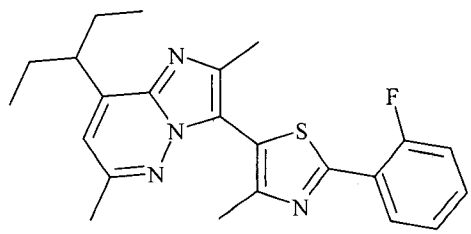
Preparación de 8-(1-etil-propil)-3-[4-metil-2-(tiofeno-2-il)-5-tiazolil]-2,6-dimetil-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 8, el ácido tiofeno-2-borónico produce el compuesto del título en 89% de rendimiento. EM, ES+ = 397.1 (M+1); 1 H-RMN (DMSO-d6) = 7.81-7.79 (d, 1H); 7.78-7.77 (d, 1H); 7.21-7.20 (m, 1H); 7.05 (s, 1H); 3.19-3.15 (m, 1H); 2.50 (s, 3H); 2.39 (s, 3H); 2.27 (s, 3H); 1.85-1.83 (m, 4H); 0.82-0.79 (m, 6H) ppm.

Ejemplo 11.

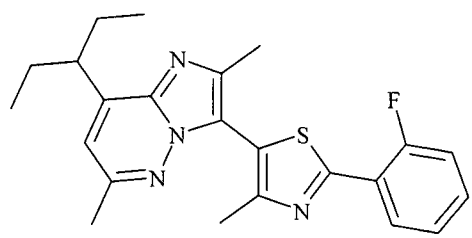
Preparación de 8-(1-etil-propil)-3-[4-metil-2-(2-fluorofenil)-5-tiazolil]-2,6-dimetil-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 8, el ácido 2-fluorofenil borónico produce el compuesto del título en 82% de rendimiento. EM, ES+ = 409.2 (M+1); 1H-RMN (DMSO-d6) = 8.32-8.28 (m, 1H); 7.60-7.58 (m, 1H); 7.57-7.41 (m, 2H); 7.05 (s, 1H); 3.13-3.12 (m, 1H); 2.49 (s, 3H); 2.40 (s, 3H); 2.35 (s, 3H); 1.91-1.780 (m, 4H); 0.87-0.79 (m, 6H) ppm.

Ejemplo 12.

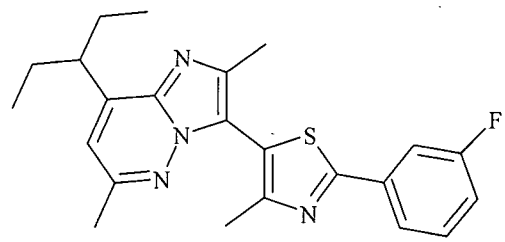
Preparación de 8-(1-etil-propil)-3-[4-metil-2-(4-fluorofenil)-5-tiazolil]-2,6-dimetil-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 8, el ácido 4-fluorofenil borónico produce el compuesto del título en 63% de rendimiento donde la mezcla cruda se purifica por cromatografía usando 2% metanol en diclorometano como un sistema de solvente. EM, ES+ = 409.2 (M+1); ^{1}H-RMN (DMSO-d6) = 8.06-8.03 (m, 2H); 7.408-7.36 (m, 2H); 7.05 (s, 1H); 3.14-3.11 (m, 1H); 2.50 (s, 3H); 2.39 (s, 3H); 2.31 (s, 3H); 1.90-1.78 (m, 4H); 0.83-0.79 (m, 6H) ppm.

Ejemplo 13.

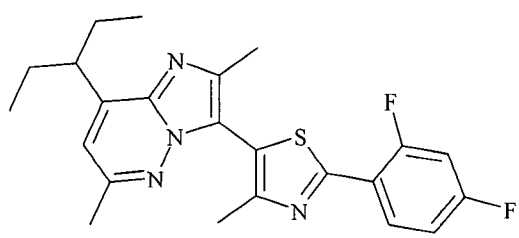
Preparación de 8-(1-etil-propil)-3-[4-metil-2-(3-fluorofenil)-5-tiazolil]-2,6-dimetil-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 8, el ácido 3-fluorofenil borónico produce el compuesto del título en 77% de rendimiento donde la mezcla cruda se purifica por cromatografía usando 2% metanol en diclorometano como un sistema de solvente. EM, ES+ = 409.2 (M+1); ^{1}H-RMN (DMSO-d6) = 7.84-7.78 (m, 2H); 7.64-7.57 (m, 2H); 7.41-7.36 (m, 1H); 7.06 (s, 1H); 3.15-3.111 (m, 1H); 2.45 (s, 3H); 2.40(s, 3H); 2.32 (s, 3H); 1.91-1.78 (m, 4H); 0.83-0.79 (m, 6H) ppm.

Ejemplo 14.

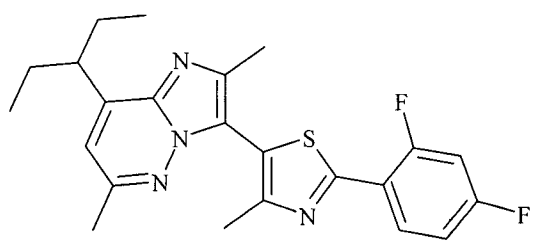
Preparación de 8-(1-etil-propil)-3-[4-metil-2-(2,4-difluorofenil)-5-tiazolil]-2,6-dimetil-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 8, el ácido 2,4-difluorofenil borónico produce el compuesto del título en 76% de rendimiento. EM, ES+ = 427.2 (M+1); 1H-RMN (DMSO-d6) = 8.370-8.310 (m, 1H); 7.586-7.540 (m, 1H); 7.36-7.32 (m, 1H); 7.054 (s, 1H); 3.14-3.13 (m, 1H); 2.492 (s, 3H); 2.391 (s, 3H); 2.345 (s, 3H); 1.906-1.797 (m, 4H); 0.826-0.788 (m, 6H) ppm.

Ejemplo 15.

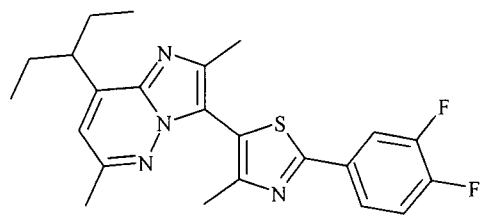
Preparación de 8-(1-etil-propil)-3-[4-metil-2-(o-toluil)-5-tiazolil]-2,6-dimetil-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 8, el ácido o-toluil borónico produce el compuesto del título en 87% de rendimiento donde la mezcla cruda se purifica por cromatografía en gel de sílice usando 2% metanol en diclorometano como un sistema de solvente. EM, ES+ = 405.2 (M+1); ^{1}H-RMN (DMSO-d6) = 7.857-7.838 (d, 1H); 7.429-7.419 (d, 2H); 7.393-7.352 (m, 1H); 7.049 (s, 1H); 3.145-3.114 (m, 1H); 2.647 (s, 3H); 2.502 (s, 3H); 2.406 (s, 3H); 2.337 (s, 3H); 1.907-1.782 (m, 4H); 0.827-0.791 (m, 6H) ppm.

Ejemplo 16.

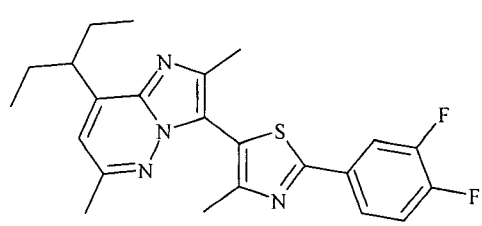
Preparación de 8-(1-etil-propil)-3-[4-metil-2-(3,4-difluorofenil)-5-tiazolil]-2,6-dimetil-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 8, el ácido 3,4-difluorofenil borónico produce el compuesto del título en 74% de rendimiento donde la mezcla cruda se purifica por cromatografía usando 2% metanol en diclorometano como un sistema de solvente. EM, ES+ = 427.2 (M+1); ^{1}H-RMN (DMSO-d6) = 8.07-8.02 (m, 1H); 7.849 (s, 1H); 7.66-7.59 (m, 1H); 7.062 (s, 1H); 3.12-3.11 (m, 1H); 2.498 (s, 3H); 2.392 (s, 3H); 2.319 (s, 3H) 1.905-1.779 (m, 4H); 0.826-0.790 (m, 6H) ppm.

Ejemplo 17.

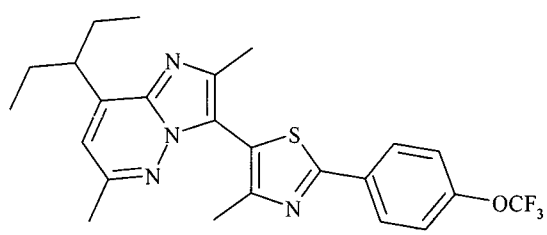
Preparación de 8-(1-etil-propil)-3-[4-metil-2-(4-fluoro-2-metilfenil)-5-tiazolil]-2,6-dimetil-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 8, el ácido 4-fluoro-2-metilfenil borónico produce el compuesto del título 0.040g (37% de rendimiento). EM, ES+ = 423.2 (M+1); ^{1}H-RMN (DMSO-d6) = 7.918-7.882 (m, 1H); 7.323-7.241 (d, 1H); 7.234-7.192 (m, 1H); 7.049 (s, 1H); 3.142-3.111 (m, 1H); 2.650 (s, 3H); 2.499 (s, 3H); 2.401 (s, 3H); 2.330 (s, 3H); 1.905-1.779 (m, 4H); 0.969-0.788 (m, 6H) ppm.

Ejemplo 18.

Preparación de 8-(1-etil-propil)-3-[4-metil-2-(4-trifluorometoxifenil)-5-tiazolil]-2,6-dimetil-imidazo[1,2-b]piridazina.

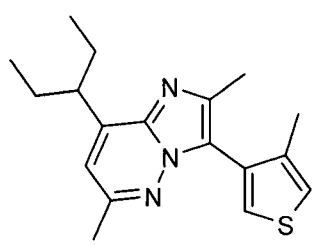


A un tubo de microondas a presión se agrega 0.100g (0.254mmol) de 8-(1-etil-propil)-3-[2-bromo-4-metil-5-tiazolil]-2,6-dimetil-imidazo[1,2-b]piridazina, 0.157g (0.762mmol) de ácido 4-(trifluorometoxi)benceno borónico, 0.147g (0.127mmol) de Pd(PPh3)4, 0.381mL (0.762mmol) de carbonato de sodio acuoso 2M, y 2mL Etanol. La mezcla de reacción se calienta en el microondas a 160°C durante hasta 1 hora. La mezcla de reacción se divide entre 50 mL de acetato de etilo y 50 mL de agua. Las capas se separan y el acuoso se

extrae 3X50mL de acetato de etilo, se seca (MgSO4), y se concentra bajo vacío. La mezcla cruda se purifica por cromatografía usando 2% metanol en diclorometano como un sistema de solvente. Las fracciones que contienen el producto se combinan para obtener 0.085g del producto, 70% de rendimiento. EM, ES+ = 475.2 (M+1); ^{1}H-RMN (DMSO-d6) = 8.134-8.112 (d, 2H); 7.553-7.532 (d, 2H); 7.059 (s, 1H); 3.142-3.113 (m, 1H); 2.500 (s, 3H); 2.399 (s, 3H); 2.330 (s, 3H); 1.907-1.782 (m, 4H); 0.827-0.791 (m, 6H) ppm.

Ejemplo 19.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(4-metil-tiofen-3-il)-imidazo[1,2-b]piridazina.



A. 4,4,5,5-Tetrametil-2-(4-metil-tiofen-3-il)-[1,3,2]dioxaborolano.

A un matraz de fondo redondo de 250 mL se agrega 3-bromo-4-metil-tiofeno (5.00 g, 28.24 mmol), bis(pinacolato)diboro (7.89 g, 31.06 mmol) y KOAc (8.32 g, 84.72 mmol) en DMSO (85 mL). La mezcla se desgasifica al burbujear N_2 durante 5 min, $PdCl_2(dppf)_2 \bullet CH_2Cl_2$ (1.15 g, 1.42

mmol) se agrega y la mezcla de reacción se calienta hasta y se agita a 85°C durante la noche. La reacción se enfría hasta temperatura ambiente, y se diluye con EtOAc (400 mL), se lava con H_2O (3 x 300 mL); se seca con $MgSO_4$, se filtra y se concentra. La purificación del material crudo por cromatografía para dar el compuesto del título (3.69 g, 16.5 mmol, 58%). ES-MS (m/z): calculado para $C_{11}H_{17}BO_2S$ (M+): 224.1; encontrado: 224.9.

B. ácido 4-Metil 3-tiofeno borónico.

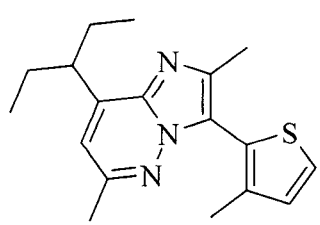
Una solución de 4,4,5,5-tetrametil-2-(4-metil-tiofen-3-il)-[1,3,2]dioxaborolano (3.69 g, 16.47 mmol) en acetona (30 mL) se trata con H_2O (30 mL), seguido por $NaIO_4$ (7.05 g, 32.95 mmol). La mezcla resultante se agita a temperatura ambiente durante la noche. El solvente orgánico se remueve in vacuo. El residuo se diluye con H_2O (50 mL), se extrae con EtOAc ((2 x 100 mL). Los extractos orgánicos se combinan, se secan con Na_2SO_4, se filtran y se concentran. La purificación del material crudo por cromatografía da el compuesto del título (0.82 g, 5.78 mmol, 35%). ^1H RMN ($CDCl_3$): δ 1.33 (s, 3H), 2.64-2.66 (m, 2H), 7.00-7.02 (m, 1H), 8.27 (d, J = 3.0 Hz, 1H). ES-MS (m/z): calculado para $C_5H_7BO_2S$ (M-H)-: 141.0; encontrado: 141.1.

C. 8-(1-Etil-propil)-2,6-dimetil-3-(4-metil-tiofen-3-il)-imidazo[1,2-b]piridazina.

A un matraz de fondo redondo de 100 ml que contiene ácido 4-metil 3-tiofeno borónico (0.27 g, 1.91 mmol), y 8-(1-etil-propil)-3-yodo-2,6-dimetil-imidazo[1,2-b]piridazina (0.65 g, 1.91 mmol) en 20 mL de una solución de reserva (DME:H_2O:EtOH = 7:3:2) se agrega 2 M Na_2CO_3 (1.9 mL). La mezcla resultante se desgasifica al burbujear N_2 durante 5 min. Luego $Pd(PPh_3)_4$ (0.11 g, 0.096 mmol) se agrega. La mezcla de reacción se puso a reflujo durante la noche. La reacción se diluye con H_2O (20 mL); se extrae con EtOAc (3 x 30 mL); se seca (Na_2SO_4), se filtra y la purificación del material crudo por cromatografía da el compuesto del título (0.52 g, 1.66 mmol, 87%). ^1H RMN ($CDCl_3$): δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.90 (m, 4H), 2.13 (d, J = 0.8 Hz, 3H), 2.44 (s, 3H), 2.49 (s, 3H), 3.30-3.39 (m, 1H), 6.64 (s, 1H), 7.08-7.11 (m, 1H), 7.34 (d, J = 3.1 Hz, 1H). ES-EM (m/z): calculado para $C_{18}H_{23}N_3S$ (M+H)+: 314.5; encontrado: 314.2.

Ejemplo 20.

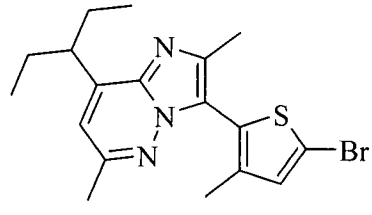
Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(3-metil-tiofen-2-il)-imidazo[1,2-b]piridazina.



A una mezcla de 8-(1-etil-propil)-3-yodo-2,6-dimetil-imidazo[1,2-b]piridazina (12.0 g, 34.96 mmol) y $PdCl_2$(dppf) (1.28 g, 1.75 mmol) se agrega una solución 0.5M de bromuro de 3-metil-2-tienilzinc en THF (100 mL, 50.0 mmol). La mezcla se agita a 65°C durante la noche, se diluye con EtOAc (500 mL), se lava con ácido cítrico al 10% (500 mL), agua (400 mL), salmuera (400 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por ISCO (10%-20% gradiente de EtOAc/hexano) resultando el compuesto del título (8.83 g, 28.17 mmol, 81%). ^{1}H RMN (CDCl3), δ 0.92 (t, J = 7.4 Hz, 6H), 1.78-1.95 (m, 4H), 2.18 (s, 3H), 2.50 (s, 3H), 2.54 (s, 3H), 3.33-3.43 (m, 1H), 6.69 (s, 1H), 7.06 (d, J = 4.9 Hz, 1H), 7.46 (d, J = 4.9 Hz, 1H). CL/EM (m/z): calculado para $C_{18}H_{23}N_3S$ (M+H)+: 314.6; encontrado: 314.2.

Ejemplo 21.

Preparación de 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

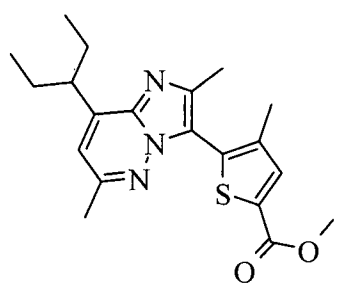


A una solución de 8-(1-Etil-propil)-2,6-dimetil-3-(3-metil-tiofen-2-il)-imidazo[1,2-b]piridazina (8.83 g, 28.17 mmol) y CH_2Cl_2 (90 mL) se agrega NBS (5.26 g, 29.58 mmol). La

solución se agita a temperatura ambiente durante 2 horas. La solución se lava con agua (3 X 75 mL), se seca sobre MgSO4, se filtra y se concentra para resultar el compuesto del título (10.5 g, 26.76 mmol, 95%). ^{1}H RMN (CDCl3), δ 0.87 (t, J = 7.3 Hz, 6H), 1.73-1.93 (m, 4H), 2.09 (s, 3H), 2.44 (s, 3H), 2.51 (s, 3H), 3.26-3.36 (m, 1H), 6.68 (s, 1H), 6.98 (d, J = 4.9 Hz, 1H) ppm. CL/EM (m/z): calculado para $C_{18}H_{22}BrN_3S$ (M+H)+: 392.6; encontrado: 392.1, 394.1.

Ejemplo 22.

Preparación de éster de metilo del ácido 5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiofeno-2-carboxílico.

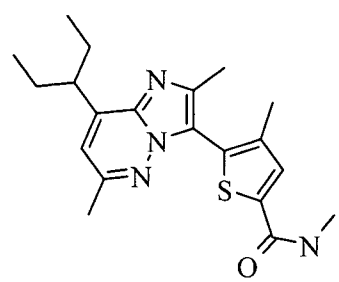


Una solución de 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (1.00 g, 2.66 mmol) en CH_3OH (12 mL), DMSO (18 mL), Et_3N (2.0 mL) con $Pd(OAc)_2$ (0.12 g, 0.538 mmol), dppf (0.937 g, 1.69 mmol) se hace reaccionar con la atmósfera CO (100 psi (7.03 kg/cm^2)) a 80°C durante 24 h. La mezcla de reacción se diluye con EtOAc (200 mL), se lava con HCl 0.1M (2 x 50 mL), salmuera (50 mL);

se seca con Na_2SO_4; se filtra a través de gel de sílice y se eluye con exceso de EtOAc. La purificación del material crudo por cromatografía da el compuesto del título (0.79 g, 2.12 mmol, 80%). ^1H RMN ($CDCl_3$): δ 0.89 (t, J = 7.7 Hz, 6H), 1.75-1.93 (m, 4H), 2.15 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 3.32-3.42 (m, 1H), 3.91 (s, 3H), 6.72 (s, 1H), 7.73 (s, 1H). ES-EM (m/z): calculado para $C_{20}H_{25}N_3O_2S$ (M+H)+: 372.5; encontrado: 372.2.

Ejemplo 23.

Preparación de metilamida del ácido 5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiofeno-2-carboxílico.



A. ácido 5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiofeno-2-carboxílico.

Una solución de éster de metilo del ácido (1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiofeno-2-carboxílico (0.78 g, 2.10 mmol) en CH_3OH (10 mL) se trata con 5.0 M NaOH (2.1 mL, 10.5 mmol). La mezcla de reacción resultante se puso a reflujo durante 4 h. El

solvente orgánico se remueve in vacuo; el residuo acuso se acidificó por la adición de 2.0 M HCl hasta pH 5~6; esto luego se extrae con EtOAc (3 x 50 mL); se seca (Na_2SO_4); se filtra y se concentra para dar el compuesto del título (0.74 g, 2.07 mmol, 98%). ^1H RMN (DMSO-d6): δ 0.79 (t, J = 7.6 Hz, 6H), 1.75-1.86 (m, 4H), 2.06 (s, 3H), 2.36 (s, 3H), 2.47 (s, 3H), 3.06-3.14 (m, 1H), 7.01 (s, 1H), 7.68 (s, 1H), 13.1 (bs, 1H). ES-EM (m/z): calculado para $C_{19}H_{23}N_3O_2S$ (M+H)+: 358.5; encontrado: 358.2.

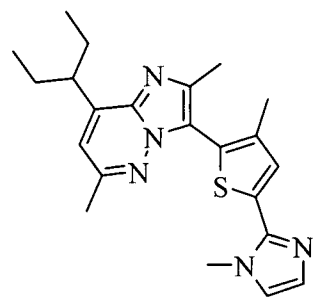
B. metilamida del ácido 5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiofeno-2-carboxílico.

El ácido 5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiofeno-2-carboxílico (0.17 g, 0.47 mmol) se hace reaccionar con 2.0 M cloruro de oxalilo en CH_2Cl_2 (3.0 mL) a temperatura ambiente durante 1h. El exceso del reactivo y solvente se removieron in vacuo. El residuo se disuelve en CH_2Cl_2 (3mL), se enfria a 0°C y se trata con 2.0 M metil amina en THF (3 mL). La reacción se agita a 0°C durante 10 min y temperatura ambiente durante 30min. Esto se diluye con EtOAc (50 mL), se lava con H_2O (15 mL0, 0.1 M NaOH (2 x 30 mL); se seca (Na_2SO_4); se filtra y se concentra. La purificación del material crudo por cromatografía para dar el compuesto del título (0.91g, 0.25 mmol, 53%). ^1H RMN ($CDCl_3$):

δ 0.89 (t, J = 7.2 Hz, 6H), 1.75-1.91 (m, 4H), 2.14 (s, 3H), 2.47 (s, 3H), 2.52 (s, 3H), 3.02 (d, J = 4.8 Hz, 3H), 3.28-3.36 (m, 1H), 5.90-6.01 (m, 1H), 6.69 (s, 1H), 7.43 (s, 1H). ES-EM (m/z): calculado para $C_{20}H_{26}N_4OS$ (M+H)+: 371.5; encontrado: 371.2.

Ejemplo 24.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(1-metil-1H-imidazol-2-il)-tiofen-2-il]-imidazo[1,2-b]piridazina.

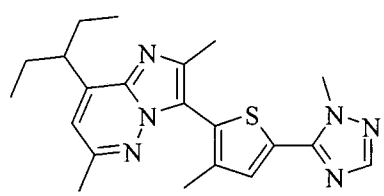


La 3-(5-Bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo-[1,2-b]piridazina (0.98 g, 2.51 mmol) y 1-metil-1H-imidazol (0.2 mL), $Pd(OAc)_2$ (34 mg, 0.15 mmol), PPh_3 (79 mg, 0.299 mmol), Cs_2CO_3 (1.95 g, 6.0 mmol) en DMF (50 mL) se agita bajo N_2 a 130-140°C durante la noche. La mezcla de reacción se enfria, se diluye con EtOAc (300 mL), se lava con H_2O (3 x 100 mL); se seca (Na_2SO_4); se filtra y se concentra. La purificación del material crudo resultante por cromatografía proporciona el compuesto del título (0.51 g,

1.29 mmol, 51%). ^{1}H RMN ($CDCl_3$): δ 0.89 (t, J = 7.5 Hz, 6H), 1.77-1.92 (m, 4H), 2.17 (s, 3H), 2.51 (s, 3H), 2.54 (s, 3H), 3.30-3.40 (m, 1H), 3.81 (s, 3H), 6.69 (s, 1H), 7.02 (s, 1H), 7.24 (s, 1H), 7.52 (s, 1H). ES-EM (m/z): calculado para $C_{22}H_{27}N_5S$ (M+H)+: 394.6; encontrado: 394.3.

Ejemplo 25.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(2-metil-2H-[1,2,4]triazol-3-il)-tiofen-2-il]-imidazo[1,2-b]piridazina.

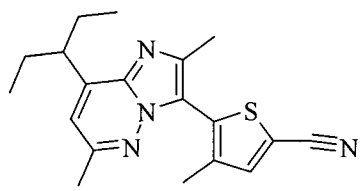


A una solución a -78°C de 1-metil-1,2,4-triazol (0.15 mL, 2.04 mmol) y THF (3 mL) se agrega a una solución 1.34 M de n-Bu-Li en hexanos (1.60 mL, 2.14 mmol) durante 20 minutos, luego se agita a -78°C durante 1.5 horas. Una solución 0.5M de $ZnCl_2$ en THF (4.28 mL, 2.14 mmol) se agrega y la solución se entibia hasta temperatura ambiente. La 3-(5-Bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.40 g, 1.019 mmol) y $PdCl_2$(dppf) (0.037 g, 0.051 mmol) se agrega y la solución se calienta a 65°C durante la noche se diluye con CH_2Cl_2 (30 mL). La capa orgánica se lava con ácido cítrico al 10% (20 mL), agua (20

mL), salmuera (20 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por ISCO (20%-60% gradiente de EtOAc/hexano). El residuo se disuelve en Et_2O, se trata con Darco®-60 durante 15 minutos, se seca con Na_2SO_4, y se filtra para resultar el compuesto del título (0.24 g, 0.61 mmol, 60%). ^1H RMN ($CDCl_3$), δ 0.88 (t, J = 7.4 Hz, 6H), 1.75-1.93 (m, 4H), 2.20 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 3.28-3.37 (m, 1H), 4.14 (s, 3H), 6.69 (s, 1H), 7.45 (s, 1H), 7.87 (s, 1H). CL/EM (m/z): calculado para $C_{21}H_{26}N_6S$ (M+H)+: 395.6; encontrado: 395.2.

Ejemplo 26.

Preparación de 5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiofeno-2-carbonitrilo.

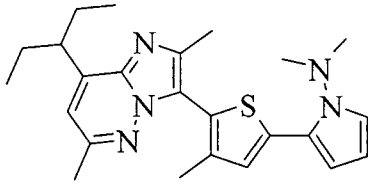


Una solución de 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.50 g, 1.28 mmol), DMF (5 mL), y $Zn(CN)_2$ (0.090 g, 0.76 mmol) se desgasifica con nitrógeno durante 15 minutos. El $Pd(PPh_3)_4$ (0.74 g, 0.064 mmol) y la solución se calienta a 100°C durante la noche. La solución se diluye con EtOAc (50 mL), se lava con 2 M NH_4OH (2 X 30 mL), salmuera (30 mL), se seca

sobre $MgSO_4$, se filtra y se concentra. El purificado por cromatografía en columna ISCO (15% - 20% gradiente de EtOAc/hexano) proporciona el compuesto del título (0.39 g, 1.15 mmol, 91%). ^1H RMN ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.15 (s, 3H), 2.46 (s, 3H), 2.51 (s, 3H), 3.26-3.34 (m, 1H), 6.72 (s, 1H), 7.53 (s, 1H). CL/EM (m/z): calculado para $C_{19}H_{22}N_4S$ $(M+H)^+$: 339.6; encontrado: 339.2.

Ejemplo 27.

Preparación de (2-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiofen-2-il}-pirrol-1-il)-dimetil-amina.

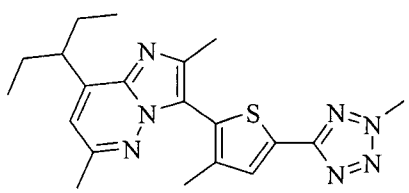


A una solución 0°C de 1-(dimetilamino)-pirrol (0.24 mL, 2.04 mmol) y THF (4 mL) se agrega 1.24 M de n-BuLi (1.73 mL, 2.14 mmol). La solución se entibia hasta temperatura ambiente y se agita durante dos horas. 0.5 M de $ZnCl_2$ (4.28 mL, 2.14 mmol) se agrega y la solución se agita durante una hora. La 3-(5-Bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.40 g, 1.02 mmol) y $PdCl_2$(dppf) (0.037 g, 0.051 mmol) se agrega y la solución se calienta a 65°C durante la noche. La solución se diluye con

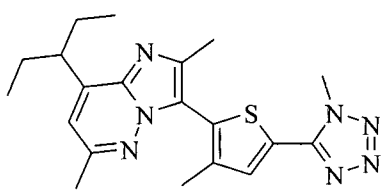
EtOAc (30 mL), se lava con NH_4Cl saturado (30 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía instantánea ISCO (15% -20% EtOAc gradiente) resulta el compuesto del título (0.41 g, 0.97 mmol, 95%). ^1H RMN ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.11 (s, 3H), 2.51 (s, 6H), 2.83 (s, 6H), 3.29-3.39 (m, 1H), 6.18-6.21 (m, 1H), 6.35 (dd, J = 4.0, 1.8 Hz, 1H), 6.65 (s, 1H), 6.98 (dd, J = 4.0, 1.8 Hz, 1H), 7.25 (s, 1H). CL/EM (m/z): calculado para $C_{24}H_{31}N_5S$ $(M+H)^+$: 422.2; encontrado: 422.4.

Ejemplo 28 y 29.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(2-metil-2,5-dihidro-1H-tetrazol-5-il)-tiofen-2-il]-imidazo[1,2-b]piridazina y 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(1-metil-1H-tetrazol-5-il)-tiofen-2-il]-imidazo[1,2b]piridazina.



Ej. 28



Ej.29

A. 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(1H-tetrazol-5-il)-tiofen-2-il]-imidazo[1,2-b]piridazina.

A una solución de 5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiofeno-2-carbonitrilo

(0.25 g, 0.74 mmol) y DMF (2.5 mL) se agrega Et_3N•HCl (0.31 g, 2.22 mmol) y NaN_3 (0.14 g, 2.20 mmol). La solución se calienta a 100°C durante la noche. La solución se diluye con agua (20 mL) y se extrajo con EtOAc (3 X 15 mL), las capas orgánicas combinadas se lavan con HCl 0.1M (20 mL), agua (20 mL), salmuera (20 mL), se secan sobre MgSO4, se filtran y se concentran. El residuo se recristaliza a partir de que el acetonitrilo proporciona el compuesto del título (0.14 g, 0.37 mmol, 50%). ^{1}H RMN ($CDCl_3$), δ 0.81 (t, J = 7.5 Hz, 6H), 1.66-1.87 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 3.26-3.35 (m, 1H), 6.83 (s, 1H), 7.84 (s, 1H). CL/EM (m/z): calculado para $C_{19}H_{23}N_7S$ (M+H)+: 382.6; encontrado: 382.2.

B. 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(2-metil-2,5-dihidro-1H-tetrazol-5-il)-tiofen-2-il]-imidazo[1,2-b]piridazina y 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(1-metil-1H-tetrazol-5-il)-tiofen-2-il]-imidazo[1,2b]piridazina.

A una solución de 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(1H-tetrazol-5-il)-tiofen-2-il]-imidazo[1,2-b]piridazina (0.14 g, 0.35 mmol) y THF (3 mL) se agrega Et_3N (0.1 mL, 0.71 mmol) y MeI (0.024 mL, 0.39 mmol). La solución se agita durante la noche, se diluye con EtOAc (20 mL), se lava con agua (15 mL), HCl 0.1M (15 mL), salmuera (15 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (20%-40% gradiente

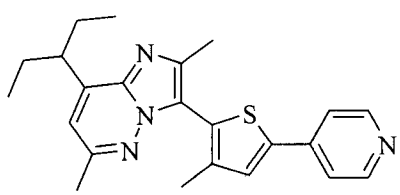
de EtOAc/hexano) proporcionando el ejemplo 28 (0.71 g, 0.18 mmol, 51%), y ejemplo 29 (0.031 g, 0.078 mmol, 22%).

Ejemplo 28: ^{1}H RMN ($CDCl_3$), δ 0.88 (t, J = 7.4 Hz, 6H), 1.75-1.92 (m, 4H), 2.18 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 3.28-3.38 (m, 1H), 4.38 (s, 3H), 6.68 (s, 1H), 7.71 (s, 1H). CL/EM (m/z): calculado para $C_{20}H_{25}N_7S$ (M+H)+: 396.6; encontrado: 396.3.

Ejemplo 29: ^{1}H RMN ($CDCl_3$), δ 0.89 (t, J = 7.4 Hz, 6H), 1.73-1.94 (m, 4H), 2.23 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.28-3.37 (m, 1H), 4.30 (s, 3H), 6.62 (s, 1H), 7.63 (s, 1H). CL/EM (m/z): calculado para $C_{20}H_{25}N_7S$ (M+H)+: 396.6; encontrado: 396.3.

Ejemplo 30.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(3-metil-5-piridin-4-il-tiofen-2-il)-imidazo[1,2-b]piridazina.



A. 3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina del ácido 3-(5-Borónico.

A una solución a -78°C de 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (1.20 g, 3.06 mmol) y THF (10 mL) se agrega n-Bu-Li 1.30 M

(2.47 mL, 3.21 mmol) gota a gota. La solución se agita a -78°C durante 1 hora. El $B(OMe)_3$ (0.38 mL, 3.65 mmol) se agrega y la solución se entibia hasta temperatura ambiente y se agita durante 2 horas. El HCl 1M se agrega y la solución se agita durante 10 minutos se extrae con CH_2Cl_2 (2 X 30 mL), se seca sobre $MgSO_4$, se filtra y se concentra para resultar el compuesto del título (0.47 g, 1.32 mmol, 43%). ^1H RMN ($CDCl_3$), δ 0.92 (t, J = 7.5 Hz, 6H), 1.71-1.98 (m, 4H), 2.02 (s, 3H), 2.64 (s, 3H), 2.69 (s, 3H), 3.64-3.83 (m, 1H), 7.06 (d, J = 5.3 Hz, 1H), 7.54 (d, J = 5.3 Hz, 1H), 7.20 (s, 1H). CL/EM (m/z): calculado para $C_{18}H_{24}BN_3O_2S$ $(M+H)^+$: 358.4; encontrado: 358.2.

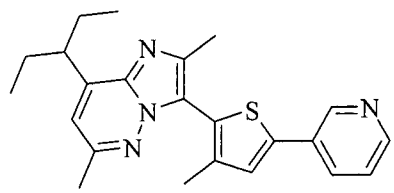
B. 8-(1-Etil-propil)-2,6-dimetil-3-(3-metil-5-piridin-4-il-tiofen-2-il)-imidazo[1,2-b]piridazina.

Una solución de 3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina del ácido 3-(5-borónico (0.25 g, 0.70 mmol), clorohidrato de 4-bromopiridina (0.16 g, 0.84 mmol), y 2 M Na_2CO_3 (0.87 mL, 1.75 mmol) y n-PrOH (2.5 mL) se desgasifica con nitrógeno durante 10 minutos. El $Pd(PPh_3)_4$ (0.040 g, 0.035 mmol) se agrega y la solución se calienta a 85°C durante la noche. La solución se diluye con CH_2Cl_2 (40 mL), se lava con 10% Na_2CO_3 (30 mL), agua (30 mL), salmuera (30 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en

columna ISCO (20%-40% gradiente de EtOAc/hexano) resulta el compuesto del título (0.16 g, 0.41 mmol, 59%). ^{1}H RMN ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.93 (m, 4H), 2.17 (s, 3H), 2.49 (s, 3H), 2.52 (s, 3H), 3.28-3.38 (m, 1H), 6.68 (s, 1H), 7.43 (s, 1H), 7.52 (d, J = 5.5 Hz, 2H), 8.62 (d, J = 5.5 Hz, 2H). CL/EM (m/z): calculado para $C_{23}H_{26}N_4S$ $(M+H)^+$: 391.2 encontrado: 391.2.

Ejemplo 31.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(3-metil-5-piridin-3-il-tiofen-2-il)-imidazo[1,2-b]piridazina.

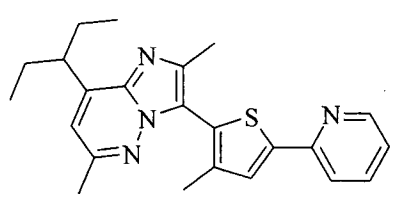


A una solución a -78°C de 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.50 g, 1.27 mmol), y THF (5 mL) se agrega n-Bu-Li 1.34 M (1.0 mL, 1.34 mmol). La solución se agita a -78°C durante 30 minutos y 0.5 M $ZnCl_2$ en THF (2.7 mL, 1.34 mmol) se agrega y la solución se entibia hasta temperatura ambiente. Después de 30 minutos 3-bromopiridina (0.15 mL, 1.53 mmol) y $PdCl_2$(dppf) (0.047 g, 0.064 mmol) se agregan y la solución se calienta a 65°C durante la noche. La solución se diluye con CH_2Cl_2 (40 mL), se lava con ácido cítrico al 10% (20 mL), agua (20 mL),

salmuera (20 mL) se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (20%-40% gradiente de EtOAc/hexano) se concentra y se redisuelve en Et_2O. La solución se trata con Darco®-60 durante 15 minutos, se seca sobre Na_2SO_4, y se filtra a través de celite® resulta el compuesto del título (0.26 g, 0.67 mmol, 52%). ^1H RMN ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.28-3.38 (m, 1H), 6.68 (s, 1H), 7.26-7.32 (m, 2H), 7.86 (dt, J = 7.9, 1.8 Hz, 1H), 850 (d, J = 3.2 Hz, 1H), 8.89 (s, 1H). CL/EM (m/z): calculado para $C_{23}H_{26}N_4S$ (M+H)+: 391.6; encontrado: 391.2.

Ejemplo 32.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(3-metil-5-piridin-2-il-tiofen-2-il)-imidazo[1,2-b]piridazina.

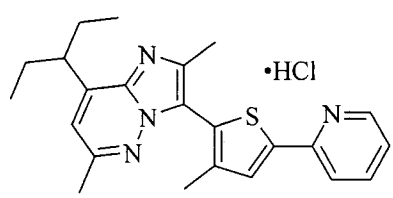


A una mezcla de 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.50 g, 1.27 mmol) y $PdCl_2$(dppf) (0.047 g, 0.064 mmol) se agrega una solución 0.5M de bromuro de 2-piridilzinc en THF (5.1 mL, 2.55 mmol). La mezcla se agita a 65°C durante la noche, se

diluye con EtOAc (50 mL), se lava con ácido cítrico al 10% (50 mL), agua (40 mL), salmuera (40 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (20%-40% gradiente de EtOAc/hexano) resulta el compuesto del título (0.45 g, 1.15 mmol, 89%). ^1H RMN ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H), 2.52 (s, 6H), 3.30-3.39 (m, 1H), 6.67 (s, 1H), 7.12-7.16 (m, 1H), 7.53 (s, 1H), 7.63-7.71 (m, 2H), 8.57 (dt, J = 1.3, 4.8 Hz, 1H). CL/EM (m/z): calculado para $C_{23}H_{26}N_4S$ $(M+H)^+$: 391.6; encontrado: 391.2.

Ejemplo 33.

Preparación de clorohidrato de 8-(1-etil-propil)-2,6-dimetil-3-(3-metil-5-piridin-2-il-tiofen-2-il)-imidazo[1,2-b]piridazina.

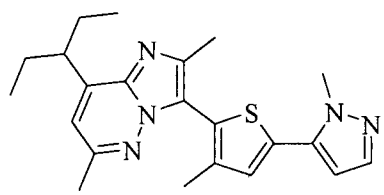


A una solución de 8-(1-etil-propil)-2,6-dimetil-3-(3-metil-5-piridin-2-il-tiofen-2-il)-imidazo[1,2-b]piridazina (0.15 g, 38 mmol) y MeOH (2 mL) se agrega AcCl (0.028 mL, 0.39 mmol). Después de una hora la solución se concentra y el residuo se recristaliza a partir de EtOAc/hexano resulta el compuesto del título (0.11 g, 0.26 mmol, 69%). ^1H RMN ($CDCl_3$),

δ 0.97 (t, J = 7.4 Hz, 6H), 1.75-2.03 (m, 4H), 2.17 (s, 3H), 2.66 (s, 3H), 2.77 (s, 3H), 3.86-3.98 (m, 1H), 7.17 (s, 1H), 7.21-7.30 (m, 2H), 7.62 (bs, 1H), 7.67-7.7.82 (m, 2H), 8.60 (d, J = 4.8 Hz, 1H). CL/EM (m/z): calculado para $C_{23}H_{26}ClN_5S$ (M+H)+: 428.1; encontrado: 391.2.

Ejemplo 34.

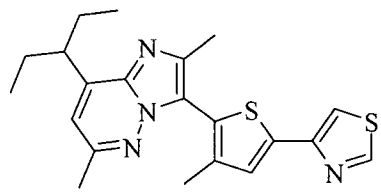
Preparación de 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(2-metil-2H-pirazol-3-il)-tiofen-2-il]-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al ejemplo 25, el 1-metilpirazol (0.17 g, 2.04 mmol), n-Bu-Li 1.56 M (1.34 mL, 2.09 mmol), $ZnCl_2$ (4.3 mL, 2.14 mmol), 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.40 g, 1.02 mmol) y $PdCl_2$(dppf) (0.037 g, 0.051 mmol) resulta el compuesto del título (0.35 g, 0.89 mmol, 88%). ^1H RMN ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.28-3.38 (m, 1H), 4.05 (s, 3H), 6.42 (d, J = 1.8 Hz, 1H), 6.68 (s, 1H), 7.08 (s, 1H), 7.46 (d, J = 1.8 Hz, 1H). CL/EM (m/z): calculado para $C_{22}H_{27}N_5S$ (M+H)+: 394.7; encontrado: 394.2.

Ejemplo 35.

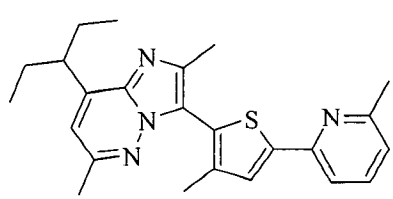
Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(3-metil-5-tiazol-4-il-tiofen-2-il)-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 31, a partir de 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.40 g, 1.02 mmol), n-Bu-Li 1.34 M (0.8 mL, 1.07 mmol), 0.5 M de $ZnCl_2$ en THF (2.14 mL, 1.07 mmol), 4-bromo-tiazol (0.20 mL, 1.22 mmol) y $PdCl_2$(dppf) (0.037 g, 0.051 mmol) resulta el compuesto del título (0.16g, 0.40 mmol, 40%). ^{1}H RMN ($CDCl_3$), δ 0.92 (t, J = 7.4 Hz, 6H), 1.70-1.96 (m, 4H), 2.17 (s, 3H), 2.64 (s, 3H), 2.66 (s, 3H), 3.38-3.48 (m, 1H), 7.16 (d, J = 1.8 Hz, 1H), 7.44 (s, 1H), 7.51 (d, J = 1.8 Hz, 1H), 7.86 (d, J = 1.8 Hz, 1H). CL/EM (m/z): calculado para $C_{21}H_{24}N_4S_2$ (M+H)+: 397.7; encontrado: 397.2.

Ejemplo 36.

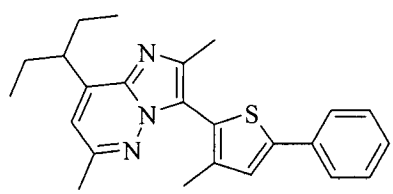
Preparación de 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(6-metil-piridin-2-il)-tiofen-2-il]-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 32, la 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.60 g, 1.53 mmol) y $PdCl_2$(dppf) (0.056 g, 0.076 mmol) y una solución 0.5 M de bromuro de 6-metil-2-piridilzinc en THF (6.0 mL, 3.06 mmol) resulta el compuesto del título (0.29 g, 0.72 mmol, 47%). ^{1}H RMN ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.73-1.93 (m, 4H), 2.16 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 2.58 (s, 3H), 3.31-3.40 (m, 1H), 6.67 (s, 1H), 7.00 (d, J = 7.9 Hz, 1H), 7.45 (d, J = 7.9 Hz, 1H), 7.52 (s, 1H), 8.56 (t, J = 7.7 Hz, 1H). CL/EM (m/z): calculado para $C_{24}H_{28}N_4$ $(M+H)^+$: 405.7; encontrado: 405.2.

Ejemplo 37.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(3-metil-5-fenil-tiofen-2-il)-imidazo[1,2-b]piridazina.

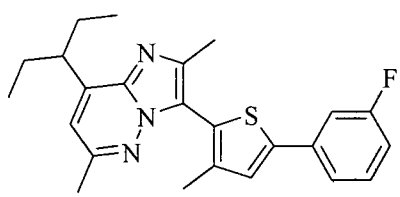


Al usar un procedimiento similar al Ejemplo 32, la 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.50 g, 1.27 mmol) y $PdCl_2$(dppf) (0.05 g, 0.069 mmol) y una solución 0.5 M de yoduro de fenilzinc en THF (5.5 mL, 2.76 mmol) resulta el compuesto del título (0.25 g, 0.64 mmol, 50%). ^{1}H RMN ($CDCl_3$), δ 0.90 (t, J

= 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.17 (s, 3H), 2.52 (s, 3H), 2.53 (s, 3H), 3.31-3.41 (m, 1H), 6.68 (s, 1H), 7.26 (s, 1H), 7.27-30 (m, 1H), 7.35-7.41 (m, 2H), 7.61-7.66 (m, 2H). CL/EM (m/z): calculado para $C_{24}H_{27}N_3S$ $(M+H)^+$: 390.3; encontrado: 390.3.

Ejemplo 38.

Preparación de 8-(1-etil-propil)-3-[5-(3-fluoro-fenil)-3-metil-tiofen-2-il]-2,6-dimetil-imidazo[1,2-b]piridazina.

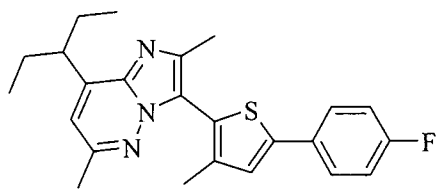


Al usar un procedimiento similar al Ejemplo 32, la 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.50 g, 1.27 mmol) y $PdCl_2$(dppf) (0.047 g, 0.063 mmol) y una solución 0.5 M de yoduro de 3-flourofenilzinc en THF (5.1 mL, 2.55 mmol) resulta el compuesto del título (0.24 g, 0.59 mmol, 46%). ^1H RMN ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.17 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.31-3.39 (m, 1H), 6.69 (s, 1H), 6.94-7.01 (m, 1H), 7.26 (s, 1H), 7.30-7.42 (m, 3H). CL/EM (m/z): calculado para $C_{24}H_{26}FN_3S$ $(M+H)^+$: 408.7; encontrado: 408.2.

310

Ejemplo 39.

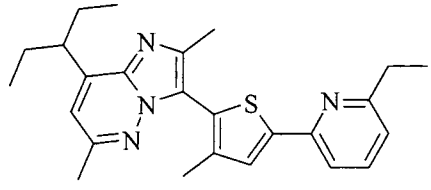
Preparación de 8-(1-etil-propil)-3-[5-(4-fluoro-fenil)-3-metil-tiofen-2-il]-2,6-dimetil-imidazo[1,2-b]piridazina.



Una suspensión espesa de 0.05 g/mL de Reike® Zn en THF (0.26 g, 4.01 mmol) y 1-bromo-4-fluoro-benceno (0.29 mL, 2.68 mmol) se calienta a reflujo durante la noche. La solución se filtra bajo nitrógeno. La 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.35 g, 0.89 mmol) y $PdCl_2$(dppf) (0.033 g, 0.045 mmol) se agregaron, y la solución se calienta a reflujo durante la noche se diluye con EtOAc (30 mL), se lava con ácido cítrico al 10% (20 mL), agua (20 mL), salmuera (20 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (10%-15% gradiente de EtOAc/hexano) resulta el compuesto del título (0.091 g, 0.22 mmol, 25%). ^1H RMN ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.15 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.30-3.38 (m, 1H), 6.68 (s, 1H), 7.08 (d, J = 8.8 Hz, 2H),7.18 (s, 1H), 7.59 (dd, J = 8.5, 5.3 Hz, 2H). CL/EM (m/z): calculado para $C_{24}H_{26}FN_3S$ $(M+H)^+$: 408.7; encontrado: 408.3.

Ejemplo 40.

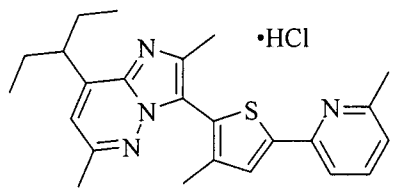
Preparación de 8-(1-etil-propil)-2,6-dimetil-3-[3-etil-5-(6-metil-piridin-2-il)-tiofen-2-il]-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 31, la 2-bromo-6-etil piridina (0.26 g, 1.41 mmol), n-Bu-Li 1.56 M (0.94 mL, 1.47 mmol), 0.5 M $ZnCl_2$ en THF (3.0 mL, 1.53 mmol), 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.50 g, 1.27 mmol) y $PdCl_2$(dppf) (0.047 g, 0.064 mmol) produce el compuesto del título (0.15 g, 0.36 mmol, 28%). ^{1}H RMN ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.34 (t, J = 7.5 Hz, 3H), 1.75-1.94 (m, 4H), 2.16 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 2.85 (q, J = 16.2, 7.5 Hz, 2H), 3.31-3.41 (m, 1H), 6.67 (s, 1H), 7.01 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 7.9 Hz, 1H), 7.53 (s, 1H), 8.59 (t, J = 7.8 Hz, 1H). CL/EM (m/z): calculado para $C_{25}H_{30}N_4S$ $(M+H)^+$: 419.3; encontrado: 419.3.

Ejemplo 41.

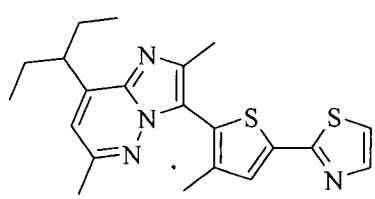
Preparación de clorohidrato de 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(6-metil-piridin-2-il)-tiofen-2-il]-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 33, la 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(6-metil-piridin-2-il)-tiofen-2-il]-imidazo[1,2-b]piridazina (0.55 g, 1.36 mmol), MeOH (6 mL) y AcCl (0.098 mL, 1.36 mmol) resulta el compuesto del título (0.11 g, 0.25 mmol, 42%). ^{1}H RMN ($CDCl_3$), δ 0.96 (t, J = 7.2 Hz, 6H), 1.74-1.89 (m, 2H), 1.89-2.02 (m, 2H), 2.22 (s, 3H), 2.68 (s, 3H), 2.78 (s, 3H), 3.08 (s, 3H), 3.88-3.98 (m, 1H), 7.23 (s, 1H), 7.40 (d, J = 6.9 Hz, 1H), 7.71 (d, J = 4.8 Hz, 1H), 8.06 (s, 1H), 8.82 (s, 1H). CL/EM (m/z): calculado para $C_{24}H_{29}ClN_4S$ $(M+H)^+$: 441.3; encontrado: 405.2.

Ejemplo 42.

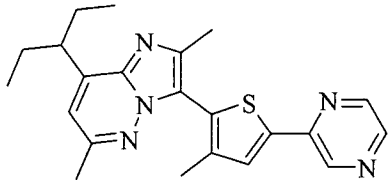
Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(3-metil-5-tiazol-2-il-tiofen-2-il)-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 32, la 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.46 g, 1.17 mmol), 0.5 M bromuro de 2-tiazolilzinc en THF (4.7 mL, 2.35 mmol) y $PdCl_2$(dppf) (0.043 g, 0.059 mmol) resulta el compuesto del título (0.32 g, 0.81 mmol, 70%). ^{1}H RMN ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.18 (s, 3H), 2.52 (s, 3H), 2.53 (s, 3H), 3.31-3.40 (m, 1H), 7.70 (s, 1H), 7.27 (d, J = 3.6 Hz, 1H), 7.47 (s, 1H), 7.78 (d, J = 3.6 Hz, 1H). CL/EM (m/z): calculado para $C_{21}H_{24}N_4S_2$ $(M+H)^+$: 397.7; encontrado: 397.1.

Ejemplo 43.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(3-metil-5-pirazin-2-il-tiofen-2-il)-imidazo[1,2-b]piridazina.

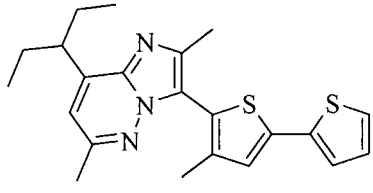


Al usar un procedimiento similar al Ejemplo 31, la 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.40 g, 1.02 mmol) (ejemplo Rupp-2), 2-cloropirazina (0.11 mL, 1.22 mmol), 1.42 M n-Bu-Li (1.52 mL, 1.07 mmol), 0.5 M $ZnCl_2$ en THF (2.14 mL, 1.07 mmol), y $PdCl_2$(dppf) (0.037 g, 0.051 mmol) resulta el compuesto del título (0.19 g, 0.49 mmol, 48%). ^{1}H RMN ($CDCl_3$),

δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.94 (m, 4H), 2.20 (s, 3H), 2.52 (s, 3H), 2.53 (s, 3H), 3.31-3.40 (m, 1H), 6.69 (s, 1H), 7.63 (s, 1H), 8.40 (d, J = 2.6 Hz, 1H), 8.51 (t, J = 1.9 Hz, 1H), 8.96 (d, J = 0.9 Hz, 1H). CL/EM (m/z): calculado para $C_{22}H_{25}N_5S$ $(M+H)^+$: 392.3; encontrado: 392.2.

Ejemplo 44.

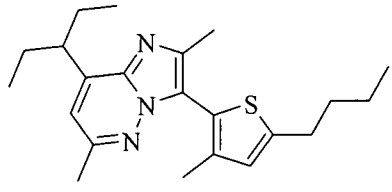
Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(4-metil-[2,2']bitiofenil-5-il)-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 32, a partir de la 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.30 g, 0.76 mmol), 0.5 M bromuro de 2-tiofenilzinc en THF (3.0 mL, 1.53 mmol) y $PdCl_2$(dppf) (0.028 g, 0.038 mmol) resulta el compuesto del título (0.25g, 0.63 mmol, 83%). ^{1}H RMN ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.14 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 3.30-3.39 (m, 1H), 6.68 (s, 1H), 7.02 (dd, J = 5.0, 3.6 Hz, 1H), 7.11 (s, 1H), 7.19 (d, J = 3.6 Hz, 1H), 7.19 (dd, J = 5.0, 1.0 Hz, 1H). CL/EM (m/z): calculado para $C_{22}H_{25}N_3S_2$ $(M+H)^+$: 396.7; encontrado: 396.2.

Ejemplo 45.

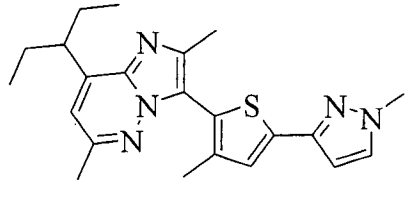
Preparación de 3-(5-butil-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 25, a partir de la 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.40 g, 0.1.02 mmol), n-Bu-Li 1.34 M (1.60 mL, 2.14 mmol), 0.5 M de $ZnCl_2$ (4.3 mL, 2.14 mmol) y $PdCl_2$(dppf) (0.037 g, 0.051 mmol) resulta el compuesto del título (0.25g, 0.69 mmol, 68%). ^1H RMN ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 0.97 (t, J = 7.5 Hz, 3H), 1.40-1.51 (m, 2H), 1.67-1.92 (m, 6H), 2.07 (s, 3H), 2.46 (s, 3H), 2.51 (s, 3H), 2.83 (t, J = 8.0 Hz, 2H), 3.30-3.38 (m, 1H), 6.64 (s, 1H), 6.70 (s, 1H) CL/EM (m/z): calculado para $C_{22}H_{31}N_3S$ $(M+H)^+$: 370.3; encontrado: 370.2.

Ejemplo 46.

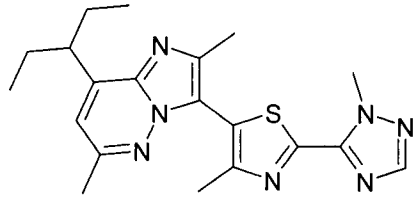
Preparación de 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(1-metil-1H-pirazol-3-il)-tiofen-2-il]-imidazo[1,2-b]piridazina.



Usando un procedimiento análogo al Ejemplo 31, la 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.40 g, 1.02 mmol), 1.42 M n-Bu-Li (0.75 mL, 1.07 mmol), 0.5 M $ZnCl_2$ en THF (2.14 mL, 1.07 mmol), 3-bromo-1-metil-1H-pirazol (Pavlik, J.; Kurzweil, E.; J. Org. Chem., 1991, 56, 22, 6313) (0.20 g, 1.22 mmol) y $PdCl_2$(dppf) (0.037 g, 0.051 mmol) resulta el compuesto del título (0.041g, 0.10 mmol, 10%). ^{1}H RMN ($CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.94 (m, 4H), 2.15 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 3.31-3.41 (m, 1H), 3.95 (s, 3H), 6.47 (d, J = 2.2 Hz, 1H), 6.67 (s, 1H), 7.25 (s, 1H), 7.36 (d, J = 2.2 Hz, 1H). CL/EM (m/z): calculado para $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.3; encontrado: 394.2.

Ejemplo 47.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-[4-metil-2-(2-metil-2H-[1,2,4]triazol-3-il)-tiazol-5-il]-imidazo[1,2-b]piridazina.

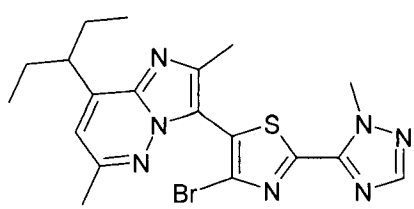


82 mg de 1-Metil-1,2,4-triazol (0.99 mmol) se disuelve en 2 ml de THF seco y se enfria hasta -78°C y 0.4 ml de n-butillitio 2.5 M en hexano (0.99 mmol) se agrega. La mezcla

de reacción se agita a -78°C a temperatura ambiente durante 10min y se enfria hasta -78°C nuevamente. 1.98 ml de 0.5 M cloruro de zinc solución 0.5M en THF (0.99 mmol) se agrega y se agita a -78°C a temperatura ambiente durante 15 min. 265 mg de 3-(2-bromo-4-metil-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.66 mmol) y 27 mg de $PdCl_2$(dppf) (0.033 mmol) se agregan y el vial se cierra con una tapa de Teflon y se calienta a 80°C durante 2 días. La reacción se enfría hasta temperatura ambiente y se apaga con NH_4Cl saturado y se extrajo con CH_2Cl_2. La capa CH_2Cl_2 separada se seca sobre Na_2SO_4 y se evapora. El producto crudo se aplica encima de una columna de cromatografía de gel de sílice (Hexano: AcOEt: 2 M NH3 en MeOH=10:2:1) para dar 57 mg del producto del título. Rendimiento 22%. espectro de masas (m/e): 396 (M+1). ^{1}H-RMN ($CDCl_3$): δ 7.96 (s, 1H), 6.77 (s, 1H), 4.45 (s, 3H), 3.36 (m, 1H), 2.55 (s, 3H), 2.52 (s, 3H), 2.47 (s, 3H), 1.88 (m, 4H), 0.92 (t, J=7.3Hz, 6H).

Ejemplo 48.

Preparación de 3-[4-bromo-2-(2-metil-2H-[1,2,4]triazol-3-il)-tiazol-5-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

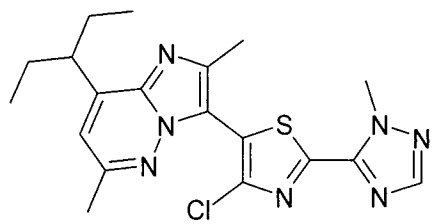


82 mg de 1-metil-1,2,4-triazol (0.99 mmol) se disuelve en 2 ml de THF seco y se enfria hasta -78°C y 0.4 ml de n-butillitio 2.5 M en hexano (0.99 mmol) se agrega. La mezcla de reacción se agita a -78°C hasta temperatura ambiente durante 10min y se enfria hasta -78°C nuevamente. 1.98 ml de 0.5 M cloruro de zinc, una solución 0.5 M en THF (0.99 mmol) se agrega y se agita a -78°C hasta temperatura ambiente durante 15min. 152 mg de 3-(2,4-dibromo-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.33 mmol) y 27 mg de PdCl2(dppf) (0.033 mmol) se agregan y el vial se cierra con una tapa de Teflon y se calienta a 80°C durante 2 días. La reacción se enfría hasta temperatura ambiente y se apaga con NH_4Cl saturado y se extrajo con CH_2Cl_2. La capa CH_2Cl_2 separada se seca sobre Na2SO4 y se evapora. El producto crudo se aplica encima de una columna de cromatografía de gel de sílice (Hexano:AcOEt:2M NH3 en MeOH=10:2:1) para dar 88mg del producto del título. Rendimiento 54%. espectro de masas(m/e):461(M+1). ^{1}H-RMN (CDCl3): 7.98 (s, 1H), 6.77 (s, 1H), 4.44 (s, 3H), 3.35 (m, 1H), 2.59 (s, 3H), 2.55 (s, 3H), 1.88 (m, 4H), 0.92 (t, J=7.5Hz, 6H).

320

Ejemplo 49.

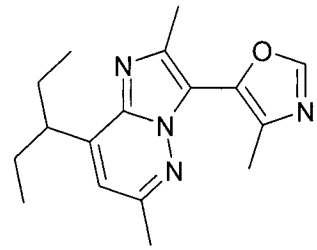
Preparación de 3-[4-cloro-2-(2-metil-2H-[1,2,4]triazol-3-il)-tiazol-5-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



175 mg de 3-[4-Bromo-2-(2-metil-2H-[1,2,4]triazol-3-il)-tiazol-5-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.38 mmol) y 56 mg de cloruro de cobre (0.57 mmol) se colocaron en un vial de 4 ml con 3.0 ml de DMF seco y el vial se cierra con una tapa de Teflon. El vial se calienta a 130°C durante la noche. La mezcla de reacción se aplica encima de una columna de cromatografía de gel de sílice (Hexano:AcOEt=3:1 y hexano:AcOEt=8:1) para dar 91 mg del producto crudo. El producto puro se recristaliza a partir de Et_2O/Hexano. 73 mg (46%). espectro de masas (m/e): 416 (M+1). ^{1}H-RMN (CDCl3): 7.98 (s, 1H), 6.80 (s, 1H), 4.44 (s, 3H), 3.35 (m, 1H), 2.59 (s, 3H), 1.88 (m, 4H), 0.92 (t, J=7.5Hz, 6H).

Ejemplo 50.

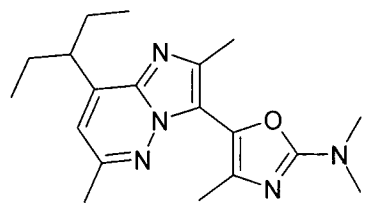
Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(4-metil-oxazol-5-il)-imidazo[1,2-b]piridazina.



686 mg de 8-(1-Etil-propil)-3-yodo-2,6-dimetil-imidazo[1,2-b]piridazina (2.0 mmol), 830 mg de 4-metil-oxazol. (10 mmol), 105 mg de trifenilfosfina (0.4 mmol) y 1.30 g de carbonato de cesio (4.0 mmol) se colocaron en el tubo con 10 ml de DMF seco. El gas N2 se burbujea durante 20min y 92 mg de Pd2dba3 (0.1 mmol) se agrega. El tubo se sella y se calienta a 130°C durante la noche. Después de enfriarse a temperatura ambiente, agua y CHCl2 se agregan a la mezcla. La capa de CHCl2 se separa, se lava con NaCl saturado, se seca sobre Na2SO4 y se evapora. El producto crudo se aplica encima de una columna de cromatografía de gel de sílice (Hexano:AcOEt=5:1) para dar 234 mg del producto del título. Rendimiento 39%. espectro de masas (m/e): 299 (M+1). ^{1}H-RMN (CDCl3): 8.06 (s, 1H), 6.75 (s, 1H), 3.34 (m, 1H), 2.56 (s, 3H), 2.50 (s, 3H), 2.29 (s, 3H), 1.86 (m, 4H), 0.90 (t, J=7.4Hz, 6H).

Ejemplo 51.

Preparación de N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-oxazol-2-il}-dimetilamina.



A. 3-(2-Bromo-4-metil-oxazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

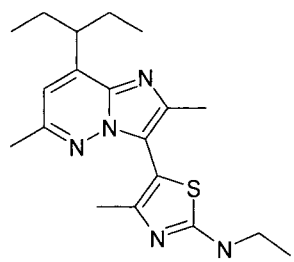
230 mg de 8-(1-Etil-propil)-2,6-dimetil-3-(4-metil-oxazol-5-il)-imidazo[1,2-b]piridazina (0.77 mmol) se disuelve en 20 ml de CH2Cl2 y 178 mg de NBS (1.0 mmol) se agrega. La mezcla de reacción se agita a temperatura ambiente durante la noche. La mezcla de reacción se lava con Na2S2O3 saturado, NaCl saturado, se seca sobre Na2SO4 y se evapora. El producto crudo se aplica encima de una columna de cromatografía de gel de sílice (Hexano:AcOEt=3:1) para dar 36 mg del compuesto del título. Rendimiento 12%. espectro de masas (m/e): 378 (M+1). ^{1}H-RMN (CDCl3): 6.82 (s, 1H), 3.39 (m, 1H), 2.58 (s, 3H), 2.53 (s, 3H), 2.26 (s, 3H), 1.85 (m, 1H), 0.89 (t, J=7.4Hz, 6H).

B. N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-oxazol-2-il}-dimetilamina.

32 mg de 3-(2-Bromo-4-metil-oxazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.08 mmol) y 78 mg de carbonato de cesio (0.24 mmol) se colocaron en un vial con 3 ml de dimetilamina 2.0 M en THF. El vial se cierra con una tapa de Teflon y se calienta a 110°C durante 3 días. La mezcla de reacción se enfría hasta temperatura ambiente, se concentra, y se aplica sobre una columna de cromatografía de gel de sílice (Hexano: AcOEt: 2M NH3 en MeOH=10:2:1) para dar 24 mg del producto del título. Rendimiento 89%. espectro de masas (m/e): 342(M+1). ^{1}H-RMN (CDCl3): 6.71(s, 1H), 3.34 (m, 1H), 3.13 (s, 6H), 2.56 (s, 3H), 2.49 (s, 3H), 2.14 (s, 3H), 1.84 (m, 4H), 0.89 (t, J=7.5Hz, 6H).

Ejemplo 52.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-[(4-metil-2-etilamino)-tiazol-5-il]-imidazo[1,2-b]piridazina.

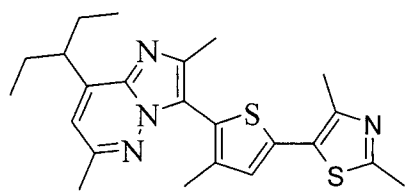


El compuesto del título se prepara esencialmente como se describe en el ejemplo 51B. Empleando 2.0 ml de etilamina 2.0 M en THF y 182 g de carbonato de cesio (0.56 mmol), 78%. espectro de masas (m/e): 358 (M+1); 1H-RMN (CDCl3): 6.69(s,

1H), 5.23(br, 1H), 3.38(m, 3H), 2.56(s, 3H), 2.46(s, 3H), 2.17(s, 3H), 1.85(m, 4H), 1.35(t, 3H, J=7.2Hz), 0.90(t, 6H, J=7.2Hz).

Ejemplo 53.

Preparación de 3-[5-(2,4-dimetil-tiazol-5-il)-3-metil-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



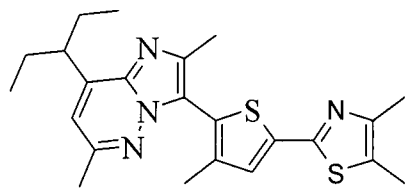
A una mezcla a -78°C de 2,4-dimetiltiazol (0.23 g, 2.04 mmol) y THF (3 mL) se agrega 1.6 M t-Bu-Li en hexano (1.30 mL, 2.09 mmol). La mezcla se agita a -78°C durante 15 minutos. 0.5 M de $ZnCl_2$ en THF (4.3 mL, 2.14 mmol) se agrega y la solución se entibia hasta temperatura ambiente. La 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.40 g, 1.02 mmol) y $PdCl_2$(dppf) (0.037 g, 0.051 mmol) se agrega y la mezcla se agita a 65°C durante la noche, se diluye con EtOAc (20 mL), se lava con ácido cítrico al 10% (15 mL), agua (15 mL), salmuera (15 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en gel de sílice (0%-15% gradiente de EtOAc/hexano) resulta el compuesto del título (0.21 g, 0.49 mmol, 49%). ^1H RMN ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H),

326

1.73-1.91 (m, 4H), 2.14 (s, 3H), 2.49 (s, 3H), 2.52 (s, 3H), 2.57 (s, 3H), 2.66 (s, 3H), 3.28-3.38 (m, 1H), 6.68 (s, 1H), 7.00 (s, 1H). CL/EM (m/z): calculado para $C_{23}H_{28}N_4S_2$ $(M+H)^+$: 425.3; encontrado: 425.2.

Ejemplo 54.

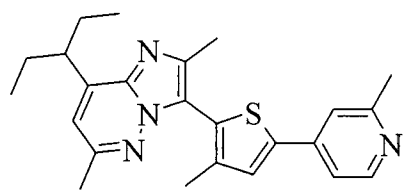
Preparación de 3-[5-(4,5-dimetil-tiazol-2-il)-3-metil-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 25, a partir de 4,5-dimetiltiazol (0.22 mL, 2.04 mmol), n-Bu-Li 1.56 M (1.34 mL, 2.09 mmol), $ZnCl_2$ (4.3 mL, 2.14 mmol), 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.40 g, 1.02 mmol) y $PdCl_2$(dppf) (0.037 g, 0.051 mmol) resulta el compuesto del título (0.27 g, 0.64 mmol, 63%). ^1H RMN ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.13 (s, 3H), 2.36 (s, 3H), 2.38 (s, 3H), 2.49 (s, 3H), 2.51(s, 3H), 3.29-3.38 (m, 1H), 6.67 (s, 1H), 7.32 (s, 1H). CL/EM (m/z): calculado para $C_{23}H_{28}N_4S_2$ $(M+H)^+$: 425.3; encontrado: 425.2.

Ejemplo 55.

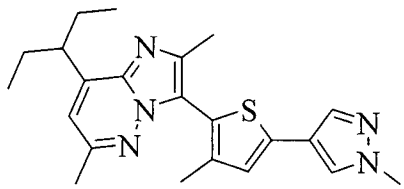
Preparación de 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(2-metil-piridin-4-il)-tiofen-2-il]-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 31, a partir de 4-bromo-2-metil piridina (Fukaya et. el. Chem. Pharm. Bull., 1990, 38, 2446) (0.21 g, 1.22 mmol), n-Bu-Li 1.56 M (0.69 mL, 1.07 mmol), 0.5 M $ZnCl_2$ en THF (2.2 mL, 1.12 mmol), 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.40 g, 1.02 mmol) y $PdCl_2$(dppf) (0.037 g, 0.051 mmol) resulta el compuesto del título (0.058 g, 0.14 mmol, 14%). ^1H RMN ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.16 (s, 3H), 2.48 (s, 3H), 2.51 (s, 3H), 2.58 (s, 3H), 3.27-3.37 (m, 1H), 6.68 (s, 1H), 7.29 (d, J = 5.3 Hz, 1H), 7.35 (s, 1H), 7.41 (s, 1H), 8.46 (t, J = 5.3 Hz, 1H). CL/EM (m/z): calculado para $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.3; encontrado: 405.2.

Ejemplo 56.

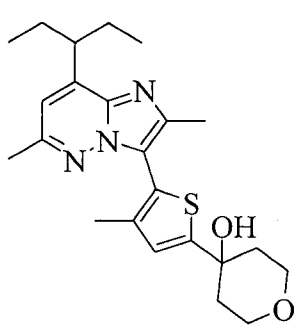
Preparación de 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(1-metil-1H-pirazol-4-il)-tiofen-2-il]-imidazo[1,2-b]piridazina.



Usando un procedimiento análogo al Ejemplo 31, a partir de la 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.40 g, 1.02 mmol), 1.42 M n-Bu-Li (0.75 mL, 1.07 mmol), 0.5 M $ZnCl_2$ en THF (2.14 mL, 1.07 mmol), 4-bromo-1-metil-1H-pirazol (0.25 g, 1.53 mmol) y $PdCl_2$(dppf) (0.037 g, 0.051 mmol) resulta el compuesto del título (0.092g, 0.23 mmol, 23%). ^1H RMN ($CDCl_3$) δ 0.88 (t, J = 7.4 Hz, 6H), 1.73-1.92 (m, 4H), 2.12 (s, 3H), 2.48 (s, 3H), 2.52 (s, 3H), 3.29-3.38 (m, 1H), 3.92 (s, 3H), 6.66 (s, 1H), 6.98 (s, 1H), 7.54 (s, 1H), 7.68 (s, 1H). CL/EM (m/z): calculado para $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.3; encontrado: 394.2.

Ejemplo 57.

Preparación de 4-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiofen-2-il}-tetrahidro-piran-4-ol.

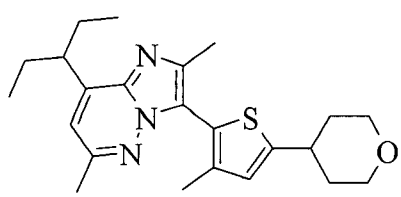


326

A una solución a -78°C de 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.60 g, 1.53 mmol) y THF (10 mL) se agrega n-Bu-Li 1.56 M (1.03 mL, 1.61 mmol). Después de 30 minutos tetrahidro-piran-4-ona (0.21 mL, 2.29 mmol) se agrega durante 5 minutos. La solución se agita a -78°C durante 2 horas, se entibia hasta temperatura ambiente, se diluye con EtOAc (50 mL), se lava con NH_4Cl saturado (50 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (20%-100% gradiente de EtOAc/hexano) resulta el compuesto del título (0.38 g, 0.92 mmol, 60%). ^1H RMN ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 1.91-2.00 (m, 2H), 2.11 (s, 3H), 2.20-2.30 (m, 2H), 2.46 (s, 3H), 2.51 (s, 3H), 3.30-3.39 (m, 1H), 3.83-3.98 (m, 5H), 6.66 (s, 1H), 6.93 (s, 1H). CL/EM (m/z): calculado para $C_{23}H_{31}N_3O_2S$ $(M+H)^+$: 414.3; encontrado: 414.2.

Ejemplo 58.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(tetrahidro-piran-4-il)-tiofen-2-il]-imidazo[1,2-b]piridazina.



Método A.

A una solución de 4-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiofen-2-il}-tetrahidro-piran-4-ol (0.25 g, 0.604 mmol) y CH_2Cl_2 (10 mL) se agrega TFA (0.79 mL, 10.28 mmol) y Et_3SiH (0.25 mL, 1.57 mmol). La solución se concentra, se disuelve en EtOAc (30 mL), se lava con $NaHCO_3$ saturado (30 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (10%-15% gradiente de EtOAc/hexano), se disuelve en EtOH (25 mL), 10 % Pd/C (0.07 g, 0.066 mmol) se agrega y la solución se agita bajo una atmósfera de H_2. Después de 2 horas la solución se filtra a través de celite® y se concentra. El residuo se purifica por cromatografía en columna ISCO (30% EtOAc en hexano) resulta el compuesto del título (0.033 g, 0.083 mmol, 14%). ^1H RMN ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.95 (m, 4H), 1.97-2.04 (m, 2H), 2.09 (s, 3H), 2.20-2.30 (m, 2H), 2.46 (s, 3H), 2.52 (s, 3H), 3.00-3.11 (m, 1H), 3.30-3.40 (m, 1H), 3.54 (dt, J = 11.8, 2.2 Hz, 2H), 4.08 (dd, J = 11.8, 2.2 Hz, 2H), 6.65 (s, 1H), 6.75 (s, 1H). CL/EM (m/z): calculado para $C_{23}H_{31}N_3OS$ $(M+H)^+$: 398.7; encontrado: 398.2.

Método B.

A. 4-(5-Bromo-4-metil-tiofen-2-il)-tetrahidro-piran-4-ol.

A una solución a -78°C de 2-bromo-3-metil-tiofeno (2.0 g, 17.75 mmol) y THF (30 mL) se agrega 2.0 M LDA (9.32 mL,

18.63 mmol). Después de 30 minutos a -78°C tetrahidro-piran-4-ona (2.3 mL, 23.07 mmol) se agrega y la solución se entibia hasta temperatura ambiente. La solución se lava con NH_4Cl saturado (30 mL). Las fases acuosas se extraen con EtOAc. Las capas orgánicas combinadas se secan sobre $MgSO_4$, se filtran y se concentran. El residuo se purifica por cromatografía en columna ISCO (30%-100% gradiente de EtOAc/hexano) resulta el compuesto del título (2.3 g, 8.30 mmol, 47%). ^1H RMN ($CDCl_3$), δ 1.82 (m, 2H), 2.00 (s, 3H), 2.06-2.15 (m, 3H), 2.16 (s, 3H), 3.77-3.84 (m, 2H), 3.87 dt, J = 11.3, 2.2 Hz, 2H), 6.67 (s, 1H). CL/EM (m/z): calculado para $C_{10}H_{13}BrO_2S$ $(M+H)^+$: 277.0; encontrado: 260.9.

B. 4-(5-Bromo-4-metil-tiofen-2-il)-tetrahidro-piran.

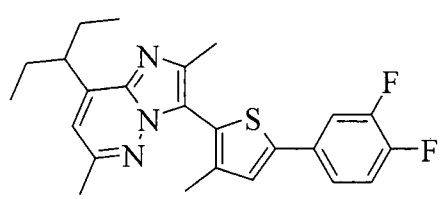
A una solución de 4-(5-bromo-4-metil-tiofen-2-il)-tetrahidro-piran-4-ol (2.3 g, 8.30 mmol) y 1,2-dicloroetano (50 mL) se agrega ZnI_2 (3.97 g, 12.45 mmol) y cianoborohidruro de sodio (3.91, 62.23 mmol). La solución se agita durante 1 hora, se filtra a través de celite y se concentra. El residuo se purifica por cromatografía en columna ISCO (5%-10% gradiente de EtOAc/hexano) resulta el compuesto del título (1.53 g, 5.86 mmol, 71%). ^1H RMN ($CDCl_3$), δ 1.69-1.82 (m, 2H), 1.84-1.92 (m, 2H), 2.14 (s, 3H), 2.84-2.98 (m, 1H), 3.49 (dt, J = 11.8, 2.2 Hz, 2H), 4.00-4.07 (m, 2H), 6.51 (s, 1H).

C. 8-(1-Etil-propil)-2,6-dimetil-3-[3-metil-5-(tetrahidro-piran-4-il)-tiofen-2-il]-imidazo[1,2-b]piridazina.

Al usar un procedimiento similar al Ejemplo 25, el 4-(5-bromo-4-metil-tiofen-2-il)-tetrahidropirano (0.83 g, 3.19 mmol), n-Bu-Li 1.56 M (2.04 mL, 3.19 mmol), $ZnCl_2$ (6.4 mL, 3.19 mmol), 8-(1-etil-propil)-3-yodo-2,6-dimetil-imidazo[1,2-b]piridazina (0.50 g, 1.56 mmol) y $Pd(PPh_3)_4$ (0.092 g, 0.008 mmol) resulta el compuesto del título (0.072 g, 0.18 mmol, 11%). Espectro idéntico a aquel del método A.

Ejemplo 59.

Preparación de 3-[5-(3,4-difluoro-fenil)-3-metil-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

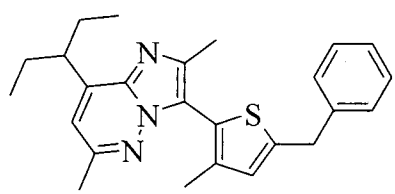


Al usar un procedimiento similar al Ejemplo 32, la 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.50 g, 1.27 mmol) y $PdCl_2$(dppf) (0.047 g, 0.064 mmol) y solución 0.5M de bromuro de 3,4-difluorofenilzinc en THF (5.1 mL, 2.55 mmol) se hicieron reaccionar. El residuo se purifica por cromatografía en columna ISCO (15%-20% gradiente de EtOAc/hexano) y se procesa

por cromatografía (columna C18 Symmetry de 50 x 250, 30-80% agua: 0.1 % TFA /ACN: 0.1% TFA gradiente) resulta el compuesto del título (0.18 g, 0.42 mmol, 33%). ^{1}H RMN ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.16 (s, 3H), 2.50 (s, 3H), 2.54 (s, 3H), 3.31-3.40 (m, 1H), 6.69 (s, 1H), 7.13-7.21 (m, 1H), 7.18 (s, 1H), 7.31-7.36 (m, 1H), 7.39-7.46 (m, 1H). CL/EM (m/z): calculado para $C_{24}H_{25}F_2N_3S$ $(M+H)^+$: 426.3; encontrado: 426.2.

Ejemplo 60.

Preparación de 3-(5-bencil-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

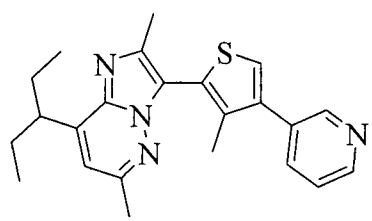


Al usar un procedimiento similar al Ejemplo 32, la 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.30 g, 0.765 mmol) y $PdCl_2$(dppf) (0.028 g, 0.038 mmol) y solución 0.5M de bromuro de bencilzinc en THF (4.6 mL, 2.29 mmol) se hicieron reaccionar. El residuo se purifica por cromatografía en columna ISCO (15%-20% gradiente de EtOAc/hexano) y se procesa por cromatografía (columna C18 Symmetry de 50 x 250, 40-65% agua: 0.1 % TFA /ACN: 0.1% TFA gradiente) resulta el compuesto del

título (0.062 g, 0.15 mmol, 20%). ^{1}H RMN ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.06 (s, 3H), 2.45 (s, 3H), 2.51 (s, 3H), 3.29-3.39 (m, 1H), 4.16 (s, 2H), 6.65 (s, 1H), 6.68(s, 1H), 7.22-7.29 (m, 1H), 7.31-7.36 (m, 4H). CL/EM (m/z): calculado para $C_{25}H_{29}N_3S$ $(M+H)^+$: 404.3; encontrado: 404.2.

Ejemplo 61.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(3-metil-4-piridin-3-il-tiofen-2-il)-imidazo[1,2-b]piridazina.

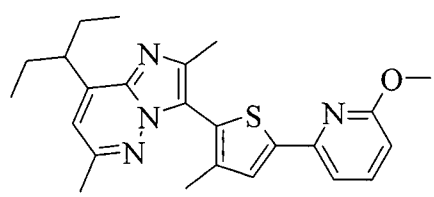


Una solución de 3-(4-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.25 g, 0.64 mmol), ácido piridina-3-borónico (0.086 g, 0.70 mmol), 2 M Na_2CO_3 (0.48 mL, 0.96 mmol) y, n-PrOH (3 mL), se desgasifica con nitrógeno durante 10 minutos. El $Pd(OAc)_2$ (2.7 mg, 0.0013 mmol) y PPh_3 (0.010 g, 0.038 mmol) se agregan y la solución se calienta a 90°C durante la noche. La solución se diluye con EtOAc (30 mL), se lava con 10% Na_2CO_3 (30 mL), agua (30 mL), salmuera (30 mL), se seca sobre $MgSO_4$, se filtra, y se concentra. El residuo se purifica por ISCO (20-40% EtOAc gradiente) resulta el compuesto del título (0.051 g, 0.13

mmol, 20%). ^{1}H RMN ($CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.09 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.29-3.40 (m, 1H), 6.69 (s, 1H), 7.33-7.43 (m, 1H), 7.47 (s, 1H), 7.80 (d, J = 7.9 Hz, 1H), 8.61 (bs, 1H), 8.78 (bs, 1H). CL/EM (m/z): calculado para $C_{23}H_{26}N_4S$ $(M+H)^+$: 391.2; encontrado: 391.4.

Ejemplo 62.

Preparación de 8-(1-etil-propil)-3-[5-(6-metoxi-piridin-2-il)-3-metil-tiofen-2-il]-2,6-dimetil-imidazo[1,2-b]piridazina.

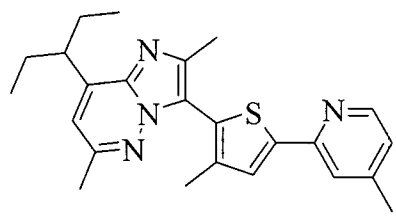


Al usar un procedimiento similar al Ejemplo 32, a partir de la 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.30 g, 0.765 mmol) y $PdCl_2$(dppf) (0.028 g, 0.038 mmol) y solución 0.5M de bromuro de 6-metoxi-2-piridilzinc en THF (3.0 mL, 1.53 mmol) resulta el compuesto del título (0.12 g, 0.29 mmol, 38%). ^{1}H RMN ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.15 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 3.98 (s, 3H), 6.61 (d, J = 7.5 Hz, 1H), 6.70(s, 1H), 7.23 (d, J = 7.5 Hz, 1H), 7.52 (s, 1H), 7.56 (d, J = 7.7 Hz, 1H). CL/EM

(m/z): calculado para $C_{24}H_{28}N_4OS$ $(M+H)^+$: 421.3; encontrado: 421.3.

Ejemplo 63.

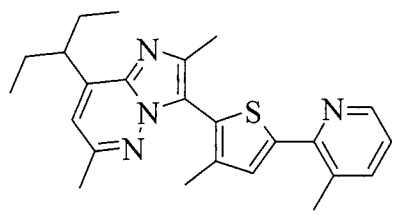
Preparación de 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(4-metil-piridin-2-il)-tiofen-2-il]-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 32, a partir de la 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.30 g, 0.765 mmol) y $PdCl_2$(dppf) (0.028 g, 0.038 mmol) y solución 0.5M de bromuro de 4-metil-2-piridilzinc en THF (3.0 mL, 1.53 mmol) resulta el compuesto del título (0.21 g, 0.52 mmol, 68%). ^{1}H RMN ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H), 2.40 (s, 3H), 2.52 (s, 6H), 3.30-3.40 (m, 1H), 6.67 (s, 1H), 6.97(d, J = 4.8 Hz, 1H), 7.49 (s, 1H), 7.52 (s, 1H), 8.42 (d, J = 4.8 Hz, 1H). CL/EM (m/z): calculado para $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.3; encontrado: 405.3.

Ejemplo 64.

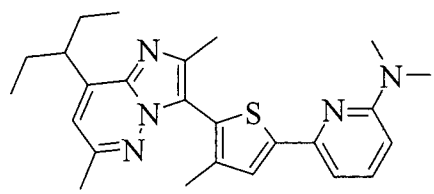
Preparación de 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(3-metil-piridin-2-il)-tiofen-2-il]-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 32, a partir de la 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina) (0.30 g, 0.765 mmol) y $PdCl_2$(dppf) (0.028 g, 0.038 mmol) y solución 0.5M de bromuro de 3-metil-2-piridilzinc en THF (5.0 mL, 2.50 mmol) resulta el compuesto del título (0.22 g, 0.54 mmol, 71%). ^{1}H RMN ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 2.63 (s, 3H), 3.29-3.39 (m, 1H), 6.67 (s, 1H), 7.06-7.14 (m, 1H), 7.44 (s, 1H), 7.74 (dd, J = 7.5, 0.9 Hz, 1H), 8.47 (dd, J = 4.9, 0.9 Hz, 1H). CL/EM (m/z): calculado para $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.3; encontrado: 405.3.

Ejemplo 65.

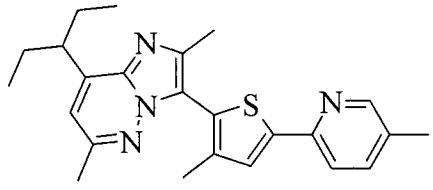
Preparación de (6-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiofen-2-il}-piridin-2-il)-dimetil-amina.



Al usar un procedimiento similar al Ejemplo 39, a partir de Rieke® Zn en THF (0.20 g, 3.06 mmol), (6-bromo-piridin-2-il)-dimetil-amina (Newkomw et. el. J. Org. Chem., 1988, 3, 786) (0.41 mL, 2.04 mmol), 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.35 g, 0.89 mmol), y $PdCl_2$(dppf) (0.037 g, 0.051 mmol) resulta el compuesto del título (0.16 g, 0.37 mmol, 36%). ^{1}H RMN ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.15 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 3.21 (s, 6H), 3.30-3.40 (m, 1H), 6.40 (d, J = 8.4 Hz, 1H), 6.66 (s, 1H), 6.95 (d, J = 7.4 Hz, 1H), 7.45 (dd, J = 8.4, 7.4 Hz, 1H), 7.46 (s, 1H). CL/EM (m/z): calculado para $C_{25}H_{31}N_5S$ $(M+H)^+$: 434.3; encontrado: 434.3.

Ejemplo 66.

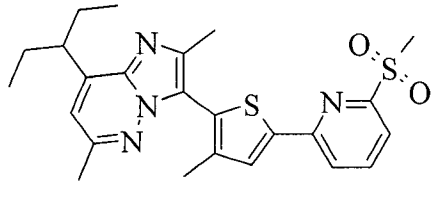
Preparación de 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(5-metil-piridin-2-il)-tiofen-2-il]-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 32, a partir de la 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.30 g, 0.765 mmol) y $PdCl_2$(dppf) (0.028 g, 0.038 mmol) y solución 0.5M de bromuro de 4-metil-2-piridilzinc en THF (3.0 mL, 1.53 mmol) resulta el compuesto del título (0.23 g, 0.57 mmol, 74%). ^{1}H RMN ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.16 (s, 3H), 2.35 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 3.31-3.41 (m, 1H), 6.67 (s, 1H), 7.48(s, 1H), 7.50 (d, J = 2.2 Hz, 1H), 7.56 (d, J = 7.9 Hz, 1H), 8.39-8.40 (m, 1H). CL/EM (m/z): calculado para $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.3; encontrado: 405.3.

Ejemplo 67.

Preparación de 8-(1-etil-propil)-3-[5-(6-metanosulfonil-piridin-2-il)-3-metil-tiofen-2-il]-2,6-dimetil-imidazo[1,2-b]piridazina.



A. 2-Bromo-6-metanosulfonil-piridina.

A una solución de 2-bromo-6-metilsulfanil-piridina (Testaferri et. el Tetrahedron, 1985, 41, 1373) (2.15 g, 10.53 mmol) y CH_2Cl_2 (30 mL) se agrega 56-87% mCPBA (12 g, 42.15 mmol). La solución se enfria con hielo a temperatura ambiente y la solución se agita durante 2 horas, se lava con $Na_2S_2O_3$ sat. (15 mL), $NaHCO_3$ saturado (2 X 15 mL) se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por recristalización a partir de EtOAc/hexano resulta el compuesto del título (1.71 g, 7.24 mmol, 69%). ^1H RMN ($CDCl_3$), δ 3.26 (s, 3H), 7.73 (dd, J = 8.0, 0.9 Hz, 1H), 7.82 (dd, J = 8.0, 7.5 Hz, 1H), 8.05 (dd, J = 7.5, 0.9 Hz, 1H). CL/EM (m/z): calculado para $C_6H_6BrNO_2S$ $(M+H)^+$: 235.9; encontrado: 235.9.

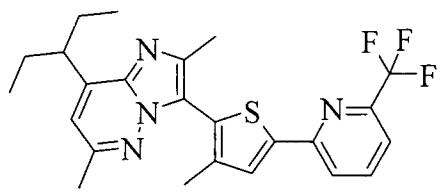
B. 8-(1-etil-propil)-3-[5-(6-metanosulfonil-piridin-2-il)-3-metil-tiofen-2-il]-2,6-dimetil-imidazo[1,2-b]piridazina.

Al usar un procedimiento similar al Ejemplo 25, la 2-bromo-6-metanosulfonil-piridina (0.29 mL, 1.22 mmol), 1.3 M n-Bu-Li (0.82 mL, 1.07 mmol), $ZnCl_2$ (2.14 mL, 1.07 mmol), 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.40 g, 1.02 mmol) y $PdCl_2$(dppf) (0.037 g, 0.051 mmol) resulta el compuesto del título (0.13 g, 0.28 mmol, 27%). ^1H RMN ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.18 (s, 3H), 2.50 (s, 3H), 2.52 (s,

3H), 3.30 (s, 3H), 3.30-3.38 (m, 1H), 6.70 (s, 1H), 7.64 (s, 1H), 7.83 (dd, J = 7.6, 0.8 Hz, 1H), 7.89 (dd, J = 7.9, 0.8 Hz, 1H), 7.93 (dd, J = 7.9, 7.6 Hz, 1H). CL/EM (m/z): calculado para $C_{24}H_{28}N_4O_2S_2$ $(M+H)^+$: 469.3; encontrado: 469.2.

Ejemplo 68.

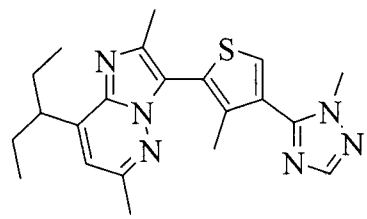
Preparación de 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(6-trifluorometil-piridin-2-il)-tiofen-2-il]-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 25, la 2-cloro-6-trifluorometil-piridina (0.29 mL, 1.22 mmol), n-Bu-Li 1.34 M (0.80 mL, 1.07 mmol), $ZnCl_2$ (2.14 mL, 1.07 mmol), 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.40 g, 1.02 mmol) y $PdCl_2$(dppf) (0.037 g, 0.051 mmol) resulta el compuesto del título (0.20 g, 0.44 mmol, 43%). ^1H RMN ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.18 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.30-3.40 (m, 1H), 6.69 (s, 1H), 7.50 (dd, J = 7.5, 0.9 Hz, 1H), 7.65 (s, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.84 (dd, J = 7.9, 7.5 Hz, 1H). CL/EM (m/z): calculado para $C_{24}H_{25}F_3N_4S$ $(M+H)^+$: 459.3; encontrado: 459.2.

Ejemplo 69.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-4-(2-metil-2H-[1,2,4]triazol-3-il)-tiofen-2-il]-imidazo[1,2-b]piridazina.



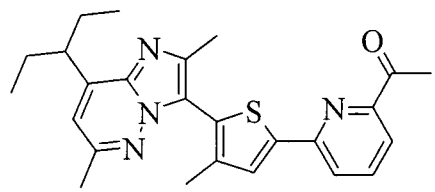
A una suspensión espesa de 0.05 g/ mL de Reike® Zn en THF (3.0 mL, 2.29 mmol) se agrega una solución de 5-bromo-1-metil-1H-[1,2,4]triazol y THF (2 mL). La solución se calienta a 65°C durante 1 hora, se enfria a temperatura ambiente y el exceso de Zn se deja asentar durante 1 hora. La solución se transfiere a un matraz que contiene 3-(4-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (ejemplo Rupp-152) (0.32 g, 0.70 mmol) y $PdCl_2$(dppf) (0.028 g, 0.038 mmol). La solución se calienta a 65°C durante la noche, se diluye con EtOAc (30 mL), se lava con NH_4Cl saturado (30 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por ISCO (50%-100% Et_2O) para resultar el compuesto del título (0.058 g, 0.15 mmol, 19%). ^1H RMN ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.11 (s, 3H), 2.47 (s, 3H), 2.49 (s, 3H), 3.27-3.37 (m, 1H), 3.97 (s, 3H), 6.68 (s, 1H), 7.64 (s, 1H), 7.99 (s, 1H).

383

CL/EM (m/z): calculado para $C_{21}H_{26}N_6S$ $(M+H)^+$: 395.2; encontrado: 395.4.

Ejemplo 70.

Preparación de 1-(6-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiofen-2-il}-piridin-2-il)-etanona.



A. 3-[5-(6-Bromo-piridin-2-il)-3-metil-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

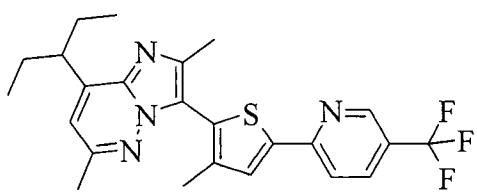
Al usar un procedimiento similar al Ejemplo 25, la 2,6-dibromo-piridina (0.91 g, 3.82 mmol), n-Bu-Li 1.34 M (1.50 mL, 2.00 mmol), $ZnCl_2$ (4.0 mL, 2.00 mmol), 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.75 g, 1.92 mmol) y $PdCl_2$(dppf) (0.070 g, 0.096 mmol) resulta el compuesto del título (0.26 g, 0.55 mmol, 29%). ^1H RMN ($CDCl_3$), δ 0.89 (t, J = 7.4 Hz, 6H), 1.74-1.93 (m, 4H), 2.16 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.30-3.39 (m, 1H), 6.68 (s, 1H), 7.31 (dd, J = 7.5, 1.3 Hz, 1H), 7.49-7.57 (m, 2H), 7.58 (s, 1H).

B. 1-(6-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiofen-2-il}-piridin-2-il)-etanona.

A una solución a -78°C de 3-[5-(6-bromo-piridin-2-il)-3-metil-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina) (0.26 g, 0.55 mmol), y THF (5 mL), se agrega n-Bu-Li 1.34 M (0.43 mL, 0.58 mmol). Después de 30 minutos N-metoxi-N-metil-acetamida (0.065 mL, 0.61 mmol) se agrega y la solución se entibia hasta temperatura ambiente. La solución se diluye con EtOAc (30 mL), se lava con NH_4Cl saturado (25 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (15-20% gradiente de EtOAc/hexano) resulta el compuesto del título (0.030 g, 0.069 mmol, 13%). ^1H RMN ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.19 (s, 3H), 2.52 (s, 3H), 2.53 (s, 3H), 2.77 (s, 3H), 3.30-3.40 (m, 1H), 6.69 (s, 1H), 7.59 (s, 1H), 7.77-7.85 (m, 2H), 7.87 (dd, J = 6.8, 2.2 Hz, 1H). CL/EM (m/z): calculado para $C_{25}H_{28}N_4OS$ $(M+H)^+$: 433.3; encontrado: 433.2.

Ejemplo 71.

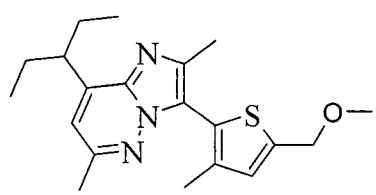
Preparación de 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(5-trifluorometil-piridin-2-il)-tiofen-2-il]-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 32, a partir de la 2-bromo-5-trifluorometil-piridina (2.14 mL, 1.07 mmol), n-Bu-Li 1.34 M (0.80 mL, 1.07 mmol), $ZnCl_2$ (2.14 mL, 1.07 mmol), 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.40 g, 1.02 mmol) y $PdCl_2$(dppf) (0.037 g, 0.051 mmol) resulta el compuesto del título (0.17 g, 0.37 mmol, 36%). ^{1}H RMN ($CDCl_3$), δ 0.90 (t, J = 7.3 Hz, 6H), 1.76-1.94 (m, 4H), 2.18 (s, 3H), 2.19 (s, 3H), 2.53 (s, 3H), 3.31-3.40 (m, 1H), 6.70 (s, 1H), 7.63 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.78 (dd, J = 8.4, 2.2 Hz, 1H), 7.79-7.82 (m, 1H). CL/EM (m/z): calculado para $C_{24}H_{25}F_3N_4S$ $(M+H)^+$: 459.3; encontrado: 459.2.

Ejemplo 72.

Preparación de 8-(1-etil-propil)-3-(5-metoximetil-3-metil-tiofen-2-il)-2,6-dimetil-imidazo[1,2-b]piridazina.

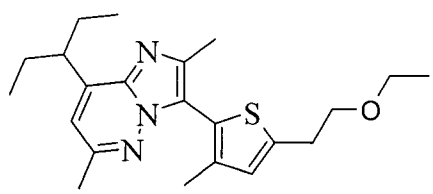


A una solución a -78°C de 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.30 g, 0.76 mmol) y THF (3 mL) se agrega n-Bu-Li 1.34 M (0.50 mL, 0.80 mmol). Después de 30 minutos el yodo-metoxi-metano (0.097 mL, 1.15 mmol) se agrega y la solución se

entibia hasta temperatura ambiente. Después de 1 hora la solución se diluye con EtOAc (40 mL) se lava con agua (30 mL), salmuera (30 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (15%-20% gradiente de EtOAc/hexano) resulta el compuesto del título (0.12 g, 0.34 mmol, 44%). ^1H RMN ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.72-1.90 (m, 4H), 2.09 (s, 3H), 2.45 (s, 3H), 2.49 (s, 3H), 3.28-3.37 (m, 1H), 3.44 (s, 3H), 4.61 (s, 2H), 6.65 (s, 1H), 6.93 (s, 1H). CL/EM (m/z): calculado para $C_{20}H_{27}N_3OS$ $(M+H)^+$: 358.3; encontrado: 358.3.

Ejemplo 73.

Preparación de 3-[5-(2-etoxi-etil)-3-metil-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

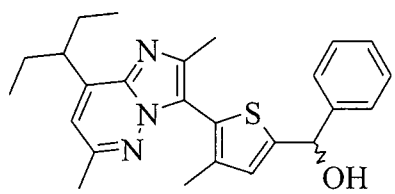


Al usar un procedimiento similar al Ejemplo 72, a partir de la 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.30 g, 0.76 mmol), n-Bu-Li 1.34 M (0.53 mL, 0.84 mmol), 1-bromo-2-etoxi-etano (0.13 mL, 1.15 mmol) y KI (0.013 g, 0.076 mmol) resulta el compuesto del título (0.11 g, 0.29 mmol, 38%). ^1H RMN ($CDCl_3$), δ 0.86 (t, J = 7.5 Hz, 6H), 1.23 (t, J = 7.0 Hz, 3H), 1.72-1.90 (m,

4H), 2.06 (s, 3H), 2.45 (s, 3H), 2.49 (s, 3H), 3.09 (t, J = 7.0 Hz, 2H), 3.28-3.37 (m, 1H), 3.55 (q, J = 7.0 Hz, 2H), 3.71 (t, J = 7.0 Hz, 2H), 6.64 (s, 1H), 6.77 (s, 1H). CL/EM (m/z): calculado para $C_{22}H_{31}N_3OS$ $(M+H)^+$: 386.3 encontrado: 386.3.

Ejemplo 74.

Preparación de {5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiofen-2-il}-fenil-metanol.



A. (5-Bromo-4-metil-tiofen-2-il)-fenil-metanol.

A una solución a -78°C de 2-bromo-3-metil-tiofeno (4.7 g, 26.54 mmol) y Et_2O (100 mL) se agrega 2.0 M LDA (14.6 mL, 29.2 mmol). Después de 1 hora el benzaldehído (3.0 mL, 29.2 mmol) se agrega y la solución se entibia hasta temperatura ambiente y se agita durante 2 hora. La solución se lava con NH_4Cl saturado (75 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (20%-30% gradiente de EtOAc/hexano) resulta el compuesto del título (3.29 g, 11.62 mmol, 44%). ^1H RMN ($CDCl_3$), δ 2.11 (s, 3H), 3.38-3.46 (m, 1H), 5.90 (s, 1H), 6.54 (s,

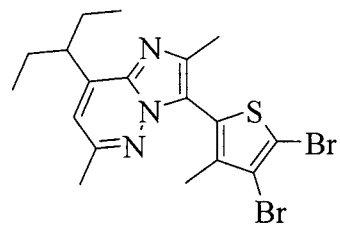
1H), 7.30-7.45 (m, 5H). CL/EM (m/z): calculado para $C_{12}H_{11}BrOS$ $(M+H)^+$: 281.0, 283.0; encontrado: 264.9, 266.9.

B. {5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiofen-2-il}-fenil-metanol.

Usando un procedimiento análogo al ejemplo 30C, a partir de la 3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina del ácido 3-(5-borónico (0.30 g, 0.1.15 mmol), (5-bromo-4-metil-tiofen-2-il)-fenil-metanol (0.33 g, 1.15 mmol), 2 M Na_2CO_3 (0.86 mL, 1.72 mmol) n-PrOH (1 mL), $Pd(OAc)_2$ (0.0052 g, 0.023 mmol), y PPh_3 (0.018 , 0.069 mmol). El residuo se purifica por cromatografía en columna ISCO (20%-30% gradiente de EtOAc/hexano) y se procesa por cromatografía (columna C18 Symmetry de 50 x 250, 25-70% agua: 0.1 % TFA /ACN: 0.1% TFA gradiente) resulta el compuesto del título (0.017 g, 0.041 mmol, 3.5%). ^1H RMN ($CDCl_3$), δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-1.90 (m, 4H), 2.04 (s, 3H), 2.43 (s, 3H), 2.49 (s, 3H), 2.75 (bs, 1H), 3.26-3.38 (m, 1H), 6.05 (s, 1H), 6.65 (s, 1H), 6.76 (s, 1H), 7.30-7.45 (m, 3H), 7.50-7.56 (m, 1H). CL/EM (m/z): calculado para $C_{25}H_{29}N_3OS$ $(M+H)^+$: 420.3; encontrado: 420.3.

Ejemplo 75.

Preparación de 3-(4,5-dibromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

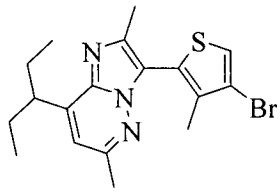


A una solución de 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (4.00 g, 10.20 mmol) y AcOH (40 mL) se agrega Br_2 (0.57 mL, 11.21 mmol) y la solución se calienta a 110°C durante la noche. El Br2 (0.57 mL, 11.21 mmol) se agrega y la solución se calienta a 110°C durante 2 horas. La solución se vacia en 5 M NaOH (200 mL) y hielo (200 mL). La suspensión espesa se extrae con EtOAc (2 x 150 mL). Las capas orgánicas combinadas se lavan con agua (200 mL), 20% $NaHSO_3$ (200 mL), $NaHCO_3$ saturado (200 mL) se secan sobre $MgSO_4$, se filtran y se concentran. El residuo se purifica por ISCO (5%-15% EtOAc gradiente) resulta el compuesto del título (2.66 g, 5.64 mmol, 55%). ^1H RMN ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-1.91 (m, 4H), 2.12 (s, 3H), 2.43 (s, 3H), 2.50 (s, 3H), 3.25-3.35 (m, 1H), 6.69 (s, 1H). CL/EM (m/z): calculado para $C_{18}H_{21}Br_2N_3S$ $(M+H)^+$: 470.0; encontrado: 470.3.

350

Ejemplo 76.

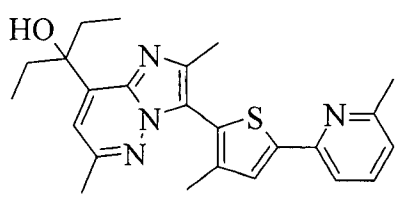
Preparación de 3-(4-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



A una solución a -78°C de 3-(4,5-dibromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.22 g, 0.47 mmol) y THF (3 mL) se agrega 1.6 M n-BuLi (0.31 mL, 0.49 mmol). Después de 20 minutos la solución se apaga con agua (1 mL), se entibia hasta temperatura ambiente, se diluye con EtOAc (30 mL), se lava con salmuera (30 mL), se seca sobre MgSO4, se filtra y se concentra. El residuo se purifica por ISCO (5%-10% EtOAc gradiente) resulta el compuesto del título (0.056 g, 0.14 mmol, 31%). ^{1}H RMN ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.93 (m, 4H), 2.09 (s, 3H), 2.44 (s, 3H), 2.49 (s, 3H), 3.27-3.36 (m, 1H), 6.68 (s, 1H), 7.44 (s, 1H). CL/EM (m/z): calculado para $C_{18}H_{22}BrN_3S$ $(M+H)^+$: 392.2; encontrado: 392.3.

Ejemplo 77.

Preparación de 3-{2,6-Dimetil-3-[3-metil-5-(6-metil-piridin-2-il)-tiofen-2-il]-imidazo[1,2-b]piridazin-8-il}-pentan-3-ol.



A. 2-(5-Bromo-4-metil-tiofen-2-il)-6-metil-piridina.

A una solución a -78°C de 2-bromo-3-metil-tiofeno (2.0 mL, 17.75 mmol) y THF (30 mL) se agrega 2.0 M LDA (9.76 mL, 19.52 mmol). Después de 45 minutos 0.5 M $ZnCl_2$ (39.0 mL, 19.50 mmol) se agrega y la solución se agita durante 30 minutos. La 2-Bromo-6-metil-piridina (2.4 mL, 21.29 mmol) y $Pd(PPh_3)_4$ (0.50 g, 0.44 mmol) se agrega y la solución se entibia hasta temperatura ambiente y se agita durante 2 hora. La solución se lava con NH_4Cl saturado (20 mL). La capa acuosa se extrae con CH_2Cl_2 (30 mL). Las capas orgánicas combinadas se lavan con NH_4Cl saturado (20 mL), se secan sobre Na_2SO_4, se filtran y se concentran. El residuo se purifica por cromatografía en columna ISCO (10%-20% gradiente de EtOAc/hexano) resulta el compuesto del título (2.34 g, 8.73 mmol, 49%). ^1H RMN ($CDCl_3$), δ 2.21 (s, 3H), 2.54 (s, 3H), 6.99 (d, J = 7.9 Hz, 1H), 7.23 (s, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.53 (dd, J = 7.9, 7.9 Hz, 1H). CL/EM (m/z): calculado para $C_{11}H_{10}BrNS$ $(M+H)^+$: 267.0, 269.0; encontrado:267.7, 269.5.

B. 2,6-Dimetil-3-[3-metil-5-(6-metil-piridin-2-il)-tiofen-2-il]-imidazo[1,2-b]piridazina.

Una solución de 2,6-dimetil-imidazo[1,2-b]piridazina (a continuación) (0.50 g, 3.39 mmol), 2-(5-bromo-4-metil-tiofen-2-il)-6-metil-piridina (1.00 g, 3.73 mmol), Cs_2CO_3 (2.32 g, 7.13 mmol) y DMF (5 mL) se desgasifica durante 15 minutos con

N_2. El $Pd_2(dba)_3$ (0.15 g, 0.16 mmol) y PPh_3 (0.17 g, 0.65 mmol) se agrega y la solución se calienta a 130°C durante la noche. La solución se diluye con CH_2Cl_2 (30 mL) se lava con agua (2 x 25 mL), salmuera (25 mL) se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (100% EtOAc), seguido por recristalización a partir de acetonitrilo/agua resulta el compuesto del título (0.45 g, 1.35 mmol, 39%). ^1H RMN ($CDCl_3$), δ 2.13 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 2.57 (s, 3H), 6.90 (d, J = 9.2 Hz, 1H), 7.01 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.52 (s, 1H), 7.56 (dd, J = 8.0, 7.5 Hz, 1H), 7.77 (d, J = 9.2 Hz, 1H). CL/EM (m/z): calculado para $C_{19}H_{18}N_4S$ $(M+H)^+$: 335.1; encontrado: 335.1.

C. 1-{2,6-Dimetil-3-[3-metil-5-(6-metil-piridin-2-il)-tiofen-2-il]-imidazo[1,2-b]piridazin-8-il}-propan-1-ona.

A una solución a -78°C de 2,6-dimetil-3-[3-metil-5-(6-metil-piridin-2-il)-tiofen-2-il]-imidazo[1,2-b]piridazina (0.34 g, 1.02 mmol) y THF (9 mL) se agrega 2.0 M LDA (0.61 mL, 1.22 mmol). Después de 3 minutos, N-metoxi-N-metil-propionamida (Wolberg et. el. Chem. Eur. J., 2001, 7, 4562) (1.17 g, 1.42 mmol) se agrega y la solución se agita durante 20 minutos, se entibia hasta temperatura ambiente y se agita durante 30 minutos. La solución se diluye con EtOAc (50 mL) se lava con NH_4Cl saturado (30 mL), se seca sobre $MgSO_4$, se

filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (20%-30% gradiente de EtOAc/hexano) resulta el compuesto del título (0.10 g, 0.26 mmol, 25%). ^{1}H RMN ($CDCl_3$), δ 1.28 (t, J = 7.0 Hz, 3H), 2.13 (s, 3H), 2.54 (s, 3H), 2.58 (s, 6H), 3.59 (q, J = 7.0 Hz, 2H), 7.03 (d, J = 7.5 Hz, 1H), 7.33 (s, 1H), 7.47 (d, J = 7.9 Hz, 1H), 7.55 (bs, 1H), 7.58 (dd, J = 7.9, 7.5 Hz, 1H). CL/EM (m/z): calculado para $C_{22}H_{22}N_4OS$ $(M+H)^+$: 391.2; encontrado: 391.2.

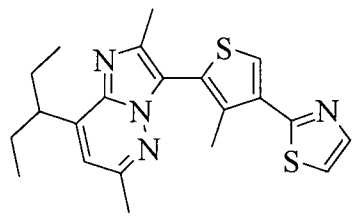
D. 3-{2,6-Dimetil-3-[3-metil-5-(6-metil-piridin-2-il)-tiofen-2-il]-imidazo[1,2-b]piridazin-8-il}-pentan-3-ol.

A una solución a-0°C de 1-{2,6-dimetil-3-[3-metil-5-(6-metil-piridin-2-il)-tiofen-2-il]-imidazo[1,2-b]piridazin-8-il}-propan-1-ona (0.040 g, 0.10 mmol) y Et_2O (5 mL) se agrega 3.0 M de bromuro de etil magnesio (0.68 mL, 2.05 mmol). La solución se entibia hasta temperatura ambiente, se diluye con EtOAc (30 mL) se lava con NH_4Cl saturado (20 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (20%-30% gradiente de EtOAc/hexano) resulta el compuesto del título (0.016 g, 0.038 mmol, 37%). ^{1}H RMN ($CDCl_3$), δ 0.89 (t, J = 7.4 Hz, 6H), 1.92-2.01 (m, 4H), 2.14 (s, 3H), 2.46 (s, 3H), 2.53 (s, 3H), 3.57 (s, 3H), 6.39 (s, 1H), 6.66 (s, 1H), 7.01 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 7.9 Hz, 1H), 7.52 (s, 1H), 7.57 (dd, J =

7.9, 7.5 Hz, 1H). CL/EM (m/z): calculado para $C_{24}H_{28}N_4OS$ $(M+H)^+$: 421.3; encontrado: 421.3.

Ejemplo 78.

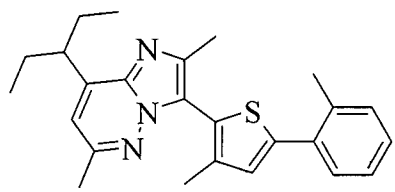
Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(3-metil-4-tiazol-2-il-tiofen-2-il)-imidazo[1,2-b]piridazina.



A un matraz que contiene 3-(4-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.25 g, 0.64 mmol) y $PdCl_2$(dppf) (0.023 g, 0.032 mmol) se agrega una solución 0.5M de bromuro de 2-tiazolilzinc (3.82 mL, 1.91 mmol). La solución se calienta a 65°C durante la noche, se diluye con EtOAc (30 mL), se lava con NH_4Cl saturado (25 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por ISCO (15%-20% EtOAc gradiente) resulta el compuesto del título (0.19 g, 0.48 mmol, 76%). ^1H RMN ($CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.92 (m, 4H), 2.36 (s, 3H), 2.47 (s, 3H), 2.50 (, 3H), 3.29-3.39 (m, 1H), 6.69 (s, 1H), 7.33 (d, J = 3.3 Hz, 1H), 7.89 (d, J = 3.3 Hz, 1H), 7.99 (s, 1H). CL/EM (m/z): calculado para $C_{21}H_{24}N_4S_2$ $(M+H)^+$: 397.2; encontrado: 397.3.

Ejemplo 79.

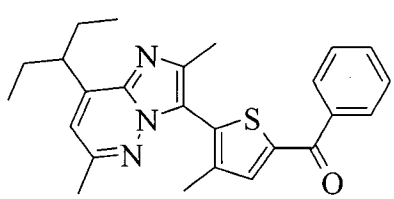
Preparación de 8-(1-Etil-propil)-2,6-dimetil-3-(3-metil-5-o-toluil-tiofen-2-il)-imidazo[1,2-b]piridazina.



Al usar el procedimiento análogo a Ejemplo 32, la 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.15 g, 0.38 mmol) y $PdCl_2$(dppf) (0.014 g, 0.019 mmol) y 0.5M solución de 2-metilyoduro de fenilzinc en THF (3 mL, 1.53 mmol) resulta el compuesto del título (0.069 g, 0.17 mmol, 46%). ^{1}H RMN ($CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.19 (s, 3H), 2.53 (s, 3H), 2.54 (s, 3H), 2.55 (s, 3H), 3.32-3.40 (m, 1H), 6.68 (s, 1H), 7.02 (s, 1H), 7.22-7.30 (m, 3H), 7.48-7.53 (m, 1H). CL/EM (m/z): calculado para $C_{25}H_{29}N_3S$ $(M+H)^+$: 404.3; encontrado: 404.3.

Ejemplo 80.

Preparación de {5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiofen-2-il}-fenil-metanona.

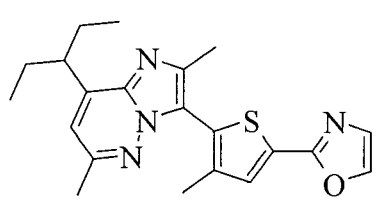


35

A una solución a -78°C de 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.30 g, 0.76 mmol) y THF (5 mL) se agrega n-Bu-Li 1.30 M (0.50 mL, 0.80 mmol). Después de 30 minutos N-metoxi-N-metil-benzamida (0.13 mL, 0.84 mmol) se agrega, la solución se entibia hasta temperatura ambiente, y se agita durante la noche. La solución se diluye con EtOAc (20 mL), se lava con NH_4Cl saturado (15 mL), agua (15 mL), salmuera (15 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (15%-20% gradiente de EtOAc/hexano) resulta el compuesto del título (0.066 g, 0.16 mmol, 21%). ^1H RMN ($CDCl_3$), δ 0.89 (t, J = 7.4 Hz, 6H), 1.74-1.93 (m, 4H), 2.18 (s, 3H), 2.52 (s, 3H), 2.54 (s, 3H), 3.29-3.38 (m, 1H), 6.71 (s, 1H), 7.49-7.54 (m, 2H), 7.56 (s, 1H), 7.57-7.62 (m, 1H), 7.89-7.94 (m, 2H). CL/EM (m/z): calculado para $C_{25}H_{27}N_3OS$ $(M+H)^+$: 418.2; encontrado: 418.2.

Ejemplo 81.

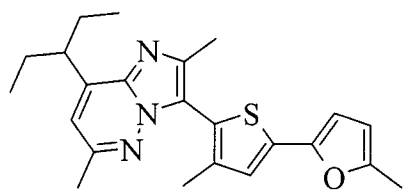
Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(3-metil-5-oxazol-2-il-tiofen-2-il)-imidazo[1,2-b]piridazina.



A una solución a -78°C de oxazol (0.14 g, 2.04 mmol) y THF (3 mL) se agrega 1.6 M t-Bu-Li en hexano (1.32 mL, 2.14 mmol). La mezcla se agita a -78°C durante 15 minutos. 0.5 M $ZnCl_2$ en THF (4.3 mL, 2.14 mmol) se agrega y la solución se entibia hasta temperatura ambiente. La 3-(5-Bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.40 g, 1.02 mmol) y $PdCl_2$(dppf) (0.037 g, 0.051 mmol) se agrega y la mezcla se agita a 65°C durante la noche, se diluye con EtOAc (30 mL), se lava con ácido cítrico al 10% (20 mL), agua (20 mL), salmuera (20 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (20% gradiente de EtOAc/hexano) y se procesa por cromatografía (columna C18 Symmetry de 50 x 250, 20-70% agua: 0.1 % TFA/ACN: 0.1% TFA gradiente) para resultar el compuesto del título (0.020 g, 0.053 mmol, 5%). ^{1}H RMN ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H), 2.49 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 6.69 (s, 1H), 7.19 (s, 1H), 7.59 (s, 1H), 7.65 (s, 1H). CL/EM (m/z): calculado para $C_{21}H_{24}N_4OS$ $(M+H)^+$: 381.3; encontrado: 381.1.

Ejemplo 82.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(5-metil-furan-2-il)-tiofen-2-il]-imidazo[1,2-b]piridazina.

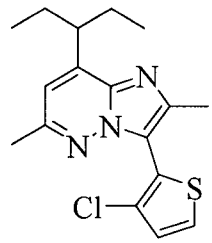


A una mezcla a 0°C de 2-metilfuran (0.18 mL, 2.04 mmol) y Et_2O (2 mL) se agrega 1.6 M t-Bu-Li en hexano (1.30 mL, 2.14 mmol). La mezcla se calienta a reflujo durante 30 minutos, se enfria a 0°C, y 0.5 M $ZnCl_2$ en THF (4.3 mL, 2.14 mmol) se agrega y la solución se entibia hasta temperatura ambiente. La 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.40 g, 1.02 mmol) y $PdCl_2$(dppf) (0.037 g, 0.051 mmol) se agrega y la mezcla se agita a 65°C durante la noche, se diluye con EtOAc (30 mL), se lava con ácido cítrico al 10% (15 mL), agua (15 mL), salmuera (15 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (20% gradiente de EtOAc/hexano) resulta el compuesto del título (0.20 g, 0.51 mmol, 50%). ^1H RMN ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.12 (s, 3H), 2.35 (s, 3H), 2.48 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 6.62 (dd, J = 3.1, 0.9 Hz, 1H), 6.40 (d, J = 3.1 Hz, 1H),

6.66 (s, 1H), 7.12 (s, 1H). CL/EM (m/z): calculado para $C_{23}H_{27}N_3OS$ $(M+H)^+$: 394.3; encontrado: 394.2.

Ejemplo 83.

Preparación de 3-(3-cloro-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

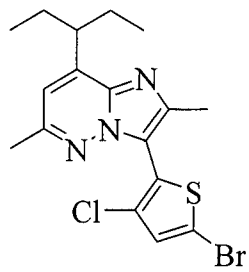


A un matraz de 2-bromo-3-cloro-tiofeno (Lemaire et. el., Synth. Commun., 1994, 24, 95) (2.53 g, 12.82 mmol) se agrega 0.05 g/mL Reike® zinc en THF (25 mL, 19.24 mmol). La solución se calienta a reflujo durante 2 horas. El exceso de zinc se permite asentar y la solución se transfiere a un matraz que contiene 8-(1-etil-propil)-3-yodo-2,6-dimetil-imidazo[1,2-b]piridazina (ejemplo KW1-A03735-193) (2.01 g, 6.41 mmol) y $PdCl_2$(dppf) (0.23 g, 0.32 mmol). La solución se calienta a reflujo durante la noche, se apaga con NH_4Cl saturado (25 mL) y se extrajo con EtOAc (2 X 25 mL). Las capas orgánicas combinadas se secan sobre $MgSO_4$, se filtran y se concentran. El residuo se purifica por cromatografía en columna ISCO (2%-15% EtOAc/hexano gradiente) resulta el compuesto del título (1.32 g, 6.68 mmol, 62%). ^1H RMN ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.48 (s, 3H), 2.49 (s, 3H), 3.37-

3.36 (m, 1H), 6.67 (s, 1H), 7.07 (d, J = 5.4 Hz, 1H), 7.48 (d, J = 5.4 Hz, 1H). CL/EM (m/z): calculado para $C_{17}H_{20}ClN_3S$ $(M+H)^+$: 334.1; encontrado: 334.1.

Ejemplo 84.

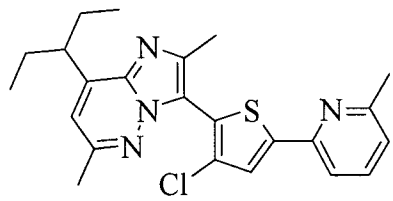
Preparación de 3-(5-bromo-3-cloro-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



A una solución de 3-(3-cloro-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina. (1.15 g, 3.44 mmol) y CH_2Cl_2 (12 mL) se agrega NBS (0.64 g, 3.62 mmol). La solución se agita a temperatura ambiente durante la noche, se lava con agua (2 x 75 mL), salmuera (75 mL), se seca sobre Na_2SO_4, se filtra y se concentra para resultar el compuesto del título (1.36 g, 3.29 mmol, 96%). ^1H RMN ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.49 (s, 3H), 2.53 (s, 3H), 3.26-3.36 (m, 1H), 6.70 (s, 1H), 7.07 (s, 1H). CL/EM (m/z): calculado para $C_{17}H_{19}BrClN_3S$ $(M+H)^+$: 412.1; encontrado: 412.0.

Ejemplo 85.

Preparación de 3-[3-cloro-5-(6-metil-piridin-2-il)-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



Método A.

A un matraz de 3-(5-bromo-3-cloro-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.30 g, 0.73 mmol) y $PdCl_2$(dppf) (0.027 g, 0.036 mmol) se agrega solución 0.5M de bromuro de 6-metil-2-piridilzinc en THF (2.9 mL, 1.45 mmol). La mezcla se agita a 65°C durante la noche, se diluye con EtOAc (50 mL), se lava con NH_4Cl saturado (40 mL), agua (40 mL), salmuera (40 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (20%-40% gradiente de EtOAc/hexano) resulta el compuesto del título (0.072 g, 0.17 mmol, 23%). ^1H RMN ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.58 (s, 3H), 3.30-3.39 (m, 1H), 6.70 (s, 1H), 7.06 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.54 (s, 1H), 7.60 (dd, J = 7.7, 7.5 Hz, 1H). CL/EM (m/z): calculado para $C_{23}H_{25}ClN_4S$ $(M+H)^+$: 425.2; encontrado: 425.2.

Método B.

A. 2-(4-Cloro-tiofen-2-il)-6-metil-piridina.

A una solución de 2-bromo-4-cloro-tiofeno (Gronowitz, Rosén Chemica Scripta, 1971, 1, 33) (1.50 g, 7.60 mmol) y solución 0.5M de bromuro de 6-metil-2-piridilzinc en THF (23.00 mL, 11.39 mmol) se agrega $Pd(PPh_3)_4$ (0.18 g, 0.15 mmol). La solución se calienta a 40°C durante la noche, se diluye con Et_2O (50 mL), se lava con NH_4Cl saturado (40 mL), se seca sobre $MgSO_4$, se filtra concentrado. El residuo se purifica por cromatografía en columna ISCO (5%-20% gradiente de EtOAc/hexano) resulta el compuesto del título (0.45 g, 2.15 mmol, 28%). ^1H RMN ($CDCl_3$), δ 2.56 (s, 3H), 7.02 (d, 7.7 Hz, 1H), 7.13 (d, J = 0.9 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.39 (d, J = 0.9 Hz, 1H), 7.54 (dd, J = 7.9, 7.7, 1H).

B. 2-(5-bromo-4-cloro-tiofen-2-il)-6-metil-piridina.

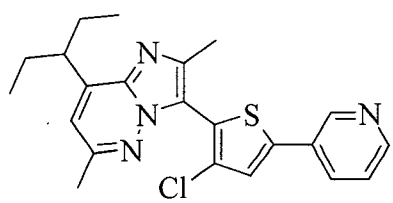
A una solución a 0°C de 2-(4-cloro-tiofen-2-il)-6-metil-piridina (ejemplo Rupp-96) (0.45 g, 1.45 mmol) y CH_2Cl_2 (10 mL) se agrega Br_2 (0.15 mL, 2.91 mmol). La solución se entibia hasta temperatura ambiente y se agita durante 1 hora. La solución se lava con $NaHCO_3$ saturado (10 mL), $Na_2S_2O_3$ sat. (10 mL), se seca sobre $MgSO_4$, se filtra y se concentra para resultar el compuesto del título (0.59 g, 2.04, 95%). ^1H RMN ($CDCl_3$), δ 2.55 (s, 3H), 7.05 (d, 7.9 Hz, 1H), 7.29 (s, 1H), 7.34 (d, J = 7.9 Hz, 1H), 7.58 (dd, J = 7.9, 7.9, 1H). CL/EM (m/z): calculado para $C_{10}H_7BrClNS$ $(M+H)^+$: 288.0; encontrado: 287.9.

C. 3-[3-Cloro-5-(6-metil-piridin-2-il)-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

Una solución de 8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.39 g, 1.78 mmol), 2-(5-bromo-4-cloro-tiofen-2-il)-6-metil-piridina (0.59 g, 2.04 mmol), Cs_2CO_3 (1.23 g, 3.77 mmol), y DMF (5 mL), se desgasifica con N2 durante 15 minutos. El PPh_3 (0.089 g, 0.34 mmol) y $Pd_2(dba)_3$ (0.079 g, 0.86 mmol) se agrega y la solución se calienta a 110°C durante 48 horas. La solución se diluye con EtOAc (30 mL), se lava con NH_4Cl saturado (25 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (20%-30% gradiente de EtOAc/hexano) y se procesa por cromatografía (columna C18 Symmetry de 19 x 300, 20-45% agua: 0.1 % TFA /ACN: 0.1% TFA gradiente) resulta el compuesto del título (0.078 g, 0.18 mmol, 10%). Espectro idéntico al Método A.

Ejemplo 86.

Preparación de 3-(3-cloro-5-piridin-3-il-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



Método A.

Una solución de 3-(5-bromo-3-cloro-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.25 g, 0.61 mmol), ácido piridina-3-borónico (0.082 g, 0.67 mmol), 2 M Na_2CO_3 (0.45 mL, 0.91 mmol) y n-PrOH (1 mL), se desgasifica con nitrógeno durante 10 minutos. El $Pd(OAc)_2$ (0.0027 g, 0.0012 mmol) y PPh_3 (0.0095 g, 0.036 mmol) se agregan y la solución se calienta a 88°C durante la noche. La solución se diluye con EtOAc (15 mL), se lava con agua (10 mL), $NaHCO_3$ saturado (10 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El purificado por cromatografía en columna ISCO (15-40% gradiente de EtOAc/hexano) resulta el compuesto del título (0.095 g, 0.23 mmol, 38%). ^1H RMN ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.29-3.38 (m, 1H), 6.71 (s, 1H), 7.32-7.37 (m, 2H), 7.85-7.90 (m, 1H), 8.57 (d, J = 4.0 Hz, 1H), 8.89 (s, 1H). CL/EM (m/z): calculado para $C_{22}H_{23}ClN_4S$ $(M+H)^+$: 411.2; encontrado: 411.2.

Método B.

A. 3-(4-Cloro-tiofen-2-il)-piridina.

Una solución de 2-bromo-4-cloro-tiofeno (Gronowitz, Rosén Chemica Scripta, 1971, 1, 33) (1.45 g, 7.34 mmol), ácido piridina-3-borónico (0.95 g, 7.71 mmol), 2 M Na_2CO_3 (5.50 mL, 11.01 mmol) y, n-PrOH (3 mL), se desgasifica con N_2 durante 10 minutos. El $Pd(OAc)_2$ (0.033 g, 0.15 mmol) y PPh_3

(0.12 g, 0.44 mmol) se agregan y la solución se calienta a 85°C durante 48 horas, se diluye con CH_2Cl_2 (50 mL), se lava con 10 % Na_2CO_3 (2 x 30 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (20%-30% gradiente de EtOAc/hexano) resulta el compuesto del título (0.74 g, 3.78 mmol, 51%). ^1H RMN ($CDCl_3$), δ 7.12-7.13 (m, 1H), 7.20 (d, J = 1.4 Hz, 1H), 7.31 (dd, J = 8.0, 4.9 Hz, 1H), 7.78-7.82 (m, 1H), 8.55 (d, J = 4.9 Hz, 1H), 8.82 (d, J = 2.2 Hz, 1H).

B. 3-(5-Bromo-4-cloro-tiofen-2-il)-piridina.

Al usar un procedimiento similar al Ejemplo 85 Método B. etapa B, la 3-(4-cloro-tiofen-2-il)-piridina (0.74 g, 3.78 mmol), y Br_2 (0.39 mL, 7.56 mmol) resulta el compuesto del título (0.99 g, 3.61 mmol, 95%). ^1H RMN ($CDCl_3$), δ 7.13 (s, 1H), 7.34 (dd, J = 8.1, 4.4 Hz, 1H), 7.74-7.78 (m, 1H), 8.58 (d, J = 4.4 Hz, 1H), 8.78 (s, 1H).

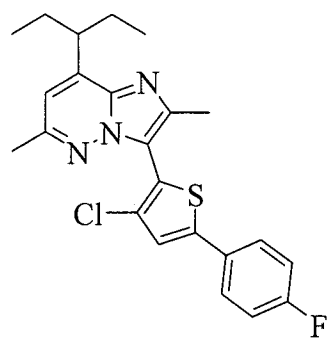
C. 3-(3-Cloro-5-piridin-3-il-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

Al usar un procedimiento similar al Ejemplo 85 Método B Etapa C, a partir de la 8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.50 g, 2.30 mmol), 3-(5-bromo-4-cloro-tiofen-2-il)-piridina) (0.76 g, 2.76 mmol), Cs_2CO_3 (1.57 g, 4.83 mmol), PPh_3 (0.11 g, 0.44 mmol) y $Pd_2(dba)_3$ (0.10 g,

0.11 mmol). El residuo se purifica por cromatografía en columna ISCO (15%-30% gradiente de EtOAc/hexano) resulta el compuesto del título (0.35 g, 0.85 mmol, 37%). Espectro idéntico al Método A.

Ejemplo 87.

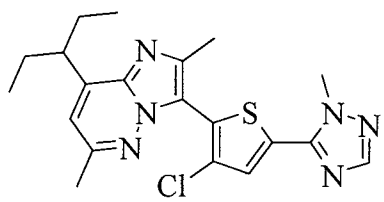
Preparación de 3-[3-cloro-5-(4-fluoro-fenil)-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 25, la 3-(5-bromo-3-cloro-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.25 g, 0.61 mmol), ácido 4-fluorofenilborónico (0.093 g, 0.67 mmol), 2 M Na_2CO_3 (0.45 mL, 0.91 mmol), n-PrOH (2 mL), $Pd(OAc)_2$ (0.0068 g, 0.030 mmol) y PPh_3 (0.016 g, 0.061 mmol) resulta el compuesto del título (0.041 g, 0.096 mmol, 16%). ^1H RMN ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.29-3.38 (m, 1H), 6.70 (s, 1H), 7.07-7.13 (m, 2H), 7.22 (s, 1H), 7.54-7.60 (m, 2H). CL/EM (m/z): calculado para $C_{23}H_{23}ClFN_3S$ $(M+H)^+$: 428.2; encontrado: 428.1.

Ejemplo 88.

Preparación de 3-[3-cloro-5-(2-metil-2H-[1,2,4]triazol-3-il)-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



Método A.

A una solución a -78°C de 1-metil-1,2,4-triazol (0.18 mL, 2.33 mmol) y THF (3 mL) se agrega una solución 1.56 M de n-Bu-Li en hexanos (1.49 mL, 2.33 mmol). La solución se agita a -78°C durante 30 minutos, solución 0.5M de $ZnCl_2$ en THF (4.70 mL, 2.33 mmol) se agrega y la solución se entibia hasta temperatura ambiente. La 3-(5-bromo-3-cloro-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.32 g, 0.78 mmol) y $PdCl_2$(dppf) (0.028 g, 0.039 mmol) se agrega y la solución se calienta a 60°C durante 2 días, se diluye con EtOAc (50 mL), se lava con NH_4Cl saturado (30 mL), agua (30 mL), salmuera (30 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (20%-10% gradiente de EtOAc/hexano) resulta el compuesto del título (0.19 g, 0.46 mmol, 59%). ^1H RMN ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.29-3.37 (m, 1H), 4.16 (s, 3H), 6.73 (s, 1H),

7.48 (s, 1H), 7.90 (s, 1H). CL/EM (m/z): calculado para $C_{20}H_{23}ClN_6S$ $(M+H)^+$: 415.2; encontrado: 415.1.

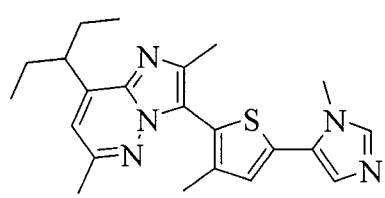
Método B.

Un matraz de reacción de 5L equipado con un baño de enfriamiento, se agita con aire, tubo de dispersión de gas y sonda de termómetro se carga con 5-(5-bromo-4-cloro-tiofen-2-il)-1-metil-1H-[1,2,4]triazol (162.0 g, 0.745 moles), 8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (250.1 g, 0.898 moles), NMP (800 mL), KOAc (366.0 g), TBABr (50.5 g), y NMP adicional (700 mL) para formar una mezcla. Mientras se agita, el N_2 se burbujea a través de la mezcla durante 1 hora. Una mezcla de $Pd(OAc)_2$ (8.37 g) y TDBPP (24.56 g) se agregan en una porción, luego se calienta a 120°C durante 3 horas. La reacción se enfría hasta 50°C y se transfiere a un matraz de 12 L. La mezcla se enfría hasta 20-25°C, luegos e agrega H_2O desionizada (3.5 L) se agrega gota a gota para precipitar un sólido pegajoso que gradualmente se solidifica con agitación durante la noche. Los sólidos se filtran, se lavan con H_2O desionizada (2 x 2L), y se filtran en el papel filtro durante 30-60 minutos. Los sólidos crudos (595 g) se calientan en EtOAc (6.0 L) hasta 30°C, luego se filtran a través de un papel GFF para remover los insolubles. El producto filtrado se seca sobre Na_2SO_4, se trata con Darco (30.0 g), se calienta a 35°C, se filtra, y se concentra para

dar sólidos cafés (432 g). Los sólidos crudos se eluyeron a través de un tapón de sílice (1.0 kg) con CH_2Cl_2 (4.0 L), seguido por EtOAc (16.0 L). Las fracciones similares se combinan y se concentran bajo vacío hasta aproximadamente 6.0 L, luego se trata con Darco durante la noche con agitación. Después de filtrarse compppletamente el Darco a través de papel GFF, el filtrado se concentra hasta sólido (336 g). Los sólidos se cristalizaron a partir de EtOAc: heptano (1:2) para proporcionar el compuesto del título como un sólido amarillo pálido (187 g, 60.5%, >98% area-% por fase inversa: Zorbax SB-C8, 4.6 mm x 250 mm, 5 micrones, UV = 218 nm, relación de flujo 1.0 mL/min., temperatura del horno 25°C, isocrática = 30% agua (0.1% TFA) & 70% AcCN.

Ejemplo 89.

Preparación de 8-(1-Etil-propil)-2,6-dimetil-3-[3-metil-5-(3-metil-3H-imidazol-4-il)-tiofen-2-il]-imidazo[1,2-b]piridazina.

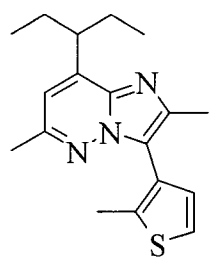


Al usar el procedimiento análogo a Ejemplo 31, la 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.40 g, 1.02 mmol), 1.34M n-Bu-Li

(0.80 mL, 1.07 mmol), 0.5M $ZnCl_2$ en THF (2.14 mL, 1.07 mmol), 5-yodo-1-metil-1H-imidazol (0.24 g, 1.22 mmol) y $PdCl_2$(dppf) (0.037 g, 0.051 mmol) resulta el compuesto del título (0.061g, 0.15 mmol, 15%). ^1H RMN ($CDCl_3$) δ 0.89 (t, J = 7.4 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 3.24-3.38 (m, 1H), 3.61 (s, 3H), 6.68 (s, 1H), 7.02 (s, 1H), 7.23 (s, 1H), 7.55 (s, 1H). CL/EM (m/z): calculado para $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.3; encontrado: 394.2.

Ejemplo 90.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(2-metil-tiofen-3-il)-imidazo[1,2-b]piridazina.



A. 4,4,5,5-Tetrametil-2-(2-metil-tiofen-3-il)-[1,3,2]dioxaborolano.

Una mezcla de 3-bromo-2-metil-tiofeno (Saika et. el. Chem. Soc. Chem. Communication, 18, 1994, 2133; Steinkopf et. el.; Justus Liebigs Ann. Chem., 513, 1934, 281; 3.1 g, 17.51 mmol), DMSO (50 mL), 4,4,5,5,4',4',5',5'-Octametil-[2,2']bi[[1,3,2]dioxaborolanilo] (4.90g, 19.26 mmol), y KOAc (5.20 g, 52.58 mmol) se desgasifica con N_2 durante 15 minutos. El $PdCl_2$(dppf) (0.70 g, 0.88 mmol) se agrega y la

solución se agita a temperatura ambiente durante la noche, luego se entibia hasta 85°C durante 3 horas. La solución se diluye con agua (200 mL), se extrae on EtOAc (2 x 100 mL). Las capas orgánicas combinadas se lavan con agua (2 x 200 mL), salmuera (200 mL) se secan sobre $MgSO_4$, se filtran y se concentran. El residuo se purifica por cromatografía en columna ISCO (5%-20% gradiente de EtOAc/hexano) resulta el compuesto del título (1.52 g, 6.78 mmol, 39%). ^1H RMN ($CDCl_3$), δ 1.34 (s, 12H), 2.72 (s, 3H), 7.04 (d, J = 5.0 Hz, 1H), 7.22 (d, 5.0 Hz, 1H).

B. ácido 2-Metil-tiofeno-3-borónico.

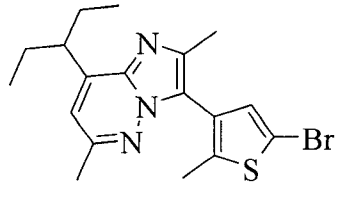
A una solución de 4,4,5,5-tetrametil-2-(2-metil-tiofen-3-il)-[1,3,2]dioxaborolano (1.52 g, 6.78 mmol), acetona (15 mL) y agua (15 mL) se agrega $NaIO_4$ (2.90 g, 13.56 mmol). La solución se agita a temperatura ambiente durante 24 horas, luego se calienta a reflujo durante 24 horas. La solución se concentra disuelta en EtOAc (1450 mL), se lava con agua (100 mL), se seca sobre $MgSO_4$, se filtra y se concentra para resultar el compuesto del título (0.75g, 5.49 mmol, 78%). ^1H RMN ($CDCl_3$), δ 2.93 (s, 3H), 7.10 (d, J = 5.3 Hz, 1H), 7.51 (d, 5.3 Hz, 1H).

C. 8-(1-Etil-propil)-2,6-dimetil-3-(2-metil-tiofen-3-il)-imidazo[1,2-b]piridazina.

(1.65 g, 4.80 mmol), ácido 2-metil-tiofeno-3-borónico (0.75 g, 5.28 mmol), Na_2CO_3 2M (3.60 mL, 7.20 mmol) y n-PrOH (20 mL) se desgasifica con N_2 durante 10 minutos. El $Pd(OAc)_2$ (0.022 g, 0.096 mmol) PPh_3 (0.076 g, 0.29 mmol) se agrega y la solución se calienta a 60°C durante 24 horas, luego se calienta a 90°C durante 24 horas. La solución se concentra, se diluye en EtOAc (50 mL) se lava con 10% Na_2CO_3 (40 mL), agua (40 mL), salmuera (40 mL) se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (10%-15% gradiente de EtOAc/hexano) resulta el compuesto del título (0.78 g, 2.49 mmol, 52%). ^1H RMN (CDCl3), δ 0.89 (t, J = 7.5 Hz, 6H), 1.74-1.94 (m, 4H), 2.38 (s, 3H), 2.44 (s, 3H), 2.50 (s, 3H), 3.30-3.40 (m, 1H), 6.64 (s, 1H), 7.11 (d, J = 5.3 Hz, 1H), 7.20 (d, J = 5.3 Hz, 1H). CL/EM (m/z): calculado para $C_{18}H_{23}N_3S$ $(M+H)^+$: 314.2; encontrado: 314.2.

Ejemplo 91.

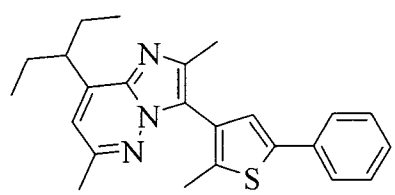
Preparación de 3-(5-bromo-2-metil-tiofen-3-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



A una solución de 8-(1-etil-propil)-2,6-dimetil-3-(2-metil-tiofen-3-il)-imidazo[1,2-b]piridazina. (0.76 g, 2.42 mmol) y CH_2Cl_2 (10 mL) se agrega NBS (0.60 g, 3.37 mmol). La solución se agita a temperatura ambiente durante 2 horas y se concentra. La solución se disuelve en Et_2O (30 mL) se lava con agua (3 x 30 mL), salmuera (30 mL) se seca sobre $MgSO_4$, se filtra y se concentra para resultar el compuesto del título (0.95 g, 2.42 mmol, >99%). ^1H RMN ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.93 (m, 4H), 2.31 (s, 3H), 2.42 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 6.66 (s, 1H), 7.04 (s, 1H). CL/EM (m/z): calculado para $C_{18}H_{22}BrN_3S$ $(M+H)^+$: 392.2; encontrado: 392.1.

Ejemplo 92.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(2-metil-5-fenil-tiofen-3-il)-imidazo[1,2-b]piridazina.

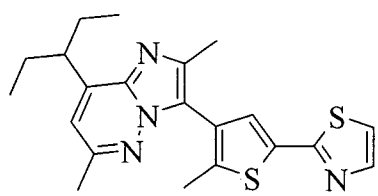


Al usar un procedimiento similar al Ejemplo 32, a partir de la 3-(5-bromo-2-metil-tiofen-3-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.20 g, 0.51 mmol) y $PdCl_2$(dppf) (0.019 g, 0.025 mmol) y una solución 0.5 M de yoduro de fenilzinc en THF (2.0 mL, 1.02 mmol). El residuo se

purifica por cromatografía de columna (0-10% gradiente de EtOAc/hexano) y se procesa por cromatografía (columna C18 Symmetry de 50 x 250, 30-70% agua: 0.1 % TFA /ACN: 0.1% TFA gradiente) resulta el compuesto del título (0.081 g, 0.21 mmol, 41%). ^{1}H RMN ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.94 (m, 4H), 2.40 (s, 3H), 2.48 (s, 3H), 2.52 (s, 3H), 3.32-3.41 (m, 1H), 6.66 (s, 1H), 7.23-7.30 (m, 1H), 7.32 (s, 1H), 7.34-7.41 (m, 2H), 7.57-7.63 (m, 2H). CL/EM (m/z): calculado para $C_{24}H_{27}N_3S$ $(M+H)^+$: 390.2; encontrado: 390.2.

Ejemplo 93.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(2-metil-5-tiazol-2-il-tiofen-3-il)-imidazo[1,2-b]piridazina.

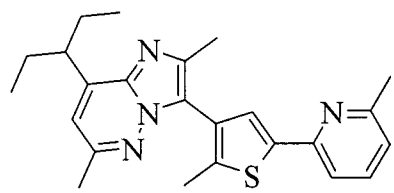


Al usar un procedimiento similar al Ejemplo 32, a partir de la 3-(5-bromo-2-metil-tiofen-3-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.20 g, 0.51 mmol), 0.5 M bromuro de 2-tiazolilzinc en THF (8.1 mL, 4.05 mmol) y $PdCl_2$(dppf) (0.019 g, 0.025 mmol) resulta el compuesto del título (0.20 g, 0.50 mmol, >99%). ^{1}H RMN ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.40 (s, 3H), 2.45 (s, 3H), 2.50 (s, 3H), 3.29-3.38 (m, 1H), 6.60 (s, 1H), 7.22 (d, J =

3.2 Hz, 1H), 7.52 (s, 1H), 7.75 (d, J = 3.2 Hz, 1H). CL/EM (m/z): calculado para $C_{21}H_{24}N_4S_2$ $(M+H)^+$: 397.1; encontrado: 397.2.

Ejemplo 94.

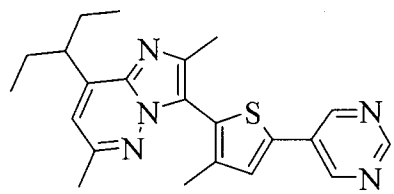
Preparación de 8-(1-etil-propil)-2,6-dimetil-3-[2-metil-5-(6-metil-piridin-2-il)-tiofen-3-il]-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 32, a partir de la 3-(5-bromo-2-metil-tiofen-3-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.24 g, 0.61 mmol) y $PdCl_2$(dppf) (0.022 g, 0.031 mmol) y solución 0.5M de bromuro de 6-metil-2-piridilzinc en THF (3.7 mL, 1.84 mmol) resulta el compuesto del título (0.086 g, 0.21 mmol, 34%). ^1H RMN ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.39 (s, 3H), 2.46 (s, 3H), 2.51 (s, 3H), 2.57 (s, 3H), 3.31-3.40 (m, 1H), 6.65 (s, 1H), 6.97 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.50-7.56 (m, 2H). CL/EM (m/z): calculado para $C_{24}H_{28}N_4$ $(M+H)^+$: 405.2; encontrado: 405.2.

Ejemplo 95.

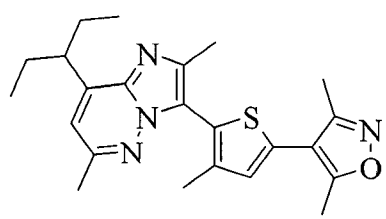
Preparación de 8-(1-Etil-propil)-2,6-dimetil-3-(3-metil-5-pirimidin-5-il-tiofen-2-il)-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 74B, a partir de la 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.20 g, 0.51 mmol), ácido 5-pirimidina borónico (0.076 g, 0.61 mmol), 2 M Na_2CO_3 (0.38 mL, 0.76 mmol), $Pd(OAc)_2$ (0.0023 g, 0.011 mmol), PPh_3 (0.0080 g, 0.0031 mmol), y n-PrOH (2 mL) resulta el compuesto del título (0.084 g, 0.21 mmol, 42%). ^1H RMN ($CDCl_3$), δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-1.91 (m, 4H), 2.17 (s, 3H), 2.48 (s, 3H), 2.51 (s, 3H), 3.26-3.36 (m, 1H), 6.69 (s, 1H), 7.74 (s, 1H), 8.95 (s, 2H), 9.10 (s, 1H). CL/EM (m/z): calculado para $C_{22}H_{25}N_5S$ $(M+H)^+$: 392.3; encontrado: 392.2.

Ejemplo 96.

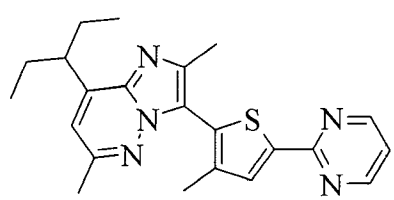
Preparación de 3-[5-(3,5-Dimetil-isoxazol-4-il)-3-metil-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



A un matraz de 4-yodo-3,5-dimetil-isoxazol (0.34 g, 1.53 mmol) se agrega una solución de Rieke® zinc 5g/100 mL en THF (3 mL, 2.29 mmol). La suspensión espesa se calienta a reflujo durante 4 horas, el zinc se permite asentar y la solución se transfiere a un matraz de 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.30 g, 0.76 mmol) y $PdCl_2$(dppf) (0.028 g, 0.038 mmol). La solución se calienta a 50°C durante la noche, se diluye con EtOAc (20 mL), se lava con HCl 0.1M (15 mL), agua (15 mL), salmuera (15 mL) se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (15%-30% gradiente de EtOAc/hexano) resulta el compuesto del título (0.22 g, 0.54 mmol, 71%). ^{1}H RMN ($CDCl_3$), δ 0.92 (t, J = 7.5 Hz, 6H), 1.78-1.96 (m, 4H), 2.21 (s, 3H), 2.47 (s, 3H), 2.53 (s, 3H), 2.56 (s, 3H), 2.61 (s, 3H), 3.33-3.42 (m, 1H), 6.72 (s, 1H), 6.98 (s, 1H). CL/EM (m/z): calculado para $C_{23}H_{28}N_4OS$ $(M+H)^+$: 409.3; encontrado: 409.2.

Ejemplo 97.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(3-metil-5-pirimidin-2-il-tiofen-2-il)-imidazo[1,2-b]piridazina.

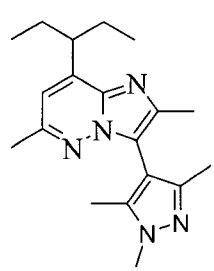


843

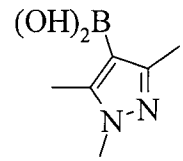
Una solución de 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.30 g, 0.76 mmol), 2-tributilestananil-pirimidina (0.34 g, 0.92 mmol) y THF (5 mL) se desgasifica con N_2 durante 10 minutos. La trifenilarsina (0.047 g, 0.15 mmol) y $Pd_2(dba)_3$ (0.035 g, 0.038 mmol) se agrega y la solución se calienta a 55°C durante 48 horas y se concentra. El residuo se purifica por cromatografía en columna ISCO (15%-30% gradiente de EtOAc/hexano), dissolved en acetonitrilo (20 mL), se lava con hexano (3 x 20 mL) y se concentra para resultar el compuesto del título (0.097 g, 0.25 mmol, 32%). ^1H RMN ($CDCl_3$), δ 0.88 (t, J = 7.4 Hz, 6H), 1.74-1.92 (m, 4H), 2.18 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 3.29-3.38 (m, 1H), 6.67 (s, 1H), 7.08 (t, J = 4.8, 1H), 7.93 (s, 1H), 8.69 (s, 2H). CL/EM (m/z): calculado para $C_{22}H_{25}N_5S$ $(M+H)^+$: 392.3; encontrado: 392.2.

Ejemplo 98.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(1,3,5-trimetil-1H-pirazol-4-il)-imidazo[1,2-b]piridazina.



A. ácido 1,3,5-Trimetilpirazol-4-borónico.



A un matraz seco se agrega 300 mg (1.59 mmol) de 4-bromo-1,3,5-trimetil pirazol hasta 4.0 ml THF. La mezcla se enfría hasta -78°C y 1eq de n-BuLi (1.6 M) se agrega por medio de jeringa. La mezcla se agita 1.5 hrs, y 0.19ml de trimetilborato (1.08 eq) se agrega. La mezcla de reacción se agita 2 hrs, permitiendo que el baño alcance -10°C, luego 1.5 ml de 5N HCl se agrega y se agita 30 minutos más. La capa acuosa se extrae 3 veces con acetato de etilo. Los productos orgánicos combinados se secaron sobre MgSO4, se filtraron, y se evaporaron hasta un aceite. El oil se disuelve en metanol/cloruro de metileno y se re-evapora. El residuo se tritura con acetona/acetato de etilo luego se filtra para obtener el compuesto del título como un sólido blanco 92.1 mg (37.6%). ^{1}H-RMN (DMSO-d_6): δ 5.92 (s); 3.72 (s, 3H); 2.34 (s, 3H); 2.26 (s, 3H) ppm.

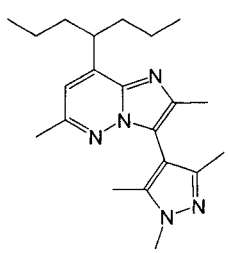
B. 8-(1-Etil-propil)-2,6-dimetil-3-(1,3,5-trimetil-1H-pirazol-4-il)-imidazo[1,2-b]piridazina.

La 3-yodo-2,6-dimetil-8-(1-etil-propil)-imidazo[1,2-b]piridazina (200mg, 0.582 mmol), ácido 1,3,5-trimetilpirazol-4-borónico (233mg, 1.53 mmol), $Pd(PPh_3)_4$

(13.4mg, 0.01 mmol) se combinan en un tubo de microondas a presión. Luego 0.58 ml de 2N Na2CO3 y 3.0ml de solución de dimetoxietano/H2O/etanol (7:3:2) se agrega. La mezcla se trata en microondas a 155°C durante 20 minutos. El agua se agrega y la mezcla se extrae cuatro veces con acetato de etilo. Los productos orgánicos combinados se secan sobre $MgSO_4$, se filtran, luego se evaporan hasta un residuo el cual se procesa por cromatografía usando hexanos, luego 1:1 hexanos: acetato de etilo, luego 100% acetato de etilo para dar el compuesto del título (6.4%) como un aceite amarillo. ^{1}H-RMN (DMSO-d_6): δ 6.86 (s, 1H); 3.73 (s, 3H); 3.06-3.10 (m, 1H); 2.41 (s, 3H); 2.22 (s, 3H); 2.03 (s, 3H); 1.93 (s, 3H); 1.74-1.83 (m, 4H); 0.77 (t, J = 7.26 Hz, 6H) ppm. EM/ ES+ = 327 (100%, M+2).

Ejemplo 99.

Preparación de 2,6-Dimetil-8-(1-propil-butil)-3-(1,3,5-trimetil-1H-pirazol-4-il)-imidazo[1,2-b]piridazina.

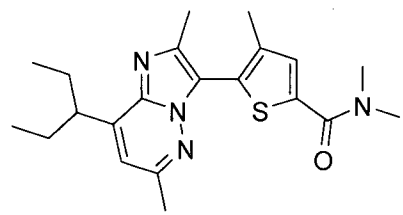


La 3-yodo-2,6-dimetil-8-(1-propil-butil)-imidazo[1,2-b]piridazina (75 mg, 0.20 mmol), ácido 1,3,5-trimetilpirazol-4-borónico (80 mg, 0.52 mmol), solución 2N Na_2CO_3 (0.22 ml), y

5.0mg (0.0004 mmol) de $Pd(PPh_3)_4$ se combinan en un recipiente de presión de microondas con 1.5ml de una solución de dimetiléter/H2O/etanol (7:3:2). La mezcla se trata en microondas a 140°C durante 25 minutos. La mezcla se evapora y se procesa por cromatografía en una columna de gel de sílice usando hexanos luego 3:1 hexano: acetato de etilo, luego 1:1 hexano:acetato de etilo para dar el compuesto del título (22.8%) como un aceite claro. ^{1}H-RMN (DMSO-d_6): δ 6.88 (s, 1H); 3.72 (s, 3H); 3.06-3.10 (m, 1H); 2.40 (s, 3H); 2.21 (s, 3H); 2.02 (s, 3H); 1.92 (s, 3H); 1.60-1.76 (m, 4H); 1.08-1.21 (m, 4H); 0.82 (t, J = 7.49 Hz, 6H) ppm. EM/ ES+ = 354 (100%, M+1).

Ejemplo 100.

Preparación de dimetilamida del ácido 5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiofeno-2-carboxílico.

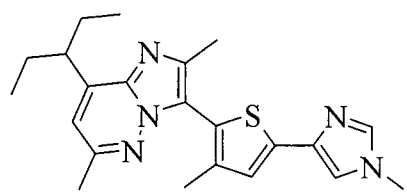


Usando un procedimiento análogo al Ejemplo 23 B, el ácido 5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiofeno-2-carboxílico (151 mg, 0.42 mmol) y 2.0 M dimetilamina (2.0 mL, 4 mmol) da el compuesto

del título (161 mg, 0.42 mmol, 100%). 1H RMN (CDCl3): δ 0.89 (t, J = 7.4 Hz, 6H), 1.75-1.94 (m, 4H), 2.14 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.15-3.50 (m, 7H), 6.72 (s, 1H), 7.30 (s, 1H). ES-EM (m/z): calculado para C21H28N4OS (M+H)+: 385.6 encontrado: 385.3.

Ejemplo 101.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(1-metil-1H-Imidazol-3-il)-tiofen-2-il]-imidazo[1,2-b]piridazina.

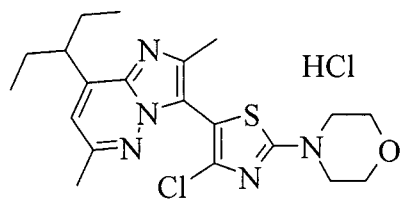


Al usar un procedimiento similar al Ejemplo 31 a partir de la 3-(5-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.40 g, 1.02 mmol), 1.34 M n-BuLi (0.80 mL, 1.07 mmol), 0.5 M $ZnCl_2$ en THF (2.14 mL, 1.07 mmol), 3-yodo-1-metil-1H-imidazol (0.24 mL, 1.22 mmol) y $PdCl_2$(dppf) (0.037 g, 0.051 mmol) resulta el compuesto del título (0.030g, 0.076 mmol, 8%). ^{1}H RMN ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.74-1.93 (m, 4H), 2.13 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 3.31-3.40 (m, 1H), 3.72 (s, 3H), 6.66 (s, 1H), 7.09 (d, J = 1.3 Hz, 1H), 7.19 (s, 1H), 7.86 (d, J = 1.3 Hz,

1H). CL/EM (m/z): calculado para $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.2; encontrado: 394.2.

Ejemplo 102.

Preparación de N-{4-cloro-5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-morfolina, sal de clorohidrato.

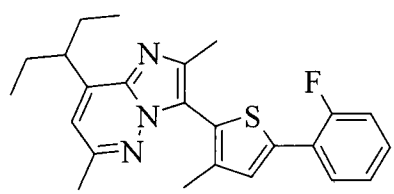


La IPA (225.0 mL) se agrega al compuesto N-{4-cloro-5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-morfolina (18.8 g, 0.0448 mmol, a continuación) en un matraz de fondo redondo de 1 cuello de 1 L. La mezcla espesa del materia de partida se calienta hasta 50°C en un baño Buchi, tiempo al cual la solución resultante nebulosa. El HCl acuoso concentrado (12 M) (3.73 mL, 0.0448 mmole, 1.0 eq) se agrega todo una vez y la solución nebulosa se agita a 50°C en el Buchi durante 10 minutos, luego se evapora hasta un sólido amarillo bajo vacío. Después de 20 minutos a temperatura ambiente bajo vacío (peso de 20.9 g), acetona (100 mL) se agrega y la mezcla espesa amarilla resultante se agita a temperatura ambiente durante 1 hora, luego se enfria con un baño de hielo y se agita durante 1 hora adicional. La

suspensión espesa se filtra, se enjuaga con acetona, y se seca durante la noche bajo vacío a 40°C para proporcionar el sólido cristalino blanco-amarillo pálido 19.18 g (94%). ^{1}H RMN (DMSO): δ 7.52 (s, 1H), 3.73 (t, J = 4.6, 4H), 3.49 (t, J = 5.2 Hz, 4H), 3.39 (m, 1H), 2.57 (s, 3H), 2.49 (s, 3H), 1.77 (m, 4H), 0.80 (t, J = 7.4 Hz, 6H).

Ejemplo 103.

Preparación de 8-(1-etil-propil)-3-[5-(2-fluoro-fenil)-3-metil-tiofen-2-il]-2,6-dimetil-imidazo[1,2-b]piridazina.

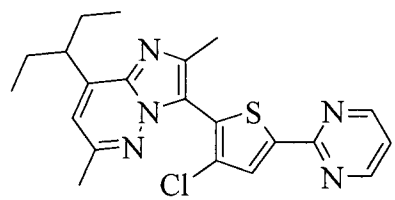


Usando un procedimiento análogo al Ejemplo 30 B, la 3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina del ácido 3-(5-borónico (0.18 g, 0.50 mmol), 1-bromo-2-fluoro-benceno (0.072 g, 0.65 mmol), y 2 M Na_2CO_3 (0.38 mL, 0.76 mmol), n-PrOH (2 mL), y $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol) resulta el compuesto del título (0.022 g, 0.054 mmol, 11%). ^{1}H RMN ($CDCl_3$), δ 0.93 (t, J = 7.4 Hz, 6H), 1.71-1.96 (m, 4H), 2.19 (s, 3H), 2.66 (s, 3H), 2.67 (s, 3H), 3.41-3.50 (m, 1H), 7.15 (s, 1H), 7.15-7.23 (m, 2H), 7.28-7.35 (m, 1H), 7.45 (d, J = 1.4 Hz, 1H), 7.66 (dt, J = 7.8, 1.6 Hz,

1H). CL/EM (m/z): calculado para $C_{24}H_{26}FN_3S$ $(M+H)^+$: 408.2; encontrado: 408.2.

Ejemplo 104.

Preparación de 3-(3-cloro-5-pirimidin-2-il-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



A. 3-(3-Cloro-tiofen-2-il-5-borónico acid)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

A una solución a -78°C de 3-(3-cloro-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (2.0 g, 5.97 mmol) y THF (30 mL) se agrega 1.6 M n-BuLi (4.1 mL). Después de 30 minutos $B(OMe)_3$ (0.74 mL, 6.59 mmol) se agrega, la solución se entibia hasta temperatura ambiente y se agita durante la noche. HCl 1M (30 mL) se agrega y la solución se agita durante 20 minutos. La solución se hizo básica con 5 M NaOH. La capa orgánica se extrae con 1 M NaOH (30 mL). Las capas orgánicas combinadas se hacen ácidas con 5 M HCl, $K_3PO_4 \cdot 3\ H_2O$ se agregan y el pH se ajusta hasta 5.5 usando 1 M NaOH. Las capas orgánicas combinadas se extraen con EtOAc (200 mL), se lavan con salmuera (150 mL), se secan sobre $MgSO_4$, se

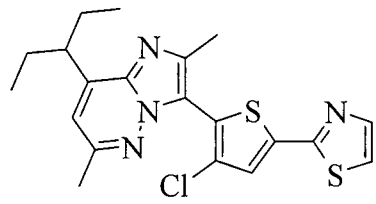
filtran y se concentran para resultar el compuesto del título (2.20 g, 5.82 mmol, 97%). CL/EM (m/z): calculado para $C_{17}H_{21}BClN_3O_2S$ $(M+H)^+$: 378.7; encontrado: 378.0.

B. 3-(3-Cloro-5-pirimidin-2-il-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

Una solución de la 8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina del ácido 3-(3-cloro-tiofen-2-il-5-borónico (0.25g, 0.66 mmol), 2-bromo-pirimidina (0.21 g, 1.32 mmol), 2 M Na_2CO_3 (0.66 mL, 1.32 mmol), y i-PrOH (3 mL) se desgasifican con N_2 durante 15 minutos. El $Pd(OAc)_2$ (7.4 mg, 0.033 mmol) y PPh_3 (0.026 g, 0.099 mmol) se agregan y la solución se calienta a 90°C durante la noche. La solución se diluye con EtOAc (35 mL), se lava con 10% Na_2CO_3 (35 mL), salmuera (35 mL), se seca sobre Na_2SO_4, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (20%-30% gradiente de EtOAc/hexano) resulta el compuesto del título (0.077 g, 0.19 mmol, 29%). ^1H RMN ($CDCl_3$) δ 0.88 (d, J = 7.4 Hz, 6H), 1.75-1.93 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.27-3.40 (m, 1H), 6.71 (s, 1H), 7.16 (t, J = 5.0 Hz, 1H), 8.00 (s, 1H), 8.74 (d, J = 5.0 Hz, 2H). CL/EM (m/z): calculado para $C_{21}H_{22}ClN_5S$ $(M+H)^+$: 412.1; encontrado: 412.2.

Ejemplo 105.

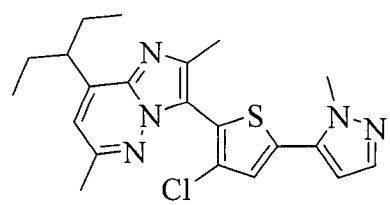
Preparación de 3-(3-cloro-5-tiazol-2-il-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 104, la 8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina del ácido 3-(3-cloro-tiofen-2-il-5-borónico (0.25g, 0.66 mmol), 2-bromo-pirimidina (0.21 g, 1.32 mmol), 2 M Na_2CO_3 (0.66 mL, 1.32 mmol) y i-PrOH (3 mL), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), y PPh_3 (0.026 g, 0.099 mmol) resulta el compuesto del título (0.099 g, 0.24 mmol, 35%). ^1H RMN ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.28-3.38 (m, 1H), 6.71 (s, 1H), 7.33 (t, J = 3.3 Hz, 1H), 7.49 (s, 1H), 7.81 (d, J = 3.3 Hz, 2H). CL/EM (m/z): calculado para $C_{21}H_{22}ClN_5S$ $(M+H)^+$: 417.1; encontrado: 417.1.

Ejemplo 106.

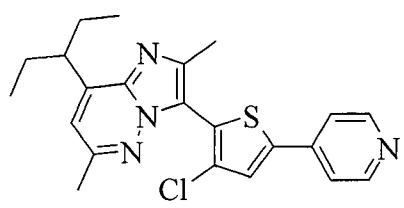
Preparación de 3-[3-cloro-5-(2-metil-2H-pirazol-3-il)-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



A una solución a -78°C de 1-metil-1H-pirazol (0.12 g, 1.45 mmol) y THF (4 mL) se agrega 1.6 M n-BuLi (0.91 mL, 1.45 mmol). Después de 45 minutos 0.5 M $ZnCl_2$ (2.9 mL, 1.45 mmol) se agrega y la soluciónse entibia hasta temperatura ambiente. Después de 30 minutos la 3-(5-bromo-3-cloro-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (ejemplo Rupp-88) (0.30 g, 0.73 mmol) y $PdCl_2$(dppf) (0.027 g, 0.036 mmol) se agregan y la solución se calienta a 65°C durante la noche, se diluye con EtOAc (30 mL), se lava con NH_4Cl saturado (2 x 30 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (15%-30% gradiente de EtOAc/hexano) resulta el compuesto del título (0.15 g, 0.36 mmol, 50%). ^1H RMN ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.52 (s, 6H), 3.26-3.36 (m, 1H), 4.05 (s, 3H), 6.45 (d, J = 1.9 Hz, 1H), 6.71 (s, 1H), 7.14(s, 1H), 7.49 (d, J = 1.9 Hz, 1H). CL/EM (m/z): calculado para $C_{21}H_{24}ClN_5S$ $(M+H)^+$: 414.2; encontrado: 414.2.

Ejemplo 107.

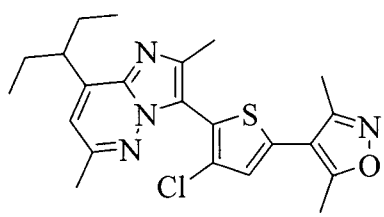
Preparación de 3-(3-cloro-5-piridin-4-il-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 104, la 8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina del ácido 3-(3-cloro-tiofen-2-il-5-borónico (0.25g, 0.66 mmol), clorohidrato de 4-bromo-piridina (0.26 g, 1.32 mmol), 2 M Na_2CO_3 (1.00 mL, 1.99 mmol), i-PrOH (3 mL), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), y PPh_3 (0.026 g, 0.099 mmol) resulta el compuesto del título (0.16 g, 0.59 mmol, 59%). ^1H RMN ($CDCl_3$) δ 0.87 (d, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.27-3.36 (m, 1H), 6.72 (s, 1H), 7.45-7.49 (m, 3H), 8.63 (d, J = 1.3 Hz, 1H), 8.64 (d, J = 1.3 Hz, 1H). CL/EM (m/z): calculado para $C_{22}H_{23}ClN_4S$ $(M+H)^+$: 411.1; encontrado: 411.1.

Ejemplo 108.

Preparación de 3-[3-cloro-5-(3,5-dimetil-isoxazol-4-il)-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

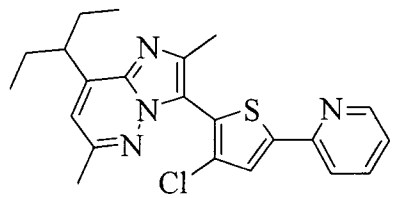


Al usar un procedimiento similar al Ejemplo 104, la 8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina del ácido 3-(3-cloro-tiofen-2-il-5-borónico (0.25g, 0.66 mmol), 4-yodo-3,5-dimetil-isoxazol (0.30 g, 1.32 mmol), 2 M Na_2CO_3

(0.66 mL, 1.32 mmol) y i-PrOH (3 mL), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), y PPh_3 (0.026 g, 0.099 mmol) resulta el compuesto del título (0.14 g, 0.50 mmol, 50%). ^1H RMN ($CDCl_3$) δ 0.87 (d, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.43 (s, 3H), 2.53 (s, 6H), 2.57 (s, 3H), 3.27-3.38 (m, 1H), 6.71 (s, 1H), 7.01 (s, 1H). CL/EM (m/z): calculado para $C_{22}H_{25}ClN_4OS$ $(M+H)^+$: 429.2; encontrado: 429.2.

Ejemplo 109.

Preparación de 3-(3-cloro-5-piridin-2-il-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

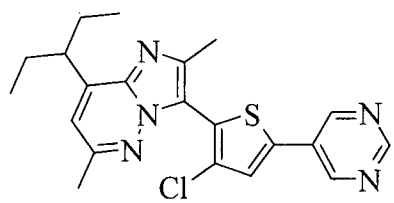


A un matraz que contiene 3-(5-bromo-3-cloro-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina(0.25 g, 0.61 mmol) y $PdCl_2$(dppf) (0.022 g, 0.030 mmol) se agrega una solución 0.5M de bromuro de 2-piridilzinc (2.40 mL, 1.21 mmol) y la solución se calienta a 65°C durante la noche, se diluye con EtOAc (30 mL), se lava con NH_4Cl saturado (2 x 30 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (20%-40% gradiente de EtOAc/hexano) seguido por recristalización de CH_3CN resulta el compuesto del título

(0.15 g, 0.36 mmol, 60%). ^{1}H RMN ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.73-1.93 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.29-3.38 (m, 1H), 6.70 (s, 1H), 7.17-7.23 (m, 1H), 7.56 (s, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.70-7.76 (m, 1H), 8.59 (d, J = 4.7 Hz, 1H). CL/EM (m/z): calculado para $C_{22}H_{23}ClN_4S$ $(M+H)^+$: 412.0; encontrado: 412.4.

Ejemplo 110.

Preparación de 3-(3-cloro-5-pirimidin-5-il-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

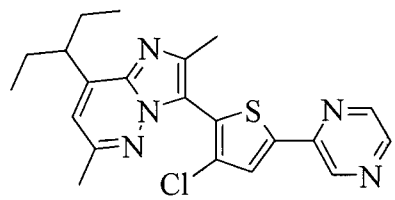


Al usar un procedimiento similar al Ejemplo 104, la 8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina del ácido 3-(3-cloro-tiofen-2-il-5-borónico (0.25g, 0.66 mmol), 4-bromo-pirimidina (0.21 g, 1.32 mmol), 2 M Na_2CO_3 (0.66 mL, 1.32 mmol), i-PrOH (3 mL), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), y PPh_3 (0.026 g, 0.099 mmol) resulta el compuesto del título (0.053 g, 0.13 mmol, 20%). ^{1}H RMN ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.27-3.37 (m, 1H), 6.73 (s, 1H), 7.40 (s, 1H), 8.97 (s, 2H), 9.18

(s, 1H). CL/EM (m/z): calculado para $C_{21}H_{22}ClN_5S$ $(M+H)^+$: 412.1; encontrado: 411.2.

Ejemplo 111.

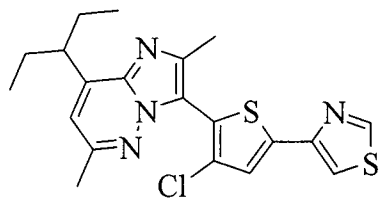
Preparación de 3-(3-cloro-5-pirazin-2-il-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 104, la 8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina del ácido 3-(3-cloro-tiofen-2-il-5-borónico (0.40g, 1.06 mmol), 2-yodo-pirazina (0.16 g, 1.59 mmol), 2 M Na_2CO_3 (1.06 mL, 2.12 mmol) y i-PrOH (5 mL), $Pd(OAc)_2$ (0.012 g, 0.053 mmol), y PPh_3 (0.042 g, 0.16 mmol) resulta el compuesto del título (0.15 g, 0.36 mmol, 34%). ^1H RMN ($CDCl_3$) δ 0.87 (d, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.51 (s, 3H), 2.52 (s, 3H), 3.25-3.37 (m, 1H), 6.71 (s, 1H), 7.66 (s, 1H), 8.45 (d, J = 2.6 Hz, 1H), 8.51-8.53 (m, 1H), 8.96 (d, J = 1.0 Hz, 1H). CL/EM (m/z): calculado para $C_{21}H_{22}ClN_5S$ $(M+H)^+$: 412.1; encontrado: 412.3.

Ejemplo 112.

Preparación de 3-(3-cloro-5-tiazol-4-il-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



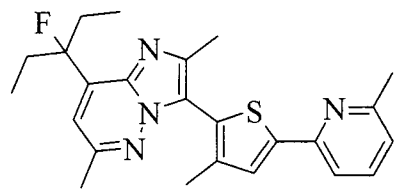
A una solución a 0°C de 3-(5-bromo-3-cloro-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.60 g, 1.45 mmol) y THF (2 mL) se agrega 0.05 g/ mL de Reike® Zn (3.80 mL, 2.91 mmol). La solución se calienta a reflujo durante 1 hora, y el exceso de Zn se deja asentar durante 1 hora a temperatura ambiente. La solución se transfiere a un matraz de 4-bromo-tiazol (Kelly, T. et al. Tetrahedron Lett. 1995, 51, 9293) (0.29 g, 1.74 mmol). El $PdCl_2$(dppf) (0.027 g, 0.036 mmol) se agrega y la solución se calienta a 65°C durante la noche, se diluye con EtOAc (40 mL), se lava con NH_4Cl saturado (30 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (15%-20% gradiente de EtOAc/hexano) seguido por cromatografía en columna ISCO (100% Et_2O) para resultar el compuesto del título (0.098 g, 0.24 mmol, 16%). ^1H RMN ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.28-3.38 (m, 1H), 6.70 (s, 1H), 7.45 (s, 1H), 7.49 (d, J = 2.0 Hz, 1H), 8.85 (d, J = 2.0 Hz, 1H). CL/EM

3019

(m/z): calculado para $C_{20}H_{21}ClN_4S_2$ $(M+H)^+$: 417.1; encontrado: 417.3.

Ejemplo 113.

Preparación de 8-(1-etil-1-fluoro-propil)-2,6-dimetil-3-[3-metil-5-(6-metil-piridin-2-il)-tiofen-2-il]-imidazo[1,2-b]piridazina.



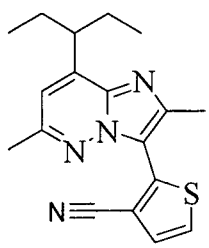
A una solución a -78°C de 3-{2,6-dimetil-3-[3-metil-5-(6-metil-piridin-2-il)-tiofen-2-il]-imidazo[1,2-b]piridazin-8-il}-pentan-3-ol (0.23 g, 0.55 mmol) y CH_2Cl_2 (3 mL) se agrega una solución de trifluoruro de [bis(2-metoxietil)amino]azufre (0.14 g, 0.60 mmol) y CH_2Cl_2 (2 mL). La solución se entibia hasta temperatura ambiente y se agita durante la noche. La solución se lava con $NaHCO_3$ saturado (5 mL) y se concentra. El residuo se purifica por cromatografía en columna ISCO (15%-20% gradiente de EtOAc/hexano) resulta el compuesto del título (0.13g, 0.31 mmol, 57%). ^1H RMN ($CDCl_3$) δ 0.80 (t, J = 7.5 Hz, 6H), 2.14 (s, 3H), 2.16-2.31 (m, 2H), 2.46 (s, 3H), 2.54 (s, 3H), 2.56 (s, 3H), 2.59-2.70 (m, 2H), 6.98 (s, 1H), 7.00 (d, J = 7.6 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.52 (s, 1H), 7.56 (dd, J = 7.8, 7.6 Hz, 1H).

395

CL/EM (m/z): calculado para $C_{24}H_{27}FN_4S$ (M+H)+: 423.2; encontrado: 423.4.

Ejemplo 114.

Preparación de 2-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiofeno-3-carbonitrilo.

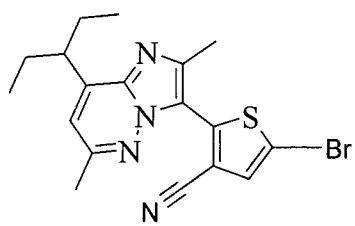


A una solución 0.05 g/mL de Reike® Zn (31 mL, 23.93 mmol) se agrega 2-bromo-tiofeno-3-carbonitrilo (Fournari, P. et al. Bull. Soc. Chim. Fr., 1967, 4115) (2.25 g, 11.96 mmol) y THF (5 mL). La solución se calienta a reflujo durante 2 horas, se enfria a temperatura ambiente y el exceso de Zn se deja asentar. La solución se transfiere por medio de una cánula a un matraz de 8-(1-etil-propil)-3-yodo-2,6-dimetil-imidazo[1,2-b]piridazina (2.5 g, 7.98 mmol) y $PdCl_2$(dppf) (0.29 g, 0.040 mmol). La mezcla se calienta a 65°C durante la noche, se diluye con EtOAc (75 mL), se lava con NH_4Cl saturado (2 x 75 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (10%-20% gradiente de EtOAc/hexano) resulta el compuesto del título (1.10 g, 3.39 mmol, 42%). ^1H RMN ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H),

1.74-1.91 (m, 4H), 2.55 (s, 3H), 2.61 (s, 3H), 3.25-3.34 (m, 1H), 6.75 (s, 1H), 7.35 (d, J = 5.2 Hz, 1H), 7.53 (d, J = 5.2 Hz, 1H). CL/EM (m/z): calculado para $C_{18}H_{20}N_4S$ $(M+H)^+$: 325.5; encontrado: 325.2.

Ejemplo 115.

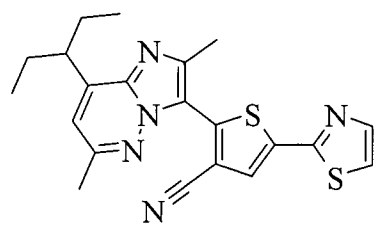
Preparación de 5-bromo-2-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiofeno-3-carbonitrilo.



A una solución de 2-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiofeno-3-carbonitrilo (0.83 g, 2.56 mmol) y CH_2Cl_2 (10 mL) se agrega NBS (0.48 g, 2.69 mmol). La solución se agita durante 1 hora, se diluye con Et_2O (100 mL), se lava con agua (3 x 100 mL), salmuera (100 mL), se seca ($MgSO_4$) se filtra y se concentra para resultar el compuesto del título (1.03 g, 2.55 mmol, >99%). ^1H RMN ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.56 (s, 3 H), 2.60 (s, 3H), 3.24-3.32 (m, 1H), 6.76 (s, 1H), 7.30 (s, 1H). CL/EM (m/z): calculado para $C_{18}H_{19}BrN_4S$ $(M+H)^+$: 404.4; encontrado: 404.1.

Ejemplo 116.

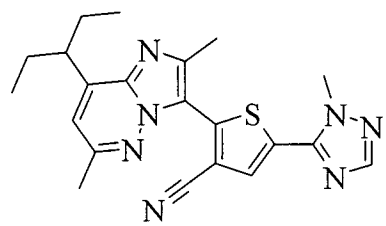
Preparación de 2-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-5-tiazol-2-il-tiofeno-3-carbonitrilo.



A un matraz que contiene 5-bromo-2-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiofeno-3-carbonitrilo (0.25 g, 0.62 mmol) y $PdCl_2$(dppf) (0.023 g, 0.031 mmol) se agrega una solución de 0.5 M bromuro de 2-tiazolilzinc (6.0 mL, 3.10 mmol). La solución se calienta a 65°C durante la noche, se diluye con EtOAc (30 mL), se lava con NH_4Cl saturado (2 x 25 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (15%-20% gradiente de EtOAc/hexano) resulta el compuesto del título (0.16 g, 0.39 mmol, 64%). ^1H RMN ($CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.58 (s, 3H), 2.66 (s, 3H), 3.25-3.35 (m, 1H), 6.78 (s, 1H), 7.38 (d, J = 3.5 Hz, 1H), 7.70 (s, 1H), 7.84 (d, J = 3.5 Hz, 1H). CL/EM (m/z): calculado para $C_{21}H_{21}N_5S_2$ $(M+H)^+$: 408.6; encontrado: 408.1.

Ejemplo 117.

Preparación de 2-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-5-tiazol-2-il-tiofeno-3-carbonitrilo.

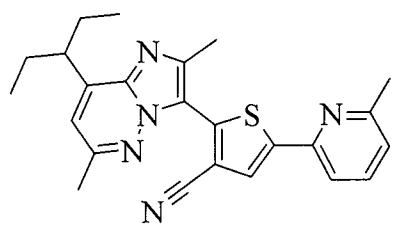


A una solución a -78°C de 1-metil-1,2,4-triazol (0.14 mL, 1.86 mmol) y THF (5 mL) se agrega a una solución 1.6 M de n-BuLi en hexanos (1.20 mL, 1.86 mmol) después de 30 minutos una solución 0.5M de $ZnCl_2$ en THF (4.70 mL, 2.33 mmol) se agrega y la solución se entibia hasta temperatura ambiente y se agita durante 30 minuto. El 5-Bromo-2-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiofeno-3-carbonitrilo (ejemplo Rupp-122) (0.25 g, 0.62 mmol) y $PdCl_2$(dppf) (0.023 g, 0.031 mmol) se agrega y la solución se calienta a 65°C durante la noche, se diluye con EtOAc (25 mL), se lava con NH_4Cl saturado (20 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (15%-60% gradiente de EtOAc/hexano), y se procesa por cromatografía (columna 50 x 250 C18 X-Terra RP, 30-90% 10 mM NH_4HCO_3/agua/5 % ACN: ACN gradiente). El residuo se disuelve en Et_2O (25 mL), se lava con $NaHCO_3$ saturado (25 mL), se seca sobre $MgSO_4$, se filtra y se concentra para resultar el compuesto del título (0.013 g,

0.032 mmol, 5%). ^{1}H RMN ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.58 (s, 3 H), 2.67 (s, 3H), 3.26-3.34 (m, 1H), 4.17 (s, 3H), 6.79 (s, 1H), 6.78 (s, 1H), 7.92 (s, 1H). CL/EM (m/z): calculado para $C_{21}H_{23}N_7S$ $(M+H)^+$: 406.5; encontrado: 406.2.

Ejemplo 118.

Preparación de 2-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-5-(6-metil-piridin-2-il)-tiofeno-3-carbonitrilo.

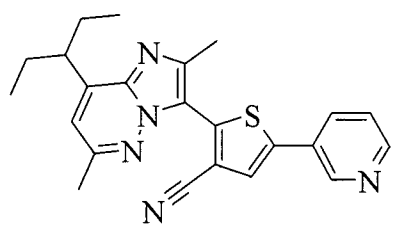


A un matraz que contiene 5-bromo-2-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiofeno-3-carbonitrilo (0.25 g, 0.62 mmol) y $PdCl_2$(dppf) (0.024 g, 0.033 mmol) se agrega una solución de 0.5 M bromuro de 6-metil-2-piridilzinc en THF (2.50 mL, 1.24 mmol). La solución se calienta a 65°C durante la noche, se diluye con EtOAc (30 mL), se lava con NH_4Cl saturado (2 x 30 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (15%-25% gradiente de EtOAc/hexano), resulta el compuesto del título (0.11 g, 0.26 mmol, 39%). ^{1}H RMN ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.76-

1.92 (m, 4H), 2.57 (s, 3 H), 2.58 (s, 3H), 2.65 (s, 3H), 3.26-3.35 (m, 1H), 6.75 (s, 1H), 7.09 (d, J = 7.5 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.63 (dd, J = 7.9, 7.5 Hz, 1H), 7.74 (s, 1H). CL/EM (m/z): calculado para $C_{24}H_{25}N_5S$ $(M+H)^+$: 416.6; encontrado: 416.2.

Ejemplo 119.

Preparación de 2-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-5-piridin-3-il-tiofeno-3-carbonitrilo.

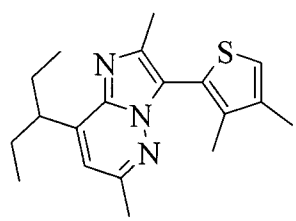


A una solución a -78°C de 3-yodo-piridina (0.32 g, 1.56 mmol), 0.5 M $ZnCl_2$ en THF (3.20 mL, 1.59 mmol), y THF (2 mL) se agrega 1.7 M t-BuLi (1.85 mL, 3.15 mmol). La solución se entibia hasta temperatura ambiente y se agita durante 30 minutos. El 5-Bromo-2-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiofeno-3-carbonitrilo (0.21 g, 0.52 mmol) y $Pd(PPh_3)_4$ (0.03 g, 0.026 mmol) se agregan y la solución se calienta a 55°C durante 1 hora, se enfria a temperatura ambiente y se agita durante la noche, se diluye con EtOAc (50 mL), se lava con NH_4Cl saturado (2 x 40 mL), se seca sobre MgSO4, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (15%-40% gradiente

de EtOAc/hexano), resulta el compuesto del título (0.15 g, 0.37 mmol, 71%). ^{1}H RMN ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.58 (s, 3 H), 2.66 (s, 3H), 3.26-3.35 (m, 1H), 6.78 (s, 1H), 7.34-7.46 (m, 1H), 7.56 (s 1H), 7.91 (d, J = 7.1 Hz, 1H), 8.62 (s, 1H), 8.91 (s, 1H). CL/EM (m/z): calculado para $C_{23}H_{23}N_5S$ $(M+H)^+$: 402.6; encontrado: 402.4.

Ejemplo 120.

Preparación de 3-(3,4-dimetil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



A. 2-Bromo-3,4-dimetil-tiofeno.

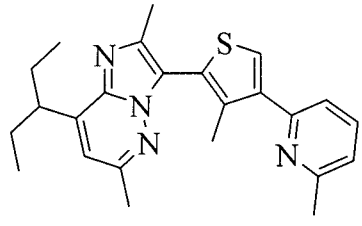
A una solución de 3,4-dimetil-tiofeno (2.0 g, 17.82 mmol) (Minato et. al., Tetrahedron 1982, 38, 3347) en CH_2Cl_2 (20 mL) se agrega NBS (3.3 g, 18.72 mmol). La solución se agita durante 1 hora, se diluye con Et_2O (100 mL), se lava con agua (3 x 100 mL), salmuera (100 mL), se seca ($MgSO_4$) se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (100% hexano) resulta el compuesto del título (3.0 g, 16.70 mmol). ^{1}H RMN ($CDCl_3$) δ 2.10 (s, 3H), 2.17 (s, 3H), 6.85 (s, 1H).

B. 3-(3,4-Dimetil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina y 8-(1-etil-propil)-2,6-dimetil-3-(3,4,3',4'-tetrametil-[2,2']bitiofenil-5-il)-imidazo[1,2-b]piridazina, respectivamente.

A una solución de 8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (2.30 g, 10.58 mmol), 2-bromo-3,4-dimetil-tiofeno (3.03 g, 15.88 mmol) y Cs_2CO_3 (7.24 g, 22.23 mmol) y DMF (50 mL) se desgasifica con N_2 durante 20 minutos. El $Pd_2(dba)_3$ (0.48 g, 0.053 mmol) y PPh_3 (0.56 g, 0.21 mmol) se agregan y la solución se calienta a 120°C durante la noche. La solución se diluye con EtOAc (200 mL), se lava con agua (3 x 200 mL), salmuera (200 mL), se seca ($MgSO_4$), se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (10%-15% gradiente de EtOAc/hexano) resulta 2.04 g de un aceite café el cual se procesa por cromatografía (columna C18 Symmetry de 50 x 250, 30-70% agua: 0.1 % TFA /ACN gradiente) resulta el compuesto del título (0.41 g, 1.25 mmol, 12%). ^1H RMN ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.94 (m, 4H), 2.00 (s, 3 H), 2.24 (d, J = 1.0 Hz, 3H), 2.45 (s, 3H), 2.50 (s, 3H), 3.29-3.38 (m, 1H), 6.65 (s, 1H), 7.10 (s, 1H). CL/EM (m/z): calculado para $C_{19}H_{25}N_3S$ $(M+H)^+$: 328.5; encontrado: 328.3.

Ejemplo 121.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-4-(6-metil-piridin-2-il)-tiofen-2-il]-imidazo[1,2-b]piridazina.

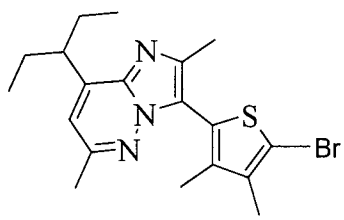


A un matraz que contiene la 3-(4-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (a continuación) (0.25 g, 0.64 mmol) y $PdCl_2$(dppf) (0.023 g, 0.032 mmol) se agrega una solución de 0.5 M bromuro de 6-metil-2-piridilzinc en THF (2.5 mL, 1.27 mmol). La solución se calienta a 65°C durante la noche, se diluye con EtOAc (25 mL), se lava con NH_4Cl saturado (20 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por ISCO (15%-20% EtOAc gradiente) y se procesa por cromatografía (columna C18 Symmetry de 50 x 250, 10-70% agua: 0.1 % TFA/ACN: 0.1% TFA gradiente). El residuo se disuelve en Et_2O (20 mL), se lava con $NaHCO_3$ saturado (15 mL) se seca sobre $MgSO_4$, se filtra y se concentra para resultar el compuesto del título (0.066 g, 1.57 mmol, 31%). ^1H RMN ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.20 (s, 3 H), 2.47 (s, 3H), 2.49 (s, 3H), 2.61 (s, 3H), 3.29-3.38 (m,

1H), 6.66 (s, 1H), 7.09 (d, J = 7.5 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.54 (dd, J = 7.5, 7.8 Hz, 1H), 7.72 (s, 1H). CL/EM (m/z): calculado para $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.2; encontrado: 405.3.

Ejemplo 122.

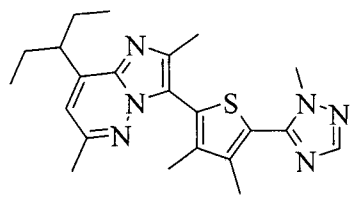
Preparación de 3-(5-bromo-3,4-dimetil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



A una solución de 3-(3,4-dimetil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.41 g, 1.25 mmol) y CH_2Cl_2 (30 mL) se agrega NBS (0.23 g, 1.32 mmol). La solución se agita durante 1 hora, se diluye con Et_2O (100 mL), se lava con agua (3 x 100 mL), salmuera (100 mL), se seca ($MgSO_4$) se filtra y se concentra para resultar el compuesto del título (0.41 g, 1.01 mmol, 80%). ^1H RMN ($CDCl_3$) δ 0.86 (t, J = 7.4 Hz, 6H), 1.72-1.94 (m, 4H), 2.02 (s, 3 H), 2.18 (s, 3H), 2.43 (s, 3H), 2.49 (s, 3H), 3.27-3.36 (m, 1H), 6.67 (s, 1H). CL/EM (m/z): calculado para $C_{19}H_{24}BrN_3S$ $(M+H)^+$: 407.4; encontrado: 407.3.

Ejemplo 123.

Preparación de 3-[3,4-dimetil-5-(2-metil-2H-[1,2,4]triazol-3-il)-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

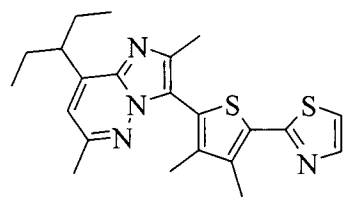


A una solución a -78°C de 1-metil-1,2,4-triazol (0.056 mL, 0.74 mmol) y THF (2 mL) se agrega a 1.6 M solución de n-BuLi en hexanos (0.46 mL, 0.74 mmol). La solución se entibia hasta temperatura ambiente y se agita durante 30 minutos. La solución se enfría hasta 0°C, una solución 0.5M de $ZnCl_2$ en THF (4.70 mL, 2.33 mmol) se agrega y la solución se entibia hasta temperatura ambiente y se agita durante 30 minuto. La 3-(5-bromo-3,4-dimetil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.10 g, 0.25 mmol) y $PdCl_2$(dppf) (0.009 g, 0.012 mmol) se agrega y la solución se calienta a 65°C durante la noche, se diluye con EtOAc (25 mL), se lava con NH_4Cl saturado (20 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (15%-60% gradiente de EtOAc/hexano), seguido por una segunda purificación por cromatografía en columna ISCO (100% Et2O) resulta el compuesto del título (0.07 g, 0.17 mmol, 70%). ^1H RMN ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.06 (s, 3 H), 2.29 (s, 3H), 2.47 (s, 3H), 2.51 (s, 3H), 3.27-3.37 (m, 1H), 3.97 (s,

3H), 6.69 (s, 1H), 8.00 (s, 1H). CL/EM (m/z): calculado para $C_{22}H_{28}N_6S$ $(M+H)^+$: 409.6; encontrado: 409.2.

Ejemplo 124.

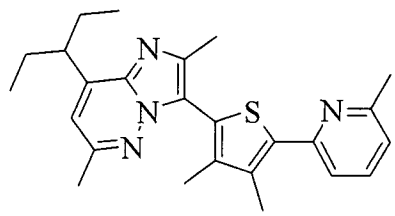
Preparación de 3-(3,4-dimetil-5-tiazol-2-il-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



A una solución a -78°C de 3-(5-bromo-3,4-dimetil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.10 g, 0.25 mmol) y THF (1 mL) se agrega 1.6 M n-BuLi (0.16 mL). La solución se agita durante 45 minutos y 0.5 M $ZnCl_2$ en THF (0.52 mL, 0.26 mmol) se agrega. La solución se entibia hasta temperatura ambiente y se agita durante 30 minutos. El 2-Bromo-tiazol (0.044 mL, 0.49 mmol), y $PdCl_2$(dppf) (0.009 g, 0.012 mmol) se agregan y la solución se calienta a 65°C durante la noche, se diluye con EtOAc (25 mL), se lava con NH_4Cl saturado (20 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (15%-20% gradiente de EtOAc/hexano), resulta el compuesto del título (6.1 mg, 0.015 mmol, 6%). ^1H RMN ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.07 (s, 3 H), 2.49 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.29-3.39 (m, 1H), 6.68 (s, 1H), 7.35 (d, J = 3.1 Hz, 1H), 7.86 (d, J = 3.1 Hz, 1H). CL/EM (m/z): calculado para $C_{22}H_{26}N_4S_2$ $(M+H)^+$: 411.6; encontrado: 411.2.

Ejemplo 125.

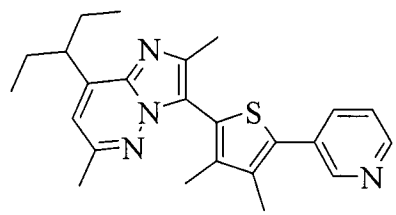
Preparación de 3-[3,4-dimetil-5-(6-metil-piridin-2-il)-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



A un matraz que contiene 3-(5-bromo-3,4-dimetil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.10 g, 0.25 mmol) y $PdCl_2$(dppf) (9 mg, 0.012 mmol) se agrega una solución de 0.5 M bromuro de 6-metil-2-piridilzinc en THF (0.98 mL, 0.49 mmol). La solución se calienta a 65°C durante la noche, se diluye con EtOAc (30 mL), se lava con NH_4Cl saturado (30 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (15%-30% gradiente de EtOAc/hexano) resulta el compuesto del título (0.029 g, 0.069 mmol, 29%). ^1H RMN ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.72-1.92 (m, 4H), 2.04 (s, 3 H), 2.45 (s, 3H), 2.47 (s, 3H), 2.50 (s, 3H), 2.59 (s, 3H), 3.29-3.38 (m, 1H), 6.66 (s, 1H), 7.04 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 8.0, 7.8 Hz, 1H). CL/EM (m/z): calculado para $C_{25}H_{30}N_4S$ $(M+H)^+$: 419.6; encontrado: 419.4.

Ejemplo 126.

Preparación de 3-[3,4-dimetil-5-(6-metil-piridin-2-il)-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

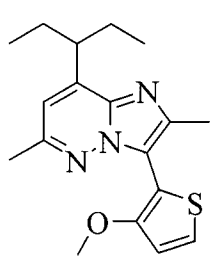


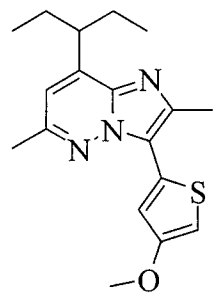
A una solución a -78°C de 3-yodo-piridina (0.15 g, 0.74 mmol) y 0.5 M $ZnCl_2$ en THF (1.5 mL, 0.75 mmol) se agrega t-BuLi (0.88 mL, 1.49 mmol). La suspensión espesa se entibia hasta temperatura ambiente y se agita durante 30 minutos. 3-(5-bromo-3,4-dimetil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.10 g, 0.25 mmol) y $Pd(PPh_3)_4$ (0.014 g, 0.012 mmol) se agregaron y la solución se agita a temperatura ambiente durante 2 días, se diluye con EtOAc (35 mL), se lava con NH_4Cl saturado (30 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (20%-30% gradiente de EtOAc/hexano) resulta el compuesto del título (6.1 mg, 0.015 mmol, 6%). ^1H RMN ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.07 (s, 3 H), 2.29 (s, 3H), 2.49 (s, 3H), 2.53 (s, 3H), 3.30-3.39 (m, 1H), 6.68 (s, 1H), 7.36 (dd, J = 8.0, 4.5 Hz, 1H), 7.79-7.83 (m 1H), 8.57 (d, J = 4.5 Hz, 1H), 8.79

(d, J = 0.9 Hz, 1H). CL/EM (m/z): calculado para $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.6; encontrado: 405.2.

Ejemplo 127 y 128.

Preparación de 8-(1-etil-propil)-3-(3-metoxi-tiofen-2-il)-2,6-dimetil-imidazo[1,2-b]piridazina y 8-(1-etil-propil)-3-(4-metoxi-tiofen-2-il)-2,6-dimetil-imidazo[1,2-b]piridazina.





Ej. 127. Ej. 128.

A una solución de 3-metoxi-tiofeno (2.19 g, 19.14 mmol) en Et_2O (50 mL) se agrega 1.6 M n-BuLi (12.20 mL, 19.46 mmol). La solución se calienta a un reflujo durante 30 minutos y se enfría hasta temperatura ambiente. Como solución de 0.5 M $ZnCl_2$ (38.9 mL, 19.5 mmol) y THF (50 mL) se agrega y la solución se agita durante 30 minutos. 8-(1-etil-propil)-3-yodo-2,6-dimetil-imidazo[1,2-b]piridazina (2.0 g, 6.38 mmol) y $PdCl_2$(dppf) (0.23 g, 0.032 mmol) se agregaron y la solución se calienta a 65°C durante 4 horas, se diluye con EtOAc (250 mL), se lava con NH_4Cl saturado (250 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (10%-25% gradiente de

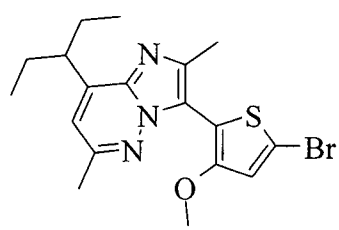
EtOAc/hexano) resulta el compuesto del títulos (1.50 g, 4.55 mmol, 71%) y (0.23 g, 0.70 mmol, 11%), respectivamente.

Ejemplo 127: ^{1}H RMN ($CDCl_3$) δ 0.83 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.59 (s, 3H), 2.70 (s, 3H), 3.26-3.35 (m, 1H), 3.86 (s, 3H), 6.32 (d, J = 1.6 Hz, 1H), 6.67 (s, 1H), 7.41 (d, J = 1.6 Hz, 1H). CL/EM (m/z): calculado para $C_{18}H_{23}N_3OS$ $(M+H)^+$: 330.5; encontrado: 330.3.

Ejemplo 128: ^{1}H RMN ($CDCl_3$) δ 0.84 (t, J = 7.5 Hz, 6H), 1.71-1.88 (m, 4H), 2.47 (s, 3H), 2.49 (s, 3H), 3.26-3.35 (m, 1H), 3.84 (s, 3H), 6.62 (s, 1H), 6.96 (d, J = 5.5 Hz, 1H), 7.39 (d, J = 5.5 Hz, 1H). CL/EM (m/z): calculado para $C_{18}H_{23}N_3OS$ $(M+H)^+$: 330.5; encontrado: 330.3.

Ejemplo 129.

Preparación de 3-(5-bromo-3-metoxi-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

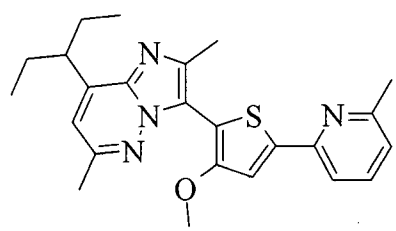


A una solución de 8-(1-etil-propil)-3-(3-metoxi-tiofen-2-il)-2,6-dimetil-imidazo[1,2-b]piridazina (0.78 g, 2.37 mmol) y CH_2Cl_2 (10 mL) se agrega NBS (0.44 g, 2.49 mmol). La solución se agita durante 1 hora, se lava con agua (3 x 10 mL), concentrado y purificado por cromatografía en columna

ISCO (5%-15% gradiente de EtOAc/hexano) para resultar el compuesto del título (0.87 g, 2.13 mmol, 90%). ^{1}H RMN ($CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.46 (s, 3H), 2.52 (s, 3H), 3.25-3.35 (m, 1H), 3.82 (s, 3H), 6.65 (s, 1H), 6.97 (s, 1H). CL/EM (m/z): calculado para $C_{18}H_{22}BrN_3OS$ $(M+H)^+$: 408.1; encontrado: 408.3.

Ejemplo 130.

Preparación de 8-(1-etil-propil)-3-[3-metoxi-5-(6-metil-piridin-2-il)-tiofen-2-il]-2,6-dimetil-imidazo[1,2-b]piridazina.

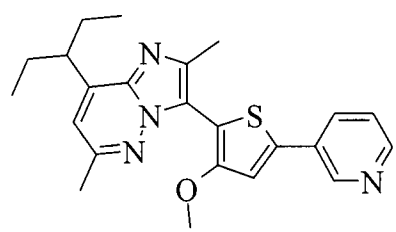


A un matraz que contiene 3-(5-bromo-3-metoxi-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.20 g, 0.49 mmol) y $PdCl_2$(dppf) (0.018 g, 0.024 mmol) se agrega una solución de 0.5 M bromuro de 6-metil-2-piridilzinc en THF (3.0 mL, 1.47 mmol). La solución se calienta a 65°C durante la noche, se diluye con EtOAc (30 mL), se lava con NH_4Cl saturado (2 x 30 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (15%-20% gradiente de EtOAc/hexano) resulta el compuesto del título (0.066 g, 1.57 mmol, 31%). ^{1}H RMN ($CDCl_3$) δ 0.85 (t,

J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.50 (s, 3 H), 2.51 (s, 3H), 2.55 (s, 3H), 3.26-3.37 (m, 1H), 3.90 (s, 3H), 6.63 (s, 1H), 6.99 (d, J = 7.4 Hz, 1H), 7.43 (d, J = 7.7 Hz, 1H), 7.49 (s, 1H), 7.54 (dd, J = 7.4, 7.7 Hz, 1H). CL/EM (m/z): calculado para $C_{24}H_{28}N_4OS$ $(M+H)^+$: 421.6; encontrado: 422.4.

Ejemplo 131.

Preparación de 8-(1-etil-propil)-3-(3-metoxi-5-piridin-3-il-tiofen-2-il)-2,6-dimetil-imidazo[1,2-b]piridazina.

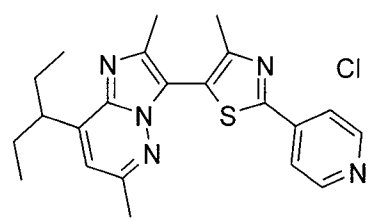


A una solución a -78°C de 3-yodo-piridina (0.32 g, 1.56 mmol) y 0.5 M $ZnCl_2$ en THF (3.20 mL, 1.59 mmol) se agrega t-BuLi (2.27 mL, 3.85 mmol). La solución se entibia hasta temperatura ambiente y se agita durante 30 minutos. 3-(5-bromo-3-metoxi-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.26 g, 0.64 mmol) y $Pd(PPh_3)_4$ (0.037 g, 0.032 mmol) se agregaron y la solución se calienta a 50°C durante 1 hora, se enfría hasta temperatura ambiente y se agita durante la noche. La solución se diluye con EtOAc (30 mL), se lava con NH_4Cl saturado (2 x 30 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (20%-50% gradiente de

EtOAc/hexano), resulta el compuesto del título (0.16 g, 0.39 mmol, 61%). ^{1}H RMN ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.52 (s, 3 H), 2.55 (s, 3H), 3.28-3.38 (m, 1H), 3.93, (3H), 6.67 (s, 1H), 7.26 (d, J = 3.5 Hz, 1H), 7.31-7.36 (m, 1H), 7.88-7.92 (m, 1H), 8.55 (d, J = 4.5 Hz, 1H), 8.92 (d, J = 1.8 Hz, 1H). CL/EM (m/z): calculado para $C_{23}H_{26}N_4OS$ $(M+H)^+$: 407.6; encontrado: 407.4.

Ejemplo 132.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(4-metil-2-piridin-4-il-tiazol-5-il)-imidazo[1,2-b]piridazina, sal de clorohidrato.

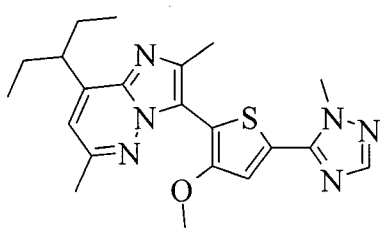


Una mezcla de 3-(2-bromo-4-metil-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (500 mg, 1.27 mmol), ácido 4-piridinaborónico (500 mg, 4 mmol), $Pd(PPh_3)_4$ (100 mg, 0.08 mmol), tolueno (2 mL), MeOH (1mL), y K_2CO_3 (2 M solución acuosa, 3.5mL) se calienta a 100°C durante 18 horas. Acetato de etilo (20mL) se agrega, y la capa orgánica se separa, se seca sobre sulfato de magnesio, se filtra, y se concentra in vacuo. La purificación se lleva a cabo por medio de cromatografía en gel de sílice usando una mezcla 3:1 de

hexanos y acetato de etilo para obtener la amina libre del compuesto del título (200 mg, 40%). El producto purificado se disuelve en acetato de etilo y una solución preparada recientemente de cloruro de hidrógeno (0.5 M en acetato de etilo, 2 mL) se agrega. El solvente se remueve in vacuo para dar el compuesto del título ^{1}H-RMN ($CDCl_3$), δ 8.2 (m, 2H); 7.05 (m,2H); 6.55 (s, 1H); 3.24 (m, 1H); 2.43 (s, 3H); 2.40 (s, 3H); 2.33 (s, 3H); 1.76 (m, 4H); 0.80 (t, 6H) ppm. EM/ES$^+$ = 391 (100%, M+1).

Ejemplo 133.

Preparación de 8-(1-etil-propil)-3-[3-metoxi-5-(2-metil-2H-[1,2,4]triazol-3-il)-tiofen-2-il]-2,6-dimetil-imidazo[1,2-b]piridazina.



A. 5-Bromo-1-metil-1H-[1,2,4]triazol.

A una solución a -78°C de 1-metil-1H-[1,2,4]triazol (1.0 mL, 13.20 mmol) y THF (100 mL) se agrega 1.6 M n-BuLi (8.70 mL, 13.86 mmol). Después de 45 minutos 1,2-dibromo-1,1,2,2-tetrafluoro-etano (1.76 mL, 14.52 mmol) se agrega, la solución se entibia hasta temperatura ambiente y se agita durante 2 horas. La solución se diluye con EtOAc (200 mL), se

lava con agua (150 mL), salmuera (150 mL), se seca sobre $MgSO_4$, se filtra y se concentra para resultar el compuesto del título (1.37 g, 8.46 mmol, 64%). ^1H RMN ($CDCl_3$) δ 3.82 (s, 3H), 7.78 (s, 1H). CL/EM (m/z): calculado para $C_3H_4BrN_3$ $(M+H)^+$: 162.0; encontrado: 161.9.

B. 8-(1-Etil-propil)-3-(5-yodo-3-metoxi-tiofen-2-il)-2,6-dimetil-imidazo[1,2-b]piridazina.

A una solución de 8-(1-etil-propil)-3-(3-metoxi-tiofen-2-il)-2,6-dimetil-imidazo[1,2-b]piridazina (0.75 g, 2.28 mmol) y CH_3CN (10 mL) se agrega NIS (0.54 g, 2.39 mmol). La solución se agita durante la noche, se concentra, se diluye con EtOAc (30 mL), se lava con agua (30 mL), NH_4Cl saturado (30 mL), 20% ($NaHSO_3$) (30 mL), salmuera (30 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (15%-20% gradiente de EtOAc/hexano) resulta el compuesto del título (0.91 g, 2.00 mmol, 88%). ^1H RMN ($CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.46 (s, 3H), 2.52 (s, 3H), 3.25-3.35 (m, 1H), 3.83 (s, 3H), 6.64 (s, 1H), 7.12 (s, 1H). CL/EM (m/z): calculado para $C_{18}H_{22}IN_3OS$ $(M+H)^+$: 456.4; encontrado: 456.0.

C. 5-Bromo-1-metil-1H-[1,2,4]triazol.

A una solución a -78°C de 1-metil-1H-[1,2,4]triazol (1.0 mL, 13.20 mmol) y THF (100 mL) se agrega 1.6 M n-BuLi (8.70

mL, 13.86 mmol). Después de 45 minutos 1,2-dibromo-1,1,2,2-tetrafluoro-etano (1.76 mL, 14.52 mmol) se agrega, la solución se entibia hasta temperatura ambiente y se agita durante 2 horas. La solución se diluye con EtOAc (200 mL), se lava con agua (150 mL), salmuera (150 mL), se seca sobre $MgSO_4$, se filtra y se concentra para resultar el compuesto del título (1.37 g, 8.46 mmol, 64%). ^1H RMN ($CDCl_3$) δ 3.82 (s, 3H), 7.78 (s, 1H). CL/EM (m/z): calculado para $C_3H_4BrN_3$ $(M+H)^+$: 162.0; encontrado: 161.9.

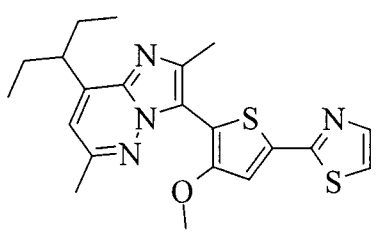
D. 8-(1-Etil-propil)-3-[3-metoxi-5-(2-metil-2H-[1,2,4]triazol-3-il)-tiofen-2-il]-2,6-dimetil-imidazo[1,2-b]piridazina.

A una suspensión espesa de 0.05 g/ mL de Reike® Zn en THF (2.8 mL, 2.11 mmol) se agrega 5-bromo-1-metil-1H-[1,2,4]triazol y THF (2 mL). La solución se calienta a 65°C durante 1 hora, se enfría hasta temperatura ambiente y el exceso de Zn se deja asentar durante 1 hora. La solución se transfiere a un matraz que contiene 8-(1-etil-propil)-3-(5-yodo-3-metoxi-tiofen-2-il)-2,6-dimetil-imidazo[1,2-b]piridazina (0.32 g, 0.70 mmol) y $Pd(PPh_3)_4$ (0.041 g, 0.035 mmol). La solución se calienta a 65°C durante la noche, se diluye con EtOAc (30 mL) se lava con NH_4Cl saturado (30 mL). La fase acuosa se extrae con EtOAc (20 mL). Las capas orgánicas combinadas se secan sobre $MgSO_4$, se filtran y se

concentran. El residuo se purifica por cromatografía en columna ISCO (20%-65% gradiente de EtOAc/hexano) seguido por cromatografía en columna ISCO (100% Et_2O) resulta el compuesto del título (0.19 g, 0.46 mmol, 62%). ^1H RMN ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.51 (s, 3 H), 2.52 (s, 3H), 3.26-3.37 (m, 1H), 3.92 (s, 3H), 4.15 (s, 3H), 6.67 (s, 1H), 7.48 (s, 1H), 7.89 (s, 1H). CL/EM (m/z): calculado para $C_{21}H_{26}N_6OS$ $(M+H)^+$: 411.5; encontrado: 411.3.

Ejemplo 134.

Preparación de 8-(1-etil-propil)-3-(3-metoxi-5-tiazol-2-il-tiofen-2-il)-2,6-dimetil-imidazo[1,2-b]piridazina.

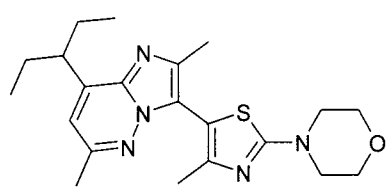


A un matraz que contiene 8-(1-etil-propil)-3-(5-yodo-3-metoxi-tiofen-2-il)-2,6-dimetil-imidazo[1,2-b]piridazina (0.45 g, 0.99 mmol) y $PdCl_2$(dppf) (0.057 g, 0.078 mmol) se agrega una solución 0.5M de bromuro de 2-tiazolilzinc (9.9 mL, 4.94 mmol). La solución se calienta a 65°C durante la noche, se diluye con EtOAc (50 mL), se lava con NH_4Cl saturado (50 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía en columna ISCO (15%-20% gradiente de EtOAc/hexano) resulta el compuesto del título (0.29 g, 0.70

mmol, 71%). ^{1}H RMN ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-1.90 (m, 4H), 2.51 (s, 3H), 2.53 (s, 3H), 3.28-3.37 (m, 1H), 3.93 (s, 3H), 6.67 (s, 1H), 7.28 (d, J = 3.3 Hz, 1H), 7.41 (s, 1H), 7.80 (d, J = 3.3 Hz, 1H). CL/EM (m/z): calculado para $C_{21}H_{24}N_4OS_2$ $(M+H)^+$: 413.6; encontrado: 414.3.

Ejemplo 135.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(4-metil-2-morfolin-4-il-tiazol-5-il)-imidazo[1,2-b]piridazina.



110 mg de 8-(1-etil-propil)-3-[2-bromo-4-metil-5-tiazolil]-2,6-dimetil-imidazo[1,2-b]piridazina (0.28 mmol) y 122 mg de morfolina (1.4 mmol) se disuelven en 3.0 ml de THF y 182 mg de carbonato de cesio (0.56 mmol) se agrega. La mezcla se coloca en 4 ml de un vial con una tapa revestida de Teflon y se calienta a 110°C durante la noche. La mezcla de reacción se concentra y se aplica a una columna de cromatografía en columna de gel de sílice con hexano:EtOAc = 3:1 eluyente para dar 98 mg del compuesto del título (88%). Espectro de masas(m/e): 400(M+1); ^{1}H-RMN($CDCl_3$): δ 6.70(s, 1H), 3.87(t, 4H, J=4.8Hz), 3.56(t, 4H, J=4.8Hz), 3.35(m, 1H) 2.56(s, 3H), 2.46(s, 3H), 1.86(m, 4H), 0.90(t, 6H, J=7.6Hz)

9/9

Los siguientes compuestos se preparan esencialmente como se describe en el Ejemplo 135. con 8-(1-etil-propil)-3-[2-bromo-4-metil-5-tiazolil]-2,6-dimetil-imidazo[1,2-b]piridazina y la amina nombrada :

Ej	Nombre	Amina	^{1}H RMN ($CDCl_3$): δ	EM (encontrado) (M+1)
136.	N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-metilamina	2M Metil-amina/THF	6.71 (s, 1H), 5.44 (s, NH), 3.35 (m, 1H), 3.06 (s, 3H), 2.57 (s, 3H), 2.47 (s, 3H), 2.19 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.6 Hz, 6H).	344
137.	N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-dimetilamina	2M Dimetil-amina/THF	6.70 (s, 1H), 3.36 (m, 1H), 3.17 (s, 6H), 2.56 (s, 3H), 2.46 (s, 3H), 2.19 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H).	358

138.	N-Etil-N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-metilamina	N-Metil-etilamina	6.70 (s, 1H), 3.59 (q, J = 7.6 Hz, 2H), 3.37 (m, 1H), 3.15 (s, 3H), 2.57 (s, 3H), 2.48 (s, 3H), 2.19 (s, 3H), 1.85 (m, 4H), 1.30 (t, J = 7.5 Hz, 2H), 0.90 (t, J = 7.1 Hz, 6H).	372
139.	N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-dietilamina	Dietil-amina	6.71 (s, 1H), 3.56 (q, J = 7.1 Hz, 4H), 3.35 (m, 1H), 2.56 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 1.30 (t, J = 7.3 Hz, 6H), 0.90 (t, J = 7.3 Hz, 6H).	386

140.	N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-N-(furan-2-ilmetil)-metilamina	N-Metil-(furan-2-il)-metil-amina	7.44 (s, 1H), 6.69 (s, 1H), 6.38 (s, 2H), 4.72 (s, 2H), 3.36 (m, 1H), 3.14 (s, 3H), 2.57 (s, 3H), 2.48 (s, 3H), 2.20 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.4 Hz, 6H).	424
141.	N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}tiomorfolina	Tio-morfolina	6.71 (s, 1H), 3.92 (m, 4H), 3.37 (m, 1H), 2.80 (m, 4H), 2.57 (s, 3H), 2.48 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.2 Hz, 6H).	416

142	N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-(2-metoxi-etil)-amina	2-metoxi-etilamina	6.71 (s, 1H), 5.90 (s, NH), 3.66 (t, J = 5.4 Hz, 2H), 3.56 (t, J = 4.6 Hz, 2H), 3.44 (s, 3H), 3.35 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.2 Hz, 6H).	388
143	N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-isopropil-amina	i-propil-amina	6.69 (s, 1H), 5.15 (s, NH), 3.74 (m, 1H), 3.35 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.17 (s, 3H), 1.84 (m, 4H), 1.35 (d, J = 5.4 Hz, 6H), 0.90 (t, J = 7.4 Hz, 6H).	372

144.	N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-pirrolidina	Pirrolidina	6.68 (s, 1H), 3.55 (m, 4H), 3.36(m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.19 (s, 3H), 2.09 (m, 4H), 1.86 (m, 4H), 0.91 (t, J = 7.6 Hz, 6H).	384
145.	N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il}-4-metil-tiazol-2-il}-n-propilamina	n-propil-amina	6.70 (s, 1H), 5.21 (s, NH), 3.39 (t, J = 7.2 Hz, 2H), 3.29 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.16 (s, 3H), 1.85 (m, 4H), 1.74 (m, 2H), 1.05 (t, J = 7.3 Hz, 3H), 0.90 (t, J = 7.4 Hz, 6H).	372

146	N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-bencilamina	Bencil-amina	7.47-7.23 (m, 5H), 6.70 (s, 1H), 5.52 (s, NH), 6.70 (s, 2H), 3.34 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.19 (s, 3H), 1.85 (m, 4H), 0.91 (t, J = 7.2 Hz, 6H).	420
147	N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-N-(2-metoxi-etil)-etilamina	N-(2-Metoxi-etil)-etilamina		416

148	N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-(2-metoxi-etil)-n-propilamina	N-(2-metoxietil)-n-propil-amina	6.69 (s, 1H), 3.72 (m, 4H), 3.47 (t, J = 7.4 Hz, 2H), 3.42 (s, 3H), 3.36 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.16 (s, 3H), 1.87 (m, 6H), 0.99 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.5 Hz, 6H).	430
149	N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-piperidina	piperidina	6.68 (s, 1H), 3.53 (t, J = 4.7 Hz, 4H), 3.36 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.86 (m, 4H), 1.71 (m, 6H), 0.90 (t, J = 7.4 Hz, 6H).	398

422

150	N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-3-pentilamina	3-amino-pentano	6.70 (s, 1H), 5.24 (s, NH), 3.32 (m, 2H), 2.57 (s, 3H), 2.47 (s, 3H), 1.94 (s, 3H), 1.85 (m, 4H), 1.72 (m, 2H), 1.60 (m, 2H), 1.02 (t, J = 7.5 Hz, 6H), 0.90 (t, J = 7.3 Hz, 6H).	400
151	N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-ciclo-propilamina	Ciclo-propil amina	6.70 (s, 1H), 6.51 (s, NH), 3.35 (m, 1H), 2.67 (m, 1H), 2.57(s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 0.91 (t, J = 7.3 Hz, 6H), 0.82 (m, 2H), 0.77 (m, 2H).	370

152	N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-allylamina	Alilamina	6.70 (s, 1H), 6.0 (m, 1H), 5.60 (s, NH), 5.38 (dd, J = 1.3, 17.4 Hz, 1H), 5.27 (dd, J = 1.2, 10.3 Hz, 1H), 4.0 (d, J = 5.2 Hz, 2H), 3.45 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.85 (m, 4H), 0.91 (t, J = 6.8 Hz, 6H).	370
153	N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-1,2,3,6-tetra-hidro-piridina	1,2,3,6-tetra-hidro-piridina	6.70 (s, 1H), 5.96 (m, 1H), 5.81 (m, 1H), 4.02 (t, J = 3.1 Hz, 2H), 3.72 (t, J = 5.5 Hz, 2H), 3.35 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.35 (m, 2H), 2.19 (s, 3H), 1.87 (m, 4H), 0.90 (t, J = 7.4 Hz, 6H).	396

154	N-Etil-N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-n-propilamina	N-etil-n-propil-amina	6.69 (s, 1H), 3.58 (q, J = 7.1 Hz, 2H), 3.43 (t, J = 7.5 Hz, 2H), 3.36 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.80 (m, 4H), 1.30 (t, J = 6.9 Hz, 3H), 1.04 (t, J = 6.9 Hz, 3H), 0.91 (t, J = 7.5 Hz, 6H).	400
155	N-Metil-N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-n-propilamina	N-metil-n-propil-amina	6.68 (s, 1H), 3.46 (t, J = 8.3 Hz, 2H), 3.35 (m, 1H), 3.16 (s, 3H), 2.56 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.80 (m, 2H), 1.00 (t, J = 7.7 Hz, 3H), 0.91 (t, J = 7.1 Hz, 6H).	386

156	N-Metil-N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-isopropil-amina	N-Metil-2-propil-amina	6.70 (s, 1H), 4.40 (m, 1H), 3.36 (m, 1H), 2.99 (s, 3H), 2.57 (s, 3H), 2.46 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 1.29 (d, J = 6.4 Hz, 6H), 0.90 (t, J = 7.1 Hz, 6H).	386
157	N-Metil-N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-2-propin-1-amina	N-Metil-2-Propin-1-amina	6.70 (s, 1H), 4.40 (d, J = 2.5 Hz, 2H), 3.35 (m, 1H), 3.17 (s, 3H), 2.56 (s, 3H), 2.45 (s, 3H), 2.34 (m, 1H), 2.19 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.1 Hz, 6H).	382

158	N-Metil-N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-3-amino-propionitrilo	N-Metil-3-amino-propio-nitrilo	6.71 (s, 1H), 3.92 (t, J = 6.4 Hz, 2H), 3.37 (m, 1H), 3.25 (s, 3H), 2.9 (t, J = 6.4 Hz, 2H), 2.58 (s, 3H), 2.48 (s, 3H), 2.18 (s, 3H), 1.86 (m, 4H), 0.91 (t, J = 7.4 Hz, 6H).	397
159	N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-ciclopropil-metilamina	Ciclo-propil-metil-amina	6.68 (s, 1H), 5.35 (s, NH), 3.34 (m, 1H), 3.19 (t, J = 6.3 Hz, 2H), 2.56 (s, 3H), 2.45 (s, 3H), 2.16 (s, 3H), 1.86 (m, 4H), 1.19 (m, 1H), 0.91 (t, J = 7.1 Hz, 6H), 0.61 (m, 2H), 0.31 (m, 2H).	384

160	N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-(2-metilsulfanil)-etilamina	2-metil-sulfanil-etilamina	6.72 (s, 1H), 5.58 (s, NH), 3.58 (m, 2H), 3.35 (m, J = 7.3, 14.4, 1H), 2.85 (m, 2H), 2.57 (s, 3H), 2.46 (s, 3H), 2.17 (s, 6H), 1.85 (m, 4H), 0.90 (t, J = 6.7 Hz, 6H).	404
161	N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}- N-{[1,3]dioxolan-2-ilmetil-metilamina	N-{[1,3]di-oxolan-2-il-metil}-metil-amina	6.72 (s, 1H), 5.22 (m, 1H), 4.05 (m, 2H), 3.94 (m, 2H), 3.73 (d, J = 4.5 Hz, 2H), 3.35 (m, J = 6.6, 14.1 Hz, 1H), 3.23 (s, 3H), 2.56 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.84 (m, 4H), 0.91 (t, J = 7.1 Hz, 6H).	430

162	N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}- N-Metil-2-propen-1-il-amina	N-Metil-2-propen-1-il-amina	6.71 (s, 1H), 5.93 (m, 2H), 5.30 (m, 2H), 4.16 (d, J = 5.9 Hz, 2H), 3.39 (m, 1H), 3.12 (s, 3H), 2.58 (s, 3H), 2.48 (s, 3H), 2.20 (s, 3H), 1.86 (m, 4H), 0.91 (t, J = 7.5 Hz, 6H).	384
163	(R)-N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-(tetrahidro-furan-2-ilmetil)-amina	(R)-(tetrahidro-furan-2-ilmetil)-amina	6.70 (s, 1H), 5.44 (s, NH), 4.20 (m, 1H), 3.94 (m, 1H), 3.84 (m, 1H), 3.60 (m, 1H), 3.35 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 2.08 (m, 1H), 1.98 (m, 2H), 1.85 (m, 4H), 1.73 (m, 2H), 0.90 (t, J = 7.3 Hz, 6H).	414

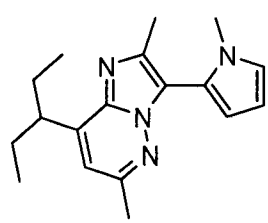
164	(S)-N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-(tetrahidro-furan-2-ilmetil)-amina	(S)-(tetrahidro-furan-2-ilmetil)-amina	6.69 (s, 1H), 5.45 (s, NH), 4.20 (m, 1H), 3.94 (m, 1H), 3.84 (m, 1H), 3.59 (m, 1H), 3.34 (m, 2H), 2.57 (s, 3H), 2.47 (s, 3H), 2.17 (s, 3H), 2.08 (m, 1H), 1.98 (m, 2H), 1.85 (m, 4H), 1.73 (m, 1H), 0.90 (t, J = 7.2 Hz, 6H).	414
165	N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-N-(2-metoxietil)-metilamina	N-Metil-2-metoxi-etil-amina	6.70 (s, 1H), 3.74 (t, J = 4.2 Hz, 2H), 3.71 (t, J = 4.1 Hz, 2H), 3.43 (s, 3H), 3.37 (m, 1H), 3.22 (s, 3H), 2.57 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.1 Hz, 6H).	402

166	N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-N-metil-Bencilamina	N-Metil-Bencil-amina	7.43-7.32 (m, 5H), 6.69 (s, 1H), 4.76 (s, 2H), 3.35 (m, 1H), 3.10 (s, 3H), 2.57(s, 3H), 2.48 (s, 3H), 2.21 (s, 3H), 1.85 (m, 4H), 0.91 (t, J = 7.3 Hz, 6H).	434
167	N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-N-etil-Bencilamina	N-Etil-Bencil-amina	7.41-7.31 (m, 5H), 6.68 (s, 1H), 4.76 (s, 2H), 3.54 (q, J = 7.3, 2H), 3.36 (m, 1H), 2.56(s, 3H), 2.49 (s, 3H), 2.20 (s, 3H), 1.85 (m, 4H), 1.26 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.1 Hz, 6H).	448
168	N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo [1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-(1-metoxi-2-butil)-amina	1-Metoxi-2-amino-butano		416

169	N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-N-metil-isobutilamina	N,2-Di-metil-n-propil-amina		400
170	N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-isobutil-amina	2-Metil-n-propil-amina		386

Ejemplo 171.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(1-metil-1H-pirrol-2-il)-imidazo[1,2-b]piridazina.



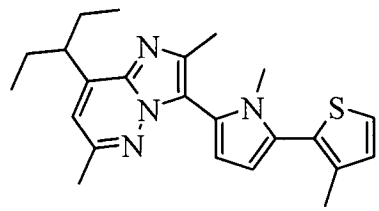
Una solución de THF (10 mL) de N-metilpirrol (Aldrich, 800 µL, 9.0 mmol) se enfría hasta -78°C bajo N_2 luego se trata con tert-BuLi (1.7 M en pentano, 5.3 mL, 9.0 mmol). La solución se entibia hasta temperatura ambiente durante 30 minutos luego se enfría hasta -78°C y se trata con $ZnCl_2$ (Aldrich, 0.5 M en THF, 18 mL, 9.0 mmol). La mezcla resultante se entibia hasta temperatura ambiente y se trata con una suspensión espesa THF (5 mL) que contiene 8-(1-etil-propil)-3-yodo-2,6-dimetil-imidazo[1,2-b]piridazina (1.02 gm, 3.0 mmol) y complejo $PdCl_2$(dppf) - CH_2Cl_2 (Aldrich, 140 mg, 0.17 mmol). La mezcla se calienta hasta 60°C durante la noche, luego se vacía en NH_4Cl acuoso saturado (50 mL) y se extrajo con éter dietílico (75 mL). El extracto orgánico se lava con salmuera acuosa, se seca sobre Na_2SO_4, se filtra, y se concentra. El producto crudo se purifica por cromatografía al usar el hexano-acetato de etilo (100% hexano hasta 20% acetato de etilo en hexano) para eluir el compuesto del título (407.5 mg, 46% de rendimiento) como un aceite.

ES-EM (m/z): calculado para $C_{18}H_{24}N_4$: 296.20; encontrado 297.5 $(M+H)^+$

^1H RMN (400 mHz, $CDCl_3$): δ 6.86 (s, 1H), 6.65 (s, 1H), 6.32-6.28 (m, 2H), 3.50 (s, 3H), 3.35 (br s, 1H), 2.49 (s, 3H), 2.46 (s, 3H), 1.87-1.75 (m, 4H), 0.87 (t, J = 7.0 Hz, 6H).

Ejemplo 172.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-[1-metil-5-(3-metil-tiofen-2-il)-1H-pirrol-2-il]- imidazo[1,2-b]piridazina.



A. 3-(5-Bromo-1-metil-1H-pirrol-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

Una solución de THF (10 mL) de 8-(1-etil-propil)-2,6-dimetil-3-(1-metil-1H-pirrol-2-il)-imidazo[1,2-b]piridazina (414 mg, 1.40 mmol) se enfría hasta 0°C y se trata con una solución de THF de NBS (250 mg, 1.40 mmol). Dentro de 5 min, la mezcla de reacción se trata con Na_2SO_3 saturado (1 mL) luego se concentra. El residuo resultante se diluye con acetato de etilo (50 mL) y se lava con 50% Na_2SO_3 acuoso saturado (2x50 mL). El extracto orgánico se seca sobre Na_2SO_4, se filtra, y se concentra. El producto crudo se purifica por cromatografía al usar el hexano-acetato de etilo (100% hexano hasta 20% acetato de etilo en hexano) para eluir el compuesto del título (374 mg, 71% de rendimiento) como un sólido. ES-EM (m/z): calculado para $C_{18}H_{23}BrN_4$: 374.11; encontrado 375 $(M+H)^+$. ^1H RMN (400 mHz, $CDCl_3$): δ 6.67 (s, 1H), 6.33 (d, J = 4.0 Hz, 1H), 6.30 (d, J = 4.0 Hz, 1H), 3.40 (s, 3H), 3.36 (br

s, 1H), 2.50 (s, 3H), 2.44 (s, 3H), 1.88-1.75 (m, 4H), 0.87 (t, J = 7.3 Hz, 6H).

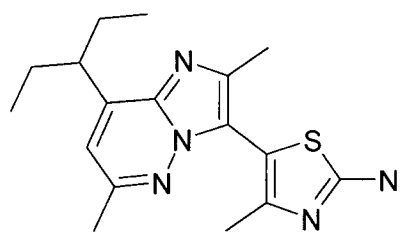
B. 8-(1-Etil-propil)-2,6-dimetil-3-[1-metil-5-(3-metil-tiofen-2-il)-1H-pirrol-2-il]-imidazo[1,2-b]piridazina.

Una suspensión espesa THF (5 mL) de 3-(5-bromo-1-metil-1H-pirrol-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (143 mg, 0.38 mmol) y complejo $PdCl_2$(dppf) - CH_2Cl_2 (Aldrich, 19 mg, 0.023 mmol) se trata con bromuro 3-metil-2-thienil zinc (Aldrich, 0.5 M en THF, 3.8 mL, 1.9 mmol) luego se calienta hasta 60°C durante 1 hr. La mezcla resultante se vació en NH_4Cl saturado (25 mL) y se extrajo con éter dietílico (35 mL). El extracto orgánico se lava con NaCl acuoso, se seca sobre Na_2SO_4, se filtra, y se concentra. El producto crudo se purifica por cromatografía al usar el hexano-acetato de etilo (100% hexano hasta 15% acetato de etilo en hexano) para eluir el producto. El material se purifica en un segundo tiempo por cromatografía instantánea al usar el hexano-acetato de etilo (100% hexano hasta 12% acetato de etilo en hexano) para eluir el producto. Solamente las fracciones que contienen el producto deseado puro, como se juzga por el análisis EM, se recolectan y dan el compuesto del título (82.6 mg, 55% de rendimiento) como un aceite. ES-EM (m/z): calculado para $C_{23}H_{28}N_4S$: 392.20; encontrado 393.1 $(M+H)^+$. ^1H RMN (400 mHz, $CDCl_3$): δ 7.28 (d, J = 5.3 Hz, 1H),

6.96 (d, J = 4.8 Hz, 1H), 6.67 (br s, 1H), 6.39 (d, J = 3.5 Hz, 1H), 6.37 (d, J = 4.0 Hz, 1H), 3.35 (br s, 1H), 3.33, (s, 3H), 2.52 (s, 3H), 2.51 (s, 3H), 2.26 (s, 3H), 1.89-1.76 (m, 4H), 0.87 (t, J = 7.5 Hz, 6H).

Ejemplo 173.

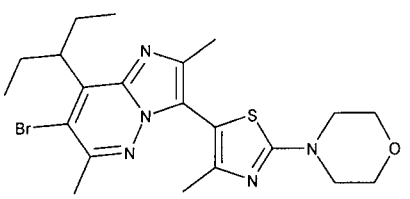
Preparación de 5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-ilamina.



50 mg de 8-(1-etil-propil)-3-[2-bromo-4-metil-5-tiazolil]-2,6-dimetil-imidazo[1,2-b]piridazina (0.13 mmol) y 10 mg de óxido de cobre (I) se agregaron a 3 ml de 2 M NH_3 en MeOH y el vial se tapa con una tapa revestida de Teflon, se calienta a 130°C durante la noche. La mezcla de reacción se concentra bajo gas de N2 y se aplica sobre una columna de cromatografía de gel de sílice (Hexano: AcOEt: 2 M NH3 en MeOH = 20:20:1) para dar 22 mg del compuesto del título. Rendimiento 54%: espectro de masas(m/e): 330(M+1); ^{1}H-RMN(CDCl3): 6.72(s,1H), 5.24(br, 2H), 3.40(m, 1H), 2.56(s, 3H), 2.47(s, 3H), 2.18(s, 3H), 1.85(m, 4H), 0.90(t, 6H, J=7.4Hz).

Ejemplo 174.

Preparación de N-{5-[7-bromo-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-morfolina.



A. 7-Bromo-3-(2-bromo-4-metil-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

547 mg de 8-(1-etil-propil)-2,6-dimetil-3-(4-metil-tiazol-5-il)-imidazo[1,2-b]piridazina (1.74 mmol) y 341 mg de NBS (1.92 mmol) se disuelven en 20 ml de CHCl3 y se agita a temperatura ambiente durante la noche. La mezcla de reacción se lava con $Na_2S_2O_3$ saturado, NaCl saturado, se seca sobre Na_2SO_4 y se evapora. Los materiales crudos se aplican en una columna de cromatografía de gel de sílice (Hexano:AcOEt=8:1) para dar 218 mg del compuesto del título. Rendimiento 27%. Espectro de masas(m/e): 473(M+1); ^{1}H-RMN($CDCl_3$): 3.44(m, 1H), 2.70(s, 3H), 2.45 (s, 3H), 2.37(s, 3H), 2.03(m, 4H), 0.90(m, 6H).

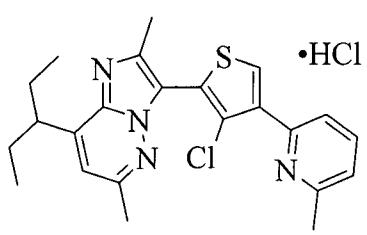
B. N-{5-[7-bromo-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-morfolina.

72 mg de 7-bromo-3-(2-bromo-4-metil-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.15 mmol) y 66 mg de morfolina (0.76 mmol) y 97 mg de carbonato de

cesio (0.3 mmol) se colocan en 4 ml de vial con 3 ml de THF seco. El vial se cierra con una tapa revestida de Teflon y se calienta a 100°C durante la noche. La mezcla de reacción se concentra y se aplica sobre una columna de cromatografía de gel de sílice (Hexano:AcOEt = 3:1) para dar 30 mg del compuesto del título. Rendimiento 42%.: espectro de masas(m/e): 479(M+1); ^{1}H-RMN($CDCl_3$): 3.87(t, 4H, J=5.0Hz), 3.55(t, 4H, J=5.0Hz), 3.45(m, 1H), 2.70(s, 3H), 2.44(s, 3H), 2.40(m, 2H), 2.18(s, 3H), 2.01(m, 2H), 0.88(t, 6H, J=7.3Hz).

Ejemplo 175.

Preparación de 3-[3-cloro-4-(6-metil-piridin-2-il)-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina, sal de clorohidrato.

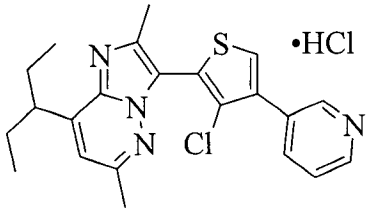


Zn Reike® (0.5 g/ mL solución en THF (1.9 mL,, 1.45 mmol) se agrega a un matraz que contiene 3-(4-bromo-3-cloro-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.30 g, 0.73 mmol). La suspensión espesa se calienta a 65°C durante 1 hora, se coloca en una centrifuga durante 5 minutos, y la solución resultante se transfiere a un matraz que contiene 2-bromo-6-metil-piridina (0.12 g, 0.73

mmol) y $PdCl_2$(dppf) (0.018 g, 0.024 mmol). La reacción se calienta a 65°C durante la noche, se diluye con acetato de etilo (20 mL), y se lava con una solución saturada de NH_4Cl (15 mL). La capa orgánica se seca sobre $MgSO_4$, se filtra, y se concentra. El residuo se purifica por cromatografía en gel de sílice usando un gradiente de hexanos y acetato de etilo. El producto resultante se disuelve en diclorometano (5 mL), se trata con una solución 1M de HCl en EtOH (0.35 mL, 0.35 mmol) y se concentra. El residuo se recristaliza a partir de acetato de etilo y hexanos resulta el compuesto del título (0.033 g, 0.072 mmol, 11%). ^{1}H-RMN ($CDCl_3$), δ 0.95 (t, J = 7.3 Hz, 6H), 1.73-2.02 (m, 4H), 2.68 (s, 3H), 2.81 (s, 3H), 3.21 (s, 3H), 3.88-3.98 (m, 1H), 7.25 (s, 1H), 7.65 (d, J = 7.5 Hz, 1H), 8.09 (d, J = 7.5 Hz, 1H), 8.33 (dd, J = 7.5, 7.1 Hz, 1H), 9.26 (s, 1H) ppm. CL/EM (m/z): calculado para $C_{23}H_{26}Cl_2N_4S$ $(M+H)^+$: 424.2; encontrado: 424.2.

Ejemplo 176.

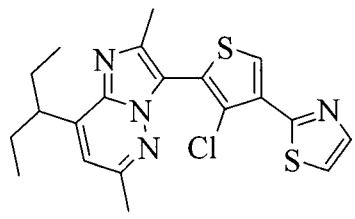
Preparación de 3-(3-cloro-4-piridin-3-il-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina, sal de clorohidrato.



Usando un procedimiento análogo al Ejemplo 175, 3-(4-bromo-3-cloro-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.40 g, 0.97 mmol), Reike® Zn (0.5 g/ mL solución en THF, 2.5 mL, 1.94 mmol), 3-yodo-piridina (0.30 g, 1.45 mmol), $PdCl_2$(dppf) (0.035 g, 0.048 mmol), y una solución 1M de HCl en EtOH (0.61 mL, 0.61 mmol) resulta el compuesto del título (0.076 g, 0.17 mmol, 18%). ^{1}H-RMN ($CDCl_3$), δ 0.95 (t, J = 7.0 Hz, 6H), 1.71-1.88 (m, 2H), 1.88-2.01 (m, 2H), 2.68 (s, 3H), 2.81 (s, 3H), 3.85-3.96 (m, 1H), 5.28 (s, 1H), 7.27 (bs, 1H), 8.09 (bs, 1H), 8.23 (bs, 1H), 8.70 (bs, 1H), 8.89 (bs, 1H), 9.18 (bs, 1H). CL/EM (m/z): calculado para $C_{22}H_{24}Cl_2N_4S$ $(M+H)^+$: 411.1; encontrado: 411.2.

Ejemplo 177.

Preparación de 3-(3-cloro-4-tiazol-2-il-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

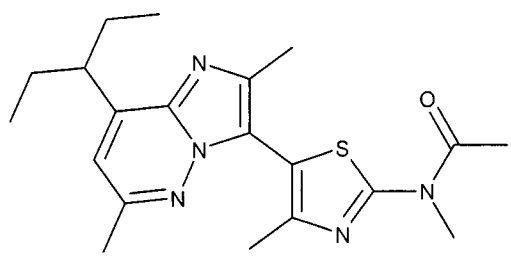


Usando un procedimiento análogo al Ejemplo 175, 3-(4-bromo-3-cloro-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.25 g, 0.61 mmol), Zn Reike® (0.5 g/ mL solución en THF, 1.6 mL, 1.21 mmol), 2-bromo-tiazol

(0.11 mL, 1.21 mmol), y $PdCl_2$(dppf) (0.022 g, 0.030 mmol) resulta el compuesto del título (0.012 g, 0.29 mmol, 6.8%). ^{1}H-RMN ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.94 (m, 4H), 2.52 (s, 6H), 3.27-3.43 (m, 1H), 6.73 (s, 1H), 7.43 (d, J = 3.3 Hz, 1H), 7.94 (d, J = 3.3 Hz, 1H), 8.30 (s,1H) ppm. CL/EM (m/z): calculado para $C_{20}H_{21}ClN_4S_2$ $(M+H)^+$: 417.1; encontrado: 417.2.

Ejemplo 178.

Preparación de N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-N-metil-acetamida.

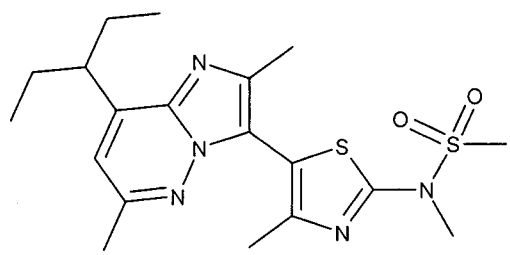


60 mg de N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-metilamina (0.17 mmol) y 86 mg de trietilamina (0.85 mmol) se disuelven en 3.0 ml de CH_2Cl_2 y 16 mg de acetilcloruro (0.2 mmol) se agrega. El vial se cierra con una tapa revestida de Teflon y se agita a temperatura ambiente durante 2h. La mezcla de reacción se concentra y se aplica sobre una columna de cromatografía de gel de sílice (Hexano :AcOEt = 3:1 y

Hexano:AcOEt=2:1) para dar 33.8 mg del compuesto del título. Rendimiento 50%: espectro de masas(m/e): 386(M+1); ^{1}H-RMN($CDCl_3$): 7.03(s,1H), 3.79(s, 3H), 3.47(m, 1H), 2.54 (s, 3H), 2.47(s, 3H), 2.46(s, 3H), 2.31(s, 3H), 1.86(m, 4H), 0.91(t, 6H, J=7.4Hz).

Ejemplo 179.

Preparación de N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-N-metanosulfonil-metilamina.

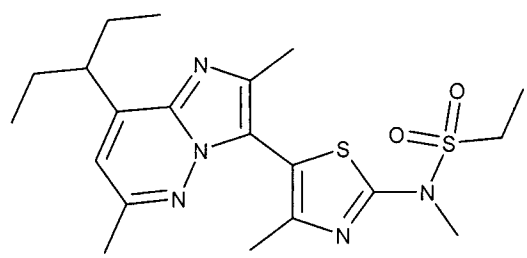


60 mg de N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-metilamina (0.17 mmol) y 86 mg de trietilamina (0.85 mmol) se disuelven en 3.0 ml de CH_2Cl_2 y 23 mg de cloruro de metanosulfonilo (0.2 mmol) se agrega. El vial se cierra con una tapa revestida de Teflon y se agita a temperatura ambiente durante 2h. La mezcla de reacción se concentra y se aplica hasta cromatografía en gel de sílice (Hexano :AcOEt = 2:1) para dar 53.8 mg del compuesto del título. Rendimiento 75%. Espectro de masas(m/e): 422(M+1); ^{1}H-

RMN($CDCl_3$): 6.96(s, 1H), 3.60(s, 3H), 3.34(m, 1H), 3.19(s, 3H), 2.56(s, 3H), 2.48(s, 3H), 2.29(s, 3H), 1.86(m, 4H), 0.90(t, 6H, J=7.4Hz).

Ejemplo 180.

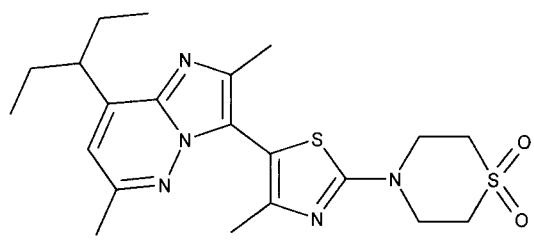
Preparación de N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-N-etanosulfonil-metilamina.



El compuesto del título se prepara por un procedimiento análogo al Ejemplo 178. Empleando 50 mg de N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-metilamina (0.15 mmol), 51 mg de trietilamina (0.5 mmol) y 39 mg de etanosulfonilcloruro (0.3 mmol). 48.9 mg, Rendimiento 75%: espectro de masas(m/e): 436(M+1); ^{1}H-RMN($CDCl_3$): 6.73(s, 1H), 3.62(s, 3H), 3.42(q, 2H, J=7.4Hz), 3.35(m, 1H), 2.55(s, 3H), 2.48(s, 3H), 2.28(s, 3H), 1.85(m, 4H), 1.46(t, 3H, J=7.4Hz), 0.90(t, 6H, J=7.5Hz).

Ejemplo 181.

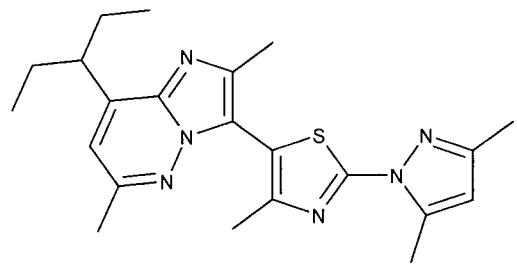
Preparación de 3-[2-(1,1-dioxo-tiomorfolin-4-il)-4-metil-tiazol-5-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



60 mg de N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}tiomorfolina(0.14 mmol) se disuelve en 3 ml de CH_2Cl_2 y 62 mg de mCPBA (0.36 mmol) se agrega. La mezcla de reacción se agita a temperatura ambiente durante 30 min. La mezcla de reacción se diluye con CH_2Cl_2, se lava con NaHCO3 saturado y NaCl saturado. La capa orgánica separada se seca sobre Na_2SO_4 y se evapora. El producto crudo se aplica encima de una columna de cromatografía de gel de sílice (Hexano:AcOEt:2 M NH3 en MeOH=10:3:1) para dar 20.3 mg del compuesto del título. Rendimiento 33%: espectro de masas(m/e): 448(M+1). ^{1}H-RMN: 6.72 (s, 1H), 4.16 (t, J = 4.7 Hz, 4H), 3.35 (m, 1H), 3.23 (t, J = 5.2 Hz, 4H), 2.57 (s, 3H), 2.48 (s, 3H), 2.19 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.1 Hz, 6H).

Ejemplo 182.

Preparación de 3-[2-(3,5-Dimetil-pirazol-1-il)-4-metil-tiazol-5-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



A. {5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-hidrazina.

El compuesto del título se prepara esencialmente como se describe en el Ejemplo 135 usando hidrazina. EM encontrado (M+1) 345.

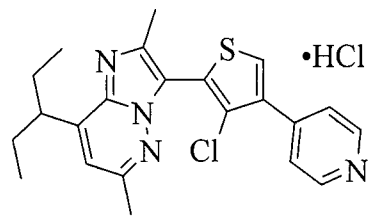
B. 3-[2-(3,5-Dimetil-pirazol-1-il)-4-metil-tiazol-5-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

28 mg de {5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-hidrazina (0.08 mmol) y 80 mg de 2,4-pentanodiona (0.8 mmol) se disuelven en 1.0 ml de AcOH y se calientan a 100°C durante 2 h. La mezcla de reacción se concentra y se aplica sobre una columna de cromatografía de gel de sílice (Hexano : AcOEt = 5:1) para dar 23 mg del compuesto del título. Rendimiento 70%: espectro de masas(m/e): 409 (M+1). 6.72 (s, 1H), 6.03 (s, 1H), 3.36

(m, J = 7.1, 14.1 Hz, 1H), 2.75 (s, 3H), 2.55 (s, 3H), 2.50 (s, 3H), 2.32(s, 3H), 2.31(s, 3H), 1.87 (m, 4H), 0.91 (t, J = 7.5 Hz, 6H).

Ejemplo 183.

Preparación de 3-(3-cloro-4-piridin-4-il-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina, sal de clorohidrato.

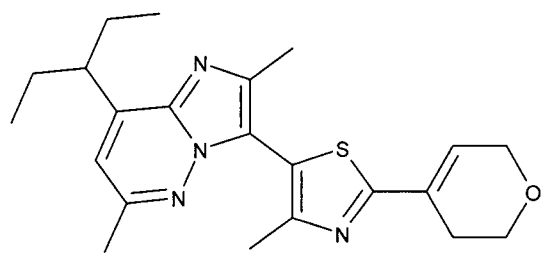


Una solución de 3-(4-bromo-3-cloro-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.25 g, 0.61 mmol), ácido 4-piridil-borónico (0.82, 0.67 mmol), una solución 2 M de Na_2CO_3 (0.5 mL, 0.91 mmol), y n-PrOH (2.5 mL) se desgasifican con nitrógeno durante 10 minutos. Pd(OAc)2 (0.0027 g, 0.012 mmol) y PPh3 (0.0095 g, 0.036 mmol) se agregan, y la solución se calienta a 90°C durante la noche. La solución se diluye con acetato de etilo (40 mL) y se lava con una solución al 10 % de Na_2CO_3 (30 mL). La capa orgánica se seca sobre $MgSO_4$, se filtra, y se concentra. El residuo se purifica por cromatografía instantánea ISCO (20%-30% gradiente EtOAc). El producto resultante se disuelve en diclorometano (5 mL), se trata con una solución 1M de HCl en

EtOH (0.35 mL, 0.35 mmol), y se concentra. El residuo se recristaliza de acetonitrilo y acetato de etilo resulta el compuesto del título (0.15 g, 0.34 mmol, 56%). ^{1}H-RMN ($CDCl_3$), δ 0.95 (t, J = 7.5 Hz, 6H), 1.73-1.88 (m, 2H), 1.89-2.04 (m, 2H), 2.68 (s, 3H), 2.82 (s, 3H), 3.87-3.97 (m, 1H), 7.28 (s, 1H), 8.26-8.34 (m, 3H), 8.95 (d, J = 5.3 Hz, 2H) ppm. CL/EM (m/z): calculado para $C_{22}H_{24}Cl_2N_4S$ $(M+H)^+$: 411.1; encontrado: 411.2.

Ejemplo 184.

Preparación de 3-[2-(3,6-dihidro-2H-piran-4-il)-4-metil-tiazol-5-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



A. 4-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-tetrahidro-piran-4-ol.

370 mg de 3-(2-Bromo-4-metil-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.93 mmol) se disuelve en 10 ml de THF seco y se enfría hasta -78°C. 0.6 ml de n-BuLi 2.0 M en hexano (1.2 mmol) se agrega y se agita a -78°C durante 30 min. 141 mg de tetrahidro-4H-piran-4-ona

(1.41 mmol) se agrega y se agita a -78°C durante 2 h. La mezcla de reacción se diluye con AcOEt, se lava con NH_4Cl saturado, se seca sobre Na_2SO_4 y se evapora. El producto crudo se aplica encima de una columna de cromatografía de gel de sílice (Hexano : AcOEt : 2 M NH3 en MeOH =10:3:1) para dar 152 mg del compuesto del título. Rendimiento 40%.: espectro de masas(m/e): 415(M+1). ^1H RMN ($CDCl_3$): δ 6.74 (s, 1H), 3.99 (t, J = 2.2 Hz, 4H), 3.97 (t, J = 2.2 Hz, 4H), 3.35 (m, 1H), 3.20 (s, OH), 2.56 (s, 3H), 2.48 (s, 3H), 2.36 (s, 3H), 1.88 (m, 4H), 0.91 (t, J = 7.3 Hz, 6H).

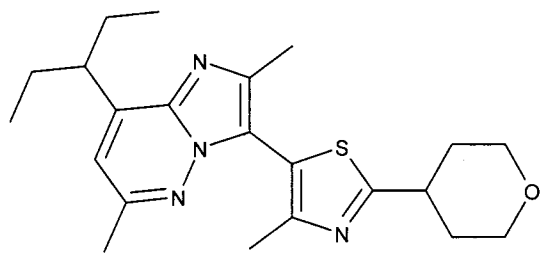
B. 3-[2-(3,6-Dihidro-2H-piran-4-il)-4-metil-tiazol-5-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

150 mg de 4-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-tetrahidro-piran-4-ol (0.36 mmol) se disuelve en 5 ml de CH2Cl2 y 112 mg de trietilsilano (0.96 mmol) y 717 mg de ácido trifluoroacético (6.3 mmol) se agregaron. La mezcla de reacción se agita a temperatura ambiente durante 1h. La mezcla de reacción se agita bajo reflujo durante 1 h y se enfría completamente hasta temperatura ambiente. El solvente se remueve in vacuo. El producto crudo se aplica encima de una columna de cromatografía de gel de sílice (Hexano : AcOEt: 2 M NH3 en MeOH =10:3:1) para dar 64 mg del compuesto del título. Rendimiento 45%. Espectro de masas(m/e):

397(M+1). 6.94 (s, 1H), 6.71 (s, 1H), 4.41 (d, J = 2.6 Hz, 2H), 3.98 (t, J = 5.3 Hz, 2H), 3.43 (m, 1H), 2.62(s, 3H), 2.75 (m, 2H), 2.56 (s, 3H), 2.37 (s, 3H), 1.86 (m, 4H), 0.92 (t, J = 8.2 Hz, 6H).

Ejemplo 185.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-[4-metil-2-(tetrahidro-piran-4-il)-tiazol-5-il]-imidazo[1,2-b]piridazina.

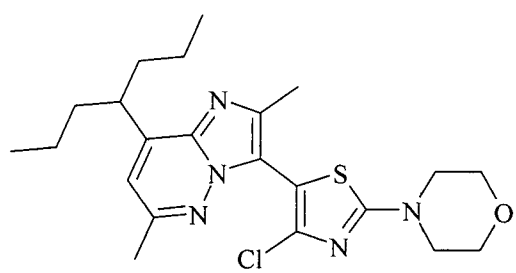


Se agrega 3-[2-(3,6-dihidro-2H-piran-4-il)-4-metil-tiazol-5-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (55 mg, 0.14 mmol), 5% de paladio en carbono (55 mg) y etanol absoluto (50 ml) a un recipiente de presión. Se pruga el recipiente de reacción con nitrógeno, se purga el recipiente de reacción con hidrógeno, se presuriza la mezcla de reacción con hidrógeno (415 KPa), se sella el recipiente, se agita la reacción y se calienta a 40°C. Se continua la reacción durante 18 horas luego se apaga el calor y se permite a la mezcla de reacción enfriarse hasta temperatura ambiente. Ventilar el exceso de

hidrógeno del recipiente y se purga el recipiente con nitrógeno. Se filtra la mezcla de reacción para remover el 5% de paladio en carbono. El producto filtrado se concentra y se aplica sobre una columna de cromatografía de gel de sílice (Hexano :AcOEt : 2 M NH_3 en MeOH = 10:3:1) para dar 12.8 mg del compuesto del título. Rendimiento 23%. Espectro de masas(m/e): 399(M+1). ^1H RMN ($CDCl_3$): δ 6.73 (s, 1H), 4.14 (m, 2H), 3.60 (m, 2H), 3.34 (m, 2H), 2.56 (s, 3H), 2.48 (s, 3H), 2.36 (s, 3H), 2.16 (m, 2H), 2.02 (m, 2H), 1.87 (m, 4H), 0.91 (t, J = 7.6 Hz, 6H).

Ejemplo 186.

Preparación de 3-(4-cloro-2-morfolin-4-il-tiazol-5-il)-2,6-dimetil-8-(1-propil-butil)-imidazo[1,2-b]piridazina.



A. 6-Metil-4-(1-propil-butil)-piridazin-3-ilamina.

6-Metil-4-(1-propil-butil)-piridazin-3-ilamina puede hacerse usando la química descrita en J. Heterocylic Chem. 1991, 28, 583. Un matraz de fondo redondo de tres cuellos de 250 mL se carga con 3-amino-6-metil piridazina (2.5 g, 0.229 moles, 1.0 equiv), agua (70 mL), y acetonitrilo (50

mL). Se concentra el ácido sulfúrico (3.51 g, 1.91 mL, 0.0344 moles, 1.5 equiv), nitrato de plata (3.87 g, 0.0229 moles, 1.0 equiv), y ácido valproico (7.21 g, 7.95 mL, 0.050 moles, 2.2 equiv) se agregaron a la mezcla de reacción. La reacción se calienta hasta 75°C. Cuando la mezcla de reacción se calienta, una solución de $(NH_4)_2S_2O_8$ (7.85 g, 0.0344 moles, 1.5 equiv) en 40 mL de agua se agrega lentamente por medio de un embudo de adición durante un periodo de 30 minutos. La mezcla de reacción se calienta a 70-80°C durante dos horas más. La mezcla de reacción se enfría y el diclorometano se agrega. La reacción se hace básica con una solución de NaOH acuoso al 30% y se filtra a través de un tapón corto Celite®. La capa orgánica se separa, y la capa acuosa se extrae dos veces más con diclorometano. Los extractos orgánicos combinados se secan sobre Na_2SO_4. El solvente se evapora y el material crudo se purifica usando cromatografía en gel de sílice con una solución 2.0 N de NH_3 en MeOH y cloruro de metileno como eluyente. Rendimiento = 0.61 g (13%). EM (APCI): 208 (M+1).

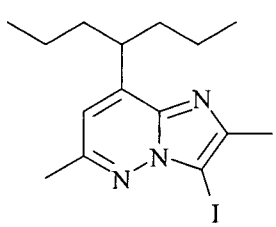
B. 2,6-Dimetil-8-(1-propil-butil)-imidazo[1,2-b]piridazina.

Un matraz de fondo redondo de 250 mL se carga con 6-metil-4-(1-propil-butil)-piridazin-3-ilamina (0.611 g, 0.00295 moles, 1 equiv), etanol 2B (30 mL), y

460

cloroacetona (0.382 g, 0.328 ml, 0.00412 moles, 1.4 equiv). La mezcla de reacción se calienta a 75°C durante la noche y luego se enfría a temperatura ambiente. El $NaHCO_3$ (0.371 g, 0.00442 moles, 1.5 equiv) se agrega lentamente a la mezcla de reacción que luego se calienta hasta 100°C durante la noche. La mezcla de reacción se enfría y el solvente se evapora. El diclorometano se agrega y la mezcla de reacción se pasa a través de un papel filtro. El solvente se evapora para obtener un aceite café el cual se purifica por medio de cromatografía en gel de sílice. El material se eluye con un gradiente de hexanos y acetato de etilo para obtener 0.511 g de los productos finales. Dos picos se identifican en el CL/EM. La mezcla se usa "como es" en la siguiente reacción. EM (APCI): 246 (M+1).

C. 3-yodo-2,6-dimetil-8-(1-propil-butil)-imidazo[1,2-b]piridazina.



Un matraz de fondo redondo de 50 mL se carga con 2,6-dimetil-8-(1-propil-butil)-imidazo[1,2-b]piridazina (0.51 g, 0.0021 moles) y acetonitrilo (3 mL). La mezcla

de reacción se coloca en un baño de hielo y NIS (0.468 g, 0.00208 moles) se agrega puro. La reacción se agita durante la noche y ls fusiones de baño de hielo. Al día siguiente, la mezcla de reacción se divide entre diclorometano y una solución acuosa saturada de $NaHCO_3$. La capa orgánica se recolecta y la capa acuosa se extrae dos veces más con diclorometano. Los extractos orgánicos se combinan, se lavan con salmuera, y se secan sobre Na_2SO_4. El solvente se evapora y el material crudo se purifica por medio de cromatografía en gel de sílice eluido con hexanos y luego una mezcla 25:75 de acetato de etilo y hexanos. Rendimiento = 0.435 g (56%). EM (APCI): 372 (M+1).

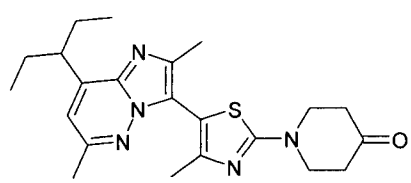
D. 3-(4-Cloro-2-morfolin-4-il-tiazol-5-il)-2,6-dimetil-8-(1-propil-butil)-imidazo[1,2-b]piridazina.

Un matraz de fondo redondo de 15 mL se carga con 3-yodo-2,6-dimetil-8-(1-propil-butil)-imidazo[1,2-b]piridazina (0.200 g, 0.000539 moles), 4-(4-cloro-tiazol-2-il)-morfolina (0.165 g, 0.000808 moles), Cs_2CO_3 (0.361 g, 0.00108 moles, 2.0 equiv), $Pd(dba)_2$ (0.0092 g, 0.0000161 moles, 0.03 equiv), PPh_3 (0.00847 gram, 0.000323 moles, 0.060 equiv) y DMF (2.0 mL). El nitrógeno se burbujea a través de la mezcla de reacción durante 15 minutos; luego, la mezcla de reacción se calienta a 130°C

durante la noche. Al día siguiente, la mezcla de reacción se divide entre Et_2O y una solución saturada de NH_4Cl. La capa acuosa se extrae dos veces más con Et_2O. Los extractos orgánicos se combinan, se lavan 2-3 veces con H_2O, se lavan una vez con salmuera, y se secan sobre Na_2SO_4. Los solventes se evaporan in vacuo y la mezcla de reacción cruda se purifica por medio de cromatografía en gel de sílice. Rendimiento = 0.1737 g (72%). ^{1}H-RMN ($CDCl_3$), δ 0.87 (t, J = 7 Hz, 6H), 1.14- 1.37 (m, 4H), 1.74 (q, J = 8 Hz, 4H), 2.54 (s, 3H), 2.50 (s, 3H), 3.48 (m, 1H), 3.53 (t, J = 5 Hz, 4H), 3.83 (t, J = 5 Hz, 4H), 6.71(br s, 1H) ppm. CL/EM (m/z): calculado para $C_{22}H_{30}ClN_5OS$ $(M+H)^+$: 448; encontrado: 448.

Ejemplo 187.

Preparación de 1-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-piperidin-4-ona.



A. 8-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-1,4-dioxa-8-aza-spiro[4.5]decano.

100 mg de 3-(2-bromo-4-metil-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina(0.25 mmol), 182 mg de 4-piperidinatileno cetal (1.27 mmol) y 244 mg de Cs_2CO_3 (0.75 mmol) se colocaron en 4.0 ml de vial con 2.0 ml de THF. El vial se cierra con una tapa revestida de Teflon y se calienta a 110°C durante 3 días. La mezcla de reacción se concentra y se aplica sobre una columna de cromatografía de gel de sílice (Hexano:AcOEt=3:1) para dar 116 mg del compuesto del título. Rendimiento 100%. espectro de masas(m/e): 456(M+1). ^1H RMN ($CDCl_3$): δ 6.69 (s, 1H), 4.05 (s, 4H), 3.70 (t, J = 6.2 Hz, 4H), 3.35 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.18 (s, 3H), 1.90-1.78 (m, 8H), 0.90 (t, J = 7.2 Hz, 6H).

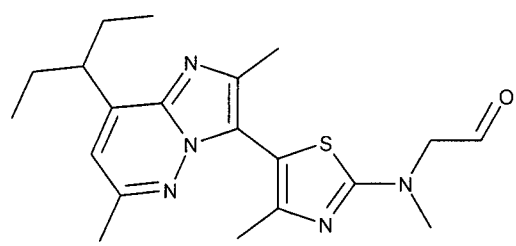
B. 1-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-piperidin-4-ona.

70 mg de 8-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-1,4-dioxa-8-aza-spiro[4.5]decano (0.15 mmol) se disuelve en 10.ml de HCl concentrado y se agita a temperatura ambiente durante 2 h. La mezcla de reacción se neutraliza con $NaHCO_3$ saturado, se extrae con CH2Cl2, se seca sobre Na2SO4 y se evapora. El producto crudo se aplica encima de una columna de cromatografía de gel de sílice (Hexano:AcOEt=2:1) para dar 33.2 mg del compuesto del título. Rendimiento 52%. Espectro

de masas(m/e): 412(M+1). ^{1}H RMN ($CDCl_3$): δ 6.70 (s, 1H), 3.94 (t, J = 6.2 Hz, 4H), 3.35 (m, 1H), 2.67 (t, J = 6.5 Hz, 4H), 2.57 (s, 3H), 2.47 (s, 3H), 2.21 (s, 3H), 1.86 (m, 4H), 0.91 (t, J = 7.1 Hz, 6H).

Ejemplo 188.

Preparación de ({5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-metil-amino)-acetaldehído.

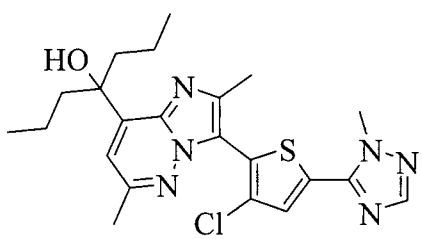


85 mg de N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-N-{[1,3]dioxolan-2-ilmetil-metilamina (0.2 mmol) se disuelve en 2 ml de HCl concentrado y se agita a 50°C durante 30 min. La mezcla se enfría hasta temperatura ambiente y se neutraliza con NaHCO3 saturado. La mezcla se extrae con CH2Cl2, se seca sobre Na2SO4 y se evapora. El producto crudo se aplica encima de una columna de cromatografía de gel de sílice (CH2Cl2:MeOH=20:1) para dar 73.4 mg del compuesto del título. Rendimiento 76%. Espectro de masas(m/e): 386(M+1). 9.79 (s, 1H), 6.72 (s,

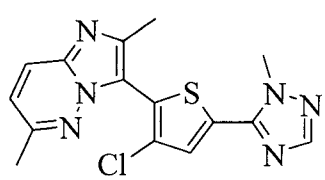
1H), 4.39 (s, 2H), 3.36 (m, 1H), 3.22 (s, 3H), 2.57 (s, 3H), 2.47 (s, 3H), 2.20 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H).

Ejemplo 189.

Preparación de 4-{3-[3-cloro-5-(2-metil-2H-[1,2,4]triazol-3-il)-tiofen-2-il]-2,6-dimetil-imidazo[1,2-b]piridazin-8-il}-heptan-4-ol.



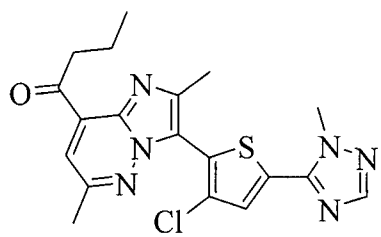
A. 3-[3-cloro-5-(2-metil-2H-[1,2,4]triazol-3-il)-tiofen-2-il]-2,6-dimetil-imidazo[1,2-b]piridazina.



Una solución de 2,6-dimetil-imidazo[1,2-b]piridazina (0.32 g, 2.17 mmol), 5-(5-bromo-4-cloro-tiofen-2-il)-1-metil-1H-[1,2,4]triazol (0.72 g, 2.61 mmol), Cs_2CO_3 (1.49 g, 4.57 mmol) y DMF (6 mL) se desgasifica durante 15 minutos con N_2. $Pd(OAc)_2$ (0.024 g, 0.11 mmol) y PPh_3 (0.057 g, 0.22 mmol) se agregaron y la solución se calienta a 135°C durante 4 horas. La solución se diluye con CH_2Cl_2 (50

mL), se lava con NH_4Cl saturado (2 x 50 mL), agua (50 mL), se filtra y se concentra. El residuo se purifica por cromatografía instantánea ISCO (30%-100% gradiente EtOAc) resulta el compuesto del título (0.29 g, 0.84 mmol, 39%). ^1H RMN ($CDCl_3$) δ 2.49 (s, 3H), 2.50 (s, 3H), 4.10 (s, 3H), 6.92 (d, J = 9.2 Hz, 1H), 7.44 (s, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.85 (s, 1H). CL/EM (m/z): calculado para $C_{15}H_{13}ClN_6S$ $(M+H)^+$: 345.1; encontrado: 345.2.

B. 1-{3-[3-Cloro-5-(2-metil-2H-[1,2,4]triazol-3-il)-tiofen-2-il]-2,6-dimetil-imidazo[1,2-b]piridazin-8-il}-butan-1-ona.



Una solución de 3-[3-cloro-5-(2-metil-2H-[1,2,4]triazol-3-il)-tiofen-2-il]-2,6-dimetil-imidazo[1,2-b]piridazina (0.20 g, 0.58 mmol), N-metoxi-N-metil-butilamida (Wolberg, M. et. al. Chem. Europ. J. 2001, 7, 4562.) (0.084 g, 0.64 mmol) en THF (3 mL) se enfría hasta a -78°C, y una solución 2.0 M de LDA en heptano/ THF/ benceno de etilo (0.58 mL, 1.16 mmol) se agrega. La solución se entibia hasta temperatura ambiente, se diluye con diclorometano (20 mL), y se lava con una solución

NH_4Cl saturada (15 mL). La capa orgánica se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía instantánea ISCO (20%-100% gradiente EtOAc) para resultar el compuesto del título (0.11 g, 0.27 mmol, 46%). ^{1}H-RMN ($CDCl_3$), δ 1.04 (t, J = 7.0 Hz, 3H), 1.76-1.86 (m, 2H), 2.56 (s, 3H), 2.59 (s, 3H), 3.51 (t, J = 7.1 Hz, 2H), 4.15 (s, 3H), 7.36 (s, 1H), 7.49 (s, 1H), 7.90 (s, 1H) ppm. CL/EM (m/z): calculado para $C_{19}H_{19}ClN_6OS$ $(M+H)^+$: 415.1; encontrado: 415.3.

C. 4-{3-[3-Cloro-5-(2-metil-2H-[1,2,4]triazol-3-il)-tiofen-2-il]-2,6-dimetil-imidazo[1,2-b]piridazin-8-il}-heptan-4-ol.

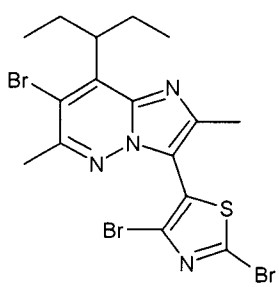
Una solución de 1-{3-[3-cloro-5-(2-metil-2H-[1,2,4]triazol-3-il)-tiofen-2-il]-2,6-dimetil-imidazo[1,2-b]piridazin-8-il}-butan-1-ona (0.15 g, 0.36 mmol) y THF (5 mL) se enfría hasta 0°C, y una solución 2.0 M de bromuro propil magnesio en dietiléter (0.22 mL, 0.43 mmol) se agrega. La reacción se entibia hasta temperatura ambiente, se diluye con acetato de etilo (30 mL), y se lava con una solución NH_4Cl saturada (30 mL). La capa orgánica se seca sobre $MgSO_4$, se filtra, y se concentra. El residuo se purifica por cromatografía instantánea ISCO (20%-40% gradiente EtOAc) para resultar el compuesto del título (0.016 g, 0.017 mmol, 47%). ^{1}H-RMN ($CDCl_3$), δ 0.90 (t, J = 7.4 Hz, 6H), 1.12-1.29 (m, 2H), 1.37-1.54 (m, 2H), 1.86-

2688

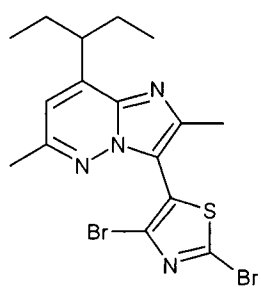
2.04 (m, 4H), 2.50 (s, 3H), 2.54 (s, 3H), 4.15 (s, 3H), 6.11 (bs, 1H), 6.73 (s, 1H), 7.48 (s, 1H), 7.90 (s, 1H) ppm. CL/EM (m/z): calculado para $C_{22}H_{27}ClN_6OS$ $(M+H)^+$: 459.2; encontrado: 459.3.

Ejemplo 190, 191, y 192.

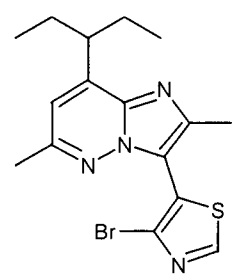
Preparación de 7-bromo-3-(2,4-dibromo-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina; 3-(2,4-dibromo-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina; y 3-(4-bromo-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



190.



191.



192.

A. 8-(1-etil-propil)-2,6-dimetil-3-tiazol-5-il-imidazo[1,2-b]piridazina.

2.41 g (7 mmol) de 8-(1-etil-propil)-3-yodo-2,6-dimetil-imidazo[1,2-b]piridazina, 3.00 g de tiazol (35.2 mmol), 378 mg de trifenilfosfina (1.44 mmol) y 4.71 g de Cs2CO3 (14.5 mmol) se combinan con 25 ml de DMF y gas de N2 gas se burbujea en durante 30 min. 330 mg de Pd2dba3 (0.36 mmol) se

agrega y el tubo se sella. La reacción tube se calienta a 130°C durante la noche. A la mezcla de reacción se agrega agua y CH2Cl2, y la capa CH2Cl2 se separa, se lava con NaCl saturado y se seca sobre Na2SO4. Los solventes se remueven in vauo y el producto crudo se aplica encima de una columna de cromatografía de gel de sílice (Hexano : AcOEt = 3:1) para dar 1.48 g del compuesto del título. Rendimiento 70%. espectro de masas(m/e): 301(M+1); ^{1}H-RMN(CDCl3): 8.93(s, 1H), 8.52(s, 1H), 6.78(s, 1H), 3.35(m, 1H), 2.76(s, 3H), 2.66(s, 3H), 1.86(m, 4H), 0.89(t, 6H, J=7.5Hz).

B. 7-bromo-3-(2,4-dibromo-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina; 3-(2,4-dibromo-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina; y 3-(4-bromo-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

1.05 g (3.5 mmol) de 8-(1-Etil-propil)-2,6-dimetil-3-tiazol-5-il-imidazo[1,2-b]piridazina y 1.56 g de NBS (8.75 mmol) se disuelven en 50 ml de CH2Cl2 y se agita a temperatura ambiente durante 3 días. La mezcla de reacción se diluye con CH2Cl2 y se lava con $Na_2S_2O_3$ saturado y NaCl saturado. La capa orgánica separada se seca sobre Na_2SO_4 y se evapora. La mezcla de reacción se aplica encima de una columna de cromatografía de gel de sílice (Hexano : AcOEt = 20:1→8:1) para dar tres productos:

149 mg de 7-bromo-3-(2,4-dibromo-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (9%);

936 mg de 3-(2,4-dibromo-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (58%); y

77 mg de 3-(4-bromo-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (6%).

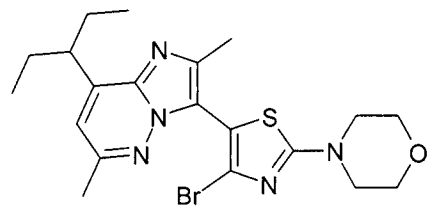
7-Bromo-3-(2,4-dibromo-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina espectro de masas(m/e): 538(M+1); ^{1}H-RMN($CDCl_3$): 3.45(m, 1H), 2.71(s, 3H), 2.52(s, 3H), 2.38(m, 2H), 2.02(m, 2H), 0.88(t, 6H, J=7.5Hz);

3-(2,4-Dibromo-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina espectro de masas(m/e): 459(M+1); ^{1}H-RMN(CDCl3): 6.79(s, 1H), 5.33(m, 1H), 2.57(s, 3H), 2.55(s, 3H), 1.87(m, 4H), 0.90(t, 6H, J=7.5Hz); y

3-(4-Bromo-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina espectro de masas(m/e): 380(M+1); ^{1}H-RMN(CDCl3): 9.01(s, 1H), 6.77(s, 1H), 3.35(m, 1H), 2.55(s, 3H), 2.54(s, 3H), 1.87(m, 4H), 0.91(t, 6H, J=7.5Hz).

Ejemplo 193.

Preparación de 3-(4-Bromo-2-morfolin-4-il-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



100 mg (0.22 mmol) de 3-(2,4-Dibromo-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.22 mmol), 96 mg de morfolina (1.1 mmol) y 215 mg de Cs2CO3 (0.66 mmol) se colocan en un vial de 4 ml con THF seco, y el vial se cierra con una tapa de Teflon. El vial se calienta a 120°C durante la noche. La mezcla de reacción se aplica encima de una columna de cromatografía de gel de sílice (Hexano:AcOEt:2 M NH3 en MeOH = 9:3:1) para dar 72.7 mg del compuesto del título. Rendimiento 71%. Espectro de masas(m/e): 465(M+1); ^{1}H-RMN(CDCl3): 6.73(s, 1H), 3.87(t, 4H, J=5.1Hz), 3.58(t, 4H, J=5.1Hz), 3.35(m, 1H), 2.57(s, 3H), 2.53(s, 3H), 1.86(m, 4H), 0.90(t, 6H, J=7.5Hz).

Los siguientes compuestos se preparan esencialmente como se describen en el ejemplo 193. Los ejemplos 194-197 usan 3-(2,4-dibromo-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.22 mmol) y la amina nombrada. El ejemplo 198. usa 7-bromo-3-(2,4-dibromo-tiazol-5-il)-8-(1-

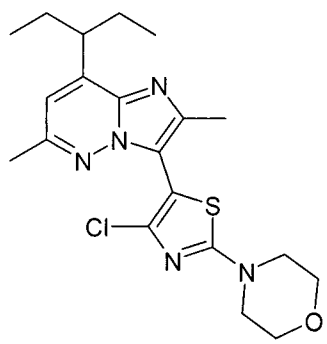
etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina y la amina nombrada:

Ej	Nombre	Amina	^{1}H RMN ($CDCl_3$): δ	EM (encontrado) (M+1)
194	N-{4-Bromo-5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-metil-amina	Metil-amina	6.75 (s, 1H), 5.85 (s, NH), 3.37 (m, 1H), 3.07 (d, J = 5.3 Hz, 3H), 2.59 (s, 3H), 2.55 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.2 Hz, 6H).	409
195	N-{4-Bromo-5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-dimetilamina	Dimetil-amina	6.72 (s, 1H), 3.36 (m, 1H), 3.19 (s, 6H), 2.57 (s, 3H), 2.52 (s, 3H), 1.85 (m, 4H), 0.90 (t, 6H, J=7.3Hz)	423

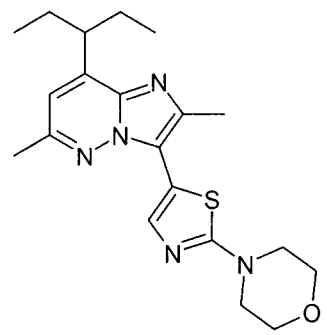
196	N-{4-Bromo-5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-N-(2-metoxi-etil)-metilamina	N-2-metoxi-etil-metil-amina	6.71 (s, 1H), 3.76 (m, 2H), 3.71 (m, 2H), 3.42 (s, 3H), 3.35 (s, 1H), 3.21 (s, 3H), 2.57(s, 3H), 2.53 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H).	467
197	N-{4-Bromo-5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-N-metil-i-propil-amina	N-metil-i-propil-amina	6.72 (s, 1H), 4.43 (m, 1H), 3.36 (m, 1H), 3.0 (s, 3H), 2.57 (s, 3H), 2.54 (s, 3H), 1.86 (m, 4H), 1.31 (s, 3H), 1.29 (s, 3H), 0.90 (t, J = 7.4 Hz, 6H).	451
198	N-{5-[7-bromo-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-bromo-tiazol-2-il}-morfolina	Morfolina	3.87 (t, J = 4.5 Hz, 4H), 3.58 (t, J = 7.8 Hz, 4H), 3.43 (m, 1H), 2.71(s, 3H), 2.50 (s, 3H), 2.38 (m, 2H), 2.01 (m, 2H), 0.88 (t, J = 7.5 Hz, 6H).	544

Ejemplo 199 y 200.

Preparación de N-{4-cloro-5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-morfolina y N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-morfolina.



199.



200.

Método A

40 mg de 3-(4-Bromo-2-morfolin-4-il-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina y 25 mg de CuCl (0.25 mmol) se colocan en un vial de 4 ml con 2 ml de DMF seco y se tapa con una tapa de Teflon. El vial se calienta a 120°C durante la noche. La mezcla de reacción se filtra, se lava con CH2Cl2 y el producto filtrado se concentra. La mezcla del producto crudo se aplica encima de una columna de cromatografía de gel de sílice (Hexano : AcOEt = 2:1 y Hexano : AcOEt = 8:1) para dar dos productos:

4.2 mg de N-{4-cloro-5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-morfolina (12%), y

7.2 mg de N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-morfolina (22%).

N-{4-Cloro-5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-morfolina espectro de masas(m/e): 420(M+1); ^{1}H-RMN(CDCl3): 6.73(s, 1H), 3.88(t, 4H, J=5.0 Hz), 3.57(t, 4H, J=5.0Hz), 3.35(m, 1H), 2.57(s, 3H), 2.52(s, 3H), 1.85(m, 4H), 0.90(t, 6H, J=7.5Hz.

N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-morfolina espectro de masas(m/e): 386(M+1); ^{1}H-RMN(CDCl3): 7.75(s, 1H), 6.70(s, 1H), 3.91(t, 4H, J=5.0Hz), 3.61(t, 4H, J=5.0Hz), 3.34(m, 1H), 2.67(s, 3H), 2.61(s, 3H), 1.85(m, 4H), 0.88(t, 6H, J=7.5Hz).

Método B N-{4-Cloro-5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-morfolina.

Un matraz de reactor de 20L bajo nitrógeno se carga con 2900 ml de DMF seco y desgasificado luego con 8-(1-etil-propil)-3-yodo-2,6-dimetil-imidazo[1,2-b]piridazina (287 g, 0.836 mol), 2-morfolino-4-clorotiazol (205.4 g, 1.01 mol, 1.2 equv.), $Pd(OAc)_2$ (3.74 g, 7.91 mmol, 0.01 equiv.), trifenilfosfina (8.77g, 33.1 mmol, 0.04 equiv.), yoduro de cobre (8 g, 41.59 mmol, 0.05 equiv.) y carbonato de cesio (544.9 g, 1.65 mol). La mezcla de reacción se calienta a 120°C. Después de 16 h a 120°C, 1.87 g de $Pd(OAc)_2$ y 4.38 g más de trifenilfosfina se agrega. Después de 1 h, la mezcla

se enfría, se apaga con solución NH_4Cl (4300 mL) y se extrajo con MTBE (2900 mL), la fase acuosa se extrae dos veces más con 2000 ml de MTBE. Las fases orgánicas se lavan con NaCl acuoso saturado (2000 mL), luego se tratan con carbón mineral 72 g en una botella de matraz y se filtra en Celite®. El producto filtrado se concentra bajo vacío para proporcionar 373.8 g (79.3%) del compuesto del título el cual es 81.4% de área análisis CLAR el resto son solvente y con Ejemplo 200 no detectable por producto.

Los siguientes compuestos del título se preparan esencialmente como se describe en los ejemplos 199 y 200 Método A:

Ejemplo #	Nombre	Material de partida	^{1}H RMN ($CDCl_3$): δ	EM (encontrado) (M+1)
201	N-{4-Cloro-5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-dimetilamina	N-{4-Bromo-5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-dimetilamina	6.72 (s, 1H), 3.36 (m, 1H), 3.19 (s, 6H), 2.57 (s, 3H), 2.51 (s, 3H), 1.84 (m, 4H), 0.90 (t, J = 7.5 Hz, 6H).	378

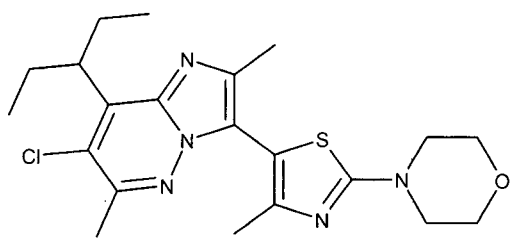
202	N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-dimetil-amina	N-{4-Bromo-5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-dimetilamina	7.74 (s, 1H), 6.67 (s, 1H), 3.35 (m, 1H), 2.23 (s, 6H), 2.67(s, 3H), 2.61 (s, 3H), 1.84 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H).	344
203	N-{4-Cloro-5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-N-(2-metoxi-etil)-metilamina	N-{4-Bromo-5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-N-(2-metoxi-etil)-metilamina	6.71 (s, 1H), 3.76 (t, J = 5.3 Hz, 2H), 3.71 (t, J = 5.1 Hz, 2H), 3.42 (s, 3H), 3.36 (m, 1H), 3.20 (s, 3H), 2.58 (s, 3H), 2.52 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.1 Hz, 6H).	423

204	N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-N-(2-metoxi-etil)-metilamina	N-{4-Bromo-5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-N-(2-metoxi-etil)-metilamina	7.72 (s, 1H), 6.68 (s, 1H), 3.80 (t, J = 5.7 Hz, 2H), 3.72 (t, J = 5.7 Hz, 2H), 3.42 (s, 3H), 3.35 (m, 1H), 3.26 (s, 3H), 2.67 (s, 3H), 2.61 (s, 3H), 1.84 (m, 4H), 0.88 (t, J = 7.7 Hz, 6H).	388
205	N-{4-Cloro-5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-N-metil-i-propil-amina	N-{4-Bromo-5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-N-metil-i-propil-amina	6.71 (s, 1H), 4.48 (m, J = 7.4, 13.2 Hz, 1H), 3.34 (m, J = 7.6, 14.4 Hz, 1H), 3.04 (s, 3H), 2.76 (s, 3H), 2.61 (s, 3H), 1.85 (m, 4H), 1.31 (d, J = 7.1 Hz, 6H), 0.88 (t, J = 7.3 Hz, 6H).	407

206	N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-N-metil-isopropil-amina	N-{4-Bromo-5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-N-metil-i-propil-amina	7.72 (s, 1H), 6.67 (s, 1H), 4.48 (m, 1H), 3.33 (m, 1H), 3.03 (s, 3H), 2.66 (s, 3H), 2.60 (s, 3H), 1.84 (m, 4H), 1.31 (d, J = 6.8, 6H), 0.88 (t, J = 7.2 Hz, 6H).	371

Ejemplo 207.

Preparación de N-{5-[7-cloro-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-morfolina.

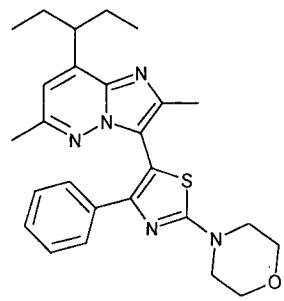


50 mg de N-{5-[7-Bromo-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-morfolina (0.1 mmol) se disuelve en 2.0 ml de DMF seco y 31 mg de CuCl (0.3 mmol) se agrega. El vial se cierra con una

microondas a 210°C durante 30 min. La mezcla de reacción se aplica encima de una columna de cromatografía de gel de sílice (Hexano:AcOEt=3:1 y CH3CN:CH2Cl2:Hexano = 5:45:50) para dar 64.3 mg del compuesto del título. Rendimiento 38%. espectro de masas(m/e): 454(M+1). ^{1}H RMN ($CDCl_3$): δ 6.72 (s, 1H), 3.88 (m, 4H), 3.60 (m, 4H), 3.32 (m, 1H), 2.54 (s, 3H), 2.47 (s, 3H), 1.85 (m, 4H), 0.89 (t, J = 7.0 Hz, 6H).

Ejemplo 210.

Preparación de N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-fenil-tiazol-2-il}-morfolina.

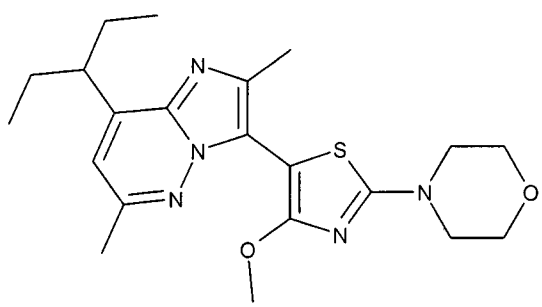


50 mg de 3-(4-Bromo-2-morfolin-4-il-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.11 mmol), 40 mg de ácido fenilborónico (0.33 mmol) y 0.27 ml de 2 M Na2CO3 acuoso (0.55 mmol) se colocan en 2.5 ml de DME / agua/EtOH = 7 / 3 / 1. El gas de N2 se burbujea en la mezcla durante 20 min y 20 mg de Pd(PPh3)4 (0.017 mmol) se agrega. El vial se sella y se calienta a 160°C durante 30 min en Microondas. La mezcla de reacción

se agregan CH2Cl2 y agua y la capa orgánica se sepan, se lava con salmuera, se secan sobre Na2SO4 y se evaporan. El producto crudo se aplica encima de una columna de cromatografía de gel de sílice (Hexano : AcOEt = 10:1) para dar 27 mg del compuesto del título. Rendimiento 54% espectro de masas(m/e): 462(M+1). δ 8.29(m, 1H), 7.60(m, 2H), 7.44(m, 1H), 7.22(m, 1H), 6.70 (s, 1H), 3.90 (t, J = 4.6 Hz, 4H), 3.64 (t, J = 5.0 Hz, 4H), 3.36 (m, 1H), 2.52 (s, 3H), 2.09 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.4 Hz, 6H).

Ejemplo 211.

Preparación de N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metoxi-tiazol-2-il}-morfolina.

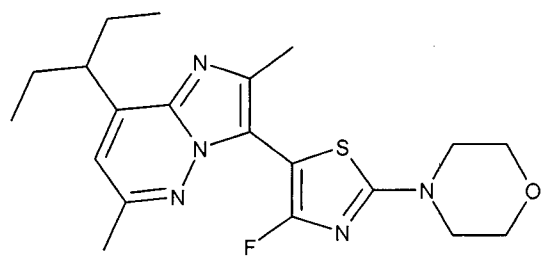


100 mg de 3-(4-Bromo-2-morfolin-4-il-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.22 mmol), 24 mg de metóxido de sodio (0.44 mmol) y 21 mg de CuI (0.11 mmol) se colocan en un vial 4 ml con MeOH 3 ml y se tapa con una tapa revestida de Teflon. El vial de reacción se

calienta a 130°C durante la noche. La mezcla de reacción se concentra y se aplica sobre una columna de cromatografía de gel de sílice (Hexano : THF = 10 : 1) para dar 32.8 mg del compuesto del título. Rendimiento 36%. Espectro de masas(m/e): 416(M+1). ^{1}H RMN ($CDCl_3$): δ 6.64 (s, 1H), 3.96 (s, 3H), 3.86 (t, J = 4.7 Hz, 4H), 3.53 (m, 4H), 3.34 (m, 1H), 2.82 (s, 3H), 2.48 (s, 3H), 1.82 (m, 4H), 0.85 (t, J = 7.4 Hz, 6H).

Ejemplo 212.

Preparación de N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-fluoro-tiazol-2-il}-morfolina.

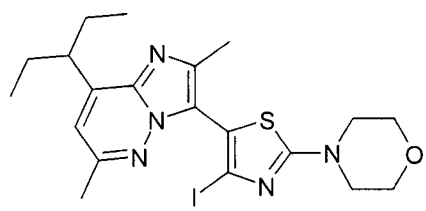


50 mg de 3-(4-Bromo-2-morfolin-4-il-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.11 mmol) se disuelve en 4 ml de dietiléter y se enfría hasta -78°C y 0.1 ml de n-BuLi 1.6M en hexano (0.16 mmol) se agrega a -78°C y se agita a -78°C durante 20 min. 104 mg de sulfonimida N-fluorobenceno (0.33 mmol) en 2 ml de tolueno se agrega a -78°C y se agita a temperatura

ambiente durante 1h. NH4Cl saturado se agrega, y la mezcla se extrae con Et2O, se seca sobre Na2SO4 y se evapora. El producto crudo se aplica encima de una columna de cromatografía de gel de sílice (Hexano:AcOEt=3:1) para dar 4.1 mg del compuesto del título. Rendimiento 10%. Espectro de masas(m/e): 404 (M+1). 6.71 (s, 1H), 3.87 (t, J = 4.6 Hz, 4H), 3.55 (t, J = 5.0 Hz, 4H), 3.34 (m, 1H), 2.58 (s, 3H), 2.54 (s, 3H), 1.84 (m, 4H), 0.88 (t, J = 7.4 Hz, 6H).

Ejemplo 213.

Preparación de N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-yodo-tiazol-2-il}-morfolina.

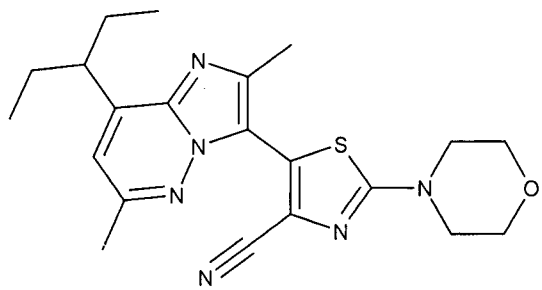


50 mg de 3-(4-Bromo-2-morfolin-4-il-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.11 mmol), 30 mg de CF_3CO_2Na (0.22 mmol) y 42 mg de CuI (0.22 mmol) se colocan en un vial de 4 ml con DMF / tolueno = 2:1. El vial se cierra con una tapa de Teflon y se calienta a 150°C durante la noche. La mezcla de reacción se aplica encima de una columna de

cromatografía de gel de sílice (Hexano:AcOEt = 5:1) para dar 54 mg del compuesto del título. 96%. Espectro de masas(m/e): 512 (M+1). ^{1}H RMN ($CDCl_3$): δ 6.71 (s, 1H), 3.87 (t, J = 5.4 Hz, 4H), 3.58 (t, J = 5.4 Hz, 4H), 3.36 (m, 1H), 2.57 (s, 3H), 2.53 (s, 3H), 1.85 (m, 4H), 0.91 (t, J = 5.4 Hz, 6H).

Ejemplo 214.

Preparación de 5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-2-morfolin-4-il-tiazol-4-carbonitrilo

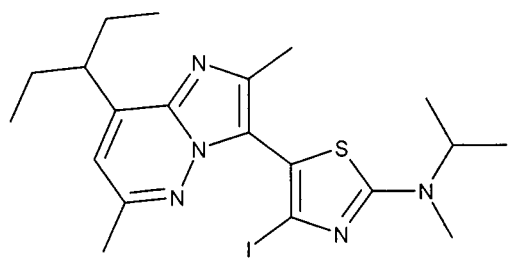


50 mg de 3-(4-Bromo-2-morfolin-4-il-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.11 mmol), y 30 mg de CuCN (0.33 mmol) se colocan en un vial de 4 ml con 2 ml de DMF y el vial se cierra con una tapa de Teflon. El vial se calienta a 150°C durante la noche. La mezcla de reacción se aplica encima de una columna de cromatografía de gel de sílice (Hexano:AcOEt=5:1) para dar 12.3 mg del compuesto del título. Rendimiento 28%. Espectro de masas(m/e): 411(M+1). 6.77 (s, 1H), 3.89 (t, J

= 4.8 Hz, 4H), 3.61 (t, J = 5.0 Hz, 4H), 3.32 (m, 1H), 2.62 (s, 3H), 2.59 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.4 Hz, 6H).

Ejemplo 215.

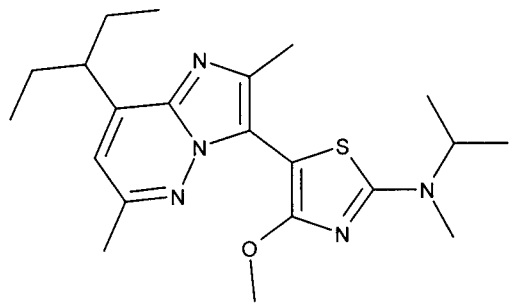
Preparación de N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-yodo-tiazol-2-il}-N-isopropil-metilamina.



El compuesto del título se prepara esencialmente como se describe en el Ejemplo 213, empleando N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-bromo-tiazol-2-il}-N-isopropil-metilamina para dar 17.9 mg. Rendimiento 22%: espectro de masas(m/e):498 (M+1). ^{1}H RMN ($CDCl_3$): δ 6.71 (s, 1H), 4.41 (m, 1H), 3.35 (m, 1H), 2.97 (s, 3H), 2.57 (s, 3H), 2.53 (s, 3H), 1.84 (m, 4H), 1.29 (d, J = 5.8 Hz, 6H), 0.90 (t, J = 7.2 Hz, 6H).

Ejemplo 216.

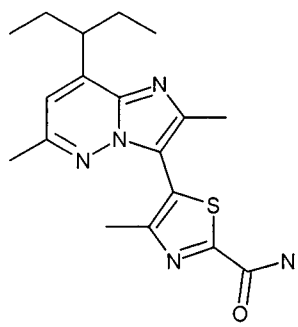
Preparación de N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metoxi-tiazol-2-il}-N-isopropil-metilamina.



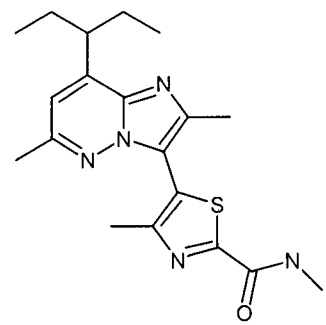
El compuesto del título se prepara esencialmente como se describe en el Ejemplo 211, empleando N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-bromo-tiazol-2-il}-N-isopropil-metilamina para dar 52.7. Rendimiento 36%: espectro de masas(m/e):402(M+1). ^{1}H RMN ($CDCl_3$): δ 6.63 (s, 1H), 4.44 (m, 1H), 3.96 (s, 3H), 3.35 (m, 1H), 2.97 (s, 3H), 2.57 (s, 3H), 2.50 (s, 3H), 1.83 (m, 4H), 1.29 (d, J = 6.7 Hz, 6H), 0.88 (t, J = 8 Hz, 6H).

Ejemplo 217 y 218.

Preparación de amida del ácido 5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-carboxílico y N-metilamida del ácido 5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-carboxílico.



217.



218.

180 mg de 8-(1-Etil-propil)-3-[2-bromo-4-metil-5-tiazolil]-2,6-dimetil-imidazo[1,2-b]piridazina (0.46 mmol) y 124 mg de cianuro de cobre (I) se colocan en un vial de 4 ml con 2 ml de DMF seco. El vial se cierra con una tapa de Teflon y se calienta a 130°C durante la noche. La mezcla de reacción cruda se aplica encima de una columna de cromatografía de gel de sílice (Hexano : AcOEt = 1:1 → 1:3) para dar

52.1 mg de amida del ácido 5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-carboxílico (32%) y

7.6 mg de metilamida del ácido 5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-carboxílico.

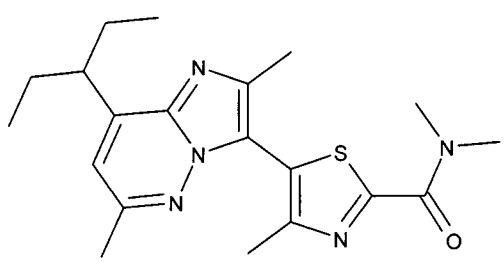
Amida del ácido 5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-carboxílico: espectro de masas(m/e): 358(M+1) ^{1}H RMN ($CDCl_3$): δ 7.21 (s, NH), 6.76 (s, 1H), 5.59 (s, NH), 3.34 (m, 1H), 2.55 (s, 3H),

2.50 (s, 3H), 2.42 (s, 3H), 1.87 (m, 4H), 0.91 (t, J = 7.2 Hz, 6H). y

Metilamida del ácido 5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-carboxílico: espectro de masas(m/e): 372(M+1). ^{1}H RMN ($CDCl_3$): 8.77 (s, NH), 6.75 (s, 1H), 4.06 (s, 3H), 3.35 (m, 1H), 2.55 (s, 3H), 2.49 (s, 3H), 2.43 (s, 3H), 1.87 (m, 4H), 0.91 (t, J = 7.6 Hz, 6H).

Ejemplo 219.

Preparación de dimetilamida del ácido 5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-carboxílico.

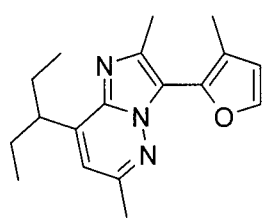


Amida del ácido 5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-carboxílico (46 mg, 0.13 mmol) y 28 mg de tert-butóxido de sodio (0.30 mmol) se colocan en 4 ml de DMSO seco y se agita attemperatura ambiente durante 5 min. 141 mg de yodometano (1.0 mmol) se agrega y se agita a temperatura ambiente durante 1 h. Se agrega agua, y la mezcla se extrae con CH_2Cl_2,

se seca sobre Na_2SO_4 y se evapora. El producto crudo se aplica encima de una columna de cromatografía de gel de sílice (Hexano:AcOEt=3:1) para dar 22.3 mg del compuesto del título. Rendimiento 45%: espectro de masas(m/e):386(M+1). 6.75 (s, 1H), 3.70 (s, 3H), 3.35 (m, 1H), 3.21 (s, 3H), 2.55 (s, 3H), 2.50 (s, 3H), 2.41 (s, 3H), 1.86 (m, 4H), 0.91 (t, J = 7.4 Hz, 6H).

Ejemplo 220.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(3-metil-furan-2-il)-imidazo[1,2-b]piridazina.

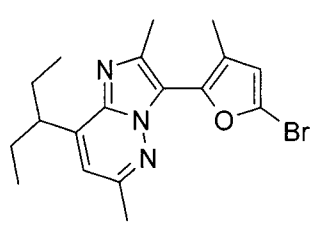


Una solución de THF (5 mL) de 3-metilfurano (Acros, 232 mg, 2.83 mmol) se enfría hasta -78°C bajo N_2 luego se trata con nBuLi (1.6 M en hexano, 1.8 mL, 2.9 mmol). Después de la adición de nBuLi, la solución se entibia hasta 0°C durante 15 minutos, luego hasta temperatura ambiente durante unos 5 minutos adicionales. La mezcla de reacción luego se enfría hasta -78°C y se trata con $ZnCl_2$ (Aldrich, 0.5 M en THF, 5.8 mL, 2.9 mmol). La mezcla resultante se entibia hasta temperatura ambiente y se trata con 8-(1-etil-propil)-3-yodo-2,6-dimetil-imidazo[1,2-b]piridazina (400 mg, 1.17 mmol) y

complejo $PdCl_2(dppf)$-CH_2Cl_2 (Aldrich, 95 mg, 0.12 mmol). La mezcla se calienta hasta 60°C durante 4 horas, luego se vacía en 1 N HCl (60 mL) y se extrae con acetato de etilo (2x60 mL). Los extractos orgánicos combinados se lavan con salmuera acuosa, se secan sobre Na_2SO_4, se filtran, y se concentran. El residuo crudo se purifica por cromatografía al usar el hexano-acetato de etilo (100% hexano hasta 20% acetato de etilo en hexano) para eluir el compuesto del título como un aceite piridazina (149 mg, 43% de rendimiento). ES-EM (m/z): calculado para $C_{18}H_{23}N_3O$: 297.2; encontrado 298.5 (M+H); ^1H RMN (400 mHz, $CDCl_3$): δ 7.59 (d, J = 1.8 Hz, 1H), 6.71 (s, 1H), 6.47 (d, J = 1.8 Hz, 1H), 3.36 (m, 1H), 2.55 (s, 3H), 2.50 (s, 3H), 2.10 (s, 3H), 1.92-1.79 (m, 4H), 0.90 (t, J = 7.5 Hz, 6H).

Ejemplo 221.

Preparación de 3-(5-bromo-3-metil-furan-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

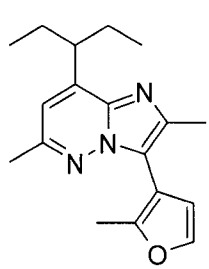


Una solución de CH_2Cl_2 (4 mL) de 8-(1-etil-propil)-2,6-dimetil-3-(3-metil-furan-2-il)-imidazo[1,2-b]piridazina (32.4 mg, 0.11 mmol) se enfría hasta 0°C

bajo un tubo de secado de $CaSO_4$ y se trata con NBS (20.1 mg, 0.11 mmol). Después de 15 minutos a 0°C, la mezcla se entibia hasta temperatura ambiente. Después de unos 10 minutos adicionales, la mezcla de reacción se vacía en H_2O (25 mL) y se extrae en CH_2Cl_2 (2x25 mL). Los extractos orgánicos combinados se lavan con salmuera acuosa, se secan sobre Na_2SO_4, se filtran, y se concentran. El producto crudo se purifica por cromatografía al usar el hexano-acetato de etilo (100% hexano hasta 10% acetato de etilo en hexano) para eluir el compuesto del título (26.3 mg, 64% de rendimiento) como un sólido. ES-EM (m/z): calculado para $C_{18}H_{22}BrN_3O$: 375.1; encontrado 376.2 (M+H); ^1H RMN (400 mHz, $CDCl_3$): δ 6.72 (s, 1H), 6.40 (s, 1H), 3.34 (m, 1H), 2.56 (s, 3H), 2.49 (s, 3H), 2.07 (s, 3H), 1.93-1.77 (m, 4H), 0.89 (t, J = 7.5 Hz, 6H).

Ejemplo 222.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(2-metil-furan-3-il)-imidazo[1,2-b]piridazina.



A. 3-Bromo-2-metil furano.

Una solución de THF (10 mL) de 2,3-dibromofurano (Lancaster, 5.54 gm, 24.5 mmol) bajo N_2 se trata con $PdCl_2(PPh_3)_2$ (860 mg, 1.2 mmol) y se agita durante 10 minutos a temperatura ambiente. La solución luego se trata con CH_3ZnCl (Aldrich, 2.0 M en THF, 15 mL, 30 mmol). La mezcla resultante se agita a temperatura ambiente durante la noche luego se vacía en 1 N HCl y se extrae en éter dietílico. El extracto orgánico se lava con NaCl saturado, se seca sobre Na_2SO_4, y se filtra. El producto filtrado luego se destila y el producto se recolecta a 120-125°C para dar el compuesto del título como un aceite incoloro (1.71 gm, 43% de rendimiento). ^1H RMN (400 mHz, $CDCl_3$): δ 7.25 (d, J = 1.8 Hz, 1H), 6.34 (d, J = 1.8 Hz, 1H), 2.28 (s, 3H).

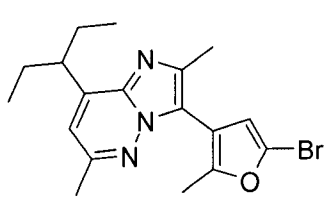
B. 8-(1-Etil-propil)-2,6-dimetil-3-(2-metil-furan-3-il)-imidazo[1,2-b]piridazina.

Una solución de THF (10 mL) de 3-bromo-2-metil furano (preparado como se describe arriba) (1.06 gm, 6.58 mmol) se enfría hasta -78°C bajo N_2 luego se trata con nBuLi (1.6 M en hexano, 4.1 mL, 6.6 mmol). Después de 10 minutos a -78°C, la mezcla se trata con $ZnCl_2$ (Aldrich, 0.5 M en THF, 13.2 mL, 6.6 mmol). La mezcla resultante se entibia hasta temperatura ambiente luego se trata con 8-(1-etil-propil)-

3-yodo-2,6-dimetil-imidazo[1,2-b]piridazina (1.13 gm, 3.29 mmol) y complejo $PdCl_2(dppf)-CH_2Cl_2$ (Aldrich, 257 mg, 0.31 mmol). La mezcla se calienta hasta 60°C durante 4 horas, luego se vacía en NH_4Cl saturado (50 mL) y se extrae con éter dietílico (2x50 mL). Los extractos orgánicos combinados se lavan con NaCl saturado, se secan sobre Na_2SO_4, se filtran, y se concentran. El producto crudo se purifica por cromatografía al usar el hexano-acetato de etilo (100% hexano hasta 20% acetato de etilo en hexano) para eluir el producto del título (685 mg, 70% de rendimiento) como un aceite. ES-EM (m/z): calculado para $C_{18}H_{23}N_3O$: 297.2; encontrado 298.2 (M+H); ^1H RMN (400 mHz, $CDCl_3$): δ 7.45 (d, J = 2.0 Hz, 1H), 6.63 (s, 1H), 6.60 (d, J = 2.0 Hz, 1H), 3.35-3.31 (m, 1H), 2.51 (s, 3H), 2.44 (s, 3H), 2.30 (s, 3H), 1.88-1.75 (m, 4H), 0.86 (t, J = 7.5 Hz, 6H).

Ejemplo 223.

Preparación de 3-(5-bromo-2-metil-furan-3-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



A. 3-Bromo-2-metil furano.

Una solución de THF (10 mL) de 2,3-dibromofurano (Lancaster, 5.54 gm, 24.5 mmol) bajo N_2 se trata con $PdCl_2(PPh_3)_2$ (860 mg, 1.2 mmol) y se agita durante 10 minutos a temperatura ambiente. La solución luego se trata con CH_3ZnCl (Aldrich, 2.0 M en THF, 15 mL, 30 mmol). La mezcla resultante se agita a temperatura ambiente durante la noche luego se vacía en 1 N HCl y se extrae en éter dietílico. El extracto orgánico se lava con NaCl saturado, se seca sobre Na_2SO_4, y se filtra. El producto filtrado luego se destila y el producto se recolecta a 120-125°C para dar el compuesto del título como un aceite incoloro (1.71 gm, 43% de rendimiento). ^1H RMN (400 mHz, $CDCl_3$): δ 7.25 (d, J = 1.8 Hz, 1H), 6.34 (d, J = 1.8 Hz, 1H), 2.28 (s, 3H).

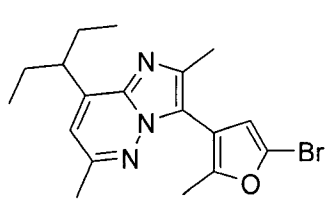
B. 8-(1-Etil-propil)-2,6-dimetil-3-(2-metil-furan-3-il)-imidazo[1,2-b]piridazina.

Una solución de THF (10 mL) de 3-bromo-2-metil furano (preparado como se describe arriba) (1.06 gm, 6.58 mmol) se enfría hasta -78°C bajo N_2 luego se trata con nBuLi (1.6 M en hexano, 4.1 mL, 6.6 mmol). Después de 10 minutos a -78°C, la mezcla se trata con $ZnCl_2$ (Aldrich, 0.5 M en THF, 13.2 mL, 6.6 mmol). La mezcla resultante se entibia hasta temperatura ambiente luego se trata con 8-(1-etil-propil)-

3-yodo-2,6-dimetil-imidazo[1,2-b]piridazina (1.13 gm, 3.29 mmol) y complejo $PdCl_2(dppf)-CH_2Cl_2$ (Aldrich, 257 mg, 0.31 mmol). La mezcla se calienta hasta 60°C durante 4 horas, luego se vacía en NH_4Cl saturado (50 mL) y se extrae con éter dietílico (2x50 mL). Los extractos orgánicos combinados se lavan con NaCl saturado, se secan sobre Na_2SO_4, se filtran, y se concentran. El producto crudo se purifica por cromatografía al usar el hexano-acetato de etilo (100% hexano hasta 20% acetato de etilo en hexano) para eluir el producto del título (685 mg, 70% de rendimiento) como un aceite. ES-EM (m/z): calculado para $C_{18}H_{23}N_3O$: 297.2; encontrado 298.2 (M+H); ^1H RMN (400 mHz, $CDCl_3$): δ 7.45 (d, J = 2.0 Hz, 1H), 6.63 (s, 1H), 6.60 (d, J = 2.0 Hz, 1H), 3.35-3.31 (m, 1H), 2.51 (s, 3H), 2.44 (s, 3H), 2.30 (s, 3H), 1.88-1.75 (m, 4H), 0.86 (t, J = 7.5 Hz, 6H).

Ejemplo 223.

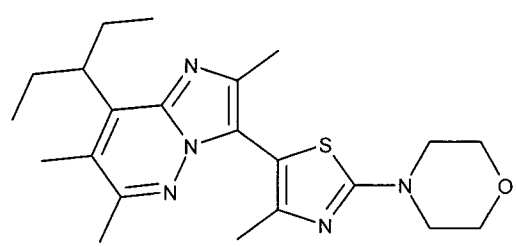
Preparación de 3-(5-bromo-2-metil-furan-3-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



tapa revestida de Teflon y se calienta a 120°C durante la noche. La mezcla de reacción se aplica encima de una columna de cromatografía de gel de sílice (Hexano:AcOEt=3:1) para dar 39.2 mg del compuesto del título. Rendimiento 87%. Espectro de masas(m/e): 435(M+1). 3.88 (t, J = 4.8 Hz, 4H), 3.57 (t, J = 5.1 Hz, 4H), 2.64(s, 3H), 2.44 (s, 3H), 2.18 (s, 3H), 2.00 (m, 4H), 0.88 (t, J = 7.4 Hz, 6H).

Ejemplo 208.

Preparación de N-{5-[7-bromo-8-(1-etil-propil)-2,6,7-trimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-morfolina.

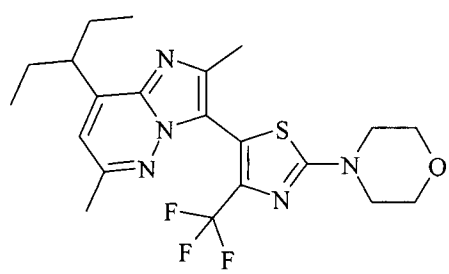


50 mg de N-{5-[7-Bromo-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-morfolina (0.1 mmol) se disuelve en 4 ml de Et2O y se enfría hasta -78°C. 0.09 ml de n-BuLi 1.6M en hexano (0.15 mmol) se agrega a -78°C y se agita a -78°C durante 20 min. 43 mg de yodometano (0.3 mmol) se agrega a la mezcla y se agita a -78°C y se permite volver a temperatura ambiente

durante la noche. La reacción se apaga con NH4Cl saturado y se extrae con Et2O. La capa orgánica separada se seca sobre Na2SO4 y se evapora. El producto crudo se aplica encima de una columna de cromatografía de gel de sílice (Hexano :AcOEt=3:1) para dar 29.6 mg del compuesto del título. Rendimiento 69%. Espectro de masas(m/e): 414(M+1). ^{1}H RMN ($CDCl_3$): δ 3.87 (t, J = 4.6 Hz, 4H), 3.56 (t, J = 4.6 Hz, 4H), 3.35 (m, 1H), 2.54 (s, 3H), 2.43 (s, 3H), 2.35 (s, 3H), 2.20 (s, 3H), 2.01 (m, 4H), 0.88 (m, 6H).

Ejemplo 209.

Preparación de N-{5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]- 4-trifluorometil-tiazol-2-il}-morfolina.

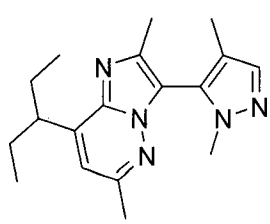


170 mg de 3-(4-Bromo-2-morfolin-4-il-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.37 mmol) y 100 mg de trifluoroacetato de sodio (0.74 mmol) se disuelven en 3 ml de DMF/tolueno = 2/1. El gas de N2 se bubujea en la mezcla durante 20 min y 141 mg de CuI (0.74 mmol) se agrega. El vial se sella y se calienta en el

Una solución CH_2Cl_2 (2 mL) de 8-(1-etil-propil)-2,6-dimetil-3-(2-metil-furan-3-il)-imidazo[1,2-b]piridazina (42.3 mg, 0.14 mmol) bajo un tubo de secado de $CaSO_4$ se trata con N-bromosuccinimida (27.6 mg, 0.16 mg). Después de 30 minutos la mezcla de reacción se vacía en H_2O (25 mL) y se extrae en CH_2Cl_2 (2x25 mL). Los extractos orgánicos combinados se lavan con NaCl saturado, se secan sobre Na_2SO_4, se filtran, y se concentran. El producto crudo se purifica por cromatografía al usar el hexano-acetato de etilo (100% hexano hasta 12% acetato de etilo en hexano) para eluir el producto del título (36.9 mg, 70% de rendimiento) como un sólido blanco. ES-EM (m/z): calculado para $C_{18}H_{22}BrN_3O$: 375.1; encontrado 376.3 (M+H); ^1H RMN (400 mHz, $CDCl_3$): δ 6.67 (s, 1H), 6.50 (s, 1H), 3.33 (m, 1H), 2.53 (s, 3H), 2.44 (s, 3H), 2.29 (s, 3H), 1.90-1.73 (m, 4H), 0.86 (t, J = 7.3 Hz, 6H).

Ejemplo 224.

Preparación de 3-(2,4-dimetil-2H-pirazol-3-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



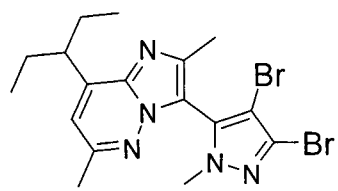
492

n-BuLi (1.3 ml, 2.09 mmol) se agita en THF (4 ml), bajo N_2, y se enfría hasta -72°C. 1,4-dimetil-1H-pirazol (170 mg, 2.04 mmol, en THF, 1 ml) se agrega lentamente, se agita durante 5 min. luego se permite calentar hasta temperatura ambiente y se agita durante 45 min. La mezcla se enfría hasta -72°C y una solución de cloruro de zinc (4.3 ml, 2.14 mmol, 0.5 M en tolueno) se agrega, se entibia hasta temperatura ambiente y se trata con 8-(1-etil-propil)-3-yodo-2,6-dimetil-imidazo[1,2-b]piridazina y complejo $PdCl_2(dppf)-CH_2Cl_2$ (Aldrich, 40 mg, 0.05 mmol). La mezcla se calienta hasta 65°C durante la noche, se enfría hasta temperatura ambiente, se agrega agua y se extrae dos veces con EtOAc. Los extractos orgánicos combinados se lavaron con salmuera, se secan sobre Na_2SO_4, se filtran y se concentran. El producto crudo se purifica por cromatografía al usar un gradiente de hexano-acetato de etilo (100% hexano hasta 50 % acetato de etilo en hexano) para eluir el producto. El compuesto del título se obtiene (0.7% de rendimiento). ES-EM (m/z): calculado para $C_{18}H_{25}N_5$: 311.4; encontrado 312.2 $(M+H)^+$. ^1H RMN (400 mHz, CDCl3): δ 7.51 (s, 1H), 6.75 (s, 1H), 3.72 (s, 3H), 3.33 (m, 1H), 2.53 (s, 3H), 2.43 (s, 3H), 2.00 (s, 3H), 1.87 (m, 4H), 0.92 (m, 6H).

198

Ejemplo 225.

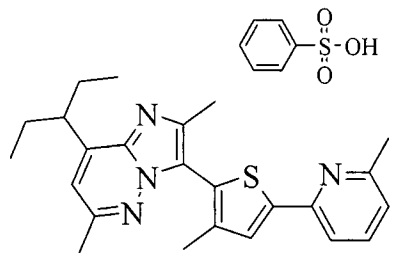
Preparación de 3-(4,5-dibromo-2-metil-2H-pirazol-3-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (300 mg, 1.4 mmol), 3,4,5-tribromo-1-metil-1H-pirazol (700 mg, 2.1 mmol) y carbonato de cesio (900 mg, 2.8 mmol) se agitan en DMF (5 ml) y se desgasifican al burbujear una corriente de nitrógeno a través de la mezcla. Se agrega $PdCl_2(PPh_3)_2$ (14 mg) se agrega y la mezcla se calienta hasta 130°C durante la noche. La mezcla se agrega hasta agua y se extrae dos veces con EtOAc. Los extractos orgánicos combinados se lavan con salmuera, se secan sobre Na_2SO_4, se filtran y se concentran. El producto crudo se purifica por cromatografía al usar un gradiente de hexano-acetato de etilo (100% hexano hasta 20% acetato de etilo en hexano) para eluir el producto del título (204 mg, 32% de rendimiento). ES-EM (m/z): calculado para $C_{17}H_{21}Br_2N_5$: 455.2; encontrado 455.9 $(M+H)^+$. ^1H RMN (400 mHz, $CDCl_3$): δ 6.75 (s, 1H), 3.72 (s, 3H), 3.33 (m, 1H), 2.51 (s, 3H), 2.45 (s, 3H), 1.84 (m, 4H), 0.88 (t, 6H).

Ejemplo 226.

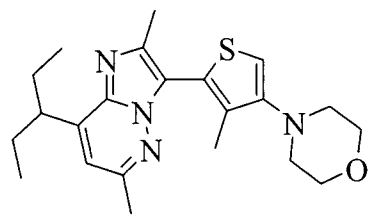
Preparación de ácido 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(6-metil-piridin-2-il)-tiofen-2-il]-imidazo[1,2-b]piridazina bencenosulfónico.



A una solución de 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(6-metil-piridin-2-il)-tiofen-2-il]-imidazo[1,2-b]piridazina (0.23 g, 0.57 mmol) y MeOH (1 mL) se agrega una solución de ácido bencenosulfónico (0.096 g, 0.57 mmol) y MeOH (1 mL). La solución se concentra para resultar el compuesto del título (0.32 g, 0.57 mmol, >99%). ^{1}H RMN ($CDCl_3$) δ 0.79 (t, J = 7.0 Hz, 6H), 1.59-1.82 (m, 4H), 2.06 (s, 3H), 2.61 (s, 6H), 2.88 (s, 3H), 3.22-3.32 (m, 1H), 6.79 (bs, 2H), 7.25 (s, 1H), 7.33-7.42 (m, 3H), 7.49 (d, J = 7.9 Hz, 1H), 7.80 (d, J = 7.4 Hz, 2H), 7.92 (dd, J = 7.4, 1.6 Hz, 1H) 8.23 (s, 1H). CL/EM (m/z): calculado para $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.2; encontrado: 405.4.

Ejemplo 227.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(3-metil-4-morfolin-4-il-tiofen-2-il)-imidazo[1,2-b]piridazina.



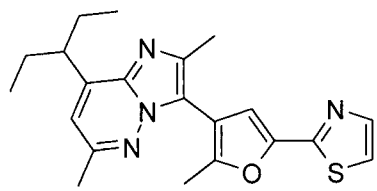
A un matraz que contiene 3-(4-bromo-3-metil-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.30g, 0.76 mmol), morfolina (0.10 mL, 1.15 mmol), $Pd_2(dba)_3$ (0.035 g, 0.038 mmol), y 2-diciclohexilfosfino-bifenil-2'-(N,N-dimetil-amino)bifenil (0.018 g, 0.046 mmol) se agrega 1 M LiHMDS (1.9 mL, 1.91 mmol). La solución se calienta a 65°C durante la noche, se diluye con EtOAc (30 mL), se lava con agua (20 mL), salmuera (20 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por ISCO (15%-30% gradiente EtOAc), se disuelve en Et_2O (20 mL) y se extrae con HCl 1M (2 x 30 mL). La capa acuosa se lava con Et_2O (20 mL), se hace básica con 5 M NaOH (15 mL), se extrae con EtOAc (2 x 20 mL), las capas orgánicas combinadas se lavan con salmuera (40 mL), se secan sobre $MgSO_4$, se filtran y se concentran para resultar el compuesto del título (0.047 g, 0.12 mmol, 16%). ^1H RMN ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.01 (s, 3H), 2.45 (s, 3H), 2.49 (s, 3H), 2.99-3.05 (m, 4H), 3.28-3.37 (m, 1H), 3.84-3.88 (m, 4H), 6.65

507

(s, 1H), 6.71 (s, 1H). CL/EM (m/z): calculado para $C_{22}H_{30}N_4OS$ $(M+H)^+$: 399.2; encontrado: 399.2.

Ejemplo 228.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-(2-metil-5-tiazol-2-il-furan-3-il)-imidazo[1,2-b]piridazina.



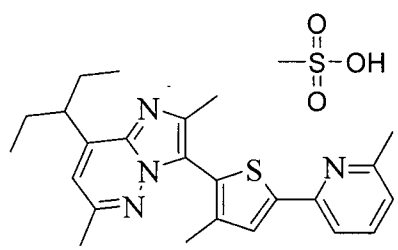
Una solución de THF (5 mL) de 2-bromotiazol (Aldrich, recientemente destilado, 75.0 µL, 0.84 mmol) se enfría hasta -78°C bajo N_2 luego se trata con nBuLi (1.6 M en hexano, 0.52 mL, 0.83 mmol). Después de 15 minutos a -78°C, la mezcla se trata con $ZnCl_2$ (Aldrich, 0.5 M en THF, 1.8 mL, 0.90 mmol). La mezcla resultante se entibia hasta temperatura ambiente luego se trata con una suspensión espesa de THF (1 mL) que contiene 3-(5-bromo-2-metil-furan-3-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (60.1 mg, 0.16 mmol) y complejo $PdCl_2(dppf)-CH_2Cl_2$ (Aldrich, 22 mg, 0.027 mmol). La mezcla se calienta durante la noche a 60°C, luego se vacía en NH_4Cl saturado y se extrae con éter dietílico. El extracto orgánico se lava con salmuera acuosa, se seca sobre Na_2SO_4, se filtra, y se concentra. El producto crudo se purifica por cromatografía al usar el hexano-acetato de etilo (100% hexano

502

hasta 20% acetato de etilo en hexano) para eluir el compuesto del título (45.8 mg, 75% de rendimiento) como un aceite. ES-EM (m/z): calculado para $C_{21}H_{24}N_4OS$: 380.17; encontrado 381.1 $(M+H)^+$. ^1H RMN (400 mHz, $CDCl_3$): δ 7.83 (d, J = 3.5 Hz, 1H), 7.29 (d, J = 3.1 Hz, 1H), 7.20 (s, 1H), 6.68 (br s, 1H), 3.35 (br s, 1H), 2.53 (s, 3H), 2.49 (s, 3H), 2.40 (s, 3H), 1.90-1.76 (m, 4H), 0.88 (t, J = 7.5 Hz, 6H).

Ejemplo 229.

Preparación de 8-(1-etil-propil)-2,6-dimetil-3-[3-metil-5-(6-metil-piridin-2-il)-tiofen-2-il]-imidazo[1,2-b]piridazina; compuesto con ácido metanosulfónico.

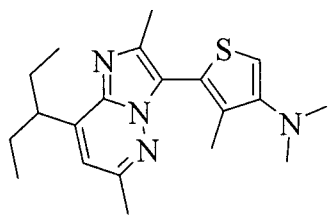


A una solución de 8-(1-etil-propil)-2,6-dimetil-3-(3-metil-5-piridin-2-il-tiofen-2-il)-imidazo[1,2-b]piridazina (0.55 g, 1.36 mmol) y MeOH (6 mL) se agrega ácido metano sulfónico (0.088 mL, 1.36 mmol). Después de una hora la solución se concentra y la solución se trata con Darco-60® durante 1 hora, se filtra y se concentra para resultar el compuesto del título (0.68 g, 1.36 mmol, >99%). ^1H RMN ($CDCl_3$: CD_3OD 95:5) δ 0.85 (t, J = 7.4 Hz, 6H), 1.67-1.91 (m, 4H), 1.96 (s, 3H), 1.97 (s, 3H), 2.20 (s, 3H), 2.61 (s, 3H), 2.90

(s, 3H), 3.17-3.29 (m, 1H), 7.33 (s, 1H), 7.64 (d, J = 7.4 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 8.18 (s, 1H), 8.34 (t, J = 7.9 Hz, 1H), 9.95 (bs, 1H). CL/EM (m/z): calculado para $C_{25}H_{32}N_4O_2S_2$ $(M+H)^+$: 405.6; encontrado: 405.6.

Ejemplo 230.

Preparación de {5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiofen-3-il}-dimetil-amina.

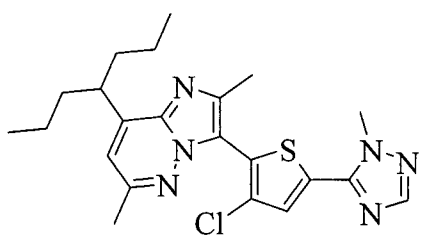


A una solución a -78°C de dimetil-(4-metil-tiofen-3-il)-amina (0.43 g, 3.06 mmol) y THF (5 mL) se agrega 1.6 M n-BuLi (1.91 mL, 3.06 mmol). La solución se agita durante 1 hora, luego 0.5 M $ZnCl_2$ (6.1 mL, 3.06 mmol) se agrega y la solución se entibia hasta temperatura ambiente. Después de 30 minutos 8-(1-etil-propil)-3-yodo-2,6-dimetil-imidazo[1,2-b]piridazina (0.70 g, 2.04 mmol) y $PdCl_2$(dppf) (0.075 g, 0.10 mmol) se agrega y la solución se calienta a 65°C durante la noche. La solución se diluye con EtOAc (35 mL), se lava con NH_4Cl saturado (30 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía instantánea ISCO (15%-30% gradiente EtOAc) resulta el compuesto del título (0.13 g, 0.36 mmol, 18%). ^1H RMN ($CDCl_3$)

δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-1.90 (m, 4H), 2.03 (s, 3H), 2.45 (s, 3H), 2.50 (s, 3H), 2.77 (s, 6H), 3.28-3.37 (m, 1H), 6.63 (s, 1H), 6.65 (s, 1H). CL/EM (m/z): calculado para $C_{20}H_{28}N_4S$ $(M+H)^+$: 357.2; encontrado: 357.2

Ejemplo 231.

Preparación de 3-[3-cloro-5-(2-metil-2H-[1,2,4]triazol-3-il)-tiofen-2-il]-2,6-dimetil-8-(1-propil-butil)-imidazo[1,2-b]piridazina.

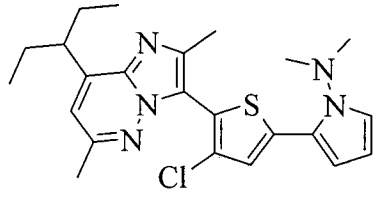


Una suspensión espesa de 2,6-dimetil-8-(1-propil-butil)-imidazo[1,2-b]piridazina (a continuación) (0.30 g, 1.22 mmol), 5-(5-bromo-4-cloro-tiofen-2-il)-1-metil-[1,2,4]triazol (a continuación) (0.41 g, 1.47 mmol), KOAc (0.60 g, 6.11 mmol), TBABr (0.39 g, 1.22 mmol), y NMP (3 mL) se desgasifica con N_2 durante 30 minutos. $Pd(OAc)_2$ (0.014 g, 0.061 mmol) y TDBPP (0.040 g, 0.061 mmol) se agregan y la solución se calienta a 125°C durante 2.5 horas. La solución se diluye con EtOAc (50 mL), se lava con agua (3 x 50 mL), salmuera (50 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía instantánea ISCO (gradiente 20%-40% EtOAc)

resulta el compuesto del título (0.30 g, 0.68 mmol, 56%). ^{1}H RMN ($CDCl_3$) δ 0.89 (t, J = 7.4 Hz, 6H), 1.14-1.39 (m, 4H), 1.76 (q, J = 16.3, 7.7 Hz, 4H), 2.51 (s, 3H), 2.52 (s, 3H), 3.41-3.50 (m, 1H), 4.15 (s, 3H), 6.73 (s, 1H), 7.48 (s, 1H), 7.90 (s, 1H). CL/EM (m/z): calculado para $C_{22}H_{27}ClN_6S$ $(M+H)^+$: 443.2; encontrado: 443.3.

Ejemplo 232.

Preparación de (2-{4-cloro-5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-tiofen-2-il}-pirrol-1-il)-dimetil-amina.

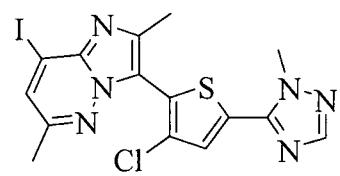


Usando un procedimiento análogo al Ejemplo 27, 1-(dimetilamino)-pirrol (0.20 mL, 1.65 mmol), THF (4 mL), 1.6 M n-BuLi (1.10 mL, 1.73 mmol), 0.5 M $ZnCl_2$ (3.46 mL, 1.73 mmol), 3-(5-bromo-3-cloro-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.34 g, 0.82 mmol) y $PdCl_2$(dppf) (0.030 g, 0.041 mmol), resulta el compuesto del título (0.17 g, 0.38 mmol, 46%). ^{1}H RMN ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.52 (s, 6H), 2.84 (s, 6H), 3.28-3.39 (m, 1H), 6.21 (dd, J = 4.1, 3.2 Hz, 1H), 6.38 (dd, J = 4.1, 1.8 Hz, 1H), 6.68 (s, 1H), 7.02 (dd, J = 3.2, 1.8

Hz, 1H), 7.29 (s, 1H). CL/EM (m/z): calculado para $C_{23}H_{28}ClN_5S$ $(M+H)^+$: 442.2; encontrado: 442.3.

Ejemplo 233.

Preparación de 3-[3-cloro-5-(2-metil-2H-[1,2,4]triazol-3-il)-tiofen-2-il]-8-yodo-2,6-dimetil-imidazo[1,2-b]piridazina.



A. 4-Cloro-tiofeno-2-carbonitrilo.

Un matraz de reacción de 22-L se equipa con un baño de enfriamiento, agitador con aire, tubo de adición de gas, y sonda de termómetro. El matraz se purga con nitrógeno, luego se carga $AlCl_3$ (1025 g, 7.69 moles) y $CHCl_3$ (6.6 L, 16.5 vol.). Después del enfriamiento la mezcla hasta 0-5°C, se carga con 2-tiofeno carbonitrilo (400 g, 3.66 moles) gota a gota por medio de un embudo de adición durante 10-15 minutos mientras se mantiene la temperatura a <10°C. La mezcla se carga con gas Cl_2 (300g, 4.23 moles, 1.16 EQ) subsuperficie a < 10°C durante 1.25 horas. El avance de la reacción se observa por GC, en donde el método que muestra GC se apaga en alícuota de la mezcla de reacción en HCl 6N, se extrae con EtOAc, se seca sobre Na_2SO_4, se filtra, y se injecta el filtrado.

Cuando la reacción se considera completa por análisis de GC [la reacción se consideró completa cuando la relación de (sm : prod : dicloro) fue aproximadamente (1:5.8:1) por área % GC.], HCl 6N (8.0 L) se agrega gota a gota por medio de embudo de adición durante 1.5 horas, mientras se mantiene la temperatura a < 20°C [La adición HCl es extremadamente exotérmica y desarrolla gas]. La reacción se transfiere a un embudo de separación y las capas se separan. Después de extraer la capa acuosa con $CHCl_3$ (4.0 L), las capas de cloroformiato se combinan y se lavan con H_2O desionizado (6.0L). La capa orgánica se seca sobre Na_2SO_4, se filtra y se concentra bajo vacío para dar un semo-sólido amarillo pálido 575g, 109.3%). GC (60°C hasta 280°C temperatura de gradiente) área-% de análisis muestra ~68% de producto (t_{ret} = 6.5 min) con mayores purezas son el material de partida no reactivo (t_{ret} = 5.1 min) y el producto diclorinado (t_{ret} = 7.4 min). Método GC: Columna: DB1; $T_{injecyt}$ = 300°C ; $T_{inicial}$ = 60°C, t = 2.0 min; T_{final} = 280°C, relación = 18 oC/min.

B. 4-Cloro-2-tiofeno carboxamida.

Un matraz de reacción de 12-L equipado con un baño de enfriamiento, agitador con aire, y sonda de termómetro se carga con KOH (288.6 g, 5.143 moles) y H_2O desionizado (6.04 L) para formar una solución que es exotermia hasta ~31°C. Después de permitir a la solución enfriarse hasta ~28.0°C, la

mezcla se carga con 4-cloro-2-tiofeno carbonitrilo (671.3 g, 4.675 moles)[1] seguido por EtOH (675 mL). Una exotermia gradual ocurre durante la adición de EtOH y se continua durante 1-1.5 horas hasta ~38°C. La reacción se agita a temperatura ambiente durante la noche.

La mezcla de reacción se filtra bajo vacío, se lava con H_2O desionizado y se seca para dar el propducto crudo. Los sólidos se disuelven en EtOAc (10.0 L) se tratan con Na_2SO_4 y Darco durante 1-2 horas; luego, se filtra y se lava con EtOAc. El producto filtrado se concentra en el Büchi hasta que los sólidos comienzan a precipitarse a 45°C en cuyo tiempo el vacío se libera, y la temperatura se incrementa hasta 60-65°C para redisolver los sólidos. Con agitación a 60°C, heptano (3.5 L) se agrega lentamente para precipitar los sólidos. Después de agitar durante 15-20 minutos a 60°C, la mezcla se enfría hasta 30-40°C y se filtra. Los sólidos se lavan con heptano (2 x 0.75 L), y se secan para dar el compuesto del título (t_{ret} = 9.9 min) como un sólido blanco (235.4 g, 31.2 % 96.4 área % por análisis de GC). Una segunda cosecha se obtiene del producto filtrado para dar 67.8 g, 9.0 %; 94.5% área-% por análisis de GC). El rendimiento general es 303.2 g, 40.1 %.

C. 4-Cloro-N-dimetilaminometileno-2-tiofeno carboxamida.

Un matraz de reacción de 5L equipado con un manto de calentamiento, agitador con aire, aparato Dean-Stark, y sonda de termómetro se carga con 4-cloro-2-tiofeno carboxamida. (300 g, 1.856 moles) y dimetilformamida dimetilacetal (872 mL) para formar una suspensión espesa que es endotermia a 1-2°C desde 22-20°C. La mezcla se calienta gradualmente hasta 96°C mientras se recolecta el destilado (mayormente MeOH). El manto de calentamiento se remueve, y la mezcla se enfría hasta < 25°C. H_2O desionizado (3.0 L) se agrega por medio de un embudo de adición y la temperatura se mantiene a < 35°C. La mezcla de reacción se extrae con EtOAc (1 x 3.0 L, 1 x 1.5 L), luego se combinan los orgánicos, se lavan con H_2O desionizado (1.5 L). La fase orgánica se seca sobre Na_2SO_4, se filtra, y se concentra bajo vacío para dar el producto crudo (400 g).

El producto crudo se disuelve en EtOAc (320 mL, 0.8 Vol) a 50-60°C; luego, heptano (1700 mL, 4.25 Vol) se agrega lentamente mientras gradualmente incrementa la temperatura hasta 70°C. Un cristal sembrado (Lote: PP6-H00086-075-1) se agrega a la solución turbia para iniciar la precipitación. La mezcla resultante se agita a temperatura ambiente durante la noche, luego se filtra y se lava con heptano. Los sólidos se secan para dar el compuesto del título (t_{ret} = 13.0 min) como un sólido blanco (329.8 g, 82%; 98.2 % área-% por análisis de GC).

510

D. 5-(4-Cloro-tiofen-2-il)-1-metil-1H-[1,2,4]triazol.

Un matraz de reacción de 3-L equipado con un baño de enfriamiento, agitador con aire, y sonda de termómetro se carga con 4-cloro-N-dimetilaminometileno-2-tiofeno carboxamida. (155 g, 0.715 moles) y HOAc (1500 mL) para formar una solución. Usando un baño de enfriamiento de hielo-agua para mantener la temperatura a <30°C, metilhidrazina (33.2 g, 0.721 moles) se agrega gota a gota por medio de un embudo de adición durante 15-20 minutos para formar una suspensión espesa amarillo ligero. Gradualmente, la reacción se calienta hasta 90°C y se mantiene a 90°C durante 30 minutos. Después del análisis de la mezcla por GC, la reacción se enfría hasta ~70°C; luego, se concentra hasta un aceite espeso/suspensión espesa. H_2O desionizado (1.67 L) se agrega lentamente para precipitar los sólidos; luego, la mezcla se enfría hasta <30°C, se filtra y se lava con H_2O desionizado (1.67 L). los sólidos húmedos (125.8 g) se redisuelven en MTBE caliente (1.64 L), se seca sobre Na_2SO_4, se filtra y se concentra hasta secado dando el compuesto del título como un sólido amarillo pálido (85.8 g, 60.1% 91.9 % área % por GC).

E. 5-(5-Bromo-4-cloro-tiofen-2-il)-1-metil-1H-[1,2,4]triazol.

Un matraz de reacción de 3-L equipado con un baño de enfriamiento, agitador con aire, y sonda de termómetro se

carga con 5-(4-Cloro-tiofen-2-il)-1-metil-1H-[1,2,4]triazol (105.3 g, 0.527 moles), ACN (1053 mL) y HOAc (105 mL) para formar una solución. NBS (103.2 g, 0.580 moles) se agrega en porciones durante 30-60 minutos mientras se mantiene la temperatura a <31°C. Después de agitar durante 1 hora[1], el análisis GC indica la reacción completa. La mezcla de reacción se vacía en H_2O desionizado (2.1 L, 20vol), se agita durante 30 minutos, se filtra, y se lava con H_2O desionizado (2 x 1 L). El producto se seca en un horno a vacío a 45°C durante la noche para dar el compuesto del título como un sólido amarillo pálido (123.0 g, 83.8 %; 96.6 % área-% por GC).

F. 2,6-Dimetil-imidazo[1,2-b]piridazina.

Un matraz de fondo redondo de 3 cuellos de 1L se carga con 6-metil-piridazin-3-ilamina (20 g, 0.18 moles), etanol 2B (200 mL), y cloroacetona (23.7 g, 20.4 mL, 0.256 moles, 1.4 equiv). La mezcla de reacción se calienta a 70°C durante la noche. NaHCO3 (23.2 g, 0.276 moles, 1.5 equiv) se agrega en porciones. Después de que la mayoría de las burbujas persiste, la reacción se calienta a 100°C durante la noche. Los solventes se remueven in vacuo y el residuo se lleva en diclorometano y se filtra a través de un papel filtro. El solvente se remueve nuevamente in vacuo. El residuo se purifica usando cromatografía en gel de sílice con un

gradiente de hexanos:acetato de etilo para obtener el compuesto del título (15.5 g, 57%). ^{1}H-RMN (DMSO-d6), δ 2.34 (s, 3H), 2.47 (s, 3H), 7.03, (d, J = 10 Hz, 1H), 7.85 (d, J = 10 Hz, 1H), 7.91 (s, 1H) ppm. EM (APCI): 148 (M+1).

G. 3-[3-cloro-5-(2-metil-2H-[1,2,4]triazol-3-il)-tiofen-2-il]-2,6-dimetil-imidazo[1,2-b]piridazina.

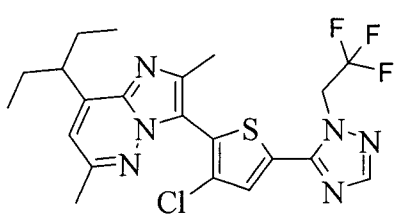
Una solución de 2,6-dimetil-imidazo[1,2-b]piridazina (0.32 g, 2..17 mmol), 5-(5-bromo-4-cloro-tiofen-2-il)-1-metil-1H-[1,2,4]triazol (0.72 g, 2.61 mmol), Cs_2CO_3 (1.49 g, 4.57 mmol) y DMF (6 mL) se desgasifica durante 15 minutos con N_2. El $Pd(OAc)_2$ (0.024 g, 0.11 mmol) y PPh_3 (0.057 g, 0.22 mmol) se agregan y la solución se calienta a 135°C durante 4 horas. La solución se diluye con CH_2Cl_2 (50 mL), se lava con NH_4Cl saturado (2 x 50 mL), agua (50 mL), se filtra y se concentra. El residuo se purifica por cromatografía instantánea ISCO (30%-100% gradiente EtOAc) resulta el compuesto del título (0.29 g, 0.84 mmol, 39%). ^{1}H RMN ($CDCl_3$) δ 2.49 (s, 3H), 2.50 (s, 3H), 4.10 (s, 3H), 6.92 (d, J = 9.2 Hz, 1H), 7.44 (s, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.85 (s, 1H). CL/EM (m/z): calculado para $C_{15}H_{13}ClN_6S$ $(M+H)^+$: 345.1; encontrado: 345.2.

H. 3-[3-Cloro-5-(2-metil-2H-[1,2,4]triazol-3-il)-tiofen-2-il]-8-yodo-2,6-dimetil-imidazo[1,2-b]piridazina.

A una solución a -78°C de 3-[3-cloro-5-(2-metil-2H-[1,2,4]triazol-3-il)-tiofen-2-il]-2,6-dimetil-imidazo[1,2-b]piridazina (1.50 g, 4.35 mmol) y THF (50 mL) se agrega I_2 (1.21 g, 4.78 mmol). Después de 10 minutos 2 M LDA (5.44 mL, 10.87 mmol) se agrega. La solución se agita durante 30 minutos, se apaga con agua, se diluye con EtOAc (100 mL), se lava con agua (100 mL), $Na_2S_2O_3$ saturado (100 mL), salmuera (100 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía instantánea ISCO (100% EtOAc) resulta el compuesto del título (0.61 g, 1.30 mmol, 30%). ^1H RMN ($CDCl_3$) δ 2.50 (s, 3H), 2.55 (s, 3H), 4.14 (s, 3H), 7.47 (s, 1H), 7.51 (s, 1H), 7.89 (s, 1H),. CL/EM (m/z): calculado para $C_{15}H_{12}ClIN_6S$ $(M+H)^+$: 471.0; encontrado: 471.0.

Ejemplo 234.

Preparación de 3-{3-cloro-5-[2-(2,2,2-trifluoro-etil)-2H-[1,2,4]triazol-3-il]-tiofen-2-il}-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



A. 5-(4-Cloro-tiofen-2-il)-1-(2,2,2-trifluoro-etil)-1H-[1,2,4]triazol.

514

A una solución de 4-cloro-N-dimetilaminometileno-2-tiofeno carboxamida (1.00 g, 4.62 mmol) y AcOH (1. mL) se agrega 70% de 2,2,2-trifluoroetil-hidrazina acuosa (0.79 mL, 4.85 mmol). La solución se calienta a 90°C durante 45 minutos, se concentra, se disuelve en Et_2O (40 mL), se lava con agua (30 mL), $NaHCO_3$ saturado (30 mL), se seca sobre $MgSO_4$, se filtra y se concentra para resultar el compuesto del título (1.24 g, 4.62 mmol, >99%). ^1H RMN ($CDCl_3$) δ 4.88 (q, J = 16.8, 7.8 Hz, 2H), 7.28 (d, J = 0.9 Hz, 1H), 7.31-7.33 (m, 1H), 7.94 (s, 1H). CL/EM (m/z): calculado para $C_8H_5ClF_3N_3S$ $(M+H)^+$: 268.0; encontrado: 268.0.

B. 5-(5-bromo-4-cloro-tiofen-2-il)-1-(2,2,2-trifluoro-etil)-1H-[1,2,4]triazol.

A una solución de 5-(4-cloro-tiofen-2-il)-1-(2,2,2-trifluoro-etil)-1H-[1,2,4]triazol (1.13 g, 4.22 mmol) y AcOH (10 mL) en un tubo sellado, se agrega Br_2 (0.23 mL, 4.43 mmol). La solución se calienta a 120°C durante 2 horas, y 140°C durante 5 horas. La solución se concentra, se diluye con Et_2O (150 mL), se lava con $NaHCO_3$ (75 mL), $Na_2S_2O_3$ saturado (75 mL), salmuera (75 mL) se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía instantánea ISCO (5%-15% gradiente EtOAc) resulta el compuesto del título

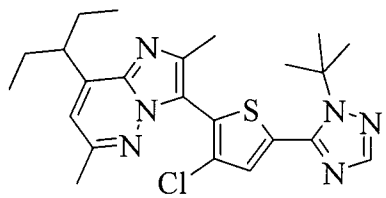
(1.04 g, 3.00 mmol, 71%). ^{1}H RMN ($CDCl_3$) δ 4.88 (q, J = 16.0, 7.9 Hz, 2H), 7.22 (s, 1H), 7.99 (s, 1H). CL/EM (m/z): calculado para $C_8H_4BrClF_3N_3S$ $(M+H)^+$: 345.9; encontrado: 346.0.

C. 3-{3-Cloro-5-[2-(2,2,2-trifluoro-etil)-2H-[1,2,4]triazol-3-il]-tiofen-2-il}-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

Usando un procedimiento análogo al Ejemplo 231, 8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.25 g, 1.14 mmol), 5-(5-bromo-4-cloro-tiofen-2-il)-1-(2,2,2-trifluoro-etil)-1H-[1,2,4]triazol (0.47 g, 1.37 mmol), KOAc (0.56 g, 5.60 mmol), TBABr (0.37 g, 1.14 mmol), y NMP (3 mL), $Pd(OAc)_2$ (0.013 g, 0.057 mmol) y TDBPP (0.037 g, 0.057 mmol) resulta el compuesto del título (0.43 g, 0.89 mmol, 78%). ^{1}H RMN ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.27-3.36 (m, 1H), 4.98 (q, J = 15.7, 7.9 Hz, 2H), 6.74 (s, 1H), 7.45 (s, 1H), 8.03 (s, 1H). CL/EM (m/z): calculado para $C_{21}H_{22}ClF_3N_6S$ $(M+H)^+$: 483.1; encontrado: 483.2.

Ejemplo 235.

Preparación de 3-[5-(2-tert-butil-2H-[1,2,4]triazol-3-il)-3-cloro-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



A. 1-tert-Butil-5-(4-cloro-tiofen-2-il)-1H-[1,2,4]triazol.

Usando un procedimiento análogo al Ejemplo 234A, 4-cloro-N-dimetilaminometileno-2-tiofeno carboxamida (5.00 g, 23.07 mmol) y AcOH (50. mL), clorohidrato de tert-butilhidrazina (3.16 g, 25.38 mmol) resulta el compuesto del título (0.20 g, 0.83 mmol, 3.6%). ^{1}H RMN ($CDCl_3$) δ 1.63 (s, 9H), 7.07 (d, J = 1.3 Hz, 1H), 7.51 (d, J = 1.3 Hz,1H), 8.08 (s, 1H).

B. 5-(5-Bromo-4-cloro-tiofen-2-il)-1-(2,2,2-trifluoro-etil)-1H-[1,2,4]triazol.

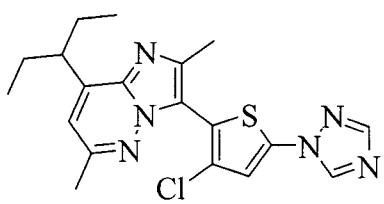
Usando un procedimiento análogo al Ejemplo 249B, 1-tert-butil-5-(4-cloro-tiofen-2-il)-1H-[1,2,4]triazol (0.20 g, 0.83 mmol), AcOH (3 mL) y Br_2 (0.051 mL, 0.99 mmol) resulta el compuesto del título (0.27 g, 0.83 mmol, >99%). ^{1}H RMN ($CDCl_3$) δ 1.62 (s, 9H), 7.42 (s, 1H), 8.08 (s, 1H). CL/EM (m/z): calculado para $C_{10}H_{11}BrClN_3S$ $(M+H)^+$: 320.0; encontrado: 320.0.

C. 3-[5-(2-tert-Butil-2H-[1,2,4]triazol-3-il)-3-cloro-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

Usando un procedimiento análogo al Ejemplo 231, 8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.15 g, 0.68 mmol), 5-(5-bromo-4-cloro-tiofen-2-il)-1-(2,2,2-trifluoro-etil)-1H-[1,2,4]triazol (0.20 g, 0.82 mmol), KOAc (0.34 g, 3.42 mmol), TBABr (0.22 g, 0.68 mmol), y NMP (3 mL), $Pd(OAc)_2$ (0.0077 g, 0.034 mmol) y TDBPP (0.022 g, 0.034 mmol) resulta el compuesto del título (0.039 g, 0.085 mmol, 13%). ^1H RMN ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.65 (s, 9H), 1.73-1.91 (m, 4H), 2.51 (s, 6H), 3.26-3.37 (m, 1H), 6.69 (s, 1H), 7.65 (s, 1H), 8.11 (s, 1H). CL/EM (m/z): calculado para $C_{23}H_{29}ClN_6S$ $(M+H)^+$: 457.2; encontrado: 457.3.

Ejemplo 236.

Preparación de 3-(3-cloro-5-[1,2,4]triazol-1-il-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



A. 3-(3-Cloro-5-yodo-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

A una solución de 3-(3-cloro-tiofén-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (2 g, 6 mmol) en 10 mL de CH_3CN anhidro bajo nitrógeno se agregó en porciones NIS (1.6 g, 7.2 mmol). La mezcla de reacción se agita a reflujo durante 14 horas. Después del enfriamiento, el solvente se concentra bajo vacío, el residuo se disuelve en EtOAc y se lava con H_2O, 5% de solución de bisulfito de sodio, H_2O y salmuera. La capa orgánica se seca sobre sulfato de magnesio, se filtra y se concentra bajo vacío. El residuo crudo se purifica por cromatografía en gel de sílice usando hex/EtOAc 8:2 como mezcla de eluyente, para obtener 2.4 g (90%) del compuesto del título; espectro de masas 460 (M+1); ^{1}H-RMN ($CDCl_3$, 300 MHz) δ 7.24 (s, 1H), 6.71 (s, 1H), 3.32 (q, 1H, J = 7.2 Hz), 2.52 (s, 3H), 2.49 (s, 3H), 1.84 (q, 4H, J = 7.2 Hz); 0.88 (t, 6H, J = 7.2 Hz) ppm.

B. 3-(3-Cloro-5-[1,2,4]triazol-1-il-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

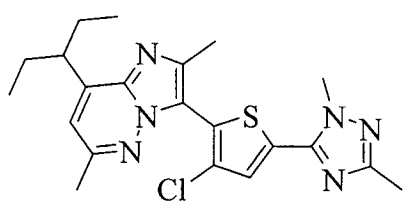
A una solución de 3-(3-cloro-5-yodo-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.30 g, 0.65 mmol), 1H-triazol (0.047 g, 0.69 mmol), CuI (0.0062, 0.033 mmol), Cs_2CO_3 (0.45 g, 1.37 mmol) y DMF (3 mL) se agrega (1S, 2S)-(+)-N,N'-dimetilciclohexano-1,2-diamina (0.014 mL, 0.098 mmol). La solución se calienta a 112°C durante la noche, se diluye con CH_2Cl_2 (10 mL) y se filtra a través de

519

Celite® y se concentra. El residuo se purifica por cromatografía instantánea ISCO (gradiente 30%-40% EtOAc resulta el compuesto del título (0.028 g, 0.070 mmol, 11%). ^{1}H RMN ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.75-1.92 (m, 4H), 2.51 (s, 3H), 2.52 (s, 3H), 3.26-3.35 (m, 1H), 6.72 (s, 1H), 7.22 (s, 1H), 8.10 (s, 1H), 8.50 (s, 1H). CL/EM (m/z): calculado para $C_{19}H_{21}ClN_6S$ $(M+H)^+$: 401.1; encontrado: 401.2.

Ejemplo 237.

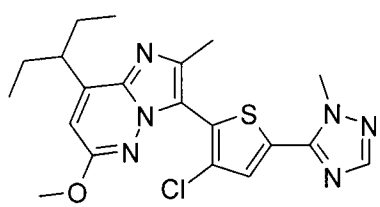
Preparación de 3-[3-cloro-5-(2,5-dimetil-2H-[1,2,4]triazol-3-il)-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



A una solución a -78°C de 3-[3-cloro-5-(2-metil-2H-[1,2,4]triazol-3-il)-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.30 g, 0.72 mmol) y THF (5 mL) se agrega tert-BuLi 1.7 M (0.47 mL, 0.80 mmol). Después de 15 minutos MeI (0.052 mL, 0.83 mmol) se agrega y la solución se entibia hasta temperatura ambiente. La solución se diluye con EtOAc (40 mL), se lava con salmuera (40 mL), se seca sobre $MgSO_4$, se filtra y se concentra. La solución se recristaliza de acetona: hexano resulta el compuesto del

título (0.13 g, 0.30 mmol, 42%). ^{1}H RMN ($CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.36 (s, 3H), 2.51 (s, 6H), 3.27-3.39(m, 1H), 3.40 (s, 3H), 6.72 (s, 1H), 8.02 (s, 1H). CL/EM (m/z): calculado para $C_{21}H_{25}ClN_6S$ $(M+H)^+$: 429.2; encontrado: 429.2.

Ejemplo 238. Preparación de 3-[3-Cloro-5-(2-metil-2H-[1,2,4]triazol-3-il)-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



A. N-(6-Metoxi-piridazin-3-il)-2,2-dimetil-propionamida.

3-Cloro-6-metoxi-piridazina (10.0 g, 69.18 mmol) se mezcla con 2,2-dimetil-propionamida (8.40 g, 83.01 mmol), BINAP (2.15 g, 3.46 mmol), Cs_2CO_3 (33.8 g, 103.77 mmol) en 1,4-dioxano (150 mL). Se desgasifica al pasar N_2 a través de durante 10 min a temperatura ambiente. $Pd_2(dba)_3$ (3.16 g, 3.46 mmol) se agrega y la mezcla resultante se puso a reflujo durante la noche. La mezcla se enfría hasta temperatura ambiente, se diluye con EtoAc (150 mL); se filtra a través de gel de sílice; se lava con EtOAc (2 x 150 mL). El producto filtrado se lava con H_2O (2 x 300 mL); se seca con $MgSO_4$; se filtra y se concentra. La purificación del material crudo por

cromatografía en gel de sílice da el compuesto del título (6.59 g, 31.53 mmol, 46%). ^{1}H RMN ($CDCl_3$): δ. 1.35 (s, 9H), 4.08 (s, 3H), 7.01 (d, J = 9.7 Hz, 1H), 8.41 (d, J = 9.7 Hz, 1H), 8.44 (bs, 1H). ES-EM (m/z): calculado para $C_{10}H_{15}N_3O_2$ $(M+H)^+$: 210.3; encontrado : 210.1.

B. N-[4-(1-Etil-propil)-6-metoxi-piridazin-3-il]-2,2-dimetil-propionamida.

Usando un procedimiento análogo al Ejemplo 6a, de N-(6-metoxi-piridazin-3-il)-2,2-dimetil-propionamida (6.09 g, 29.14 mmol) y un reactivo de Grignard preparado de bromuro 3-pentilo (18.1 mL, 160.3 mmol) y Mg (3.84 g, 160.26 mmol) da el compuesto del título (5.32 g, 19.08 mmol, 65%). ^{1}H RMN ($CDCl_3$): δ. 0.84 (t, J = 7.5 Hz, 6H), 1.36 (s, 9H), 1.50-1.72 (m, 4H), 3.50-3.70 (m, 1H), 4.07 (s, 3H), 6.96 (s, 1H). ES-EM (m/z): calculado para $C_{15}H_{25}N_3O_2$ $(M+H)^+$: 280.4; encontrado: 280.2.

C. 4-(1-Etil-propil)-2-metoxi-6-metil-pirrolo[1,2-b]piridazina.

Una solución de N-[4-(1-etil-propil)-6-metoxi-piridazin-3-il]-2,2-dimetil-propionamida (5.32 g, 19.08 mmol) en EtOH (250 mL) se trata con $ZnCl_2$ (26.0 g, 190.8 mmol) y se pone a reflujo durante 48 h. La reacción se enfría hasta temperatura

ambiente y se concentra. El residuo se lleva con EtOAc (250 mL), y H_2O (100 mL). Se lava con H_2O (2 x 100 mL); se seca con Na_2SO_4; se filtra y se concentra. El residuo luego se disuelve en EtOAc (80 mL), se hace reaccionar con cloroacetona (1.6 mL, 20.03 mmoL) a reflujo durante la noche. Mientras no está calienta, $NaHCO_3$ (8.10 g) se agrega y la reacción se pone a reflujo durante 1 h. Se enfría hasta temperatura ambiente y se filtra a través de gel de sílice se lava con EtOAc y concentrated. La purificación del material crudo por cromatografía da el compuesto del título (0.48 g, 2.07 mmol, 11%). ^1H RMN ($CDCl_3$): δ. 0.84 (t, J = 7.5 Hz, 6H), 1.69-1.869 (m, 4H), 2.45 (s, 3H), 3.19-3.30 (m, 1H), 3.94 (s, 3H), 6.39 (s, 1H), 7.49 (s, 1H). ES-EM (m/z): calculado para $C_{14}H_{20}N_2O$ $(M+H)^+$: 233.3; encontrado : 234.1.

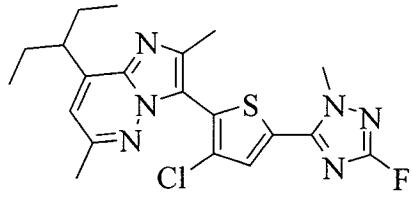
D. 3-[3-Cloro-5-(2-metil-2H-[1,2,4]triazol-3-il)-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

Una solución de 4-(1-etil-propil)-2-metoxi-6-metil-pirrolo[1,2-b]piridazina (74.8 mg, 0.32 mmol), 5-(5-bromo-4-cloro-tiofen-2-il)-1-metil-1H-[1,2,4]triazol (107.5 mg, 0.38 mmol), TDBPP (10.4 mg, 0.016 mmol), bromuro de tetrabutilamonio (103.0 mg, 0.32 mmol), KOAc (158 mg, 1.61 mmol) en NMP (15 mL) se purga con N2 durante 5 min. Se agrega $Pd(OAc)_2$ (3.6 mg, 0.016 mmol) y la mezcla resultante se agita a 125°C durante 6 h. La reacción se enfría hasta temperatura

ambiente, y se diluye con EtOAc (10 mL); se filtra a través de gel de sílice; se lava con EtOAc (3 x 30 mL). El producto filtrado se lava con H2O (3 x 30 m); se seca con Na2SO4, se filtra y se concentra. La purificación del material crudo por cromatografía en gel de sílice da el compuesto del título (0.1062 g, 0.2469 mmol, 77%). ^{1}H RMN (CDCl3): δ. 0.89 (t, J = 7.6 Hz, 6H), 1.75-1.90 (m, 4H), 2.52 (s, 3H), 3.22-3.38 (m, 1H), 3.93 (s, 3H), 4.15 (s, 3H), 6.52 (s, 1H), 7.48 (s, 1H), 7.91 (s, 1H). ES-EM (m/z): calculado para $C_{20}H_{23}ClN_6OS$ $(M+H)^+$: 431.9; encontrado: 431.3.

Ejemplo 239.

Preparación de 3-[3-cloro-5-(5-fluoro-2-metil-2H-[1,2,4]triazol-3-il)-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



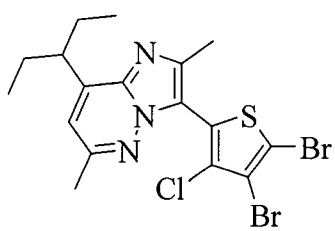
A una solución a -78°C de 3-[3-cloro-5-(2-metil-2H-[1,2,4]triazol-3-il)-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.40 g, 0.72 mmol) y THF (8 mL) se agrega tert-BuLi 1.7 M (0.47 mL, 0.80 mmol). Después de 30 minutos la solución se transfiere por medio de una cánula en una solución de N-fluorobencenosulfonamida (0.40 g,

524

1.25 mmol) y THF. Después de 30 minutos la solución se entibia hasta temperatura ambiente. La solución se diluye con EtOAc (40 mL), se lava con agua (30 mL), salmuera (30 mL), se seca sobre $MgSO_4$, se filtra y se concentra. La solución se purifica por ISCO (20%-30% gradiente EtOAc) resulta el compuesto del título (0.068 g, 0.16 mmol, 16%). ^1H RMN ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.71-1.93 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.26-3.36 (m, 1H), 4.08 (d J = 2.7 Hz, 3H), 6.75 (s, 1H), 7.97 (s, 1H). CL/EM (m/z): calculado para $C_{20}H_{22}ClFN_6S$ $(M+H)^+$: 433.2; encontrado: 433.2.

Ejemplo 240.

Preparación de 3-(4,5-dibromo-3-cloro-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

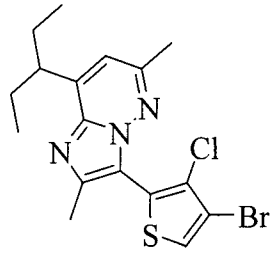


A una solución de 3-(5-bromo-3-cloro-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (5.92 g, 14.34 mmol) y ácido trifluoroacético (40 mL) y 98% de H_2SO_4 (10 ml) se agrega NBS (3.83 g, 21.15 mmol). Después de 10 minutos la solución se vacía en hielo, y se hace básica con 5M NaOH. La suspensión espesa se extrae con EtOAc (3 x 100 mL), las capas orgánicas combinadas se lavan con agua (2 x

400 mL), salmuera (400 mL), se seca sobre $MgSO_4$, se filtra y se concentra para resultar el compuesto del título (6.61 g, 13.44 mmol, 94%). ^1H RMN ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.72-1.92 (m, 4H), 2.47 (s, 3H), 2.52 (s, 3H), 3.25-3.34 (m, 1H), 6.72 (s, 1H). CL/EM (m/z): calculado para $C_{17}H_{18}Br_2ClN_3S$ $(M+H)^+$: 489.9; encontrado: 490.0.

Ejemplo 241.

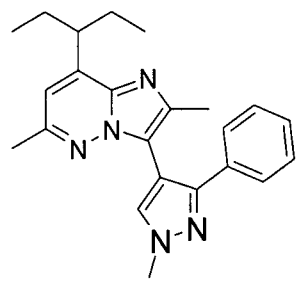
Preparación de 3-(4-bromo-3-cloro-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



Al usar un procedimiento similar al Ejemplo 76, 3-(4,5-dibromo-3-cloro-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (1.83 g, 3.72 mmol), 1.6 M n-BuLi (2.56 mL, 4.09 mmol), y THF (30 mL) resulta el compuesto del título (1.05 g, 2.54 mmol, 68%). ^1H RMN ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.48 (s, 3H), 2.51 (s, 3H), 3.27-3.36 (m, 1H), 6.71 (s, 1H), 7.55 (s, 1H). CL/EM (m/z): calculado para $C_{17}H_{19}BrClN_3S$ $(M+H)^+$: 412.0; encontrado: 412.1.

Ejemplo 242.

Preparación de 3-(1-metil-3-fenil-1H-pirazol-4-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



A. 1-metil-3-fenil-1H-pirazol y 1-metil-5-fenil-1H-pirazol.

Hidruro de sodio (60% dispersión en aceite mineral, 0.83 g, 20.8 mmol) se suspende en THF (45 ml) y se agita bajo una atmósfera de nitrógeno. 3-Fenil pirazol (2.5 g, 17.3 mmol disuelto en THF, 15 ml) se agrega lentamente, se agita durante 30 minutos luego yodometano (1.3 ml, 20..8 mmol) se agrega y se agita durante 3 hrs. La reacción se agrega hasta agua y se extrae dos veces con acetato de etilo. Los extractos orgánicos combinados se lavan con salmuera, se secan sobre Na_2SO_4, se filtran y se concentran. El producto crudo se purifica por cromatografía al usar un gradiente de hexano-acetato de etilo (100% hexano hasta 40% acetato de etilo en hexano) para eluir el compuesto del título. se obtiene una mezcla de 1-metil-3-fenil-1H-pirazol y 1-metil-5-fenil-1H-pirazol (2.6g, 95% de rendimiento).

B. 4-Bromo-1-metil-3-fenil-1H-pirazol y 4-bromo-1-metil-5-fenil-1H-pirazol.

La mezcla de isómeros, 1-metil-3-fenil-1H-pirazol y 1-metil-5-fenil-1H-pirazol (1.0g, 6.3 mmol) y NBS (1.1g, 6.3 mmol) se combinan en acetonitrilo (25 ml), se agitan y se calientan hasta 70°C durante 1 hr. La solución se concentra y el producto crudo se purifica por cromatografía al usar un gradiente de hexano-acetato de etilo (100% hexano hasta 25% acetato de etilo en hexano) para eluir 4-bromo-1-metil-3-fenil-1H-pirazol (504 mg, 34% de rendimiento) y 4-bromo-1-metil-5-fenil-1H-pirazol (295 mg, 20% de rendimiento), respectivamente:

^{1}H RMN: (400 mHz, DMSO): δ 8.01 (s, 1H), 7.95 (d, 2H), 7.41 (t, 2H), 7.38 (d, 1H), 3.85 (s, 3H).

^{1}H RMN: (400 mHz, DMSO): δ 7.63 (s, 1H), 7.50 (m, 5H) 3.77 (s, 3H).

C. 3-(1-Metil-3-fenil-1H-pirazol-4-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

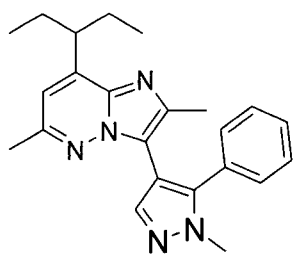
8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (160 mg, 0.73 mmol), 4-bromo-1-metil-3-fenil-1H-pirazol (250 mg, 1.1 mmol) y carbonato de cesio (490 mg, 1.50 mmol) se agitaron en DMF (5 ml) y se desgasifica al burbujear una corriente de nitrógeno a través de la mezcla. $PdCl_2(PPh_3)_2$ (15

528

mg) se agrega y la mezcla se calienta hasta 130°C durante la noche. La mezcla se agrega hasta agua y se extrae dos veces con acetato de etilo. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran y se concentran. El producto crudo se purifica por cromatografía al usar un gradiente de hexano-acetato de etilo (100% hexano hasta 50% acetato de etilo en hexano) para eluir el compuesto del título (17.5 mg, 4% de rendimiento). ES-EM (m/z): calculado para $C_{23}H_{27}N_5$: 373.5; encontrado 374.2 $(M+H)^+$. ^1H RMN (400 mHz, $CDCl_3$): δ 7.68 (s, 1H), 7.37 (m, 2H), 7.20 (m, 3H), 6.59 (s, 1H), 4.04 (s, 3H), 3.36 (m, 1H), 2.38 (s, 3H), 2.15 (s, 3H), 1.82 (m, 4H), 0.86 (t, 6H).

Ejemplo 243.

Preparación de 3-(1-metil-5-fenil-1H-pirazol-4-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

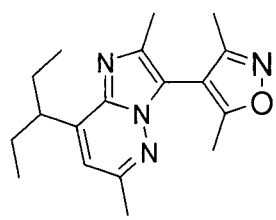


Al usar el procedimiento análogo al Ejemplo 242, a partir de 8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (160 mg, 0.73 mmol), 4-bromo-1-metil-5-fenil-1H-pirazol (250 mg, 1.1 mmol), carbonato de cesio (490 mg, 1.50

mmol) y $PdCl_2(PPh_3)_2$ (15 mg) en DMF (5 ml) da el compuesto del título (18 mg, 4% de rendimiento). ES-EM (m/z): calculado para $C_{23}H_{27}N_5$: 373.5; encontrado 374.2 $(M+H)^+$. ^1H RMN (400 mHz, $CDCl_3$): δ 7.85 (s, 1H), 7.32 (m, 3H), 7.23 (m, 2H), 6.55 (s, 1H), 3.94 (s, 3H), 3.27 (m, 1H), 2.38 (s, 3H), 2.03 (s, 3H), 1.76 (m, 4H), 0.83 (t, 6H).

Ejemplo 244.

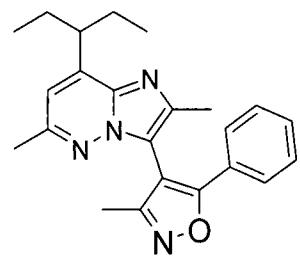
Preparación de 3-(3,5-dimetil isoxazol-4-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.,



Al usar el procedimiento análogo al Ejemplo 242, de 8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (200 mg, 0.90 mmol), 4-bromo-3,5-dimetil isoxazol (Alfa, 320 mg, 1.8 mmol), carbonato de cesio (880 mg, 2.70 mmol) y $PdCl_2(PPh_3)_2$ (25mg) en DMF (5 ml), se calienta a 130 durante 4 hrs, luego durante la noche a temperatura ambiente da el compuesto del título (65 mg, 23% de rendimiento). ES-EM (m/z): calculado para $C_{18}H_{24}N_4O$: 312.4; encontrado 313.2 $(M+H)^+$. ^1H RMN (400 mHz, $CDCl_3$): δ 6.68 (s, 1H), 3.32 (m, 1H), 2.50 (s, 3H), 2.39 (s, 3H), 2.33 (s, 3H), 2.19 (s, 3H), 1.82 (m, 4H), 0.87 (m, 6H).

Ejemplo 245.

Preparación de 3-(3-metil-5-fenil-isoxazol-4-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.



A. 4-Bromo-3-metil-5-fenil isoxazol.

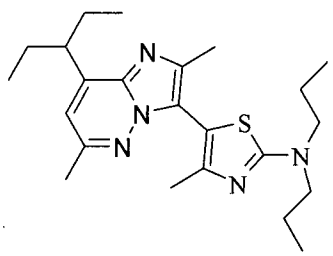
3-Metil-5-fenil isoxazol (Synthesis, 1997, 439-442) (1.0g, 6.3 mmol) y N-bromosuccinimida (1.2 g, 6.9 mmol) se combinan juntos en ácido acético (30 ml) y se calienta hasta reflujo con agitación durante 2 hrs. La solución se agrega hasta agua y se extrae dos veces con acetato de etilo. Los extractos orgánicos combinados se lavan con bicarbonato de sodio (saturado) y NaCl saturado luego se seca sobre Na_2SO_4, se filtra y se concentra. El producto crudo se purifica por cromatografía al usar un gradiente de hexano-acetato de etilo (100% hexano hasta 10% acetato de etilo en hexano) para eluir el compuesto del título (1.5 g, 100% de rendimiento). ^1H RMN (400 mHz, $CDCl_3$): δ 8.02 (m, 2H), 7.49 (m, 3H), 6.34, 2.35 (s, 3H).

B. 3-(3-Metil-5-fenil-isoxazol-4-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

Al usar el procedimiento análogo al Ejemplo 257, 8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (200 mg, 0.90 mmol), 4-bromo-3-metil-5-fenil isoxazol (430 mg, 1.8 mmol), carbonato de cesio (880 mg, 2.70 mmol) y $PdCl_2(PPh_3)_2$ (25mg) en DMF (5 ml) se combinan y se calientan a 130°C. durante 5 hrs para dar el compuesto del título (65 mg, 23% de rendimiento). ES-EM (m/z): calculado para $C_{23}H_{26}N_4O$: 374.5; encontrado 375.1 $(M+H)^+$. ^1H RMN (400 mHz, $CDCl_3$): δ 7.50 (d, 2H), 7.31 (m, 3H), 6.69 (s, 1H), 3.39 (m, 1H), 2.48 (s, 3H), 2.20 (s, 6H), 2.33 (s, 3H), 1.84 (m, 4H), 0.88 (m, 6H).

Ejemplo 246.

{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-metil-tiazol-2-il}-dipropil-amina.

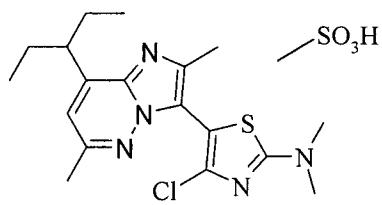


35 mg de 3-(2-Bromo-4-metil-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.09mmol) y 45 mg de di-n-propilamina (0.44 mmol) y 57 mg de carbonato de cesio (0.18 mmol) se colocan en 4 ml de un vial de reacción con 3 ml de THF seco y el vial se cierra con una tapa de Teflon. El vial de reacción se calienta a 100°C durante 4h.

La mezcla de reacción se transfiere dentro de un recipiente de reacción para microondas y se sella. La mezcla de reacción se calienta a 160°C durante 30 min por microondas. La mezcla se concentra y se aplica en columna de cromatografía de gel de sílice (Hexano:AcOEt=3:1) para dar el compuesto del título. 5.3 mg (14%); espectro de masa (m/e): 414; ^{1}H-RMN ($CDCl_3$): 5.59(s, 1H), 3.45(m, 4H), 3.36(m, 1H), 2.57(s, 3H), 2.47(s, 3H), 2.17(s, 3H), 1.80(m, 8H), 0.99(t, 6H, J=7.5Hz), 0.89(t, 6H, J=9.4Hz).

Ejemplo 247.

N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-cloro-tiazol-2-il}-dimetilamina, sal de mesilato.

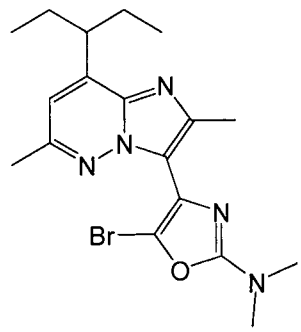


89 mg de N-{5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-cloro-tiazol-2-il}-dimetilamina (0.236 mmol) se disuelve en 2.0 ml de acetato de etilo y 0.236 ml de 1M ácido metanosulfónico en acetato de etilo (0.236 mmol) se agrega. Los solventes se remueven bajo gas N_2 y los cristales precipitados se recolectan, se lava con Et2O y se secan. 92 mg (83%); espectro de masa (m/e): 378(M+1); ^{1}H-RMN($CDCl_3$): 7.30(s, 1H), 3.67(m, 1H), 3.22(s,

6H), 2.93(s, 3H), 2.78(s, 3H), 2.78(s, 3H), 2.71(s, 3H), 1.95(m, 2H), 1.82(m, 2H), 0.96(t, 6H, J=7.3Hz).

Ejemplo 248.

Preparación de {5-Bromo-4-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-oxazol-2-il}-dimetil-amina.



A. 8-(1-Etil-propil)-2,6-dimetil-3-oxazol-4-il-imidazo[1,2-b]piridazina.

500 mg de 8-(1-etil-propil)-3-yodo-2,6-dimetil-imidazo[1,2-b]piridazina (1.46 mmol), 622 mg de oxazol (9.0 mmol), 79 mg de trifenilfosfina (0.3 mmol) y 989 mg de carbonato de cesio (3.03 mmol) se colocan en un vial de reacción con 7 ml de DMF seco. El gas N_2 se burbujea en la mezcla durante 30 min y 67 mg de Pd_2dba_3 (0.07 mmol) se agrega. El vial de reacción se tapa con una tapa de Teflon y se agita a 130°C durante 3 días. La mezcla de reacción se diluye con diclorometano, se lava con NaCl saturado, se seca sobre Na_2SO_4 y se evapora. El producto crudo se aplica encima de una columna de cromatografía de gel de sílice (Hexano:EtOAc = 3:1) para dar el compuesto del título 172 mg

(42%); espectro de masa (m/e): 285; ^{1}H-RMN($CDCl_3$): 8.04(s, 1H), 7.97(s, 1H), 6.78(s, 1H), 3.35(m, 1H), 2.80(s, 3H), 2.65(s, 3H), 1.86(m, 4H), 0.88(t, 6H).

B. 3-(2,5-Dibromo-oxazol-4-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

172 mg de 8-(1-etil-propil)-2,6-dimetil-3-oxazol-4-il-imidazo[1,2-b]piridazina (0.60 mmol) y 270 mg de NBS (1.51 mmol) se disuelven en 8.0 ml de diclorometano y se agita a temperatura ambiente durante la noche. La mezcla de reacción se concentra y se aplica sobre una columna de cromatografía de gel de sílice (Hexano:EtOAc = 3:1) para dar 70 mg del compuesto del título (26%); espectro de masa (m/e): 442; ^{1}H-RMN($CDCl_3$): 6.82(s, 1H), 3.32(m, 1H), 2.59(s, 3H), 2.54(s, 3H), 1.86(m, 4H), 0.89(t, 6H, J=7.4Hz).

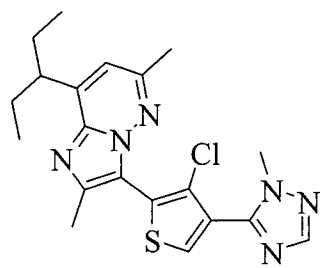
C. {5-Bromo-4-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-oxazol-2-il}-dimetil-amina.

67 mg de 3-(2,5-Dibromo-oxazol-4-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.15 mmol), 146 mg de carbonato de cesio (0.45 mmol) y 3.0 ml de dimetilamina 2.0M en THF (6 mmol) se colocan en un vial de reacción 4 ml y el vial se cierra con una tapa de Teflon. El vial de reacción se calienta a 130°C durante la noche. La mezcla de reacción se concentra y se aplica sobre una columna de cromatografía de

gel de sílice (Hexano:AcOE t = 3:1) para dar 53 mg del compuesto del título (87%); espectro de masa (m/e): 406; ^{1}H-RMN($CDCl_3$): 6.72(s, 1H), 3.37(m, 1H), 3.15(s, 6H), 2.58(s, 3H), 2.53(s, 3H), 1.85(m, 4H), 0.90(t, 6H, J=7.2Hz).

Ejemplo 249.

Preparación de 3-[3-cloro-4-(2-metil-2H-[1,2,4]triazol-3-il)-tiofen-2-il]-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

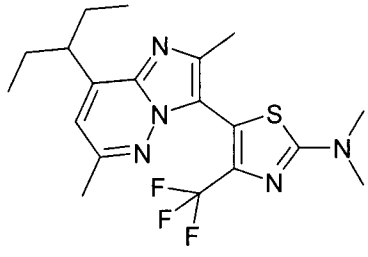


A un matraz de 3-(4-bromo-3-cloro-tiofen-2-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.20 g, 0.49 mmol) se agrega 0.5 g/ mL de Zn Reike® (1.3 mL, 0.97 mmol). La suspensión espesa se calienta a 65°C durante 1 hora, se coloca en una centrifuga durante 5 minutos, y la solución se transfiere a un matraz que contiene 5-bromo-1-metil-1H-[1,2,4]triazol (0.12 g, 0.73 mmol) y PdCl2(dppf) (0.018 g, 0.024 mmol). La solución se calienta a 65°C durante la noche, se diluye con EtOAc (20 mL), se lava con NH_4Cl saturado (15 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por cromatografía

instantánea ISCO (20%-50% gradiente EtOAc) resulta el compuesto del título (0.018 g, 0.043 mmol, 9%). ^{1}H RMN ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.51 (s, 3H), 2.52 (s, 3H), 3.26-3.37 (m, 1H), 3.95 (s, 3H), 6.72 (s, 1H), 7.82 (s, 1H), 8.01 (s, 1H). CL/EM (m/z): calculado para $C_{20}H_{23}ClN_6S$ $(M+H)^+$: 415.2; encontrado: 415.3.

Ejemplo 250.

Preparación de {5-[8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-trifluorometil-tiazol-2-il}-dimetil-amina.



A. 8-(1-Etil-propil)-2,6-dimetil-3-tiazol-5-il-imidazo[1,2-b]piridazina.

Yodoimidazopiridazina (6.75 g, 19.7 mmol), trifenilfosfina (1.03 g, 3.94 mmol), Cs_2CO_3 (12.84 g, 39.4 mmol) y $Pd_2(dba)_3$ (900 mg, 0.98 mmol) se colocan en un tubo sellado con 65 mL de DMF seco y gas N_2 se burbujea en la mezcla durante 5 minutos. Tiazol (8.36 g, 6.7 mL, 98.4 mmol) se agrega, y la mezcla se calienta a 130°C durante la noche. La mezcla se enfría hasta temperatura ambiente y se apaga por

la adición de solución NH_4Cl saturada (200 mL). La mezcla se extrae con Et_2O (3 x 100 mL) y las capas orgánicas se lava con agua (2 x 100 mL) y NaCl saturado (100 mL), se seca sobre $MgSO_4$ y se concentra. El producto crudo se purifica por cromatografía instantánea sobre gel de sílice (eluyente; hexano:EtOAc= 4:1) para dar 3.80 g del compuesto del título (rendimiento: 64%). ESIEM: m/z 301 [M+H]+.

B. 3-(2,4-Dibromo-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

A una solución de 8-(1-etil-propil)-2,6-dimetil-3-tiazol-5-il-imidazo[1,2-b]piridazina. (3.80 g, 12.6 mmol) en CH_3CN (55 mL) a temperatura ambiente se agrega NBS (5.18 g, 29.1 mmol), y la mezcla se agita a temperatura ambiente durante 3 horas. Un precipitado blanco se forma tal que se filtra in vacuo, para dar 4.86 g del compuesto del título (Rendimiento: 84%). ESIEM: m/z 459, 461 [M+H]+.

C. 3-(4-Bromo-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

A una solución de 3-(2,4-dibromo-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (4.86 g, 10.6 mmol) en THF (150 mL) bajo atmósfera de N_2 a -78°C, BuLi (6.63 mL 1.6 M en hexano, 10.6 mmol) se agrega gota a gota durante un periodo de 10 minutos. La mezcla se agita a -78°C

durante 30 minutos. Agua se agrega, y la mezcla se extrae con Et_2O (3 x 100 mL), se seca sobre $MgSO_4$ y se concentra in vacuo. El producto crudo se purifica por cromatografía instantánea sobre gel de sílice (eluyente hexano:EtOAc 5:1) para dar 3.28 g del compuesto del título (Rendimiento: 82%). ESIEM: m/z 379, 381 [M+H]+.

D. 8-(1-Etil-propil)-2,6-dimetil-3-(4-trifluorometil-tiazol-5-il)-imidazo[1,2-b]piridazina.

A una solución de 3-(4-bromo-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (2.45 g, 6.5 mmol) en NMP (35 mL) en un tubo sellado se agrega $FSO_2CF_2CO_2Me$ (2.5 g, 1.65 mL, 13 mmol) y CuI (2.48 g, 13 mmol). Gas N_2 se burbujea en la mezcla durante 5 minutos, y la mezcla se calienta a 120°C durante 9 horas. Después del enfriamiento hasta temperatura ambiente, agua (100 mL) y solución NaCl saturado (100 mL) se agregan a la mezcla. La mezcla se extrae con Et_2O (5 x 80 mL); se lava con agua (2 x 100 mL), y se seca sobre $MgSO_4$ y se concentra. El producto crudo se purifica por cromatografía instantánea sobre gel de sílice (eluyente hexano:EtOAc 5:1) para obtener 960 mg del compuesto del título (Rendimiento: 40%). ESIEM: m/z 369 [M+H]+.

E. 3-(2-bromo-4-trifluorometil-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina.

A una solución de 8-(1-etil-propil)-2,6-dimetil-3-(4-trifluorometil-tiazol-5-il)-imidazo[1,2-b]piridazina (915 mg, 2.48 mmol) en 40 mL de THF bajo atmósfera de N_2 al -78°C, BuLi (1.86 mL 1.6 M en hexano, 2.98 mmol) se agrega lentamente. La mezcla se agita a -78°C durante 30 minutos. Luego, una solución de CBr_4 (989 mg, 2.98 mmol) en 3 mL de THF se agrega, y la mezcla se agita a -78°C durante 45 minutos. La reacción se apaga por la adición de solución NH_4Cl saturada (50 mL), se extrae con Et_2O (2 x 50 mL), se seca sobre $MgSO_4$, y se concentra in vacuo. El producto crudo se purifica por cromatografía instantánea sobre gel de sílice (eluyente CH_2Cl_2) para obtener 685 mg del compuesto del título (Rendimiento: 62%). ^1H RMN ($CDCl_3$): δ 0.86 (t, J = 7.5 Hz, 6H), 1.82 (m, 4H), 2.45 (s, 3H), 2.51 (s, 3H), 3.27 (m, 1H), 6.74 (s, 1H). ESIEM: m/z 447, 449 [M+H]+.

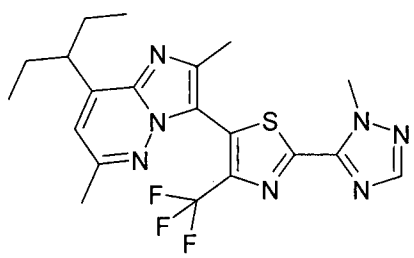
F. {5-[8-(1-Etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazin-3-il]-4-trifluorometil-tiazol-2-il}-dimetil-amina.

100 mg de 3-(2-Bromo-4-trifluorometil-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina (0.22 mmol) y 218 mg de carbonato de cesio (0.66 mmol) se colocan en 4 ml de vial de reacción y 3 ml de dimetilamina 2 M en THF se agrega. El vial de reacción se tapa con una tapa de Teflon y se calienta a 120°C durante la noche. La mezcla de reacción se filtra y se concentra y se aplica sobre una columna de

cromatografía de gel de sílice (Hexano :AcOEt =3:1) para dar 85 mg del compuesto del título. Rendimiento 94%. espectro de masas(m/e): 412 (M+1).

Ejemplo 251.

Preparación de 8-(1-Etil-propil)-2,6-dimetil-3-[2-(2-metil-2H-[1,2,4]triazol-3-il)-4-trifluorometil-tiazol-5-il]-imidazo[1,2-b]piridazina

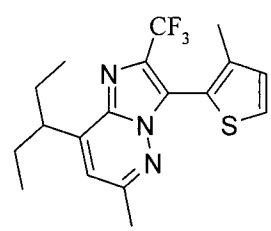


164 mg de 1-Metil-1,2,4-triazol (1.96 mmol) se disuelve en 2 ml de THF y se enfría hasta -78°C. 0.8 ml de 2.5M n-butillitio en hexano (1.96 mmol) se agrega lentamente y se agita a -78°C, se calienta hasta temperatura ambiente y se agita a temperatura ambiente durante 15 min y se enfría hasta -78°C. 3.96 ml de 0.5 M $ZnCl_2$ en THF (1.98 mmol) se agrega y se agita a temperatura ambiente durante 15 min. 180 mg de 3-(2-bromo-4-trifluorometil-tiazol-5-il)-8-(1-etil-propil)-2,6-dimetil-imidazo[1,2-b]piridazina y 54 mg de PdCl2(pddf) (0.06 mmol) se agregan. El vial se cierra con una tapa de Teflon y se calienta a 80°C durante la noche. NH_4Cl acuoso se agrega para apagar la reacción y la mezcla se extrae por CH_2Cl_2, se

seca sobre Na2SO4 y se evapora. El producto crudo se coloca en columna de cromatografía de gel de sílice (Hexano:AcOEt =3:1) para dar 119 mg del compuesto del título. Rendimiento 58%. espectro de masas(m/e) : 449(M+1).

Ejemplo 252.

Preparación de 8-(1-Etil-propil)-6-metil-3-(3-metil-tiofen-2-il)-2-trifluorometil-imidazo[1,2-b]piridazina.



A. 8-(1-Etil-propil)-6-metil-2-trifluorometil-imidazo[1,2-b]piridazina.

α-Bromotrifluoroacetona (402 mg, 2.93 mmol) se agrega a un tubo de reacción de microondas 10 mL seco que contiene 4-(1-etil-propil)-6-metil-piridazin-3-ilamina (500 mg, 2.79 mmol) en EtOH (2.0 mL). La mezcla resultante se calienta a 110°C en el microondas durante 1 hora. $NaHCO_3$ (246.5 mg, 2.93 mmol) se agrega, y la reacción se mezcla bien durante 5 minutos. Luego, la reacción se calienta a 110°C en el microondas durante 1 hora. El solvente se remueve por medio de presión reducida, y la reacción se diluye con acetato de etilo (30 mL). La capa orgánica se lava con H_2O (3 X 10 mL), y las capas orgánicas combinadas se extraen con acetato de

etilo (2 X 20 mL). Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y purifican por cromatografía en gel de sílice para dar el compuesto del título (29.5 mg, 0.068 mmol, 9.8 %). ^{1}H-RMN ($CDCl_3$), δ 0.87 (t, J = 7.6 Hz, 6H), 1.86 (m, 4H), 2.60 (s, 3H), 3.30 (m, 1H), 6.80 (s, 1H), 8.14 (s, 1H) ppm. ES-EM (m/z): calculado para $C_{13}H_{16}F_3N_3$ $(M+H)^+$: 271.29; encontrado: 272.2

B. 8-(1-Etil-propil)-6-metil-3-(3-metil-tiofen-2-il)-2-trifluorometil-imidazo[1,2-b]piridazina.

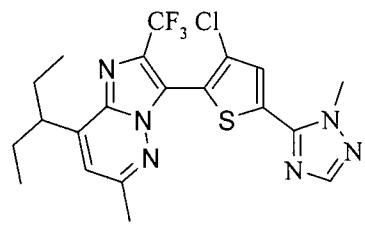
A un matraz de fondo redondo de 10 ml seco con condensador a reflujo que contiene 8-(1-etil-propil)-6-metil-2-trifluorometil-imidazo[1,2-b]piridazina (300 mg, 1.11 mmol), 2-bromo-3-metil-tiofeno (216 mg, 1.22 mmol), y Cs_2CO_3 (760 mg, 2.33 mmol) se agrega NMP (1.7 ml). La mezcla se desgasifica con N_2 burbujeado durante 15 min y $Pd_2(dba)_3$ (50.8 mg, 0.055 mmol) y PPh_3 (58.2 mg, 0.222 mmol) se agrega. La mezcla de reacción se agita a 130°C durante la noche. La mezcla se enfría hasta temperatura ambiente, se diluye con H_2O; y se extrajo con EtOAc (3 x 20 ml). Las capas orgánicas se secan (Na_2SO_4), se filtran y purifican por CLAR para dar el compuesto del título (32 mg, 0.087 mmol, 8%). ^{1}H-RMN ($CDCl_3$), δ 0.93 (t, J = 7.2 Hz, 6H), 1.91 (m, 4H), 2.15 (s, 3H), 2.58 (s, 3H), 3.36 (m, 1H), 6.91 (s, 1H), 7.08 (d, J = 5.3 Hz,

543

1H), 7.55 (d, J = 5.5 Hz, 1H) ppm. ES-EM (m/z): calculado para $C_{18}H_{20}F_3N_3S$ $(M+H)^+$: 367.44; encontrado: 368.1.

Ejemplo 253.

Preparación de 3-[3-Cloro-5-(2-metil-2H-[1,2,4]triazol-3-il)-tiofen-2-il]-8-(1-etil-propil)-6-metil-2-trifluorometil-imidazo[1,2-b]piridazina.

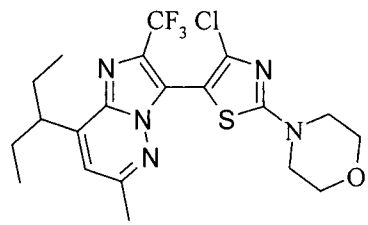


En un matraz de fondo redondo seco de 25 mL, 8-(1-etil-propil)-6-metil-2-trifluorometil-imidazo[1,2-b]piridazina (182 mg, 0.671 mmol), 5-(5-bromo-4-cloro-tiofen-2-il)-1-metil-1H-[1,2,4]triazol (225 mg, 0.805 mmol), KOAc (330.2 mg, 3.36 mmol), y TBAB (217 mg, 0.671 mmol) se disuelven en NMP (3 mL). La mezcla se desgasifica con nitrógeno burbujeado durante 20 minutos. Luego, $Pd(OAc)_2$ (8 mg, 0.034 mmol) y TDBPP (20.4 g, 0.34 moles) se agregan. La mezcla de reacción se calienta hasta 125°C durante 3 horas para dar el compuesto del título (125 mg, 0.267 mmol, 40%). ^{1}H-RMN ($CDCl_3$), δ 0.88 (t, J = 7.2 Hz, 6H), 1.87 (m, 4H), 2.537 (s, 3H), 3.32 (m, 1H), 4.16 (s, 3H), 6.86 (s, 1H), 7.51 (s, 1H), 7.91 (s, 1H) ppm. ES-EM (m/z): calculado para $C_{20}H_{20}ClF_3N_6S$ $(M+H)^+$: 468.93; encontrado: 469.2.

549

Ejemplo 254.

Preparación de 3-(4-Cloro-2-morfolin-4-il-tiazol-5-il)-8-(1-etil-propil)-6-metil-2-trifluorometil-imidazo[1,2-b]piridazina.



A. 8-(1-Etil-propil)-3-yodo-6-metil-2-trifluorometil-imidazo[1,2-b]piridazina.

En un matraz de fondo redondo seco de 25 mL, 8-(1-etil-propil)-6-metil-2-trifluorometil-imidazo[1,2-b]piridazina (460 mg, 1.70 mmol) se disuelven en THF seco (3.5 mL) y se enfrían hasta -78°C. Una solución de 2.5 M n-butillitio en hexanos (748 µL, 1.87 mmol) se agrega gota a gota. La mezcla de reacción se agita durante 20 minutos a -78°C, luego se entibia hasta 0°C durante 15 minutos. Una solución de I_2 (453 mg, 1.79 moles) en THF (2.0 mL) se agrega gota a gota. La reacción se agita durante 15 minutos a 0°C, y luego se entibia hasta temperatura ambiente. La reacción se agita durante la noche, y el solvente se remueve por medio de presión reducida. La mezcla de reacción se redisuelve en acetato de etilo (50 mL) y se lava con una solución 1 N de $Na_2S_2O_3$ (2 X 20 mL). La capa acuosa se extrae con acetato de etilo (2 X 40 mL). Los extractos orgánicos combinados se

secan con Na_2SO_4, se filtran, y purifican por medio de cromatografía en gel de sílice para dar el compuesto del título (595 mg, 1.50 mmol, 88%). ^{1}H-RMN ($CDCl_3$), δ 0.82 (t, J = 8.0 Hz, 6H), 1.83 (m, 4H), 2.64 (s, 3H), 3.27 (m, 1H), 6.82 (s, 1H) ppm. ES-EM (m/z): calculado para $C_{13}H_{15}F_3IN_3$ $(M+H)^+$: 397.18; encontrado: 398.3.

B. 2,4-Dicloro-tiazol.

En un matraz de fondo redondo de 250 mL, 2.4-tiazolidina diona (12.5 g, 107 mmol) se disuelve en oxicloruro de fósforo (70 mL) y piridina (8.5 mL). La mezcla se agita bajo reflujo durante 3 horas y se enfría hasta temperatura ambiente. La mezcla de reacción se vacía en agua con hielo lentamente y se extrajo con diclorometano. Los extractos orgánicos combinados se secan con Na_2SO_4, se filtran, y se concentran. El residuo se purifica por medio de cromatografía en gel de sílice para dar el compuesto del título (9.18 g, 59.6 mmol, 56%). ^{1}H-RMN ($CDCl_3$), δ 7.01 (s, 1H) ppm.

C. 4-(4-Cloro-tiazol-2-il)-morfolina.

En un recipiente de presión seco de 75 mL, 2,4-dicloro-tiazol (500 mg, 3.2 mmol) y morfolina (560 µL, 6.4 mmol) se disuelven en THF seco (2.0 mL). Cs_2CO_3 (1.56 g, 4.8 mmol) se agrega, y el recipiente de reacción se sella. La mezcla de

reacción se calienta hasta 110°C durante la noche. El solvente se remueven por medio de presión reducida, y la mezcla de reacción cruda se purifica por medio de cromatografía en gel de sílice para dar el compuesto del título (597 mg, 2.92 mmol, 91%). ^{1}H-RMN ($CDCl_3$), δ 3.45 (m, 4H), 3.79 (m, 4H), 6.31 (s, 1H) ppm. ES-EM (m/z): calculado para $C_7H_9ClN_2OS$ $(M+H)^+$: 204.68; encontrado: 205.2.

D. 3-(4-Cloro-2-morfolin-4-il-tiazol-5-il)-8-(1-etil-propil)-6-metil-2-trifluorometil-imidazo[1,2-b]piridazina.

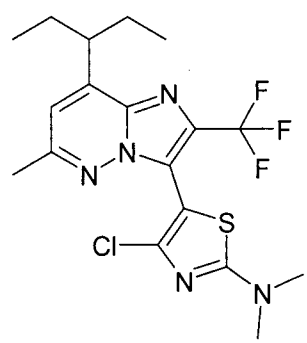
En un matraz de fondo redondo seco de 25 mL, 8-(1-etil-propil)-3-yodo-6-metil-2-trifluorometil-imidazo[1,2-b]piridazina (250 mg, 0.630 mmol), 4-(4-cloro-tiazol-2-il)-morfolina (194 mg, 0.945 mmol), y Cs_2CO_3 (410 mg, 1.26 mmol) se disuelven en DMF. La mezcla se desgasifica con nitrógeno burbujeado durante 15 minutos. Luego, $Pd_2(dba)_3$ (18 mg, 0.032 mmol) y PPh_3 (33 mg, 0.126 mmol) se agregan. La mezcla de reacción se calienta hasta 130°C durante la noche. La reacción se enfría hasta temperatura ambiente, se apaga con una solución de NH_4Cl saturado (20 mL), y se extrajo con Et_2O (3 X 50 mL). Los extractos orgánicos combinados se lavan con salmuera (30 mL), se secan con Na_2SO_4, se filtran y se concentran. El residuo se purifica por medio de CLAR de fase inversa con un gradiente al 30-80% de CH_3CN en 10mM NH_4HCO_3/H_2O/5% CH_3CN (pH 10.0)para dar el compuesto del título

551

(11 mg, 0.023 mmol, 4%). ^{1}H-RMN ($CDCl_3$), δ 0.86 (t, J = 7.3 Hz, 6H), 1.84 (m, 4H), 2.55 (s, 3H), 3.31 (m, 1H), 3.54 (dd, J = 5.2, 4H), 3.84 (dd, J = 5.2 Hz, 4H), 6.82 (s, 1H) ppm. ES-EM (m/z): calculado para $C_{20}H_{23}ClF_3N_5OS$ $(M+H)^+$: 473.95; encontrado: 474.2.

Ejemplo 255.

Preparación de {4-Cloro-5-[8-(1-etil-propil)-6-metil-2-trifluorometil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-dimetil-amina.



A. (4-Cloro-tiazol-2-il)-dimetil-amina.

Usando un procedimiento análogo al Ejemplo 254C, 2,4-dicloro-tiazol (500 mg, 3.2 mmol) y dimetilamina (una solución 2.0 M en THF, 3 mL, 6.4 mmol) se hace reaccionar para dar el compuesto del título (60 mg, 0.152 mmol, 15%). ^{1}H-RMN ($CDCl_3$), δ 3.09 (s, 6H), 6.22 (s, 1H) ppm. ES-EM (m/z): calculado para $C_5H_7ClN_2S$ $(M+H)^+$: 162.64; encontrado: 163.2.

552

B. {4-Cloro-5-[8-(1-etil-propil)-6-metil-2-trifluorometil-imidazo[1,2-b]piridazin-3-il]-tiazol-2-il}-dimetil-amina.

Usando un procedimiento análogo al Ejemplo 254D, 8-(1-etil-propil)-3-yodo-6-metil-2-trifluorometil-imidazo[1,2-b]piridazina (250 mg, 0.630 mmol) se acopla con (4-cloro-tiazol-2-il)-dimetil-amina (154 mg, 0.945 mmol) para proporcionar el producto deseado. ^{1}H-RMN ($CDCl_3$), δ 0.85 (t, J = 7.4 Hz, 6H), 1.83 (m, 4H), 2.55 (s, 3H), 3.16 (s, 6H), 3.31 (m, 1H), 6.81 (s, 1H) ppm. ES-EM (m/z): calculado para $C_{18}H_{21}ClF_3N_5S$ $(M+H)^+$: 431.91; encontrado: 432.2.

Ejemplo A

Evaluación de Potencia In Vivo usando Enlace Ex Vivo

Para evaluar potencia in vivo, un compuesto de la presente invención se evaluó usando enlaceo ex vivo. Usando los procedimientos como se proporcionan en D. R. Gehlert y colaboradores, *EJP* 509: 145-153 (2005), un compuesto se administra a una rata vía la ruta oral. El enlace de ^{125}I-sauvagine al cerebelo se evalúa luego ex vivo como se describe en Gehlert y colaboradores, Por ejemplo, el Ejemplo 199 proporciona un resultado de ED_{50} de 1.3 mg/kg.

Ejemplo B

Ensayo de Enlaceo del Filtro CRF1

Las limitaciones de expresión de CRF1 humano de base de plásmido, en términos de generación de una línea de célula recombinante con densidad de receptor suficiente para desarrollar un ensayo de enlace, son superados por el uso de un sistema de expresión retroviral de Phoenix licenciado de Standford. La línea de células HEK-hCRF1 estable se usa para preparar membranas y reacciones de enlace (200 µl) se establecen como sigue: 50 µl de ^{125}I-sauvagina (0.2 nM final), 50 µl de compuesto y 100 µl de membrana CRF1 (25 µg/reacción). Las reacciones se incubaron a temperatura de habitación por 2 horas y luego se terminaron por filtración a través de placas (96 pozos) de filtro de fibra de cristal de FB Millipore pretratadas. Las placas se lavan dos veces con solución amortiguadora de ensayo frías a hielo (50 mM de tris, 12.5 mM de NaCl, 1mM de EDTA, 10 mM de $MgCl_2$, 0.05% BSA, pH 7.2), se secaron durante la noche y se contaron con Microscint 40 de 100 µl en un contador de MicroBeta. El enlace no específico (NSB) se determinó en la presencia de 0.5 µM de sauvagina no etiquetada. Las determinaciones triplicadas comúnmente se corren y los puntos de los datos medios se dibujan mediante Graph Pad Prism.

Usando este ensayo, los compuestos ejemplificados reivindicados de la presente invención inhiben el enlace de

^{125}I-Sauvagina (4 nM) en células enrolladotas/adherentes con un Ki (constante de inhibición por debajo de 1 µM. Por ejemplo, los Ejemplos 102 y 199 exhiben un Ki de 4.92 ± 0.57 nM y 9.98 ± 0.72 nM, respectivamente.

Ejemplo C

Ensayo de Enlace de Filtro CRF2

Las limitaciones de la expresión de CRF2 humano de base plásmido, en términos de generación de una línea de célula recombinante con densidad de receptor suficiente para desarrollar un ensayo de enlace, se superan mediante el uso del sistema de expresión retroviral de Phoenix licenciado por Standford. La línea de células HEK-hCRF2 estable se usa para preparar membranas y reacciones de enlace (200 µl) se establecen como sigue: 50 µl de ^{125}I-sauvagina (0.2 nM de concentración final), 50 µl de compuesto y 100 µl de membrana CRF2 (25 µg/reacción). Las reacciones se incubaron a temperatura de habitación por 2 horas y luego se terminaron por filtración a través de placas (96 pozos) de filtro de fibra de cristal de FB Millipore pretratadas. Las placas se lavan dos veces con solución amortiguadora de ensayo frías a hielo (50 mM de tris, 12.5 mM de NaCl, 1mM de EDTA, 10 mM de $MgCl_2$, 0.05% BSA, pH 7.2), se secaron durante la noche y se contaron con Microscint 40 de 100 µl en un contador de MicroBeta. El enlace no específico (NSB) se determinó en la

presencia de 0.5 µM de sauvagine no etiquetada. Alternativamente, los compuestos se evaluaron usando un ensayo de Proximidad de Escintilación. Este ensayo se establece como sigue: 50 µl de ^{125}I-sauvagina (0.2 nM de concentración final), 50 µl de compuesto o sauvagina no etiquetada (NSB) y 100 µl que contienen 250 µg de aglutinina de germen de trigo (WGA) perlas de SPA y membrana de CRF2 (1.5 µg/reacción). Las placas se incubaron por 4-5 horas a temperatura de habitación y luego se centrifugaron a 200 X g por 10 minutos. La reactividad asociada se evalúa usando un contador de escintilación Wallac Trilux. El enlace se evalúa comúnmente usando determinaciones por triplicado y los puntos de los datos promedio se dibujan mediante Graph Pad Prism. Los compuestos son seleccionados por exclusión inicialmente a una concentración fija y, si la actividad es suficiente se nota, subsiguientemente se generan las curvas de respuesta de concentración.

Los compuestos de la presente invención se evalúan en el ensayo de enlace de CRF2 y exhiben pico de afinidad para el receptor CRF2. Por ejemplo, los Ejemplos 102 y 199 exhiben un porcentaje de inhibición a 50 µM de 9.0 ± 2.6 y 16.9 ± 1.9, respectivamente. Estos resultados sugieren que los compuestos de la presente invención son altamente selectivos para el receptor CRF1.

556

Ejemplo D

Biocapacidad y Propiedades Farmacocinéticas

Los compuestos de la Fórmula I son antagonistas de CRF1, y sorpresivamente poseen propiedades relacionadas con su farmacocinética y biocapacidad.

El volumen de distribución (Vdist) relaciona la cantidad del fármaco en el cuerpo para la concentración del fármaco en la sangre o plasma. El volumen de distribución se refiere al volumen de fluido que podría ser requerido para contener la cantidad total del fármaco en el cuerpo en la misma concentración como en la sangre o plasma: Vdist=cantidad de fármaco en el cuerpo/concentración de fármaco en sangre o plasma (Goodman and Gillman). Para una dosis de 10 mg y una concentración de plasma de 10 mg/L, el volumen de distribución podría ser de 1 litro. El volumen de distribución refleja la extensión a la cual el fármaco está presente en el tejido extravascular. Un volumen grande de distribución refleja la tendencia de un compuesto a enlazar a los componentes del tejido comparados con enlace de proteína en plasma. En un establecimiento de clínica, el Vdist se puede usar para determinar una dosis de carga que logra una concentración de estado estable.

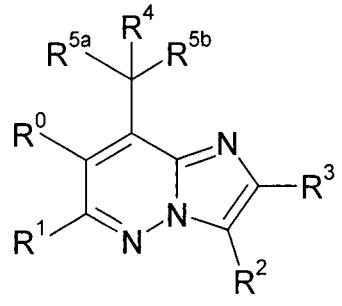
Para la prueba de volumen de distribución, ratas macho Sprague Dawley (N=3) son administradas con una dosis única intravenosa de 3 mg/kg de compuesto. Las muestras de plasma

múltiple se recolectan en momentos en el tiempo desde 0.08 hasta 24 horas después de dosis. Las muestras de plasma son analizadas por CL/EM/EM para determinar las concentraciones de plasma. Los cálculos farmacocinéticos de plasma se desarrollan para determinar los parámetros farmacocinéticas que incluyen Vdist y espacio de plasma (Clp).

La gran mayoría de fármacos del SNC y cardiovasculares comerciales exhiben un Vdist Humano de <10 L/Kg. En comparación con los antagonistas CRF CP154526 (Schulz y colaboradores, *Proc. Natl. Acad. Sci. (USA)*, 93:10477 (1996)) y NBI30775 (Chen y colaboradores, *Drug Development Research*, 65:216 (2005)) los cuales exhiben un Vdist de rata de 114 L/Kg y 76 L/Kg, respectivamente, después de una dosis intravenosa, los Ejemplos 48 y 199 de tiazol de la presente invención exhiben un Vdist de rata de solamente 9 y 2 L/Kg, respectivamente. Además, los Ejemplos 88 y 39 de tiofeno de la presente invención exhiben un Vdist de solamente 44 y 17 L/Kg, respectivamente.

REIVINDICACIONES

1. Un compuesto de la fórmula I



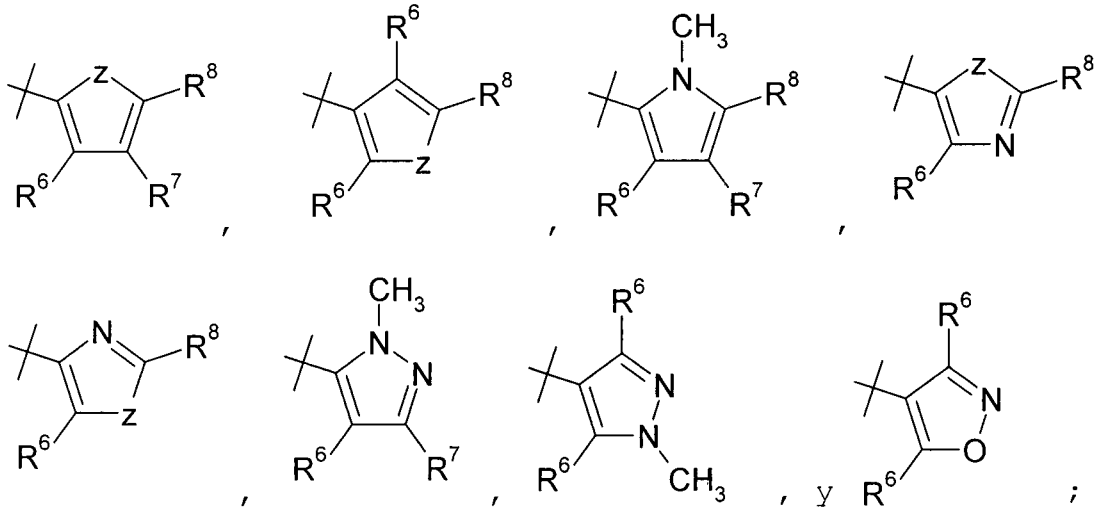
Fórmula I

caracterizado porque:

R^0 es hidrógeno, halo, metilo o etilo;

R^1 y R^3 son independientemente metilo, metoxi, o trifluorometilo;

R^2 se selecciona del grupo que consiste de :



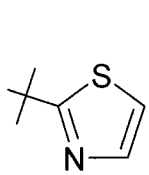
; y

R^4 es hidrógeno, halo, o hidroxi;

R^{5a} y R^{5b} son independientemente etilo o n-propilo;

R^6 cada que se preenta es independientemente hidrógeno, halo, ciano, alquilo (C_1-C_4), trifluorometilo, metoxi, o fenilo;

R^7 es hidrógeno, halo, metilo, metoxi, dimetilamino,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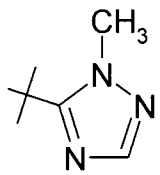
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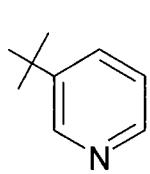
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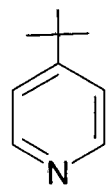
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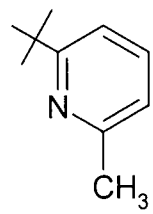
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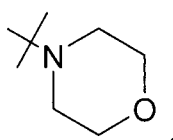
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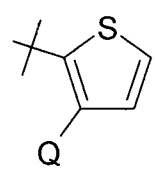
R^8 se selecciona del grupo que consiste de hidrógeno, halo, ciano, alquilo (C_1-C_4), R^aR^bN-, carbamilo, alcoxi (C_1-C_2)alquilo (C_1-C_2), R^{11}-C(O)-,

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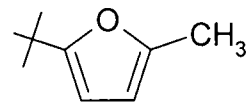
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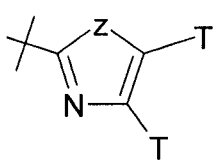
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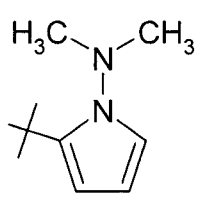
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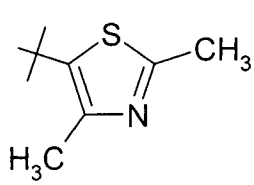
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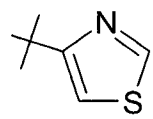
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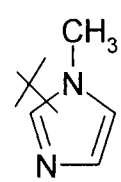
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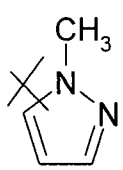
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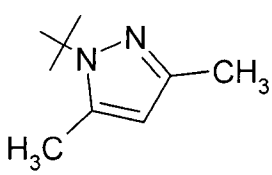
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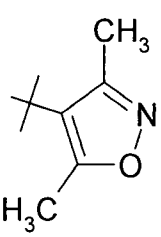
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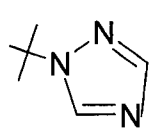
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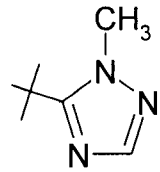
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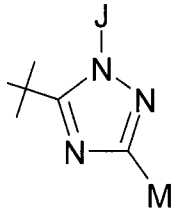
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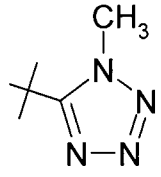
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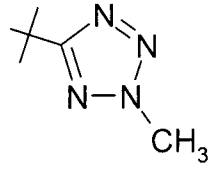
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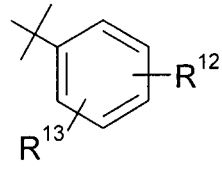
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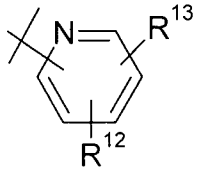
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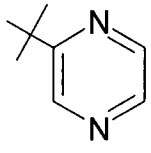
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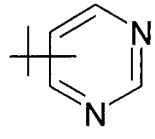
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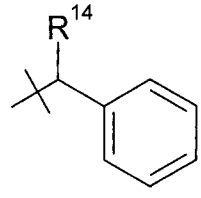
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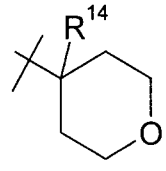
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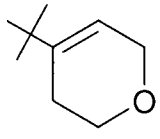
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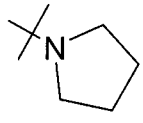
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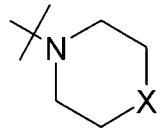
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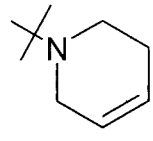
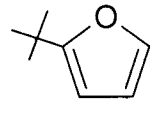

;

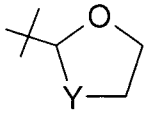
R^{11} es metoxi, metilamino, dimetilamino, o fenilo;

R^{12} es hidrógeno, halo, metilo, etilo, trifluorometilo, metoxi, trifluorometoxi dimetilamino, acetilo, o metilsulfonilo;

R^{13} es hidrógeno, metilo o halo;

R^{14} es hidrógeno o hidroxi;

R^{15} es metiltio, ciclopropilo, fenilo,  o;


;

R^a es hidrógeno, alquilo (C_1-C_5), cicloalquilo (C_3-C_5), metoxialquilo (C_2-C_4), acetilo, alquilsulfonilo (C_1-C_2), alquenilo (C_3), R^{15}-$(CH_2)_n$-, o alquilo (C_1-C_2) substituido con ciano, formilo, vinilo, o etinilo;

R^b es hidrógeno o alquilo (C_1-C_3);

X es $-CH_2-$, $-CO-$, $-O-$, $-S-$ o $-SO_2-$;

Y es $-CH_2-$ o $-O-$;

z es S o O;

n es 1 o 2;

Q es hidrógeno o metilo;

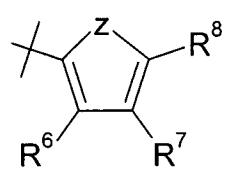
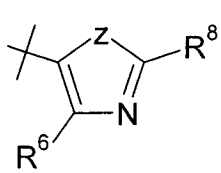
T es hidrógeno o metilo;

J es metilo, trifluoroetilo, o tert-butilo; y

M es metilo o halo;

y sales farmacéuticamente aceptables de los mismos.

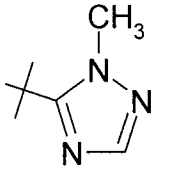
2. El compuesto de conformidad con la reivindicación 1 caracterizado porque R^0 y R^4 son hidrógeno, R^1 y R^3 son metilo, y R^{5a} y R^{5b} son etilo.

3. El compuesto de conformidad con cualesquiera de las reivindicaciones 1 hasta 2, caracterizado porque R^2 se selecciona del grupo que consiste de  o  y donde z es S.

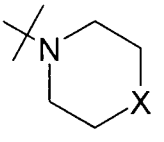
4. El compuesto de conformidad con cualesquiera de las reivindicaciones 1 hasta 3, caracterizado porque R^7 es hidrógeno.

5. El compuesto de conformidad con cualesquiera de las reivindicaciones 1 hasta 4, caracterizado porque R^6 es halo o metilo.

6. El compuesto de conformidad con cualesquiera de las reivindicaciones 1 hasta 5, caracterizado porque R^8 es



o



y donde X es O.

7. Una composición farmacéutica caracterizada porque comprende un compuesto de conformidad con cualesquiera de las reivindicaciones 1 hasta 6, o una sal farmacéuticamente aceptable del mismos, y un portador, diluyente o excipiente farmacéuticamente aceptable.

8. Un compuesto de conformidad con cualesquiera de las reivindicaciones 1 hasta 6 para uso como un medicamento.

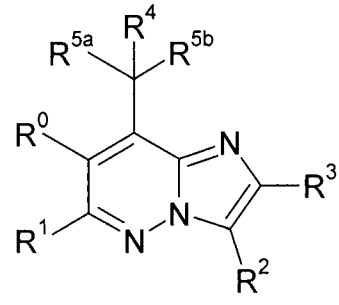
9. El uso de un compuesto de conformidad con cualesquiera de las reivindicaciones 1 hasta 6 para la

manufactura de un medicamento para tratar la ansiedad, depresión, trastorno depresivo mayor, síntomas del retiro de alcohol, o síndrome de intestino irritable en un mamífero.

10. El uso de un compuesto de conformidad con la reivindicación 9 caracterizado porque el mamífero es un humano.

RESUMEN DE LA INVENCION

La presente invención se refiere a compuestos imidazo[1,2-b]piridazina substituidos novedosos de la Fórmula I:



Fórmula I

composiciones farmacéuticas del mismo, y el uso de tales compuestos como antagonistas del receptor del factor 1 que libera la corticotropina (CRF1) en el tratamiento de trastornos psiquiátricos y enfermedades neurológicas.

569

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-098431- -00000-0000

Fecha: 2007-09-21 16:36:48 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 563

SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Descripción de la invención [ ]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Edgar Navarro
Firma Responsable

Fecha 21-09-07

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio 565

2020
Bogotá D.C.,

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
ELI-LILLY AND COMPANY

REFERENCIA	Radicación No.	7 98431
	Solicitud internacional	PCT/US2006/009942
	Fecha inicio fase nacional	21/10/2006
	Trámite	11
	Evento	379
	Actuación	416
	Oficio No.	4681
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC,

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

adpa11