SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 13-047157- -00000-0000
Fecha: 2013-03-08 16:46:40 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 5

Industria y Comercio
SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL
DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: IMIDAZOPIRIDAZINAS SUSTITUIDAS.

SOLICITANTE: BAYER INTELLECTUAL PROPERTY GmbH.

DIRECCIÓN: Alfred-Nobel-Str. 10, 40789 Monheim, Alemania.

APODERADO: CARLOS R. OLARTE

BOGOTÁ 08 de marzo de 2013

P2013/000048

OLARTE MOURE

OLARTE MOURE & A

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 13-047157- -00000-0000
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PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2013/000048**

SOLICITUD DE:

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**	**Nombre:** BAYER INTELLECTUAL PROPERTY GmbH **Dirección:** Alfred-Nobel-Str. 10, 40789 Monheim, Alemania. **Nacionalidad o Domicilio:** Alemana **Lugar de Constitución:** Alemania **Teléfono:** _____ **Fax:** _____ **E-mail:** _____	**IDENTIFICACIÓN** **C.C.** [ ] **NIT** [ ] **C.E.** [ ] **Otro** [ ] **Cual** _____ **Número** _____
REPRESENTANTE O APODERADO	**Nombre:** CARLOS R. OLARTE **Dirección:** Carrera 5 No. 34-03 Bogotá **Teléfono:** 601-7700 **Fax:** 601-7799 **E-mail:** office@olartemoure.com	**IDENTIFICACIÓN** **C.C.** [x] **NIT** [ ] **C.E.** [ ] **Otro** [ ] **Cual** _____ **Número** 79.782.747Bta **TP** 74.295
INVENTOR (ES) (72)	**Nombre:** VER PÁGINA ADJUNTA. **Dirección:** VER PÁGINA ADJUNTA. **Nacionalidad o Domicilio:** VER PÁGINA ADJUNTA.	

(5) **PCT (86)**

Solicitud Internacional No. PCT/EP2011/065368 Fecha Septiembre 06, 2011

Publicación Internacional No. WO 2012/032031 A1 Fecha Marzo 15, 2012

(6) **Título (54)** **IMIDAZOPIRIDAZINAS SUSTITUIDAS.**

Clasificación Internacional (51) C07D 487/04; A61K 31/5025; A61P 35/00.

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

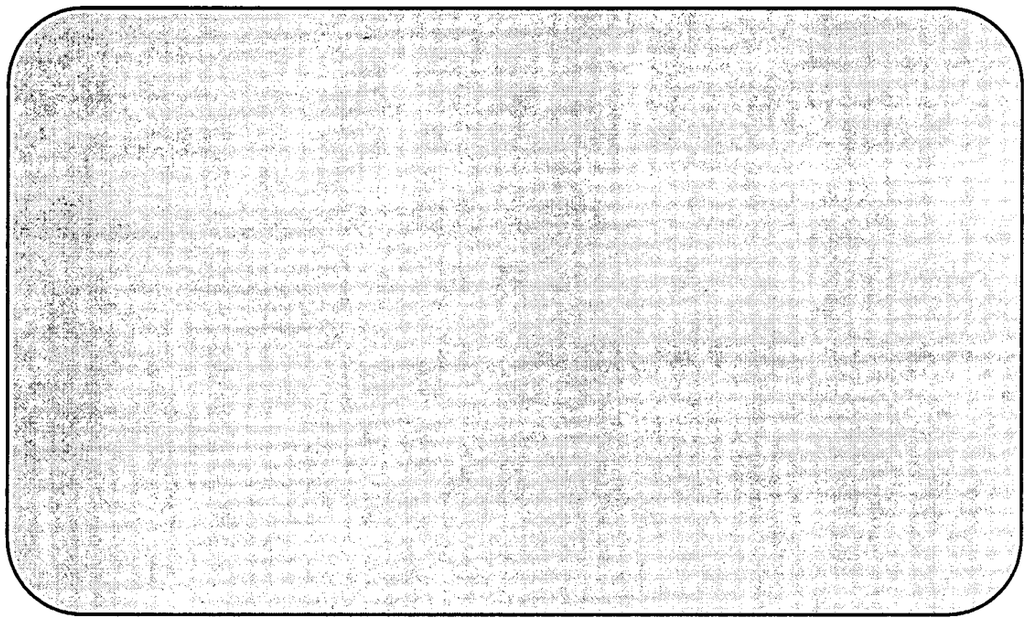
(33) País de Origen	(32) Fecha	(31) Número de Solicitud
EP	Septiembre 10, 2010	10176134.4
EP	Febrero 04, 2011	11075022.1
EP	Junio 21, 2011	11170775.8
EP	Junio 21, 2011	11170771.7

(9) **Comprobante de pago No.** 13- **Fecha** _____

(10) ANEXOS

- [X] Comprobante de pago de la tasa de presentación de la solicitud.
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [X] Poderes, si fuere el caso.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones. Bajo la Regla 4.17 (ii) del PCT.
- [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.
- [X] De ser el caso, modificaciones efectuadas a la solicitud internacional. PCT/IB306.
- [X] Otros. Búsqueda Internacional.

(11) FIGURA CARACTERÍSTICA:



(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747Bta T.P. 74.295

LISTA DE INVENTORES

PCT/EP2011/065368

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Nacionalidad: Alemana

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 13 - 0023672

Bogotá D.C., Marzo 08 de 2013 - 16:26:40

RECIBIDO DE : OLARTE MOURE & ASOCIADOS NI 830.122.870

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	197794995	08/03/2013	2.000.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	500.000.00	500.000.00
				$500.000.00

SON: **QUINIENTOS MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 13-047157- -00000-0000

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Act. 411 PRESENTACION Folios: 5

PATENTE DE INVENCIÓN ☐ MODELO DE U ☐ Art.35 Decisión 486/00

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☒ MODELO DE UTILIDAD PCT ☐ Art.33 Decisión 486/00, Circular Única

- ☐ Indicación que se solicita una PCT
- ☐ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☒ Incompleta ☐

DISEÑO INDUSTRIAL ☐ (Art. 119 Decisión 486/00)

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ (Art. 92 Decisión 486/00)

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

Industria y Comercio
SUPERINTENDENCIA

PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA
RELACIÓN DE ANEXOS

Dependencia:	Fecha: ____/____/____/ AAAA MM DD	Recorrido:

Tipo de Radicación: Entrada: ☐ Salida: ☐ Traslado: ☐ Convenio: ☐

Radicador: | Planilla:

ID	No. Radicación	Consecutivo	Item
1			
2			
3			
4			
5	13-47157		
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			

Item	Unidad de Conservación
1	Bolsa
2	Caja
3	Libro
4	Sobre
5	Tomo
6	Otro
Item	*Soporte Documental*
7	CD
8	Disquete
9	DVD
10	Folleto
11	Foto
12	Periódico
13	Plano
14	Publicación Periódica
15	USB
10	Otro

Observaciones:

Anexo 1 CD

COLEGIO DE ESCRIBANOS · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL · REPUBLICA ARGENTINA

ACTUACION NOTARIAL
LEY 404

PO 84 157

N 015080567

FOLIO 283.- PRIMERA COPIA.- ESCRITURA NÚMERO: SETENTA Y CINCO.- SUSTITUCIÓN PARCIAL DE PODER: MESSERER, Dagmar a favor de OLARTE, Carlos Reinaldo y otro del Poder otorgado por BAYER INTELLECTUAL PROPERTY GmbH.- -

En la Ciudad Autónoma de Buenos Aires, Capital de la República Argentina, el día **VEINTICUATRO** de **MAYO** del año **DOS MIL DOCE**, ante mí, María Silvina Lasarte, Escribana Autorizante, titular del Registro Notarial Número 1.788, **COMPARECE**: **Dagmar MESSERER,** argentina, nacida el 28 de mayo de 1.968, hija de Walter Messerer y Elsa Onelia Romanelli, soltera, titular del Documento Nacional de Identidad Número 20.383.892, con domicilio en la Avenida Del Libertador 5.954, Piso 7°, de esta Ciudad de Buenos Aires.- La compareciente es mayor de edad.- **INTERVIENE**: por su propio derecho.- Y la compareciente **EXPRESA**: **PRIMERO**: Que la Sociedad **"BAYER INTELLECTUAL PROPERTY GmbH"**, con domicilio en Alfred-Nobel-Strasse 10, 40789 Monheim, Alemania, le confirió, con fecha 25 de Abril de 2.012, en dicho país, un Poder, el cual mediante escritura número 72, del día de la fecha, otorgada ante mi, al folio 274, protocolo corriente, de este Registro Notarial Número 1788, a mi cargo, fue incorporado y transcripto al mismo, cuya primera copia tengo para este acto a la vista y en lo pertinente transcribiré en la presente.- **SEGUNDO**: Manifiesta bajo juramento que el referido poder invocado se encuentra plenamente vigente en virtud de no haberle sido revocado, suspendido ni limitado en ninguna de sus partes.- **TERCERO**: En consecuencia, **DICE**: Que en uso de la facultad conferida **SUSTITUYE PARCIALMENTE** el poder mencionado a favor de **Carlos Reinaldo Olarte** y/o **Juan Guillermo Moure Pérez**, al solo y único objeto de que en nombre y representación de la Sociedad **"BAYER INTELLECTUAL PROPERTY GmbH"**,

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y actuando en forma individual, indistinta y/o alternadamente, se presenten **exclusivamente** ante las autoridades de **COLOMBIA**, que correspondan y realicen los actos enumerados en el citado poder y con las facultades que surgen del mismo, el que transcripto en lo pertinente dice: "FOLIO 274.- PRIMERA COPIA.- ESCRITURA NÚMERO: SETENTA Y DOS.- ...- En la Ciudad Autónoma de Buenos Aires, ..., el día VEINTICUATRO de MAYO del año DOS MIL DOCE, ante mí ..., COMPARECE: Dagmar MESSERER, argentina, nacida el 28 de mayo de 1.968, hija de Walter Messerer y Elsa Onelia Romanelli, soltera, titular del Documento Nacional de Identidad Número 20.383.892, con domicilio en la Avenida Del Libertador 5.954, Piso 7°, de esta Ciudad de Buenos Aires.- La compareciente es mayor de edad.- INTERVIENE: por su propio derecho.- Y la compareciente EXPRESA: Que a los efectos que hubiere lugar, solicita de mí, la Autorizante, LA INCORPORACIÓN y TRANSCRIPCIÓN en este protocolo del PODER que fuera conferido en Leverkusen, Alemania, el día 25 de Abril de 2.012, por la Sociedad "BAYER INTELLECTUAL PROPERTY GmbH", con domicilio Alfred-Nobel-Strasse 10, 40789 Monheim, Alemania, a favor de Gerardo Messerer y/o Dagmar Messerer y/o Karen Messerer y/o Moeller & CO. S.A., indistintamente, sobre cuya plena vigencia responde la requirente bajo juramento.- Yo, la Autorizante, hago constar: a) Que el instrumento de poder cuya incorporación y transcripción a este protocolo solicita la compareciente, se encuentra extendido en idioma castellano, certificadas las firmas por notario en idiomas inglés y alemán, debidamente legalizado en idioma alemán (Sello de Apostilla de la Convención de La Haya del 5 de octubre de 1961) y traducido en lo pertinente al idioma nacional por la Traductora Pública Laura Thieberger.- b) Que la compareciente en virtud de lo manifestado tiene interés legítimo en su requerimiento.- En consecuencia, me hace entrega en este acto del

original del instrumento de poder relacionado con su respectiva traducción al idioma nacional, el que agrego a la presente y transcripto dice: "PODER Los abajo firmante/s Bayer Intellectual Property GmbH domiciliados en Alfred-Nobel-Strasse 10 40789 Monheim, Alemania declaran por el presente otorgar a Gerardo MESSERER y/o Dagmar MESSERER y/o Karen MESSERER y/o MOELLER & CO. S.A. indistintamente poder general amplio y suficiente para recabar de las autoridades ..., sud y centroamericanas ... que correspondan, la obtención de patentes de invención, el registro y la renovación de marcas y modelos y/o derechos de propiedad intelectual y/o nombres de dominio, a cuyo efecto los faculta/n para llevar a cabo ante dichas autoridades todas las gestiones necesarias al objeto indicado, presentar solicitudes, formular descripciones, oposiciones, protestos, declaraciones, apelaciones y reclamos, oblar impuestos, justificar explotaciones, solicitar testimonios, aceptar transferencias, recibir documentos y valores, percibir y hacer cuanto fuere necesario ante las autoridades administrativas de cualquier orden. Por otra parte, les confieren mandato para que en su nombre y representación puedan iniciar y proseguir cualquier juicio que actualmente los que suscriben tengan o en el futuro tuvieran ..., en Sudamérica, Centroamérica ..., con motivo de su nombre, marcas de fábrica o de comercio, patentes de invención y modelos y/o de sus derechos de propiedad intelectual que actualmente posean o adquieran en lo sucesivo, promover juicios de cualquier jurisdicción, criminales, correccionales, civiles o comerciales, contra los falsificadores, usurpadores o imitadores y contra los tenedores de artículos que infrinjan su nombre, marcas o patentes de invención, seguir los juicios por oposición u otros en que fueran parte como actores o demandados, defender el nombre, las marcas, patentes y modelos y/o de derechos de propiedad intelectual y/o nombres de dominio, haciendo las protestas del caso o diciendo de nulidad. Al efecto, podrán

N 015080568

presentarse con escritos, querellas, pedidos, y lo que fuere necesario ante cualquier autoridad judicial, presentar testigos, documentos y demás justificativos, rendir pruebas de cualquier especie, pedir nombramientos de peritos, pedir y absolver posiciones, asistir a juicios verbales, declinar y prorrogar de jurisdicción, tachar, recusar, apelar, transar, someter a arbitraje o mediación, hacer renuncias, exigir y dar cauciones, pedir embargos preventivos, definitivos o inhibiciones y su levantamiento, pedir la venta de los bienes de los deudores, solicitar y obtener el cumplimiento de sentencias, prestar juramentos, decir de nulidad, desistir, percibir, otorgar recibos y en general practicar todos los actos y diligencias que sean precisos al desempeño de este mandato. Podrán asimismo sustituir el presente poder en todo o en parte. ... Dado y firmado en - Sigue una firma ilegible (Aclarado:) Dr. J. Thomaier, ppa. - Sigue una firma ilegible (Aclarado:) C. Linder".- ES COPIA FIEL, doy fe.- En hoja adjunta consta: a) La certificación notarial de las firmas obrantes en el poder en idioma inglés y alemán, efectuada por el Escribano Público de Leverkusen, Alemania, Klaus Striewski; y b) La respectiva legalización de la firma y sello del nombrado Notario (Sello de Apostilla de la Convención de La Haya del 5 de octubre de 1961), en idioma alemán, efectuada por el Vicepresidente del Tribunal Regional de Colonia, Alemania, Doctor Dumke.- En hoja adjunta sigue la referida traducción al idioma nacional la que transcripta textualmente, dice: "TRADUCCIÓN PUBLICA (A continuación de un PODER otorgado en idioma nacional por la Sociedad "Bayer Intellectual Property GmbH", con sede en Alfred-Nobel-Strasse 10 - 40789 Monheim, Alemania, figuran los siguientes textos, que traducidos dicen:) ... Acta N° 656/2012 – 1. Certifico que las personas llamadas: - Dr. Jörg Thomaier, domicilio comercial: D-40789 Monheim, Alfred-Nobel-Strasse 10, Alemania, - Sra. Claudia Linder, domicilio comercial: 51368 Leverkusen, Chempark, Alemania, comparecieron ante mí y otorgaron el siguiente

documento firmándolo personalmente – todas personas de mi conocimiento – Confirmo que el Dr. Jörg Thomaier y la Sra. Claudia Linder están autorizados como representantes de "Bayer Intellectual Property GmbH", de Monheim, habiendo tenido a la vista electrónicamente en el día de la fecha el Registro de Comercio del Tribunal Regional de Düsseldorf constatando que los mismos, según el capítulo B 67604 son representantes autorizados.- 2. (Siguen los textos en alemán de su original en inglés) – Leverkusen, 25 de abril de 2012 - (Hay un sello en oblea adherido sobre precinto: Klaus Striewski - Escribano de Leverkusen - Firma (Firmado y aclarado:) Klaus Striewski – Escribano de Leverkusen.- APOSTILLA – (Convención de La Haya del 5 octubre de 1961) – País: República Federal de Alemania - Este instrumento público fue firmado por Klaus Striewski en su carácter de Escribano, estando provisto del sello del Escribano Klaus Striewski de Leverkusen.- Certificado en Colonia, el 03.05.2012 por el Vicepresidente del Tribunal Regional con el N° 1880/2012 – Sello (Hay un sello:) Presidente del Tribunal Regional de Colonia – 2 - Firma (Firmado y aclarado:) Doctor Dumke.- … - ES TRADUCCIÓN FIEL de las partes pertinentes del documento de referencia que en los idiomas alemán e inglés he tenido a la vista y he vertido al idioma nacional, en Buenos Aires, el 21 de mayo de 2012. Hay una firma ilegible. Hay un sello que dice: "Laura Thieberger-Matrícula de Traductores Alemán-Francés-Tomo II Folio 254 (Cap.) Tomo III 98- (La Plata)- Inglés-Tomo III: Folio 14 (Cap.)- Tomo III Folio 329 (La Plata)- Colegio de Traductores Públicos N° 173".- ES COPIA FIEL, doy fe.- A continuación hay un sello que dice: "Colegio de Traductores Públicos de la Ciudad de Buenos Aires Corresponde a la Legalización N° 29177/12. Sigue una firma ilegible. Mayra Fiorella Pugliese".- ...- A continuación sigue la legalización de la firma de la nombrada traductora ...- Constancias Notariales: Identidad de la compareciente (Artículo 1.002 del Código Civil): Se justifica la misma

CECBA - LEY404 GCBA
APOSTILLA
120528 129072
28/05/2012 10 45 21

CECBA - LEY404 GCBA
LEGALIZACION
120528 252762
28/05/2012 10.45 21

COLEGIO DE ESCRIBANOS · CIUDAD DE BUENOS AIRES CAPITAL FEDERAL · REPUBLICA ARGENTINA

N 015080569

por conocimiento de la Autorizante.- ...- LEO esta escritura a la compareciente, quien así la otorga y en prueba de conformidad, la firma ante mí, doy fe.- Dagmar MESSERER. Ante mí: MARÍA SILVINA LASARTE. Escribana. Está mi sello.-".- **ES COPIA FIEL**, de las partes pertinentes de la escritura de referencia, doy fe.- **CUARTO**: Finalmente la compareciente expresa: **a)** Que el presente otorgamiento no significa renunciar al ejercicio de las facultades sustituidas; **b)** Que los nombrados apoderados sustitutos no podrán sustituir el presente poder en ninguna de sus partes; y **c)** Que el presente instrumento no se encuentra alcanzado por el Impuesto de Sellos, en virtud de no revestir el carácter de oneroso.- **Constancias Notariales: Identidad de la Compareciente (Artículo 1.002 del Código Civil):** Se justifica la misma por conocimiento de la Autorizante.- Informo a la compareciente respecto de los alcances de las cláusulas contenidas en la presente escritura y del derecho de leer por sí este instrumento.- **LEO** esta escritura a la compareciente, quien así la otorga y en prueba de conformidad la firma ante mí, doy fe.- Dagmar MESSERER. Ante mí: MARÍA SILVINA LASARTE. Escribana. Está mi sello. **CONCUERDA** con su escritura matriz que pasó ante mí, al folio 283 del Registro Notarial número 1788, a mi cargo. PARA LA PODERDANTE expido la presente **PRIMERA COPIA** en tres (3) sellos de actuación notarial numerados correlativamente desde el número N 015080567 al presente inclusive, que sello y firmo en la fecha y lugar de su otorgamiento, doy fe.-

ESCRIBANA MARIA SILVINA LASARTE

COLEGIO DE ESCRIBANOS • CIUDAD DE BUENOS AIRES • CAPITAL FEDERAL - REPUBLICA ARGENTINA • NIHIL PEQUE PIDE

LEGALIZACION
LEY 404

L 010811293

EL COLEGIO DE ESCRIBANOS de la Ciudad de Buenos Aires, Capital Federal de la República Argentina, en virtud de las facultades que le confiere la ley orgánica vigente, LEGALIZA la firma y sello del escribano MARIA SILVINA LASARTE **obrantes en el documento anexo, presentado en el día de la fecha bajo el Nº** 120528252762/0 **. La presente legalización no juzga sobre el contenido y forma del documento.**

Buenos Aires, Lunes 28 de Mayo de 2012

COLEGIO DE ESCRIBANOS • LEGALIZACION • CIUDAD DE BUENOS AIRES • CAPITAL FEDERAL - REPUBLICA ARGENTINA

ESC. JUAN MANUEL SANCLEMENTE
COLEGIO DE ESCRIBANOS
CONSEJERO

SERIE A 0074636

CFNA

REPÚBLICA ARGENTINA

MINISTERIO *de*
RELACIONES EXTERIORES
COMERCIO INTERNACIONAL Y CULTO

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. País: REPÚBLICA ARGENTINA
   El presente documento público DE LEGALIZACIÓN
2. Ha sido firmado por JUAN MANUEL SANGUINETTI
3. Quien actúa en calidad de CONSEJERO
4. Lleva el sello/timbre del COLEGIO DE ESCRIBANOS DE LA CIUDAD DE BUENOS AIRES.
5. En LA CIUDAD DE BUENOS AIRES
6. El día 28/05/2012
7. Por EL COLEGIO DE ESCRIBANOS DE LA CIUDAD DE BUENOS AIRES MINISTERIO DE RELACIONES EXTERIORES, COMERCIO INTERNACIONAL Y CULTO (Convenio 02/09/2003)
8. Bajo el Número: 120528129072
9. Sello/Timbre:
10. Firma

COLEGIO DE ESCRIBANOS APOSTILLA CAPITAL FEDERAL - REPÚBLICA ARGENTINA

CANCILLERIA ARGENTINA

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 March 2012 (15.03.2012)

PCT

(10) International Publication Number
WO 2012/032031 A1

(51) International Patent Classification:
C07D 487/04 (2006.01) *A61P 35/00* (2006.01)
A61K 31/5025 (2006.01)

(21) International Application Number:
PCT/EP2011/065368

(22) International Filing Date:
6 September 2011 (06.09.2011)

(25) Filing Language: English

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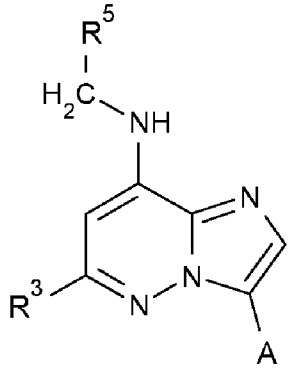
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(54) **Title**: SUBSTITUTED IMIDAZOPYRIDAZINES



(I)

(57) **Abstract**: The present invention relates to substituted imidazopyridazine compounds of general formula (I), which are Mps -1 (Monopolar Spindle 1) Kinase inhibitors (also known as Tyrosine Threonine Kinase, TTK) in which R^3, R^5, and A are as defined in the claims, to methods of preparing said compounds, to pharmaceutical compositions and combinations comprising said compounds and to the use of said compounds for manufacturing a pharmaceutical composition for the treatment or prophylaxis of a disease, in particular of a hyper-proliferative and/or angiogenesis disorder, as a sole agent or in combination with other active ingredients.

WO 2012/032031 A1

SUBSTITUTED IMIDAZOPYRIDAZINES

The present invention relates to substituted imidazopyridazine compounds of general formula I as described and defined herein, to methods of preparing said compounds, to pharmaceutical compositions and combinations comprising said compounds, to the use of said compounds for manufacturing a pharmaceutical composition for the treatment or prophylaxis of a disease, as well as to intermediate compounds useful in the preparation of said compounds.

BACKGROUND OF THE INVENTION

The present invention relates to chemical compounds that inhibit Mps-1 (Monopolar Spindle 1) kinase (also known as Tyrosine Threonine Kinase, TTK). Mps-1 is a dual specificity Ser/Thr kinase which plays a key role in the activation of the mitotic checkpoint (also known as spindle checkpoint, spindle assembly checkpoint) thereby ensuring proper chromosome segregation during mitosis [Abrieu A *et al.*, Cell, 2001, 106, 83-93]. Every dividing cell has to ensure equal separation of the replicated chromosomes into the two daughter cells. Upon entry into mitosis, chromosomes are attached at their kinetochores to the microtubules of the spindle apparatus. The mitotic checkpoint is a surveillance mechanism that is active as long as unattached kinetochores are present and prevents mitotic cells from entering anaphase and thereby completing cell division with unattached chromosomes [Suijkerbuijk SJ and Kops GJ, Biochemica et Biophysica Acta, 2008, 1786, 24-31; Musacchio A and Salmon ED, Nat Rev Mol Cell Biol., 2007, 8, 379-93]. Once all kinetochores are attached in a correct amphitelic, *i.e.* bipolar, fashion with the mitotic spindle, the checkpoint is satisfied and the cell enters anaphase and proceeds through mitosis. The mitotic checkpoint consists of complex network of a number of essential proteins, including members of the MAD (mitotic arrest deficient, MAD 1-3) and Bub (Budding uninhibited by benzimidazole, Bub 1-3) families, the motor protein CENP-E, Mps-1 kinase as well as other components, many of these being over-expressed in proliferating cells (*e.g.* cancer cells) and tissues [Yuan B *et al.*, Clinical Cancer Research, 2006, 12, 405-10]. The essential role of Mps-1 kinase activity in mitotic checkpoint signalling has been shown by

shRNA-silencing, chemical genetics as well as chemical inhibitors of Mps-1 kinase [Jelluma N *et al.*, PLos ONE, 2008, 3, e2415; Jones MH *et al.*, Current Biology, 2005, 15, 160-65; Dorer RK *et al.*, Current Biology, 2005, 15, 1070-76; Schmidt M *et al.*, EMBO Reports, 2005, 6, 866-72].

There is ample evidence linking reduced but incomplete mitotic checkpoint function with aneuploidy and tumourigenesis [Weaver BA and Cleveland DW, Cancer Research, 2007, 67, 10103-5; King RW, Biochimica et Biophysica Acta, 2008, 1786, 4-14]. In contrast, complete inhibition of the mitotic checkpoint has been recognised to result in severe chromosome missegregation and induction of apoptosis in tumour cells [Kops GJ *et al.*, Nature Reviews Cancer, 2005, 5, 773-85; Schmidt M and Medema RH, Cell Cycle, 2006, 5, 159-63; Schmidt M and Bastians H, Drug Resistance Updates, 2007, 10, 162-81]. Therefore, mitotic checkpoint abrogation through pharmacological inhibition of Mps-1 kinase or other components of the mitotic checkpoint represents a new approach for the treatment of proliferative disorders including solid tumours such as carcinomas and sarcomas and leukaemias and lymphoid malignancies or other disorders associated with uncontrolled cellular proliferation.

Established anti-mitotic drugs such as vinca alkaloids, taxanes or epothilones activate the SAC inducing a mitotic arrest either by stabilising or destabilising microtubule dynamics. This arrest prevents separation of sister chromatids to form the two daughter cells. Prolonged arrest in mitosis forces a cell either into mitotic exit without cytokinesis or into mitotic catastrophe leading to cell death.
In contrast, inhibitors of Mps-1 induce a SAC inactivation that accelerates progression of cells through mitosis resulting in severe chromosomal missegregation and finally in cell death.

These findings suggest that Mps-1 inhibitors should be of therapeutic value for the treatment of proliferative disorders associated with enhanced uncontrolled proliferative cellular processes such as, for example, cancer, inflammation, arthritis, viral diseases, neurodegenerative diseases such as Alzheimer's disease, cardiovascular diseases, or fungal diseases in a warm-blooded animal such as man.

Therefore, inhibitors of Mps-1 represent valuable compounds that should complement therapeutic options either as single agents or in combination with other drugs.

Different compounds have been disclosed in prior art which show an inhibitory effect on Mps-1 kinase. WO2010/124826A1 discloses substituted imidazoquinoxaline compounds as inhibitors of Mps-1 kinase or TTK. WO2011/026579A1 discloses substituted aminoquinoxalines as Mps-1 inhibitors. WO2011/063908A1, WO2011/064328A1 as well as WO2011/063907 A1 disclose triazolopyridine derivates as inhibitors of Mps-1 kinase.

Imidazopyridazine derivates have been disclosed for the treatment or prophylaxis of different diseases:

WO 2007/038314 A2 (Bristol-Myers Squibb Company) relates to fused heterocyclic compounds useful as kinase modulators, including MK2 modulation. In particular, WO 2007/038314 A2 relates to imidazo[1,2-b]pyridazines.

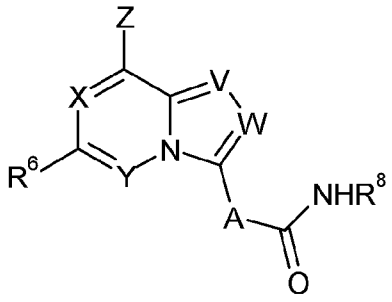
US patent application publication US 2008/0045536 A1 (Bristol-Myers Squibb Company) similarly relates to fused heterocyclic compounds useful as kinase modulators, including MK2 modulation. In particular, it relates to imidazo[1,2-b]pyridazines.

WO 2010/042699 A1 (Bristol-Myers Squibb Company) relates to fused heterocyclic compounds useful as kinase modulators, particularly CK2 modulation. In particular, WO 2010/042699 A1 relates to imidazo[1,2-b]pyridazines which are substituted with a nitrile group in position 3.

WO 2007/025090 A2 (Kalypsis, Inc.) relates to heterocyclic compounds useful as inhibitors of MEK kinase. In particular, WO 2007/025090 A2 relates *inter alia* to imidazo[1,2-b]pyridazines.

WO 1998/08847 A1 (Pfizer, Inc.) relates to heterocyclic compounds useful as corticotropin releasing factor (hormone) CRF (CRH) antagonists. In particular, WO 1998/08847 A1 relates inter alia to imidazo[1,2-b]pyridazines.

WO 2011/013729A1 discloses fused imidazole derivatives as Mps-1 inhibitors. Among the disclosed fused imidazole derivates there are also imidazo[1,2-b]pyridazines. For example, WO 2011/013729A1 discloses compounds of formula **C1**:



C1

in which (X, Y, V, W) is (-N=, =CR^1-, =N-, -CR^7=), (-CR^2=, =N-, =N-, -CR^7=), (-N=, =CR^1-, =N-, -N=) or (-N=, =CR^1-, -O-, -N=) ;

R^8 is substituted or unsubstituted cycloalkyl ;

Z is a group represented by formula -NR^3R^4 or a group represented by formula -OR^5;

A is substituted or unsubstituted aromatic hydrocarbon ring, substituted or unsibstituted aromatic heterocyclic ring, substituted or unsubstituted non-aromatic hydrocarbon ring or substituted or unsubstituted non-aromatic heterocyclic ring ;

R^1, R^3, R^4, R^5, and R^6 represent a large variety of substituents (see WO 2011/013729A1, e.g. claim 1).

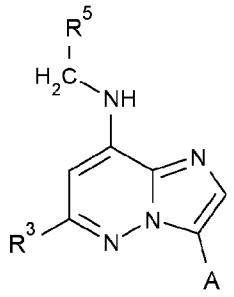
The inventors of the present invention surprisingly observed that compounds of general formula I as described and defined herein show a high activity in Mps-1 inhibition and show a high metabolic stability.

The state of the art described above does not describe the imidazopyridazine compounds of claims 1 to 8, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same, as described and defined herein, and as hereinafter referred to as "compounds of the present invention", or their pharmacological activity and stability. It has now been found, and this constitutes the basis of the present invention, that said compounds of the present invention have surprising and advantageous properties.

In particular, said compounds of the present invention have surprisingly been found to effectively inhibit Mps-1 kinase and may therefore be used for the treatment or prophylaxis of diseases of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses or diseases which are accompanied with uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, particularly in which the uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses is mediated by Mps-1 kinase, such as, for example, haemotological tumours, solid tumours, and/or metastases thereof, *e.g.* leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

SUMMARY of the INVENTION

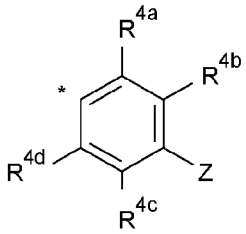
The present invention covers compounds of general formula I :



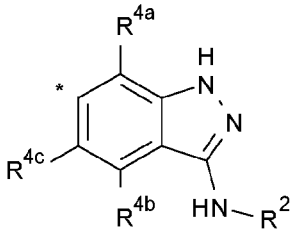
I

in which :

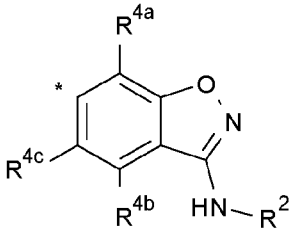
A represents a



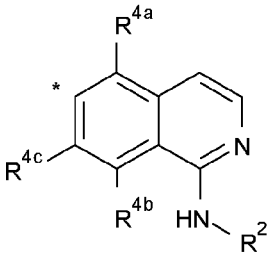
or



or



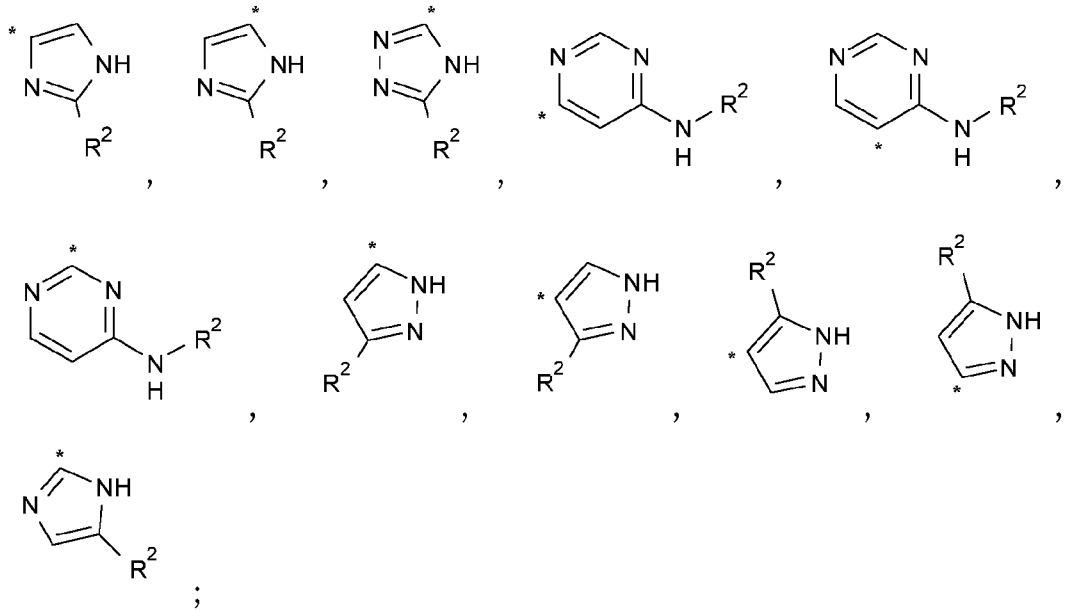
or



-group ;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a $-C(=O)N(H)R^2$ or $-C(=S)N(H)R^2$ group, or a group selected from



wherein * indicates the point of attachment of said groups with the rest of the molecule ;

R^2 represents a hydrogen atom, or a C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl- or C_3-C_6-cycloalkyl- group ;
wherein said C_3-C_6-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 groups selected from: halogen, -OH, -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkyl-;

R^3 represents a hydrogen atom or a halogen atom, or a -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, -$(CH_2)_m$-C_2-C_6-alkenyl, -$(CH_2)_m$-C_4-C_8-cycloalkenyl, -$(CH_2)_m$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl-, -C_1-C_6-alkyl-aryl, -C_1-C_6-alkyl-heteroaryl, heteroaryl-, C_1-C_6-alkyl-X-, -X-$(CH_2)_m$-C_2-C_6-alkenyl, -X-$(CH_2)_m$-C_4-C_8-cycloalkenyl, -X-$(CH_2)_m$-C_2-C_6-alkynyl, -X-$(CH_2)_m$-C_3-C_6-cycloalkyl, -X-$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -X-$(CH_2)_m$-(4- to 8-membered

heterocycloalkenyl), aryl-X-, heteroaryl-X-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -OR^6, -SR^6, -S(=O)R^6, -S(=O)$_2R^6$, -S(=O)(=NR^{6a})R^{6b}, -S(=O)$_2$N(R^{6b})R^{6c}, -S-(CH_2)$_n$-N(R^{6a})R^{6b} or -S-(CH_2)$_n$-(3- to 7-membered heterocycloalkyl) group ;

wherein said C_1-C_6-alkyl-, C_1-C_6-alkoxy-, -(CH_2)$_m$-C_2-C_6-alkenyl, -(CH_2)$_m$-C_2-C_6-alkynyl, -(CH_2)$_m$-C_3-C_6-cycloalkyl, aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl-, C_1-C_6-alkyl-X-, -X-(CH_2)$_m$-C_2-C_6-alkenyl, -X-(CH_2)$_m$-C_4-C_8-cycloalkenyl, -X-(CH_2)$_m$-C_2-C_6-alkynyl, -X-(CH_2)$_m$-C_3-C_6-cycloalkyl, -X-(CH_2)$_m$-(3- to 7-membered heterocycloalkyl), -X-(CH_2)$_m$-(4- to 8-membered heterocycloalkenyl), aryl-X-, heteroaryl-X-, -C_1-C_6-alkyl-aryl, -C_1-C_6-alkyl-heteroaryl or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^7 groups ;

R^{4a}, R^{4b}, R^{4c}, R^{4d}

represent, independently from each other, a hydrogen or halogen atom, or a -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkyl-, R^{6a}(R^{6b})N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2R^6$, -N(R^{6c})S(=O)$_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -S(=O)$_2R^6$, -S(=O)$_2$N(H)R^{6a}, -S(=O)$_2$N(R^{6a})R^{6b}, -S(=O)(=NR^{6c})R^6 group ;

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, -(CH_2)$_n$-C_2-C_6-alkenyl, -(CH_2)$_n$-C_2-C_6-alkynyl, -(CH_2)$_m$-C_3-C_6-cycloalkyl, -(CH_2)$_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, R^{6a}(R^{6b})N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-,aryl- or heteroaryl- group ;

wherein said C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_4-C_8-cycloalkenyl-, aryl- or heteroaryl-group is optionally substituted, identically or differently, with 1, 2, 3 or 4 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c}
represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl-, H O-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, C_2-C_6-alkenyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, aryl-C_1-C_6-alkyl- or heteroaryl-C_1-C_6-alkyl- group ;

R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)$S(=O)_2R^6$, -N(R^{6c})$S(=O)_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -$S(=O)_2R^6$, -$S(=O)_2$N(H)R^6, -$S(=O)_2$N(R^{6a})R^{6b} or -S(=O)(=NR^{6c})R^6 group ;
wherein said C_1-C_6-alkoxy-, aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2 or 3 C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-, -C(=O)O-R^6 or -OH groups;
or
when 2 R^7 groups are present ortho to each other on an aryl- or heteroaryl-ring, said 2 R^7 groups together form a bridge :
$O(CH_2)_2O$, *$O(CH_2)O$*, *NH(C(=O))NH*, wherein * represent the point of attachment to said aryl- or heteroaryl- ring ;

R^8 represents a hydrogen or halogen atom, or a -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ or $-S(=O)_2$-(3- to 7-membered heterocycloalkyl) group;
wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 C_1-C_6-alkyl- groups ;

m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

n is an integer of 0, 1, 2, 3, 4 or 5 ;

X represents $S(=O)_p$, O, NR^6, $CR^{6a}R^{6b}$ or $C=CR^{6a}R^{6b}$;

p is an integer of 0, 1 or 2 ;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

The present invention also relates to methods of preparing said compounds, to pharmaceutical compositions and combinations comprising said compounds, to the use of said compounds for manufacturing a pharmaceutical composition for the treatment or prophylaxis of a disease, as well as to intermediate compounds useful in the preparation of said compounds.

DETAILLED DESCRIPTION of the INVENTION

The terms as mentioned in the present text have preferably the following meanings :

The term "halogen atom" or "halo-" is to be understood as meaning a fluorine, chlorine, bromine or iodine atom, preferably a fluorine, chlorine, bromine or iodine atom.

The term "C_1-C_6-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent hydrocarbon group having 1, 2, 3, 4, 5, or 6 carbon atoms, *e.g.* a methyl, ethyl, propyl, butyl, pentyl, hexyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl, iso-pentyl, 2-methylbutyl, 1-methylbutyl, 1-ethylpropyl, 1,2-dimethylpropyl, neo-pentyl, 1,1-dimethylpropyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 2-ethylbutyl, 1-ethylbutyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 2,3-dimethylbutyl, 1,3-dimethylbutyl, or 1,2-dimethylbutyl group, or an isomer thereof. Particularly, said group has 1, 2, 3 or 4 carbon atoms ("C_1-C_4-alkyl"), *e.g.* a methyl, ethyl, propyl, butyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl group, more particularly 1, 2 or 3 carbon atoms ("C_1-C_3-alkyl"), *e.g.* a methyl, ethyl, n-propyl- or iso-propyl group.

The term "halo-C_1-C_6-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent hydrocarbon group in which the term "C_1-C_6-alkyl" is defined *supra*, and in which one or more hydrogen atoms is replaced by a halogen atom, in identically or differently, *i.e.* one halogen atom being independent from another. Particularly, said halogen atom is F. Said halo-C_1-C_6-alkyl group is, for example, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CF_2CF_3$, or $-CH_2CF_3$.

The term "C_1-C_6-alkoxy" is to be understood as preferably meaning a linear or branched, saturated, monovalent, hydrocarbon group of formula -O-C_1-C_6-alkyl, in which the term "C_1-C_6-alkyl" is defined *supra*, *e.g.* a methoxy, ethoxy, n-propoxy,

iso-propoxy, n-butoxy, iso-butoxy, tert-butoxy, sec-butoxy, pentoxy, iso-pentoxy, or n-hexoxy group, or an isomer thereof.

The term "halo-C_1-C_6-alkoxy" is to be understood as preferably meaning a linear or branched, saturated, monovalent C_1-C_6-alkoxy group, as defined *supra*, in which one or more of the hydrogen atoms is/are replaced, in identically or differently, by one or more halogen atoms. Particularly, said halogen atom is F. Said halo-C_1-C_6-alkoxy group is, for example, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-OCF_2CF_3$, or $-OCH_2CF_3$.

The term "C_1-C_6-alkoxy-C_1-C_6-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent C_1-C_6-alkyl group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, in identically or differently, by a C_1-C_6-alkoxy group, as defined *supra*, *e.g.* methoxyalkyl, ethoxyalkyl, propyloxyalkyl, iso-propoxyalkyl, butoxyalkyl, iso-butoxyalkyl, tert-butoxyalkyl, sec-butoxyalkyl, pentyloxyalkyl, iso-pentyloxyalkyl, hexyloxyalkyl group, or an isomer thereof.

The term "halo-C_1-C_6-alkoxy-C_1-C_6-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent C_1-C_6-alkoxy-C_1-C_6-alkyl group, as defined *supra*, in which one or more of the hydrogen atoms is/are replaced, in identically or differently, by one or more halogen atoms. Particularly, said halogen atom is F. Said halo-C_1-C_6-alkoxy-C_1-C_6-alkyl group is, for example, $-CH_2CH_2OCF_3$, $-CH_2CH_2OCHF_2$, $-CH_2CH_2OCH_2F$, $-CH_2CH_2OCF_2CF_3$, or $-CH_2CH_2OCH_2CF_3$.

The term "C_2-C_6-alkenyl" is to be understood as preferably meaning a linear or branched, monovalent hydrocarbon group, which contains one or more double bonds, and which has 2, 3, 4, 5 or 6 carbon atoms, particularly 2 or 3 carbon atoms ("C_2-C_3-alkenyl"), it being understood that in the case in which said alkenyl group contains more than one double bond, then said double bonds may be isolated from, or conjugated with, each other. Said alkenyl group is, for example, a vinyl, allyl, (E)-2-methylvinyl, (Z)-2-methylvinyl, homoallyl, (E)-but-2-enyl, (Z)-but-2-enyl, (E)-but-1-enyl, (Z)-but-1-enyl, pent-4-enyl, (E)-pent-3-enyl, (Z)-pent-3-enyl,

(E)-pent-2-enyl, (Z)-pent-2-enyl, (E)-pent-1-enyl, (Z)-pent-1-enyl, hex-5-enyl, (E)-hex-4-enyl, (Z)-hex-4-enyl, (E)-hex-3-enyl, (Z)-hex-3-enyl, (E)-hex-2-enyl, (Z)-hex-2-enyl, (E)-hex-1-enyl, (Z)-hex-1-enyl, isopropenyl, 2-methylprop-2-enyl, 1-methylprop-2-enyl, 2-methylprop-1-enyl, (E)-1-methylprop-1-enyl, (Z)-1-methylprop-1-enyl, 3-methylbut-3-enyl, 2-methylbut-3-enyl, 1-methylbut-3-enyl, 3-methylbut-2-enyl, (E)-2-methylbut-2-enyl, (Z)-2-methylbut-2-enyl, (E)-1-methylbut-2-enyl, (Z)-1-methylbut-2-enyl, (E)-3-methylbut-1-enyl, (Z)-3-methylbut-1-enyl, (E)-2-methylbut-1-enyl, (Z)-2-methylbut-1-enyl, (E)-1-methylbut-1-enyl, (Z)-1-methylbut-1-enyl, 1,1-dimethylprop-2-enyl, 1-ethylprop-1-enyl, 1-propylvinyl, 1-isopropylvinyl, 4-methylpent-4-enyl, 3-methylpent-4-enyl, 2-methylpent-4-enyl, 1-methylpent-4-enyl, 4-methylpent-3-enyl, (E)-3-methylpent-3-enyl, (Z)-3-methylpent-3-enyl, (E)-2-methylpent-3-enyl, (Z)-2-methylpent-3-enyl, (E)-1-methylpent-3-enyl, (Z)-1-methylpent-3-enyl, (E)-4-methylpent-2-enyl, (Z)-4-methylpent-2-enyl, (E)-3-methylpent-2-enyl, (Z)-3-methylpent-2-enyl, (E)-2-methylpent-2-enyl, (Z)-2-methylpent-2-enyl, (E)-1-methylpent-2-enyl, (Z)-1-methylpent-2-enyl, (E)-4-methylpent-1-enyl, (Z)-4-methylpent-1-enyl, (E)-3-methylpent-1-enyl, (Z)-3-methylpent-1-enyl, (E)-2-methylpent-1-enyl, (Z)-2-methylpent-1-enyl, (E)-1-methylpent-1-enyl, (Z)-1-methylpent-1-enyl, 3-ethylbut-3-enyl, 2-ethylbut-3-enyl, 1-ethylbut-3-enyl, (E)-3-ethylbut-2-enyl, (Z)-3-ethylbut-2-enyl, (E)-2-ethylbut-2-enyl, (Z)-2-ethylbut-2-enyl, (E)-1-ethylbut-2-enyl, (Z)-1-ethylbut-2-enyl, (E)-3-ethylbut-1-enyl, (Z)-3-ethylbut-1-enyl, 2-ethylbut-1-enyl, (E)-1-ethylbut-1-enyl, (Z)-1-ethylbut-1-enyl, 2-propylprop-2-enyl, 1-propylprop-2-enyl, 2-isopropylprop-2-enyl, 1-isopropylprop-2-enyl, (E)-2-propylprop-1-enyl, (Z)-2-propylprop-1-enyl, (E)-1-propylprop-1-enyl, (Z)-1-propylprop-1-enyl, (E)-2-isopropylprop-1-enyl, (Z)-2-isopropylprop-1-enyl, (E)-1-isopropylprop-1-enyl, (Z)-1-isopropylprop-1-enyl, (E)-3,3-dimethylprop-1-enyl, (Z)-3,3-dimethylprop-1-enyl, 1-(1,1-dimethylethyl)ethenyl, buta-1,3-dienyl, penta-1,4-dienyl, hexa-1,5-dienyl, or methylhexadienyl group. Particularly, said group is vinyl or allyl.

The term "C_2-C_6-alkynyl" is to be understood as preferably meaning a linear or branched, monovalent hydrocarbon group which contains one or more triple bonds,

and which contains 2, 3, 4, 5 or 6 carbon atoms, particularly 2 or 3 carbon atoms ("C_2-C_3-alkynyl"). Said C_2-C_6-alkynyl group is, for example, ethynyl, prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl, but-3-ynyl, pent-1-ynyl, pent-2-ynyl, pent-3-ynyl, pent-4-ynyl, hex-1-ynyl, hex-2-inyl, hex-3-inyl, hex-4-ynyl, hex-5-ynyl, 1-methylprop-2-ynyl, 2-methylbut-3-ynyl, 1-methylbut-3-ynyl, 1-methylbut-2-ynyl, 3-methylbut-1-ynyl, 1-ethylprop-2-ynyl, 3-methylpent-4-ynyl, 2-methylpent-4-ynyl, 1-methylpent-4-ynyl, 2-methylpent-3-ynyl, 1-methylpent-3-ynyl, 4-methylpent-2-ynyl, 1-methylpent-2-ynyl, 4-methylpent-1-ynyl, 3-methylpent-1-ynyl, 2-ethylbut-3-ynyl, 1-ethylbut-3-ynyl, 1-ethylbut-2-ynyl, 1-propylprop-2-ynyl, 1-isopropylprop-2-ynyl, 2,2-dimethylbut-3-inyl, 1,1-dimethylbut-3-ynyl, 1,1-dimethylbut-2-ynyl, or 3,3-dimethylbut-1-ynyl group. Particularly, said alkynyl group is ethynyl, prop-1-ynyl, or prop-2-inyl.

The term "C_3-C_6-cycloalkyl" is to be understood as meaning a saturated, monovalent, mono-, or bicyclic hydrocarbon ring which contains 3, 4, 5 or 6 carbon atoms ("C_3-C_6-cycloalkyl"). Said C_3-C_6-cycloalkyl group is for example, a monocyclic hydrocarbon ring, *e.g.* a cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl or a bicyclic hydrocarbon ring.

The term "C_4-C_8-cycloalkenyl" is to be understood as preferably meaning a monovalent, mono-, or bicyclic hydrocarbon ring which contains 4, 5, 6, 7 or 8 carbon atoms and one, two, three or four double bonds, in conjugation or not, as the size of said cycloalkenyl ring allows. Said C_4-C_8-cycloalkenyl group is for example, a monocyclic hydrocarbon ring, *e.g.* a cyclobutenyl, cyclopentenyl, or cyclohexenyl or a bicyclic hydrocarbon ring, *e.g.* a cyclooctadienyl ring.

The term "3- to 7-membered heterocycloalkyl", is to be understood as meaning a saturated, monovalent, mono- or bicyclic hydrocarbon ring which contains 2, 3, 4, 5, or 6 carbon atoms, and one or more heteroatom-containing groups selected from C(=O), O, S, S(=O), $S(=O)_2$, NR^a, in which R^a represents a hydrogen atom, or a C_1-C_6-alkyl- or halo-C_1-C_6-alkyl- group ; it being possible for said heterocycloalkyl group to be attached to the rest of the molecule via any one of the carbon atoms or, if present, the nitrogen atom.

Particularly, said 3- to 7-membered heterocycloalkyl can contain 2, 3, 4, or 5 carbon atoms, and one or more of the above-mentioned heteroatom-containing groups (a "3- to 6-membered heterocycloalkyl"), more particularly said heterocycloalkyl can contain 4 or 5 carbon atoms, and one or more of the above-mentioned heteroatom-containing groups (a "5- to 6-membered heterocycloalkyl").

Particularly, without being limited thereto, said heterocycloalkyl can be a 4-membered ring, such as an azetidinyl, oxetanyl, or a 5-membered ring, such as tetrahydrofuranyl, dioxolinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, pyrrolinyl, or a 6-membered ring, such as tetrahydropyranyl, piperidinyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, or trithianyl, or a 7-membered ring, such as a diazepanyl ring, for example. Optionally, said heterocycloalkyl can be benzo fused.

Said heterocyclyl can be bicyclic, such as, without being limited thereto, a 5,5-membered ring, e.g. a hexahydrocyclopenta[c]pyrrol-2(1H)-yl) ring, or a 5,6-membered bicyclic ring, e.g. a hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl ring, or for example.

As mentioned *supra*, said nitrogen atom-containing ring can be partially unsaturated, *i.e.* it can contain one or more double bonds, such as, without being limited thereto, a 2,5-dihydro-1H-pyrrolyl, 4H-[1,3,4]thiadiazinyl, 4,5-dihydrooxazolyl, or 4H-[1,4]thiazinyl ring, for example, or, it may be benzo-fused, such as, without being limited thereto, a dihydroisoquinolinyl ring, for example.

The term "4- to 8-membered heterocycloalkenyl", is to be understood as meaning an unsaturated, monovalent, mono- or bicyclic hydrocarbon ring which contains 4, 5, 6, 7 or 8 carbon atoms, and one or more heteroatom-containing groups selected from C(=O), O, S, S(=O), $S(=O)_2$, NR^a, in which R^a represents a hydrogen atom, or a C_1-C_6-alkyl- or halo-C_1-C_6-alkyl- group ; it being possible for said heterocycloalkenyl group to be attached to the rest of the molecule via any one of the carbon atoms or, if present, the nitrogen atom. Examples of said heterocycloalkenyl may contain

one or more double bonds, *e.g.* 4H-pyranyl, 2H-pyranyl, 3H-diazirinyl, 2,5-dihydro-1H-pyrrolyl, [1,3]dioxolyl, 4H-[1,3,4]thiadiazinyl, 2,5-dihydrofuranyl, 2,3-dihydrofuranyl, 2,5-dihydrothiophenyl, 2,3-dihydrothiophenyl, 4,5-dihydrooxazolyl, or 4H-[1,4]thiazinyl group, or, it may be benzo fused.

The term "aryl" is to be understood as preferably meaning a monovalent, aromatic or partially aromatic, mono-, or bi- or tricyclic hydrocarbon ring having 6, 7, 8, 9, 10, 11, 12, 13 or 14 carbon atoms (a "C_6-C_{14}-aryl" group), particularly a ring having 6 carbon atoms (a "C_6-aryl" group), *e.g.* a phenyl group; or a biphenyl group, or a ring having 9 carbon atoms (a "C_9-aryl" group), *e.g.* an indanyl or indenyl group, or a ring having 10 carbon atoms (a "C_{10}-aryl" group), *e.g.* a tetralinyl, dihydronaphthyl, or naphthyl group, or a ring having 13 carbon atoms, (a "C_{13}-aryl" group), *e.g.* a fluorenyl group, or a ring having 14 carbon atoms, (a "C_{14}-aryl" group), *e.g.* an anthranyl group.

The term "heteroaryl" is understood as preferably meaning a monovalent, monocyclic- , bicyclic- or tricyclic aromatic ring system having 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 ring atoms (a "5- to 14-membered heteroaryl" group), particularly 5 or 6 or 9 or 10 atoms, and which contains at least one heteroatom which may be identical or different, said heteroatom being such as oxygen, nitrogen or sulfur, and in addition in each case can be benzocondensed. Particularly, heteroaryl is selected from thienyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, thia-4H-pyrazolyl *etc.*, and benzo derivatives thereof, such as, for example, benzofuranyl, benzothienyl, benzoxazolyl, benzisoxazolyl, benzimidazolyl, benzotriazolyl, indazolyl, indolyl, isoindolyl, *etc.*; or pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, *etc.*, and benzo derivatives thereof, such as, for example, quinolinyl, quinazolinyl, isoquinolinyl, *etc.*; or azocinyl, indolizinyl, purinyl, *etc.*, and benzo derivatives thereof; or cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthpyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, xanthenyl, or oxepinyl, *etc.*.

In general, and unless otherwise mentioned, the heteroarylic or heteroarylenic radicals include all the possible isomeric forms thereof, e.g. the positional isomers

thereof. Thus, for some illustrative non-restricting example, the term pyridinyl or pyridinylene includes pyridin-2-yl, pyridin-2-ylene, pyridin-3-yl, pyridin-3-ylene, pyridin-4-yl and pyridin-4-ylene; or the term thienyl or thienylene includes thien-2-yl, thien-2-ylene, thien-3-yl and thien-3-ylene.

The term "C_1-C_6", as used throughout this text, *e.g.* in the context of the definition of "C_1-C_6-alkyl", "C_1-C_6-haloalkyl", "C_1-C_6-alkoxy", or "C_1-C_6-haloalkoxy" is to be understood as meaning an alkyl group having a finite number of carbon atoms of 1 to 6, *i.e.* 1, 2, 3, 4, 5, or 6 carbon atoms. It is to be understood further that said term "C_1-C_6" is to be interpreted as any sub-range comprised therein, *e.g.* C_1-C_6, C_2-C_5, C_3-C_4, C_1-C_2, C_1-C_3, C_1-C_4, C_1-C_5, C_1-C_6; particularly C_1-C_2, C_1-C_3, C_1-C_4, C_1-C_5, C_1-C_6; more particularly C_1-C_4; in the case of "C_1-C_6-haloalkyl" or "C_1-C_6-haloalkoxy" even more particularly C_1-C_2.

Similarly, as used herein, the term "C_2-C_6", as used throughout this text, *e.g.* in the context of the definitions of "C_2-C_6-alkenyl" and "C_2-C_6-alkynyl", is to be understood as meaning an alkenyl group or an alkynyl group having a finite number of carbon atoms of 2 to 6, *i.e.* 2, 3, 4, 5, or 6 carbon atoms. It is to be understood further that said term "C_2-C_6" is to be interpreted as any sub-range comprised therein, *e.g.* C_2-C_6, C_3-C_5, C_3-C_4, C_2-C_3, C_2-C_4, C_2-C_5; particularly C_2-C_3.

Further, as used herein, the term "C_3-C_6", as used throughout this text, *e.g.* in the context of the definition of "C_3-C_6-cycloalkyl", is to be understood as meaning a cycloalkyl group having a finite number of carbon atoms of 3 to 6, *i.e.* 3, 4, 5 or 6 carbon atoms. It is to be understood further that said term "C_3-C_6" is to be interpreted as any sub-range comprised therein, *e.g.* C_3-C_6, C_4-C_5, C_3-C_5, C_3-C_4, C_4-C_6, C_5-C_6; particularly C_3-C_6.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

Ring system substituent means a substituent attached to an aromatic or nonaromatic ring system which, for example, replaces an available hydrogen on the ring system.

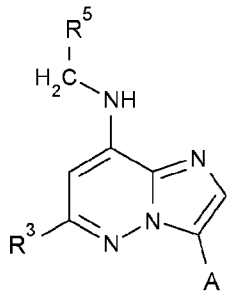
As used herein, the term "leaving group" refers to an atom or a group of atoms that is displaced in a chemical reaction as stable species taking with it the bonding electrons. Preferably, a leaving group is selected from the group comprising: halo, in particular chloro, bromo or iodo, methanesulfonyloxy, p-toluenesulfonyloxy, trifluoromethanesulfonyloxy, nonafluorobutanesulfonyloxy, (4-bromo-benzene)sulfonyloxy, (4-nitro-benzene)sulfonyloxy, (2-nitro-benzene)-sulfonyloxy, (4-isopropyl-benzene)sulfonyloxy, (2,4,6-tri-isopropyl-benzene)-sulfonyloxy, (2,4,6-trimethyl-benzene)sulfonyloxy, (4-tertbutyl-benzene)sulfonyloxy, benzenesulfonyloxy, and (4-methoxy-benzene)sulfonyloxy.

As used herein, the term "one or more times", *e.g.* in the definition of the substituents of the compounds of the general formulae of the present invention, is understood as meaning "one, two, three, four or five times, particularly one, two, three or four times, more particularly one, two or three times, even more particularly one or two times".

Where the plural form of the word compounds, salts, polymorphs, hydrates, solvates and the like, is used herein, this is taken to mean also a single compound, salt, polymorph, isomer, hydrate, solvate or the like.

By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

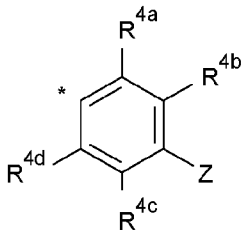
In accordance with a first aspect, the present invention is directed to compounds of general formula I :



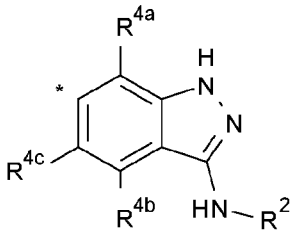
I

in which :

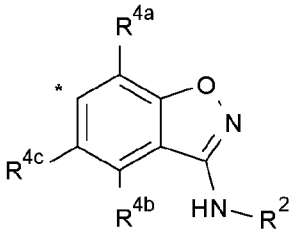
A represents a



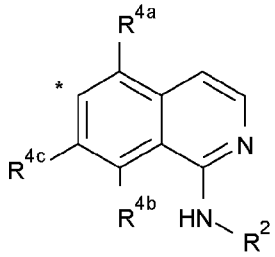
or



or



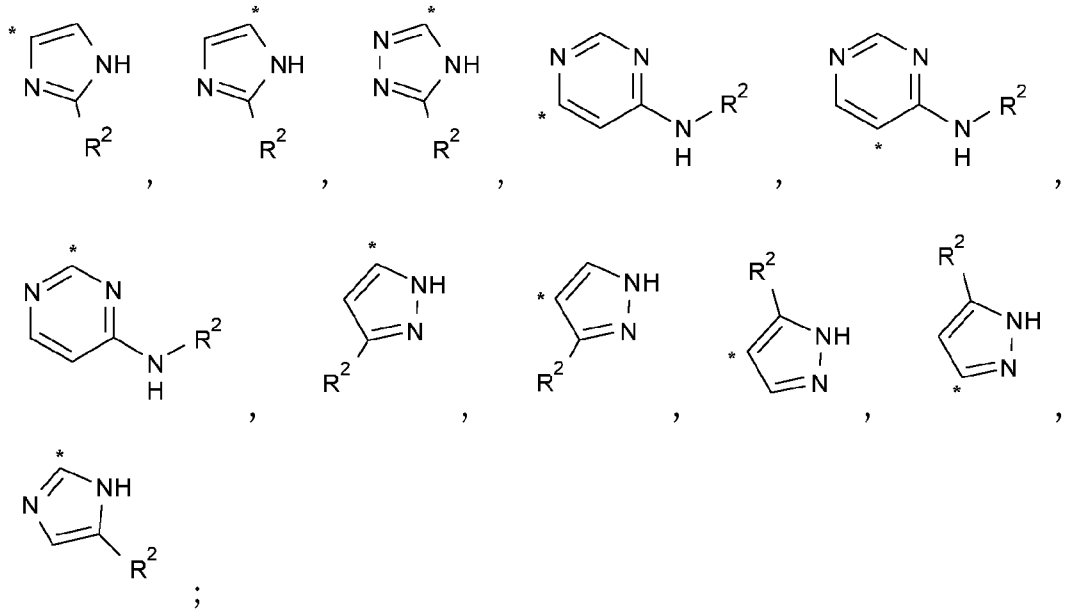
or



-group ;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a $-C(=O)N(H)R^2$ or $-C(=S)N(H)R^2$ group, or a group selected from



wherein * indicates the point of attachment of said groups with the rest of the molecule ;

R^2 represents a hydrogen atom, or a C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl- or C_3-C_6-cycloalkyl- group ;
wherein said C_3-C_6-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 groups selected from: halogen, -OH, -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkyl-;

R^3 represents a hydrogen atom or a halogen atom, or a -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, -$(CH_2)_m$-C_2-C_6-alkenyl, -$(CH_2)_m$-C_4-C_8-cycloalkenyl, -$(CH_2)_m$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl-, -C_1-C_6-alkyl-aryl, -C_1-C_6-alkyl-heteroaryl, heteroaryl-, C_1-C_6-alkyl-X-, -X-$(CH_2)_m$-C_2-C_6-alkenyl, -X-$(CH_2)_m$-C_4-C_8-cycloalkenyl, -X-$(CH_2)_m$-C_2-C_6-alkynyl, -X-$(CH_2)_m$-C_3-C_6-cycloalkyl, -X-$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -X-$(CH_2)_m$-(4- to 8-membered

heterocycloalkenyl), aryl-X-, heteroaryl-X-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -OR^6, -SR^6, -S(=O)R^6, -S(=O)$_2R^6$, -S(=O)(=NR^{6a})R^{6b}, -S(=O)$_2$N(R^{6b})R^{6c}, -S-(CH_2)$_n$-N(R^{6a})R^{6b} or -S-(CH_2)$_n$-(3- to 7-membered heterocycloalkyl) group ;

wherein said C_1-C_6-alkyl-, C_1-C_6-alkoxy-, -(CH_2)$_m$-C_2-C_6-alkenyl, -(CH_2)$_m$-C_2-C_6-alkynyl, -(CH_2)$_m$-C_3-C_6-cycloalkyl, aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl-, C_1-C_6-alkyl-X-, -X-(CH_2)$_m$-C_2-C_6-alkenyl, -X-(CH_2)$_m$-C_4-C_8-cycloalkenyl, -X-(CH_2)$_m$-C_2-C_6-alkynyl, -X-(CH_2)$_m$-C_3-C_6-cycloalkyl, -X-(CH_2)$_m$-(3- to 7-membered heterocycloalkyl), -X-(CH_2)$_m$-(4- to 8-membered heterocycloalkenyl), aryl-X-, heteroaryl-X-, -C_1-C_6-alkyl-aryl, -C_1-C_6-alkyl-heteroaryl or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^7 groups ;

R^{4a}, R^{4b}, R^{4c}, R^{4d}

represent, independently from each other, a hydrogen or halogen atom, or a -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkyl-, R^{6a}(R^{6b})N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2R^6$, -N(R^{6c})S(=O)$_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -S(=O)$_2R^6$, -S(=O)$_2$N(H)R^{6a}, -S(=O)$_2$N(R^{6a})R^{6b}, -S(=O)(=NR^{6c})R^6 group ;

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, -(CH_2)$_n$-C_2-C_6-alkenyl, -(CH_2)$_n$-C_2-C_6-alkynyl, -(CH_2)$_m$-C_3-C_6-cycloalkyl, -(CH_2)$_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, R^{6a}(R^{6b})N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-,aryl- or heteroaryl- group ;

wherein said C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_4-C_8-cycloalkenyl-, aryl- or heteroaryl-group is optionally substituted, identically or differently, with 1, 2, 3 or 4 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c}
represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl-, H O-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, C_2-C_6-alkenyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, aryl-C_1-C_6-alkyl- or heteroaryl-C_1-C_6-alkyl- group ;

R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)$S(=O)_2R^6$, -N(R^{6c})$S(=O)_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -$S(=O)_2R^6$, -$S(=O)_2$N(H)R^6, -$S(=O)_2$N(R^{6a})R^{6b} or -S(=O)(=NR^{6c})R^6 group ;
wherein said C_1-C_6-alkoxy-, aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2 or 3 C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-, -C(=O)O-R^6 or -OH groups;
or
when 2 R^7 groups are present ortho to each other on an aryl- or heteroaryl-ring, said 2 R^7 groups together form a bridge :
$O(CH_2)_2O$, *$O(CH_2)O$*, *NH(C(=O))NH*, wherein * represent the point of attachment to said aryl- or heteroaryl- ring ;

R^8 represents a hydrogen or halogen atom, or a -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, H O-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)$S(=O)_2R^6$, -N(R^{6c})$S(=O)_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, -S(=O)(=NR^{6c})R^6 or $-S(=O)_2$-(3- to 7-membered heterocycloalkyl) group;

wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 C_1-C_6-alkyl- groups ;

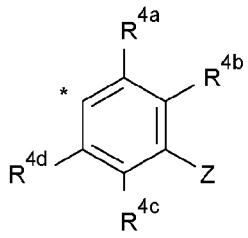
m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

n is an integer of 0, 1, 2, 3, 4 or 5 ;

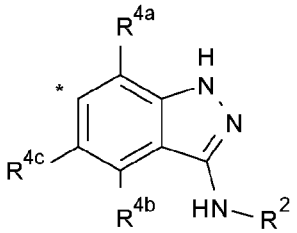
X represents $S(=O)_p$, O, NR^6, $CR^{6a}R^{6b}$ or $C=CR^{6a}R^{6b}$; and

p is an integer of 0, 1 or 2.

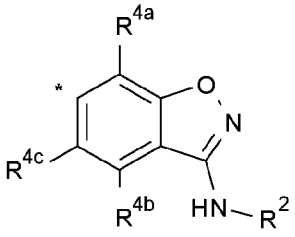
As defined *supra*, A represents a



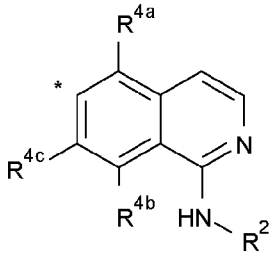
or



or



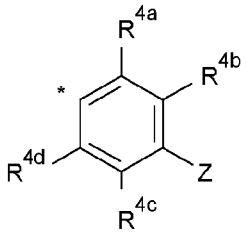
or



-group ;

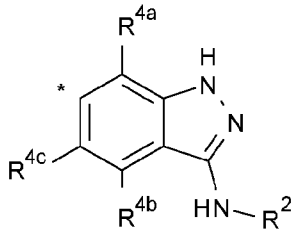
wherein * indicates the point of attachment of said groups with the rest of the molecule.

In a preferred embodiment A represents a



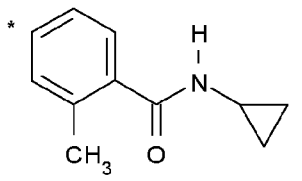
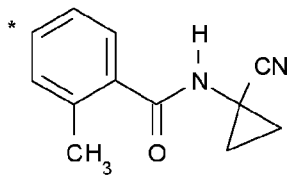
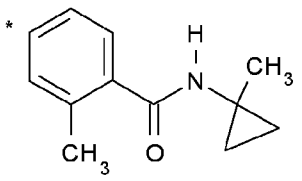
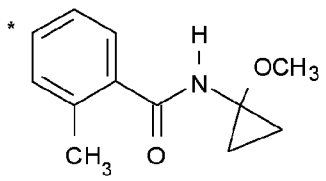
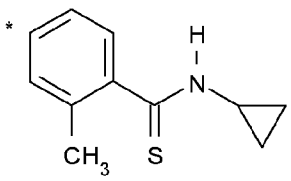
-group.

In another preferred embodiment A represents a



-group.

In another preferred embodiment, the invention relates to compounds of formula I, *supra*, wherein A is selected from the group consisting of:


,

,

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,

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As defined *supra*, R^2 represents a hydrogen atom, or a C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl- or C_3-C_6-cycloalkyl- group ;

wherein said C_3-C_6-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 groups selected from: halogen, -OH, -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkyl-.

In a preferred embodiment, the invention relates to compounds of formula I, wherein :

R^2 represents a C_3-C_6-cycloalkyl- group ;
wherein said C_3-C_6-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 groups selected from: halogen, -OH, -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkyl-.

In another preferred embodiment, the invention relates to compounds of formula I, wherein :

R^2 represents a C_3-C_6-cycloalkyl- group ;
wherein said C_3-C_6-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2, or 3 groups selected from:
halogen, -OH, -CN, -C_1-C_6-alkyl, -C_1-C_6-alkoxy.
Preferably, the C_3-C_6-cycloalkyl- group is a cyclopropyl- group.

In another preferred embodiment, the invention relates to compounds of formula I, wherein :

R^2 represents a C_3-C_6-cycloalkyl- group ;
wherein said C_3-C_6-cycloalkyl- group is optionally substituted, identically or differently, with 1 or 2 groups selected from:
-CN, -C_1-C_3-alkyl, -C_1-C_3-alkoxy.
Preferably, the C_3-C_6-cycloalkyl- group is a cyclopropyl- group.

In another preferred embodiment, the invention relates to compounds of formula I, wherein :

R^2 represents a cyclopropyl- group ;
wherein said cyclopropyl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 groups selected from:
halogen, -OH, -CN, -C_1-C_6-alkyl, -C_1-C_6-alkoxy.

In another preferred embodiment, the invention relates to compounds of formula I, wherein :

R^2 represents a cyclopropyl- group ;
wherein said cyclopropyl- group is optionally substituted, identically or differently, with 1 or 2 groups selected from:
halogen, -OH, -CN, -C_1-C_6-alkyl, -C_1-C_6-alkoxy.

In another preferred embodiment, the invention relates to compounds of formula I, wherein :

R^2 represents a cyclopropyl- group ;
wherein said cyclopropyl- group is substituted, identically or differently, with 1 or 2 groups selected from:
halogen, -CN, -C_1-C_3-alkyl, -C_1-C_3-alkoxy.

In another preferred embodiment, the invention relates to compounds of formula I, wherein :

R^2 represents a halo-C_1-C_6-alkyl- group.

In another preferred embodiment, the invention relates to compounds of formula I, wherein :

R^2 represents a C_1-C_6-alkyl- group ;
wherein said C_1-C_6-alkyl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 groups selected from:
halogen, -OH, -CN, C_1-C_6-alkoxy-.

In another preferred embodiment, the invention relates to compounds of formula I, wherein :

R^2 represents a C_1-C_4-alkyl- group ;
wherein said C_1-C_4-alkyl- group is optionally substituted, identically or differently, with 1, 2 or 3 groups selected from:
halogen, -OH, -CN, -C_1-C_4-alkoxy.

In another preferred embodiment, the invention relates to compounds of formula I, wherein :

R^2 represents a methyl- or ethyl- group ;
wherein said methyl- or ethyl- group is optionally substituted, identically or differently, with 1, 2 or 3 groups selected from:
halogen, -OH, -CN.

In another preferred embodiment, the invention relates to compounds of formula I, wherein :

R^2 represents CH_3 or C_2H_5.

In another preferred embodiment, the invention relates to compounds of formula I, wherein :

R^2 represents a C_1-C_3-alkyl- group ;
wherein said C_1-C_3-alkyl- group is optionally substituted, identically or differently, with 1, 2 or 3 groups selected from:
halogen, -OH, -CN, -C_1-C_3-alkoxy.

The invention relates to compounds of formula I, wherein :

R^3 represents a hydrogen atom or a halogen atom, or a -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, -$(CH_2)_m$-C_2-C_6-alkenyl, -$(CH_2)_m$-C_4-C_8-cycloalkenyl, -$(CH_2)_m$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl-, -C_1-C_6-alkyl-aryl, -C_1-C_6-alkyl-heteroaryl, heteroaryl-, C_1-C_6-alkyl-X-, -X-$(CH_2)_m$-C_2-C_6-alkenyl, -X-$(CH_2)_m$-C_4-C_8-cycloalkenyl, -X-$(CH_2)_m$-C_2-C_6-alkynyl, -X-$(CH_2)_m$-C_3-C_6-cycloalkyl, -X-$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -X-$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-X-, heteroaryl-X-, -$C(=O)R^6$, -$C(=O)N(H)R^{6a}$, -$C(=O)N(R^{6a})R^{6b}$, -$C(=O)O$-R^6, -$N(R^{6a})R^{6b}$, -NO_2, -$N(H)C(=O)R^6$, -OR^6, -SR^6, -$S(=O)R^6$, -$S(=O)_2R^6$, -$S(=O)(=NR^{6a})R^{6b}$, -$S(=O)_2N(R^{6b})R^{6c}$, -S-$(CH_2)_n$-$N(R^{6a})R^{6b}$ or -S-$(CH_2)_n$-(3- to 7-membered heterocycloalkyl) group ;

wherein said C_1-C_6-alkyl-, C_1-C_6-alkoxy-, -$(CH_2)_m$-C_2-C_6-alkenyl, -$(CH_2)_m$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl-, C_1-C_6-alkyl-X-, -X-$(CH_2)_m$-C_2-C_6-alkenyl, -X-$(CH_2)_m$-C_4-C_8-cycloalkenyl, -X-$(CH_2)_m$-C_2-C_6-alkynyl, -X-$(CH_2)_m$-C_3-C_6-cycloalkyl, -X-$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -X-$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-X-, heteroaryl-X-, -C_1-C_6-alkyl-aryl, -C_1-C_6-alkyl-heteroaryl or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^7 groups.

In a preferred embodiment, the invention relates to compounds of formula I, *supra*, wherein:

R^3 represents a

C_1-C_6-alkyl-X-, -X-$(CH_2)_m$-C_2-C_6-alkenyl, -X-$(CH_2)_m$-C_4-C_8-cycloalkenyl, -X-$(CH_2)_m$-C_2-C_6-alkynyl, -X-$(CH_2)_m$-C_3-C_6-cycloalkyl, -X-$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -X-$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-, heteroaryl-, aryl-X- or heteroaryl-X- group;

wherein said C_1-C_6-alkyl-X-, -X-$(CH_2)_m$-C_2-C_6-alkenyl, -X-$(CH_2)_m$-C_4-C_8-cycloalkenyl, -X-$(CH_2)_m$-C_2-C_6-alkynyl, -X-$(CH_2)_m$-C_3-C_6-cycloalkyl, -X-$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -X-$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-, heteroaryl-, aryl-X- or heteroaryl-X- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 R^7 groups.

In another preferred embodiment, the invention relates to compounds of formula I, *supra*, wherein:

R^3 represents a hydrogen atom or a halogen atom, or a C_1-C_6-alkoxy-, -$(CH_2)_m$-C_2-C_6-alkenyl, aryl-, aryl-X-, heteroaryl-X-, heteroaryl-, -$(CH_2)_m$-C_4-C_8-cycloalkenyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-, -C(=O)N(H)R^{6a}, -OR^6, -SR^6, -S(=O)R^6, -$S(=O)_2R^6$, -S-$(CH_2)_n$-N(R^{6a})R^{6b} or -S-$(CH_2)_n$-(3- to 7-membered heterocycloalkyl) group ;

wherein said C_1-C_6-alkoxy-, aryl-, aryl-X-, heteroaryl-X- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^7 groups.

In another preferred embodiment, the invention relates to compounds of formula I, *supra*, wherein:

R^3 represents a hydrogen atom or a halogen atom, or a -$(CH_2)_m$-C_2-C_6-alkenyl, -$(CH_2)_m$-C_4-C_8-cycloalkenyl -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-, heteroaryl-, aryl-X-, heteroaryl-X-, -C(=O)N(H)R^{6a}, -OR^6, -SR^6, -S(=O)R^6, -$S(=O)_2R^6$, -S-$(CH_2)_n$-N(R^{6a})R^{6b}, or -S-$(CH_2)_n$-(3- to 7-membered heterocycloalkyl) group ;
wherein said aryl-, aryl-X-, heteroaryl-X- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 R^7 groups.

In another preferred embodiment, the invention relates to compounds of formula I, *supra*, wherein:

R^3 represents an aryl-, -C_1-C_6-alkyl-aryl, aryl-X-, heteroaryl-X-, heteroaryl-, -C_1-C_6-alkyl-heteroaryl, heteroaryl-group; wherein said aryl-, aryl-X-, heteroaryl-X-, heteroaryl-, -C_1-C_6-alkyl-aryl or -C_1-C_6-alkyl-heteroaryl-group is optionally substituted, identically or differently, with 1, 2, 3 or 4 R^7 groups.

In another preferred embodiment, the invention relates to compounds of formula I, *supra*, wherein:

R^3 represents

a substituted or unsubstituted aryl-X- group, or

a substituted or unsubstituted heteroaryl-X- group.

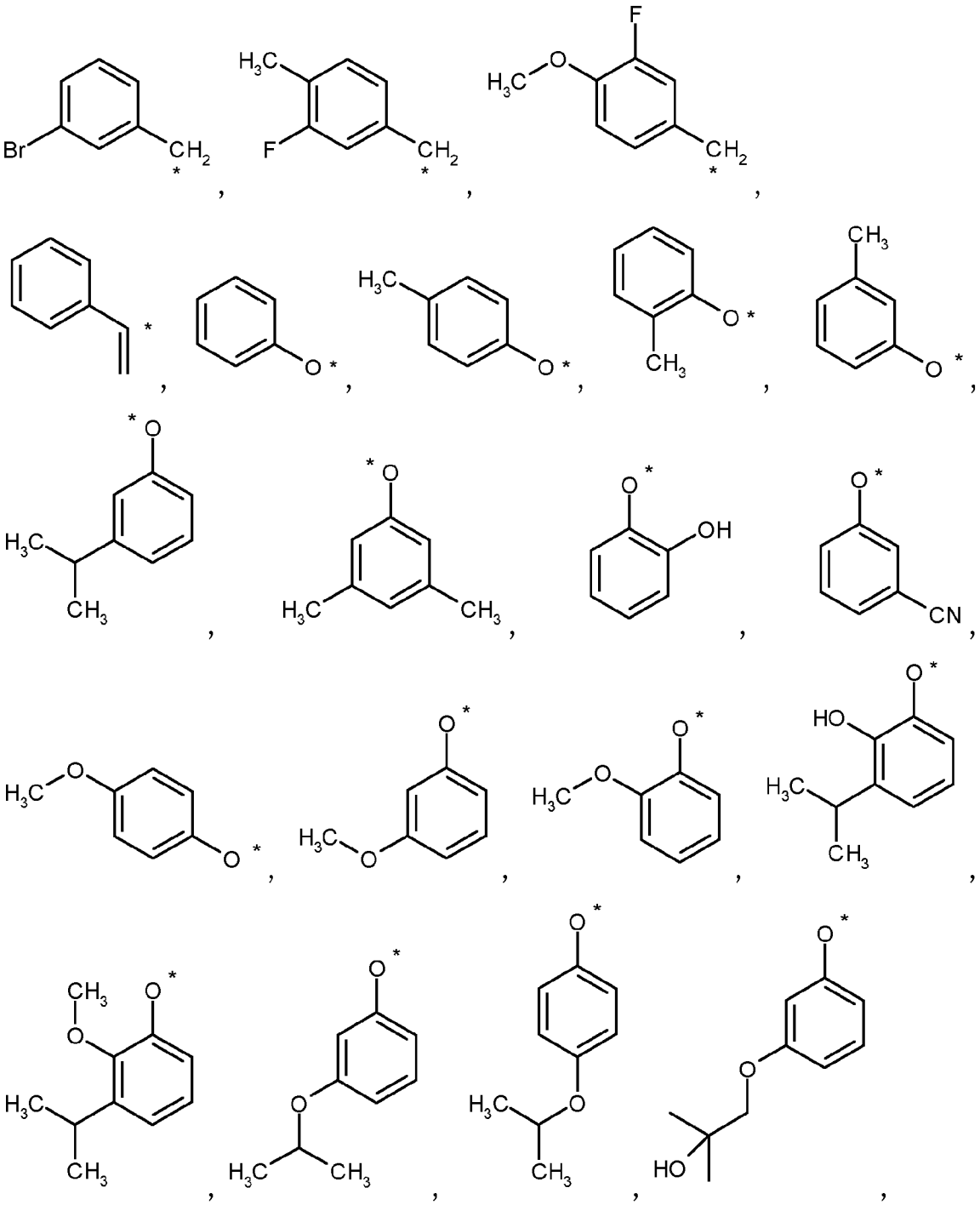
A preferred aryl-X- group is phenyl-X-.

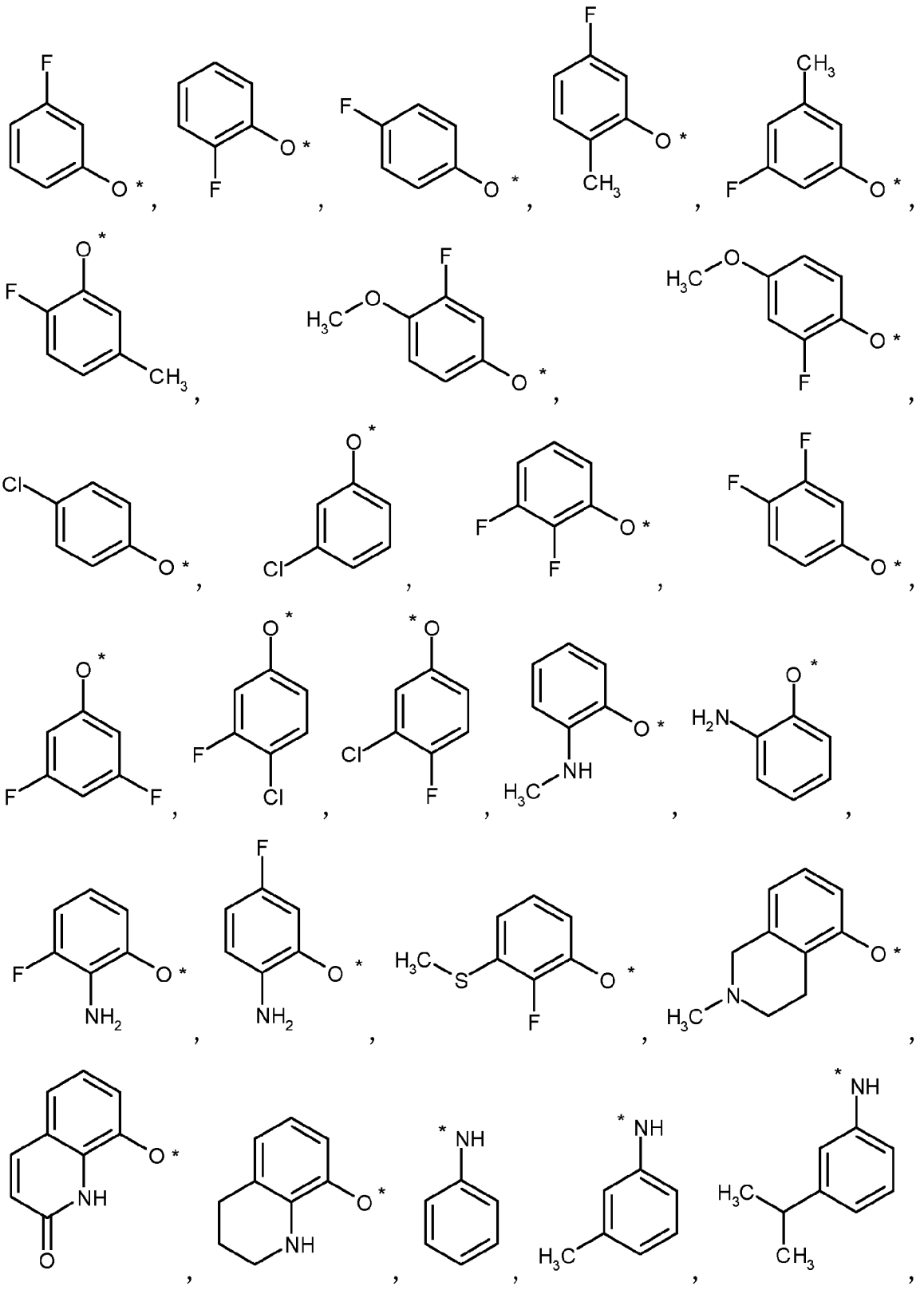
Preferred heteroaryl-X- groups are quinolinyl-X-, pyridyl-X-, thienyl-X-, pyrazinyl-X-, imidazyl-X-, triazyl-X- and pyrazyl-X-.

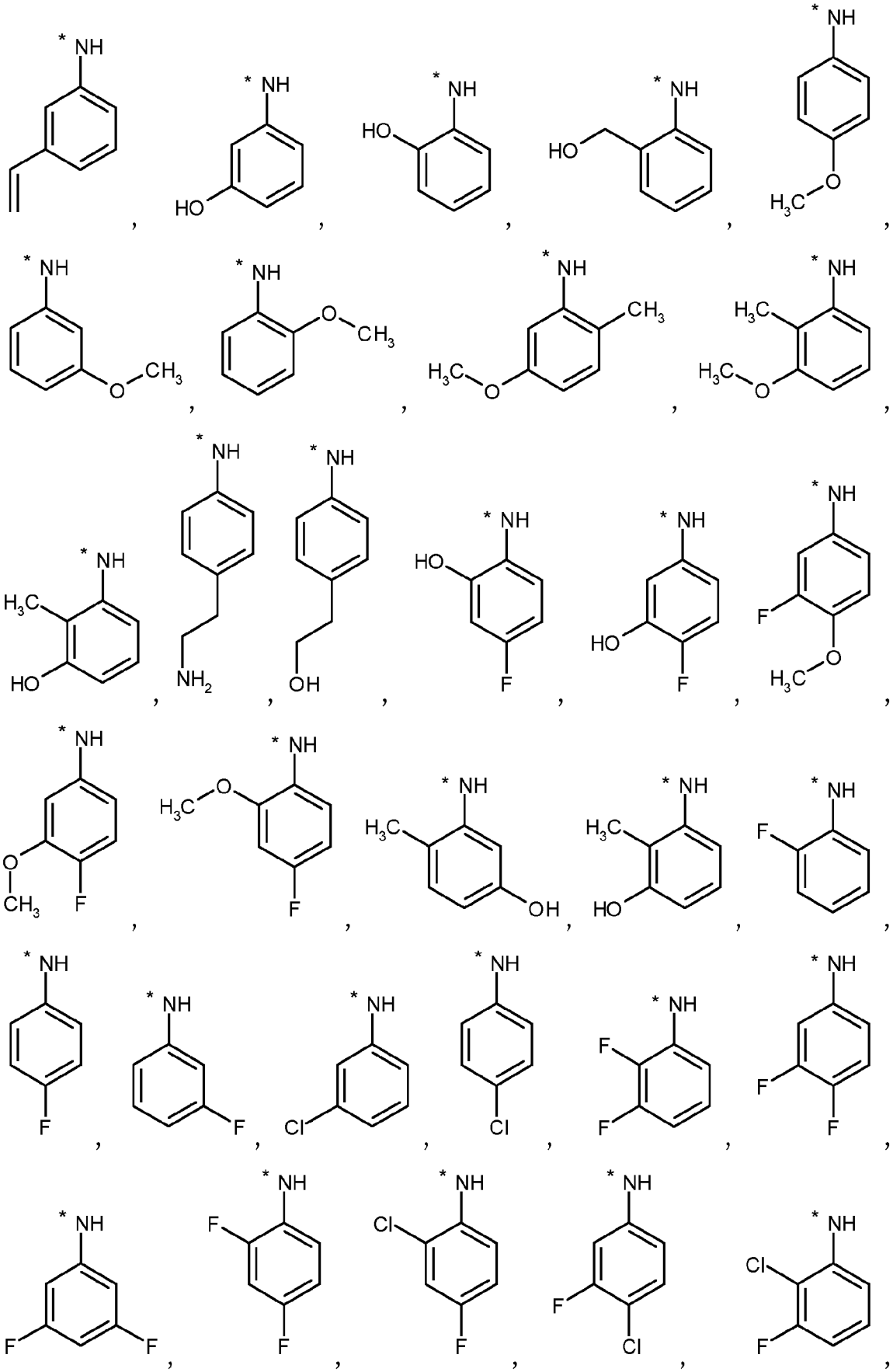
R^3 is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^7 groups.

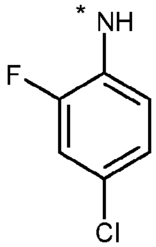
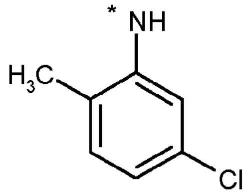
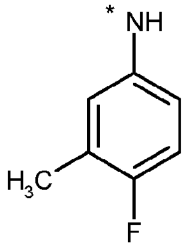
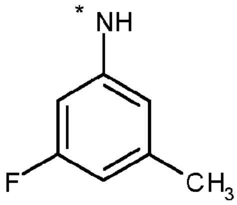
In a preferred embodiment, the invention relates to compounds of formula I, wherein R^3 is optionally substituted, identically or differently, with 1 or 2 R^7 groups.

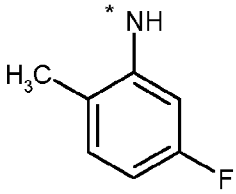
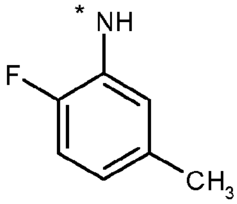
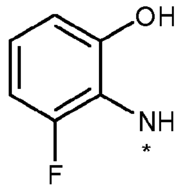
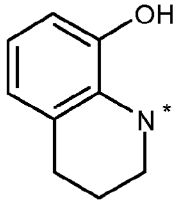
In another preferred embodiment, the invention relates to compounds of formula I, wherein R^3 is selected from the group consisting of:

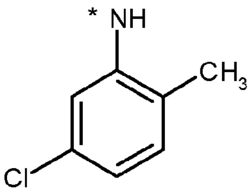
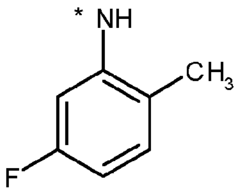
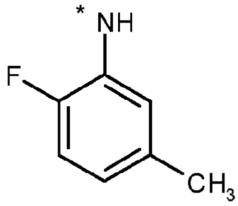
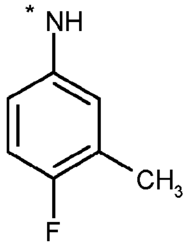


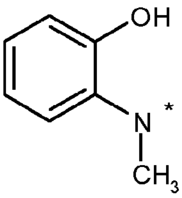
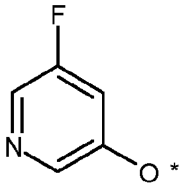
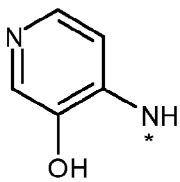
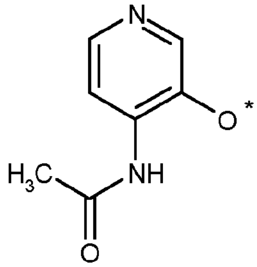


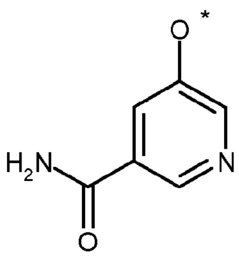
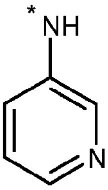
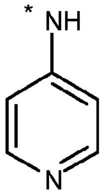
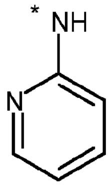
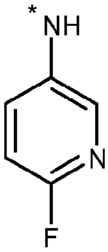
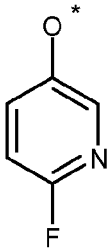
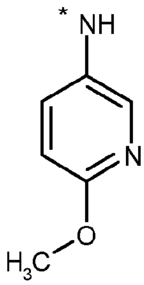


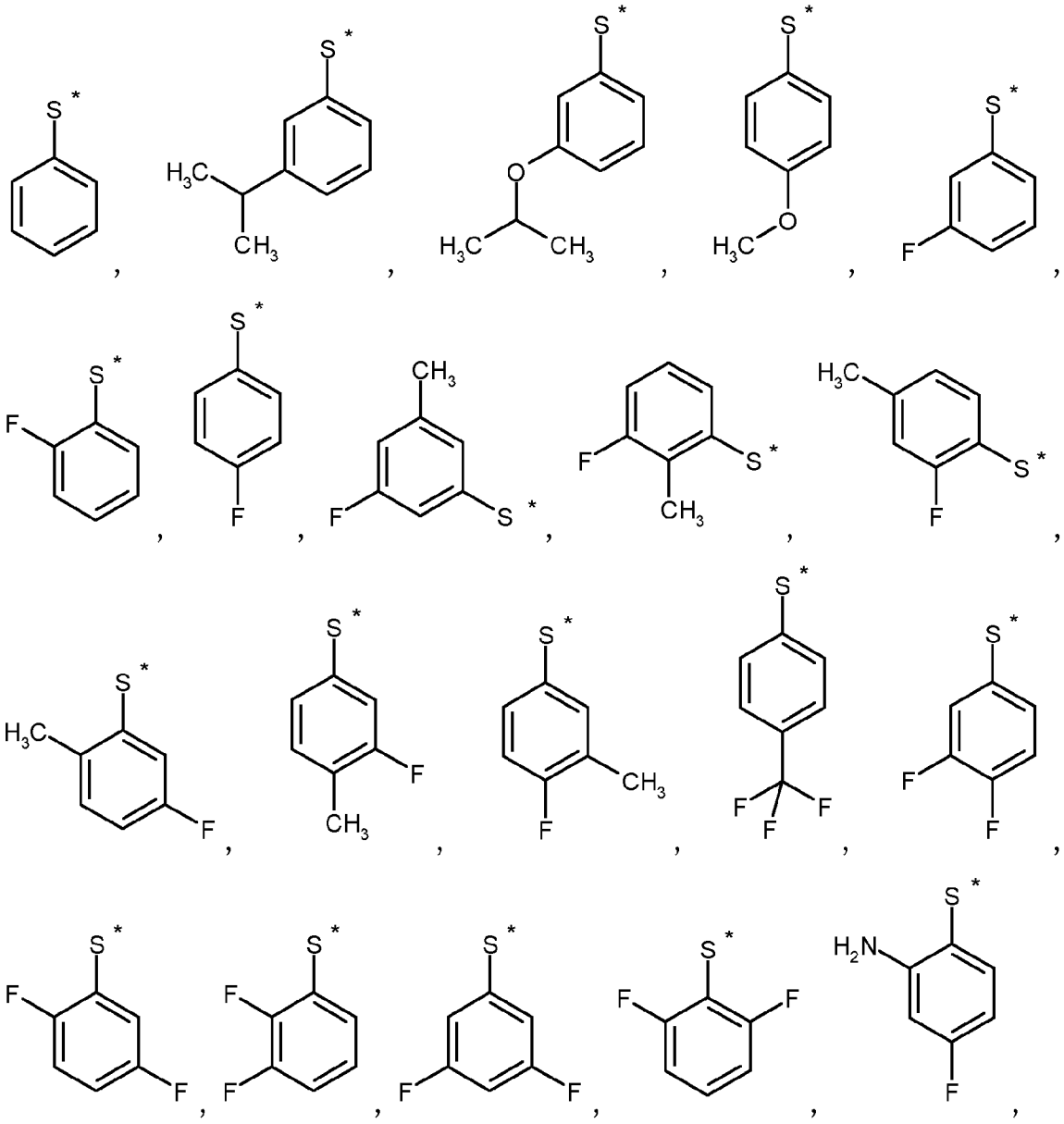
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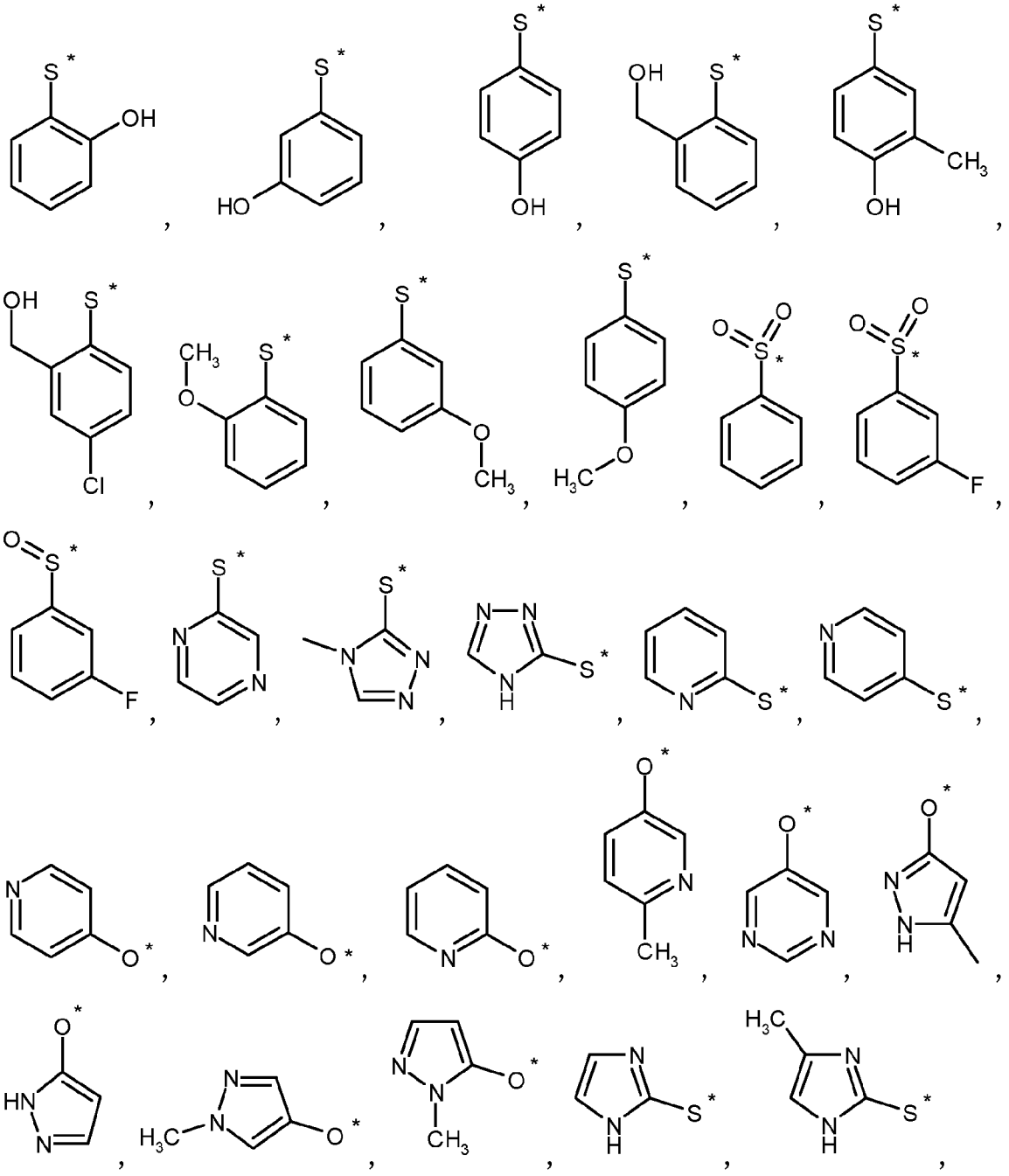
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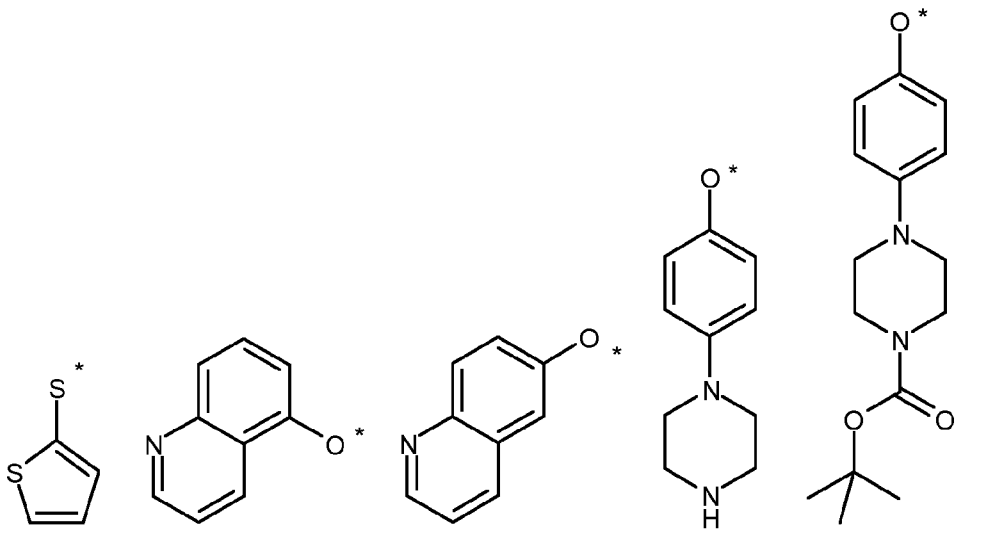
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The invention relates to compounds of formula I, *supra*, wherein :

R^{4a}, R^{4b}, R^{4c}, R^{4d}

represent, independently from each other, a hydrogen or halogen atom, or a -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, $-NO_2$, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)$S(=O)_2R^6$, -N(R^{6c})$S(=O)_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^{6a}$, $-S(=O)_2N(R^{6a})R^{6b}$, -S(=O)(=NR^{6c})R^6 group.

In a preferred embodiment, the invention relates to compounds of formula I, *supra*, wherein:

R^{4a}, R^{4c}, R^{4d} represent a hydrogen atom, and

R^{4b} represents a hydrogen atom, halogen atom or a C_1-C_6-alkyl- group.

In another preferred embodiment, the invention relates to compounds of formula I, *supra*, wherein:

R^{4b}, R^{4c}, R^{4d} represent a hydrogen atom, and

R^{4a} represents a halogen atom, C_1-C_6-alkyl-, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^{6a}$, $-S(=O)_2N(R^{6a})R^{6b}$, or $-S(=O)(=NR^{6c})R^6$ group.

In another preferred embodiment, the invention relates to compounds of formula I, *supra*, wherein:

R^{4b}, R^{4c}, R^{4d} represent a hydrogen atom, and

R^{4a} represents a halogen atom, C_1-C_6-alkyl- or $-OR^6$ group.

In another preferred embodiment, the invention relates to compounds of formula I, *supra*, wherein:

R^{4a}, R^{4b}, R^{4c}, and R^{4d} represent, independently from each other, a hydrogen or halogen atom, or a -CN, -OH, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, NC-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl- group; with the proviso that at least one of the groups R^{4b} and R^{4c} is not a hydrogen atom.

In another preferred embodiment of the present invention R^{4a} and R^{4d} represent, independently from each other, a hydrogen or halogen atom, or a -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkyl- or a halo-C_1-C_6-alkoxy- group.

In another preferred embodiment of the present invention R^{4a} and R^{4d} represent, independently from each other, a hydrogen or halogen atom, or a C_1-C_6-alkyl-, C_1-C_6-alkoxy-, or a halo-C_1-C_6-alkyl- group.

In another preferred embodiment of the present invention R^{4a} and R^{4d} represent hydrogen.

In another preferred embodiment of the present invention R^{4b} and R^{4c} represent independently from each other, a hydrogen or halogen atom, or a -CN, -OH, C_1-C_6-alkyl-, C_1-C_6-alkoxy- group; with the proviso that at least one of the groups R^{4b} and R^{4c} is not a hydrogen atom.

In another preferred embodiment of the present invention R^{4b} and R^{4c} represent independently from each other, a hydrogen or a C_1-C_6-alkyl- group; with the proviso that at least one of the groups R^{4b} and R^{4c} is not a hydrogen atom.

In another preferred embodiment of the present invention R^{4b} and R^{4c} represent independently from each other, a hydrogen or a C_1-C_4-alkyl- group; with the proviso that at least one of the groups R^{4b} and R^{4c} is not a hydrogen atom.

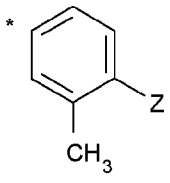
In another preferred embodiment of the present invention one of the groups R^{4b} and R^{4c} represents a hydrogen atom while the other one represents a group selected from: halo-, -CN, -OH, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, NC-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, and halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-.

In another preferred embodiment of the present invention one of the groups R^{4b} and R^{4c} represents a hydrogen atom while the other one represents a group selected from: halo-, -CN, -OH, C_1-C_6-alkyl- and C_1-C_6-alkoxy-.

In another preferred embodiment of the present invention
either: R^{4b} = C_1-C_4-akyl- and R^{4c} = hydrogen;
or: R^{4b} = hydrogen and R^{4c} = C_1-C_4-akyl-.

In another preferred embodiment, the invention relates to compounds of formula I, wherein :

A represents a



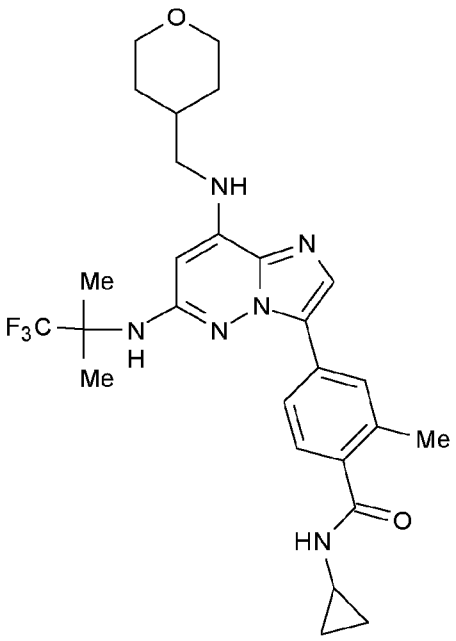
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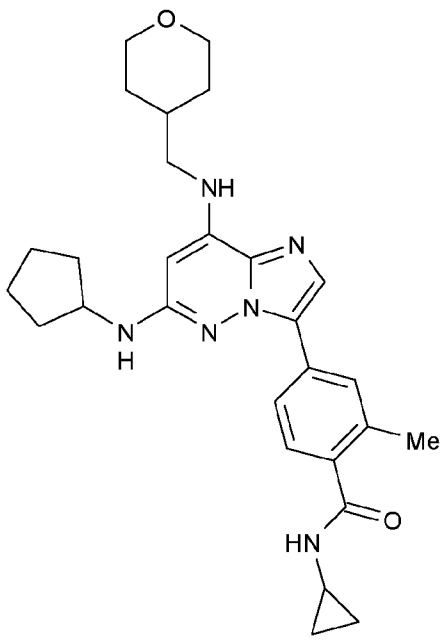
wherein * indicates the point of attachment of said groups with the rest of the molecule ; and

Z represents a -C(=O)N(H)R^2 or a -C(=S)N(H)R^2 group.

Preferably Z represents a -C(=O)N(H)R^2 group.

In another preferred embodiment, the invention relates to compounds of formula I, *supra*, wherein the following compounds (which are specificall disclosed in WO 2011/013729A1) are excluded:





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The invention relates to compounds of formula I, *supra*, wherein :

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-,aryl- or heteroaryl- group ;

wherein said C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_4-C_8-cycloalkenyl-, aryl- or heteroaryl-

group is optionally substituted, identically or differently, with 1, 2, 3 or 4 R^8 groups.

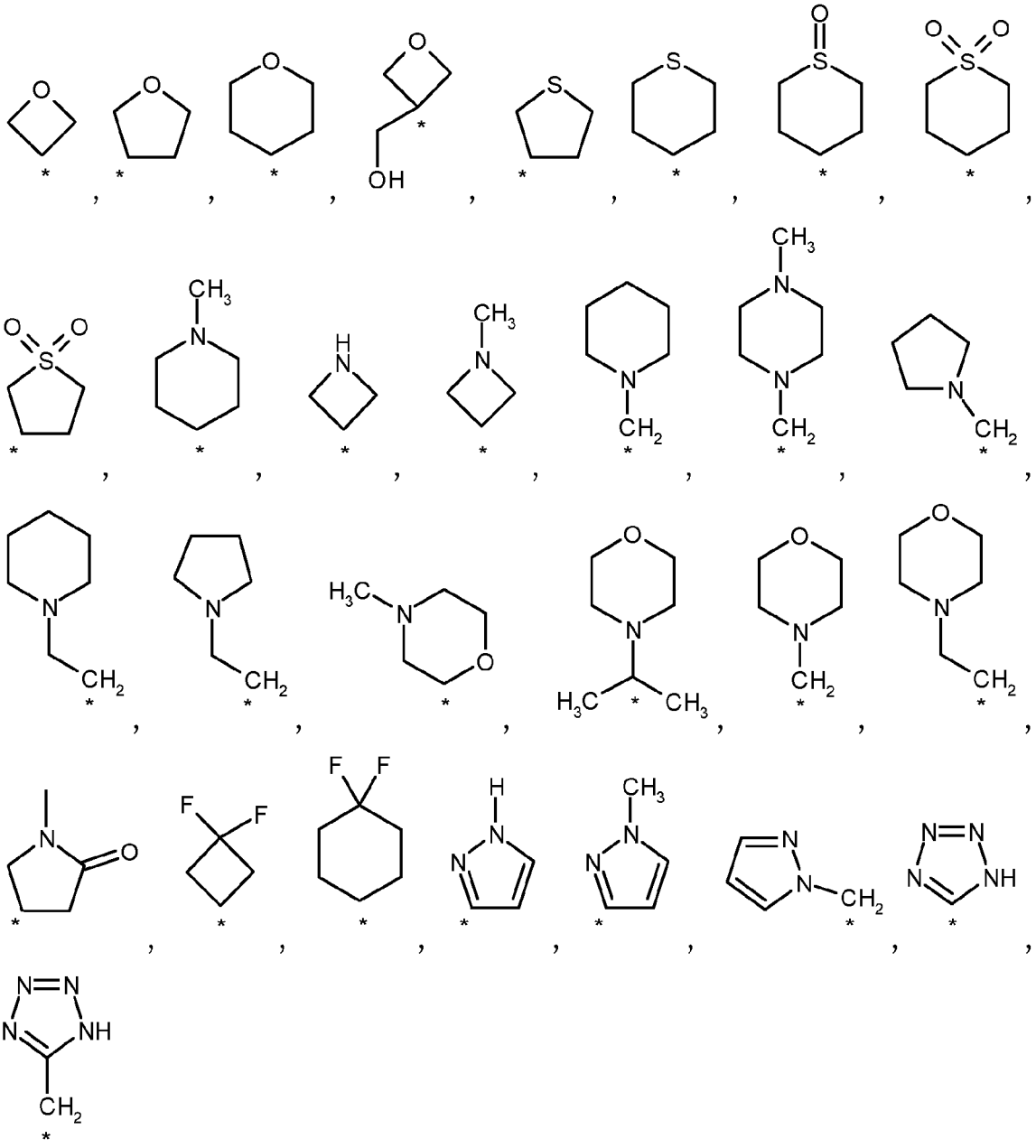
In a preferred embodiment, the invention relates to compounds of formula I, *supra*, wherein:

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl- or heteroaryl- group ;
wherein said C_1-C_6-alkyl-, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-, or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 R^8 groups.

In another preferred embodiment, the invention relates to compounds of formula I, *supra*, wherein:

R^5 represents a C_1-C_6-alkyl-, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl- or heteroaryl- group ;
wherein said C_1-C_6-alkyl-, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-, heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 R^8 groups.

In another preferred embodiment, the invention relates to compounds of formula I, wherein R^5 is selected from the group consisting of:
H, $(CH_3)_2CH$-, CHF_2-, CF_3-, CF_3-CH_2-, CF_3-CH_2-CH_2-, CF_3-CH(OH)-, HO-CH_2-, HO-$C(CH_3)_2$-, HO-$C(CH_3)_2CH_2$-, HO-CH_2-CH(OH)-, H_3C-O-CH_2-, H_2N-CH_2-CH_2-, H_2N-$C(CH_3)_2$-, $(CH_3)_2N$-CH_2-, $(CH_3)_2N$-CH_2-CH_2-, $(CH_3)_2N$-CH_2-CH_2-CH_2-, $(CH_3)_2N$-$C(CH_3)_2$-, H_3C-$S(=O)_2$-CH_2-, H_3C-$S(=O)_2$-CH_2-CH_2-, HO-$S(=O)_2$-CH_2-, HO-$S(=O)_2$-CH_2-CH_2-, NC-CH_2-, H_3C-C(=O)-N(H)-CH_2, H_3C-C(=O)-N(H)-CH_2-CH_2-, H_2N-C(=O)-CH_2-, $(CH_3)_2N$-C(=O)-CH_2-, H_3C-N(H)-C(=O)-N(CH_3)-CH_2-CH_2-,



In another preferred embodiment, with respect to compounds of formula I, *supra*, R^5 represents a 1,1,1-trifluoroethyl group.

The invention relates to compounds of formula I, *supra*, wherein :

R^6, R^{6a}, R^{6b} and R^{6c}

represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl-, H O-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, C_2-C_6-alkenyl-, 3- to

7-membered heterocycloalkyl-, aryl-, heteroaryl-, aryl-C_1-C_6-alkyl- or heteroaryl-C_1-C_6-alkyl- group.

In a preferred embodiment, the invention relates to compounds of formula I, *supra*, wherein:

R^6, R^{6a}, R^{6b}, R^{6c},

represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl- or aryl- group.

In another preferred embodiment, the invention relates to compounds of formula I, wherein

R^6, R^{6a}, R^{6b}, and R^{6c} represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl- group.

The invention relates to compounds of formula I, *supra*, wherein :

R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$ or $-S(=O)(=NR^{6c})R^6$ group ;

wherein said C_1-C_6-alkoxy-, aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2 or 3 C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-, $-C(=O)O-R^6$ or -OH groups;

or

when 2 R^7 groups are present ortho to each other on an aryl- or heteroaryl-ring, said 2 R^7 groups together form a bridge :

$*O(CH_2)_2O*$, $*O(CH_2)O*$, *NH(C(=O))NH*, wherein * represent the point of attachment to said aryl- or heteroaryl- ring.

In a preferred embodiment, the invention relates to compounds of formula I, wherein R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, H_2N-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, or $-S(=O)(=NR^{6c})R^6$ group ;

wherein said C_1-C_6-alkoxy-, aryl-, 3- to 7-membered heterocycloalkyl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, or 3 C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-, $-C(=O)O-R^6$ or -OH groups.

In another preferred embodiment, the invention relates to compounds of formula I, *supra*, wherein:

R^7 represents a hydrogen or halogen atom, or an HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, aryl-, heteroaryl-, $-C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-OR^6$, $-S(=O)R^6$, or $-S(=O)_2R^6$, group ;

wherein said C_1-C_6-alkoxy- or heteroaryl- group is optionally substituted, identically or differently, with a C_1-C_4-alkyl-, halo-C_1-C_6-alkoxy-, $-C(=O)O-R^6$ or -OH group;

or

when 2 R^7 groups are present ortho- to each other on an aryl- or heteroaryl-ring, said 2 R^7 groups together form a bridge :

$*O(CH_2)_2O*$, $*O(CH_2)O*$, *NH(C(=O))NH*, wherein * represent the point of attachment to said aryl- or heteroaryl- ring.

In another preferred embodiment, the invention relates to compounds of formula I, *supra*, wherein:

R^7 represents a hydrogen or halogen atom, or an HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, aryl-, heteroaryl-, $-C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-OR^6$, $-S(=O)R^6$, or $-S(=O)_2R^6$, group ;

wherein said C_1-C_6-alkoxy- or heteroaryl- group is optionally substituted, identically or differently, with a C_1-C_4-alkyl-, halo-C_1-C_6-alkoxy-, -C(=O)O-R^6 or -OH group.

In another preferred embodiment, the invention relates to compounds of formula I, *supra*, wherein:

R^7 represents a hydrogen or halogen atom, or an HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, aryl-, heteroaryl-, -C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -OR^6, -S(=O)R^6, or -S(=O)$_2R^6$ group; wherein said heteroaryl- group is optionally substituted with a C_1-C_4-alkyl group;

or

when 2 R^7 groups are present ortho- to each other on an aryl- or heteroaryl-ring, said 2 R^7 groups together form a bridge :

O(CH_2)$_2$O, *O(CH_2)O*, *NH(C(=O))NH*, wherein * represent the point of attachment to said aryl- or heteroaryl- ring.

In another preferred embodiment, the invention relates to compounds of formula I, wherein R^7 represents a halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, H_2N-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, -C(=O)N(H)R^{6a}, -N(R^{6a})R^{6b}, -N(H)C(=O)R^6, or -SR^6 group ;

wherein said C_1-C_6-alkoxy-, or 3- to 7-membered heterocycloalkyl- group is optionally substituted, identically or differently, with 1, 2, or 3 C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-, -C(=O)O-R^6 or -OH groups.

In another preferred embodiment, the invention relates to compounds of formula I, wherein R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, R^{6a}(R^{6b})N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, H_2N-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, aryl-, heteroaryl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2R^6$, -N(R^{6c})S(=O)$_2R^6$,

-N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -S(=O)$_2R^6$, - S(=O)$_2$N(H)R^6, -S(=O)$_2$N(R^{6a})R^{6b}, or -S(=O)(=NR^{6c})R^6 group ;

wherein said C_1-C_6-alkoxy-, aryl-, 3- to 7-membered heterocycloalkyl, or heteroaryl- group is optionally substituted, identically or differently, with 1 C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-, -C(=O)O-R^6 or -OH group.

In another preferred embodiment, the invention relates to compounds of formula I, wherein R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, H_2N-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, -C(=O)N(H)R^{6a}, -N(R^{6a})R^{6b}, -N(H)C(=O)R^6 or -SR^6 group ;

wherein said C_1-C_6-alkoxy- or 3- to 7-membered heterocycloalkyl- group is optionally substituted, identically or differently, with one -C(=O)O-R^6 or -OH group.

In another preferred embodiment, the invention relates to compounds of formula I, *supra*, wherein 2 R^7 groups are present ortho to each other on the aryl- or heteroarly- ring of the R^3 group ;

said 2 R^7 groups together form a bridge :

O(CH_2)$_2$O, *O(CH_2)O*, *CH_2(CH_2)$_2$NH*, *CH_2CH_2N(R^{6a})CH_2*, *NH(C(=O))NH*, *C(H)=C(H)-C(=O)-N(H)*,

wherein * represent the point of attachment to said aryl- or heteroaryl- ring.

Preferably the 2 R^7 groups together form a bridge selected from:

CH_2(CH_2)$_2$NH, *CH_2CH_2N(R^{6a})CH_2*, *C(H)=C(H)-C(=O)-N(H)*.

The invention relates to compounds of formula I, *supra*, wherein

R^8 represents a hydrogen or halogen atom, or a -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, R^{6a}(R^{6b})N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2R^6$, -N(R^{6c})S(=O)$_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6,

$-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ or $-S(=O)_2$-(3- to 7-membered heterocycloalkyl) group;

wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 C_1-C_6-alkyl-groups.

In a preferred embodiment, the invention relates to compounds of formula I, *supra*, wherein:

R^8 represents a halogen atom, or a -CN, -OH, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, HO-C_1-C_6-alkyl, $-C(=O)N(R^{6a})R^{6b}$, $-N(R^{6a})R^{6b}$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$ or $-S(=O)_2OH$ group.

In another preferred embodiment, the invention relates to compounds of formula I, *supra*, wherein:

R^8 represents a halogen atom, a -CN, $-N(R^{6a})R^{6b}$, or $-OR^6$ group.

Preferably, R^8 represents a halogen atom, a $-N(R^{6a})R^{6b}$ or a $-OR^6$ group.

The invention relates to compounds of formula I, wherein

m is an integer of 0, 1, 2, 3, 4, 5 or 6.

In a preferred embodiment, with respect to compounds of formula I, *supra*, m is 0.

In another preferred embodiment, with respect to compounds of formula I, *supra*, m is 1.

The invention relates to compounds of formula I, wherein

n is an integer of 0, 1, 2, 3, 4 or 5.

In a preferred embodiment, with respect to compounds of formula I, *supra*, n is 1.

The invention relates to compounds of formula I, wherein

X is S, S(=O), $S(=O)_2$, O, NR^6, $CR^{6a}R^{6b}$ or $C=CR^{6a}R^{6b}$.

In a preferred embodiment, the invention relates to compounds of formula I, wherein

X is S.

In another preferred embodiment, the invention relates to compounds of formula I, wherein

X is S(=O).

In another preferred embodiment, the invention relates to compounds of formula I, wherein

X is $S(=O)_2$.

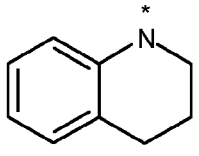
In another preferred embodiment, the invention relates to compounds of formula I, wherein

X is O.

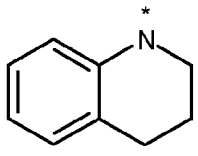
In another preferred embodiment, the invention relates to compounds of formula I, wherein

X is NR^6. Preferably, X is NH or $N(CH_3)$. Most preferably, X is NH.

It should be noted that in a group of e.g. formula aryl-NR^6- or heteroaryl-NR^6- the substituent R^6 optionally can be attached to the aryl- or heteroaryl- ring, thereby - together with the N-atom - forming a heterocyclic ring fused to the aryl- or heteroaryl- ring. An example of such a fused ring system is the group :



, in which * indicates the point of attachment of said group with the rest of the molecule. In other words, a group with the formula

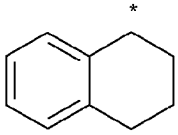


, in which * indicates the point of attachment of said group with the rest of the molecule, is an example of an aryl-X- group.

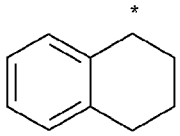
In another preferred embodiment, the invention relates to compounds of formula I, wherein

X is $CR^{6a}R^{6b}$. Preferably, X is CH_2.

It should be noted that in a group of e.g. formula aryl-$CR^{6a}R^{6b}$- or heteroaryl-$CR^{6a}R^{6b}$- the substituents R^{6a} and/or R^{6b} optionally can be attached to the aryl- or heteroaryl- ring, thereby forming one or more carbocyclic rings fused to the aryl- or heteroaryl- ring. An example of such a fused ring system is the group



, in which * indicates the point of attachment of said group with the rest of the molecule. In other words, a group with the formula



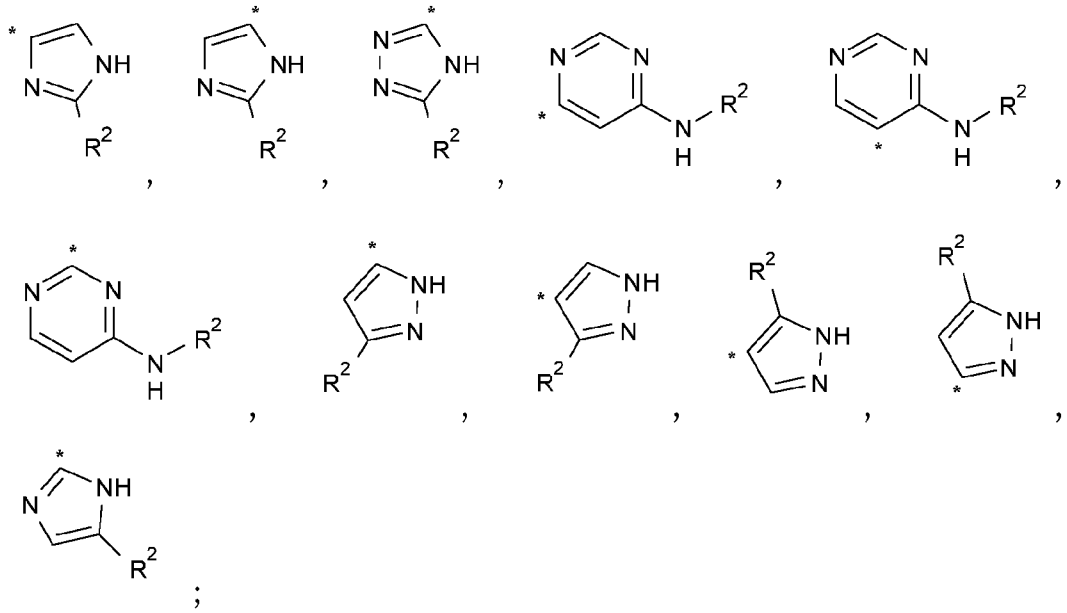
, in which * indicates the point of attachment of said group with the rest of the molecule, is an example of an aryl-X- group.

In another preferred embodiment, the invention relates to compounds of formula I, wherein

X is $C{=}CR^{6a}R^{6b}$. Preferably, X is $C{=}CH_2$.

The invention relates to compounds of formula I, wherein

Z represents a $-C(=O)N(H)R^2$ or $-C(=S)N(H)R^2$ group, or a group selected from



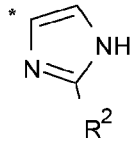
;

wherein * indicates the point of attachment of said groups with the rest of the molecule.

In a preferred embodiment Z represents a -C(=O)N(H)R^2 group.

In another preferred embodiment Z represents a -C(=S)N(H)R^2 group.

In another preferred embodiment Z represents a



group.

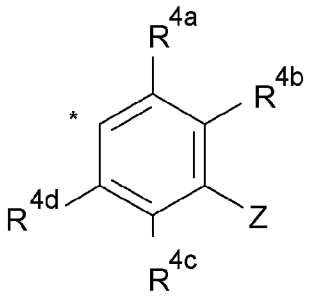
In an embodiment of the above-mentioned aspects, the invention relates to compounds of formula I, according to any of the above-mentioned embodiments, in the form of or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

It is to be understood that the present invention relates also to any combination of the preferred embodiments described above.

Some examples of combinations are given hereinafter. However, the invention is not limited to these combinations.

In a preferred embodiment, the invention relates to compounds of general formula I, *supra*, in which :

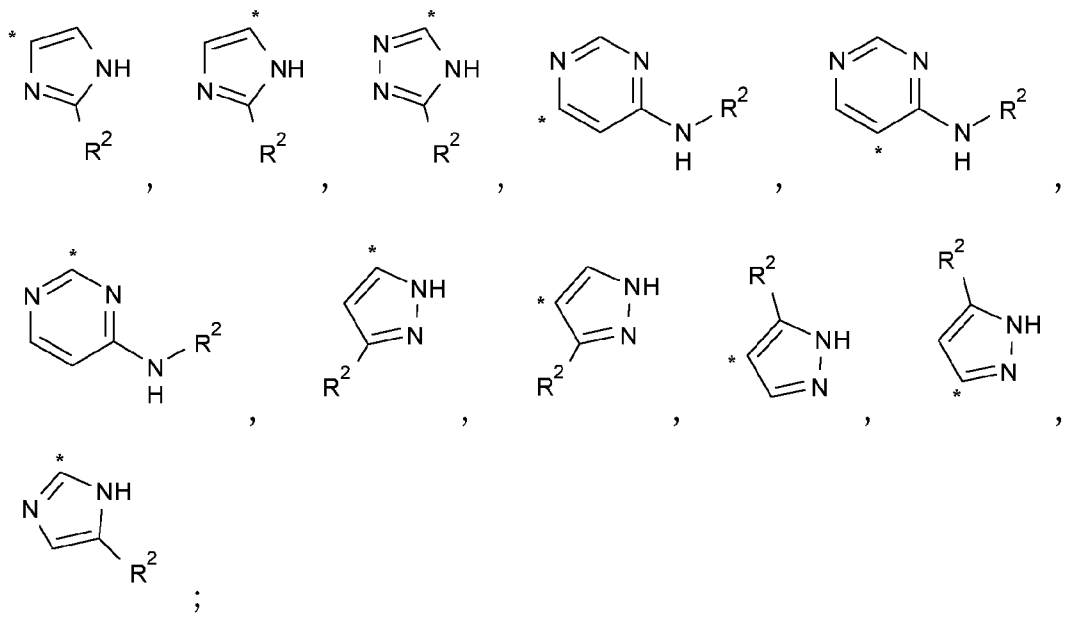
A represents a



-group;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a -C(=O)N(H)R^2 or -C(=S)N(H)R^2 group, or a group selected from



wherein * indicates the point of attachment of said groups with the rest of the molecule ;

R^2 represents a hydrogen atom, or a C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl- or C_3-C_6-cycloalkyl-group ;

wherein said C_3-C_6-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 - groups selected from: halogen, OH, -CN, C_1-C_6-alkyl, -C_1-C_6-alkoxy, halo-C_1-C_6-alkyl- ;

R^3 represents a hydrogen atom or a halogen atom, or a -CN, C_1-C_6-alkyl-, -$(CH_2)_m$-C_2-C_6-alkenyl, , -$(CH_2)_m$-C_4-C_8-cycloalkenyl -$(CH_2)_m$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, a 3- to 7-membered heterocycloalkyl, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl-, -C1-C6-alkyl-aryl, -C1-C6-alkyl-heteroaryl, heteroaryl-, C_1-C_6-alkyl-X-, -X-$(CH_2)_m$-C_2-C_6-alkenyl, -X-$(CH_2)_m$-C_4-C_8-cycloalkenyl, -X-$(CH_2)_m$-C_2-C_6-alkynyl, -X-$(CH_2)_m$-C_3-C_6-cycloalkyl, -X-$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -X-$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-X-, heteroaryl-X-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)_2R^6$, $-S(=O)(=NR^{6a})R^{6b}$, $-S(=O)_2N(R^{6b})R^{6c}$, -S-$(CH_2)_n$-$N(R^{6a})R^{6b}$, or -S-$(CH_2)_n$-(3- to 7-membered heterocycloalkyl) group ;

wherein said C_1-C_6-alkyl-, -$(CH_2)_m$-C_2-C_6-alkenyl, -$(CH_2)_m$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, a 3- to 7-membered heterocycloalkyl, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl-, C_1-C_6-alkyl-X-, -X-$(CH_2)_m$-C_2-C_6-alkenyl, -X-$(CH_2)_m$-C_4-C_8-cycloalkenyl, -X-$(CH_2)_m$-C_2-C_6-alkynyl, -X-$(CH_2)_m$-C_3-C_6-cycloalkyl, -X-$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -X-$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-X-, heteroaryl-X-, -C_1-C_6-alkyl-aryl, -C_1-C_6-alkyl-heteroaryl or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 R^7 groups ;

R^{4a}, R^{4b}, R^{4c}, R^{4d}

represent, independently from each other, a hydrogen or halogen atom, or a -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^{6a}$, $-S(=O)_2N(R^{6a})R^{6b}$ or $-S(=O)(=NR^{6c})R^6$ group.

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, $-(CH_2)_n$-C_2-C_6-alkenyl, $-(CH_2)_n$-C_2-C_6-alkynyl, $-(CH_2)_m$-C_3-C_6-cycloalkyl, $-(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-,aryl- or heteroaryl group ;
wherein said C_1-C_6-alkyl-, $-(CH_2)_n$-C_2-C_6-alkenyl, $-(CH_2)_n$-C_2-C_6-alkynyl, $-(CH_2)_m$-C_3-C_6-cycloalkyl, $-(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_4-C_8-cycloalkenyl-, aryl- or heteroaryl-group is optionally substituted, identically or differently, with 1, 2, 3, or 4 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c},
represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, aryl-C_1-C_6-alkyl-, or heteroaryl-C_1-C_6-alkyl- group ;

R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-,

C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, aryl-, heteroaryl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2R^6$, -N(R^{6c})S(=O)$_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, - S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -S(=O)$_2R^6$, -S(=O)$_2$N(H)R^6, -S(=O)$_2$N(R^{6a})R^{6b}, -S(=O)(=NR^{6c})R^6 group ;

wherein said aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, or 3 C_1-C_6-alkyl groups;

or

when 2 R^7 groups are present ortho- to each other on an aryl- ring, said 2 R^7 groups together form a bridge :

O$(CH_2)_2$O, *O(CH_2)O*, *NH(C(=O))NH*, wherein * represent the point of attachment to said aryl- ring ;

R^8 represents a hydrogen or halogen atom, or a -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, aryl-, heteroaryl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2R^6$, -N(R^{6c})S(=O)$_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -S(=O)$_2R^6$, -S(=O)$_2$N(H)R^6, -S(=O)$_2$N(R^{6a})R^{6b}, -S(=O)(=NR^{6c})R^6 group or - S(=O)$_2$-(3- to 7-membered heterocycloalkyl);

wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 C_1-C_6-alkyl- groups ;

m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

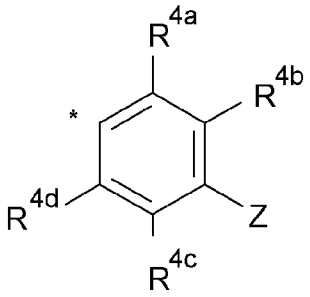
n is an integer of 0, 1, 2, 3, 4 or 5 ;

X is S, S(=O), S(=O)$_2$, O, NR^6;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another preferred embodiment, the invention relates to compounds of general formula I, *supra*, in which :

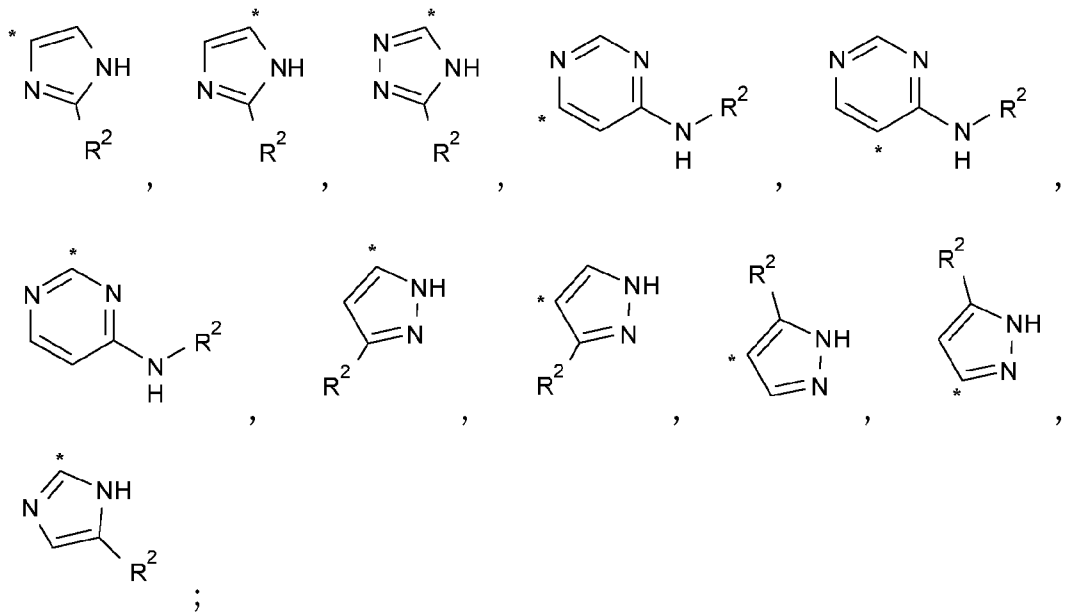
A represents a



-group;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a -C(=O)N(H)R^2 or -C(=S)N(H)R^2 group, or a group selected from



;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

R^2 represents a hydrogen atom, or a C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl- or C_3-C_6-cycloalkyl- group ;

wherein said C_3-C_6-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 - groups selected from: halogen, OH, -CN, C_1-C_6-alkyl, -C_1-C_6-alkoxy, halo-C_1-C_6-alkyl-;

R^3 represents a hydrogen atom or a halogen atom, or a -CN, C_1-C_6-alkyl-, -$(CH_2)_m$-C_2-C_6-alkenyl-, -$(CH_2)_m$-C_4-C_8-cycloalkenyl, -$(CH_2)_m$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl-, -C_1-C_6-alkyl-aryl, -C_1-C_6-alkyl-heteroaryl, heteroaryl-, C_1-C_6-alkyl-X-, -X-$(CH_2)_m$-C_2-C_6-alkenyl, -X-$(CH_2)_m$-C_4-C_8-cycloalkenyl, -X-$(CH_2)_m$-C_2-C_6-alkynyl, -X-$(CH_2)_m$-C_3-C_6-cycloalkyl, -X-$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -X-$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-X-, heteroaryl-X-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -OR^6, -SR^6, -S(=O)R^6, -$S(=O)_2R^6$, -S(=O)(=NR^{6a})R^{6b}, -$S(=O)_2$N(R^{6b})R^{6c}, -S-$(CH_2)_n$-N(R^{6a})R^{6b}, or -S-$(CH_2)_n$-(3- to 7-membered heterocycloalkyl) group ;

wherein said C_1-C_6-alkyl-, -$(CH_2)_m$-C_2-C_6-alkenyl, -$(CH_2)_m$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl-, C_1-C_6-alkyl-X-, -X-$(CH_2)_m$-C_2-C_6-alkenyl, -X-$(CH_2)_m$-C_4-C_8-cycloalkenyl, -X-$(CH_2)_m$-C_2-C_6-alkynyl, -X-$(CH_2)_m$-C_3-C_6-cycloalkyl, -X-$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -X-$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-X-, heteroaryl-X-, -C_1-C_6-alkyl-aryl,

-C_1-C_6-alkyl-heteroaryl, or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 R^7 groups ;

either

R^{4a}, R^{4c}, R^{4d} represent a hydrogen atom, and
R^{4b} represents a hydrogen atom or a halogen atom or a C_1-C_6-alkyl- group;

or

R^{4b}, R^{4c}, R^{4d} represent a hydrogen atom, and
R^{4a} represents a halogen atom or an C_1-C_6-alkyl-, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^{6a}$, $-S(=O)_2N(R^{6a})R^{6b}$ or $-S(=O)(=NR^{6c})R^6$ group ;

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, $-(CH_2)_n$-C_2-C_6-alkenyl, $-(CH_2)_n$-C_2-C_6-alkynyl, $-(CH_2)_m$-C_3-C_6-cycloalkyl, $-(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, a 3- to 7-membered heterocycloalkyl, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-,aryl- or heteroaryl- group ;
wherein said C_1-C_6-alkyl-, $-(CH_2)_n$-C_2-C_6-alkenyl, $-(CH_2)_n$-C_2-C_6-alkynyl, $-(CH_2)_m$-C_3-C_6-cycloalkyl, $-(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl, C_4-C_8-cycloalkenyl-, aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c},
represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, C_2-C_6-alkenyl-, 3- to 7-membered

heterocycloalkyl-, aryl-, heteroaryl-, aryl-C_1-C_6-alkyl-, or heteroaryl-C_1-C_6-alkyl- group ;

R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, or $-S(=O)(=NR^{6c})R^6$ group ;
wherein said aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, or 3 C_1-C_6-alkyl- groups;
or
when 2 R^7 groups are present ortho to each other on an aryl- ring, said 2 R^7 groups together form a bridge :
$*O(CH_2)_2O*$, $*O(CH_2)O*$, *NH(C(=O))NH*, wherein * represent the point of attachment to said aryl- ring ;

R^8 represents a hydrogen or halogen atom, or a -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ or $-S(=O)_2$-(3- to 7-membered heterocycloalkyl) group;

wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 C_1-C_6-alkyl- groups ;

m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

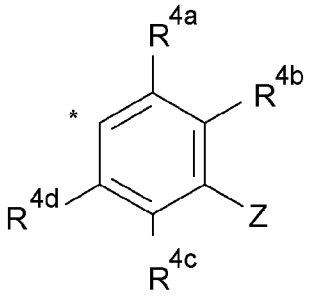
n is an integer of 0, 1, 2, 3, 4 or 5 ;

X is S, S(=O), $S(=O)_2$, O, NR^6;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another preferred embodiment, the invention relates to compounds of general formula I, *supra*, in which :

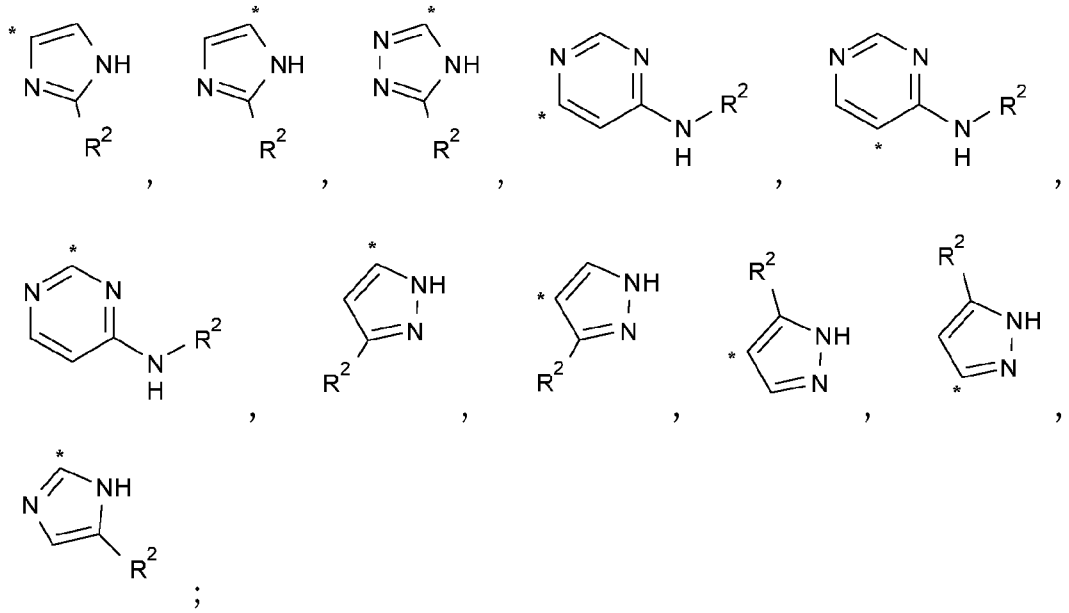
A represents a



-group;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a $-C(=O)N(H)R^2$ or $-C(=S)N(H)R^2$ group, or a group selected from



wherein * indicates the point of attachment of said groups with the rest of the molecule ;

R^2 represents a hydrogen atom, or a C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl- or C_3-C_6-cycloalkyl- group ;
wherein said C_3-C_6-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 - groups selected from: halogen, OH, -CN, C_1-C_6-alkyl, -C_1-C_6-alkoxy, halo-C_1-C_6-alkyl-;

R^3 represents a hydrogen atom or a halogen atom, or a -CN, C_1-C_6-alkyl-, -$(CH_2)_m$-C_2-C_6-alkenyl, , -$(CH_2)_m$-C_4-C_8-cycloalkenyl -$(CH_2)_m$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl-, -C1-C6-alkyl-aryl, -C1-C6-alkyl-heteroaryl, heteroaryl-, C_1-C_6-alkyl-X-, -X-$(CH_2)_m$-C_2-C_6-alkenyl, -X-$(CH_2)_m$-C_4-C_8-cycloalkenyl, -X-$(CH_2)_m$-C_2-C_6-alkynyl, -X-$(CH_2)_m$-C_3-C_6-cycloalkyl, -X-$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -X-$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-X-, heteroaryl-X-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -

$C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)_2R^6$, $-S(=O)(=NR^{6a})R^{6b}$, $-S(=O)_2N(R^{6b})R^{6c}$, $-S-(CH_2)_n-N(R^{6a})R^{6b}$, or $-S-(CH_2)_n-$(3- to 7-membered heterocycloalkyl) group ;

wherein said C_1-C_6-alkyl-, $-(CH_2)_m-C_2$-C_6-alkenyl, $-(CH_2)_m-C_2$-C_6-alkynyl, $-(CH_2)_m-C_3$-C_6-cycloalkyl, aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl-, C_1-C_6-alkyl-X-, $-X-(CH_2)_m-C_2$-C_6-alkenyl, $-X-(CH_2)_m-C_4$-C_8-cycloalkenyl, $-X-(CH_2)_m-C_2$-C_6-alkynyl, $-X-(CH_2)_m-C_3$-C_6-cycloalkyl, $-X-(CH_2)_m-$(3- to 7-membered heterocycloalkyl), $-X-(CH_2)_m-$(4- to 8-membered heterocycloalkenyl), aryl-X-, heteroaryl-X-, $-C_1$-C_6-alkyl-aryl, $-C_1$-C_6-alkyl-heteroaryl, or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 R^7 groups ;

either

R^{4a}, R^{4c}, R^{4d} represent a hydrogen atom, and

R^{4b} represents a hydrogen atom or a halogen atom or a C_1-C_6-alkyl group;

or

R^{4b}, R^{4c}, R^{4d} represent a hydrogen atom, and

R^{4a} represents a halogen atom or a C_1-C_6-alkyl-, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^{6a}$, $-S(=O)_2N(R^{6a})R^{6b}$, or $-S(=O)(=NR^{6c})R^6$ group ;

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, $-(CH_2)_m-$(3- to 7-membered heterocycloalkyl), aryl- or heteroaryl- group ;

wherein said C_1-C_6-alkyl-, $-(CH_2)_m-$(3- to 7-membered heterocycloalkyl), aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c}

represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, C_2-C_6-alkenyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, aryl-C_1-C_6-alkyl-, or heteroaryl-C_1-C_6-alkyl- group ;

R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ group ;
wherein said aryl-, heteroaryl- is optionally substituted, identically or differently, with 1, 2, or 3 C_1-C_6-alkyl groups;
or
when 2 R^7 groups are present ortho- to each other on an aryl- ring, said 2 R^7 groups together form a bridge :
$*O(CH_2)_2O*$, $*O(CH_2)O*$, *NH(C(=O))NH*, wherein * represent the point of attachment to said aryl- ring ;

R^8 represents a hydrogen or halogen atom, or a -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ group , $-S(=O)_2$-(3- to 7-membered heterocycloalkyl);

wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- is optionally substituted, identically or differently, with 1, 2, 3 or 4 C_1-C_6-alkyl- groups ;

m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

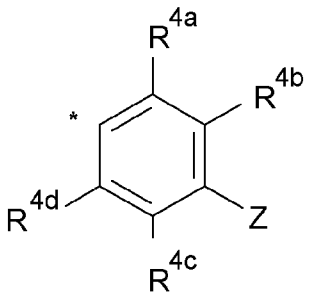
n is an integer of 0, 1, 2, 3, 4 or 5 ;

X is S, S(=O), $S(=O)_2$, O, NR^6;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another preferred embodiment, the invention relates to compounds of general formula I, *supra*, in which :

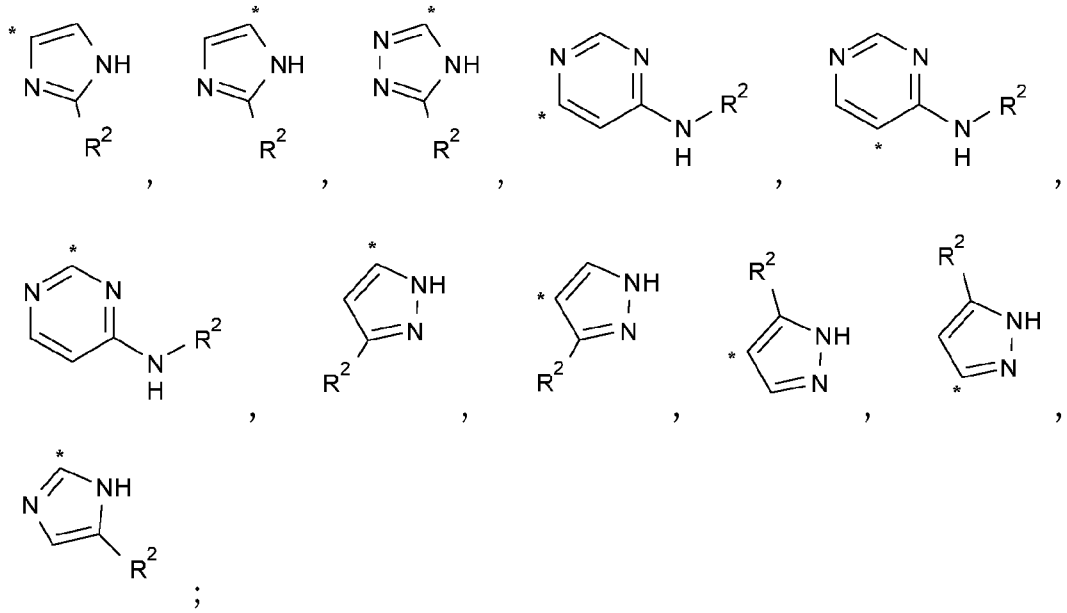
A represents a



-group;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a $-C(=O)N(H)R^2$ or $-C(=S)N(H)R^2$ group, or a group selected from



wherein * indicates the point of attachment of said groups with the rest of the molecule ;

R^2 represents a hydrogen atom, or a C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl- or C_3-C_6-cycloalkyl- group ;
wherein said C_3-C_6-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 groups selected from: halogen, OH, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy-, halo-C_1-C_6-alkyl-;

R^3 represents a hydrogen atom or a halogen atom, or a -CN, C_1-C_6-alkyl-, -$(CH_2)_m$-C_2-C_6-alkenyl, , -$(CH_2)_m$-C_4-C_8-cycloalkenyl -$(CH_2)_m$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl-, -C1-C6-alkyl-aryl, -C1-C6-alkyl-heteroaryl, heteroaryl-, C_1-C_6-alkyl-X-, -X-$(CH_2)_m$-C_2-C_6-alkenyl, -X-$(CH_2)_m$-C_4-C_8-cycloalkenyl, -X-$(CH_2)_m$-C_2-C_6-alkynyl, -X-$(CH_2)_m$-C_3-C_6-cycloalkyl, -X-$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -X-$(CH_2)_m$-(4- to 8-membered

heterocycloalkenyl), aryl-X-, heteroaryl-X-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -OR^6, -SR^6, -S(=O)R^6, -$S(=O)_2R^6$, -S(=O)(=NR^{6a})R^{6b}, -$S(=O)_2$N(R^{6b})R^{6c}, -S-$(CH_2)_n$-N(R^{6a})R^{6b}, or -S-$(CH_2)_n$-(3- to 7-membered heterocycloalkyl) group ;

wherein said C_1-C_6-alkyl-, -$(CH_2)_m$-C_2-C_6-alkenyl, -$(CH_2)_m$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl-, C_1-C_6-alkyl-X-, -X-$(CH_2)_m$-C_2-C_6-alkenyl, -X-$(CH_2)_m$-C_4-C_8-cycloalkenyl, -X-$(CH_2)_m$-C_2-C_6-alkynyl, -X-$(CH_2)_m$-C_3-C_6-cycloalkyl, -X-$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -X-$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-X-, heteroaryl-X-, -C_1-C_6-alkyl-aryl, -C_1-C_6-alkyl-heteroaryl, or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 R^7 groups ;

either

R^{4a}, R^{4c}, R^{4d} represent a hydrogen atom, and
R^{4b} represents a hydrogen atom or a halogen atom or a C_1-C_6-alkyl group;

or

R^{4b}, R^{4c}, R^{4d} represent a hydrogen atom, and
R^{4a} represents a halogen atom or a C_1-C_6-alkyl-, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -$S(=O)_2R^6$, -$S(=O)_2$N(H)R^{6a}, -$S(=O)_2$N(R^{6a})R^{6b}, -S(=O)(=NR^{6c})R^6 group ;

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl- or heteroaryl group ;
said C_1-C_6-alkyl-, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c},

represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, C_2-C_6-alkenyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, aryl-C_1-C_6-alkyl-, or heteroaryl-C_1-C_6-alkyl- group ;

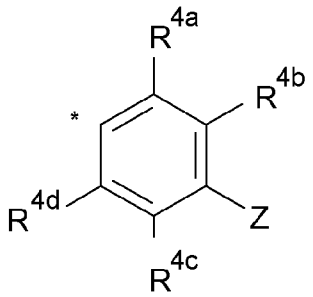
R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ group ;
wherein said aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, or 3 C_1-C_6-alkyl groups;
or
when 2 R^7 groups are present ortho- to each other on an aryl ring, said 2 R^7 groups together form a bridge :
$*O(CH_2)_2O*$, $*O(CH_2)O*$, *NH(C(=O))NH*, wherein * represent the point of attachment to said aryl ring ;

R^8 represents a halogen atom, an $-N(R^{6a})R^{6b}$ or $-OR^6$ group ;

m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;
n is an integer of 0, 1, 2, 3, 4 or 5 ;
X is S, S(=O), $S(=O)_2$, O, NR^6;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

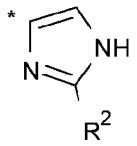
In another preferred embodiment, the invention relates to compounds of general formula I, *supra*, in which :



A represents a -group;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a $-C(=O)N(H)R^2$ or $-C(=S)N(H)R^2$ group,
or a



group ;
wherein * indicates the point of attachment of said groups with the rest of the molecule ;

R^2 represents a hydrogen atom, or a C_1-C_6-alkyl- or C_3-C_6-cycloalkyl- group ;

R^3 represents a hydrogen atom or a halogen atom, or a $-(CH_2)_m$-C_2-C_6-alkenyl, $-(CH_2)_m$-C_4-C_8-cycloalkenyl $-(CH_2)_m$-C_3-C_6-cycloalkyl, $-(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-, aryl-X-, heteroaryl-X-, heteroaryl-, $-C(=O)N(H)R^{6a}$, $-OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)_2R^6$, $-S-(CH_2)_n-N(R^{6a})R^{6b}$, or $-S-(CH_2)_n$-(3- to 7-membered heterocycloalkyl) group ;
wherein said aryl-, aryl-X-, heteroaryl-X- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 R^7 groups ;

either

R^{4a}, R^{4c}, R^{4d} represent a hydrogen atom, and
R^{4b} represents a hydrogen atom or a halogen atom or a C_1-C_6-alkyl group;

or

R^{4b}, R^{4c}, R^{4d} represent a hydrogen atom, and
R^{4a} represents a halogen atom or a C_1-C_6-alkyl-, or -OR^6 group ;

R^5 represents a C_1-C_6-alkyl-, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl- or heteroaryl- group ;
said C_1-C_6-alkyl-, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c},
represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl- or aryl- group ;

R^7 represents a hydrogen or halogen atom, or an HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, aryl-, heteroaryl-, -$C(=O)N(R^{6a})R^{6b}$, -$N(H)C(=O)R^6$, -$N(H)C(=O)N(R^{6a})R^{6b}$, -OR^6, -$S(=O)R^6$, or -$S(=O)_2R^6$ group ;
wherein said heteroaryl- group is optionally substituted with a C_1-C_4-alkyl group;
or
when 2 R^7 groups are present ortho- to each other on an aryl ring, said 2 R^7 groups together form a bridge :
$O(CH_2)_2O$, *$O(CH_2)O$*, *$NH(C(=O))NH$*, wherein * represent the point of attachment to said aryl ring ;

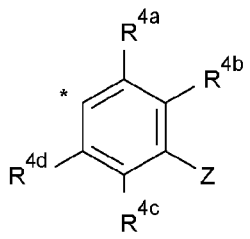
R^8 represents a halogen atom, a -$N(R^{6a})R^{6b}$, or -OR^6 group ;

m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;
X is S, S(=O), $S(=O)_2$, O, NR^6;

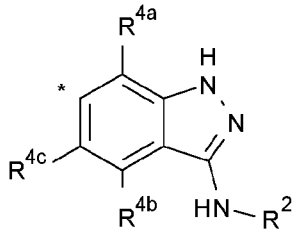
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another preferred embodiment, the invention relates to compounds of general formula I, *supra*, in which :

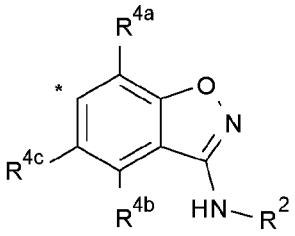
A represents a



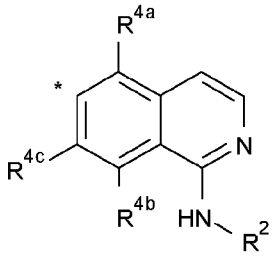
or



or



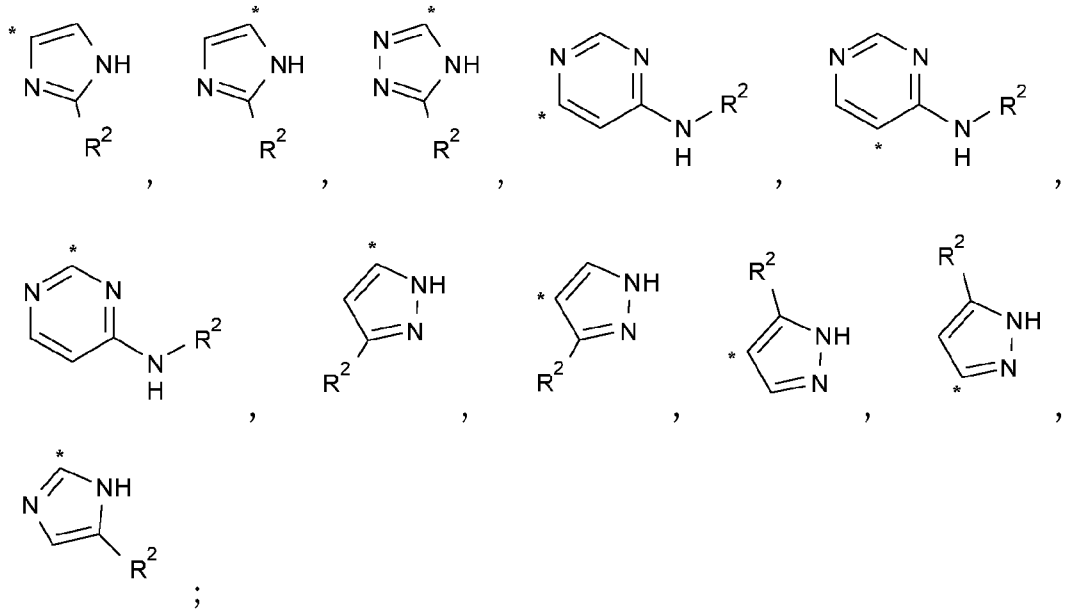
or



-group ;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a $-C(=O)N(H)R^2$ or $-C(=S)N(H)R^2$ group, or a group selected from



wherein * indicates the point of attachment of said groups with the rest of the molecule ;

R^2 represents a hydrogen atom, or a C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl- or C_3-C_6-cycloalkyl- group ;
wherein said C_3-C_6-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 - groups selected from: halogen, OH, -CN, C_1-C_6-alkyl, -C_1-C_6-alkoxy, halo-C_1-C_6-alkyl-;

R^3 represents a hydrogen atom or a halogen atom, or a -CN, C_1-C_6-alkyl-, -C_1-C_6-alkoxy, -$(CH_2)_m$-C_2-C_6-alkenyl, , -$(CH_2)_m$-C_4-C_8-cycloalkenyl -$(CH_2)_m$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl-, -C1-C6-alkyl-aryl, -C1-C6-alkyl-heteroaryl, heteroaryl-, C_1-C_6-alkyl-X-, -X-$(CH_2)_m$-C_2-C_6-alkenyl, -X-$(CH_2)_m$-C_4-C_8-cycloalkenyl, -X-$(CH_2)_m$-C_2-C_6-alkynyl, -X-$(CH_2)_m$-C_3-C_6-cycloalkyl, -X-$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -X-$(CH_2)_m$-(4- to 8-membered

heterocycloalkenyl), aryl-X-, heteroaryl-X-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -OR^6, -SR^6, -S(=O)R^6, -S(=O)$_2R^6$, -S(=O)(=NR^{6a})R^{6b}, -S(=O)$_2$N(R^{6b})R^{6c}, -S-(CH_2)$_n$-N(R^{6a})R^{6b}, or -S-(CH_2)$_n$-(3- to 7-membered heterocycloalkyl) group ;

said C_1-C_6-alkyl-, -C_1-C_6-alkoxy, -(CH_2)$_m$-C_2-C_6-alkenyl, -(CH_2)$_m$-C_2-C_6-alkynyl, -(CH_2)$_m$-C_3-C_6-cycloalkyl, aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl-, C_1-C_6-alkyl-X-, -X-(CH_2)$_m$-C_2-C_6-alkenyl, -X-(CH_2)$_m$-C_4-C_8-cycloalkenyl, -X-(CH_2)$_m$-C_2-C_6-alkynyl, -X-(CH_2)$_m$-C_3-C_6-cycloalkyl, -X-(CH_2)$_m$-(3- to 7-membered heterocycloalkyl), -X-(CH_2)$_m$-(4- to 8-membered heterocycloalkenyl), aryl-X-, heteroaryl-X-, -C_1-C_6-alkyl-aryl, -C_1-C_6-alkyl-heteroaryl or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^7 groups ;

R^{4a}, R^{4b}, R^{4c}, R^{4d}

represent, independently from each other, a hydrogen or halogen atom, or a -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkyl-, R^{6a}(R^{6b})N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2R^6$, -N(R^{6c})S(=O)$_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6 , -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -S(=O)$_2R^6$, -S(=O)$_2$N(H)R^{6a}, -S(=O)$_2$N(R^{6a})R^{6b}, -S(=O)(=NR^{6c})R^6 group ;

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, -(CH_2)$_n$-C_2-C_6-alkenyl, -(CH_2)$_n$-C_2-C_6-alkynyl, -(CH_2)$_m$-C_3-C_6-cycloalkyl, -(CH_2)$_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, R^{6a}(R^{6b})N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl- or heteroaryl- group ;

wherein said C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, a 3- to 7-membered heterocycloalkyl, C_4-C_8-cycloalkenyl-, aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c},
represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, C_2-C_6-alkenyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, aryl-C_1-C_6-alkyl-, or heteroaryl-C_1-C_6-alkyl- group ;

R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, aryl-, heteroaryl-, -$C(=O)R^6$, -$C(=O)N(H)R^{6a}$, -$C(=O)N(R^{6a})R^{6b}$, -$C(=O)O$-R^6, -$N(R^{6a})R^{6b}$, -NO_2, -$N(H)C(=O)R^6$, -$N(R^{6c})C(=O)R^6$, -$N(H)C(=O)N(R^{6a})R^{6b}$, -$N(R^{6c})C(=O)N(R^{6a})R^{6b}$, -$N(H)C(=O)OR^6$, -$N(R^{6c})C(=O)OR^6$, -$N(H)S(=O)R^6$, -$N(R^{6c})S(=O)R^6$, -$N(H)S(=O)_2R^6$, -$N(R^{6c})S(=O)_2R^6$, -$N=S(=O)(R^{6a})R^{6b}$, -$OR^6$, -$O(C=O)R^6$, -$O(C=O)N(R^{6a})R^{6b}$, -$O(C=O)OR^6$, -$SR^6$, -$S(=O)R^6$, -$S(=O)N(H)R^6$, -$S(=O)N(R^{6a})R^{6b}$, -$S(=O)_2R^6$, -$S(=O)_2N(H)R^6$, -$S(=O)_2N(R^{6a})R^{6b}$, -$S(=O)(=NR^{6c})R^6$ group ;
wherein said C_1-C_6-alkoxy-, aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, or 3 C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-, -$C(=O)O$-R^6 or -OH groups;
or
when 2 R^7 groups are present ortho- to each other on an aryl ring, said 2 R^7 groups together form a bridge :
$O(CH_2)_2O$, *$O(CH_2)O$*, *$NH(C(=O))NH$*, wherein * represent the point of attachment to said aryl ring ;

R^8 represents a hydrogen or halogen atom, or a -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ or $-S(=O)_2$-(3- to 7-membered heterocycloalkyl) group;
wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 C_1-C_6-alkyl- groups ;

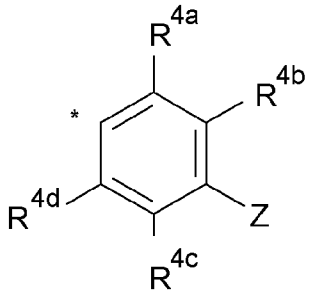
m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

n is an integer of 0, 1, 2, 3, 4 or 5 ;

X is S, S(=O), $S(=O)_2$, O, NR^6;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

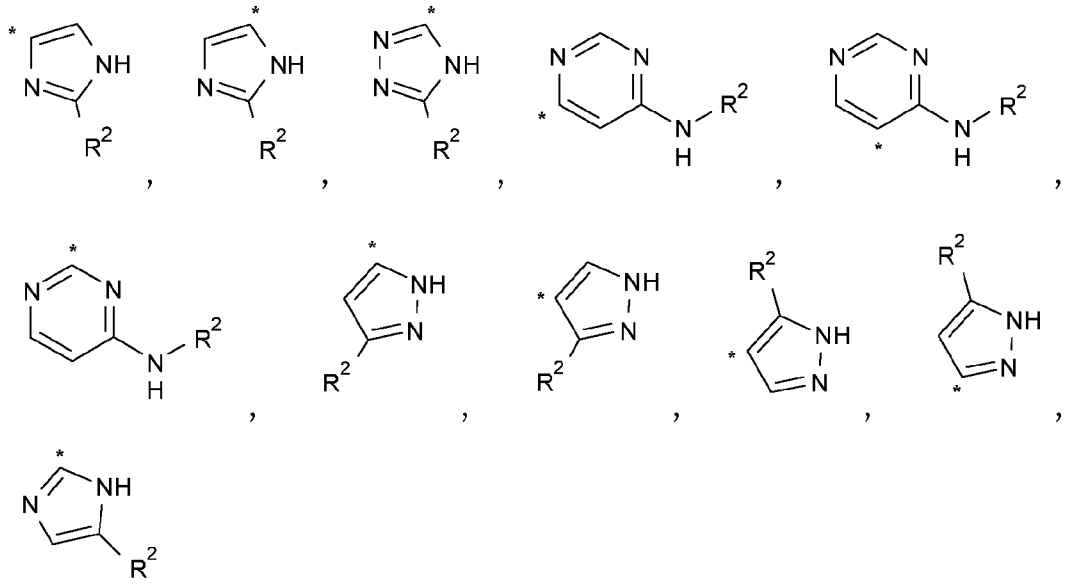
In another preferred embodiment, the invention relates to compounds of general formula I, *supra*, in which :



A represents a -group;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a -C(=O)N(H)R^2 or -C(=S)N(H)R^2 group,
or a group selected from



;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

R^2 represents a hydrogen atom, or a C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl- or C_3-C_6-cycloalkyl- group ;
wherein said C_3-C_6-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 - groups selected from: halogen, OH, -CN, C_1-C_6-alkyl, -C_1-C_6-alkoxy, halo-C_1-C_6-alkyl-;

R^3 represents a hydrogen atom or a halogen atom, or a -CN, C_1-C_6-alkyl-, -C_1-C_6-alkoxy, -$(CH_2)_m$-C_2-C_6-alkenyl, -$(CH_2)_m$-C_4-C_8-cycloalkenyl, -$(CH_2)_m$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to

7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl-, -C1-C6-alkyl-aryl, -C1-C6-alkyl-heteroaryl, heteroaryl-, C_1-C_6-alkyl-X-, -X-$(CH_2)_m$-C_2-C_6-alkenyl, -X-$(CH_2)_m$-C_4-C_8-cycloalkenyl, -X-$(CH_2)_m$-C_2-C_6-alkynyl, -X-$(CH_2)_m$-C_3-C_6-cycloalkyl, -X-$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -X-$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-X-, heteroaryl-X-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -OR^6, -SR^6, -S(=O)R^6, -S(=O)$_2R^6$, -S(=O)(=NR^{6a})R^{6b}, -S(=O)$_2$N(R^{6b})R^{6c}, -S-$(CH_2)_n$-N(R^{6a})R^{6b}, or -S-$(CH_2)_n$-(3- to 7-membered heterocycloalkyl) group ;

wherein said C_1-C_6-alkyl-, -C_1-C_6-alkoxy, -$(CH_2)_m$-C_2-C_6-alkenyl, -$(CH_2)_m$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl-, C_1-C_6-alkyl-X-, -X-$(CH_2)_m$-C_2-C_6-alkenyl, -X-$(CH_2)_m$-C_4-C_8-cycloalkenyl, -X-$(CH_2)_m$-C_2-C_6-alkynyl, -X-$(CH_2)_m$-C_3-C_6-cycloalkyl, -X-$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -X-$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-X-, heteroaryl-X-, -C_1-C_6-alkyl-aryl, -C_1-C_6-alkyl-heteroaryl or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^7 groups ;

R^{4a}, R^{4b}, R^{4c}, R^{4d}

represent, independently from each other, a hydrogen or halogen atom, or a -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkyl-, R^{6a}(R^{6b})N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2R^6$, -N(R^{6c})S(=O)$_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -S(=O)$_2R^6$, -S(=O)$_2$N(H)R^{6a}, -S(=O)$_2$N(R^{6a})R^{6b}, -S(=O)(=NR^{6c})R^6 group ;

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-,

$R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, a 3- to 7-membered heterocycloalkyl, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-,aryl- or heteroaryl group ;

wherein said C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, a 3- to 7-membered heterocycloalkyl, C_4-C_8-cycloalkenyl-, aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c}

represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, C_2-C_6-alkenyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, aryl-C_1-C_6-alkyl-, or heteroaryl-C_1-C_6-alkyl- group ;

R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, aryl-, heteroaryl-, -$C(=O)R^6$, -$C(=O)N(H)R^{6a}$, -$C(=O)N(R^{6a})R^{6b}$, -$C(=O)O$-R^6, -$N(R^{6a})R^{6b}$, -NO_2, -$N(H)C(=O)R^6$, -$N(R^{6c})C(=O)R^6$, -$N(H)C(=O)N(R^{6a})R^{6b}$, -$N(R^{6c})C(=O)N(R^{6a})R^{6b}$, -$N(H)C(=O)OR^6$, -$N(R^{6c})C(=O)OR^6$, -$N(H)S(=O)R^6$, -$N(R^{6c})S(=O)R^6$, -$N(H)S(=O)_2R^6$, -$N(R^{6c})S(=O)_2R^6$, -$N=S(=O)(R^{6a})R^{6b}$, -$OR^6$, -$O(C=O)R^6$, -$O(C=O)N(R^{6a})R^{6b}$, -$O(C=O)OR^6$, -$SR^6$, -$S(=O)R^6$, - $S(=O)N(H)R^6$, -$S(=O)N(R^{6a})R^{6b}$, -$S(=O)_2R^6$, -$S(=O)_2N(H)R^6$, -$S(=O)_2N(R^{6a})R^{6b}$ or - $S(=O)(=NR^{6c})R^6$ group ;

wherein said C_1-C_6-alkoxy-, aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, or 3 C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-, -$C(=O)O$-R^6 or -OH groups;

or

when 2 R^7 groups are present ortho- to each other on an aryl ring, said 2 R^7 groups together form a bridge :

O(CH$_2$)$_2$O, *O(CH$_2$)O*, *NH(C(=O))NH*, wherein * represent the point of attachment to said aryl group ;

R^8 represents a hydrogen or halogen atom, or a -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2$$R^6$, -N($R^{6c}$)S(=O)$_2$$R^6$, -N=S(=O)($R^{6a}$)$R^{6b}$, -O$R^6$, -O(C=O)$R^6$, -O(C=O)N($R^{6a}$)$R^{6b}$, -O(C=O)O$R^6$, -S$R^6$, -S(=O)$R^6$, -S(=O)N(H)$R^6$, -S(=O)N($R^{6a}$)$R^{6b}$, -S(=O)$_2$$R^6$, -S(=O)$_2$N(H)$R^6$, -S(=O)$_2$N($R^{6a}$)$R^{6b}$, -S(=O)(=N$R^{6c}$)$R^6$ group , -S(=O)$_2$-(3- to 7-membered heterocycloalkyl);
wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl-, is optionally substituted, identically or differently, with 1, 2, 3, or 4 C_1-C_6-alkyl- groups ;

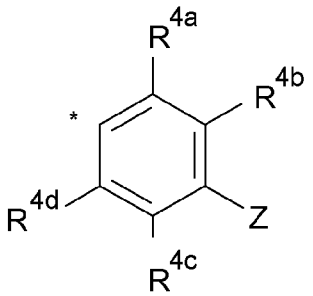
m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

n is an integer of 0, 1, 2, 3, 4 or 5 ;

X is S, S(=O), S(=O)$_2$, O, NR^6;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

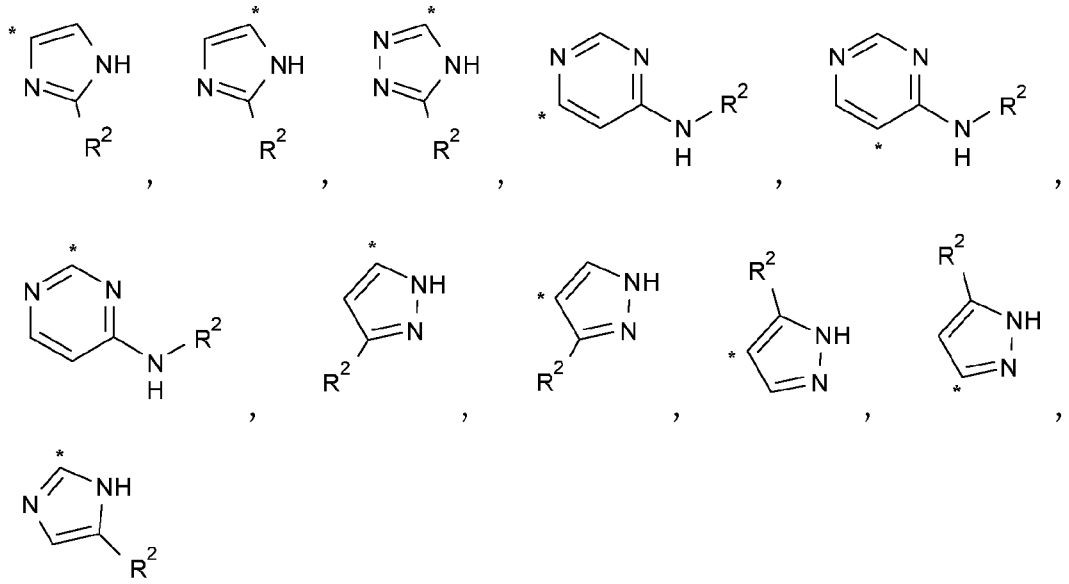
In another preferred embodiment, the invention relates to compounds of general formula I, *supra*, in which :



A represents a -group;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a -C(=O)N(H)R^2 or -C(=S)N(H)R^2 group,
or a group selected from



;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

R^2 represents a hydrogen atom, or a C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl- or C_3-C_6-cycloalkyl- group ;
wherein said C_3-C_6-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 - groups selected from: halogen, OH, -CN, C_1-C_6-alkyl, -C_1-C_6-alkoxy, halo-C_1-C_6-alkyl-;

R^3 represents a hydrogen atom or a halogen atom, or a -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, -$(CH_2)_m$-C_2-C_6-alkenyl, -$(CH_2)_m$-C_4-C_8-cycloalkenyl -$(CH_2)_m$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to

7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl-, -C1-C6-alkyl-aryl, -C1-C6-alkyl-heteroaryl, heteroaryl-, C_1-C_6-alkyl-X-, -X-$(CH_2)_m$-C_2-C_6-alkenyl, -X-$(CH_2)_m$-C_4-C_8-cycloalkenyl, -X-$(CH_2)_m$-C_2-C_6-alkynyl, -X-$(CH_2)_m$-C_3-C_6-cycloalkyl, -X-$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -X-$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-X-, heteroaryl-X-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -OR^6, -SR^6, -S(=O)R^6, -S(=O)$_2R^6$, -S(=O)(=NR^{6a})R^{6b}, -S(=O)$_2$N(R^{6b})R^{6c}, -S-$(CH_2)_n$-N(R^{6a})R^{6b}, or -S-$(CH_2)_n$-(3- to 7-membered heterocycloalkyl) group ;

wherein said C_1-C_6-alkyl-, -C_1-C_6-alkoxy, -$(CH_2)_m$-C_2-C_6-alkenyl, -$(CH_2)_m$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl-, C_1-C_6-alkyl-X-, -X-$(CH_2)_m$-C_2-C_6-alkenyl, -X-$(CH_2)_m$-C_4-C_8-cycloalkenyl, -X-$(CH_2)_m$-C_2-C_6-alkynyl, -X-$(CH_2)_m$-C_3-C_6-cycloalkyl, -X-$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -X-$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-X-, heteroaryl-X-, -C_1-C_6-alkyl-aryl, -C_1-C_6-alkyl-heteroaryl or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^7 groups ;

either

R^{4a}, R^{4c}, R^{4d} represent a hydrogen atom, and
R^{4b} represents a hydrogen atom or a halogen atom or a C_1-C_6-alkyl group;

or

R^{4b}, R^{4c}, R^{4d} represent a hydrogen atom, and
R^{4a} represents a halogen atom or an C_1-C_6-alkyl-, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -S(=O)$_2R^6$, -S(=O)$_2$N(H)R^{6a}, -S(=O)$_2$N(R^{6a})R^{6b}, -S(=O)(=NR^{6c})R^6 group ;

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, a 3- to 7-membered heterocycloalkyl, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-,aryl- or heteroaryl group ;

wherein said C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, a 3- to 7-membered heterocycloalkyl, C_4-C_8-cycloalkenyl-, aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c},

represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, C_2-C_6-alkenyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, aryl-C_1-C_6-alkyl-, or heteroaryl-C_1-C_6-alkyl- group ;

R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2$$R^6$, -N($R^{6c}$)S(=O)$_2$$R^6$, -N=S(=O)($R^{6a}$)$R^{6b}$, -O$R^6$, -O(C=O)$R^6$, -O(C=O)N($R^{6a}$)$R^{6b}$, -O(C=O)O$R^6$, -S$R^6$, -S(=O)$R^6$, -S(=O)N(H)$R^6$, -S(=O)N($R^{6a}$)$R^{6b}$, -S(=O)$_2$$R^6$, -S(=O)$_2$N(H)$R^6$, -S(=O)$_2$N($R^{6a}$)$R^{6b}$, -S(=O)(=N$R^{6c}$)$R^6$ group ;

wherein said C_1-C_6-alkoxy-, aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2 or 3 C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-, -C(=O)O-R^6 or -OH groups;

or

when 2 R^7 groups are present ortho- to each other on an aryl ring, said 2 R^7 groups together form a bridge :

$O(CH_2)_2O$, *$O(CH_2)O$*, *$NH(C(=O))NH$*, wherein * represent the point of attachment to said aryl ring ;

R^8 represents a hydrogen or halogen atom, or a -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ group , $-S(=O)_2$-(3- to 7-membered heterocycloalkyl);

wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 C_1-C_6-alkyl- groups ;

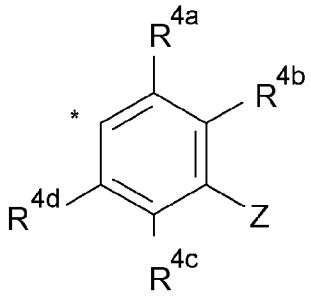
m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

n is an integer of 0, 1, 2, 3, 4 or 5 ;

X is S, S(=O), $S(=O)_2$, O, NR^6;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

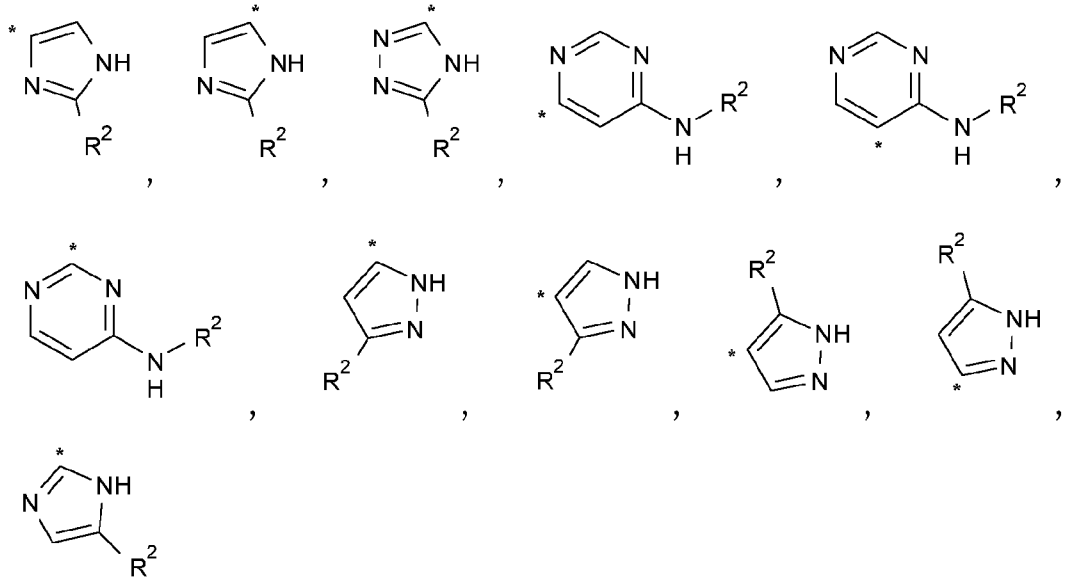
In another preferred embodiment, the invention relates to compounds of general formula I, *supra*, in which :



A represents a -group;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a $-C(=O)N(H)R^2$ or $-C(=S)N(H)R^2$ group,
or a group selected from



;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

R^2 represents a hydrogen atom, or a C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl- or C_3-C_6-cycloalkyl-group ;

wherein said C_3-C_6-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 - groups selected from: halogen, OH, -CN, C_1-C_6-alkyl, -C_1-C_6-alkoxy, halo-C_1-C_6-alkyl-;

R^3 represents a hydrogen atom or a halogen atom, or a -CN, C_1-C_6-alkyl-, -C_1-C_6-alkoxy, -$(CH_2)_m$-C_2-C_6-alkenyl, , -$(CH_2)_m$-C_4-C_8-cycloalkenyl -$(CH_2)_m$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl-, -C1-C6-alkyl-aryl, -C1-C6-alkyl-heteroaryl, heteroaryl-, C_1-C_6-alkyl-X-, -X-$(CH_2)_m$-C_2-C_6-alkenyl, -X-$(CH_2)_m$-C_4-C_8-cycloalkenyl, -X-$(CH_2)_m$-C_2-C_6-alkynyl, -X-$(CH_2)_m$-C_3-C_6-cycloalkyl, -X-$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -X-$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-X-, heteroaryl-X-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -OR^6, -SR^6, -S(=O)R^6, -$S(=O)_2R^6$, -S(=O)(=NR^{6a})R^{6b}, -$S(=O)_2$N(R^{6b})R^{6c}, -S-$(CH_2)_n$-N(R^{6a})R^{6b}, or -S-$(CH_2)_n$-(3- to 7-membered heterocycloalkyl) group ;

wherein said C_1-C_6-alkyl-, -C_1-C_6-alkoxy, -$(CH_2)_m$-C_2-C_6-alkenyl, -$(CH_2)_m$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl-, C_1-C_6-alkyl-X-, -X-$(CH_2)_m$-C_2-C_6-alkenyl, -X-$(CH_2)_m$-C_4-C_8-cycloalkenyl, -X-$(CH_2)_m$-C_2-C_6-alkynyl, -X-$(CH_2)_m$-C_3-C_6-cycloalkyl, -X-$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -X-$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-X-, heteroaryl-X-, -C_1-C_6-alkyl-aryl, -C_1-C_6-alkyl-heteroaryl or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^7 groups ;

either

R^{4a}, R^{4c}, R^{4d} represent a hydrogen atom, and

R^{4b} represents a hydrogen atom or a halogen atom or a C_1-C_6-alkyl group;

or

R^{4b}, R^{4c}, R^{4d} represent a hydrogen atom, and

R^{4a} represents a halogen atom or an C_1-C_6-alkyl-, or -OR^6 $O)R^6$, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -S(=O)$_2$$R^6$, -S(=O)$_2$N(H)$R^{6a}$, -S(=O)$_2$N($R^{6a}$)$R^{6b}$, -S(=O)(=N$R^{6c}$)$R^6$ group ;

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl- or heteroaryl group ;
said C_1-C_6-alkyl-, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c},
represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, C_2-C_6-alkenyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, aryl-C_1-C_6-alkyl-, or heteroaryl-C_1-C_6-alkyl- group ;

R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, R^{6a}(R^{6b})N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2$$R^6$, -N($R^{6c}$)S(=O)$_2$$R^6$, -N=S(=O)($R^{6a}$)$R^{6b}$, -O$R^6$, -O(C=O)$R^6$, -O(C=O)N($R^{6a}$)$R^{6b}$, -O(C=O)O$R^6$, -S$R^6$, -S(=O)$R^6$, -S(=O)N(H)$R^6$, -S(=O)N($R^{6a}$)$R^{6b}$, -S(=O)$_2$$R^6$, -S(=O)$_2$N(H)$R^6$, -S(=O)$_2$N($R^{6a}$)$R^{6b}$, -S(=O)(=N$R^{6c}$)$R^6$ group ;
wherein said C_1-C_6-alkoxy-, aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, or 3 C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-, -C(=O)O-R^6 or -OH groups;

or

when 2 R^7 groups are present ortho- to each other on an aryl ring, said 2 R^7 groups together form a bridge :

$O(CH_2)_2O$, *$O(CH_2)O$*, *$NH(C(=O))NH$*, wherein * represent the point of attachment to said aryl ring ;

R^8 represents a hydrogen or halogen atom, or a -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ group , $-S(=O)_2$-(3- to 7-membered heterocycloalkyl);

wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 C_1-C_6-alkyl- groups ;

m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

n is an integer of 0, 1, 2, 3, 4 or 5 ;

X is S, S(=O), $S(=O)_2$, O, NR^6;

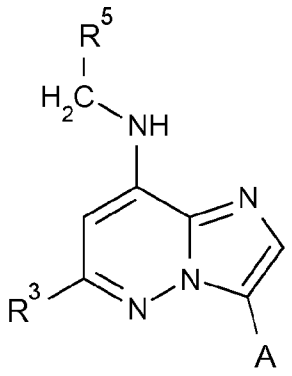
or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

WO 2011/013729A1 discloses IC_{50} values for the inhibition of Mps-1 (TTK) for a couple of compounds of formula **C1**, *supra*. However, WO 2011/013729A1 does not disclose any information about the metabolic stability of the compounds.

The inventors of the present invention surprisingly observed that compounds of general formula I, *supra*, in which R^3 is an aryl-X- or heteroaryl-X- group, and in

which at least one of the groups R^{4c} and R^{4b} is not a hydrogen atom show a high inhibitory activity as well as a high metabolic stability.

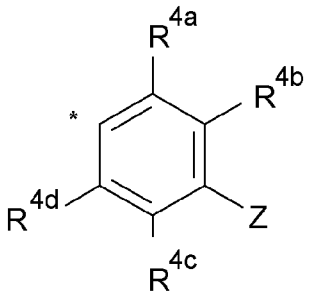
Hence, in another preferred embodiment, the invention relates to compounds of general formula I :



I

in which :

A represents



;

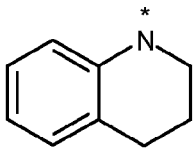
wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a $-C(=O)N(H)R^2$ or a $-C(=S)N(H)R^2$ group ;

R^2 represents a hydrogen atom, or a C_1-C_6-alkyl- or C_3-C_6-cycloalkyl- group ; wherein said C_1-C_6-alkyl- or C_3-C_6-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 groups selected from:

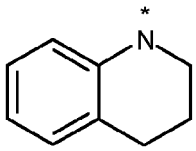
halogen, -OH, -CN, -C_1-C_6-alkyl, -C_1-C_6-alkoxy ;

R^3 represents an aryl-X- or a heteroaryl-X- group, or a



group, in which * indicates the point of attachment of said group with the rest of the molecule ;

wherein said aryl-X-, heteroaryl-X- or



group

is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^7 groups ;

R^{4a}, R^{4b}, R^{4c}, R^{4d}

represent, independently from each other, a hydrogen or halogen atom, or a -CN, -OH, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, NC-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl- group;
with the proviso that at least one of the groups R^{4b} and R^{4c} is not a hydrogen atom;

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl- or heteroaryl- group ;
said C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-,

$R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, H O-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl, C_4-C_8-cycloalkenyl-, aryl- or heteroaryl-group

is optionally substituted, identically or differently, with 1, 2, 3, or 4 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c},

represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl, HO-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, aryl, heteroaryl, aryl-C_1-C_6-alkyl-, or heteroaryl-C_1-C_6-alkyl- group ;

R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, H_2N-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, aryl-, heteroaryl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2R^6$, -N(R^{6c})S(=O)$_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, - S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -S(=O)$_2R^6$, - S(=O)$_2$N(H)R^6, -S(=O)$_2$N(R^{6a})R^{6b}, or -S(=O)(=NR^{6c})R^6 group ;

wherein said C_1-C_6-alkoxy-, aryl-, 3- to 7-membered heterocycloalkyl, or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, or 3 C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-, -C(=O)O-R^6 or -OH groups;

or

when 2 R^7 groups are present ortho to each other on an aryl or heteroarly ring, said 2 R^7 groups together form a bridge :

O(CH_2)$_2$O, *O(CH_2)O*, *CH_2(CH_2)$_2$NH*, *$CH_2CH_2N(R^{6a})CH_2$*, *NH(C(=O))NH*, *C(H)=C(H)-C(=O)-N(H)*,

wherein * represent the point of attachment to said aryl or heteroaryl ring ;

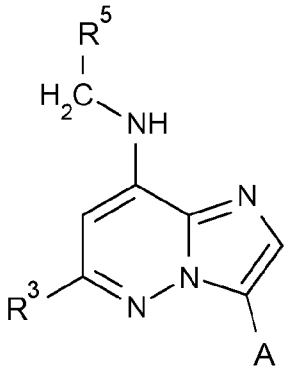
R^8 represents a hydrogen or halogen atom, or a -CN, -OH, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2OH$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ group , $-S(=O)_2$-(3- to 7-membered heterocycloalkyl);
wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 C_1-C_6-alkyl- groups ;

m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

n is an integer of 0, 1, 2, 3, 4 or 5 ; and

X is S, S(=O), $S(=O)_2$, O, NR^6, $CR^{6a}R^{6b}$, $C=CR^{6a}R^{6b}$.

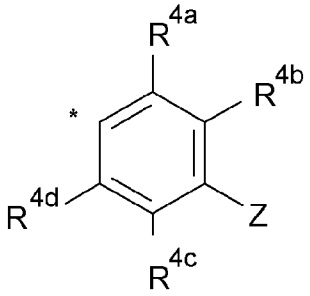
In another preferred embodiment, the invention relates to compounds of formula I



I

in which :

A represents



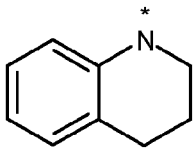
;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a -C(=O)N(H)R^2 or a -C(=S)N(H)R^2 group ;

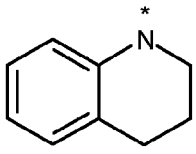
R^2 represents a hydrogen atom, or a C_1-C_6-alkyl- or C_3-C_6-cycloalkyl- group ; wherein said C_1-C_6-alkyl- or C_3-C_6-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 groups selected from: halogen, -OH, -CN, -C_1-C_6-alkyl, -C_1-C_6-alkoxy ;

R^3 represents an aryl-X- or a heteroaryl-X- group, or a



group, in which * indicates the point of attachment of said group with the rest of the molecule ;

wherein said aryl-X-, heteroaryl-X- or



group

is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^7 groups ;

R^{4a} represents hydrogen;

R^{4d} represents hydrogen;

one of the groups R^{4b} and R^{4c} represents a hydrogen atom while the other one represents a group selected from: halo-, -CN, -OH, C_1-C_6-alkyl- and C_1-C_6-alkoxy-;

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl- or heteroaryl- group ;
said C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl, C_4-C_8-cycloalkenyl-, aryl- or heteroaryl- group
is optionally substituted, identically or differently, with 1, 2, 3, or 4 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c},
represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl, HO-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, aryl, heteroaryl, aryl-C_1-C_6-alkyl-, or heteroaryl-C_1-C_6-alkyl- group ;

R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, H_2N-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, aryl-, heteroaryl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2,

$-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, or $-S(=O)(=NR^{6c})R^6$ group ;

wherein said C_1-C_6-alkoxy-, aryl-, 3- to 7-membered heterocycloalkyl, or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, or 3 C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-, $-C(=O)O-R^6$ or -OH groups;

or

when 2 R^7 groups are present ortho to each other on an aryl or heteroarly ring, said 2 R^7 groups together form a bridge :

$*O(CH_2)_2O*$, $*O(CH_2)O*$, $*CH_2(CH_2)_2NH*$, $*CH_2CH_2N(R^{6a})CH_2*$, *NH(C(=O))NH*, *C(H)=C(H)-C(=O)-N(H)*,

wherein * represent the point of attachment to said aryl or heteroaryl ring ;

R^8 represents a hydrogen or halogen atom, or a -CN, -OH, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2OH$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ group , $-S(=O)_2$-(3- to 7-membered heterocycloalkyl);

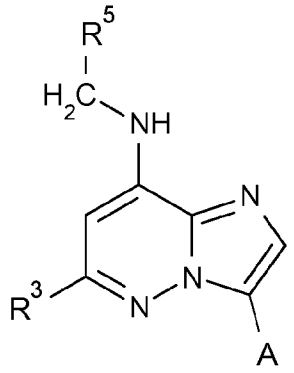
wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 C_1-C_6-alkyl- groups ;

m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

n is an integer of 0, 1, 2, 3, 4 or 5 ; and

X is S, S(=O), $S(=O)_2$, O, NR^6, $CR^{6a}R^{6b}$, $C=CR^{6a}R^{6b}$.

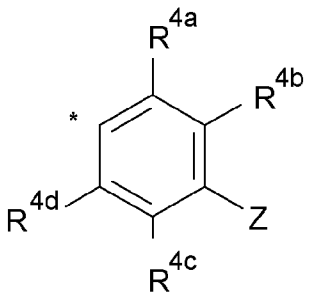
In another preferred embodiment, the invention relates to compounds of formula I



I

in which :

A represents



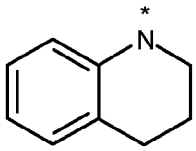
;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a $-C(=O)N(H)R^2$ or a $-C(=S)N(H)R^2$ group ;

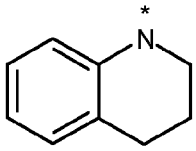
R^2 represents a C_1-C_3-alkyl- or C_3-C_6-cycloalkyl- group ;
wherein said C_1-C_3-alkyl- or C_3-C_6-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2 or 3 groups selected from:
halogen, -OH, -CN, -C_1-C_6-alkyl, -C_1-C_6-alkoxy ;

R^3 represents an aryl-X- or a heteroaryl-X- group, or a



group, in which * indicates the point of attachment of said group with the rest of the molecule ;

wherein said aryl-X-, heteroaryl-X- or



group

is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^7 groups ;

R^{4a} represents hydrogen;

R^{4d} represents hydrogen;

one of the groups R^{4b} and R^{4c} represents a hydrogen atom while the other one represents a group selected from: halo-, -CN, -OH, C_1-C_6-alkyl- and C_1-C_6-alkoxy-;

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl- or heteroaryl- group ;

said C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3-

to 7-membered heterocycloalkyl, C_4-C_8-cycloalkenyl-, aryl- or heteroaryl-group
is optionally substituted, identically or differently, with 1, 2, 3, or 4 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c},
represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl, HO-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, aryl, heteroaryl, aryl-C_1-C_6-alkyl-, or heteroaryl-C_1-C_6-alkyl- group ;

R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, H_2N-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, aryl-, heteroaryl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)$S(=O)_2R^6$, -N(R^{6c})$S(=O)_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, - S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -$S(=O)_2R^6$, - $S(=O)_2$N(H)R^6, -$S(=O)_2$N(R^{6a})R^{6b}, or -S(=O)(=NR^{6c})R^6 group ;

wherein said C_1-C_6-alkoxy-, aryl-, 3- to 7-membered heterocycloalkyl, or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, or 3 C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-, -C(=O)O-R^6 or -OH groups;

or
when 2 R^7 groups are present ortho to each other on an aryl or heteroarly ring, said 2 R^7 groups together form a bridge :
O$(CH_2)_2$O, *O(CH_2)O*, *$CH_2(CH_2)_2$NH*, *CH_2CH_2N(R^{6a})CH_2*, *NH(C(=O))NH*, *C(H)=C(H)-C(=O)-N(H)*,
wherein * represent the point of attachment to said aryl or heteroaryl ring ;

R^8 represents a hydrogen or halogen atom, or a -CN, -OH, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2OH$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ group , $-S(=O)_2$-(3- to 7-membered heterocycloalkyl);

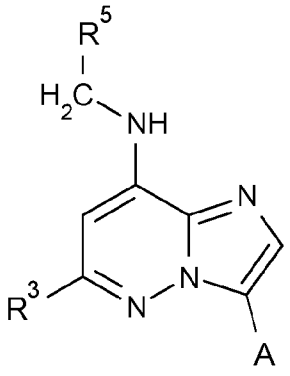
wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 C_1-C_6-alkyl- groups ;

m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

n is an integer of 0, 1, 2, 3, 4 or 5 ; and

X is S, S(=O), $S(=O)_2$, O, NR^6, $CR^{6a}R^{6b}$, $C=CR^{6a}R^{6b}$.

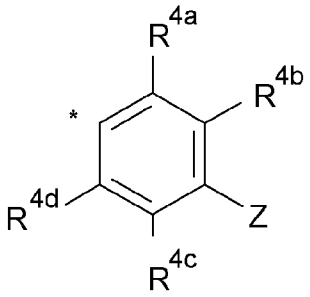
In another preferred embodiment, the invention relates to compounds of formula I



I

in which :

A represents



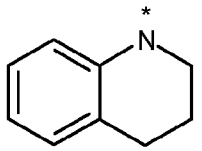
;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a -C(=O)N(H)R^2 or a -C(=S)N(H)R^2 group ;

R^2 represents a C_1-C_3-alkyl- or C_3-C_6-cycloalkyl- group ;
wherein said C_1-C_3-alkyl- or C_3-C_6-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2 or 3 groups selected from:
halogen, -OH, -CN, -C_1-C_6-alkyl, -C_1-C_6-alkoxy ;

R^3 represents a group selected from:
phenyl-X, quinolinyl-X-, pyridyl-X-, thienyl-X-, pyrazinyl-X-, imidazyl-X-, triazyl-X-, pyrazyl-X- and



;

wherein said group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^7 groups ;

R^{4a} represents hydrogen;

R^{4d} represents hydrogen;

one of the groups R^{4b} and R^{4c} represents a hydrogen atom while the other one represents halo- or a C_1-C_6-alkyl- group;

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl- or heteroaryl- group ;

said C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl, C_4-C_8-cycloalkenyl-, aryl- or heteroaryl- group

is optionally substituted, identically or differently, with 1, 2, 3, or 4 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c}

represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl, HO-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, aryl, heteroaryl, aryl-C_1-C_6-alkyl-, or heteroaryl-C_1-C_6-alkyl- group ;

R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, H_2N-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, aryl-, heteroaryl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2$$R^6$, -N($R^{6c}$)S(=O)$_2$$R^6$, -N=S(=O)($R^{6a}$)$R^{6b}$, -O$R^6$, -O(C=O)$R^6$, -O(C=O)N($R^{6a}$)$R^{6b}$, -O(C=O)O$R^6$, -S$R^6$, -S(=O)$R^6$, - S(=O)N(H)$R^6$, -S(=O)N($R^{6a}$)$R^{6b}$, -S(=O)$_2$$R^6$, - S(=O)$_2$N(H)$R^6$, -S(=O)$_2$N($R^{6a}$)$R^{6b}$, or -S(=O)(=N$R^{6c}$)$R^6$ group ;

wherein said C_1-C_6-alkoxy-, aryl-, 3- to 7-membered heterocycloalkyl, or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, or 3 C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-, -C(=O)O-R^6 or -OH groups;

or

when 2 R^7 groups are present ortho to each other on an aryl or heteroarly ring, said 2 R^7 groups together form a bridge :

$O(CH_2)_2O$, *$O(CH_2)O$*, *$CH_2(CH_2)_2NH$*, *$CH_2CH_2N(R^{6a})CH_2$*, *NH(C(=O))NH*, *C(H)=C(H)-C(=O)-N(H)*,

wherein * represent the point of attachment to said aryl or heteroaryl ring ;

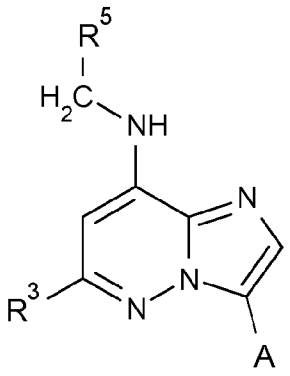
R^8 represents a hydrogen or halogen atom, or a -CN, -OH, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, aryl-, heteroaryl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)$S(=O)_2R^6$, -N(R^{6c})$S(=O)_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -$S(=O)_2R^6$, -$S(=O)_2$OH, -$S(=O)_2$N(H)R^6, -$S(=O)_2$N(R^{6a})R^{6b}, -S(=O)(=NR^{6c})R^6 group , -$S(=O)_2$-(3- to 7-membered heterocycloalkyl);
wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 C_1-C_6-alkyl- groups ;

m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

n is an integer of 0, 1, 2, 3, 4 or 5 ; and

X is S, S(=O), $S(=O)_2$, O, NR^6, $CR^{6a}R^{6b}$, $C=CR^{6a}R^{6b}$.

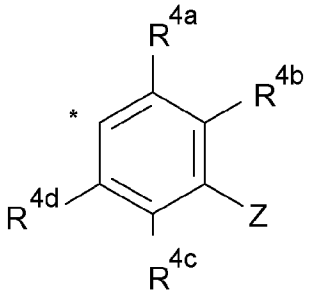
In another preferred embodiment, the invention relates to compounds of formula I



I

in which :

A represents



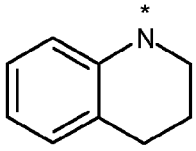
;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a -C(=O)N(H)R^2 or a -C(=S)N(H)R^2 group ;

R^2 represents a C_1-C_3-alkyl- or C_3-C_6-cycloalkyl- group ;
wherein said C_1-C_3-alkyl- or C_3-C_6-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2 or 3 groups selected from:
halogen, -OH, -CN, -C_1-C_6-alkyl, -C_1-C_6-alkoxy ;

R^3 represents a group selected from:
phenyl-X, quinolinyl-X-, pyridyl-X-, thienyl-X-, pyrazinyl-X-, imidazyl-X-, triazyl-X-, pyrazyl-X- and



;

wherein said group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^7 groups ;

R^{4a} represents hydrogen;

R^{4d} represents hydrogen;

one of the groups R^{4b} and R^{4c} represents a hydrogen atom while the other one represents a C_1-C_4-alkyl- group;

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl, or heteroaryl- group ;

said C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, , C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl, heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c},

represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl, HO-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, aryl, heteroaryl, aryl-C_1-C_6-alkyl-, or heteroaryl-C_1-C_6-alkyl- group ;

R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, H_2N-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, aryl-, heteroaryl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6,

$-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, or $-S(=O)(=NR^{6c})R^6$ group ;

wherein said C_1-C_6-alkoxy-, aryl-, 3- to 7-membered heterocycloalkyl, or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, or 3 C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-, $-C(=O)O-R^6$ or -OH groups;

or

when 2 R^7 groups are present ortho to each other on an aryl or heteroarly ring, said 2 R^7 groups together form a bridge :

$*O(CH_2)_2O*$, $*O(CH_2)O*$, $*CH_2(CH_2)_2NH*$, $*CH_2CH_2N(R^{6a})CH_2*$, *NH(C(=O))NH*, *C(H)=C(H)-C(=O)-N(H)*,

wherein * represent the point of attachment to said aryl or heteroaryl ring ;

R^8 represents a hydrogen or halogen atom, or a -CN, -OH, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2OH$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ group , $-S(=O)_2$-(3- to 7-membered heterocycloalkyl);

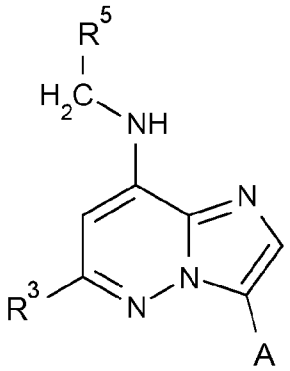
wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 C_1-C_6-alkyl- groups ;

m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

n is an integer of 0, 1, 2, 3, 4 or 5 ; and

X is S, S(=O), $S(=O)_2$, O, NR^6, $CR^{6a}R^{6b}$, $C=CR^{6a}R^{6b}$.

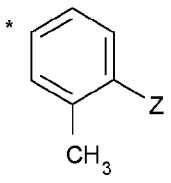
In another preferred embodiment, the invention relates to compounds of formula I



I

in which :

A represents a



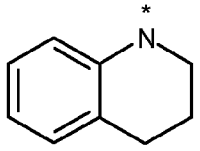
group ;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a -C(=O)N(H)R^2 or a -C(=S)N(H)R^2 group ;

R^2 represents a C_1-C_3-alkyl- or C_3-C_6-cycloalkyl- group ;
wherein said C_1-C_3-alkyl- or C_3-C_6-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2 or 3 groups selected from:
halogen, -OH, -CN, -C_1-C_6-alkyl, -C_1-C_6-alkoxy ;

R^3 represents a group selected from:
phenyl-X, quinolinyl-X-, pyridyl-X-, thienyl-X-, pyrazinyl-X-, imidazyl-X-, triazyl-X-, pyrazyl-X- and



;

wherein said group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^7 groups ;

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl, or heteroaryl- group ;

said C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, , C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl, heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c},

represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl, HO-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, aryl, heteroaryl, aryl-C_1-C_6-alkyl-, or heteroaryl-C_1-C_6-alkyl- group ;

R^7 represents a halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, H_2N-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, -C(=O)N(H)R^{6a}, -N(R^{6a})R^{6b}, -N(H)C(=O)R^6, or -SR^6 group ;

wherein said C_1-C_6-alkoxy-, or 3- to 7-membered heterocycloalkyl- group is optionally substituted, identically or differently, with 1, 2, or 3 C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-, -C(=O)O-R^6 or -OH groups;

or

when 2 R^7 groups are present ortho to each other on an aryl or heteroarly ring, said 2 R^7 groups together form a bridge :

$CH_2(CH_2)_2NH$, *$CH_2CH_2N(R^{6a})CH_2$*, *C(H)=C(H)-C(=O)-N(H)*,

wherein * represent the point of attachment to said aryl or heteroaryl ring ;

R^8 represents a hydrogen or halogen atom, or a -CN, -OH, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2OH$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ group , $-S(=O)_2$-(3- to 7-membered heterocycloalkyl);

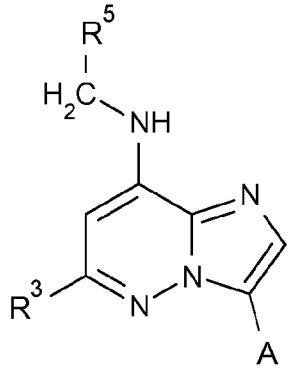
wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 C_1-C_6-alkyl- groups ;

m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

n is an integer of 0, 1, 2, 3, 4 or 5 ; and

X is S, S(=O), $S(=O)_2$, O, NR^6, $CR^{6a}R^{6b}$, $C=CR^{6a}R^{6b}$.

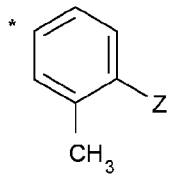
In another preferred embodiment, the invention relates to compounds of formula I



I

in which :

A represents a



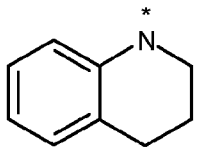
group ;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a -C(=O)N(H)R^2 or a -C(=S)N(H)R^2 group ;

R^2 represents a C_1-C_3-alkyl- or C_3-C_6-cycloalkyl- group ;
wherein said C_1-C_3-alkyl- or C_3-C_6-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2 or 3 groups selected from:
halogen, -OH, -CN, -C_1-C_6-alkyl, -C_1-C_6-alkoxy ;

R^3 represents a group selected from:
phenyl-X, quinolinyl-X-, pyridyl-X-, thienyl-X-, pyrazinyl-X-, imidazyl-X-, triazyl-X-, pyrazyl-X- and



;

wherein said group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^7 groups ;

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl, or heteroaryl- group ;
said C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, , C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl, heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c},
represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl- group ;

R^7 represents a halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, H_2N-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, -C(=O)N(H)R^{6a}, -N(R^{6a})R^{6b}, -N(H)C(=O)R^6, or -SR^6 group ;

wherein said C_1-C_6-alkoxy-, or 3- to 7-membered heterocycloalkyl- group is optionally substituted, identically or differently, with 1, 2, or 3 C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-, -C(=O)O-R^6 or -OH groups;

or

when 2 R^7 groups are present ortho to each other on an aryl or heteroarly ring, said 2 R^7 groups together form a bridge :

$CH_2(CH_2)_2NH$, *$CH_2CH_2N(R^{6a})CH_2$*, *C(H)=C(H)-C(=O)-N(H)*,

wherein * represent the point of attachment to said aryl or heteroaryl ring ;

R^8 represents a hydrogen or halogen atom, or a -CN, -OH, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, aryl-, heteroaryl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)$S(=O)_2R^6$, -N(R^{6c})$S(=O)_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -$S(=O)_2R^6$, -$S(=O)_2$OH, -$S(=O)_2$N(H)R^6, -$S(=O)_2$N(R^{6a})R^{6b}, -S(=O)(=NR^{6c})R^6 group , -$S(=O)_2$-(3- to 7-membered heterocycloalkyl);

wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 C_1-C_6-alkyl- groups ;

m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

n is an integer of 0, 1, 2, 3, 4 or 5 ; and

X is S, S(=O), $S(=O)_2$, O, NR^6, $CR^{6a}R^{6b}$, $C=CR^{6a}R^{6b}$.

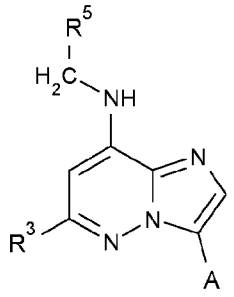
WO 2011/013729 A1 teaches that compounds of formula **C1**, *supra,* in which R^8 represents a cyclopropyl-group are preferred because they tendentially show

higher activity in Mps-1 inhibition than compounds of formula **C1** in which R^8 does not represent a cyclopropyl-group.

The inventors of the present invention surprisingly observed that compounds of formula **C1** in which R^8 is a non-cyclic group rather than a cycloalkyl-group show higher metabolic stability. The inventors of the present invention surprisingly observed that compounds of formula **C1** show especially high inhibitory effect on Mps-1 kinase if R^6 represents an aryl-X- or a heteroaryl-X- group in which X is defined as for compounds of formula I, supra.

So the combination of R^8 being a non-cyclic group with R^6 being an aryl-X- or a heteroaryl-X- group, results in compounds of superior inhibitory and metabolic properties.

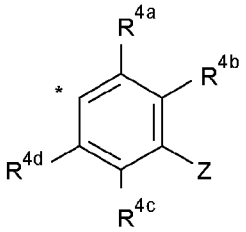
Hence, in another preferred embodiment, the invention relates to compounds of formula I



I

in which :

A represents



wherein * indicates the point of attachment of said group with the rest of the molecule ;

Z represents a $-C(=O)N(H)R^2$ or $-C(=S)N(H)R^2$ group ;

R^2 represents a hydrogen atom, or a C_1-C_6-alkyl- group ;
wherein said C_1-C_6-alkyl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 groups selected from: halogen, -OH, -CN, C_1-C_6-alkyl- , C_1-C_6-alkoxy- ;

R^3 represents an aryl-X- or a heteroaryl-X- group, wherein said aryl-X- or heteroaryl-X- group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^7 groups ;

R^{4a}, R^{4b}, R^{4c}, R^{4d}
represent, independently from each other, a hydrogen or halogen atom, or a -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, NC-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl- group ;

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_4-C_8-cycloalkenyl-, aryl- or heteroaryl-group ;
said C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_4-C_8-cycloalkenyl-, aryl- or heteroaryl-group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c},
represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, C_2-C_6-alkenyl-, 3- to

7-membered heterocycloalkyl-, aryl-, heteroaryl-, aryl-C_1-C_6-alkyl- or heteroaryl-C_1-C_6-alkyl- group ;

R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, H O-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O_2)R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ group ;

wherein said aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2 or 3 C_1-C_6-alkyl- groups;

or

when 2 R^7 groups are present ortho- to each other on an aryl- or heteroaryl-ring, said 2 R^7 groups together form a bridge :

$*O(CH_2)_2O*$, $*O(CH_2)O*$, *NH(C(=O))NH*, wherein * represent the point of attachment to said aryl- or heteroaryl- ring ;

R^8 represents a hydrogen or halogen atom, or a -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O_2)R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ or $-S(=O)_2$-(3- to 7-membered heterocycloalkyl) group;

wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group, is optionally substituted, identically or differently, with 1, 2, 3 or 4 C_1-C_6-alkyl-groups

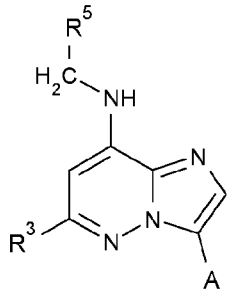
m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

n is an integer of 0, 1, 2, 3, 4 or 5 ; and

X is selected from: S, S(=O), $S(=O)_2$, O, NR^6, $CR^{6a}R^{6b}$;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

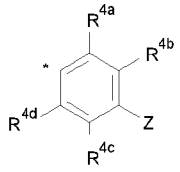
In another preferred embodiment, the invention relates to compounds of general formula I :



I

in which :

A represents



wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a $-C(=O)N(H)R^2$ or $-C(=S)N(H)R^2$ group ;
wherein * indicates the point of attachment of said groups with the rest of the molecule ;

R^2 represents a hydrogen atom, or a C_1-C_6-alkyl- group ;
wherein said C_1-C_6-alkyl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 groups selected from: halogen, OH, -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy- ;

R^3 represents an aryl-X- or a heteroaryl-X- group, wherein said aryl-X- or heteroaryl-X- group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^7 groups ;

R^{4a}, R^{4b}, R^{4c}, R^{4d}
are selected, independently from each other, from hydrogen, halogen, -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy- ;

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_4-C_8-cycloalkenyl-, aryl- or heteroaryl-group ;
said C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_4-C_8-cycloalkenyl-, aryl- or heteroaryl-group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c},
represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, C_2-C_6-alkenyl-, 3- to

7-membered heterocycloalkyl-, aryl-, heteroaryl-, aryl-C_1-C_6-alkyl-, or heteroaryl-C_1-C_6-alkyl- group ;

R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O_2)R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ group ;

wherein said aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2 or 3 C_1-C_6-alkyl- groups;

or

when 2 R^7 groups are present ortho- to each other on an aryl- or heteroaryl-ring, said 2 R^7 groups together form a bridge :

$*O(CH_2)_2O*$, $*O(CH_2)O*$, *NH(C(=O))NH*, wherein * represent the point of attachment to said aryl- or heteroaryl- ring ;

R^8 represents a hydrogen or halogen atom, or a -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, - $S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ group , $-S(=O)_2$-(3- to 7-membered heterocycloalkyl);

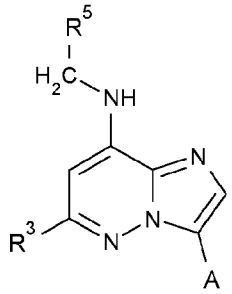
wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group, is optionally substituted, identically or differently, with 1, 2, 3 or 4 C_1-C_6-alkyl- groups ;

m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

n is an integer of 0, 1, 2, 3, 4 or 5 ; and

X is S, S(=O), $S(=O)_2$, O, NR^6 or $CR^{6a}R^{6b}$.

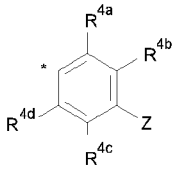
In another preferred embodiment, the invention relates to compounds of general formula I :



I

in which :

A represents



wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a $-C(=O)N(H)R^2$ or $-C(=S)N(H)R^2$ group ;

R^2 represents a C_1-C_4-alkyl- group ;
wherein said C_1-C_4-alkyl- group is optionally substituted, identically or differently, with 1 or 2 groups selected from: halogen, -OH, -CN, C_1-C_3-alkyl-, C_1-C_4-alkoxy- ;

R^3 represents an aryl-X- or a heteroaryl-X- group, wherein said aryl-X- or heteroaryl-X- group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^7 groups ;

R^{4a}, R^{4b}, R^{4c}, R^{4d}

are selected, independently from each other, from hydrogen, halogen, -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy- ;

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_4-C_8-cycloalkenyl-, aryl- or heteroaryl-group ;
said C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_4-C_8-cycloalkenyl-, aryl- or heteroaryl-group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c},

represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, C_2-C_6-alkenyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, aryl-C_1-C_6-alkyl-, or heteroaryl-C_1-C_6-alkyl- group ;

R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-,

C_2-C_6-alkynyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2$$R^6$, -N($R^{6c}$)S(=O)$_2$$R^6$, -N=S(=O)($R^{6a}$)$R^{6b}$, -O$R^6$, -O(C=O)$R^6$, -O(C=O)N($R^{6a}$)$R^{6b}$, -O(C=O)O$R^6$, -S$R^6$, -S(=O)$R^6$, -S(=O)N(H)$R^6$, -S(=O)N($R^{6a}$)$R^{6b}$, -S(=O$_2$)$R^6$, -S(=O)$_2$N(H)$R^6$, -S(=O)$_2$N($R^{6a}$)$R^{6b}$, -S(=O)(=N$R^{6c}$)$R^6$ group ;

wherein said aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, or 3 C_1-C_6-alkyl- groups;

or

when 2 R^7 groups are present ortho- to each other on an aryl- or heteroaryl- ring, said 2 R^7 groups together form a bridge :

O(CH_2)$_2$O, *O(CH_2)O*, *NH(C(=O))NH*, wherein * represent the point of attachment to said aryl- or heteroaryl- ring ;

R^8 represents a hydrogen or halogen atom, or a -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, R^{6a}(R^{6b})N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2$$R^6$, -N($R^{6c}$)S(=O)$_2$$R^6$, -N=S(=O)($R^{6a}$)$R^{6b}$, -O$R^6$, -O(C=O)$R^6$, -O(C=O)N($R^{6a}$)$R^{6b}$, -O(C=O)O$R^6$, -S$R^6$, -S(=O)$R^6$, - S(=O)N(H)$R^6$, -S(=O)N($R^{6a}$)$R^{6b}$, -S(=O)$_2$$R^6$, -S(=O)$_2$N(H)$R^6$, -S(=O)$_2$N($R^{6a}$)$R^{6b}$, -S(=O)(=N$R^{6c}$)$R^6$ or -S(=O)$_2$-(3- to 7-membered heterocycloalkyl) group;

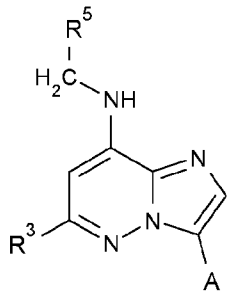
wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group, is optionally substituted, identically or differently, with 1, 2, 3, or 4 C_1-C_6-alkyl- groups ;

m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

n is an integer of 0, 1, 2, 3, 4 or 5 ; and

X is S, S(=O), S(=O)$_2$, O, NR^6 or C$R^{6a}R^{6b}$.

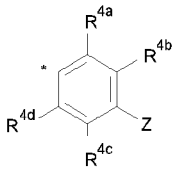
In another preferred embodiment, the invention relates to compounds of general formula I :



I

in which :

A represents



wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a $-C(=O)N(H)R^2$ or $-C(=S)N(H)R^2$ group ;

R^2 represents a methyl- or ethyl-group ;
wherein said methyl- or ethyl- group is optionally substituted, identically or differently, with 1 or 2 groups selected from: halogen, -OH, -CN, C_1-C_3-alkoxy- ;

R^3 represents an aryl-X- or a heteroaryl-X- group, wherein said aryl-X- or heteroaryl-X- group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^7 groups ;

R^{4a}, R^{4b}, R^{4c}, R^{4d}
are selected, independently from each other, from hydrogen, halogen, -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy- ;

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_4-C_8-cycloalkenyl-, aryl- or heteroaryl-group ;

said C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_4-C_8-cycloalkenyl-, aryl- or heteroaryl-group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c},

represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, C_2-C_6-alkenyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, aryl-C_1-C_6-alkyl-, or heteroaryl-C_1-C_6-alkyl- group ;

R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)$S(=O)_2R^6$, -N(R^{6c})$S(=O)_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -$S(=O_2)R^6$, -$S(=O)_2$N(H)R^6, -$S(=O)_2$N(R^{6a})R^{6b}, -S(=O)(=NR^{6c})R^6 group ;

wherein said aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2 or 3 C_1-C_6-alkyl- groups;

or

when 2 R^7 groups are present ortho- to each other on an aryl- or heteroaryl- ring, said 2 R^7 groups together form a bridge :

$O(CH_2)_2O$, *$O(CH_2)O$*, *NH(C(=O))NH*, wherein * represent the point of attachment to said aryl- or heteroaryl- ring ;

R^8 represents a hydrogen or halogen atom, or a -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ group , $-S(=O)_2$-(3- to 7-membered heterocycloalkyl);

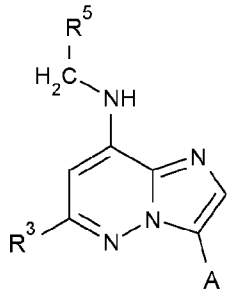
wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group, is optionally substituted, identically or differently, with 1, 2, 3, or 4 C_1-C_6-alkyl- groups ;

m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

n is an integer of 0, 1, 2, 3, 4 or 5 ; and

X is S, S(=O), $S(=O)_2$, O, NR^6 or $CR^{6a}R^{6b}$.

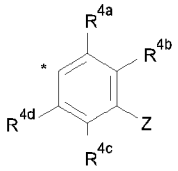
In another preferred embodiment, the invention relates to compounds of general formula I :



I

in which :

A represents



wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a $-C(=O)N(H)R^2$ or $-C(=S)N(H)R^2$ group ;

R^2 represents a C_1-C_4-alkyl- group ;
wherein said C_1-C_4-alkyl- group is optionally substituted, identically or differently, with 1 or 2 groups selected from: halogen, OH, -CN, C_1-C_3-alkyl-, C_1-C_4-alkoxy- ;

R^3 represents an aryl-X- or heteroaryl-X- group ; wherein said aryl-X- or heteroaryl-X- group is optionally substituted, identically or differently, with 1 or 2 R^7 groups ;

R^{4a}, R^{4b}, R^{4c}, R^{4d}
are selected, independently from each other, from hydrogen, halogen, -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy- ;

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_4-C_8-cycloalkenyl-, aryl- or heteroaryl-group ;

said C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_4-C_8-cycloalkenyl-, aryl- or heteroaryl-group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c},

represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, C_2-C_6-alkenyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, aryl-C_1-C_6-alkyl-, or heteroaryl-C_1-C_6-alkyl- group ;

R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})$N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2$$R^6$, -N($R^{6c}$)S(=O)$_2$$R^6$, -N=S(=O)($R^{6a}$)$R^{6b}$, -O$R^6$, -O(C=O)$R^6$, -O(C=O)N($R^{6a}$)$R^{6b}$, -O(C=O)O$R^6$, -S$R^6$, -S(=O)$R^6$, -S(=O)N(H)$R^6$, -S(=O)N($R^{6a}$)$R^{6b}$, -S(=$O_2$)$R^6$, -S(=O)$_2$N(H)$R^6$, -S(=O)$_2$N($R^{6a}$)$R^{6b}$, -S(=O)(=N$R^{6c}$)$R^6$ group ;

wherein said aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2 or 3 C_1-C_6-alkyl- groups;

or

when 2 R^7 groups are present ortho- to each other on an aryl- or heteroaryl-ring, said 2 R^7 groups together form a bridge :

$O(CH_2)_2O$, *$O(CH_2)O$*, *$NH(C(=O))NH$*, wherein * represent the point of attachment to said aryl- or heteroaryl- ring ;

R^8 represents a hydrogen or halogen atom, or a -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ group , $-S(=O)_2$-(3- to 7-membered heterocycloalkyl);

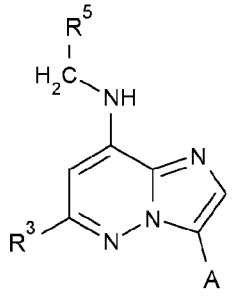
wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group, is optionally substituted, identically or differently, with 1, 2, 3 or 4 C_1-C_6-alkyl- groups ;

m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

n is an integer of 0, 1, 2, 3, 4 or 5 ; and

X is S, S(=O), $S(=O)_2$, O, NR^6 or $CR^{6a}R^{6b}$.

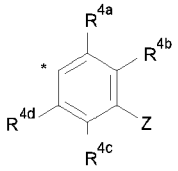
In another preferred embodiment, the invention relates to compounds of general formula I :



I

in which :

A represents



wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a -C(=O)N(H)R^2 or -C(=S)N(H)R^2 group ;

R^2 represents a C_1-C_4-alkyl- group ;
wherein said C_1-C_4-alkyl- group is optionally substituted, identically or differently, with 1 or 2 groups selected from: halogen, -OH, -CN, C_1-C_3-alkyl-, C_1-C_4-alkoxy- ;

R^3 is selected from aryl-X- or heteroaryl-X- ; wherein said aryl-X- or heteroaryl-X- group is optionally substituted, identically or differently, with 1 or 2 R^7 groups ;

R^{4a}, R^{4b}, R^{4c}, R^{4d}
are selected, independently from each other, from hydrogen, halogen, -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkyl-, or halo-C_1-C_6-alkoxy- ;

R^5 represents a hydrogen atom, C_1-C_6-alkyl-, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl- or heteroaryl- group ;
wherein said C_1-C_6-alkyl-, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c},

represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl-, H O-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, C_2-C_6-alkenyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, aryl-C_1-C_6-alkyl-, or heteroaryl-C_1-C_6-alkyl- group ;

R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2R^6$, -N(R^{6c})S(=O)$_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -S(=O_2)R^6, -S(=O)$_2$N(H)R^6, -S(=O)$_2$N(R^{6a})R^{6b}, -S(=O)(=NR^{6c})R^6 group ;

wherein said aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2 or 3 C_1-C_6-alkyl- groups;

or

when 2 R^7 groups are present ortho- to each other on an aryl- or heteroaryl- ring, said 2 R^7 groups together form a bridge :

O(CH_2)$_2$O, *O(CH_2)O*, *NH(C(=O))NH*, wherein * represent the point of attachment to said aryl- or heteroaryl- ring ;

R^8 represents a hydrogen or halogen atom, or a -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2R^6$, -N(R^{6c})S(=O)$_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, - S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -S(=O)$_2R^6$, -S(=O)$_2$N(H)R^6, -S(=O)$_2$N(R^{6a})R^{6b}, -S(=O)(=NR^{6c})R^6 group , -S(=O)$_2$-(3- to 7-membered heterocycloalkyl);

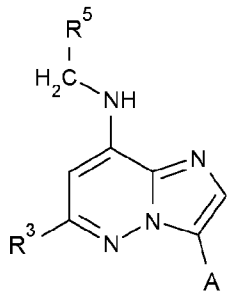
wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 C_1-C_6-alkyl-groups ;

m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

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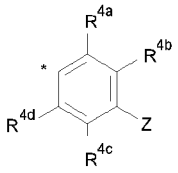
In another preferred embodiment, the invention relates to compounds of general formula I :



I

in which :

A represents



wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a $-C(=O)N(H)R^2$ or $-C(=S)N(H)R^2$ group ;

R^2 represents a C_1-C_4-alkyl- group ;

wherein said C_1-C_4-alkyl- group is optionally substituted, identically or differently, with 1 or 2 groups selected from: halogen, OH, -CN, C_1-C_3-alkyl-, C_1-C_4-alkoxy- ;

R^3 represent an aryl-X- or heteroaryl-X- group ; wherein said aryl-X- or heteroaryl-X- group is optionally substituted, identically or differently, with 1 or 2 R^7 groups ;

R^{4a}, R^{4b}, R^{4c}, R^{4d}
are selected, independently from each other, from hydrogen, halogen, -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy- ;

R^5 represents a hydrogen atom, C_1-C_6-alkyl-, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl- or heteroaryl- group ;
wherein said C_1-C_6-alkyl-, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c},
represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl-, H O-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, C_2-C_6-alkenyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, aryl-C_1-C_6-alkyl-, or heteroaryl-C_1-C_6-alkyl- group ;

R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2$$R^6$, -N($R^{6c}$)S(=O)$_2$$R^6$, -N=S(=O)($R^{6a}$)$R^{6b}$, -O$R^6$, -O(C=O)$R^6$, -O(C=O)N($R^{6a}$)$R^{6b}$, -O(C=O)O$R^6$, -S$R^6$, -S(=O)$R^6$, -S(=O)N(H)$R^6$, -S(=O)N($R^{6a}$)$R^{6b}$, -S(=$O_2$)$R^6$, -S(=O)$_2$N(H)$R^6$, -S(=O)$_2$N($R^{6a}$)$R^{6b}$, -S(=O)(=N$R^{6c}$)$R^6$ group ;

wherein said aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2 or 3 C_1-C_6-alkyl- groups;
or
when 2 R^7 groups are present ortho- to each other on an aryl- or heteroaryl- ring, said 2 R^7 groups together form a bridge :
$O(CH_2)_2O$, *$O(CH_2)O$*, *$NH(C(=O))NH$*, wherein * represent the point of attachment to said aryl- or heteroaryl- ring ;

R^8 represents a halogen atom, a -CN, $-N(R^{6a})R^{6b}$, or $-OR^6$ group ;

m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;
n is an integer of 0, 1, 2, 3, 4 or 5 ; and
X is S, S(=O), $S(=O)_2$, O, NR^6 or $CR^{6a}R^{6b}$.

It is to be understood that the present invention relates to any sub-combination within any embodiment or aspect of the present invention of compounds of general formula I, *supra*.

More particularly still, the present invention covers compounds of general formula I which are disclosed in the Experimental Section of this text, *infra*.

The compounds of this invention may contain one or more asymmetric centre, depending upon the location and nature of the various substituents desired. Asymmetric carbon atoms may be present in the (R) or (S) configuration, resulting in racemic mixtures in the case of a single asymmetric centre, and diastereomeric mixtures in the case of multiple asymmetric centres. In certain instances, asymmetry may also be present due to restricted rotation about a given bond, for example, the central bond adjoining two substituted aromatic rings of the specified compounds.

Substituents on a ring may also be present in either cis or trans form. It is intended that all such configurations (including enantiomers and diastereomers), are included within the scope of the present invention.

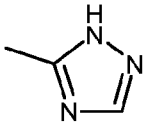
Preferred compounds are those which produce the more desirable biological activity. Separated, pure or partially purified isomers and stereoisomers or racemic or diastereomeric mixtures of the compounds of this invention are also included within the scope of the present invention. The purification and the separation of such materials can be accomplished by standard techniques known in the art.

The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base or formation of covalent diastereomers. Examples of appropriate acids are tartaric, diacetyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of diastereoisomers can be separated into their individual diastereomers on the basis of their physical and/or chemical differences by methods known in the art, for example, by chromatography or fractional crystallisation. The optically active bases or acids are then liberated from the separated diastereomeric salts. A different process for separation of optical isomers involves the use of chiral chromatography (*e.g.*, chiral HPLC columns), with or without conventional derivatisation, optimally chosen to maximise the separation of the enantiomers. Suitable chiral HPLC columns are manufactured by Diacel, *e.g.*, Chiracel OD and Chiracel OJ among many others, all routinely selectable. Enzymatic separations, with or without derivatisation, are also useful. The optically active compounds of this invention can likewise be obtained by chiral syntheses utilizing optically active starting materials.

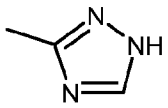
In order to limit different types of isomers from each other reference is made to IUPAC Rules Section E (Pure Appl Chem 45, 11-30, 1976).

The present invention includes all possible stereoisomers of the compounds of the present invention as single stereoisomers, or as any mixture of said stereoisomers, in any ratio. Isolation of a single stereoisomer, *e.g.* a single enantiomer or a single diastereomer, of a compound of the present invention may be achieved by any suitable state of the art method, such as chromatography, especially chiral chromatography, for example.

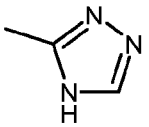
Further, the compounds of the present invention may exist as tautomers. For example, any compound of the present invention which contains a pyrazole moiety as a heteroaryl group for example can exist as a 1H tautomer, or a 2H tautomer, or even a mixture in any amount of the two tautomers, or a triazole moiety for example can exist as a 1H tautomer, a 2H tautomer, or a 4H tautomer, or even a mixture in any amount of said 1H, 2H and 4H tautomers, namely :



1H-tautomer



2H-tautomer



4H-tautomer.

The present invention includes all possible tautomers of the compounds of the present invention as single tautomers, or as any mixture of said tautomers, in any ratio.

Further, the compounds of the present invention can exist as N-oxides, which are defined in that at least one nitrogen of the compounds of the present invention is oxidised. The present invention includes all such possible N-oxides.

Furthermore, the present invention includes all possible crystalline forms, or polymorphs, of the compounds of the present invention, either as single polymorphs, or as a mixture of more than one polymorph, in any ratio.

The compounds of the present invention can exist as a hydrate, or as a solvate, wherein the compounds of the present invention contain polar solvents, in particular water, methanol or ethanol for example as structural element of the crystal lattice of the compounds. The amount of polar solvents, in particular water, may exist in a stoichiometric or non-stoichiometric ratio. In the case of stoichiometric solvates, *e.g.* a hydrate, hemi-, (semi-), mono-, sesqui-, di-, tri-, tetra-, penta- *etc.* solvates or hydrates, respectively, are possible. The present invention includes all such hydrates or solvates.

In an embodiment of the above-mentioned aspects, the invention relates to compounds of formula I, according to any of the above-mentioned embodiments, in the form of or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

The compounds of the present invention have surprisingly been found to effectively inhibit Mps-1 kinase and may therefore be used for the treatment or prophylaxis of diseases of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses or diseases which are accompanied with uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, particularly in which the uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses is mediated by Mps-1 kinase, such as, for example, haemotological tumours, solid tumours, and/or metastases thereof, *e.g.* leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

Therefore, the compounds of formula I, *supra*, are expected to be valuable as therapeutic agents.

Accordingly, in another embodiment, the present invention is directed to a compound of general formula I, *supra*, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, for use in the treatment or prophylaxis of a disease.

In another embodiment, the present invention provides a method of treating disorders associated with enhanced uncontrolled proliferative cellular processes in

a patient in need of such treatment, comprising administering to the patient an effective amount of a compound of formula I.

The term "treating" or "treatment" as stated throughout this document is used conventionally, e.g., the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving the condition of a disease or disorder, such as a carcinoma.

The term "subject" or "patient" includes organisms which are capable of suffering from a cell proliferative disorder or who could otherwise benefit from the administration of a compound of the invention, such as human and non-human animals. Preferred humans include human patients suffering from or prone to suffering from a cell proliferative disorder or associated state, as described herein. The term "non-human animals" includes vertebrates, e.g., mammals, such as non-human primates, sheep, cow, dog, cat and rodents, e.g., mice, and non-mammals, such as chickens, amphibians, reptiles, etc.

The terms "cell proliferative disorder" or "disorder associated with enhanced uncontrolled proliferative cellular processes" include disorders involving the undesired or uncontrolled proliferation of a cell. The compounds of the present invention can be utilized to prevent, inhibit, block, reduce, decrease, control, etc., cell proliferation and/or cell division, and/or produce apoptosis. This method comprises administering to a subject in need thereof, including a mammal, including a human, an amount of a compound of this invention, or a pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate or solvate thereof which is effective to treat or prevent the disorder.

In another embodiment, the present invention is directed to a compound of general formula I, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, for use in the treatment or prophylaxis of a disease, wherein said disease is a disease of uncontrolled cell growth, proliferation and/or survival, an inappropriate cellular immune response, or an inappropriate cellular inflammatory

response, particularly in which the uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune response, or inappropriate cellular inflammatory response is mediated by the mitogen-activated protein kinase (MEK-ERK) pathway, more particularly in which the disease of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune response, or inappropriate cellular inflammatory response is a haemotological tumour, a solid tumour and/or metastases thereof, *e.g.* leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

The present invention also relates to useful forms of the compounds as disclosed herein, such as metabolites, hydrates, solvates, prodrugs, salts, in particular pharmaceutically acceptable salts, *in vivo* hydrolysable esters, and co-precipitates.

The term "pharmaceutically acceptable salt" refers to a relatively non-toxic, inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M. Berge, *et al.* "Pharmaceutical Salts," J. Pharm. Sci. **1977**, 66, 1-19.

A suitable pharmaceutically acceptable salt of the compounds of the present invention may be, for example, an acid-addition salt of a compound of the present invention bearing a nitrogen atom, in a chain or in a ring, for example, which is sufficiently basic, such as an acid-addition salt with an inorganic acid, such as hydrochloric, hydrobromic, hydroiodic, sulfuric, bisulfuric, phosphoric, or nitric acid, for example, or with an organic acid, such as formic, acetic, acetoacetic, pyruvic, trifluoroacetic, propionic, butyric, hexanoic, heptanoic, undecanoic, lauric, benzoic, salicylic, 2-(4-hydroxybenzoyl)-benzoic, camphoric, cinnamic, cyclopentanepropionic, digluconic, 3-hydroxy-2-naphthoic, nicotinic, pamoic, pectinic, persulfuric, 3-phenylpropionic, picric, pivalic, 2-hydroxyethanesulfonate, itaconic, sulfamic, trifluoromethanesulfonic, dodecylsulfuric, ethansulfonic, benzenesulfonic, para-toluenesulfonic, methansulfonic, 2-naphthalenesulfonic, naphthalinedisulfonic, camphorsulfonic acid, citric, tartaric, stearic, lactic, oxalic,

malonic, succinic, malic, adipic, alginic, maleic, fumaric, D-gluconic, mandelic, ascorbic, glucoheptanoic, glycerophosphoric, aspartic, sulfosalicylic, hemisulfuric, or thiocyanic acid, for example.

Further, another suitably pharmaceutically acceptable salt of a compound of the present invention which is sufficiently acidic, is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically acceptable cation, for example a salt with N-methyl-glucamine, dimethyl-glucamine, ethyl-glucamine, lysine, dicyclohexylamine, 1,6-hexadiamine, ethanolamine, glucosamine, sarcosine, serinol, tris-hydroxy-methyl-aminomethane, aminopropandiol, sovak-base, 1-amino-2,3,4-butantriol. Additionally, basic nitrogen containing groups may be quaternised with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides ; dialkyl sulfates like dimethyl, diethyl, and dibutyl sulfate ; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and strearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

Those skilled in the art will further recognise that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts of acidic compounds of the invention are prepared by reacting the compounds of the invention with the appropriate base via a variety of known methods.

The present invention includes all possible salts of the compounds of the present invention as single salts, or as any mixture of said salts, in any ratio.

As used herein, the term "*in vivo* hydrolysable ester" is understood as meaning an *in vivo* hydrolysable ester of a compound of the present invention containing a carboxy or hydroxy group, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include for example alkyl, cycloalkyl and optionally substituted phenylalkyl, in particular benzyl esters, C_1-C_6 alkoxymethyl esters, *e.g.* methoxymethyl, C_1-C_6 alkanoyloxymethyl esters, *e.g.*

pivaloyloxymethyl, phthalidyl esters, C_3-C_8 cycloalkoxy-carbonyloxy-C_1-C_6 alkyl esters, *e.g.* 1-cyclohexylcarbonyloxyethyl ; 1,3-dioxolen-2-onylmethyl esters, *e.g.* 5-methyl-1,3-dioxolen-2-onylmethyl ; and C_1-C_6-alkoxycarbonyloxyethyl esters, *e.g.* 1-methoxycarbonyloxyethyl, and may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the present invention containing a hydroxy group includes inorganic esters such as phosphate esters and [alpha]-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of [alpha]-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. The present invention covers all such esters.

Compounds of formula I may be administered as the sole pharmaceutical agent or in combination with one or more additional therapeutic agents where the combination causes no unacceptable adverse effects. This combination therapy includes administration of a single pharmaceutical dosage formulation which contains a compound of formula I and one or more additional therapeutic agents, as well as administration of the compound of formula I and each additional therapeutic agent in its own separate pharmaceutical dosage formulation. For example, a compound of formula I and a therapeutic agent may be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent may be administered in separate dosage formulations.

Where separate dosage formulations are used, the compound of formula I and one or more additional therapeutic agents may be administered at essentially the same time (e.g., concurrently) or at separately staggered times (e.g., sequentially).

In another aspect, the invention provides a pharmaceutical composition comprising a compound of general formula I, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable

salt thereof, or a mixture of same, and a pharmaceutically acceptable diluent or carrier.

Preferably, the pharmaceutical combination comprises :
- one or more compounds of general formula I, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same; and
- one or more agents selected from : a taxane, such as Docetaxel, Paclitaxel, or Taxol; an epothilone, such as Ixabepilone, Patupilone, or Sagopilone; Mitoxantrone; Predinisolone; Dexamethasone; Estramustin; Vinblastin; Vincristin; Doxorubicin; Adriamycin; Idarubicin; Daunorubicin; Bleomycin; Etoposide; Cyclophosphamide; Ifosfamide; Procarbazine; Melphalan; 5-Fluorouracil; Capecitabine; Fludarabine; Cytarabine; Ara-C; 2-Chloro-2´-deoxyadenosine; Thioguanine; an anti-androgen, such as Flutamide, Cyproterone acetate, or Bicalutamide; Bortezomib; a platinum derivative, such as Cisplatin, or Carboplatin; Chlorambucil; Methotrexate; and Rituximab.

In still another aspect, the invention provides a process for preparing a pharmaceutical composition. The process includes the step of combining at least one compound of formula I as defined above with at least one pharmaceutically acceptable carrier, and bringing the resulting combination into a suitable administration form.

In still another aspect, the invention provides use of a compound of formula I as defined above for manufacturing a pharmaceutical composition for the treatment or prevention of a cell proliferative disorder. In certain embodiments, the cell proliferative disorder is cancer.

The active component of formula I can act systemically and/or locally. For this purpose, it can be applied in a suitable manner, for example orally, parenterally, pulmonally, nasally, sublingually, lingually, buccally, rectally, transdermally, conjunctivally, otically, or as an implant or stent.

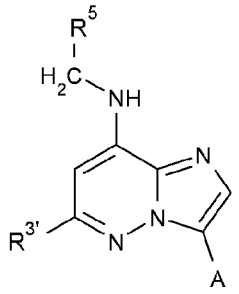
When the compounds of the present invention are administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

Regardless of the route of administration selected, the compounds of the invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels and time course of administration of the active ingredients in the pharmaceutical compositions of the invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

In accordance with another aspect, the present invention covers methods of preparing compounds of the present invention.

In accordance with a first embodiment, the present invention relates to a method of preparing a compound of general formula I, *supra*, said method comprising the step of allowing an intermediate compound of general formula IV :



IV

in which A, and R^5 are as defined for general formula I, *supra*, and $R^{3'}$ is a leaving group ;

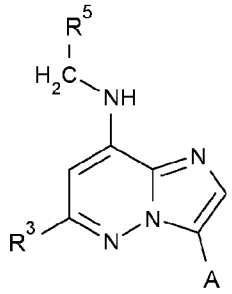
to react with a compound of general formula **IVa** :

R^3-Y

IVa

in which R^3 is as defined for general formula I, *supra*, and Y is a substituent which is displaced in a coupling reaction, such as a hydrogen atom, or a boronic acid group, or a boronic ester group, for example ;

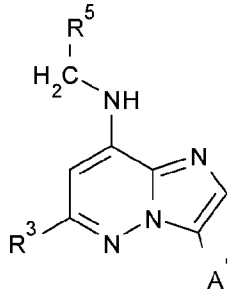
thereby giving a compound of general formula **I** :



I

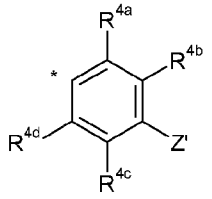
in which A, R^3, and R^5 are as defined for general formula **I**, *supra*.

In accordance with a second embodiment, the present invention also relates to a method of preparing a compound of general formula **I**, *supra*, said method comprising the step of allowing an intermediate compound of general formula **Ia** :



Ia

in which R^3 and R^5 are as defined for general formula I, *supra*;
and A' is



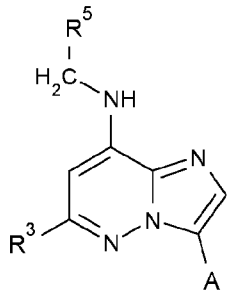
wherein * indicates the point of attachment of said group with the rest of the molecule; R^{4a}, R^{4b}, R^{4c} and R^{4d} are as defined for general formula I, *supra*, and Z' represents a group selected from:
-C(=O)OH, -C(=S)OH, -C(=O)O-(C_1-C_6-alkyl) or -C(=S)O-(C_1-C_6-alkyl);

to react with a compound of general formula Ib :

H_2NR^2

Ib

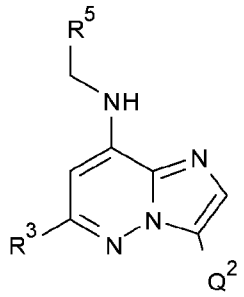
in which R^2 is as defined as for general formula I, *supra*, thereby giving, upon optional deprotection, a compound of general formula I:



I

in which R^3, R^5 and A are as defined for general formula I, *supra*.

In accordance with a third embodiment, the present invention also relates to a method of preparing a compound of general formula I, *supra*, said method comprising the step of allowing an intermediate compound of general formula II :



II

in which R^3 and R^5 are as defined for general formula I, *supra*, and Q^2 is a leaving group, preferably Q^2 is a halogen atom ;

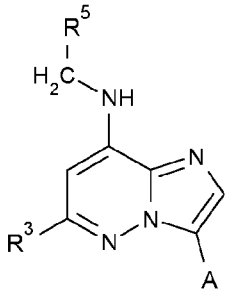
to react with a compound of general formula IIa :

A-Y

IIa

in which A is as defined for general formula I, *supra*, and Y is a substituent which is displaced in a coupling reaction, such as a boronic acid group, or an ester of a boronic acid group, for example,

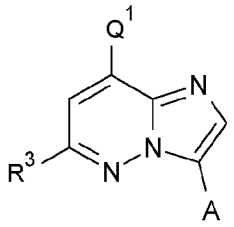
thereby giving, upon optional deprotection, a compound of general formula I :



I

in which R^3, R^5 and A are as defined for general formula I, *supra*.

In accordance with a fourth embodiment, the present invention also relates to a method of preparing a compound of general formula I, *supra*, said method comprising the step of allowing an intermediate compound of general formula VII :



VII

in which R^3 and A are as defined for general formula I, *supra*, and Q^1 is a leaving group, for example a halogen atom,

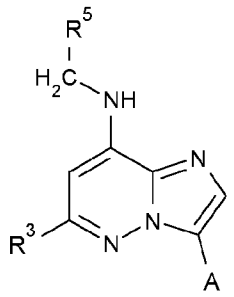
to react with a compound of general formula VIIa :

$$R^5\text{-}CH_2\text{-}NH_2$$

VIIa

in which R^5 is as defined for general formula I, *supra*,

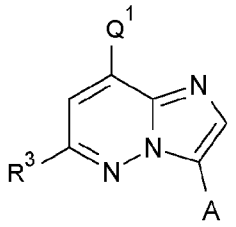
thereby giving, upon optional deprotection, a compound of general formula I :



I

in which R^3, R^5 and A are as defined for general formula I, *supra*.

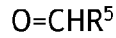
In accordance with a forth embodiment, the present invention also relates to a method of preparing a compound of general formula I, *supra*, said method comprising the step of allowing an intermediate compound of general formula VII :



VII

in which R^3 and A are as defined for general formula I, *supra*, and Q^1 is an optionally protected NH_2-group

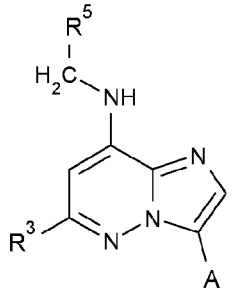
to react with a compound of general formula VIIb :



VIIb

in which R^5 is as defined for general formula I, *supra*,

thereby giving, upon optional deprotection, a compound of general formula I :

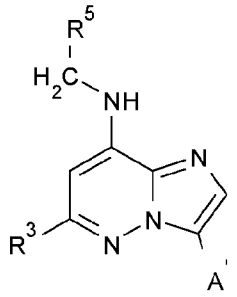


I

in which R^3, R^5 and A are as defined for general formula I, *supra*.

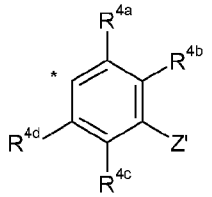
In accordance with a further aspect, the present invention covers intermediate compounds which are useful in the preparation of compounds of the present invention of general formula I, particularly in the method described herein.

In particular, the present invention covers intermediate compounds of general formula **Ia** :



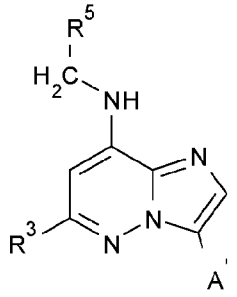
Ia

in which R^3 and R^5 are as defined for general formula I, *supra*;
and A' is



wherein * indicates the point of attachment of said group with the rest of the molecule; R^{4a}, R^{4b}, R^{4c} and R^{4d} are as defined for general formula I, *supra*, and Z' represents a group selected from:
-C(=O)OH, -C(=S)OH, -C(=O)O-(C_1-C_6-alkyl) or -C(=S)O-(C_1-C_6-alkyl).

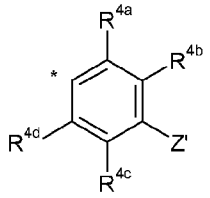
In accordance with yet another aspect, the present invention covers the use of the intermediate compounds of general formula **Ia** :



Ia

in which R^3 and R^5 are as defined for general formula I, *supra*;

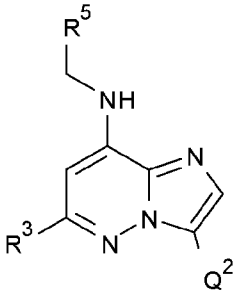
and A' is



wherein * indicates the point of attachment of said group with the rest of the molecule; R^{4a}, R^{4b}, R^{4c} and R^{4d} are as defined for general formula I, *supra*, and Z' represents a group selected from:
-C(=O)OH, -C(=S)OH, -C(=O)O-(C_1-C_6-alkyl) or -C(=S)O-(C_1-C_6-alkyl);

for the preparation of a compound of general formula I as defined *supra*.

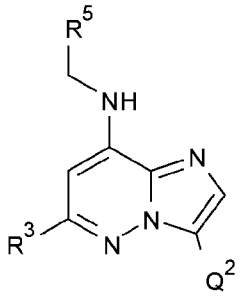
In accordance with yet another aspect, the present invention covers intermediate compounds of general formula II :



II

in which R^3 and R^5 are as defined for general formula I, *supra*, and Q^2 is a leaving group, preferably Q^2 is a halogen atom.

In accordance with yet another aspect, the present invention covers the use of the intermediate compounds of general formula II :

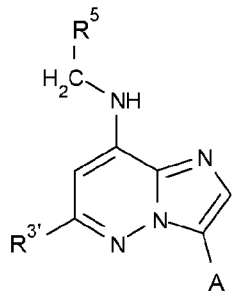


II

in which R^3 and R^5 are as defined for general formula I, *supra*, and Q^2 is a leaving group, preferably Q^2 is a halogen atom ;

for the preparation of a compound of general formula I as defined *supra*.

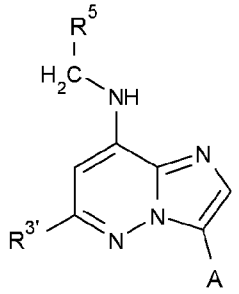
In accordance with yet another aspect, the present invention covers intermediate compounds of general formula IV :



IV

in which A, and R^5 are as defined for general formula I, *supra*, and $R^{3'}$ is a leaving group.

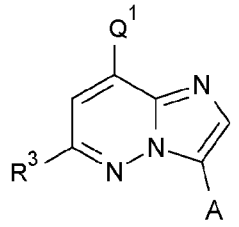
In accordance with yet another aspect, the present invention covers the use of the intermediate compounds of general formula **IV** :



IV

in which A, and R^5 are as defined for general formula I, *supra*, and $R^{3'}$ is a leaving group, for the preparation of a compound of general formula I as defined *supra*.

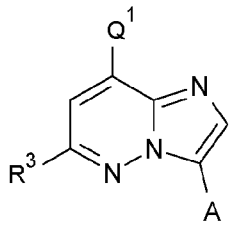
In accordance with a further aspect, the present invention covers intermediate compounds of general formula **VII** :



VII

in which A, and R^3 are as defined for general formula I, *supra*, and Q^1 represents an optionally protected NH_2-group or a leaving group.

In accordance with yet another aspect, the present invention covers the use of the intermediate compounds of general formula **VII** :



VII

in which A, and R^3 are as defined for general formula I, *supra*, and Q^1 represents an optionally protected NH_2-group or a leaving group;

for the preparation of a compound of general formula I as defined *supra*.

EXPERIMENTAL SECTION

The following Table lists the abbreviations used in this paragraph, and in the Examples section.

Abbreviation	Meaning
EDC	1-Ethyl-3-(3-dimethyllaminopropyl)carbodiimide
DIPEA	N,N-diisopropylethylamine
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide
$Pd(dppf)Cl_2$	Dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II)
NMR	nuclear magnetic resonance spectroscopy
Rt	Room temperature
RT	Retention time in minutes
MW	molecular weight
NMP	*N*-methylpyrrolidinone
Oxone	Potassium peroxymonosulfate
UPLC	ultra performance liquid chromatography

Synthesis of compounds of general formula I of the present invention

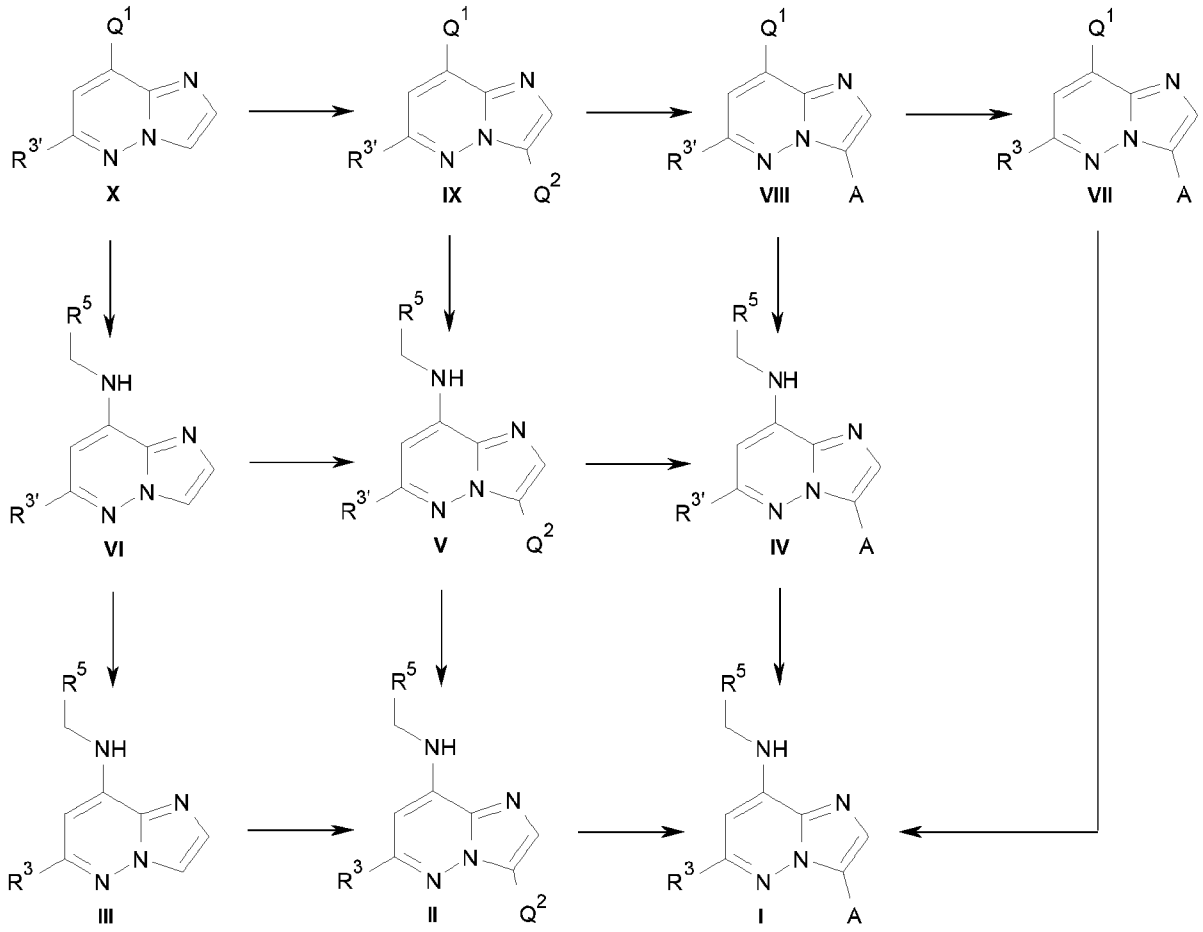
Compounds of general formula I can be synthesized as depicted in the Scheme, with

A, R^3, R^5 having the meaning as given for general formula I, *supra* ;

$R^{3'}$, Q^2 representing leaving groups ; and

Q^1 represents an optionally protected NH_2-group or a leaving group.

Examples for typical leaving groups include but are not limited to halogen atoms like a chlorine, bromine or iodine atom, or $S(O)_pR^6$-groups (wherein p is 0, 1, or 2, and R^6 is as defined for general formula I, *supra*) like a methylsulfonyl- group, or a triflate- or nonaflate-group.



Scheme

The Scheme exemplifies routes that allow variations for R^3, $R^{3'}$, R^5, Q^1, Q^2 and A during the synthesis. Functional moieties in R^3, $R^{3'}$, R^5, Q^1, Q^2 and A can be converted at every suitable stage of the synthesis.

However, also other routes were used for synthesis of the target compounds.

Compounds of formula **X** may be commercially available or can be synthesized according to procedures known to persons skilled in the art, for example applying procedures described in WO2007/38314A2.

A leaving group Q^2 can be introduced in compounds of general formula **X**, **VI** or **III** by procedures known to persons skilled in the art to give compounds of general formula **IX**, **V** or **II**. As an example, halogens can be introduced using halogenation reagents like N-iodosuccinimide (NIS), N-bromosuccinimide (NBS), or N-chlorosuccinimide (NCS), in an inert solvent like N,N-dimethylformamide or 1-methylpyrrolidin-2-one, for example, at temperatures ranging from room temperature to the boiling point of the solvent, for example.

Compounds of general formula **I**, **IV** or **VIII** can be obtained from compounds of general formula **II**, **V** or **IX** via a coupling reaction between a reagent of formula Y-A, in which A is defined *supra* and Y represents a suitable functional group by which the group A can be transferred to the Q-group bearing carbon atom of compounds of formula **II**, **V** or **IX**. Examples of suitable functional groups for Y in A-Y include boronic acids A-$B(OH)_2$, or esters of boronic acids A-$B(OC_1$-C_6-alkyl$)_2$. Said coupling reactions are performed in the presence of suitable catalysts, such as, for example, palladium based catalysts like, for example, Palladium (II) acetate, tetrakis(triphenylphosphine)palladium (0), bis(triphenylphosphine)-palladium (II) chloride or (1,1,-bis(diphenylphosphino) ferrocene)-dichloropalladium (II) and optionally suitable additives such as, for example, phosphines like, for example, $P(oTol)_3$ or triphenylphosphine and optionally with a suitable base, such as, for example, potassium carbonate, sodium 2-methylpropan-2-olate, tetrabutylammonium fluoride or tribasic potassium phosphate in a suitable solvent, such as, for example, tetrahydrofuran.
Examples of such coupling reactions may be found in the textbook entitled "Metal-Catalyzed Cross-Coupling Reactions", Armin de Meijere (Editor), François Diederich (Editor) September 2004, Wiley Interscience ISBN: 978-3-527-30518-6.

Compounds of general formula **I**, **II**, **III** or **VII** can be obtained from compounds of general formula **IV**, **V**, **VI** or **VIII** via a coupling reaction using a reagent of formula Y-R^3 in which R^3 is defined *supra* and Y represents a suitable functional group by

which the group R^3 can be transferred to the $R^{3'}$ bearing carbon atom of compounds of formula **IV**, **V**, **VI** or **VIII**. Examples of suitable functional groups Y for the use in coupling reactions are given *supra* for the preparation of compounds of general formula **I**, **IV** or **VIII** from compounds of general formula **II**, **V** or **IX**.

The coupling reactions include metal catalyzed coupling reactions like Sonogashira coupling reactions with alkynes for alkyne introduction, Heck coupling reactions with alkenes for alkene introduction, Hartwig Buchwald coupling reactions with amines for amine introduction.

Y in Y-R^3 may also represent an acidic hydrogen that can be removed by suitable bases, for example sodium hydride, in a suitable solvent, such as DMSO or tetrahydrofuran at temperatures ranging from rt to the boiling point. The resulting nucleophiles, like, for example, primary or secondary amines, alkoxides, thiolates or carbon anion bearing groups can be used to replace $R^{3'}$ in compounds of general formula **IV**, **V**, **VI** or **VIII** to add secondary or tertiary amines, ethers, thioethers or carbon-atom attached groups to give compounds of general formula **I**, **II**, **III** or **VII**.

Compounds of general formula **I**, **II**, **III** or **VII** containing primary or secondary amines, ethers or thioether can also be build by Ullmann-type coupling reactions in the presence of suitable catalysts, such as, for example, copper based catalysts like copper(II)diacetate in presence of a suitable base, like for example, caesium carbonate staring from compounds of general formula **IV**, **V**, **VI** or **VIII** in which $R^{3'}$ represents a leaving group such as, for example, an iodine, bromine or chlorine atom. Optionally, suitable ligands like N,N-dimethylglycine or phenyl hydrogen pyrrolidin-2-ylphosphonate can be added.

In the case Q^1 represents a leaving group, the introduction of a R^5-CH_2-group can be achieved by nucleophilic substitution of Q^1 in compounds of formula **VII**, **VIII**, **IX** or **X** i. e. by a reaction with suitable amines R^5-CH_2-NH_2 in the presence of a suitable base, such as, for example DIPEA in a suitable solvent such as N,N-dimethylformamide or 1-methylpyrrolidin-2-one, at temperatures ranging from

room temperature to the boiling point of the solvent to give amines of general formula **I**, **IV**, **V** or **VI**.

In the case Q^1 represents a leaving group, the introduction of a R^5-CH_2-group can also be achieved in a coupling reaction in which Q^1 in compounds of formula **VII**, **VIII**, **IX** or **X** is reacted with suitable amines R^5-CH_2-NH_2 optionally in the presence of a suitable catalyst, such as Pd_2dba_3 and BINAP for example, and optionally with a suitable base, such as, for example, sodium tert-butylate in a suitable solvent, such as, for example, N,N-dimethylformamide or 1-methylpyrrolidin-2-one to give amines of general formula **I**, **IV**, **V** or **VI**.

In the case Q^1 represents an optionally protected NH_2-group the introduction of a R^5-CH_2-group, after deprotection to a NH_2-group, can be achieved by a reductive amination reaction using an aldehyde of formula $O=CHR^5$, a suitable reducing agent, for example sodium tris(acetato-kappaO)(hydrido)borate or sodium cyanoborohydride in a suitable solvent like, for example, acetic acid at reaction temperatures ranging from room temperature to the boiling point of the solvent.

Residues in compounds of formula **I**, **II**, **III**, **IV**, **V**, **VI**, **VII**, **VIII**, **IX** or **X** can be optionally modified. For example, thioethers can be oxidized using oxidation reagents like 3-chlorobenzenecarboperoxoic acid, oxone or dimethyldioxirane in inert solvents like dichloromethane or acetone, respectively. Depending on the stoichiometric ratio of oxidation reagent to the afore mentioned compounds sulfoxides or sulfones or mixtures thereof will be obtained.

Further, the compounds of formula **I** of the present invention can be converted to any salt as described herein, by any method which is known to the person skilled in the art. Similarly, any salt of a compound of formula **I** of the present invention can be converted into the free compound, by any method which is known to the person skilled in the art.

The compounds and intermediates produced according to the methods of the invention may require purification. Purification of organic compounds is well known to the person skilled in the art and there may be several ways of purifying the same compound. In some cases, no purification may be necessary. In some cases, the compounds may be purified by crystallisation. In some cases, impurities may be removed by stirring using a suitable solvent. In some cases, the compounds may be purified by chromatography, particularly flash chromatography, using for example pre-packed silica gel cartridges, *e.g.* from Separtis such as Isolute® Flash silica gel or Isolute® Flash NH2 silica gel in combination with a suitable chromatographic system such as a Flashmaster II (Separtis) or an Isolera system (Biotage) and eluents such as, for example, gradients of hexane/EtOAc or DCM/methanol. In some cases, the compounds may be purified by preparative HPLC using, for example, a Waters autopurifier equipped with a diode array detector and/or on-line electrospray ionisation mass spectrometer in combination with a suitable pre-packed reverse phase column and eluants such as, for example, gradients of water and acetonitrile which may contain additives such as trifluoroacetic acid, formic acid or aqueous ammonia.

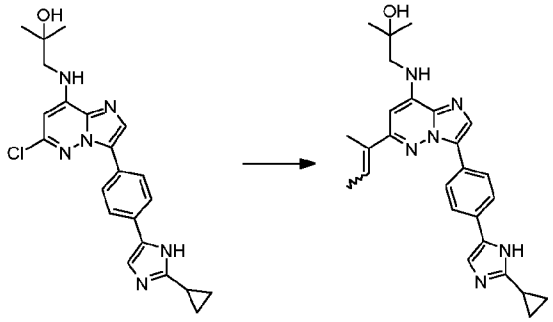
Examples

Analytical UPLC-MS was performed as follows:
Method A: System: UPLC Acquity (Waters) with PDA Detector und Waters ZQ mass spectrometer; Column: Acquity BEH C18 1.7µm 2.1x50mm; Temperature: 60°C; Solvent A: Water + 0.1% formic acid; Solvent B: acetonitrile; Gradient: 99 % A → 1 % A (1.6 min) → 1 % A (0.4 min) ; Flow: 0.8 mL/min; Injection Volume: 1.0 µl (0.1mg-1mg/mL sample concentration); Detection: PDA scan range 210-400 nm - Fixed and ESI (+),scan range 170-800 m/z

General:
All reactions were run under an atmosphere of argon in degassed solvents unless stated otherwise.

Example 1

1-({6-[(2E/Z)-But-2-en-2-yl]-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl] imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol

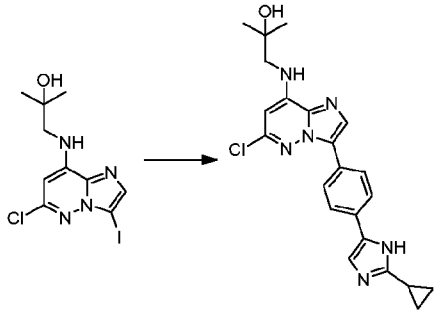


A mixture of 47.5 mg (112 µmol) 1-({6-chloro-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol which was prepared according to intermediate example 1a, 47.3 mg (2E/Z)-but-2-en-2-ylboronic acid, 1.6 mL n-propanol, 228 µL 1-methylpyrrolidin-2-one, 168 µL of an aqueous 2M potassium carbonate solution, 1.47 mg triphenylphosphine, and 7.9 mg bis(triphenylphosphine)palladium (II) chloride was stirred at 120°C for 2 hours under microwave irradiation. Solvent was removed and the residue was purified by chromatography to give 20.7 mg (40%) of the title compounds.

^{1}H-NMR (DMSO-d6): δ= 0.81-0.91 (4H), 1.15 (6H), 1.72 (3H), 1.93 (1H), 2.05 (3H), 3.13+3.26 (2H), 4.75+4.77 (1H), 5.73 (1H), 6.16+6.18 (1H), 6.75 (1H), 7.19+7.45 (1H), 7.65+7.76 (2H), 7.90+7.95 (1H), 8.06+8.14 (2H), 11.79+12.09 (1H) ppm.

Intermediate Example 1a

1-({6-Chloro-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol

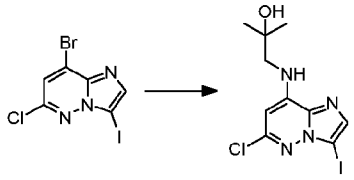


A mixture comprising 700 mg (1.91 mmol) 1-[(6-chloro-3-iodoimidazo[1,2-b]pyridazin-8-yl)amino]-2-methylpropan-2-ol which was prepared according to intermediate example 1b, 610 mg [4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]boronic acid, which was prepared according to intermediate example 1d, 156 mg

(1,1,-bis(diphenylphosphino)ferrocene)-dichloropalladium (II), 2.86 mL aqueous 2M tribasic potassium phosphate solution and 8.2 mL tetrahydrofuran was stirred at 45°C for 12 hours. Water was added and the mixture was extracted with ethyl acetate and methanol. The organic layer was washed with brine and dried over sodium sulfate. After filtration and removal of the solvent the residue was purified by chromatography to give 345 mg (43%) of the title compound.

Intermediate Example 1b

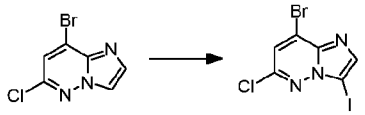
1-[(6-Chloro-3-iodoimidazo[1,2-b]pyridazin-8-yl)amino]-2-methylpropan-2-ol



To a solution of 1.20 g (3.35 mmol) 8-bromo-6-chloro-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 1c in 24 mL N,N-dimethylformamide were added 895 mg 1-amino-2-methylpropan-2-ol and the mixture was stirred at 40°C overnight. Water was added and the mixture was extracted with dichloromethane and methanol. The organic phase was washed with water and dried over sodium sulfate. After filtration and removal of solvent the residue was purified by chromatography to give 798 mg (65%) of the title compound.

Intermediate Example 1c

8-Bromo-6-chloro-3-iodoimidazo[1,2-b]pyridazine

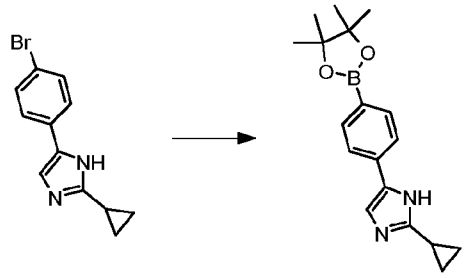


A mixture comprising 100 g (430 mmol) 8-bromo-6-chloroimidazo[1,2-b]pyridazine which was prepared according to a procedure described in US2007/78136 (WO2007/38314), 145 g N-iodosuccinimide, 5 percent per weight conc. hydrochloric acid and 1 L trichloromethane was heated at reflux for 6 hours. 20 g N-iodosuccinimide were added and heating was continued for additional 3 hours. The precipitate was removed and the filtrate was washed with 1N sodium hydroxide solution, brine and dried over sodium sulfate. After filtration and removal of solvent diisopropyl ether was added and the residue was stirred at 23°C

overnight. The precipitate was filtered off and dried to give 66.6 g (43%) of the title compound.

Intermediate Example 1d

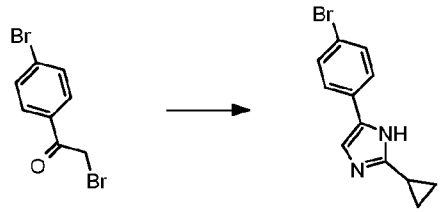
2-Cyclopropyl-5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1H-imidazole



A mixture comprising 42.1 g (160 mmol) 5-(4-bromophenyl)-2-cyclopropyl-1H-imidazole which was prepared according to intermediate example 1e, 60.9 g 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane, 3.05 g dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine, 1.46 g tris-(dibenzylidenacetone)-dipalladium(0), 23.5 g potassium acetate and 267 mL 1,4-dioxane was stirred at 110°C for 4 hours. After cooling to 23°C, ethyl acetate and 1M hydrochloric acid were added and the pH was adjusted to 8.0 by adding 5% sodium hydroxide solution. The mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. After filtration and removal of the solvent the residue was purified by crystallisation to give 33.5 g (67%) of the title compound.

Intermediate Example 1e

5-(4-Bromophenyl)-2-cyclopropyl-1H-imidazole

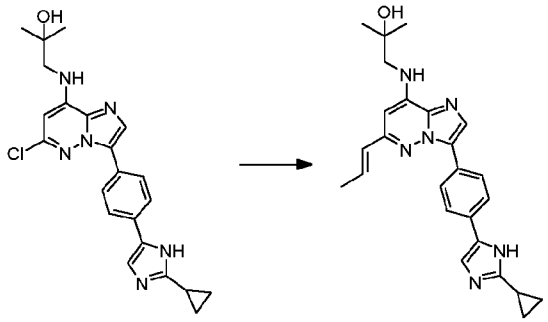


To a solution of 89.0 g (320 mmol) 2-bromo-1-(4-bromophenyl)ethanone in 2.0 L *N,N*-dimethylformamide were added cyclopropanecarboximidamide hydrochloride, 132.8 g potassium carbonate and the mixture was stirred at 23°C overnight. After

removal of the solvent, water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. After filtration and removal of the solvent the residue was purified by crystallisation to give 42.1 g (50%) of the title compound.

Example 2

1-({3-[4-(2-Cyclopropyl-1H-imidazol-5-yl)phenyl]-6-[(1E/Z)-prop-1-en-1-yl] imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol

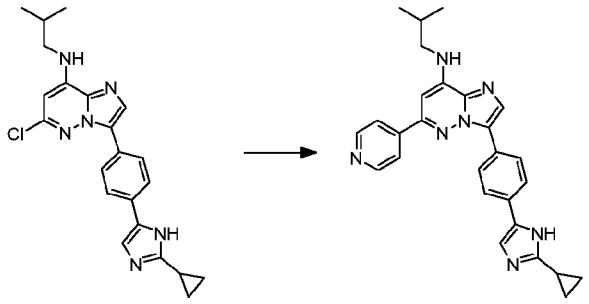


47.5 mg (112 µmol) 1-({6-chloro-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol which was prepared according to intermediate example 1a were transformed in analogy to example 1 using (1E/Z)-prop-1-en-1-ylboronic acid to give after working up and purification 34.1 mg (71%) of the title compounds.

^{1}H-NMR (DMSO-d6): δ= 0.81-0.93 (4H), 1.16 (6H), 1.83-1.98 (4H), 3:13+3.26 (2H), 4.76 (1H), 6.34-6.46 (2H), 6.59-6.78 (2H), 7.19+7.45 (1H), 7.66+7.76 (2H), 7.85+7.91 (1H), 8.08+8.15 (2H), 11.79+12.11 (1H) ppm.

Example 3

3-[4-(2-Cyclopropyl-1H-imidazol-5-yl)phenyl]-N-isobutyl-6-(pyridin-4-yl) imidazo[1,2-b]pyridazin-8-amine

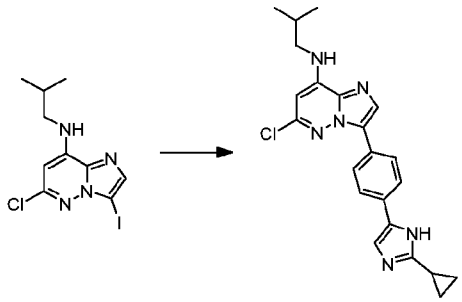


50 mg (123 µmol) 6-chloro-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-N-isobutylimidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 3a were transformed in analogy to example 1 using pyridin-4-ylboronic acid to give after working up and purification 10.9 mg (20%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.82-0.91 (4H), 0.94 (6H), 1.94 (1H), 2.04 (1H), 3.26 (2H), 6.74 (1H), 7.49 (1H), 7.68 (1H), 7.82 (2H), 7.98 (1H), 8.05 (2H), 8.16 (2H), 8.72 (2H), 11.82+12.13 (1H) ppm.

Intermediate Example 3a

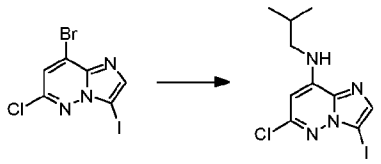
6-Chloro-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-N-isobutylimidazo[1,2-b]pyridazin-8-amine



200 mg (570 µmol) 6-chloro-3-iodo-N-isobutylimidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 3b were transformed in analogy to intermediate example 1a to give after working up and purification 114 mg (49%) of the title compound.

Intermediate Example 3b

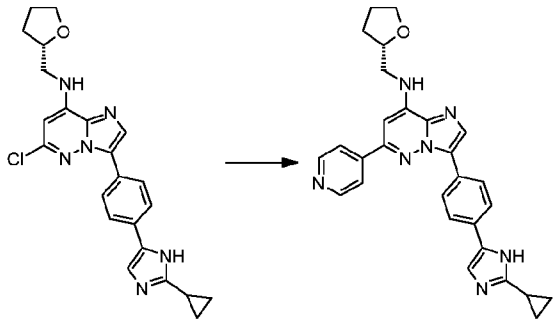
6-Chloro-3-iodo-N-isobutylimidazo[1,2-b]pyridazin-8-amine



200 mg (558 µmol) 8-bromo-6-chloro-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 1c were transformed in analogy to intermediate example 1b using 2-methylpropan-1-amine to give after working up and purification 188 mg (96%) of the title compound.

Example 4

3-[4-(2-Cyclopropyl-1H-imidazol-5-yl)phenyl]-6-(pyridin-4-yl)-N-[(2S)-tetrahydrofuran-2-ylmethyl]imidazo[1,2-b]pyridazin-8-amine

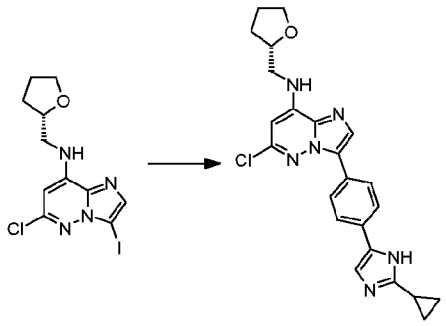


50 mg (115 µmol) 6-chloro-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-N-[(2S)-tetrahydrofuran-2-ylmethyl]imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 4a were transformed in analogy to example 1 using pyridin-4-ylboronic acid to give after working up and purification 4.4 mg (8%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 1.01-1.12 (4H), 1.73 (1H), 1.95 (2H), 2.09 (2H), 3.44 (1H), 3.53 (1H), 3.78 (1H), 3.92 (1H), 4.21 (1H), 6.50 (1H), 7.21 (1H), 7.70 (2H), 7.74 (1H), 7.85 (2H), 8.07 (2H), 8.17 (1H), 8.63 (2H) ppm.

Intermediate Example 4a

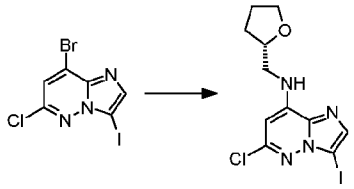
6-Chloro-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-N-[(2S)-tetrahydrofuran-2-ylmethyl]imidazo[1,2-b]pyridazin-8-amine



232 mg (613 µmol) 6-chloro-3-iodo-N-[(2S)-tetrahydrofuran-2-ylmethyl]imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 4b were transformed in analogy to intermediate example 1a to give after working up and purification 118 mg (44%) of the title compound.

Intermediate Example 4b

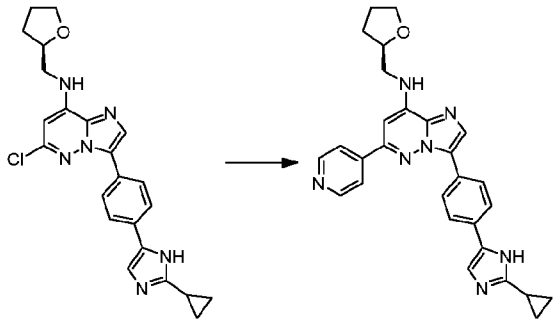
6-Chloro-3-iodo-N-[(2S)-tetrahydrofuran-2-ylmethyl]imidazo[1,2-b]pyridazin-8-amine



500 mg (1,40 mmol) 8-bromo-6-chloro-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 1c were transformed in analogy to intermediate example 1b using 1-[(2S)-tetrahydrofuran-2-yl]methanamine to give after working up and purification 497 mg (94%) of the title compound.

Example 5

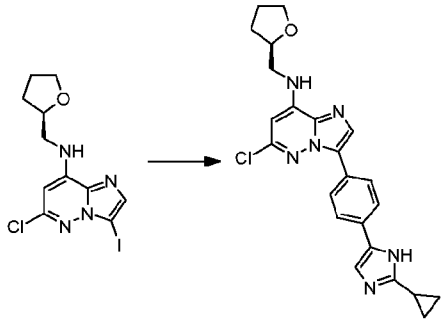
3-[4-(2-Cyclopropyl-1H-imidazol-5-yl)phenyl]-6-(pyridin-4-yl)-N-[(2R)-tetrahydrofuran-2-ylmethyl]imidazo[1,2-b]pyridazin-8-amine



50 mg (115 µmol)
6-chloro-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-N-[(2R)-tetrahydrofuran-2-yl methyl]imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 5a were transformed in analogy to example 1 using pyridin-4-ylboronic acid to give after working up and purification 6.1 mg (11%) of the title compound.

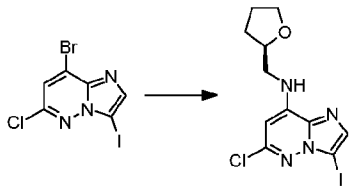
^{1}H-NMR ($CDCl_3$): δ= 1.01-1.12 (4H), 1.73 (1H), 1.95 (2H), 2.09 (2H), 3.44 (1H), 3.53 (1H), 3.78 (1H), 3.92 (1H), 4.21 (1H), 6.50 (1H), 7.21 (1H), 7.70 (2H), 7.74 (1H), 7.85 (2H), 8.07 (2H), 8.17 (1H), 8.63 (2H) ppm.

Intermediate Example 5a
6-Chloro-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-N-[(2R)-tetrahydrofuran-2-yl methyl]imidazo[1,2-b]pyridazin-8-amine



247 mg (652 µmol)
6-chloro-3-iodo-N-[(2R)-tetrahydrofuran-2-ylmethyl]imidazo[1,2-b]pyridazin-8-amin e which was prepared according to intermediate example 5b were transformed in analogy to intermediate example 1a to give after working up and purification 112 mg (39%) of the title compound.

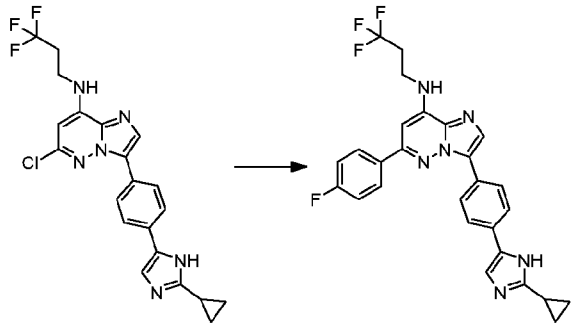
Intermediate Example 5b
6-Chloro-3-iodo-N-[(2R)-tetrahydrofuran-2-ylmethyl]imidazo[1,2-b]pyridazin-8-amine



500 mg (1,40 mmol) 8-bromo-6-chloro-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 1c were transformed in analogy to intermediate example 1b using 1-[(2R)-tetrahydrofuran-2-yl]methanamine to give after working up and purification 513 mg (97%) of the title compound.

Example 6

3-[4-(2-Cyclopropyl-1H-imidazol-5-yl)phenyl]-6-(4-fluorophenyl)-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine

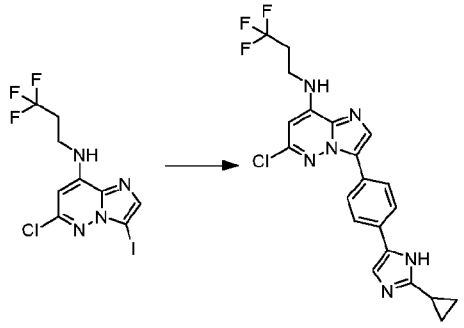


40 mg (90 µmol) 6-chloro-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 6a were transformed in analogy to example 1 using (4-fluorophenyl)boronic acid to give after working up and purification 3.6 mg (7%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.97-1.09 (4H), 2.00 (2H), 2.59 (2H), 3.73 (2H), 5.97 (1H), 6.37 (1H), 7.14-7.26 (3H), 7.75-7.84 (3H), 7.96 (2H), 8.13 (2H) ppm.

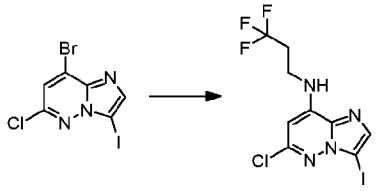
Intermediate Example 6a

6-Chloro-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine



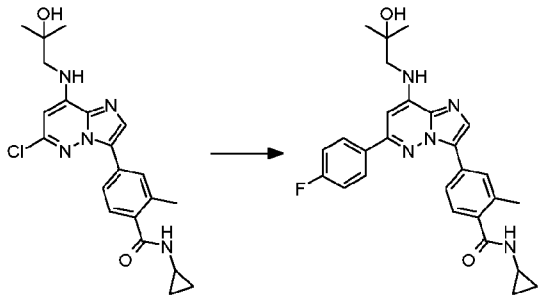
330mg (845 µmol)
6-chloro-3-iodo-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 6b were transformed in analogy to intermediate example 1a to give after working up and purification 220 mg (58%) of the title compound.

Intermediate Example 6b
6-Chloro-3-iodo-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine



1.96 g (5.46 mmol) 8-bromo-6-chloro-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 1c were transformed in analogy to intermediate example 1b using 3,3,3-trifluoropropan-1-amine to give after working up and purification 1.58 g (74%) of the title compound.

Example 7
N-cyclopropyl-4-{6-(4-fluorophenyl)-8-[(2-hydroxy-2-methylpropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

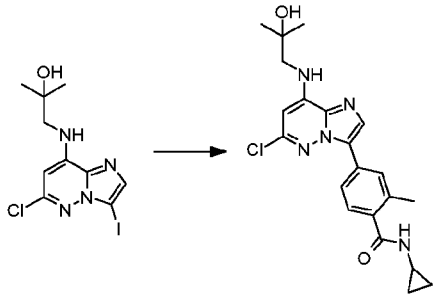


76 mg (184 µmol)
4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 1 using (4-fluorophenyl)boronic acid to give after working up and purification 25.7 mg (30%) of the title compound.

^{1}H-NMR ($CDCl_3/CD_3OD$): δ= 0.61 (2H), 0.86 (2H), 1.37 (6H), 2.47 (3H), 2.88 (1H), 3.33 (2H), 6.38 (1H), 7.13 (2H), 7.39 (1H), 7.69 (1H), 7.83-7.91 (3H), 7.94 (1H) ppm.

Intermediate Example 7a

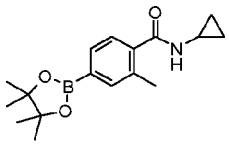
4-{6-Chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



700 mg (1.91 mmol) 1-[(6-chloro-3-iodoimidazo[1,2-b]pyridazin-8-yl)amino]-2-methylpropan-2-ol which was prepared according to intermediate example 1b were transformed in analogy to intermediate example 1a using N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide which was prepared according to intermediate example 7b to give after working up and purification 360 mg (46%) of the title compound.

Intermediate Example 7b

N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide



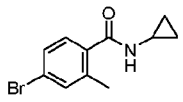
To a solution of 260g (1.02 mol) 4-bromo-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7c in 2L dioxane at 23°C were added 390 g bis-(pinacolato)-diboron, 19.5 g 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, 150.g potassium acetate and 9.37 g tris-(dibenzylidenaceton)-dipalladium(0) and the mixture was refluxed for 6 h. After cooling to 23°C, water and ethyl acetate were added and the mixture stirred for 15 min. The organic phase was washed with water, dried over sodium

sulfate, filtered and evaporated. The residue was purified by chromatography to give 308g (56%) of the title compound.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.59 (2H), 0.85 (2H), 1.33 (6H), 2.41 (3H), 2.87 (1H), 5.94 (1H), 7.28 (1H), 7.60 (1H), 7.63 (1H) ppm.

Intermediate Example 7c

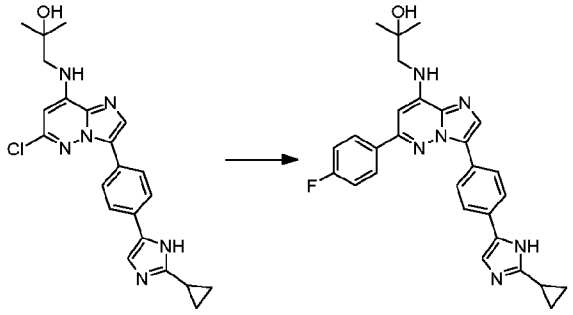
4-Bromo-N-cyclopropyl-2-methylbenzamide



To a stirred solution of 300g (1.4 mol) 4-bromo-2-methylbenzoic acid in 8.4L dichloromethane at 23°C were added 79.6g cyclopropanamine and 320.9g EDC. After stirring overnight, the solution was washed with water and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over sodium sulfate, filtered and evaporated. The remaining solid was triturated with diisopropyl ether, filtered, washed and dried in vaccuo to yield 260g (73%)of the title compound.

Example 8

1-({3-[4-(2-Cyclopropyl-1H-imidazol-5-yl)phenyl]-6-(4-fluorophenyl)imidazo [1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol



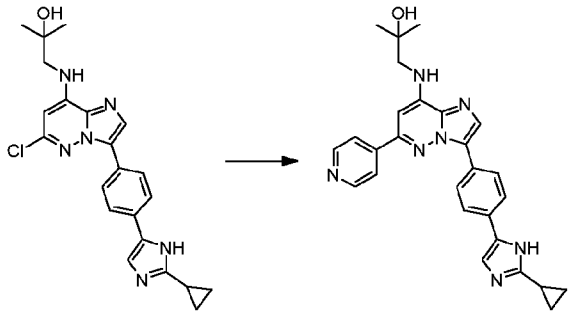
70 mg (166 µmol)

1-({6-chloro-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol which was prepared according to intermediate example 1a were transformed in analogy to example 1 using (4-fluorophenyl)boronic acid to give after working up and purification 4.9 mg (6%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.80-0.94 (4H), 1.18 (6H), 1.93 (1H), 3.39 (2H), 4.79 (1H), 6.77 (1H), 6.86 (1H), 7.21+7.48 (1H), 7.85 (2H), 7.70+7.81 (2H), 7.94+7.99 (1H), 8.06-8.24 (4H), 11.81+12.12 (1H) ppm.

Example 9

1-({3-[4-(2-Cyclopropyl-1H-imidazol-5-yl)phenyl]-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol



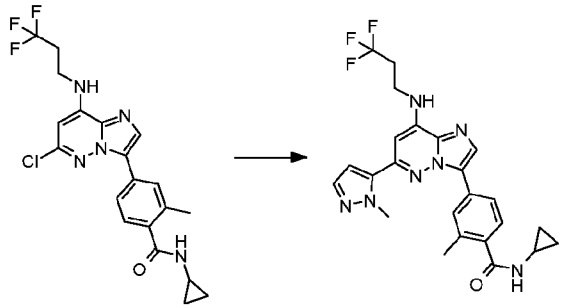
47,5 mg (112 µmol)

1-({6-chloro-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol which was prepared according to intermediate example 1a were transformed in analogy to example 1 using pyridin-4-ylboronic acid to give after working up and purification 12.5 mg (23%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.82-0.92 (4H), 1.19 (6H), 1.93 (1H), 3.42 (2H), 4.79 (1H), 6.89 (1H), 7.01 (1H), 7.22+7.49 (1H), 7.72+7.83 (2H), 7.97-8.08 (3H), 8.15+8.23 (2H), 8.73 (2H), 7.82+12.13 (1H) ppm.

Example 10

N-cyclopropyl-2-methyl-4-{6-(1-methyl-1H-pyrazol-5-yl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide

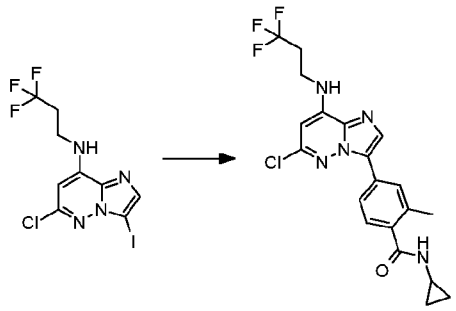


40 mg (91 µmol) 4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 10a were transformed in analogy to example 1 using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole to give after working up and purification 7.2 mg (16%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.64 (2H), 0.90 (2H), 2.52 (3H), 2.58 (2H), 2.93 (1H), 3.72 (2H), 4.20 (3H), 5.95 (1H), 6.01 (1H), 6.28 (1H), 6.66 (1H), 7.42 (1H), 7.55 (1H), 7.79 (1H), 7.85 (1H), 7.89 (1H) ppm.

Intermediate Example 10a

4-{6-Chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

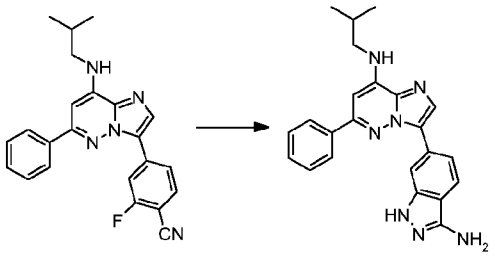


500 mg (1.28 mmol) 6-chloro-3-iodo-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 6b were transformed in analogy to intermediate example 1a using

N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide to give after working up and purification 139 mg (25%) of the title compound.

Example 11

3-(3-Amino-1H-indazol-6-yl)-N-isobutyl-6-phenylimidazo[1,2-b]pyridazin-8-amine

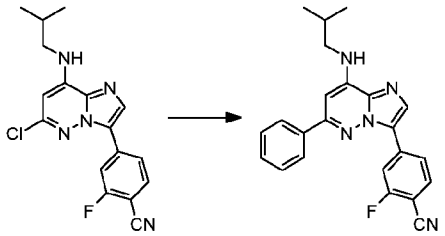


To a solution of 46 mg (119 µmol) 2-fluoro-4-[8-(isobutylamino)-6-phenylimidazo[1,2-b]pyridazin-3-yl]benzonitrile which was prepared according to intermediate example 11a in 2.5 mL n-butanol were added 232 µL hydrazine hydrate and the mixture was heated at 120°C overnight. The precipitate was filtered, washed with 2-propanol and dried to give 26.5 mg (53%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.94 (6H), 2.04 (1H), 3.26 (2H), 5.33 (2H), 6.63 (1H), 7.46-7.58 (5H), 7.74 (1H), 8.00 (1H), 8.07 (2H), 8.38 (1H), 11.53 (1H) ppm.

Intermediate Example 11a

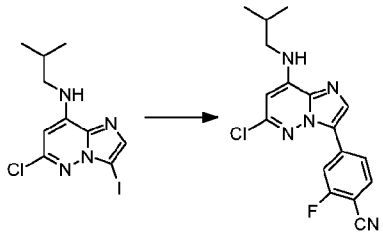
2-Fluoro-4-[8-(isobutylamino)-6-phenylimidazo[1,2-b]pyridazin-3-yl]benzonitrile



100 mg (291 µmol) 4-[6-chloro-8-(isobutylamino)imidazo[1,2-b]pyridazin-3-yl]-2-fluorobenzonitrile which was prepared according to intermediate example 11b were transformed in analogy to example 1 using phenylboronic acid to give after working up and purification 49 mg (44%) of the title compound.

Intermediate Example 11b

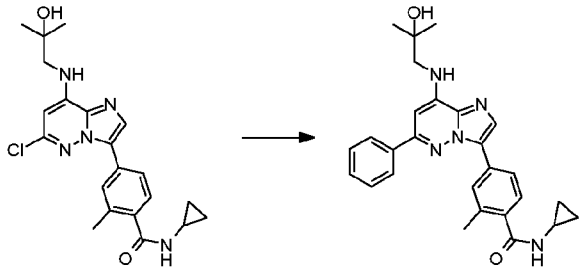
4-[6-Chloro-8-(isobutylamino)imidazo[1,2-b]pyridazin-3-yl]-2-fluorobenzonitrile



500 mg (1.43 mmol) 6-Chloro-3-iodo-N-isobutylimidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 3b were transformed in analogy to intermediate example 1a using (4-cyano-3-fluorophenyl)boronic acid to give after working up and purification 217 mg (44%) of the title compound.

Example 12

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-phenylimidazo[1,2-b] pyridazin-3-yl}-2-methylbenzamide

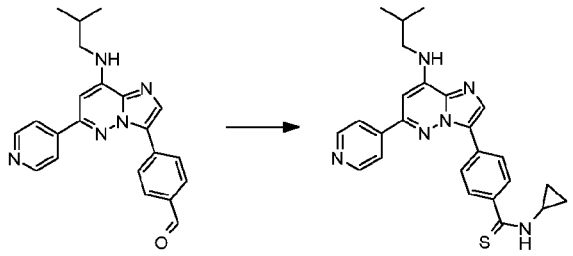


250 mg (604 µmol) 4-{6-Chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 1 using phenylboronic acid to give after working up and purification 48 mg (17%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 1.18 (6H), 2.39 (3H), 2.81 (1H), 3.39 (2H), 4.78 (1H), 6.80 (1H), 6.90 (1H), 7.40 (1H), 7.46-7.55 (3H), 8.00-8.07 (4H), 8.13 (1H), 8.30 (1H) ppm.

Example 13

N-cyclopropyl-4-[8-(isobutylamino)-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl] benzenecarbothioamide

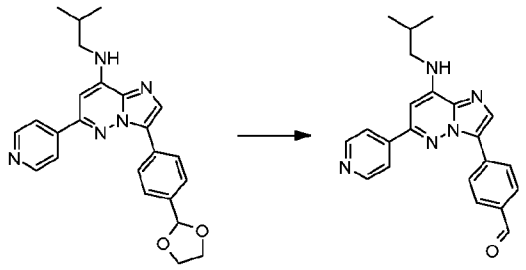


A mixture of 40 mg (108 µmol) 4-[8-(isobutylamino)-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl]benzaldehyde which was prepared according to intermediate example 13a, 3.45 mg sulfur, 37 µL cyclopropanamine and 250 µL dimethyl sulfoxide were heated at 100°C under microwave irradiation for 4 hours. The mixture was stirred at 90°C overnight, the solvent was evaporated and the residue purified by chromatography to give 4.8 mg (10%) of the title compound.

^{1}H-NMR ($CDCl_3/CD_3OD$): δ= 0.80 (2H), 1.03 (2H), 1.08 (6H), 2.08 (1H), 3.21 (2H), 3.40 (1H), 6.40 (1H), 7.78-7.89 (5H), 8.12 (2H), 8.69 (2H) ppm.

Intermediate Example 13a

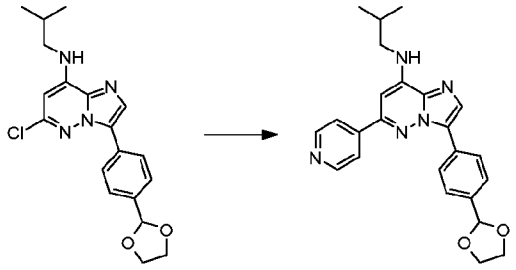
4-[8-(Isobutylamino)-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl]benzaldehyde



To a solution of 63 mg (152 µmol) 3-[4-(1,3-dioxolan-2-yl)phenyl]-N-isobutyl-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 13b, in 2.8 mL acetone were added 190 µL 4N hydrochloric acid and the mixture was stirred at 23°C for 2 hours. Saturated hydrogen carbonate solution was added and the mixture was extracted with dichloromethane. The organic phase was dried over sodium sulfate. After filtration and removal of solvent the residue was purified by chromatography to give 41 mg (73%) of the title compound.

Intermediate Example 13b

3-[4-(1,3-Dioxolan-2-yl)phenyl]-N-isobutyl-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-8-amine

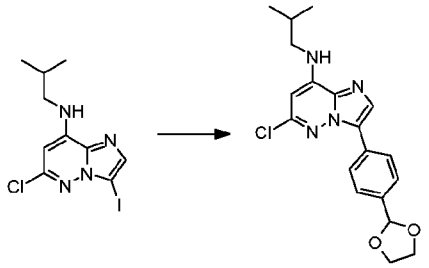


105 mg (282 µmol)

6-chloro-3-[4-(1,3-dioxolan-2-yl)phenyl]-N-isobutylimidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 13c were transformed in analogy to example 1 using pyridin-4-ylboronic acid to give after working up and purification 64 mg (55%) of the title compound.

Intermediate Example 13c

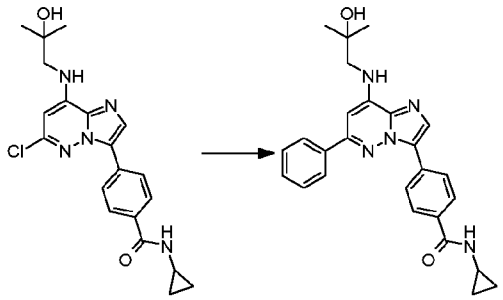
6-Chloro-3-[4-(1,3-dioxolan-2-yl)phenyl]-N-isobutylimidazo[1,2-b]pyridazin-8-amine



500 mg (1.43 mmol) 6-Chloro-3-iodo-N-isobutylimidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 3b were transformed in analogy to intermediate example 1a using 2-[4-(1,3-dioxolan-2-yl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane to give after working up and purification 314 mg (47%) of the title compound.

Example 14

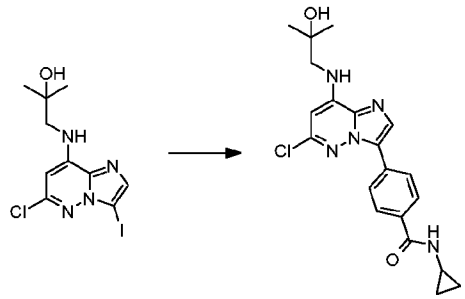
N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-phenylimidazo[1,2-b]pyridazin-3-yl}benzamide



176 mg (440 µmol) which
4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide was prepared according to intermediate example 14a were transformed in analogy to example 1 using phenylboronic acid to give after working up and purification 42 mg (21%) of the title compound.

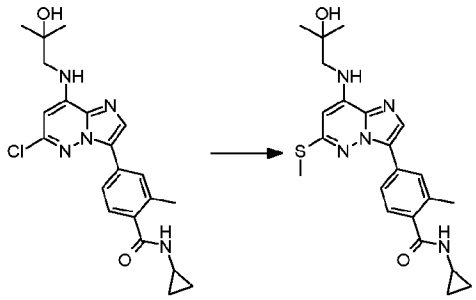
^{1}H-NMR (DMSO-d6): δ= 0.56 (2H), 0.67 (2H), 1.19 (6H), 2.85 (1H), 3.40 (2H), 4.78 (1H), 6.82 (1H), 6.93 (1H), 7.46-7.55 (3H), 7.93 (2H), 8.05 (2H), 8.09 (1H), 8.33 (2H), 8.45 (1H) ppm.

Intermediate Example 14a
4-{6-Chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide



976 mg (2.66 mmol)
1-[(6-chloro-3-iodoimidazo[1,2-b]pyridazin-8-yl)amino]-2-methylpropan-2-ol which was prepared according to intermediate example 1b were transformed in analogy to intermediate example 1a using [4-(cyclopropylcarbamoyl)phenyl]boronic acid to give after working up and purification 602 mg (57%) of the title compound.

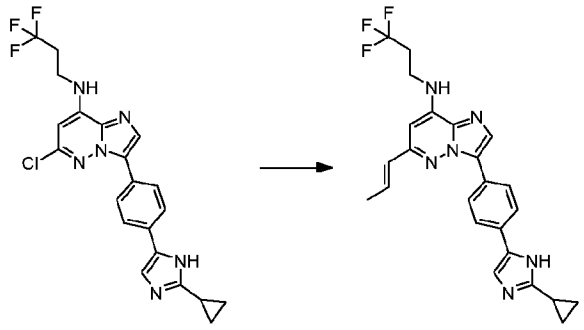
Example 15
N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(methylsulfanyl) imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



To a solution of 83 mg (201 µmol) 4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a in 1,0 mL dimethyl sulfoxide were added 70 mg sodium methanethiolate and the mixture was heated under microwave irradiation at 70°C for 1 hour. The mixture was poured into water and extracted with dichloromethane and methanol. The organic layer was washed with brine and dried over sodium sulfate. After filtration and removal of the solvent the residue was purified by recrystallisation to give 46.7 mg (55%) of the title compound.

Example 16

3-[4-(2-Cyclopropyl-1H-imidazol-5-yl)phenyl]-6-[(1E)-prop-1-en-1-yl]-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine

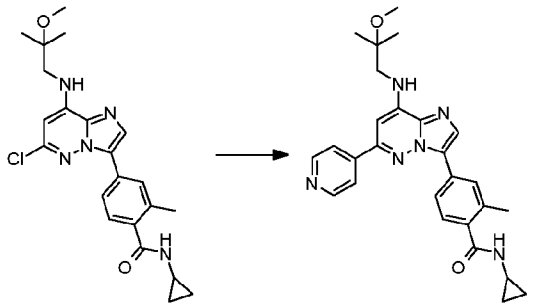


35 mg (78 µmol) 6-chloro-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 6a were transformed in analogy to example 1 using (1E)-prop-1-en-1-ylboronic acid to give after working up and purification 3.6 mg (10%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.95-1.04 (4H), 1.95 (3H), 2.00 (1H), 2.55 (2H), 3.62 (2H), 6.10 (1H), 6.46 (1H), 6.61 (1H), 7.16 (1H), 7.67 (1H), 7.70 (2H), 8.05 (2H) ppm.

Example 17

N-cyclopropyl-4-{8-[(2-methoxy-2-methylpropyl)amino]-6-(pyridin-4-yl) imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

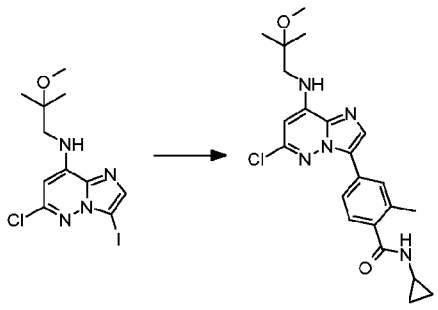


60 mg (140 µmol) 4-{6-Chloro-8-[(2-methoxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 17a were transformed in analogy to example 1 using pyridin-4-ylboronic acid to give after working up and purification 18.7 mg (28%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.64 (2H), 0.90 (2H), 1.33 (6H), 2.54 (3H), 2.93 (1H), 3.28 (3H), 3.38 (2H), 6.11 (1H), 6.18 (1H), 6.42 (1H), 7.44 (1H), 7.80-7.85 (3H), 7.92 (1H), 8.00 (1H), 8.71 (2H) ppm.

Intermediate Example 17a

4-{6-Chloro-8-[(2-methoxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

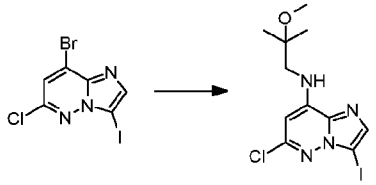


145 mg (380 µmol) 6-chloro-3-iodo-N-(2-methoxy-2-methylpropyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 17b were transformed in analogy to intermediate example 1a using

N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide to give after working up and purification 131 mg (81%) of the title compound.

Intermediate Example 17b

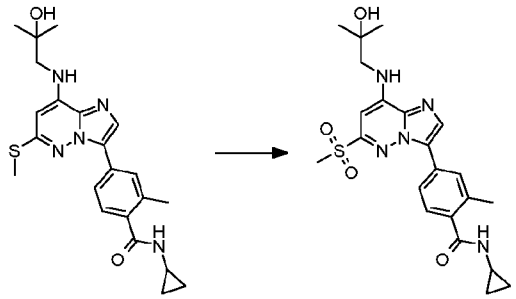
6-Chloro-3-iodo-N-(2-methoxy-2-methylpropyl)imidazo[1,2-b]pyridazin-8-amine



250 mg (698 µmol) 8-bromo-6-chloro-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 1c were transformed in analogy to intermediate example 1b using 2-methoxy-2-methylpropan-1-amine to give after working up and purification 260 mg (98%) of the title compound.

Example 18

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(methylsulfonyl) imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

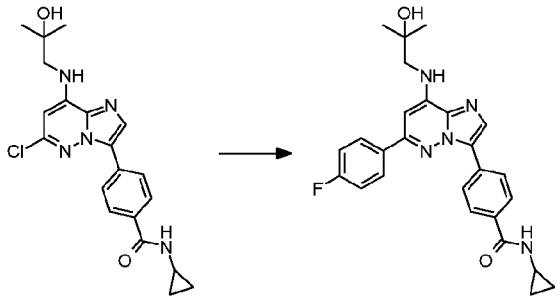


To a solution of 38.7 mg (91 µmol) N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(methylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 15 in 1.2 mL N,N-dimethylformamide were added 168 mg Oxone and the mixture was stirred at 23°C for 2.5 days. Water was added and the mixture was extracted with dichloromethane. The organic phase was washed with water and dried over sodium sulfate. After filtration and removal of solvent the residue was purified by chromatography to give 18.5 mg (39%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.65 (2H), 1.15 (6H), 2.37 (3H), 2.80 (1H), 3.34 (2H), 3.38 (3H), 4.79 (1H), 6.76 (1H), 7.40 (1H), 7.71 (1H), 7.95 (1H), 7.99 (1H), 8.16 (1H), 8.32 (1H) ppm.

Example 19

N-cyclopropyl-4-{6-(4-fluorophenyl)-8-[(2-hydroxy-2-methylpropyl)amino] imidazo[1,2-b]pyridazin-3-yl}benzamide



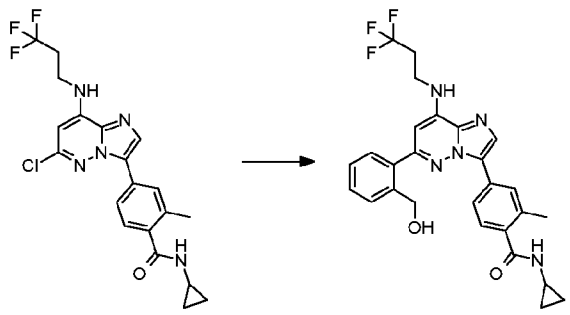
200 mg (500 µmol)

4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide which was prepared according to intermediate example 14a were transformed in analogy to example 1 using (4-fluorophenyl)boronic acid to give after working up and purification 136 mg (59%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.56 (2H), 0.68 (2H), 1.18 (6H), 2.85 (1H), 3.39 (2H), 4.79 (1H), 6.81 (1H), 6.94 (1H), 7.35 (2H), 7.93 (2H), 8.09 (1H), 8.11 (2H), 8.31 (2H), 8.46 (1H) ppm.

Example 20

N-cyclopropyl-4-{6-[2-(hydroxymethyl)phenyl]-8-[(3,3,3-trifluoropropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



172 mg (393 µmol)

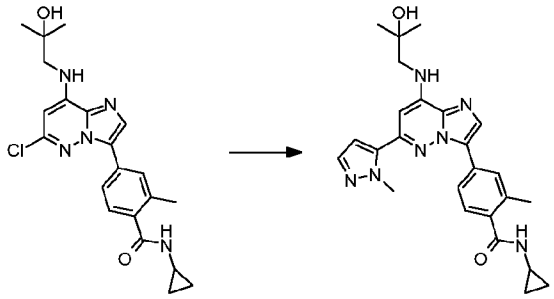
4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopr

opyl-2-methylbenzamide which was prepared according to intermediate example 10a were transformed in analogy to example 1 using [2-(hydroxymethyl)phenyl] boronic acid to give after working up and purification 29.1 mg (14%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.58 (2H), 0.85 (2H), 2.48 (3H), 2.58 (2H), 2.88 (1H), 3.72 (2H), 3.96 (1H), 4.41 (2H), 6.16 (1H), 6.19 (1H), 6.24 (1H), 7.38 (1H), 7.45-7.52 (3H), 7.60 (1H), 7.61 (1H), 7.70 (1H), 7.72 (1H) ppm.

Example 21

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

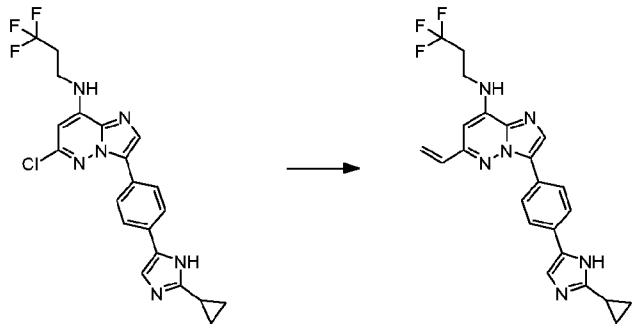


100 mg (242 µmol) 4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 1 using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole to give after working up and purification 35.9 mg (31%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.65 (2H), 1.17 (6H), 2.35 (3H), 2.80 (1H), 3.35 (2H), 4.13 (3H), 4.76 (1H), 6.62 (1H), 6.89 (1H), 7.00 (1H), 7.37 (1H), 7.51 (1H), 7.93 (1H), 7.97 (1H), 7.98 (1H), 8.30 (1H) ppm.

Example 22

3-[4-(2-Cyclopropyl-1H-imidazol-5-yl)phenyl]-6-ethenyl-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine

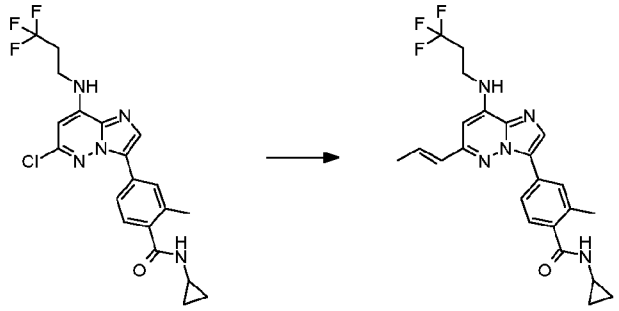


55 mg (123 µmol)
6-chloro-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 6a were transformed in analogy to example 1 using 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane to give after working up and purification 3.2 mg (6%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.95-1.03 (4H), 1.99 (1H), 2.56 (2H), 3.64 (2H), 5.58 (1H), 6.07 (1H), 6.18 (1H), 6.76 (1H), 7.16 (1H), 7.68-7.74 (3H), 8.05 (2H) ppm.

Example 23

N-cyclopropyl-2-methyl-4-{6-[(1E/Z)-prop-1-en-1-yl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide

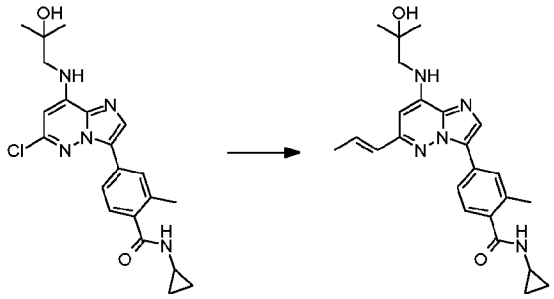


75 mg (171 µmol)
4-{6-Chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 10a were transformed in analogy to example 1 using (1E)-prop-1-en-1-ylboronic acid to give after working up and purification 3.0 mg (4%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.63 (2H), 0.90 (2H), 1.98 (3H), 2.47-2.65 (2H), 2.54 (3H), 2.92 (1H), 3.67 (2H), 5.91 (1H), 5.98 (1H), 6.46 (1H), 6.60+6.66 (1H), 7.25 (1H), 7.43 (1H), 7.73 (1H), 7.90 (1H), 7.96 (1H) ppm.

Example 24

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(1E/Z)-prop-1-en-1-yl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

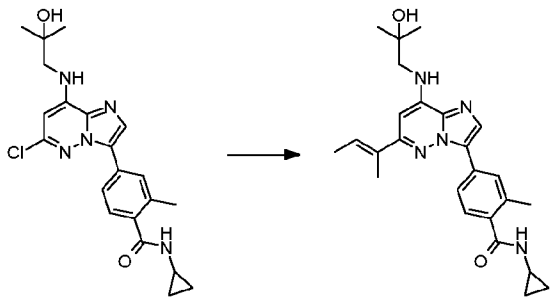


75 mg (181 µmol) 4-{6-Chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 1 using (1E)-prop-1-en-1-ylboronic acid to give after working up and purification 22 mg (29%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.63 (2H), 0.89 (2H), 1.43 (6H), 1.95+2.16 (3H), 2.51 (3H), 2.92 (1H), 3.32 (2H), 4.33 (1H), 5.99 (1H), 6.07+6.14 (1H), 6.37 (1H), 6.41 (1H), 6.57+6.63 (1H), 7.39 (1H), 7.66+7.70 (1H), 7.84+7.87 (1H), 7.94 (1H) ppm.

Example 25

4-{6-[(2E)-But-2-en-2-yl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

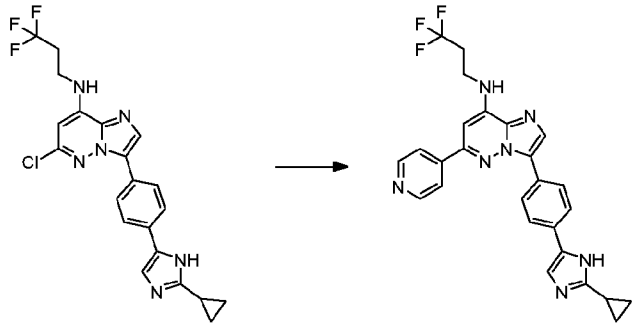


75 mg (181 µmol) 4-{6-Chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 1 to give after working up and purification 7.0 mg (8%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.62 (2H), 0.88 (2H), 1.45 (6H), 1.79 (3H), 2.11 (3H), 2.50 (3H), 2.91 (1H), 3.32 (2H), 5.02 (1H), 5.77 (1H), 5.97 (1H), 6.00 (1H), 6.50 (1H), 7.38 (1H), 7.70 (1H), 7.89 (1H), 7.91 (1H) ppm.

Example 26

3-[4-(2-Cyclopropyl-1H-imidazol-5-yl)phenyl]-6-(pyridin-4-yl)-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine



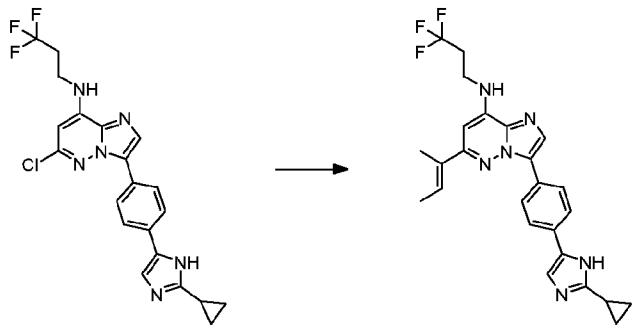
70 mg (157 µmol)

6-Chloro-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 6a were transformed in analogy to example 1 using pyridin-4-ylboronic acid to give after working up and purification 3.2 mg (4%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.92-0.98 (4H), 1.98 (1H), 2.58 (2H), 3.32 (2H), 3.69 (2H), 6.42 (1H), 7.15 (1H), 7.72 (2H), 7.75 (1H), 7.87 (2H), 8.04 (2H), 8.65 (2H) ppm.

Example 27

6-[(2E)-But-2-en-2-yl]-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine



50 mg (112 µmol)

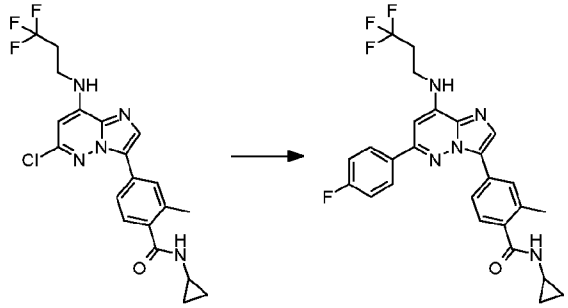
6-Chloro-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-N-(3,3,3-trifluoropropyl)imid

azo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 6a were transformed in analogy to example 1 to give after working up and purification 3.0 mg (5%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.95-1.02 (4H), 1.78 (3H), 1.99 (1H), 2.12 (3H), 2.46-2.63 (2H), 3.62 (2H), 5.78 (1H), 5.96 (1H), 7.16 (1H), 7.69 (2H), 7.73 (1H), 8.05 (2H) ppm.

Example 28

N-cyclopropyl-4-{6-(4-fluorophenyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo [1,2-b]pyridazin-3-yl}-2-methylbenzamide

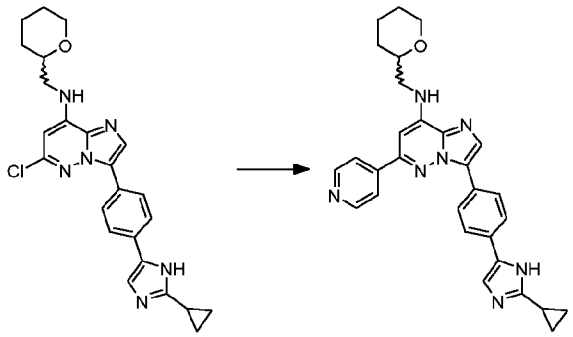


50 mg (114 µmol) 4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 10a were transformed in analogy to example 1 using (4-fluorophenyl)boronic acid to give after working up and purification 5.4 mg (9%) of the title compound.

^{1}H-NMR ($CDCl_3$/CD_3OD): δ= 0.59 (2H), 0.86 (2H), 2.48 (3H), 2.58 (2H), 2.86 (1H), 3.68 (2H), 6.36 (1H), 7.16 (2H), 7.41 (1H), 7.74 (1H), 7.85-8.03 (4H) ppm.

Example 29

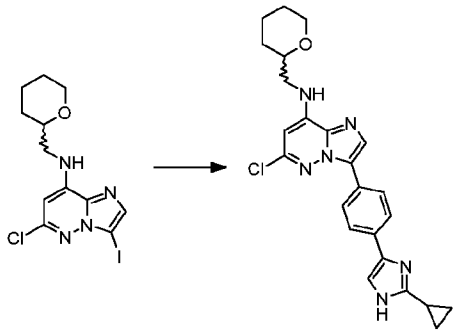
(RS) 3-[4-(2-Cyclopropyl-1H-imidazol-5-yl)phenyl]-6-(pyridin-4-yl)-N-(tetrahydro-2H-pyran-2-ylmethyl)imidazo[1,2-b]pyridazin-8-amine



53 mg (118 µmol)
(RS)-6-Chloro-3-[4-(2-cyclopropyl-1H-imidazol-4-yl)phenyl]-N-(tetrahydro-2H-pyran-2-ylmethyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 29a were transformed in analogy to example 1 using pyridin-4-ylboronic acid to give after working up and purification 6.2 mg (10%) of the title compound.

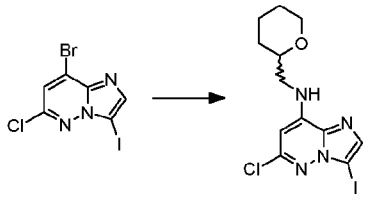
^{1}H-NMR ($CDCl_3$): δ= 0.99-1.09 (4H), 1.45-2.07 (7H), 3.34-3.55 (3H), 3.67 (1H), 4.06 (1H), 6.26 (1H), 6.44 (1H), 7.24 (1H), 7.79 (2H), 7.83 (1H), 7.88 (2H), 8.13 (2H), 8.74 (2H) ppm.

Intermediate Example 29a
(RS)-6-Chloro-3-[4-(2-cyclopropyl-1H-imidazol-4-yl)phenyl]-N-(tetrahydro-2H-pyran-2-ylmethyl)imidazo[1,2-b]pyridazin-8-amine



105 mg (267 µmol)
(RS)-6-chloro-3-iodo-N-(tetrahydro-2H-pyran-2-ylmethyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 29b were transformed in analogy to intermediate example 1a to give after working up and purification 61 mg (51%) of the title compound.

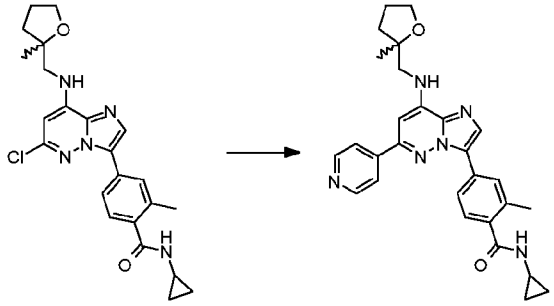
Intermediate Example 29b
(RS)-6-Chloro-3-iodo-N-(tetrahydro-2H-pyran-2-ylmethyl)imidazo[1,2-b]pyridazin-8-amine



530 mg (1.48 mmol) 8-bromo-6-chloro-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 1c were transformed in analogy to intermediate example 1b using 1-[(2RS)-tetrahydro-2H-pyran-2-yl]methanamine to give after working up and purification 214 mg (37%) of the title compound.

Example 30

(RS)-N-cyclopropyl-2-methyl-4-[8-{[(2-methyltetrahydrofuran-2-yl)methyl] amino}-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl]benzamide

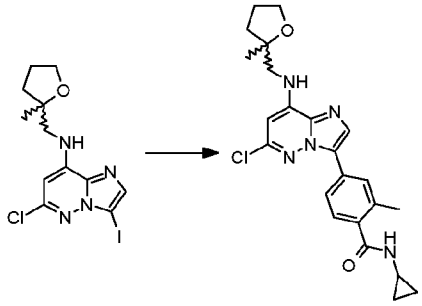


50 mg (114 µmol) (RS)-4-(6-Chloro-8-{[(2-methyltetrahydrofuran-2-yl)methyl]amino}imidazo[1,2-b] pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 30a were transformed in analogy to example 1 using pyridin-4-ylboronic acid to give after working up and purification 12.5 mg (22%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.64 (2H), 0.89 (2H), 1.35 (3H), 1.81 (1H), 1.91-2.10 (3H), 2.54 (3H), 2.93 (1H), 3.45 (2H), 3.93 (2H), 6.10 (1H), 6.20 (1H), 6.50 (1H), 7.44 (1H), 7.79-7.84 (3H), 7.92 (1H), 7.99 (1H), 8.71 (2H) ppm.

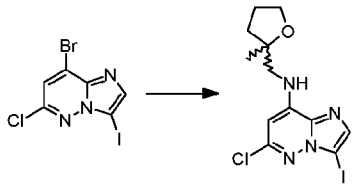
Intermediate Example 30a

(RS)-4-(6-Chloro-8-{[(2-methyltetrahydrofuran-2-yl)methyl]amino}imidazo[1,2-b] pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide



150 mg (382 µmol)
(RS)-6-chloro-3-iodo-N-[(2-methyltetrahydrofuran-2-yl)methyl]imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 30b were transformed in analogy to intermediate example 1a using
N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide to give after working up and purification 110 mg (65%) of the title compound.

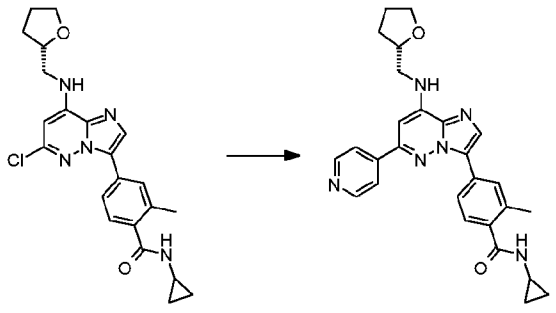
Intermediate Example 30b
(RS)
6-Chloro-3-iodo-N-[(2-methyltetrahydrofuran-2-yl)methyl]imidazo[1,2-b]pyridazin-8-amine



250 mg (698 µmol) 8-bromo-6-chloro-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 1c were transformed in analogy to intermediate example 1b using
1-[(2RS)-2-methyltetrahydrofuran-2-yl]methanamine to give after working up and purification 262 mg (96%) of the title compound.

Example 31

N-cyclopropyl-2-methyl-4-[6-(pyridin-4-yl)-8-{[(2S)-tetrahydrofuran-2-ylmethyl]amino}imidazo[1,2-b]pyridazin-3-yl]benzamide

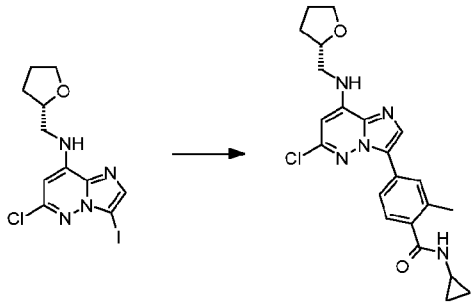


49 mg (115 µmol)
4-(6-Chloro-8-{[(2S)-tetrahydrofuran-2-ylmethyl]amino}imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate

example 31a were transformed in analogy to example 1 using pyridin-4-ylboronic acid to give after working up and purification 3.6 mg (6%) of the title compound. ^{1}H-NMR ($CDCl_3$): δ= 0.64 (2H), 0.90 (2H), 1.75 (1H), 1.98 (2H), 2.11 (1H), 2.55 (3H), 2.93 (1H), 3.46 (1H), 3.60 (1H), 3.82 (1H), 3.96 (1H), 4.24 (1H), 6.01 (1H), 6.23 (1H), 6.50 (1H), 7.45 (1H), 7.83 (1H), 7.84 (2H), 7.93 (1H), 8.00 (1H), 8.74 (2H) ppm.

Intermediate Example 31a

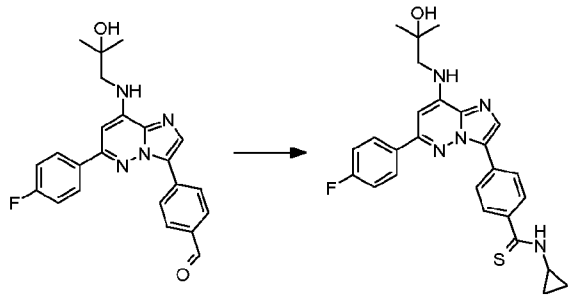
4-(6-Chloro-8-{[(2S)-tetrahydrofuran-2-ylmethyl]amino}imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide



232 mg (613 µmol) 6-chloro-3-iodo-N-[(2S)-tetrahydrofuran-2-ylmethyl]imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 4b were transformed in analogy to intermediate example 1a using N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide to give after working up and purification 98 mg (38%) of the title compound.

Example 32

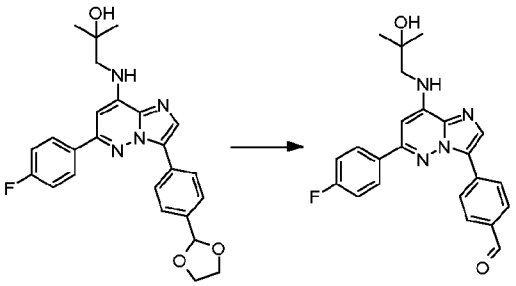
N-cyclopropyl-4-{6-(4-fluorophenyl)-8-[(2-hydroxy-2-methylpropyl)amino] imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide



33 mg (82 µmol)
4-{6-(4-fluorophenyl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzaldehyde which was prepared according to intermediate example 32a were transformed in analogy to example 13 to give after working up and purification 3.3 mg (8%) of the title compound.

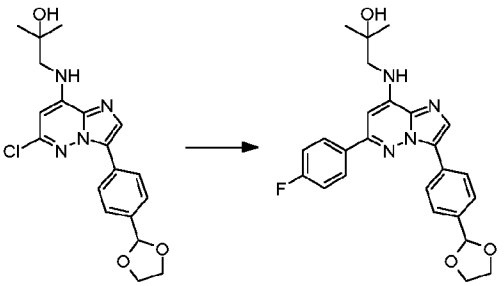
^{1}H-NMR (DMSO-d6): δ= 0.75-0.88 (4H), 1.18 (6H), 3.40 (2H), 3.47 (1H), 4.78 (1H), 6.81 (1H), 6.95 (1H), 7.35 (2H), 7.84 (2H), 8.07 (1H), 8.11 (2H), 8.26 (2H), 10.16 (1H) ppm.

Intermediate Example 32a
4-{6-(4-Fluorophenyl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzaldehyde



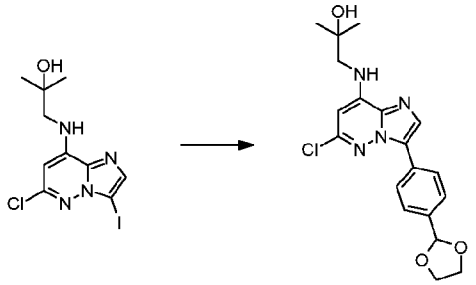
48 mg (107 µmol)
1-({3-[4-(1,3-dioxolan-2-yl)phenyl]-6-(4-fluorophenyl)imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol which was prepared according to intermediate example 32b were transformed in analogy to intermediate example 13a to give after working up and purification 34.6 mg (76%) of the title compound.

Intermediate Example 32b
1-({3-[4-(1,3-Dioxolan-2-yl)phenyl]-6-(4-fluorophenyl)imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol



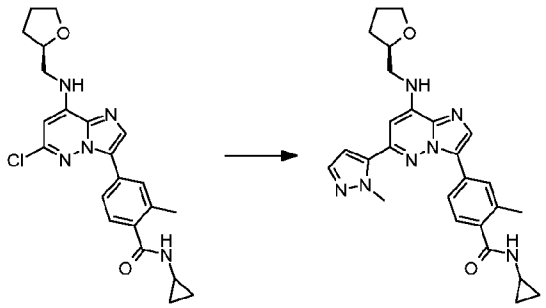
100 mg (257 µmol)
1-({6-chloro-3-[4-(1,3-dioxolan-2-yl)phenyl]imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol which was prepared according to intermediate example 32c were transformed in analogy to example 1 using (4-fluorophenyl)boronic acid to give after working up and purification 50.0 mg (43%) of the title compound.

Intermediate Example 32c
1-({3-[4-(1,3-Dioxolan-2-yl)phenyl]-6-(4-fluorophenyl)imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol



2.65 g (7.2 mmol)
1-[(6-chloro-3-iodoimidazo[1,2-b]pyridazin-8-yl)amino]-2-methylpropan-2-ol which was prepared according to intermediate example 1b were transformed in analogy to intermediate example 1a using
2-[4-(1,3-dioxolan-2-yl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane to give after working up and purification 1.36 g (48%) of the title compound.

Example 33
N-cyclopropyl-2-methyl-4-[6-(1-methyl-1H-pyrazol-5-yl)-8-{[(2R)-tetrahydrofuran-2-ylmethyl]amino}imidazo[1,2-b]pyridazin-3-yl]benzamide



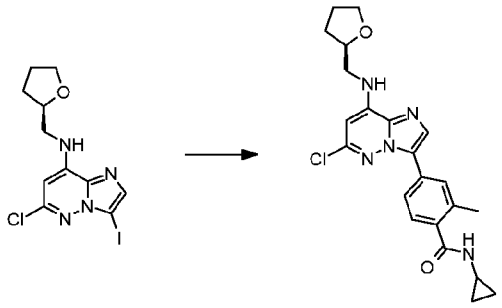
63 mg (148 µmol)
4-(6-chloro-8-{[(2R)-tetrahydrofuran-2-ylmethyl]amino}imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate

example 33a were transformed in analogy to example 1 using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole to give after working up and purification 10.6 mg (14%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.64 (2H), 0.89 (2H), 1.72 (1H), 1.97 (2H), 2.09 (1H), 2.50 (3H), 2.92 (1H), 3.40 (1H), 3.53 (1H), 3.81 (1H), 3.95 (1H), 4.17 (3H), 4.21 (1H), 6.05 (1H), 6.17 (1H), 6.30 (1H), 6.63 (1H), 7.39 (1H), 7.52 (1H), 7.76 (1H), 7.83 (1H), 7.88 (1H) ppm.

Intermediate Example 33a

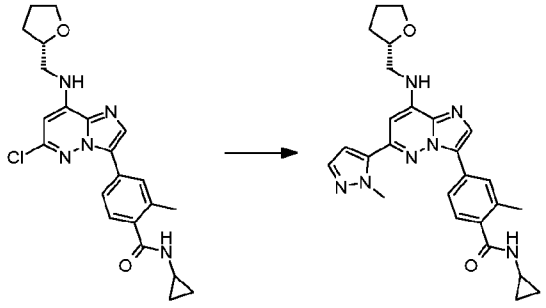
4-(6-Chloro-8-{[(2R)-tetrahydrofuran-2-ylmethyl]amino}imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide



247 mg (652 µmol) 6-chloro-3-iodo-N-[(2R)-tetrahydrofuran-2-ylmethyl]imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 5b were transformed in analogy to intermediate example 1a using N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide to give after working up and purification 127 mg (46%) of the title compound.

Example 34

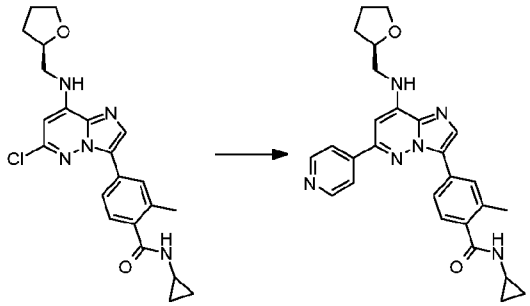
N-cyclopropyl-2-methyl-4-[6-(1-methyl-1H-pyrazol-5-yl)-8-{[(2S)-tetrahydrofuran-2-ylmethyl]amino}imidazo[1,2-b]pyridazin-3-yl]benzamide



49 mg (115 µmol)
4-(6-chloro-8-{[(2S)-tetrahydrofuran-2-ylmethyl]amino}imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 31a were transformed in analogy to example 1 using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole to give after working up and purification 8.5 mg (15%) of the title compound.
^{1}H-NMR ($CDCl_3$): δ= 0.64 (2H), 0.89 (2H), 1.72 (1H), 1.97 (2H), 2.09 (1H), 2.50 (3H), 2.92 (1H), 3.40 (1H), 3.53 (1H), 3.81 (1H), 3.95 (1H), 4.17 (3H), 4.21 (1H), 6.05 (1H), 6.17 (1H), 6.30 (1H), 6.63 (1H), 7.39 (1H), 7.52 (1H), 7.76 (1H), 7.83 (1H), 7.88 (1H) ppm.

Example 35

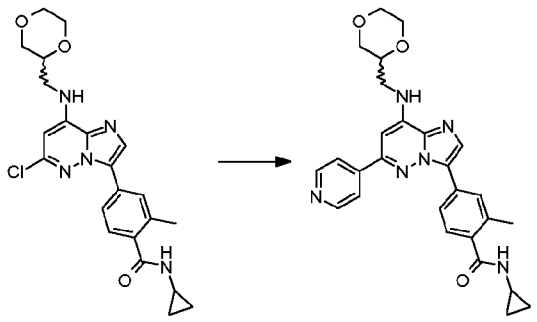
N-cyclopropyl-2-methyl-4-[6-(pyridin-4-yl)-8-{[(2R)-tetrahydrofuran-2-ylmethyl]amino}imidazo[1,2-b]pyridazin-3-yl]benzamide



63 mg (148 µmol)
4-(6-chloro-8-{[(2R)-tetrahydrofuran-2-ylmethyl]amino}imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 33a were transformed in analogy to example 1 using pyridin-4-ylboronic acid to give after working up and purification 4.2 mg (6%) of the title compound.
^{1}H-NMR ($CDCl_3$): δ= 0.64 (2H), 0.90 (2H), 1.75 (1H), 1.98 (2H), 2.11 (1H), 2.55 (3H), 2.93 (1H), 3.46 (1H), 3.59 (1H), 3.82 (1H), 3.96 (1H), 4.24 (1H), 6.02 (1H), 6.20 (1H), 6.49 (1H), 7.45 (1H), 7.83 (1H), 7.84 (2H), 7.93 (1H), 8.01 (1H), 8.73 (2H) ppm.

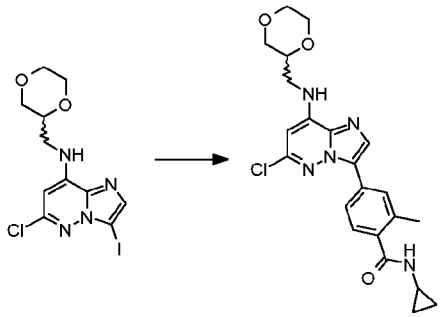
Example 36

(RS)-N-cyclopropyl-4-{8-[(1,4-dioxan-2-ylmethyl)amino]-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



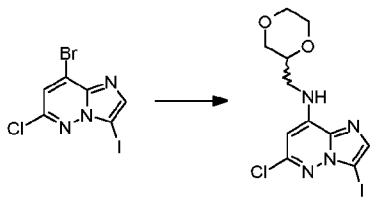
88 mg (199 µmol)
(RS)-4-{6-chloro-8-[(1,4-dioxan-2-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 36a were transformed in analogy to example 1 using pyridin-4-ylboronic acid to give after working up and purification 2.9 mg (3%) of the title compound.
^{1}H-NMR ($CDCl_3$): δ= 0.62 (2H), 0.88 (2H), 2.52 (3H), 2.90 (1H), 3.36-4.01 (9H), 6.06 (1H), 6.23 (1H), 6.46 (1H), 7.44 (1H), 7.80 (1H), 7.84 (2H), 7.90 (1H), 7.98 (1H), 8.70 (2H) ppm.

Intermediate Example 36a
(RS)-4-{6-Chloro-8-[(1,4-dioxan-2-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



200 mg (507 µmol)
(RS)-6-chloro-N-(1,4-dioxan-2-ylmethyl)-3-iodoimidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 36b were transformed in analogy to intermediate example 1a using N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide to give after working up and purification 93.6 mg (42%) of the title compound.

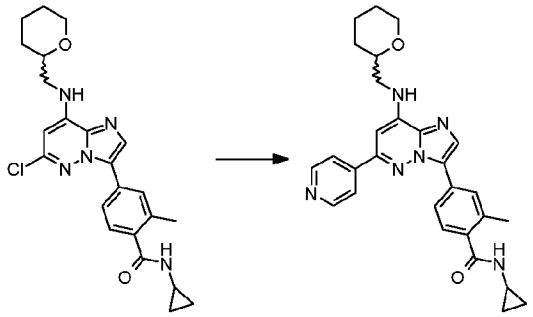
Intermediate Example 36b
(RS)-6-Chloro-N-(1,4-dioxan-2-ylmethyl)-3-iodoimidazo[1,2-b]pyridazin-8-amine



500 mg (1.40 mmol) 8-bromo-6-chloro-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 1c were transformed in analogy to intermediate example 1b using 1-[(2RS)-1,4-dioxan-2-yl]methanamine to give after working up and purification 520 mg (94%) of the title compound.

Example 37

(RS)-N-cyclopropyl-2-methyl-4-{6-(pyridin-4-yl)-8-[(tetrahydro-2H-pyran-2-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide



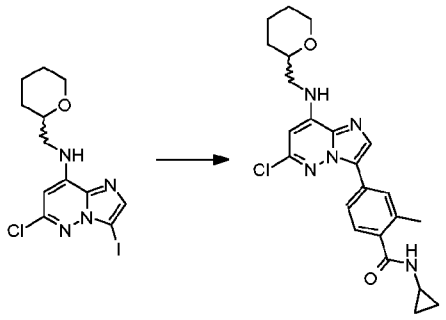
63 mg (143µmol) which

(RS)-4-{6-chloro-8-[(tetrahydro-2H-pyran-2-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide was prepared according to intermediate example 37a were transformed in analogy to example 1 using pyridin-4-ylboronic acid to give after working up and purification 4.0 mg (5%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.63 (2H), 0.88 (2H), 1.40-2.03 (6H), 2.53 (3H), 2.91 (1H), 3.33-3.55 (3H), 3.66 (1H), 4.05 (1H), 6.18 (1H), 6.43 (1H), 6.47 (1H), 7.44 (1H), 7.80 (1H), 7.83 (2H), 7.91 (1H), 7.98 (1H), 8.70 (2H) ppm.

Intermediate Example 37a

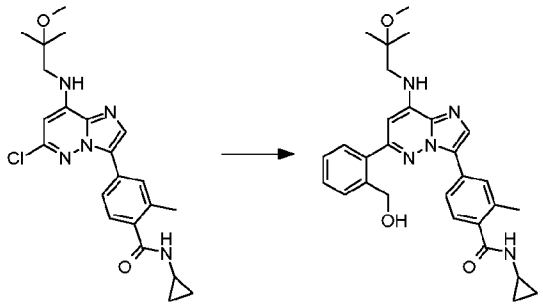
(RS)-4-{6-Chloro-8-[(tetrahydro-2H-pyran-2-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



100 mg (255 µmol)
6-chloro-3-iodo-N-(tetrahydro-2H-pyran-2-ylmethyl)imidazo[1,2-b]pyridazin-8-amin
e which was prepared according to intermediate example 29b were transformed in
analogy to intermediate example 1a using
N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide
to give after working up and purification 68 mg (61%) of the title compound.

Example 38

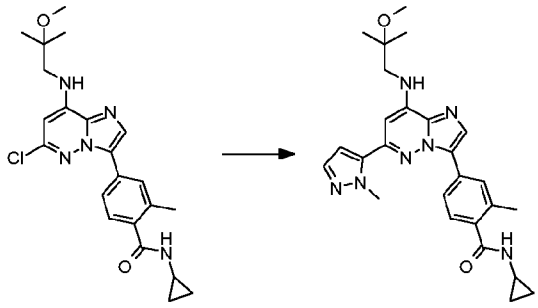
**N-cyclopropyl-4-{6-[2-(hydroxymethyl)phenyl]-8-[(2-methoxy-2-methylpropyl)
amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide**



62 mg (145 µmol)
4-{6-chloro-8-[(2-methoxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cy
clopropyl-2-methylbenzamide which was prepared according to intermediate
example 17a were transformed in analogy to example 1 using
[2-(hydroxymethyl)phenyl] boronic acid to give after working up and purification
24.8 mg (33%) of the title compound.
^{1}H-NMR ($CDCl_3$): δ= 0.58 (2H), 0.84 (2H), 1.31 (6H), 2.47 (3H), 2.87 (1H), 3.28 (3H),
3.34 (2H), 4.13 (1H), 4.38 (2H), 6.19 (1H), 6.21 (1H), 6.25 (1H), 7.36 (1H),
7.42-7.49 (3H), 7.59 (1H), 7.61 (1H), 7.70 (1H), 7.72 (1H) ppm.

Example 39

N-cyclopropyl-4-{8-[(2-methoxy-2-methylpropyl)amino]-6-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



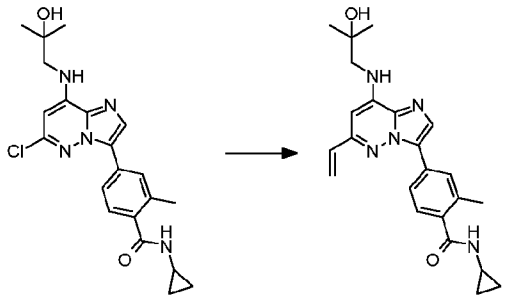
70 mg (164 µmol)

4-{6-chloro-8-[(2-methoxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 17a were transformed in analogy to example 1 using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole to give after working up and purification 30 mg (37%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.63 (2H), 0.89 (2H), 1.31 (6H), 2.50 (3H), 2.91 (1H), 3.27 (3H), 3.32 (2H), 4.16 (3H), 6.10 (1H), 6.17 (1H), 6.25 (1H), 6.62 (1H), 7.38 (1H), 7.51 (1H), 7.76 (1H), 7.83 (1H), 7.87 (1H) ppm.

Example 40

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-vinylimidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



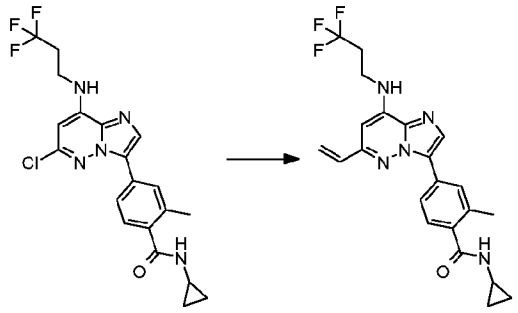
100 mg (242 µmol)

4-{6-Chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 1 using 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane to give after working up and purification 13 mg (12%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.63 (2H), 0.89 (2H), 1.43 (6H), 2.52 (3H), 2.92 (1H), 3.35 (2H), 5.56 (1H), 5.97 (1H), 6.07 (1H), 6.22 (1H), 6.37 (1H), 6.73 (1H), 7.40 (1H), 7.71 (1H), 7.50 (1H), 7.94 (1H) ppm.

Example 41

N-cyclopropyl-2-methyl-4-{8-[(3,3,3-trifluoropropyl)amino]-6-vinylimidazo [1,2-b]pyridazin-3-yl}benzamide



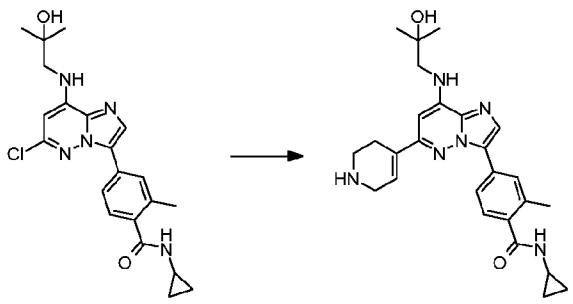
100 mg (228 µmol)

4-{6-Chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 10a were transformed in analogy to example 1 using 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane to give after working up and purification 11.4 mg (10%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.62 (2H), 0.89 (2H), 2.52 (3H), 2.56 (2H), 2.92 (1H), 3.69 (2H), 5.60 (1H), 5.92 (1H), 5.95 (1H), 6.09 (1H), 6.20 (1H), 6.77 (1H), 7.42 (1H), 7.75 (1H), 7.91 (1H), 7.95 (1H) ppm.

Example 42

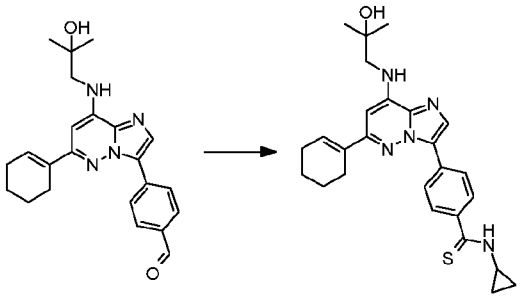
N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



50 mg (121 µmol)
4-{6-Chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 1 using
4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine to give after working up and purification 10.5 mg (18%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.65 (2H), 1.16 (6H), 2.37 (3H), 2.61 (2H), 2.80 (1H), 3.05 (2H), 3.31 (2H), 3.56 (1H), 6.54 (1H), 6.66-6.74 (2H), 7.35 (1H), 7.97 (1H), 8.03 (1H), 8.04 (1H), 8.26 (1H), 8.28 (1H) ppm.

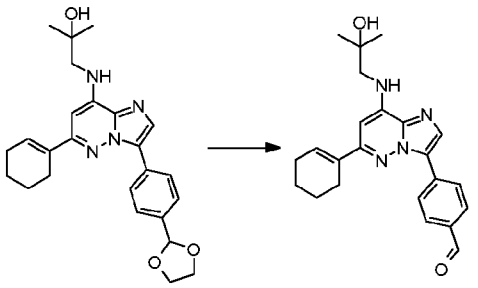
Example 43

4-{6-(Cyclohex-1-en-1-yl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzenecarbothioamide



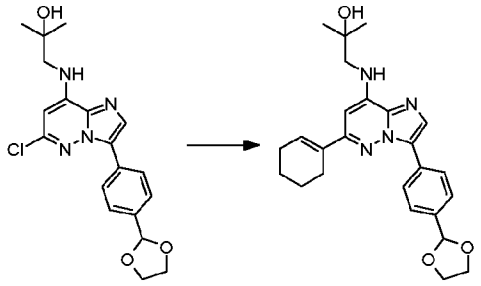
20,6 mg (53 µmol)
4-{6-(cyclohex-1-en-1-yl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzaldehyde which was prepared according to intermediate example 43a were transformed in analogy to example 13 to give after working up and purification 3.2 mg (13%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.75-0.85 (4H), 1.15 (6H), 1.61 (2H), 1.71 (2H), 2.22 (2H), 2.52 (2H), 3.13 (2H), 3.49 (1H), 4.77 (1H), 6.51 (1H), 6.63 (1H), 6.68 (1H), 7.83 (2H), 8.01 (1H), 8.21 (2H), 10.12 (1H) ppm.

Intermediate Example 43a
4-{6-(Cyclohex-1-en-1-yl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzaldehyde



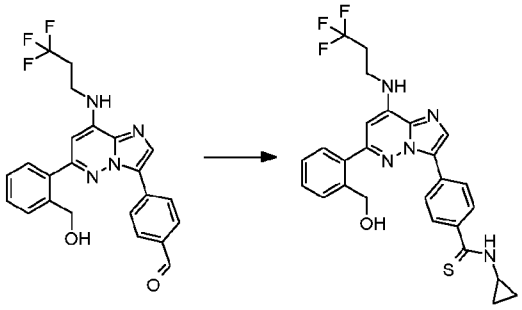
97 mg (223 µmol)
1-({6-(cyclohex-1-en-1-yl)-3-[4-(1,3-dioxolan-2-yl)phenyl]imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol which was prepared according to intermediate example 43b were transformed in analogy to intermediate example 13a to give after working up and purification 24 mg (25%) of the title compound.

Intermediate Example 43b
1-({6-(Cyclohex-1-en-1-yl)-3-[4-(1,3-dioxolan-2-yl)phenyl]imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol



100 mg (257 µmol)
1-({6-chloro-3-[4-(1,3-dioxolan-2-yl)phenyl]imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol which was prepared according to intermediate example 32c were transformed in analogy to example 1 using cyclohex-1-en-1-ylboronic acid to give after working up and purification 97 mg (87%) of the title compound.

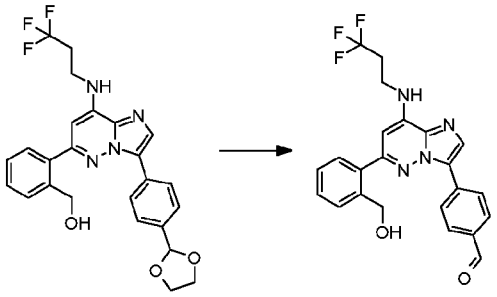
Example 44
N-cyclopropyl-4-{6-[2-(hydroxymethyl)phenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide



72.3 mg (164 µmol)
4-{6-[2-(hydroxymethyl)phenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzaldehyde which was prepared according to intermediate example 44a were transformed in analogy to example 13 to give after working up and purification 6.6 mg (7%) of the title compound.

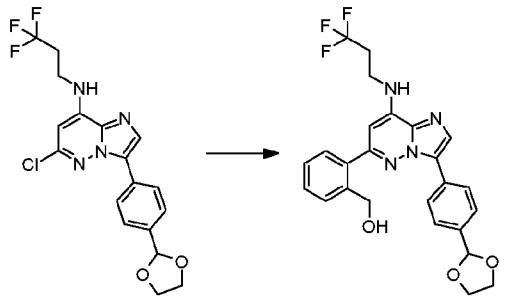
^{1}H-NMR ($CDCl_3$): δ= 0.76 (2H), 1.00 (2H), 2.58 (2H), 3.37 (1H), 3.72 (2H), 3.96 (1H), 4.40 (2H), 6.16 (1H), 6.25 (1H), 7.46-7.51 (3H), 7.59 (1H), 7.76 (1H), 7.77 (2H), 7.84 (2H), 7.89 (1H) ppm.

Intermediate Example 44a
4-{6-[2-(Hydroxymethyl)phenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzaldehyde



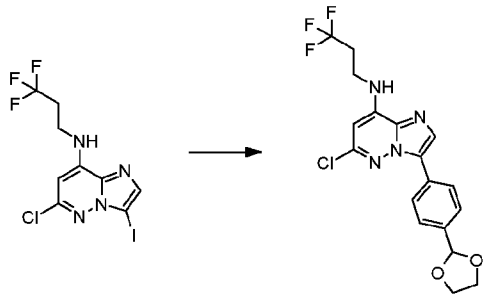
52 mg (107 µmol)
(2-{3-[4-(1,3-dioxolan-2-yl)phenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-6-yl}phenyl)methanol which was prepared according to intermediate example 44b were transformed in analogy to intermediate example 13a to give after working up and purification 72.3 mg (76%) of the title compound.

Intermediate Example 44b
(2-{3-[4-(1,3-Dioxolan-2-yl)phenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-6-yl}phenyl)methanol



100 mg (242 µmol)
6-chloro-3-[4-(1,3-dioxolan-2-yl)phenyl]-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 44c were transformed in analogy to example 1 using [2-(hydroxymethyl)phenyl]boronic acid to give after working up and purification 52 mg (44%) of the title compound.

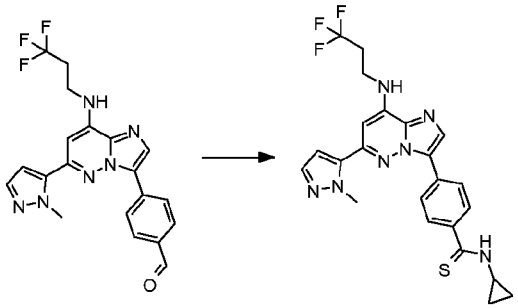
Intermediate Example 44c
6-Chloro-3-[4-(1,3-dioxolan-2-yl)phenyl]-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine



800 mg (2.05 Mmol)
6-chloro-3-iodo-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 6b were transformed in analogy to intermediate example 1a using
2-[4-(1,3-dioxolan-2-yl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane to give after working up and purification 332 mg (35%) of the title compound.

Example 45

N-cyclopropyl-4-{6-(1-methyl-1H-pyrazol-5-yl)-8-[(3,3,3-trifluoropropyl)amino] imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide

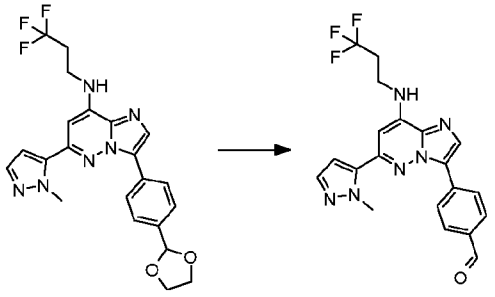


27 mg (65 µmol) 4-{6-(1-methyl-1H-pyrazol-5-yl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzaldehyde which was prepared according to intermediate example 45a were transformed in analogy to example 13 to give after working up and purification 1.8 mg (5%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.82 (2H), 1.07 (2H), 2.59 (2H), 3.42 (1H), 3.73 (2H), 4.19 (3H), 6.08 (1H), 6.29 (1H), 6.66 (1H), 7.56 (1H), 7.64 (1H), 7.84 (2H), 7.85 (1H), 8.07 (2H) ppm.

Intermediate Example 45a

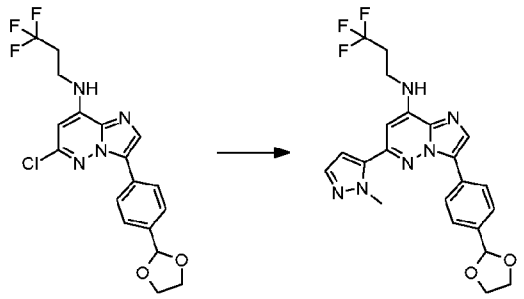
4-{6-(1-Methyl-1H-pyrazol-5-yl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b] pyridazin-3-yl}benzaldehyde



73 mg (159 µmol) 3-[4-(1,3-dioxolan-2-yl)phenyl]-6-(1-methyl-1H-pyrazol-5-yl)-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 45b were transformed in analogy to intermediate example 13a to give after working up and purification 27 mg (41%) of the title compound.

Intermediate Example 45b

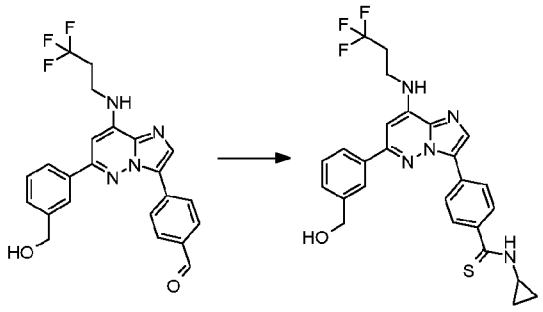
3-[4-(1,3-Dioxolan-2-yl)phenyl]-6-(1-methyl-1H-pyrazol-5-yl)-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine



100 mg (242 µmol) 6-chloro-3-[4-(1,3-dioxolan-2-yl)phenyl]-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 44c were transformed in analogy to example 1 using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole to give after working up and purification 73 mg (66%) of the title compound.

Example 46

N-cyclopropyl-4-{6-[3-(hydroxymethyl)phenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide

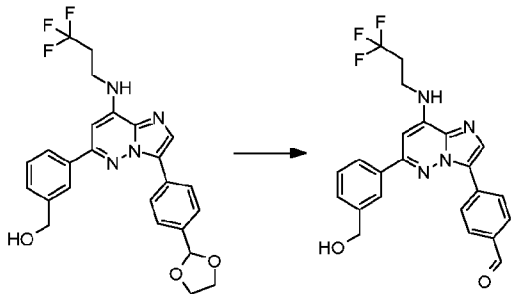


39.1 mg (89 µmol) 4-{6-[3-(hydroxymethyl)phenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzaldehyde which was prepared according to intermediate example 46a were transformed in analogy to example 13 to give after working up and purification 2,0 mg (4%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.83 (2H), 1.07 (2H), 2.56 (2H), 3.43 (1H), 3.68 (2H), 4.82 (2H), 6.00 (1H), 6.40 (1H), 7.50 (2H), 7.71 (1H), 7.79-7.90 (5H), 8.15 (2H) ppm.

Intermediate Example 46a

4-{6-[3-(Hydroxymethyl)phenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzaldehyde

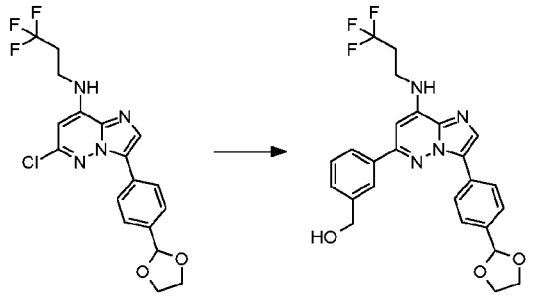


167 mg (µmol)

(3-{3-[4-(1,3-dioxolan-2-yl)phenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-6-yl}phenyl)methanol which was prepared according to intermediate example 46b were transformed in analogy to intermediate example 13a to give after working up and purification 39.1 mg (37%) of the title compound.

Intermediate Example 46b

(3-{3-[4-(1,3-Dioxolan-2-yl)phenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-6-yl}phenyl)methanol

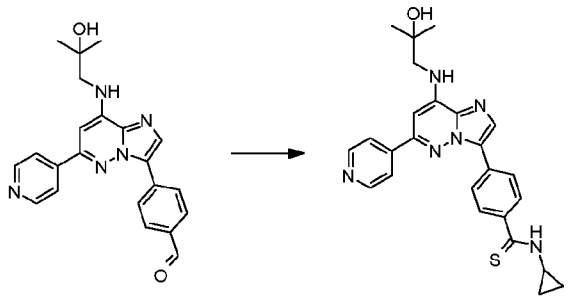


100 mg (242 µmol)

6-chloro-3-[4-(1,3-dioxolan-2-yl)phenyl]-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 44c were transformed in analogy to example 1 using [3-(hydroxymethyl)phenyl]boronic acid to give after working up and purification 83.5 mg (71%) of the title compound.

Example 47

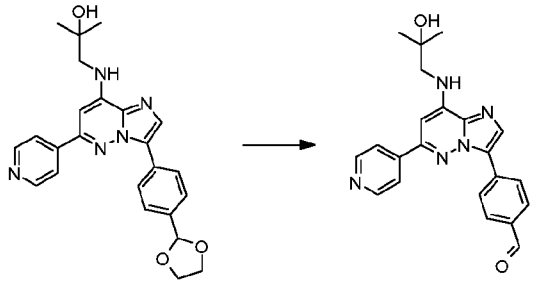
N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide



48 mg (124 µmol)
4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl}benzaldehyde which was prepared according to intermediate example 47a were transformed in analogy to example 13 to give after working up and purification 4.7 mg (6%) of the title compound.

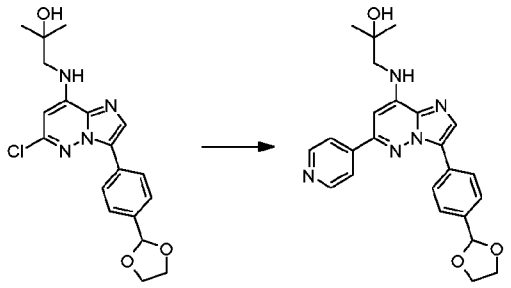
^{1}H-NMR (DMSO-d6): δ= 0.76-0.88 (4H), 1.18 (6H), 3.38-3.52 (3H), 4.79 (1H), 6.93 (1H), 7.09 (1H), 7.86 (2H), 8.04 (2H), 8.12 (1H), 8.27 (2H), 8.73 (2H), 10.16 (1H) ppm.

Intermediate Example 47a
4-{8-[(2-Hydroxy-2-methylpropyl)amino]-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl}benzaldehyde



69 mg (160 µmol)
1-({3-[4-(1,3-dioxolan-2-yl)phenyl]-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol which was prepared according to intermediate example 47b were transformed in analogy to intermediate example 13a to give after working up and purification 51.5 mg (83%) of the title compound.

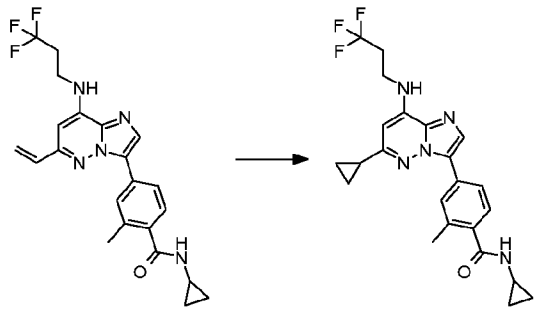
Intermediate Example 47b
1-({3-[4-(1,3-Dioxolan-2-yl)phenyl]-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol



200 mg (514 µmol) 1-({6-chloro-3-[4-(1,3-dioxolan-2-yl)phenyl]imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol which was prepared according to intermediate example 32c were transformed in analogy to example 1 using pyridin-4-ylboronic acid to give after working up and purification 51.5 mg (23%) of the title compound.

Example 48

N-cyclopropyl-4-{6-cyclopropyl-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

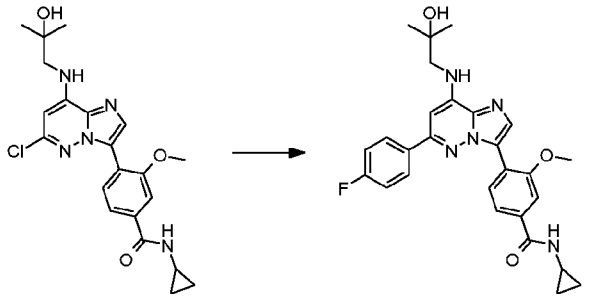


A solution of 31 mg (72 µmol) N-cyclopropyl-2-methyl-4-{8-[(3,3,3-trifluoropropyl)amino]-6-vinylimidazo[1,2-b]pyridazin-3-yl}benzamide which was prepared according to example 41 in 3.5 mL tetrahydrofuran was cooled to 3°C, 5 mL of diazomethane solution in diethyl ether was added followed by 0.81 mg palladium(II) diacetate and the mixture was stirred for 1 hour. The solvents were removed and the residue was purified by chromatography to give 5.8 mg (18%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.63 (2H), 0.89 (2H), 1.00-1.11 (4H), 2.00 (1H), 2.53 (3H), 2.47-2.61 (2H), 2.92 (1H), 3.65 (2H), 5.78 (1H), 5.91 (1H), 5.93 (1H), 7.41 (1H), 7.73 (1H), 7.91 (1H), 7.92 (1H) ppm.

Example 49

N-cyclopropyl-4-{6-(4-fluorophenyl)-8-[(2-hydroxy-2-methylpropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-3-methoxybenzamide

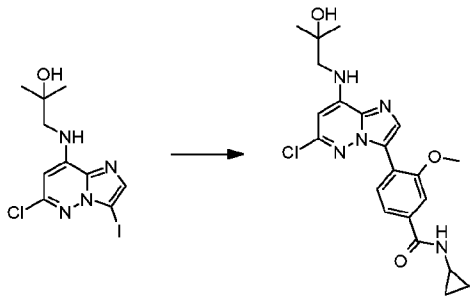


75 mg (174 µmol) 4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-3-methoxybenzamide which was prepared according to intermediate example 49a were transformed in analogy to example 1 using (4-fluorophenyl)boronic acid to give after working up and purification 18.5 mg (22%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.57 (2H), 0.69 (2H), 1.19 (6H), 2.85 (1H), 3.39 (2H), 3.89 (3H), 4.78 (1H), 6.77 (1H), 6.87 (1H), 7.31 (2H), 7.54 (1H), 7.56 (1H), 7.87 (1H), 8.03 (2H), 8.25 (1H), 8.51 (1H) ppm.

Example 49a

4-{6-Chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-3-methoxybenzamide

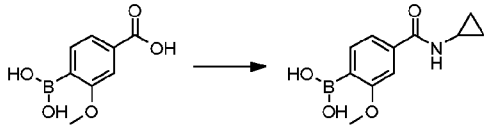


1.0 g (2.73 mmol) 1-[(6-Chloro-3-iodoimidazo[1,2-b]pyridazin-8-yl)amino]-2-methylpropan-2-ol which was prepared according to intermediate example 1b were transformed in analogy to intermediate example 1a using [4-(cyclopropylcarbamoyl)-2-methoxyphenyl]boronic acid which was prepared

according to intermediate example 49b to give after working up and purification 741 mg (60%) of the title compound.

Example 49b

[4-(Cyclopropylcarbamoyl)-2-methoxyphenyl]boronic acid

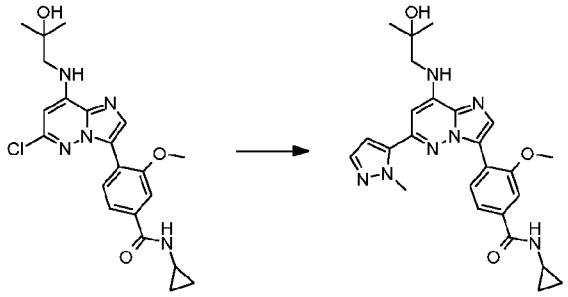


A suspension of 3,0 g (15.3 mmol) 4-(dihydroxyboryl)-3-methoxybenzoic acid, 874 mg cyclopropanamine and 3.5 g N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide in 93 mL dichloromethane was stirred overnight at 23°C.

Water was added and the mixture was extracted with dichloromethane. The organic layer was washed with brine and dried over sodium sulfate. After filtration and removal of the solvent the residue was purified by chromatography to give 2.60 g (72%) of the title compound.

Example 50

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-3-yl}-3-methoxybenzamide



75 mg (174 µmol)

4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-3-methoxybenzamide which was prepared according to intermediate example 49a were transformed in analogy to example 1 using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole to give after working up and purification 14.8 mg (18%) of the title compound.

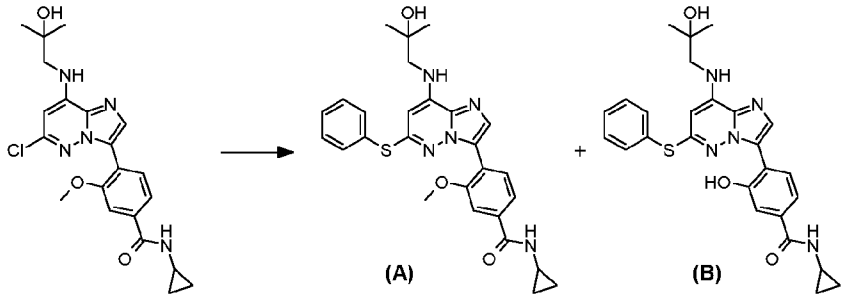
^{1}H-NMR (DMSO-d6): δ= 0.57 (2H), 0.69 (2H), 1.17 (6H), 2.83 (1H), 3.35 (2H), 3.85 (3H), 4.01 (3H), 4.77 (1H), 6.59 (1H), 6.85 (1H), 6.95 (1H), 7.47 (1H), 7.51 (1H), 7.53 (1H), 7.81 (1H), 8.03 (1H), 8.49 (1H) ppm.

Example 51

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(phenylsulfanyl) imidazo[1,2-b]pyridazin-3-yl}-3-methoxybenzamide (A)

and

N-cyclopropyl-3-hydroxy-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}benzamide (B)



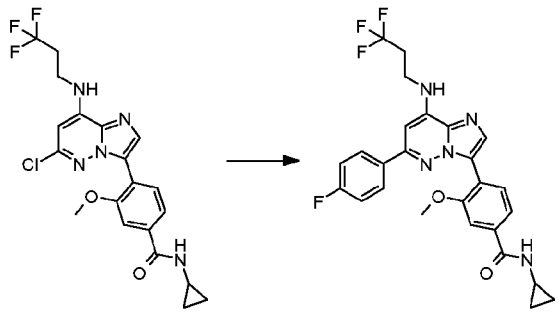
To a solution of 76.9 mg benzenethiol in 1.0 mL dimethyl sulfoxide were added 27.9 mg sodium hydride (60%) and the mixture was stirred at 23°C for 1 hour. Then 50 mg (116 µmol) 4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-3-methoxybenzamide which was prepared according to intermediate example 49a were added and the mixture was heated at 120°C using microwave irradiation for 1 hour. Water was added and the mixture was extracted with dichloromethane and methanol. The organic layer was washed with brine and dried over sodium sulfate. After filtration and removal of the solvent the residue was purified by chromatography to give 8.0 mg (18%) of the title compound A and 15.3 mg (27%) of the title compound B.

^{1}H-NMR (DMSO-d6) of A: δ= 0.56 (2H), 0.69 (2H), 1.10 (6H), 2.82 (1H), 3.19 (2H), 3.27 (3H), 4.70 (1H), 6.19 (1H), 6.97 (1H), 7.22 (1H), 7.41-7.47 (4H), 7.53-7.58 (2H), 7.85 (1H), 7.86 (1H), 8.44 (1H) ppm.

^{1}H-NMR (DMSO-d6) of B: δ= 0.54 (2H), 0.66 (2H), 1.10 (6H), 2.80 (1H), 3.18 (2H), 4.70 (1H), 6.17 (1H), 6.98 (1H), 7.04 (1H), 7.33 (1H), 7.42-7.48 (3H), 7.55-7.61 (2H), 7.87 (1H), 7.95 (1H), 8.33 (1H), 10.13 (1H) ppm.

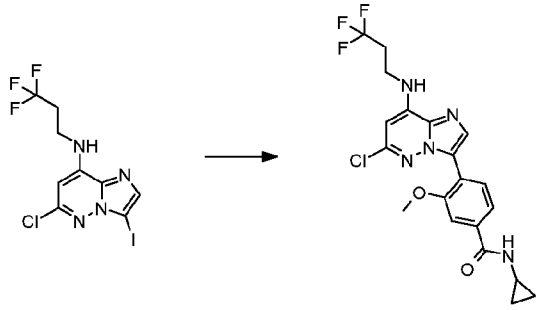
Example 52

N-cyclopropyl-4-{6-(4-fluorophenyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo [1,2-b]pyridazin-3-yl}-3-methoxybenzamide



65 mg (143 µmol)
4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-3-methoxybenzamide which was prepared according to intermediate example 52a were transformed in analogy to example 1 using (4-fluorophenyl)boronic acid to give after working up and purification 14.3 mg (18%) of the title compound.
^{1}H-NMR ($CDCl_3$): δ= 0.66 (2H), 0.91 (2H), 2.59 (2H), 2.95 (1H), 3.75 (2H), 3.97 (3H), 6.00 (1H), 6.32 (1H), 6.39 (1H), 7.17 (2H), 7.33 (1H), 7.58 (1H), 7.90 (2H), 8.01 (1H), 8.37 (1H) ppm.

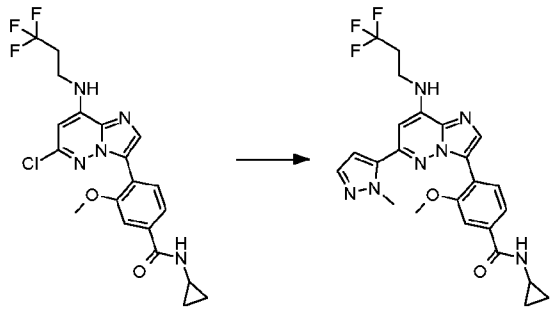
Intermediate example 52a
4-{6-Chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-3-methoxybenzamide



484 mg (1.24 mmol)
6-chloro-3-iodo-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 6b were transformed in analogy to intermediate example 1a using [4-(cyclopropylcarbamoyl)-2-methoxyphenyl]boronic acid which was prepared according to intermediate example 49b to give after working up and purification 163 mg (29%) of the title compound.

Example 53

N-cyclopropyl-3-methoxy-4-{6-(1-methyl-1H-pyrazol-5-yl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide

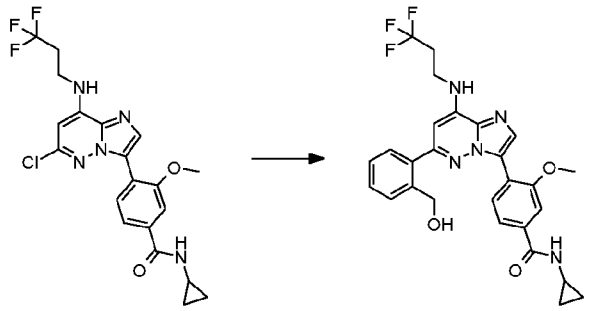


65 mg (143 µmol) 4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-3-methoxybenzamide which was prepared according to intermediate example 52a were transformed in analogy to example 1 using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole to give after working up and purification 3.6 mg (5%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.66 (2H), 0.91 (2H), 2.58 (2H), 2.94 (1H), 3.72 (2H), 3.94 (3H), 4.11 (3H), 6.04 (1H), 6.27 (1H), 6.31 (1H), 6.64 (1H), 7.27 (1H), 7.53 (1H), 7.58 (1H), 7.95 (1H), 8.13 (1H) ppm.

Example 54

N-cyclopropyl-4-{6-[2-(hydroxymethyl)phenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-3-methoxybenzamide



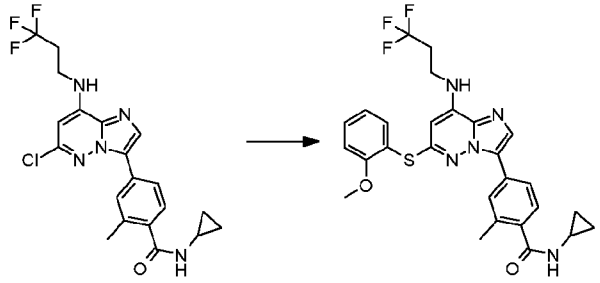
50 mg (110 µmol) 4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-3-methoxybenzamide which was prepared according to intermediate example 52a were transformed in analogy to example 1 using

[2-(hydroxymethyl)phenyl]boronic acid to give after working up and purification 11.8 mg (18%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.60 (2H), 0.85 (2H), 2.58 (2H), 2.88 (1H), 3.73 (2H), 3.90 (3H), 4.39 (2H), 5.12 (1H), 6.13 (1H), 6.24 (1H), 6.34 (1H), 7.22 (1H), 7.43-7.49 (3H), 7.55 (1H), 7.58 (1H), 7.79 (1H), 7.84 (1H) ppm.

Example 55

N-cyclopropyl-4-{6-[(2-methoxyphenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

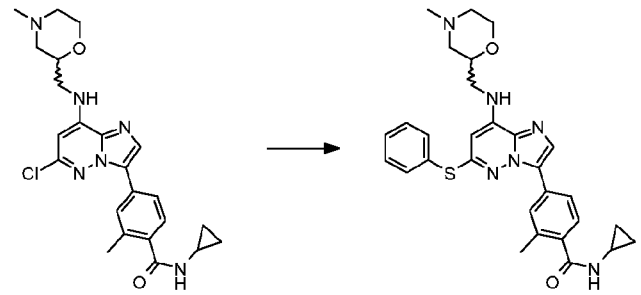


50 mg (114 µmol) 4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 10a were transformed in analogy to example 51 using 2-methoxybenzenethiol to give after working up and purification 9.2 mg (14%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.61 (2H), 0.88 (2H), 2.36 (3H), 2.47 (2H), 2.89 (1H), 3.52 (2H), 3.77 (3H), 5.88 (1H), 6.01 (1H), 6.28 (1H), 6.97-7.07 (2H), 7.16 (1H), 7.48 (1H), 7.57-7.65 (3H), 7.67 (1H) ppm.

Example 56

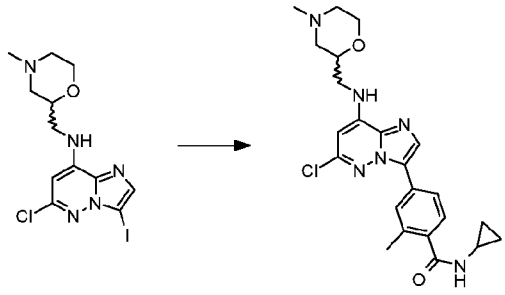
(RS)-N-cyclopropyl-2-methyl-4-[8-{[(4-methylmorpholin-2-yl)methyl]amino}-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl]benzamide



75 mg (165 µmol)
(RS)-4-(6-chloro-8-{[(4-methylmorpholin-2-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 56a were transformed in analogy to example 51 using benzenethiol to give after working up and purification 21.6 mg (25%) of the title compound.

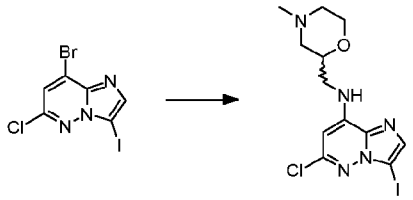
^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.65 (2H), 1.70 (1H), 1.93 (1H), 2.13 (3H), 2.20 (3H), 2.53 (1H), 2.64 (1H), 2.79 (1H), 3.25-3.34 (2H), 3.43 (1H), 3.62 (1H), 3.73 (1H), 6.10 (1H), 7.10 (1H), 7.42 (1H), 7.45-7.51 (3H), 7.59-7.67 (3H), 7.71 (1H), 7.92 (1H), 8.23 (1H) ppm.

Intermediate example 56a
(RS)-4-(6-Chloro-8-{[(4-methylmorpholin-2-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide



352 mg (864 µmol)
(RS)-6-chloro-3-iodo-N-[(4-methylmorpholin-2-yl)methyl]imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 56b were transformed in analogy to intermediate example 1a using N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide to give after working up and purification 372 mg (95%) of the title compound.

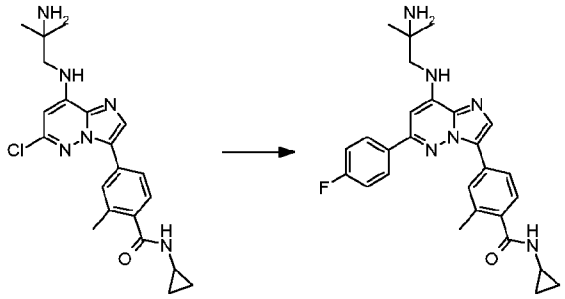
Intermediate example 56b
(RS)-6-Chloro-3-iodo-N-[(4-methylmorpholin-2-yl)methyl]imidazo[1,2-b]pyridazin-8-amine



370 mg (1.03 mmol) 8-bromo-6-chloro-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 1c were transformed in analogy to intermediate example 1b using 1-[(2RS)-4-methylmorpholin-2-yl]methanamine to give after working up and purification 359 mg (85%) of the title compound.

Example 57

4-{8-[(2-Amino-2-methylpropyl)amino]-6-(4-fluorophenyl)imidazo[1,2-b] pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

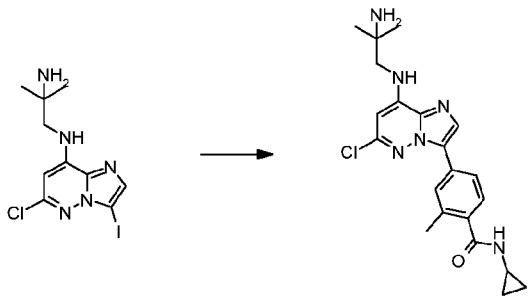


100 mg (242 µmol) 4-{8-[(2-amino-2-methylpropyl)amino]-6-chloroimidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 57a were transformed in analogy to example 1 using (4-fluorophenyl)boronic acid to give after working up and purification 17.9 mg (14%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.63 (2H), 0.90 (2H), 1.25 (2H), 1.29 (6H), 2.55 (3H), 2.93 (1H), 3.27 (2H), 5.94 (1H), 6.34 (1H), 6.41 (1H), 7.17 (2H), 7.45 (1H), 7.81 (1H), 7.91-7.98 (3H), 8.04 (1H) ppm.

Intermediate example 57a

4-{8-[(2-Amino-2-methylpropyl)amino]-6-chloroimidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



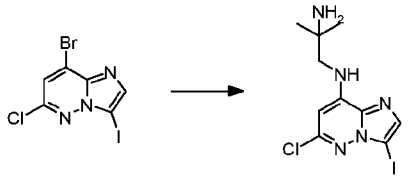
1.07 g (2.93 mmol)

N^1-(6-chloro-3-iodoimidazo[1,2-b]pyridazin-8-yl)-2-methylpropane-1,2-diamine which was prepared according to intermediate example 57b were transformed in analogy to intermediate example 1a using

N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide to give after working up and purification 809 mg (64%) of the title compound.

Intermediate example 57b

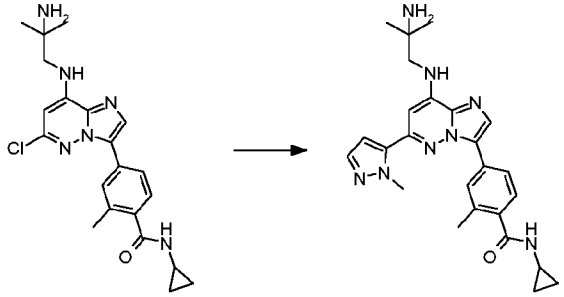
N^1-(6-chloro-3-iodoimidazo[1,2-b]pyridazin-8-yl)-2-methylpropane-1,2-diamine



2.00 g (5.58 mmol) 8-bromo-6-chloro-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 1c were transformed in analogy to intermediate example 1b using 2-methylpropane-1,2-diamine to give after working up and purification 1.08 g (53%) of the title compound.

Example 58

4-{8-[(2-Amino-2-methylpropyl)amino]-6-(1-methyl-1H-pyrazol-5-yl)imidazo [1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



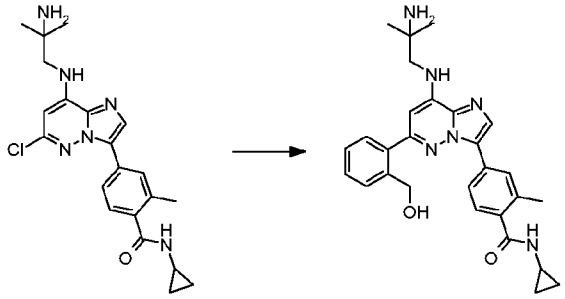
100 mg (242 µmol)

4-{8-[(2-amino-2-methylpropyl)amino]-6-chloroimidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 57a were transformed in analogy to example 1 using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole to give after working up and purification 27.5 mg (22%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.64 (2H), 0.90 (2H), 1.25 (2H), 1.28 (6H), 2.52 (3H), 2.93 (1H), 3.23 (2H), 4.20 (3H), 5.97 (1H), 6.29 (1H), 6.42 (1H), 6.64 (1H), 7.41 (1H), 7.53 (1H), 7.79 (1H), 7.86 (1H), 7.90 (1H) ppm.

Example 59

4-{8-[(2-Amino-2-methylpropyl)amino]-6-[2-(hydroxymethyl)phenyl]imidazo [1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



100 mg (242 µmol)

4-{8-[(2-amino-2-methylpropyl)amino]-6-chloroimidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 57a were transformed in analogy to example 1 using [2-(hydroxymethyl)phenyl]boronic acid to give after working up and purification 30.0 mg (23%) of the title compound.

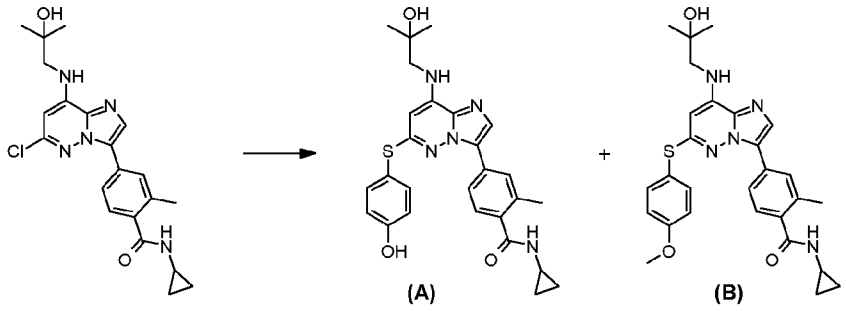
^{1}H-NMR ($CDCl_3$): δ= 0.59 (2H), 0.85 (2H), 1.25 (2H), 1.28 (6H), 2.49 (3H), 2.89 (1H), 3.25 (2H), 4.40 (2H), 5.30 (1H), 6.07 (1H), 6.30 (1H), 6.47 (1H), 7.38 (1H), 7.43-7.50 (3H), 7.60 (1H), 7.64 (1H), 7.73 (1H), 7.74 (1H) ppm.

Example 60

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(4-hydroxyphenyl) sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide (A)

and

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(4-methoxyphenyl) sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide (B)



75 mg (181 µmol)
4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using 4-methoxybenzenethiol to give after working up and purification 50 mg (43%) of the title compound A and 8.8 mg (5%) of the title compound B.

^{1}H-NMR (DMSO-d6) of A: δ= 0.49 (2H), 0.65 (2H), 1.11 (6H), 2.21 (3H), 2.79 (1H), 3.19 (2H), 4.72 (1H), 6.12 (1H), 6.82-6.91 (3H), 7.12 (1H), 7.42 (2H), 7.65 (1H), 7.70 (1H), 7.91 (1H), 8.22 (1H), 10.04 (1H) ppm.

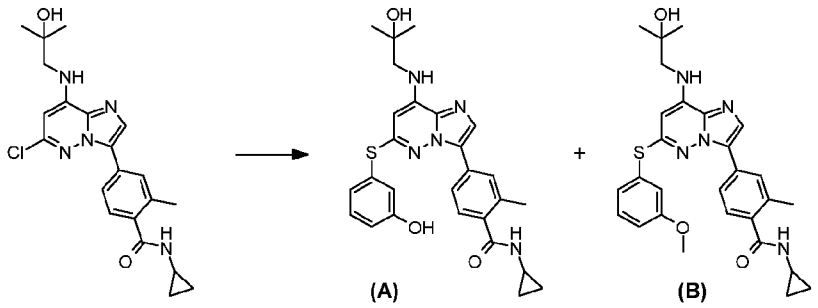
^{1}H-NMR ($CDCl_3$) of B: δ= 0.64 (2H), 0.90 (2H), 1.39 (6H), 2.37 (3H), 2.92 (1H), 3.24 (2H), 3.88 (3H), 4.09 (1H), 5.30 (1H), 5.92 (1H), 5.97 (1H), 6.36 (1H), 6.96 (2H), 7.12 (1H), 7.50-7.58 (3H), 7.61 (1H) ppm.

Example 61

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-hydroxyphenyl) sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide (A)

and

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-methoxyphenyl) sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide (B)



75 mg (181 µmol)
4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cy

clopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using 3-methoxybenzenethiol to give after working up and purification 26.9 mg (21%) of the title compound A and 14.9 mg (15%) of the title compound B.

^{1}H-NMR (DMSO-d6) of A: δ= 0.49 (2H), 0.65 (2H), 1.11 (6H), 2.22 (3H), 2.79 (1H), 3.20 (2H), 4.71 (1H), 6.21 (1H), 6.85 (1H), 6.94-7.02 (3H), 7.15 (1H), 7.25 (1H), 7.73 (1H), 7.74 (1H), 7.94 (1H), 8.23 (1H), 9.73 (1H) ppm.

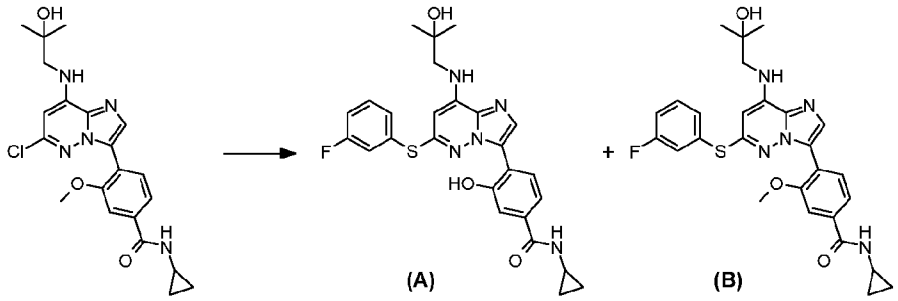
^{1}H-NMR ($CDCl_3$) of B: δ= 0.63 (2H), 0.90 (2H), 1.40 (6H), 2.37 (3H), 2.92 (1H), 3.23 (2H), 3.73 (3H), 5.94 (1H), 6.02 (1H), 6.50 (1H), 6.97 (1H), 7.13-7.20 (3H), 7.22 (1H), 7.33 (1H), 7.56-7.63 (3H) ppm.

Example 62

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-3-hydroxybenzamide (A)

and

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-3-methoxybenzamide (B)



150 mg (349 µmol)

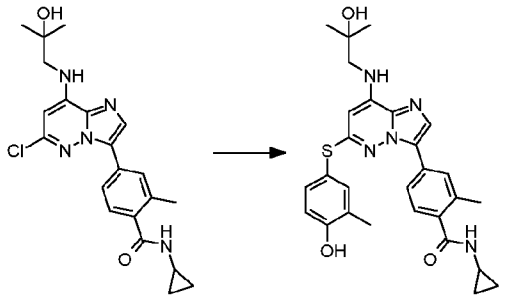
4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-3-methoxybenzamide which was prepared according to intermediate example 49a were transformed in analogy to example 51 using 3-fluorobenzenethiol to give after working up and purification 3.3 mg (2%) of the title compound A and 2.5 mg (1%) of the title compound B.

^{1}H-NMR (DMSO-d6) of A: δ= 0.53 (2H), 0.66 (2H), 1.11 (6H), 2.80 (1H), 3.21 (2H), 4.71 (1H), 6.24 (1H), 7.06 (2H), 7.26 (1H), 7.33-7.52 (4H), 7.86 (1H), 7.94 (1H), 8.33 (1H), 10.18 (1H) ppm.

^{1}H-NMR (DMSO-d6) of B: δ= 0.55 (2H), 0.69 (2H), 1.11 (6H), 2.82 (1H), 3.22 (2H), 3.84 (3H), 4.70 (1H), 6.26 (1H), 7.04 (1H), 7.21-7.30 (2H), 7.36 (1H), 7.39-7.49 (3H), 7.84 (1H), 7.85 (1H), 8.44 (1H) ppm.

Example 63

N-cyclopropyl-4-{6-[(4-hydroxy-3-methylphenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



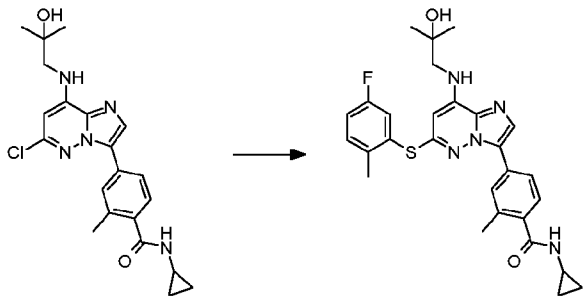
75 mg (181 µmol)

4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using 2-methyl-4-sulfanylphenol to give after working up and purification 27.6 mg (28%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.65 (2H), 1.11 (6H), 2.10 (3H), 2.20 (3H), 2.79 (1H), 3.18 (2H), 4.70 (1H), 6.11 (1H), 6.86 (1H), 6.88 (1H), 7.10 (1H), 7.25 (1H), 7.32 (1H), 7.67 (1H), 7.71 (1H), 7.92 (1H), 8.21 (1H), 9.87 (1H) ppm.

Example 64

N-cyclopropyl-4-{6-[(5-fluoro-2-methylphenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



75 mg (181 µmol)

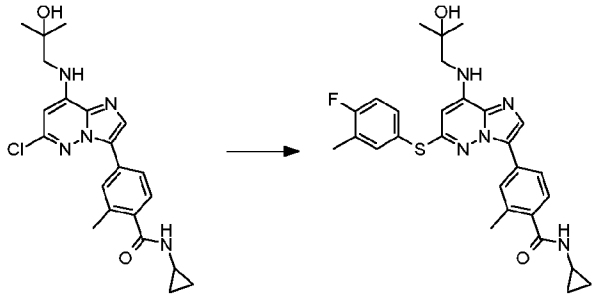
4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cy

clopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using 5-fluoro-2-methylbenzenethiol to give after working up and purification 47.7 mg (48%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.65 (2H), 1.12 (6H), 2.19 (3H), 2.31 (3H), 2.79 (1H), 3.23 (2H), 4.71 (1H), 6.27 (1H), 7.01 (1H), 7.06 (1H), 7.29 (1H), 7.42-7.49 (2H), 7.57 (1H), 7.67 (1H), 7.94 (1H), 8.23 (1H) ppm.

Example 65

N-cyclopropyl-4-{6-[(4-fluoro-3-methylphenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

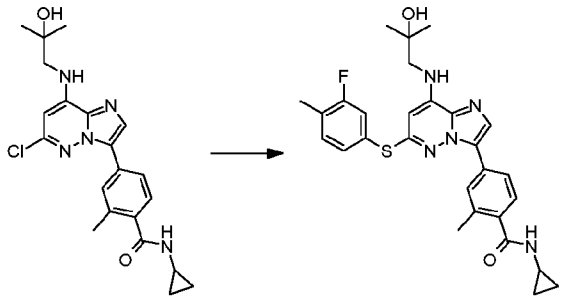


75 mg (181 µmol) 4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using 4-fluoro-3-methylbenzenethiol to give after working up and purification 25.9 mg (26%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.65 (2H), 1.11 (6H), 2.18 (3H), 2.22 (3H), 2.79 (1H), 3.22 (2H), 4.71 (1H), 6.22 (1H), 6.97 (1H), 7.08 (1H), 7.25 (1H), 7.48 (1H), 7.59 (2H), 7.67 (1H), 7.93 (1H), 7.23 (1H) ppm.

Example 66

N-cyclopropyl-4-{6-[(3-fluoro-4-methylphenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

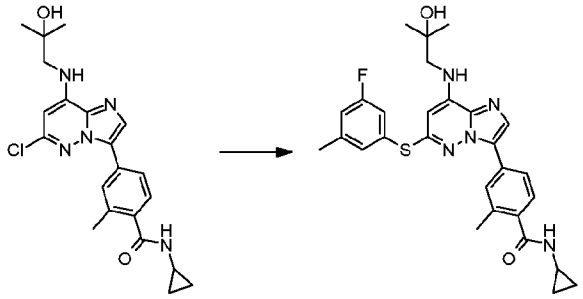


75 mg (181 µmol)
4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using 3-fluoro-4-methylbenzenethiol to give after working up and purification 41.7 mg (42%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.65 (2H), 1.12 (6H), 2.19 (3H), 2.28 (3H), 2.79 (1H), 3.23 (2H), 4.72 (1H), 6.27 (1H), 6.99 (1H), 7.07 (1H), 7.34 (1H), 7.39 (1H), 7.44 (1H), 7.63 (1H), 7.69 (1H), 7.94 (1H), 8.25 (1H) ppm.

Example 67

N-cyclopropyl-4-{6-[(3-fluoro-5-methylphenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

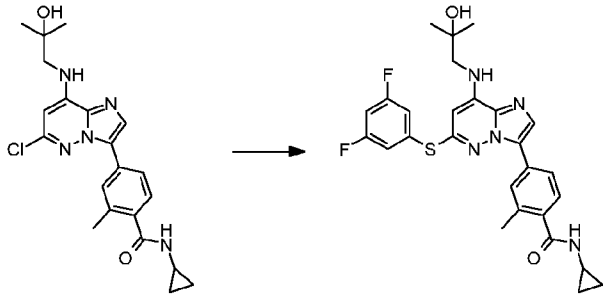


75 mg (181 µmol)
4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using 3-fluoro-5-methylbenzenethiol to give after working up and purification 33 mg (33%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.65 (2H), 1.12 (6H), 2.21 (3H), 2.30 (3H), 2.79 (1H), 3.22 (2H), 4.70 (1H), 6.27 (1H), 7.05 (1H), 7.13 (1H), 7.16 (1H), 7.26 (1H), 7.27 (1H), 7.70 (1H), 7.73 (1H), 7.95 (1H), 8.24 (1H) ppm.

Example 68

N-cyclopropyl-4-{6-[(3,5-difluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

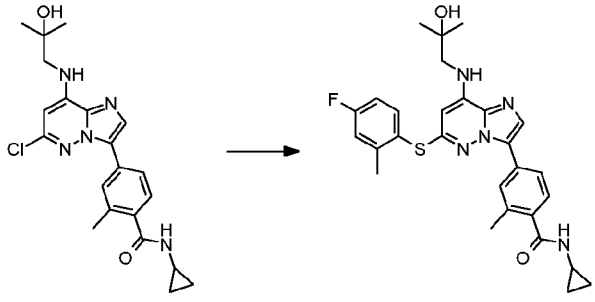


75 mg (181 µmol) 4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using 3,5-difluorobenzenethiol to give after working up and purification 5.7 mg (6%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.65 (2H), 1.12 (6H), 2.22 (3H), 2.79 (1H), 3.24 (2H), 4.71 (1H), 6.34 (1H), 7.12 (1H), 7.16 (1H), 7.35-7.40 (3H), 7.71 (1H), 7.74 (1H), 7.96 (1H), 8.25 (1H) ppm.

Example 69

N-cyclopropyl-4-{6-[(4-fluoro-2-methylphenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



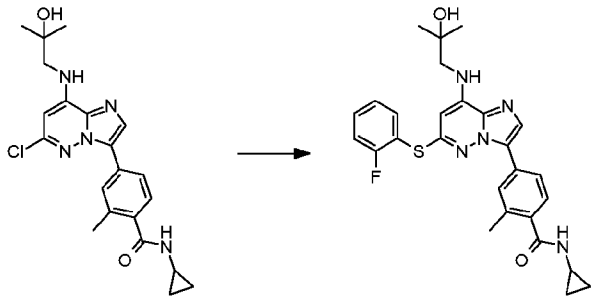
75 mg (181 µmol) 4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using

4-fluoro-3-methylbenzenethiol to give after working up and purification 32.1 mg (32%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.65 (2H), 1.12 (6H), 2.18 (3H), 2.35 (3H), 2.79 (1H), 3.22 (2H), 4.72 (1H), 6.23 (1H), 6-95 (1H), 7.05 (1H), 7.15 (1H), 7.34 (1H), 7.53 (1H), 7.63 (1H), 7.65 (1H), 7.92 (1H), 8.23 (1H) ppm.

Example 70

N-cyclopropyl-4-{6-[(2-fluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

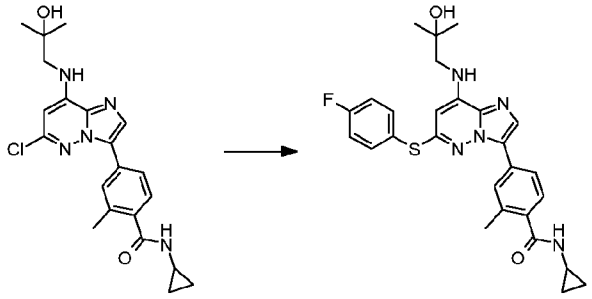


75 mg (181 µmol) 4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using 2-fluorobenzenethiol to give after working up and purification 36.8 mg (38%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.65 (2H), 1.13 (6H), 2.18 (3H), 2.78 (1H), 3.24 (2H), 4.72 (1H), 6.31 (1H), 7.00 (1H), 7.03 (1H), 7.32 (1H), 7.40 (1H), 7.53 (1H), 7.61 (1H), 7.64 (1H), 7.69 (1H), 7.93 (1H), 8.22 (1H) ppm.

Example 71

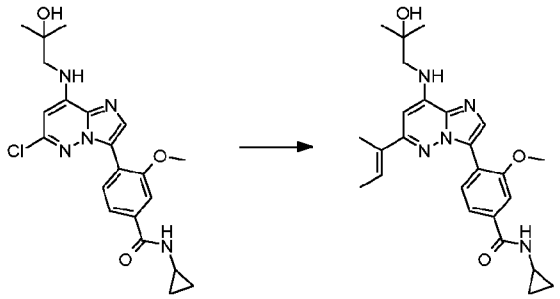
N-cyclopropyl-4-{6-[(4-fluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



75 mg (181 µmol)
4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using 4-fluorobenzenethiol to give after working up and purification 31.6 mg (33%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.65 (2H), 1.12 (6H), 2.19 (3H), 2.79 (1H), 3.22 (2H), 4.72 (1H), 6.24 (1H), 6.97 (1H), 7.08 (1H), 7.33 (2H), 7.58 (1H), 7.64-7.71 (3H), 7.92 (1H), 8.23 (1H) ppm.

Example 72

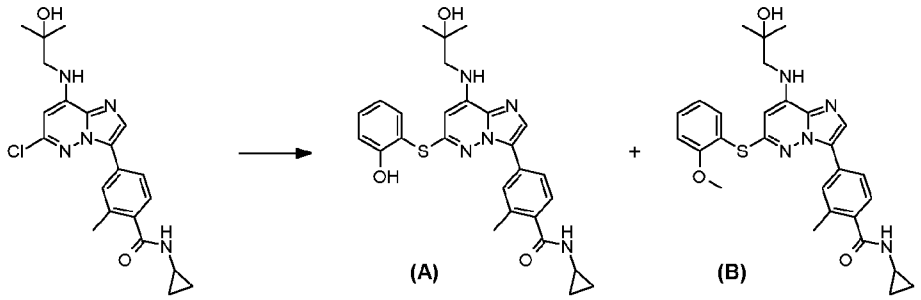
4-{6-[(2E)-But-2-en-2-yl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-3-methoxybenzamide



75 mg (174 µmol)
4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-3-methoxybenzamide which was prepared according to intermediate example 49a were transformed in analogy to example 1 using (2Z)-but-2-en-2-ylboronic acid to give after working up and purification 26.9 mg (33%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.57 (2H), 0.68 (2H), 1.16 (6H), 1.81 (3H), 1.99 (3H), 2.84 (1H), 3.28 (2H), 3.89 (3H), 4.75 (1H), 6.40 (1H), 6.48 (1H), 6.58 (1H), 7.51 (1H), 7.53 (1H), 7.85 (1H), 8.32 (1H), 8.47 (1H) ppm.

Example 73

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(2-hydroxyphenyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide (A)
and
N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(2-methoxyphenyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide (B)



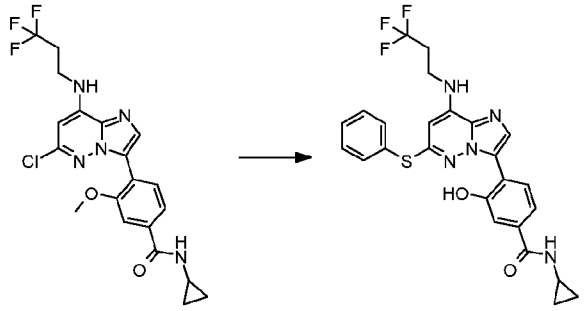
100 mg (242 µmol)
4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using 2-methoxybenzenethiol to give after working up and purification 43.1 mg (35%) of the title compound A and 5.8 mg (4%) of the title compound B.

^{1}H-NMR (DMSO-d6) of A: δ= 0.49 (2H), 0.65 (2H), 1.11 (6H), 2.20 (3H), 2.78 (1H), 3.19 (2H), 4.72 (1H), 6.14 (1H), 6.82-6.90 (2H), 6.97 (1H), 7.07 (1H), 7.33 (1H), 7.44 (1H), 7.66 (1H), 7.71 (1H), 7.91 (1H), 8.22 (1H), 9.96 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ= 0.63 (2H), 0.89 (2H), 1.39 (6H), 2.35 (3H), 2.91 (1H), 3.23 (2H), 3.77 (3H), 4.62 (1H), 5.92 (1H), 5.97 (1H), 6.42 (1H), 6.99 (1H), 7.03 (1H), 7.13 (1H), 7.47 (1H), 7.56-7.64 (4H) ppm.

Example 74

N-cyclopropyl-3-hydroxy-4-{6-(phenylsulfanyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide

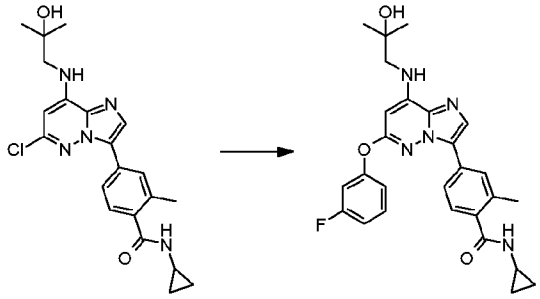


29.5 mg (67 µmol)
4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-3-methoxybenzamide which was prepared according to intermediate example 52a were transformed in analogy to example 51 using benzenethiol to give after working up and purification 19 mg (52%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.63 (2H), 0.88 (2H), 2.44 (2H), 2.92 (1H), 3.55 (2H), 5.81 (1H), 6.12 (1H), 6.22 (1H), 7.22 (1H), 7.33 (1H), 7.41-7.54 (4H), 7.58-7.66 (3H), 9.01 (1H) ppm.

Example 75

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



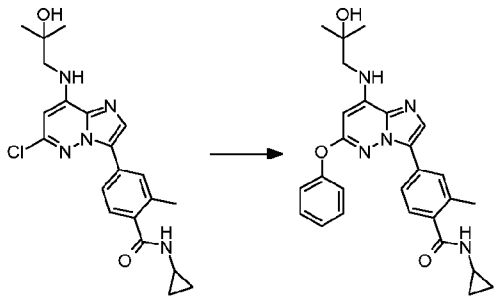
50 mg (121 µmol)

4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using 3-fluorophenol to give after working up and purification 13.9 mg (22%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.47 (2H), 0.63 (2H), 1.16 (6H), 2.14 (3H), 2.76 (1H), 3.27 (2H), 4.74 (1H), 6.18 (1H), 7.02 (1H), 7.08-7.14 (2H), 7.16 (1H), 7.24 (1H), 7.47 (1H), 7.67 (1H), 7.77 (1H), 7.92 (1H), 8.21 (1H) ppm.

Example 76

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-phenoxyimidazo [1,2-b]pyridazin-3-yl}-2-methylbenzamide



50 mg (121 µmol)

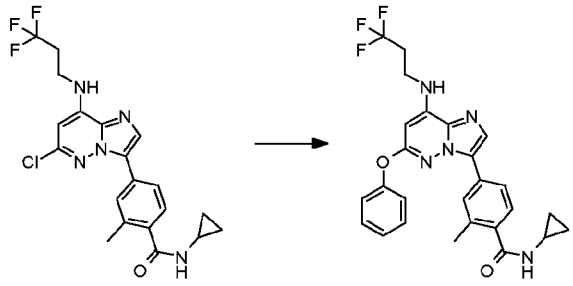
4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cy

clopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using phenol to give after working up and purification 15.1 mg (25%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.59 (2H), 0.86 (2H), 1.38 (6H), 2.26 (3H), 2.86 (1H), 3.29 (2H), 3.74 (1H), 5.91 (1H), 6.02 (1H), 6.42 (1H), 7.19 (2H), 7.23 (2H), 7.41 (2H), 7.57 (1H), 7.66 (1H), 7.70 (1H) ppm.

Example 77

N-cyclopropyl-2-methyl-4-{6-phenoxy-8-[(3,3,3-trifluoropropyl)amino]imidazo [1,2-b]pyridazin-3-yl}benzamide

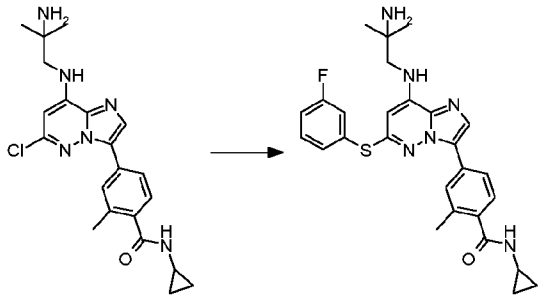


50 mg (114 µmol) 4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 10a were transformed in analogy to example 51 using phenol to give after working up and purification 5.7 mg (9%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.60 (2H), 0.87 (2H), 2.29 (3H), 2.57 (2H), 2.88 (1H), 1.97 (2H), 5.84 (1H), 5.90 (1H), 5.97 (1H), 7.20-7.30 (4H), 7.44 (2H), 7.60 (1H), 7.73 (1H), 7.74 (1H) ppm.

Example 78

4-{8-[(2-Amino-2-methylpropyl)amino]-6-[(3-fluorophenyl)sulfanyl]imidazo [1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

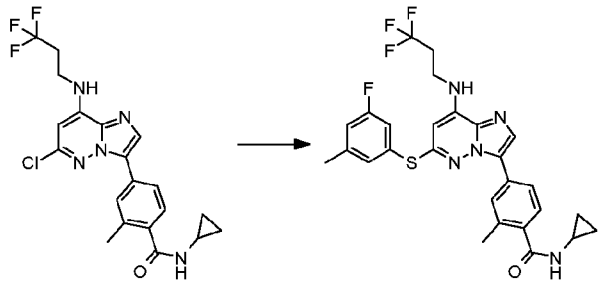


250 mg (605 µmol)
4-{8-[(2-amino-2-methylpropyl)amino]-6-chloroimidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 57a were transformed in analogy to example 51 using 3-fluorobenzenethiol to give after working up and purification 9.8 mg (3%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.63 (2H), 0.89 (2H), 1.24 (6H), 1.80 (2H), 2.39 (3H), 2.91 (1H), 3.14 (2H), 5.91 (1H), 5.97 (1H), 6.34 (1H), 7.12 (1H), 7.22 (1H), 7.32-7.42 (3H), 7.62 (1H), 7.64 (1H), 7.69 (1H) ppm.

Example 79

N-cyclopropyl-4-{6-[(3-fluoro-5-methylphenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

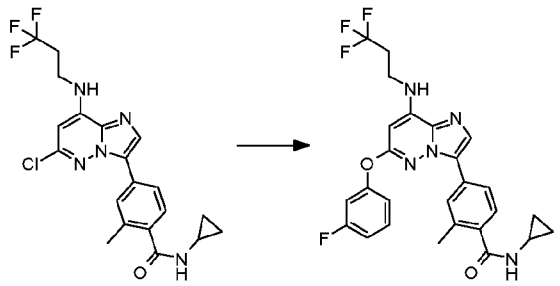


50 mg (114 µmol)
4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 10a were transformed in analogy to example 51 using 3-fluoro-5-methylbenzenethiol to give after working up and purification 6.9 mg (11%) of the title compound.

^{1}H-NMR ($CDCl_3$ + CD_3OD): δ= 0.61 (2H), 0.88 (2H), 2.35 (3H), 2.39 (3H), 2.48 (2H), 2.89 (1H), 3.54 (2H), 5.89 (1H), 6.07 (1H), 6.46 (1H), 6.96 (1H), 7.17 (1H), 7.21 (1H), 7.23 (1H), 7.63 (1H), 7.66 (1H), 7.68 (1H) ppm.

Example 80

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

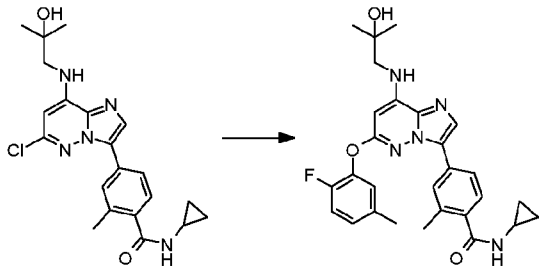


50 mg (114 µmol)
4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 10a were transformed in analogy to example 51 using 3-fluorophenol to give after working up and purification 9.1 mg (15%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.60 (2H), 0.87 (2H), 2.32 (3H), 2.57 (2H), 2.89 (1H), 3.67 (2H), 5.87 (1H), 5.89 (1H), 6.12 (1H), 6.94-7.08 (3H), 7.25 (1H), 7.39 (1H), 7.60 (1H), 7.72 (2H) ppm.

Example 81

N-cyclopropyl-4-{6-(2-fluoro-5-methylphenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

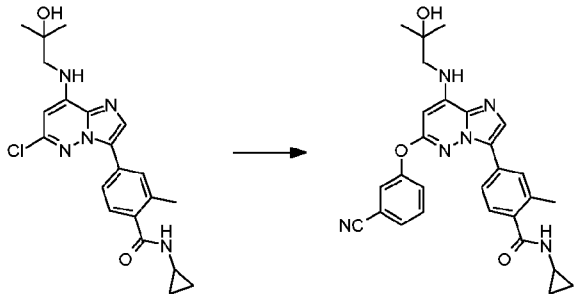


50 mg (121 µmol)
4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using 2-fluoro-5-methylphenol to give after working up and purification 5.2 mg (8%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.46 (2H), 0.63 (2H), 1.17 (6H), 2.09 (3H), 2.29 (3H), 2.76 (1H), 3.29 (2H), 4.75 (1H), 6.23 (1H), 7.02 (1H), 7.10-7.16 (2H), 7.23 (1H), 7.27 (1H), 7.62 (1H), 7.70 (1H), 7.92 (1H), 8.21 (1H) ppm.

Example 82

4-{6-(3-Cyanophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b] pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

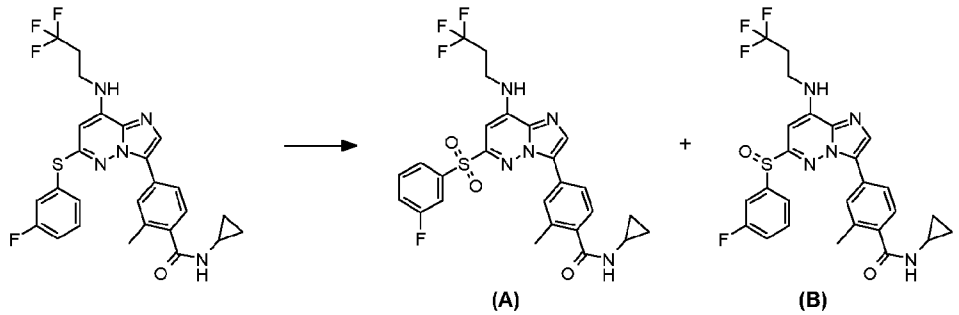


50 mg (121 µmol) 4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using 3-hydroxybenzonitrile to give after working up and purification 5.8 mg (9%) of the title compound.

^{1}H-NMR ($CDCl_3$ + CD_3OD): δ= 0.63 (2H), 0.86 (2H), 1.42 (6H), 2.35 (3H), 2.90 (1H), 3.32 (2H), 5.88 (1H), 6.26 (1H), 6.66 (1H), 7.30 (1H), 7.46 (1H), 7.49-7.60 (4H), 7.65 (1H), 7.72 (1H) ppm.

Example 83

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfonyl]-8-[(3,3,3-trifluoropropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide (A) and (RS)-N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfinyl]-8-[(3,3,3-trifluoropropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide (B)



(A) (B)

To a solution of 50 mg (121 µmol) N-cyclopropyl-4-{6-[(3-fluorophenyl) sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide, which was prepared according to intermediate example 209 in 1.0 mL dichloromethane were added 0.71 mg methyl(trioxo)rhenium, 1.77 mg isonicotinonitrile and 58 µL aqueous hydrogen peroxide (30%). The mixture was

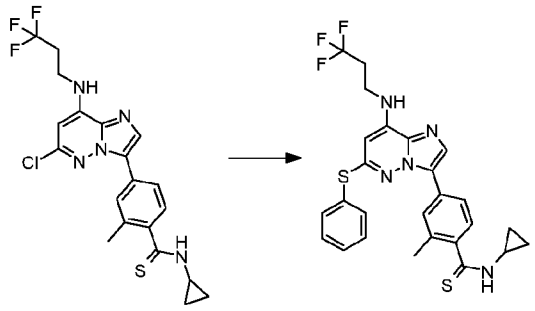
stirred for two days at 23°C, poured into sodium thiosulfate solution and extracted with dichloromethane. The organic phase was dried over sodium sulfate. After filtration and removal of solvent the residue was purified by chromatography to give 14.9 mg (53%) of the title compound A and 4.5 mg (8%) of the title compound B.

^{1}H-NMR ($CDCl_3$ + CD_3OD) of A: δ= 0.65 (2H), 0.90 (2H), 2.47 (3H), 2.59 (2H), 2.92 (1H), 3.75 (2H), 6.08 (1H), 6.76 (1H), 6.77 (1H), 7.33 (1H), 7.38 (1H), 7.53-7.65 (3H), 7.81 (1H), 7.82 (1H), 7.88 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ= 0.65 (2H), 0.92 (2H), 2.55 (5H), 2.94 (1H), 3.73 (2H), 5.98 (1H), 6.37 (1H), 6.60 (1H), 7.17 (1H), 7.46 (1H), 7.50 (1H), 7.56 (1H), 7.60 (1H), 7.74-7.84 (3H) ppm.

Example 84

N-cyclopropyl-2-methyl-4-{6-(phenylsulfanyl)-8-[(3,3,3-trifluoropropyl)amino] imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide

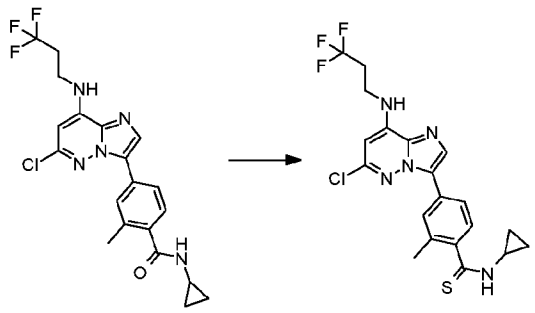


59.1 mg (130 µmol) 4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b] pyridazin-3-yl}-N-cyclopropyl-2-methylbenzenecarbothioamide which was prepared according to intermediate example 84a were transformed in analogy to example 51 using benzenethiol to give after working up and purification 7.1 mg (9%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.75 (2H), 1.05 (2H), 2.30 (3H), 2.47 (2H), 3.41 (1H), 3.56 (2H), 5.87 (2H), 7.16 (1H), 7.27 (1H), 7.41-7.50 (3H), 7.57-7.71 (5H) ppm.

Intermediate example 84a

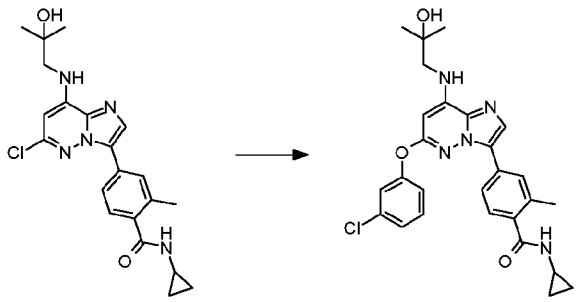
4-{6-Chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzenecarbothioamide



A mixture comprising 100 mg (228 µmol) 4-{6-chloro-8-[(3,3,3-trifluoropropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 10a, 25.4 mg phosphorus pentasulfide and 0.47 mL pyridine were heated at 115°C for 4 hours. Water and brine were added and the mixture was extracted several times with ethyl acetate. The combined organic layers were dried over sodium sulfate. After filtration and removal of the solvent the residue was purified by chromatography to give 65.7 mg (63%) of the title compound.

Example 85

4-{6-(3-Chlorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b] pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

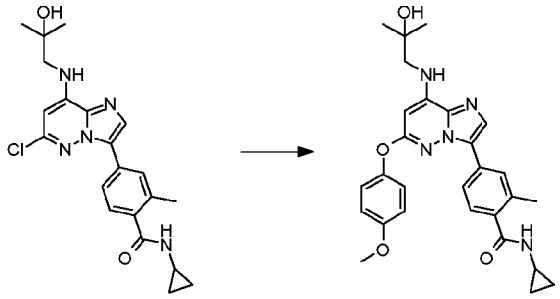


50 mg (121 µmol) 4-{6-Chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using 3-chlorophenol to give after working up and purification 9.3 mg (14%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.47 (2H), 0.63 (2H), 1.16 (6H), 2.14 (3H), 2.77 (1H), 3.29 (2H), 4.74 (1H), 6.18 (1H), 7.03 (1H), 7.17 (1H), 7.25 (1H), 7.33 (1H), 7.44 (1H), 7.47 (1H), 7.67 (1H), 7.74 (1H), 7.93 (1H), 8.22 (1H) ppm.

Example 86

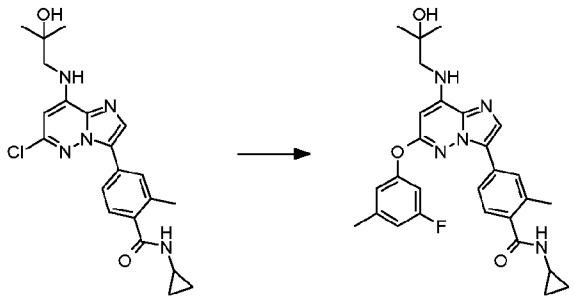
N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(4-methoxyphenoxy) imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



50 mg (121 µmol)
4-{6-Chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using 4-methoxyphenol to give after working up and purification 22.5 mg (35%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.47 (2H), 0.63 (2H), 1.16 (6H), 2.11 (3H), 2.77 (1H), 3.27 (2H), 3.75 (3H), 4.75 (1H), 6.13 (1H), 6.91 (1H), 6.98 (2H), 7.15 (1H), 7.18 (2H), 7.65 (1H), 7.77 (1H), 7.91 (1H), 8.21 (1H) ppm.

Example 87

N-cyclopropyl-4-{6-(3-fluoro-5-methylphenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

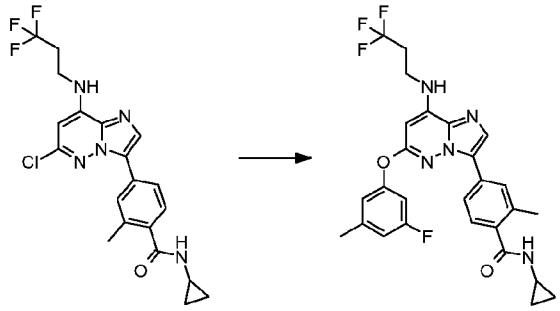


50 mg (121 µmol)
4-{6-Chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using 3-fluoro-5-methylphenol to give after working up and purification 12.0 mg (19%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.47 (2H), 0.63 (2H), 1.15 (6H), 2.15 (3H), 2.31 (3H), 2.77 (1H), 3.27 (2H), 4.73 (1H), 6.16 (1H), 6.90-7.06 (4H), 7.17 (1H), 7.69 (1H), 7.78 (1H), 7.92 (1H), 8.22 (1H) ppm.

Example 88

N-cyclopropyl-4-{6-(3-fluoro-5-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



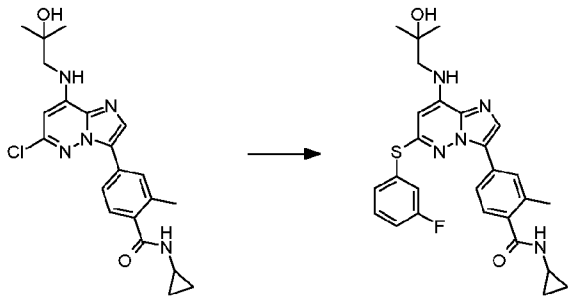
50 mg (114 µmol)

4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 10a were transformed in analogy to example 51 using 3-fluoro-5-methylphenol to give after working up and purification 7.6 mg (12%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.47 (2H), 0.63 (2H), 2.15 (3H), 2.32 (3H), 2.67 (2H), 2.77 (1H), 3.59 (2H), 6.11 (1H), 6.95 (2H), 7.03 (1H), 7.17 (1H), 7.65-7.75 (2H), 7.78 (1H), 7.93 (1H), 8.22 (1H) ppm.

Example 89

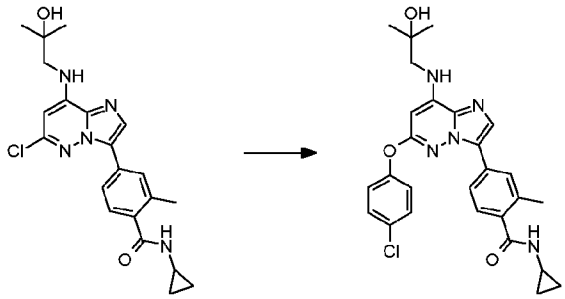
N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



300 mg (725 µmol)
4-{6-Chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using 3-fluorobenzenethiol to give after working up and purification 27.9 mg (7%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.65 (2H), 1.12 (6H), 2.20 (3H), 2.79 (1H), 3.23 (2H), 4.71 (1H), 6.29 (1H), 7.04 (1H), 7.12 (1H), 7.33 (1H), 7.43 (1H), 7.46-7.53 (2H), 7.66 (1H), 7.71 (1H), 7.94 (1H), 8.23 (1H) ppm.

Example 90

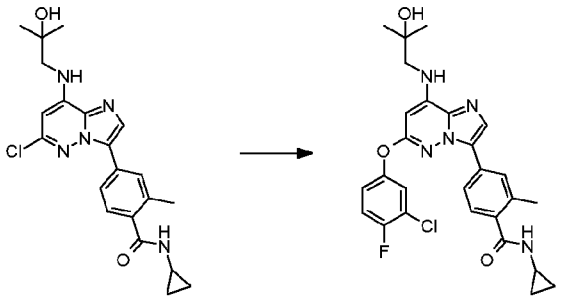
4-{6-(4-Chlorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



50 mg (121 µmol)
4-{6-Chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using 4-chlorophenol to give after working up and purification 14.5 mg (23%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.47 (2H), 0.64 (2H), 1.16 (6H), 2.13 (3H), 2.77 (1H), 3.28 (2H), 4.74 (1H), 6.18 (1H), 7.00 (1H), 7.17 (1H), 7.30 (2H), 7.50 (2H), 7.64 (1H), 7.73 (1H), 7.92 (1H), 8.22 (1H) ppm.

Example 91

4-{6-(3-Chloro-4-fluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

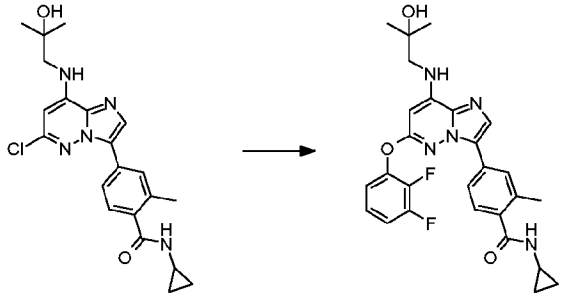


50 mg (121 µmol)
4-{6-Chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using 3-chloro-4-fluorophenol to give after working up and purification 16.2 mg (24%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.47 (2H), 0.64 (2H), 1.16 (6H), 2.13 (3H), 2.77 (1H), 3.28 (2H), 4.74 (1H), 6.18 (1H), 7.02 (1H), 7.18 (1H), 7.32 (1H), 7.51 (1H), 7.66 (2H), 7.72 (1H), 7.93 (1H), 8.22 (1H) ppm.

Example 92

N-cyclopropyl-4-{6-(2,3-difluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

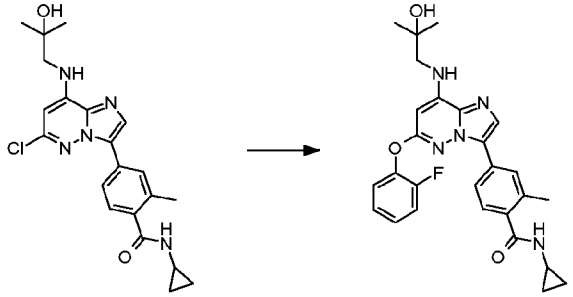


50 mg (121 µmol)
4-{6-Chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using 2,3-difluorophenol to give after working up and purification 5.8 mg (9%) of the title compound.

^{1}H-NMR ($CDCl_3$ + CD_3OD): δ= 0.59 (2H), 0.85 (2H), 1.38 (6H), 2.24 (3H), 2.86 (1H), 3.31 (2H), 5.98 (1H), 6.16 (1H), 6.53 (1H), 7.02-7.14 (3H), 7.17 (1H), 7.47 (1H), 7.61 (2H), ppm.

Example 93

N-cyclopropyl-4-{6-(2-fluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

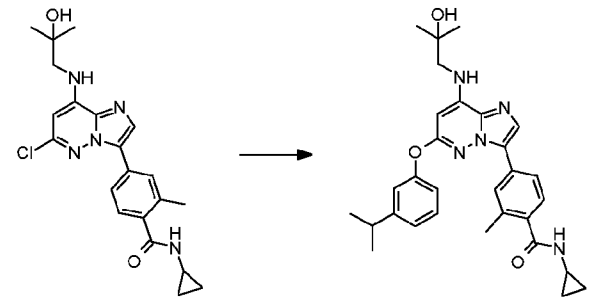


50 mg (121 µmol) 4-{6-Chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using 2-fluorophenol to give after working up and purification 4.2 mg (7%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.46 (2H), 0.63 (2H), 1.17 (6H), 2.08 (3H), 2.46 (2H), 2.76 (1H), 4.75 (1H), 6.25 (1H), 7.03 (1H), 7.11 (1H), 7.24-7.45 (4H), 7.59 (1H), 7.67 (1H), 7.92 (1H), 8.21 (1H) ppm.

Example 94

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(3-isopropylphenoxy) imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



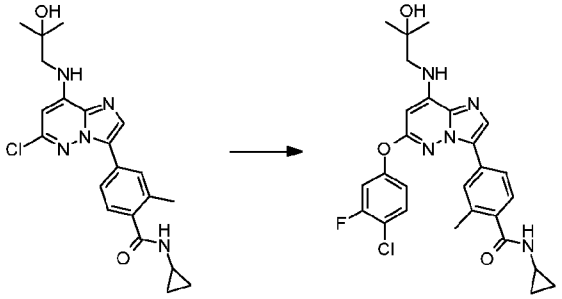
50 mg (121 µmol) 4-{6-Chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate

example 7a were transformed in analogy to example 51 using 3-isopropylphenol to give after working up and purification 9.0 mg (14%) of the title compound.

^{1}H-NMR ($CDCl_3$ + CD_3OD): δ= 0.58 (2H), 0.84 (2H), 1.22 (6H), 1.36 (6H), 2.24 (3H), 2.33 (1H), 2.85 (1H), 2.89 (1H), 3.27 (2H), 5.88 (1H), 6.15 (1H), 6.44 (1H), 7.02 (1H), 7.03 (1H), 7.10 (1H), 7.17 (1H), 7.31 (1H), 7.59 (1H), 7.64 (1H), 7.68 (1H) ppm.

Example 95

4-{6-(4-Chloro-3-fluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo [1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

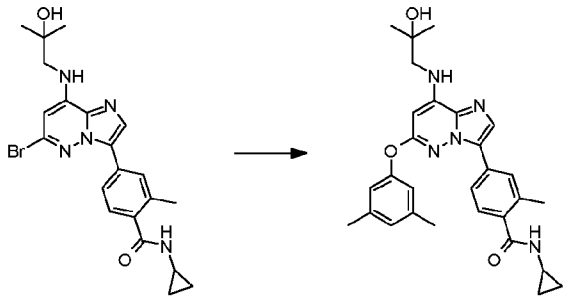


50 mg (121 µmol) 4-{6-Chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using 4-chloro-3-fluorophenol to give after working up and purification 4.0 mg (6%) of the title compound.

^{1}H-NMR ($CDCl_3$ + CD_3OD): δ= 0.60 (2H), 086 (2H), 1.37 (6H), 2.31 (3H), 2.34 (1H), 2.87 (1H), 3.29 (2H), 5.89 (1H), 6.09 (1H), 6.57 (1H), 6.98 (1H), 7.09 (1H), 7.15 (1H), 7.42 (1H), 7.55 (1H), 7.67 (2H) ppm.

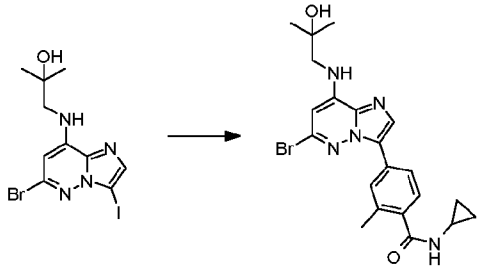
Example 96

N-cyclopropyl-4-{6-(3,5-dimethylphenoxy)-8-[(2-hydroxy-2-methylpropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



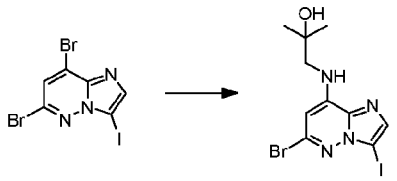
50 mg (109 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using 3,5-dimethylphenol to give after working up and purification 14.6 mg (27%) of the title compound.
^{1}H-NMR ($CDCl_3$): δ= 0.61 (2H), 0.87 (2H), 1.45 (6H), 2.28 (3H), 2.33 (6H), 2.89 (1H), 3.31 (2H), 3.83 (1H), 5.86 (1H), 5.92 (1H), 6.59 (1H), 6.83 (2H), 6.87 (1H), 7.21 (1H), 7.63 (1H), 7.65 (1H), 7.73 (1H) ppm.

Intermediate example 96a
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide (



809 mg (1.97 mmol)
1-[(6-bromo-3-iodoimidazo[1,2-b]pyridazin-8-yl)amino]-2-methylpropan-2-ol which was prepared according to intermediate example 96b were transformed in analogy to intermediate example 1a using
N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide to give after working up and purification 659 mg (73%) of the title compound.

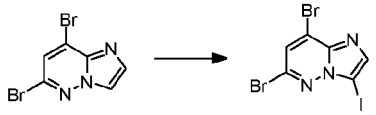
Intermediate example 96b
1-[(6-bromo-3-iodoimidazo[1,2-b]pyridazin-8-yl)amino]-2-methylpropan-2-ol



1.0 g (2.48 mmol) 6,8-dibromo-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 96c were transformed in analogy to intermediate example 1b using 1-amino-2-methylpropan-2-ol to give after working up and purification 915 mg (90%) of the title compound.

Intermediate example 96c

6,8-dibromo-3-iodoimidazo[1,2-b]pyridazine



A mixture comprising 3.64 g (10.5 mmol) 6,8-dibromoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 96d, 2.8 g N-iodosuccinimide, 72.6 mL N,N-dimethylformamide was heated at 60°C for 3 hours. 1.4 g N-iodosuccinimide were added and heating was continued for additional 4 hours. Most of the solvent was removed, water was added and the mixture was extracted with dichloromethane. The organic phase was washed with water, sodium thiosulfate solution and dried over sodium sulfate. After filtration and removal of solvent the residue was purified by chromatography to give 3.64 g (86%) of the title compound.

Intermediate example 96d

6,8-dibromoimidazo[1,2-b]pyridazine

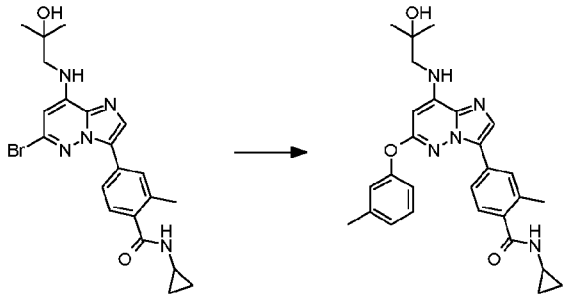


A mixture of 5.0 (14.0 mmol) 8-bromo-6-chloro-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 1c, 30 mL of hydrogen bromide solution in acetic acid (33%) was stirred at 120°C for 1 hour under microwave irradiation. The mixture was poured into water and extracted with dichloromethane. The organic phase was washed with sodium thiosulfate and sodium hydrogencarbonate solution and dried over sodium sulfate. After filtration

and removal of solvent the residue was purified by chromatography to give 3.0 g (78%) of the title compound.

Example 97

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(3-methylphenoxy) imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

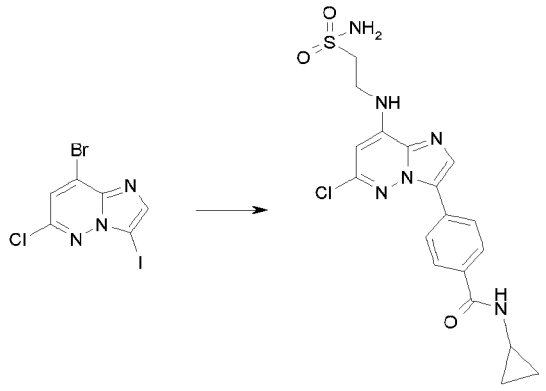


50 mg (109 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using 3-methylphenol to give after working up and purification 17.1 mg (32%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.61 (2H), 0.87 (2H), 1.46 (6H), 2.26 (3H), 2.37 (3H), 2.89 (1H), 3.31 (2H), 5.87 (1H), 5.94 (1H), 6.61 (1H), 6.98-7.09 (3H), 7.19 (1H), 7.29 (1H), 7.59 (1H), 7.63 (1H), 7.70 (1H) ppm.

Example 98

4-{6-Chloro-8-[(2-sulfamoylethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide

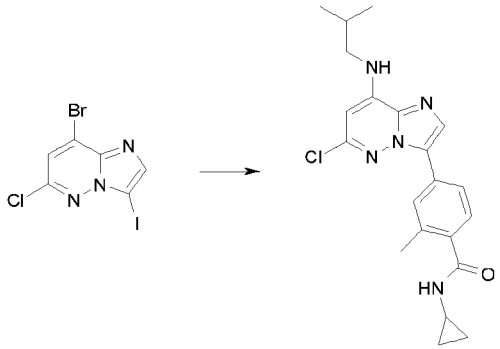


8-Bromo-6-chloro-3-iodoimidazo[1,2-b]pyridazine (0.3 mmol) which was prepared according to intermediate example 1c , 2-aminoethanesulfonamide hydrochloride

(1:1) (0.3 mmol, 1.0 eq)) and DIPEA (3 eq, 157 µL) were combined with 3mL NMP in a sealed vial and heated at 160 °C under microwave irradiation for 30 min. After cooling, [4-(cyclopropylcarbamoyl)phenyl]boronic acid (1.2 eq, 74 mg), Pd(dppf)Cl2 (0.2 eq, 49 mg) and potassium carbonate (3 eq, 900 µL, 1M in water) were added and the mixture was heated at 80 °C overnight. After cooling, the solution was filtered and subjected to preparative HPLC to give 4-{6-chloro-8-[(2-sulfamoylethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl benzamide (45 mg, 35 %): UPLC-MS: RT = = 0.92 min; m/z (ES+) 435.9 [MH+]; required MW = 434.9.

Intermediate example 99

4-{6-Chloro-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



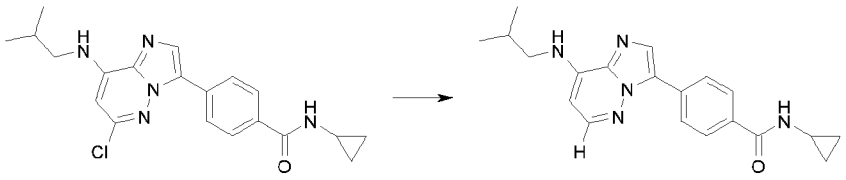
6 g (16.7 mmol) 8-Bromo-6-chloro-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 1c were transformed in analogy to example 98 using 2-methylpropan-1-amine and N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide to give after working up and purification 1.27 g (19%) of the title compound.

UPLC-MS: RT = 1.32 min; m/z (ES+) 398.9 [MH+]; required MW = 397.9.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.65 (2H), 0.90 (6H), 1.96 (1H), 2.35 (3H), 2.80 (1H), 3.12 (2H), 6.29 (1H), 7.36 (1H), 7.84 (1H), 7.91 (1H), 7.96 (1H), 7.99 (1H), 8.29 (1H) ppm.

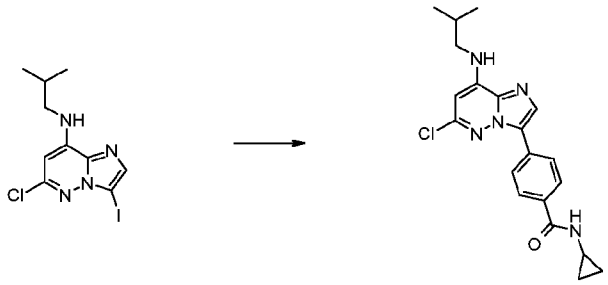
Example 100

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl} benzamide



100 mg (260 µmol) 4-{6-chloro-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylb enzamide which was prepared according to intermediate example 100a were dissolved in 50 mL ethanol and subjected to flow hydrogenation using an H-Cube with cartridge Pd/C 10% CATCART 30 at 30°C, 10 bar and 0.8 mL/min flow. Purification by RP-HPLC yielded 21.1 mg (23%) of the title compound.
UPLC-MS: RT = 1.13 min; m/z (ES+) 350.4 [MH+]; required MW = 349.4.
^{1}H-NMR (DMSO-d6): δ= 0.56 (2H), 0.67 (2H), 0.90 (6H), 1.96 (1H), 2.82 (1H), 3.11 (2H), 6.15 (1H), 7.54 (1H), 7.87 (2H), 8.04 (1H), 8.12 (1H),-8.21 (2H), 8.43 (1H) ppm.

Intermediate Example 100a
4-{6-chloro-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylb enzamide

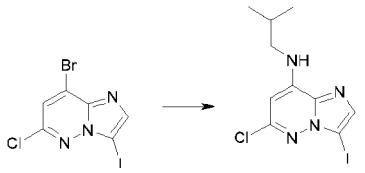


1 mmol 6-chloro-3-iodo-N-(2-methylpropyl)imidazo[1,2-b]pyridazin-8-amine (10 mL, 0.1 M in NMP), which was prepared according to intermediate example 100b, 1.5 mmol [4-(cyclopropylcarbamoyl)phenyl]boronic acid, 0.2 mmol Pd(dppf)Cl_2 and 3 mmol potassium carbonate (3 mL, 1M in water, 3 eq) were combined in a sealed vial and heated at 150 °C for 180 min. After cooling, the mixture was treated with water and extracted with ethyl acetate, the combined organic layers were dried and concentrated, purified by flash silica gel column chromatography (Ethyl acetate:Petroleum ether 1:5) give 115 mg (30 %) of the title compound.
UPLC-MS: RT = 1.29 min; m/z (ES+) 384.9 [MH+]; required MW 383.9.

^{1}H-NMR (DMSO-d6): δ= 0.60 (2H), 0.72 (2H), 0.93 (6H), 2.0 (1H), 2.87 (1H), 3.34 (2H), 6.33 (1H), 7.92 (1H), 8.07 (2H), 8.16 (2H), 8.48 (1H) ppm.

Intermediate Example 100b

6-chloro-3-iodo-N-(2-methylpropyl)imidazo[1,2-b]pyridazin-8-amine



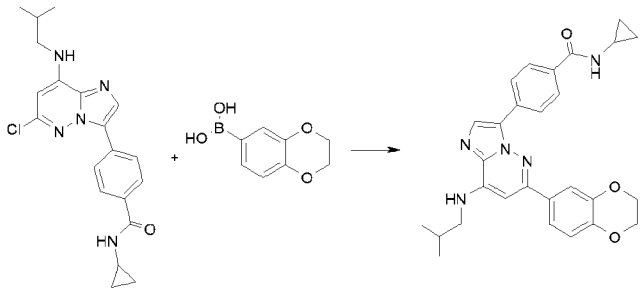
To a solution of 200 mg (0.558 mmol) 8-bromo-6-chloro-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 1c in 4 mL N,N-dimethylformamide were added 122 mg 2-methylpropan-1-amine and the mixture was stirred at rt overnight. Water was added and the mixture was extracted with dichloromethane and methanol. The organic phase was washed with water and dried over sodium sulfate. After filtration and removal of solvent the residue was purified by chromatography to give 188 mg (96%) of the title compound.

UPLC-MS: RT = 1.36 min; m/z (ES+) 351.6 [MH+]; required MW 350.6.

^{1}H-NMR (DMSO-d6): δ= 1.04 (6H), 2.00 (1H), 3.13 (2H), 6.00 (1H), 7.27 (1H), 7.53 (1H) ppm.

Example 101

3-[4-(2-Cyclopropyl-1H-imidazol-5-yl)phenyl]-6-ethenyl-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine

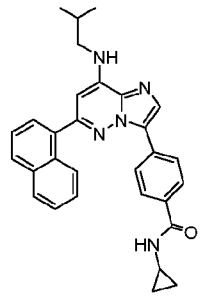
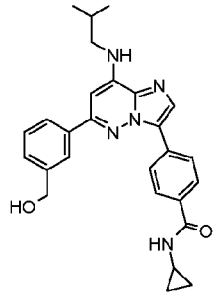
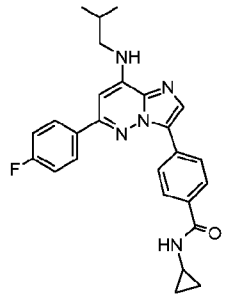


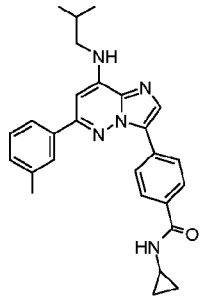
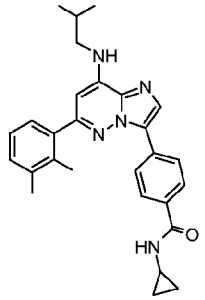
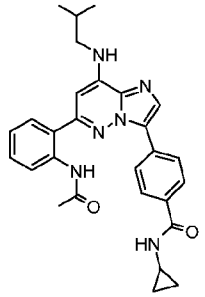
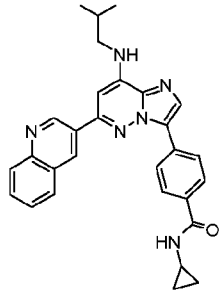
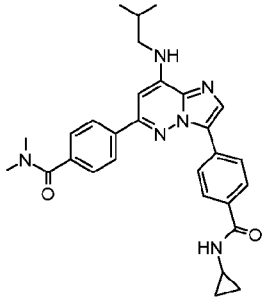
0.1 mmol 4-{6-chloro-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide (1 mL, 0.1 M in NMP), which was prepared according to intermediate example 100a, 0.4 mmol 2,3-dihydro-1,4-benzodioxin-6-ylboronic acid (0.8 mL, 0.5 M in NMP, 4 eq), 0.02 mmol $Pd(dppf)Cl_2$ (0.3 eq, 800 µL, 0.0375 M in

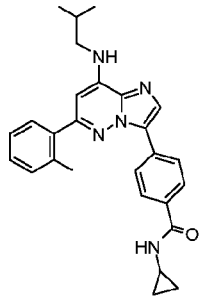
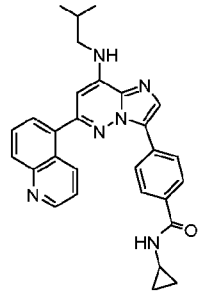
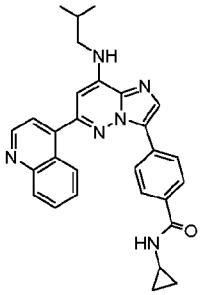
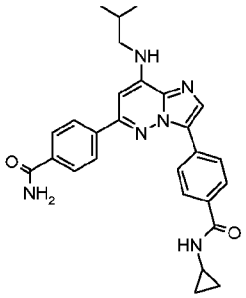
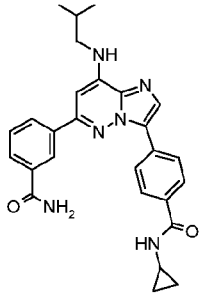
NMP) and 0.3 mmol potassium carbonate (0.3 mL, 1M in water, 3 eq) were combined in a sealed vial and heated at 150 °C under microwave irradiation for 90 min. After cooling, the solution was filtered and subjected to preparative HPLC to give 4.2 mg (8 %) of the title compound.

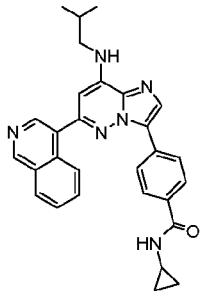
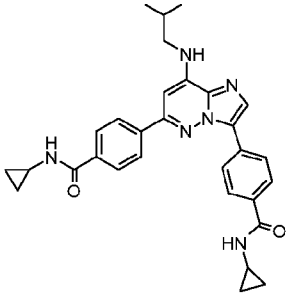
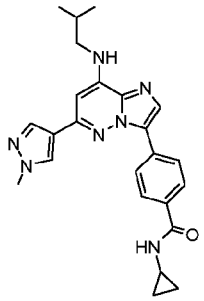
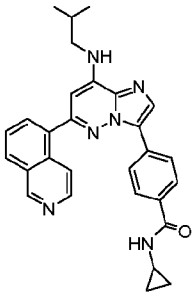
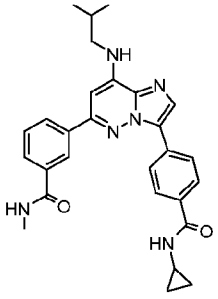
UPLC-MS: RT = 1.34 min; m/z (ES+) 484.6 [MH+]; required MW = 483.6.

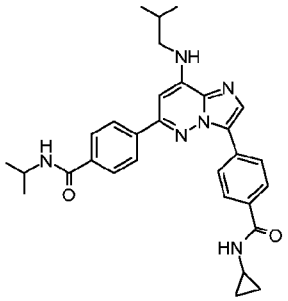
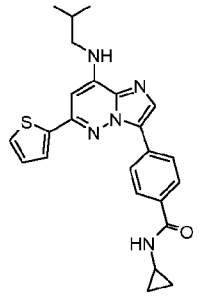
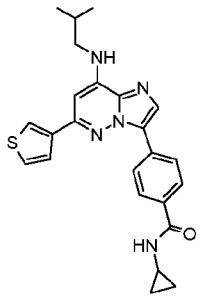
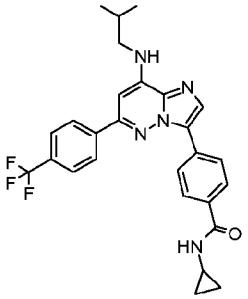
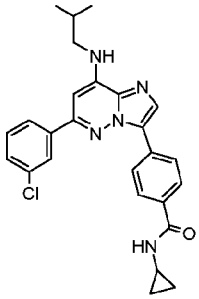
The following compound examples were prepared analogously to the procedure described above using the appropriate intermediate and the appropriate boronic acid building block [LC-MS data such as retention time (RT in min) or observed mass peak were collected using LC-MS Method A unless explicitly stated]:

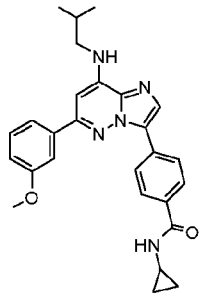
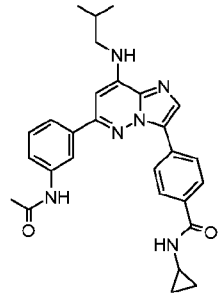
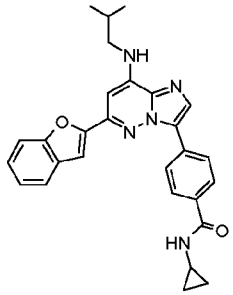
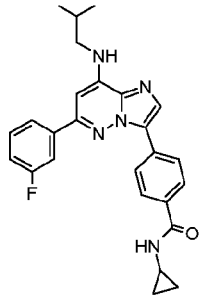
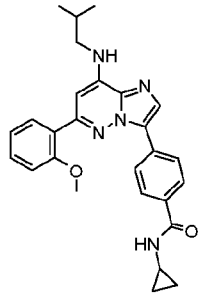
Example	Structure	Name	Analytical Data
102		N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(naphthalen-1-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.47 MWfound = 476.6 MWcalc = 475.6
103		N-cyclopropyl-4-{6-[3-(hydroxymethyl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.18 MWfound = 456.6 MWcalc = 455.6
104		N-cyclopropyl-4-{6-(4-fluorophenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.39 MWfound = 444.5 MWcalc = 443.5

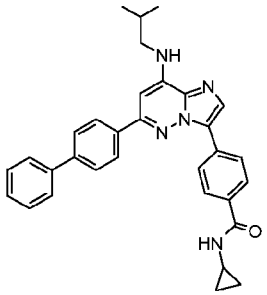
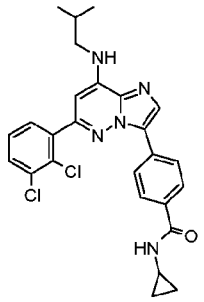
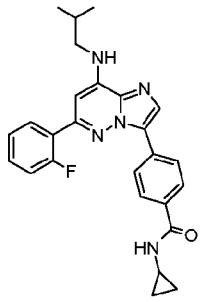
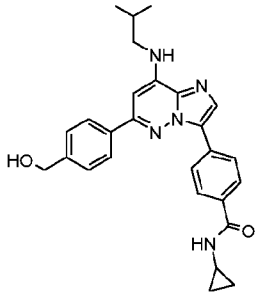
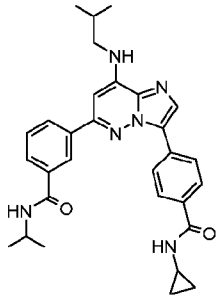
Example	Structure	Name	Analytical Data
105		N-cyclopropyl-4-{6-(3-methylphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.44 MWfound = 440.6 MWcalc = 439.6
106		N-cyclopropyl-4-{6-(2,3-dimethylphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.46 MWfound = 454.6 MWcalc = 453.6
107		4-{6-[2-(Acetylamino)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide	RT = 1.22 MWfound = 483.6 MWcalc = 482.6
108		N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(quinolin-3-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.32 MWfound = 477.6 MWcalc = 476.6
109		4-{3-[4-(Cyclopropylcarbamoyl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}-N,N-dimethylbenzamide	RT = 1.19 MWfound = 497.6 MWcalc = 496.6

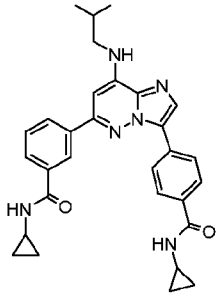
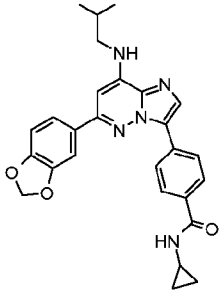
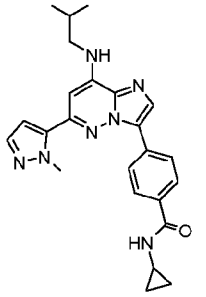
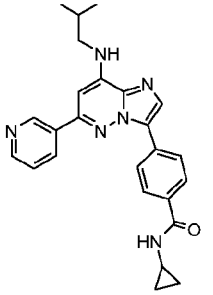
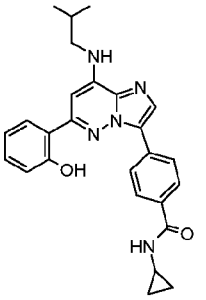
Example	Structure	Name	Analytical Data
110		N-cyclopropyl-4-{6-(2-methylphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.41 MWfound = 440.6 MWcalc = 439.6
111		N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(quinolin-5-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.18 MWfound = 477.6 MWcalc = 476.6
112		N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(quinolin-4-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.23 MWfound = 477.6 MWcalc = 476.6
113		4-{6-(4-Carbamoylphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide	RT = 1.10 MWfound = 469.6 MWcalc = 468.6
114		4-{6-(3-Carbamoylphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide	RT = 1.11 MWfound = 469.6 MWcalc = 468.6

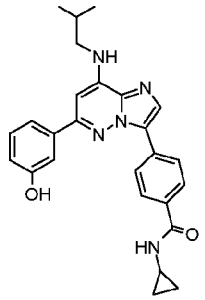
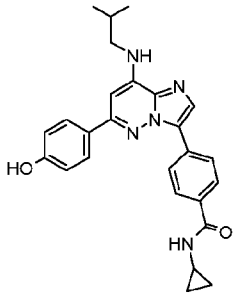
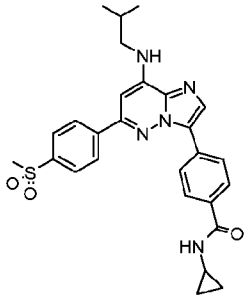
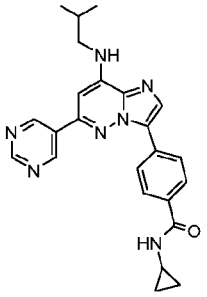
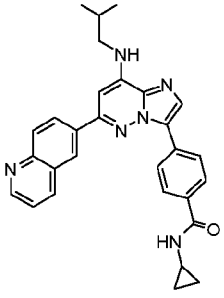
Example	Structure	Name	Analytical Data
115		N-cyclopropyl-4-{6-(isoquinolin-4-yl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.21 MWfound = 477.6 MWcalc = 476.6
116		4,4'-{8-[(2-Methylpropyl)amino]imidazo[1,2-b]pyridazine-3,6-diyl}bis(N-cyclopropylbenzamide)	RT = 1.21 MWfound = 509.6 MWcalc = 508.6
117		N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.12 MWfound = 430.5 MWcalc = 429.5
118		N-cyclopropyl-4-{6-(isoquinolin-5-yl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.09 MWfound = 477.6 MWcalc = 476.6
119		3-{3-[4-(Cyclopropylcarbamoyl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}-N-methylbenzamide	RT = 1.16 MWfound = 483.6 MWcalc = 482.6

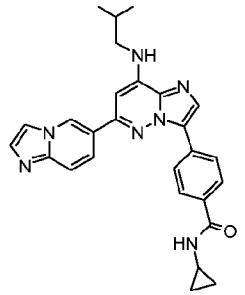
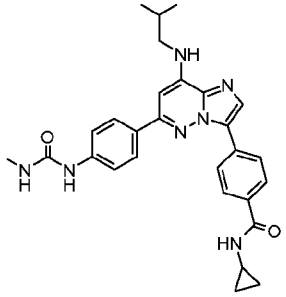
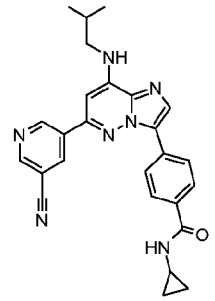
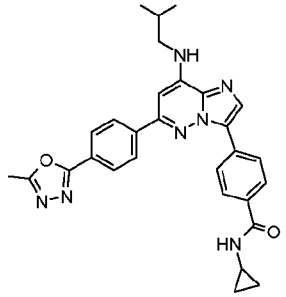
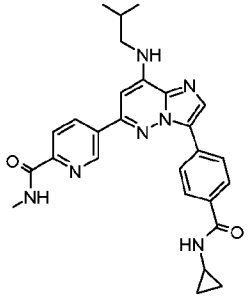
Example	Structure	Name	Analytical Data
120		4-{3-[4-(Cyclopropylcarbamoyl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}-N-(propan-2-yl)benzamide	RT = 1.25 MWfound = 511.6 MWcalc = 510.6
121		N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(thiophen-2-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.36 MWfound = 432.6 MWcalc = 431.6
122		N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(thiophen-3-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.35 MWfound = 432.6 MWcalc = 431.6
123		N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-[4-(trifluoromethyl)phenyl]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.49 MWfound = 494.5 MWcalc = 493.5
124		4-{6-(3-Chlorophenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide	RT = 1.48 MWfound = 461.0 MWcalc = 460.0

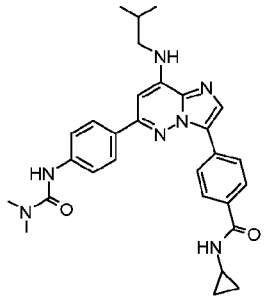
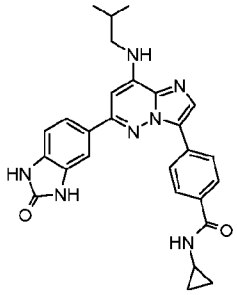
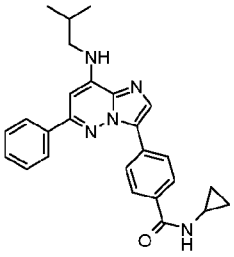
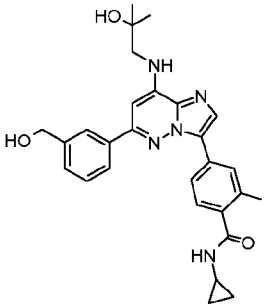
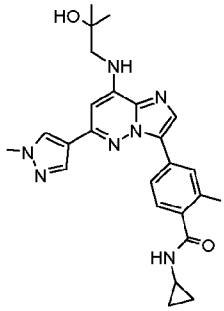
Example	Structure	Name	Analytical Data
125		N-cyclopropyl-4-{6-(3-methoxyphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.38 MWfound = 456.6 MWcalc = 455.6
126		4-{6-[3-(Acetylamino)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide	RT = 1.19 MWfound = 483.6 MWcalc = 482.6
127		4-{6-(1-Benzofuran-2-yl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide	RT = 1.48 MWfound = 466.5 MWcalc = 465.5
128		N-cyclopropyl-4-{6-(3-fluorophenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.40 MWfound = 444.5 MWcalc = 443.5
129		N-cyclopropyl-4-{6-(2-methoxyphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.34 MWfound = 456.6 MWcalc = 455.6

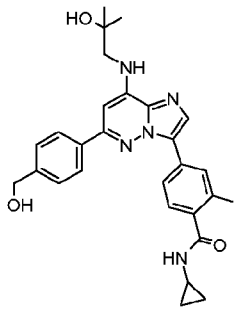
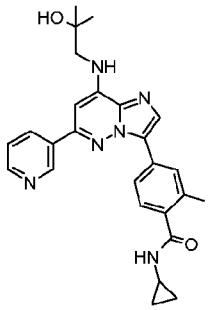
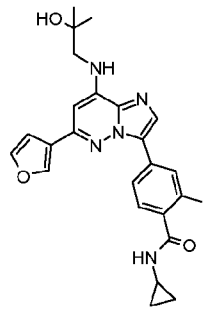
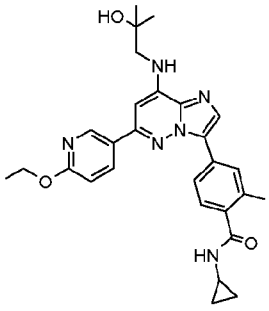
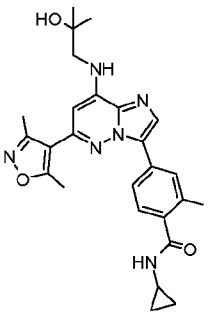
Example	Structure	Name	Analytical Data
130		4-{6-(Biphenyl-4-yl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide	RT = 1.56 MWfound = 502.6 MWcalc = 501.6
131		N-cyclopropyl-4-{6-(2,3-dichlorophenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.49 MWfound = 495.4 MWcalc = 494.4
132		N-cyclopropyl-4-{6-(2-fluorophenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.38 MWfound = 444.5 MWcalc = 443.5
133		N-cyclopropyl-4-{6-[4-(hydroxymethyl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.17 MWfound = 456.6 MWcalc = 455.6
134		3-{3-[4-(Cyclopropylcarbamoyl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}-N-(propan-2-yl)benzamide	RT = 1.26 MWfound = 511.6 MWcalc = 510.6

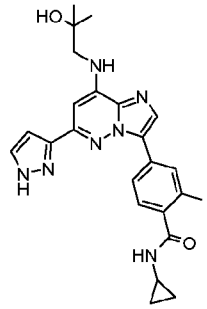
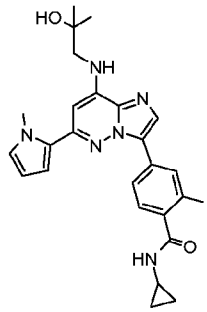
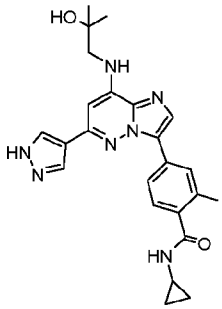
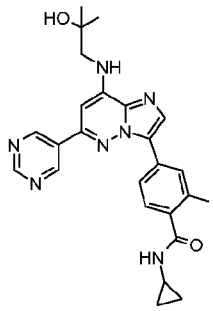
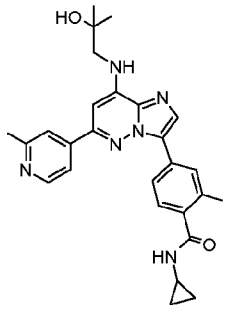
Example	Structure	Name	Analytical Data
135		N-cyclopropyl-3-{3-[4-(cyclopropylcarbamoyl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}benzamide	RT = 1.21 MWfound = 509.6 MWcalc = 508.6
136		4-{6-(1,3-Benzodioxol-5-yl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide	RT = 1.34 MWfound = 470.5 MWcalc = 469.5
137		N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.19 MWfound = 430.5 MWcalc = 429.5
138		N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(pyridin-3-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.11 MWfound = 427.5 MWcalc = 426.5
139		N-cyclopropyl-4-{6-(2-hydroxyphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.35 MWfound = 442.5 MWcalc = 441.5

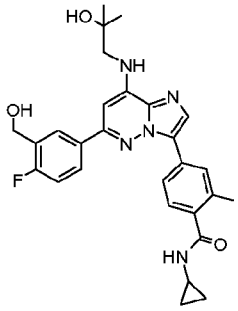
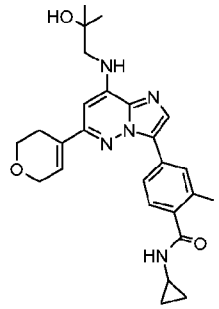
Example	Structure	Name	Analytical Data
140		N-cyclopropyl-4-{6-(3-hydroxyphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.21 MWfound = 442.5 MWcalc = 441.5
141		N-cyclopropyl-4-{6-(4-hydroxyphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.18 MWfound = 442.5 MWcalc = 441.5
142		N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-[4-(methylsulfonyl)phenyl]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.21 MWfound = 504.6 MWcalc = 503.6
143		N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(pyrimidin-5-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.13 MWfound = 428.5 MWcalc = 427.5
144		N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(quinolin-6-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.21 MWfound = 477.6 MWcalc = 476.6

Example	Structure	Name	Analytical Data
145		N-cyclopropyl-4-{6-(imidazo[1,2-a]pyridin-6-yl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 0.84 MWfound = 466.5 MWcalc = 465.5
146		N-cyclopropyl-4-(6-{4-[(methylcarbamoyl)amino]phenyl}-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl)benzamide	RT = 1.13 MWfound = 498.6 MWcalc = 497.6
147		4-{6-(5-Cyanopyridin-3-yl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide	RT = 1.23 MWfound = 452.5 MWcalc = 451.5
148		N-cyclopropyl-4-{6-[4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.26 MWfound = 508.6 MWcalc = 507.6
149		5-{3-[4-(Cyclopropylcarbamoyl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}-N-methylpyridine-2-carboxamide	RT = 1.18 MWfound = 484.6 MWcalc = 483.6

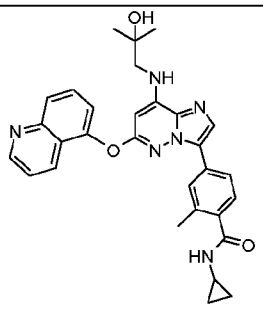
Example	Structure	Name	Analytical Data
150		N-cyclopropyl-4-(6-{4-[(dimethylcarbamoyl)amino]phenyl}-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl)benzamide	RT = 1.18 MWfound = 512.6 MWcalc = 511.6
151		N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.07 MWfound = 482.5 MWcalc = 481.5
152		N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-phenylimidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.39 MWfound = 426.5 MWcalc = 425.5
153		N-cyclopropyl-4-{6-[3-(hydroxymethyl)phenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.00 MWfound = 486.6 MWcalc = 485.6
154		N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 0.93 MWfound = 460.5 MWcalc = 459.5

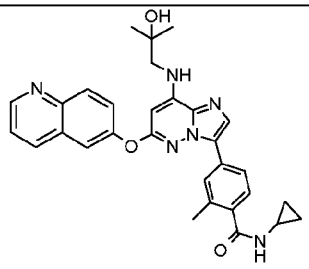
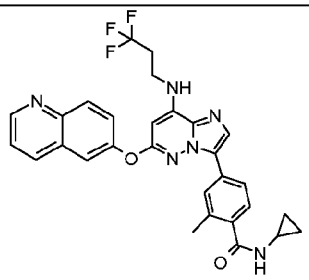
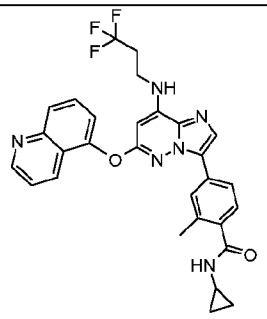
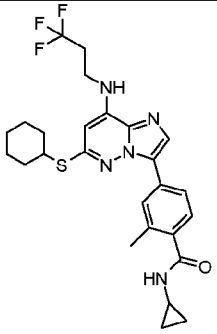
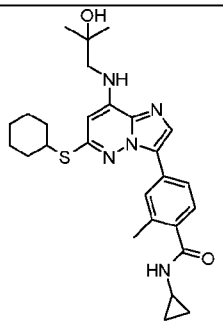
Example	Structure	Name	Analytical Data
155		N-cyclopropyl-4-{6-[4-(hydroxymethyl)phenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 0.97 MWfound = 486.6 MWcalc = 485.6
156		N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-3-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 0.91 MWfound = 457.5 MWcalc = 456.5
157		N-cyclopropyl-4-{6-(furan-3-yl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.09 MWfound = 446.5 MWcalc = 445.5
158		N-cyclopropyl-4-{6-(6-ethoxypyridin-3-yl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.20 MWfound = 501.6 MWcalc = 500.6
159		N-cyclopropyl-4-{6-(3,5-dimethyl-1,2-oxazol-4-yl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.06 MWfound = 475.6 MWcalc = 474.6

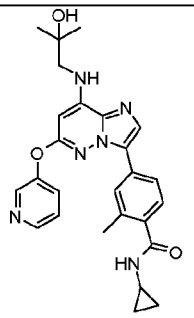
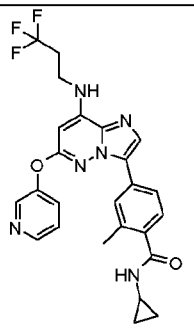
Example	Structure	Name	Analytical Data
160		N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1H-pyrazol-3-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 0.90 MWfound = 446.5 MWcalc = 445.5
161		N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1-methyl-1H-pyrrol-2-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.12 MWfound = 459.6 MWcalc = 458.6
162		N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 0.84 MWfound = 446.5 MWcalc = 445.5
163		N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyrimidin-5-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 0.94 MWfound = 458.5 MWcalc = 457.5
164		N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(2-methylpyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 0.80 MWfound = 471.6 MWcalc = 470.6

Example	Structure	Name	Analytical Data
165		N-cyclopropyl-4-{6-[4-fluoro-3-(hydroxymethyl)phenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.04 MWfound = 504.6 MWcalc = 503.6
166		N-cyclopropyl-4-{6-(3,6-dihydro-2H-pyran-4-yl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.06 MWfound = 462.6 MWcalc = 461.6

The following compound examples were prepared analogously to the procedure described for example 51 using the appropriate alcohol or thiol building block [LC-MS data such as retention time (RT in min) or observed mass peak were collected using LC-MS Method A unless explicitly stated]:

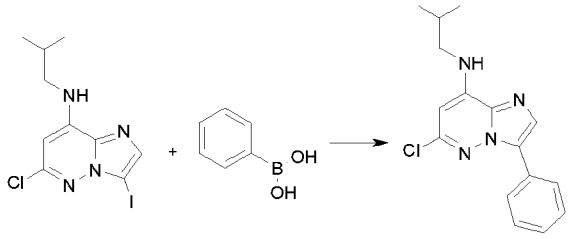
Example	Structure	Name	Analytical Data
167		N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(quinolin-5-yloxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.03 MW_{found} = 523.6 MW_{calc} = 522.6

Example	Structure	Name	Analytical Data
168		N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(quinolin-6-yloxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 0.99 MW_{found} = 523.6 MW_{calc} = 522.6
169		N-cyclopropyl-2-methyl-4-{6-(quinolin-6-yloxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.17 MW_{found} = 547.6 MW_{calc} = 546.6
170		N-cyclopropyl-2-methyl-4-{6-(quinolin-5-yloxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.20 MW_{found} = 547.6 MW_{calc} = 546.6
171		4-{6-(cyclohexylsulfanyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide	RT = 1.51 MW_{found} = 518.6 MW_{calc} = 517.6
172		4-{6-(cyclohexylsulfanyl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide	RT = 1.36 MW_{found} = 494.7 MW_{calc} = 493.7

Example	Structure	Name	Analytical Data
173		N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-3-yloxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 0.96 MW_{found} = 473.6 MW_{calc} = 472.6
174		N-cyclopropyl-2-methyl-4-{6-(pyridin-3-yloxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.14 MW_{found} = 497.5 MW_{calc} = 496.5

Example 175

3-[4-(2-Cyclopropyl-1H-imidazol-5-yl)phenyl]-6-ethenyl-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine

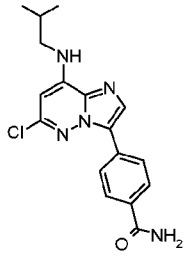
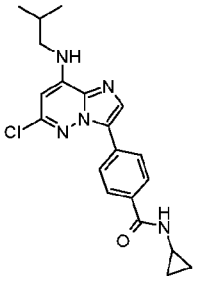
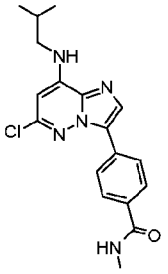
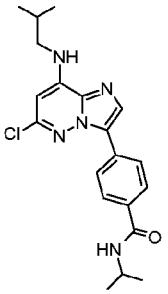


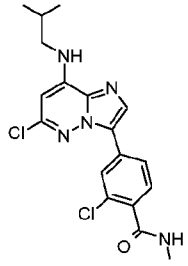
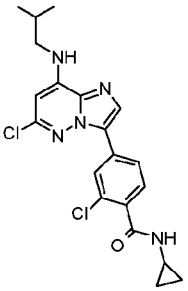
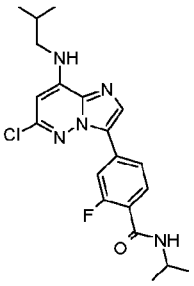
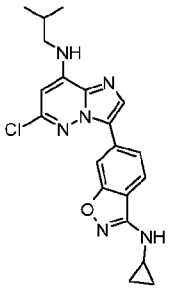
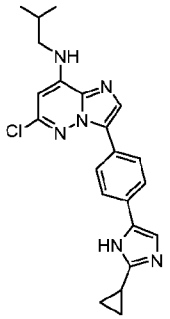
52 mg (150 µmol) 6-chloro-3-iodo-N-(2-methylpropyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 100b were transformed in analogy to intermediate example 1a using phenylboronic acid to give after working up and purification 7.4 mg (17%) of the title compound.

UPLC-MS: RT = 1.50 min; m/z (ES+) 301.8 [MH+]; required MW = 300.8.

The following compound examples were prepared analogously to the procedure described above using the appropriate boronic acid building block [LC-MS data such

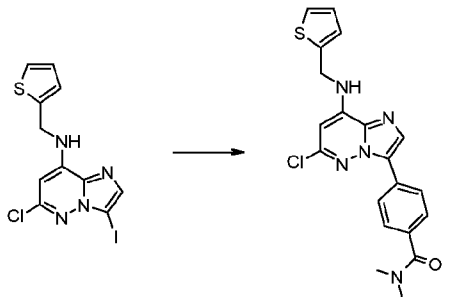
as retention time (RT in min) or observed mass peak were collected using LC-MS Method A unless explicitly stated]:

Example	Structure	Name	Analytical Data
176		4-{6-Chloro-8-[(2-methylpropyl) amino]imidazo[1,2-b]pyridazin-3 -yl}benzamide	RT = 1.17 MW_{found} = 344.8 MW_{calc} = 343.8
177		4-{6-Chloro-8-[(2-methylpropyl) amino]imidazo[1,2-b]pyridazin-3 -yl}-N-cyclopropylbenzamide	RT = 1.29 MW_{found} = 384.9 MW_{calc} = 383.9
178		4-{6-Chloro-8-[(2-methylpropyl) amino]imidazo[1,2-b]pyridazin-3 -yl}-N-methylbenzamide	RT = 1.22 MW_{found} = 358.8 MW_{calc} = 357.8
179		4-{6-Chloro-8-[(2-methylpropyl) amino]imidazo[1,2-b]pyridazin-3 -yl}-N-(propan-2-yl)benzamide	RT = 1.34 MW_{found} = 386.9 MW_{calc} = 385.9

Example	Structure	Name	Analytical Data
180		2-Chloro-4-{6-chloro-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-methylbenzamide	RT = 1.27 MW_{found} = 393.3 MW_{calc} = 392.3
181		2-Chloro-4-{6-chloro-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide	RT = 1.34 MW_{found} = 419.3 MW_{calc} = 418.3
182		4-{6-Chloro-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-fluoro-N-(propan-2-yl)benzamide	RT = 1.42 MW_{found} = 404.9 MW_{calc} = 403.9
183		6-Chloro-3-[3-(cyclopropylamino)-1,2-benzoxazol-6-yl]-N-(2-methylpropyl)imidazo[1,2-b]pyridazin-8-amine	RT = 1.40 MW_{found} = 397.9 MW_{calc} = 396.9
184		6-Chloro-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-N-(2-methylpropyl)imidazo[1,2-b]pyridazin-8-amine	RT = 0.95 MW_{found} = 407.9 MW_{calc} = 406.9

Example 185

4-{6-Chloro-8-[(thiophen-2-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,N-dimethylbenzamide

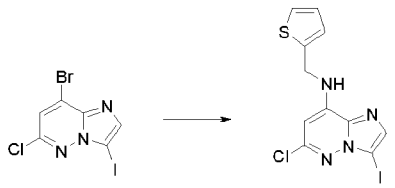


117 mg (300 µmol) 6-chloro-3-iodo-N-(thiophen-2-ylmethyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 185a were transformed in analogy to intermediate example 100a using [4-(dimethylcarbamoyl)phenyl]boronic acid to give after working up and purification 15 mg (12%) of the title compound.

UPLC-MS: RT = 1.25 min; m/z (ES+) 412.9 [MH+]; required MW 411.9.

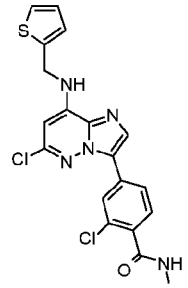
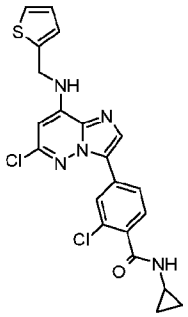
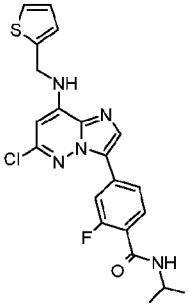
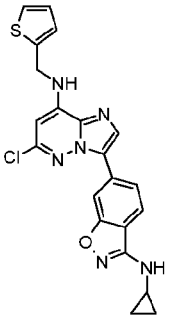
Intermediate Example 185a

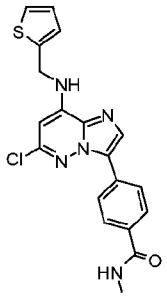
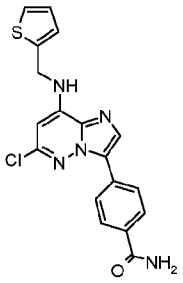
6-chloro-3-iodo-N-(thiophen-2-ylmethyl)imidazo[1,2-b]pyridazin-8-amine



6-chloro-3-iodo-N-(thiophen-2-ylmethyl)imidazo[1,2-b]pyridazin-8-amine was prepared in analogy to example 100b using 1-(thiophen-2-yl)methanamine which was prepared according to intermediate example 1c to give after working up and purification 80% of the title compound.

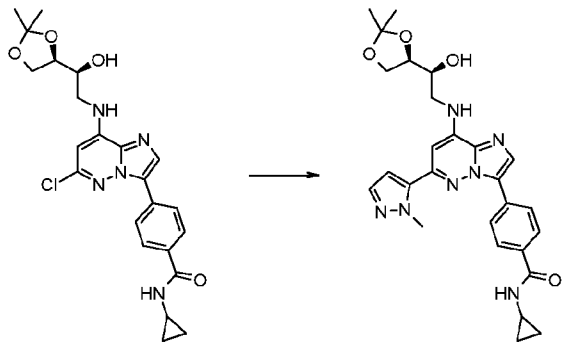
The following compound examples were prepared analogously to the procedure described for example 185 using the appropriate boronic acid building block [LC-MS data such as retention time (RT in min) or observed mass peak were collected using LC-MS Method A unless explicitly stated]:

Example	Structure	Name	Analytical Data
186		2-Chloro-4-{6-chloro-8-[(thiophen-2-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-methylbenzamide	RT = 1.24 MW_{found} = 433.3 MW_{calc} = 432.3
187		2-Chloro-4-{6-chloro-8-[(thiophen-2-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide	RT = 1.31 MW_{found} = 459.4 MW_{calc} = 458.4
188		4-{6-Chloro-8-[(thiophen-2-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-fluoro-N-(propan-2-yl)benzamide	RT = 1.40 MW_{found} = 444.9 MW_{calc} = 443.9
189		6-Chloro-3-[3-(cyclopropylamino)-1,2-benzoxazol-6-yl]-N-(thiophen-2-ylmethyl)imidazo[1,2-b]pyridazin-8-amine	RT = 1.37 MW_{found} = 437.9 MW_{calc} = 436.9

190		4-{6-Chloro-8-[(thiophen-2-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-methylbenzamide	RT = 1.45 MW_{found} = 398.9 MWcalc = 397.9
191		4-{6-Chloro-8-[(thiophen-2-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.14 MW_{found} = 384.9 MW_{calc} = 383.9

Example 192

N-cyclopropyl-4-[8-({(2S)-2-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-hydroxyethyl}amino)-6-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-3-yl] benzamide

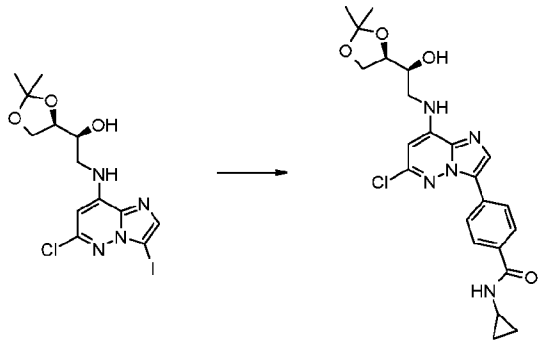


To a mixture of 52 mg (94 µmol) 4-[6-chloro-8-({(2S)-2-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-hydroxyethyl}amino)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropylbenzamide which was prepared according to intermediate example 192a, 33 mg 1-methyl-1H-pyrazol-5-yl) boronic acid, 6.5 mg tetrakis(triphenylphosphin)palladium in 1 mL of ethanol and 1 mL of toluene was added 0.26 mL of an aqueous 10% sodiumbicarbonate solution and the mixture was stirred at 120°C for 2 hours under microwave irradiation. Then the mixture was filtered, the solvent was removed and the residue was purified by chromatography to give 36 mg of the title compounds.

1H-NMR (DMSO-d6): δ= 0.49-0.68 (4H), 1.24 (3H), 1.32 (3H), 2.62 (1H), 3.31 - 3.95 (3H), 3.60 - 4.05 (3H), 4.12 (3H), 6.54 (1H), 6.85 (1H), 7.31 (1H) 7.90 (2H), 8.07 (1H), 8.18 (2H), 8.45 (1H), ppm.

Intermediate example 192a

4-[6-chloro-8-({(2S)-2-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-hydroxyethyl}amino) imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropylbenzamide

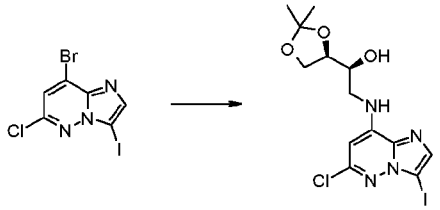


300 mg (684 µmol)

(1S)-2-[(6-chloro-3-iodoimidazo[1,2-b]pyridazin-8-yl)amino]-1-[(4R)-2,2-dimethyl-1, 3-dioxolan-4-yl]ethanol which was prepared according to intermediate example 192b were transformed in analogy to intermediate example 1a using [4-(cyclopropylcarbamoyl)phenyl]boronic acid to give after working up and purification 17 mg (5%) of the title compound.

Intermediate example 192b

(1S)-2-[(6-chloro-3-iodoimidazo[1,2-b]pyridazin-8-yl)amino]-1-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]ethanol

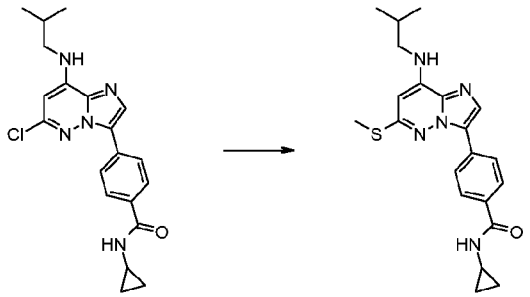


700 mg (1.95 mmol) 8-bromo-6-chloro-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 1c were transformed in analogy to intermediate example 1b using

(1S)-2-amino-1-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]ethanol to give after working up and purification 512 mg (60%) of the title compound.

Example 193

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(methylsulfanyl)imidazo[1,2-b] pyridazin-3-yl}benzamide

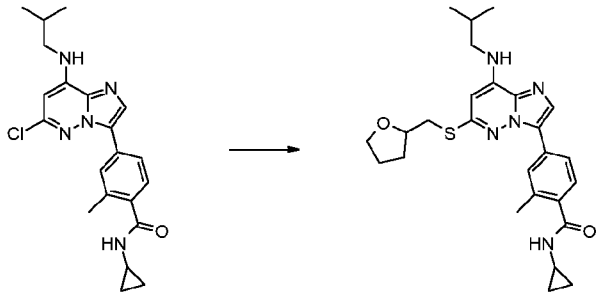


A solution of 450 mg (1172 µmol) of 4-[6-chloro-8-(isobutylamino)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropylbenzamide , which was prepared according to intermediate example 100a, and 330 mg (4690 µmol) sodiummethylsulfide in 8 mL of dimethylsulfoxide was heated for 60 min at 70°C in the microwave. Then the mixture was poored onto water and the precipitate was collected and dried under vaccum to yield 460 mg of the title compound as a white solid.

^{1}H-NMR (DMSO-d6): δ= 0.52-0.71 (4H), 0.88 (6H), 1.94 (1H), 2.56 (3H), 2.84 (1H), 3.08 (2H), 6.08 (1H), 7.49 (1H), 7.88 (2H), 7.97 (1H), 8.22 (2H), 8.43 (1H) ppm.

Example 194

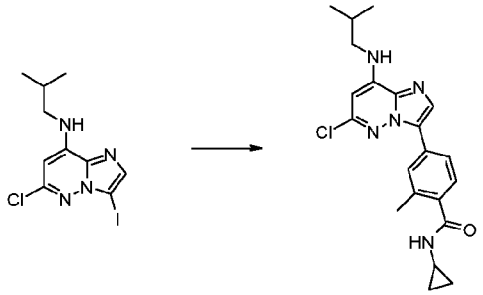
(RS)-N-cyclopropyl-2-methyl-4-{8-[(2-methylpropyl)amino]-6-[(tetrahydrofuran-2-ylmethyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}benzamide



A solution of 45 mg (377 µmol) of (RS)-tetrahydrofuran-2-ylmethanethiol in 1 mL of dimethylsulfoxide was treated with 14 mg (350 µmol) of sodium hydride and stirred at room temperature for 2 hours. Then 100 mg (251 µmol) of 4-[6-chloro-8-(isobutylamino)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylb enzamide, which was prepared according to intermediate example 194a, was

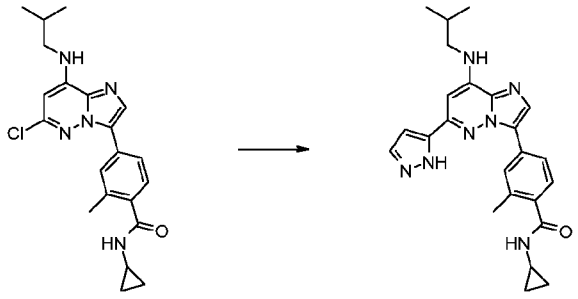
added and the mixture was heated for 2 hours at 70°C. Then the mixture was purified by reversed phase chromatography to yield 12 mg of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.48-0.68 (4H), 0.88 (6H), 1.63-1.99 (4H), 2.36 (3H), 2.81 (1H), 3.08 (2H), 3.22-3.36 (2H), 3.62 (1H), 3.76 (1H), 4.12 (1H), 6.04 (1H), 7.32 (1H), 7.50 (1H), 7.90 (1H), 7.93 (1H), 8.04 (1H), 8.29 (1H) ppm.

Intermediate example 194a
4-[6-chloro-8-(isobutylamino)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide



3.54 g (10.1 mmol) 6-Chloro-3-iodo-N-isobutylimidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 3b were transformed in analogy to intermediate example 1a using [4-(cyclopropylcarbamoyl)-3-methylphenyl]boronic acid to give after working up and purification 1.79 g (45%) of the title compound.

Example 195
N-cyclopropyl-2-methyl-4-{8-[(2-methylpropyl)amino]-6-(1H-pyrazol-5-yl) imidazo[1,2-b]pyridazin-3-yl}benzamide



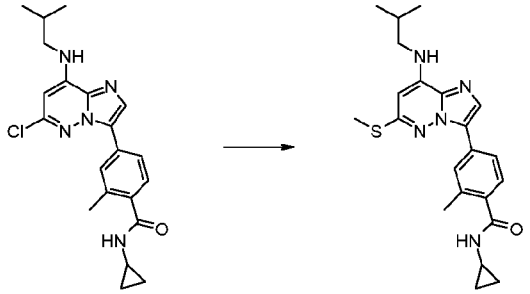
To a mixture of 125 mg (314 µmol) 4-[6-chloro-8-(isobutylamino)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide, which was prepared according to example 194a, 111 mg (942 µmol) 1H-pyrazol-5-yl boronic acid, 44 mg Tetrakis(triphenylphosphin)palladium in 2 mL

of ethanol and 2 mL of toluene was added 0.63 mL of an aqueous 10% sodiumbicarbonate solution and the mixture was stirred at 120°C for 2 hours under microwave irradiation. Then the mixture was filtered and concentrated and purified by chromatography to give 41 mg of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48-0.69 (4H), 0.91 (6H), 2.02 (1H), 2.39 (3H), 2.82 (1H), 3.17 (2H), 6.72 (1H), 6.78 (1H), 7.39 (1H), 7.85 (1H), 8.00 (1H), 8.10 - 8.17 (2H), 8.29 (1H), ppm.

Example 196

N-cyclopropyl-2-methyl-4-{8-[(2-methylpropyl)amino]-6-(methylsulfanyl) imidazo[1,2-b]pyridazin-3-yl}benzamide

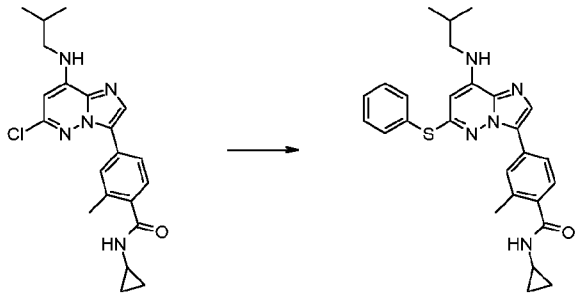


A solution of 50 mg (126 µmol) of 4-[6-chloro-8-(isobutylamino)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylb enzamide, which was prepared according to example 194a, and 35 mg (503 µmol) sodiummethylsulfide in 1 mL of dimethylsulfoxide was heated for 30 min at 70°C in the microwave. Then the mixture was poored onto water and the precipitate was collected and dried under vaccum to yield 26 mg of the title compound as a yellow solid.

^{1}H-NMR (DMSO-d6): δ= 0.47-0.68 (4H), 0.88 (6H), 1.94 (1H), 2.35 (3H), 2.55 (3H) 2.80 (1H), 3.08 (2H), 6.06 (1H), 7.32 (1H), 7.47 (1H), 7.90 (1H), 7.98 (1H), 8.05 (1H), 8.29 (1H), ppm.

Example 197

N-cyclopropyl-2-methyl-4-{8-[(2-methylpropyl)amino]-6-(phenylsulfanyl) imidazo[1,2-b]pyridazin-3-yl}benzamide

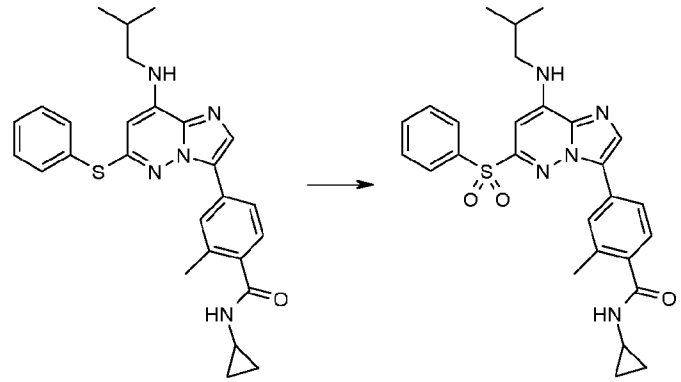


A solution of 180 mg (1634 µmol) of thiophenol in 10 mL of dimethylsulfoxide was treated with 64 mg (1608 µmol) of sodium hydride and stirred at room temperature for 2 hours. Then 100 mg (251 µmol) of 4-[6-chloro-8-(isobutylamino)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide, which was prepared according to intermediate example 194a, was added and the mixture was heated for 1.5 hours at 140°C. Then the mixture poured onto ice water and the precipitate was collected and subsequently purified by normal phase chromatography to yield 112 mg of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48-0.69 (4H), 0.84 (6H), 1.87 (1H), 2.21 (3H), 2.79 (1H), 3.03 (2H), 5.99 (1H), 7.10 (1H), 7.49 (3H), 7.61-7.71 (5H), 7.92 (1 H), 8.24 (1H), ppm.

Example 198

N-cyclopropyl-2-methyl-4-{8-[(2-methylpropyl)amino]-6-(phenylsulfonyl) imidazo[1,2-b]pyridazin-3-yl}benzamide



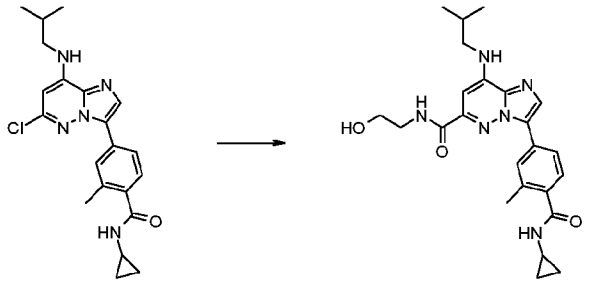
To a solution of 105 mg (223 µmol) of N-cyclopropyl-2-methyl-4-{8-[(2-methylpropyl)amino]-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}benzamide, which was prepared according to example 197, in 15 mL of DMF was added and 684 mg (1113 µmol) OXONE (potassium peroxymonosulfate) in small portions. The mixture was stirred over night, then

cooled to 0 °C and poored onto 200 mL of cold water. The precipitate was collected and purified with normal phase chromatography to yield 97 mg of the title compound as a yellow solid.

^{1}H-NMR (DMSO-d6): δ= 0.50-0.69 (4H), 0.91 (6H), 1.99 (1H), 2.30 (3H), 2.56 (1H), 3.41 (2H), 4.31 (1H), 6.71 (1H), 7.28 (1H), 7.66-7.81 (5H), 8.03 (2 H), 8.12 (1H), 8.31 (1H), 8.43 (1H) ppm.

Example 199

3-[4-(Cyclopropylcarbamoyl)-3-methylphenyl]-N-(2-hydroxyethyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazine-6-carboxamide

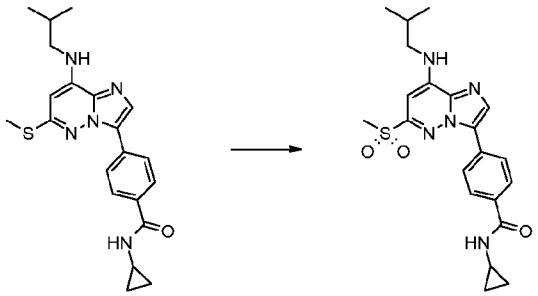


A solution of 100 mg (251 µmol) of 4-[6-chloro-8-(isobutylamino)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide, which was prepared according to example 194a, 46 mg (754 µmol) aminoethanol, 66 mg (251 µmol) molybdonhexacarbonyl, 80 mg (754 µmol) sodiumbicarbonate, 5.6 mg (25 µmol) palladium(II) acetate and 7.3 mg (25 µmol) tri-tert-butylphosphine tetrafluorborate in 3 mL of dioxane was heated in the microwave for 2 hours at 140 °C. Then the mixture was directly submitted to reversed phase chromatography to yield 13 mg of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48-0.69 (4H), 0.91 (6H), 1.99 (1H), 2.38 (3H), 2.81 (1H), 3.17 (2H), 3.38 (3H), 3.53 (2H), 5.99 (1H), 6.61 (1H), 7.36 (1H), 7.84 (1H), 8.00-8.09 (3H), 8.16 (1 H), 8.29 (1H), ppm.

Example 200

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(methylsulfonyl)imidazo[1,2-b]pyridazin-3-yl}benzamide

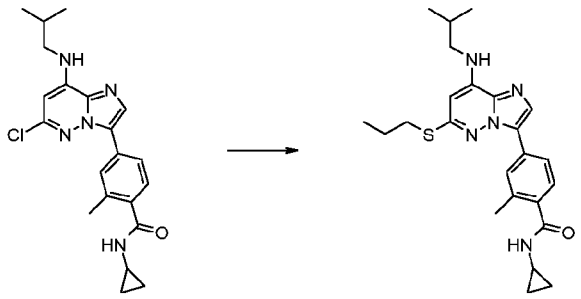


To a solution of 410 mg (1037 µmol) of N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(methylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}benzamide, which was prepared according to example 193, in 15 mL of DMF was added and 1912 mg (3110 µmol) OXONE (potassium peroxymonosulfate) in small portions. The mixture was stirred over night, then cooled to 0 °C and poored onto 200 mL of cold water. The precipitate was collected and dried under vaccum to yield 291 mg of the title compound as a yellow solid.

^{1}H-NMR (DMSO-d6): δ= 0.53-0.71 (4H), 0.91 (6H), 2.00 (1H), 2.84 (1H), 3.20 (2H), 3.38 (3H), 6.58 (1H), 7.92 (2H), 8.19-8.23 (3H), 8.37 (1 H), 8.46 (1H), ppm.

Example 201

N-cyclopropyl-2-methyl-4-{8-[(2-methylpropyl)amino]-6-(propylsulfanyl) imidazo[1,2-b]pyridazin-3-yl}benzamide

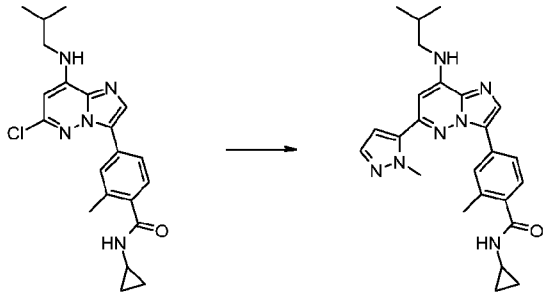


A solution of 100 mg (251 µmol) of 4-[6-chloro-8-(isobutylamino)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide, which was prepared according to example 194a, and 49 mg (503 µmol) sodium propane-1-thiolate in 1 mL of dimethylsulfoxide was heated for 60 min at 70°C in the microwave. Then the mixture was purified by reversed phase chromatography to yield 18.5 mg of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49-0.66 (4H), 0.88 (6H), 1.00 (3H), 1.74 (2H), 1.94 (1H), 2.36 (3H), 2.79 (1H), 3.05-3.15 (4H), 6.02 (1H), 7.33 (1H), 7.47 (1H), 7.90 (1H), 7.96 (1H), 8.03 (1H), 8.29 (1H) ppm.

Example 202

N-cyclopropyl-2-methyl-4-{8-[(2-methylpropyl)amino]-6-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide

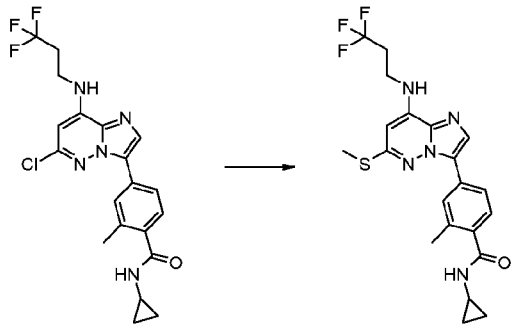


To a mixture of 100 mg (251 µmol) 4-[6-chloro-8-(isobutylamino)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide, which was prepared according to example 194a, 95 mg (750 µmol) 1-methyl-1H-pyrazol-5-yl) boronic acid, 35 mg Tetrakis(triphenylphosphin)palladium in 2 mL of ethanol and 2 mL of toluene was added 0.5 mL of an aqueous 10% sodiumbicarbonate solution and the mixture was stirred at 120°C for 2 hours under microwave irradiation. Then water and was added and the organic layer was washed with water and brine, concentrated and purified by chromatography to give 99 mg of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49-0.67 (4H), 0.93 (6H), 2.00 (1H), 2.36 (3H), 2.80 (1H), 3.21 (3H), 4.13 (3H), 6.46 (1H), 6.90 (1H), 7.37 (1H), 7.50 (1H), 7.65 (1H), 7.92 - 7.97 (3H), 8.29 (1H) ppm.

Example 203

N-cyclopropyl-2-methyl-4-{6-(methylsulfanyl)-8-[(3,3,3-trifluoropropyl) amino]imidazo[1,2-b]pyridazin-3-yl}benzamide

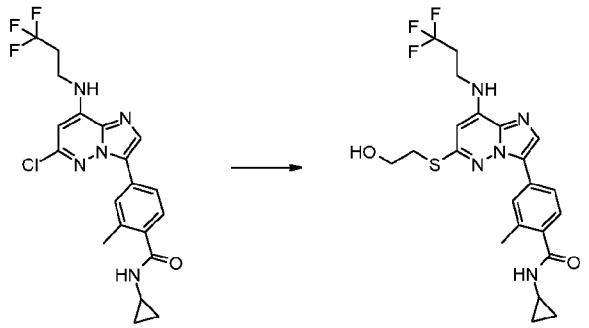


The title compound was prepared according to the procedure described for example 193 employing 4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide, which was prepared according to intermediate example 10a.

^{1}H-NMR (DMSO-d6): δ= 0.48-0.70 (4H), 2.36 (3H), 2.54-2.70 (6H), 2.82 (1H), 3.54 (2H), 6.16 (1H), 7.35 (1H), 7.51 (1H), 7.92 (1H), 7.97 (1H), 8.05 (1H), 8.28 (1H), ppm.

Example 204

N-cyclopropyl-4-{6-[(2-hydroxyethyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

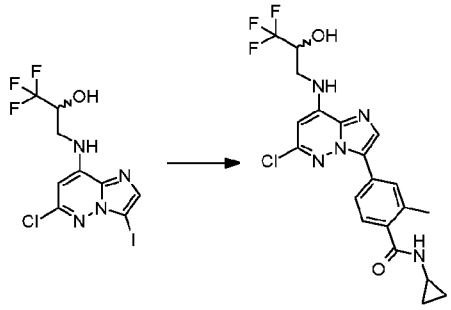


The title compound was prepared according to the procedure described for example 194 employing 4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide, which was prepared according to intermediate example 10a.

^{1}H-NMR (DMSO-d6): δ= 0.47-0.70 (4H), 2.36 (3H), 2.53-2.70 (4H), 2.81 (1H), 3.52 (2H), 3.71 (2H), 4.97 (1H), 6.13 (1H), 7.33 (1H), 7.53 (1H), 7.92 (1H), 8.02 (1H), 8.29 (1H), ppm.

Intermediate example 205

(RS)-4-{6-Chloro-8-[(3,3,3-trifluoro-2-hydroxypropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

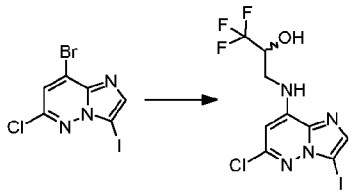


650 mg (1.60 mmol) (RS)-3-[(6-chloro-3-iodoimidazo[1,2-b]pyridazin-8-yl)amino]-1,1,1-trifluoropropan-2-ol which was prepared according to intermediate example 205a were transformed in analogy to intermediate example 1a using N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide which was prepared according to intermediate example 7b to give after working up and purification 430 mg (59%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48-0.68 (4H), 2.36 (3H), 2.81 (1H), 3.45 -3.62 (2H), 4.31 (1H), 6.40 (2H), 6.58 (1H), 7.37 (1H), 7.81 (1H), 7.85 (1H), 7.90 (1H), 8.00 (1H), 8.29 (1H), ppm.

Intermediate example 205a

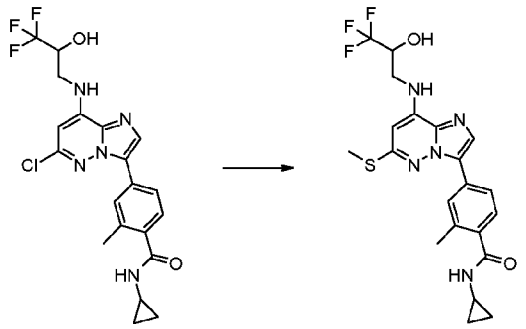
(RS)-3-[(6-chloro-3-iodoimidazo[1,2-b]pyridazin-8-yl)amino]-1,1,1-trifluoropropan-2-ol



8-bromo-6-chloro-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 1c was transformed in analogy to intermediate example 1b using (RS)-(3,3,3-trifluoro-2-hydroxypropyl)amine to provide the title compound.

Example 206

(RS) N-cyclopropyl-2-methyl-4-{6-(methylsulfanyl)-8-[(3,3,3-trifluoro-2-hydroxypropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide

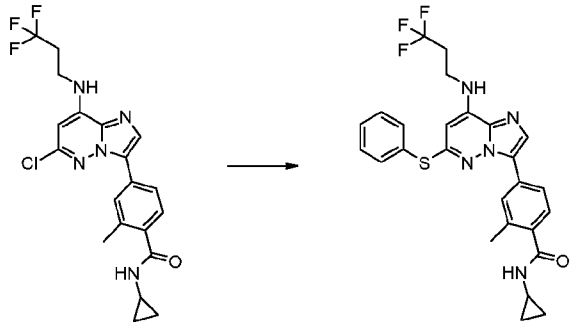


The title compound was prepared according to the procedure described for example 193 employing (RS)-4-{6-chloro-8-[(3,3,3-trifluoro-2-hydroxypropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide, which was prepared according to example 205.

^{1}H-NMR (DMSO-d6): δ= 0.48-0.70 (4H), 2.36 (3H), 2.56 (3H), 2.80 (1H), 3.47 (1H), 3.58 (1H), 4.30 (1H), 6.19 (1H), 6.56 (1H), 7.29 (1H), 7.35 (1H), 7.93 (1H), 7.97 (1H), 8.06 (1H), 8.28 (1H), ppm.

Example 207

N-cyclopropyl-2-methyl-4-{6-(phenylsulfanyl)-8-[(3,3,3-trifluoropropyl)amino] imidazo[1,2-b]pyridazin-3-yl}benzamide

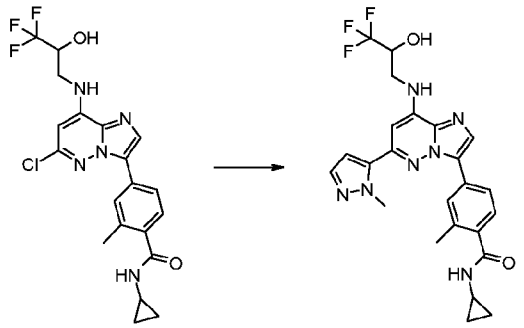


The title compound was prepared according to the procedure described for example 197 employing 4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide, which was prepared according to intermediate example 10a.

^{1}H-NMR (DMSO-d6): δ= 0.48-0.70 (4H), 2.20 (3H), 2.54-2.70 (4H), 2.82 (1H), 3.50 (2H), 6.13 (1H), 7.09 (1H), 7.46 - 7.70 (8H), 7.94 (1H), 8.22 (1H), ppm.

Example 208

(RS)-N-cyclopropyl-2-methyl-4-{6-(1-methyl-1H-pyrazol-5-yl)-8-[(3,3,3-trifluoro-2-hydroxypropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide

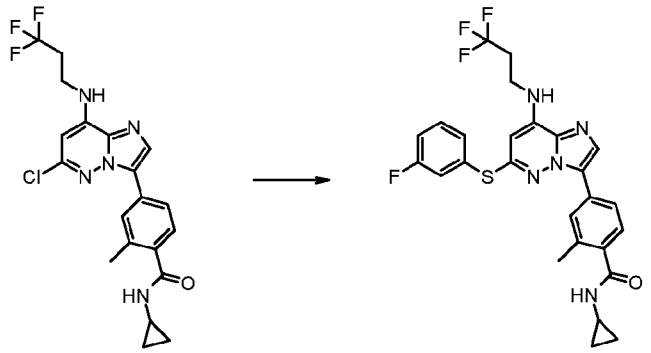


The title compound was prepared according to the procedure described for example 211 employing (RS)-4-{6-chloro-8-[(3,3,3-trifluoro-2-hydroxypropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide, which was prepared according to example 205.

^{1}H-NMR (DMSO-d6): δ= 0.48-0.67 (4H), 2.36 (3H), 2.80 (1H), 3.47 (1H), 3.58 (1H), 4.32 (1H), 6.58 (2H), 6.90 (1H), 7.37 (1H), 7.48 (1H), 7.51 (1H), 7.91-8.00 (3H), 8.29 (1H), ppm.

Example 209

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

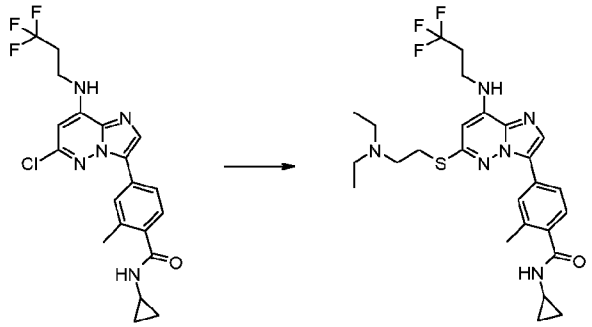


The title compound was prepared according to the procedure described for example 194 employing 4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide, which was prepared according to intermediate example 10a.

^{1}H-NMR (DMSO-d6): δ= 0.49-0.66 (4H), 2.20 (3H), 2.53-2.70 (4H), 2.78 (1H), 3.54 (2H), 6.20 (1H), 7.12 (1H), 7.34 (1H), 7.43 - 7.71 (6H), 7.95 (1H), 8.23 (1H), ppm.

Example 210

N-cyclopropyl-4-(6-{[2-(diethylamino)ethyl]sulfanyl}-8-[(3,3,3-trifluoropropyl) amino]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide



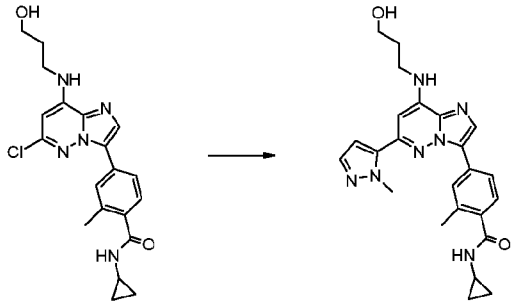
The title compound was prepared according to the procedure described for example 194 employing

4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide, which was prepared according to intermediate example 10a.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.65 (2H), 0.86 (6H), 2.36 (3H), 2.59-2.71 (4H), 2.79 (1H), 3.23 - 3.33 (multiple H, overlaps with water peak), 3.54 (2H), 6.13 (1H), 7.32 (1H), 7.52 (1H), 7.91 (1H), 7.95 (1H), 8.02 (1H) 8.28 (1H), ppm.

Example 211

N-cyclopropyl-4-{8-[(3-hydroxypropyl)amino]-6-(1-methyl-1H-pyrazol-5-yl) imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



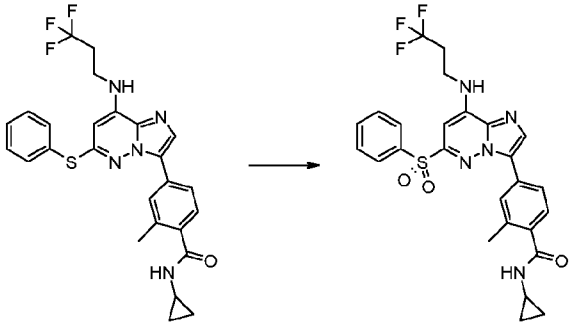
To a mixture of 51 mg (128 µmol) 4-{6-chloro-8-[(3-hydroxypropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide , which was prepared in analogy to example 205 employing

3-hydroxy-n-propylamine, 80 mg (380 µmol) 1-methyl-1H-pyrazol-5-yl) boronic acid pinacol ester, 18 mg Tetrakis(triphenylphosphin)palladium in 1 mL of ethanol and 1 mL of toluene was added 0.27 mL of an aqueous 10% sodiumbicarbonate solution and the mixture was stirred at 120°C for 2 hours under microwave irradiation. Then water and ethyl acetate was added and the organic layer was washed with water and brine, concentrated and treated with dichloromethane. The remaining undisolved solid yielded 25 mg of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.66 (2H), 1.78 (2H), 2.35 (3H), 2.80 (1H), 3.41 - 3.51 (4H), 6.47 (1H), 6.88 (1H), 7.36 (1H), 7.51 (1H), 7.62 (1H), 7.91 - 7.97 (3H), (1H), 8.29 (1H), ppm.

Example 212

N-cyclopropyl-2-methyl-4-{6-(phenylsulfonyl)-8-[(3,3,3-trifluoropropyl)amino] imidazo[1,2-b]pyridazin-3-yl}benzamide

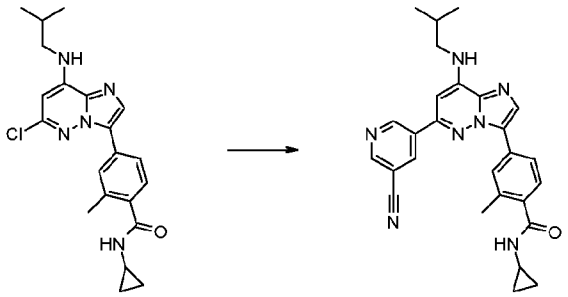


50 mg (98 µmol) N-cyclopropyl-2-methyl-4-{6-(phenylsulfanyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide which was prepared according to example 207 were transformed in analogy to example 18 to give after working up and purification 30.2 mg (57%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.67 (2H), 2.31 (3H), 2.70 (2H), 2.81 (1H), 3.29 (2H), 6.81 (1H), 7.28 (1H), 7.65-7.82 (5H), 8.03 (1H), 8.06 (1H), 8.15 (1H), 8.30 (1H), 8.36 (1H) ppm.

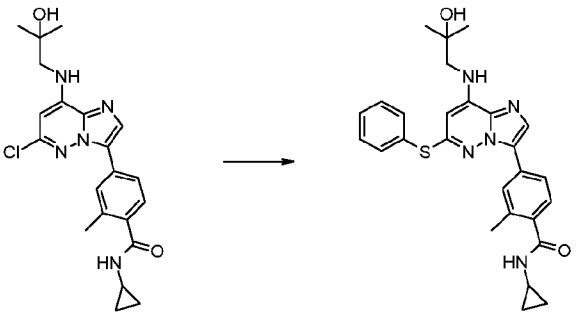
Example 213

4-[6-(5-Cyanopyridin-3-yl)-8-(isobutylamino)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide



200 mg (503 µmol)
4-[6-chloro-8-(isobutylamino)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylb
enzamide which was prepared according to intermediate example 194a were transformed in analogy to example 202 using 5-cyanopyridin-3-yl boronic acid to give after working up and purification 80.9 mg (33%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.62 (2H), 0.92 (6H), 2.04 (1H), 2.39 (3H), 2.81 (1H), 3.26 (2H), 6.83 (1H), 7.41 (1H), 7.76 (1H), 8.01 - 8.10 (3H), 8.30 (1H), 8.93 (1H), 9.10 (1H), 9.49 (1H), ppm.

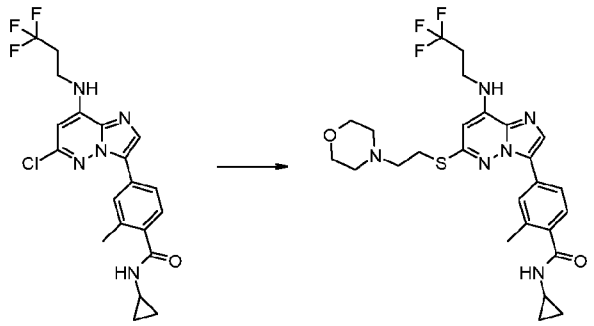
Example 214
N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(phenylsulfanyl) imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



100 mg (242 µmol)
4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cy
clopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 55 using benzenethiol to give after working up and purification 113.5 mg (96%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.65 (2H), 1.11 (6H), 2.19 (3H), 2.79 (1H), 3.21 (2H), 4.71 (1H), 6.23 (1H), 6.97 (1H), 7.08 (1H), 7.44-7.52 (3H), 7.58-7.65 (3H), 7.70 (1H), 7.93 (1H), 8.22 (1H) ppm.

Example 215

N-cyclopropyl-2-methyl-4-(6-{[2-(morpholin-4-yl)ethyl]sulfanyl}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)benzamide

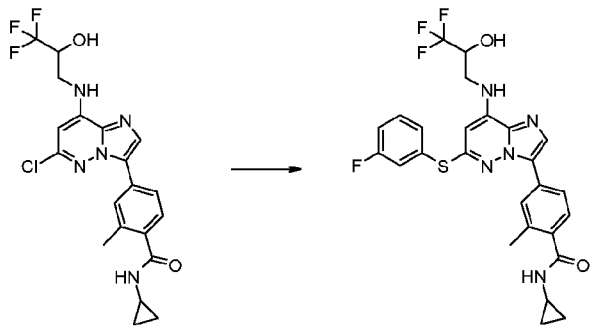


100 mg (228 µmol) 4-{6-Chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 10a were transformed in analogy to example 55 using 2-(morpholin-4-yl)ethanethiol to give after working up and purification 78.2 mg (59%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.65 (2H), 2.30-2.39 (4H), 2.37 (3H), 2.57-2.71 (4H), 2.80 (1H), 3.28 (2H), 3.47-3.57 (6H), 6.13 (1H), 7.33 (1H), 7.53 (1H), 7.90 (1H), 7.96 (1H), 7.98 (1H), 8.29 (1H) ppm.

Example 216

(RS)-N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(3,3,3-trifluoro-2-hydroxypropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

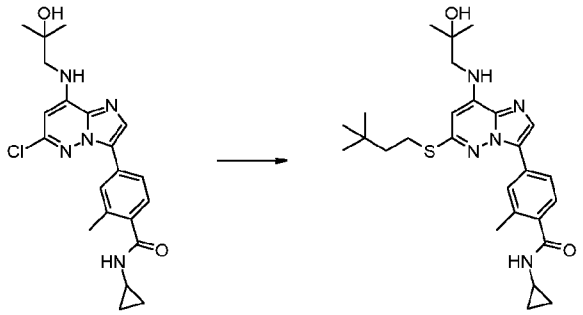


95 mg (191 µmol) (RS)-4-{6-chloro-8-[(3,3,3-trifluoro-2-hydroxypropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 205 were transformed in analogy to example 194 using 3-fluorobenzenethiol to give after working up and purification 54 mg (49%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.65 (2H), 2.20 (3H), 2.79 (1H), 3.45 -3.62 (2H), 4.26 (1H), 6.24 (1H), 6.56 (1H), 7.13 (1H), 7.35 (1H), 7.50 (1H), 7.51 - 7.56 (3H), 7.65 (1H), 7.71 (1H), 7.97 (1H), 8.25 (1H), ppm.

Example 217

N-cyclopropyl-4-{6-[(3,3-dimethylbutyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



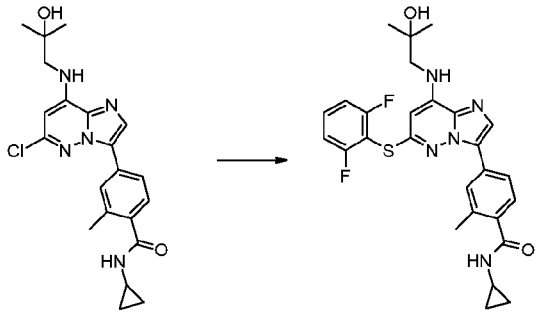
75 mg (181 µmol)

4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using 3,3-dimethylbutane-1-thiol to give after working up and purification 29.2 mg (31%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.65 (2H), 0.89 (9H), 1.13 (6H), 1.54 (2H), 2.35 (3H), 2.79 (1H), 3.13 (2H), 3.21 (2H), 4.72 (1H), 6.17 (1H), 6.81 (1H), 7.29 (1H), 7.91 (1H), 7.98 (1H), 7.99 (1H), 8.28 (1H) ppm.

Example 218

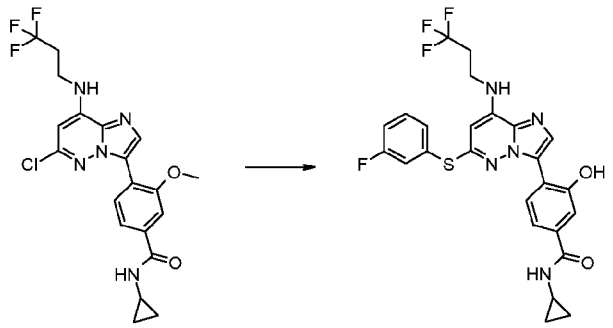
N-cyclopropyl-4-{6-[(2,6-difluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



75 mg (181 µmol)
4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using
2,6-difluorobenzenethiol to give after working up and purification 6.5 mg (6%) of the title compound.
^{1}H-NMR ($CDCl_3$): δ= 0.63 (2H), 0.89 (2H), 1.40 (6H), 2.33 (3H), 2.91 (1H), 3.29 (2H), 5.96 (1H), 6.05 (1H), 6.55 (1H), 7.00-7.11 (3H), 7.41-7.53 (3H), 7.57 (1H) ppm.

Example 219

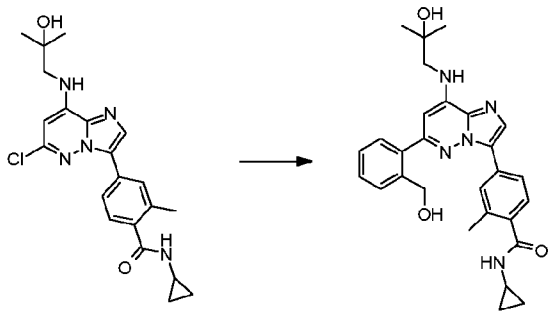
N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-3-hydroxybenzamide



75 mg (165 µmol)
4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-3-methoxybenzamide which was prepared according to intermediate example 52a were transformed in analogy to intermediate example 51 using 3-fluorobenzenethiol to give after working up and purification 24.0 mg (27%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.54 (2H), 0.66 (2H), 2.60 (2H), 2.80 (1H), 3.52 (2H), 6.13 (1H), 7.07 (1H), 7.28 (1H), 7.34 (1H), 7.38-7.53 (3H), 7.71 (1H), 7.85 (1H), 7.94 (1H), 8.34 (1H), 10.12 (1H) ppm.

Example 220

N-cyclopropyl-4-{6-[2-(hydroxymethyl)phenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

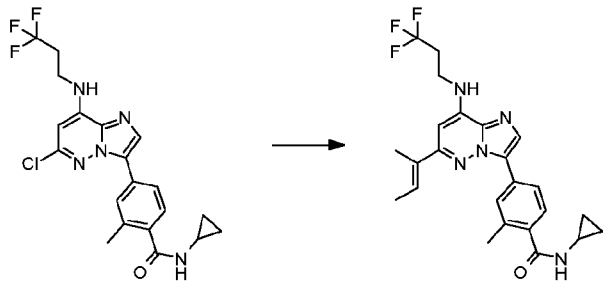


5.25 g (12.7 mmol) 4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 1 using [2-(hydroxymethyl)phenyl]boronic acid to give after working up and purification 4.90 g (80%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 1.18 (6H), 2.36 (3H), 2.82 (1H), 3.32 (2H), 4.66 (2H), 4.75 (1H), 5.13 (1H), 6.45 (1H), 6.95 (1H), 7.35 (1H), 7.39 (1H), 7.45-7.52 (2H), 7.66 (1H), 7.95 (1H), 8.00 (1H), 8.01 (1H), 8.26 (1H) ppm.

Example 221

4-{6-[(2E)-but-2-en-2-yl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b] pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

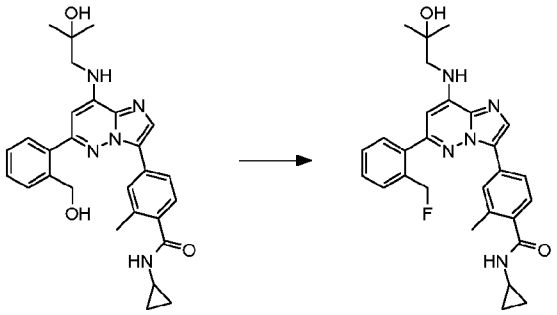


115 mg (262 µmol) 4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 10a were transformed in analogy to example 1 using (2Z)-but-2-en-2-ylboronic acid to give after working up and purification 7.2 mg (6%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.65 (2H), 1.84 (3H), 2.07 (3H), 2.36 (3H), 2.67 (2H), 2.80 (1H), 3.61 (2H), 6.43 (1H), 6.49 (1H), 7.32 (1H), 7.35 (1H), 7.97 (1H), 8.03 (1H), 8.07 (1H), 8.27 (1H) ppm.

Example 222

N-cyclopropyl-4-{6-[2-(fluoromethyl)phenyl]-8-[(2-hydroxy-2-methylpropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

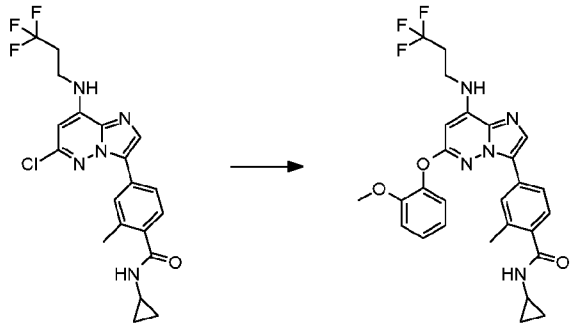


To a solution of 329 mg (677 µmol) N-cyclopropyl-4-{6-[2-(hydroxymethyl)phenyl]-8-[(2-hydroxy-2-methylpropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide which was prepared according to example 220 in 13 mL dichloromethane at 3°C were added 98 µL N-ethyl-N-(trifluoro-lambda^4-sulfanyl)ethanamine. After stirring for 10 minutes, the solution was poured into water and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with sodium hydrogencarbonate solution and dried over sodium sulfate. After filtration and removal of solvent the residue was purified by chromatography to give 28.6 mg (8%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.61 (2H), 0.87 (2H), 1.47 (6H), 2.48 (3H), 2.90 (1H), 3.36 (2H), 5.21 (1H), 5.58 (2H), 5.97 (1H), 6.26 (1H), 6.71 (1H), 7.37 (1H), 7.46 (1H), 7.51 (1H), 7.58 (1H), 7.64 (1H), 7.74 (1H), 7.81 (1H), 7.88 (1H) ppm.

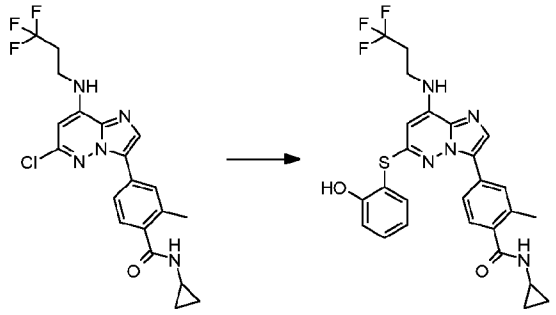
Example 223

N-cyclopropyl-4-{6-(2-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



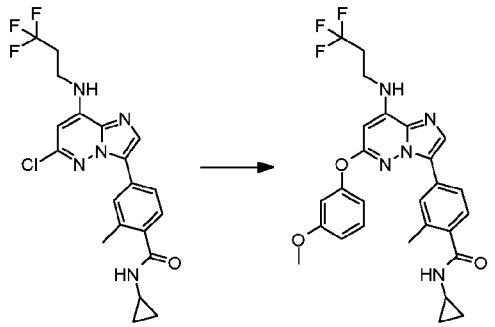
150 mg (343 µmol)
4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 10a were transformed in analogy to example 51 using 2-methoxyphenol to give after working up and purification 8.1 mg (5%) of the title compound.
^{1}H-NMR ($CDCl_3$): δ= 0.60 (2H), 0.88 (2H), 2.26 (3H), 2.57 (2H), 2.89 (1H), 3.68 (2H), 3.78 (3H), 5.82 (1H), 5.94 (1H), 5.98 (1H), 7.01 (1H), 7.05 (1H), 7.18 (1H), 7.22 (1H), 7.27 (1H), 7.55 (1H), 7.70 (1H), 7.72 (1H) ppm.

Example 224
N-cyclopropyl-4-{6-[(2-hydroxyphenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



100 mg (228 µmol)
4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 10a were transformed in analogy to example 51 using 2-methoxybenzenethiol to give after working up and purification 5.1 mg (4%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.65 (2H), 2.21 (3H), 2.59 (2H), 2.79 (1H), 3.49 (2H), 6.05 (1H), 6.87 (1H), 6.98 (1H), 7.07 (1H), 7.34 (1H), 7.46 (1H), 7.56 (1H), 7.67 (1H), 7.72 (1H), 7.93 (1H), 8.23 (1H), 9.96 (1H) ppm.

Example 225
N-cyclopropyl-4-{6-(3-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

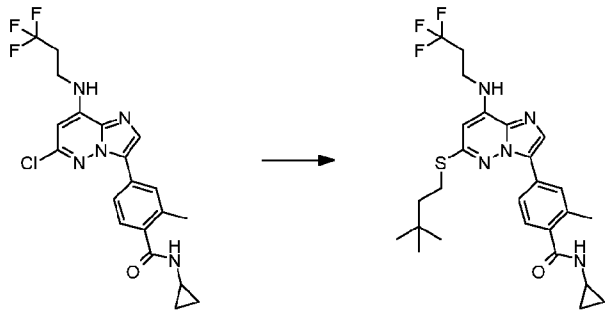


150 mg (343 µmol)
4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 10a were transformed in analogy to example 51 using 3-methoxyphenol to give after working up and purification 5.1 mg (3%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.60 (2H), 0.87 (2H), 2.31 (3H), 2.56 (2H), 2.89 (1H), 3.66 (2H), 3.80 (3H), 5.85 (1H), 5.88 (1H), 6.03 (1H), 6.79-6.88 (3H), 7.24 (1H), 7.33 (1H), 7.63 (1H), 7.73 (1H), 7.79 (1H) ppm.

Example 226

N-cyclopropyl-4-{6-[(3,3-dimethylbutyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

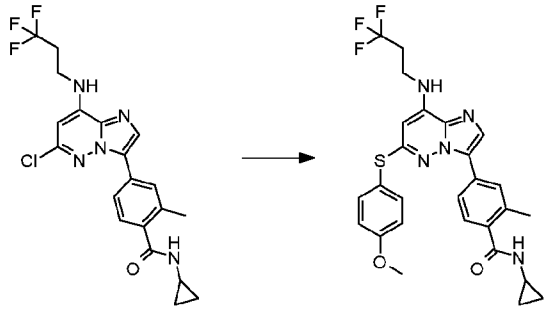


100 mg (228 µmol)
4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 10a were transformed in analogy to example 51 using 3,3-dimethylbutane-1-thiol to give after working up and purification 3.6 mg (3%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.63 (2H), 0.90 (2H), 0.94 (9H), 1.62 (2H), 2.51 (3H), 2.52 (2H), 2.92 (1H), 3.19 (2H), 3.61 (2H), 5.84-5.93 (3H), 7.37 (1H), 7.69 (1H), 7.88 (1H), 7.91 (1H) ppm.

Example 227

N-cyclopropyl-4-{6-[(4-methoxyphenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

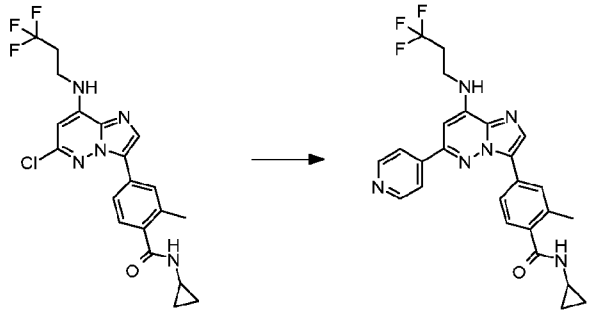


100 mg (228 µmol) 4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 10a were transformed in analogy to example 51 using 4-methoxybenzenethiol to give after working up and purification 16.8 mg (13%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.63 (2H), 0.90 (2H), 2.40 (3H), 2.47 (2H), 2.92 (1H), 3.57 (2H), 3.88 (3H), 5.82-5.93 (3H), 6.98 (2H), 7.17 (1H), 7.54-7.63 (4H), 7.69 (1H) ppm.

Example 228

N-cyclopropyl-2-methyl-4-{6-(pyridin-4-yl)-8-[(3,3,3-trifluoropropyl)amino] imidazo[1,2-b]pyridazin-3-yl}benzamide

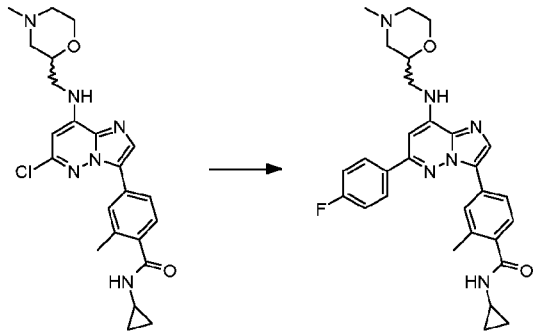


250 mg (571 µmol) 4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 10a were transformed in analogy to example 1 using pyridin-4-ylboronic acid to give after working up and purification 6.7 mg (2%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.63 (2H), 0.89 (2H), 2.53 (3H), 2.61 (2H), 2.91 (1H), 3.72 (2H), 6.20 (1H), 6.43 (1H), 6.67 (1H), 7.44 (1H), 7.80 (1H), 7.82 (2H), 7.89 (1H), 7.96 (1H), 8.72 (2H) ppm.

Example 229

(RS)-N-cyclopropyl-4-[6-(4-fluorophenyl)-8-{[(4-methylmorpholin-2-yl)methyl] amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide



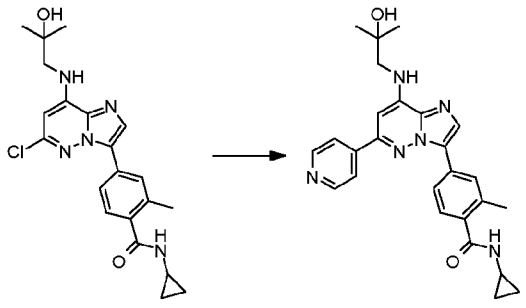
50 mg (110 µmol)

(RS)-4-[6-chloro-8-({[(2S)-4-methylmorpholin-2-yl]methyl}amino)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 56a were transformed in analogy to example 1 using (4-fluorophenyl)boronic acid to give after working up and purification 12.2 mg (22%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 1.80 (1H), 1.96 (1H), 2.14 (3H), 2.39 (3H), 2.54 (1H), 2.74 (1H), 2.81 (1H), 3.45-3.55 (3H), 3.72-3.80 (2H), 6.72 (1H), 7.34 (2H), 7.39 (2H), 8.00 (1H), 8.03 (1H), 8.06-8.12 (3H), 8.30 (1H), ppm.

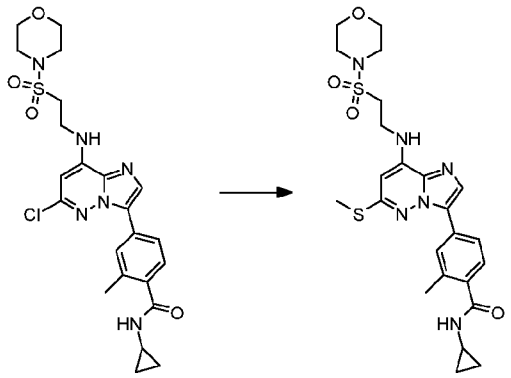
Example 230

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-4-yl)imidazo [1,2-b]pyridazin-3-yl}-2-methylbenzamide



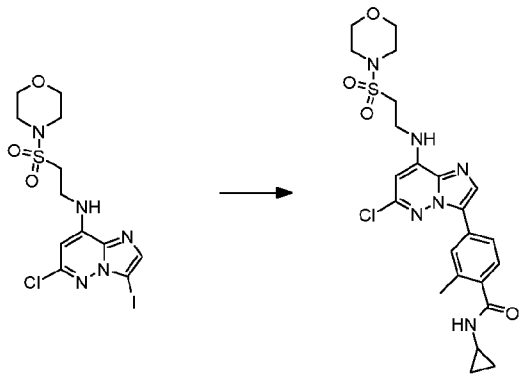
200 mg (483 µmol)
4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 1 using pyridin-4-ylboronic acid to give after working up and purification 28.3 mg (12%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.69 (2H), 0.91 (2H), 1.49 (6H), 2.46 (3H), 2.96 (1H), 3.33 (2H), 4.99 (1H), 6.23 (1H), 6.53 (1H), 6.58 (1H), 7.29 (1H), 7.66 (2H), 7.70 (1H), 7.76 (1H), 7.82 (1H), 8.57 (2H) ppm.

Example 231
N-cyclopropyl-2-methyl-4-[6-(methylsulfanyl)-8-{[2-(morpholin-4-ylsulfonyl) ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]benzamide



46 mg (89 µmol)
4-(6-chloro-8-{[2-(morpholin-4-ylsulfonyl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 231a were transformed in analogy to example 51 using sodium methanethiolate to give after working up and purification 12 mg (25%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.65 (2H), 2.36 (3H), 2.57 (3H), 2.80 (1H), 3.14 (4H), 3.44 (2H), 3.60 (4H), 3.69 (2H), 6.15 (1H), 7.35 (1H), 7.43 (1H), 7.93 (1H), 7.98 (1H), 8.06 (1H), 8.28 (1H) ppm.

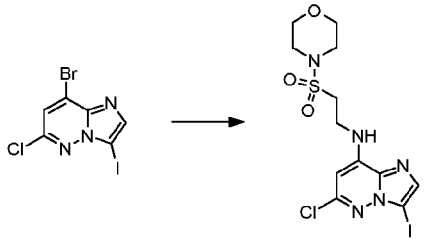
Intermediate example 231a
4-(6-chloro-8-{[2-(morpholin-4-ylsulfonyl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide



650 mg (1.38 mmol) 6-chloro-3-iodo-N-[2-(morpholin-4-ylsulfonyl)ethyl]imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 231b were transformed in analogy to intermediate example 1a using N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide to give after working up and purification 102 mg (14%) of the title compound.

Intermediate example 231b

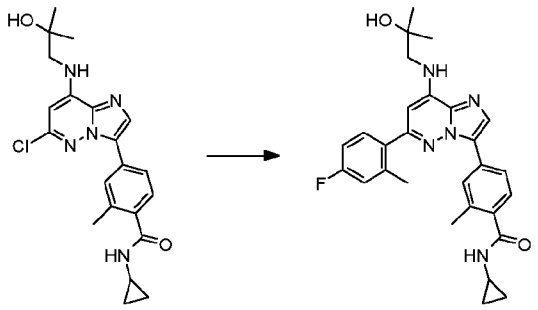
6-chloro-3-iodo-N-[2-(morpholin-4-ylsulfonyl)ethyl]imidazo[1,2-b]pyridazin-8-amine



1.00 g (2.79 mmol) 8-bromo-6-chloro-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 1c were transformed in analogy to intermediate example 1b using 2-(morpholin-4-ylsulfonyl)ethanamine to give after working up and purification 650 mg (49%) of the title compound.

Example 232

N-cyclopropyl-4-{6-(4-fluoro-2-methylphenyl)-8-[(2-hydroxy-2-methylpropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

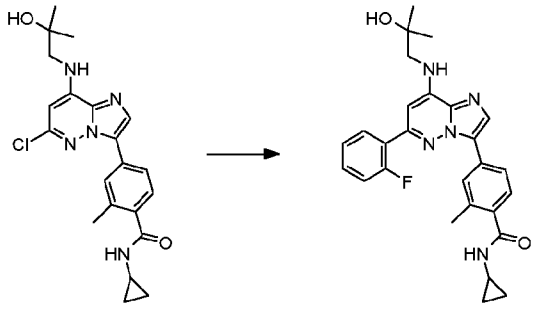


100 mg (242 µmol) 4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 1 using (4-fluoro-2-methylphenyl)boronic acid to give after working up and purification 19.0 mg (15%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.47 (2H), 0.64 (2H), 1.15 (6H), 2.33 (3H), 2.38 (3H), 2.78 (1H), 3.31 (2H), 4.71 (1H), 6.36 (1H), 6.95 (1H), 7.12 (1H), 7.19 (1H), 7.32 (1H), 7.47 (1H), 7.92 (1H), 7.98 (1H), 7.99 (1H), 8.24 (1H) ppm.

Example 233

N-cyclopropyl-4-{6-(2-fluorophenyl)-8-[(2-hydroxy-2-methylpropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

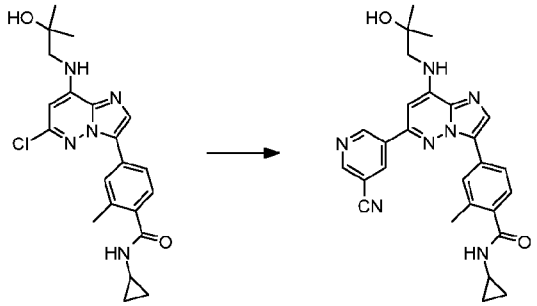


100 mg (242 µmol) 4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 1 using (2-fluorophenyl)boronic acid to give after working up and purification 10.0 mg (8%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.64 (2H), 1.16 (6H), 2.36 (3H), 2.79 (1H), 3.31 (2H), 4.74 (1H), 6.57 (1H), 7.00 (1H), 7.31-7.40 (3H), 7.52 (1H), 7.78 (1H), 8.01 (1H), 8.03 (1H), 8.06 (1H), 8.26 (1H) ppm.

Example 234

4-{6-(5-cyanopyridin-3-yl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



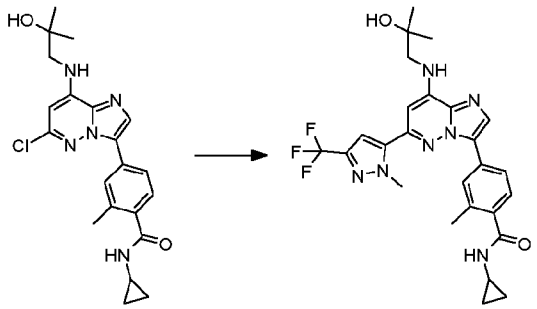
200 mg (483 µmol)

4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 1 using (5-cyanopyridin-3-yl)boronic acid to give after working up and purification 19.0 mg (8%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 1.19 (6H), 2.39 (3H), 2.81 (1H), 3.42 (2H), 4.79 (1H), 6.96 (1H), 7.08 (1H), 7.41 (1H), 8.01 (1H), 8.04 (1H), 8.10 (1H), 8.31 (1H), 8.91 (1H), 9.11 (1H), 9.50 (1H) ppm.

Example 235

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

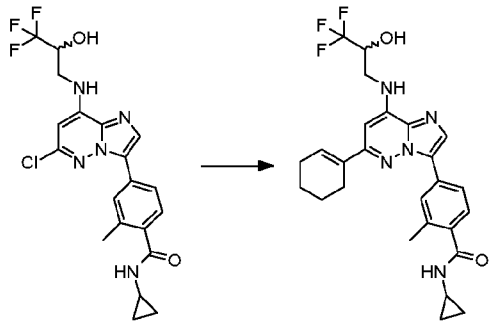


100 mg (242 µmol)
4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 1 using
[1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]boronic acid to give after working up and purification 25 mg (19%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.65 (2H), 1.17 (6H), 2.36 (3H), 2.80 (1H), 3.37 (2H), 4.22 (3H), 4.77 (1H), 6.73 (1H), 7.07 (1H), 7.37 (1H), 7.46 (1H), 7.91 (1H), 7.94 (1H), 8.00 (1H), 8.30 (1H) ppm.

Example 236

(RS)-4-{6-(cyclohex-1-en-1-yl)-8-[(3,3,3-trifluoro-2-hydroxypropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

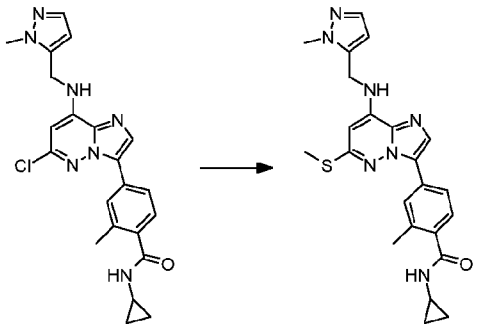


85 mg (187 µmol)
(RS)-4-{6-chloro-8-[(3,3,3-trifluoro-2-hydroxypropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to example 205 were transformed in analogy to intermediate example 1 using cyclohex-1-en-1-ylboronic acid to give after working up and purification 4.0 mg (4%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.62 (2H), 1.58 (2H), 1.68 (2H), 2.20 (2H), 2.34 (3H), 2.49 (2H), 2.77 (1H), 3.48 (1H), 3.64 (1H), 4.28 (1H), 6.46 (1H), 6.54 (1H), 6.65 (1H), 7.05 (1H), 7.33 (1H), 7.94 (1H), 8.01 (1H), 8.02 (1H), 8.23 (1H) ppm.

Example 237

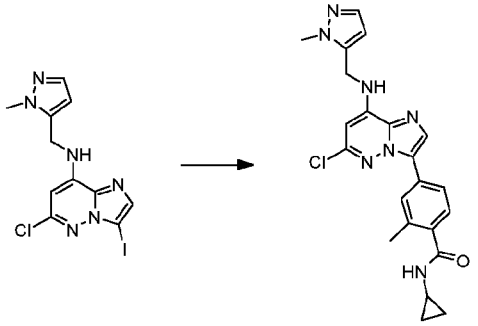
N-cyclopropyl-2-methyl-4-[8-{[(1-methyl-1H-pyrazol-5-yl)methyl]amino}-6-(methylsulfanyl)imidazo[1,2-b]pyridazin-3-yl]benzamide



100 mg (229 µmol)
4-(6-chloro-8-{[(1-methyl-1H-pyrazol-5-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 237a were transformed in analogy to example 51 using sodium methanethiolate to give after working up and purification 75 mg (72%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.65 (2H), 2.35 (3H), 2.53 (3H), 2.80 (1H), 3.79 (3H), 4.58 (2H), 6.14 (2H), 7.25 (1H), 7.34 (1H), 7.92-8.02 (3H), 8.05 (1H), 8.28 (1H) ppm.

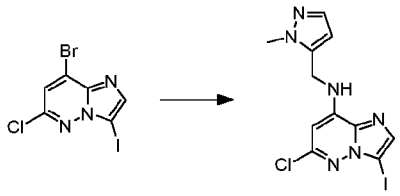
Intermediate example 237a
4-(6-chloro-8-{[(1-methyl-1H-pyrazol-5-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide



500 mg (1.29 mmol)
6-chloro-3-iodo-N-[(1-methyl-1H-pyrazol-5-yl)methyl]imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 237b were transformed in analogy to intermediate example 1a using N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide to give after working up and purification 277 mg (47%) of the title compound.

Intermediate example 237b

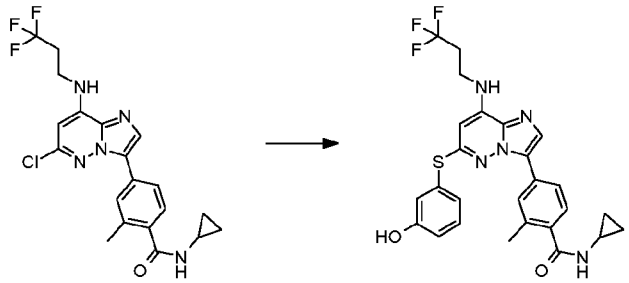
6-chloro-3-iodo-N-[(1-methyl-1H-pyrazol-5-yl)methyl]imidazo[1,2-b]pyridazin-8-amine



1.00 g (2.79 mmol) 8-bromo-6-chloro-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 1c were transformed in analogy to intermediate example 1b using 1-(1-methyl-1H-pyrazol-5-yl)methanamine to give after working up and purification 1.00 g (92%) of the title compound.

Example 238

N-cyclopropyl-4-{6-[(3-hydroxyphenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



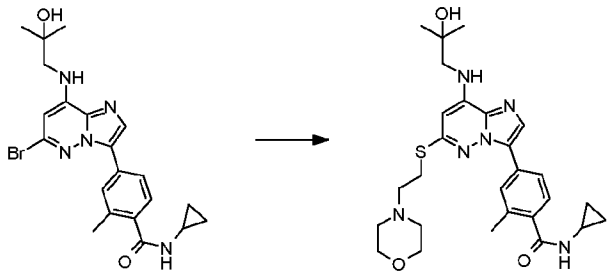
100 mg (228 µmol)

4-{6-chloro-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 10a were transformed in analogy to example 51 using 3-methoxybenzenethiol to give after working up and purification 68 mg (65%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.65 (2H), 2.23 (3H), 2.60 (2H), 2.79 (1H), 3.52 (2H), 6.11 (1H), 6.86 (1H), 6.98 (1H), 7.01 (1H), 7.15 (1H), 7.26 (1H), 7.63 (1H), 7.73 (1H), 7.74 (1H), 7.94 (1H), 8.21 (1H), 9.69 (1H) ppm.

Example 239

N-cyclopropyl-4-(8-[(2-hydroxy-2-methylpropyl)amino]-6-{[2-(morpholin-4-yl)ethyl]sulfanyl}imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide

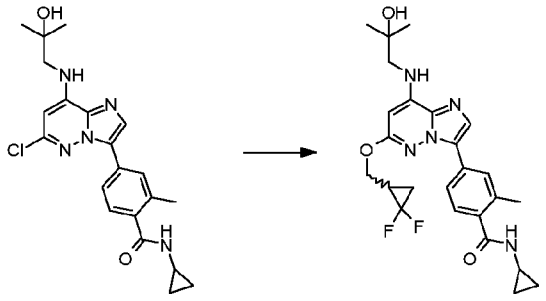


75 mg (164 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using 2-(morpholin-4-yl)ethanethiol to give after working up and purification 45.4 mg (50%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.65 (2H), 1.13 (6H), 2.30-2.40 (4H), 2.37 (3H), 2.61 (2H), 2.80 (1H), 3.22 (2H), 3.27 (2H), 3.51 (4H), 4.71 (1H), 6.18 (1H), 6.81 (1H), 7.33 (1H), 7.89 (1H), 7.96 (1H), 7.98 (1H), 8.28 (1H) ppm.

Example 240

(RS)-N-cyclopropyl-4-{6-[(2,2-difluorocyclopropyl)methoxy]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



325 mg (785 µmol)
4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using [(1RS)-2,2-difluorocyclopropyl]methanol to give after working up and purification 12.3 mg (3%) of the title compound.

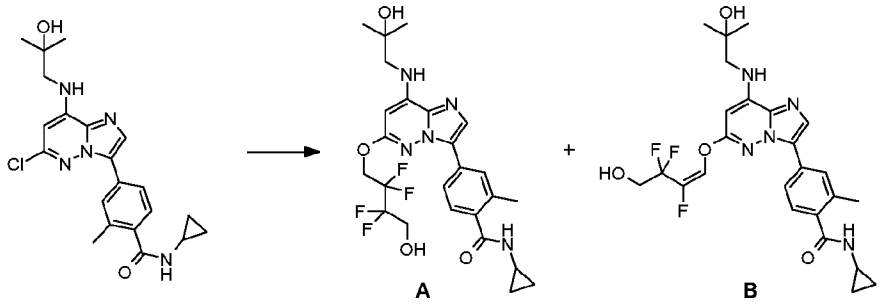
^{1}H-NMR ($CDCl_3$): δ= 0.64 (2H), 0.89 (2H), 1.29 (1H), 1.43 (6H), 1.56 (1H), 2.15 (1H), 2.49 (3H), 2.92 (1H), 3.27 (2H), 4.34 (2H), 4.78 (1H), 5.70 (1H), 6.01 (1H), 6.42 (1H), 7.38 (1H), 7.60 (1H), 7.80 (1H), 7.83 (1H) ppm.

Example 241

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(2,2,3,3-tetrafluoro-4-hydroxybutoxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide (A)

and

N-cyclopropyl-4-(8-[(2-hydroxy-2-methylpropyl)amino]-6-{[(1E)-2,3,3-trifluoro-4-hydroxybut-1-en-1-yl]oxy}imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide



250 mg (604 µmol)

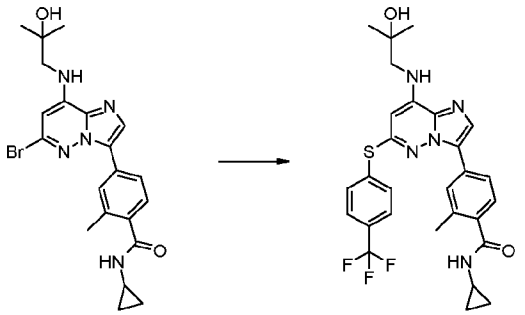
4-{6-chloro-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to example 51 using 2,2,3,3-tetrafluorobutane-1,4-diol to give after working up and purification 38.3 mg (12%) of the title compound A and 88.7 mg (28%) of the title compound B.

^{1}H-NMR (DMSO-d6) of A: δ= 0.50 (2H), 0.65 (2H), 1.14 (6H), 2.35 (3H), 2.80 (1H), 3.26 (2H), 3.90 (2H), 4.71 (1H), 4.89 (2H), 6.01 (2H), 6.89 (1H), 7.33 (1H), 7.90 (1H), 7.93 (1H), 7.97 (1H), 7.28 (1H) ppm.

^{1}H-NMR (DMSO-d6) of B: δ= 0.50 (2H), 0.65 (2H), 1.14 (6H), 2.35 (3H), 2.80 (1H), 3.26 (2H), 3.85 (2H), 4.70 (1H), 5.93 (1H), 6.18 (1H), 7.17 (1H), 7.33 (1H), 7.70 (1H), 7.89 (1H), 7.96 (1H), 8.02 (1H), 8.29 (1H) ppm.

Example 242

N-cyclopropyl-4-(8-[(2-hydroxy-2-methylpropyl)amino]-6-{[4-(trifluoromethyl)phenyl]sulfanyl}imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide

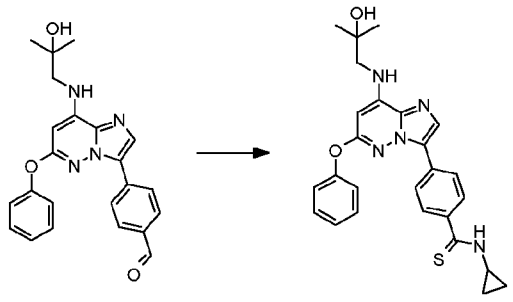


50 mg (109 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using 4-(trifluoromethyl)benzenethiol to give after working up and purification 23 mg (36%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.47 (2H), 0.65 (2H), 1.13 (6H), 2.17 (3H), 2.78 (1H), 3.25 (2H), 4.70 (1H), 6.37 (1H), 7.04-7.10 (2H), 7.59 (1H), 7.69 (1H), 7.79 (4H), 7.95 (1H), 8.18 (1H) ppm.

Example 243

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-phenoxyimidazo [1,2-b]pyridazin-3-yl}benzenecarbothioamide

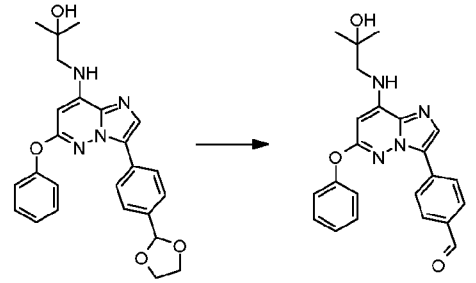


127 mg (316 µmol)
4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-phenoxyimidazo[1,2-b]pyridazin-3-yl}benzaldehyde which was prepared according to intermediate example 243a were transformed in analogy to example 13 to give after working up and purification 47 mg (30%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.71-0.87 (4H), 1.16 (6H), 3.26 (2H), 3.41 (1H), 4.72 (1H), 6.16 (1H), 6.99 (1H), 7.21-7.30 (3H), 7.44 (2H), 7.57 (2H), 7.91 (2H), 7.99 (1H), 10.05 (1H) ppm.

Intermediate example 243a

4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-phenoxyimidazo[1,2-b]pyridazin-3-yl}benzaldehyde

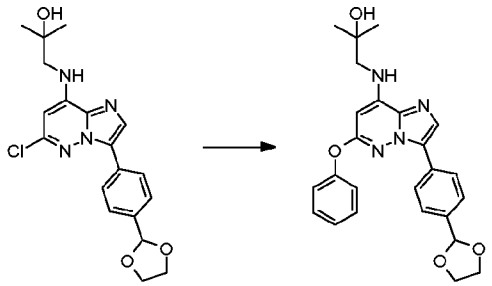


152 mg (340 µmol)

1-({3-[4-(1,3-dioxolan-2-yl)phenyl]-6-phenoxyimidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol which was prepared according to intermediate example 243b were transformed in analogy to intermediate example 13a to give after working up and purification 132 mg (96%) of the title compound.

Intermediate example 243b

1-({3-[4-(1,3-dioxolan-2-yl)phenyl]-6-phenoxyimidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol

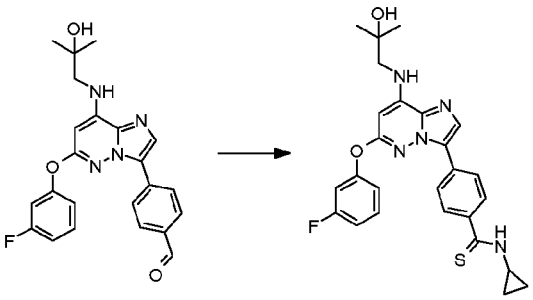


250 mg (643 µmol)

1-({6-chloro-3-[4-(1,3-dioxolan-2-yl)phenyl]imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol which was prepared according to intermediate example 32c were transformed in analogy to example 51 using phenol to give after working up and purification 157 mg (55%) of the title compound.

Example 244

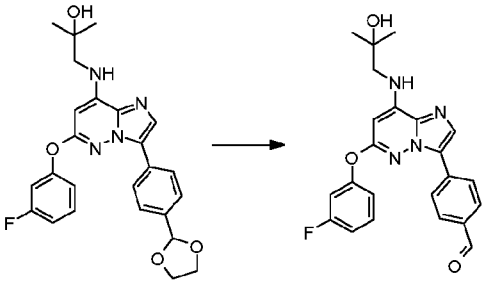
N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide



79 mg (188 µmol)
4-{6-(3-fluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzaldehyde which was prepared according to intermediate example 244a were transformed in analogy to example 13 to give after working up and purification 22 mg (22%) of the title compound.

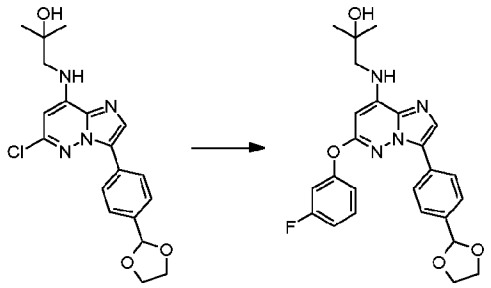
^{1}H-NMR (DMSO-d6): δ= 0.72-0.86 (4H), 1.15 (6H), 3.41 (2H), 3.49 (1H), 4.72 (1H), 6.18 (1H), 7.03-7.15 (3H), 7.21 (1H), 7.47 (1H), 7.60 (2H), 7.92 (2H), 8.00 (1H), 10.07 (1H) ppm.

Intermediate example 244a
4-{6-(3-fluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzaldehyde



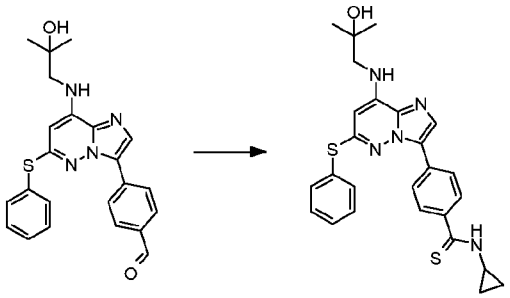
92 mg (198 µmol)
1-({3-[4-(1,3-dioxolan-2-yl)phenyl]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol which was prepared according to intermediate example 244b were transformed in analogy to intermediate example 13a to give after working up and purification 80 mg (96%) of the title compound.

Intermediate example 244b
1-({3-[4-(1,3-dioxolan-2-yl)phenyl]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol



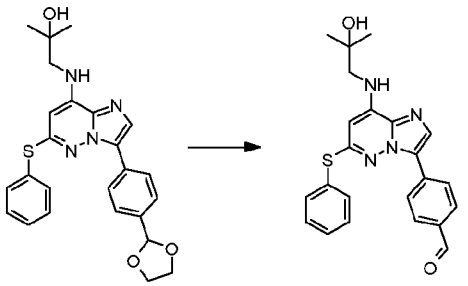
250 mg (643 µmol)
1-({6-chloro-3-[4-(1,3-dioxolan-2-yl)phenyl]imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol which was prepared according to intermediate example 32c were transformed in analogy to example 51 using 3-fluorophenol to give after working up and purification 94.2 mg (32%) of the title compound.

Example 245
N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(phenylsulfanyl) imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide



105 mg (251 µmol)
4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}benzaldehyde which was prepared according to intermediate example 245a were transformed in analogy to example 13 to give after working up and purification 27.3 mg (21%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.75-0.87 (4H), 1.12 (6H), 3.22 (2H), 3.43 (1H), 4.69 (1H), 6.24 (1H), 6.98 (1H), 7.46-7.59 (5H), 7.63 (2H), 7.82 (2H), 7.99 (1H), 10.07 (1H) ppm.

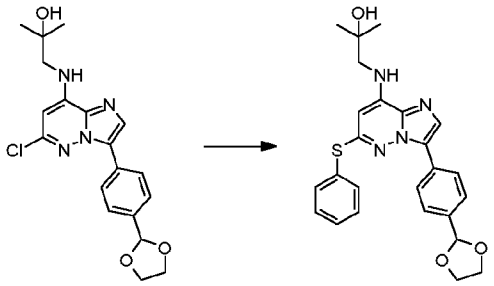
Intermediate example 245a
4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}benzaldehyde



155 mg (335 µmol) 1-({3-[4-(1,3-dioxolan-2-yl)phenyl]-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol which was prepared according to intermediate example 245b were transformed in analogy to intermediate example 13a to give after working up and purification 109 mg (78%) of the title compound.

Intermediate example 245b

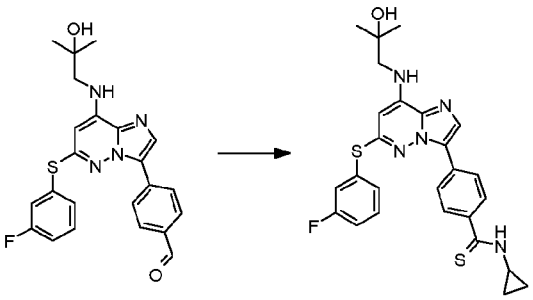
1-({3-[4-(1,3-dioxolan-2-yl)phenyl]-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol



250 mg (643 µmol) 1-({6-chloro-3-[4-(1,3-dioxolan-2-yl)phenyl]imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol which was prepared according to intermediate example 32c were transformed in analogy to example 51 using benzenethiol to give after working up and purification 154 mg (52%) of the title compound.

Example 246

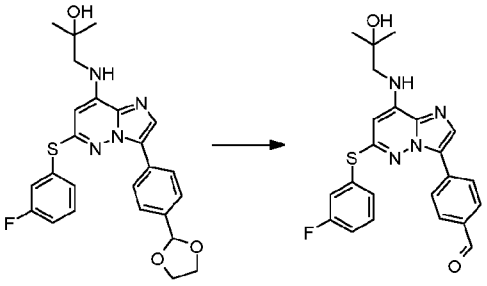
N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide



94 mg (215 µmol)
4-{6-[(3-fluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzaldehyde which was prepared according to intermediate example 246a were transformed in analogy to example 13 to give after working up and purification 9.2 mg (8%) of the title compound.

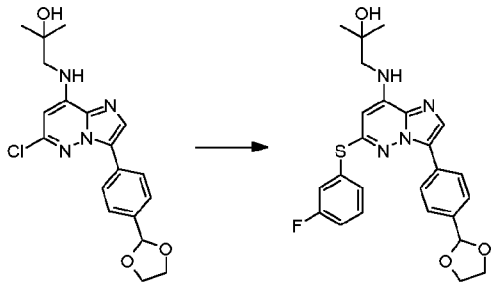
^{1}H-NMR (DMSO-d6): δ= 0.75-0.87 (4H), 1.12 (6H), 3.23 (2H), 3.44 (1H), 4.71 (1H), 6.31 (1H), 7.07 (1H), 7.35 (1H), 7.44 (1H), 7.48-7.55 (2H), 7.58 (2H), 7.85 (2H), 8.01 (1H), 10.10 (1H) ppm.

Intermediate example 246a
4-{6-[(3-fluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzaldehyde



108 mg (225 µmol)
1-({3-[4-(1,3-dioxolan-2-yl)phenyl]-6-[(3-fluorophenyl)sulfanyl]imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol which was prepared according to intermediate example 246b were transformed in analogy to intermediate example 13a to give after working up and purification 95 mg (97%) of the title compound.

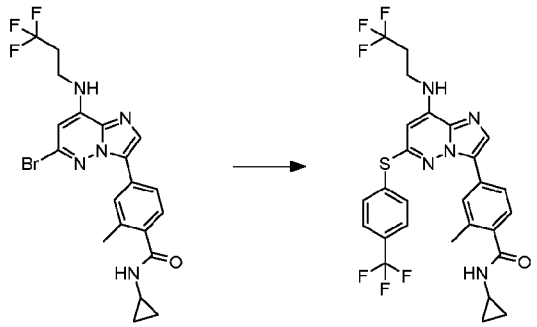
Intermediate example 246b
1-({3-[4-(1,3-dioxolan-2-yl)phenyl]-6-[(3-fluorophenyl)sulfanyl]imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol



250 mg (643 µmol)
1-({6-chloro-3-[4-(1,3-dioxolan-2-yl)phenyl]imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol which was prepared according to intermediate example 32c were transformed in analogy to example 51 using 3-fluorobenzenethiol to give after working up and purification 103.2 mg (33%) of the title compound.

Example 247

N-cyclopropyl-2-methyl-4-(6-{[4-(trifluoromethyl)phenyl]sulfanyl}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)benzamide

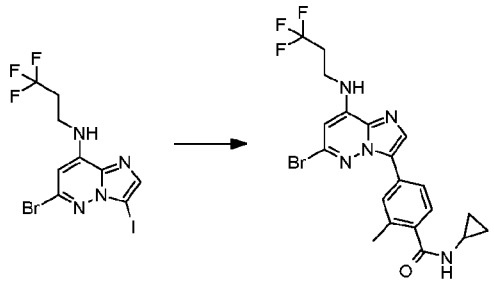


50 mg (104 µmol)
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using 4-(trifluoromethyl)benzenethiol to give after working up and purification 20.2 mg (32%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.60 (2H), 0.86 (2H), 2.37 (3H), 2.51 (2H), 2.87 (1H), 3.57 (2H), 5.95 (1H), 6.04 (1H), 6.54 (1H), 7.08 (1H), 7.48 (1H), 7.55 (1H), 7.66 (2H), 7.68 (1H), 7.73 (2H) ppm.

Intermediate example 247a

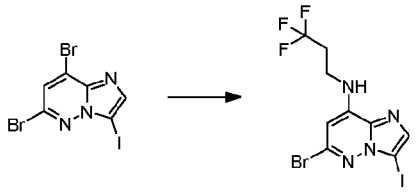
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



1.00 g (2.3 mmol) 6-bromo-3-iodo-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 247b were transformed in analogy to intermediate example 1a using N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide which was prepared according to intermediate example 7b to give after working up and purification 580 mg (52%) of the title compound.

Intermediate example 247b

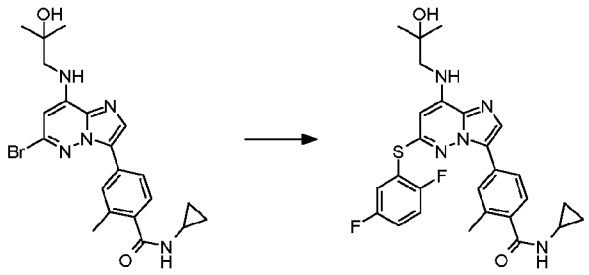
6-bromo-3-iodo-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine



2.30 g (5.71 mmol) 6,8-dibromo-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 96c were transformed in analogy to intermediate example 1b using 3,3,3-trifluoropropan-1-amine to give after working up and purification 2.0 g (81%) of the title compound.

Example 248

N-cyclopropyl-4-{6-[(2,5-difluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

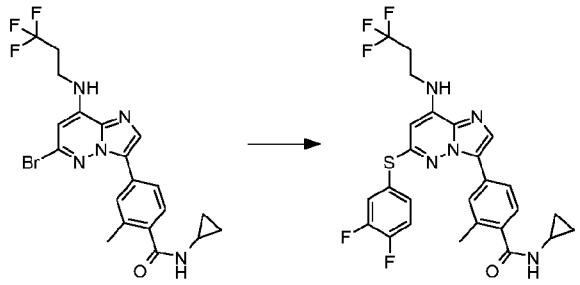


50 mg (109 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using 2,5-difluorobenzenethiol to give after working up and purification 10.4 mg (17%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.65 (2H), 1.14 (6H), 2.20 (3H), 2.79 (1H), 3.25 (2H), 4.71 (1H), 6.35 (1H), 7.04 (1H), 7.08 (1H), 7.42-7.51 (2H), 7.57 (1H), 7.62 (1H), 7.66 (1H), 7.94 (1H), 8.22 (1H) ppm.

Example 249

N-cyclopropyl-4-{6-[(3,4-difluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

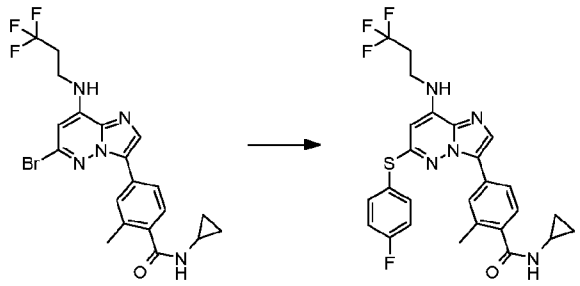


50 mg (104 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using 3,4-difluorobenzenethiol to give after working up and purification 5.0 mg (8%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.64 (2H), 0.90 (2H), 2.42 (3H), 2.52 (2H), 2.93 (1H), 3.61 (2H), 5.88 (1H), 8.90 (1H), 5.94 (1H), 7.20-7.28 (2H), 7.39 (1H), 7.51 (1H), 7.56 (1H), 7.57 (1H), 7.70 (1H) ppm.

Example 250

N-cyclopropyl-4-{6-[(4-fluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

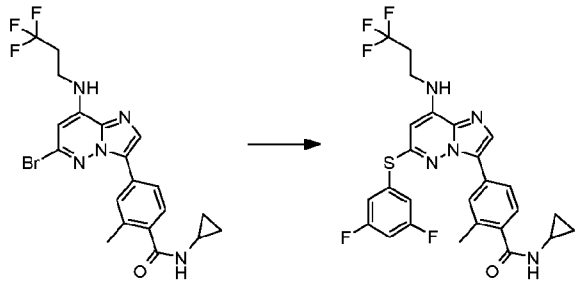


50 mg (104 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using 4-fluorobenzenethiol to give after working up and purification 3.8 mg (7%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.64 (2H), 0.90 (2H), 2.41 (3H), 2.50 (2H), 2.93 (1H), 3.59 (2H), 5.87 (1H), 5.88 (1H), 5.96 (1H), 7.15 (2H), 7.19 (1H), 7.55 (1H), 7.59 (1H), 7.64 (2H), 7.70 (1H) ppm.

Example 251

N-cyclopropyl-4-{6-[(3,5-difluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

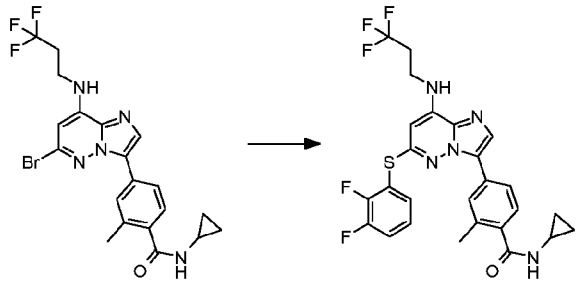


50 mg (104 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using 3,5-difluorobenzenethiol to give after working up and purification 2.9 mg (5%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.63 (2H), 0.90 (2H), 2.43 (3H), 2.52 (2H), 2.93 (1H), 3.62 (2H), 5.86 (1H), 5.96 (1H), 6.00 (1H), 6.88 (1H), 7.18 (2H), 7.29 (1H), 7.65 (1H), 7.69 (1H), 7.73 (1H) ppm.

Example 252

N-cyclopropyl-4-{6-[(2,3-difluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



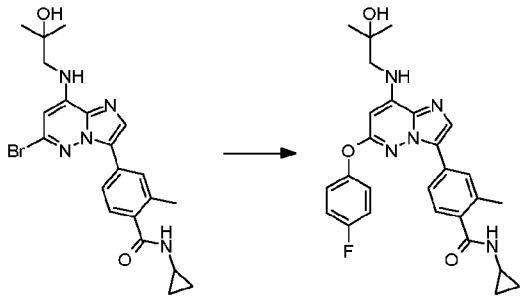
50 mg (104 µmol)

4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using 2,3-difluorobenzenethiol to give after working up and purification 1.6 mg (3%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.63 (2H), 0.90 (2H), 2.39 (3H), 2.54 (2H), 2.93 (1H), 3.62 (2H), 5.85 (1H), 5.97 (1H), 6.10 (1H), 7.16 (1H), 7.20 (1H), 7.33 (1H), 7.41 (1H), 7.56 (1H), 7.57 (1H), 7.69 (1H) ppm.

Example 253

N-cyclopropyl-4-{6-(4-fluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



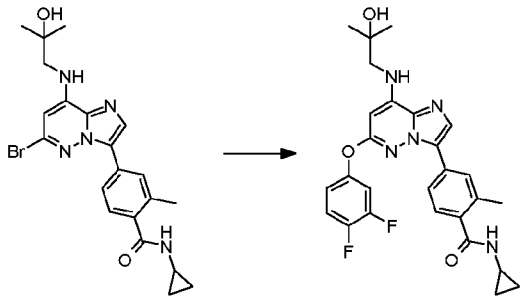
50 mg (109 µmol)

4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate

example 96a were transformed in analogy to example 51 using 4-fluorophenol to give after working up and purification 27.5 mg (49%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.47 (2H), 0.63 (2H), 1.16 (6H), 2.13 (3H), 2.77 (1H), 3.27 (2H), 4.73 (1H), 6.16 (1H), 6.95 (1H), 7.16 (1H), 7.24-7.34 (4H), 7.64 (1H), 7.73 (1H), 7.91 (1H), 8.19 (1H) ppm.

Example 254

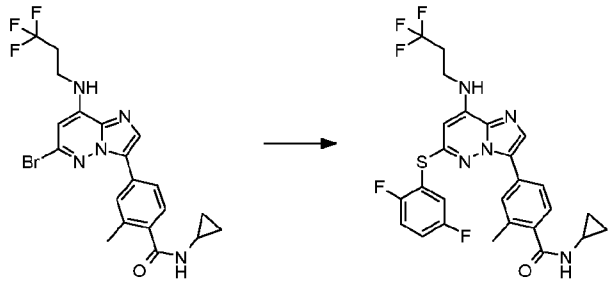
N-cyclopropyl-4-{6-(3,4-difluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



50 mg (109 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using 3,4-difluorophenol to give after working up and purification 18.1 mg (31%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.47 (2H), 0.64 (2H), 1.16 (6H), 2.14 (3H), 2.77 (1H), 3.27 (2H), 4.73 (1H), 6.17 (1H), 7.00 (1H), 7.13 (1H), 7.18 (1H), 7.51 (1H), 7.56 (1H), 7.65 (1H), 7.75 (1H), 7.91 (1H), 8.21 (1H) ppm.

Example 255

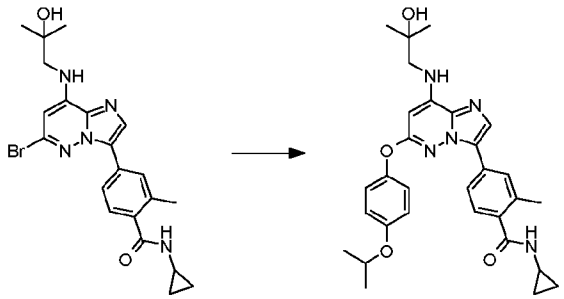
N-cyclopropyl-4-{6-[(2,5-difluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



50 mg (104 µmol)
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using 2,5-difluorobenzenethiol to give after working up and purification 13.3 mg (22%) of the title compound.
^{1}H-NMR ($CDCl_3$): δ= 0.62 (2H), 0.90 (2H), 2.39 (3H), 2.53 (2H), 2.92 (1H), 3.62 (2H), 5.87 (1H), 5.97 (1H), 6.06 (1H), 7.14-7.23 (3H), 7.39 (1H), 7.57 (1H), 7.59 (1H), 7.70 (1H) ppm.

Example 256

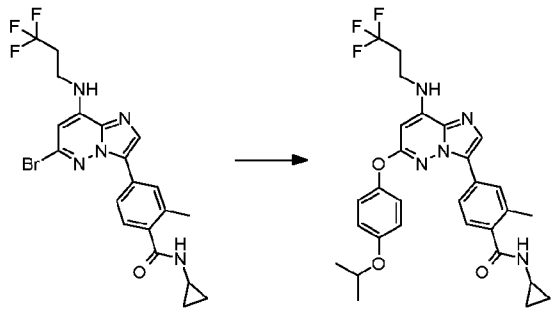
N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(4-isopropoxyphenoxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



75 mg (164 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using 4-isopropoxyphenol to give after working up and purification 13.7 mg (15%) of the title compound.
^{1}H-NMR ($CDCl_3$): δ= 0.60 (2H), 0.87 (2H), 1.36 (6H), 1.44 (6H), 2.30 (3H), 2.89 (1H), 3.31 (2H), 4.52 (1H), 5.87 (1H), 5.93 (1H), 6.52 (1H), 6.91 (2H), 7.11 (2H), 7.19 (1H), 7.58 (1H), 7.64 (1H), 7.74 (1H) ppm.

Example 257

N-cyclopropyl-4-{6-(4-isopropoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

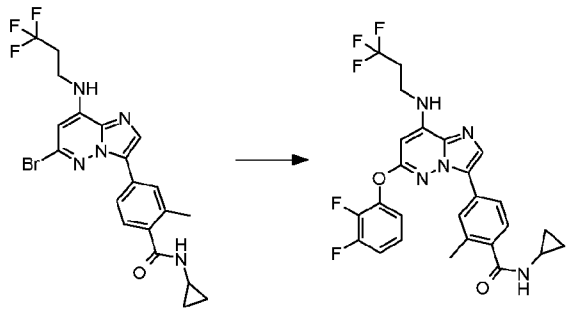


75 mg (156 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using 4-isopropoxyphenol to give after working up and purification 9.3 mg (10%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.59 (2H), 0.88 (2H), 1.37 (6H), 2.32 (3H), 2.56 (2H), 2.88 (1H), 3.66 (2H), 4.53 (1H), 5.84 (1H), 5.88 (1H), 5.91 (1H), 6.93 (2H), 7.14 (2H), 7.22 (1H), 7.62 (1H), 7.73 (1H), 7.79 (1H) ppm.

Example 258

N-cyclopropyl-4-{6-(2,3-difluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

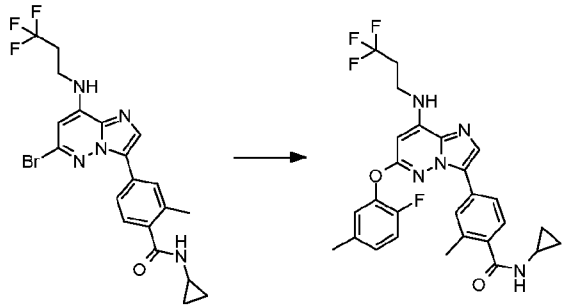


100 mg (207 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using 2,3-difluorophenol to give after working up and purification 22 mg (19%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.60 (2H), 0.88 (2H), 2.29 (3H), 2.58 (2H), 2.89 (1H), 3.70 (2H), 5.86 (1H), 5.96 (1H), 6.07 (1H), 7.06-7.17 (3H), 7.22 (1H), 7.53 (1H), 7.66 (1H), 7.71 (1H) ppm.

Example 259

N-cyclopropyl-4-{6-(2-fluoro-5-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

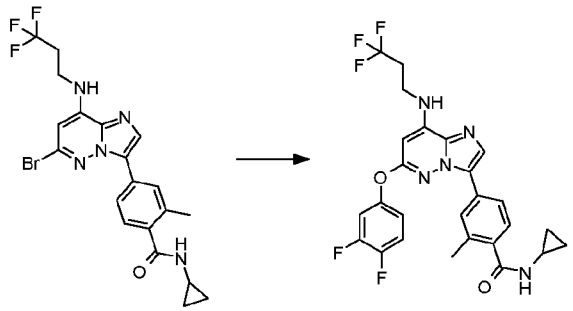


100 mg (207 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using 2-fluoro-5-methylphenol to give after working up and purification 23 mg (20%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.60 (2H), 0.88 (2H), 2.27 (3H), 2.35 (3H), 2.58 (2H), 2.89 (1H), 3.68 (2H), 5.84 (1H), 5.95 (1H), 6.11 (1H), 7.00-7.16 (3H), 7.21 (1H), 7.55 (1H), 7.71 (2H) ppm.

Example 260

N-cyclopropyl-4-{6-(3,4-difluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

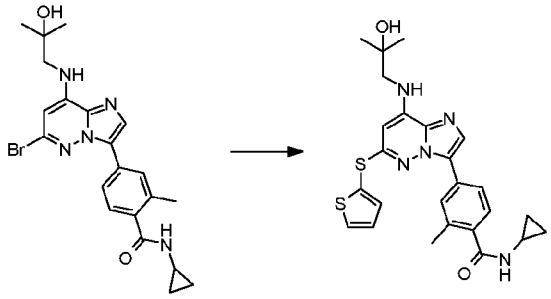


100 mg (207 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using 3,4-difluorophenol to give after working up and purification 36 mg (31%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.61 (2H), 0.88 (2H), 2.34 (3H), 2.57 (2H), 2.90 (1H), 3.68 (2H), 5.86 (1H), 5.87 (1H), 6.04 (1H), 6.99 (1H), 7.11-7.29 (3H), 7.59 (1H), 7.71 (1H), 7.72 (1H) ppm.

Example 261

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(2-thienylsulfanyl) imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



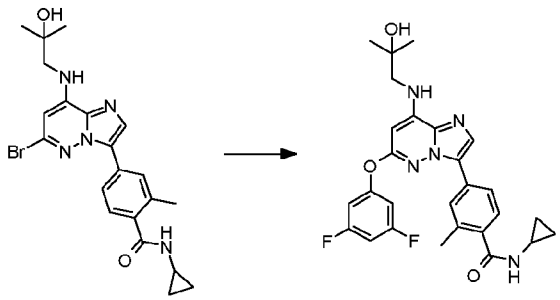
75 mg (164 µmol)

4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using thiophene-2-thiol to give after working up and purification 34 mg (41%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.65 (2H), 1.12 (6H), 2.26 (3H), 2.80 (1H), 1.64 (2H), 4.70 (1H), 6.21 (1H), 7.01 (1H), 7.17 (1H), 7.23 (1H), 7.47 (1H), 7.71 (1H), 7.76 (1H), 7.94 (2H), 8.23 (1H) ppm.

Example 262

N-cyclopropyl-4-{6-(3,5-difluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



200 mg (436 µmol)

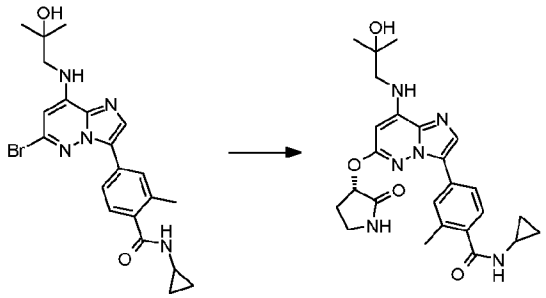
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cy

clopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using 3,5-difluorophenol to give after working up and purification 34.6 mg (15%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.47 (2H), 0.63 (2H), 1.15 (6H), 2.17 (3H), 2.77 (1H), 3.27 (2H), 4.74 (1H), 6.19 (1H), 7.08 (1H), 7.12-7.22 (4H), 7.68 (1H), 7.79 (1H), 7.93 (1H), 8.23 (1H) ppm.

Example 263

N-cyclopropyl-4-(8-[(2-hydroxy-2-methylpropyl)amino]-6-{[(3S)-2-oxopyrrolidin-3-yl]oxy}imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide

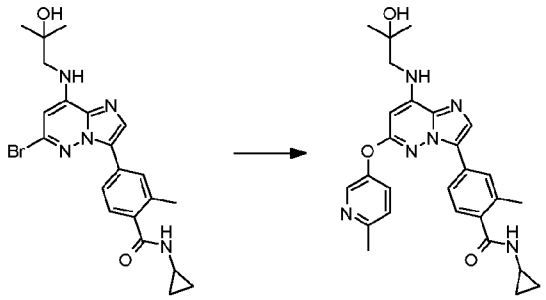


75 mg (164 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using (3S)-3-hydroxypyrrolidin-2-one to give after working up and purification 3.2 mg (4%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.64 (2H), 0.89 (2H), 1.40 (6H), 2.20 (1H), 2.49 (3H), 2.80 (1H), 2.92 (1H), 3.27 (2H), 3.37-3.51 (2H), 4.04 (1H), 5.33 (1H), 5.82 (1H), 6.09 (1H), 6.18 (1H), 6.34 (1H), 7.38 (1H), 7.57 (1H), 7.74 (1H), 7.80 (1H) ppm.

Example 264

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(6-methylpyridin-3-yl)oxy]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

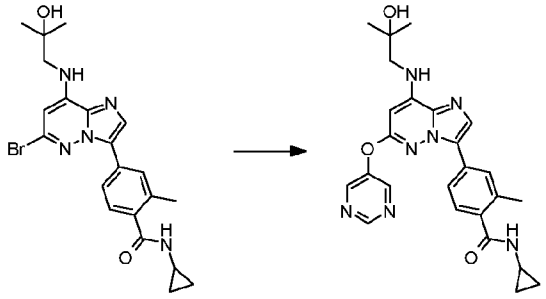


75 mg (164 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using 6-methylpyridin-3-ol to give after working up and purification 24.5 mg (30%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.66 (2H), 1.19 (6H), 2.14 (3H), 2.51 (3H), 2.80 (1H), 3.32 (2H), 4.76 (1H), 6.23 (1H), 7.02 (1H), 7.19 (1H), 7.37 (1H), 7.64 (1H), 7.68 (1H), 7.73 (1H), 7.94 (1H), 8.22 (1H), 8.43 (1H) ppm.

Example 265

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyrimidin-5-yloxy) imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

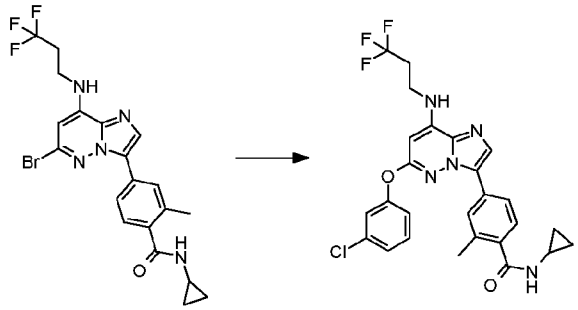


200 mg (436 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using pyrimidin-5-ol to give after working up and purification 34.6 mg (15%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.64 (2H), 0.89 (2H), 1.48 (6H), 2.30 (3H), 2.92 (1H), 3.35 (2H), 4.81 (1H), 5.87 (1H), 6.41 (1H), 6.62 (1H), 7.23 (1H), 7.45 (1H), 7.51 (1H), 7.58 (1H), 8.52 (2H), 9.05 (1H) ppm.

Example 266

4-{6-(3-chlorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b] pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

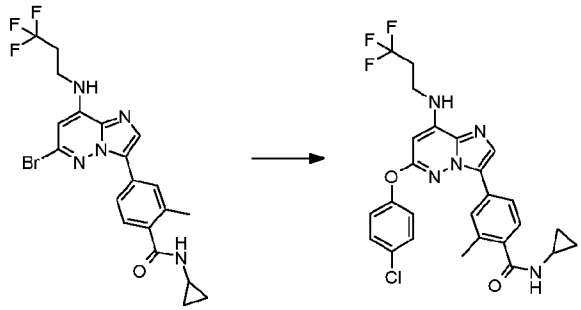


75 mg (156 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using 3-chlorophenol to give after working up and purification 13.9 mg (17%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.61 (2H), 0.88 (2H), 2.34 (3H), 2.58 (2H), 2.90 (1H), 3.68 (2H), 5.82 (1H), 5.89 (1H), 5.97 (1H), 7.15 (1H), 7.25 (1H), 7.27 (1H), 7.31 (1H), 7.36 (1H), 7.63 (1H), 7.72 (1H), 7.74 (1H) ppm.

Example 267

4-{6-(4-chlorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b] pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

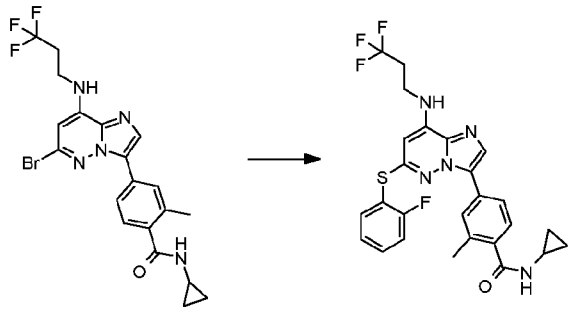


75 mg (156 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using 4-chlorophenol to give after working up and purification 12.6 mg (12.6%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.61 (2H), 0.88 (2H), 2.33 (3H), 2.57 (2H), 2.90 (1H), 3.68 (2H), 5.83 (1H), 5.89 (1H), 5.96 (1H), 7.19 (2H), 7.25 (1H), 7.40 (2H), 7.58 (1H), 7.72 (1H), 7.73 (1H) ppm.

Example 268

N-cyclopropyl-4-{6-[(2-fluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



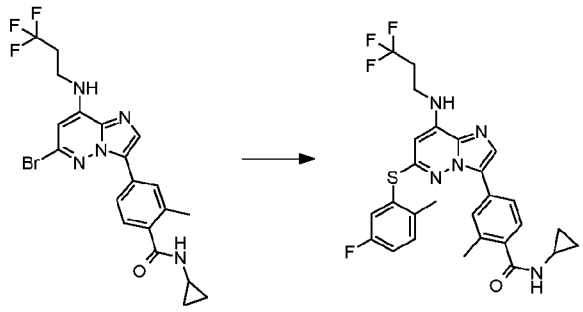
75 mg (156 µmol)

4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using 2-fluorobenzenethiol to give after working up and purification 31.8 mg (39%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.62 (2H), 0.90 (2H), 2.37 (3H), 2.51 (2H), 2.92 (1H), 3.60 (2H), 5.83 (1H), 5.89 (1H), 5.94 (1H), 7.16 (1H), 7.20 (1H), 7.25 (1H), 7.51 (1H), 7.56 (1H), 7.59 (1H), 7.66 (1H), 7.70 (1H) ppm.

Example 269

N-cyclopropyl-4-{6-[(5-fluoro-2-methylphenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



75 mg (156 µmol)

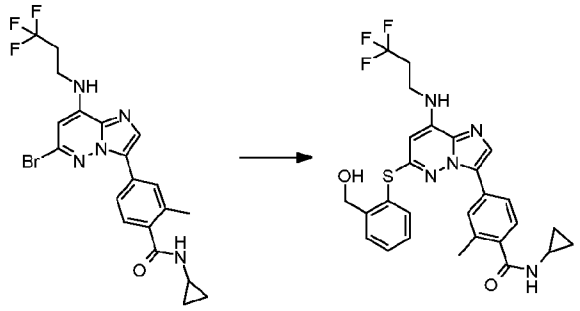
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopr

opyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using 5-fluoro-2-methylbenzenethiol to give after working up and purification 6.1 mg (7%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.63 (2H), 0.90 (2H), 2.39 (3H), 2.40 (3H), 2.50 (2H), 2.92 (1H), 3.59 (2H), 5.86 (1H), 5.89 (1H), 5.93 (1H), 7.10 (1H), 7.19 (1H), 7.31 (1H), 7.38 (1H), 7.57 (1H), 7.60 (1H), 7.71 (1H) ppm.

Example 270

N-cyclopropyl-4-(6-{[2-(hydroxymethyl)phenyl]sulfanyl}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide

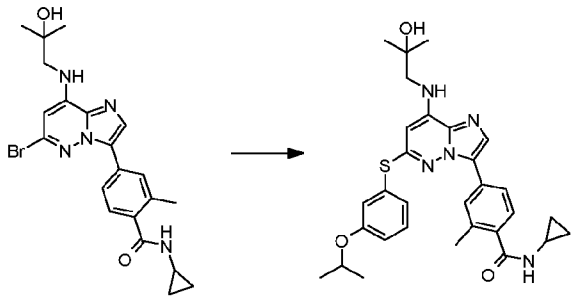


75 mg (156 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using (2-sulfanylphenyl)methanol to give after working up and purification 12.3 mg (15%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.63 (2H), 0.90 (2H), 2.34 (3H), 2.51 (2H), 2.92 (1H), 3.61 (2H), 4.83 (2H), 5.86 (1H), 5.89 (1H), 5.94 (1H), 7.14 (1H), 7.41 (1H), 7.42 (1H), 7.50 (1H), 7.57 (1H), 7.65 (1H), 7.68 (1H), 7.70 (1H) ppm.

Example 271

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-methoxyphenyl) sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

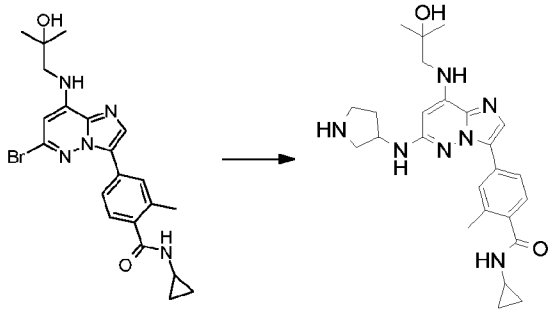


75 mg (164 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using 3-isopropoxybenzenethiol to give after working up and purification 18.5 mg (20%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.65 (2H), 1.11 (6H), 1.18 (6H), 2.21 (3H), 2.78 (1H), 3.20 (2H), 4.58 (1H), 4.71 (1H), 6.21 (1H), 6.95-7.05 (2H), 7.08-7.16 (3H), 7.34 (1H), 7.71 (1H), 7.73 (1H), 7.94 (1H), 8.23 (1H) ppm.

Example 272

(RS)-N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyrrolidin-3-ylamino)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



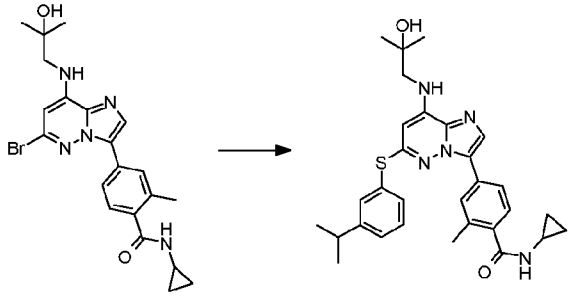
50 mg (109 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using (RS)-pyrrolidin-3-amine to give after working up and purification 18 mg (36%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.65 (2H), 1.16 (6H), 1.86 (1H), 2.15 (1H), 2.36 (3H), 2.80 (1H), 3.21 (2H), 3.28 (1H), 3.45 (1H), 3.53-3.65 (2H), 3.71 (1H), 4.27

(1H), 5.68 (1H), 6.36 (1H), 7.31 (1H), 7.78 (1H), 8.07 (1H), 8.10 (1H), 8.26 (1H), 8.29 (1H) ppm.

Example 273

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-isopropylphenyl) sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

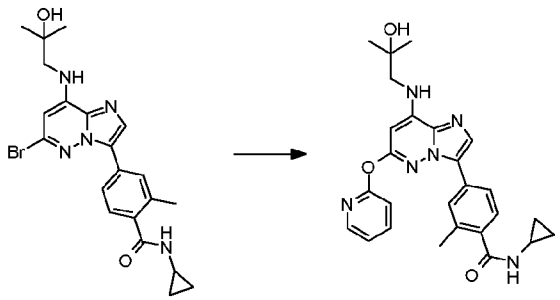


75 mg (164 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using 3-isopropylbenzenethiol to give after working up and purification 14.0 mg (15%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.64 (2H), 1.10 (6H), 1.14 (6H), 2.18 (3H), 2.78 (1H), 2.88 (1H), 3.18 (2H), 4.71 (1H), 6.18 (1H), 6.98 (1H), 7.08 (1H), 7.34-7.43 (3H), 7.45 (1H), 7.64 (1H), 7.71 (1H), 7.94 (1H), 8.22 (1H) ppm.

Example 274

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-2-yloxy) imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



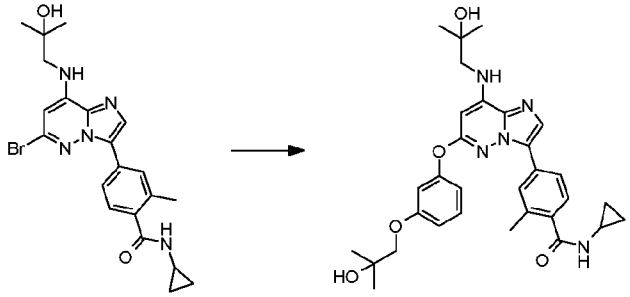
75 mg (164 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate

example 96a were transformed in analogy to example 51 using pyridin-2-ol to give after working up and purification 11.0 mg (14%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.64 (2H), 1.14 (6H), 2.33 (3H), 2.79 (1H), 3.27 (2H), 4.73 (1H), 6.33 (1H), 6.47 (1H), 6.48 (1H), 7.21 (1H), 7.33 (1H), 7.54 (1H), 7.79 (1H), 7.82 (1H), 7.91 (1H), 8.03 (1H), 8.24 (1H) ppm.

Example 275

N-cyclopropyl-4-{6-[3-(2-hydroxy-2-methylpropoxy)phenoxy]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

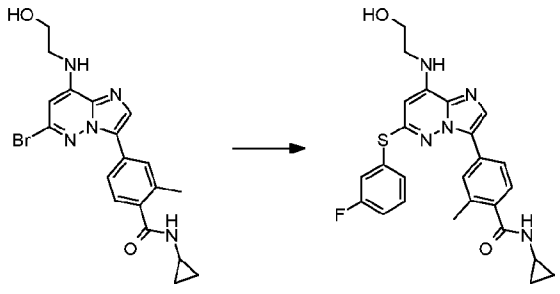


50 mg (109 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using 3-{2-methyl-2-[(triisopropylsilyl)oxy]propoxy}phenol to give after working up and purification 2.3 mg (4%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.46 (2H), 0.63 (2H), 1.14 (6H), 1.15 (6H), 2.14 (3H), 2.76 (1H), 3.27 (2H), 3.66 (2H), 4.59 (1H), 4.74 (1H), 6.14 (1H), 6.76-6.86 (3H), 6.97 (1H), 7.16 (1H), 7.31 (1H), 7.70 (1H), 7.79 (1H), 7.92 (1H), 8.21 (1H) ppm.

Example 276

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(2-hydroxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

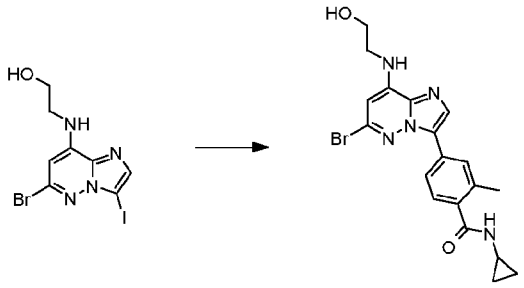


75 mg (174 µmol) 4-{6-bromo-8-[(2-hydroxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 276a were transformed in analogy to example 51 using 3-fluorobenzenethiol to give after working up and purification 14.5 mg (17%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.65 (2H), 2.20 (3H), 2.78 (1H), 3.33 (2H), 3.57 (2H), 4.82 (1H), 6.19 (1H), 7.12 (1H), 7.33 (1H), 7.38-7.54 (4H), 7.66 (1H), 7.71 (1H), 7.94 (1H), 8.23 (1H) ppm.

Intermediate example 276a

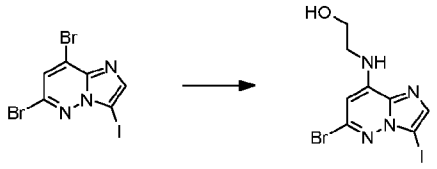
4-{6-bromo-8-[(2-hydroxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



1.98 g (5.17 mmol) 2-[(6-bromo-3-iodoimidazo[1,2-b]pyridazin-8-yl)amino]ethanol which was prepared according to intermediate example 276b were transformed in analogy to intermediate example 1a using N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide to give after working up and purification 1.27 g (51%) of the title compound.

Intermediate example 276b

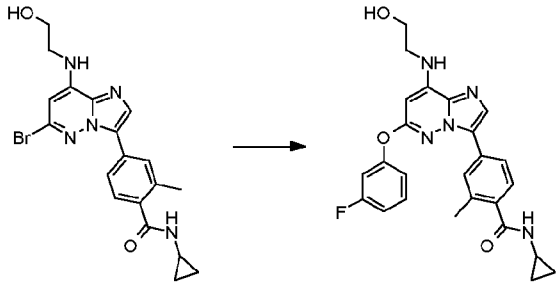
2-[(6-bromo-3-iodoimidazo[1,2-b]pyridazin-8-yl)amino]ethanol



2.50 g (6.21 mmol) 6,8-dibromo-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 96c were transformed in analogy to intermediate example 1b using 2-aminoethanol to give after working up and purification 1.99 g (81%) of the title compound.

Example 277

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(2-hydroxyethyl)amino]imidazo [1,2-b]pyridazin-3-yl}-2-methylbenzamide



75 mg (174 µmol) 4-{6-bromo-8-[(2-hydroxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamid which was prepared according to intermediate example 276a were transformed in analogy to example 51 using 3-fluorophenol to give after working up and purification 17.2 mg (21%) of the title compound.

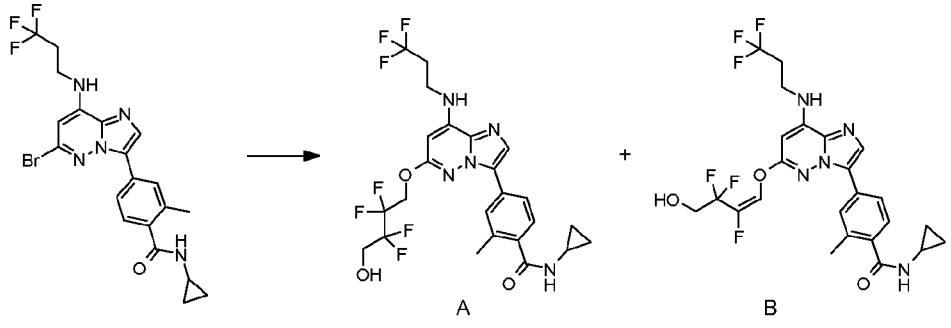
^{1}H-NMR (DMSO-d6): δ= 0.46 (2H), 0.63 (2H), 2.14 (3H), 2.76 (1H), 3.38 (2H), 3.62 (2H), 4.84 (1H), 6.08 (1H), 7.07-7.20 (3H), 7.24 (1H), 7.41 (1H), 7.48 (1H), 7.66 (1H), 7.76 (1H), 7.92 (1H), 8.21 (1H) ppm.

Example 278

N-cyclopropyl-2-methyl-4-{6-(2,2,3,3-tetrafluoro-4-hydroxybutoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide (A)

and

N-cyclopropyl-2-methyl-4-(6-{[(1E)-2,3,3-trifluoro-4-hydroxybut-1-en-1-yl]oxy}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)benzamide



A B

100 mg (207 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using

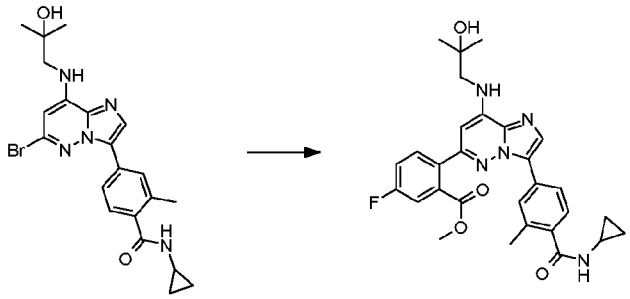
2,2,3,3-tetrafluorobutane-1,4-diol to give after working up and purification 5.2 mg (4%) of the title compound A and 5.3 mg (4%) of the title compound B.

^{1}H-NMR (DMSO-d6) of A: δ= 0.50 (2H), 0.65 (2H), 2.35 (3H), 2.65 (2H), 2.80 (1H), 3.56 (2H), 3.91 (2H), 4.91 (2H), 5.97 (1H), 6.00 (1H), 7.33 (1H), 7.60 (1H), 7.90 (1H), 7.92 (1H), 7.97 (1H), 8.27 (1H) ppm.

^{1}H-NMR (DMSO-d6) of B: δ= 0.50 (2H), 0.66 (2H), 2.35 (3H), 2.66 (2H), 2.80 (1H), 3.59 (2H), 3.86 (2H), 5.92 (1H), 6.14 (1H), 7.33 (1H), 7.70 (1H), 7.84 (1H), 7.89 (1H), 7.97 (1H), 8.02 (1H), 8.28 (1H) ppm.

Example 279

2-{3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-8-[(2-hydroxy-2-methylpropyl) amino]imidazo[1,2-b]pyridazin-6-yl}-5-fluoro-benzoic acid methyl ester



600 mg (1.31 mmol)

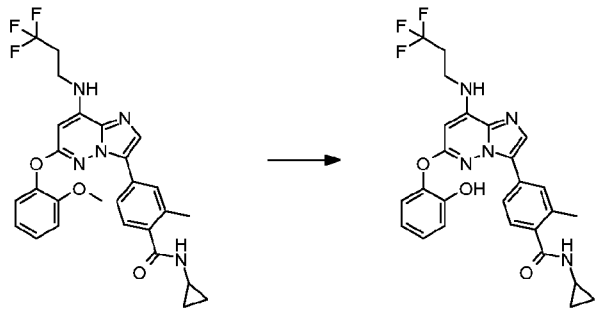
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 1 using [4-fluoro-2-(methoxycarbonyl)phenyl]boronic acid. After working up 19 mL tetrahydrofuran were added to the crude product and the suspension was cooled to 3°C. 21.8 mL of a freshly prepared diazomethane solution in diethyl ether were added in portions over 2 hours. The solvent was removed and the residue purified by chromatography to give 52.7 mg (9%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.65 (2H), 1.17 (6H), 2.36 (3H), 2.80 (1H), 3.33 (2H), 3.47 (3H), 4.75 (1H), 6.52 (1H), 6.96 (1H), 7.30 (1H), 7.51-7.59 (2H), 7.78 (1H), 7.92 (1H), 7.97 (1H), 8.04 (1H), 8.23 (1H) ppm.

Example 280

N-cyclopropyl-4-{6-(2-hydroxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]

imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

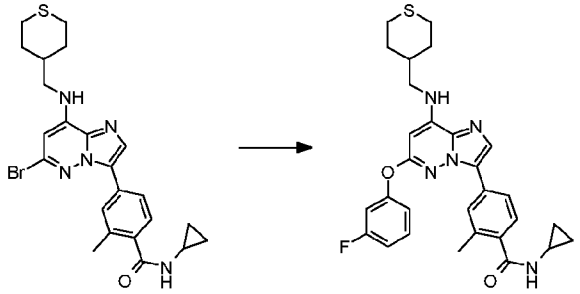


A mixture of 28.0 mg (53 µmol) N-cyclopropyl-4-{6-(2-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide which was prepared according to example 223, 44.8 mg sodium methanethiolate and 350 µL *N,N*-dimethylformamide was heated under microwave irradiation for 30 minutes at 120°C. The mixture was pured into water, the pH was adjusted between 7 and 8 by addition of ammonium chloride and extracted with a mixture of dichloromethane and methanol. The combined organic phases were dried over sodium sulfate. After filtration and removal of solvent the residue was purified by chromatography to give 11.5 mg (40%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.47 (2H), 0.63 (2H), 2.09 (3H), 2.68 (2H), 2.76 (1H), 3.59 (2H), 6.08 (1H), 6.83 (1H), 6.97 (1H), 7.05-7.17 (3H), 7.55 (1H), 7.62 (1H), 7.75 (1H), 7.90 (1H), 8.18 (1H), 9.53 (1H) ppm.

Example 281

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



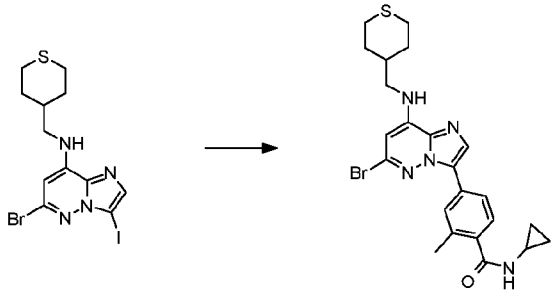
75 mg (150 µmol) 4-{6-bromo-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 281a were transformed in analogy to example 51 using

3-fluorophenol to give after working up and purification 33.7 mg (40%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.66 (2H), 1.32 (2H), 1.78 (1H), 2.04 (2H), 2.17 (3H), 2.59 (4H), 2.79 (1H), 3.22 (2H), 6.09 (1H), 7.15 (2H), 7.18 (1H), 7.27 (1H), 7.50 (1H), 7.68 (1H), 7.72 (1H), 7.78 (1H), 7.93 (1H), 8.22 (1H) ppm.

Intermediate example 281a

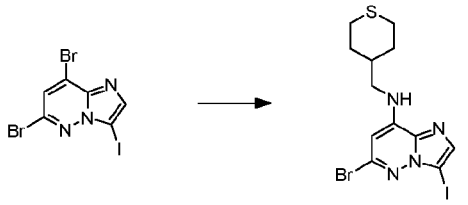
4-{6-bromo-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



2.22 g (4.90 mmol) 6-bromo-3-iodo-N-(tetrahydro-2H-thiopyran-4-ylmethyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 281b were transformed in analogy to intermediate example 1a using N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide to give after working up and purification 1.49 g (55%) of the title compound.

Intermediate example 281b

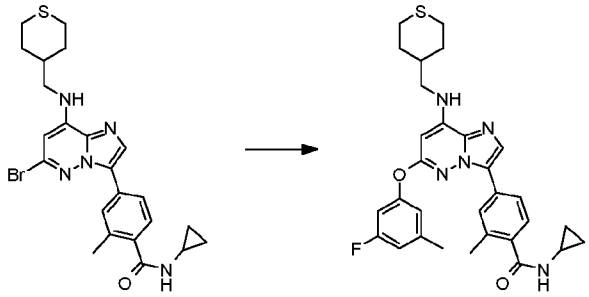
6-bromo-3-iodo-N-(tetrahydro-2H-thiopyran-4-ylmethyl)imidazo[1,2-b]pyridazin-8-amine



2.31 g (5.75 mmol) 6,8-dibromo-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 96c were transformed in analogy to intermediate example 1b using 1-(tetrahydro-2H-thiopyran-4-yl)methanamine to give after working up and purification 2.23 g (81%) of the title compound.

Example 282

N-cyclopropyl-4-{6-(3-fluoro-5-methylphenoxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

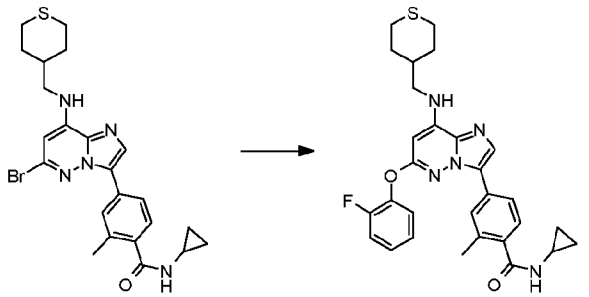


75 mg (150 µmol) 4-{6-bromo-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 281a were transformed in analogy to example 51 using 3-fluoro-5-methylphenol to give after working up and purification 14.1 mg (16%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.66 (2H), 1.32 (2H), 1.77 (1H), 2.04 (2H), 2.18 (3H), 2.34 (3H), 2.59 (4H), 2.79 (1H), 3.22 (2H), 6.07 (1H), 6.96 (1H), 6.97 (1H), 7.04 (1H), 7.20 (1H), 7.68-7.74 (2H), 7.80 (1H), 7.93 (1H), 8.23 (1H) ppm.

Example 283

N-cyclopropyl-4-{6-(2-fluorophenoxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

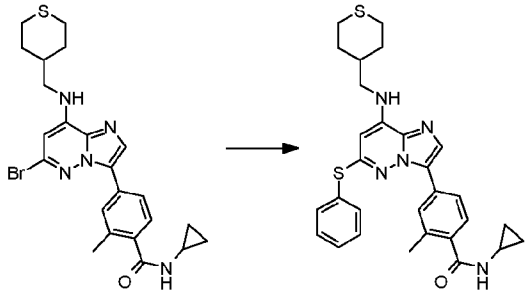


75 mg (150 µmol) 4-{6-bromo-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 281a were transformed in analogy to example 51 using 2-fluorophenol to give after working up and purification 26.6 mg (32%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.66 (2H), 1.33 (2H), 1.80 (1H), 2.06 (2H), 2.11 (3H), 2.60 (4H), 2.78 (1H), 3.23 (2H), 6.16 (1H), 7.13 (1H), 7.30 (1H), 7.37 (1H), 7.43 (1H), 7.47 (1H), 7.61 (1H), 7.69 (1H), 7.74 (1H), 7.93 (1H), 8.21 (1H) ppm.

Example 284

N-cyclopropyl-2-methyl-4-{6-(phenylsulfanyl)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide



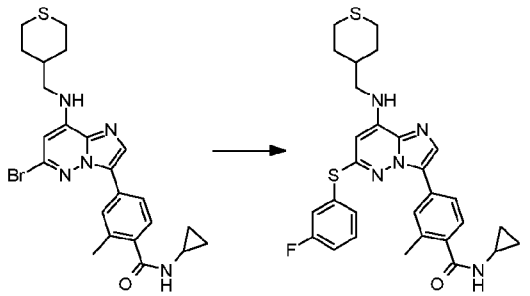
75 mg (150 µmol)

4-{6-bromo-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 281a were transformed in analogy to example 51 using benzenethiol to give after working up and purification 45.3 mg (54%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.65 (2H), 1.22 (2H), 1.60 (1H), 1.91 (2H), 2.21 (3H), 2.52 (4H), 2.78 (1H), 3.08 (2H), 5.99 (1H), 7.10 (1H), 7.44-7.53 (3H), 7.59-7.73 (5H), 7.91 (1H), 8.24 (1H) ppm.

Example 285

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



75 mg (150 µmol)

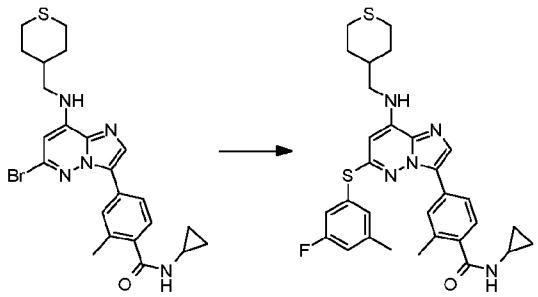
4-{6-bromo-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-

3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 281a were transformed in analogy to example 51 using 3-fluorobenzenethiol to give after working up and purification 9.8 mg (11%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.65 (2H), 1.23 (2H), 1.64 (1H), 1.93 (2H), 2.21 (3H), 2.53 (4H), 2.79 (1H), 3.11 (2H), 6.10 (1H), 7.13 (1H), 7.34 (1H), 7.44 (1H), 7.48-7.54 (2H), 7.68 (1H), 7.72 (1H), 7.74 (1H), 7.93 (1H), 8.25 (1H) ppm.

Example 286

N-cyclopropyl-4-{6-[(3-fluoro-5-methylphenyl)sulfanyl]-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

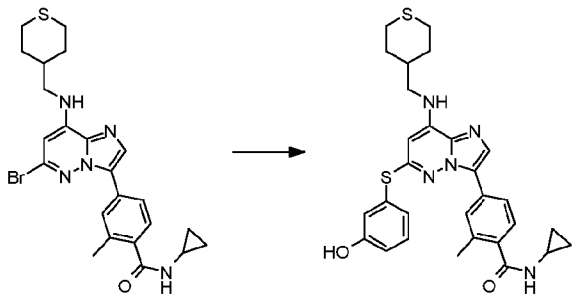


75 mg (150 µmol) 4-{6-bromo-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 281a were transformed in analogy to example 51 using 3-fluoro-5-methylbenzenethiol to give after working up and purification 9.1 mg (10%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.65 (2H), 1.23 (2H), 1.62 (1H), 1.92 (2H), 2.21 (3H), 2.31 (3H), 2.52 (4H), 2.79 (1H), 3.11 (2H), 6.07 (1H), 7.14 (1H), 7.17 (1H), 7.26-7.32 (2H), 7.68-7.76 (3H), 7.93 (1H), 8.25 (1H) ppm.

Example 287

N-cyclopropyl-4-{6-[(3-hydroxyphenyl)sulfanyl]-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

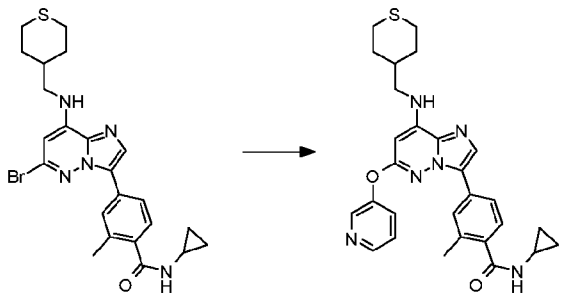


100 mg (200 µmol)
4-{6-bromo-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 281a were transformed in analogy to example 51 using 3-methoxybenzenethiol to give after working up and purification 14 mg (12%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.65 (2H), 1.22 (2H), 1.58 (1H), 1.90 (2H), 2.24 (3H), 2.52 (4H), 2.79 (1H), 3.07 (2H), 5.95 (1H), 6.86 (1H), 6.96 (1H), 7.01 (1H), 7.17 (1H), 7.26 (1H), 7.69 (1H), 7.73-7.80 (2H), 7.92 (1H), 8.24 (1H), 9.76 (1H) ppm.

Example 288

N-cyclopropyl-2-methyl-4-{6-(pyridin-3-yloxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide

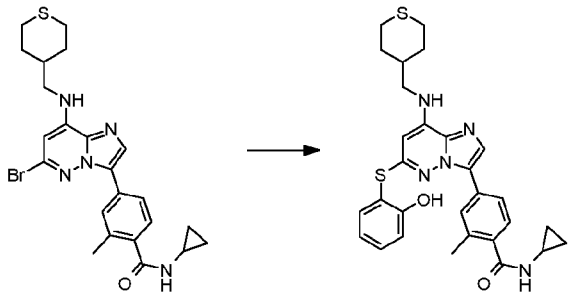


75 mg (150 µmol)
4-{6-bromo-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 281a were transformed in analogy to example 51 using pyridin-3-ol to give after working up and purification 25.2 mg (31%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.46 (2H), 0.63 (2H), 1.30 (2H), 1.76 (1H), 2.02 (2H), 2.12 (3H), 2.57 (4H), 2.76 (1H), 3.20 (2H), 6.13 (1H), 7.13 (1H), 7.51 (1H), 7.60 (1H), 7.68 (1H), 7.76 (1H), 7.80 (1H), 7.90 (1H), 8.21 (1H), 8.48 (1H), 8.57 (1H) ppm.

Example 289

N-cyclopropyl-4-{6-[(2-hydroxyphenyl)sulfanyl]-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



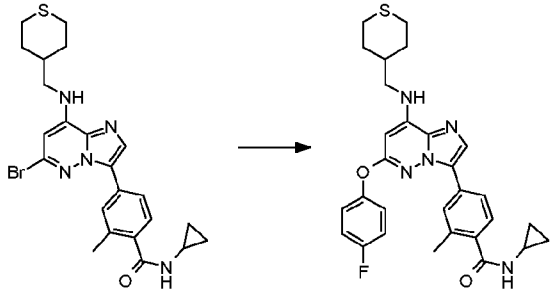
75 mg (150 µmol)

4-{6-bromo-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 281a were transformed in analogy to example 51 using 2-methoxybenzenethiol to give after working up and purification 40.9 mg (48%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.65 (2H), 1.20 (2H), 1.57 (1H), 1.88 (2H), 2.23 (3H), 2.52 (4H), 2.79 (1H), 3.03 (2H), 5.86 (1H), 6.87 (1H), 6.98 (1H), 7.12 (1H), 7.34 (1H), 7.46 (1H), 7.60 (1H), 7.72 (1H), 7.74 (1H), 7.90 (1H), 8.23 (1H), 10.01 (1H) ppm.

Example 290

N-cyclopropyl-4-{6-(4-fluorophenoxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

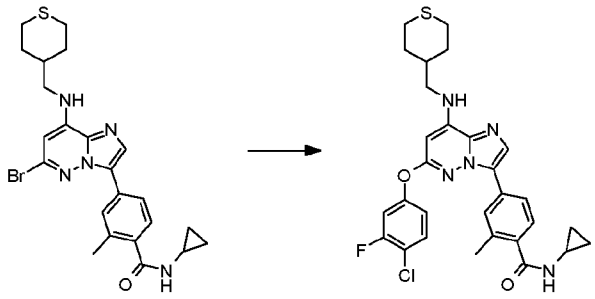


75 mg (150 µmol)
4-{6-bromo-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 281a were transformed in analogy to example 51 using 4-fluorophenol to give after working up and purification 45.6 mg (54%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.46 (2H), 0.63 (2H), 1.29 (2H), 1.75 (1H), 2.02 (2H), 2.12 (3H), 2.56 (4H), 2.76 (1H), 3.19 (2H), 6.06 (1H), 7.15 (1H), 7.23-7.35 (4H), 7.63 (1H), 7.68 (1H), 7.72 (1H), 7.90 (1H), 8.21 (1H) ppm.

Example 291

4-{6-(4-chloro-3-fluorophenoxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

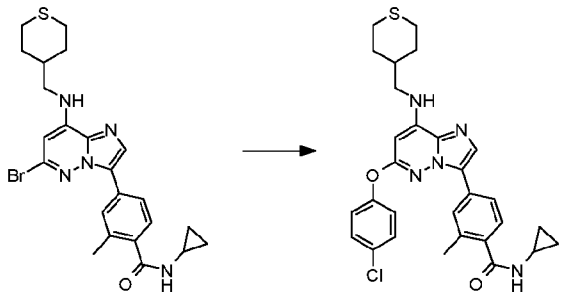


75 mg (150 µmol)
4-{6-bromo-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 281a were transformed in analogy to example 51 using 4-chloro-3-fluorophenol to give after working up and purification 5.4 mg (6%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.64 (2H), 0.91 (2H), 1.54 (2H), 1.80 (1H), 2.20 (2H), 2.37 (3H), 2.65-2.79 (4H), 2.93 (1H), 3.26 (2H), 5.86 (1H), 5.87 (1H), 5.97 (1H), 7.04 (1H), 7.16 (1H), 7.30 (1H), 7.46 (1H), 7.62 (1H), 7.74 (2H) ppm.

Example 292

4-{6-(4-chlorophenoxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

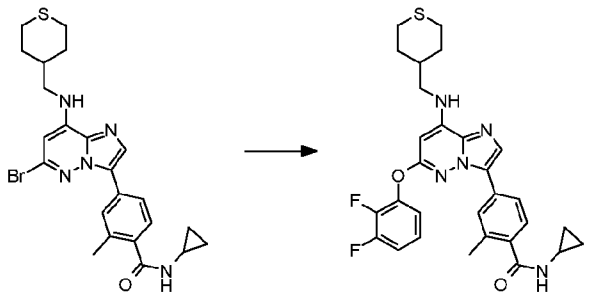


75 mg (150 µmol)
4-{6-bromo-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 281a were transformed in analogy to example 51 using 4-chlorophenol to give after working up and purification 30.7 mg (36%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.46 (2H), 0.63 (2H), 1.29 (2H), 1.75 (1H), 2.02 (2H), 2.12 (3H), 2.56 (4H), 2.77 (1H), 3.19 (2H), 6.07 (1H), 7.16 (1H), 7.31 (2H), 7.50 (2H), 7.62 (1H), 7.72 (2H), 7.90 (1H), 8.21 (1H) ppm.

Example 293

N-cyclopropyl-4-{6-(2,3-difluorophenoxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



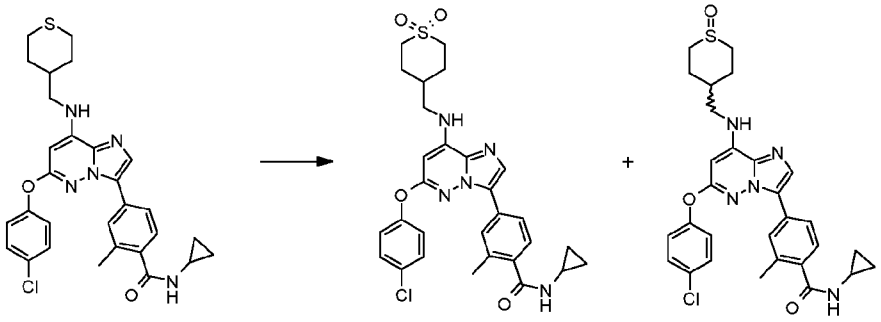
75 mg (150 µmol)
4-{6-bromo-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 281a were transformed in analogy example 51 using 2,3-difluorophenol to give after working up and purification 19.1 mg (22%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.60 (2H), 0.88 (2H), 1.52 (2H), 1.79 (1H), 2.19 (2H), 2.30 (3H), 2.61-2.79 (4H), 2.89 (1H), 3.25 (2H), 5.82 (1H), 5.92 (2H), 7.05-7.17 (3H), 7.22 (1H), 7.54 (1H), 7.68 (1H), 7.70 (1H) ppm.

Example 294

4-[6-(4-chlorophenoxy)-8-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide (A) and

4-[6-(4-chlorophenoxy)-8-({[(cis/trans)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide (B)



A B

To a solution of 22.4 mg (41 µmol) 4-{6-(4-chlorophenoxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to example 292 in 327 µL trichloromethane were added 13.7 mg 3-chlorobenzenecarboperoxoic acid (77%) and the mixture was stirred at 23°C for 40 minutes. Saturated sodium hydrogencarbonate solution was added and the solvents were removed. The residue was purified by chromatography to give 9.1 mg (38%) of the title compound A and 3.1 mg (13%) of a cis/trans-mixture of the title compounds B.

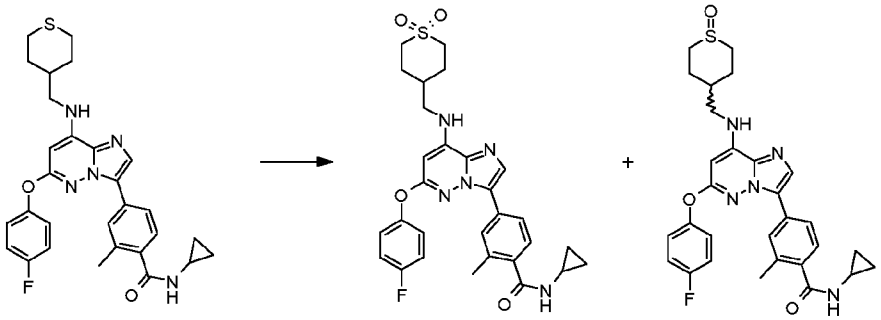
^{1}H-NMR (DMSO-d6) of A: δ= 0.47 (2H), 0.63 (2H), 1.66 (2H), 1.98-2.15 (3H), 2.12 (3H), 2.77 (1H), 2.97-3.15 (4H), 3.25 (2H), 6.16 (1H), 7.17 (1H), 7.30 (2H), 7.50 (2H), 7.62 (1H), 7.72 (1H), 7.79 (1H), 7.91 (1H), 8.19 (1H) ppm.

^{1}H-NMR (DMSO-d6) of B: δ= 0.46 (2H), 0.63 (2H), 1.65 (2H), 1.95-2.17 (3H), 2.12 (3H), 2.76 (1H), 2.96-3.16 (4H), 3.27 (2H), 6.17 (1H), 7.16 (1H), 7.30 (2H), 7.50 (2H), 7.62 (1H), 7.72 (1H), 7.82 (1H), 7.91 (1H), 8.22 (1H) ppm.

Example 295

N-cyclopropyl-4-[8-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}-

6-(4-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide (A)
and
N-cyclopropyl-4-[6-(4-fluorophenoxy)-8-({[(cis/trans)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide (B)



A B

37 mg (70 µmol) N-cyclopropyl-4-{6-(4-fluorophenoxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide which was prepared according to example 290 were transformed in analogy to example 294 to give after working up and purification 5.2 mg (13%) of the title compound A and 1.7 mg (4%)of a cis/trans-mixture of the title compounds B.

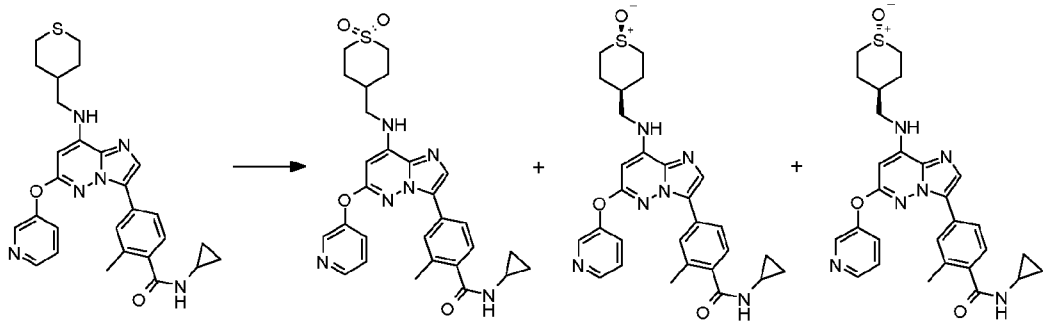
^{1}H-NMR (DMSO-d6) of A: δ= 0.47 (2H), 0.63 (2H), 1.66 (2H), 1.95-2.17 (3H), 2.12 (3H), 2.76 (1H), 2.97-3.16 (4H), 3.22 (2H), 6.15 (1H), 7.15 (1H), 7.23-7.36 (4H), 7.63 (1H), 7.72 (1H), 7.76 (1H), 7.90 (1H), 8.19 (1H) ppm.

^{1}H-NMR (DMSO-d6) of B: δ= 0.47 (2H), 0.63 (2H), 1.38 (1H), 1.64-2.26 (5H), 2.12 (3H), 2.57 (2H), 2.67-2.88 (2H), 3.19 (2H), 6.11 (1H), 7.15 (1H), 7.22-7.35 (4H), 7.63 (1H), 7.68-7.77 (2H), 7.90 (1H), 8.19 (1H) ppm.

Example 296

N-cyclopropyl-4-[8-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}-6-(pyridin-3-yloxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide (A)
and
N-cyclopropyl-2-methyl-4-[8-({[(cis)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)-6-(pyridin-3-yloxy)imidazo[1,2-b]pyridazin-3-yl]benzamide (B)
and
N-cyclopropyl-2-methyl-4-[8-({[(trans)-1-oxidotetrahydro-2H-thiopyran-4-yl]

methyl}amino)-6-(pyridin-3-yloxy)imidazo[1,2-b]pyridazin-3-yl]benzamide (C)



A B C

17.1 mg (33 µmol) N-cyclopropyl-2-methyl-4-{6-(pyridin-3-yloxy)-8-[(tetrahydro-2H-thiopyran-4-ylmeth yl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide which was prepared according to example 288 were transformed in analogy to example 294 to give after working up and purification 6.7 mg (37%) of the title compound A, 2.4 mg (12%)of the title compound B and 3.1 mg (16%)of the title compound C.

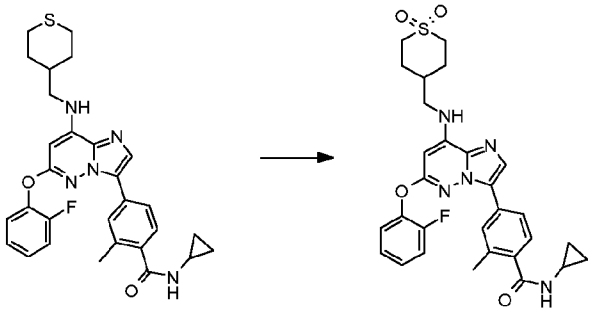
^{1}H-NMR ($CDCl_3$) of A: δ= 0.61 (2H), 0.88 (2H), 1.96-2.11 (3H), 2.29 (2H), 2.32 (3H), 2.89 (1H), 3.04 (2H), 3.14 (2H), 3.37 (2H), 5.90 (1H), 5.92 (1H), 6.51 (1H), 7.24 (1H), 7.40 (1H), 7.55 (1H), 7.62 (1H), 7.64 (1H), 7.72 (1H), 8.54 (1H), 8.61 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ= 0.61 (2H), 0.88 (2H), 1.87-2.01 (3H), 2.24 (2H), 2.32 (3H), 2.48 (2H), 2.89 (1H), 3.10 (2H), 3.33 (2H), 5.89 (1H), 5.92 (1H), 6.02 (1H), 7.24 (1H), 7.39 (1H), 7.56 (1H), 7.62 (1H), 7.66 (1H), 7.71 (1H), 8.53 (1H), 8.60 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of C: δ= 0.61 (2H), 0.88 (2H), 1.57 (2H), 1.99 (1H), 2.29 (2H), 2.31 (3H), 2.68 (2H), 2.89 (1H), 3.30 (2H), 3.40 (2H), 5.87-5.92 (2H), 5.99 (1H), 7.23 (1H), 7.39 (1H), 7.55 (1H), 7.62 (1H), 7.65 (1H), 7.71 (1H), 8.53 (1H), 8.60 (1H) ppm.

Example 297

N-cyclopropyl-4-[8-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}-6-(2-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide

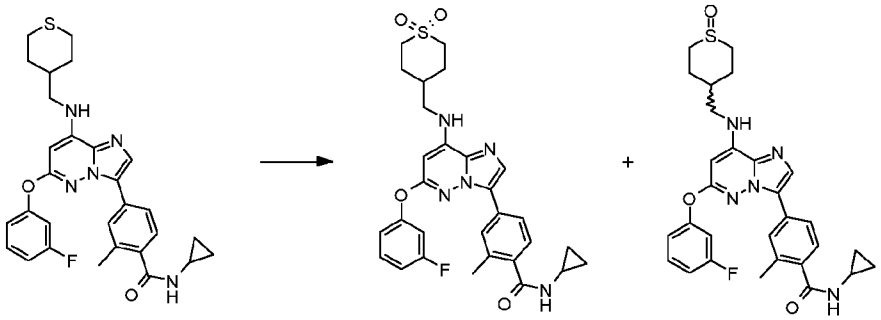


19.7 mg (37 µmol)
N-cyclopropyl-4-{6-(2-fluorophenoxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide which was prepared according to example 283 were transformed in analogy to example 294 to give after working up and purification 9.8 mg (47%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.60 (2H), 0.88 (2H), 1.94-2.08 (3H), 2.26 (3H), 2.28 (2H), 2.89 (1H), 3.02 (2H), 3.13 (2H), 3.36 (2H), 5.82 (1H), 5.94 (1H), 5.99 (1H), 7.17-7.33 (5H), 7.53 (1H), 7.68 (1H), 7.71 (1H) ppm.

Example 298

N-cyclopropyl-4-[8-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide (A)
and
N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-({[(cis/trans)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide (B)



A B

25.5 mg (48 µmol)
N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide which was prepared according to example 281 were transformed in analogy to example 294 to give after working

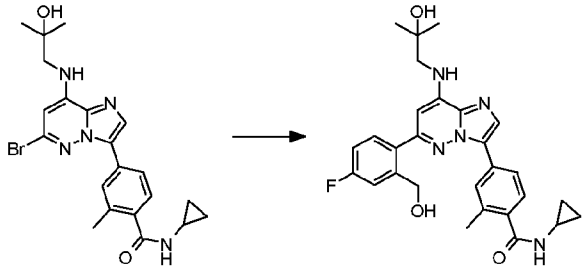
up and purification 12.3 mg (43%) of the title compound A and 5.6 mg (21%)of a cis/trans-mixture of the title compounds B.

^{1}H-NMR ($CDCl_3$) of A: δ= 0.61 (2H), 0.88 (2H), 1.93-2.08 (3H), 2.28 (2H), 2.33 (3H), 2.89 (1H), 3.02 (2H), 3.13 (2H), 3.35 (2H), 5.84 (1H), 5.86 (1H), 6.04 (1H), 6.95-7.09 (3H), 7.25 (1H), 7.39 (1H), 7.61 (1H), 7.72 (1H), 7.74 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ= 0.60 (2H), 0.88 (2H), 1.55 (1H), 1.89 (1H), 1.97 (1H), 2.15-2.31 (2H), 2.32 (3H), 2.47+2.67 (2H), 2.89 (1H), 3.08+3.39 (2H), 3.29 (2H), 5.84+5.87 (1H), 5.89 (1H), 6.13 (1H), 6.95-7.07 (3H), 7.25 (1H), 7.39 (1H), 7.61 (1H), 7.72 (1H), 7.74 (1H) ppm.

Example 299

N-cyclopropyl-4-{6-[4-fluoro-2-(hydroxymethyl)phenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

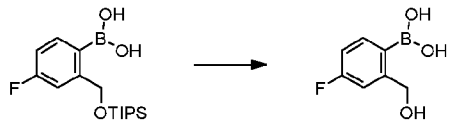


250 mg (545 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 1 using [4-fluoro-2-(hydroxymethyl)phenyl]boronic acid which was prepared according to intermediate example 299a to give after working up and purification 239 mg (87%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.64 (2H), 1.15 (6H), 2.34 (3H), 2.79 (1H), 3.28 (2H), 4.65 (2H), 4.73 (1H), 5.31 (1H), 6.41 (1H), 6.97 (1H), 7.19 (1H), 7.32 (1H), 7.40 (1H), 7.53 (1H), 7.91 (1H), 7.95 (1H), 7.99 (1H), 8.26 (1H) ppm.

Intermediate example 299a

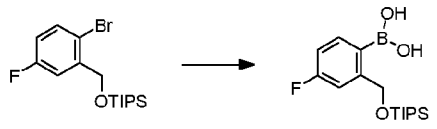
[4-fluoro-2-(hydroxymethyl)phenyl]boronic acid



To a solution of 2.60 g (7.97 mmol) (4-fluoro-2-{[(triisopropylsilyl)oxy]methyl} phenyl)boronic acid which was prepared according to intermediate example 299b in 10 mL dichloromethane were added 6.14 mL trifluoroacetic acid and the mixture was stirred for 16 hours at 23°C. The solvent was removed and the residue christallized from n-hexane to give 682 mg (50%) of the title compound.

Intermediate example 299b

(4-fluoro-2-{[(triisopropylsilyl)oxy]methyl}phenyl)boronic acid



To a solution of 6.00 g (16.6 mmol) [(2-bromo-5-fluorobenzyl)oxy](triisopropyl)silane which was prepared according to intermediate example 299c in 60 mL tetrahydrofuran were added 7.31 mL n-butyllithium (2.5M in hexane) at -78°C. After 20 minutes of stirring 5.58 mL trimethyl borate were added and stirring was continued for additional 60 minutes. The mixture was allowed to warm to 23°C, poured into a saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. After filtration and removal of the solvent the residue was purified by chromatography to give 3.16 g (58%) of the title compound.

Intermediate example 299c

[(2-bromo-5-fluorobenzyl)oxy](triisopropyl)silane

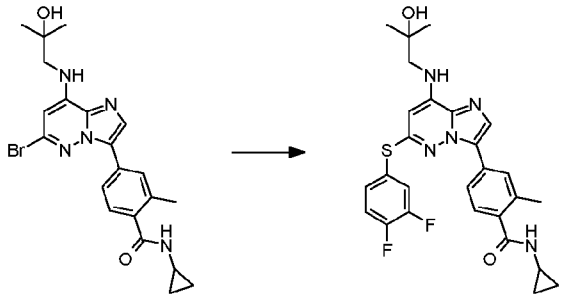


To a solution of 5.00 g (24.4 mmol) (2-bromo-5-fluorophenyl)methanol in 100 mL N,N-dimethylformamide were added 2.49 g imidazole, 6.20 mL chloro(triisopropyl)silane, 1.49 g N,N-dimethylpyridin-4-amine and the mixture was stirred at 23°C for 2 days. Water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium

sulfate. After filtration and removal of the solvent the residue was purified by chromatography to give 8.17 g (93%) of the title compound.

Example 300

N-cyclopropyl-4-{6-[(3,4-difluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

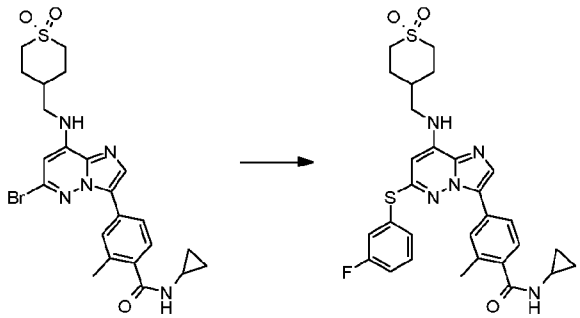


200 mg (436 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using 3,4-difluorobenzenethiol to give after working up and purification 5.8 mg (2%) of the title compound.

^{1}H-NMR ($CDCl_3/CD_3OD$): δ= 0.62 (2H), 0.88 (2H), 1.33 (6H), 2.37 (3H), 2.89 (1H), 3.22 (2H), 5.95 (1H), 6.13 (1H), 6.42 (1H), 7.17 (1H), 7.21 (1H), 7.35 (1H), 7.47 (1H), 7.51 (1H), 7.52 (1H), 7.62 (1H) ppm.

Example 301

N-cyclopropyl-4-(8-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}-6-[(3-fluorophenyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide



25 mg (47 µmol)
4-(6-bromo-8-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}imidazo[1,2

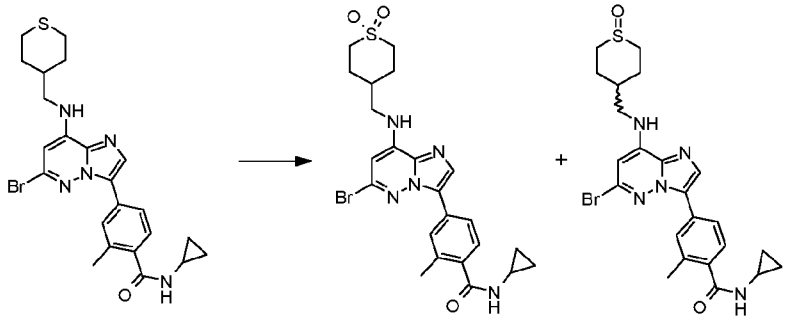
-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 301a were transformed in analogy to example 51 using 3-fluorobenzenethiol to give after working up and purification 13.0 mg (48%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.65 (2H), 1.62 (2H), 1.94 (1H), 2.01 (2H), 2.20 (3H), 2.79 (1H), 2.96-3.11 (4H), 3.23 (2H), 6.25 (1H), 7.11 (1H), 7.34 (1H), 7.44 (1H), 7.49 (1H), 7.54 (1H), 7.65 (1H), 7.70 (1H), 7.82 (1H), 7.94 (1H), 8.24 (1H) ppm.

Intermediate example 301a

4-(6-bromo-8-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide (A) and

4-(6-bromo-8-({[(cis/trans)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide (B)

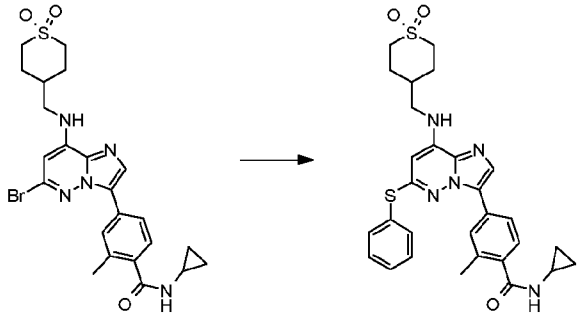


A B

328 mg (655 µmol) 4-{6-bromo-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 281a were transformed in analogy to example 294 to give after working up and purification 167 mg (48%) of the title compound A and 128 mg (38%) of the title compounds B.

Example 302

N-cyclopropyl-4-[8-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide



25 mg (47 µmol)
4-(6-bromo-8-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 301a were transformed in analogy to example 51 using benzenethiol to give after working up and purification 10.1 mg (26%) of the title compound.

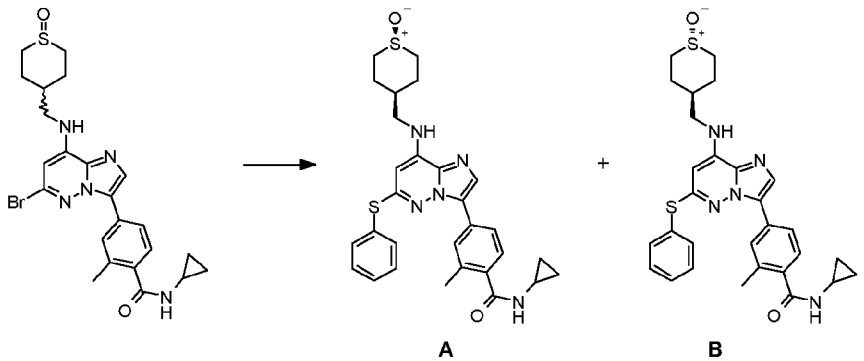
^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.65 (2H), 1.61 (2H), 1.91 (1H), 1.99 (2H), 2.19 (3H), 2.78 (1H), 2.96-3.12 (4H), 3.20 (2H), 6.15 (1H), 7.08 (1H), 7.44-7.53 (3H), 7.58-7.65 (3H), 7.69 (1H), 7.77 (1H), 7.93 (1H), 8.23 (1H) ppm.

Example 303

N-cyclopropyl-2-methyl-4-[8-({[(cis)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl]benzamide (A)

and

N-cyclopropyl-2-methyl-4-[8-({[(trans)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl]benzamide (B)



A B

25 mg (48 µmol)
4-(6-bromo-8-({[(cis/trans)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 301a were transformed in analogy to example

51 using benzenethiol to give after working up and purification 3.7 mg (14%) of the title compound A and 2.5 mg (9%) of the title compound B.

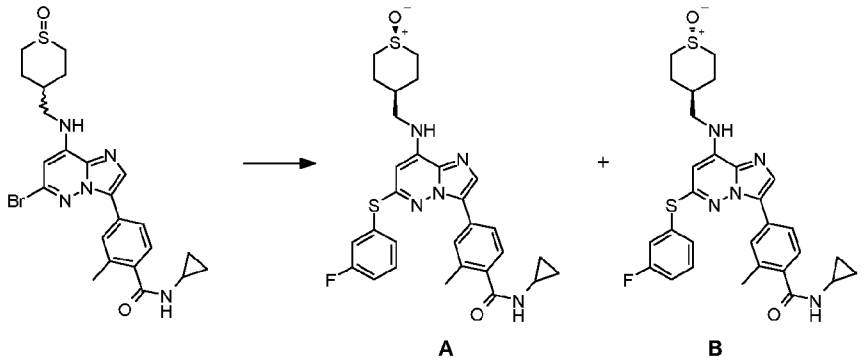
^{1}H-NMR ($CDCl_3$) of A: δ= 0.62 (2H), 0.89 (2H), 1.75-1.88 (3H), 2.15 (2H), 2.38 (3H), 2.42 (2H), 2.91 (1H), 3.05 (2H), 3.19 (2H), 5.87 (1H), 5.89 (1H), 5.97 (1H), 7.20 (1H), 7.41-7.50 (3H), 7.61-7.686 (4H), 7.69 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ= 0.62 (2H), 0.89 (2H), 1.46 (2H), 1.83 (1H), 2.17 (2H), 2.39 (3H), 2.60 (2H), 2.92 (1H), 3.15 (2H), 3.34 (2H), 5.82 (1H), 5.85 (1H), 5.90 (1H), 7.21 (1H), 7.42-7.51 (3H), 7.61-7.68 (4H), 7.70 (1H) ppm.

Example 304

N-cyclopropyl-4-(6-[(3-fluorophenyl)sulfanyl]-8-({[(cis)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide (A) and

N-cyclopropyl-4-(6-[(3-fluorophenyl)sulfanyl]-8-({[(trans)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide (B)



A B

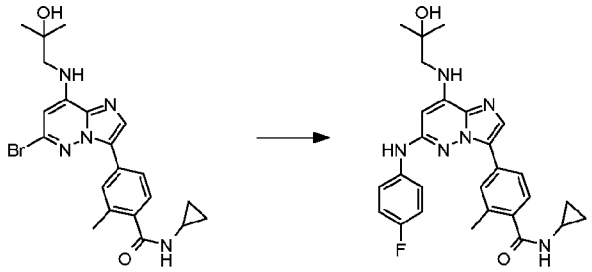
25 mg (48 µmol) 4-(6-bromo-8-({[(cis/trans)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 301a were transformed in analogy to example 81 using 3-fluorobenzenethiol to give after working up and purification 7.4 mg (27%) of the title compound A and 4.8 mg (18%) of the title compound B.

^{1}H-NMR ($CDCl_3$) of A: δ= 0.63 (2H), 0.89 (2H), 1.74-1.89 (3H), 2.17 (2H), 2.40 (3H), 2.43 (2H), 2.92 (1H), 3.06 (2H), 3.22 (2H), 5.90 (1H), 5.92 (1H), 5.98 (1H), 7.15 (1H), 7.23 (1H), 7.35-7.44 (3H), 7.63 (1H), 7.65 (1H), 7.69 (1H) ppm.

^{1}H-NMR ($CDCl_3$) of B: δ= 0.62 (2H), 0.90 (2H), 1.49 (2H), 0.87 (1H), 2.20 (2H), 2.40 (3H), 2.62 (2H), 2.92 (1H), 3.19 (2H), 3.35 (2H), 5.87 (2H), 5.93 (1H), 7.15 (1H), 7.24 (1H), 7.35-7.44 (3H), 7.64 (1H), 7.65 (1H), 7.70 (1H) ppm.

Example 305

N-cyclopropyl-4-{6-[(4-fluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

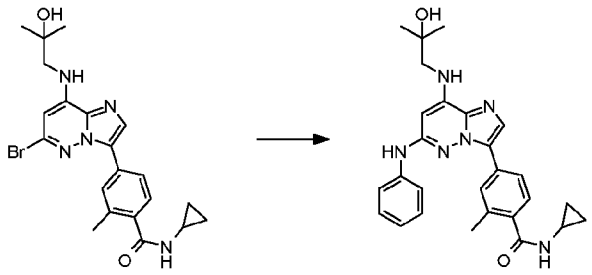


A mixture comprising 75 mg (164 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a, 3 mL dimethyl sulfoxide, 61.1 mg 1,1'-binaphthalene-2,2'-diylbis(diphenylphosphine), 30.0 mg tris(dibenzylideneacetone)dipalladium (0) and 55 mg sodium 2-methylpropan-2-olate were heated to 160°C under microwave irradiation for one hour. The reaction mixture was poured into water and extracted with dichloromethane. The combined organic phases were dried over sodium sulfate. After filtration and removal of solvent the residue was purified by chromatography to give 11.3 mg (14%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.52 (2H), 0.66 (2H), 1.18 (6H), 2.37 (3H), 2.81 (1H), 3.15 (2H), 4.81 (1H), 5.85 (1H), 6.55 (1H), 7.10 (2H), 7.35 (1H), 7.65 (2H), 7.76 (1H), 7.84 (1H), 8.04 (1H), 8.29 (1H), 8.94 (1H) ppm.

Example 306

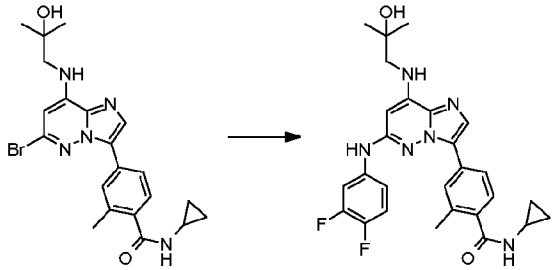
4-{6-anilino-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



75 mg (164 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using aniline to give after working up and purification 15.8 mg (21%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 1.18 (6H), 2.38 (3H), 2.81 (1H), 3.16 (2H), 4.81 (1H), 5.89 (1H), 6.53 (1H), 6.90 (1H), 7.27 (2H), 7.34 (1H), 7.66 (2H), 7.77 (1H), 7.85 (1H), 8.12 (1H), 8.30 (1H), 8.92 (1H) ppm.

Example 307

N-cyclopropyl-4-{6-[(3,4-difluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

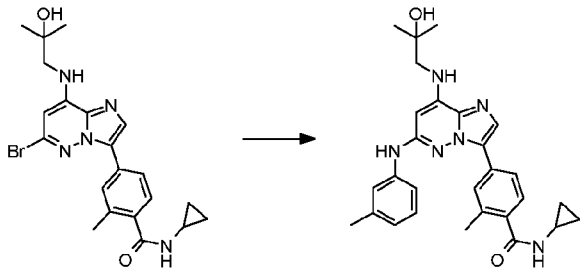


50 mg (109 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using 3,4-difluoroaniline to give after working up and purification 8.3 mg (14%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 1.18 (6H), 2.36 (3H), 2.81 (1H), 3.16 (2H), 4.80 (1H), 5.85 (1H), 6.65 (1H), 7.22 (1H), 7.31 (1H), 7.34 (1H), 7.76 (1H), 7.82 (1H), 7.91 (1H), 8.00 (1H), 8.30 (1H), 9.17 (1H) ppm.

Example 308

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-methylphenyl)

amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

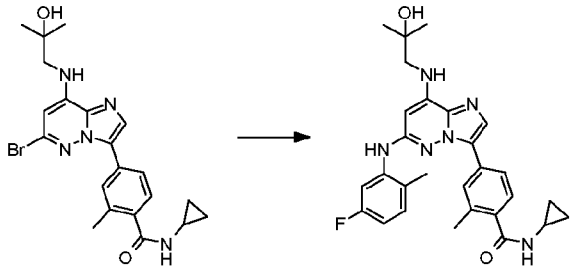


50 mg (109 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using m-toluidine to give after working up and purification 8.3 mg (16%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.66 (2H), 1.18 (6H), 2.25 (3H), 2.36 (3H), 2.81(1H), 3.15 (2H), 4.81 (1H), 5.89 (1H), 6.51 (1H), 6.71 (1H), 7.14 (1H), 7.33 (1H), 7.40 (1H), 7.51 (1H), 7.77 (1H), 7.95 (1H), 8.01 (1H), 8.29 (1H), 8.83 (1H) ppm.

Example 309

N-cyclopropyl-4-{6-[(5-fluoro-2-methylphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide e

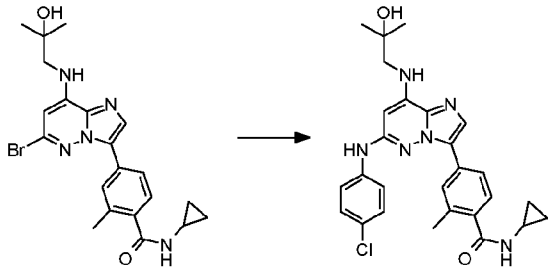


50 mg (109 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using 5-fluoro-2-methylaniline to give after working up and purification 5.9 mg (11%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.64 (2H), 1.19 (6H), 2.23 (3H), 2.26 (3H), 2.79 (1H), 3.17 (2H), 4.82 (1H), 6.15 (1H), 6.51 (1H), 6.74 (1H), 7.18 (1H), 7.23 (1H), 7.77-7.87 (3H), 7.95 (1H), 8.01 (1H), 8.25 (1H) ppm.

Example 310

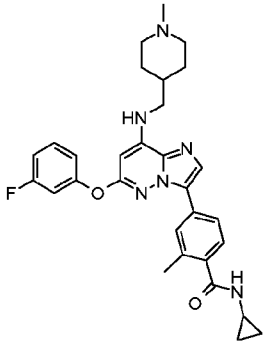
4-{6-[(4-chlorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

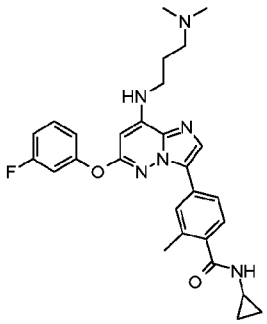
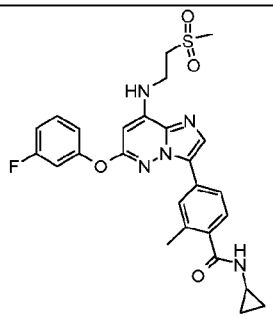


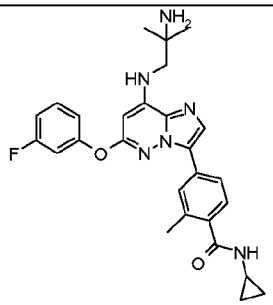
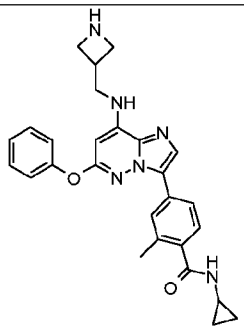
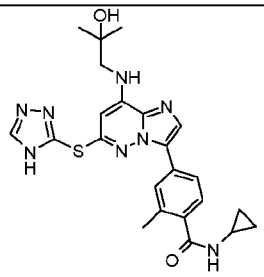
50 mg (109 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using 4-chloroaniline to give after working up and purification 8.1 mg (15%) of the title compound.

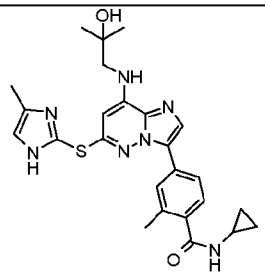
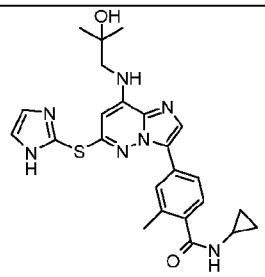
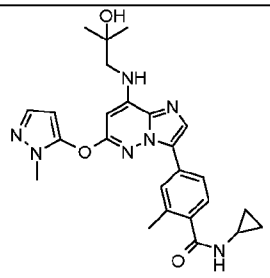
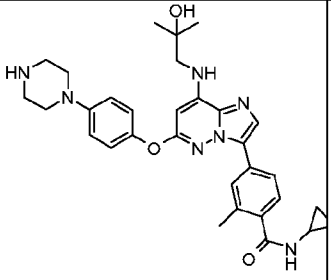
^{1}H-NMR (DMSO-d6): δ= 0.52 (2H), 0.67 (2H), 1.18 (6H), 2.38 (3H), 2.81 (1H), 3.16 (2H), 4.80 (1H), 5.87 (1H), 6.60 (1H), 7.29 (2H), 7.37 (1H), 7.67 (2H), 7.77 (1H), 7.84 (1H), 8.02 (1H), 8.30 (1H), 9.08 (1H) ppm.

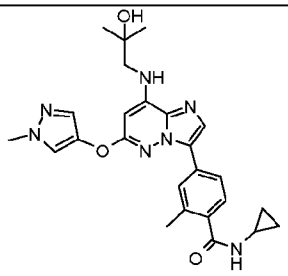
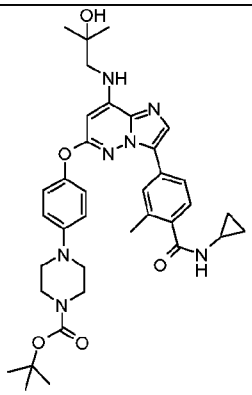
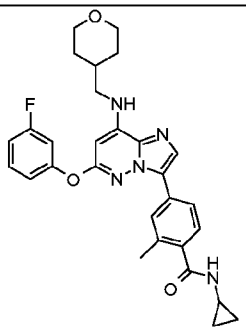
The following compound examples were prepared analogously to the procedure described for example 51 using the appropriate intermediate and the appropriate alcohols, thiols, or amines [LC-MS data such as retention time (RT in min) or observed mass peak were collected using LC-MS Method A unless explicitly stated]:

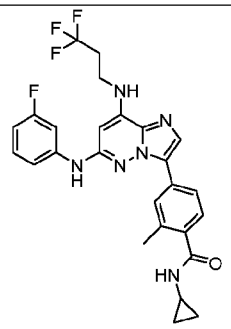
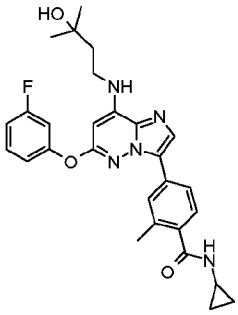
Example	Structure	Name	Analytical Data
311		N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[(1-methylpiperidin-4-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	^{1}H-NMR (DMSO-d6): δ= 0.47 (2H), 0.63 (2H), 1.33 (2H), 1.77 (3H), 2.14 (3H), 2.37 (2H), 2.40 (3H), 2.77 (1H), 3.05 (2H), 3.23 (2H), 6.10 (1H), 7.09 - 7.14 (2H), 7.16 (1H), 7.25

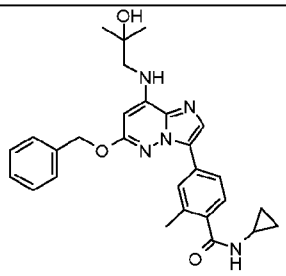
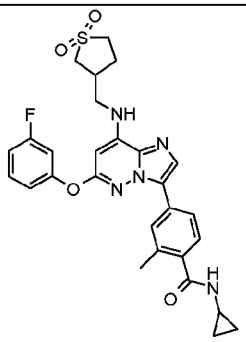
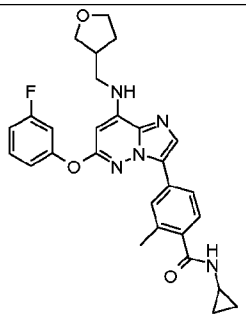
Example	Structure	Name	Analytical Data
			(1H), 7.47 (1H), 7.65 (1H), 7.76 (1H), 7.78 (1H), 7.91 (1H), 8.23 (1H), 8.26 (1H) ppm RT = 0.95 MW_{found} = 529.6 MW_{calc} =528.6
312		N-cyclopropyl-4-[8-{[3-(dimethylamino)propyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	^{1}H-NMR (DMSO-d6): δ= 0.47 (2H), 0.62 (2H), 1.85 (2H), 2.14 (3H), 2.38 (6H), 2.63 (2H, 2.77 (1H), 3.36 (2H), 6.07 (1H), 7.08 - 7.15 (3H), 7.17 (1H), 7.24 (1H), 7.48 (1H), 7.66 (1H), 7.76 (1H), 7.78 (1H), 7.92 (1H) ppm RT = 0.93 MW_{found} = 503.6 MW_{calc} =502.6
313		N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[2-(methylsulfonyl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 1.12 MW_{found} = 524.6 MW_{calc} =523.6

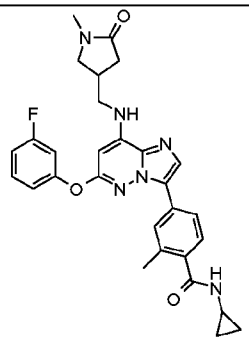
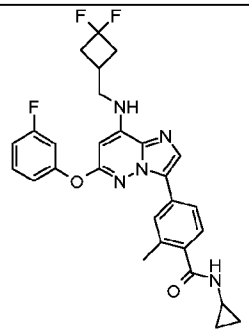
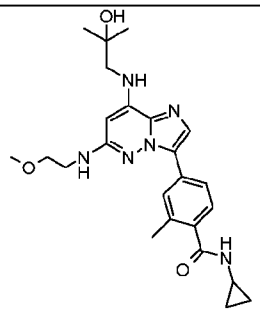
Example	Structure	Name	Analytical Data
314		4-{8-[(2-amino-2-methylpropyl)amino]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide	^{1}H-NMR (DMSO-d6): δ= 0.47 (2H), 0.63 (2H), 1.25 (6H), 2.14 (3H), 2.76 (1H), 3.50 (2H), 6.31 (1H), 7.12 (2H), 7.17 (1H), 7.24 (1H), 7.48 (1H), 7.67 (1H), 7.77 (1H), 7.95 (1H), 8.24 (1H), 8.36 (1H) ppm RT = 0.94 MW_{found} = 489.6 MW_{calc} =488.6
315		4-{8-[(azetidin-3-ylmethyl)amino]-6-phenoxyimidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide	RT = 0.90 MW_{found} = 469.6 MW_{calc} =468.6
316		N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(4H-1,2,4-triazol-3-ylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.65 (2H), 1.11 (6H), 2.28 (3H), 2.79 (1H), 3.21 (2H), 6.28 (1H), 7.06 (1H), 7.23 (1H), 7.41 - 7.59 (2H), 7.68 (2H), 7.95 (1H), 8.27 (1H), 8.82 (1H) ppm RT = 0.85 MW_{found} = 479.6 MW_{calc} =478.6

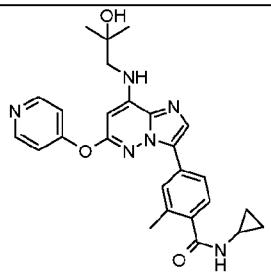
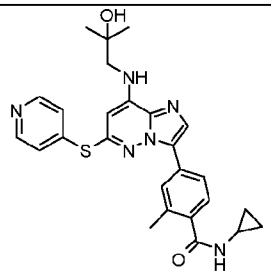
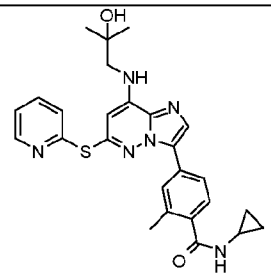
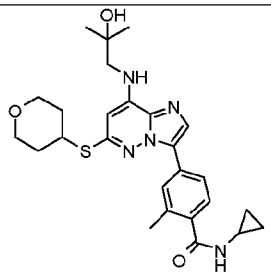
Example	Structure	Name	Analytical Data
317		N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(4-methyl-1H-imidazol-2-yl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 0.71 MW_{found} = 492.6 MW_{calc} =491.6
318		N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1H-imidazol-2-ylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.65 (2H), 1.11 (6H), 2.29 (3H), 2.79 (1H), 3.19 (2H), 6.13 (1H), 7.00 (1H), 7.20 (1H), 7.69 (1H), 7.74 (1H), 7.94 (1H), 8.10 (2H), 8.24 (1H) ppm RT = 0.73 MW_{found} = 478.6 MW_{calc} =477.6
319		N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(1-methyl-1H-pyrazol-5-yl)oxy]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 0.97 MW_{found} = 476.6 MW_{calc} =475.6
320		N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[4-(piperazin-1-yl)phenoxy]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 0.81 MW_{found} = 556.7 MW_{calc} =555.7

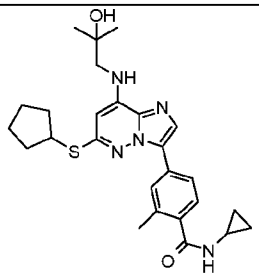
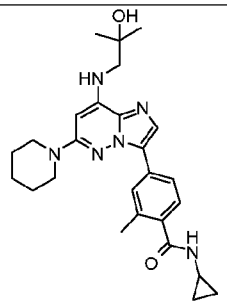
Example	Structure	Name	Analytical Data
321		N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(1-methyl-1H-pyrazol-4-yl)oxy]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	^{1}H-NMR (DMSO-d6): δ= 0.55 (2H), 0.78 (2H), 1.30 (6H), 2.28 (3H), 2.82 (1H), 3.19 (2H), 3.75 (3H), 5.73 (1H), 6.36 (1H), 6.78 (1H), 7.18 (2H), 7.33 (2H), 7.44 (2H), 7.58 (1H), 8.06 (1H) ppm RT = 0.96 MW_{found} = 476.6 MW_{calc} =475.6
322		tert-butyl 4-[4-({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]piperazine-1-carboxylate	RT = 1.36 MW_{found} = 666.8 MW_{calc} =665.8
323		N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	^{1}H-NMR (DMSO-d6): δ= 0.46 (2H), 0.64 (2H), 1.21 (2H), 1.60 (2H), 1.93 (1H), 2.14 (3H), 2.76 (1H), 3.23 (2H), 3.27 (2H), 3.82 (2H), 6.09 (1H), 7.07 - 7.19 (3H), 7.25 (1H), 7.47 (1H), 7.66 (1H), 7.73 (1H), 7.76 (1H), 7.91 (1H), 8.22 (1H) ppm

Example	Structure	Name	Analytical Data
			RT = 1.30 MW_{found} = 516.9 MW_{calc} =515.9
324		N-cyclopropyl-4-{6-[(3-fluorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.65 (2H), 2.35 (3H), 2.67 (2H), 2.80 (1H), 3.49 325(2H), 5.82 (1H), 6.70 (1H), 7.21 - 7.40 (4H), 7.72 (1H), 7.78 (1H), 7.82 (1H), 8.05 (1H), 8.30 (1H), 9.21 (1H) ppm RT = 1.24 MW_{found} = 513.5 MW_{calc} =512.5
325		N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(3-hydroxy-3-methylbutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	^{1}H-NMR ($CDCl_3$): δ= 0.60 (2H), 0.87 (2H), 1.35 (6H), 1.94 (2H), 2.31 (3H), 2.89 (1H), 3.50 (2H), 5.88 (2H), 6.72 (1H), 6.93 - 7.09 (3H), 7.23 (1H), 7.36 (1H), 7.60 (1H), 7.70 (2H) ppm RT = 1.25 MW_{found} = 504.6 MW_{calc} =505.6

Example	Structure	Name	Analytical Data
326		4-{6-(benzyloxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide	1H-NMR (CDCl3): δ= 0.63 (2H), 0.88 (2H), 1.39 (2H), 2.50 (3H), 2.93 (1H), 3.27 (2H), 5.35 (2H), 5.78 (1H), 5.95 (1H), 6.33 (1H), 7.32 - 7.51 (6H), 7.63 (1H), 7.84 (2H) ppm RT = 1.19 MWfound = 486.6 MWcalc = 485.6
327		N-cyclopropyl-4-[8-{[(1,1-dioxidotetrahydrothiophen-3-yl)methyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 1.16 MW_{found} = 550.6 MW_{calc} = 549.6
328		N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(tetrahydrofuran-3-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	^{1}H-NMR ($CDCl_3$): δ= 0.61 (2H), 0.88 (2H), 1.69 (1H), 2.12 (1H), 2.32 (3H), 2.68 (1H), 2.90 (1H), 3.32 (2H), 3.72 - 4.00 (4H), ppm RT = 1.25 MW_{found} = 502.6 MW_{calc} = 501.6

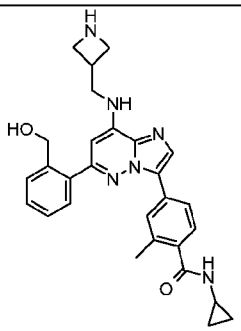
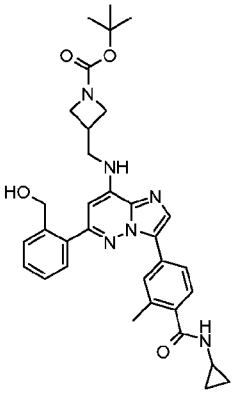
Example	Structure	Name	Analytical Data
329		N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[(1-methyl-5-oxopyrrolidin-3-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 1.12 MW_{found} = 529.6 MW_{calc} = 528.6
330		N-cyclopropyl-4-[8-{[(3,3-difluorocyclobutyl)methyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	^{1}H-NMR ($CDCl_3$): δ= 0.60 (2H), 0.88 (2H), 2.33 (3H), 2.39 (2H), 2.61 (1H), 2.71 - 2.95 (3H), 3.48 (2H), 5.87 (1H), 5.91 (1H), 6.27 (1H), 6.97 - 7.07 (3H), 7.25 (1H), 7.38 (1H), 7.60 (1H), 7.72 (2H) ppm RT = 1.38 MW_{found} = 522.6 MW_{calc} = 521.6
331		N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	1H-NMR (DMSO-d6): δ= 0.52 (2H), 0.77 (2H, (2H), 1.28 (6H), 2.38 (3H), 2.81 (1H), 3.11 (2H), 3.28 (3H), 3.41 (2H), 3.51 (2H), 5.37 (1H), 5.92 (1H), 6.28 (1H), 7.15 (2H), 7.26 (1H), 7.44 (1H), 7.77 (1H), 7.80 (1H) ppm RT = 0.83 MWfound = 453.6

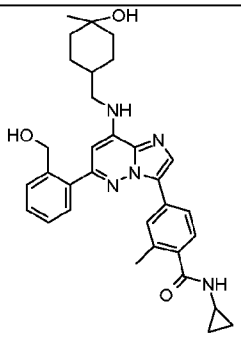
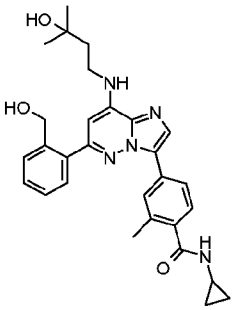
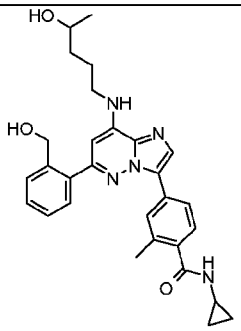
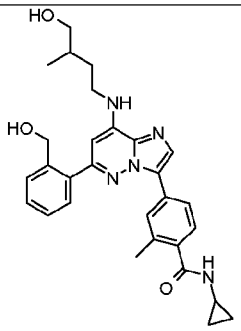
Example	Structure	Name	Analytical Data
			MWcalc = 452.6
332		N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-4-yloxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	^{1}H-NMR (DMSO-d6): δ= 0.56 (2H), 0.70 (2H), 1.22 (6H), 2.42 (3H), 2.85 (1H), 3.41 (2H), 4.82 (1H), 6.32 (2H), 6.69 (1H), 7.40 (1H), 7.42 (1H), 7.93 (1H), 8.01 (1H), 8.05 (1H), 8.32 (2H), 8.34 (1H) ppm RT = 0.82 MW_{found} = 473.6 MW_{calc} = 472.6
333		N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-4-ylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 87 MW_{found} = 489.6 MW_{calc} = 488.6
334		N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-2-ylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.05 MW_{found} = 489.6 MW_{calc} = 488.6
335		N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(tetrahydro-2H-pyran-4-ylsulfanyl)imidazo[1,2-b]pyridazin-3-	1H-NMR (DMSO-d6): δ= 0.51 (2H), 0.65 (2H), 1.13 (6H), 1.65 (2H), 2.06 (2H), 2.38 (3H), 2.81 (1H), 3.22 (2H),

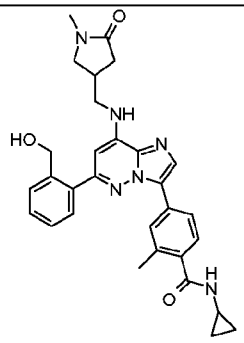
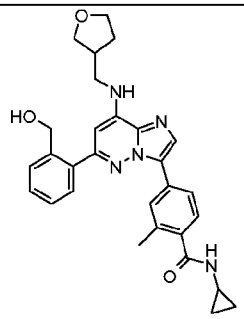
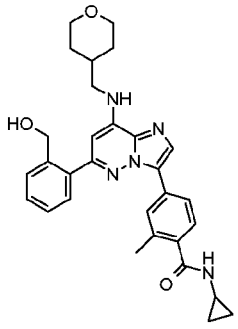
Example	Structure	Name	Analytical Data
		yl}-2-methylbenzamide	3.47 (2H), 3.97 (2H), 4.71 (1H), 6.14 (1H), 6.84 (1H)7.35 (1H), 7.92 (2H), 7.97 (1H), 8.28 (1H) ppm RT = 1.09 MWfound = 496.7 MWcalc = 495.7
336		4-{6-(cyclopentylsulfanyl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide	1H-NMR (DMSO-d6): δ= 0.50 (2H), 0.65 (2H), 1.13 (6H), 1.52 - 1.76 (6H), 2.20 (2H), 2.35 (3H), 2.80 (1H), 3.21 (2H), 4.00 (1H), 4.71 (1H), 6.13 (1H), 6.78 (1H), 7.33 (1H), 7.90 (1H), 7.95 (1H), 8.05 (1H), 8.28 (1H) ppm RT = 1.31 MWfound = 480.7 MWcalc = 479.7
337		N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	1H-NMR (DMSO-d6): δ= 0.50 (2H), 0.65 (2H), 1.15 (6H), 1.58 (6H), 2.27 (4H), 2.35 (3H), 2.78 (1H), 3.23 (2H), 4.75 (1H), 6.07 (1H), 6.40 (1H), 7.33 (1H), 7.86 (1H), 7.98 (1H), 8.03 (1H), 8.27 (1H) ppm

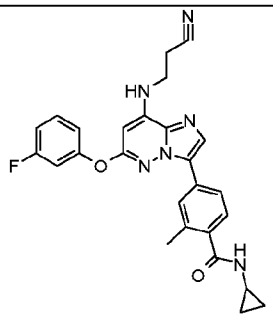
Example	Structure	Name	Analytical Data
			RT = 1.08 MWfound = 463.6 MWcalc = 462.6

The following compound examples were prepared analogously to the procedure described for example 101 using the appropriate intermediate and the appropriate boronic acid building block [LC-MS data such as retention time (RT in min) or observed mass peak were collected using LC-MS Method A unless explicitly stated]:

Example	Structure	Name	Analytical Data
338		4-{8-[(azetidin-3-ylmethyl)amino]-6-[2-(hydroxymethyl)phenyl]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide	RT = 0.77 MWfound = 483.6 MWcalc = 482.6
339		tert-butyl 3-[({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-6-[2-(hydroxymethyl)phenyl]imidazo[1,2-b]pyridazin-8-yl}amino)methyl]azetidine-1-carboxylate	RT = 1.24 MWfound = 583.7 MWcalc = 582.7

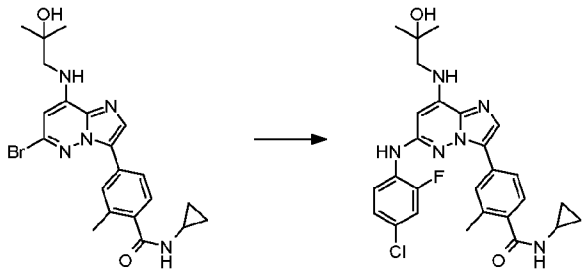
Example	Structure	Name	Analytical Data
340		N-cyclopropyl-4-(8-{[(4-hydroxy-4-methylcyclohexyl)methyl]amino}-6-[2-(hydroxymethyl)phenyl]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide	RT = 1.13 MWfound = 540.7 MWcalc = 539.7
341		N-cyclopropyl-4-{8-[(3-hydroxy-3-methylbutyl)amino]-6-[2-(hydroxymethyl)phenyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.05 MWfound = 500.6 MWcalc = 499.6
342		(RS)-N-cyclopropyl-4-{6-[2-(hydroxymethyl)phenyl]-8-[(4-hydroxypentyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.03 MWfound = 500.6 MWcalc = 499.6
343		(RS)-N-cyclopropyl-4-{8-[(4-hydroxy-3-methylbutyl)amino]-6-[2-(hydroxymethyl)phenyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.04 MWfound = 500.6 MWcalc = 499.6

Example	Structure	Name	Analytical Data
344		N-cyclopropyl-4-(6-[2-(hydroxymethyl)phenyl]-8-{[(1-methyl-5-oxopyrrolidin-3-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide	RT = 0.95 MWfound = 525.6 MWcalc = 524.6
345		(RS)-N-cyclopropyl-4-{6-[2-(hydroxymethyl)phenyl]-8-[(tetrahydrofuran-3-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.06 MWfound = 498.6 MWcalc = 497.6
346		N-cyclopropyl-4-{6-[2-(hydroxymethyl)phenyl]-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	1H-NMR (DMSO-d6): δ= 0.59 (2H), 0.86 (2H), 1.44 (2H), 1.78 (2H), 2.02 (1H), 2.47 (3H), 2.89 (1H), 3.31 (2H), 3.41 (2H), 4.02 (2H), 4.40 (2H), 6.17 (1H), 6.22 (1H), 6.38 (1H), 7.26 (2H), 7.38 (1H), 7.48

Example	Structure	Name	Analytical Data
			(2H), 7.60 (2H), 7.69 (2H) ppm RT = 1.09 MWfound = 512.6 MWcalc = 511.6
347		4-{8-[(2-cyanoethyl)amino]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide	RT = 1.18 MW_{found} = 471.5 MW_{calc} =470.5 ^{1}H-NMR (DMSO-d6): δ= 0.47 (2H), 0.63 (2H), 2.14 (3H), 2.76 (1H), 2.86 (2H), 3.65 (2H). 6.26 (1H), 7.07 - 7.20 (3H), 7.25 (1H), 7.49 (1H), 7.67 (1H), 7.76 (1H), 7.87 (1H), 7.94 (1H), 8.22 (1H) ppm.

Example 348

4-{6-[(4-chloro-2-fluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

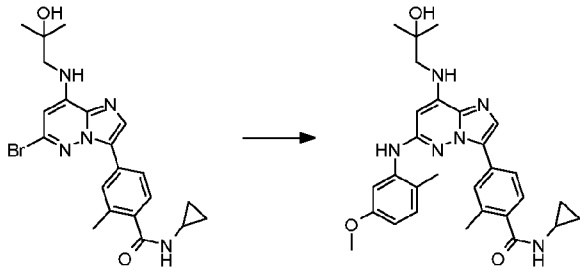


75 mg (164 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using 4-chloro-2-fluoroaniline to give after working up and purification 3.1 mg (3%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.65 (2H), 1.18 (6H), 2.31 (3H), 2.79 (1H), 3.16 (2H), 4.79 (1H), 6.15 (1H), 6.59 (1H), 7.19 (1H), 7.31 (1H), 7.43 (1H), 7.77 (1H), 7.79 (1H), 7.95 (1H), 8.15 (1H), 8.27 (1H), 8.63 (1H) ppm.

Example 349

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(5-methoxy-2-methylphenyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

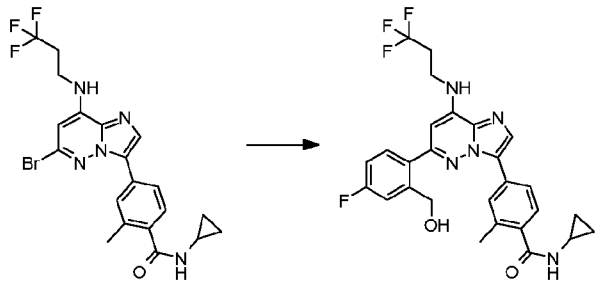


75 mg (164 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using 5-methoxy-2-methylaniline to give after working up and purification 9.1 mg (10%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.64 (2H), 1.18 (6H), 2.17 (3H), 2.22 (3H), 2.78 (1H), 3.16 (2H), 3.62 (3H), 4.81 (1H), 6.04 (1H), 6.43 (1H), 6.56 (1H), 7.08 (1H), 7.20 (1H), 7.34 (1H), 7.80 (1H), 7.85 (1H), 7.88 (1H), 8.02 (1H), 8.23 (1H) ppm.

Example 350

N-cyclopropyl-4-{6-[4-fluoro-2-(hydroxymethyl)phenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

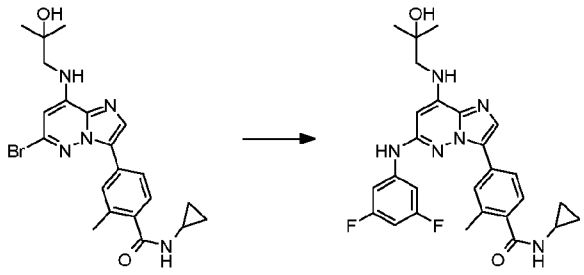


50 mg (104 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 1 using [4-fluoro-2-(hydroxymethyl)phenyl]boronic acid to give after working up and purification 10.4 mg (18%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.64 (2H), 2.34 (3H), 2.67 (2H), 2.79 (1H), 3.61 (2H), 4.65 (2H), 5.34 (1H), 6.36 (1H), 7.20 (1H), 7.33 (1H), 7.41 (1H), 7.59 (1H), 7.67 (1H), 7.91 (1H), 7.95 (1H), 8.01 (1H), 8.27 (1H) ppm.

Example 351

N-cyclopropyl-4-{6-[(3,5-difluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

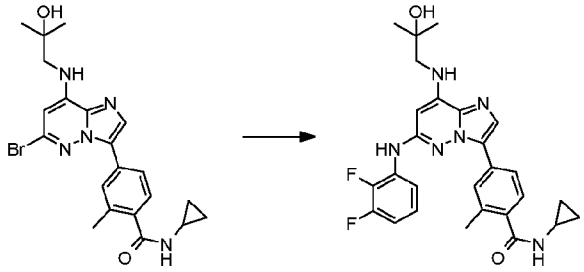


75 mg (164 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using 3,5-difluoroaniline to give after working up and purification 4.9 mg (6%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.66 (2H), 1.18 (6H), 2.35 (3H), 2.81 (1H), 3.17 (2H), 4.80 (1H), 5.87 (1H), 6.67 (1H), 6.73 (1H), 7.30-7.39 (3H), 7.77 (1H), 7.79 (1H), 8.01 (1H), 8.31 (1H), 9.40 (1H) ppm.

Example 352

N-cyclopropyl-4-{6-[(2,3-difluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



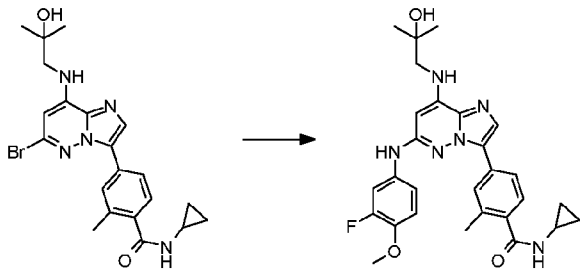
75 mg (164µmol)

4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using 2,3-difluoroaniline to give after working up and purification 4.3 mg (5%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.65 (2H), 1.18 (6H), 2.30 (3H), 2.79 (1H), 3.17 (2H), 4.80 (1H), 6.16 (1H), 6.62 (1H), 7.02 (1H), 7.12 (1H), 7.28 (1H), 7.80 (2H), 7.92 (1H), 8.00 (1H), 8.27 (1H), 8.77 (1H) ppm.

Example 353

N-cyclopropyl-4-{6-[(3-fluoro-4-methoxyphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



75 mg (164µmol)

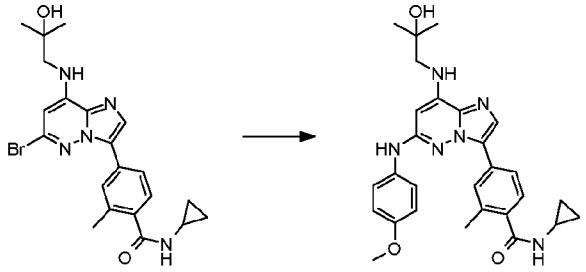
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using

3-fluoro-4-methoxyaniline to give after working up and purification 16.8 mg (19%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.66 (2H), 1.18 (6H), 2.35 (3H), 2.81 (1H), 3.15 (2H), 3.77 (3H), 4.80 (1H), 5.82 (1H), 6.55 (1H), 7.06 (1H), 7.21 (1H), 7.32 (1H), 7.70 (1H), 7.75 (1H), 7.83 (1H), 8.04 (1H), 8.29 (1H), 8.91 (1H) ppm.

Example 354

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(4-methoxyphenyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



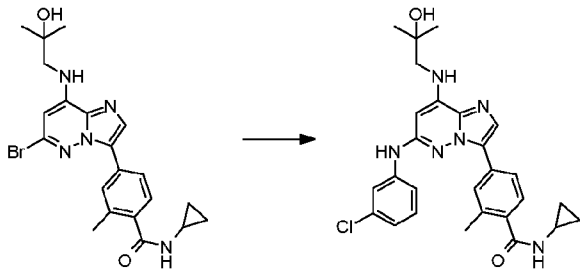
75 mg (164 µmol)

4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using 4-methoxyaniline to give after working up and purification 11.4 mg (13%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 1.18 (6H), 2.37 (3H), 2.81 (1H), 3.14 (2H), 3.70 (3H), 4.80 (1H), 5.83 (1H), 6.46 (1H), 6.86 (2H), 7.33 (1H), 7.55 (2H), 7.75 (1H), 7.85 (1H), 8.10 (1H), 8.29 (1H), 8.71 (1H) ppm.

Example 355

4-{6-[(3-chlorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo [1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



75 mg (164 µmol)

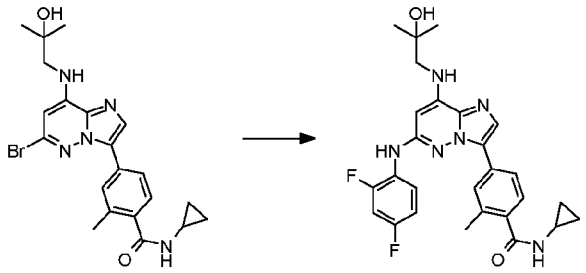
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cy

clopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using 3-chloroaniline to give after working up and purification 15.4 mg (18%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.66 (2H), 1.18 (6H), 2.36 (3H), 2.81 (1H), 3.16 (2H), 4.80 (1H), 5.88 (1H), 6.64 (1H), 6.92 (1H), 7.27 (1H), 7.36 (1H), 7.71 (1H), 7.58 (1H), 7.83 (1H), 7.93 (1H), 7.95 (1H), 8.28 (1H), 9.15 (1H) ppm.

Example 356

N-cyclopropyl-4-{6-[(2,4-difluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

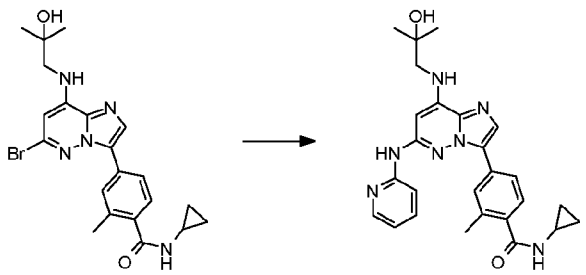


75 mg (164 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using 2,4-difluoroaniline to give after working up and purification 5.0 mg (6%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.65 (2H), 1.18 (6H), 2.28 (3H), 2.79 (1H), 3.14 (2H), 4.80 (1H), 6.06 (1H), 6.54 (1H), 7.04 (1H), 7.27 (1H), 7.30 (1H), 7.78 (1H), 7.79 (1H), 7.94 (1H), 7.99 (1H), 8.25 (1H), 8.48 (1H) ppm.

Example 357

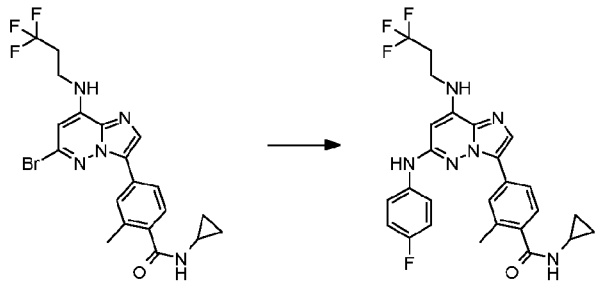
N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-2-ylamino) imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



75 mg (164 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using pyridin-2-amine to give after working up and purification 10.1 mg (12%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 1.18 (6H), 2.39 (3H), 2.81 (1H), 3.16 (2H), 4.80 (1H), 6.27 (1H), 6.60 (1H), 6.91 (1H), 7.36 (1H), 7.69 (1H), 7.80 (1H), 7.86 (1H), 8.01 (1H), 8.08 (1H), 8.23 (1H), 8.31 (1H), 9.48 (1H) ppm.

Example 358

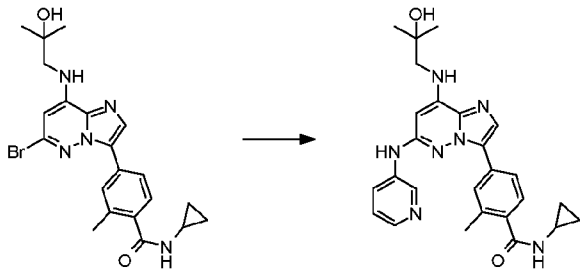
N-cyclopropyl-4-{6-[(4-fluorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



75 mg (156 µmol)
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using 4-fluoroaniline to give after working up and purification 20.1 mg (24%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.52 (2H), 0.66 (2H), 2.37 (3H), 2.68 (2H), 2.81 (1H), 3.49 (2H), 5.79 (1H), 7.11 (2H), 7.28 (1H), 7.35 (1H), 7.65 (2H), 7.77 (1H), 7.84 (1H), 8.04 (1H), 8.29 (1H), 8.98 (1H) ppm.

Example 359

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-3-ylamino)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

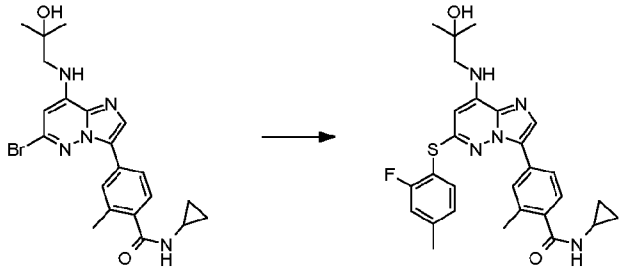


75 mg (164 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using pyridin-2-amine to give after working up and purification 12.6 mg (13%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 1.19 (6H), 2.39 (3H), 2.81 (1H), 3.17 (2H), 4.82 (1H), 5.91 (1H), 6.66 (1H), 7.28 (1H), 7.34 (1H), 7.78 (1H), 7.81 (1H), 8.06 (1H), 8.11 (1H), 8.13 (1H), 8.31 (1H), 8.80 (1H), 9.13 (1H) ppm.

Example 360

N-cyclopropyl-4-{6-[(2-fluoro-4-methylphenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

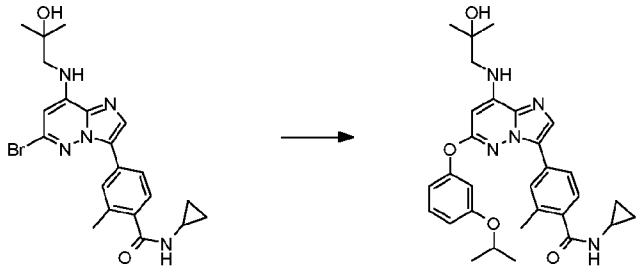


75 mg (164 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using 2-fluoro-4-methylbenzenethiol to give after working up and purification 43.2 mg (48%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.65 (2H), 1.13 (6H), 2.19 (3H), 2.39 (3H), 2.79 (1H), 3.24 (2H), 4.72 (1H), 6.29 (1H), 6.97 (1H), 7.00 (1H), 7.14 (1H), 7.25 (1H), 7.52 (1H), 7.57 (1H), 7.64 (1H), 7.93 (1H), 8.24 (1H) ppm.

Example 361

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(3-isopropoxyphenoxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



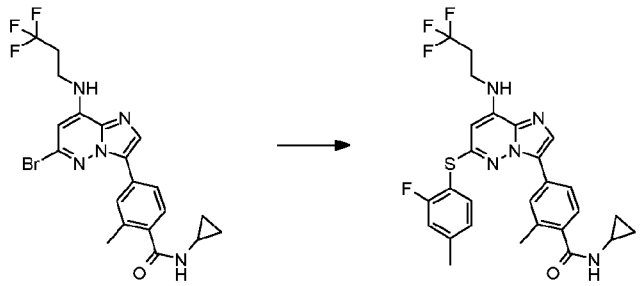
75 mg (164 µmol)

4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using 3-isopropoxyphenol to give after working up and purification 33.3 mg (37%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.46 (2H), 0.63 (2H), 1.15 (6H), 1.20 (6H), 2.14 (3H), 2.76 (1H), 3.27 (2H), 4.58 (1H), 4.74 (1H), 6.14 (1H), 6.73-6.83 (3H), 6.96 (1H), 7.15 (1H), 7.30 (1H), 7.70 (1H), 7.80 (1H), 7.92 (1H), 8.21 (1H) ppm.

Example 362

N-cyclopropyl-4-{6-[(2-fluoro-4-methylphenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



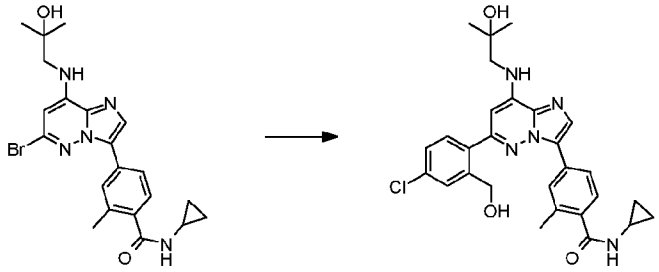
75 mg (156µmol)

4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using 2-fluoro-4-methylbenzenethiol to give after working up and purification 30.3 mg (34%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.66 (2H), 2.19 (3H), 2.40 (3H), 2.64 (2H), 2.80 (1H), 3.55 (2H), 6.23 (1H), 7.01 (1H), 7.15 (1H), 7.26 (1H), 7.53 (1H), 7.57 (1H), 7.64 (1H), 7.66 (1H), 7.94 (1H), 8.25 (1H) ppm.

Example 363

4-{6-[4-chloro-2-(hydroxymethyl)phenyl]-8-[(2-hydroxy-2-methylpropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



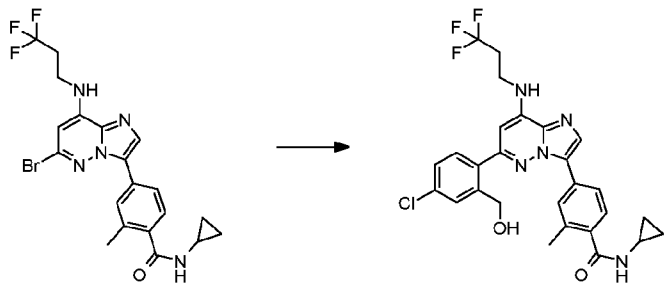
75 mg (164 µmol)

4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 1 using [4-chloro-2-(hydroxymethyl)phenyl]boronic acid to give after working up and purification 22.5 mg (26%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.64 (2H), 1.15 (6H), 2.33 (3H), 2.79 (1H), 3.31 (2H), 4.64 (2H), 4.73 (1H), 5.32 (1H), 6.42 (1H), 7.00 (1H), 7.32 (1H), 7.43 (1H), 7.51 (1H), 7.65 (1H), 7.91 (1H), 7.95 (1H), 8.00 (1H), 8.26 (1H) ppm.

Example 364

4-{6-[4-chloro-2-(hydroxymethyl)phenyl]-8-[(3,3,3-trifluoropropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



75 mg (156 µmol)

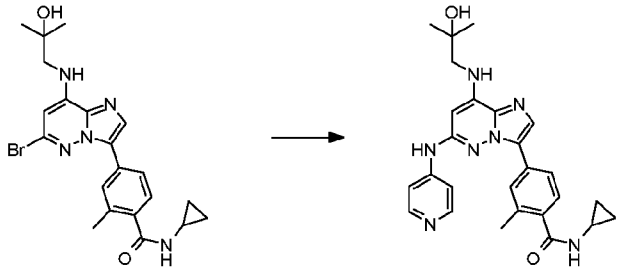
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopr

opyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 1 using [4-chloro-2-(hydroxymethyl)phenyl]boronic acid to give after working up and purification 15.6 mg (18%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.64 (2H), 2.33 (3H), 2.67 (2H), 2.79 (1H), 3.61 (2H), 4.64 (2H), 5.35 (1H), 6.37 (1H), 7.32 (1H), 7.43 (1H), 7.57 (1H), 7.65 (1H), 7.68 (1H), 7.91 (1H), 7.94 (1H), 8.01 (1H), 8.26 (1H) ppm.

Example 365

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-4-ylamino) imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

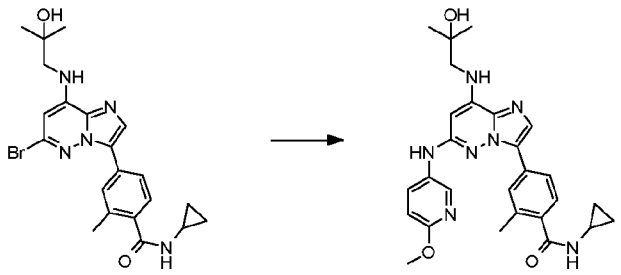


75 mg (164 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using pyridin-4-amine to give after working up and purification 10.7 mg (14%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.52 (2H), 0.67 (2H), 1.18 (6H), 2.40 (3H), 2.82 (1H), 3.18 (2H), 4.81 (1H), 5.95 (1H), 6.77 (1H), 7.38 (1H), 7.59 (2H), 7.81 (1H), 7.83 (1H), 8.06 (1H), 8.27-8.35 (3H), 9.45 (1H) ppm.

Example 366

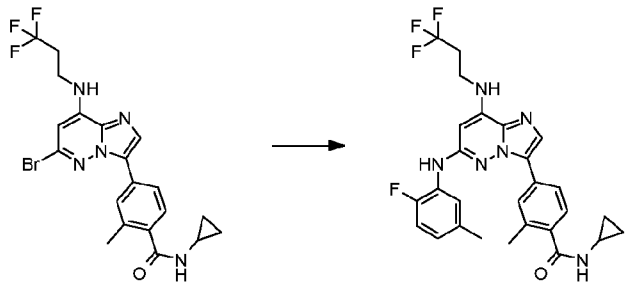
N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(6-methoxypyridin-3-yl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



75 mg (164 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using 4-methoxyaniline to give after working up and purification 27 mg (33%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.65 (2H), 1.18 (6H), 2.36 (3H), 2.80 (1H), 3.15 (2H), 3.79 (3H), 4.80 (1H), 5.83 (1H), 6.55 (1H), 6.77 (1H), 7.30 (1H), 7.76 (1H), 7.77 (1H), 7.92 (1H), 8.09 (1H), 8.28 (1H), 8.45 (1H), 8.82 (1H) ppm.

Example 367

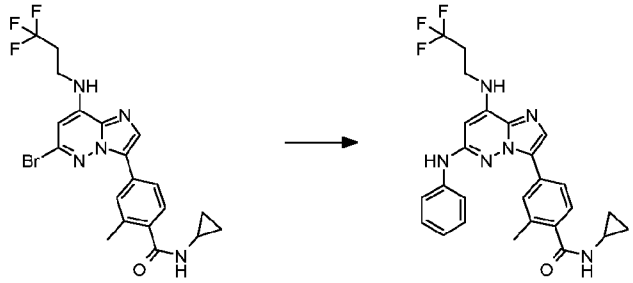
N-cyclopropyl-4-{6-[(2-fluoro-5-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



75 mg (156 µmol)
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using 2-fluoro-5-methylaniline to give after working up and purification 18.7 mg (22%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.65 (2H), 2.23 (3H), 2.28 (2H), 2.68 (3H), 2.79 (1H), 3.48 (2H), 6.10 (1H), 6.79 (1H), 7.09 (1H), 7.24-7.32 (2H), 7.78 (1H), 7.87 (1H), 7.90 (1H), 7.94 (1H), 8.25 (1H), 8.47 (1H) ppm.

Example 368

4-{6-anilino-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

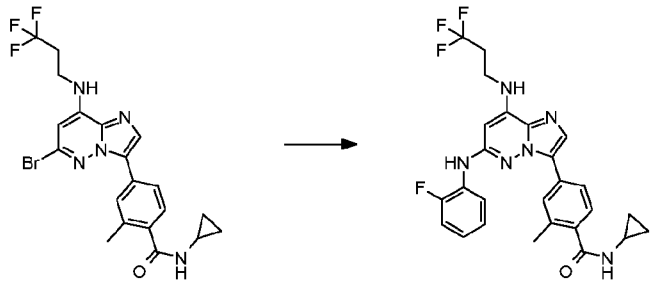


75 mg (156 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using aniline to give after working up and purification 21.1 mg (26%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 2.38 (3H), 2.68 (2H), 2.81 (1H), 3.49 (2H), 5.84 (1H), 6.90 (1H), 7.23-7.31 (3H), 7.34 (1H), 7.66 (2H), 7.78 (1H), 7.84 (1H), 8.12 (1H), 8.30 (1H), 8.96 (1H) ppm.

Example 369

N-cyclopropyl-4-{6-[(2-fluorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

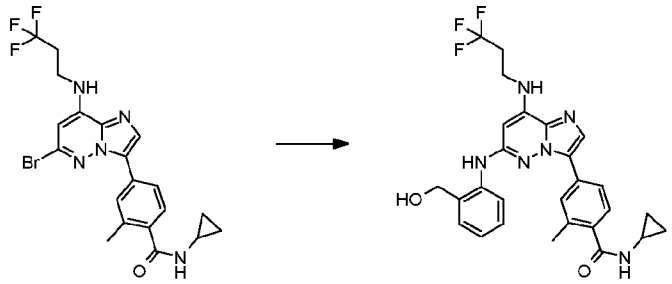


75 mg (156 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using 2-fluoroaniline to give after working up and purification 12.0 mg (14%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.65 (2H), 2.32 (3H), 2.68 (2H), 2.80 (1H), 3.49 (2H), 6.14 (1H), 7.00 (1H), 7.14 (1H), 7.23 (1H), 7.26-7.34 (2H), 7.79 (1H), 7.81 (1H), 8.02 (1H), 8.17 (1H), 8.27 (1H), 8.57 (1H) ppm.

Example 370

N-cyclopropyl-4-(6-{[2-(hydroxymethyl)phenyl]amino}-8-[(3,3,3-trifluoropropyl) amino]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide



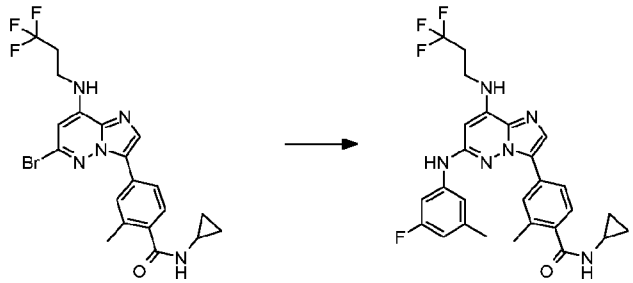
75 mg (156 µmol)

4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using (2-aminophenyl)methanol to give after working up and purification 5.2 mg (6%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.64 (2H), 2.25 (3H), 2.69 (2H), 2.78 (1H), 3.50 (2H), 4.55 (2H), 5.30 (1H), 5.94 (1H), 7.05 (1H), 7.18-7.29 (3H), 7.38 (1H), 7.77-7.87 (3H), 8.01 (1H), 8.07 (1H), 8.24 (1H) ppm.

Example 371

N-cyclopropyl-4-{6-[(3-fluoro-5-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



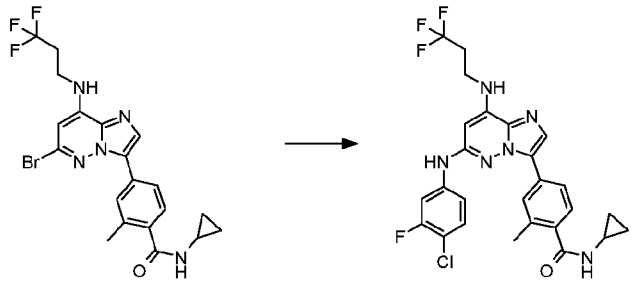
75 mg (156 µmol)

4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using 3-fluoro-5-methylaniline to give after working up and purification 20.2 mg (23%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.66 (2H), 2.25 (3H), 2.35 (3H), 2.68 (2H), 2.81 (1H), 3.49 (2H), 5.82 (1H), 6.53 (1H), 7.05 (1H), 7.29-7.39 (2H), 7.54 (1H), 7.77 (1H), 7.87 (1H), 7.98 (1H), 8.30 (1H), 9.12 (1H) ppm.

Example 372

4-{6-[(4-chloro-3-fluorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo [1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

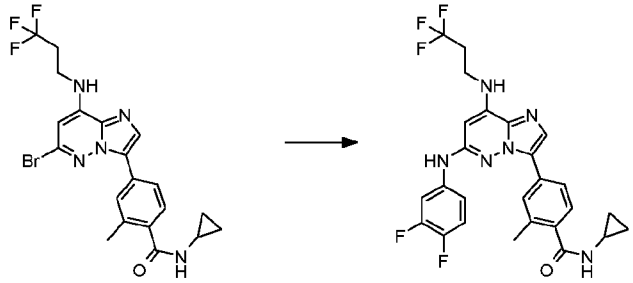


75 mg (156 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using 4-chloro-3-fluoroaniline to give after working up and purification 16.9 mg (19%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 2.36 (3H), 2.68 (2H), 2.81 (1H), 3.50 (2H), 5.81 (1H), 7.26 (1H), 7.35 (1H), 7.39 (1H), 7.44 (1H), 7.77 (1H), 7.80 (1H), 7.95 (1H), 7.98 (1H), 8.31 (1H), 9.36 (1H) ppm.

Example 373

N-cyclopropyl-4-{6-[(3,4-difluorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

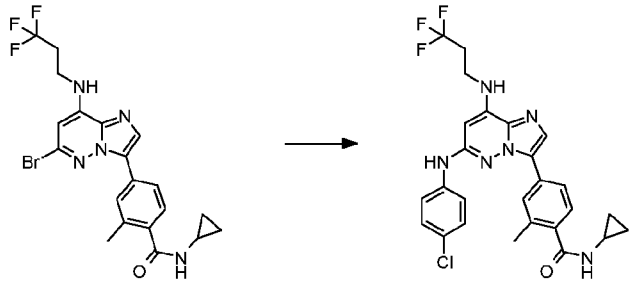


75 mg (156 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using 3,4-difluoroaniline to give after working up and purification 11.9 mg (14%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 2.36 (3H), 2.68 (2H), 2.81 (1H), 3.50 (2H), 5.79 (1H), 7.22 (1H), 7.28-7.39 (3H), 7.77 (1H), 7.81 (1H), 7.91 (1H), 8.00 (1H), 8.30 (1H), 9.20 (1H) ppm.

Example 374

4-{6-[(4-chlorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b] pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



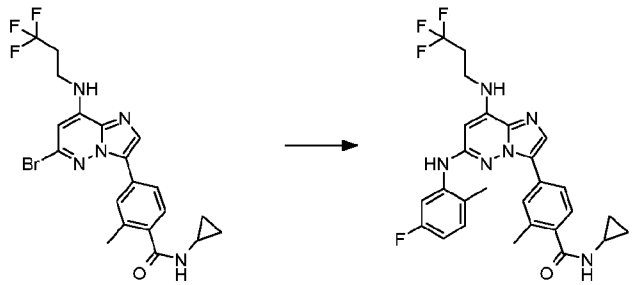
75 mg (156 µmol)

4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using 4-chloroaniline to give after working up and purification 14.3 mg (17%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.52 (2H), 0.67 (2H), 2.38 (3H), 2.68 (2H), 2.81 (1H), 3.49 (2H), 5.82 (1H), 7.30 (2H), 7.33 (1H), 7.38 (1H), 7.68 (2H), 7.78 (1H), 7.84 (1H), 8.02 (1H), 8.30 (1H), 9.12 (1H) ppm.

Example 375

N-cyclopropyl-4-{6-[(5-fluoro-2-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



75 mg (156 µmol)

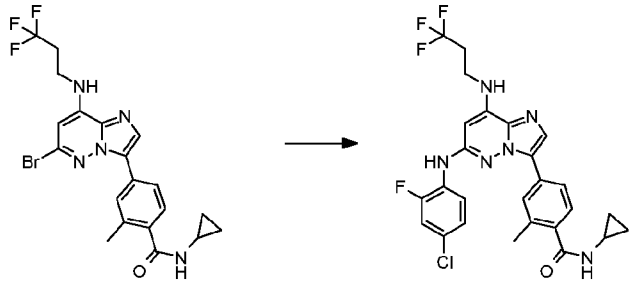
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example

247a were transformed in analogy to example 305 using 5-fluoro-2-methylaniline to give after working up and purification 6.6 mg (8%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.64 (2H), 2.24 (3H), 2.26 (3H), 2.63-2.85 (3H), 3.50 (2H), 6.11 (1H), 6.75 (1H), 7.19 (1H), 7.24 (1H), 7.29 (1H), 7.78-7.86 (3H), 7.96-8.03 (2H), 8.25 (1H) ppm.

Example 376

4-{6-[(4-chloro-2-fluorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

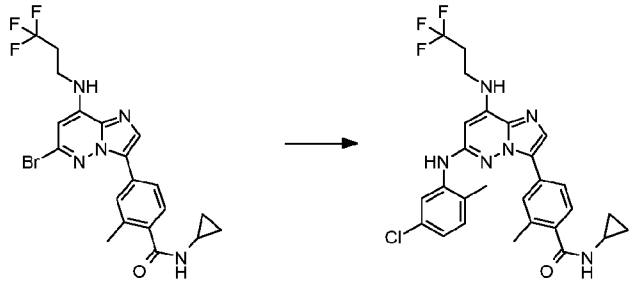


75 mg (156 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using 4-chloro-2-fluoroaniline to give after working up and purification 10.8 mg (12%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 2.31 (3H), 2.68 (2H), 2.80 (1H), 3.49 (2H), 6.12 (1H), 7.21 (1H), 7.32 (1H), 7.35 (1H), 7.46 (1H), 7.79 (1H), 7.80 (1H), 7.96 (1H), 8.18 (1H), 8.28 (1H), 8.69 (1H) ppm.

Example 377

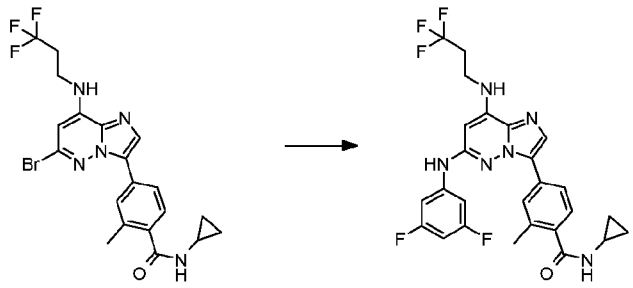
4-{6-[(5-chloro-2-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



75 mg (156 µmol)
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using 5-chloro-2-methylaniline to give after working up and purification 9.7 mg (11%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.64 (2H), 2.24 (3H), 2.26 (3H), 2.70 (2H), 2.78 (1H), 3.50 (2H), 6.06 (1H), 7.00 (1H), 7.21 (1H), 7.26 (1H), 7.29 (1H), 7.83 (1H), 7.89 (1H), 7.91-7.95 (2H), 8.04 (1H), 8.23 (1H) ppm.

Example 378

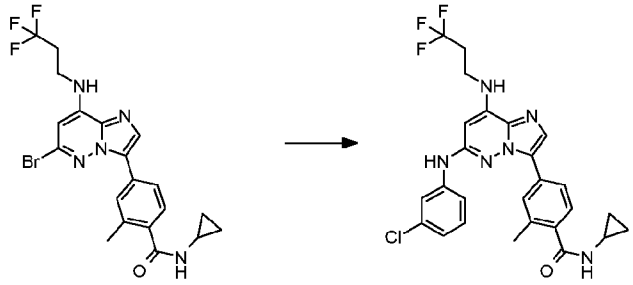
N-cyclopropyl-4-{6-[(3,5-difluorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



75 mg (156 µmol)
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using 3,5-difluoroaniline to give after working up and purification 14.7 mg (17%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.66 (2H), 2.35 (3H), 2.68 (2H), 2.81 (1H), 3.51 (2H), 5.80 (1H), 6.69 (1H), 7.31-7.38 (3H), 7.43 (1H), 7.78 (1H), 7.79 (1H), 8.00 (1H), 8.31 (1H), 9.43 (1H) ppm.

Example 379

4-{6-[(3-chlorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

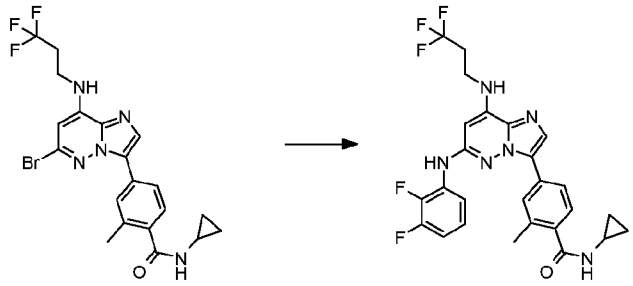


75 mg (156 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using 3-chloroaniline to give after working up and purification 16.7 mg (19%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.66 (2H), 2.36 (3H), 2.68 (2H), 2.81 (1H), 3.50 (2H), 5.82 (1H), 6.93 (1H), 7.28 (1H), 7.32-7.39 (2H), 7.50 (1H), 7.79 (1H), 7.83 (1H), 7.92 (1H), 7.94 (1H), 8.28 (1H), 9.18 (1H) ppm.

Example 380

N-cyclopropyl-4-{6-[(2,3-difluorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

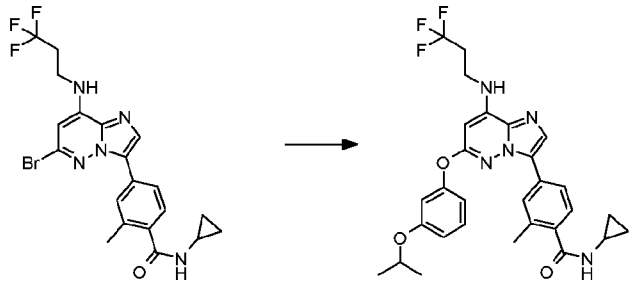


75 mg (156 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using 2,3-difluoroaniline to give after working up and purification 6.6 mg (8%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.65 (2H), 2.31 (3H), 2.68 (2H), 2.80 (1H), 3.50 (2H), 6.13 (1H), 7.02 (1H), 7.13 (1H), 7.28 (1H), 7.37 (1H), 7.79 (1H), 7.81 (1H), 7.95 (1H), 7.99 (1H), 8.28 (1H), 8.81 (1H) ppm.

Example 381

N-cyclopropyl-2-methyl-4-{6-[3-(propan-2-yloxy)phenoxy]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide



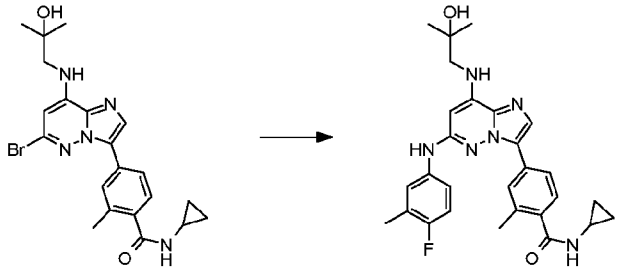
75 mg (156 µmol)

4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using 3-isopropoxyaniline to give after working up and purification 4.8 mg (5%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.46 (2H), 0.63 (2H), 1.21 (6H), 2.14 (3H), 2.67 (2H), 2.76 (1H), 3.58 (2H), 4.58 (1H), 6.09 (1H), 6.75-6.84 (3H), 7.15 (1H), 7.31 (1H), 7.66 (1H), 7.70 (1H), 7.79 (1H), 7.93 (1H), 8.21 (1H) ppm.

Example 382

N-cyclopropyl-4-{6-[(4-fluoro-3-methylphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



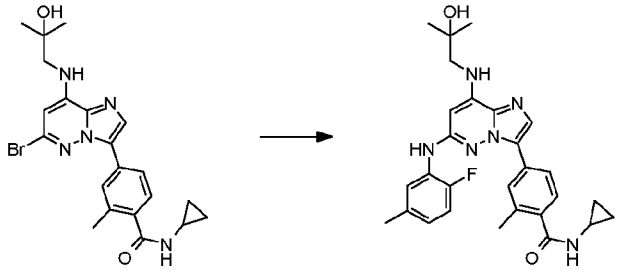
75 mg (164 µmol)

4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using 4-fluoro-3-methylaniline to give after working up and purification 16.5 mg (19%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.66 (2H), 1.18 (6H), 2.18 (3H), 2.34 (3H), 2.81 (1H), 3.15 (2H), 4.80 (1H), 5.84 (1H), 6.52 (1H), 7.02 (1H), 7.34 (1H), 7.44-7.51 (2H), 7.75 (1H), 7.92 (1H), 7.96 (1H), 8.27 (1H), 8.83 (1H) ppm.

Example 383

N-cyclopropyl-4-{6-[(2-fluoro-5-methylphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



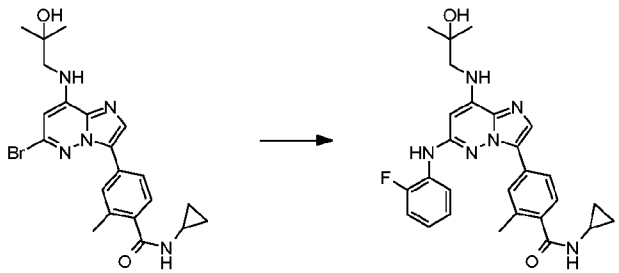
75 mg (164 µmol)

4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using 2-fluoro-5-methylaniline to give after working up and purification 10.5 mg (12%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.65 (2H), 1.18 (6H), 2.23 (3H), 2.28 (3H), 2.79 (1H), 3.15 (2H), 4.79 (1H), 6.13 (1H), 6.52 (1H), 6.79 (1H), 7.09 (1H), 7.27 (1H), 7.78 (1H), 7.86 (1H), 7.88 (1H), 7.95 (1H), 8.25 (1H), 8.42 (1H) ppm.

Example 384

N-cyclopropyl-4-{6-[(2-fluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



75 mg (164 µmol)

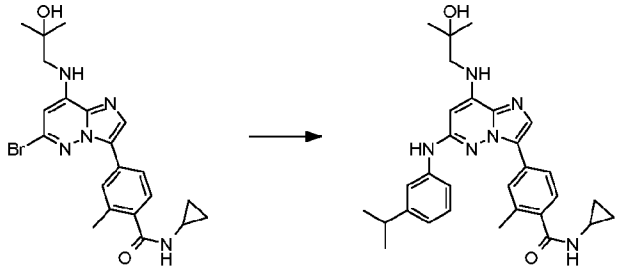
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate

example 96a were transformed in analogy to example 305 using 2-fluoroaniline to give after working up and purification 8.3 mg (10%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.65 (2H), 1.18 (6H), 2.31 (3H), 2.80 (1H), 3.16 (2H), 4.79 (1H), 6.17 (1H), 6.54 (1H), 7.00 (1H), 7.14 (1H), 7.22 (1H), 7.28 (1H), 7.78 (1H), 7.81 (1H), 8.02 (1H), 8.14 (1H), 8.27 (1H), 8.52 (1H) ppm.

Example 385

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-isopropylphenyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

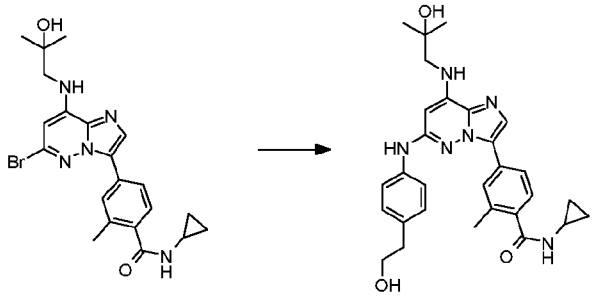


75 mg (164 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using 3-isopropylaniline to give after working up and purification 11.6 mg (14%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.66 (2H), 1.16 (6H), 1.18 (6H), 2.37 (3H), 2.74-2.87 (2H), 3.15 (2H), 4.79 (1H), 5.89 (1H), 6.51 (1H), 6.79 (1H), 7.18 (1H), 7.26 (1H), 7.32 (1H), 7.68 (1H), 7.76 (1H), 7.93 (1H), 8.02 (1H), 8.28 (1H), 8.84 (1H) ppm.

Example 386

N-cyclopropyl-4-(6-{[4-(2-hydroxyethyl)phenyl]amino}-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide

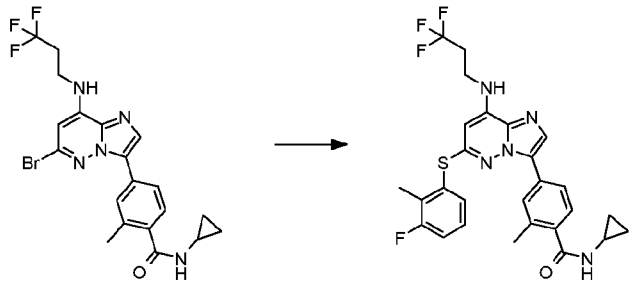


75 mg (164 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using
2-(4-aminophenyl)ethanol to give after working up and purification 10.6 mg (13%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.52 (2H), 0.66 (2H), 1.18 (6H), 2.38 (3H), 2.64 (2H), 2.81 (1H), 3.15 (2H), 3.54 (2H), 4.57 (1H), 4.80 (1H), 5.87 (1H), 6.49 (1H), 7.10 (2H), 7.34 (1H), 7.55 (2H), 7.76 (1H), 7.84 (1H), 8.12 (1H), 8.31 (1H), 8.82 (1H) ppm.

Example 387

N-cyclopropyl-4-{6-[(3-fluoro-2-methylphenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

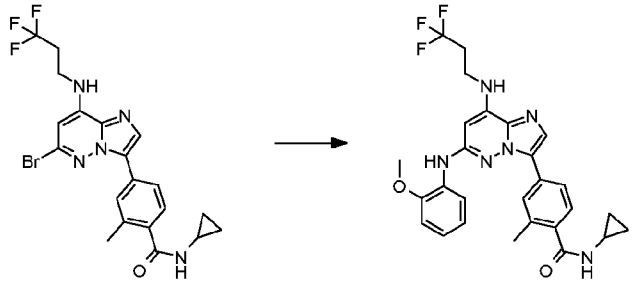


75 mg (156 µmol)
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using
3-fluoro-2-methylbenzenethiol to give after working up and purification 35.3 mg (42%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.65 (2H), 2.18 (3H), 2.27 (3H), 2.62 (2H), 2.79 (1H), 3.54 (2H), 6.19 (1H), 7.06 (1H), 7.30-7.42 (2H), 7.48 (1H), 7.55 (1H), 7.65 (1H), 7.68 (1H), 7.95 (1H), 8.24 (1H) ppm.

Example 388

N-cyclopropyl-4-{6-[(2-methoxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

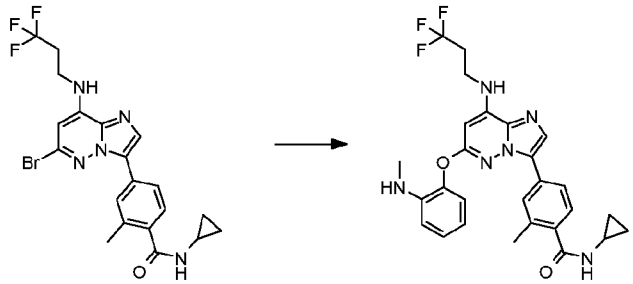


200 mg (415 µmol)
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using 2-methoxyaniline to give after working up and purification 68.3 mg (31%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.65 (2H), 2.35 (3H), 2.69 (2H), 2.80 (1H), 3.29 (3H), 3.49 (2H), 6.28 (1H), 6.87-7.05 (3H), 7.21 (1H), 7.31 (1H), 7.78 (1H), 7.84 (1H), 8.02 (1H), 8.09 (1H), 8.24-8.32 (2H) ppm.

Example 389

N-cyclopropyl-2-methyl-4-{6-[2-(methylamino)phenoxy]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide

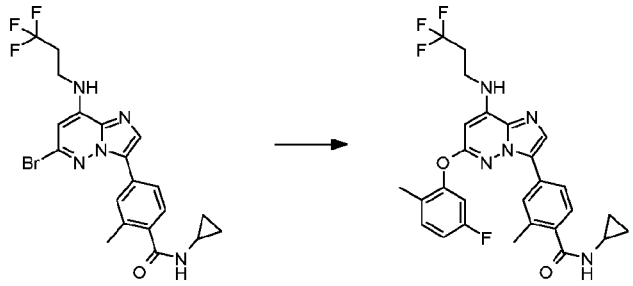


75 mg (156 µmol)
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using 2-(methylamino)phenol to give after working up and purification 35.1 mg (43%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.65 (2H), 2.33 (3H), 2.46 (2H), 2.80 (1H), 3.25 (2H), 3.29 (3H), 5.21 (1H), 6.84 (1H), 6.95 (1H), 7.06 (1H), 7.14 (1H), 7.19 (1H), 7.31 (1H), 7.82 (1H), 8.04 (1H), 8.09 (1H), 8.26 (1H), 9.54 (1H) ppm.

Example 390

N-cyclopropyl-4-{6-(5-fluoro-2-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



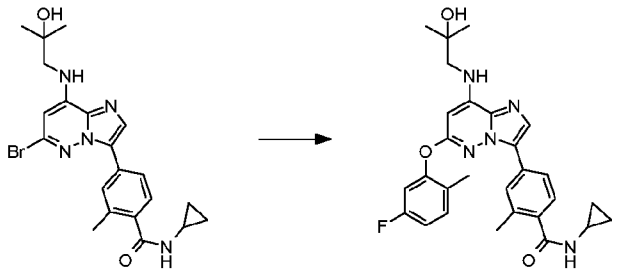
75 mg (156 µmol)

4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using 5-fluoro-2-methylphenol to give after working up and purification 31.5 mg (38%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.46 (2H), 0.63 (2H), 2.10 (6H), 2.69 (2H), 2.76 (1H), 3.60 (2H), 6.16 (1H), 7.07 (1H), 7.13 (1H), 7.18 (1H), 7.37 (1H), 7.60 (1H), 7.69 (1H), 7.72 (1H), 7.93 (1H), 8.21 (1H) ppm.

Example 391

N-cyclopropyl-4-{6-(5-fluoro-2-methylphenoxy)-8-[(2-hydroxy-2-methylpropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



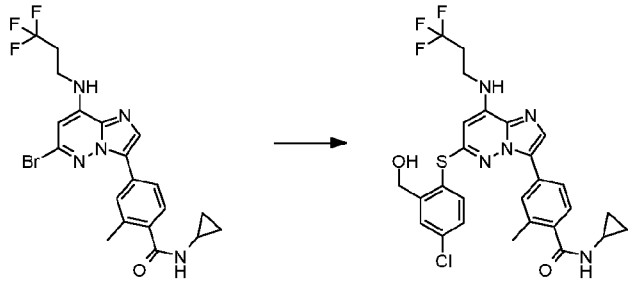
50 mg (109 µmol)

4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using 5-fluoro-2-methylphenol to give after working up and purification 29.4 mg (54%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.46 (2H), 0.73 (2H), 1.17 (6H), 2.10 (6H), 2.76 (1H), 3.28 (2H), 4.76 (1H), 6.20 (1H), 6.98 (1H), 7.06 (1H), 7.13 (1H), 7.17 (1H), 7.36 (1H), 7.61 (1H), 7.71 (1H), 7.92 (1H), 8.21 (1H) ppm.

Example 392

4-(6-{[4-chloro-2-(hydroxymethyl)phenyl]sulfanyl}-8-[(3,3,3-trifluoropropyl) amino]imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide



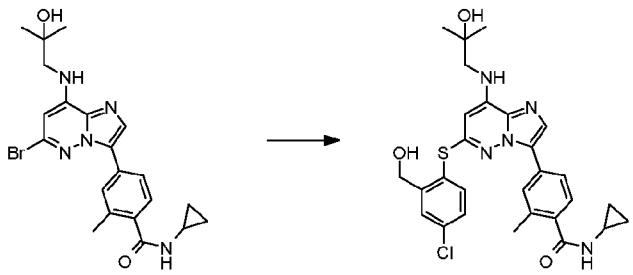
75 mg (156 µmol)

4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using (5-chloro-2-sulfanylphenyl)methanol to give after working up and purification 49.0 mg (55%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.65 (2H), 2.19 (3H), 2.63 (2H), 2.79 (1H), 3.54 (2H), 4.58 (2H), 5.43 (1H), 6.21 (1H), 7.06 (1H), 7.42 (1H), 7.47 (1H), 7.58-7.70 (4H), 7.94 (1H), 8.24 (1H) ppm.

Example 393

4-(6-{[4-chloro-2-(hydroxymethyl)phenyl]sulfanyl}-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide

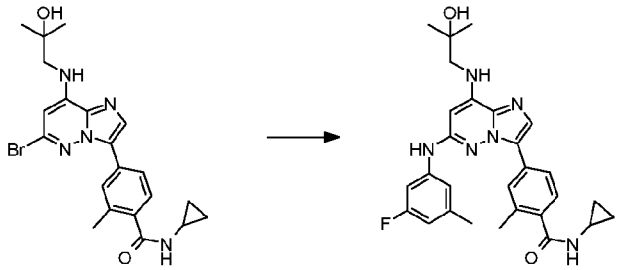


75 mg (164 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using (5-chloro-2-sulfanylphenyl)methanol to give after working up and purification 57.0 mg (63%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.65 (2H), 1.13 (6H), 2.19 (3H), 2.79 (1H), 3.24 (2H), 4.57 (2H), 4.72 (1H), 5.42 (1H), 6.28 (1H), 6-98 (1H), 7.06 (1H), 7.41 (1H), 7.48 (1H), 7.59 (1H), 7.61 (1H), 7.64 (1H), 7.92 (1H), 8.23 (1H) ppm.

Example 394

N-cyclopropyl-4-{6-[(3-fluoro-5-methylphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

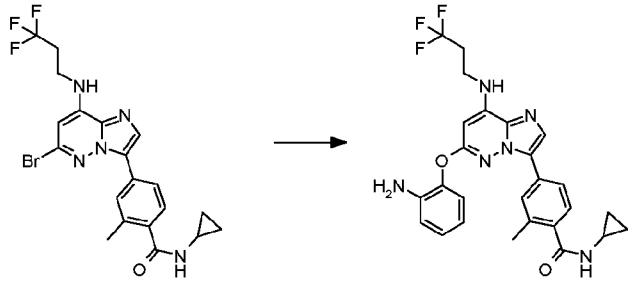


75 mg (164 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using 3-fluoro-5-methylaniline to give after working up and purification 9.7 mg (11%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.65 (2H), 1.18 (6H), 2.24 (3H), 2.34 (3H), 2.81 (1H), 3.16 (2H), 4.81 (1H), 5.89 (1H), 6.52 (1H), 6.61 (1H), 7.05 (1H), 7.32 (1H), 7.53 (1H), 7.76 (1H), 7.88 (1H), 7.98 (1H), 8.29 (1H), 9.11 (1H) ppm.

Example 395

4-{6-(2-aminophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

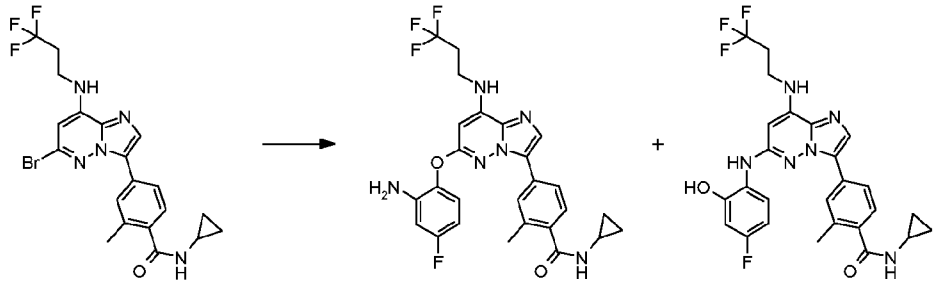


75 mg (156 µmol)
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using 2-aminophenol to give after working up and purification 25.6 mg (32%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.47 (2H), 0.63 (2H), 2.13 (3H), 2.69 (2H), 2.76 (1H), 3.58 (2H), 4.92 (2H), 6.08 (1H), 6.58 (1H), 6.79 (1H), 6.97 (1H), 7.03 (1H), 7.13 (1H), 7.59 (1H), 7.67 (1H), 7.83 (1H), 7.91 (1H), 8.20 (1H) ppm.

Example 396

4-{6-(2-amino-4-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide (A) and N-cyclopropyl-4-{6-[(4-fluoro-2-hydroxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide (B)



A B

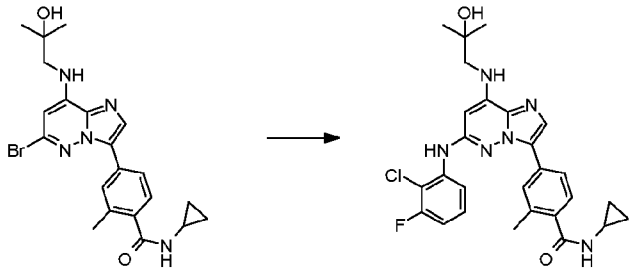
75 mg (156 µmol)
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using 2-amino-5-fluorophenol to give after working up and purification 14.8 mg (18%) of the title compound A and 12.6 mg (15%) of the title compound B.

^{1}H-NMR (DMSO-d6) of A: δ= 0.47 (2H), 0.64 (2H), 2.15 (3H), 2.69 (2H), 2.77 (1H), 3.58 (2H), 5.27 (2H), 6.08 (1H), 6.34 (1H), 6.55 (1H), 7.03 (1H), 7.15 (1H), 7.60 (1H), 7.67 (1H), 7.83 (1H), 7.92 (1H), 8.22 (1H) ppm.

^{1}H-NMR (DMSO-d6) of B: δ= 0.50 (2H), 0.66 (2H), 2.34 (3H), 2.68 (2H), 2.81 (1H), 3.49 (2H), 6.38 (1H), 6.55 (1H), 6.79 (1H), 7.26 (1H), 7.30 (1H), 7.76 (1H), 7.82 (1H), 8.04 (1H), 8.09 (1H), 8.14 (1H), 8.29 (1H), 9.86 (1H) ppm.

Example 397

4-{6-(2-chloro-3-fluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo [1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

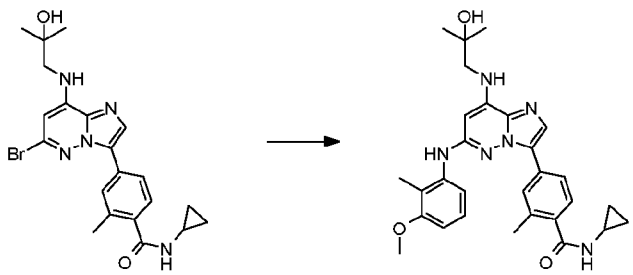


75 mg (164 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using 2-chloro-3-fluoroaniline to give after working up and purification 6.0 mg (6%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 1.17 (6H), 2.36 (3H), 2.81 (1H), 3.17 (2H), 4.83 (1H), 5.95 (1H), 6.68 (1H), 7.28 (1H), 7.35 (1H), 7.40 (1H), 7.76 (1H), 7.81 (1H), 7.95 (1H), 7.99 (1H), 8.31 (1H), 9.51 (1H) ppm.

Example 398

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-methoxy-2-methylphenyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

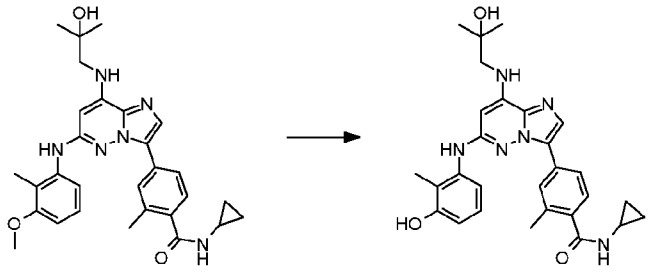


75 mg (164 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using 3-methoxy-2-methylaniline to give after working up and purification 16.7 mg (20%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.64 (2H), 1.18 (6H), 2.06 (3H), 2.21 (3H), 2.78 (1H), 3.15 (2H), 3.77 (3H), 4.81 (1H), 5.97 (1H), 6.40 (1H), 6.73 (1H), 7.13 (1H), 7.18 (1H), 7.24 (1H), 7.79 (2H), 8.01 (2H), 8.22 (1H) ppm.

Example 399

N-cyclopropyl-4-{6-[(2-hydroxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

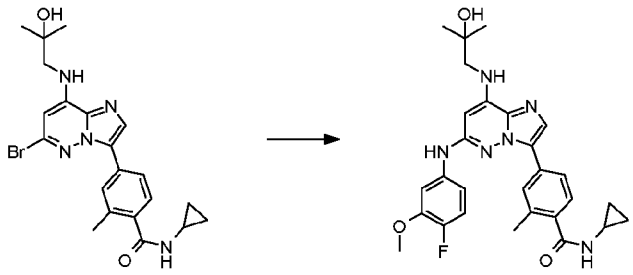


40 mg (76 µmol)
N-cyclopropyl-4-{6-[(2-methoxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide which was prepared according to example 388 were transformed in analogy to intermediate example 280 to give after working up and purification 14.7 mg (36%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 2.35 (3H), 2.68 (2H), 2.80 (1H), 3.48 (2H), 6.28 (1H), 6.73-6.88 (3H), 7.17 (1H), 7.30 (1H), 7.77 (1H), 7.83 (1H), 7.91 (1H), 8.10 (1H), 8.18 (1H), 8.28 (1H), 9.80 (1H) ppm.

Example 400

N-cyclopropyl-4-{6-[(4-fluoro-3-methoxyphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

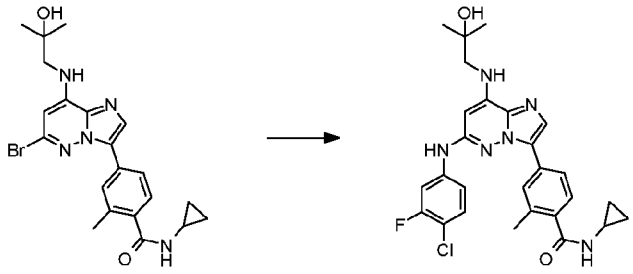


75 mg (164 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to intermediate example 305 using 4-fluoro-3-methoxyaniline to give after working up and purification 20.3 mg (24%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 1.18 (6H), 2.33 (3H), 2.81 (1H), 3.16 (2H), 3.67 (3H), 4.80 (1H), 5.85 (1H), 6.57 (1H), 7.08 (1H), 7.23 (1H), 7.28 (1H), 7.33 (1H), 7.75 (1H), 7.86 (1H), 7.99 (1H), 8.27 (1H), 8.91 (1H) ppm.

Example 401

4-{6-[(4-chloro-3-fluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

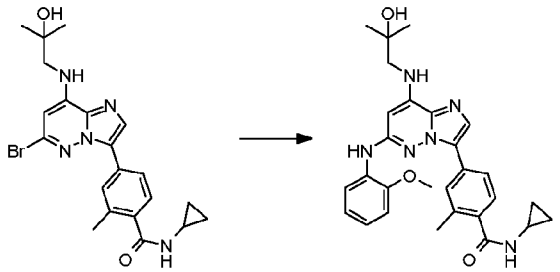


75 mg (164 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to intermediate example 305 using 4-chloro-3-fluoroaniline to give after working up and purification 5.6 mg (7%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.52 (2H), 0.66 (2H), 1.18 (6H), 2.37 (3H), 2.82 (1H), 3.17 (2H), 4.81 (1H), 5.91 (1H), 6.69 (1H), 7.28 (1H), 7.35 (1H), 7.41 (1H), 7.76 (1H), 7.81 (1H), 7.95 (1H), 7.99 (1H), 8.31 (1H), 9.41 (1H) ppm.

Example 402

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(2-methoxyphenyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

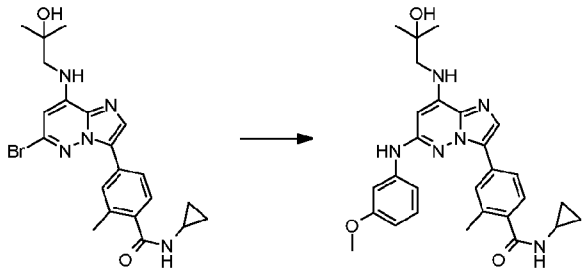


50 mg (109 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using 2-methoxyaniline to give after working up and purification 59.7 mg (35%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 1.18 (6H), 2.35 (3H), 2.80 (1H), 3.17 (2H), 3.84 (3H), 4.78 (1H), 6.29 (1H), 6.43 (1H), 6.88-6.96 (2H), 7.00 (1H), 7.31 (1H), 7.77 (1H), 7.84 (1H), 7.92 (1H), 8.09 (1H), 8.25 (1H), 8.29 (1H) ppm.

Example 403

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-methoxyphenyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

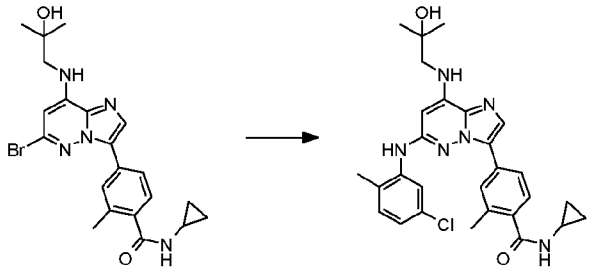


150 mg (327 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using 3-methoxyaniline to give after working up and purification 44.4 mg (24%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.67 (2H), 1.18 (6H), 2.36 (3H), 2.81 (1H), 3.15 (2H), 3.66 (3H), 4.80 (1H), 5.88 (1H), 6.48 (1H), 6.55 (1H), 7.16 (1H), 7.20-7.28 (2H), 7.32 (1H), 7.77 (1H), 7.86 (1H), 8.08 (1H), 8.29 (1H), 8.90 (1H) ppm.

Example 404

4-{6-[(5-chloro-2-methylphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

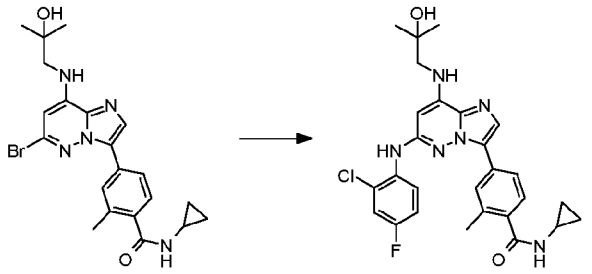


75 mg (164 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using 5-chloro-2-methylaniline to give after working up and purification 6.2 mg (7%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.64 (2H), 1.19 (6H), 2.23 (3H), 2.26 (3H), 2.78 (1H), 3.17 (2H), 4.82 (1H), 6.10 (1H), 6.52 (1H), 6.99 (1H), 7.20 (1H), 7.26 (1H), 7.82 (1H), 7.88-7.96 (3H), 8.01 (1H), 8.23 (1H) ppm.

Example 405

4-{6-[(2-chloro-4-fluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

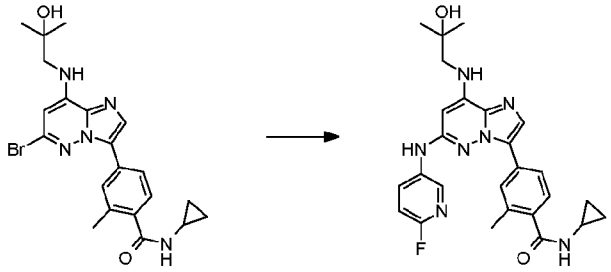


75 mg (164 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using 2-chloro-4-fluoroaniline to give after working up and purification 7.3 mg (8%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.64 (2H), 1.18 (6H), 2.24 (3H), 2.78 (1H), 3.17 (2H), 4.80 (1H), 5.72 (1H), 6.09 (1H), 6.53 (1H), 7.23 (1H), 7.49 (1H), 7.76 (1H), 7.79 (1H), 7.90 (1H), 7.92 (1H), 8.23 (1H), 8.25 (1H) ppm.

Example 406

N-cyclopropyl-4-{6-[(6-fluoropyridin-3-yl)amino]-8-[(2-hydroxy-2-methylpropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



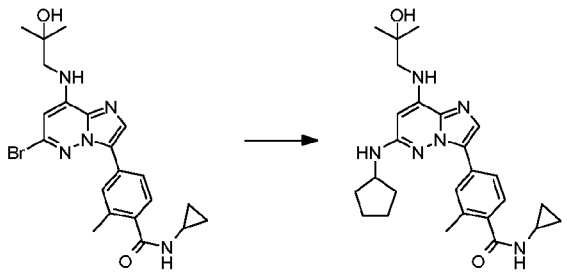
50 mg (109 µmol)

4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using 6-fluoropyridin-3-amine to give after working up and purification 9.9 mg (18%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 1.18 (6H), 2.37 (3H), 2.81 (1H), 3.17 (2H), 4.80 (1H), 5.87 (1H), 6.67 (1H), 7.10 (1H), 7.34 (1H), 7.76 (1H), 7.78 (1H), 8.00 (1H), 8.16 (1H), 8.29 (1H), 8.50 (1H), 9.17 (1H) ppm.

Example 407

4-{6-(cyclopentylamino)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b] pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



50 mg (109 µmol)

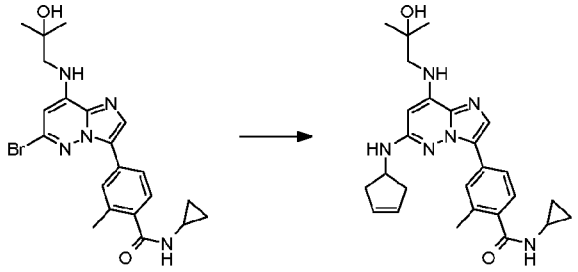
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate

example 96a were transformed in analogy to example 305 using cyclopentanamine to give after working up and purification 10.8 mg (20%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.64 (2H), 1.15 (6H), 1.43-1.72 (6H), 1.97 (2H), 2.34 (3H), 2.79 (1H), 3.06 (2H), 3.99 (1H), 4.76 (1H), 5.61 (1H), 6.17 (1H), 6.37 (1H), 7.29 (1H), 7.72 (1H), 7.99 (1H), 8.17 (1H), 8.24 (1H) ppm.

Example 408

4-{6-(cyclopent-3-en-1-ylamino)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

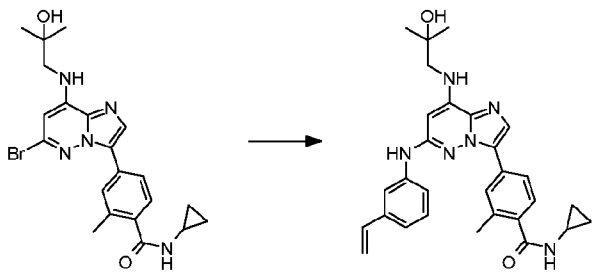


100 mg (218 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using cyclopent-3-en-1-amine to give after working up and purification 12.8 mg (12%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.64 (2H), 1.15 (6H), 2.25 (1H), 2.28 (1H), 2.34 (3H), 2.73-2.83 (3H), 3.07 (2H), 4.32 (1H), 4.76 (1H), 5.61 (1H), 5.73 (2H), 6.21 (1H), 6.57 (1H), 7.31 (1H), 7.73 (1H), 8.02 (1H), 8.13 (1H), 8.25 (1H) ppm.

Example 409

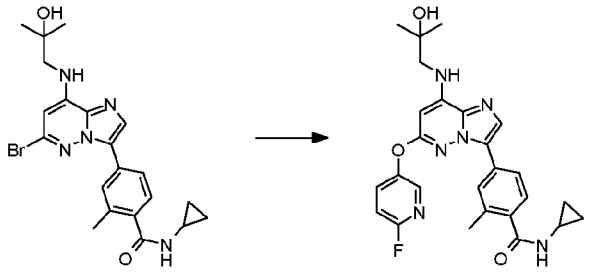
N-cyclopropyl-4-{6-[(3-ethenylphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



75 mg (164 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using 3-vinylaniline to give after working up and purification 28.0 mg (33%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 1.18 (6H), 2.34 (3H), 2.81 (1H), 3.16 (2H), 4.81 (1H), 5.18 (1H), 5.67 (1H), 5.89 (1H), 6.56 (1H), 6.64 (1H), 7.03 (1H), 7.24 (1H), 7.31 (1H), 7.62 (1H), 7.63 (1H), 7.77 (1H), 7.91 (1H), 8.01 (1H), 8.29 (1H), 8.94 (1H) ppm.

Example 410

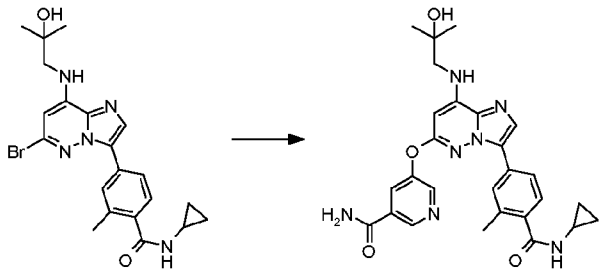
N-cyclopropyl-4-{6-[(6-fluoropyridin-3-yl)oxy]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



75 mg (164 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using 6-fluoropyridin-3-ol to give after working up and purification 4.1 mg (5%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.47 (2H), 0.64 (2H), 1.17 (6H), 2.14 (3H), 2.77 (1H), 3.28 (2H), 4.75 (1H), 6.24 (1H), 7.07 (1H), 7.17 (1H), 7.32 (1H), 7.61 (1H), 7.68 (1H), 7.92 (1H), 8.03 (1H), 8.23 (1H), 8.25 (1H) ppm.

Example 411

5-({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)nicotinamide

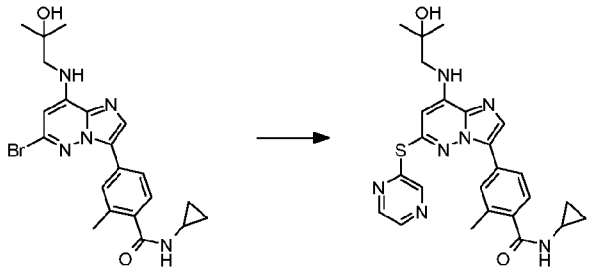


75 mg (164 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using 5-hydroxynicotinamide to give after working up and purification 22.0 mg (25%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.46 (2H), 0.63 (2H), 1.17 (6H), 2.09 (3H), 2.76 (1H), 3.13 (2H), 4.75 (1H), 6.27 (1H), 7.10 (1H), 7.13 (1H), 7.61 (1H), 7.64 (1H), 7.69 (1H), 7.92 (1H), 8.17-8.22 (3H), 8.72 (1H), 8.96 (1H) ppm.

Example 412

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyrazin-2-ylsulfanyl) imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

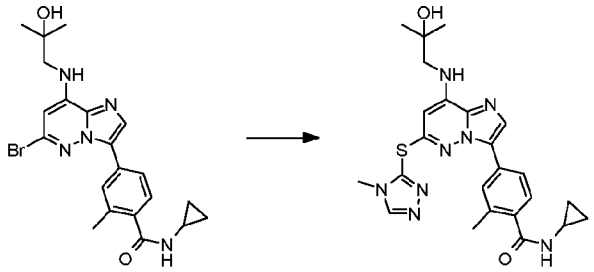


75 mg (164 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using pyrazine-2-thiol to give after working up and purification 17.5 mg (21%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.65 (2H), 1.13 (6H), 2.23 (3H), 2.79 (1H), 3.25 (2H), 4.71 (1H), 6.48 (1H), 7.16 (1H), 7.19 (1H), 7.66 (1H), 7.71 (1H), 7.97 (1H), 8.25 (1H), 8.58 (1H), 8.61 (1H), 8.83 (1H) ppm.

Example 413

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(4-methyl-4H-1,2,4-triazol-3-yl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



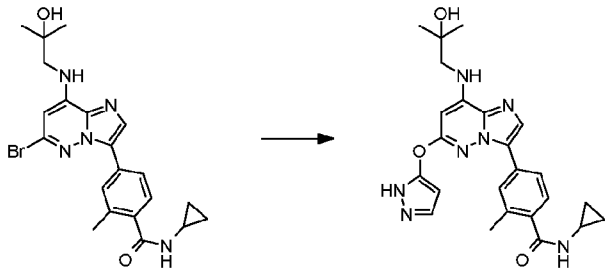
75 mg (164 µmol)

4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using 4-methyl-4H-1,2,4-triazole-3-thiol to give after working up and purification 17.5 mg (21%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 1.14 (6H), 2.28 (3H), 2.80 (1H), 3.25 (2H), 3.61 (3H), 4.73 (1H), 6.38 (1H), 7.17 (1H), 7.21 (1H), 7.48 (1H), 7.60 (1H), 7.96 (1H), 8.28 (1H), 8.93 (1H) ppm.

Example 414

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1H-pyrazol-5-yloxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



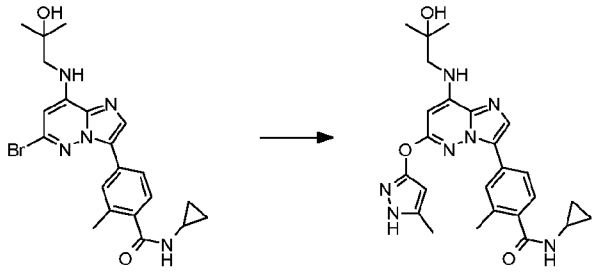
75 mg (164 µmol)

4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using 1H-pyrazol-5-ol to give after working up and purification 5.5 mg (7%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.64 (2H), 1.15 (6H), 2.25 (3H), 2.78 (1H), 3.26 (2H), 4.75 (1H), 6.13 (1H), 6.16 (1H), 6.98 (1H), 7.23 (1H), 7.73-7.80 (2H), 7.91 (1H), 7.93 (1H), 8.26 (1H), 12.45 (1H) ppm.

Example 415

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(5-methyl-1H-pyrazol-3-yl)oxy]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

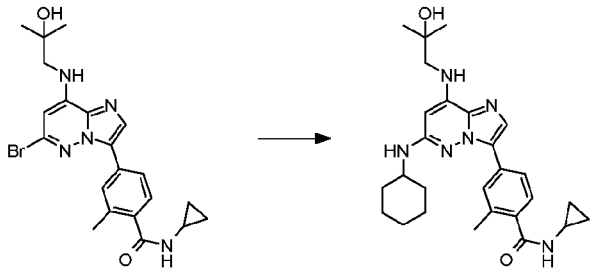


75 mg (164 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using 5-methyl-1H-pyrazol-3-ol to give after working up and purification 6.3 mg (8%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.64 (2H), 1.15 (6H), 2.23 (3H), 2.26 (3H), 2.79 (1H), 3.26 (2H), 4.74 (1H), 5.92 (1H), 6.11 (1H), 6.96 (1H), 7.24 (1H), 7.77 (1H), 7.90 (1H), 7.96 (1H), 8.26 (1H), 12.13 (1H) ppm.

Example 416

4-{6-(cyclohexylamino)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

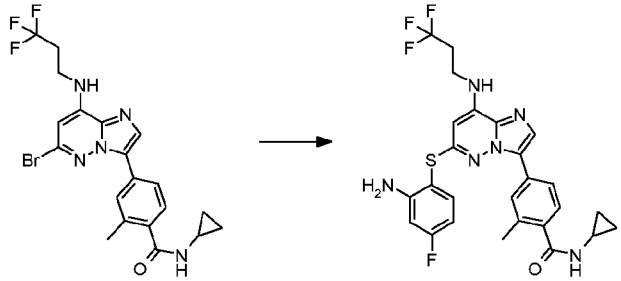


75 mg (164 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using cyclohexanamine to give after working up and purification 7.8 mg (10%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.64 (2H), 1.11-1.42 (5H), 1.15 (6H), 1.60 (1H), 1.73 (2H), 2.03 (2H), 2.35 (3H), 2.79 (1H), 3.06 (2H), 3.56 (1H), 4.77 (1H), 5.61 (1H), 6.17 (1H), 6.25 (1H), 7.28 (1H), 7.72 (1H), 7.95 (1H), 8.16 (1H), 8.26 (1H) ppm.

Example 417

4-{6-[(2-amino-4-fluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

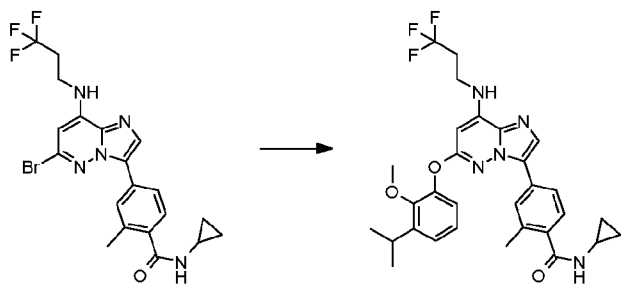


75 mg (156 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using 2-amino-4-fluorobenzenethiol to give after working up and purification 23.7 mg (27%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.65 (2H), 2.24 (3H), 2.60 (2H), 2.79 (1H), 3.49 (2H), 5.75 (2H), 6.02 (1H), 6.40 (1H), 6.58 (1H), 7.12 (1H), 7.38 (1H), 7.60 (1H), 7.74 (1H), 7.75 (1H), 7.93 (1H), 8.24 (1H) ppm.

Example 418

N-cyclopropyl-4-{6-[2-methoxy-3-(propan-2-yl)phenoxy]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

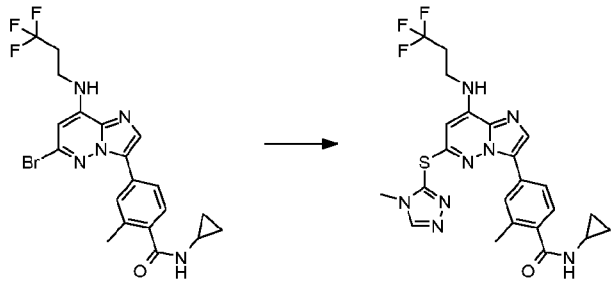


75 mg (156 µmol)
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using
3-isopropyl-2-methoxyphenol to give after working up and purification 45 mg (48%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.45 (2H), 0.63 (2H), 1.16 (6H), 2.06 (3H), 2.60-2.80 (3H), 3.17-3.26 (1H), 3.60 (2H), 3.71 (3H), 6.17 (1H), 7.04-7.23 (4H), 7.61 (1H), 7.67 (1H), 7.71 (1H), 7.94 (1H), 8.19 (1H) ppm.

Example 419

N-cyclopropyl-2-methyl-4-{6-[(4-methyl-4H-1,2,4-triazol-3-yl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide

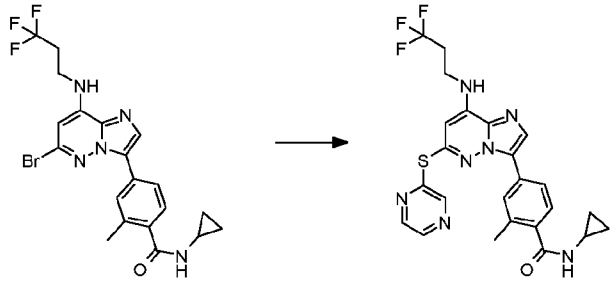


75 mg (156 µmol)
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using
4-methyl-4H-1,2,4-triazole-3-thiol to give after working up and purification 29.4 mg (35%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 2.28 (3H), 2.66 (2H), 2.80 (1H), 3.57 (2H), 3.61 (3H), 6.35 (1H), 7.20 (1H), 7.46 (1H), 7.59 (1H), 7.84 (1H), 7.96 (1H), 8.27 (1H), 8.93 (1H) ppm.

Example 420

N-cyclopropyl-2-methyl-4-{6-(pyrazin-2-ylsulfanyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide

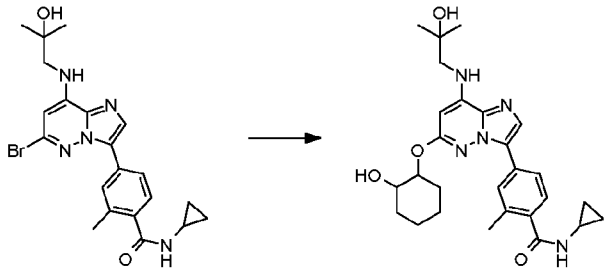


75 mg (156 µmol)
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using pyrazine-2-thiol to give after working up and purification 28.6 mg (34%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.64 (2H), 2.23 (3H), 2.64 (2H), 2.79 (1H), 3.57 (2H), 6.43 (1H), 7.18 (1H), 7.64 (1H), 7.69 (1H), 7.83 (1H), 7.97 (1H), 8.25 (1H), 8.57-8.62 (2H), 8.86 (1H) ppm.

Example 421

N-cyclopropyl-4-(6-{[(1RS,2RS)-2-hydroxycyclohexyl]oxy}-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide

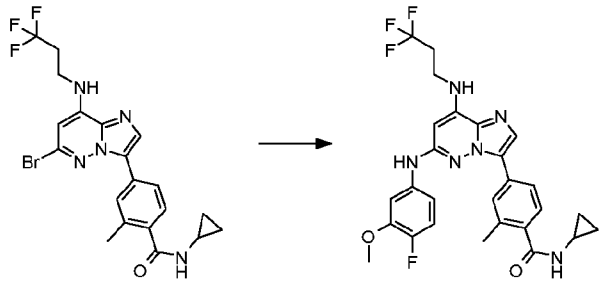


50 mg (109 µmol)
4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using (1RS,2RS)-cyclohexane-1,2-diol to give after working up and purification 2.8 mg (5%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.65 (2H), 1.13 (6H), 1.23-1.39 (4H), 1.66 (2H), 1.89 (1H), 2.36 (3H), 2.80 (1H), 3.19 (2H), 3.54 (1H), 4.65 (1H), 4.72 (1H), 4.82 (1H), 5.72 (1H), 5.84 (1H), 6.66 (1H), 7.33 (1H), 7.87 (1H), 7.91 (1H), 8.08 (1H), 8.29 (1H) ppm.

Example 422

N-cyclopropyl-4-{6-[(4-fluoro-3-methoxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

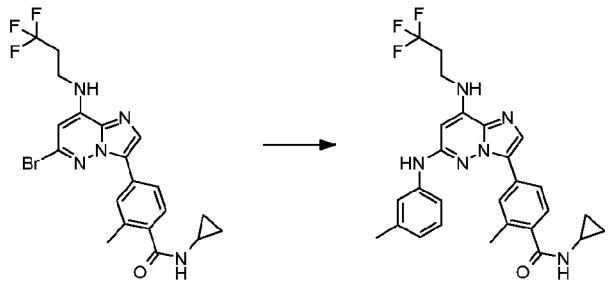


100 mg (207 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using 4-fluoro-3-methoxyaniline to give after working up and purification 43.1 mg (38%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 2.33 (3H), 2.67 (2H), 2.81 (1H), 3.49 (2H), 3.67 (3H), 5.78 (1H), 7.08 (1H), 7.19-7.37 (4H), 7.76 (1H), 7.85 (1H), 7.99 (1H), 8.27 (1H), 8.94 (1H) ppm.

Example 423

N-cyclopropyl-2-methyl-4-{6-[(3-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide

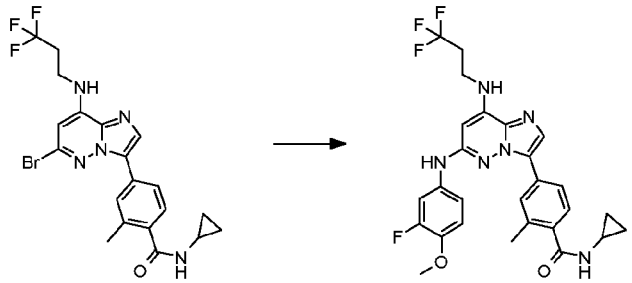


75 mg (156 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using m-toluidine to give after working up and purification 14.5 mg (17%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.63 (2H), 0.90 (2H), 2.35 (3H), 2.43-2.58 (2H), 2.51 (3H), 2.61 (1H), 2.92 (1H), 3.59 (2H), 5.64 (1H), 5.78 (1H), 5.91 (1H), 6.25 (1H), 6.89 (1H), 7.22 (1H), 7.35 (1H), 7.40 (1H), 7.65 (1H), 7.90 (1H), 7.92 (1H) ppm.

Example 424

N-cyclopropyl-4-{6-[(3-fluoro-4-methoxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



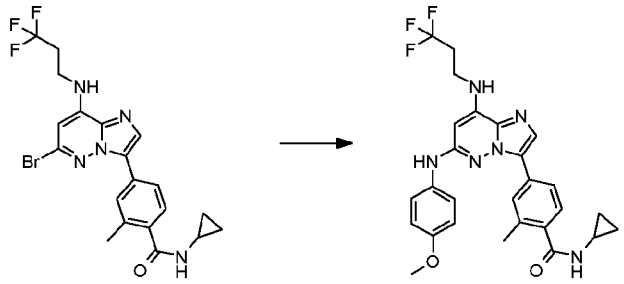
75 mg (156 µmol)

4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using 3-fluoro-4-methoxyaniline to give after working up and purification 21.0 mg (24%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.64 (2H), 0.90 (2H), 2.44-2.60 (2H), 2.51 (3H), 2.92 (1H), 3.59 (2H), 3.89 (3H), 5.55 (1H), 5.78 (1H), 5.94 (1H), 6.20 (1H), 6.92 (1H), 7.06 (1H), 7.41 (1H), 7.55 (1H), 7.64 (1H), 7.83 (1H), 7.92 (1H) ppm.

Example 425

N-cyclopropyl-4-{6-[(4-methoxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



75 mg (156 µmol)

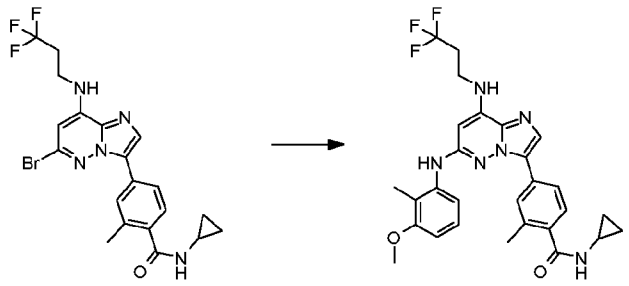
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example

247a were transformed in analogy to example 305 using 4-methoxyaniline to give after working up and purification 17.8 mg (21%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.63 (2H), 0.90 (2H), 2.43-2.60 (2H), 2.51 (3H), 2.92 (1H), 3.57 (2H), 3.82 (3H), 5.56 (1H), 5.77 (1H), 5.91 (1H), 6.10 (1H), 6.91 (2H), 7.35-7.42 (3H), 7.64 (1H), 7.83 (1H), 7.98 (1H) ppm.

Example 426

N-cyclopropyl-4-{6-[(3-methoxy-2-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

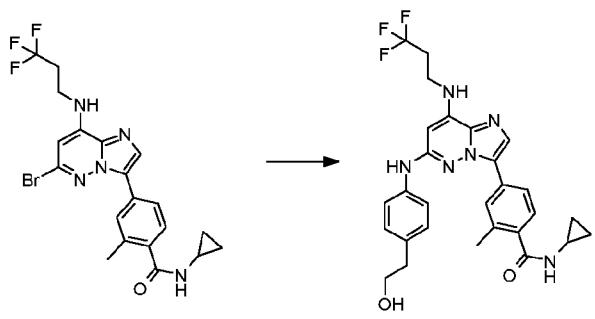


150 mg (311 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using 3-methoxy-2-methylaniline to give after working up and purification 21.3 mg (12%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.62 (2H), 0.89 (2H), 2.20 (3H), 2.47 (3H), 2.50 (2H), 2.92 (1H), 3.55 (2H), 3.87 (3H), 5.63 (1H), 5.81 (1H), 5.89 (1H), 6.00 (1H), 6.72 (1H), 7.16-7.25 (2H), 7.36 (1H), 7.65 (1H), 7.84 (1H); 7.93 (1H) ppm.

Example 427

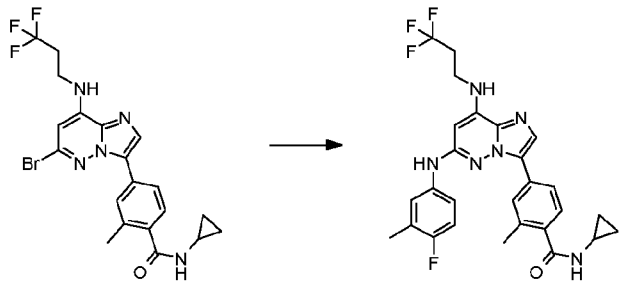
N-cyclopropyl-4-(6-{[4-(2-hydroxyethyl)phenyl]amino}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide



75 mg (156 µmol)
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using 2-(4-aminophenyl)ethanol to give after working up and purification 9.2 mg (10%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.52 (2H), 0.66 (2H), 2.38 (3H), 2.58-2.77 (4H), 2.82 (1H), 3.41-3.59 (4H), 4.59 (1H), 5.82 (1H), 7.11 (2H), 7.24 (1H), 7.34 (1H), 7.56 (2H), 7.77 (1H), 7.83 (1H), 8.12 (1H), 8.32 (1H), 8.86 (1H) ppm.

Example 428

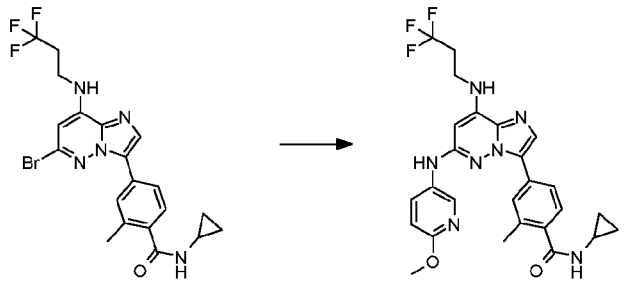
N-cyclopropyl-4-{6-[(4-fluoro-3-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



75 mg (156 µmol)
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using 4-fluoro-3-methylaniline to give after working up and purification 11.9 mg (14%) of the title compound.
^{1}H-NMR ($CDCl_3$): δ= 0.63 (2H), 0.89 (2H), 2.25 (3H), 2.42-2.56 (2H), 2.48 (3H), 2.92 (1H), 3.53 (2H), 5.57 (1H), 5.87 (1H), 5.99 (1H), 6.39 (1H), 6.95 (1H), 7.21-7.34 (2H), 7.36 (1H), 7.62 (1H), 7.85 (1H), 7.87 (1H) ppm.

Example 429

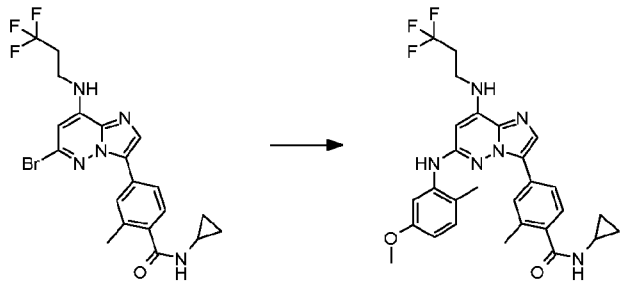
N-cyclopropyl-4-{6-[(6-methoxypyridin-3-yl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



75 mg (156 µmol)
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using 6-methoxypyridin-3-amine to give after working up and purification 8.7 mg (10%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.64 (2H), 2.37 (3H), 2.68 (2H), 2.80 (1H), 3.30 (3H), 3.49 (2H), 5.77 (1H), 6.78 (1H), 7.25-7.35 (2H), 7.77 (2H), 7.93 (1H), 8.09 (1H), 8.29 (1H), 8.46 (1H), 8.86 (1H) ppm.

Example 430

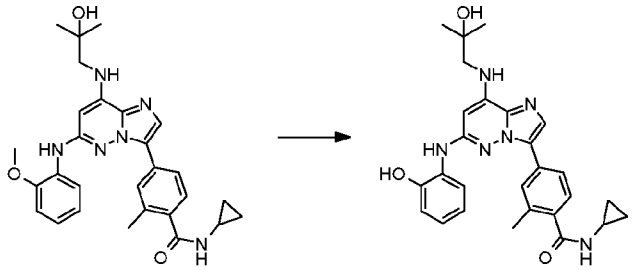
N-cyclopropyl-4-{6-[(5-methoxy-2-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



150 mg (311 µmol)
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using 5-methoxy-2-methylaniline to give after working up and purification 15.5 mg (9%) of the title compound.
^{1}H-NMR ($CDCl_3$): δ= 0.62 (2H), 0.89 (2H), 2.26 (3H), 2.48 (3H), 2.52 (2H), 2.92 (1H), 3.58 (2H), 3.73 (3H), 5.65 (1H), 5.79 (1H), 5.89 (1H), 5.96 (1H), 6.62 (1H), 7.14 (1H), 7.31 (1H), 7.38 (1H), 7.66 (1H), 7.87 (1H), 7.90 (1H) ppm.

Example 431

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(2-hydroxyphenyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



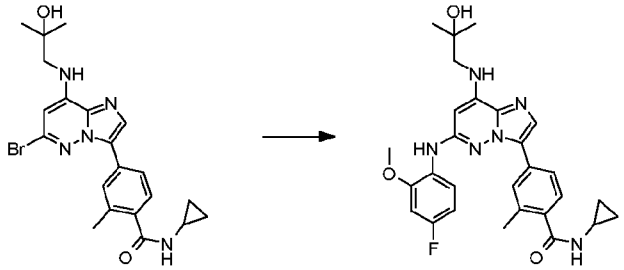
40 mg (80 µmol)

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(2-methoxyphenyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide which was prepared according to example 402 were transformed in analogy to example 280 to give after working up and purification 5.8 mg (13%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 1.17 (6H), 2.36 (3H), 2.81 (1H), 3.17 (2H), 4.76 (1H), 6.28 (1H), 6.40 (1H), 6.71-6.89 (3H), 7.30 (1H), 7.76 (1H), 7.80-7.91 (2H), 8.11 (1H), 8.16 (1H), 8.29 (1H), 9.90 (1H) ppm.

Example 432

N-cyclopropyl-4-{6-[(4-fluoro-2-methoxyphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



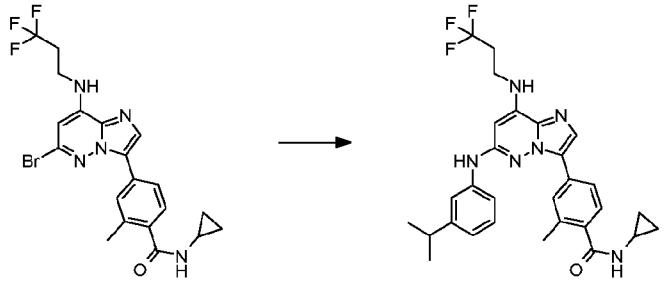
150 mg (327 µmol)

4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using 4-fluoro-2-methoxyaniline to give after working up and purification 12.2 mg (6%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.65 (2H), 1.18 (6H), 2.32 (3H), 2.80 (1H), 3.15 (2H), 3.84 (3H), 4.79 (1H), 6.21 (1H), 6.42 (1H), 6.72 (1H), 6.96 (1H), 7.30 (1H), 7.76 (1H), 7.82 (1H), 7.91 (1H), 8.01 (1H), 8.10 (1H), 8.27 (1H) ppm.

Example 433

N-cyclopropyl-2-methyl-4-(6-{[3-(propan-2-yl)phenyl]amino}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)benzamide

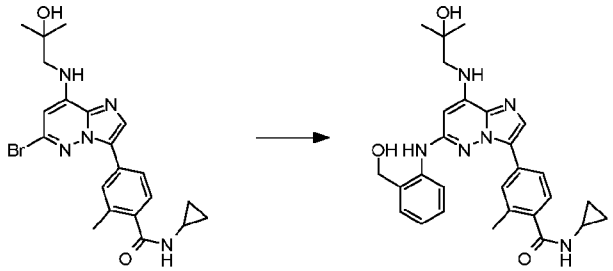


75 mg (156 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using 3-isopropylaniline to give after working up and purification 22.8 mg (26%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.66 (2H), 1.16 (6H), 2.37 (3H), 2.49-2.88 (4H), 3.49 (2H), 5.84 (1H), 6.79 (1H), 7.19 (1H), 7.23-7.29 (2H), 7.33 (1H), 7.70 (1H), 7.77 (1H), 7.92 (1H), 8.02 (1H), 8.29(1H), 8.88 (1H) ppm.

Example 434

N-cyclopropyl-4-(6-{[2-(hydroxymethyl)phenyl]amino}-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide

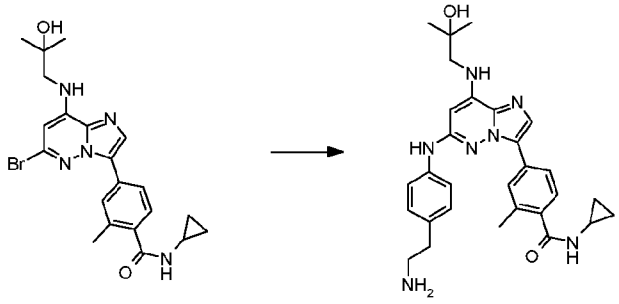


75 mg (164 µmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using (2-aminophenyl)methanol to give after working up and purification 2.0 mg (2%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.49 (2H), 0.64 (2H), 1.18 (6H), 2.26 (3H), 2.78 (1H), 3.18 (2H), 4.54 (2H), 4.80 (1H), 5.35 (1H), 5.96 (1H), 6.46 (1H), 7.03 (1H), 7.24 (2H), 7.36 (1H), 7.77-7.91 (3H), 8.02 (1H), 8.06 (1H), 8.24 (1H) ppm.

Example 435

4-(6-{[4-(2-aminoethyl)phenyl]amino}-8-[(2-hydroxy-2-methylpropyl)amino] imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide



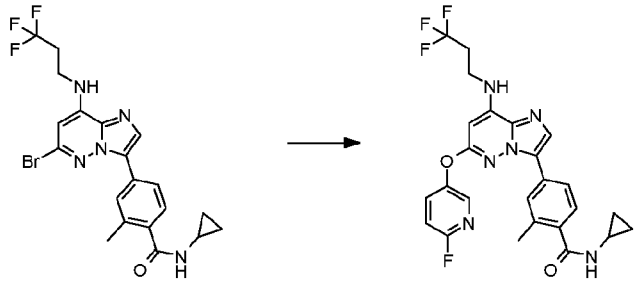
75 mg (164 µmol)

4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 305 using 4-(2-aminoethyl)aniline to give after working up and purification 11 mg (12%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 1.18 (6H), 2.38 (3H), 2.59-2.65 (2H), 2.74-2.85 (3H), 3.15 (2H), 4.82 (1H), 5.88 (1H), 6.51 (1H), 7.10 (2H), 7.34 (1H), 7.58 (2H), 7.76 (1H), 7.84 (1H), 8.12 (1H), 8.32 (1H), 8.87 (1H) ppm.

Example 436

N-cyclopropyl-4-{6-[(6-fluoropyridin-3-yl)oxy]-8-[(3,3,3-trifluoropropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



200 mg (415 µmol)

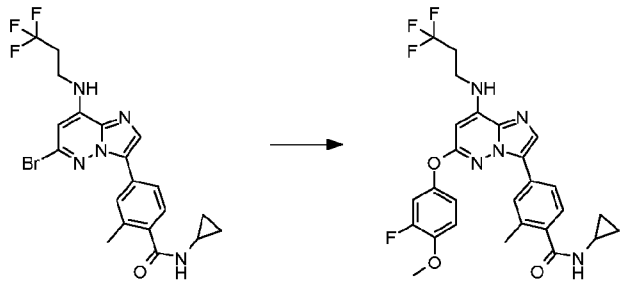
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopr

opyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using 6-fluoropyridin-3-ol to give after working up and purification 4.8 mg (2%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.47 (2H), 0.64 (2H), 2.13 (3H), 2.60-2.80 (3H), 3.61 (2H), 6.19 (1H), 7.17 (1H), 7.32 (1H), 7.60 (1H), 7.67 (1H), 7.77 (1H), 7.93 (1H), 8.04 (1H), 8.22 (1H), 8.26 (1H) ppm.

Example 437

N-cyclopropyl-4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

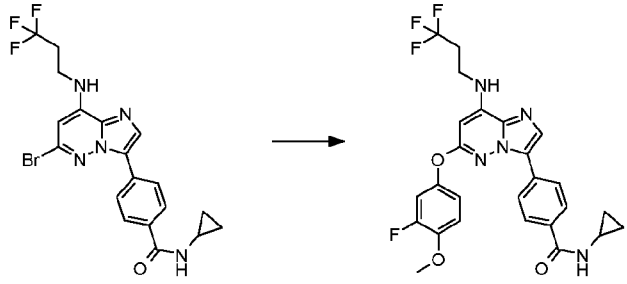


400 mg (829 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 51 using 2-fluoro-4-methoxyphenol to give after working up and purification 194 mg (41%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.46 (2H), 0.64 (2H), 2.08 (3H), 2.60-2.80 (3H), 3.60 (2H), 3.78 (3H), 6.16 (1H), 6.84 (1H), 7.06 (1H), 7.15 (1H), 7.33 (1H), 7.61 (1H), 7.67-7.74 (2H), 7.94 (1H), 8.21 (1H) ppm.

Example 438

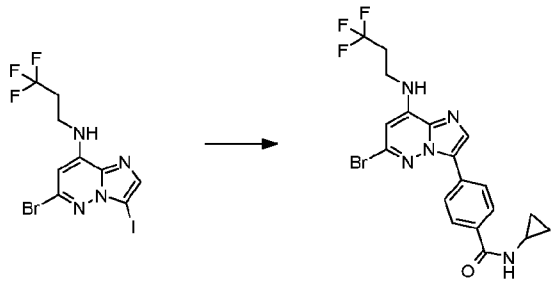
N-cyclopropyl-4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl) amino]imidazo[1,2-b]pyridazin-3-yl}benzamide



400 mg (854 µmol)
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopr opylbenzamide which was prepared according to intermediate example 438a were transformed in analogy to example 51 using 2-fluoro-4-methoxyphenol to give after working up and purification 219 mg (46%) of the title compound.

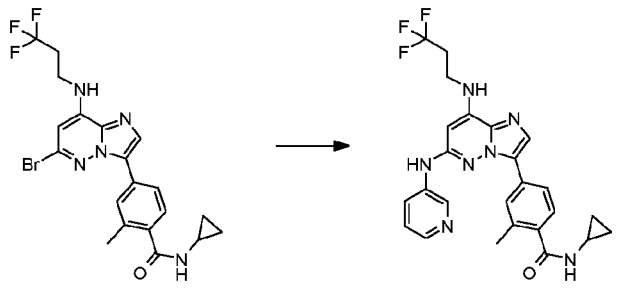
^{1}H-NMR (DMSO-d6): δ= 0.53 (2H), 0.66 (2H), 2.69 (2H), 2.79 (1H), 3.60 (2H), 3.81 (3H), 6.17 (1H), 6.85 (1H), 7.08 (1H), 7.34 (1H), 7.65 (2H), 7.74 (1H), 7.89 (2H), 8.01 (1H), 8.40 (1H) ppm.

Intermediate example 438a
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopr opylbenzamide



1.50 g (3.45 mmol)
6-bromo-3-iodo-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 247b were transformed in analogy to intermediate example 1a using [4-(cyclopropylcarbamoyl)phenyl]boronic acid to give after working up and purification 1.05 g (65%) of the title compound.

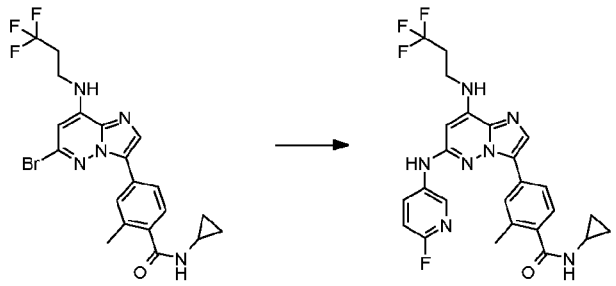
Example 439
N-cyclopropyl-2-methyl-4-{6-(pyridin-3-ylamino)-8-[(3,3,3-trifluoropropyl) amino]imidazo[1,2-b]pyridazin-3-yl}benzamide



75 mg (156 µmol)
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using pyridin-3-amine to give after working up and purification 15.5 mg (19%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 2.38 (3H), 2.68 (2H), 2.81 (1H), 3.51 (2H), 5.84 (1H), 7.29 (1H), 7.34 (1H), 7.38 (1H), 7.79 (1H), 7.80 (1H), 8.06 (1H), 8.10-8.16 (2H), 8.32 (1H), 8.80 (1H), 9.18 (1H) ppm.

Example 440

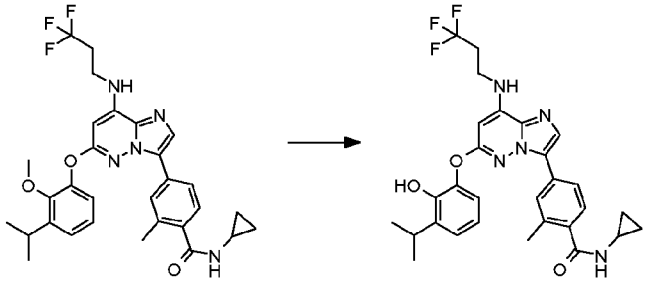
N-cyclopropyl-4-{6-[(6-fluoropyridin-3-yl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



75 mg (156 µmol)
4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a were transformed in analogy to example 305 using 6-fluoropyridin-3-amine to give after working up and purification 25.5 mg (30%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 2.37 (3H), 2.68 (2H), 2.81 (1H), 3.50 (2H), 5.80 (1H), 7.12 (1H), 7.34 (1H), 7.39 (1H), 7.76-7.80 (2H), 8.00 (1H), 8.16 (1H), 8.31 (1H), 8.51 (1H), 9.21 (1H) ppm.

Example 441

N-cyclopropyl-4-{6-[2-hydroxy-3-(propan-2-yl)phenoxy]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

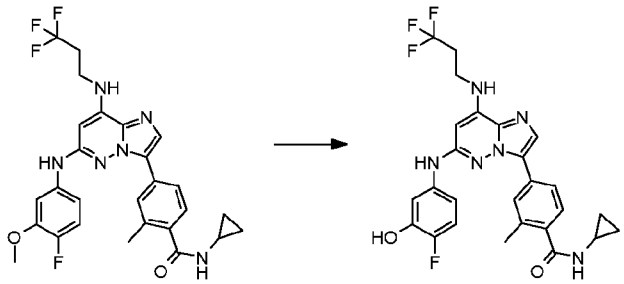


32 mg (56 µmol) N-cyclopropyl-4-{6-[2-methoxy-3-(propan-2-yl)phenoxy]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide which was prepared according to example 418 were transformed in analogy to example 280 to give after working up and purification 8.2 mg (25%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.46 (2H), 0.62 (2H), 1.07 (6H), 2.05 (3H), 2.69 (2H), 2.75 (1H), 3.04 (1H), 3.60 (2H), 6.14 (1H), 6.76 (1H), 6.82 (1H), 7.03-7.09 (2H), 7.56 (1H), 7.62 (1H), 7.77 (1H), 7.93 (1H), 8.19 (1H), 9.37 (1H) ppm.

Example 442

N-cyclopropyl-4-{6-[(4-fluoro-3-hydroxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

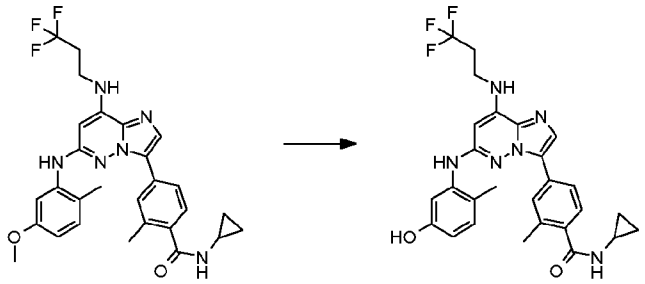


33 mg (61 µmol) N-cyclopropyl-4-{6-[(4-fluoro-3-methoxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide which was prepared according to example 422 were transformed in analogy to example 280 to give after working up and purification 9.3 mg (27%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 2.36 (3H), 2.67 (2H), 2.81 (1H), 3.47 (2H), 5.78 (1H), 7.00 (1H), 7.05 (1H), 7.20-7.27 (2H), 7.33 (1H), 7.78 (1H), 7.87 (1H), 8.06 (1H), 8.28 (1H), 8.79 (1H), 9.71 (1H) ppm.

Example 443

N-cyclopropyl-4-{6-[(5-hydroxy-2-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



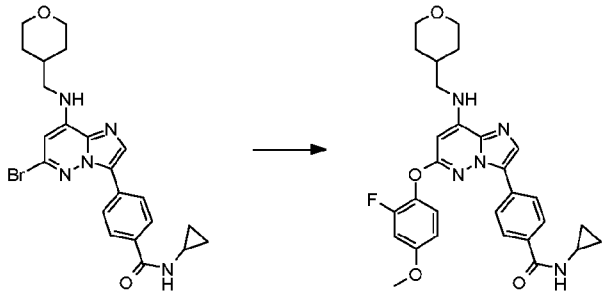
10.5 mg (19 µmol)

N-cyclopropyl-4-{6-[(5-methoxy-2-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide which was prepared according to example 430 were transformed in analogy to example 280 to give after working up and purification 2.0 mg (20%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.47 (2H), 0.64 (2H), 2.11 (3H), 2.24 (3H), 2.69 (2H), 2.77 (1H), 3.48 (2H), 5.94 (1H), 6.42 (1H), 6.95 (1H), 7.10 (1H), 7.16 (1H), 7.20 (1H), 7.65-7.95 (3H), 8.01 (1H), 8.21 (1H), 9.06 (1H) ppm.

Example 444

N-cyclopropyl-4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide



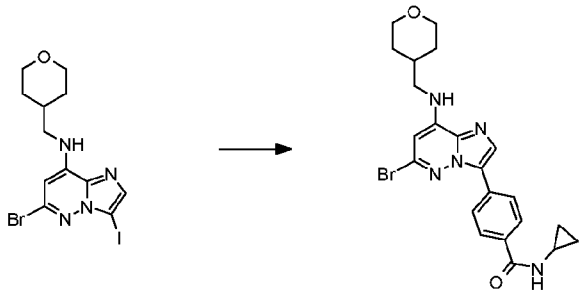
400 mg (850 µmol)

4-{6-bromo-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide which was prepared according to intermediate example 444a were transformed in analogy to example 51 using 2-fluoro-4-methoxyphenol to give after working up and purification 257 mg (54%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.53 (2H), 0.66 (2H), 1.22 (2H), 1.62 (2H), 1.94 (1H), 2.80 (1H), 3.17-3.32 (4H), 3.81 (3H), 3.84 (2H), 6.12 (1H), 6.84 (1H), 7.07 (1H), 7.34 (1H), 7.64 (2H), 7.74 (1H), 7.89 (2H), 7.98 (1H), 8.39 (1H) ppm.

Intermediate example 444a

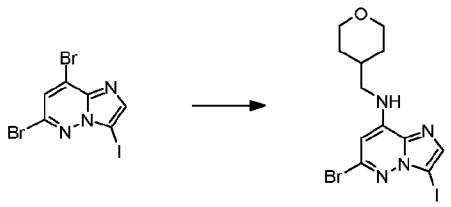
4-{6-bromo-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide



1.20 g (2.75 mmol) 6-bromo-3-iodo-N-(tetrahydro-2H-pyran-4-ylmethyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 444b were transformed in analogy to intermediate example 1a using [4-(cyclopropylcarbamoyl)phenyl]boronic acid to give after working up and purification 1.08 g (84%) of the title compound.

Intermediate example 444b

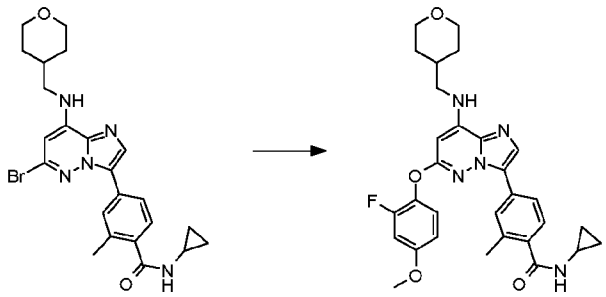
6-bromo-3-iodo-N-(tetrahydro-2H-pyran-4-ylmethyl)imidazo[1,2-b]pyridazin-8-amine



3.00 g (7.45 mmol) 6,8-dibromo-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 96c were transformed in analogy to intermediate example 1b using 1-(tetrahydro-2H-pyran-4-yl)methanamine to give after working up and purification 2.81 g (81%) of the title compound.

Example 445

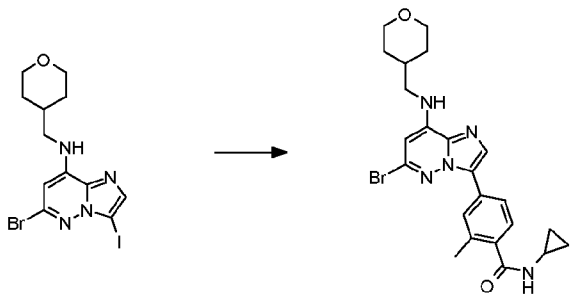
N-cyclopropyl-4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



400 mg (826 µmol)
4-{6-bromo-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 445a were transformed in analogy to example 51 using 2-fluoro-4-methoxyphenol to give after working up and purification 295 mg (65%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.46 (2H), 0.63 (2H), 1.22 (2H), 1.62 (2H), 1.95 (1H), 2.08 (3H), 2.77 (1H), 3.19-3.27 (4H), 3.77 (3H), 3.83 (2H), 6.12 (1H), 6.83 (1H), 7.05 (1H), 7.14 (1H), 7.33 (1H), 7.61 (1H), 7.67-7.74 (2H), 7.91 (1H), 8.21 (1H) ppm.

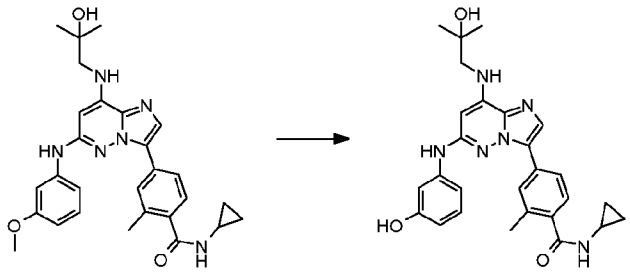
Intermediate example 445a
4-{6-bromo-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



1.58 g (3.62 mmol)
6-bromo-3-iodo-N-(tetrahydro-2H-pyran-4-ylmethyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 444b were transformed in analogy to intermediate example 1a using N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide to give after working up and purification 1.05 g (57%) of the title compound.

Example 446
N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-hydroxyphenyl)

amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

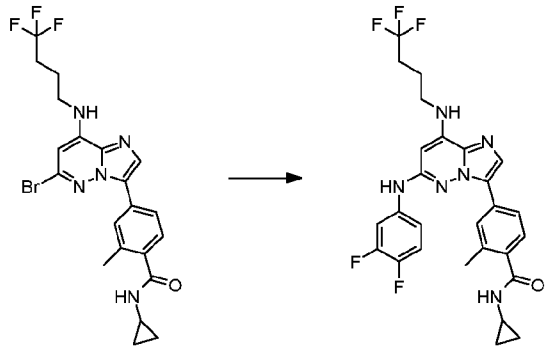


30 mg (60 µmol)
N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-methoxyphenyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide which was prepared according to example 403 were transformed in analogy to example 280 to give after working up and purification 9.60 mg (31%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.65 (2H), 1.18 (6H), 2.37 (3H), 2.81 (1H), 3.14 (2H), 4.81 (1H), 5.88 (1H), 6.33 (1H), 6.49 (1H), 6.94 (1H), 7.03 (1H), 7.23 (1H), 7.32 (1H), 7.77 (1H), 7.89 (1H), 8.12 (1H), 8.29 (1H), 8.77 (1H), 9.25 (1H) ppm.

Example 447

N-cyclopropyl-4-{6-[(3,4-difluorophenyl)amino]-8-[(4,4,4-trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

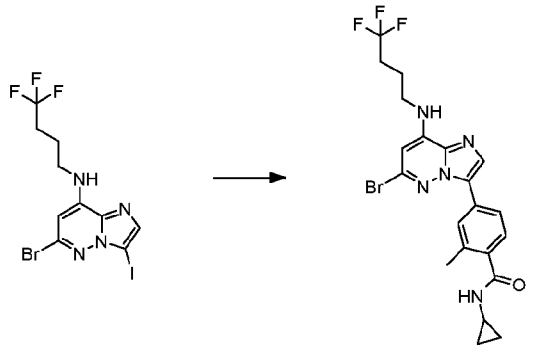


75 mg (151µmol)
4-{6-bromo-8-[(4,4,4-trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 447a were transformed in analogy to example 305 using 3,4-difluoroaniline to give after working up and purification 6.3 mg (7%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.51 (2H), 0.66 (2H), 1.86 (2H), 2.26-2.43 (2H), 2.36 (3H), 2.81 (1H), 3.32-3.38 (2H), 5.75 (1H), 7.20-7.39 (4H), 7.75 (1H), 7.81 (1H), 7.90 (1H), 7.99 (1H), 8.28 (1H), 9.14 (1H) ppm.

Intermediate example 447a

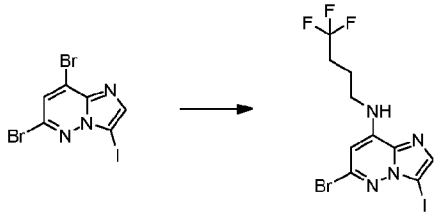
4-{6-bromo-8-[(4,4,4-trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



4,27 g (9.51 mmol) 6-bromo-3-iodo-N-(4,4,4-trifluorobutyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 447b were transformed in analogy to intermediate example 1a using N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide to give after working up and purification 2.37 g (50%) of the title compound.

Intermediate example 447b

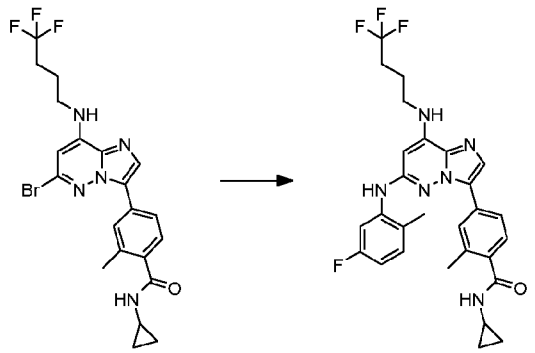
6-bromo-3-iodo-N-(4,4,4-trifluorobutyl)imidazo[1,2-b]pyridazin-8-amine



3.96 g (9.83 mmol) 6,8-dibromo-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 96c were transformed in analogy to intermediate example 1b using 4,4,4-trifluorobutan-1-amine to give after working up and purification 3.43 g (74%) of the title compound.

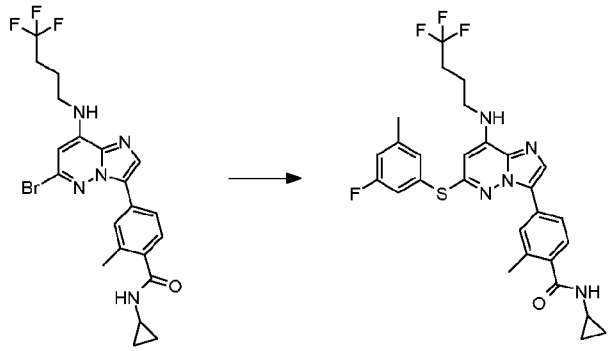
Example 448

N-cyclopropyl-4-{6-[(5-fluoro-2-methylphenyl)amino]-8-[(4,4,4-trifluorobutyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



75 mg (151 µmol)
4-{6-bromo-8-[(4,4,4-trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 447a were transformed in analogy to example 305 using 5-fluoro-2-methylaniline to give after working up and purification 10.5 mg (12%) of the title compound.
^{1}H-NMR ($CDCl_3$): δ= 0.63 (2H), 0.89 (2H), 2.00 (2H), 2.20-2.33 (2H), 2.30 (3H), 2.50 (3H), 2.92 (1H), 3.39 (2H), 5.62 (1H), 5.77 (1H), 5.92 (1H), 6.02 (1H), 6.70 (1H), 7.14 (1H), 7.40 (1H), 7.65 (1H), 7.76 (1H), 7.84 (1H), 7.87 (1H) ppm.

Example 449
N-cyclopropyl-4-{6-[(3-fluoro-5-methylphenyl)sulfanyl]-8-[(4,4,4-trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

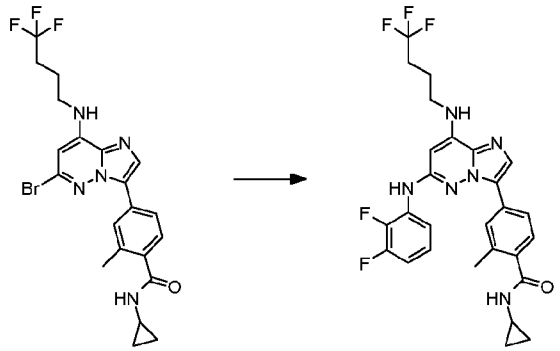


75 mg (151 µmol)
4-{6-bromo-8-[(4,4,4-trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 447a were transformed in analogy to example 51 using
3-fluoro-5-methylbenzenethiol to give after working up and purification 44.6 mg (50%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.63 (2H), 0.90 (2H), 1.97 (2H), 2.23 (2H), 2.36 (3H), 2.41 (3H), 2.92 (1H), 3.38 (2H), 5.79 (1H), 5.87 (1H), 5.91 (1H), 6.96 (1H), 7.17-7.29 (3H), 7.66 (1H), 7.69 (1H), 7.72 (1H) ppm.

Example 450

N-cyclopropyl-4-{6-[(2,3-difluorophenyl)amino]-8-[(4,4,4-trifluorobutyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



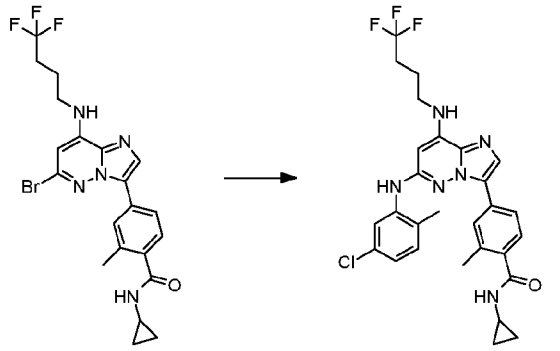
75 mg (151 µmol)

4-{6-bromo-8-[(4,4,4-trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 447a were transformed in analogy to example 305 using 2,3-difluoroaniline to give after working up and purification 10.6 mg (12%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.63 (2H), 0.90 (2H), 2.03 (2H), 2.28 (2H), 2.52 (3H), 2.93 (1H), 3.43 (2H), 5.64 (1H), 5.75 (1H), 5.91 (1H), 6.40 (1H), 6.81 (1H), 7.03 (1H), 7.40 (1H), 7.66 (1H), 7.78 (1H), 7.98 (1H), 8.07 (1H) ppm.

Example 451

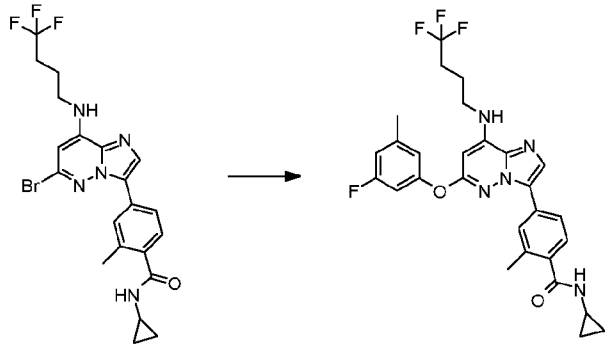
4-{6-[(5-chloro-2-methylphenyl)amino]-8-[(4,4,4-trifluorobutyl)amino]imidazo [1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



75 mg (151 µmol)
4-{6-bromo-8-[(4,4,4-trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 447a were transformed in analogy to example 305 using 5-chloro-2-methylaniline to give after working up and purification 12.7 mg (14%) of the title compound.
^{1}H-NMR ($CDCl_3$): δ= 0.61 (2H), 0.88 (2H), 1.99 (2H), 2.17-2.38 (2H), 2.29 (3H), 2.48 (3H), 2.92 (1H), 3.38 (2H), 5.60 (1H), 5.73 (1H), 5.90 (1H), 5.98 (1H), 6.99 (1H), 7.13 (1H), 7.43 (1H), 7.65 (1H), 7.76 (1H), 7.91 (1H), 7.93 (1H) ppm.

Example 452

N-cyclopropyl-4-{6-(3-fluoro-5-methylphenoxy)-8-[(4,4,4-trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

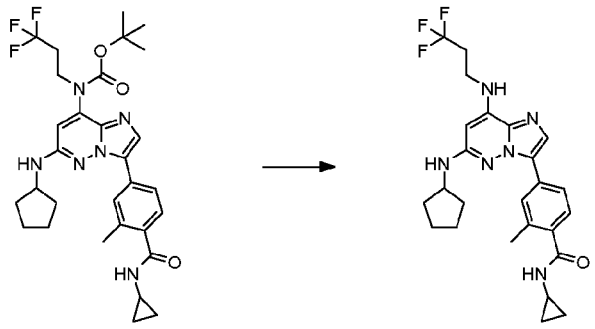


75 mg (151 µmol)
4-{6-bromo-8-[(4,4,4-trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 447a were transformed in analogy to example 51 using 3-fluoro-5-methylphenol to give after working up and purification 27.7 mg (32%) of the title compound.
^{1}H-NMR ($CDCl_3$): δ= 0.60 (2H), 0.88 (2H), 2.04 (2H), 2.28 (2H), 2.34 (3H), 2.37 (3H), 2.90 (1H), 3.46 (2H), 5.81-5.89 (3H), 6.77-6.87 (3H), 7.27 (1H), 7.66 (1H), 7.73 (1H), 7.77 (1H) ppm.

Example 453

4-{6-(cyclopentylamino)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]

pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

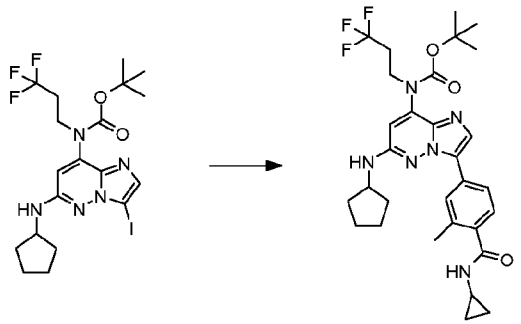


To a solution of 90 mg (153 µmol) ert-butyl {6-(cyclopentylamino)-3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]imidazo[1,2-b]pyridazin-8-yl}(3,3,3-trifluoropropyl)carbamate which was prepared according to intermediate example 453a in 1 mL dichloromethane were added 177 µL trifluoroacetic acid and the mixture was stirred for 2 hours at 23°C. The mixture was poured into water and extracted with dichloromethane. The organic phase was washed with sodium hydrogencarbonate solution and dried over sodium sulfate. After filtration and removal of solvent the residue was purified by chromatography to give 64.1 mg (82%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.64 (2H), 1.44-1.72 (6H), 1.90-2.05 (2H), 2.34 (3H), 2.62 (2H), 2.79 (1H), 3.41 (2H), 3.99 (1H), 5.57 (1H), 6.43 (1H), 6.92 (1H), 7.30 (1H), 7.73 (1H), 7.98 (1H), 8.17 (1H), 8.24 (1H) ppm.

Intermediate example 453a

4-{6-(cyclopentylamino)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

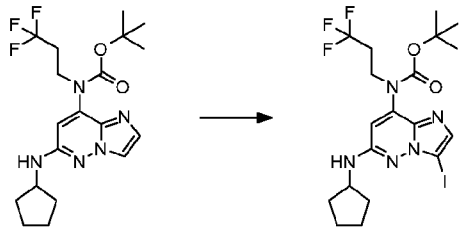


135 mg (250 µmol) tert-butyl [6-(cyclopentylamino)-3-iodoimidazo[1,2-b]pyridazin-8-yl](3,3,3-trifluoropropyl)carbamate which was prepared according to intermediate example 453b were transformed in analogy to intermediate example 1a using

[4-(cyclopropylcarbamoyl)-3-methylphenyl]boronic acid to give after working up and purification 101 mg (65%) of the title compound.

Intermediate example 453b

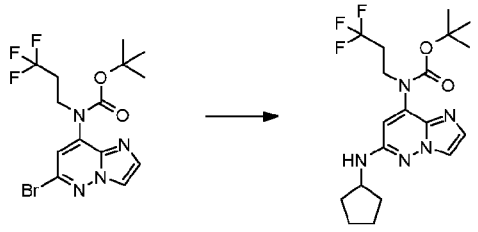
tert-butyl [6-(cyclopentylamino)-3-iodoimidazo[1,2-b]pyridazin-8-yl](3,3,3-trifluoropropyl) carbamate



197 mg (405 µmol) tert-butyl [6-(cyclopentylamino)imidazo[1,2-b]pyridazin-8-yl](3,3,3-trifluoropropyl)carbamate which was prepared according to intermediate example 453c were transformed in analogy to intermediate example 96c to give after working up and purification 141 mg (58%) of the title compound.

Intermediate example 453c

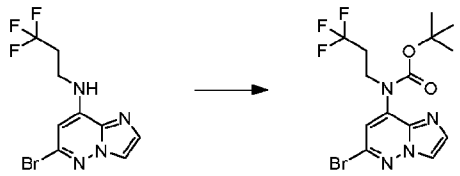
tert-butyl [6-(cyclopentylamino)imidazo[1,2-b]pyridazin-8-yl](3,3,3-trifluoropropyl)carbamate



200 mg (489 µmol) tert-butyl (6-bromoimidazo[1,2-b]pyridazin-8-yl)(3,3,3-trifluoropropyl)carbamate which was prepared according to intermediate example 453d were transformed in analogy to intermediate example 305 using cyclopentanamine to give after working up and purification 205 mg (101%) of the title compound that contains some reagent.

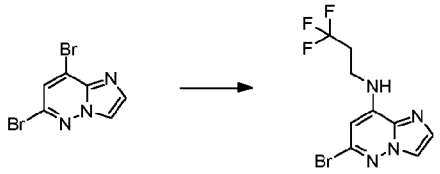
Intermediate example 453d

tert-butyl (6-bromoimidazo[1,2-b]pyridazin-8-yl)(3,3,3-trifluoropropyl)carbamate



To a solution of 1.88 g (6.08 mmol) 6-bromo-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 453e in 7.0 mL tetrahydrofuran were added 2.92 g di-tert-butyl dicarbonate, 74.3 mg N,N-dimethylpyridin-4-amine and the mixture was heated for 2 hours at 55°C. Ethyl acetate was added and the organic phase was washed with saturated sodium hydrogencarbonate solution and dried over sodium sulfate. After filtration and removal of solvent the residue was purified by chromatography to give 2.15 g (82%) of the title compound.

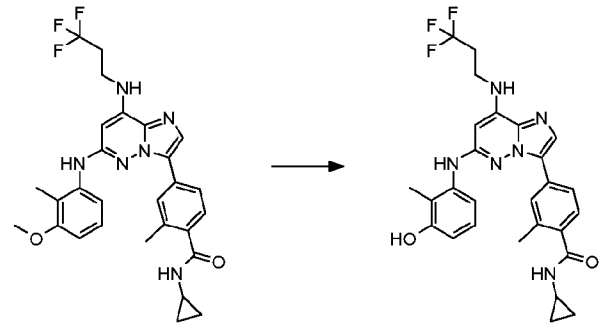
Intermediate example 453e
6-bromo-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine



5.00 g (18.06 mmol) 6,8-dibromoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 96d were transformed in analogy to intermediate example 1b using 3,3,3-trifluoropropan-1-amine to give after working up and purification 3.04 g (49%) of the title compound.

Example 454

N-cyclopropyl-4-{6-[(3-hydroxy-2-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

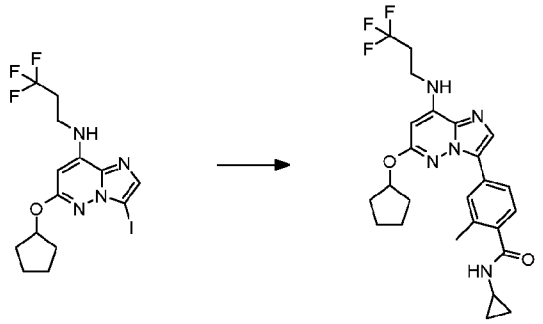


14.1 mg (26 µmol)
N-cyclopropyl-4-{6-[(3-methoxy-2-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide which was prepared according to example 426 were transformed in analogy to example 280 to give after working up and purification 4.7 mg (33%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.64 (2H), 2.04 (3H), 2.23 (3H), 2.60-2.82 (3H), 3.48 (2H), 5.94 (1H), 6.58 (1H), 6.95 (1H), 7.06-7.29 (3H), 7.79 (1H), 7.81 (1H), 7.93 (1H), 8.03 (1H), 8.22 (1H), 9.24 (1H) ppm.

Example 455

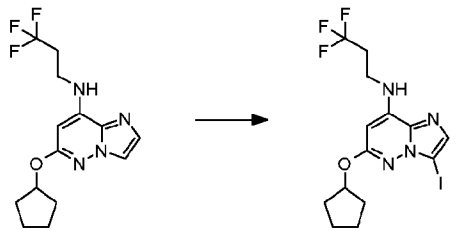
4-{6-(cyclopentyloxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



32 mg (73 µmol)
6-(cyclopentyloxy)-3-iodo-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 455a were transformed in analogy to intermediate example 1a using [4-(cyclopropylcarbamoyl)-3-methylphenyl]boronic acid to give after working up and purification 17.4 mg (47%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.65 (2H), 0.91 (2H), 1.50-1.73 (6H), 1.84 (2H), 2.40 (2H), 2.48 (3H), 2.94 (1H), 4.08 (2H), 4.82 (1H), 5.26 (1H), 5.93 (1H), 7.10 (1H), 7.13 (1H), 7.40 (1H), 7.45 (1H), 7.64 (1H) ppm.

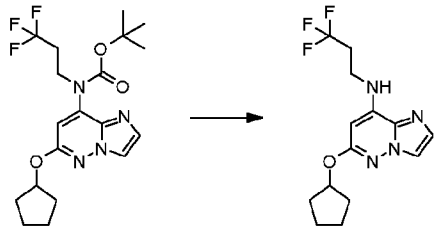
Intermediate example 455a
6-(cyclopentyloxy)-3-iodo-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine



42 mg (134 µmol) 6-(cyclopentyloxy)-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 455b were transformed in analogy to intermediate example 96c to give after working up and purification 33 mg (56%) of the title compound.

Intermediate example 455b

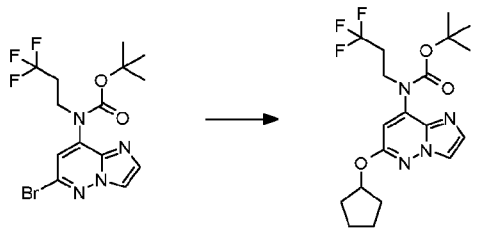
6-(cyclopentyloxy)-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine



361 mg (max. 784 µmol) tert-butyl [6-(cyclopentyloxy)imidazo[1,2-b]pyridazin-8-yl](3,3,3-trifluoropropyl)carbamate which was prepared according to intermediate example 455c were transformed in analogy to example 453 to give after working up and purification 43 mg (17%) of the title compound.

Intermediate example 455c

tert-butyl [6-(cyclopentyloxy)imidazo[1,2-b]pyridazin-8-yl](3,3,3-trifluoropropyl)carbamate

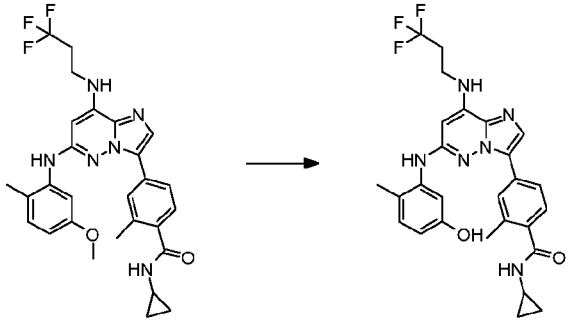


321 mg (784 µmol) tert-butyl (6-bromoimidazo[1,2-b]pyridazin-8-yl)(3,3,3-trifluoropropyl)carbamate which was prepared according to intermediate example 453d were transformed in analogy to intermediate example 51 using cyclopentanol to give after working up 361 mg of

the title compound that contains starting material and products in which the carbanate was cleaved.

Example 456

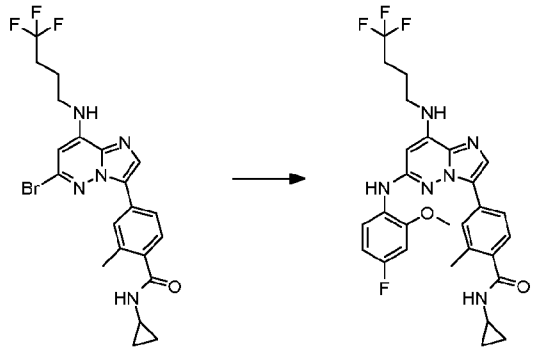
N-cyclopropyl-4-{6-[(5-hydroxy-2-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



10.5 mg (19 µmol)
N-cyclopropyl-4-{6-[(5-methoxy-2-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide which was prepared according to example 430 were transformed in analogy to example 280 to give after working up and purification 2.0 mg (18%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 0.48 (2H), 0.64 (2H), 2.21 (3H), 2.24 (3H), 2.60-2.83 (3H), 3.48 (2H), 5.94 (1H), 6.42 (1H), 6.95 (1H), 7.10 (1H), 7.16 (1H), 7.20 (1H), 7.79-7.90 (3H), 8.01 (1H), 8.21 (1H), 9.06 (1H) ppm.

Example 457

N-cyclopropyl-4-{6-[(4-fluoro-2-methoxyphenyl)amino]-8-[(4,4,4-trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



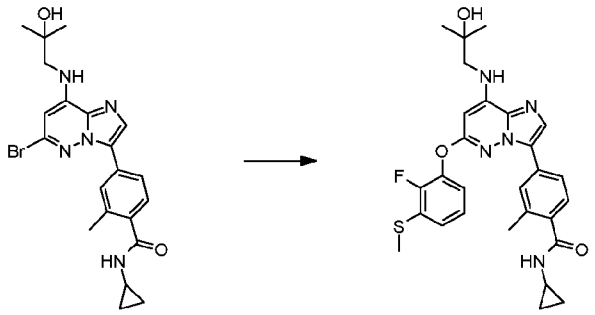
150 mg (302µmol)
4-{6-bromo-8-[(4,4,4-trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopro

pyl-2-methylbenzamide which was prepared according to intermediate example 447a were transformed in analogy to example 305 using 4-fluoro-2-methoxyaniline to give after working up and purification 43.1 mg (24%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.65 (2H), 0.91 (2H), 2.02 (2H), 2.28 (2H), 2.54 (3H), 2.94 (1H), 3.42 (2H), 3.92 (3H), 5.58 (1H), 5.66 (1H), 5.93 (1H), 6.63-6.71 (3H), 7.41 (1H), 7.63 (1H), 7.81 (1H), 8.01 (1H), 8.28 (1H) ppm.

Example 458

N-cyclopropyl-4-{6-[2-fluoro-3-(methylsulfanyl)phenoxy]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

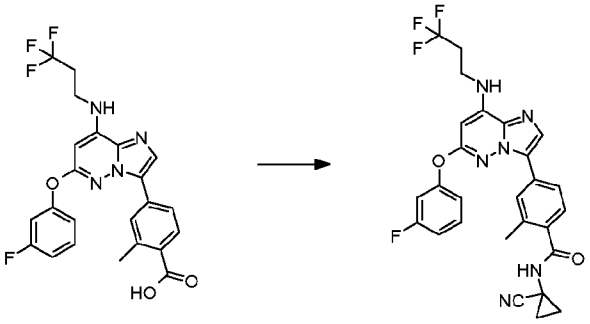


2.00 g (4.36 mmol) 4-{6-bromo-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 96a were transformed in analogy to example 51 using 2,3-difluorophenol to give after working up and purification 4.6 mg (0.2%) of the title compound and 933 mg (42%) of the title compound described in example 92.

^{1}H-NMR (DMSO-d6): δ= 0.50 (2H), 0.67 (2H), 1.21 (6H), 2.14 (3H), 2.52 (3H), 2.80 (1H), 3.33 (2H), 4.78 (1H), 6.27 (1H), 7.05 (1H), 7.17 (1H), 7.26 (1H), 7.28-7.34 (2H), 7.64 (1H), 7.70 (1H), 7.95 (1H), 8.23 (1H) ppm.

Example 459

4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methyl-N-(1-methylcyclopropyl)benzamide

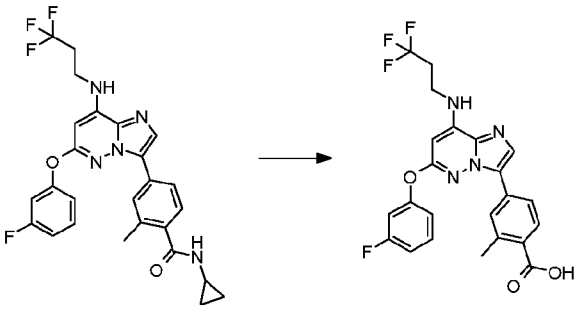


A mixture comprising 10.5 mg (22 µmol) 4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzoic acid which was prepared according to intermediate example 459a, 3.94 mg 1-cyanocyclopropanaminium chloride, 12.6 mg N-[(dimethylamino)(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy)methylene]-N-methylmethanaminium hexafluorophosphate, 4.06 mg N,N-dimethylpyridin-4-amine and 0.5 mL N,N-dimethylformamide was stirred at 23°C overnight. The solvent was removed and the residue purified by chromatography to give 4.5 mg (36%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 1.21 (2H), 1.50 (2H), 2.16 (3H), 2.68 (2H), 3.60 (2H), 6.14 (1H), 7.14 (2H), 7.25 (2H), 7.49 (1H), 7.67-7.76 (2H), 7.81 (1H), 7.97 (1H), 9.09 (1H) ppm.

Intermediate example 459a

4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzoic acid

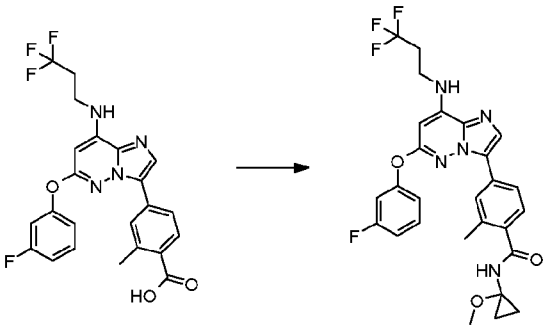


A mixture comprising 231.8 mg (451 µmol) N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide which was prepared according to example 80 and 7.73 mL hydrobromic acid was heated at 120°C for 10 hours. Water was added, the precipitate filtered off and purified by chromatography to give 74 mg (24%) of

title compound that contained about 30% 4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide.

Example 460

4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b] pyridazin-3-yl}-N-(1-methoxycyclopropyl)-2-methylbenzamide

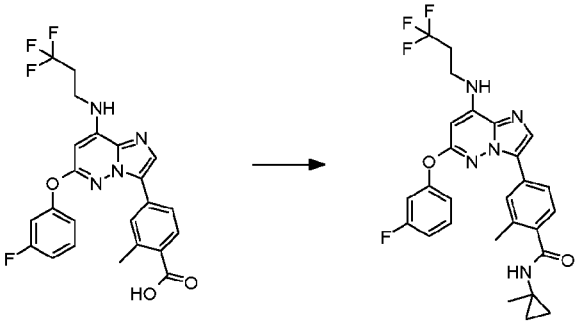


10.5 mg (22 µmol) 4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzoic acid which was prepared according to intermediate example 459a were transformed in analogy to example 459 using 1-methoxycyclopropanaminium chloride to give after working up and purification 10.7 mg (85%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 0.84 (2H), 0.97 (2H), 2.15 (3H), 2.68 (2H), 3.24 (3H), 3.60 (2H), 6.13 (1H), 7.09-7.16 (2H), 7.21 (1H), 7.25 (1H), 7.49 (1H), 7.67 (1H), 7.71 (1H), 7.78 (1H), 7.94 (1H), 9.04 (1H) ppm.

Example 461

4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b] pyridazin-3-yl}-2-methyl-N-(1-methylcyclopropyl)benzamide

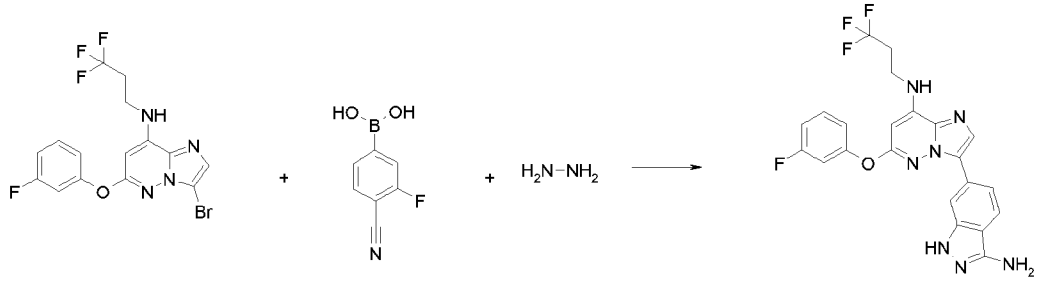


10.5 mg (22 µmol) 4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzoic acid which was prepared according to intermediate example 459a were transformed in analogy to example 459 using 1-methylcyclopropanaminium chloride to give after working up and purification 12.0 mg (98%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.74 (2H), 0.85 (2H), 1.51 (3H), 2.31 (3H), 2.58 (2H), 3.68 (2H), 5.89 (1H), 5.99 (1H), 6.07 (1H), 6.94-7.09 (3H), 7.23 (1H), 7.39 (1H), 7.61 (1H), 7.73 (2H) ppm.

Example 462

3-(3-amino-1H-indazol-6-yl)-6-(3-fluorophenoxy)-N-(3,3,3-trifluoropropyl) imidazo[1,2-b]pyridazin-8-amine

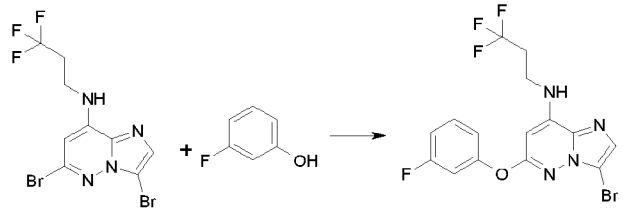


42 mg (100 µmol) 3-bromo-6-(3-fluorophenoxy)-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 462a were transformed in analogy to example 101 using (4-cyano-3-fluorophenyl)boronic acid to give 2-fluoro-4-[6-(3-fluoro-phenoxy)-8-(3,3,3-trifluoro-propylamino)-imidazo[1,2-b]pyridazin-3-yl]-benzonitrile. 62 µL (2 mmol) hydrazine hydrate were added and the mixture was heated at 80°C overnight. After working up and purification 5.1 mg (11%) of the title compound were obtained.

UPLC-MS: RT = 1.14, MWfound = 472.4, MWcalc = 471.4. 1H-NMR (300 MHz ,DMSO-d6), δ [ppm]= 2.65 (3H), 3.58 (3H), 5.32 (2H), 6.06 (1H), 7.00-7.21 (3H), 7.38 (1H), 7.49 (1H), 7.59 (1H), 7.73 (1H), 7.83 (1H), 7.91 (1H), 11.31 (1H)

Intermediate example 462a

3-bromo-6-(3-fluorophenoxy)-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-am



ine

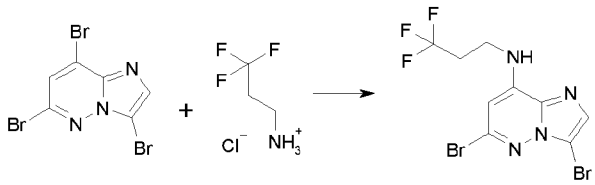
448.9 mg (1.16 mmol)

3,6-dibromo-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 462b were transformed in analogy to example 51 using 3-fluorophenol to give after working up and purification 105.7 mg (22%) of the title compound.

^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 2.55-2.73 (2H), 3.55 (2H), 6.06 (1H), 7.00-7.09 (2H), 7.11-7.22 (1H), 7.33-7.49 (1H), 7.56 (1H), 7.82 (1H)

Intermediate example 462b

3,6-dibromo-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine



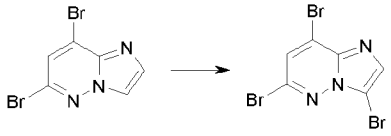
3,6-dibromo-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine

3.00 g (8.43 mmol) 3,6,8-tribromoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 462c were transformed in analogy to intermediate example 1b using 3,3,3-trifluoropropan-1-aminium chloride to give after working up and purification 2.97 g (91%) of the title compound.

^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 2.52-2.73 (2H), 3.56 (2H), 6.45 (1H), 7.61 (1H), 8.01 (1H)

Intermediate example 462c

3,6,8-tribromoimidazo[1,2-b]pyridazine

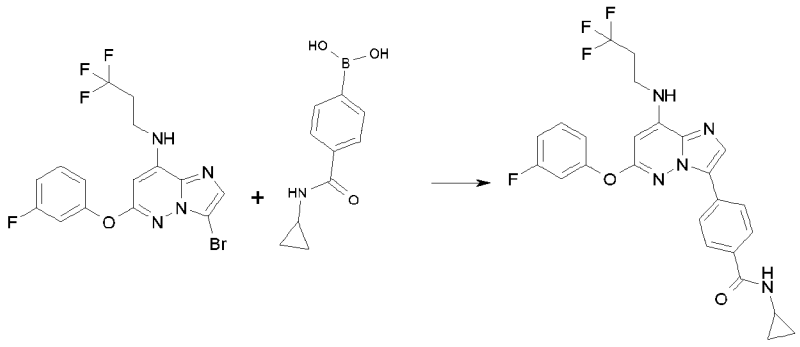


To a stirred suspension of 100.00 g (361.1 mmol) 6,8-dibromoimidazo[1,2-b]pyridazine, which was prepared according to intermediate example 96d, in 1.6 L acetic acid were added 69.2 g (433.3 mmol) bromine at rt and the mixture was stirred for 1 h. The precipitate was filtered, washed with water and dissolved in 10 L DCM. The organic üphase was washed with saturated sodium hydrogen carbonate solution, dried over sodium sulfate, filtered and evaporated to give 81.99 g (64%) of the title compound.

^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 7.96 (1H), 8.04 (1H).

Example 463

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo [1,2-b]pyridazin-3-yl}benzamide

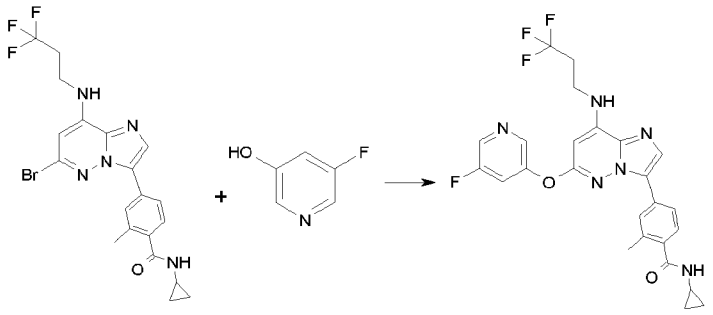


42 mg (100 µmol) 3-bromo-6-(3-fluorophenoxy)-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine which was prepared according to intermediate example 462a were transformed in analogy to example 101 using [4-(cyclopropylcarbamoyl)phenyl]boronic acid to give after working up and purification 2.9 mg (5%) of the title compound.

UPLC-MS: RT = 1.31, MW_{found} = 500.5, MW_{calc} = 499.5. ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.52 (2H), 0.66 (2H), 2.67 (2H), 2.79 (1H), 3.59 (2H), 6.14 (1H), 7.08-7.17 (2H), 7.24 (1H), 7.33-7.60 (2H), 7.68 (1H), 7.77 (1H), 7.95 (1H), 8.01 (1H), 8.40 (1H).

Example 464

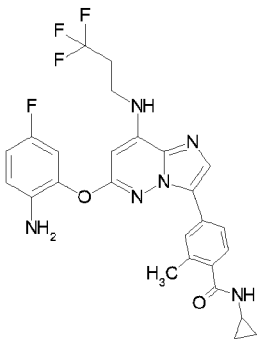
N-cyclopropyl-4-{6-[(5-fluoropyridin-3-yl)oxy]-8-[(3,3,3-trifluoropropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

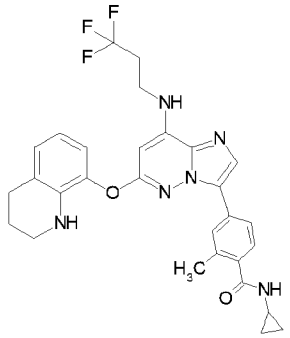
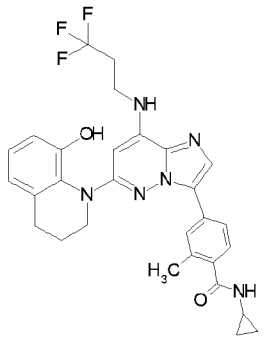


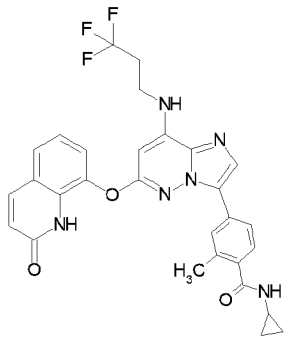
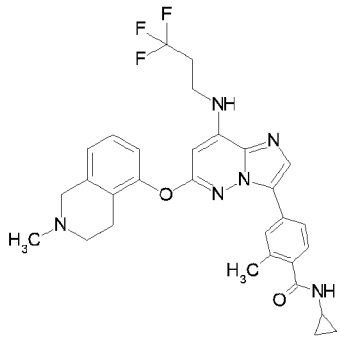
48 mg (100 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamidewhich was prepared according to intermediate example 247a were transformed in analogy to example 51 using 5-fluoropyridin-3-ol to give after working up and purification 8.1 mg (16%) of the title compound.

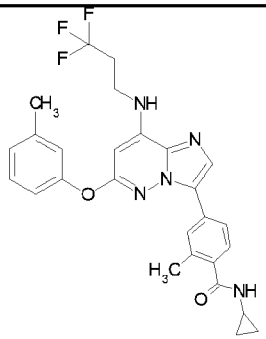
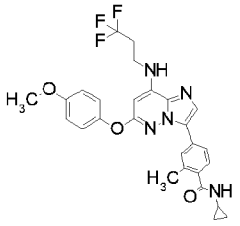
UPLC-MS: RT = 1.19, MW_{found} = 515.5, MW_{calc} = 514.5. ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.41-0.54 (2H), 0.58-0.71 (2H), 2.14 (3H), 2.59-2.85 (3H), 3.61 (2H), 6.21 (1H), 7.17 (1H), 7.61 (1H), 7.70 (1H), 7.81 (1H), 7.93 (1H), 7.95-8.06 (1H), 8.22 (1H), 8.46-8.63 (2H)

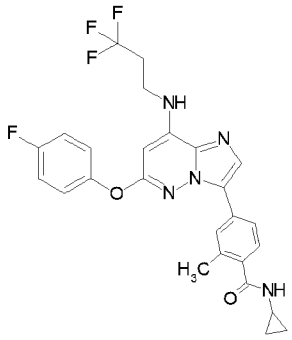
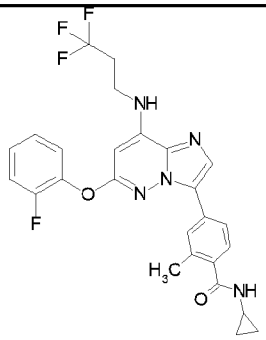
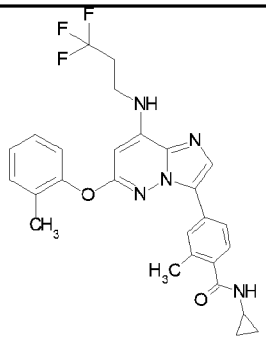
The following compound examples were prepared analogously to the procedure described for example 51 using the appropriate phenols or anilines [LC-MS data such as retention time (RT in min) or observed mass peak were collected using LC-MS Method A unless explicitly stated]:

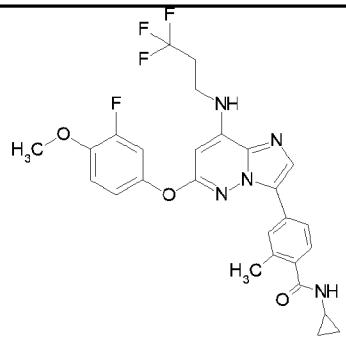
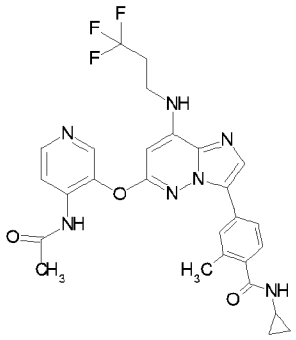
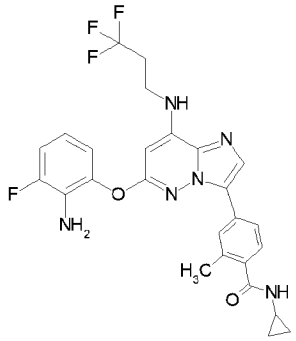
Example	Structure	Name	Analytical Data
465		4-{6-(2-amino-5-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide	RT = 1.25 MW_{found} = 529.5 MW_{calc} = 528.5 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.43-0.51 (2H), 0.58-0.69 (2H), 2.15 (3H), 2.60-2.82 (3H), 3.59 (2H), 4.83 (2H), 6.10 (1H), 6.74-6.82 (1H), 6.85 (1H), 7.03

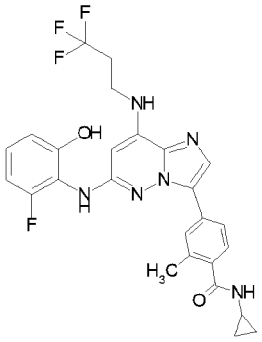
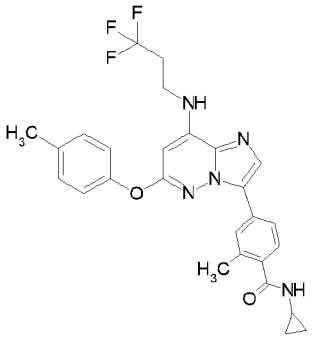
Example	Structure	Name	Analytical Data
			(1H), 7.15 (1H), 7.61-7.70 (2H), 7.84 (1H), 7.92 (1H), 8.22 (1H)
466		N-cyclopropyl-2-methyl-4-{6-(1,2,3,4-tetrahydroquinolin-8-yloxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.36 MW_{found} = 551.6 MW_{calc} = 550.6 ^{1}H-NMR (600 MHz ,DMSO-d_6), δ [ppm]= 0.48-0.54 (2H), 0.63-0.70 (2H), 1.76-1.82 (2H), 2.19 (3H), 2.66-2.78 (4H), 2.80 (1H), 3.12-3.20 (2H), 3.61 (2H), 5.24 (1H), 6.08 (1H), 6.50 (1H), 6.82 (1H), 6.90 (1H), 7.18 (1H), 7.60 (1H), 7.72-7.77 (1H), 7.87 (1H), 7.95 (1H), 8.23 (1H)
467		N-cyclopropyl-4-{6-(8-hydroxy-3,4-dihydroquinolin-1(2H)-yl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.19 MW_{found} = 551.6 MW_{calc} = 550.6 ^{1}H-NMR (600 MHz ,DMSO-d_6), δ [ppm]= 0.50-0.56 (2H), 0.64-0.71 (2H), 1.88 (2H), 2.31 (3H), 2.62 (2H), 2.69 (2H), 2.83 (1H), 3.44 (2H), 3.84 (2H), 5.72 (1H), 6.66

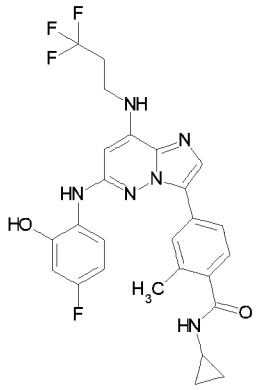
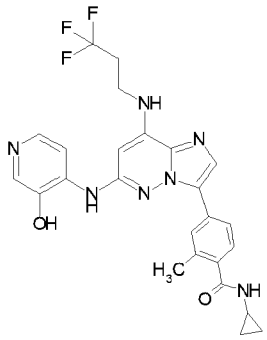
Example	Structure	Name	Analytical Data
			(1H), 6.74 (1H), 6.90-6.94 (1H), 7.11 (1H), 7.27 (1H), 7.84 (1H), 7.92 (1H), 7.96 (1H), 8.25 (1H), 9.29 (1H) Isomer!
468		N-cyclopropyl-2-methyl-4-{6-[(2-oxo-1,2-dihydroquinolin-8-yl)oxy]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.01 MW_{found} = 563.5 MW_{calc} = 562.5 ^{1}H-NMR (600 MHz ,DMSO-d_6), δ [ppm]= 0.47-0.51 (2H), 0.64-0.69 (2H), 2.06 (3H), 2.71-2.82 (3H), 3.66 (2H), 6.25 (1H), 6.55 (1H), 7.08 (1H), 7.26 (1H), 7.54 (1H), 7.57 (1H), 7.62-7.65 (2H), 7.66-7.71 (1H), 7.93 (1H), 8.02 (1H), 8.20 (1H)
469		N-cyclopropyl-2-methyl-4-{6-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)oxy]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 0.95 MW_{found} = 565.6 MW_{calc} = 564.6 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.42-0.50 (2H), 0.58-0.68 (2H), 2.09 (3H), 2.28 (3H), 2.53 (2H), 2.60-2.81 (5H), 3.51 (2H), 3.59 (2H), 6.11 (1H), 6.97-7.06

Example	Structure	Name	Analytical Data
			(2H), 7.12 (1H), 7.16-7.24 (1H), 7.58-7.67 (2H), 7.71 (1H), 7.91 (1H), 8.18 (1H)
470		N-cyclopropyl-2-methyl-4-{6-(3-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.42 MW_{found} = 510.5 MW_{calc} = 509.5
471		N-cyclopropyl-4-{6-(4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.34 MW_{found} = 526.5 MW_{calc} = 525.5 ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 0.43-0.50 (2H), 0.60-0.68 (2H), 2.11 (3H), 2.60-2.73 (2H), 2.77 (1H), 3.59 (2H), 3.75 (3H), 6.07 (1H), 6.99 (2H), 7.13-7.22 (3H), 7.58-7.67 (2H), 7.77 (1H), 7.91 (1H), 8.19 (1H)

Example	Structure	Name	Analytical Data
472		N-cyclopropyl-4-{6-(4-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.36 MW_{found} = 514.5 MW_{calc} = 513.5 ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 0.47 (2H), 0.63 (2H), 2.13 (3H), 2.60-2.73 (2H), 2.73-2.82 (1H), 3.60 (2H), 6.11 (1H), 7.16 (1H), 7.23-7.36 (4H), 7.60-7.70 (2H), 7.72 (1H), 7.92 (1H), 8.20 (1H)
473		N-cyclopropyl-4-{6-(2-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.36 MW_{found} = 514.5 MW_{calc} = 513.5
474		N-cyclopropyl-2-methyl-4-{6-(2-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.40 MW_{found} = 510.5 MW_{calc} = 509.5

Example	Structure	Name	Analytical Data
475		N-cyclopropyl-4-{6-(3-fluoro-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.35 MW_{found} = 544.5 MW_{calc} = 543.5
476		4-(6-{[4-(acetylamino)pyridin-3-yl]oxy}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide	RT = 0.89 MW_{found} = 554.5 MW_{calc} = 553.5 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.44-0.55 (2H), 0.60-0.69 (2H), 2.20-2.27 (3H), 2.36 (3H), 2.65-2.85 (3H), 3.69 (2H), 6.76 (1H), 7.38 (1H), 7.84-7.93 (2H), 7.95-8.04 (2H), 8.09 (1H), 8.23-8.34 (3H), 8.36 (1H)
477		4-{6-(2-amino-3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide	RT = 1.28 MW_{found} = 529.5 MW_{calc} = 528.5 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.42-0.53 (2H), 0.58-0.69 (2H), 2.13 (3H), 2.59-2.85 (3H), 3.50-3.66 (2H), 4.98 (2H), 6.11 (1H), 6.53-6.63 (1H), 6.93 (1H), 6.96-7.03 (1H),

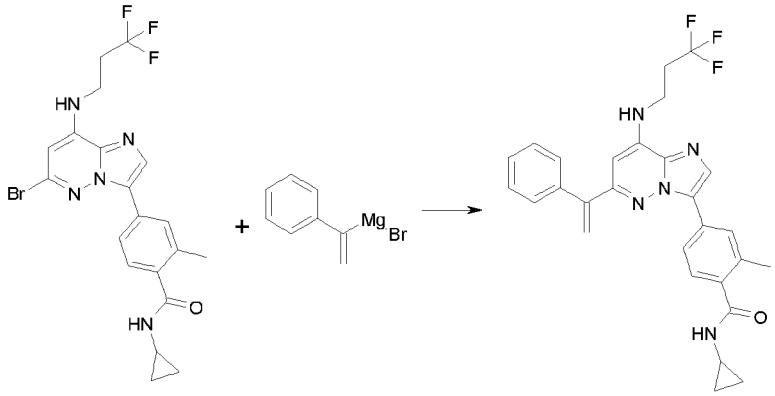
Example	Structure	Name	Analytical Data
			7.14 (1H), 7.60-7.68 (2H), 7.80 (1H), 7.89-7.95 (1H), 8.22 (1H)
478		N-cyclopropyl-4-{6-[(2-fluoro-6-hydroxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.10 MW_{found} = 529.5 MW_{calc} = 528.5 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.42-0.52 (2H), 0.59-0.69 (2H), 2.17 (3H), 2.58-2.82 (3H), 3.49 (2H), 5.89 (1H), 6.67-6.77 (2H), 6.99-7.10 (1H), 7.10-7.19 (2H), 7.68-7.75 (1H), 7.77 (1H), 7.92 (1H), 7.87 (1H), 8.21 (1H), 9.78 (1H)Isomer
479		N-cyclopropyl-2-methyl-4-{6-(4-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.41 MW_{found} = 510.5 MW_{calc} = 509.5 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.42-0.50 (2H), 0.59-0.67 (2H), 2.09 (3H), 2.31 (3H), 2.59-2.82 (3H), 3.58 (2H), 6.09 (1H), 7.15 (3H), 7.25 (2H), 7.60-7.68 (2H), 7.75

Example	Structure	Name	Analytical Data
			(1H), 7.92 (1H), 8.21 (1H)
480		N-cyclopropyl-4-{6-[(4-fluoro-2-hydroxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.25 MW_{found} = 529.5 MW_{calc} = 528.5 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.45-0.55 (2H), 0.60-0.71 (2H), 2.33 (3H), 2.67 (2H), 2.80 (1H), 3.43-3.53 (2H), 6.21 (1H), 6.53-6.63 (1H), 6.67 (1H), 7.18 (1H), 7.30 (1H), 7.76 (1H), 7.78-7.86 (1H), 7.90 (1H), 7.98-8.14 (3H), 8.28 (1H), 10.28 (1H)
481		N-cyclopropyl-4-{6-[(3-hydroxypyridin-4-yl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 0.84 MW_{found} = 512.5 MW_{calc} = 511.5 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.47-0.56 (2H), 0.62-0.71 (2H), 2.39 (3H), 2.68 (2H), 2.82 (1H), 3.45-3.56 (2H), 6.46 (1H), 7.32-7.42 (2H), 7.77-7.85 (2H), 7.88 (1H), 8.00 (1H), 8.06 (1H), 8.14 (2H), 8.29 (2H)

Example	Structure	Name	Analytical Data

Example 482

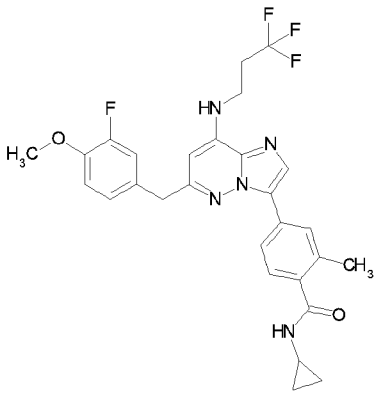
N-cyclopropyl-2-methyl-4-{6-(1-phenylethenyl)-8-[(3,3,3-trifluoropropyl)amino] imidazo[1,2-b]pyridazin-3-yl}benzamide

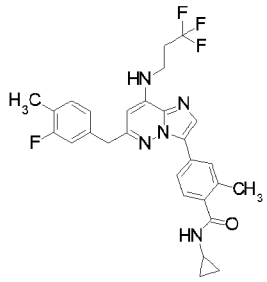


To a stirred solution of 24 mg (50 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 247a in 1 mL THF is dropwise added 1.0 mL (0.5 mmol) of a 0.5 M solution of bromo(1-phenylethenyl)magnesium in THF at rt. After stirring overnight at rt, the mixture is heated at 50°C and stirred for 3 more days to give after working up and purification 1.7 mg (5%) of the title compound.

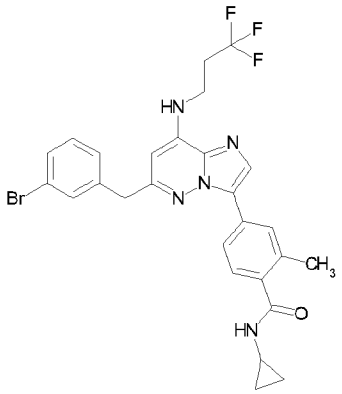
UPLC-MS: RT = 1.36, MW_{found} = 506.5, MW_{calc} = 505.5. ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 0.42-0.50 (2H), 0.59-0.66 (2H), 2.15 (3H), 2.61-2.71 (2H), 2.77 (1H), 3.60 (2H), 5.74 (1H), 5.99 (1H), 6.36 (1H), 7.16-7.20 (2H), 7.34-7.45 (3H), 7.55 (2H), 7.79-7.84 (1H), 7.86 (1H), 8.01 (1H), 8.22 (1H)

The following compound examples were prepared analogously to the procedure described for example 482 using the appropriate Grignard reagents [LC-MS data such as retention time (RT in min) or observed mass peak were collected using LC-MS Method A unless explicitly stated]:

Example	Structure	Name	Analytical Data
483		N-cyclopropyl-4-{6-(3-fluoro-4-methoxybenzyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.33 MW_{found} = 542.5 MW_{calc} = 541.5 ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 0.47-0.53 (2H), 0.62-0.69 (2H), 2.32 (3H), 2.64 (2H), 2.77-2.84 (1H), 3.53 (2H), 3.76 (3H), 3.96 (2H), 6.20 (1H), 7.04-7.12 (2H), 7.17-7.23 (1H), 7.30 (1H), 7.47 (1H), 7.93-7.98 (3H), 8.27 (1H)

Example	Structure	Name	Analytical Data
484		N-cyclopropyl-4-{6-(3-fluoro-4-methylbenzyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.25 MW_{found} = 526.5 MW_{calc} = 525.5 ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 0.47-0.53 (2H), 0.62-0.68 (2H), 2.14-2.17 (3H), 2.31 (3H), 2.59-2.71 (2H), 2.80 (1H), 3.53 (2H), 3.99 (2H), 6.21 (1H), 7.06 (1H), 7.13 (1H), 7.16-7.22 (1H), 7.30 (1H), 7.47 (1H), 7.92-7.99

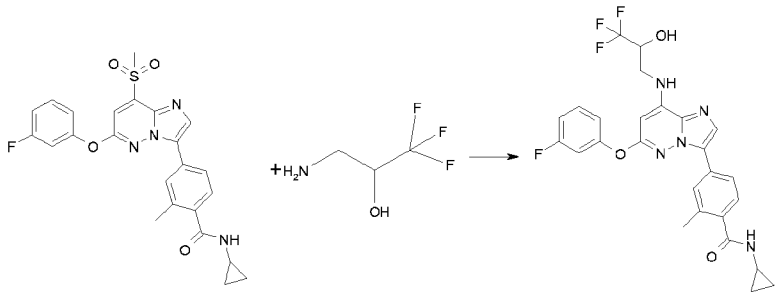
			(3H), 8.27 (1H)

Example	Structure	Name	Analytical Data
485		4-{6-(3-bromobenzyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide	RT = 1.44 MW_{found} = 573.4 MW_{calc} = 572.4 ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 0.47-0.53 (2H), 0.62-0.68 (2H), 2.33 (3H), 2.58-2.70 (2H), 2.80 (1H), 3.54 (2H), 4.03 (2H), 6.24 (1H), 7.27 (1H), 7.31 (1H), 7.36 (1H), 7.39-7.44 (1H), 7.47-7.53

			(1H), 7.57-7.61 (1H), 7.95 (3H), 8.27 (1H)

Example 486

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoro-2-hydroxypropyl) amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

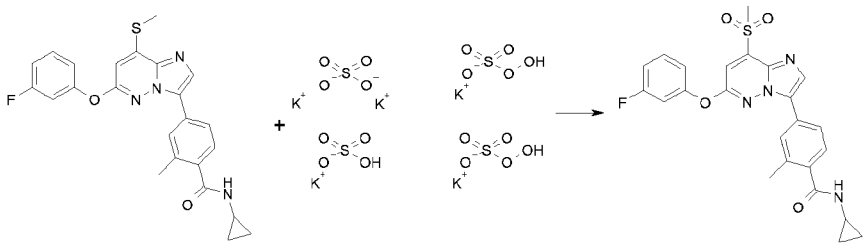


To a stirred solution of 96 mg (200 µmol) N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-(methylsulfonyl)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide which was prepared according to intermediate example 486a in 2 mL NMP is added 77.5 mg (0.6 mmol) 3-amino-1,1,1-trifluoropropan-2-ol and 77.5 mg (0.6 mmol) DIPEA and the mixture is heated at 160°C for 30 min in a microwave oven. After working up and purification 10.5 mg (9%) of the title compound are obtained.

UPLC-MS: RT = 1.23, MW_{found} = 530.5, MW_{calc} = 529.5)

Intermediate example 486a

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-(methylsulfonyl)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide

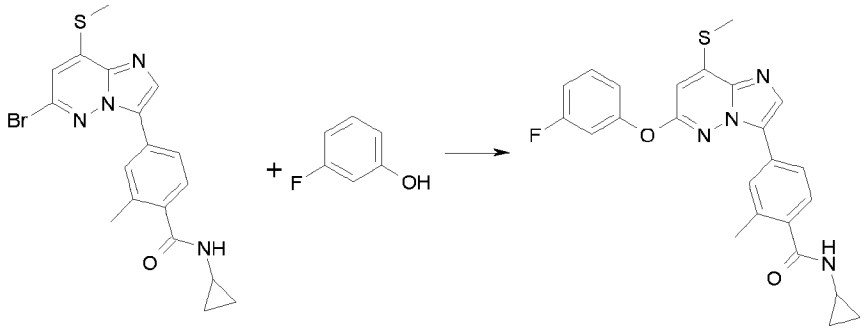


To a stirred solution of 4.96 g (11.06 mmol) N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-(methylsulfanyl)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide which was prepared according to intermediate example 486b in DMF (250 mL) were added 20.4 g (33.18 mmol) oxone in one portion at rt. After reaction for 72 h, further 30 g (55 mmol) oxone are added and the mixture is heated at 70°C for one hour. Extraction with ethyl acetate / water, filtration of the organic phase through a Whatman filter and evaporation of the organic phase yielded the crude product (4.96 g, 93%) which was used without further purification.

^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 0.44-0.50 (2H), 0.64 (2H), 2.73-2.82 (1H), 3.65 (3H), 7.19-7.24 (2H), 7.24-7.29 (1H), 7.39-7.45 (1H), 7.53-7.61 (2H), 7.68 (1H), 7.72 (1H), 8.28 (1H), 8.37 (1H)

Intermediate example 486b

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-(methylsulfanyl)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide



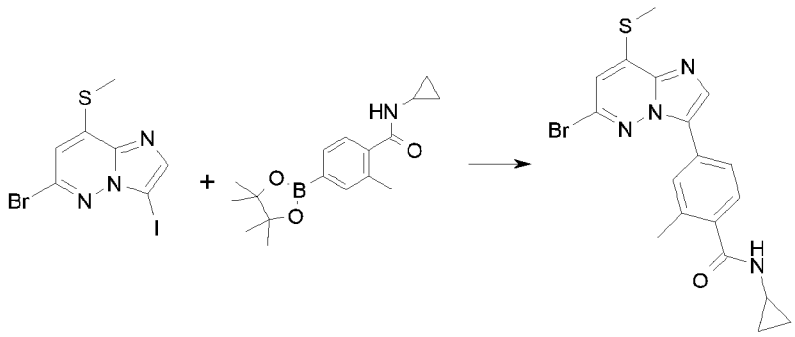
8 g (19.2 mmol) 4-[6-bromo-8-(methylsulfanyl)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methyl benzamide which was prepared according to intermediate example 486c were transformed in analogy to example 51 using 3-fluorophenol to give after working up and purification 4.96 g (46%) of the title compound.

^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 0.44-0.50 (2H), 0.60-0.67 (2H), 2.13 (3H), 2.65 (3H), 2.76 (1H), 6.99 (1H), 7.15-7.25 (3H), 7.37 (1H), 7.49-7.56 (1H), 7.65 (1H), 7.73 (1H), 8.06 (1H), 8.24 (1H)

Intermediate example 486c

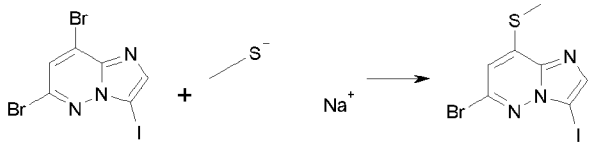
4-[6-bromo-8-(methylsulfanyl)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-

2-methylbenzamide



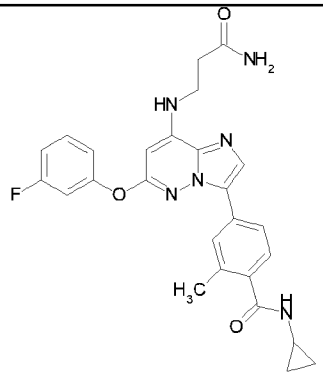
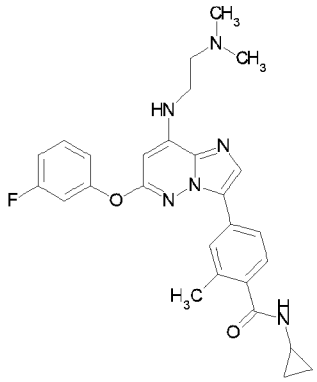
42.1 g (113.9 mmol) 6-bromo-3-iodo-8-(methylsulfanyl)imidazo[1,2-b]pyridazine which was prepared according to intermediate example 486d were transformed in analogy to example 1a using N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide to give after working up and purification 17.78 g (34%) of the title compound.
^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.47-0.53 (2H), 0.62-0.70 (2H), 2.36 (4H), 2.64 (3H), 2.81 (1H), 7.19 (1H), 7.40 (1H), 7.86 (1H), 7.90 (1H), 8.12 (1H), 8.31 (1H)

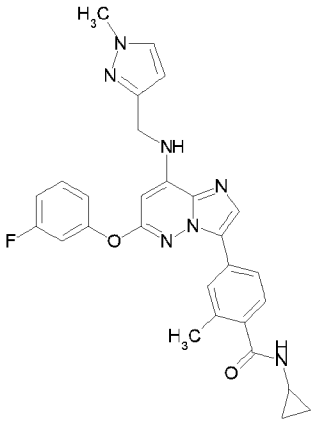
Intermediate example 486d
6-bromo-3-iodo-8-(methylsulfanyl)imidazo[1,2-b]pyridazine

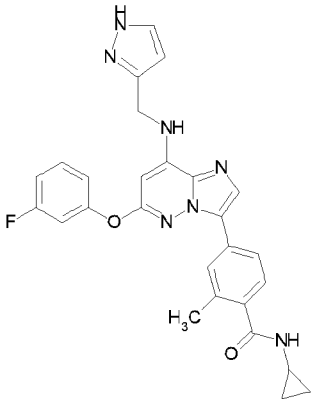


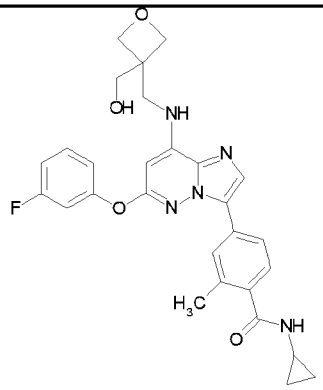
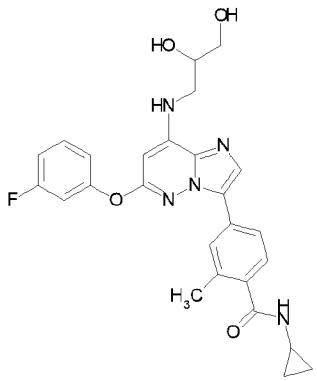
To a stirred solution of 51.2 g (146.8 mmol) 6,8-dibromo-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 96c in NMP (450 mL) are added 12.35 g (176.2 mmol) sodium methanethiolate in one portion at 0° C. After reaction for 15 min, 700 mL water are added and the precipitate is filtered off and dried. Trituration with ether, filtration and drying in vaccuo . yields 44.3 g (65%) of the title compound
^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 2.62 (4H), 7.15 (1H), 7.75 (1H)

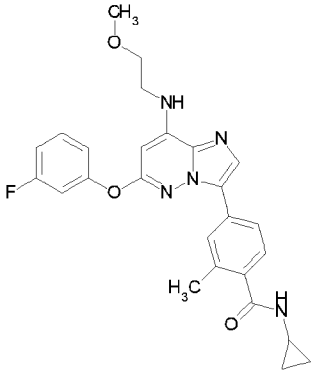
The following compound examples were prepared analogously to the procedure described for example 486 using the appropriate amine [LC-MS data such as retention time (RT in min) or observed mass peak were collected using LC-MS Method A unless explicitly stated]:

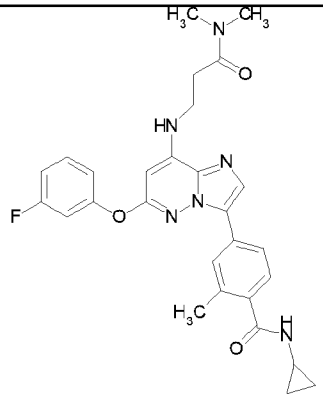
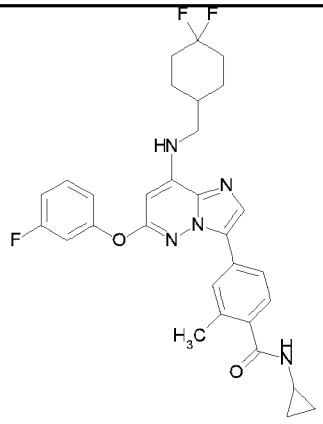
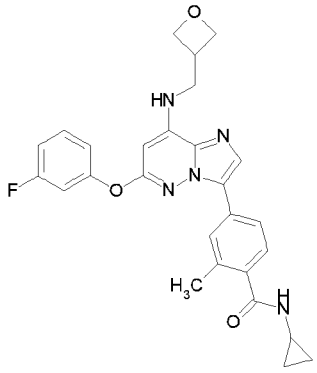
Example	Structure	Name	Analytical Data
549		4-{8-[(3-amino-3-oxopropyl)amino]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide	RT = 1.01 MW_{found} = 489.5 MW_{calc} = 488.5
487		N-cyclopropyl-4-[8-{[2-(dimethylamino)ethyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 0.88 MW_{found} = 489.6 MW_{calc} = 488.6 ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 0.46 (2H), 0.63 (2H), 2.14 (3H), 2.19 (6H), 2.52 (2H), 2.76 (1H), 3.39 (2H), 6.06 (1H), 7.09-7.19 (4H), 7.24 (2H), 7.48 (1H), 7.66 (1H), 7.76 (1H), 7.90 (1H), 8.21

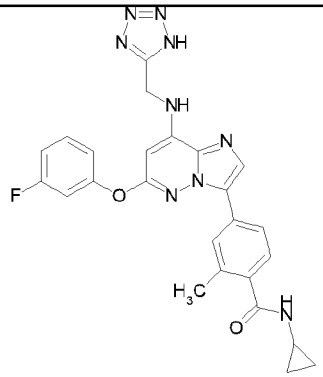
Example	Structure	Name	Analytical Data
			(1H)
488		N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[(1-methyl-1H-pyrazol-3-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 1.17 MW_{found} = 512.6 MW_{calc} = 511.6 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.42-0.51 (2H), 0.58-0.68 (2H), 2.14 (3H), 2.76 (1H), 3.76 (3H), 4.45 (2H), 6.00 (1H), 6.15 (1H), 7.06-7.26 (5H), 7.46 (1H), 7.58 (1H), 7.66 (1H), 7.75 (1H), 7.92 (1H), 7.93-8.01 (1H), 8.21 (1H)

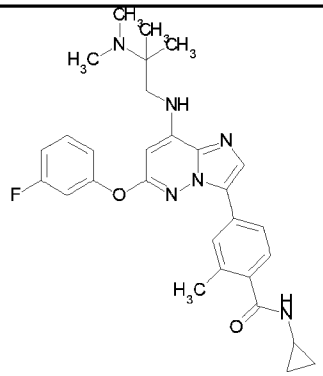
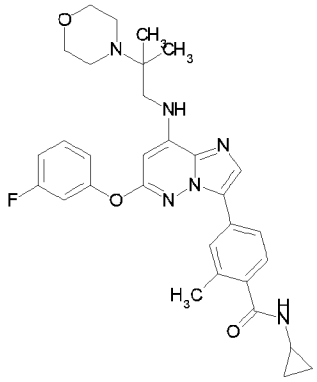
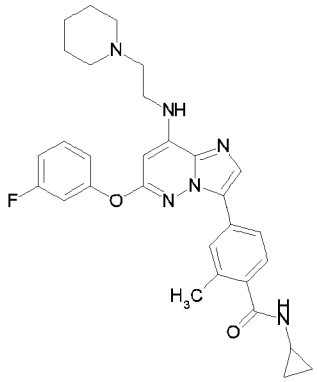
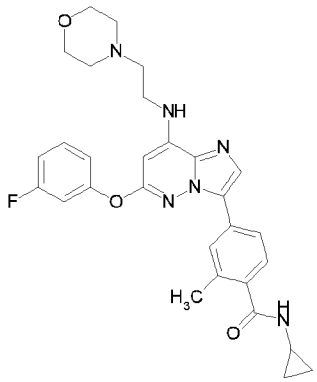
Example	Structure	Name	Analytical Data
489		N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(1H-pyrazol-3-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.14 MW_{found} = 498.5 MW_{calc} = 497.5 ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 0.43-0.50 (2H), 0.59-0.66 (2H), 2.13 (3H), 2.76 (1H), 4.51 (2H), 6.06 (1H), 6.19 (1H), 7.07-7.19 (4H), 7.23 (1H), 7.42-7.51 (2H), 7.65 (2H), 7.75 (1H), 7.87-7.95 (1H), 7.95-8.05 (1H), 8.21 (2H)

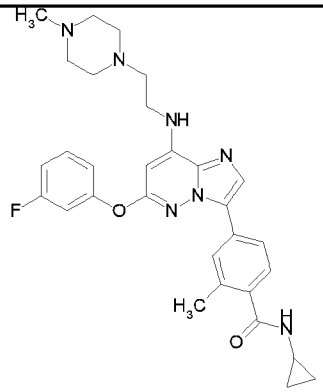
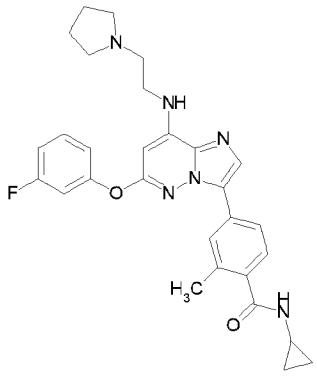
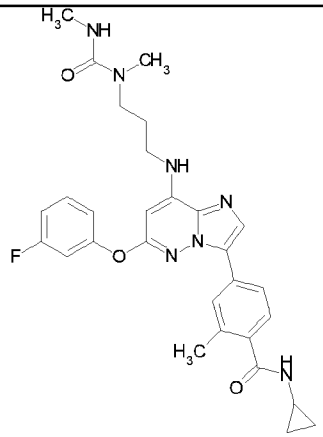
Example	Structure	Name	Analytical Data
490		N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-({[3-(hydroxymethyl)oxetan-3-yl]methyl}amino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 1.08 MW_{found} = 518.6 MW_{calc} = 517.6
491		N-cyclopropyl-4-{8-[(2,3-dihydroxypropyl)amino]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.04 MW_{found} = 492.5 MW_{calc} = 491.5 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.39-0.51 (2H), 0.58-0.69 (2H), 2.14 (3H), 2.76 (1H), 3.39 (3H), 3.73 (1H), 4.70 (1H), 4.98 (1H), 6.08 (1H), 7.02-7.20 (3H), 7.20-7.37 (2H), 7.41-7.55

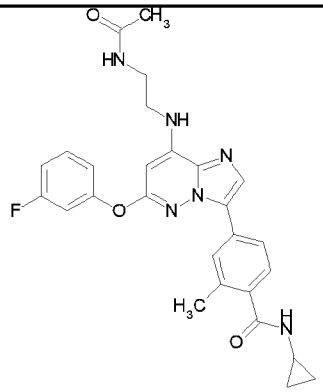
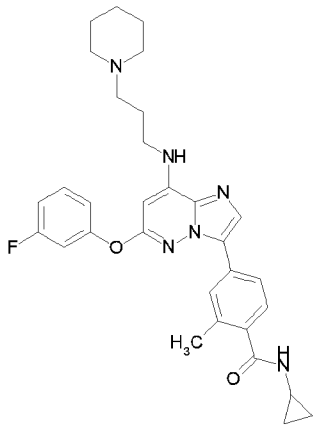
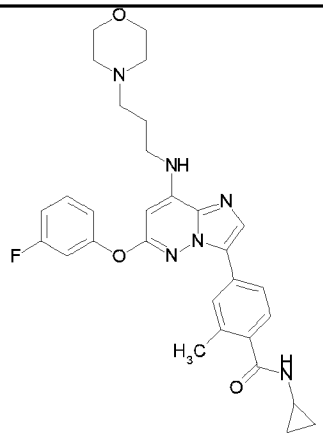
Example	Structure	Name	Analytical Data
			(1H), 7.66 (1H), 7.76 (1H), 7.91 (1H), 8.21 (1H)
492		N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.26 MW_{found} = 476.5 MW_{calc} = 475.5 ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 0.42-0.50 (2H), 0.60-0.67 (2H), 2.14 (3H), 2.77 (1H), 3.26 (3H), 3.51 (2H), 3.53-3.58 (2H), 6.10 (1H), 7.08-7.19 (3H), 7.25 (1H), 7.43-7.52 (2H), 7.66 (1H), 7.76

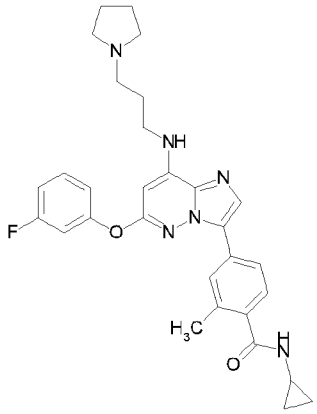
Example	Structure	Name	Analytical Data
			(1H), 7.92 (1H), 8.21 (1H)
493		N-cyclopropyl-4-[8-{[3-(dimethylamino)-3-oxopropyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 1.26 MW_{found} = 517.6 MW_{calc} = 516.6
494		N-cyclopropyl-4-[8-{[(4,4-difluorocyclohexyl)methyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 1.45 MW_{found} = 550.6 MW_{calc} = 549.6
495		N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(oxetan-3-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.17 MW_{found} = 488.5 MW_{calc} = 487.5 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.40-0.51 (2H), 0.56-0.69

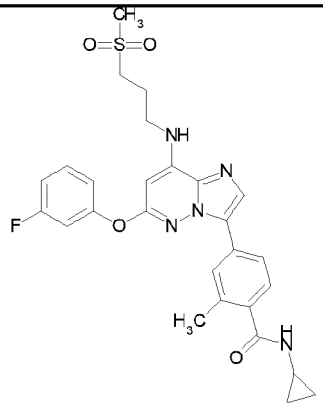
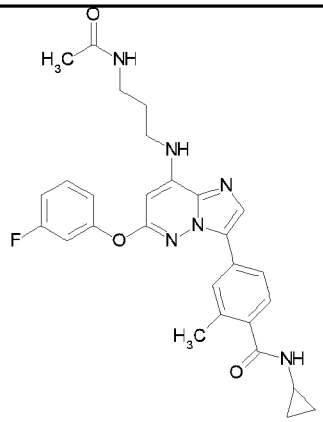
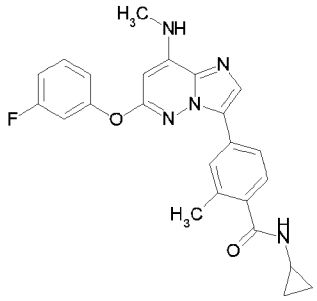
Example	Structure	Name	Analytical Data
			(2H), 0.75-0.89 (1H), 2.13 (3H), 2.76 (1H), 3.61 (2H), 4.34 (2H), 4.63 (2H), 6.13 (1H), 7.05-7.20 (3H), 7.25 (1H), 7.41-7.54 (1H), 7.65 (1H), 7.75 (1H), 7.85-7.96 (2H), 8.21 (1H)
496		N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(1H-tetrazol-5-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.03 MW_{found} = 500.5 MW_{calc} = 499.5

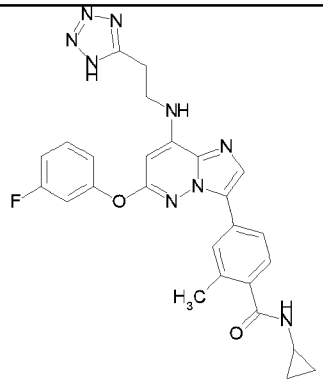
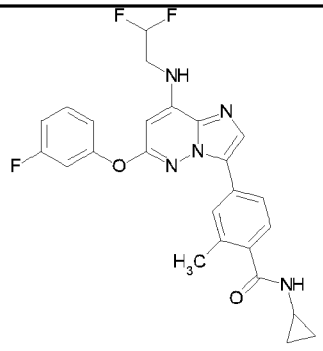
Example	Structure	Name	Analytical Data
497		N-cyclopropyl-4-[8-{[2-(dimethylamino)-2-methylpropyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 0.97 MW_{found} = 517.6 MW_{calc} = 516.6
498		N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[2-methyl-2-(morpholin-4-yl)propyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 0.99 MW_{found} = 559.6 MW_{calc} = 558.6
499		N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[2-(piperidin-1-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 0.98 MW_{found} = 529.6 MW_{calc} = 528.6
500		N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 0.93 MW_{found} = 531.6 MW_{calc} = 530.6

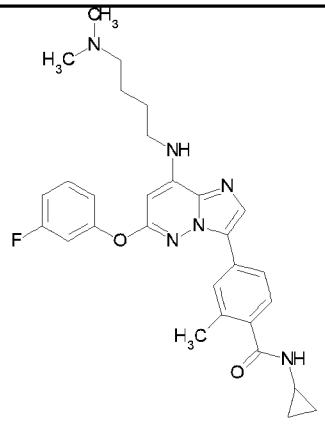
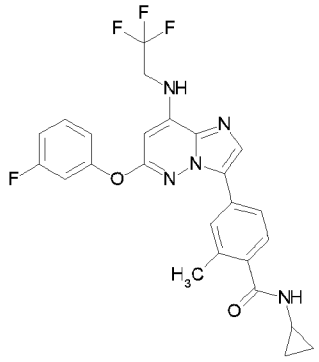
Example	Structure	Name	Analytical Data
501		N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[2-(4-methylpiperazin-1-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 0.96 MW_{found} = 544.6 MW_{calc} = 543.6
502		N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[2-(pyrrolidin-1-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 0.96 MW_{found} = 515.6 MW_{calc} = 514.6
503		N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-({3-[methyl(methylcarbamoyl)amino]propyl}amino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 1.17 MW_{found} = 546.6 MW_{calc} = 545.6

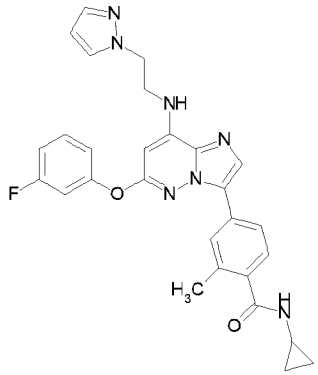
Example	Structure	Name	Analytical Data
504		4-[8-{[2-(acetylamino)ethyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide	RT = 1.10 MW_{found} = 503.5 MW_{calc} = 502.5
505		N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[3-(piperidin-1-yl)propyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 1.01 MW_{found} = 543.6 MW_{calc} = 542.6
506		N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[3-(morpholin-4-yl)propyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 0.96 MW_{found} = 545.6 MW_{calc} = 544.6

Example	Structure	Name	Analytical Data
507		N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[3-(pyrrolidin-1-yl)propyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 0.98 MW_{found} = 529.6 MW_{calc} = 528.6 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.43-0.50 (2H), 0.58-0.67 (2H), 1.68 (4H), 1.78 (2H), 2.14 (3H), 2.48-2.54 (2H), 2.76 (1H), 3.36 (6H), 6.04 (1H), 7.06-7.19 (4H), 7.23 (1H), 7.42-7.52 (1H), 7.62-7.70 (1H), 7.76 (1H), 7.82-7.92 (2H), 8.17-8.24

Example	Structure	Name	Analytical Data
			(1H)
508		N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[3-(methylsulfonyl)propyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 1.15 MW_{found} = 538.6 MW_{calc} = 537.6
509		4-[8-{[3-(acetylamino)propyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide	RT = 1.12 MW_{found} = 517.6 MW_{calc} = 516.6
510		N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-(methylamino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 1.26 MW_{found} = 432.5 MW_{calc} = 431.5 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.40-0.52 (2H), 0.57-0.73 (2H), 2.20 (3H),

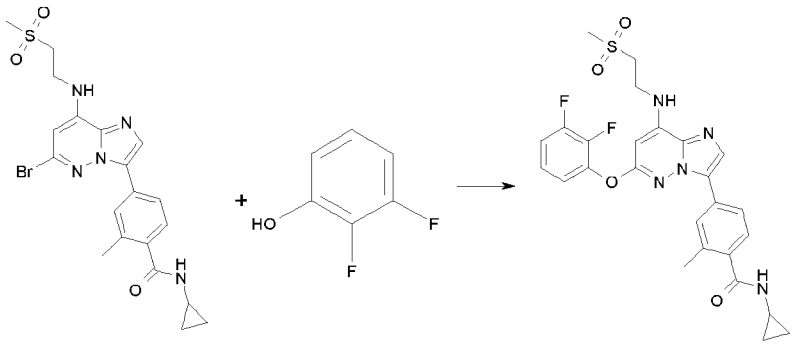
Example	Structure	Name	Analytical Data
			2.69-2.82 (1H), 2.90 (3H), 5.95 (1H), 7.04-7.20 (3H), 7.24 (1H), 7.41-7.55 (1H), 7.59-7.73 (2H), 7.76 (1H), 7.90 (1H), 8.21 (1H)
511		N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[2-(1H-tetrazol-5-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 1.10 MW_{found} = 514.5 MW_{calc} = 513.5
512		N-cyclopropyl-4-{8-[(2,2-difluoroethyl)amino]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.28 MW_{found} = 482.5 MW_{calc} = 481.5

Example	Structure	Name	Analytical Data
513		N-cyclopropyl-4-[8-{[4-(dimethylamino)butyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 0.99 MW_{found} = 517.6 MW_{calc} = 516.6
514		N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(2,2,2-trifluoroethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.06 MW_{found} = 500.5 MW_{calc} = 499.5 ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 0.43-0.51 (2H), 0.59-0.69 (2H), 2.14 (3H), 2.72-2.81 (1H), 5.20 (2H), 6.96 (1H), 7.15-7.27 (4H), 7.39 (1H), 7.54 (1H), 7.67 (1H), 7.74 (1H), 8.17

Example	Structure	Name	Analytical Data
			(1H), 8.25 (1H)
515		N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[2-(1H-pyrazol-1-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 1.22 MW_{found} = 512.6 MW_{calc} = 511.6

Example 516

N-cyclopropyl-4-[6-(2,3-difluorophenoxy)-8-{[2-(methylsulfonyl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide



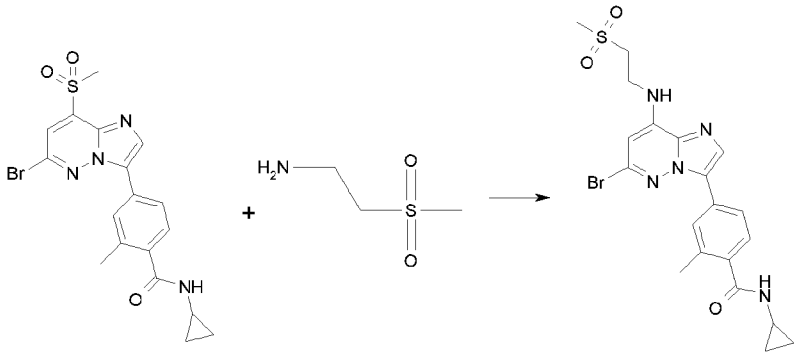
147 mg (300 µmol) 4-(6-bromo-8-{[2-(methylsulfonyl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 516a were transformed in analogy to example 51 using 2,3-difluorophenol to give after working up and purification 38 mg (21%) of the title compound.

UPLC-MS: RT = 1.14, MW_{found} = 542.6, MW_{calc} = 541.6

Intermediate example 516a

4-(6-bromo-8-{[2-(methylsulfonyl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl)-

N-cyclopropyl-2-methylbenzamide

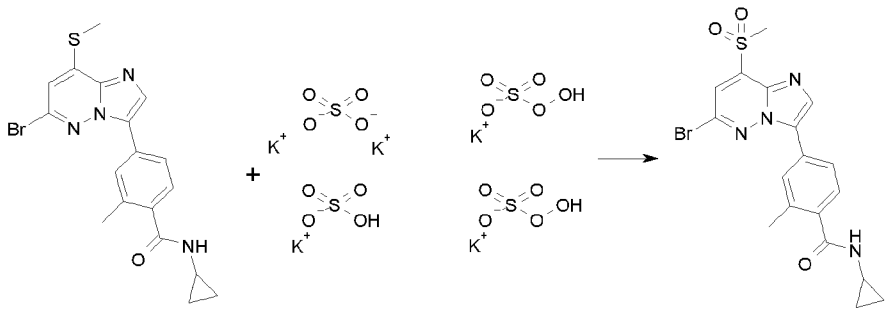


To a stirred solution of 1.12 g (2.5 mmol) 4-[6-bromo-8-(methylsulfonyl)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methyl benzamide which was prepared according to intermediate example 516b in 15 mL NMP is added 924 mg (7.5 mmol) 2-(methylsulfonyl)ethanamine and 1.94 g (15 mmol) DIPEA and the mixture is heated at 160°C for 4 h in a heating block. After working up and without further purification 1.18 g (96%) of the title compound are obtained.

UPLC-MS: RT = 0.95, MW_{found} = 493.4, MW_{calc} = 492.4

Intermediate example 516b

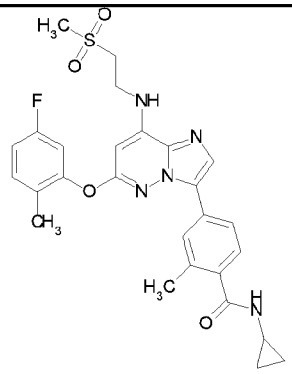
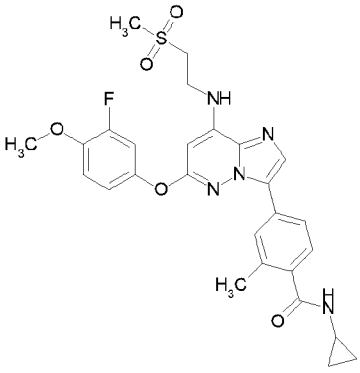
4-[6-bromo-8-(methylsulfonyl)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide

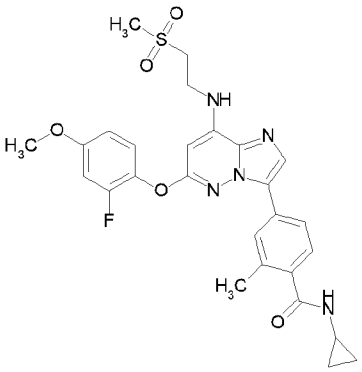


12 g (28.8 mmol) 4-[6-bromo-8-(methylsulfanyl)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methyl benzamide which was prepared according to intermediate example 486b were transformed in analogy to intermediate example 486a to give after working up and purification 8.61 g (59%) of the title compound.

UPLC-MS: RT = 0.98, MW_{found} = 450.4, MW_{calc} = 449.4

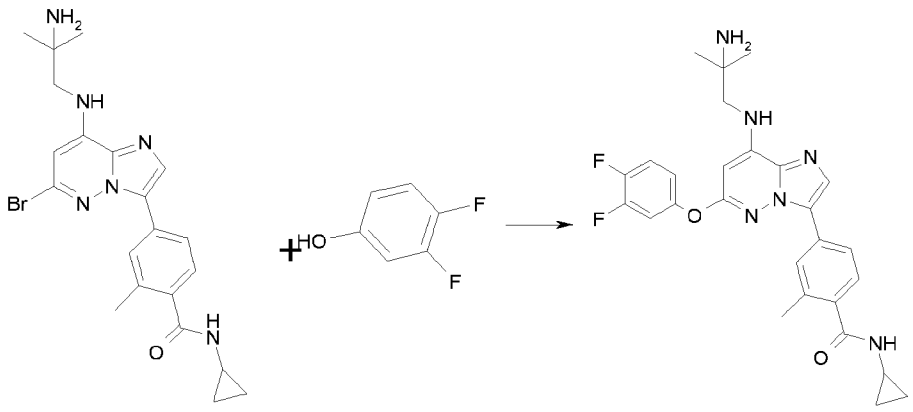
The following compound examples were prepared analogously to the procedure described for example 516 using the appropriate phenol or aniline building block [LC-MS data such as retention time (RT in min) or observed mass peak were collected using LC-MS Method A unless explicitly stated]:

Example	Structure	Name	Analytical Data
517		N-cyclopropyl-4-[6-(5-fluoro-2-methylphenoxy)-8-{[2-(methylsulfonyl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 1.17 MW_{found} = 538.6 MW_{calc} = 537.6
518		N-cyclopropyl-4-[6-(3-fluoro-4-methoxyphenoxy)-8-{[2-(methylsulfonyl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 1.33 MW_{found} = 554.6 MW_{calc} = 553.6 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.43-0.51 (2H), 0.59-0.68 (2H), 2.12 (3H), 2.77 (1H), 3.05 (3H), 3.49 (2H), 3.73-3.81 (2H), 3.84 (3H), 6.13 (1H), 7.07 (1H), 7.17 (1H), 7.19-7.26 (1H), 7.30 (1H), 7.49-7.69 (2H), 7.77 (1H), 7.92 (1H), 8.20 (1H)

Example	Structure	Name	Analytical Data
519		N-cyclopropyl-4-[6-(2-fluoro-4-methoxyphenoxy)-8-{[2-(methylsulfonyl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 1.12 MW_{found} = 554.6 MW_{calc} = 553.6 ^{1}H-NMR (500 MHz ,DMSO-d_6), δ [ppm]= 0.49-0.53 (2H), 0.66-0.71 (2H), 2.13 (3H), 2.81 (1H), 3.11 (3H), 3.55 (2H), 3.82 (5H), 6.25 (1H), 6.89 (1H), 7.11 (1H), 7.19 (1H), 7.38 (1H), 7.66 (1H), 7.74-7.79 (2H), 7.99 (1H), 8.26 (1H)

Example 520

4-{8-[(2-amino-2-methylpropyl)amino]-6-(3,4-difluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

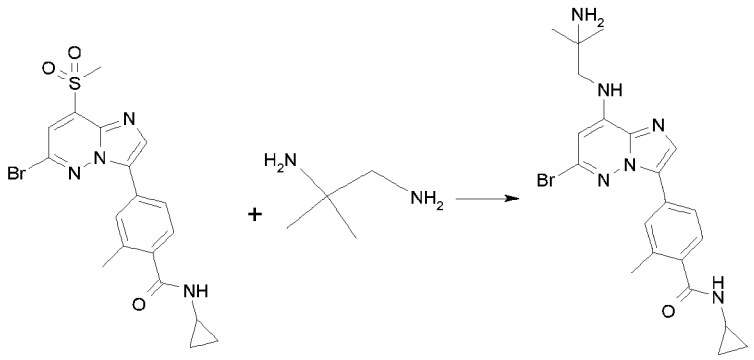


78 mg (171 µmol) 4-{8-[(2-amino-2-methylpropyl)amino]-6-bromoimidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 520a were transformed in analogy to example 51 using 2,3-difluorophenol to give after working up and purification 8 mg (8%) of the title compound.

UPLC-MS: RT = 0.97 MW_{found} = 507.5 MW_{calc} = 506.5

Intermediate example 520a

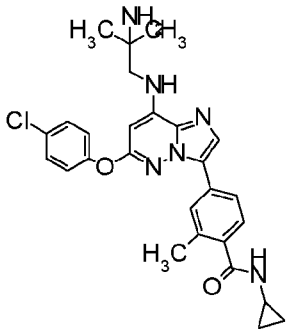
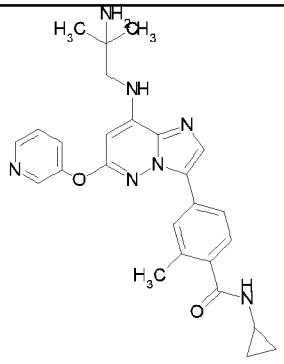
4-{8-[(2-amino-2-methylpropyl)amino]-6-bromoimidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



449 mg (1 mmol) 4-[6-bromo-8-(methylsulfonyl)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 516b were transformed in analogy to intermediate example 516a using 2-methylpropane-1,2-diamine to give after working up and purification 395 mg (86%) of the title compound.

UPLC-MS: RT = 0.75, MW_{found} = 458.4, MW_{calc} = 457.4. ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.46-0.53 (2H), 0.62-0.69 (2H), 1.07 (6H), 2.35 (3H), 2.80 (1H), 3.16 (2H), 6.50 (1H), 7.36 (1H), 7.85 (1H), 7.91 (1H), 7.93-7.96 (1H), 8.29 (1H)

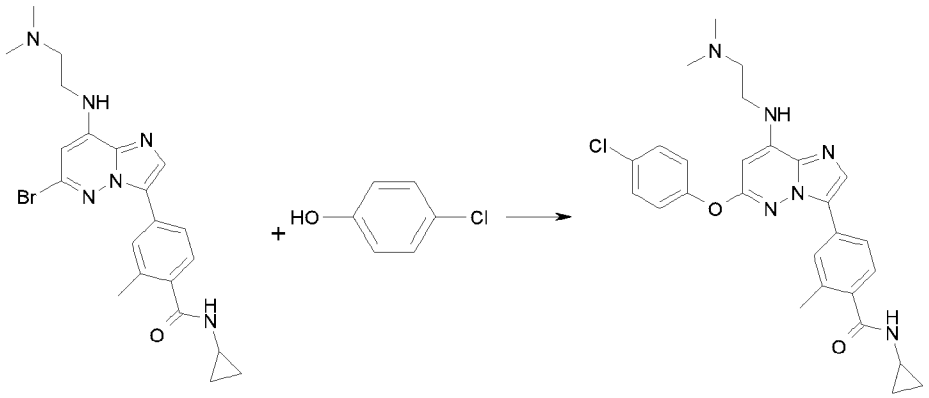
The following compound examples were prepared analogously to the procedure described for example 520 using the appropriate phenol or aniline building block [LC-MS data such as retention time (RT in min) or observed mass peak were collected using LC-MS Method A unless explicitly stated]:

Example	Structure	Name	Analytical Data
521		4-{8-[(2-amino-2-methylpropyl)amino]-6-(4-chlorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide	RT = 0.97 MW_{found} = 506.0 MW_{calc} = 505.0 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.44-0.52 (2H), 0.59-0.68 (2H), 1.12 (6H), 2.14 (3H), 2.77 (1H), 3.27 (3H), 6.20 (1H), 7.11-7.22 (3H), 7.34 (1H), 7.46-7.61 (2H), 7.62-7.68 (1H), 7.74 (1H), 7.92 (1H), 8.23 (1H)
522		4-{8-[(2-amino-2-methylpropyl)amino]-6-(pyridin-3-yloxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide	RT = 0.76 MW_{found} = 472.6 MW_{calc} = 471.6 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.43-0.50 (2H),

Example	Structure	Name	Analytical Data
			0.59-0.68 (2H), 1.14 (6H), 2.12 (3H), 2.76 (1H), 3.30 (3H), 6.27 (1H), 7.14 (1H), 7.40 (1H), 7.51 (1H), 7.58-7.64 (1H), 7.69 (1H), 7.76-7.82 (1H), 7.92 (1H), 8.21 (1H), 8.49 (1H), 8.57 (1H)

Example 523

4-[6-(4-chlorophenoxy)-8-{[2-(dimethylamino)ethyl]amino}imidazo[1,2-b] pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide

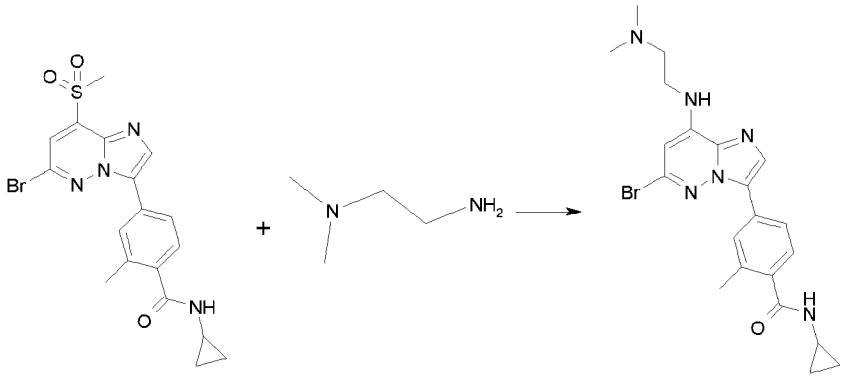


68 mg (150 µmol) 4-(6-bromo-8-{[2-(dimethylamino)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 523a were transformed in analogy to example 51 using 4-chlorophenol to give after working up and purification 20 mg (27%) of the title compound.

UPLC-MS: RT = 0.97, MW_{found} = 506.0, MW_{calc} = 505.0. ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.47 (2H), 0.59-0.68 (2H), 2.12 (3H), 2.18 (6H), 2.52 (2H), 2.76 (1H), 3.39 (2H), 6.06 (1H), 7.13-7.25 (2H), 7.27-7.35 (2H), 7.46-7.54 (2H), 7.63 (1H), 7.72 (1H), 7.90 (1H), 8.22 (1H)

Intermediate example 523a

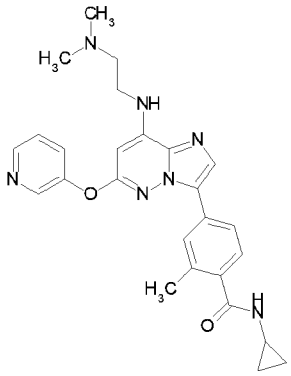
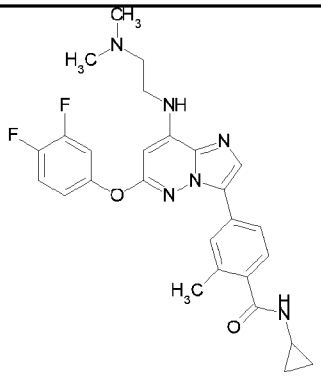
4-(6-bromo-8-{[2-(dimethylamino)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide



449 mg (1 mmol) 4-[6-bromo-8-(methylsulfonyl)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methyl benzamide which was prepared according to intermediate example 516b were transformed in analogy to intermediate example 516a using N,N-dimethylethane-1,2-diamine to give after working up and purification 367 mg (80%) of the title compound.

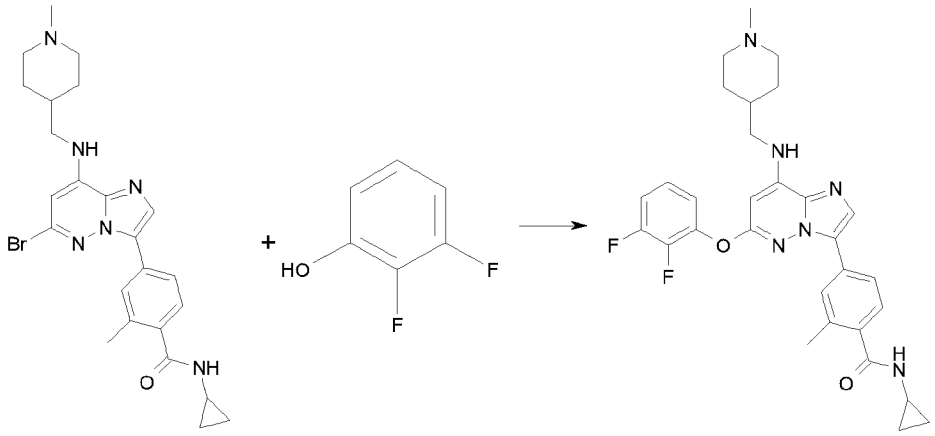
UPLC-MS: RT = 0.70, MW_{found} = 458.4, MW_{calc} = 457.4. ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.50 (2H), 0.65 (2H), 2.17 (6H), 2.35 (3H), 2.51 (2H), 2.80 (1H), 3.39 (2H), 6.38 (1H), 7.36 (1H), 7.44-7.50 (1H), 7.84 (1H), 7.91 (1H), 7.94 (1H), 8.28 (1H)

The following compound examples were prepared analogously to the procedure described for example 523 using the appropriate phenol or aniline building block [LC-MS data such as retention time (RT in min) or observed mass peak were collected using LC-MS Method A unless explicitly stated]:

Example	Structure	Name	Analytical Data
524		N-cyclopropyl-4-[8-{[2-(dimethylamino)ethyl]amino}-6-(pyridin-3-yloxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 0.74 MW_{found} = 472.6 MW_{calc} = 471.6 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.43-0.50 (2H), 0.59-0.67 (2H), 2.12 (3H), 2.20 (6H), 2.49-2.59 (2H), 2.76 (1H), 3.37-3.47 (2H), 6.11 (1H), 7.13 (1H), 7.26 (1H), 7.51 (1H), 7.57-7.64 (1H), 7.68 (1H), 7.80 (1H), 7.88-7.92 (1H), 8.21 (1H), 8.49 (1H), 8.57 (1H)
525		N-cyclopropyl-4-[6-(3,4-difluorophenoxy)-8-{[2-(dimethylamino)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 0.95 MW_{found} = 507.5 MW_{calc} = 506.5

Example 526

N-cyclopropyl-4-[6-(2,3-difluorophenoxy)-8-{[(1-methylpiperidin-4-yl)methyl] amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide



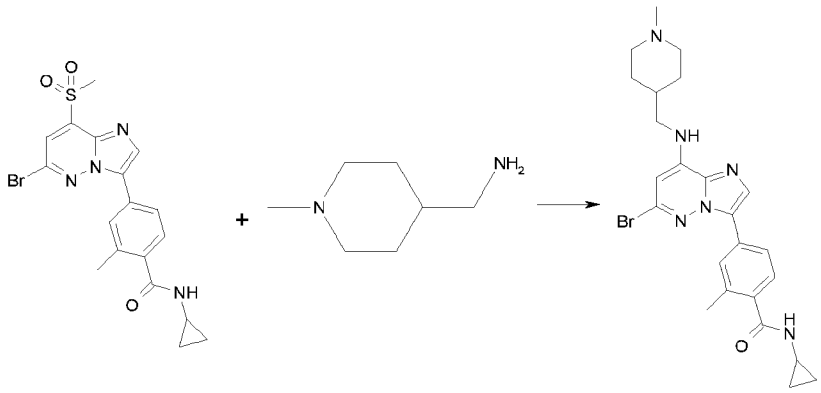
90 mg (181 µmol)

4-(6-bromo-8-{[(1-methylpiperidin-4-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl) -N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 526a were transformed in analogy to example 51 using 2,3-difluorophenol to give after working up and purification 16 mg (15%) of the title compound.

UPLC-MS: RT = 0.97 ,MW_{found} = 547.6, MW_{calc} = 546.6. ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.41-0.52 (2H), 0.58-0.69 (2H), 1.20 (2H), 1.67 (3H), 1.80 (2H), 2.11 (6H), 2.67-2.82 (3H), 3.22 (2H), 6.16 (1H), 6.69-6.81 (1H), 7.13 (1H), 7.26-7.34 (2H), 7.42 (1H), 7.59 (1H), 7.67 (1H), 7.79 (1H), 7.92 (1H), 8.22 (1H).

Intermediate example 526a

4-(6-bromo-8-{[(1-methylpiperidin-4-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl) -N-cyclopropyl-2-methylbenzamide



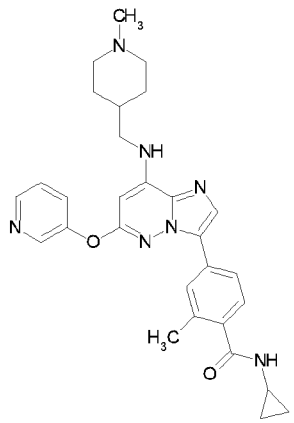
449 mg (1 mmol)

4-[6-bromo-8-(methylsulfonyl)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methyl

benzamide which was prepared according to intermediate example 516b were transformed in analogy to intermediate example 516a using 1-(1-methylpiperidin-4-yl)methanamine to give after working up and purification 460 mg (92%) of the title compound.

UPLC-MS: RT = 0.76, MW_{found} = 498.5, MW_{calc} = 497.5. ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.46-0.53 (2H), 0.61-0.70 (2H), 1.18 (2H), 1.53-1.68 (3H), 1.75 (2H), 2.08 (3H), 2.34 (3H), 2.63-2.76 (2H), 2.80 (1H), 3.18 (2H), 6.38 (1H), 7.36 (1H), 7.84 (1H), 7.87-7.98 (3H), 8.28 (1H)

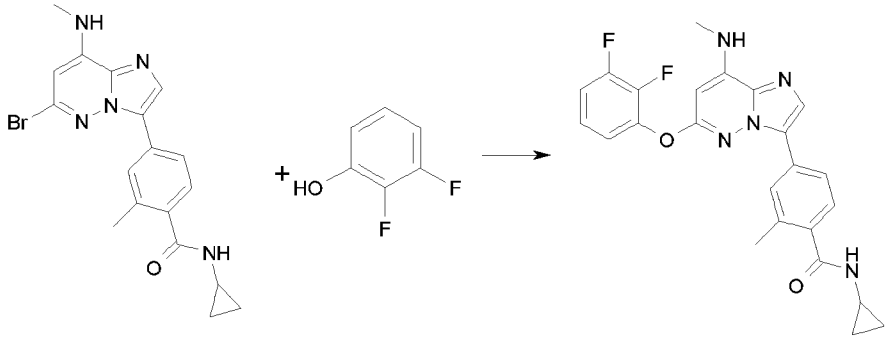
The following compound examples were prepared analogously to the procedure described for example 526 using the appropriate phenol or aniline building block [LC-MS data such as retention time (RT in min) or observed mass peak were collected using LC-MS Method A unless explicitly stated]:

Example	Structure	Name	Analytical Data
527		N-cyclopropyl-2-methyl-4-[8-{[(1-methylpiperidin-4-yl)methyl]amino}-6-(pyridin-3-yloxy)imidazo[1,2-b]pyridazin-3-yl]benzamide	RT = 0.77 MW_{found} = 512.6 MW_{calc} = 511.6 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.43-0.50 (2H), 0.59-0.68 (2H), 1.21 (2H), 1.67 (3H), 1.85 (2H), 2.12 (3H), 2.14 (3H), 2.70-2.81 (3H), 3.22 (2H), 6.11 (1H), 7.13 (1H), 7.51 (1H), 7.56-7.62 (1H), 7.68 (1H), 7.74

Example	Structure	Name	Analytical Data
			(1H), 7.78-7.83 (1H), 7.90 (1H), 8.18-8.23 (1H), 8.48 (1H), 8.57 (1H)

Example 528

N-cyclopropyl-4-[6-(2,3-difluorophenoxy)-8-(methylamino)imidazo[1,2-b] pyridazin-3-yl]-2-methylbenzamide

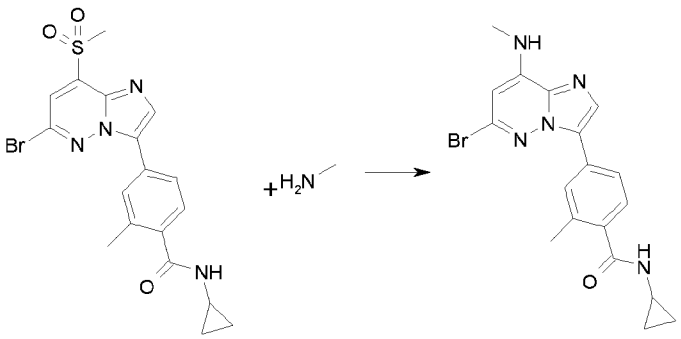


80 mg (200 µmol) 4-[6-bromo-8-(methylamino)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 528a were transformed in analogy to example 51 using 2,3-difluorophenol to give after working up and purification 18 mg (14%) of the title compound.

UPLC-MS: RT = 1.27, MW_{found} = 450.5, MW_{calc} = 449.

Intermediate example 528a

4-[6-bromo-8-(methylamino)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-



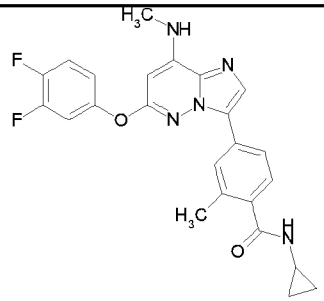
2-methylbenzamide

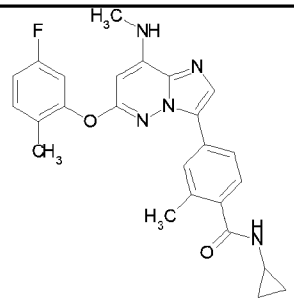
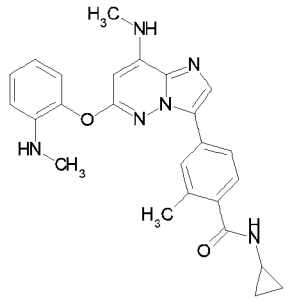
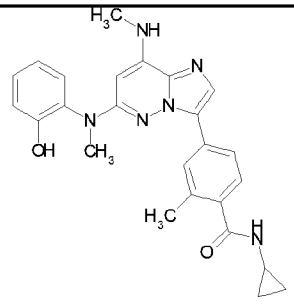
1123 mg (2.5 mmol)

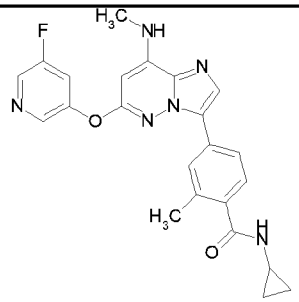
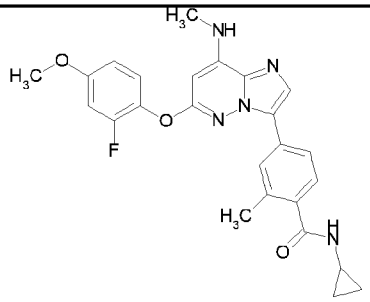
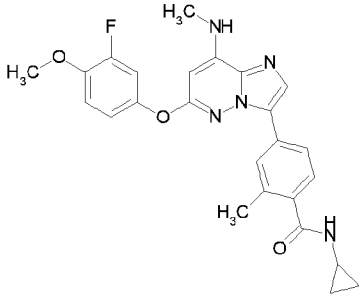
4-[6-bromo-8-(methylsulfonyl)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methyl benzamide which was prepared according to intermediate example 516b were transformed in analogy to intermediate example 516a using methanamine to give after working up and purification 1000 mg (100%) of the title compound.

UPLC-MS: RT = 1.08, MW_{found} = 401.3, MW_{calc} = 400.3.

The following compound examples were prepared analogously to the procedure described for example 528 using the appropriate phenol or aniline building block [LC-MS data such as retention time (RT in min) or observed mass peak were collected using LC-MS Method A unless explicitly stated]:

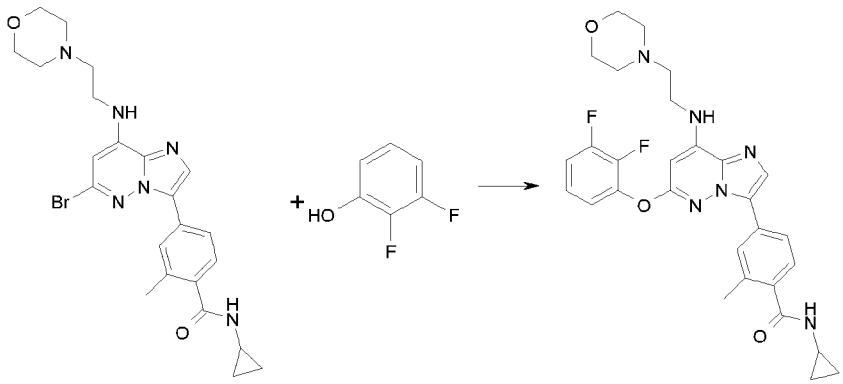
Example	Structure	Name	Analytical Data
529		N-cyclopropyl-4-[6-(3,4-difluorophenoxy)-8-(methylamino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 1.27 MW_{found} = 450.5 MW_{calc} = 449.5

Example	Structure	Name	Analytical Data
530		N-cyclopropyl-4-[6-(5-fluoro-2-methylphenoxy)-8-(methylamino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 1.31 MW_{found} = 446.5 MW_{calc} = 445.5
531		N-cyclopropyl-2-methyl-4-{8-(methylamino)-6-[2-(methylamino)phenoxy]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 0.97 MW_{found} = 443.5 MW_{calc} = 442.5 ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 0.51-0.56 (2H), 0.65-0.70 (2H), 2.36 (3H), 2.61 (3H), 2.83 (1H), 3.29 (3H), 5.16 (1H), 6.84-6.90 (1H), 6.99 (2H), 7.15-7.23 (2H), 7.33 (1H), 7.82 (1H), 8.06 (1H), 8.12 (1H), 8.26 (1H)
532		N-cyclopropyl-4-{6-[(2-hydroxyphenyl)(methyl)amino]-8-(methylamino)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.21 MW_{found} = 443.5 MW_{calc} = 442.5

Example	Structure	Name	Analytical Data
533		N-cyclopropyl-4-{6-[(5-fluoropyridin-3-yl)oxy]-8-(methylamino)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.06 MW_{found} = 433.5 MW_{calc} = 432.5
534		N-cyclopropyl-4-[6-(2-fluoro-4-methoxyphenoxy)-8-(methylamino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 1.24 MW_{found} = 462.5 MW_{calc} = 461.5
535		N-cyclopropyl-4-[6-(3-fluoro-4-methoxyphenoxy)-8-(methylamino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 1.23 MW_{found} = 462.5 MW_{calc} = 461.5 ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 0.44-0.50 (2H), 0.61-0.67 (2H), 2.12 (3H), 2.74-2.81 (1H), 2.90 (3H), 3.84 (3H), 5.91 (1H), 7.03-7.08 (1H), 7.17 (1H), 7.19-7.25 (1H), 7.29 (1H), 7.61 (1H), 7.65 (1H), 7.78 (1H), 7.89 (1H), 8.20 (1H)

Example 536

N-cyclopropyl-4-[6-(2,3-difluorophenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino} imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide

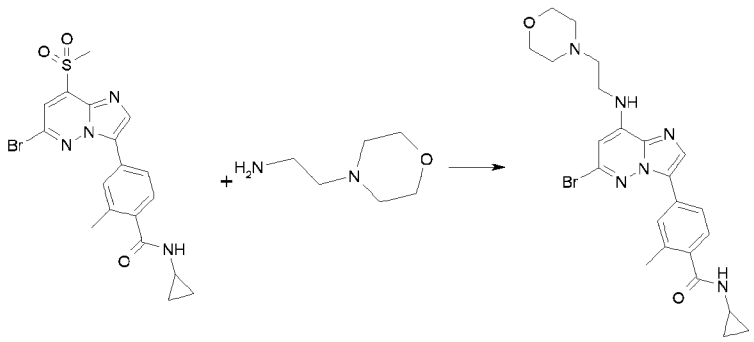


100 mg (200 µmol) 4-(6-bromo-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 536a were transformed in analogy to example 51 using 2,3-difluorophenol to give after working up and purification 25 mg (21%) of the title compound.

UPLC-MS: RT = 0.93, MW_{found} = 549.6, MW_{calc} = 548.6. ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 0.44-0.50 (2H), 0.60-0.67 (2H), 2.11 (3H), 2.46 (4H), 2.61 (2H), 2.77 (1H), 3.46 (2H), 3.57 (4H), 6.17 (1H), 7.14 (1H), 7.27-7.34 (2H), 7.39-7.46 (2H), 7.59 (1H), 7.67 (1H), 7.93 (1H), 8.11 (1H), 8.23 (1H)

Intermediate example 536a

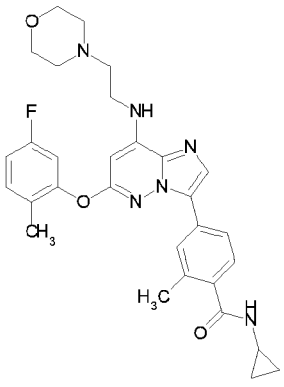
4-(6-bromo-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide

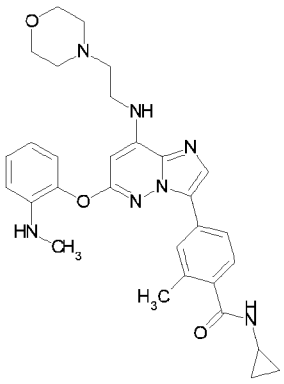
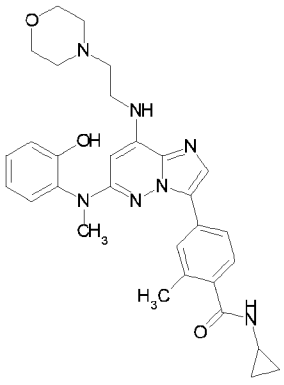


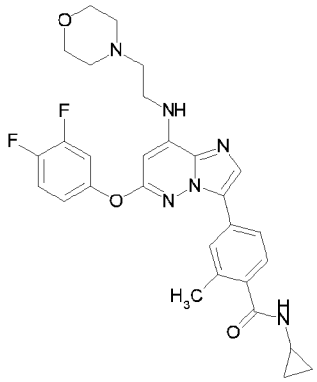
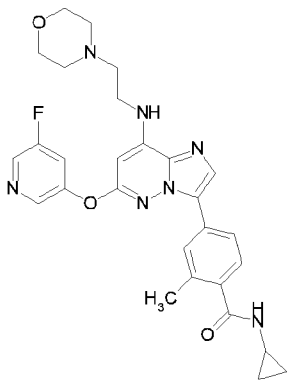
1123 mg (2.5 mmol) 4-[6-bromo-8-(methylsulfonyl)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methyl benzamide which was prepared according to intermediate example 516b were transformed in analogy to intermediate example 516a using 2-(morpholin-4-yl)ethanamine to give after working up and purification 1360 mg (108%) of the title compound.

UPLC-MS: RT = 0.74, MW_{found} = 500.4, MW_{calc} = 499.4.

The following compound examples were prepared analogously to the procedure described for example 536 using the appropriate phenol or aniline building block [LC-MS data such as retention time (RT in min) or observed mass peak were collected using LC-MS Method A unless explicitly stated]:

Example	Structure	Name	Analytical Data
537		N-cyclopropyl-4-[6-(5-fluoro-2-methylphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 0.95 MW_{found} = 545.6 MW_{calc} = 544.6 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.44-0.51 (2H), 0.60-0.67 (2H), 2.11 (6H), 2.40-2.49 (4H), 2.59 (2H), 2.77

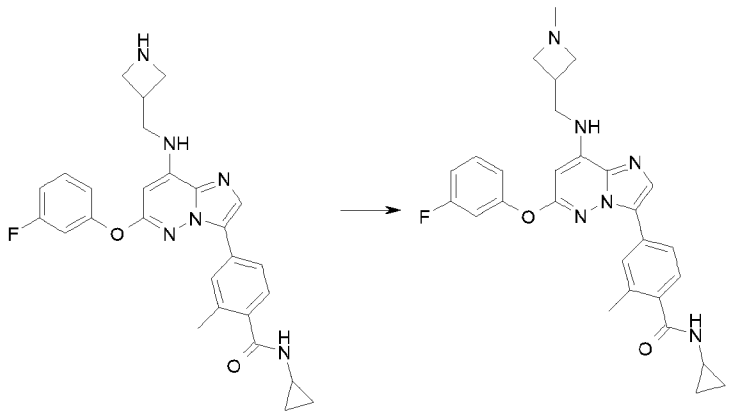
			(1H), 3.38-3.49 (2H), 3.53-3.60 (4H), 6.09 (1H), 7.06 (1H), 7.11-7.20 (2H), 7.27 (1H), 7.32-7.39 (1H), 7.58-7.64 (1H), 7.71 (1H), 7.91 (1H), 8.20 (1H)
538		N-cyclopropyl-2-methyl-4-(6-[2-(methylamino)phenoxy]-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl)benzamide	RT = 0.85 MW_{found} = 542.6 MW_{calc} = 541.6
539		N-cyclopropyl-4-(6-[(2-hydroxyphenyl)(methyl)amino]-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide	RT = 0.81 MW_{found} = 542.6 MW_{calc} = 541.6 ^{1}H-NMR (300 MHz ,$CDCl_3$), δ [ppm]= 0.70 (2H),

			0.89 (2H), 2.38 (7H), 2.52 (2H), 2.98 (3H), 3.30 (2H), 3.71 (4H), 5.06 (1H), 5.92 (1H), 6.42 (1H), 6.89-6.99 (1H), 7.10 (2H), 7.22 (3H), 7.65 (1H), 7.78 (1H), 7.90 (1H)
540		N-cyclopropyl-4-[6-(3,4-difluorophenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 0.94 MW_{found} = 549.6 MW_{calc} = 548.6
541		N-cyclopropyl-4-(6-[(5-fluoropyridin-3-yl)oxy]-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide	RT = 1.06 MW_{found} = 532.6 MW_{calc} = 531.6 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.44-0.52

			(2H), 0.59-0.68 (2H), 2.14 (3H), 2.39-2.44 (4H), 2.58 (2H), 2.73-2.81 (1H), 3.45 (2H), 3.51-3.59 (4H), 6.14 (1H), 7.17 (1H), 7.41 (1H), 7.59-7.64 (1H), 7.70 (1H), 7.91 (1H), 7.98 (1H), 8.22 (1H), 8.50 (1H), 8.54 (1H)

Example 542

tert-butyl 3-[({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-8-yl}amino)methyl]azetidine-1-carboxylate

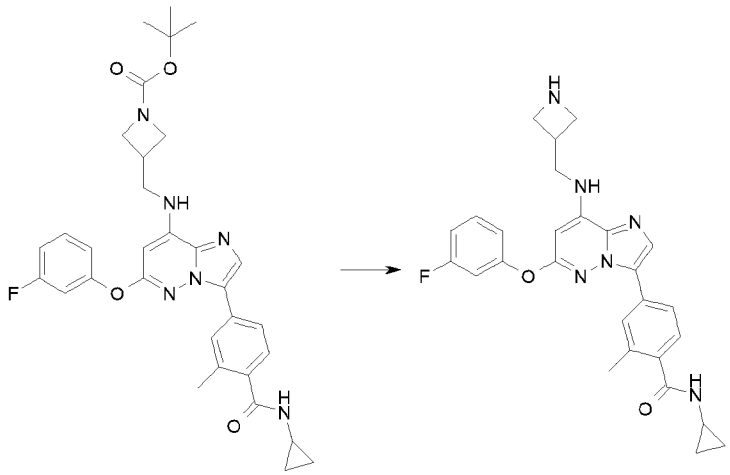


To a stirred solution of 10 mg (21 µmol) 4-{8-[(azetidin-3-ylmethyl)amino]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 542a in 1 mL DCE are added 1.2 mg (42 µmol) formaldehyde, 44 mg (204 µmol) sodium triacetoxyborohydride and 24 µL (411 µmol) HOAc at rt. After 72h the mixture is worked up and purified to give 2 mg (18%) of the title compound.

UPLC-MS: RT = 0.93, MW_{found} = 501.6, MW_{calc} = 500.6. ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.43-0.50 (2H), 0.59-0.67 (2H), 2.14 (3H), 2.30 (3H), 2.77 (1H), 3.15 (3H), 3.40 (2H), 3.51 (2H), 6.08 (1H), 7.07-7.19 (2H), 7.24 (1H), 7.47 (1H), 7.66 (1H), 7.76 (1H), 7.82 (1H), 7.91 (1H), 8.18-8.26 (2H)

Intermediate example 542a

tert-butyl 3-[({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-8-yl}amino)methyl]azetidine-1-carboxylate

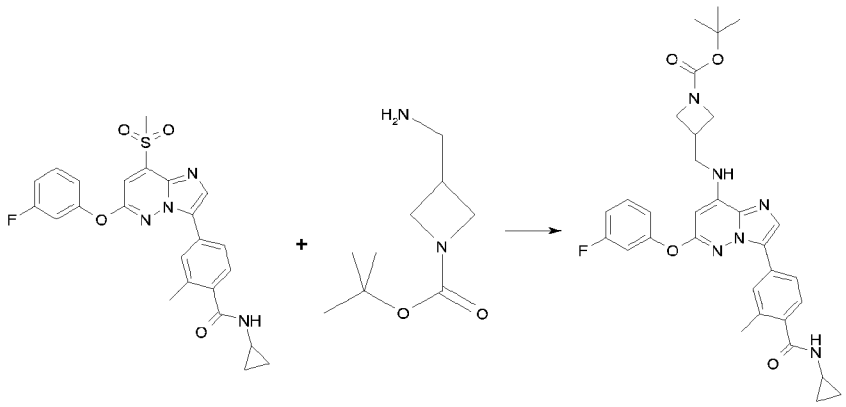


To a stirred solution of 43 mg (74 µmol) tert-butyl 3-[({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-8-yl}amino)methyl]azetidine-1-carboxylate which was prepared according to intermediate example 542b in 3 mL DCM are added 1mL TFA and two drops of water at rt. After 1h the mixture is worked up to give 34 mg (93%) of the title compound.

UPLC-MS: RT = 0.82, MW_{found} = 487.5, MW_{calc} = 486.5.

Intermediate example 542b

tert-butyl-3-[({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-6-(3-fluorophenoxy) imidazo[1,2-b]pyridazin-8-yl}amino)methyl]azetidine-1-carboxylate

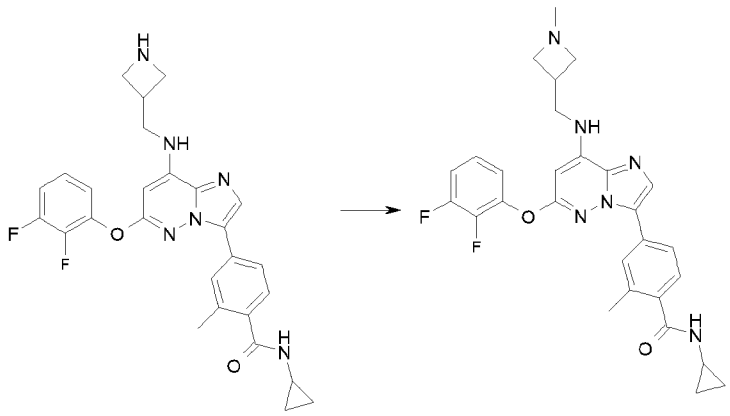


192 mg (400 µmol) N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-(methylsulfonyl)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide which was prepared according to intermediate example 486a were transformed in analogy to example 486 using tert-butyl 3-(aminomethyl)azetidine-1-carboxylate to give after working up and purification 43 mg (18%) of the title compound.

UPLC-MS: RT = 1.36, MW_{found} = 587.7, MW_{calc} = 586.7.

Example 543

N-cyclopropyl-4-[6-(2,3-difluorophenoxy)-8-{[(1-methylazetidin-3-yl)methyl] amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide

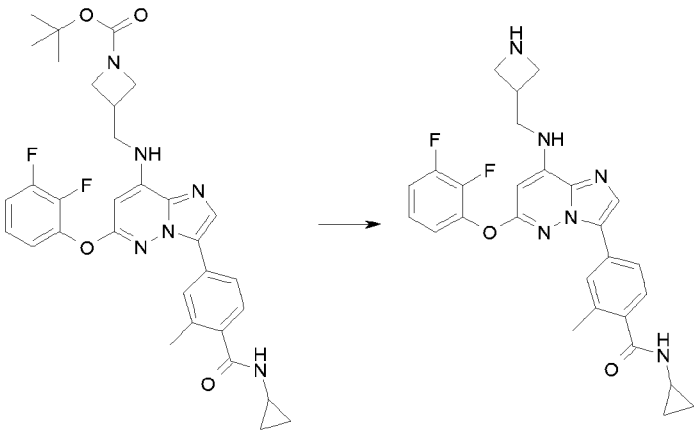


10 mg (21 µmol) 4-{8-[(azetidin-3-ylmethyl)amino]-6-(2,3-difluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 543a were transformed in analogy to example 542 to give after working up and purification 0.8 mg (6%) of the title compound.

UPLC-MS: RT = 0.94, MW_{found} = 519.6, MW_{calc} = 518.6.

Intermediate example 543a

4-{8-[(azetidin-3-ylmethyl)amino]-6-(2,3-difluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

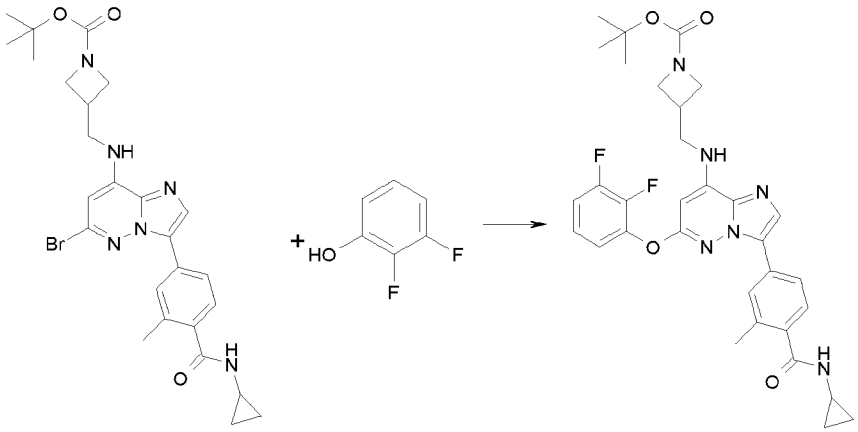


120 mg (200 µmol) tert-butyl 3-[({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-6-(2,3-difluorophenoxy)imidazo[1,2-b]pyridazin-8-yl}amino)methyl]azetidine-1-carboxylate which was prepared according to intermediate example 543b were transformed in analogy to intermediate example 542a to give after working up and purification 13 mg (13%) of the title compound.

UPLC-MS: RT = 0.92, MW_{found} = 505.5, MW_{calc} = 504.5. ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 0.44-0.50 (2H), 0.60-0.68 (2H), 2.11 (3H), 2.72-2.81 (1H), 3.08-3.18 (1H), 3.59 (2H), 3.66-3.74 (2H), 3.91 (2H), 6.26 (1H), 6.74 (2H), 6.93 (1H), 7.14 (1H), 7.26-7.34 (1H), 7.43 (1H), 7.59 (1H), 7.67 (1H), 7.94 (1H), 7.99 (1H), 8.21 (1H)

Intermediate example 543b

tert-butyl-3-[({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-6-(2,3-difluorophenoxy)imidazo[1,2-b]pyridazin-8-yl}amino)methyl]azetidine-1-carboxylat



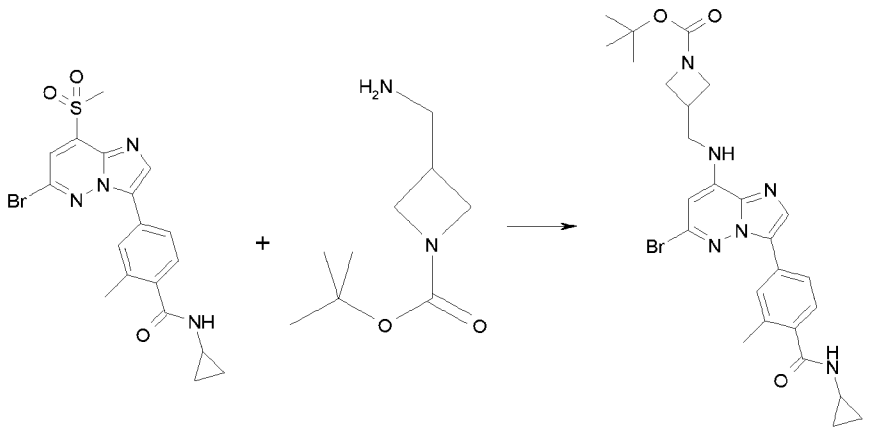
e

195 mg (200 µmol) tert-butyl 3-[({6-bromo-3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]imidazo[1,2-b]pyridazin-8-yl}amino)methyl]azetidine-1-carboxylate which was prepared according to intermediate example 543c were transformed in analogy to example 51 using 2,3-difluorophenol and the product was used without working up in the next step.

UPLC-MS: RT = 0.1.37, MW_{found} = 605.7, MW_{calc} = 605.7.

Intermediate example 543c

tert-butyl 3-[({6-bromo-3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]imidazo[1,2-b]pyridazin-8-yl}amino)methyl]azetidine-1-carboxylate

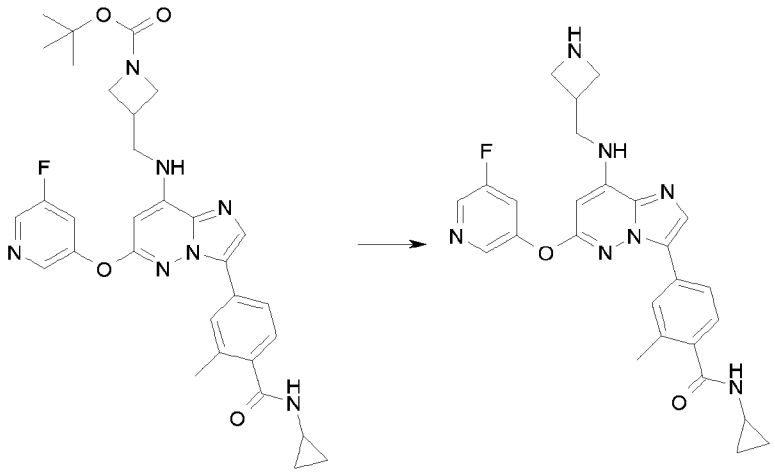


1348 mg (3 mmol) 4-[6-bromo-8-(methylsulfonyl)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methyl benzamide which was prepared according to intermediate example 516a were transformed in analogy to example 516 to give after working up and purification 1.67 g (100%) of the title compound.

UPLC-MS: RT = 1.28, MW_{found} = 556.5, MW_{calc} = 555.5

Example 544

4-{8-[(azetidin-3-ylmethyl)amino]-6-[(5-fluoropyridin-3-yl)oxy]imidazo [1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



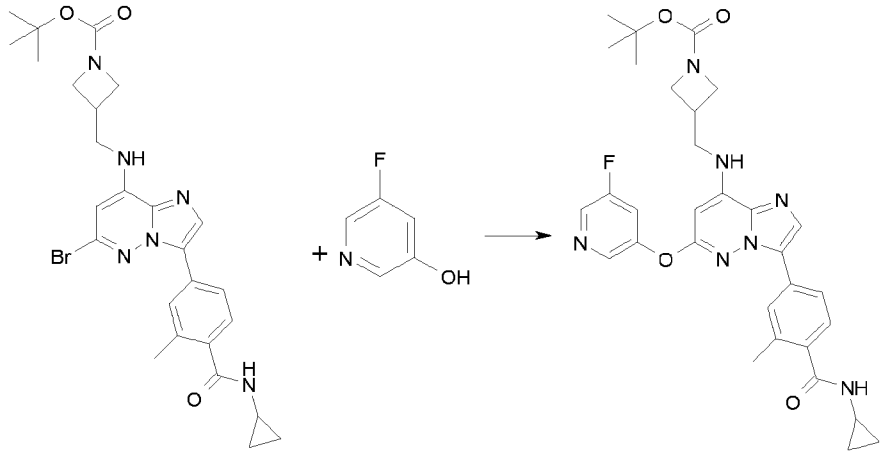
5 mg (8 µmol) tert-butyl 3-[({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-6-[(5-fluoropyridin-3-yl)oxy]imidazo[1,2-b]pyridazin-8-yl}amino)methyl]azetidine-1-carboxylate which was prepared according to intermediate example 544a were transformed in analogy to

intermediate example 542a to give after working up and purification 3.7 mg (99%) of the title compound.

RT = 0.80, MW_{found} = 488.5, MW_{calc} = 487.5. ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.43-0.51 (2H), 0.59-0.69 (2H), 2.15 (3H), 2.77 (1H), 3.17 (1H), 3.59 (2H), 3.73-3.85 (2H), 3.92-4.04 (2H), 6.21-6.26 (1H), 7.17 (1H), 7.64 (1H), 7.70 (1H), 7.73 (1H), 7.92-8.01 (2H), 8.20 (1H), 8.33 (1H), 8.39 (1H), 8.55 (1H).

Intermediate example 544a

tert-butyl 3-[({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-6-[(5-fluoropyridin-3-yl)oxy] imidazo[1,2-b]pyridazin-8-yl}amino)methyl]azetidine-1-carboxylate

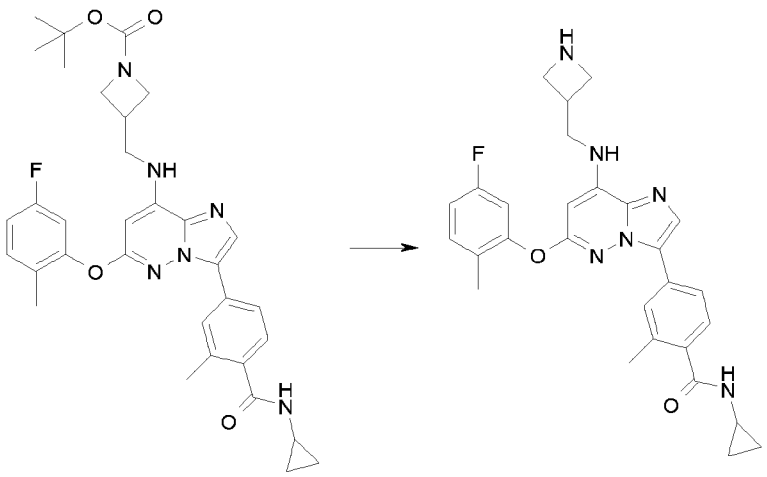


111 mg (200 µmol) tert-butyl 3-[({6-bromo-3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]imidazo[1,2-b]pyridazin-8-yl}amino)methyl]azetidine-1-carboxylate which was prepared according to intermediate example 543c were transformed in analogy to example 51 using 5-fluoropyridin-3-ol to give after working up and purification 5 mg (4%) of the title compound.

UPLC-MS: RT = 1.25, MW_{found} = 588.7, MW_{calc} = 587.7.

Example 545

4-{8-[(azetidin-3-ylmethyl)amino]-6-(5-fluoro-2-methylphenoxy)imidazo [1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

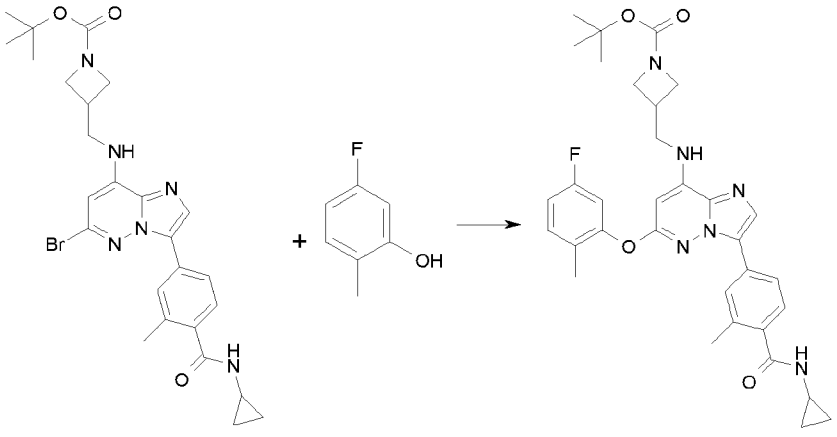


120 mg (200 µmol) tert-butyl 3-[({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-6-(5-fluoro-2-methylphenoxy)imidazo[1,2-b]pyridazin-8-yl}amino)methyl]azetidine-1-carboxylate which was prepared according to intermediate example 545a were transformed in analogy to intermediate example 542a to give after working up and purification 13 mg (13%) of the title compound.

UPLC-MS: RT = 0.94 MW_{found} = 501.6 MW_{calc} = 500.6

Intermediate example 545a

tert-butyl 3-[({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-6-(5-fluoro-2-methylphenoxy)imidazo[1,2-b]pyridazin-8-yl}amino)methyl]azetidine-1-carboxylate

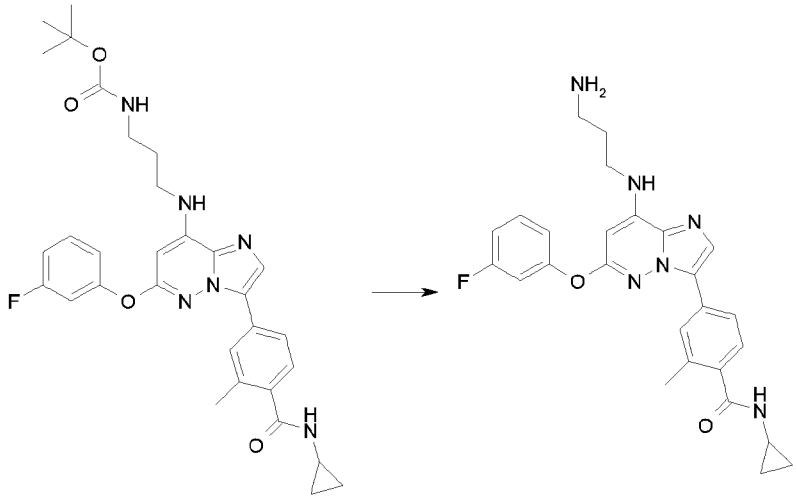


111 mg (200 µmol) tert-butyl 3-[({6-bromo-3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]imidazo[1,2-b]pyridazin-8-yl}amino)methyl]azetidine-1-carboxylate which was prepared according to

intermediate example 543c were transformed in analogy to example 51 using 2,3-difluorophenol and the product was used without working up in the next step. UPLC-MS: RT = 0.1.43, MW_{found} = 601.7, MW_{calc} = 600.7.

Example 546

4-{8-[(3-aminopropyl)amino]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

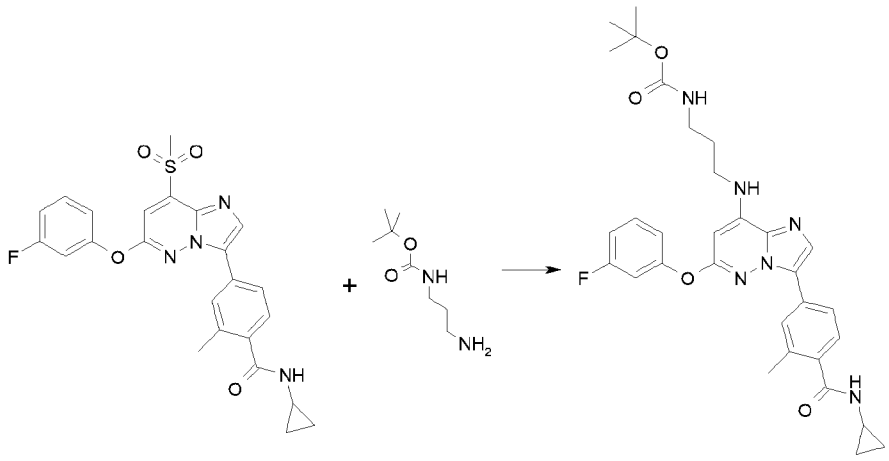


23 mg (40 µmol) tert-butyl [3-({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-8-yl}amino)propyl]carbamate which was prepared according to intermediate example 546a were transformed in analogy to intermediate example 542a to give after working up and purification 7 mg (36%) of the title compound.

UPLC-MS: RT = 0.94, MW_{found} = 475.5, MW_{calc} = 474.5. ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.43-0.51 (2H), 0.59-0.68 (2H), 1.81-1.97 (2H), 2.14 (3H), 2.76 (1H), 2.87 (2H), 3.41 (2H), 6.14 (1H), 7.08-7.19 (4H), 7.19-7.28 (1H), 7.49 (1H), 7.60-7.73 (3H), 7.73-7.82 (2H), 7.93 (1H), 8.21 (1H)

Intermediate example 546a

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoro-2-hydroxypropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



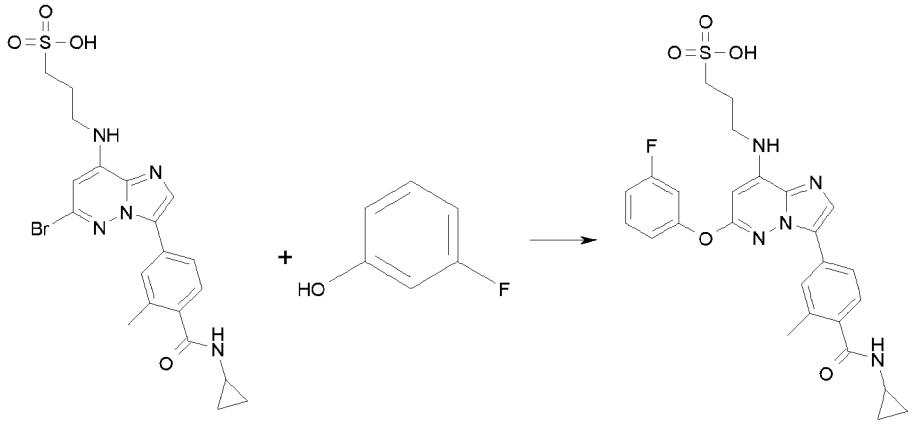
67 mg (140 µmol)

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-(methylsulfonyl)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide which was prepared according to intermediate example 486a were transformed in analogy to example 486 to give after working up and purification 23 mg (29%) of the title compound.

UPLC-MS: RT = 1.38, MW_{found} = 575.7, MW_{calc} = 574.7.

Example 547

3-({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-8-yl}amino)propane-1-sulfonic acid



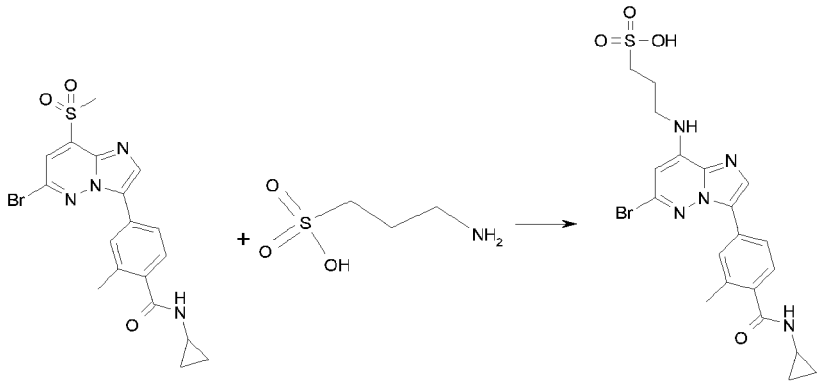
101 mg (200 µmol)

3-({6-bromo-3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]imidazo[1,2-b]pyridazin-8-yl}amino)propane-1-sulfonic acid which was prepared according to intermediate example 547a were transformed in analogy to example 51 to give after working up and purification 12 mg (9%) of the title compound.

UPLC-MS: RT = 0.98, MW_{found} = 540.6, MW_{calc} = 539.6. ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 0.40-0.54 (2H), 0.58-0.70 (2H), 1.81-1.99 (2H), 2.14 (3H), 2.49-2.62 (2H), 2.77 (1H), 3.46 (2H), 6.29 (1H), 7.11-7.21 (3H), 7.27 (1H), 7.42-7.55 (1H), 7.64 (2H), 7.74 (2H), 8.11 (1H), 8.22 (1H)

Intermediate example 547a

3-({6-bromo-3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]imidazo[1,2-b]pyridazin-8-yl}amino)propane-1-sulfonic acid

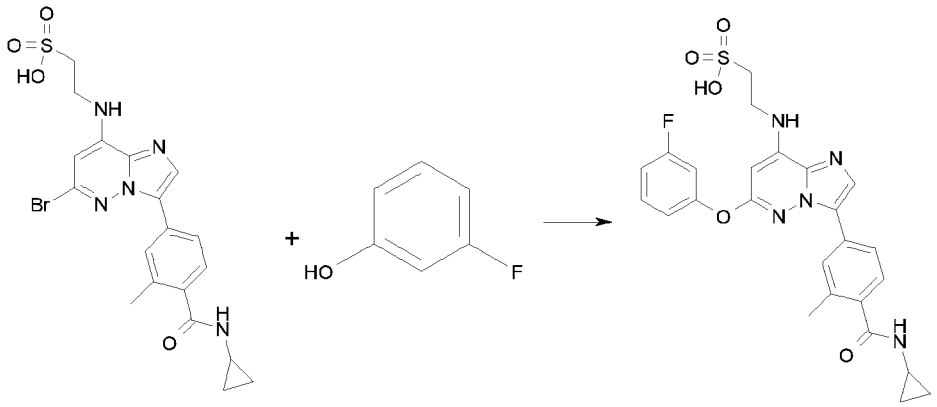


To a stirred solution of 41 mg (300 µmol) 3-aminopropane-1-sulfonic acid in 2 mL DMSO is added 24 mg (600 µmol) sodium hydride at rt. After 30 min, 90 mg (200 µmol) 4-[6-bromo-8-(methylsulfonyl)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methyl benzamide are added which was prepared according to intermediate example 516b to give after stirring for 2 h, the crude title compound which was used after evaporation of the solvent without further workup.

UPLC-MS: RT = 0.82, MW_{found} = 509.4, MW_{calc} = 508.4.

Example 548

2-({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-6-(3-fluorophenoxy)imidazo [1,2-b]pyridazin-8-yl}amino)ethanesulfonic acid



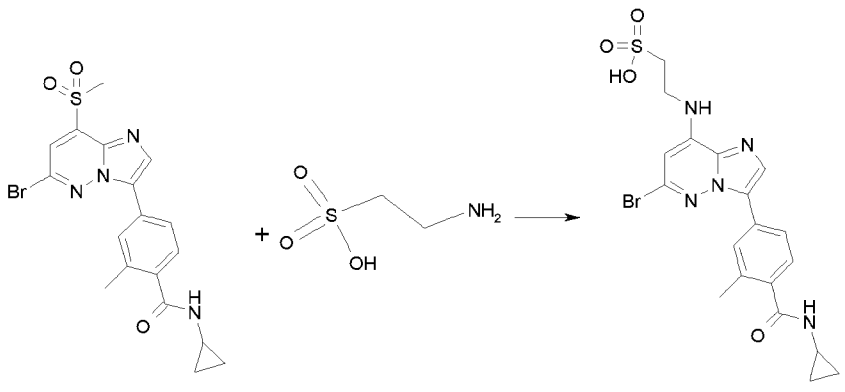
99 mg (200 µmol)

2-({6-bromo-3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]imidazo[1,2-b]pyridazin-8-yl}amino)ethanesulfonic acid which was prepared according to intermediate example 548a were transformed in analogy to example 51 to give after working up and purification 9 mg (7%) of the title compound.

UPLC-MS: RT = 0.97, MW_{found} = 526.6, MW_{calc} = 525.6. ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 0.44-0.54 (2H), 0.59-0.70 (2H), 2.14 (3H), 2.71-2.84 (3H), 3.59 (2H), 6.22 (1H), 7.09-7.21 (4H), 7.27 (1H), 7.49 (1H), 7.61-7.67 (1H), 7.73 (2H), 8.12 (1H), 8.23 (1H)

Intermediate example 548a

2-({6-bromo-3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]imidazo[1,2-b]pyridazin-8-yl}amino)ethanesulfonic acid



89 mg (200 µmol)

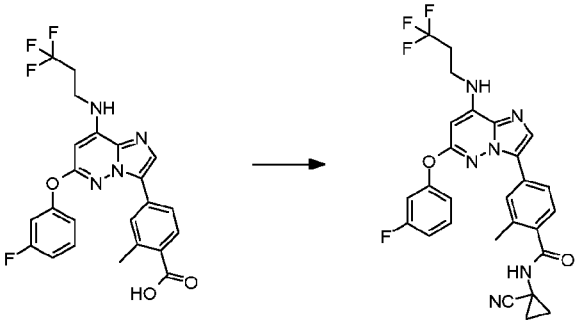
4-[6-bromo-8-(methylsulfonyl)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methyl benzamide which was prepared according to intermediate example 516b were

transformed in analogy to example 547a to give the crude title compound that was used in the next step without further purification.

UPLC-MS: RT = 0.84, MW_{found} = 495.4, MW_{calc} = 494.4.

Example 549

N-(1-cyanocyclopropyl)-4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

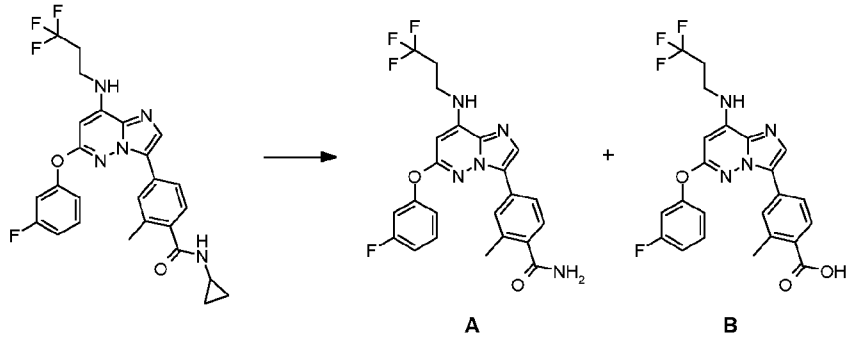


10.5 mg (22 µmol) 4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzoic acid which was prepared according to intermediate example 459a were transformed in analogy to example 459 using 1-cyanocyclopropanaminium chloride to give after working up and purification 4.5 mg (36%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 1.21 (2H), 1.50 (2H), 2.16 (3H), 2.61-2.76 (2H), 3.60 (2H), 6.14 (1H), 7.14 (2H), 7.25 (2H), 7.49 (1H), 7.66-7.76 (2H), 7.81 (1H), 7.97 (1H), 9.09 (1H) ppm.

Example 550

4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b] pyridazin-3-yl}-2-methylbenzamide (A) and 4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b] pyridazin-3-yl}-2-methylbenzoic acid (B)



A B

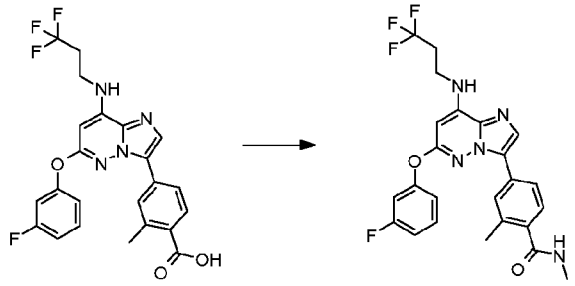
A mixture comprising 50 mg (97 µmol) N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide and 0.5 mL hydrobromic acid was heated at 120°C for 10 minutes under microwave irradiation. Water was added, the precipitate filtered off and purified by chromatography to give 30.0 mg (62%) of title compound A and 4.1 mg (9%) of title compound B.

^{1}H-NMR (DMSO-d6) of A: δ= 2.20 (3H), 2.68 (2H), 3.60 (2H), 6.13 (1H), 7.13 (2H), 7.22-7.30 (3H), 7.48 (1H), 7.60-7.78 (4H), 7.93 (1H) ppm.

^{1}H-NMR (DMSO-d6) of B: δ= 2.35 (3H), 2.68 (2H), 3.59 (2H), 6.15 (1H), 7.14 (2H), 7.26 (1H), 7.49 (1H), 7.64-7.77 (3H), 7.82 (1H), 7.99 (1H), 8.20 (1H) ppm.

Example 551

4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide



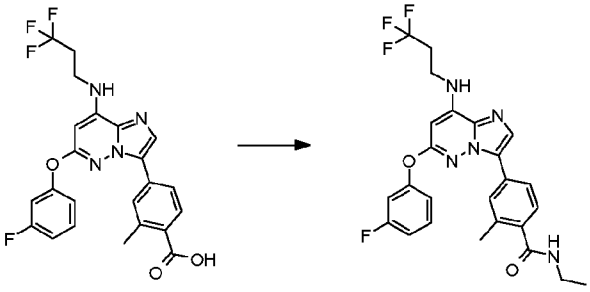
A mixture comprising 30 mg (63 µmol) 4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzoic acid which was prepared according to example 550, 2.94 mg methanamine, 36.1 mg N-[(dimethylamino)(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy)methylene]-N-methylmethanaminium hexafluorophosphate, 11.6 mg N,N-dimethylpyridin-4-amine and 1.5 mL N,N-dimethylformamide was stirred at 23°C overnight. The solvent was

removed and the residue purified by chromatography to give 30.0 mg (92%) of title compound.

^{1}H-NMR (DMSO-d6): δ= 2.16 (3H), 2.49-2.76 (2H), 2.69 (3H), 3.60 (2H), 6.13 (1H), 7.13 (2H), 7.20 (1H), 7.25 (1H), 7.48 (1H), 7.63-7.74 (2H), 7.76 (1H), 7.93 (1H), 8.08 (1H) ppm.

Example 552

N-ethyl-4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b] pyridazin-3-yl}-2-methylbenzamide

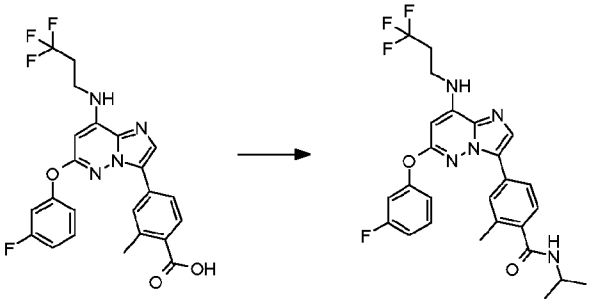


30 mg (63 µmol) 4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzoic acid which was prepared according to example 550 were transformed in analogy to example 2 using ethanamine to give after working up and purification 29.7 mg (89%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 1.06 (3H), 2.16 (3H), 2.68 (2H), 3.19 (2H), 3.60 (2H), 6.13 (1H), 7.13 (2H), 7.19 (1H), 7.25 (1H), 7.48 (1H), 7.64-7.74 (2H), 7.76 (1H), 7.93 (1H), 8.15 (1H) ppm.

Example 553

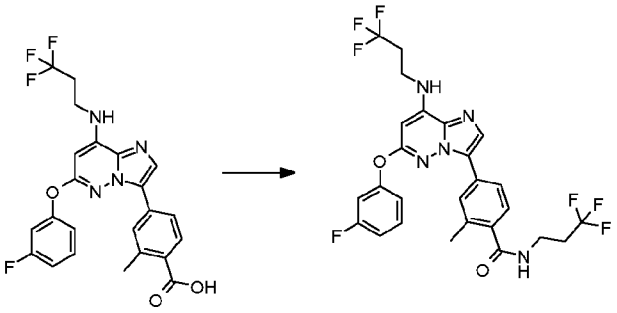
4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b] pyridazin-3-yl}-N-isopropyl-2-methylbenzamide



30 mg (63 µmol)
4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzoic acid which was prepared according to example 550 were transformed in analogy to example 2 using propan-2-amine to give after working up and purification 13.4 mg (39%) of the title compound.
^{1}H-NMR (DMSO-d6): δ= 1.09 (6H), 2.14 (3H), 2.68 (2H), 3.60 (2H), 3.99 (1H), 6.13 (1H), 7.08-7.19 (3H), 7.26 (1H), 7.48 (1H), 7.66 (1H), 7.72 (1H), 7.77 (1H), 7.92 (1H), 8.03 (1H) ppm.

Example 554

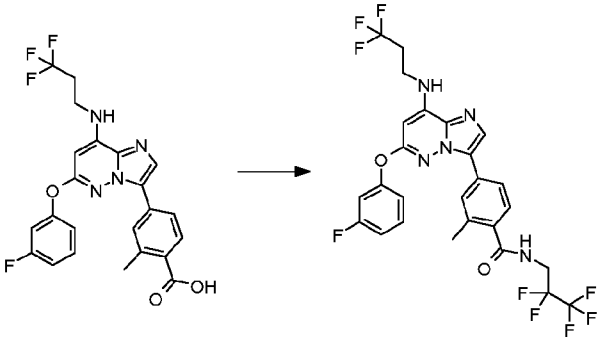
4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methyl-N-(3,3,3-trifluoropropyl)benzamide



11.8 mg (25 µmol)
4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzoic acid which was prepared according to example 550 were transformed in analogy to example 2 using 3,3,3-trifluoropropan-1-amine to give after working up and purification 12.0 mg (83%) of the title compound.
^{1}H-NMR ($CDCl_3$): δ= 2.34 (3H), 2.41-2.65 (4H), 3.69 (4H), 5.90 (1H), 5.97 (2H), 6.94-7.08 (3H), 7.28 (1H), 7.39 (1H), 7.65 (1H), 7.75 (1H), 7.77 (1H) ppm.

Example 555

4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methyl-N-(2,2,3,3,3-pentafluoropropyl)benzamide

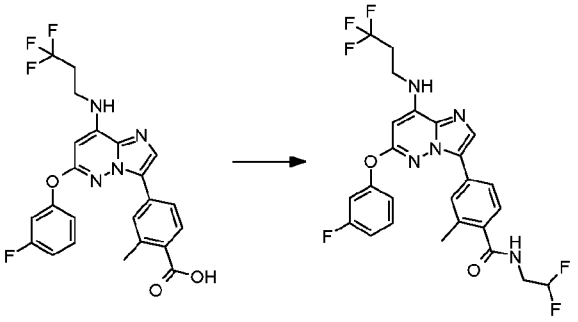


11.8 mg (25 µmol) 4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzoic acid which was prepared according to example 550 were transformed in analogy to example 552 using 2,2,3,3,3-pentafluoropropan-1-amine to give after working up and purification 12.5 mg (82%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 2.34 (3H), 2.50-2.65 (2H), 3.69 (2H), 4.16 (2H), 5.91 (1H), 5.96 (2H), 6.93-7.08 (3H), 7.32 (1H), 7.40 (1H), 7.67 (1H), 7.76 (1H), 7.80 (1H) ppm.

Example 556

N-(2,2-difluoroethyl)-4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

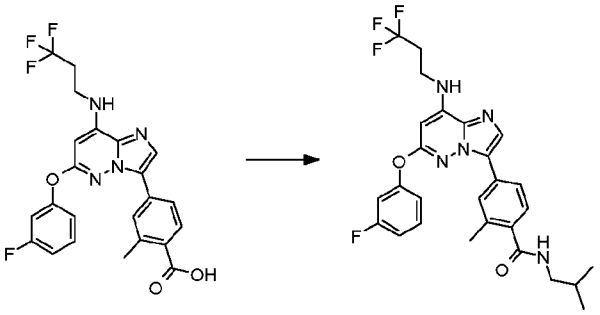


11.8 mg (25 µmol) 4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzoic acid which was prepared according to example 550 were transformed in analogy to example 551 using 2,2-difluoroethanamine to give after working up and purification 13.4 mg (93%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 2.35 (3H), 2.58 (2H), 3.69 (2H), 3.82 (2H), 5.90 (1H), 5.93-6.02 (2H), 5.99 (1H) 6.95-7.08 (3H), 7.33 (1H), 7.40 (1H), 7.66 (1H), 7.76 (1H), 7.79 (1H) ppm.

Example 557

4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b] pyridazin-3-yl}-N-isobutyl-2-methylbenzamide

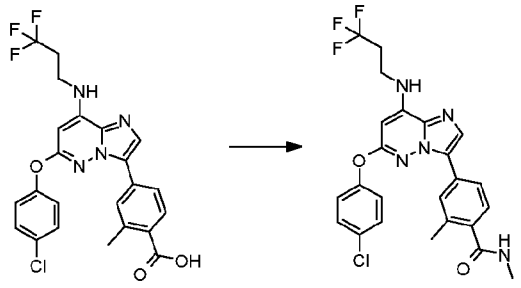


11.8 mg (25 µmol) 4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl }-2-methylbenzoic acid which was prepared according to example 550 were transformed in analogy to example 551 using 2-methylpropan-1-amine to give after working up and purification 12.8 mg (96%) of the title compound.

^{1}H-NMR ($CDCl_3$): δ= 0.99 (6H), 1.89 (1H), 2.35 (3H), 2.58 (2H), 3.28 (2H), 3.68 (2H), 5.74 (1H), 5.89 (1H), 5.97 (1H), 6.92-7.08 (3H), 7.30 (1H), 7.39 (1H), 7.64 (1H), 7.74 (1H), 7.76 (1H) ppm.

Example 558

4-{6-(4-chlorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b] pyridazin-3-yl}-N,2-dimethylbenzamide

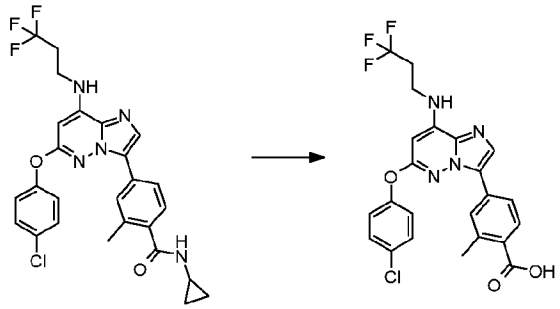


25 mg (51µmol) 4-{6-(4-chlorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl }-2-methylbenzoic acid which was prepared according to intermediate example 558a were transformed in analogy to example 551 to give after working up and purification 11.1 mg (43%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 2.15 (3H), 2.61-2.75 (2H), 2.70 (3H), 3.60 (2H), 6.13 (1H), 7.21 (1H), 7.32 (2H), 7.51 (2H), 7.64 (1H), 7.69 (1H), 7.74 (1H), 7.93 (1H), 8.09 (1H) ppm.

Intermediate Example 558a

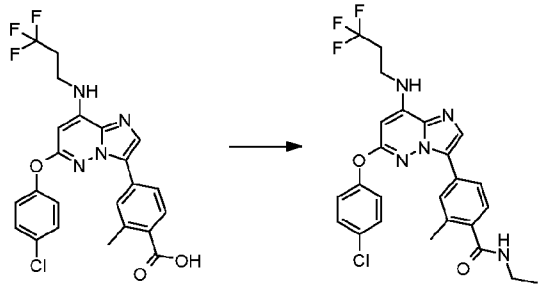
4-{6-(4-chlorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzoic acid



A mixture comprising 300 mg (566 µmol) 4-{6-(4-chlorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide and 13.4 mL hydrobromic acid was heated at 120°C for 2.5 days. Water was added, the precipitate filtered off to give the crude title compound that was used without further purification.

Example 559

4-{6-(4-chlorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-ethyl-2-methylbenzamide

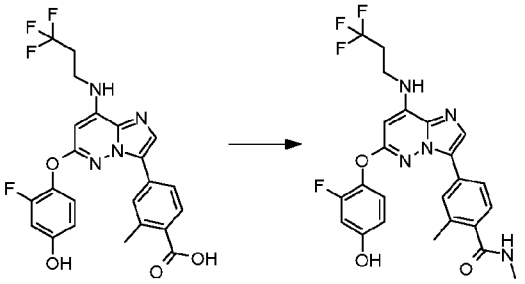


25 mg (51 µmol) 4-{6-(4-chlorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzoic acid which was prepared according to intermediate example 558a were transformed in analogy to example 2 using ethanamine to give after working up and purification 10.4 mg (37%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 1.07 (3H), 2.14 (3H), 2.62-2.75 (2H), 3.20 (2H), 3.60 (2H), 6.13 (1H), 7.20 (1H), 7.32 (2H), 7.51 (2H), 7.64 (1H), 7.69 (1H), 7.74 (1H), 7.93 (1H), 8.15 (1H) ppm.

Example 560

4-{6-(2-fluoro-4-hydroxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo [1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide



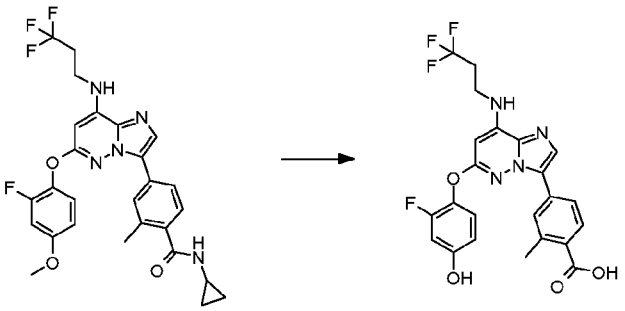
12.8 mg (26 µmol)

4-{6-(2-fluoro-4-hydroxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzoic acid which was prepared according to intermediate example 560a were transformed in analogy to example 551 to give after working up and purification 5.6 mg (43%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 2.15 (3H), 2.61-2.79 (2H), 2.70 (3H), 3.60 (2H), 6.13 (1H), 6.64 (1H), 6.73 (1H), 7.13-7.25 (2H), 7.58-7.70 (2H), 7.75 (1H), 7.93 (1H), 8.09 (1H), 9.87 (1H) ppm.

Example 560a

4-{6-(2-fluoro-4-hydroxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b] pyridazin-3-yl}-2-methylbenzoic acid



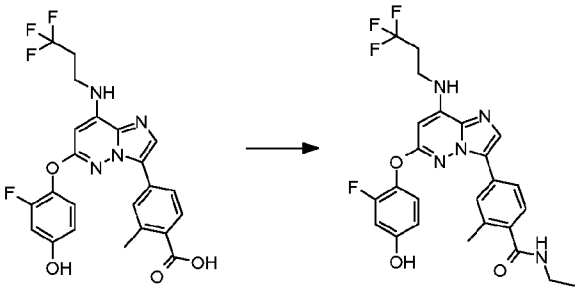
75 mg (138µmol)

N-cyclopropyl-4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]im

idazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide were transformed in analogy to intermediate example 558a to give after working up 76.6 mg of the title compound with a purity of 85% that was used without further purification.

Example 561

N-ethyl-4-{6-(2-fluoro-4-hydroxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide



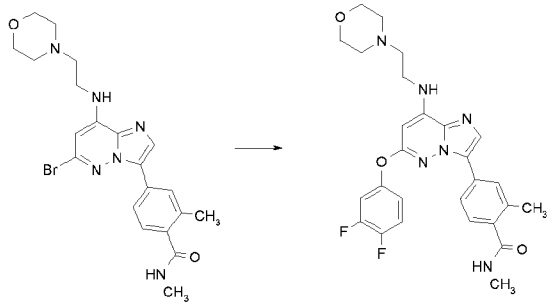
12.8 mg (26 µmol)

4-{6-(2-fluoro-4-hydroxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzoic acid which was prepared according to intermediate example 560a were transformed in analogy to example 551 using ethanamine to give after working up and purification 9.6 mg (713%) of the title compound.

^{1}H-NMR (DMSO-d6): δ= 1.07 (3H), 2.15 (3H), 2.68 (2H), 3.20 (2H), 3.60 (2H), 6.13 (1H), 6.64 (1H), 6.74 (1H), 7.14-7.23 (2H), 7.60-7.70 (2H), 7.75 (1H), 7.92 (1H), 8.16 (1H), 9.86 (1H) ppm.

Example 562

4-[6-(3,4-difluorophenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo [1,2-b]pyridazin-3-yl]-N,2-dimethylbenzamide



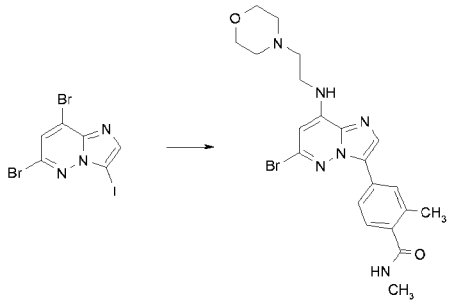
To a stirred solution of 48 mg (1200 µmol) sodium hydride in 1.2 mL DMSO were added 156 mg (1200 µmol) 3,4-difluorophenol in one portion at rt. After 1 h, 95 mg (200 µmol) 4-(6-bromo-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-

3-yl)-N,2-dimethylbenzamide which was prepared according to intermediate example 562a in 1 mL DMSO were added and the mixture was heated for 8 h at 140°C in a microwave oven. After working up and purification 7.42 mg (7%) of the title compound were obtained.

UPLC-MS: RT = 0.82, MW_{found} = 523.5, MW_{calc} = 522.5. ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 2.16 (3H), 2.45-2.47 (3H), 2.59 (2H), 2.67-2.75 (4H), 3.44 (2H), 3.53-3.60 (4H), 6.07 (1H), 7.12-7.19 (1H), 7.22 (1H), 7.31 (1H), 7.47-7.60 (2H), 7.66 (1H), 7.74 (1H), 7.91 (1H), 8.09 (1H).

Intermediate example 562a

4-(6-bromo-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl)-N,2-dimethylbenzamide

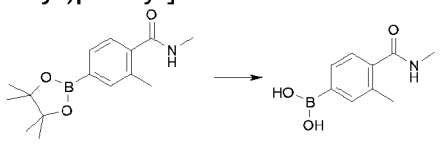


To a stirred solution of 2.01 g (5 mmol) 6,8-dibromo-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 96c in NMP (15 mL) were added 1.94 g (15 mmol) DIPEA and 1.30 g (10 mmol) 2-(morpholin-4-yl)ethanamine in one portion at rt. After heating for 2 h at 70°C, 100 mL DCM were added and the mixture was washed with water (3 x 100 mL). The organic phase was dried over sodium sulphate and evaporated to yield a brownish solid which was used without further purification in the next step. To a stirred solution of the remaining solid in 20 mL THF were added 1.16 g (6 mmol) [3-methyl-4-(methylcarbamoyl)phenyl]boronic acid which was prepared according to intermediate example 562b, 15 mL aqueous potassium carbonate solution (15 mmol, 1M), 816 mg Pd(dppf)Cl_2 (1 mmol) and the mixture was heated for 41 h at 70°C, to yield after working up and purification 2.35 g (99%) of the title compound.

UPLC-MS: RT = 0.71, MW_{found} = 474.4, MW_{calc} = 473.4. ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 2.37 (3H), 2.42 (4H), 2.54 (2H), 2.73 (3H), 3.26 (2H), 3.49-3.59 (4H), 6.42 (1H), 7.40 (2H), 7.56-7.63 (1H), 7.86 (1H), 7.92 (1H), 7.96 (1H), 8.18 (1H)

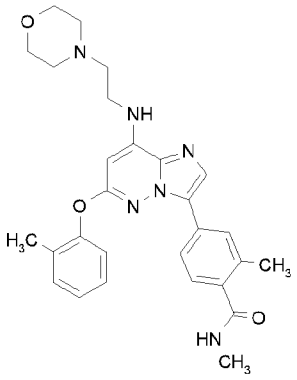
Intermediate example 562b

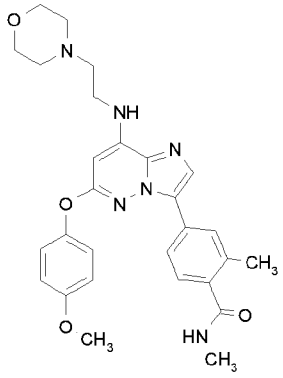
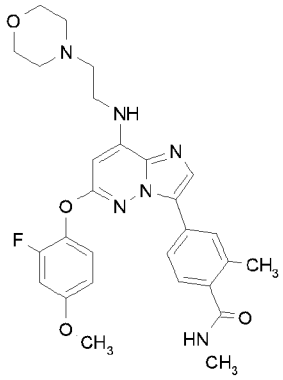
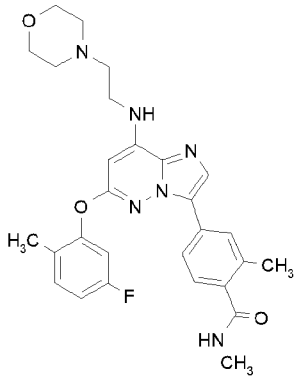
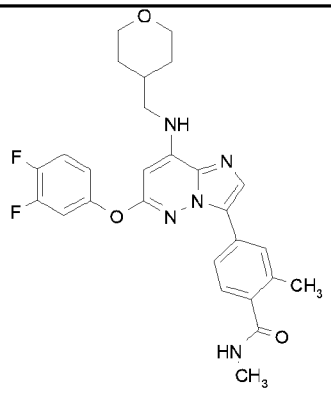
[3-methyl-4-(methylcarbamoyl)phenyl]boronic acid

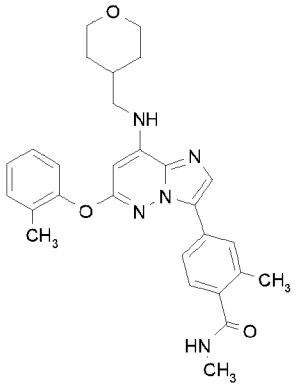
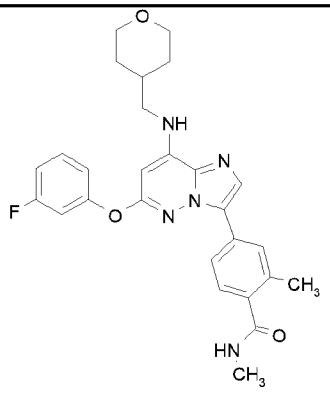
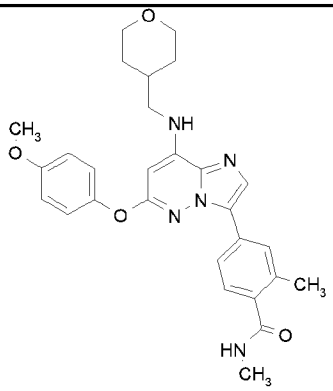


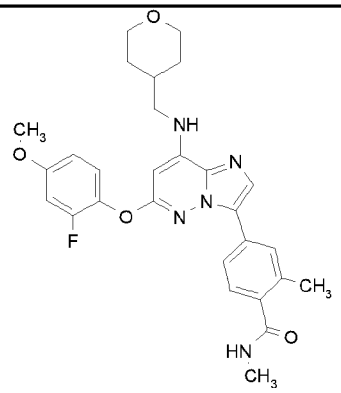
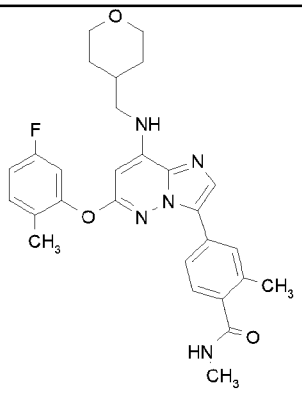
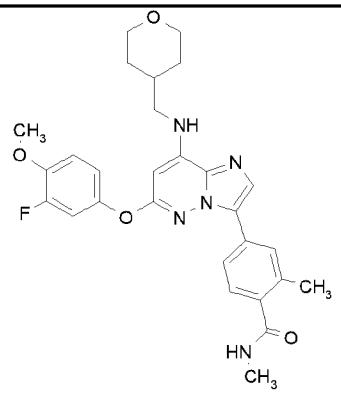
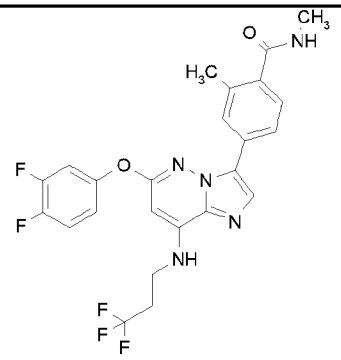
To a stirred solution of 20.22 g (67 mmol) N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide in acetone (300 mL) were added 43.08 g (201 mmol) sodium periodate 134 mL ammonium acetate (134 mmol, 1M in water) and the mixture was stirred for 3 h at rt and 2 h at 40°C. 4 N HCl was added (32 mL) and the organic phase was removed in vaccuo. The mixture was extracted with ethyl acetate, and the organic phase was washed with water, dried and removed in vaccuo to yield 14.59 g (94.2 %) of the title compound. ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 0.44-0.52 (2H), 0.59-0.67 (2H), 2.26 (3H), 2.78 (1H), 7.18 (1H), 7.53-7.61 (2H), 8.01 (2H), 8.19 (1H).

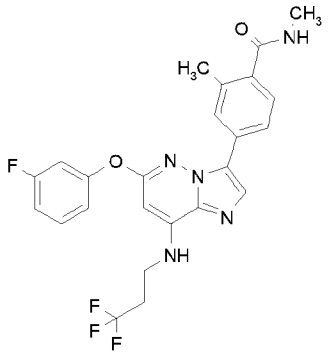
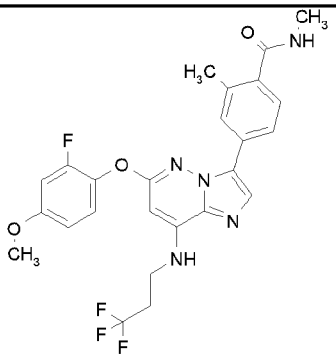
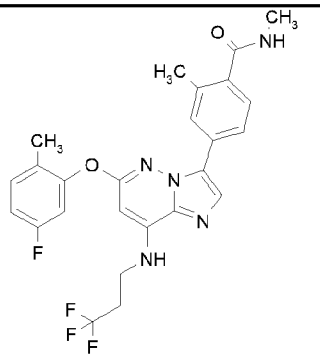
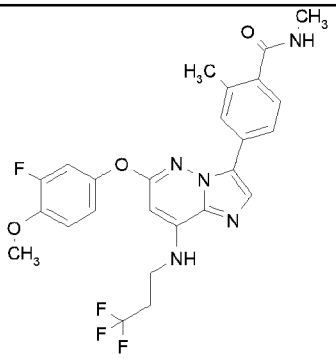
The following compound examples were prepared analogously to the procedure described above for example 562 using the appropriate intermediate example and the appropriate phenol [LC-MS data such as retention time (RT in min) or observed mass peak were collected using LC-MS Method A unless explicitly stated]:

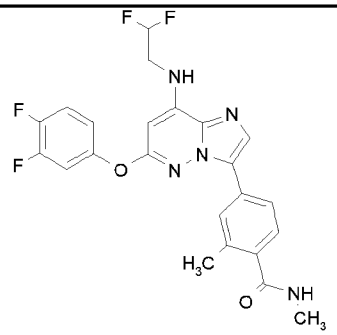
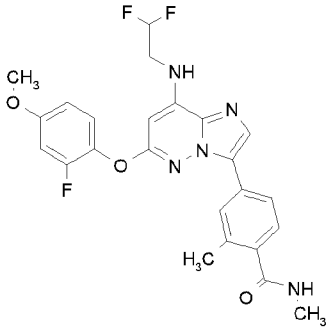
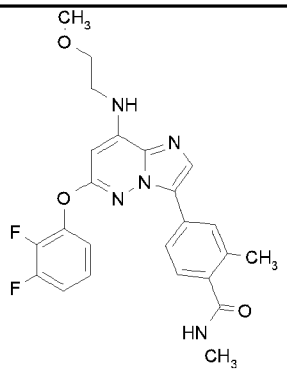
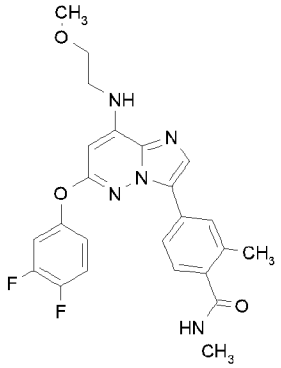
Example	Structure	Name	Analytical Data
563		N,2-dimethyl-4-[6-(2-methylphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]benzamide	RT = 0.82 MW_{found} = 501.6 MW_{calc} = 500.6

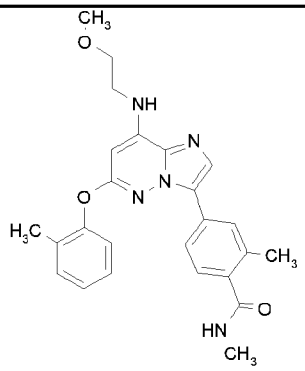
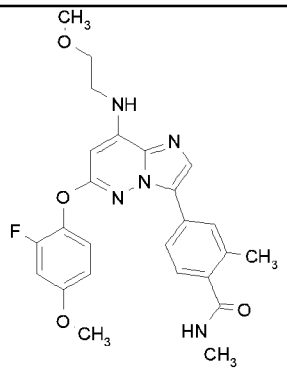
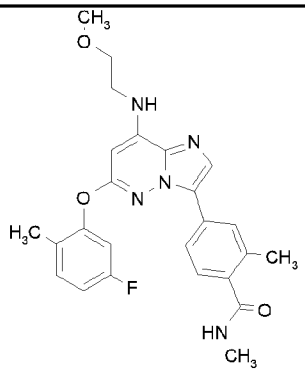
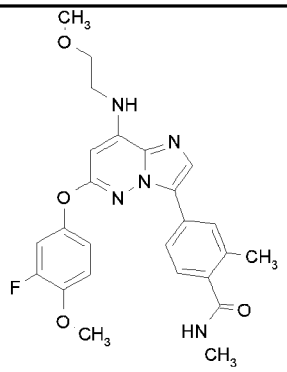
Example	Structure	Name	Analytical Data
564		4-[6-(4-methoxyphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-N,2-dimethylbenzamide	RT = 0.78 MW_{found} = 517.6 MW_{calc} = 516.6
565		4-[6-(2-fluoro-4-methoxyphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-N,2-dimethylbenzamide	RT = 0.80 MW_{found} = 535.6 MW_{calc} = 534.6
566		4-[6-(5-fluoro-2-methylphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-N,2-dimethylbenzamide	RT = 0.84 MW_{found} = 519.6 MW_{calc} = 518.6
567		4-{6-(3,4-difluorophenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide	RT = 1.22 MW_{found} = 508.5 MW_{calc} = 507.5

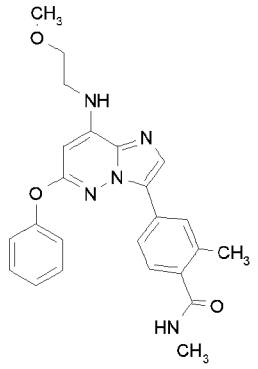
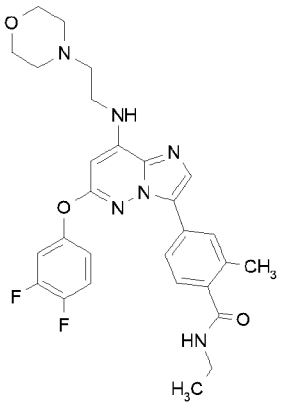
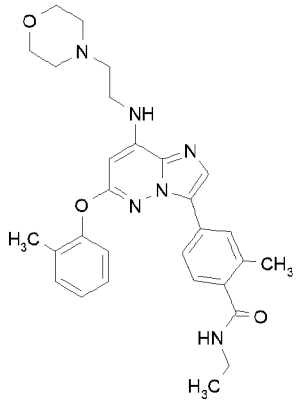
Example	Structure	Name	Analytical Data
568		N,2-dimethyl-4-{6-(2-methylphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.22 MW_{found} = 486.6 MW_{calc} = 485.6 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 1.14-1.32 (2H), 1.63 (2H), 1.86-2.03 (1H), 2.50 (6H), 2.68 (3H), 3.22 (4H), 3.83 (2H), 6.08 (1H), 7.13 (1H), 7.15-7.23 (2H), 7.23-7.28 (1H), 7.33 (1H), 7.57-7.65 (2H), 7.69 (1H), 7.89 (1H), 8.05 (1H)
569		4-{6-(3-fluorophenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide	RT = 1.20 MW_{found} = 490.5 MW_{calc} = 489.5
570		4-{6-(4-methoxyphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide	RT = 1.16 MW_{found} = 502.6 MW_{calc} = 501.6

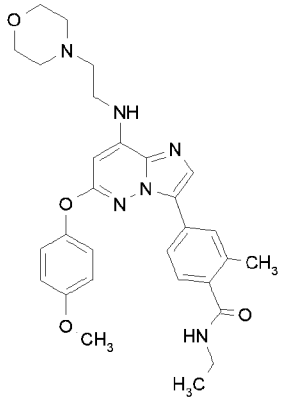
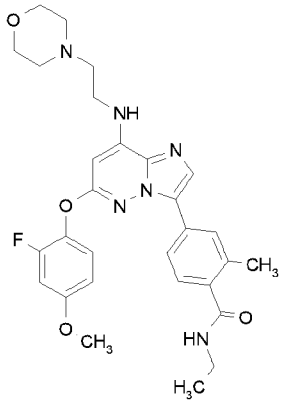
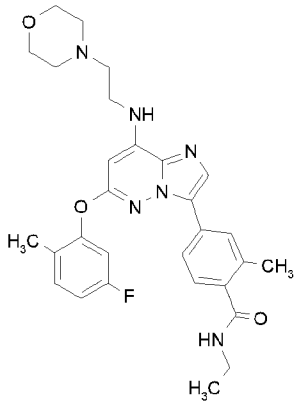
Example	Structure	Name	Analytical Data
571		4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide	RT = 1.19 MW_{found} = 520.6 MW_{calc} = 519.6
572		4-{6-(5-fluoro-2-methylphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide	RT = 1.24 MW_{found} = 504.6 MW_{calc} = 503.6
573		4-{6-(3-fluoro-4-methoxyphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide	RT = 1.17 MW_{found} = 520.6 MW_{calc} = 519.6
574		4-{6-(3,4-difluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide	RT = 1.29 MW_{found} = 506.4 MW_{calc} = 505.4

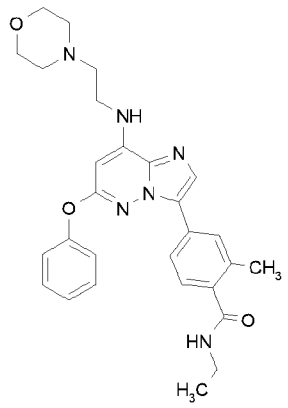
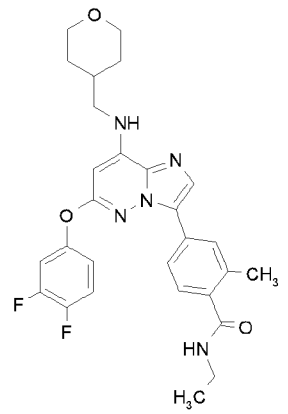
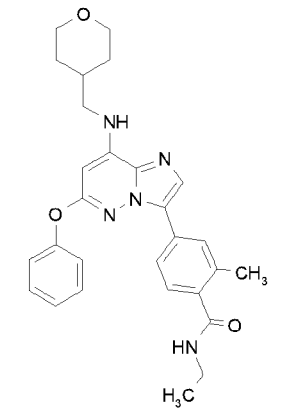
Example	Structure	Name	Analytical Data
575		4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide	RT = 1.29 MW_{found} = 488.5 MW_{calc} = 487.5 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 2.16 (3H), 2.59-2.76 (5H), 3.54-3.66 (2H), 6.13 (1H), 7.13 (2H), 7.20 (1H), 7.25 (1H), 7.43-7.53 (1H), 7.64-7.74 (2H), 7.76 (1H), 7.93 (1H), 8.08 (1H)
576		4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide	RT = 1.26 MW_{found} = 518.5 MW_{calc} = 517.5
577		4-{6-(5-fluoro-2-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide	RT = 1.32 MW_{found} = 502.5 MW_{calc} = 501.5
578		4-{6-(3-fluoro-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide	RT = 1.25 MW_{found} = 518.5 MW_{calc} = 517.5

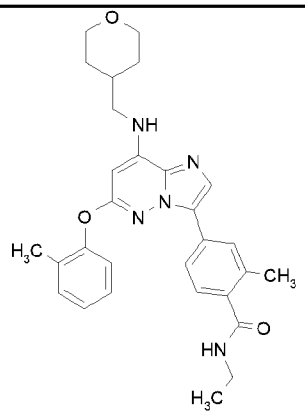
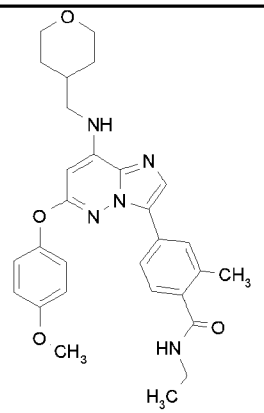
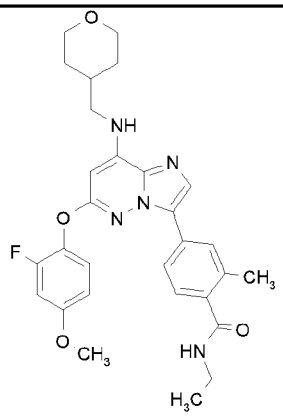
Example	Structure	Name	Analytical Data
579		4-{8-[(2,2-difluoroethyl)amino]-6-(3,4-difluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide	RT = 1.17 MW_{found} = 474.4 MW_{calc} = 473.4
580		4-{8-[(2,2-difluoroethyl)amino]-6-(2-fluoro-4-methoxyphenoxy)imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide	RT = 1.16 MW_{found} = 486.5 MW_{calc} = 485.5 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 2.10 (3H), 2.70 (3H), 3.78 (3H), 3.86 (3H), 6.23 (1H), 6.32 (1H), 6.84 (1H), 7.05 (1H), 7.19 (1H), 7.34 (1H), 7.62 (1H), 7.70-7.79 (1H), 7.97 (1H), 8.08 (1H)
581		4-{6-(2,3-difluorophenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide	RT = 1.17 MW_{found} = 468.5 MW_{calc} = 467.5
582		4-{6-(3,4-difluorophenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide	RT = 1.18 MW_{found} = 468.5 MW_{calc} = 467.5 ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 2.16 (3H), 2.70 (3H), 3.27 (3H), 3.52 (2H), 3.54-3.59 (2H), 6.10 (1H), 7.13-7.19 (1H), 7.22 (1H), 7.45

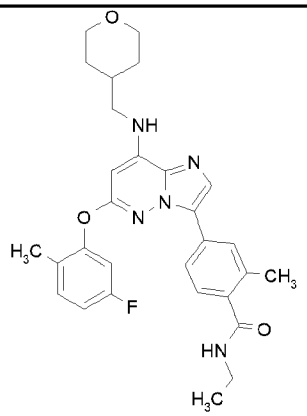
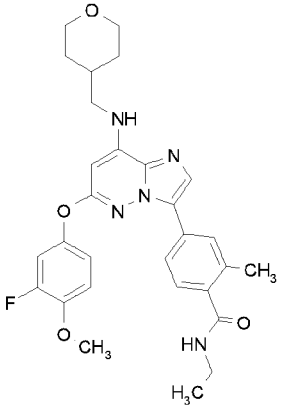
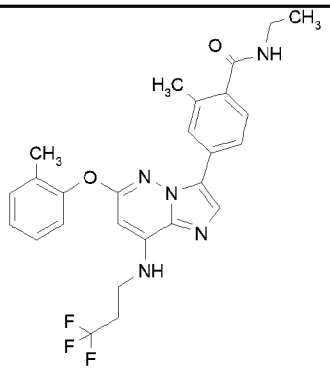
Example	Structure	Name	Analytical Data
			(1H), 7.50-7.60 (2H), 7.66 (1H), 7.75 (1H), 7.92 (1H), 8.09 (1H)
583		4-{8-[(2-methoxyethyl)amino]-6-(2-methylphenoxy)imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide	RT = 1.18 MW_{found} = 446.5 MW_{calc} = 445.5
584		4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide	RT = 1.15 MW_{found} = 480.5 MW_{calc} = 479.5
585		4-{6-(5-fluoro-2-methylphenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide	RT = 1.20 MW_{found} = 464.5 MW_{calc} = 463.5
586		4-{6-(3-fluoro-4-methoxyphenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide	RT = 1.13 MW_{found} = 480.5 MW_{calc} = 479.5

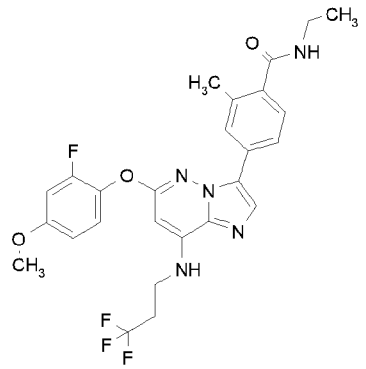
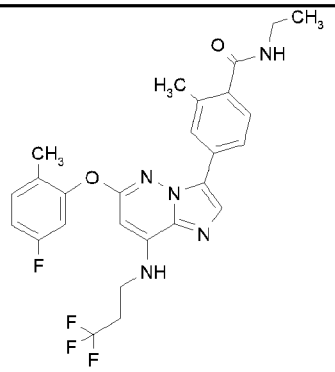
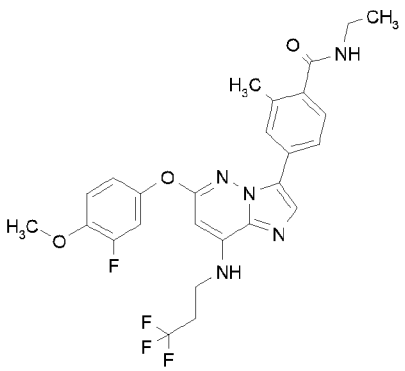
Example	Structure	Name	Analytical Data
587		4-{8-[(2-methoxyethyl)amino]-6-phenoxyimidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide	RT = 1.14 MW_{found} = 432.5 MW_{calc} = 431.5 ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 2.14 (3H), 2.69 (3H), 3.17-3.29 (3H), 3.51 (2H), 3.53-3.59 (2H), 6.08 (1H), 7.18 (1H), 7.24-7.29 (3H), 7.38 (1H), 7.41-7.48 (2H), 7.67 (1H), 7.75 (1H), 7.91 (1H), 8.09 (1H)
588		4-[6-(3,4-difluorophenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-N-ethyl-2-methylbenzamide	RT = 0.88 MW_{found} = 537.6 MW_{calc} = 536.6
589		N-ethyl-2-methyl-4-[6-(2-methylphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]benzamide	RT = 0.88 MW_{found} = 515.6 MW_{calc} = 514.6

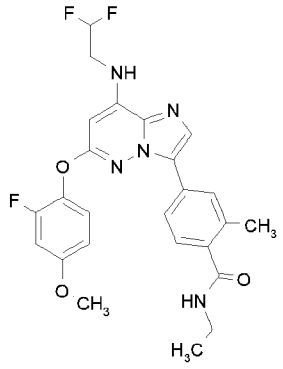
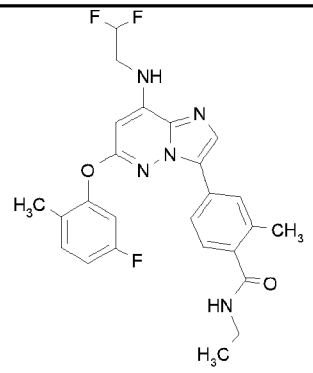
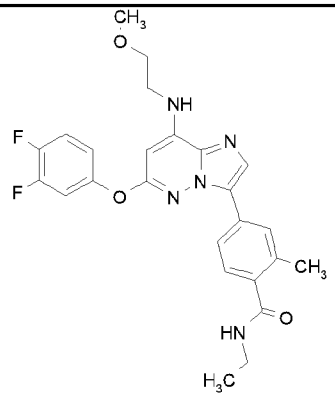
Example	Structure	Name	Analytical Data
590		N-ethyl-4-[6-(4-methoxyphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 0.83 MW_{found} = 531.6 MW_{calc} = 530.6
591		N-ethyl-4-[6-(2-fluoro-4-methoxyphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 0.86 MW_{found} = 549.6 MW_{calc} = 548.6 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 1.06 (3H), 2.10 (3H), 2.42 (4H), 2.59 (2H), 3.14-3.24 (2H), 3.44 (2H), 3.53-3.59 (4H), 3.77 (3H), 6.10 (1H), 6.54 (1H), 6.67-6.88 (1H), 7.05 (1H), 7.17 (1H), 7.25-7.32 (1H), 7.62 (1H), 7.72 (1H), 7.92 (1H), 8.16 (1H)
592		N-ethyl-4-[6-(5-fluoro-2-methylphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide	RT = 0.89 MW_{found} = 533.6 MW_{calc} = 532.6

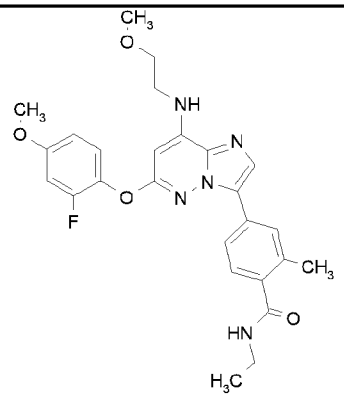
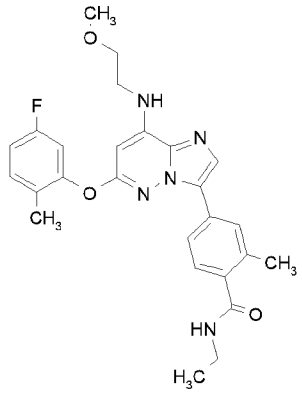
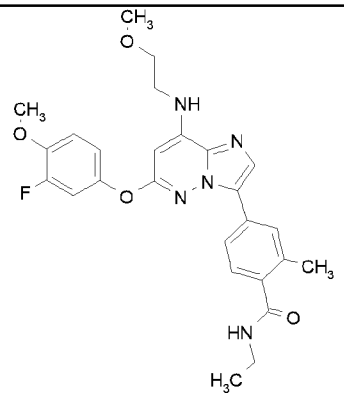
Example	Structure	Name	Analytical Data
593		N-ethyl-2-methyl-4-(8-{[2-(morpholin-4-yl)ethyl]amino}-6-phenoxyimidazo[1,2-b]pyridazin-3-yl)benzamide	RT = 0.89 MW_{found} = 501.6 MW_{calc} = 500.6 ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 1.06 (3H), 2.14 (3H), 2.59 (2H), 3.19 (4H), 3.43 (3H), 3.56 (5H), 6.05 (1H), 7.17 (1H), 7.26 (5H), 7.41-7.50 (2H), 7.66 (1H), 7.75 (1H), 7.90 (1H), 8.13 (2H)
594		4-{6-(3,4-difluorophenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-ethyl-2-methylbenzamide	RT = 1.28 MW_{found} = 522.6 MW_{calc} = 521.6 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 1.07 (3H), 1.14-1.32 (2H), 1.62 (2H), 1.86-2.01 (1H), 2.16 (3H), 3.14-3.25 (6H), 3.83 (2H), 6.09 (1H), 7.11-7.23 (2H), 7.46-7.60 (2H), 7.61-7.68 (1H), 7.68-7.77 (2H), 7.90 (1H), 8.15 (1H)
595		N-ethyl-2-methyl-4-{6-phenoxy-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.26 MW_{found} = 486.6 MW_{calc} = 485.6 ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 1.06 (3H), 1.15-1.29 (4H), 1.62 (2H), 1.89-2.00 (1H), 2.13 (3H), 3.15-3.29 (4H), 3.83 (2H), 6.07 (1H), 7.16 (1H), 7.27 (3H), 7.41-7.48

Example	Structure	Name	Analytical Data
			(2H), 7.62-7.68 (2H), 7.75 (1H), 7.90 (1H), 8.10-8.18 (1H)
596		N-ethyl-2-methyl-4-{6-(2-methylphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.29 MW_{found} = 500.6 MW_{calc} = 499.6
597		N-ethyl-4-{6-(4-methoxyphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.22 MW_{found} = 516.6 MW_{calc} = 515.6
598		N-ethyl-4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.24 MW_{found} = 534.6 MW_{calc} = 533.6

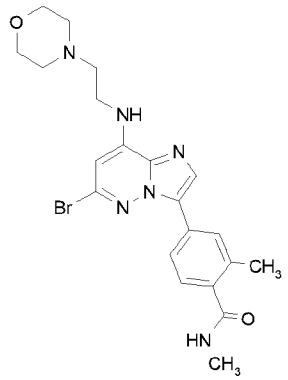
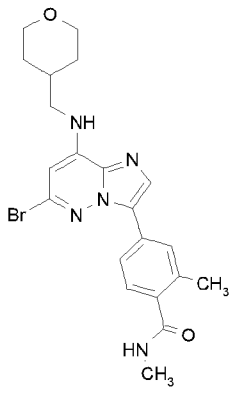
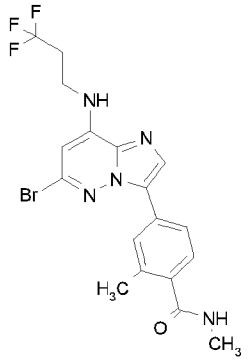
Example	Structure	Name	Analytical Data
599		N-ethyl-4-{6-(5-fluoro-2-methylphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.31 MW_{found} = 518.6 MW_{calc} = 517.6
600		N-ethyl-4-{6-(3-fluoro-4-methoxyphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.25 MW_{found} = 534.6 MW_{calc} = 533.6 ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 1.07 (3H), 1.15-1.29 (2H), 1.62 (2H), 1.94 (1H), 2.13 (3H), 3.15-3.26 (6H), 3.78-3.83 (2H), 3.84 (3H), 6.05 (1H), 7.03-7.09 (1H), 7.16-7.25 (2H), 7.30 (1H), 7.62-7.69 (2H), 7.78 (1H), 7.90 (1H), 8.15 (1H)
601		N-ethyl-2-methyl-4-{6-(2-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide	RT = 1.36 MW_{found} = 498.5 MW_{calc} = 497.5

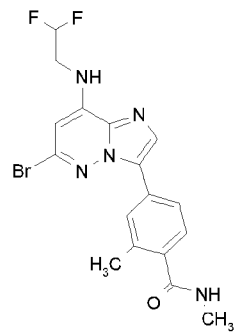
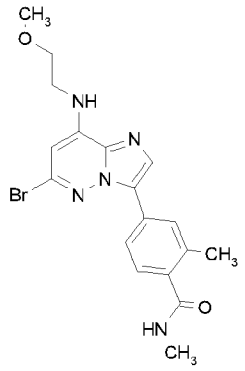
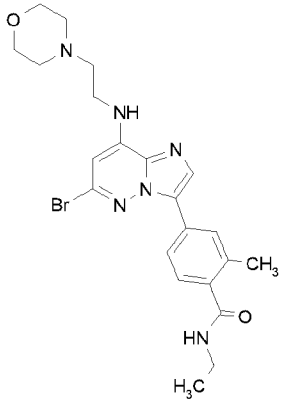
Example	Structure	Name	Analytical Data
602		N-ethyl-4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.31 MW_{found} = 532.5 MW_{calc} = 531.5 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 1.06 (3H), 2.10 (3H), 2.69 (2H), 3.13-3.24 (2H), 3.61 (2H), 3.77 (3H), 6.16 (1H), 6.84 (1H), 7.06 (1H), 7.17 (1H), 7.34 (1H), 7.58-7.65 (1H), 7.68 (1H), 7.72 (1H), 7.93 (1H), 8.15 (1H)
603		N-ethyl-4-{6-(5-fluoro-2-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.37 MW_{found} = 516.5 MW_{calc} = 515.5
604		N-ethyl-4-{6-(3-fluoro-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.32 MW_{found} = 532.5 MW_{calc} = 531.5 ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 1.07 (3H), 2.13 (3H), 2.61-2.74 (2H), 3.20 (2H), 3.59 (2H), 3.84 (3H), 6.09 (1H), 7.04-7.09 (1H), 7.17-7.20 (1H), 7.20-7.25 (1H), 7.31 (1H), 7.63-7.68 (2H), 7.78 (1H), 7.93 (1H), 8.15 (1H)

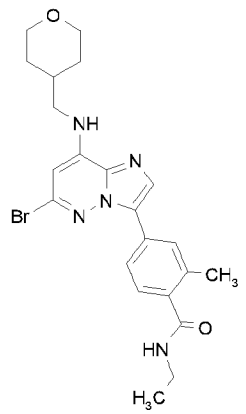
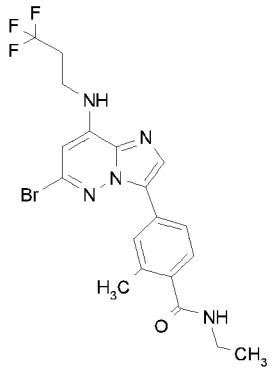
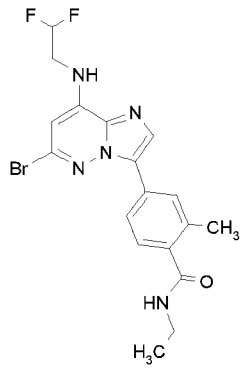
Example	Structure	Name	Analytical Data
605		4-{8-[(2,2-difluoroethyl)amino]-6-(2-fluoro-4-methoxyphenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-ethyl-2-methylbenzamide	RT = 1.22 MW_{found} = 500.5 MW_{calc} = 499.5 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 1.06 (3H), 2.10 (3H), 3.19 (2H), 3.77 (2H), 3.86 (1H), 6.32 (1H), 6.84 (1H), 7.06 (1H), 7.17 (1H), 7.34 (1H), 7.59-7.65 (1H), 7.69-7.79 (2H), 7.96 (1H), 8.15 (1H)
606		4-{8-[(2,2-difluoroethyl)amino]-6-(5-fluoro-2-methylphenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-ethyl-2-methylbenzamide	RT = 1.28 MW_{found} = 484.5 MW_{calc} = 483.5
607		4-{6-(3,4-difluorophenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-ethyl-2-methylbenzamide	RT = 1.24 MW_{found} = 482.5 MW_{calc} = 481.5

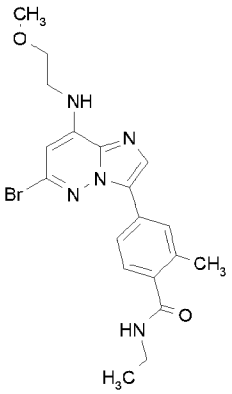
Example	Structure	Name	Analytical Data
608		N-ethyl-4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.21 MW_{found} = 494.5 MW_{calc} = 493.5
609		N-ethyl-4-{6-(5-fluoro-2-methylphenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.27 MW_{found} = 478.5 MW_{calc} = 477.5 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 1.06 (3H), 2.11 (3H), 2.12 (3H), 3.19 (4H), 3.46-3.61 (5H), 6.12 (1H), 7.06 (1H), 7.12-7.21 (2H), 7.32-7.44 (2H), 7.62 (1H), 7.71 (1H), 7.91 (1H), 8.14 (1H)
610		N-ethyl-4-{6-(3-fluoro-4-methoxyphenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide	RT = 1.19 MW_{found} = 494.5 MW_{calc} = 493.5

The following intermediate examples were prepared analogously to the procedure described above for example 562a using the appropriate amine and the appropriate boronic acid [LC-MS data such as retention time (RT in min) or observed mass peak were collected using LC-MS Method A unless explicitly stated]:

Intermediate Example	Structure	Name	Analytical Data
562a		4-(6-bromo-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl)-N,2-dimethylbenzamide	RT = 0.71 MW_{found} = 474.4 MW_{calc} = 473.4 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 2.37 (3H), 2.42 (4H), 2.54 (2H), 2.73 (3H), 3.26 (2H), 3.49-3.59 (4H), 6.42 (1H), 7.40 (2H), 7.56-7.63 (1H), 7.86 (1H), 7.92 (1H), 7.96 (1H), 8.18 (1H)
567a		4-{6-bromo-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide	RT = 1.09 MW_{found} = 459.4 MW_{calc} = 458.4 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 1.11-1.31 (2H), 1.59 (2H), 1.83-1.98 (1H), 2.37 (3H), 2.69-2.78 (3H), 3.15-3.27 (4H), 3.81 (2H), 6.42 (1H), 7.40 (1H), 7.86 (1H), 7.89-8.00 (3H), 8.18 (1H)
574a		4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide	RT = 1.18 MW_{found} = 457.3 MW_{calc} = 456.3 ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 2.37 (3H), 2.59-2.71 (2H), 2.73 (3H), 3.59 (2H), 6.46 (1H), 7.41 (1H), 7.86 (1H), 7.89-7.96 (2H), 7.97 (1H), 8.17 (1H)

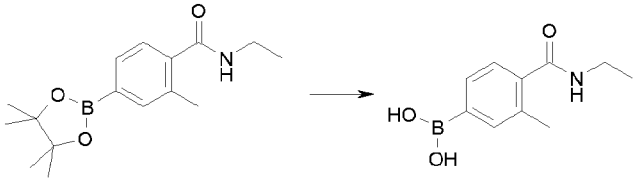
Intermediate Example	Structure	Name	Analytical Data
579a		4-{6-bromo-8-[(2,2-difluoroethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide	RT = 1.03 MW_{found} = 425.3 MW_{calc} = 424.3 ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 2.37 (3H), 2.73 (3H), 3.25 (1H), 3.85 (2H), 6.62 (1H), 7.41 (1H), 7.87 (1H), 7.92 (1H), 7.97-8.03 (2H), 8.17 (1H)
581a		4-{6-bromo-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide	RT = 1.02 MW_{found} = 419.3 MW_{calc} = 418.3 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 2.37 (3H), 2.73 (3H), 3.25 (3H), 3.53 (4H), 6.42 (1H), 7.41 (1H), 7.71 (1H), 7.86 (1H), 7.89-7.94 (1H), 7.95 (1H), 8.16 (1H)
588a		4-(6-bromo-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl)-N-ethyl-2-methylbenzamide	RT = 0.75 MW_{found} = 488.4 MW_{calc} = 487.4 ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 1.06-1.12 (3H), 2.37 (3H), 2.42 (4H), 2.56 (2H), 3.18-3.26 (2H), 3.43 (2H), 3.52-3.58 (4H), 6.41 (1H), 7.39 (1H), 7.57 (1H), 7.85 (1H), 7.91 (1H), 7.95 (1H), 8.22 (1H)

Intermediate Example	Structure	Name	Analytical Data
594a		4-{6-bromo-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-ethyl-2-methylbenzamide	RT = 1.1.17 MW_{found} = 473.4 MW_{calc} = 472.4 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 1.05-1.12 (3H), 1.13-1.31 (2H), 1.59 (2H), 1.89 (1H), 2.37 (3H), 3.16-3.25 (6H), 3.81 (2H), 6.42 (1H), 7.39 (1H), 7.85 (1H), 7.88-7.98 (3H), 8.22 (1H)
601a		4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-ethyl-2-methylbenzamide	RT = 1.25 MW_{found} = 471.3 MW_{calc} = 470.3 ^{1}H-NMR (400 MHz ,DMSO-d_6), δ [ppm]= 1.09 (3H), 2.37 (3H), 2.66 (2H), 3.18-3.26 (2H), 3.59 (2H), 6.46 (1H), 7.40 (1H), 7.85 (1H), 7.89-7.96 (2H), 7.96 (1H), 8.23 (1H)
605a		4-{6-bromo-8-[(2,2-difluoroethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-ethyl-2-methylbenzamide	RT = 1.10 MW_{found} = 439.3 MW_{calc} = 438.3 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 1.09 (3H), 2.37 (3H), 3.18-3.26 (3H), 3.86 (2H), 6.61 (1H), 7.40 (1H), 7.86 (1H), 7.89-7.95 (1H), 7.99 (2H), 8.23 (1H)

Intermediate Example	Structure	Name	Analytical Data
607a		4-{6-bromo-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-ethyl-2-methylbenzamide	RT = 1.09 MW_{found} = 433.3 MW_{calc} = 432.3 ^{1}H-NMR (300 MHz ,DMSO-d_6), δ [ppm]= 1.09 (3H), 2.37 (3H), 3.18-3.27 (4H), 3.43-3.59 (5H), 6.43 (1H), 7.39 (2H), 7.75 (1H), 7.86 (1H), 7.92 (1H), 7.95 (1H), 8.24 (1H)

Intermediate example 582b

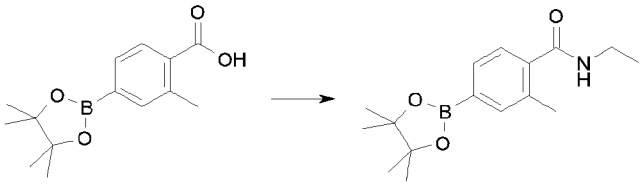
[4-(ethylcarbamoyl)-3-methylphenyl]boronic acid



17.72 g (61.27 mmol) N-ethyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide which was prepared according to intermediate example 582c were transformed in analogy to intermediate example 562b to give after working up and purification 8.75 g (70%) of the title compound.

Intermediate example 582c

N-ethyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide



To a stirred solution of 15 g (57 mmol) 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid in NMP (20 mL) were added 85.84 mL (171.68 mmol) ethylamine and 72.8 mL 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-

trioxide (114.45 mmol, 2M in THF) and the mixture was stirred for 2 h at rt to give after working up and purification 16.00 g (96.7 %) of the title compound.

Pharmaceutical compositions of the compounds of the invention

This invention also relates to pharmaceutical compositions containing one or more compounds of the present invention. These compositions can be utilised to achieve the desired pharmacological effect by administration to a patient in need thereof. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for the particular condition or disease. Therefore, the present invention includes pharmaceutical compositions that are comprised of a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound, or salt thereof, of the present invention. A pharmaceutically acceptable carrier is preferably a carrier that is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active ingredient so that any side effects ascribable to the carrier do not vitiate the beneficial effects of the active ingredient. A pharmaceutically effective amount of compound is preferably that amount which produces a result or exerts an influence on the particular condition being treated. The compounds of the present invention can be administered with pharmaceutically-acceptable carriers well known in the art using any effective conventional dosage unit forms, including immediate, slow and timed release preparations, orally, parenterally, topically, nasally, ophthalmically, optically, sublingually, rectally, vaginally, and the like.

For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, troches, lozenges, melts, powders, solutions, suspensions, or emulsions, and may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions. The solid unit dosage forms can be a capsule that can be of the ordinary hard- or soft-shelled gelatine type containing, for example, surfactants, lubricants, and inert fillers such as lactose, sucrose, calcium phosphate, and corn starch.

In another embodiment, the compounds of this invention may be tableted with conventional tablet bases such as lactose, sucrose and cornstarch in combination

with binders such as acacia, corn starch or gelatine, disintegrating agents intended to assist the break-up and dissolution of the tablet following administration such as potato starch, alginic acid, corn starch, and guar gum, gum tragacanth, acacia, lubricants intended to improve the flow of tablet granulation and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example talc, stearic acid, or magnesium, calcium or zinc stearate, dyes, colouring agents, and flavouring agents such as peppermint, oil of wintergreen, or cherry flavouring, intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the patient. Suitable excipients for use in oral liquid dosage forms include dicalcium phosphate and diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent or emulsifying agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance tablets, pills or capsules may be coated with shellac, sugar or both.

Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example those sweetening, flavouring and colouring agents described above, may also be present.

The pharmaceutical compositions of this invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as liquid paraffin or a mixture of vegetable oils. Suitable emulsifying agents may be (1) naturally occurring gums such as gum acacia and gum tragacanth, (2) naturally occurring phosphatides such as soy bean and lecithin, (3) esters or partial esters derived form fatty acids and hexitol anhydrides, for example, sorbitan monooleate, (4) condensation products of said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil or coconut oil,

or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate ; one or more colouring agents ; one or more flavouring agents ; and one or more sweetening agents such as sucrose or saccharin.

Syrups and elixirs may be formulated with sweetening agents such as, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, and preservative, such as methyl and propyl parabens and flavouring and colouring agents.

The compounds of this invention may also be administered parenterally, that is, subcutaneously, intravenously, intraocularly, intrasynovially, intramuscularly, or interperitoneally, as injectable dosages of the compound in preferably a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid or mixture of liquids such as water, saline, aqueous dextrose and related sugar solutions, an alcohol such as ethanol, isopropanol, or hexadecyl alcohol, glycols such as propylene glycol or polyethylene glycol, glycerol ketals such as 2,2-dimethyl-1,1-dioxolane-4-methanol, ethers such as poly(ethylene glycol) 400, an oil, a fatty acid, a fatty acid ester or, a fatty acid glyceride, or an acetylated fatty acid glyceride, with or without the addition of a pharmaceutically acceptable surfactant such as a soap or a detergent, suspending agent such as pectin, carbomers, methycellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agent and other pharmaceutical adjuvants.

Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum and mineral oil. Suitable fatty acids include oleic acid, stearic acid, isostearic acid and myristic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable soaps include fatty acid alkali metal, ammonium, and triethanolamine salts and suitable detergents include cationic detergents, for example dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates ; anionic detergents, for example, alkyl, aryl, and

olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates ; non-ionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene-oxypropylene)s or ethylene oxide or propylene oxide copolymers ; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quarternary ammonium salts, as well as mixtures.

The parenteral compositions of this invention will typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Preservatives and buffers may also be used advantageously. In order to minimise or eliminate irritation at the site of injection, such compositions may contain a non-ionic surfactant having a hydrophile-lipophile balance (HLB) preferably of from about 12 to about 17. The quantity of surfactant in such formulation preferably ranges from about 5% to about 15% by weight. The surfactant can be a single component having the above HLB or can be a mixture of two or more components having the desired HLB.

Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

The pharmaceutical compositions may be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia ; dispersing or wetting agents which may be a naturally occurring phosphatide such as lecithin, a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadeca-ethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived form a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or a condensation product of an ethylene oxide with a partial

ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents and solvents that may be employed are, for example, water, Ringer's solution, isotonic sodium chloride solutions and isotonic glucose solutions. In addition, sterile fixed oils are conventionally employed as solvents or suspending media. For this purpose, any bland, fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can be used in the preparation of injectables.

A composition of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritation excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are, for example, cocoa butter and polyethylene glycol.

Another formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art (see, e.g., US Patent No. 5,023,252, issued June 11, 1991, incorporated herein by reference). Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Controlled release formulations for parenteral administration include liposomal, polymeric microsphere and polymeric gel formulations that are known in the art.

It may be desirable or necessary to introduce the pharmaceutical composition to the patient via a mechanical delivery device. The construction and use of mechanical delivery devices for the delivery of pharmaceutical agents is well known in the art. Direct techniques for, for example, administering a drug directly to the brain usually involve placement of a drug delivery catheter into the

patient's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of agents to specific anatomical regions of the body, is described in US Patent No. 5,011,472, issued April 30, 1991.

The compositions of the invention can also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized. Such ingredients and procedures include those described in the following references, each of which is incorporated herein by reference: Powell, M.F. *et al.*, "Compendium of Excipients for Parenteral Formulations" PDA Journal of Pharmaceutical Science & Technology **1998**, 52(5), 238-311 ; Strickley, R.G "Parenteral Formulations of Small Molecule Therapeutics Marketed in the United States (1999)-Part-1" PDA Journal of Pharmaceutical Science & Technology **1999**, 53(6), 324-349 ; and Nema, S. *et al.*, "Excipients and Their Use in Injectable Products" PDA Journal of Pharmaceutical Science & Technology **1997**, 51(4), 166-171.

Commonly used pharmaceutical ingredients that can be used as appropriate to formulate the composition for its intended route of administration include:

acidifying agents (examples include but are not limited to acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid) ;

alkalinizing agents (examples include but are not limited to ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, trolamine) ;

adsorbents (examples include but are not limited to powdered cellulose and activated charcoal) ;

aerosol propellants (examples include but are not limited to carbon dioxide, CCl_2F_2, $F_2ClC\text{-}CClF_2$ and $CClF_3$)

air displacement agents (examples include but are not limited to nitrogen and argon) ;

antifungal preservatives (examples include but are not limited to benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate) ;

antimicrobial preservatives (examples include but are not limited to benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal) ;

antioxidants (examples include but are not limited to ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite) ;

binding materials (examples include but are not limited to block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones, polysiloxanes and styrene-butadiene copolymers) ;

buffering agents (examples include but are not limited to potassium metaphosphate, dipotassium phosphate, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate)

carrying agents (examples include but are not limited to acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection)

chelating agents (examples include but are not limited to edetate disodium and edetic acid)

colourants (examples include but are not limited to FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red) ;

clarifying agents (examples include but are not limited to bentonite) ;

emulsifying agents (examples include but are not limited to acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyoxyethylene 50 monostearate) ;

encapsulating agents (examples include but are not limited to gelatin and cellulose acetate phthalate)

flavourants (examples include but are not limited to anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin) ;

humectants (examples include but are not limited to glycerol, propylene glycol and sorbitol) ;

levigating agents (examples include but are not limited to mineral oil and glycerin) ;

oils (examples include but are not limited to arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil) ;

ointment bases (examples include but are not limited to lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment) ;

penetration enhancers (transdermal delivery) (examples include but are not limited to monohydroxy or polyhydroxy alcohols, mono-or polyvalent alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas)

plasticizers (examples include but are not limited to diethyl phthalate and glycerol) ;

solvents (examples include but are not limited to ethanol, corn oil, cottonseed oil, glycerol, isopropanol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation) ;

stiffening agents (examples include but are not limited to cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax) ;

suppository bases (examples include but are not limited to cocoa butter and polyethylene glycols (mixtures)) ;

surfactants (examples include but are not limited to benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan mono-palmitate) ;

suspending agents (examples include but are not limited to agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum) ;

sweetening agents (examples include but are not limited to aspartame, dextrose, glycerol, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose) ;

tablet anti-adherents (examples include but are not limited to magnesium stearate and talc) ;

tablet binders (examples include but are not limited to acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, non-crosslinked polyvinyl pyrrolidone, and pregelatinized starch) ;

tablet and capsule diluents (examples include but are not limited to dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch) ;

tablet coating agents (examples include but are not limited to liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac) ;

tablet direct compression excipients (examples include but are not limited to dibasic calcium phosphate) ;

tablet disintegrants (examples include but are not limited to alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, cross-linked polyvinylpyrrolidone, sodium alginate, sodium starch glycollate and starch) ;

tablet glidants (examples include but are not limited to colloidal silica, corn starch and talc) ;

tablet lubricants (examples include but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate) ;

tablet/capsule opaquants (examples include but are not limited to titanium dioxide) ;

tablet polishing agents (examples include but are not limited to carnuba wax and white wax) ;

thickening agents (examples include but are not limited to beeswax, cetyl alcohol and paraffin) ;

tonicity agents (examples include but are not limited to dextrose and sodium chloride) ;

viscosity increasing agents (examples include but are not limited to alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, polyvinyl pyrrolidone, sodium alginate and tragacanth) ; and

wetting agents (examples include but are not limited to heptadecaethylene oxycetanol, lecithins, sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate).

Pharmaceutical compositions according to the present invention can be illustrated as follows:

Sterile IV Solution: A 5 mg/mL solution of the desired compound of this invention can be made using sterile, injectable water, and the pH is adjusted if necessary. The solution is diluted for administration to 1 - 2 mg/mL with sterile 5% dextrose and is administered as an IV infusion over about 60 minutes.

Lyophilised powder for IV administration: A sterile preparation can be prepared with (i) 100 - 1000 mg of the desired compound of this invention as a lyophilised powder, (ii) 32- 327 mg/mL sodium citrate, and (iii) 300 - 3000 mg Dextran 40. The formulation is reconstituted with sterile, injectable saline or dextrose 5% to a

concentration of 10 to 20 mg/mL, which is further diluted with saline or dextrose 5% to 0.2 - 0.4 mg/mL, and is administered either IV bolus or by IV infusion over 15 - 60 minutes.

Intramuscular suspension: The following solution or suspension can be prepared, for intramuscular injection:

50 mg/mL of the desired, water-insoluble compound of this invention

5 mg/mL sodium carboxymethylcellulose

4 mg/mL TWEEN 80

9 mg/mL sodium chloride

9 mg/mL benzyl alcohol

Hard Shell Capsules: A large number of unit capsules are prepared by filling standard two-piece hard galantine capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate.

Soft Gelatin Capsules: A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into molten gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules are washed and dried. The active ingredient can be dissolved in a mixture of polyethylene glycol, glycerin and sorbitol to prepare a water miscible medicine mix.

Tablets: A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 mg of active ingredient, 0.2 mg. of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg. of starch, and 98.8 mg of lactose. Appropriate aqueous and non-aqueous coatings may be applied to increase palatability, improve elegance and stability or delay absorption.

Immediate Release Tablets/Capsules: These are solid oral dosage forms made by conventional and novel processes. These units are taken orally without water for immediate dissolution and delivery of the medication. The active ingredient is

mixed in a liquid containing ingredient such as sugar, gelatin, pectin and sweeteners. These liquids are solidified into solid tablets or caplets by freeze drying and solid state extraction techniques. The drug compounds may be compressed with viscoelastic and thermoelastic sugars and polymers or effervescent components to produce porous matrices intended for immediate release, without the need of water.

Combination therapies

The compounds of this invention can be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutical agents where the combination causes no unacceptable adverse effects. The present invention relates also to such combinations. For example, the compounds of this invention can be combined with known anti-hyper-proliferative or other indication agents, and the like, as well as with admixtures and combinations thereof. Other indication agents include, but are not limited to, anti-angiogenic agents, mitotic inhibitors, alkylating agents, anti-metabolites, DNA-intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzyme inhibitors, toposisomerase inhibitors, biological response modifiers, or anti-hormones.

The additional pharmaceutical agent can be afinitor, aldesleukin, alendronic acid, alfaferone, alitretinoin, allopurinol, aloprim, aloxi, altretamine, aminoglutethimide, amifostine, amrubicin, amsacrine, anastrozole, anzmet, aranesp, arglabin, arsenic trioxide, aromasin, 5-azacytidine, azathioprine, BCG or tice BCG, bestatin, betamethasone acetate, betamethasone sodium phosphate, bexarotene, bleomycin sulfate, broxuridine , bortezomib, busulfan, calcitonin, campath, capecitabine, carboplatin, casodex, cefesone, celmoleukin, cerubidine, chlorambucil, cisplatin, cladribine, cladribine, clodronic acid, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, DaunoXome, decadron, decadron phosphate, delestrogen, denileukin diftitox, depo-medrol, deslorelin, dexrazoxane, diethylstilbestrol, diflucan, docetaxel, doxifluridine, doxorubicin, dronabinol, DW-166HC, eligard, elitek, ellence, emend, epirubicin, epoetin alfa, epogen, eptaplatin, ergamisol, estrace, estradiol, estramustine phosphate sodium, ethinyl estradiol, ethyol, etidronic acid, etopophos, etoposide, fadrozole, farston,

filgrastim, finasteride, fligrastim, floxuridine, fluconazole, fludarabine, 5-fluorodeoxyuridine monophosphate, 5-fluorouracil (5-FU), fluoxymesterone, flutamide, formestane, fosteabine, fotemustine, fulvestrant, gammagard, gemcitabine, gemtuzumab, gleevec, gliadel, goserelin, granisetron HCl, histrelin, hycamtin, hydrocortone, eyrthro-hydroxynonyladenine, hydroxyurea, ibritumomab tiuxetan, idarubicin, ifosfamide, interferon alpha, interferon-alpha 2, interferon alfa-2A, interferon alfa-2B, interferon alfa-n1, interferon alfa-n3, interferon beta, interferon gamma-1a, interleukin-2, intron A, iressa, irinotecan, kytril, lapatinib, lentinan sulfate, letrozole, leucovorin, leuprolide, leuprolide acetate, levamisole, levofolinic acid calcium salt, levothroid, levoxyl, lomustine, lonidamine, marinol, mechlorethamine, mecobalamin, medroxyprogesterone acetate, megestrol acetate, melphalan, menest, 6-mercaptopurine, Mesna, methotrexate, metvix, miltefosine, minocycline, mitomycin C, mitotane, mitoxantrone, Modrenal, Myocet, nedaplatin, neulasta, neumega, neupogen, nilutamide, nolvadex, NSC-631570, OCT-43, octreotide, ondansetron HCl, orapred, oxaliplatin, paclitaxel, pediapred, pegaspargase, Pegasys, pentostatin, picibanil, pilocarpine HCl, pirarubicin, plicamycin, porfimer sodium, prednimustine, prednisolone, prednisone, premarin, procarbazine, procrit, raltitrexed, RDEA 119, rebif, rhenium-186 etidronate, rituximab, roferon-A, romurtide, salagen, sandostatin, sargramostim, semustine, sizofiran, sobuzoxane, solu-medrol, sparfosic acid, stem-cell therapy, streptozocin, strontium-89 chloride, sunitinib, synthroid, tamoxifen, tamsulosin, tasonermin, tastolactone, taxotere, teceleukin, temozolomide, teniposide, testosterone propionate, testred, thioguanine, thiotepa, thyrotropin, tiludronic acid, topotecan, toremifene, tositumomab, trastuzumab, treosulfan, tretinoin, trexall, trimethylmelamine, trimetrexate, triptorelin acetate, triptorelin pamoate, UFT, uridine, valrubicin, vesnarinone, vinblastine, vincristine, vindesine, vinorelbine, virulizin, zinecard, zinostatin stimalamer, zofran, ABI-007, acolbifene, actimmune, affinitak, aminopterin, arzoxifene, asoprisnil, atamestane, atrasentan, sorafenib (BAY 43-9006), avastin, CCI-779, CDC-501, celebrex, cetuximab, crisnatol, cyproterone acetate, decitabine, DN-101, doxorubicin-MTC, dSLIM, dutasteride, edotecarin, eflornithine, exatecan, fenretinide, histamine dihydrochloride, histrelin hydrogel implant, holmium-166 DOTMP, ibandronic acid, interferon gamma, intron-PEG, ixabepilone, keyhole limpet hemocyanin, L-651582, lanreotide, lasofoxifene, libra, lonafarnib, miproxifene, minodronate, MS-209,

liposomal MTP-PE, MX-6, nafarelin, nemorubicin, neovastat, nolatrexed, oblimersen, onco-TCS, osidem, paclitaxel polyglutamate, pamidronate disodium, PN-401, QS-21, quazepam, R-1549, raloxifene, ranpirnase, 13-cis -retinoic acid, satraplatin, seocalcitol, T-138067, tarceva, taxoprexin, thymosin alpha 1, tiazofurine, tipifarnib, tirapazamine, TLK-286, toremifene, TransMID-107R, valspodar, vapreotide, vatalanib, verteporfin, vinflunine, Z-100, zoledronic acid or combinations thereof.

Optional anti-hyper-proliferative agents which can be added to the composition include but are not limited to compounds listed on the cancer chemotherapy drug regimens in the 11th Edition of the Merck Index, (1996), which is hereby incorporated by reference, such as asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, epothilone, an epothilone derivative, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

Other anti-hyper-proliferative agents suitable for use with the composition of the invention include but are not limited to those compounds acknowledged to be used in the treatment of neoplastic diseases in Goodman and Gilman's The Pharmacological Basis of Therapeutics (Ninth Edition), editor Molinoff *et al.*, publ. by McGraw-Hill, pages 1225-1287, (1996), which is hereby incorporated by reference, such as aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2',2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyl adenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

Other anti-hyper-proliferative agents suitable for use with the composition of the invention include but are not limited to other anti-cancer agents such as epothilone and its derivatives, irinotecan, raloxifen and topotecan.

The compounds of the invention may also be administered in combination with protein therapeutics. Such protein therapeutics suitable for the treatment of cancer or other angiogenic disorders and for use with the compositions of the invention include, but are not limited to, an interferon (e.g., interferon .alpha., .beta., or .gamma.) supraagonistic monoclonal antibodies, Tuebingen, TRP-1 protein vaccine, Colostrinin, anti-FAP antibody, YH-16, gemtuzumab, infliximab, cetuximab, trastuzumab, denileukin diftitox, rituximab, thymosin alpha 1, bevacizumab, mecasermin, mecasermin rinfabate, oprelvekin, natalizumab, rhMBL, MFE-CP1 + ZD-2767-P, ABT-828, ErbB2-specific immunotoxin, SGN-35, MT-103, rinfabate, AS-1402, B43-genistein, L-19 based radioimmunotherapeutics, AC-9301, NY-ESO-1 vaccine, IMC-1C11, CT-322, rhCC10, r(m)CRP, MORAb-009, aviscumine, MDX-1307, Her-2 vaccine, APC-8024, NGR-hTNF, rhH1.3, IGN-311, Endostatin, volociximab, PRO-1762, lexatumumab, SGN-40, pertuzumab, EMD-273063, L19-IL-2 fusion protein, PRX-321, CNTO-328, MDX-214, tigapotide, CAT-3888, labetuzumab, alpha-particle-emitting radioisotope-llinked lintuzumab, EM-1421, HyperAcute vaccine, tucotuzumab celmoleukin, galiximab, HPV-16-E7, Javelin - prostate cancer, Javelin - melanoma, NY-ESO-1 vaccine, EGF vaccine, CYT-004-MelQbG10, WT1 peptide, oregovomab, ofatumumab, zalutumumab, cintredekin besudotox, WX-G250, Albuferon, aflibercept, denosumab, vaccine, CTP-37, efungumab, or 131I-chTNT-1/B. Monoclonal antibodies useful as the protein therapeutic include, but are not limited to, muromonab-CD3, abciximab, edrecolomab, daclizumab, gentuzumab, alemtuzumab, ibritumomab, cetuximab, bevicizumab, efalizumab, adalimumab, omalizumab, muromomab-CD3, rituximab, daclizumab, trastuzumab, palivizumab, basiliximab, and infliximab.

The compounds of the invention may also be combined with biological therapeutic agents, such as antibodies (e.g. avastin, rituxan, erbitux, herceptin), or recombinant proteins.

The compounds of the invention may also be in combination with antiangiogenesis agents, such as, for example, with avastin, axitinib, DAST, recentin, sorafenib or

sunitinib. Combinations with inhibitors of proteasomes or mTOR inhibitors, or anti-hormones or steroidal metabolic enzyme inhibitors are also possible.

Generally, the use of cytotoxic and/or cytostatic agents in combination with a compound or composition of the present invention will serve to:

(1) yield better efficacy in reducing the growth of a tumour or even eliminate the tumour as compared to administration of either agent alone,

(2) provide for the administration of lesser amounts of the administered chemotherapeutic agents,

(3) provide for a chemotherapeutic treatment that is well tolerated in the patient with fewer deleterious pharmacological complications than observed with single agent chemotherapies and certain other combined therapies,

(4) provide for treating a broader spectrum of different cancer types in mammals, especially humans,

(5) provide for a higher response rate among treated patients,

(6) provide for a longer survival time among treated patients compared to standard chemotherapy treatments,

(7) provide a longer time for tumour progression, and/or

(8) yield efficacy and tolerability results at least as good as those of the agents used alone, compared to known instances where other cancer agent combinations produce antagonistic effects.

Methods of Sensitizing Cells to Radiation

In a distinct embodiment of the present invention, a compound of the present invention may be used to sensitize a cell to radiation. That is, treatment of a cell with a compound of the present invention prior to radiation treatment of the cell renders the cell more susceptible to DNA damage and cell death than the cell

would be in the absence of any treatment with a compound of the invention. In one aspect, the cell is treated with at least one compound of the invention.

Thus, the present invention also provides a method of killing a cell, wherein a cell is administered one or more compounds of the invention in combination with conventional radiation therapy.

The present invention also provides a method of rendering a cell more susceptible to cell death, wherein the cell is treated one or more compounds of the invention prior to the treatment of the cell to cause or induce cell death. In one aspect, after the cell is treated with one or more compounds of the invention, the cell is treated with at least one compound, or at least one method, or a combination thereof, in order to cause DNA damage for the purpose of inhibiting the function of the normal cell or killing the cell.

In one embodiment, a cell is killed by treating the cell with at least one DNA damaging agent. That is, after treating a cell with one or more compounds of the invention to sensitize the cell to cell death, the cell is treated with at least one DNA damaging agent to kill the cell. DNA damaging agents useful in the present invention include, but are not limited to, chemotherapeutic agents (*e.g.*, cisplatinum), ionizing radiation (X-rays, ultraviolet radiation), carcinogenic agents, and mutagenic agents.

In another embodiment, a cell is killed by treating the cell with at least one method to cause or induce DNA damage. Such methods include, but are not limited to, activation of a cell signalling pathway that results in DNA damage when the pathway is activated, inhibiting of a cell signalling pathway that results in DNA damage when the pathway is inhibited, and inducing a biochemical change in a cell, wherein the change results in DNA damage. By way of a non-limiting example, a DNA repair pathway in a cell can be inhibited, thereby preventing the repair of DNA damage and resulting in an abnormal accumulation of DNA damage in a cell.

In one aspect of the invention, a compound of the invention is administered to a cell prior to the radiation or other induction of DNA damage in the cell. In another aspect of the invention, a compound of the invention is administered to a cell concomitantly with the radiation or other induction of DNA damage in the cell. In

yet another aspect of the invention, a compound of the invention is administered to a cell immediately after radiation or other induction of DNA damage in the cell has begun.

In another aspect, the cell is in vitro. In another embodiment, the cell is in vivo.

As mentioned supra, the compounds of the present invention have surprisingly been found to effectively inhibit Mps-1 and may therefore be used for the treatment or prophylaxis of diseases of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, or diseases which are accompanied with uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, particularly in which the uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses is mediated by Mps-1, such as, for example, haematological tumours, solid tumours, and/or metastases thereof, e.g. leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

In accordance with another aspect therefore, the present invention covers a compound of general formula I, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, as described and defined herein, for use in the treatment or prophylaxis of a disease, as mentioned supra.

Another particular aspect of the present invention is therefore the use of a compound of general formula I, described *supra*, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, for the prophylaxis or treatment of a disease.

Another particular aspect of the present invention is therefore the use of a compound of general formula I described supra for manufacturing a pharmaceutical composition for the treatment or prophylaxis of a disease.

The diseases referred to in the two preceding paragraphs are diseases of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, or diseases which are accompanied with uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, particularly in which the uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses is mediated by Mps-1, such as, for example, haematological tumours, solid tumours, and/or metastases thereof, e.g. leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

The term "inappropriate" within the context of the present invention, in particular in the context of "inappropriate cellular immune responses, or inappropriate cellular inflammatory responses", as used herein, is to be understood as preferably meaning a response which is less than, or greater than normal, and which is associated with, responsible for, or results in, the pathology of said diseases.

Preferably, the use is in the treatment or prophylaxis of diseases, wherein the diseases are haemotological tumours, solid tumours and/or metastases thereof.

Method of treating hyper-proliferative disorders

The present invention relates to a method for using the compounds of the present invention and compositions thereof, to treat mammalian hyper-proliferative

disorders. Compounds can be utilized to inhibit, block, reduce, decrease, etc., cell proliferation and/or cell division, and/or produce apoptosis. This method comprises administering to a mammal in need thereof, including a human, an amount of a compound of this invention, or a pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate, solvate or ester thereof ; etc. which is effective to treat the disorder. Hyper-proliferative disorders include but are not limited, e.g., psoriasis, keloids, and other hyperplasias affecting the skin, benign prostate hyperplasia (BPH), solid tumours, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases. Those disorders also include lymphomas, sarcomas, and leukaemias.

Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ.

Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to brain stem and hypophtalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumour.

Tumours of the male reproductive organs include, but are not limited to prostate and testicular cancer. Tumours of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

Tumours of the digestive tract include, but are not limited to anal, colon, colorectal, oesophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers. Tumours of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, urethral and human papillary renal cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

Head-and-neck cancers include, but are not limited to laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer and squamous cell. Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Burkitt lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

These disorders have been well characterized in humans, but also exist with a similar etiology in other mammals, and can be treated by administering pharmaceutical compositions of the present invention.

The term "treating" or "treatment" as stated throughout this document is used conventionally, *e.g.*, the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving the condition of, *etc.*, of a disease or disorder, such as a carcinoma.

Methods of treating kinase disorders

The present invention also provides methods for the treatment of disorders associated with aberrant mitogen extracellular kinase activity, including, but not limited to stroke, heart failure, hepatomegaly, cardiomegaly, diabetes, Alzheimer's disease, cystic fibrosis, symptoms of xenograft rejections, septic shock or asthma.

Effective amounts of compounds of the present invention can be used to treat such disorders, including those diseases (*e.g.*, cancer) mentioned in the Background section above. Nonetheless, such cancers and other diseases can be treated with compounds of the present invention, regardless of the mechanism of action and/or the relationship between the kinase and the disorder.

The phrase "aberrant kinase activity" or "aberrant tyrosine kinase activity," includes any abnormal expression or activity of the gene encoding the kinase or of the polypeptide it encodes. Examples of such aberrant activity, include, but are not limited to, over-expression of the gene or polypeptide ; gene amplification ; mutations which produce constitutively-active or hyperactive kinase activity ; gene mutations, deletions, substitutions, additions, etc.

The present invention also provides for methods of inhibiting a kinase activity, especially of mitogen extracellular kinase, comprising administering an effective amount of a compound of the present invention, including salts, polymorphs, metabolites, hydrates, solvates, prodrugs (*e.g.*: esters) thereof, and diastereoisomeric forms thereof. Kinase activity can be inhibited in cells (*e.g.*, *in vitro*), or in the cells of a mammalian subject, especially a human patient in need of treatment.

Methods of treating angiogenic disorders

The present invention also provides methods of treating disorders and diseases associated with excessive and/or abnormal angiogenesis.

Inappropriate and ectopic expression of angiogenesis can be deleterious to an organism. A number of pathological conditions are associated with the growth of extraneous blood vessels. These include, e.g., diabetic retinopathy, ischemic retinal-vein occlusion, and retinopathy of prematurity [Aiello et al. New Engl. J. Med. **1994**, 331, 1480 ; Peer et al. Lab. Invest. **1995**, 72, 638], age-related macular degeneration [AMD ; see, Lopez et al. Invest. Opththalmol. Vis. Sci. **1996**, 37, 855], neovascular glaucoma, psoriasis, retrolental fibroplasias, angiofibroma, inflammation, rheumatoid arthritis (RA), restenosis, in-stent restenosis, vascular graft restenosis, etc. In addition, the increased blood supply associated with

cancerous and neoplastic tissue, encourages growth, leading to rapid tumour enlargement and metastasis. Moreover, the growth of new blood and lymph vessels in a tumour provides an escape route for renegade cells, encouraging metastasis and the consequence spread of the cancer. Thus, compounds of the present invention can be utilized to treat and/or prevent any of the aforementioned angiogenesis disorders, e.g., by inhibiting and/or reducing blood vessel formation ; by inhibiting, blocking, reducing, decreasing, etc. endothelial cell proliferation or other types involved in angiogenesis, as well as causing cell death or apoptosis of such cell types.

Dose and administration

Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of hyper-proliferative disorders and angiogenic disorders, by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the compounds of this invention can readily be determined for treatment of each desired indication. The amount of the active ingredient to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

The total amount of the active ingredient to be administered will generally range from about 0.001 mg/kg to about 200 mg/kg body weight per day, and preferably from about 0.01 mg/kg to about 20 mg/kg body weight per day. Clinically useful dosing schedules will range from one to three times a day dosing to once every four weeks dosing. In addition, "drug holidays" in which a patient is not dosed with a drug for a certain period of time, may be beneficial to the overall balance between pharmacological effect and tolerability. A unit dosage may contain from about 0.5 mg to about 1500 mg of active ingredient, and can be administered one or more times per day or less than once a day. The average daily dosage for administration

by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The average daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

Of course the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compound employed, the age and general condition of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a compound of the present invention or a pharmaceutically acceptable salt or ester or composition thereof can be ascertained by those skilled in the art using conventional treatment tests.

Preferably, the diseases of said method are haematological tumours, solid tumour and/or metastases thereof.

The compounds of the present invention can be used in particular in therapy and prevention, i.e. prophylaxis, of tumour growth and metastases, especially in solid tumours of all indications and stages with or without pre-treatment of the tumour growth.

Methods of testing for a particular pharmacological or pharmaceutical property are well known to persons skilled in the art.

The example testing experiments described herein serve to illustrate the present invention and the invention is not limited to the examples given.

Biological assay: Proliferation Assay

Cultivated tumour cells (MCF7, hormone dependent human mammary carcinoma cells, ATCC HTB22; NCI-H460, human non-small cell lung carcinoma cells, ATCC HTB-177; DU 145, hormone-independent human prostate carcinoma cells, ATCC HTB-81; HeLa-MaTu, human cervical carcinoma cells, EPO-GmbH, Berlin; HeLa-MaTu-ADR, multidrug-resistant human cervical carcinoma cells, EPO-GmbH, Berlin; HeLa human cervical tumour cells, ATCC CCL-2; B16F10 mouse melanoma cells, ATCC CRL-6475) were plated at a density of 5000 cells/well (MCF7, DU145, HeLa-MaTu-ADR), 3000 cells/well (NCI-H460, HeLa-MaTu, HeLa), or 1000 cells/well (B16F10) in a 96-well multititer plate in 200 µL of their respective growth medium supplemented 10% fetal calf serum. After 24 hours, the cells of one plate (zero-point plate) were stained with crystal violet (see below), while the medium of the other plates was replaced by fresh culture medium (200 µl), to which the test substances were added in various concentrations (0 µM, as well as in the range of 0.01-30 µM; the final concentration of the solvent dimethyl sulfoxide was 0.5%). The cells were incubated for 4 days in the presence of test substances. Cell proliferation was determined by staining the cells with crystal violet: the cells were fixed by adding 20 µl/measuring point of an 11% glutaric aldehyde solution for 15 minutes at room temperature. After three washing cycles of the fixed cells with water, the plates were dried at room temperature. The cells were stained by adding 100 µl/measuring point of a 0.1% crystal violet solution (pH 3.0). After three washing cycles of the stained cells with water, the plates were dried at room temperature. The dye was dissolved by adding 100 µl/measuring point of a 10% acetic acid solution. The extinction was determined by photometry at a wavelength of 595 nm. The change of cell number, in percent, was calculated by normalization of the measured values to the extinction values of the zero-point plate (=0%) and the extinction of the untreated (0 µm) cells (=100%). The IC50 values were determined by means of a 4 parameter fit using the company's own software.

Mps-1 kinase assay

The human kinase Mps-1 phosphorylates a biotinylated substrate peptide. Detection of the phosphorylated product is achieved by time-resolved fluorescence resonance energy transfer (TR-FRET) from Europium-labelled anti-phospho-Serine/Threonine antibody as donor to streptavidin labelled with cross-linked allophycocyanin (SA-XLent) as acceptor. Compounds are tested for their inhibition of the kinase activity.

N-terminally GST-tagged human full length recombinant Mps-1 kinase (purchased from Invitrogen, Karslruhe, Germany, cat. no PV4071) was used. As substrate for the kinase reaction a biotinylated peptide of the amino-acid sequence PWDPDDADITEILG (C-terminus in amide form, purchased from Biosynthan GmbH, Berlin) was used.

For the assay 50 nL of a 100-fold concentrated solution of the test compound in DMSO was pipetted into a black low volume 384well microtiter plate (Greiner Bio-One, Frickenhausen, Germany), 2 µl of a solution of Mps-1 in assay buffer [0.1 mM sodium-ortho-vanadate, 10 mM $MgCl_2$, 2 mM DTT, 25 mM Hepes pH 7.7, 0.05% BSA, 0.001% Pluronic F-127] were added and the mixture was incubated for 15 min at 22°C to allow pre-binding of the test compounds to Mps-1 before the start of the kinase reaction. Then the kinase reaction was started by the addition of 3 µl of a solution of 16.7 adenosine-tri-phosphate (ATP, 16.7 µM => final conc. in the 5 µl assay volume is 10 µM) and peptide substrate (1.67 µM => final conc. in the 5 µl assay volume is 1 µM) in assay buffer and the resulting mixture was incubated for a reaction time of 60 min at 22°C. The concentration of Mps-1 in the assay was adjusted to the activity of the enzyme lot and was chosen appropriate to have the assay in the linear range, typical enzyme concentrations were in the range of about 1 nM (final conc. in the 5 µl assay volume). The reaction was stopped by the addition of 3 µl of a solution of HTRF detection reagents (100 mM Hepes pH 7.4, 0.1% BSA, 40 mM EDTA, 140 nM Streptavidin-XLent [# 61GSTXLB, Fa. Cis Biointernational, Marcoule, France], 1.5 nM anti-phospho(Ser/Thr)-Europium-antibody [#AD0180, PerkinElmer LAS, Rodgau-Jügesheim, Germany].

The resulting mixture was incubated 1 h at 22°C to allow the binding of the phosphorylated peptide to the anti-phospho(Ser/Thr)-Europium-antibody. Subsequently the amount of phosphorylated substrate was evaluated by measurement of the resonance energy transfer from the Europium-labelled anti-phospho(Ser/Thr) antibody to the Streptavidin-XLent. Therefore, the fluorescence emissions at 620 nm and 665 nm after excitation at 350 nm was measured in a Viewlux TR-FRET reader (PerkinElmer LAS, Rodgau-Jügesheim, Germany). The "blank-corrected normalized ratio" (a Viewlux specific readout, similar to the traditional ratio of the emissions at 665 nm and at 622 nm, in which blank and Eu-donor crosstalk are subtracted from the 665 nm signal before the ratio is calculated) was taken as the measure for the amount of phosphorylated substrate. The data were normalised (enzyme reaction without inhibitor = 0 % inhibition, all other assay components but no enzyme = 100 % inhibition). Test compounds were tested on the same microtiter plate at 10 different concentrations in the range of 20 µM to 1 nM (20 µM, 6.7 µM, 2.2 µM, 0.74 µM, 0.25 µM, 82 nM, 27 nM, 9.2 nM, 3.1 nM and 1 nM, dilution series prepared before the assay at the level of the 100fold conc. stock solutions by serial 1:3 dilutions) in duplicate values for each concentration and IC_{50} values were calculated by a 4 parameter fit using an in-house software.

It was surprisingly found that the inhibitory activity of compounds of general formula I can be positively influenced by R^3 being an aryl-X- or heteroaryl-X- group. Therefore, compounds of general formula I, *supra*, in which R^3 represents an aryl-X- or heteroaryl-X- group are preferred.

Table 1

Example	Mps1 IC50 [nM]
1	61.1
2	90.5
3	13.7
4	20.6
5	13.3
6	43.6
7	1.2
8	111.0
9	25.0
10	<1.0
11	2.4
12	3.2
13	1.8
14	1.2
15	21.5
16	27.3
17	3.2
18	228.0
19	1.6
20	1.2
21	3.7
22	35.7
23	2.4
24	23.8
25	13.1

Example	Mps1 IC50 [nM]
26	4.1
27	33.2
28	<1.0
29	80.2
30	2.1
31	1.1
32	4.3
33	1.5
34	2.4
35	2.5
36	3.0
37	<1.0
38	10.3
39	3.7
40	111.0
41	7.1
42	7.8
43	21.1
44	2.6
45	1.1
46	1.1
47	2.0
48	1.4
49	11.9
50	84.8

Table 1 (cont.)

Example	Mps1 IC50 [nM]
51A	58.0
51B	1.2
52	3.2
53	7.1
54	7.6
55	1.2
56	< 1.0
57	4.4
58	20.5
59	32.5
60A	0.2
60B	< 0.1
61A	0.2
61B	0.3
62A	0.2
62B	11.5
63	< 0.1
64	0.1
65	0.7
66	0.2
67	0.1
68	< 0.1
69	1.0
70	0.3
71	0.8

Example	Mps1 IC50 [nM]
72	44.4
73A	< 0.7
73B	3.8
74	< 0.7
75	< 0.7
76	< 0.7
77	< 0.7
78	0.2
79	0.7
80	0.2
81	0.2
82	0.3
83A	0.2
83B	0.8
84	0.3
85	0.2
86	0.1
87	0.2
88	0.4
89	0.2
90	0.5
91	0.5
92	0.2
93	0.3
94	0.3

Table 1 (cont.)

Example	Mps1 IC50 [nM]
95	0.3
96	0.8
97	0.2
98	52.3
99	29.5
100	7.6
101	6.3
102	24.6
103	<1.0
104	<1.0
105	3.5
106	8.9
107	35.5
108	7.0
109	2.1
110	1.3
111	6.3
112	5.1
113	2.0
114	<1.0
115	27.5
116	4.0
117	3.3
118	4.3
119	<1.0
120	2.5

Example	Mps1 IC50 [nM]
121	1.8
122	2.9
123	7.6
124	4.7
125	3.8
126	2.0
127	40.0
128	2.7
129	3.3
130	5.9
131	10.0
132	1.5
133	<1.0
134	<1.0
135	<1.0
136	4.0
137	<1.0
138	2.0
139	3.7
140	3.9
141	2.4
142	1.4
143	4.7
144	2.3
145	<1.0
146	3.8

Table 1 (cont.)

Example	Mps1 IC50 [nM]
147	2.2
148	1.5
149	2.2
150	3.7
151	3.1
152	3.3
153	3.6
154	25.0
155	3.6
156	5.1
157	12.0
158	6.4
159	14.8
160	13.6
161	6.2
162	64.9
163	30.5
164	6.3
165	1.8
166	5.3
167	2.3
168	0.3
169	0.1
170	0.7
171	0.8

Example	Mps1 IC50 [nM]
172	0.8
173	0.4
174	< 0.1
175	7280.0
176	465.0
177	32.2
178	172.0
179	601.0
180	327.0
181	39.9
182	Nt
183	290.0
184	101.0
185	Nt
186	338.0
187	49.8
188	Nt
189	Nt
190	660.0
191	20000.0
192	21.5
193	1.3
194	2.5
195	3.2
196	2.7

Table 1 (cont.)

Example	Mps1 IC50 [nM]
197	< 1.0
198	2.6
199	6.9
200	Nt
201	2.3
202	1.5
203	1.4
204	< 1.0
205	72.7
206	6.2
207	< 1.0
208	2.0
209	0.6
210	6.9
211	5.8
212	< 1.0
213	< 1.0
214	< 1.0
215	1.7
216	< 1.0
217	3.6
218	3.7
219	Nt
220	Nt
221	1.2
222	2.1
223	0.2
224	< 0.1

Example	Mps1 IC50 [nM]
225	0.2
226	1.3
227	0.2
228	0.6
229	2.6
230	2.7
231	14.3
232	1.0
233	1.7
234	6.1
235	6.2
236	Nt
237	5.6
238	< 0.1
239	25.5
240	1.2
241A	Nt
241B	3.4
242	3.7
243	0.9
244	0.3
245	0.7
246	0.6
247	1.7
248	0.5
249	0.2
250	0.3
251	0.2

Table 1 (cont.)

Example	Mps1 IC50 [nM]
252	0.2
253	0.3
254	0.1
255	0.2
256	0.2
257	0.4
258	0.2
259	0.3
260	0.2
261	0.5
262	0.2
263	32.4
264	2.0
265	0.9
266	0.3
267	0.3
268	0.2
269	0.3
270	0.1
271	1.0
272	21.1
273	0.5
274	73.8
275	5.4
276	0.1
277	< 0.1
278A	0.4

Example	Mps1 IC50 [nM]
278B	1.0
279	148.0
280	0.1
281	0.3
282	0.4
283	0.3
284	0.4
285	0.4
286	0.4
287	0.3
288	0.1
289	0.2
290	0.3
291	0.6
292	0.5
293	0.4
294A	0.3
294B	0.2
295A	0.4
295B	0.2
296A	0.5
296B	0.5
296C	0.2
297	0.1
298A	< 0.1
298B	0.1
299	6.9

5

Table 1 (cont.)

300	0.8	323	0.2
301	0.2	324	0.3
302	0.3	325	0.1
303A	Nt	326	1.9
303B	0.2	327	0.3
304A	< 0.1	328	0.3
304B	0.1	329	< 0.1
305	0.6	330	0.2
306	0.6	331	12.6
307	0.5	332	26.8
308	1.0	333	9.5
309	Nt	334	30.0
310	Nt	335	3.6
311	0.2	336	1.0
312	0.2	337	3.9
313	0.1	338	83.9
314	0.2	339	95.9
315	0.3	340	3.3
316	118.0	341	10.6
317	7.4	342	6.9
318	64.3	343	4.3
319	121.0	344	23.0
320	3.3	345	3.0
321	0.6	346	1.6
322	70.6	347	0.1

5

Table 1 (cont.)

348	1.5
349	0.4
351	1.0
352	0.2
353	0.4
354	0.4
355	0.9
356	0.6
357	4.4
358	0.1
359	1.2
360	0.9
361	0.3
362	0.2
365	4.4
366	1.1
367	0.1
368	0.1
369	0.1
370	0.1
371	0.2
372	0.2
373	0.2
374	0.3
375	0.1
376	0.2
377	0.3
378	0.2
379	0.2

380	0.1
381	0.6
382	1.2
383	0.3
384	0.4
385	0.9
386	1.5
387	0.3
388	0.4
389	0.1
390	0.1
391	0.1
392	0.4
393	2.3
394	0.2
395	0.3
396	0.1
396	0.3
397	1.0
398	0.4
399	0.1
400	3.1
401	1.0
402	3.4
403	1.0
404	0.3
405	0.2
406	0.4
409	0.7

5

Table 1 (cont.)

410	0.5
411	4.8
412	19.2
413	45.7
414	6.7
415	8.2
417	0.2
418	1.2
419	3.5
420	2.8
422	0.4
423	0.3
424	0.2
425	0.1
426	0.2
427	0.2
428	0.4
429	0.1
430	0.3
431	0.1
432	4.6
433	0.6
434	1.3
435	1.6
436	0.1
437	0.4
439	0.2
440	0.1
441	0.5

442	0.1
443	0.1
445	0.2
446	0.4
447	1.1
448	0.6
449	0.6
450	0.3
451	1.3
452	0.8
454	0.1
456	nt
457	5.4
458	1.1
459	0.4
460	0.3
461	0.2
464	0.1
465	nt
466	4.8
467	1.6
468	7.5
469	1.7
470	0.4
471	0.2
472	0.2
473	0.4
474	0.3
475	0.2

5

Table 1 (cont.)

476	10.3	505	0.2
477	0.3	506	0.1
478	0.3	507	0.2
479	0.2	508	0.2
480	nt	509	0.1
481	3.1	510	0.1
482	0.6	511	0.3
483	0.1	512	0.1
484	0.3	513	0.2
485	0.4	514	8.0
486	0.1	515	0.4
487	0.1	516	0.3
488	0.1	517	0.2
489	0.2	518	0.1
490	1.5	519	0.1
491	0.1	520	0.2
492	0.1	521	0.3
493	0.3	522	1.8
494	0.3	523	0.7
495	0.1	524	2.3
496	8.9	525	0.7
497	0.2	526	0.1
498	0.3	527	0.6
499	0.2	528	0.7
500	0.1	529	0.4
501	0.1	530	0.6
502	0.2	531	14.8
503	0.2	532	0.2
504	0.2	533	1.2

5

Table 1 (cont.)

534	0.1
535	0.1
536	0.3
537	0.2
538	0.8
539	0.2
540	0.1
541	0.4
542	0.1
543	0.2
544	1.1
545	0.1
546	0.1
547	0.2
548	0.7
549	0.2

550	0.5
551	0.2
552	0.2
553	0.7
554	1.6
555	9.4
556	0.3
557	2.2
558	0.3
559	0.6
560	0.1
561	0.6

5

Example	Mps1 IC50 [nM]
562	2.7
563	4.3
564	Nt
565	3.5
566	1.7
567	< 1.0
568	< 1.0
569	< 1.0
570	< 1.0
571	< 1.0
572	< 1.0
573	< 1.0
574	Nt
575	< 1.0
576	< 1.0
577	1.4
578	Nt
579	Nt
580	< 1.0
581	< 1.0
582	3.8
583	6.9
584	2.3
585	5.4
586	1.0

Example	Mps1 IC50 [nM]
587	3.2
588	2.2
589	4.3
590	Nt
591	2.5
592	1.5
593	9.0
594	< 1.0
596	1.1
597	1.1
598	< 1.0
599	1.0
600	< 1.0
601	< 1.0
602	< 1.0
603	< 1.0
604	< 1.0
605	1.2
606	Nt
607	3.7
608	3.9
609	2.9
610	< 1.0

In the above Table, Nt = not tested

Spindle Assembly Checkpoint Assay

The spindle assembly checkpoint assures the proper segregation of chromosomes during mitosis. Upon entry into mitosis, chromosomes begin to condensate which is accompanied by the phosphorylation of histone H3 on serine 10. Dephosphorylation of histone H3 on serine 10 begins in anaphase and ends at early telophase. Accordingly, phosphorylation of histone H3 on serine 10 can be utilized as a marker of cells in mitosis. Nocodazole is a microtubule destabilizing substance. Thus, nocodazole interferes with microtubule dynamics and mobilises the spindle assembly checkpoint. The cells arrest in mitosis at G2/M transition and exhibit phosphorylated histone H3 on serine 10. An inhibition of the spindle assembly checkpoint by Mps-1 inhibitors overrides the mitotic blockage in the presence of nocodazole, and the cells complete mitosis prematurely. This alteration is detected by the decrease of cells with phosphorylation of histone H3 on serine 10. This decline is used as a marker to determine the capability of compounds of the present invention to induce a mitotic breakthrough.

Cultivated cells of the human cervical tumour cell line HeLa (ATCC CCL-2) were plated at a density of 2500 cells/well in a 384-well microtiter plate in 20 µl Dulbeco's Medium (w/o phenol red, w/o sodium pyruvate, w 1000 mg/ml glucose, w pyridoxine) supplemented with 1% (v/v) glutamine, 1% (v/v) penicillin, 1% (v/v) streptomycin and 10% (v/v) fetal calf serum. After incubation overnight at 37°C, 10 µl/well nocodazole at a final concentration of 0.1 µg/ml were added to cells. After 24 h incubation, cells were arrested at G2/M phase of the cell cycle progression. Test compounds solubilised in dimethyl sulfoxide (DMSO) were added at various concentrations (0 µM, as well as in the range of 0.005 µM - 10 µM; the final concentration of the solvent DMSO was 0.5% (v/v)). Cells were incubated for 4 h at 37°C in the presence of test compounds. Thereafter, cells were fixed in 4% (v/v) paraformaldehyde in phosphate buffered saline (PBS) at 4°C overnight then permeabilised in 0.1% (v/v) Triton X™ 100 in PBS at room temperature for 20 min and blocked in 0.5% (v/v) bovine serum albumin (BSA) in PBS at room temperature for 15 min. After washing with PBS, 20 µl/well antibody solution (anti-phospho-histone H3 clone 3H10, FITC; Upstate, Cat# 16-222; 1:200 dilution) was added to cells, which were incubated for 2 h at room temperature.

Afterwards, cells were washed with PBS and 20 µl/well HOECHST 33342 dye solution (5 µg/ml) was added to cells and cells were incubated 12 min at room temperature in the dark. Cells were washed twice with PBS then covered with PBS and stored at 4°C until analysis. Images were acquired with a Perkin Elmer OPERA™ High-Content Analysis reader. Images were analyzed with image analysis software MetaXpress™ from Molecular devices utilizing the Cell Cycle application module. In this assay both labels HOECHST 33342 and phosphorylated Histone H3 on serine 10 were measured. HOECHST 33342 labels DNA and is used to count cell number. The staining of phosphorylated Histone H3 on serine 10 determines the number of mitotic cells. Inhibition of Mps-1 decreases the number of mitotic cells in the presence of nocodazole indicating an inappropriate mitotic progression. The raw assay data were further analysed by four parameter logistic regression analysis to determine the IC_{50} value for each tested compound.

It will be apparent to persons skilled in the art that assays for other Mps kinases may be performed in analogy using the appropriate reagents.

Thus the compounds of the present invention effectively inhibit one or more Mps-1 kinases and are therefore suitable for the treatment or prophylaxis of diseases of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, particularly in which the uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses is mediated by Mps-1, more particularly in which the diseases of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses are haemotological tumours, solid tumours and/or metastases thereof, *e.g.* leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

Investigation of *in vitro* metabolic stability in rat hepatocytes (including calculation of hepatic *in vivo* blood clearance (CL))

Hepatocytes from Han Wistar rats were isolated via a 2-step perfusion method. After perfusion, the liver was carefully removed from the rat: the liver capsule was opened and the hepatocytes were gently shaken out into a Petri dish with ice-cold WME. The resulting cell suspension was filtered through sterile gaze in 50 ml falcon tubes and centrifuged at 50 × *g* for 3 min at room temperature. The cell pellet was resuspended in 30 ml WME and centrifuged through a Percoll® gradient for 2 times at 100 × *g*. The hepatocytes were washed again with Williams' medium E (WME) and resuspended in medium containing 5% FCS. Cell viability was determined by trypan blue exclusion.

For the metabolic stability assay liver cells were distributed in WME containing 5% FCS to glas vials at a density of 1.0×10^6 vital cells/ml. The test compound was added to a final concentration of 1 µM. During incubation, the hepatocyte suspensions were continuously shaken and aliquots were taken at 2, 8, 16, 30, 45 and 90 min, to which equal volumes of cold methanol were immediately added. Samples were frozen at -20° C over night, after subsequently centrifuged for 15 minutes at 3000 rpm and the supernatant was analyzed with an Agilent 1200 HPLC-system with LCMS/MS detection.

The half-life of a test compound was determined from the concentration-time plot. From the half-life the intrinsic clearances were calculated. Together with the additional parameters liver blood flow, amount of liver cells *in vivo* and *in vitro*. The hepatic *in vivo* blood clearance (CL) and the maximal oral bioavailability (F_{max}) was calculated. The following parameter values were used: Liver blood flow - 4.2 L/h/kg rat; specific liver weight - 32 g/kg rat body weight; liver cells *in vivo*- 1.1×10^8 cells/g liver, liver cells *in vitro* - 0.5×10^6/ml.

It was surprisingly found that the metabolic stability of compounds of general formula I can be positively influenced by at least one of the groups R^{4b} and R^{4c} being different from a hydrogen atom.

For example, the replacement of a hydrogen atom for R^{4c} or R^{4b} by a methyl group increases the metabolic stability by 700% (Table 2a) or by 177% (Table 2b), respectively.

Therefore, in a preferred embodiment, R^{4a}, R^{4b}, R^{4c} and R^{4d} represent, independently from each other, a hydrogen or halogen atom, or a -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, NC-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl- group; with the proviso that at least one of the groups R^{4b} and R^{4c} is not a hydrogen atom.

Table 2a:

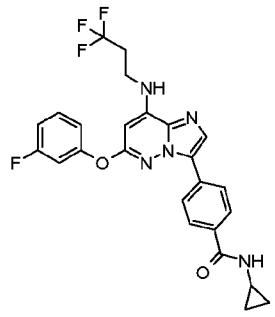
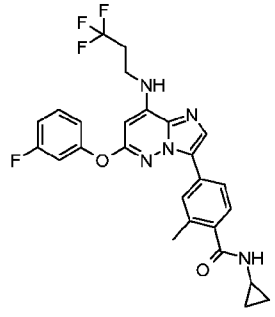
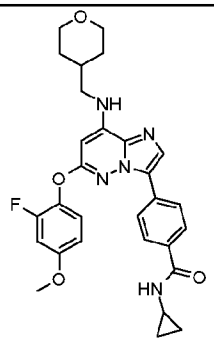
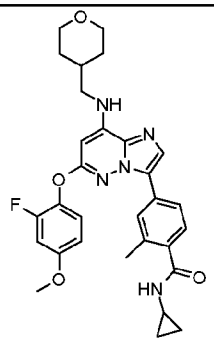
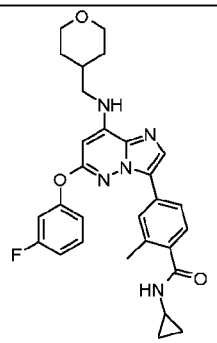
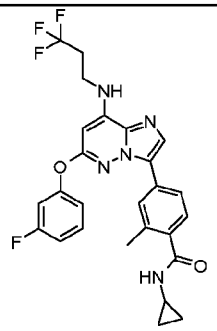
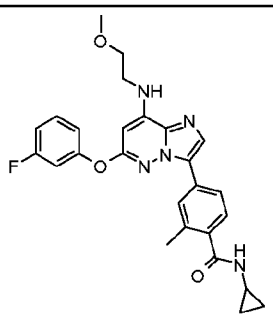
Example	Structure	Fmax [%]
463		7
80		56

Table 2b:

Example	Structure	Fmax [%]
444		22
445		61

It was surprisingly found that the metabolic stability of compounds of general formula I can be positively influenced by R^5 (Tables 3a, 3b, and 3c). For example, the replacement of a 4-tetrahydropyranyl-group for R^5 (compound of example 323) by a 1,1,1-trifluoroethyl group (compound of example 80) increases the metabolic stability by 81% (Table 3a).

Table 3a

Example	Structure	Fmax [%]
323		31
80		56
492		42

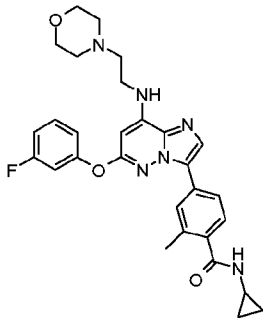
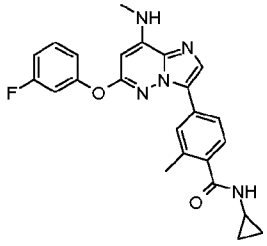
Example	Structure	Fmax [%]
500		40
510		39

Table 3b

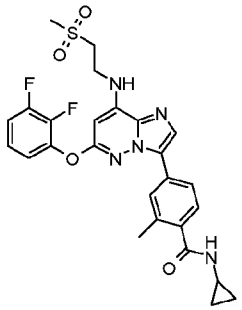
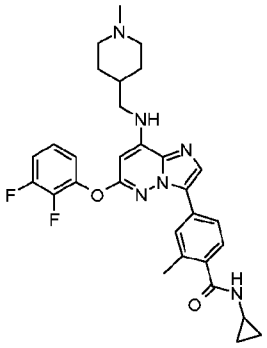
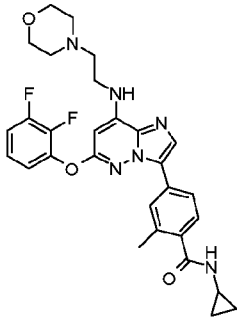
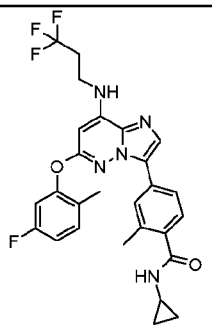
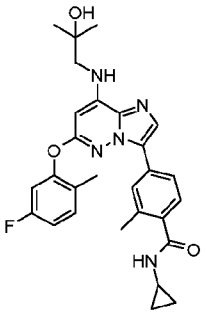
Example	Structure	Fmax [%]
516		69
526		50
536		37

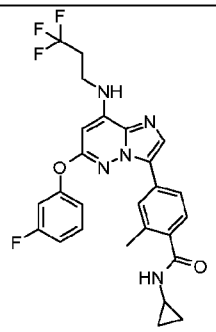
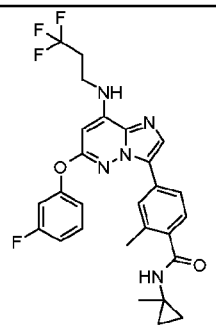
Table 3c

Example	Structure	Fmax [%]
390		55
391		47

It was surprisingly found that the metabolic stability of compounds of general formula I can be positively influenced by R^2.

For example, the replacement of a cylopropyl-group for R^2 by a substituted cylopropyl-group such as a 1-methylcyclopropyl group increases the metabolic stability by 34% (Table 4).

Table 4

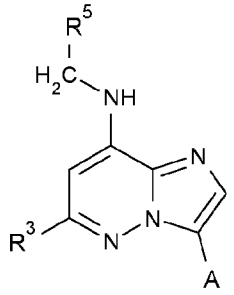
Example	Structure	Fmax [%]
80		56
461		75

It was surprisingly found that the metabolic stability of compounds of general formula I can be positively influenced by R^2.

For example, the replacement of a cylopropyl-group for R^2 by a non-cyclic alkyl-group increases the metabolic stability significantly.

CLAIMS

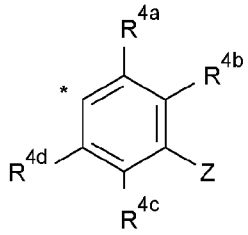
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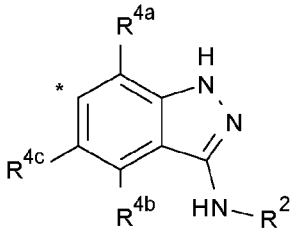
I

in which :

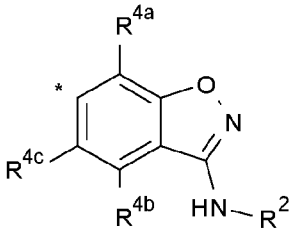
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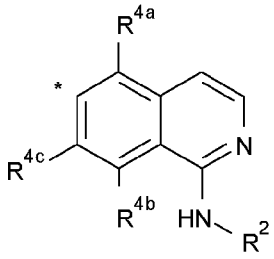
or



or



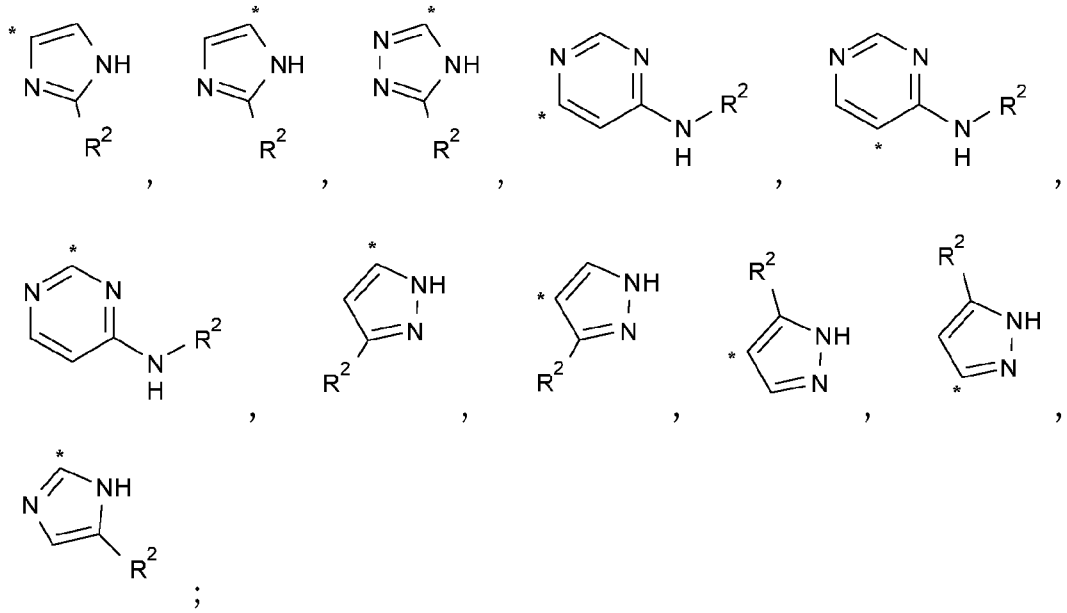
or



-group ;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a $-C(=O)N(H)R^2$ or $-C(=S)N(H)R^2$ group, or a group selected from



wherein * indicates the point of attachment of said groups with the rest of the molecule ;

R^2 represents a hydrogen atom, or a C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl- or C_3-C_6-cycloalkyl- group ;
wherein said C_3-C_6-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 groups selected from: halogen, -OH, -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkyl-;

R^3 represents a hydrogen atom or a halogen atom, or a -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, -$(CH_2)_m$-C_2-C_6-alkenyl, -$(CH_2)_m$-C_4-C_8-cycloalkenyl, -$(CH_2)_m$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl-, -C_1-C_6-alkyl-aryl, -C_1-C_6-alkyl-heteroaryl, heteroaryl-, C_1-C_6-alkyl-X-, -X-$(CH_2)_m$-C_2-C_6-alkenyl, -X-$(CH_2)_m$-C_4-C_8-cycloalkenyl, -X-$(CH_2)_m$-C_2-C_6-alkynyl, -X-$(CH_2)_m$-C_3-C_6-cycloalkyl, -X-$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -X-$(CH_2)_m$-(4- to 8-membered

heterocycloalkenyl), aryl-X-, heteroaryl-X-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -OR^6, -SR^6, -S(=O)R^6, -S(=O)$_2R^6$, -S(=O)(=NR^{6a})R^{6b}, -S(=O)$_2$N(R^{6b})R^{6c}, -S-(CH_2)$_n$-N(R^{6a})R^{6b} or -S-(CH_2)$_n$-(3- to 7-membered heterocycloalkyl) group ;

wherein said C_1-C_6-alkyl-, C_1-C_6-alkoxy-, -(CH_2)$_m$-C_2-C_6-alkenyl, -(CH_2)$_m$-C_2-C_6-alkynyl, -(CH_2)$_m$-C_3-C_6-cycloalkyl, aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-, aryl-, C_1-C_6-alkyl-X-, -X-(CH_2)$_m$-C_2-C_6-alkenyl, -X-(CH_2)$_m$-C_4-C_8-cycloalkenyl, -X-(CH_2)$_m$-C_2-C_6-alkynyl, -X-(CH_2)$_m$-C_3-C_6-cycloalkyl, -X-(CH_2)$_m$-(3- to 7-membered heterocycloalkyl), -X-(CH_2)$_m$-(4- to 8-membered heterocycloalkenyl), aryl-X-, heteroaryl-X-, -C_1-C_6-alkyl-aryl, -C_1-C_6-alkyl-heteroaryl or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^7 groups ;

R^{4a}, R^{4b}, R^{4c}, R^{4d}

represent, independently from each other, a hydrogen or halogen atom, or a -CN, C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkyl-, R^{6a}(R^{6b})N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2R^6$, -N(R^{6c})S(=O)$_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -S(=O)$_2R^6$, -S(=O)$_2$N(H)R^{6a}, -S(=O)$_2$N(R^{6a})R^{6b}, -S(=O)(=NR^{6c})R^6 group ;

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, -(CH_2)$_n$-C_2-C_6-alkenyl, -(CH_2)$_n$-C_2-C_6-alkynyl, -(CH_2)$_m$-C_3-C_6-cycloalkyl, -(CH_2)$_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, R^{6a}(R^{6b})N-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_2-C_6-alkenyl-, C_4-C_8-cycloalkenyl-, C_2-C_6-alkynyl-,aryl- or heteroaryl- group ;

wherein said C_1-C_6-alkyl-, -$(CH_2)_n$-C_2-C_6-alkenyl, -$(CH_2)_n$-C_2-C_6-alkynyl, -$(CH_2)_m$-C_3-C_6-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-C_1-C_6-alkyl-, heteroaryl-C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, C_4-C_8-cycloalkenyl-, aryl- or heteroaryl-group is optionally substituted, identically or differently, with 1, 2, 3 or 4 R^8 groups ;

R^6, R^{6a}, R^{6b}, R^{6c},
represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl-, H O-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, C_2-C_6-alkenyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, aryl-C_1-C_6-alkyl- or heteroaryl-C_1-C_6-alkyl- group ;

R^7 represents a hydrogen or halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)$S(=O)_2R^6$, -N(R^{6c})$S(=O)_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -$S(=O)_2R^6$, -$S(=O)_2$N(H)R^6, -$S(=O)_2$N(R^{6a})R^{6b} or -S(=O)(=NR^{6c})R^6 group ;
wherein said C_1-C_6-alkoxy-, aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2 or 3 C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-, -C(=O)O-R^6 or -OH groups;
or
when 2 R^7 groups are present ortho to each other on an aryl- or heteroaryl-ring, said 2 R^7 groups together form a bridge :
$O(CH_2)_2O$, *$O(CH_2)O$*, *NH(C(=O))NH*, wherein * represent the point of attachment to said aryl- or heteroaryl- ring ;

R^8 represents a hydrogen or halogen atom, or a -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ or $-S(=O)_2$-(3- to 7-membered heterocycloalkyl) group;

wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 C_1-C_6-alkyl- groups ;

m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

n is an integer of 0, 1, 2, 3, 4 or 5 ;

X represents $S(=O)_p$, O, NR^6, $CR^{6a}R^{6b}$ or $C=CR^{6a}R^{6b}$;

p is an integer of 0, 1 or 2 ;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

2. A compound according to claim 1, wherein

R^{4a} represents hydrogen;

R^{4d} represents hydrogen; and

one of the groups R^{4b} and R^{4c} represents a hydrogen atom while the other one represents a group selected from: halo-, -CN, -OH, C_1-C_6-alkyl- and C_1-C_6-alkoxy-;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

3. A compound according to any one of claims 1 to 2, wherein

R^2 is selected from the groups consisting of :

C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, $R^{6a}(R^{6b})N$-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, -C_1-C_6-alkyl-CN, C_1-C_6-alkoxy-C_1-C_6-alkyl-, halo-C_1-C_6-alkoxy-C_1-C_6-alkyl-, C_2-C_6-alkenyl-, C_2-C_6-alkynyl-;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

4. A compound according to any one of claims 1 to 3, wherein

R^3 represents an aryl-X- or heteroaryl-X- group;

wherein said aryl-X- or heteroaryl-X- group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 R^7 groups ;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

5. A compound according to any one of claims 1 to 4, wherein

R^5 represents a hydrogen atom, or a C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl, or heteroaryl- group ;

said C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, , C_3-C_6-cycloalkyl-, 3- to 7-membered heterocycloalkyl, heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 R^8 groups ;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

6. A compound according to any one of claims 1 to 5, wherein

R^7 represents a halogen atom, or a HO-, -CN, C_1-C_6-alkoxy-, C_1-C_6-alkyl-, halo-C_1-C_6-alkyl-, HO-C_1-C_6-alkyl-, H_2N-C_1-C_6-alkyl-, C_2-C_6-alkenyl, 3- to 7-membered heterocycloalkyl, -C(=O)N(H)R^{6a}, -N(R^{6a})R^{6b}, -N(H)C(=O)R^6, or -SR^6 group ;

wherein said C_1-C_6-alkoxy-, or 3- to 7-membered heterocycloalkyl- group is optionally substituted, identically or differently, with 1, 2, or 3 C_1-C_6-alkyl-, C_1-C_6-alkoxy-, halo-C_1-C_6-alkoxy-, -C(=O)O-R^6 or -OH groups;

or

when 2 R^7 groups are present ortho to each other on an aryl or heteroarly ring, said 2 R^7 groups together form a bridge :

$CH_2(CH_2)_2NH$, *$CH_2CH_2N(R^{6a})CH_2$*, *C(H)=C(H)-C(=O)-N(H)*, wherein * represent the point of attachment to said aryl or heteroaryl ring ;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

7. A compound according to any one of claims 1 to 6, wherein

R^6, R^{6a}, R^{6b}, and R^{6c} represent, independently from each other, a hydrogen atom, or a C_1-C_6-alkyl- group;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

8. A compound according to claim 1, which is selected from the group consisting of :

1-({6-[(2E/Z)-but-2-en-2-yl]-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol,

1-({3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-6-[(1E/Z)-prop-1-en-1-yl]imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol,

3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-N-isobutyl-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-8-amine,

3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-6-(pyridin-4-yl)-N-[(2S)-tetrahydrofuran-2-ylmethyl]imidazo[1,2-b]pyridazin-8-amine,

3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-6-(pyridin-4-yl)-N-[(2R)-tetrahydrofuran-2-ylmethyl]imidazo[1,2-b]pyridazin-8-amine,

3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-6-(4-fluorophenyl)-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine,

N-cyclopropyl-4-{6-(4-fluorophenyl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

1-({3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-6-(4-fluorophenyl)imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol,

1-({3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol,

N-cyclopropyl-2-methyl-4-{6-(1-methyl-1H-pyrazol-5-yl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

3-(3-amino-1H-indazol-6-yl)-N-isobutyl-6-phenylimidazo[1,2-b]pyridazin-8-amine,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-phenylimidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-[8-(isobutylamino)-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl]benzenecarbothioamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-phenylimidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(methylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-6-[(1E)-prop-1-en-1-yl]-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine,

N-cyclopropyl-4-{8-[(2-methoxy-2-methylpropyl)amino]-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(methylsulfonyl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(4-fluorophenyl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[2-(hydroxymethyl)phenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-6-ethenyl-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine,

N-cyclopropyl-2-methyl-4-{6-[(1E)-prop-1-en-1-yl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(1E)-prop-1-en-1-yl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-[(2E)-but-2-en-2-yl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-6-(pyridin-4-yl)-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine,

6-[(2E)-but-2-en-2-yl]-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine,

N-cyclopropyl-4-{6-(4-fluorophenyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-6-(pyridin-4-yl)-N-(tetrahydro-2H-pyran-2-ylmethyl)imidazo[1,2-b]pyridazin-8-amine,

(RS)-N-cyclopropyl-2-methyl-4-[8-{[(2-methyltetrahydrofuran-2-yl)methyl]amino}-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-2-methyl-4-[6-(pyridin-4-yl)-8-{[(2S)-tetrahydrofuran-2-ylmethyl]amino}imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-4-{6-(4-fluorophenyl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide,

N-cyclopropyl-2-methyl-4-[6-(1-methyl-1H-pyrazol-5-yl)-8-{[(2R)-tetrahydrofuran-2-ylmethyl]amino}imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-2-methyl-4-[6-(1-methyl-1H-pyrazol-5-yl)-8-{[(2S)-tetrahydrofuran-2-ylmethyl]amino}imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-2-methyl-4-[6-(pyridin-4-yl)-8-{[(2R)-tetrahydrofuran-2-ylmethyl]amino}imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-4-{8-[(1,4-dioxan-2-ylmethyl)amino]-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(pyridin-4-yl)-8-[(tetrahydro-2H-pyran-2-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[2-(hydroxymethyl)phenyl]-8-[(2-methoxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-methoxy-2-methylpropyl)amino]-6-(1-methyl-1H-pyrazol-5-

yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-vinylimidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{8-[(3,3,3-trifluoropropyl)amino]-6-vinylimidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(cyclohex-1-en-1-yl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzenecarbothioamide,

N-cyclopropyl-4-{6-[2-(hydroxymethyl)phenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide,

N-cyclopropyl-4-{6-(1-methyl-1H-pyrazol-5-yl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide,

N-cyclopropyl-4-{6-[3-(hydroxymethyl)phenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide,

N-cyclopropyl-4-{6-cyclopropyl-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(4-fluorophenyl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-3-methoxybenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-3-yl}-3-methoxybenzamide,

N-cyclopropyl-3-hydroxy-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}-3-methoxybenzamide,

N-cyclopropyl-4-{6-(4-fluorophenyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-3-methoxybenzamide,

N-cyclopropyl-3-methoxy-4-{6-(1-methyl-1H-pyrazol-5-yl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[2-(hydroxymethyl)phenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-3-methoxybenzamide,

N-cyclopropyl-4-{6-[(2-methoxyphenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

(RS)-N-cyclopropyl-2-methyl-4-[8-{[(4-methylmorpholin-2-yl)methyl]amino}-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl]benzamide,

4-{8-[(2-amino-2-methylpropyl)amino]-6-(4-fluorophenyl)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{8-[(2-amino-2-methylpropyl)amino]-6-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{8-[(2-amino-2-methylpropyl)amino]-6-[2-(hydroxymethyl)phenyl]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(4-hydroxyphenyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(4-methoxyphenyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-hydroxyphenyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-methoxyphenyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-3-hydroxybenzamide,

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-3-methoxybenzamide

N-cyclopropyl-4-{6-[(4-hydroxy-3-methylphenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(5-fluoro-2-methylphenyl)sulfanyl]-8-[(2-hydroxy-2-

methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluoro-3-methylphenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluoro-4-methylphenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluoro-5-methylphenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3,5-difluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluoro-2-methylphenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2-fluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-[(2E)-but-2-en-2-yl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-3-methoxybenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(2-hydroxyphenyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(2-methoxyphenyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-3-hydroxy-4-{6-(phenylsulfanyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-phenoxyimidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-phenoxy-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

4-{8-[(2-amino-2-methylpropyl)amino]-6-[(3-fluorophenyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluoro-5-methylphenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(2-fluoro-5-methylphenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(3-cyanophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

(RS)-N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfinyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfonyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(phenylsulfanyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide,

4-{6-(3-chlorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(4-methoxyphenoxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluoro-5-methylphenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluoro-5-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

4-{6-(4-chlorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{6-(3-chloro-4-fluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-

b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-(2,3-difluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(2-fluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(3-isopropylphenoxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(4-chloro-3-fluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-(3,5-dimethylphenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(3-methylphenoxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-chloro-8-[(2-sulfamoylethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide,

4-{6-chloro-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(2,3-dihydro-1,4-benzodioxin-6-yl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(naphthalen-1-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[3-(hydroxymethyl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(4-fluorophenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(3-methylphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(2,3-dimethylphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-

b]pyridazin-3-yl}benzamide,

4-{6-[2-(acetylamino)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(quinolin-3-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

4-{3-[4-(cyclopropylcarbamoyl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}-N,N-dimethylbenzamide,

N-cyclopropyl-4-{6-(2-methylphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(quinolin-5-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(quinolin-4-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

4-{6-(4-carbamoylphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide,

4-{6-(3-carbamoylphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide,

N-cyclopropyl-4-{6-(isoquinolin-4-yl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

4,4'-{8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazine-3,6-diyl}bis(N-cyclopropylbenzamide),

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(isoquinolin-5-yl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

3-{3-[4-(cyclopropylcarbamoyl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}-N-methylbenzamide,

4-{3-[4-(cyclopropylcarbamoyl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}-N-(propan-2-yl)benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(thiophen-2-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(thiophen-3-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-[4-(trifluoromethyl)phenyl]imidazo[1,2-b]pyridazin-3-yl}benzamide,

4-[6-(3-chlorophenyl)-8-(isobutylamino)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropylbenzamide,

N-cyclopropyl-4-{6-(3-methoxyphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

4-{6-[3-(acetylamino)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide,

4-{6-(1-benzofuran-2-yl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide,

N-cyclopropyl-4-{6-(3-fluorophenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(2-methoxyphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

4-{6-(biphenyl-4-yl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide,

N-cyclopropyl-4-{6-(2,3-dichlorophenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(2-fluorophenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[4-(hydroxymethyl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

3-{3-[4-(cyclopropylcarbamoyl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}-N-(propan-2-yl)benzamide,

N-cyclopropyl-3-{3-[4-(cyclopropylcarbamoyl)phenyl]-8-[(2-

methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}benzamide,

4-{6-(1,3-benzodioxol-5-yl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(pyridin-3-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(2-hydroxyphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(3-hydroxyphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(4-hydroxyphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-[4-(methylsulfonyl)phenyl]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(pyrimidin-5-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(quinolin-6-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(imidazo[1,2-a]pyridin-6-yl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-(6-{4-[(methylcarbamoyl)amino]phenyl}-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl)benzamide,

4-{6-(5-cyanopyridin-3-yl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide,

N-cyclopropyl-4-{6-[4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

5-{3-[4-(cyclopropylcarbamoyl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}-N-methylpyridine-2-carboxamide,

N-cyclopropyl-4-(6-{4-[(dimethylcarbamoyl)amino]phenyl}-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl)benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-phenylimidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[3-(hydroxymethyl)phenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[4-(hydroxymethyl)phenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-3-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(furan-3-yl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(6-ethoxypyridin-3-yl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3,5-dimethyl-1,2-oxazol-4-yl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1H-pyrazol-3-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1-methyl-1H-pyrrol-2-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyrimidin-5-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(2-methylpyridin-4-

yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[4-fluoro-3-(hydroxymethyl)phenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3,6-dihydro-2H-pyran-4-yl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(quinolin-5-yloxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(quinolin-6-yloxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(quinolin-6-yloxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{6-(quinolin-5-yloxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

4-{6-(cyclohexylsulfanyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{6-(cyclohexylsulfanyl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-3-yloxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(pyridin-3-yloxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-6-ethenyl-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine,

4-{6-chloro-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

4-{6-chloro-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide,

4-{6-chloro-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-methylbenzamide,

4-{6-chloro-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-(propan-2-

yl)benzamide,

2-chloro-4-{6-chloro-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-methylbenzamide,

2-chloro-4-{6-chloro-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide,

4-{6-chloro-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-fluoro-N-(propan-2-yl)benzamide,

6-chloro-3-[3-(cyclopropylamino)-1,2-benzoxazol-6-yl]-N-(2-methylpropyl)imidazo[1,2-b]pyridazin-8-amine,

6-chloro-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-N-(2-methylpropyl)imidazo[1,2-b]pyridazin-8-amine,

4-{6-chloro-8-[(thiophen-2-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,N-dimethylbenzamide,

2-chloro-4-{6-chloro-8-[(thiophen-2-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-methylbenzamide,

2-chloro-4-{6-chloro-8-[(thiophen-2-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide,

4-{6-chloro-8-[(thiophen-2-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-fluoro-N-(propan-2-yl)benzamide,

6-chloro-3-[3-(cyclopropylamino)-1,2-benzoxazol-6-yl]-N-(thiophen-2-ylmethyl)imidazo[1,2-b]pyridazin-8-amine,

4-{6-chloro-8-[(thiophen-2-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-methylbenzamide,

4-{6-chloro-8-[(thiophen-2-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-[8-({(2S)-2-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-hydroxyethyl}amino)-6-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(methylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

(RS)-N-cyclopropyl-2-methyl-4-{8-[(2-methylpropyl)amino]-6-[(tetrahydrofuran-2-ylmethyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{8-[(2-methylpropyl)amino]-6-(1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{8-[(2-methylpropyl)amino]-6-(methylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{8-[(2-methylpropyl)amino]-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{8-[(2-methylpropyl)amino]-6-(phenylsulfonyl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-N-(2-hydroxyethyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazine-6-carboxamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(methylsulfonyl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{8-[(2-methylpropyl)amino]-6-(propylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{8-[(2-methylpropyl)amino]-6-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{6-(methylsulfanyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[(2-hydroxyethyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-chloro-8-[(3,3,3-trifluoro-2-hydroxypropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(methylsulfanyl)-8-[(3,3,3-trifluoro-2-hydroxypropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{6-(phenylsulfanyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{6-(1-methyl-1H-pyrazol-5-yl)-8-[(3,3,3-trifluoro-2-

hydroxypropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-(6-{[2-(diethylamino)ethyl]sulfanyl}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-{8-[(3-hydroxypropyl)amino]-6-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(phenylsulfonyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

4-{6-(5-cyanopyridin-3-yl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-(6-{[2-(morpholin-4-yl)ethyl]sulfanyl}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)benzamide,

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(3,3,3-trifluoro-2-hydroxypropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3,3-dimethylbutyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2,6-difluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-3-hydroxybenzamide,

N-cyclopropyl-4-{6-[2-(hydroxymethyl)phenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-[(2E)-but-2-en-2-yl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[2-(fluoromethyl)phenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(2-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2-hydroxyphenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3,3-dimethylbutyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-methoxyphenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(pyridin-4-yl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

(RS)-N-cyclopropyl-4-[6-(4-fluorophenyl)-8-{[(4-methylmorpholin-2-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-[6-(methylsulfanyl)-8-{[2-(morpholin-4-ylsulfonyl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-4-{6-(4-fluoro-2-methylphenyl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(2-fluorophenyl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(5-cyanopyridin-3-yl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

(RS)-4-{6-(cyclohex-1-en-1-yl)-8-[(3,3,3-trifluoro-2-hydroxypropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-[8-{[(1-methyl-1H-pyrazol-5-yl)methyl]amino}-6-

(methylsulfanyl)imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-4-{6-[(3-hydroxyphenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-(8-[(2-hydroxy-2-methylpropyl)amino]-6-{[2-(morpholin-4-yl)ethyl]sulfanyl}imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

(RS)-N-cyclopropyl-4-{6-[(2,2-difluorocyclopropyl)methoxy]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-(8-[(2-hydroxy-2-methylpropyl)amino]-6-{[(1E)-2,3,3-trifluoro-4-hydroxybut-1-en-1-yl]oxy}imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(2,2,3,3-tetrafluoro-4-hydroxybutoxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-(8-[(2-hydroxy-2-methylpropyl)amino]-6-{[4-(trifluoromethyl)phenyl]sulfanyl}imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-phenoxyimidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(2-hydroxy-2-methylpropyl) amino]imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide,

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide,

N-cyclopropyl-2-methyl-4-(6-{[4-(trifluoromethyl)phenyl]sulfanyl}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)benzamide,

N-cyclopropyl-4-{6-[(2,5-difluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3,4-difluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3,5-difluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2,3-difluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(4-fluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3,4-difluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2,5-difluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(4-isopropoxyphenoxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(4-isopropoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(2,3-difluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(2-fluoro-5-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3,4-difluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(2-thienylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3,5-difluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-(8-[(2-hydroxy-2-methylpropyl)amino]-6-{[(3S)-2-oxopyrrolidin-3-yl]oxy}imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(6-methylpyridin-3-yl)oxy]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyrimidin-5-

yloxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(3-chlorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{6-(4-chlorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2-fluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(5-fluoro-2-methylphenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-(6-{[2-(hydroxymethyl)phenyl]sulfanyl}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-methoxy-phenyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

(RS)-N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyrrolidin-3-ylamino)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-isopropyl-phenyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-2-yloxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[3-(2-hydroxy-2-methylpropoxy)phenoxy]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(2-hydroxy-ethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(2-hydroxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-(6-{[(1E)-2,3,3-trifluoro-4-hydroxybut-1-en-1-yl]oxy}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)benzamide,

N-cyclopropyl-2-methyl-4-{6-(2,2,3,3-tetrafluoro-4-hydroxybutoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

2-{3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}-5-fluoro-benzoic acid methyl ester,

N-cyclopropyl-4-{6-(2-hydroxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluoro-5-methylphenoxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(2-fluorophenoxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(phenylsulfanyl)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluoro-5-methylphenyl)sulfanyl]-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-hydroxyphenyl)sulfanyl]-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(pyridin-3-yloxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[(2-hydroxyphenyl)sulfanyl]-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(4-fluorophenoxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

4-{6-(4-chloro-3-fluorophenoxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{6-(4-chlorophenoxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-(2,3-difluorophenoxy)-8-[(tetrahydro-2H-thiopyran-4-

ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-[6-(4-chlorophenoxy)-8-({[(cis/trans)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide,

4-[6-(4-chlorophenoxy)-8-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-[6-(4-fluorophenoxy)-8-({[(cis/trans)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[8-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}-6-(4-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-[8-({[(cis)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)-6-(pyridin-3-yloxy)imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-2-methyl-4-[8-({[(trans)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)-6-(pyridin-3-yloxy)imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-4-[8-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}-6-(pyridin-3-yloxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[8-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}-6-(2-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-({[(cis/trans)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[8-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-{6-[4-fluoro-2-(hydroxymethyl)phenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3,4-difluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-(8-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}-6-[(3-fluorophenyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-[8-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-[8-({[(cis)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-2-methyl-4-[8-({[(trans)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-4-(6-[(3-fluorophenyl)sulfanyl]-8-({[(cis)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-(6-[(3-fluorophenyl)sulfanyl]-8-({[(trans)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-anilino-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3,4-difluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-methylphenyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(5-fluoro-2-methylphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-[(4-chlorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[(1-methylpiperidin-4-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[8-{[3-(dimethylamino)propyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[2-(methylsulfonyl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

4-{8-[(2-amino-2-methylpropyl)amino]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{8-[(azetidin-3-ylmethyl)amino]-6-phenoxyimidazo[1,2-b]pyridazin-3-yl}-N-

cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(4H-1,2,4-triazol-3-ylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(4-methyl-1H-imidazol-2-yl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1H-imidazol-2-ylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(1-methyl-1H-pyrazol-5-yl)oxy]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[4-(piperazin-1-yl)phenoxy]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(1-methyl-1H-pyrazol-4-yl)oxy]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

tert-butyl 4-[4-({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]piperazine-1-carboxylate,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(3-hydroxy-3-methylbutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(benzyloxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-[8-{[(1,1-dioxidotetrahydrothiophen-3-yl)methyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(tetrahydrofuran-3-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[(1-methyl-5-oxopyrrolidin-3-

yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[8-{[(3,3-difluorocyclobutyl)methyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-4-yloxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-4-ylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-2-ylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(tetrahydro-2H-pyran-4-ylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(cyclopentylsulfanyl)-8-[(2-hydroxy-2-methylpropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{8-[(azetidin-3-ylmethyl)amino]-6-[2-(hydroxymethyl)phenyl] imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

tert-butyl 3-[({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-6-[2-(hydroxymethyl)phenyl]imidazo[1,2-b]pyridazin-8-yl}amino)methyl]azetidine-1-carboxylate,

N-cyclopropyl-4-(8-{[(4-hydroxy-4-methylcyclohexyl)methyl]amino}-6-[2-(hydroxymethyl)phenyl]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-{8-[(3-hydroxy-3-methylbutyl)amino]-6-[2-(hydroxymethyl)phenyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

(RS)-N-cyclopropyl-4-{6-[2-(hydroxymethyl)phenyl]-8-[(4-hydroxypentyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

(RS)-N-cyclopropyl-4-{8-[(4-hydroxy-3-methylbutyl)amino]-6-[2-

(hydroxymethyl)phenyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-(6-[2-(hydroxymethyl)phenyl]-8-{[(1-methyl-5-oxopyrrolidin-3-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

(RS)-N-cyclopropyl-4-{6-[2-(hydroxymethyl)phenyl]-8-[(tetrahydrofuran-3-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[2-(hydroxymethyl)phenyl]-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{8-[(2-cyanoethyl)amino]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{6-[(4-chloro-2-fluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(5-methoxy-2-methylphenyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[4-fluoro-2-(hydroxymethyl)phenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3,5-difluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2,3-difluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluoro-4-methoxyphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(4-methoxyphenyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-[(3-chlorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2,4-difluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-2-

ylamino)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-3-ylamino)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2-fluoro-4-methylphenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(3-isopropoxyphenoxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2-fluoro-4-methylphenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

4-{6-[4-chloro-2-(hydroxymethyl)phenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{6-[4-chloro-2-(hydroxymethyl)phenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-4-ylamino)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(6-methoxypyridin-3-yl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2-fluoro-5-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-anilino-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2-fluorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-(6-{[2-(hydroxymethyl)phenyl]amino}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluoro-5-methylphenyl)amino]-8-[(3,3,3-

trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-[(4-chloro-3-fluorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3,4-difluorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-[(4-chlorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(5-fluoro-2-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-[(4-chloro-2-fluorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{6-[(5-chloro-2-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3,5-difluorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-[(3-chlorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2,3-difluorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-[3-(propan-2-yloxy)phenoxy]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[(4-fluoro-3-methylphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2-fluoro-5-methylphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2-fluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-isopropylphenyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-(6-{[4-(2-hydroxyethyl)phenyl]amino}-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluoro-2-methylphenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2-methoxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-[2-(methylamino)phenoxy]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(5-fluoro-2-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(5-fluoro-2-methylphenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-(6-{[4-chloro-2-(hydroxymethyl)phenyl]sulfanyl}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide,

4-(6-{[4-chloro-2-(hydroxymethyl)phenyl]sulfanyl}-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluoro-5-methylphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(2-aminophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{6-(2-amino-4-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluoro-2-hydroxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(2-chloro-3-fluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-methoxy-2-methylphenyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2-hydroxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluoro-3-methoxyphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-[(4-chloro-3-fluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(2-methoxyphenyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-methoxyphenyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-[(5-chloro-2-methylphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{6-[(2-chloro-4-fluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(6-fluoropyridin-3-yl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(cyclopentylamino)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{6-(cyclopent-3-en-1-ylamino)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-ethenylphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(6-fluoropyridin-3-yl)oxy]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

5-({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)nicotinamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyrazin-2-

ylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(4-methyl-4H-1,2,4-triazol-3-yl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1H-pyrazol-5-yloxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(5-methyl-1H-pyrazol-3-yl)oxy]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(cyclohexylamino)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{6-[(2-amino-4-fluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[2-methoxy-3-(propan-2-yl)phenoxy]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-[(4-methyl-4H-1,2,4-triazol-3-yl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{6-(pyrazin-2-ylsulfanyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-(6-{[(1RS,2RS)-2-hydroxycyclohexyl]oxy}-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluoro-3-methoxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-[(3-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[(3-fluoro-4-methoxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-methoxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-methoxy-2-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-(6-{[4-(2-hydroxyethyl)phenyl]amino}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluoro-3-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(6-methoxypyridin-3-yl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(5-methoxy-2-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(2-hydroxyphenyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluoro-2-methoxyphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-(6-{[3-(propan-2-yl)phenyl]amino}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)benzamide,

N-cyclopropyl-4-(6-{[2-(hydroxymethyl)phenyl]amino}-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

4-(6-{[4-(2-aminoethyl)phenyl]amino}-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(6-fluoropyridin-3-yl)oxy]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{6-(pyridin-3-ylamino)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[(6-fluoropyridin-3-yl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[2-hydroxy-3-(propan-2-yl)phenoxy]-8-[(3,3,3-

trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluoro-3-hydroxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(5-hydroxy-2-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-hydroxyphenyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3,4-difluorophenyl)amino]-8-[(4,4,4-trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(5-fluoro-2-methylphenyl)amino]-8-[(4,4,4-trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluoro-5-methylphenyl)sulfanyl]-8-[(4,4,4-trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2,3-difluorophenyl)amino]-8-[(4,4,4-trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-[(5-chloro-2-methylphenyl)amino]-8-[(4,4,4-trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluoro-5-methylphenoxy)-8-[(4,4,4-trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(cyclopentylamino)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-hydroxy-2-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(cyclopentyloxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(5-hydroxy-2-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluoro-2-methoxyphenyl)amino]-8-[(4,4,4-trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[2-fluoro-3-(methylsulfanyl)phenoxy]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methyl-N-(1-methylcyclopropyl)benzamide,

4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-(1-methoxycyclopropyl)-2-methylbenzamide,

N-(1-cyanocyclopropyl)-4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

3-(3-amino-1H-indazol-6-yl)-6-(3-fluorophenoxy)-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[(5-fluoropyridin-3-yl)oxy]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(2-amino-5-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(1,2,3,4-tetrahydroquinolin-8-yloxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(8-hydroxy-3,4-dihydroquinolin-1(2H)-yl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-[(2-oxo-1,2-dihydroquinolin-8-yl)oxy]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{6-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)oxy]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{6-(3-methylphenoxy)-8-[(3,3,3-

trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(4-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(2-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(2-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(3-fluoro-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-(6-{[4-(acetylamino)pyridin-3-yl]oxy}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide,

4-{6-(2-amino-3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2-fluoro-6-hydroxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(4-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[(4-fluoro-2-hydroxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-hydroxypyridin-4-yl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(1-phenylethenyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(3-fluoro-4-methoxybenzyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluoro-4-methylbenzyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(3-bromobenzyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoro-2-hydroxypropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-[8-{[2-(dimethylamino)ethyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[(1-methyl-1H-pyrazol-3-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(1H-pyrazol-3-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-({[3-(hydroxymethyl)oxetan-3-yl]methyl}amino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2,3-dihydroxypropyl)amino]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-[8-{[3-(dimethylamino)-3-oxopropyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[8-{[(4,4-difluorocyclohexyl)methyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(oxetan-3-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(1H-tetrazol-5-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-[8-{[2-(dimethylamino)-2-methylpropyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[2-methyl-2-(morpholin-4-yl)propyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[2-(piperidin-1-yl)ethyl]amino}imidazo[1,2-

b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[2-(4-methylpiperazin-1-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[2-(pyrrolidin-1-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-({3-[methyl(methylcarbamoyl)amino]propyl}amino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

4-[8-{[2-(acetylamino)ethyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[3-(piperidin-1-yl)propyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[3-(morpholin-4-yl)propyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[3-(pyrrolidin-1-yl)propyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[3-(methylsulfonyl)propyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

4-[8-{[3-(acetylamino)propyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-(methylamino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[2-(1H-tetrazol-5-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2,2-difluoroethyl)amino]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-[8-{[4-(dimethylamino)butyl]amino}-6-(3-

fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(2,2,2-trifluoroethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[2-(1H-pyrazol-1-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(2,3-difluorophenoxy)-8-{[2-(methylsulfonyl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(5-fluoro-2-methylphenoxy)-8-{[2-(methylsulfonyl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluoro-4-methoxyphenoxy)-8-{[2-(methylsulfonyl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(2-fluoro-4-methoxyphenoxy)-8-{[2-(methylsulfonyl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

4-{8-[(2-amino-2-methylpropyl)amino]-6-(3,4-difluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{8-[(2-amino-2-methylpropyl)amino]-6-(4-chlorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

4-{8-[(2-amino-2-methylpropyl)amino]-6-(pyridin-3-yloxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-[6-(4-chlorophenoxy)-8-{[2-(dimethylamino)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-[8-{[2-(dimethylamino)ethyl]amino}-6-(pyridin-3-yloxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3,4-difluorophenoxy)-8-{[2-(dimethylamino)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(2,3-difluorophenoxy)-8-{[(1-methylpiperidin-4-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-[8-{[(1-methylpiperidin-4-yl)methyl]amino}-6-(pyridin-3-yloxy)imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-4-[6-(2,3-difluorophenoxy)-8-(methylamino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3,4-difluorophenoxy)-8-(methylamino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(5-fluoro-2-methylphenoxy)-8-(methylamino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{8-(methylamino)-6-[2-(methylamino)phenoxy]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[(2-hydroxyphenyl)(methyl)amino]-8-(methylamino)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(5-fluoropyridin-3-yl)oxy]-8-(methylamino)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-[6-(2-fluoro-4-methoxyphenoxy)-8-(methylamino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluoro-4-methoxyphenoxy)-8-(methylamino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(2,3-difluorophenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(5-fluoro-2-methylphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-(6-[2-(methylamino)phenoxy]-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl)benzamide,

N-cyclopropyl-4-(6-[(2-hydroxyphenyl)(methyl)amino]-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-[6-(3,4-difluorophenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-(6-[(5-fluoropyridin-3-yl)oxy]-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[(1-methylazetidin-3-

yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

4-{8-[(azetidin-3-ylmethyl)amino]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-[6-(2,3-difluorophenoxy)-8-{[(1-methylazetidin-3-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

4-{8-[(azetidin-3-ylmethyl)amino]-6-(2,3-difluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{8-[(azetidin-3-ylmethyl)amino]-6-[(5-fluoropyridin-3-yl)oxy]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{8-[(azetidin-3-ylmethyl)amino]-6-(5-fluoro-2-methylphenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{8-[(3-aminopropyl)amino]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

3-({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-8-yl}amino)propane-1-sulfonic acid,

2-({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-8-yl}amino)ethanesulfonic acid,

N-(1-cyanocyclopropyl)-4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

N-ethyl-4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-isopropyl-2-methylbenzamide,

4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methyl-N-(3,3,3-trifluoropropyl)benzamide,

4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methyl-N-(2,2,3,3,3-pentafluoropropyl)benzamide,

N-(2,2-difluoroethyl)-4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-isobutyl-2-methylbenzamide,

4-{6-(4-chlorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(4-chlorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-ethyl-2-methylbenzamide,

4-{6-(2-fluoro-4-hydroxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

N-ethyl-4-{6-(2-fluoro-4-hydroxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-[6-(3,4-difluorophenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-N,2-dimethylbenzamide,

N,2-dimethyl-4-[6-(2-methylphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]benzamide,

4-[6-(4-methoxyphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-N,2-dimethylbenzamide,

4-[6-(2-fluoro-4-methoxyphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-N,2-dimethylbenzamide,

4-[6-(5-fluoro-2-methylphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-N,2-dimethylbenzamide,

4-{6-(3,4-difluorophenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

N,2-dimethyl-4-{6-(2-methylphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

4-{6-(3-fluorophenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-

b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(4-methoxyphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(5-fluoro-2-methylphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(3-fluoro-4-methoxyphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(3,4-difluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(5-fluoro-2-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(3-fluoro-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{8-[(2,2-difluoroethyl)amino]-6-(3,4-difluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{8-[(2,2-difluoroethyl)amino]-6-(2-fluoro-4-methoxyphenoxy)imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(2,3-difluorophenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(3,4-difluorophenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{8-[(2-methoxyethyl)amino]-6-(2-methylphenoxy)imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(5-fluoro-2-methylphenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(3-fluoro-4-methoxyphenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{8-[(2-methoxyethyl)amino]-6-phenoxyimidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-[6-(3,4-difluorophenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-N-ethyl-2-methylbenzamide,

N-ethyl-2-methyl-4-[6-(2-methylphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-ethyl-4-[6-(4-methoxyphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-ethyl-4-[6-(2-fluoro-4-methoxyphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-ethyl-4-[6-(5-fluoro-2-methylphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-ethyl-2-methyl-4-(8-{[2-(morpholin-4-yl)ethyl]amino}-6-phenoxyimidazo[1,2-b]pyridazin-3-yl)benzamide,

4-{6-(3,4-difluorophenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-ethyl-2-methylbenzamide,

N-ethyl-2-methyl-4-{6-(2-methylphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-ethyl-4-{6-(4-methoxyphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-ethyl-4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-ethyl-4-{6-(5-fluoro-2-methylphenoxy)-8-[(tetrahydro-2H-pyran-4-

ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-ethyl-4-{6-(3-fluoro-4-methoxyphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-ethyl-2-methyl-4-{6-(2-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-ethyl-4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-ethyl-4-{6-(5-fluoro-2-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-ethyl-4-{6-(3-fluoro-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{8-[(2,2-difluoroethyl)amino]-6-(2-fluoro-4-methoxyphenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-ethyl-2-methylbenzamide,

4-{8-[(2,2-difluoroethyl)amino]-6-(5-fluoro-2-methylphenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-ethyl-2-methylbenzamide,

4-{6-(3,4-difluorophenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-ethyl-2-methylbenzamide,

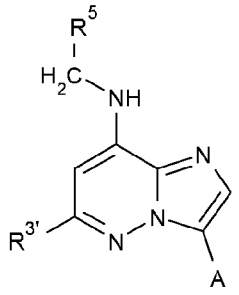
N-ethyl-4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-ethyl-4-{6-(5-fluoro-2-methylphenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-ethyl-4-{6-(3-fluoro-4-methoxyphenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

9. A method of preparing a compound according to any one of claims 1 to 8, said method comprising the step of allowing an intermediate compound of general formula **IV** :



IV

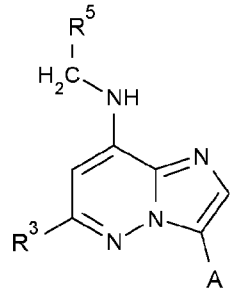
in which A, and R^5 are as defined for general formula I in any one of claims 1 to 8, and $R^{3'}$ is a leaving group ;

to react with a compound of general formula **IVa** :

R^3-Y

IVa

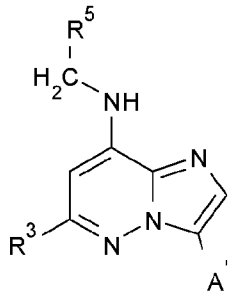
in which R^3 is as defined for general formula I in any one of claims 1 to 8, and Y is a substituent which is displaced in a coupling reaction, such as a hydrogen atom, or a boronic acid group, or a boronic ester group, for example,
thereby giving a compound of general formula I :



I

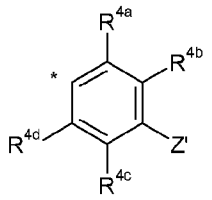
in which A, R^3, and R^5 are as defined for general formula I in any one of claims 1 to 8.

10. A method of preparing a compound according to any one of claims 1 to 8, said method comprising the step of allowing an intermediate compound of general formula **Ia** :



Ia

in which R^3 and R^5 are as defined for general formula I in any one of claims 1 to 8; and A' is



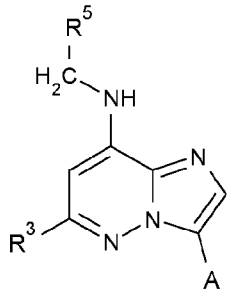
wherein * indicates the point of attachment of said group with the rest of the molecule; R^{4a}, R^{4b}, R^{4c} and R^{4d} are as defined for general formula I in any one of claims 1 to 8, and Z' represents a group selected from:
-C(=O)OH, -C(=S)OH, -C(=O)O-(C_1-C_6-alkyl) or -C(=S)O-(C_1-C_6-alkyl);

to react with a compound of general formula **Ib** :

H_2NR^2

Ib

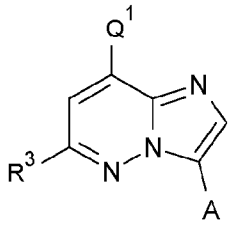
in which R^2 is as defined for general formula I in any one of the claims 1 to 8, thereby giving, upon optional deprotection, a compound of general formula I:



I

in which R^3, R^5 and A are as defined for general formula I in any one of claims 1 to 8.

11. A method of preparing a compound according to any one of claims 1 to 8, said method comprising the step of allowing an intermediate compound of general formula VII :



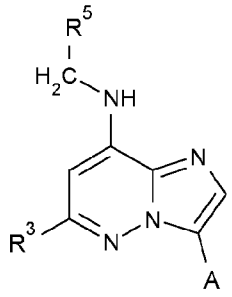
VII

in which R^3 and A are as defined for general formula I in any one of claims 1 to 8, and Q^1 is a leaving group,
to react with a compound of general formula VIIa :

R^5-CH_2-NH_2

VIIa

in which R^5 is as defined for general formula I, in any one of claims 1 to 8,
thereby giving, upon optional deprotection, a compound of general formula I :



I

in which R^3, R^5 and A are as defined for general formula I in any one of claims 1 to 8.

12. A compound according to any one of claims 1 to 8, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, for use in the treatment or prophylaxis of a disease.

13. A pharmaceutical composition comprising a compound according to any one of claims 1 to 8, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, and a pharmaceutical acceptable diluent or carrier.

14. A pharmaceutical combination comprising :

- one or more compounds according to any one of claims 1 to 8, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same;

and

- one or more agents selected from : a taxane, such as Docetaxel, Paclitaxel, or Taxol; an epothilone, such as Ixabepilone, Patupilone, or Sagopilone; Mitoxantrone; Predinisolone; Dexamethasone; Estramustin; Vinblastin; Vincristin; Doxorubicin; Adriamycin; Idarubicin; Daunorubicin; Bleomycin; Etoposide; Cyclophosphamide; Ifosfamide; Procarbazine; Melphalan; 5-Fluorouracil; Capecitabine; Fludarabine; Cytarabine; Ara-C; 2-Chloro-2´-deoxyadenosine; Thioguanine; an anti-androgen, such as Flutamide, Cyproterone acetate, or Bicalutamide; Bortezomib; a platinum

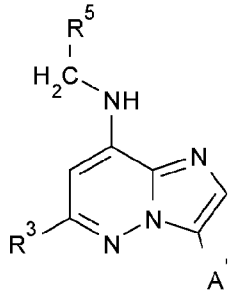
derivative, such as Cisplatin, or Carboplatin; Chlorambucil; Methotrexate; and Rituximab.

15. Use of a compound according to any one of claims 1 to 8, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, for the prophylaxis or treatment of a disease.

16. Use of a compound according to any one of claims 1 to 8, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, for the preparation of a medicament for the prophylaxis or treatment of a disease.

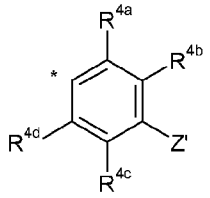
17. Use according to claim 12, 15 or 16, wherein said disease is a disease of uncontrolled cell growth, proliferation and/or survival, an inappropriate cellular immune response, or an inappropriate cellular inflammatory response, particularly in which the uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune response, or inappropriate cellular inflammatory response is mediated by the mitogen-activated protein kinase (MEK-ERK) pathway, more particularly in which the disease of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune response, or inappropriate cellular inflammatory response is a haemotological tumour, a solid tumour and/or metastases thereof, *e.g.* leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

18. A compound of general formula **Ia** :



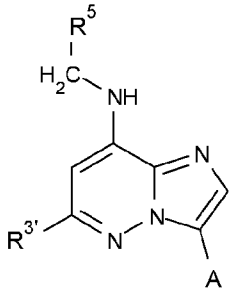
Ia

in which R^3 and R^5 are as defined for the compounds of general formula I in any one of the claims 1 to 8, and A' is



wherein * indicates the point of attachment of said group with the rest of the molecule; R^{4a}, R^{4b}, R^{4c} and R^{4d} are as defined for the compounds of general formula I in any one of the claims 1 to 8, and Z' represents a group selected from: -C(=O)OH, -C(=S)OH, -C(=O)O-(C_1-C_6-alkyl) or -C(=S)O-(C_1-C_6-alkyl).

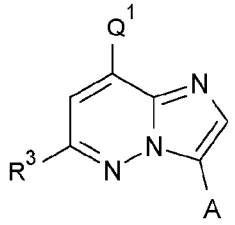
19. A compound of general formula **IV** :



IV

in which A, and R^5 are as defined for the compounds of general formula I in any one of the claims 1 to 8, and $R^{3'}$ is a leaving group.

20. A compound of general formula **VII** :



VII

in which A, and R^3 are as defined for the compounds of general formula **I** in any one of the claims 1 to 8, and Q^1 represents an optionally protected NH_2-group or a leaving group.

21. Use of a compound of any one of the claims 18, 19 or 20 for the preparation of a compound of general formula I.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/065368

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/5025 A61P35/00
ADD.

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.
X,P	WO 2011/013729 A1 (ONCOTHERAPY SCIENCE INC [JP]; KUSAKABE KEN-ICHI [JP]; YOSHIDA HIROSHI) 3 February 2011 (2011-02-03) cited in the application pages 66-68,15; claim 1	1-21
A	WO 2007/038314 A2 (SQUIBB BRISTOL MYERS CO [US]; VACCARO WAYNE [US]; CHEN ZHONG [US]; DOD) 5 April 2007 (2007-04-05) cited in the application page 44, line 4; claim 1	1-21

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 November 2011	18/11/2011

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

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2011/065368

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011013729 A1	03-02-2011	TW 201107329 A	01-03-2011
WO 2007038314 A2	05-04-2007	AR 055177 A1	08-08-2007
		AU 2006295439 A1	05-04-2007
		BR PI0616393 A2	21-06-2011
		CA 2623369 A1	05-04-2007
		EA 200800873 A1	29-08-2008
		EP 1928879 A2	11-06-2008
		JP 2009509961 A	12-03-2009
		KR 20080063344 A	03-07-2008
		NZ 566663 A	31-03-2011
		PE 05202007 A1	29-08-2007
		TW 200804385 A	16-01-2008
		US 2007078136 A1	05-04-2007
		US 2008045536 A1	21-02-2008
		US 2010204212 A1	12-08-2010

IMIDAZOPIRIDAZINAS SUSTITUIDAS

La presente invención se relaciona con compuestos de imidazopiridazina sustituida que tienen la fórmula general I, tal como se describe y se define en la presente, con métodos para preparar dichos compuestos, con composiciones y combinaciones farmacéuticas que comprenden dichos compuestos, con el uso de dichos compuestos para preparar una composición farmacéutica para el tratamiento o la profilaxis de una enfermedad, y también con compuestos intermediarios útiles para preparar dichos compuestos.

ANTECEDENTES DE LA INVENCIÓN

La presente invención se relaciona con compuestos químicos que inhiben la quinasa Mps-1 (del huso monopolar 1) (que también se conoce como quinasa de tirosina y treonina, TTK). Mps-1 es una quinasa de Ser/Thr con especificidad doble que cumple una función fundamental en la activación del punto de verificación de la mitosis (también conocido como punto de verificación del huso o punto de verificación del ensamblaje del huso), que permite asegurar una segregación apropiada de los cromosomas durante la mitosis [Abrieu A *et al*., Cell, 2001, 106, 83-93]. Es necesario que en cada célula en división tenga lugar una separación equitativa de los cromosomas replicados entre las células hijas. Una vez que comienza la mitosis, los cromosomas se unen a los microtúbulos del aparato del huso a través de sus cinetocoros. El punto de verificación de la mitosis es un mecanismo de vigilancia que presenta actividad siempre que hay cinetocoros no unidos presentes, por lo que impide que las células en mitosis ingresen en la anafase, y que de esta manera

completen la división los cromosomas no unidos [Suijkerbuijk SJ y Kops GJ, Biochemica et Biophysica Acta, 2008, 1786, 24-31; Musacchio A y Salmon ED, Nat Rev Mol Cell Biol., 2007, 8, 379-93]. Una vez que los cinetocoros están unidos al huso mitótico de una manera anfitélica correcta, es decir, bipolar, se cumple con la verificación y la célula ingresa en la anafase y procede en la mitosis. El punto de verificación de la mitosis consiste en una red compleja de diversas proteínas esenciales, incluyendo miembros de las familias MAD (con deficiencias en la detención de la mitosis, MAD 1-3) y Bub (con una brotación no inhibida por el benzimidazol, Bub 1-3), la proteína motora CENP-E, la quinasa Mps-1 y otros componentes, muchos de los cuales se sobreexpresan en las células (por ejemplo, las células cancerosas) y los tejidos en proliferación [Yuan B *et al.*, Clinical Cancer Research, 2006, 12, 405-10]. La función esencial de la actividad de la quinasa Mps-1 en la señalización del punto de verificación de la mitosis ha sido demostrada a través de un silenciamiento con ARNph, por medio de la genética química y con inhibidores químicos de la quinasa Mps-1 [Jelluma N *et al.*, PLos ONE, 2008, 3, e2415; Jones MH *et al.*, Current Biology, 2005, 15, 160-65; Dorer RK *et al.*, Current Biology, 2005, 15, 1070-76; Schmidt M *et al.*, EMBO Reports, 2005, 6, 866-72].

Hay numerosas evidencias que permiten establecer una relación entre una función reducida pero incompleta del punto de verificación de la mitosis y la aneuploidía y la tumorigénesis [Weaver BA y Cleveland DW, Cancer Research, 2007, 67, 10103-5; King RW, Biochimica et Biophysica Acta, 2008, 1786, 4-14]. En contraste, se ha reconocido que la inhibición completa del punto

de verificación de la mitosis da como resultado la agregación severamente inapropiada de los cromosomas de las células tumorales y la inducción de la apoptosis en ellas [Kops GJ *et al.*, Nature Reviews Cancer, 2005, 5, 773-85; Schmidt M y Medema RH, Cell Cicle, 2006, 5, 159-63; Schmidt M y Bastians H, Drug Resisance Updates, 2007, 10, 162-81]. Entonces, la anulación del punto de verificación de la mitosis a través de la inhibición farmacológica de la quinasa Mps-1 o de otros componentes del punto de verificación de la mitosis representa un nuevo abordaje para el tratamiento de trastornos proliferativos, incluyendo los tumores sólidos, tales como los carcinomas, los sarcomas, las leucemias o los tumores malignos linfáticos, o de otros trastornos asociados a una proliferación celular descontrolada.

Las drogas antimitóticas establecidas, tales como los alcaloides de vinca, taxanos o epotilonas activan la SAC induciendo un arresto mitótico ya sea estabilizando o desestabilizando la dinámica de los microtúbulos. Este arresto impide la separación de cromátidas hermanas para formar las dos células hijas. Un prolongado arresto de la mitosis fuerza a la célula ya sea hacia una salida mitótica sin citoquinesis o a una catástrofe mitótica que lleva a la muerte celular.

Al contrario, los inhibidores de Mps-1 inducen una inactivación de la SAC que acelera el progreso de las células a través de la mitosis que da como resultado una grave segregación cromosómica defectuosa y finalmente la muerte celular.

Dichos descubrimientos sugieren que los inhibidores de Mps-1 deberían tener valor terapéutico para el tratamiento de

trastornos proliferativos asociados con la intensificación de procesos celulares proliferativos descontrolados tales como, por ejemplo, cáncer, inflamación, artritis, enfermedades virales, enfermedades neurodegenerativas tales como la enfermedad de Alzheimer, enfermedades cardiovasculares, o enfermedades fúngicas en un animal de sangre caliente tal como un ser humano.

Por lo tanto, los inhibidores de Mps-1 representan compuestos valiosos que deberían complementar las opciones terapéuticas ya sea como agentes únicos o en combinación con otras drogas.

En los antecedentes técnicos se han descripto diversos compuestos que presentan un efectoo de inhibición sobre la quinasa Mps-1. WO2010/124826A1 divulga compuestos de imidazoquinoxalina sustituidos, como inhibidores de Mps-1 quinasa o TTK. WO2011/026579A1 divulga aminoquinoxalinas sustituidas como inhibidores de Mps-1. WO2011/063908A1, WO2011/064328A1 así como WO2011/063907 A1 divulgan derivados de triazolopiridina como inhibidores de Mps-1 quinasa.

Se han divulgado derivados de imidazopiridazina para el tratamiento o la profilaxis de diferentes enfermedades:

WO 2007/038314 A2 (Bristol-Myers Squibb Company) se refiere a compuestos heterocíclicos fusionados útiles como moduladores de quinasa, incluyendo la modulación de MK2. En particular, WO 2007/038314 A2 se refiere a imidazo[1,2-b]piridazinas.

De manera similar, la publicación de solicitud de patente de los EE.UU. US 2008/0045536 A1 (Bristol-Myers Squibb Company) se refiere a compuestos heterocíclicos fusionados útiles como

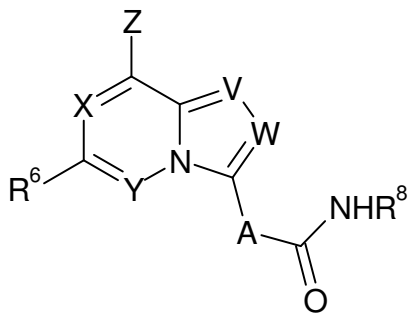
moduladores de quinasa, que incluyen la modulación de MK2. En particular, se refiere a imidazo[1,2-b]piridazinas.

WO 2010/042699 A1 (Bristol-Myers Squibb Company) se refiere a compuestos heterocíclicos fusionados útiles como moduladores de quinasa, en particular a la modulación de CK2. En particular, WO 2010/042699 A1 se refiere a imidazo[1,2-b]piridazinas que están sustituidas con un grupo nitrilo en posición 3.

WO 2007/025090 A2 (Kalypsis, Inc.) se refiere a compuestos heterocíclicos útiles como inhibidores de MEK quinasa. En particular, WO 2007/025090 A2 se refiere *entre otras cosas*, a imidazo[1,2-b]piridazinas.

WO 1998/08847 A1 (Pfizer, Inc.) se refiere a compuestos heterocíclicos útiles como antagonistas del factor de liberación de corticotropina (hormona) CRF (CRH). En particular, WO 1998/08847 A1 se refiere, entre otras cosas, a imidazo[1,2-b]piridazinas.

WO 2011/013729A1 divulga derivados imidazol fusionados como inhibidores de Mps-1. Entre los derivados imidazol fusionados que se divulgan figuran también las imidazo[1,2-b]piridazinas. Por ejemplo, WO 2011/013729A1 divulga compuestos de fórmula **C1**:



C1

en donde (X, Y, V, W) es (–N=, =CR^1–, =N–, –CR^7=), (–CR^2=, =N–, =N–, –CR^7=), (–N=, =CR^1–, =N–, –N=) o (–N=, =CR^1–, –O–, –N=);

R^8 es cicloalquilo sustituido o no sustituido;

Z es un grupo representado por la fórmula –NR^3R^4 o un grupo representado por la fórmula –OR^5;

A es un anillo hidrocarburo aromático sustituido o no sustituido, anillo heterocíclico aromático sustituido o no sustituido, anillo hidrocarburo no aromático sustituido o no sustituido o anillo heterocíclico no aromático sustituido o no sustituido;

R^1, R^3, R^4, R^5, y R^6 representan una gran variedad de sustituyentes (véase WO 2011/013729A1, por ejemplo la reivindicación 1).

Los inventores de la presente invención observaron sorprendentemente que los compuestos con la fórmula general **I** según se describen y definen aquí muestran una alta actividad en la inhibición de Mps–1 y muestran una alta estabilidad metabólica.

Sin embargo, en los antecedentes técnicos anteriores no se describen los compuestos de imidazopiridina de las reivindicaciones 1 a 8, o estereoisómeros, tautómeros, N–óxidos, hidratos, solvatos o sales de éstos, o mezclas que los contengan, como sí se los describe y se los define en la presente, y en adelante llamados “compuestos de la presente invención”, ni su actividad ni estabilidad

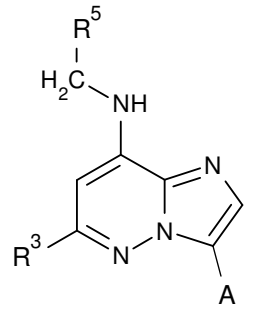
farmacológica. Recientemente, se ha descubierto que los compuestos de la presente invención presentan propiedades sorprendentes y ventajosas, y esto constituye la base de la presente invención.

En particular, sorprendentemente se ha descubierto que los compuestos de la presente invención inhiben de manera efectiva la quinasa Mps-1, por lo que pueden ser usados para el tratamiento o la profilaxis de enfermedades relacionadas con un crecimiento, una proliferación y/o una supervivencia celular descontrolada, con una respuesta inmune celular inapropiada o con una respuesta inflamatoria celular inapropiada, o de enfermedades que están acompañadas por un crecimiento, una proliferación y/o una supervivencia celular descontrolada, por una respuesta inmune celular inapropiada o por una respuesta inflamatoria celular inapropiada, particularmente donde el crecimiento, la proliferación y/o la supervivencia celular descontrolada, la respuesta inmune celular inapropiada o la respuesta inflamatoria celular inapropiada están mediados por Mps-1, por ejemplo, los tumores hematológicos, los tumores sólidos y/o sus metástasis, por ejemplo, las leucemias y el síndrome mielodisplástico, los linfomas malignos, los tumores de la cabeza y el cuello, incluyendo los tumores cerebrales y las metástasis cerebrales, los tumores del tórax, incluyendo los tumores de las células pulmonares no pequeñas y de las células pulmonares pequeñas, los tumores gastrointestinales, los tumores endocrinos, los tumores mamarios y otros tumores

ginecológicos, los tumores del tracto urinario, incluyendo los tumores renales, vesicales y prostáticos, los tumores en la piel y los sarcomas, y/o sus metástasis.

RESUMEN DE LA INVENCIÓN

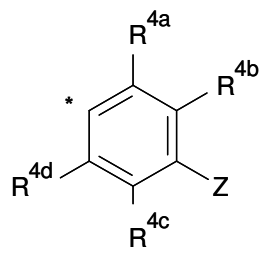
La presente invención comprende compuestos de fórmula general I:



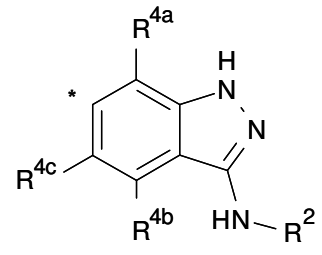
I

donde:

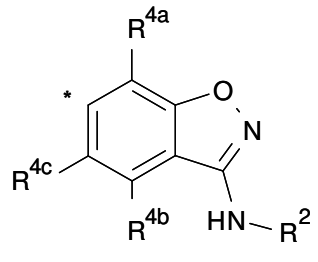
A representa un grupo



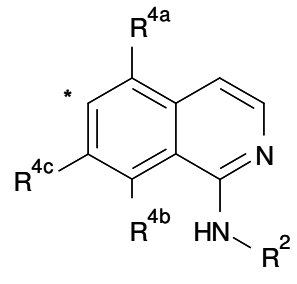
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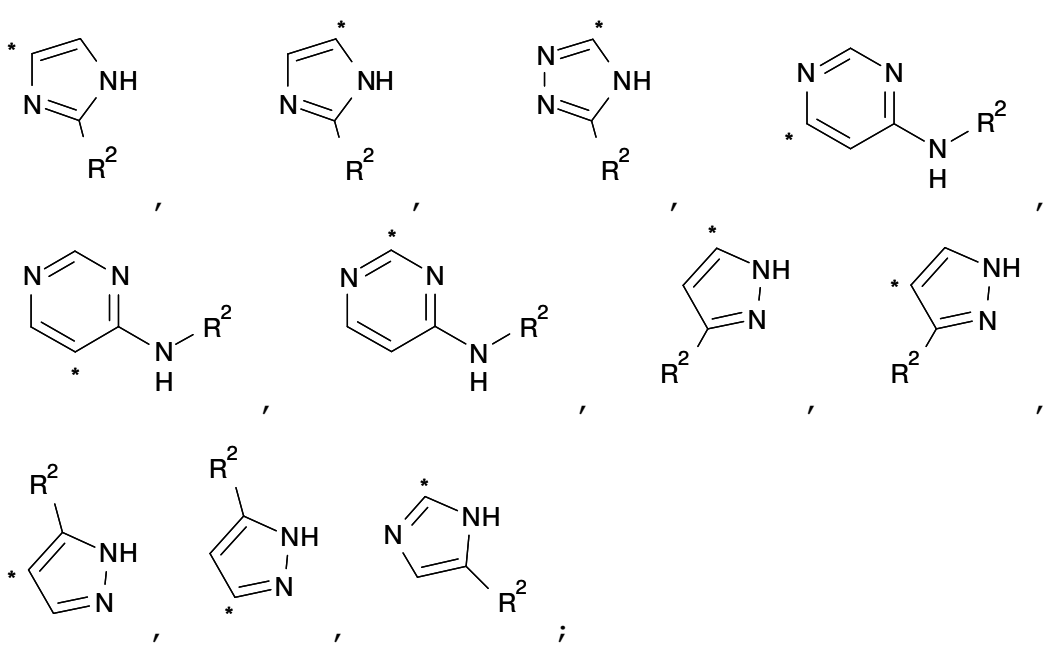


–;

donde * indica el punto de unión de dichos grupos con el

resto de la molécula;

Z representa un grupo $-C(=O)N(H)R^2$ o $-C(=S)N(H)R^2$, o un grupo seleccionado entre



donde * indica el punto de unión de dichos grupos con el resto de la molécula;

R^2 representa un átomo de hidrógeno, o un grupo C1-C6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, C_2-C_6-alquinilo- o C3-C6-cicloalquilo-;

donde dicho grupo C_3-C_6-cicloalquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos seleccionados entre: halógeno, -OH, -CN, C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alquilo-;

R^3 representa un átomo de hidrógeno o un átomo de halógeno, o un grupo -CN, C_1-C_6-alquilo-, C_1-C_6-alcoxi-, $-(CH_2)_m$-C_2-C_6-

alquenilo, $-(CH_2)_m-C_4-C_8$-cicloalquenilo, $-(CH_2)_m-C_2-C_6$-alquinilo, $-(CH_2)_m-C_3-C_6$-cicloalquilo, $-(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), $-(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N-C_1-C_6$-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo-, $-C_1-C_6$-alquil-arilo, $-C_1-C_6$-alquil-heteroarilo, heteroarilo-, C_1-C_6-alquil-X-, $-X-(CH_2)_m-C_2-C_6$-alquenilo, $-X-(CH_2)_m-C_4-C_8$-cicloalquenilo, $-X-(CH_2)_m-C_2-C_6$-alquinilo, $-X-(CH_2)_m-C_3-C_6$-cicloalquilo, $-X-(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), $-X-(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-X-, heteroaril-X-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)_2R^6$, $-S(=O)(=NR^{6a})R^{6b}$, $-S(=O)_2N(R^{6b})R^{6c}$, $-S-(CH_2)_n-N(R^{6a})R^{6b}$ o $-S-(CH_2)_n$-(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho grupo C_1-C_6-alquilo-, C_1-C_6-alcoxi-, $-(CH_2)_m-C_2-C_6$-alquenilo, $-(CH_2)_m-C_2-C_6$-alquinilo, $-(CH_2)_m-C_3-C_6$-cicloalquilo, aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo-, C_1-C_6-alquil-X-, $-X-(CH_2)_m-C_2-C_6$-alquenilo, $-X-(CH_2)_m-C_4-C_8$-cicloalquenilo, $-X-(CH_2)_m-C_2-C_6$-alquinilo, $-X-(CH_2)_m-C_3-C_6$-cicloalquilo, $-X-(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), $-X-(CH_2)_m$-

(heterocicloalquenilo de entre 4 y 8 miembros), aril-X-, heteroaril-X-, -C_1-C_6-alquil-arilo, -C_1-C_6-alquil-heteroarilo o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, 4 o 5 grupos R^7;

R^{4a}, R^{4b}, R^{4c}, R^{4d}

representan, en forma independiente entre sí, un átomo de hidrógeno o halógeno, o un grupo -CN, C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^{6a}$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$;

R^5 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, -$(CH_2)_n$-C_2-C_6-alquenilo, -$(CH_2)_n$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-,arilo- o

heteroarilo-;

donde dicho grupo C_1-C_6-alquilo-, -$(CH_2)_n$-C_2-C_6-alquenilo, -$(CH_2)_n$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_4-C_8-cicloalquenilo-, arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos R^8;

R^6, R^{6a}, R^{6b}, R^{6c}

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, C_2-C_6-alquenilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, aril-C_1-C_6-alquilo- o heteroaril-C_1-C_6-alquilo-;

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, -$C(=O)R^6$, -$C(=O)N(H)R^{6a}$, -$C(=O)N(R^{6a})R^{6b}$, -$C(=O)O$-R^6, -$N(R^{6a})R^{6b}$, -NO_2, -$N(H)C(=O)R^6$, -$N(R^{6c})C(=O)R^6$, -$N(H)C(=O)N(R^{6a})R^{6b}$, -$N(R^{6c})C(=O)N(R^{6a})R^{6b}$, -$N(H)C(=O)OR^6$, -$N(R^{6c})C(=O)OR^6$, -$N(H)S(=O)R^6$, -$N(R^{6c})S(=O)R^6$, -$N(H)S(=O)_2R^6$, -$N(R^{6c})S(=O)_2R^6$, -$N=S(=O)(R^{6a})R^{6b}$, -$OR^6$, -

$O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$ o $-S(=O)(=NR^{6c})R^6$;

donde dicho grupo C_1-C_6-alcoxi-, arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2 o 3 grupos C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alcoxi-, $-C(=O)O-R^6$ o $-OH$;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo- o heteroarilo-, donde dichos 2 grupos R^7 juntos forman un puente:

$*O(CH_2)_2O*$, $*O(CH_2)O*$, $*NH(C(=O))NH*$, donde * representa el punto de unión a dicho anillo arilo- o heteroarilo-;

R^8 representa un átomo de hidrógeno o halógeno, o un grupo -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ o $-S(=O)_2$-(heterocicloalquilo

de entre 3 y 7 miembros);

donde dicho heterocicloalquilo- o heteroarilo- de entre 3 y 7 miembros está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos C_1-C_6 alquilo-;

m es el entero 0, 1, 2, 3, 4, 5 o 6;

n es el entero 0, 1, 2, 3, 4 o 5;

X representa $S(=O)_p$, O, NR^6, $CR^{6a}R^{6b}$ o $C=CR^{6a}R^{6b}$;

p es el entero 0, 1 o 2;

o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato o una sal de los mismos, o una mezcla de los mismos.

La presente invención también se relaciona con métodos para preparar dichos compuestos, con composiciones y combinaciones farmacéuticas que comprenden dichos compuestos, con el uso de dichos compuestos en la manufactura de una composición farmacéutica para tratar o prevenir una enfermedad y con compuestos intermediarios útiles en la preparación de los compuestos mencionados.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Los términos mencionados en el presente texto tienen preferentemente los siguientes significados:

El término “átomo de halógeno” o “halo-” debe entenderse como un átomo de flúor, cloro, bromo o yodo, preferiblemente un átomo de flúor, cloro, bromo o yodo.

El término “C_1-C_6-alquilo” debe entenderse preferentemente como un grupo hidrocarburo monovalente lineal o ramificado,

saturado que tiene 1, 2, 3, 4, 5, o 6 átomos de carbono, por ejemplo un grupo metilo, etilo, propilo, butilo, pentilo, hexilo, iso-propilo, iso-butilo, sec-butilo, tert-butilo, iso-pentilo, 2-metilbutilo, 1-metilbutilo, 1-etilpropilo, 1,2-dimetilpropilo, neo-pentilo, 1,1-dimetilpropilo, 4-metilpentilo, 3-metilpentilo, 2-metilpentilo, 1-metilpentilo, 2-etilbutilo, 1-etilbutilo, 3,3-dimetilbutilo, 2,2-dimetilbutilo, 1,1-dimetilbutilo, 2,3-dimetilbutilo, 1,3-dimetilbutilo, o 1,2-dimetilbutilo, o un isómero del mismo. Particularmente, dicho grupo tiene 1, 2, 3 o 4 átomos de carbono ("C_1-C_4-alquilo"), por ejemplo un grupo metilo, etilo, propilo, butilo, iso-propilo, iso-butilo, sec-butilo, tert-butilo, más particularmente 1, 2 o 3 átomos de carbono ("C_1-C_3-alquilo"), por ejemplo un grupo metilo, etilo, n-propil- o iso-propilo.

El término "halo-C_1-C_6-alquilo" debe entenderse preferentemente como un grupo hidrocarburo monovalente lineal o ramificado saturado en el cual el término "C_1-C_6-alquilo" tiene los valores que se definen precedentemente, y en el cual uno o más átomos de hidrógeno se reemplaza por un átomo de halógeno, de igual o diferente manera, por ejemplo un átomo de halógeno en forma independiente de otro. Particularmente, dicho átomo de halógeno es F. Dicho grupo halo-C_1-C_6-alquilo es, por ejemplo, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CF_2CF_3$, o $-CH_2CF_3$.

El término "C_1-C_6-alcoxi" debe entenderse preferentemente como un grupo hidrocarburo monovalente saturado lineal o ramificado de fórmula $-O-(C_1$-C_6-alquilo), en el cual el término "C_1-C_6-alquilo" tiene los valores que

se definen precedentemente, por ejemplo un grupo metoxi, etoxi, n-propoxi, iso-propoxi, n-butoxi, iso-butoxi, tert-butoxi, sec-butoxi, pentoxi, iso-pentoxi, o n-hexoxi, o un isómero del mismo.

El término "halo-C_1-C_6-alcoxi" debe entenderse preferentemente como un grupo C_1-C_6-alcoxi lineal o ramificado saturado monovalente, como se define precedentemente, en el cual uno o más de los átomos de hidrógeno se reemplaza, de igual o diferente manera, por uno o más átomos de halógeno. Particularmente, dicho átomo de halógeno es F. Dicho grupo halo-C_1-C_6-alcoxi es, por ejemplo, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-OCF_2CF_3$, o $-OCH_2CF_3$.

El término "C_1-C_6-alcoxi-C_1-C_6-alquilo" debe entenderse preferentemente como un grupo C_1-C_6-alquilo monovalente saturado lineal o ramificado, como se define precedentemente, en el cual uno o más de los átomos de hidrógeno se reemplaza, de igual o diferente manera, por un grupo C_1-C_6-alcoxi, como se define precedentemente, por ejemplo un grupo metoxialquilo, etoxialquilo, propiloxialquilo, iso-propoxialquilo, butoxialquilo, iso-butoxialquilo, tert-butoxialquilo, sec-butoxialquilo, pentiloxialquilo, iso-pentiloxialquilo, hexiloxialquilo, o un isómero del mismo.

El término "halo-C_1-C_6-alcoxi-C_1-C_6-alquilo" debe entenderse preferentemente como un grupo C_1-C_6-alcoxi-C_1-C_6-alquilo lineal o ramificado monovalente saturado, como se define precedentemente, en el cual uno o más de los átomos de hidrógeno se reemplaza, de igual o diferente manera, por

uno o más átomos de halógeno. Particularmente, dicho átomo de halógeno es F. Dicho grupo halo-C_1-C_6-alcoxi-C_1-C_6-alquilo es, por ejemplo, $-CH_2CH_2OCF_3$, $-CH_2CH_2OCHF_2$, $-CH_2CH_2OCH_2F$, $-CH_2CH_2OCF_2CF_3$, o $-CH_2CH_2OCH_2CF_3$.

El término "C_2-C_6-alquenilo" debe entenderse preferentemente como un grupo hidrocarburo monovalente lineal o ramificado, que contiene una o más uniones dobles, y el cual tiene 2, 3, 4, 5 o 6 átomos de carbono, particularmente 2 o 3 átomos de carbono ("C_2-C_3-alquenilo"), debiéndose entender que en el caso en el cual dicho grupo alquenilo contiene más de una unión doble, luego dichas uniones dobles pueden estar aisladas o conjugadas entre sí. Dicho grupo alquenilo es, por ejemplo, un grupo vinilo, alilo, (E)-2-metilvinilo, (Z)-2-metilvinilo, homoalilo, (E)-but-2-enilo, (Z)-but-2-enilo, (E)-but-1-enilo, (Z)-but-1-enilo, pent-4-enilo, (E)-pent-3-enilo, (Z)-pent-3-enilo, (E)-pent-2-enilo, (Z)-pent-2-enilo, (E)-pent-1-enilo, (Z)-pent-1-enilo, hex-5-enilo, (E)-hex-4-enilo, (Z)-hex-4-enilo, (E)-hex-3-enilo, (Z)-hex-3-enilo, (E)-hex-2-enilo, (Z)-hex-2-enilo, (E)-hex-1-enilo, (Z)-hex-1-enilo, isopropenilo, 2-metilprop-2-enilo, 1-metilprop-2-enilo, 2-metilprop-1-enilo, (E)-1-metilprop-1-enilo, (Z)-1-metilprop-1-enilo, 3-metilbut-3-enilo, 2-metilbut-3-enilo, 1-metilbut-3-enilo, 3-metilbut-2-enilo, (E)-2-metilbut-2-enilo, (Z)-2-metilbut-2-enilo, (E)-1-metilbut-2-enilo, (Z)-1-metilbut-2-enilo, (E)-3-metilbut-1-enilo, (Z)-3-metilbut-1-enilo, (E)-2-metilbut-1-enilo, (Z)-2-metilbut-1-enilo, (E)-1-metilbut-1-enilo, (Z)-1-metilbut-1-enilo, 1,1-

dimetilprop-2-enilo, 1-etilprop-1-enilo, 1-propilvinilo, 1-isopropilvinilo, 4-metilpent-4-enilo, 3-metilpent-4-enilo, 2-metilpent-4-enilo, 1-metilpent-4-enilo, 4-metilpent-3-enilo, (E)-3-metilpent-3-enilo, (Z)-3-metilpent-3-enilo, (E)-2-metilpent-3-enilo, (Z)-2-metilpent-3-enilo, (E)-1-metilpent-3-enilo, (Z)-1-metilpent-3-enilo, (E)-4-metilpent-2-enilo, (Z)-4-metilpent-2-enilo, (E)-3-metilpent-2-enilo, (Z)-3-metilpent-2-enilo, (E)-2-metilpent-2-enilo, (Z)-2-metilpent-2-enilo, (E)-1-metilpent-2-enilo, (Z)-1-metilpent-2-enilo, (E)-4-metilpent-1-enilo, (Z)-4-metilpent-1-enilo, (E)-3-metilpent-1-enilo, (Z)-3-metilpent-1-enilo, (E)-2-metilpent-1-enilo, (Z)-2-metilpent-1-enilo, (E)-1-metilpent-1-enilo, (Z)-1-metilpent-1-enilo, 3-etilbut-3-enilo, 2-etilbut-3-enilo, 1-etilbut-3-enilo, (E)-3-etilbut-2-enilo, (Z)-3-etilbut-2-enilo, (E)-2-etilbut-2-enilo, (Z)-2-etilbut-2-enilo, (E)-1-etilbut-2-enilo, (Z)-1-etilbut-2-enilo, (E)-3-etilbut-1-enilo, (Z)-3-etilbut-1-enilo, 2-etilbut-1-enilo, (E)-1-etilbut-1-enilo, (Z)-1-etilbut-1-enilo, 2-propilprop-2-enilo, 1-propilprop-2-enilo, 2-isopropilprop-2-enilo, 1-isopropilprop-2-enilo, (E)-2-propilprop-1-enilo, (Z)-2-propilprop-1-enilo, (E)-1-propilprop-1-enilo, (Z)-1-propilprop-1-enilo, (E)-2-isopropilprop-1-enilo, (Z)-2-isopropilprop-1-enilo, (E)-1-isopropilprop-1-enilo, (Z)-1-isopropilprop-1-enilo, (E)-3,3-dimetilprop-1-enilo, (Z)-3,3-dimetilprop-1-enilo, 1-(1,1-dimetiletil)etenilo, buta-1,3-dienilo, penta-1,4-dienilo, hexa-1,5-dienilo, o metilhexadienilo.

Particularmente, dicho grupo es vinilo o alilo.

El término "C_2-C_6-alquinilo" debe entenderse preferentemente como un grupo hidrocarburo monovalente lineal o ramificado que contiene una o más uniones triples, y que contiene 2, 3, 4, 5 o 6 átomos de carbono, particularmente 2 o 3 átomos de carbono ("C_2-C_3-alquinilo"). Dicho grupo C_2-C_6-alquinilo es, por ejemplo, un grupo etinilo, prop-1-inilo, prop-2-inilo, but-1-inilo, but-2-inilo, but-3-inilo, pent-1-inilo, pent-2-inilo, pent-3-inilo, pent-4-inilo, hex-1-inilo, hex-2-inilo, hex-3-inilo, hex-4-inilo, hex-5-inilo, 1-metilprop-2-inilo, 2-metilbut-3-inilo, 1-metilbut-3-inilo, 1-metilbut-2-inilo, 3-metilbut-1-inilo, 1-etilprop-2-inilo, 3-metilpent-4-inilo, 2-metilpent-4-inilo, 1-metilpent-4-inilo, 2-metilpent-3-inilo, 1-metilpent-3-inilo, 4-metilpent-2-inilo, 1-metilpent-2-inilo, 4-metilpent-1-inilo, 3-metilpent-1-inilo, 2-etilbut-3-inilo, 1-etilbut-3-inilo, 1-etilbut-2-inilo, 1-propilprop-2-inilo, 1-isopropilprop-2-inilo, 2,2-dimetilbut-3-inilo, 1,1-dimetilbut-3-inilo, 1,1-dimetilbut-2-inilo, o 3,3-dimetilbut-1-inilo. Particularmente, dicho grupo alquinilo es etinilo, prop-1-inilo, o prop-2-inilo.

El término "C_3-C_6-cicloalquilo" debe entenderse preferentemente como un anillo mono o bicíclico saturado monovalente que contiene 3, 4, 5 o 6 átomos de carbono ("C_3-C_6-cicloalquilo"). Dicho grupo C_3-C_6-cicloalquilo es por ejemplo, un anillo hidrocarburo monocíclico, por ejemplo ciclopropilo, ciclobutilo, ciclopentilo, o ciclohexilo o un anillo hidrocarburo bicíclico.

Se debe entender que el término "C_4-C_8-cicloalquenilo" significa preferiblemente un anillo hidrocarburo monovalente, mono, o bicíclico que contiene 4, 5, 6, 7 u 8 átomos de carbono y uno, dos, tres o cuatro dobles uniones, conjugadas o no, si lo permite el tamaño de dicho anillo cicloalquenilo. Dicho grupo C_4-C_8-cicloalquenilo es por ejemplo, un anillo hidrocarburo monocíclico, *por ejemplo* un ciclobutenilo, ciclopentenilo, o ciclohexenilo o un anillo hidrocarburo bicíclico, *por ejemplo* un anillo ciclooctadienilo.

Se debe entender que el término "heterocicloalquilo de 3 a 7 miembros", significa un anillo hidrocarburo saturado, monovalente, mono- o bicíclico que contiene 2, 3, 4, 5, ó 6 átomos de carbono, y uno o más grupos que contienen heteroátomos que se seleccionan entre C(=O), O, S, S(=O), $S(=O)_2$, NR^a, en los cuales R^a representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo- o halo-C_1-C_6-alquilo-; donde es posible que dicho grupo heterocicloalquilo esté unido al resto de la molécula a través de cualquiera de los átomos de carbono o, si está presente, del átomo de nitrógeno.

En particular, dicho heterocicloalquilo de 3 a 7 miembros puede contener 2, 3, 4, ó 5 átomos de carbono, y uno o más de los grupos que contienen heteroátomos mencionados anteriormente (un "heterocicloalquilo de 3 a 6 miembros"), más en particular dicho heterocicloalquilo puede contener 4 ó 5 átomos de carbono, y uno o más de los grupos que contienen heteroátomos mencionados anteriormente (un "heterocicloalquilo de 5 a 6 miembros").

En particular, sin limitarse a esto, dicho heterocicloalquilo puede ser un anillo de 4 miembros, como por ejemplo un azetidinilo, oxetanilo, o un anillo 5 de miembros, como por ejemplo tetrahidrofuranilo, dioxolinilo, pirrolidinilo, imidazolidinilo, pirazolidinilo, pirrolinilo, o un anillo 6 de miembros, como por ejemplo tetrahidropiranilo, piperidinilo, morfolinilo, ditianilo, tiomorfolinilo, piperazinilo, o tritianilo, o un anillo 7 de miembros, como por ejemplo un anillo diazepanilo, por ejemplo. Opcionalmente, dicho heterocicloalquilo puede estar fusionado con un grupo benzo.

Dicho heterociclilo puede ser bicíclico, por ejemplo, pero de manera no taxativa, un anillo bicíclico de 5,5 miembros, por ejemplo un anillo hexahidrociclopenta[c]pirrol-2(1H)-il), o un anillo bicíclico de 5,6 de miembros, por ejemplo un anillo hexahidropirrolo[1,2-a]pirazin-2(1H)-ilo, o por ejemplo.

Como se mencionó anteriormente, dicho anillo que contiene átomo(s) de nitrógeno puede estar parcialmente insaturado, *es decir* puede contener una o más dobles uniones, por ejemplo, pero de manera no taxativa, un anillo 2,5-dihidro-1H-pirrolilo, 4H-[1,3,4]tiadiazinilo, 4,5-dihidrooxazolilo, o 4H-[1,4]tiazinilo, por ejemplo, o, puede estar fusionado con un grupo benzo, por ejemplo, pero de manera no taxativa, un anillo dihidroisoquinolinilo, por ejemplo.

Se debe entender que el término “heterocicloalquenilo de 4 a 8 miembros”, significa un anillo hidrocarburo insaturado, monovalente, mono o bicíclico que contiene 4, 5, 6, 7 u 8

átomos de carbono, y uno o más grupos que contienen heteroátomos que se seleccionan entre C(=O), O, S, S(=O), $S(=O)_2$, NR^a, en los cuales R^a representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo- o halo-C_1-C_6-alquilo-; donde es posible que dicho grupo heterocicloalquenilo esté unido al resto de la molécula a través de cualquiera de los átomos de carbono o, si está presente, del átomo de nitrógeno. Los ejemplos de dichos heterocicloalquenilos pueden contener una o más uniones dobles, *por ejemplo* los grupos 4H-piranilo, 2H-piranilo, 3H-diazirinilo, 2,5-dihidro-1H-pirrolilo, [1,3]dioxolilo, 4H-[1,3,4]tiadiazinilo, 2,5-dihidrofuranilo, 2,3-dihidrofuranilo, 2,5-dihidrotiofenilo, 2,3-dihidrotiofenilo, 4,5-dihidrooxazolilo, o 4H-[1,4]tiazinilo, o, el mismo puede estar fusionado con un grupo benzo.

El término “arilo” debe entenderse preferentemente como un anillo hidrocarburo mono, bi o tricíclico monovalente aromático o parcialmente aromático que tiene 6, 7, 8, 9, 10, 11, 12, 13 o 14 átomos de carbono (un grupo “C_6-C_{14}-arilo”), particularmente un anillo que tiene 6 átomos de carbono (un grupo “C_6-arilo”), por ejemplo un grupo fenilo, o un grupo bifenilo, o un anillo que tiene 9 átomos de carbono (un grupo “C_9-arilo”), por ejemplo un grupo indanilo o indenilo, o un anillo que tiene 10 átomos de carbono (un grupo “C_{10}-arilo”), por ejemplo un grupo tetralinilo, dihidronaftilo, o naftilo, o un anillo que tiene 13 átomos de carbono, (un grupo “C_{13}-arilo”), por

ejemplo un grupo fluorenilo, o un anillo que tiene 14 átomos de carbono, (un grupo "C_{14}-arilo"), por ejemplo un grupo antranilo.

El término "heteroarilo" se entiende preferentemente como un sistema de anillos monovalente, mono, bi, o tricíclico aromático que tiene 5, 6, 7, 8, 9, 10, 11, 12, 13 o 14 átomos del anillo (un grupo "heteroarilo de 5 a 14 miembros"), particularmente 5 o 6 o 9 o 10 átomos, y el cual contiene al menos un heteroátomo el cual puede ser idéntico o diferente, donde dicho heteroátomo es tal como oxígeno, nitrógeno o azufre, y además en cada caso puede ser benzocondensado. Particularmente, heteroarilo se selecciona entre tienilo, furanilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, pirazolilo, isoxazolilo, isotiazolilo, oxadiazolilo, triazolilo, tiadiazolilo, tia-4H-pirazolilo *etc*., y benzo derivados de los mismos, tales como, por ejemplo, benzofuranilo, benzotienilo, benzoxazolilo, bencisoxazolilo, bencimidazolilo, benzotriazolilo, indazolilo, indolilo, isoindolilo, *etc*.; o piridilo, piridazinilo, pirimidinilo, pirazinilo, triazinilo, *etc*., y benzo derivados de los mismos, tales como, por ejemplo, quinolinilo, quinazolinilo, isoquinolinilo, *etc*.; o azocinilo, indolizinilo, purinilo, *etc*., y benzo derivados de los mismos; o cinnolinilo, ftalazinilo, quinazolinilo, quinoxalinilo, naftpiridinilo, pteridinilo, carbazolilo, acridinilo, fenazinilo, fenotiazinilo, fenoxazinilo, xantenilo, o oxepinilo, *etc*.

En general, y a no ser que se mencione otra cosa, los radicales heteroarílicos o heteroarilénicos incluyen a todas las posibles

formas isoméricas de los mismos, por ejemplo los isómeros posicionales de los mismos. Por lo tanto, para algunos ejemplos ilustrativos no taxativos, el término piridinilo o piridinileno incluye piridin-2-ilo, piridin-2-ileno, piridin-3-ilo, piridin-3-ileno, piridin-4-ilo y piridin-4-ileno; o el término tienilo o tienileno incluye tien-2-ilo, tien-2-ileno, tien-3-ilo y tien-3-ileno.

El término "C_1-C_6", según se lo utiliza a lo largo de este texto, por ejemplo en el contexto de la definición de "C_1-C_6-alquilo", "C_1-C_6-haloalquilo", "C_1-C_6-alcoxi", o "C_1-C_6-haloalcoxi" debe entenderse como un grupo alquilo que tiene un número finito de átomos de carbono de 1 a 6, por ejemplo 1, 2, 3, 4, 5, o 6 átomos de carbono. Debe entenderse además que dicho término "C_1-C_6" debe interpretarse como cualquier subrango comprendido por el mismo, por ejemplo C_1-C_6, C_2-C_5, C_3-C_4, C_1-C_2, C_1-C_3, C_1-C_4, C_1-C_5, C_1-C_6; en particular C_1-C_2, C_1-C_3, C_1-C_4, C_1-C_5, C_1-C_6; más particularmente C_1-C_4; en el caso de "C_1-C_6-haloalquilo" o "C_1-C_6-haloalcoxi" aún más particularmente C_1-C_2.

De manera similar, según se lo utiliza aquí, el término "C_2-C_6", según se lo utiliza a lo largo de este texto, por ejemplo en el contexto de las definiciones de "C_2-C_6-alquenilo" y "C_2-C_6-alquinilo", debe entenderse como un grupo alquenilo o un grupo alquinilo que tiene un número finito de átomos de carbono de 2 a 6, por ejemplo 2, 3, 4, 5, o 6 átomos de carbono. Debe entenderse además que dicho término "C_2-C_6" debe interpretarse como cualquier subrango comprendido por el mismo, por ejemplo C_2-C_6, C_3-C_5, C_3-C_4, C_2-C_3, C_2-C_4, C_2-C_5; particularmente C_2-C_3.

Además, según se lo utiliza aquí, el término "C_3-C_6", según se lo utiliza a lo largo de este texto, por ejemplo en el contexto de la definición de "C_3-C_6-cicloalquilo", debe entenderse como un grupo cicloalquilo que tiene un número finito de átomos de carbono de 3 a 6, por ejemplo 3, 4, 5 o 6 átomos de carbono. Debe entenderse además que dicho término "C_3-C_6" debe interpretarse como cualquier subrango comprendido por el mismo, por ejemplo C_3-C_6, C_4-C_5, C_3-C_5, C_3-C_4, C_4-C_6, C_5-C_6; particularmente C_3-C_6.

El término "sustituido" significa que uno o más hidrógenos sobre el átomo que se designa son reemplazados por un grupo que se selecciona entre los indicados, con la condición de que no se debe superar la valencia normal del átomo que se designa en las circunstancias existentes, y que la sustitución debe dar como resultado un compuesto estable. Las combinaciones de sustituyentes y/o variables están permitidas solo si dichas combinaciones dan como resultado compuestos estables.

El término "opcionalmente sustituido" significa una sustitución opcional con los grupos, radicales o unidades que se especifican.

Un sustituyente que es un sistema de anillo significa un sustituyente unido a un sistema de anillo aromático o no aromático que, por ejemplo, reemplaza a un hidrógeno disponible sobre el sistema de anillo.

Como se lo usa en la presente, el término "grupo saliente" hace referencia a un átomo o un grupo de átomos que es desplazado en una reacción química, en forma de una especie

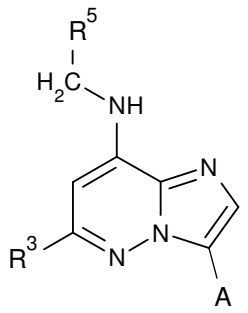
estable que arrastra los electrones del enlace. Preferiblemente, el grupo saliente se selecciona del grupo que comprende un grupo halógeno, particularmente cloro, bromo o iodo, metanosulfoniloxilo, p-toluenosulfoniloxilo, trifluorometanosulfoniloxilo, nonafluorobutanosulfoniloxilo, (4-bromo-benceno)sulfoniloxilo, (4-nitro-benceno)sulfoniloxilo, (2-nitro-benceno)-sulfoniloxilo, (4-isopropil-benceno)sulfoniloxilo, (2,4,6-tri-isopropil-benceno)-sulfoniloxilo, (2,4,6-trimetil-benceno)sulfoniloxilo, (4-tertbutil-benceno)sulfoniloxilo, benzenosulfoniloxilo y (4-metoxi-benceno)sulfoniloxilo.

Como se lo usa en la presente, el término “una o más veces”, por ejemplo, en la definición de los sustituyentes de los compuestos de las fórmulas generales de la presente invención, ha de interpretarse como “una, dos, tres, cuatro o cinco veces”, particularmente una, dos, tres o cuatro veces, más particularmente una, dos o tres veces, más particularmente una o dos veces”.

Cuando en la presente se usa la forma en plural de la palabra, los compuestos, sales, formas polimórficas, hidratos, solvatos y semejantes, se considera que también comprende un solo compuesto, sal, forma polimórfica, isómero, hidrato, solvato o semejantes.

“Compuesto estable” o “estructura estable” significa un compuesto que es suficientemente robusto como para sobrevivir a la aislación hasta un grado de pureza útil desde una mezcla de reacción, y a la formulación para dar un agente terapéutico eficaz.

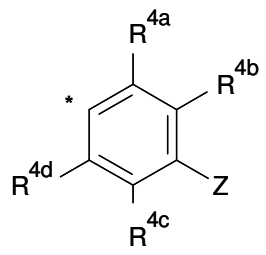
De acuerdo con un primer aspecto, la presente invención hace referencia a compuestos de fórmula general I:



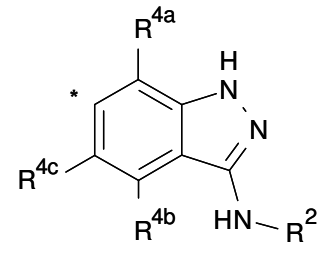
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donde:

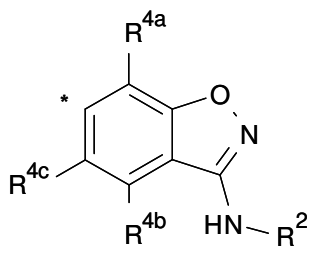
A representa un grupo



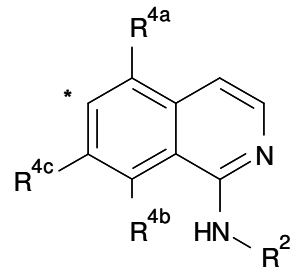
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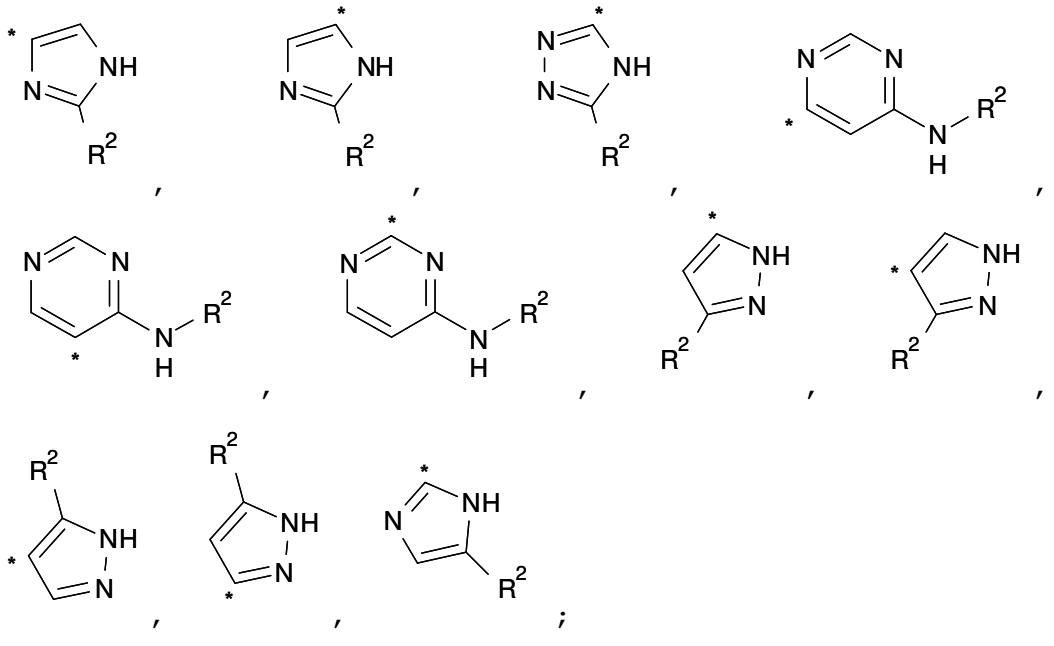
o



–;

donde * indica el punto de unión de dichos grupos con el resto de la molécula;

Z representa un grupo $-C(=O)N(H)R^2$ o $-C(=S)N(H)R^2$, o un grupo seleccionado entre



donde * indica el punto de unión de dichos grupos con el resto de la molécula;

R^2 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, C_2-C_6-alquinilo- o C_3-C_6-cicloalquilo-;

donde dicho grupo C_3-C_6-cicloalquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos seleccionados entre: halógeno, -OH, -CN, C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alquilo-;

R^3 representa un átomo de hidrógeno o un átomo de halógeno, o un grupo -CN, C_1-C_6-alquilo-, C_1-C_6-alcoxi-, -$(CH_2)_m$-C_2-C_6-alquenilo, -$(CH_2)_m$-C_4-C_8-cicloalquenilo, -$(CH_2)_m$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-C_1-C_6-

alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo-, -C_1-C_6-alquil-arilo, -C_1-C_6-alquil-heteroarilo, heteroarilo-, C_1-C_6-alquil-X-, -X-$(CH_2)_m$-C_2-C_6-alquenilo, -X-$(CH_2)_m$-C_4-C_8-cicloalquenilo, -X-$(CH_2)_m$-C_2-C_6-alquinilo, -X-$(CH_2)_m$-C_3-C_6-cicloalquilo, -X-$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -X-$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-X-, heteroaril-X-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)_2R^6$, $-S(=O)(=NR^{6a})R^{6b}$, $-S(=O)_2N(R^{6b})R^{6c}$, -S-$(CH_2)_n$-$N(R^{6a})R^{6b}$ o -S-$(CH_2)_n$-(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho grupo C_1-C_6-alquilo-, C_1-C_6-alcoxi-, -$(CH_2)_m$-C_2-C_6-alquenilo, -$(CH_2)_m$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo-, C_1-C_6-alquil-X-, -X-$(CH_2)_m$-C_2-C_6-alquenilo, -X-$(CH_2)_m$-C_4-C_8-cicloalquenilo, -X-$(CH_2)_m$-C_2-C_6-alquinilo, -X-$(CH_2)_m$-C_3-C_6-cicloalquilo, -X-$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -X-$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-X-, heteroaril-X-, -C_1-C_6-alquil-arilo, -C_1-C_6-alquil-heteroarilo o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, 4 o 5 grupos

R^7;

R^{4a}, R^{4b}, R^{4c}, R^{4d}

representan, en forma independiente entre sí, un átomo de hidrógeno o halógeno, o un grupo -CN, C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^{6a}$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$;

R^5 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, $-(CH_2)_n$-C_2-C_6-alquenilo, $-(CH_2)_n$-C_2-C_6-alquinilo, $-(CH_2)_m$-C_3-C_6-cicloalquilo, $-(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-,arilo- o heteroarilo-;

donde dicho grupo C_1-C_6-alquilo-, $-(CH_2)_n$-C_2-C_6-alquenilo, $-(CH_2)_n$-C_2-C_6-alquinilo, $-(CH_2)_m$-C_3-C_6-cicloalquilo, $-(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-

alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_4-C_8-cicloalquenilo-, arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos R^8;

R^6, R^{6a}, R^{6b}, R^{6c}

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, C_2-C_6-alquenilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, aril-C_1-C_6-alquilo- o heteroaril-C_1-C_6-alquilo-;

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2R^6$, -N(R^{6c})S(=O)$_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -S(=O)$_2R^6$, -S(=O)$_2$N(H)R^6, -S(=O)$_2$N(R^{6a})R^{6b} o -S(=O)(=NR^{6c})R^6;

donde dicho grupo C_1-C_6-alcoxi-, arilo- o heteroarilo- está

opcionalmente sustituido, en forma idéntica o diferente, con 1, 2 o 3 grupos C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alcoxi-, -C(=O)O-R^6 o -OH;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo- o heteroarilo-, donde dichos 2 grupos R^7 juntos forman un puente:

O$(CH_2)_2$O, *O(CH_2)O*, *NH(C(=O))NH*, donde * representa el punto de unión a dicho anillo arilo- o heteroarilo-;

R^8 representa un átomo de hidrógeno o halógeno, o un grupo -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})$N-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2R^6$, -N(R^{6c})S(=O)$_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -S(=O)$_2R^6$, -S(=O)$_2$N(H)R^6, -S(=O)$_2$N(R^{6a})R^{6b}, -S(=O)(=NR^{6c})R^6 o -S(=O)$_2$-(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho heterocicloalquilo- o heteroarilo- de entre 3 y 7 miembros está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos C_1-C_6 alquilo-;

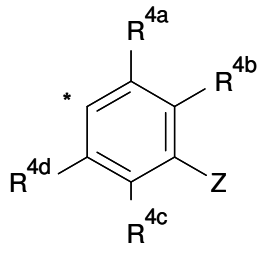
m es el entero 0, 1, 2, 3, 4, 5 o 6;

n es el entero 0, 1, 2, 3, 4 o 5;

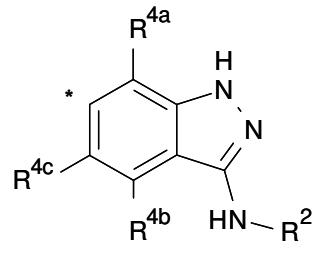
X representa $S(=O)_p$, O, NR^6, $CR^{6a}R^{6b}$ o $C=CR^{6a}R^{6b}$; y

p es el entero 0, 1 o 2.

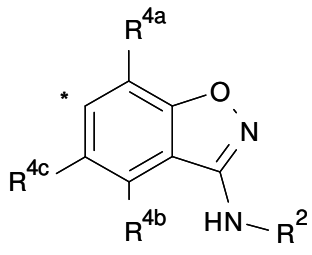
Como se ha definido, A representa un grupo



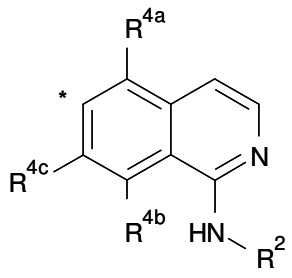
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o



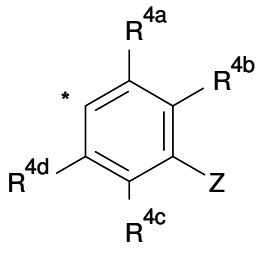
o



o –;

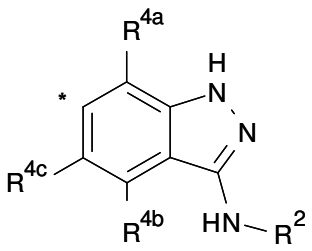
donde * indica el punto de unión de dichos grupos con el resto de la molécula.

En una forma de realización preferida A representa un grupo



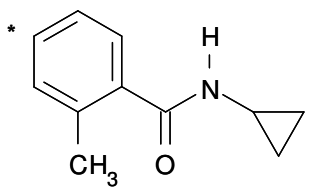
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En otra forma de realización preferida A representa un grupo

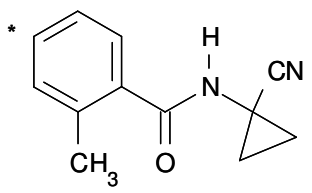


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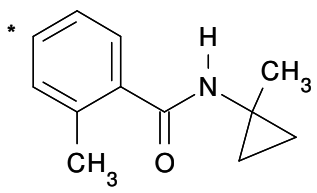
En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, como se ha definido, donde A se selecciona entre el grupo que consiste en:



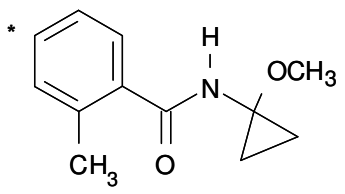
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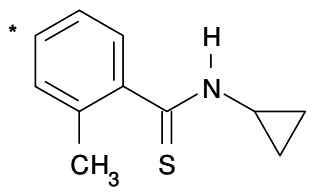
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Como se ha definido, R^2 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, C_2-C_6-alquinilo- o C_3-C_6-cicloalquilo-;

donde dicho grupo C_3-C_6-cicloalquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos seleccionados entre: halógeno, -OH, -CN, C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alquilo-.

En una forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, donde:

R^2 representa un grupo C_3-C_6-cicloalquilo-;

donde dicho grupo C_3-C_6-cicloalquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos seleccionados entre: halógeno, -OH, -CN, C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alquilo-.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, donde:

R^2 representa un grupo C_3-C_6-cicloalquilo-;

donde dicho grupo C_3-C_6-cicloalquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, o 3 grupos seleccionados entre:

halógeno, -OH, -CN, -C_1-C_6-alquilo, -C_1-C_6-alcoxi.

Preferentemente, C_3-C_6-cicloalquilo- es un grupo ciclopropilo-.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, donde:

R^2 representa un grupo C_3-C_6-cicloalquilo-;

donde dicho grupo C_3-C_6-cicloalquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1 o 2 grupos seleccionados entre:

-CN, -C_1-C_3-alquilo, -C_1-C_3-alcoxi.

Preferentemente, C_3-C_6-cicloalquilo- es un grupo ciclopropilo-.

En otra forma de realización preferida, la invención se

relaciona con los compuestos de fórmula I, donde:

R^2 representa un grupo ciclopropilo-;

donde dicho ciclopropilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos seleccionados entre:

halógeno, -OH, -CN, $-C_1-C_6$-alquilo, $-C_1-C_6$-alcoxi.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, donde:

R^2 representa un grupo ciclopropilo-;

donde dicho ciclopropilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1 o 2 grupos seleccionados entre:

halógeno, -OH, -CN, $-C_1-C_6$-alquilo, $-C_1-C_6$-alcoxi.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, donde:

R^2 representa un grupo ciclopropilo-;

donde dicho ciclopropilo- está sustituido, en forma idéntica o diferente, con 1 o 2 grupos seleccionados entre:

halógeno, -CN, $-C_1-C_3$-alquilo, $-C_1-C_3$-alcoxi.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, donde:

R^2 representa un grupo halo-C_1-C_6-alquilo-.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, donde:

R^2 representa un grupo C_1-C_6-alquilo-;

donde dicho grupo C_1-C_6-alquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos seleccionados entre:

halógeno, -OH, -CN, C_1-C_6-alcoxi-.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, donde:

R^2 representa un grupo C_1-C_4-alquilo-;

donde dicho grupo C_1-C_4-alquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2 o 3 grupos seleccionados entre:

halógeno, -OH, -CN, $-C_1$-C_4-alcoxi.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, donde:

R^2 representa un grupo metilo- o etilo-;

donde dicho metilo- o etilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2 o 3 grupos seleccionados entre:

halógeno, -OH, -CN.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, donde:

R^2 representa CH3 o C2H5.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, donde:

R^2 representa un grupo C_1-C_3-alquilo-;

donde dicho grupo C_1-C_3-alquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2 o 3 grupos seleccionados entre:

halógeno, -OH, -CN, -C_1-C_3-alcoxi.

La invención se relaciona con los compuestos de fórmula I, donde:

R^3 representa un átomo de hidrógeno o un átomo de halógeno, o un grupo -CN, C_1-C_6-alquilo-, C_1-C_6-alcoxi-, -$(CH_2)_m$-C_2-C_6-alquenilo, -$(CH_2)_m$-C_4-C_8-cicloalquenilo, -$(CH_2)_m$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo-, -C_1-C_6-alquil-arilo, -C_1-C_6-alquil-heteroarilo, heteroarilo-, C_1-C_6-alquil-X-, -X-$(CH_2)_m$-C_2-C_6-alquenilo, -X-$(CH_2)_m$-C_4-C_8-cicloalquenilo, -X-$(CH_2)_m$-C_2-C_6-alquinilo, -X-$(CH_2)_m$-C_3-C_6-cicloalquilo, -X-$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -X-$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-X-, heteroaril-X-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)_2R^6$, $-S(=O)(=NR^{6a})R^{6b}$, $-S(=O)_2N(R^{6b})R^{6c}$, -$(CH_2)_n$-$N(R^{6a})R^{6b}$ o -S-$(CH_2)_n$-(heterocicloalquilo de entre 3 y

7 miembros);

donde dicho grupo C_1-C_6-alquilo-, C_1-C_6-alcoxi-, -$(CH_2)_m$-C_2-C_6-alquenilo, -$(CH_2)_m$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo-, C_1-C_6-alquil-X-, -X-$(CH_2)_m$-C_2-C_6-alquenilo, -X-$(CH_2)_m$-C_4-C_8-cicloalquenilo, -X-$(CH_2)_m$-C_2-C_6-alquinilo, -X-$(CH_2)_m$-C_3-C_6-cicloalquilo, -X-$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -X-$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-X-, heteroaril-X-, -C_1-C_6-alquil-arilo, -C_1-C_6-alquil-heteroarilo o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, 4 o 5 grupos R^7.

En una forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, como se ha definido, donde:

R^3 representa un grupo

C_1-C_6-alquil-X-, -X-$(CH_2)_m$-C_2-C_6-alquenilo, -X-$(CH_2)_m$-C_4-C_8-cicloalquenilo, -X-$(CH_2)_m$-C_2-C_6-alquinilo, -X-$(CH_2)_m$-C_3-C_6-cicloalquilo, -X-$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -X-$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), arilo-, heteroarilo-, aril-X- o heteroaril-X-;

donde dicho grupo C_1-C_6-alquil-X-, -X-$(CH_2)_m$-C_2-C_6-alquenilo, -X-$(CH_2)_m$-C_4-C_8-cicloalquenilo, -X-$(CH_2)_m$-C_2-C_6-alquinilo, -X-$(CH_2)_m$-C_3-C_6-cicloalquilo, -X-$(CH_2)_m$-(heterocicloalquilo de

entre 3 y 7 miembros), –X–$(CH_2)_m$–(heterocicloalquenilo de entre 4 y 8 miembros), arilo–, heteroarilo–, aril–X– o heteroaril–X– está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos R^7.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, como se ha definido, donde:

R^3 representa un átomo de hidrógeno o un átomo de halógeno, o un grupo C_1–C_6–alcoxi–, –$(CH_2)_m$–C_2–C_6–alquenilo, arilo–, aril–X–, heteroaril–X–, heteroarilo–, –$(CH_2)_m$–C_4–C_8–cicloalquenilo, –$(CH_2)_m$–C_3–C_6–cicloalquilo, –$(CH_2)_m$–(heterocicloalquenilo de entre 4 y 8 miembros), arilo–, –C(=O)N(H)R^{6a}, –OR^6, –SR^6, –S(=O)R^6, –$S(=O)_2R^6$, –S–$(CH_2)_n$–N(R^{6a})R^{6b} o –S–$(CH_2)_n$–(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho grupo C_1–C_6–alcoxi–, arilo–, aril–X–, heteroaril–X– o heteroarilo– está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, 4 o 5 grupos R^7.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, como se ha definido, donde:

R^3 representa un átomo de hidrógeno o un átomo de halógeno, o un grupo –$(CH_2)_m$–C_2–C_6–alquenilo, –$(CH_2)_m$–C_4–C_8–cicloalquenilo –$(CH_2)_m$–C_3–C_6–cicloalquilo, –$(CH_2)_m$–(heterocicloalquenilo de entre 4 y 8 miembros), arilo–, heteroarilo–, aril–X–, heteroaril–X–, –C(=O)N(H)R^{6a}, –OR^6, –

SR^6, $-S(=O)R^6$, $-S(=O)_2R^6$, $-S-(CH_2)_n-N(R^{6a})R^{6b}$, o $-S-(CH_2)_n-$(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho arilo-, aril-X-, heteroaril-X- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos R^7.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, como se ha definido, donde:

R^3 representa un grupo arilo-, $-C_1-C_6$-alquil-arilo, aril-X-, heteroaril-X-, heteroarilo-, $-C_1-C_6$-alquil-heteroarilo, heteroarilo-; donde dicho arilo-, aril-X-, heteroaril-X-, heteroarilo-, $-C_1-C_6$-alquil-arilo o $-C_1-C_6$-alquil-heteroaril-está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos R^7.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, como se ha definido, donde:

R^3 representa

un grupo aril-X- sustituido o no sustituido, o

un grupo heteroaril-X- sustituido o no sustituido.

Un grupo aril-X- preferido es fenil-X-.

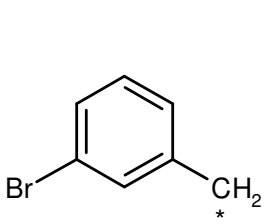
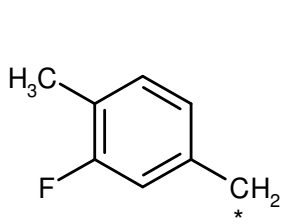
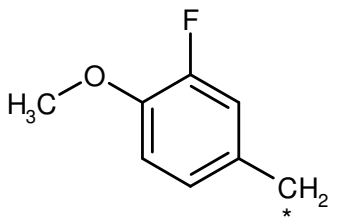
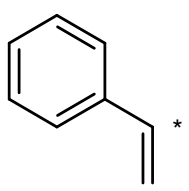
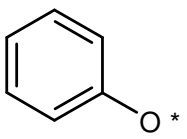
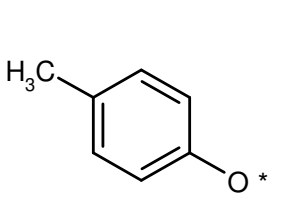
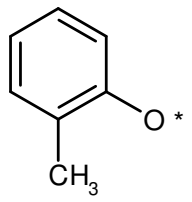
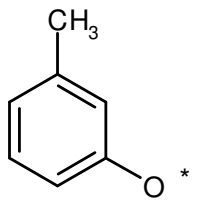
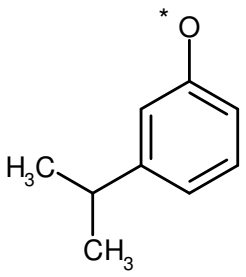
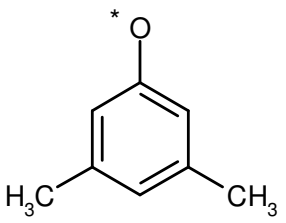
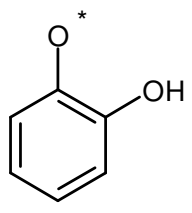
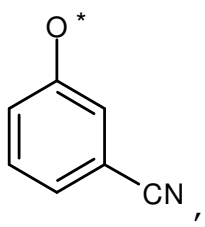
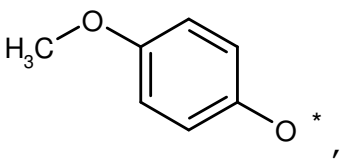
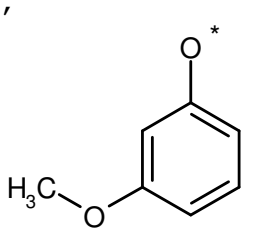
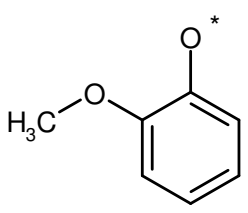
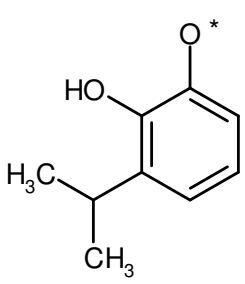
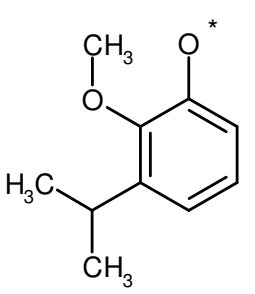
Los grupos heteroaril-X- preferidos son quinolinil-X-, piridil-X-, tienil-X-, pirazinil-X-, imidazil-X-, triazil-X- y pirazil-X-.

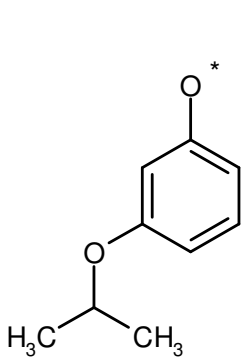
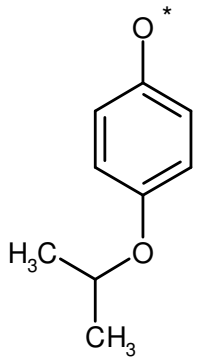
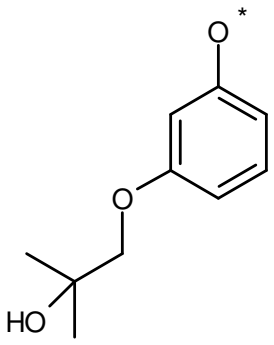
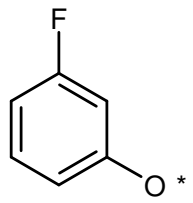
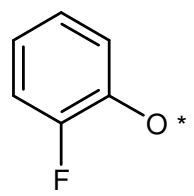
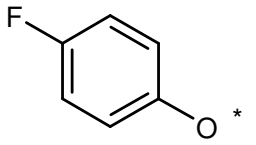
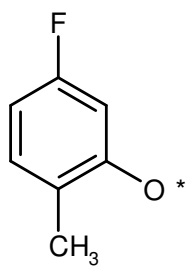
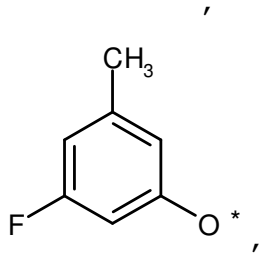
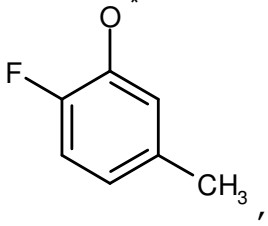
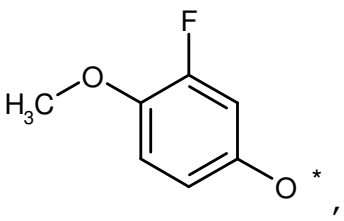
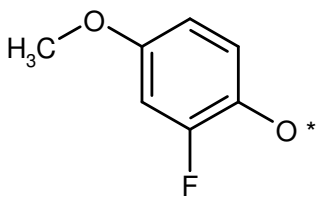
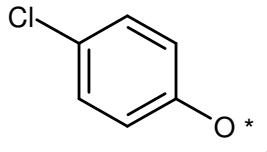
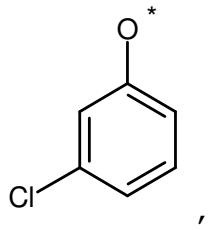
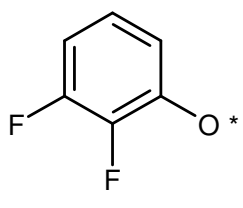
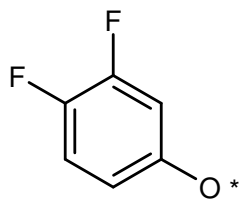
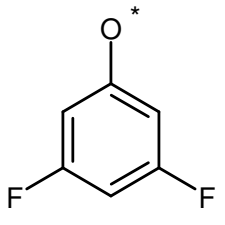
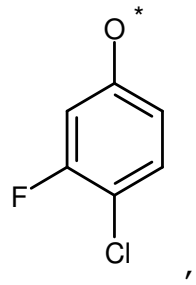
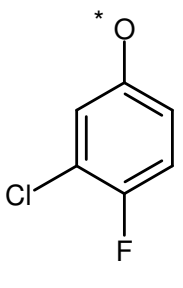
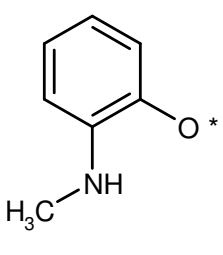
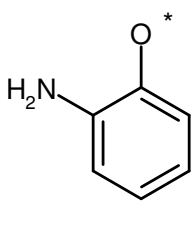
R^3 está opcionalmente sustituido, en forma idéntica o

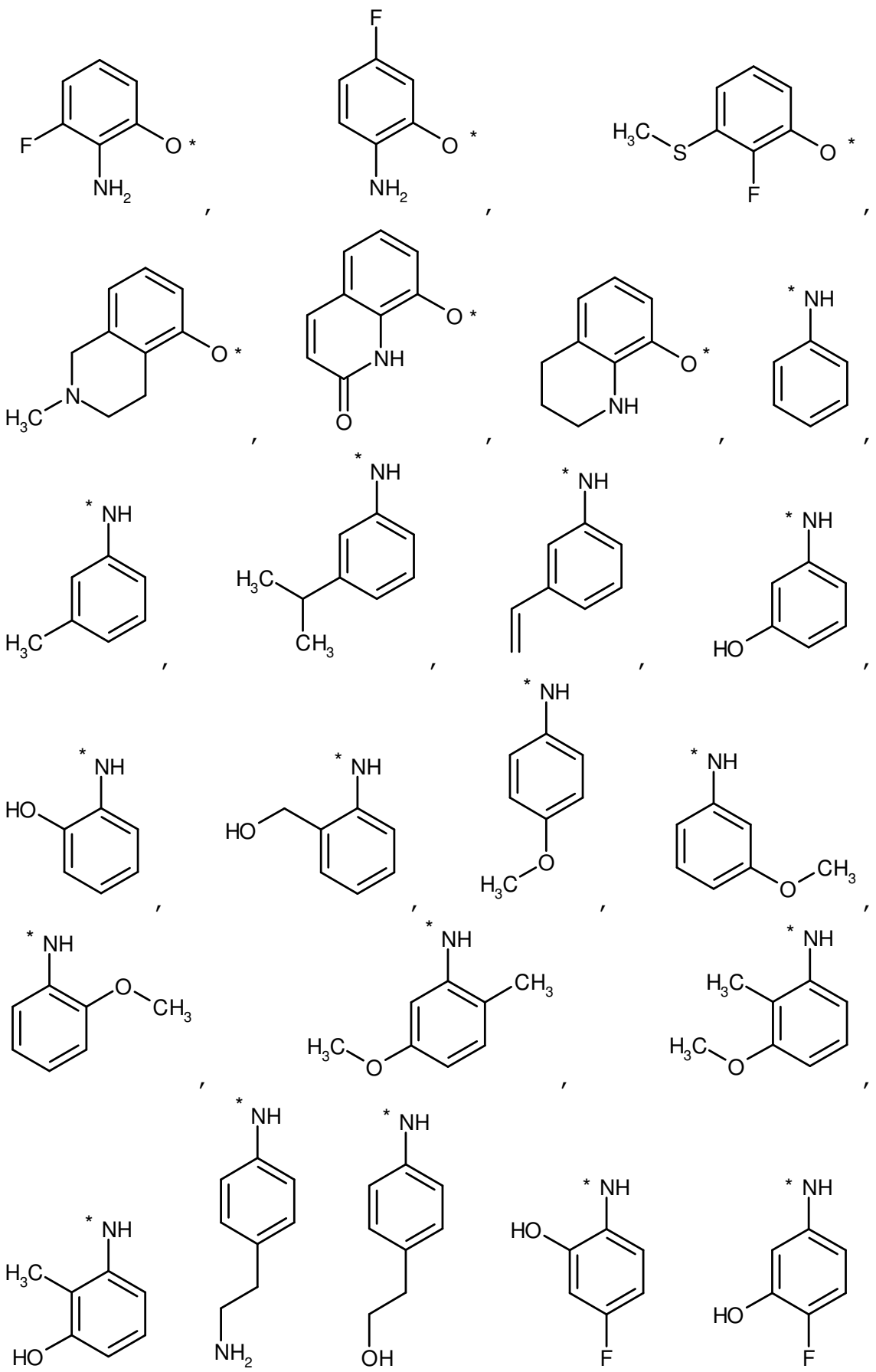
diferente, con 1, 2, 3, 4 o 5 grupos R^7.

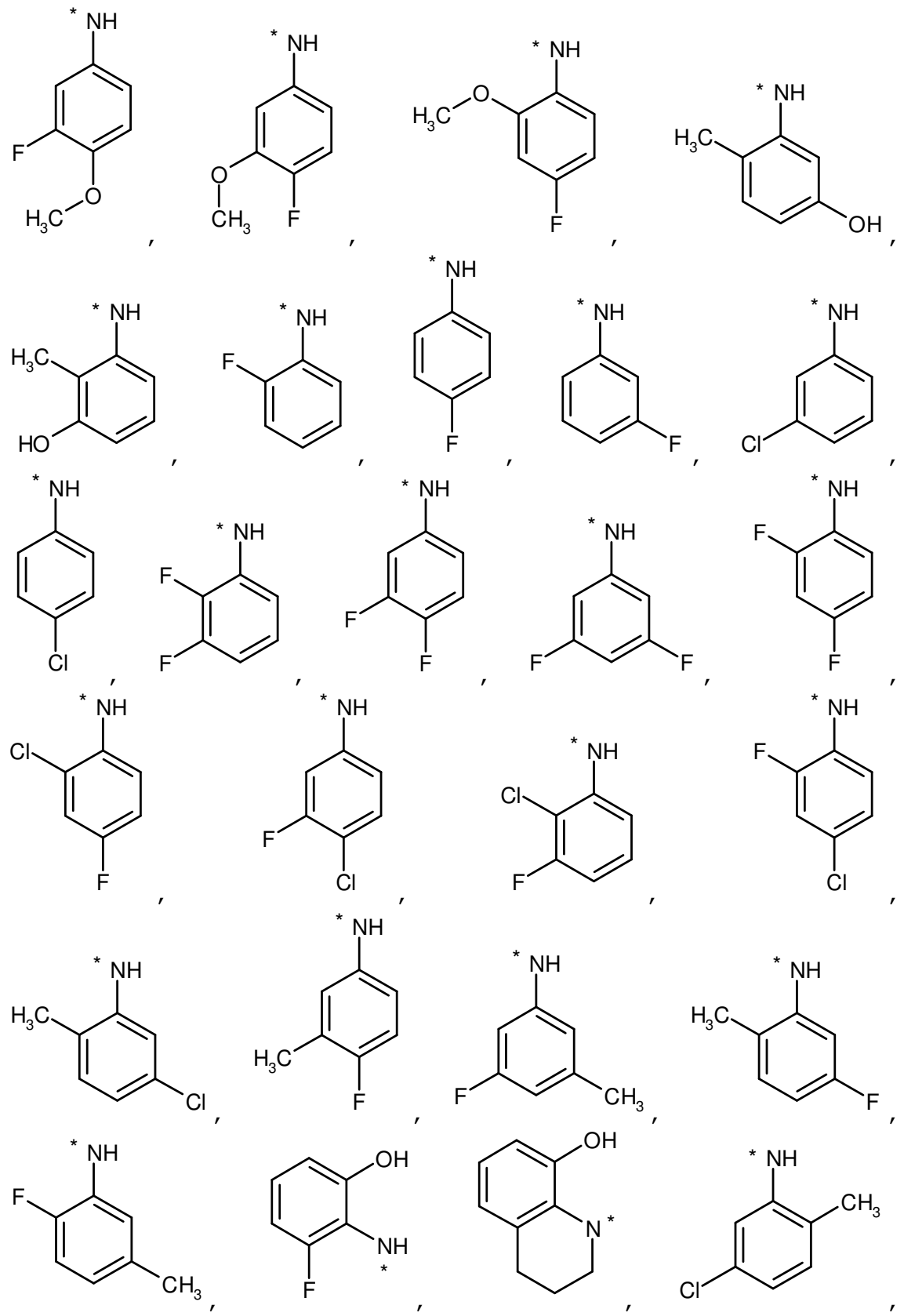
En una forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, donde R^3 está opcionalmente sustituido, en forma idéntica o diferente, con 1 o 2 grupos R^7.

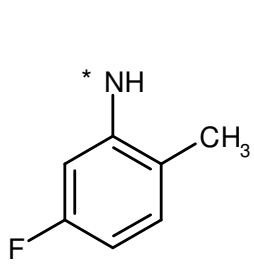
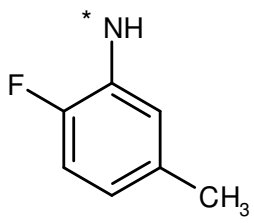
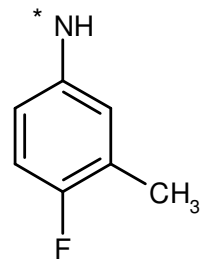
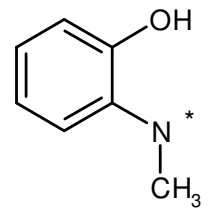
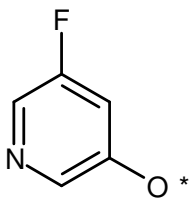
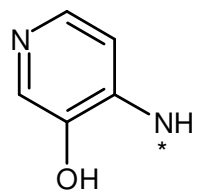
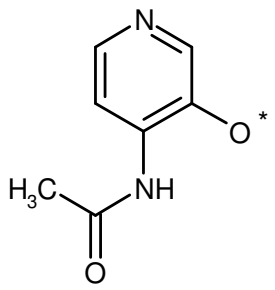
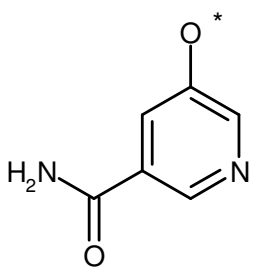
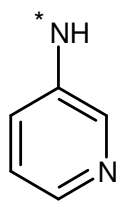
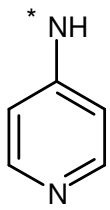
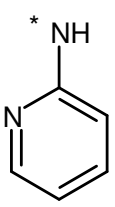
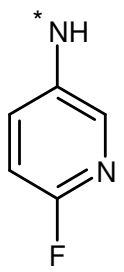
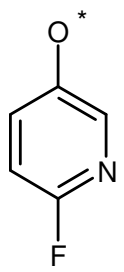
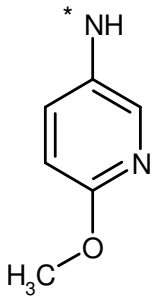
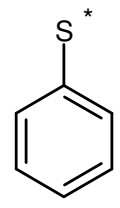
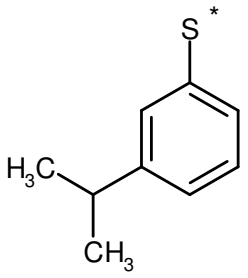
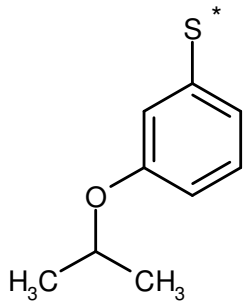
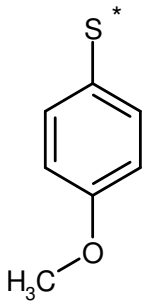
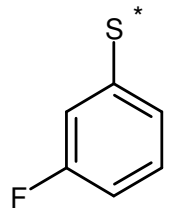
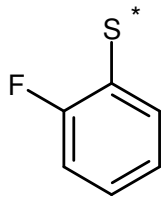
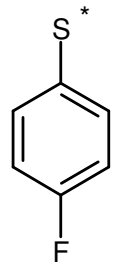
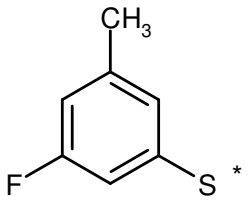
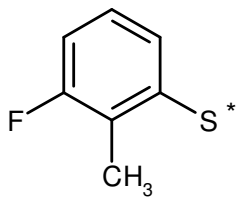
En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, donde R^3 se selecciona entre el grupo que consiste en:

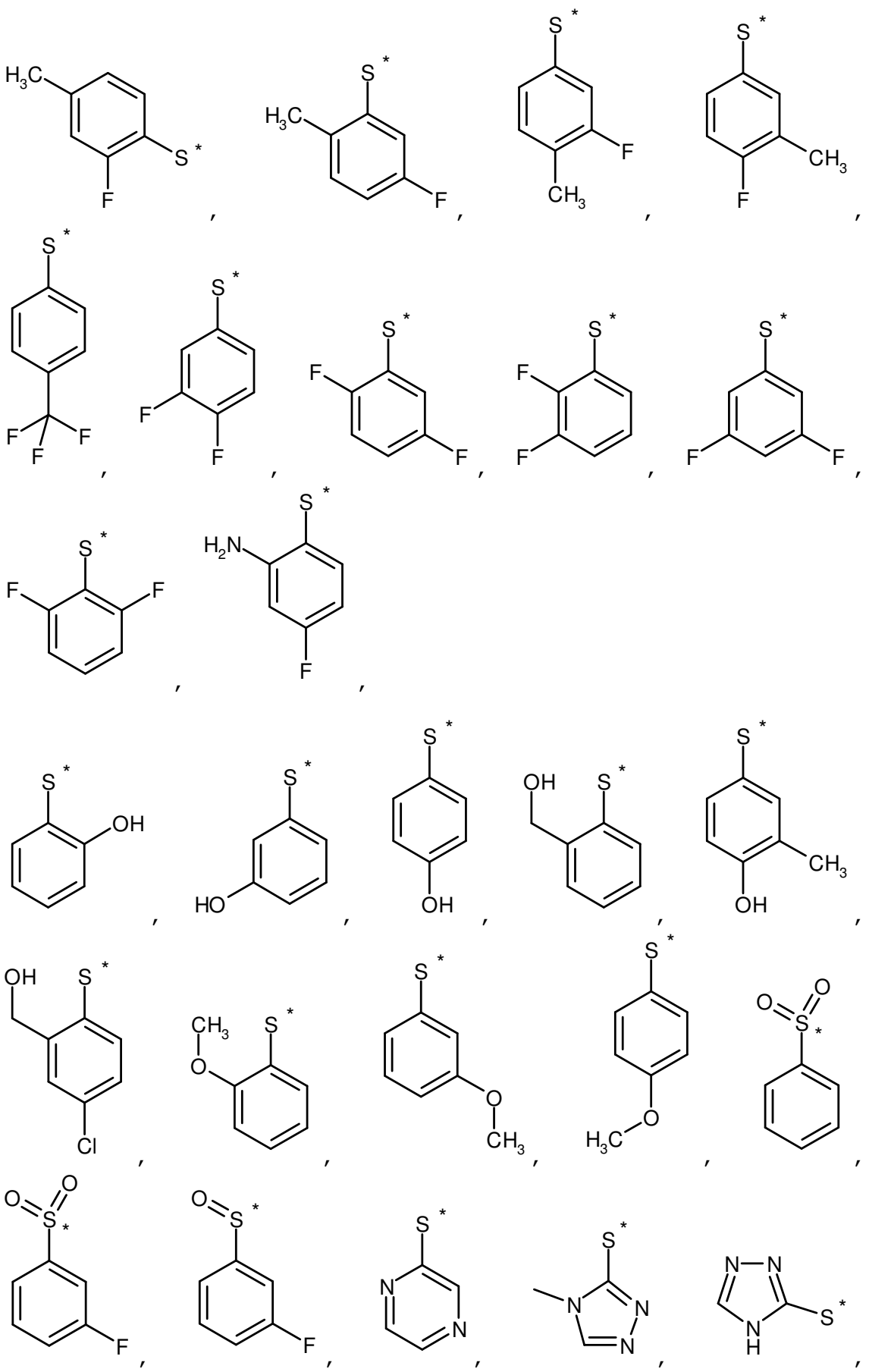


















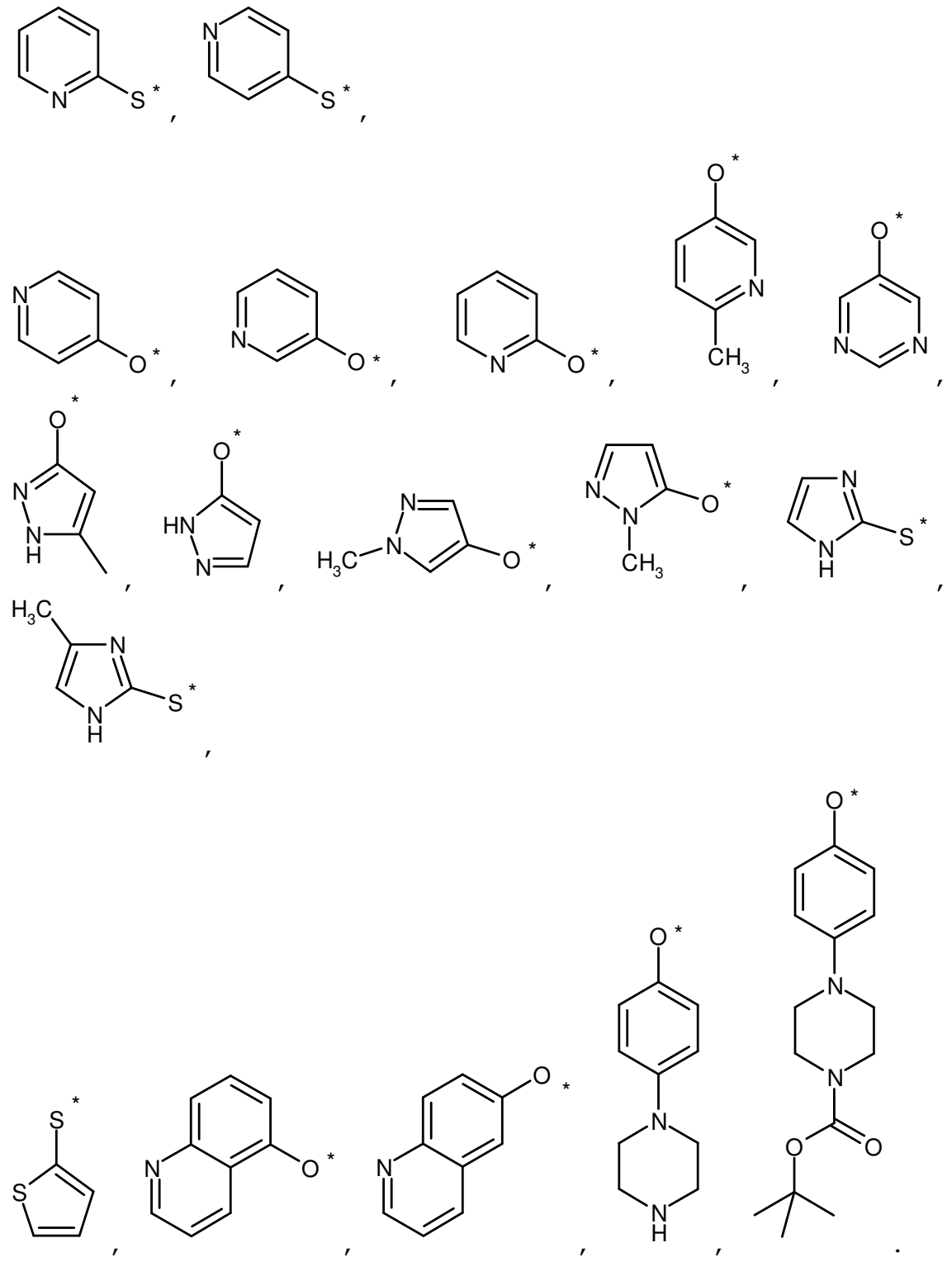





























La invención se relaciona con los compuestos de fórmula I, como se ha definido, donde:

R^{4a}, R^{4b}, R^{4c}, R^{4d} representan, en forma independiente entre sí, un átomo de

hidrógeno o halógeno, o un grupo –CN, C_1–C_6–alquilo–, C_1–C_6–alcoxi–, halo–C_1–C_6–alquilo–, $R^{6a}(R^{6b})N$–C_1–C_6–alquilo–, HO–C_1–C_6–alquilo–, C_1–C_6–alcoxi–C_1–C_6–alquilo–, halo–C_1–C_6–alcoxi–C_1–C_6–alquilo–, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^{6a}$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$.

En una forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, como se ha definido, donde:

R^{4a}, R^{4c}, R^{4d} representan un átomo de hidrógeno, y

R^{4b} representa un átomo de hidrógeno, un átomo de halógeno o un grupo C_1–C_6–alquilo–.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, como se ha definido, donde:

R^{4b}, R^{4c}, R^{4d} representan un átomo de hidrógeno, y

R^{4a} representa un átomo de halógeno, C_1–C_6–alquilo–, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^{6a}$, $-S(=O)_2N(R^{6a})R^{6b}$, o

$-S(=O)(=NR^{6c})R^{6}$.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, como se ha definido, donde:

R^{4b}, R^{4c}, R^{4d} representan un átomo de hidrógeno, y

R^{4a} representa un átomo de halógeno, C_1-C_6-alquilo- o $-OR^{6}$.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, como se ha definido, donde:

R^{4a}, R^{4b}, R^{4c}, y R^{4d} representan, en forma independiente entre sí, un átomo de hidrógeno o halógeno, o un grupo -CN, -OH, C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, NC-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-; con la condición de que al menos uno de los grupos R^{4b} y R^{4c} no es un átomo de hidrógeno.

En otra forma de realización preferida de la presente invención R^{4a} y R^{4d} representan, en forma independiente entre sí, un átomo de hidrógeno o halógeno, o un grupo -CN, C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alquilo- o un grupo halo-C_1-C_6-alcoxi-.

En otra forma de realización preferida de la presente invención R^{4a} y R^{4d} representan, en forma independiente entre sí, un átomo de hidrógeno o halógeno, o un grupo C_1-C_6-alquilo-, C_1-C_6-alcoxi-, o un grupo halo-C_1-C_6-alquilo-.

En otra forma de realización preferida de la presente invención R^{4a} y R^{4d} representan hidrógeno.

En otra forma de realización preferida de la presente invención R^{4b} y R^{4c} representan en forma independiente entre sí, un átomo de hidrógeno o halógeno, o un grupo –CN, –OH, C_1–C_6–alquilo–, C_1–C_6–alcoxi–; con la condición de que al menos uno de los grupos R^{4b} y R^{4c} no es un átomo de hidrógeno.

En otra forma de realización preferida de la presente invención R^{4b} y R^{4c} representan en forma independiente entre sí, un átomo de hidrógeno o un grupo C_1–C_6–alquilo–; con la condición de que al menos uno de los grupos R^{4b} y R^{4c} no es un átomo de hidrógeno.

En otra forma de realización preferida de la presente invención R^{4b} y R^{4c} representan en forma independiente entre sí, un átomo de hidrógeno o un grupo C_1–C_4–alquilo–; con la condición de que al menos uno de los grupos R^{4b} y R^{4c} no es un átomo de hidrógeno.

En otra forma de realización preferida de la presente invención uno de los grupos R^{4b} y R^{4c} representa un átomo de hidrógeno mientras que el otro representa un grupo seleccionado entre: halo–, –CN, –OH, C_1–C_6–alquilo–, C_1–C_6–alcoxi–, halo–C_1–C_6–alquilo–, halo–C_1–C_6–alcoxi–, $R^{6a}(R^{6b})$N–C_1–C_6–alquilo–, HO–C_1–C_6–alquilo–, NC–C_1–C_6–alquilo–, C_1–C_6–alcoxi–C_1–C_6–alquilo–, y halo–C_1–C_6–alcoxi–C_1–C_6–alquilo–.

En otra forma de realización preferida de la presente invención uno de los grupos R^{4b} y R^{4c} representa un átomo de hidrógeno mientras que el otro representa un grupo seleccionado entre: halo–, –CN, –OH, C_1–C_6–alquilo– y C_1–C_6–alcoxi–.

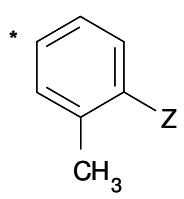
En otra forma de realización preferida de la presente invención

R^{4b} = C_1–C_4–alquilo– y R^{4c} = hidrógeno;

o R^{4b} = hidrógeno y R^{4c} = C_1–C_4–alquilo–.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, donde:

A representa un grupo

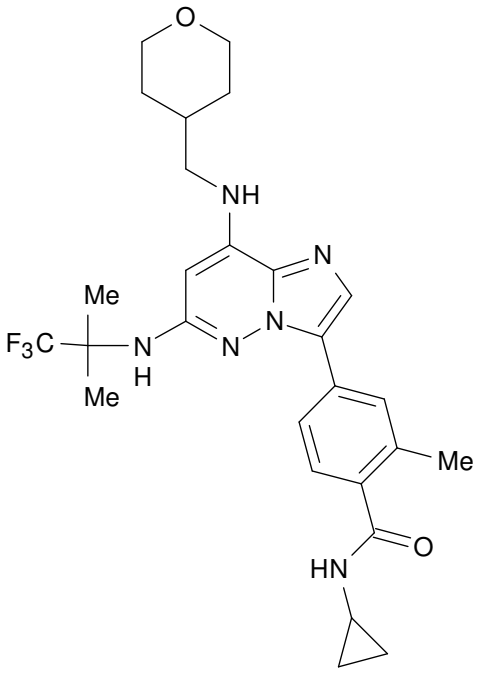


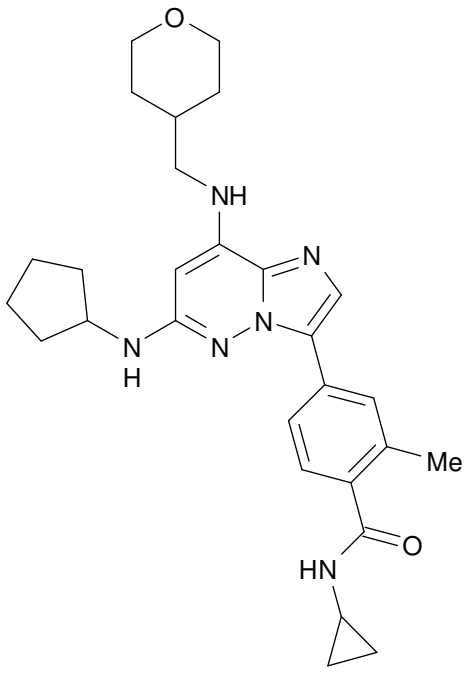
donde * indica el punto de unión de dichos grupos con el resto de la molécula; y

Z representa un grupo $-C(=O)N(H)R^2$ o un grupo $-C(=S)N(H)R^2$.

Preferentemente Z representa un grupo $-C(=O)N(H)R^2$.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, como se ha definido, donde se excluyen los siguientes compuestos (que se describen específicamente en WO 2011/013729A1):





La invención se relaciona con los compuestos de fórmula I, como se ha definido, donde:

R^5 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, -$(CH_2)_n$-C_2-C_6-alquenilo, -$(CH_2)_n$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-,arilo- o heteroarilo-;

donde dicho grupo C_1-C_6-alquilo-, -$(CH_2)_n$-C_2-C_6-alquenilo, -$(CH_2)_n$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-,

$R^{6a}(R^{6b})N-C_1-C_6$-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_4-C_8-cicloalquenilo-, arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos R^8.

En una forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, como se ha definido, donde:

R^5 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), arilo- o heteroarilo-;

donde dicho grupo C_1-C_6-alquilo-, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros),

arilo-, o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos R^8.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, como se ha definido, donde:

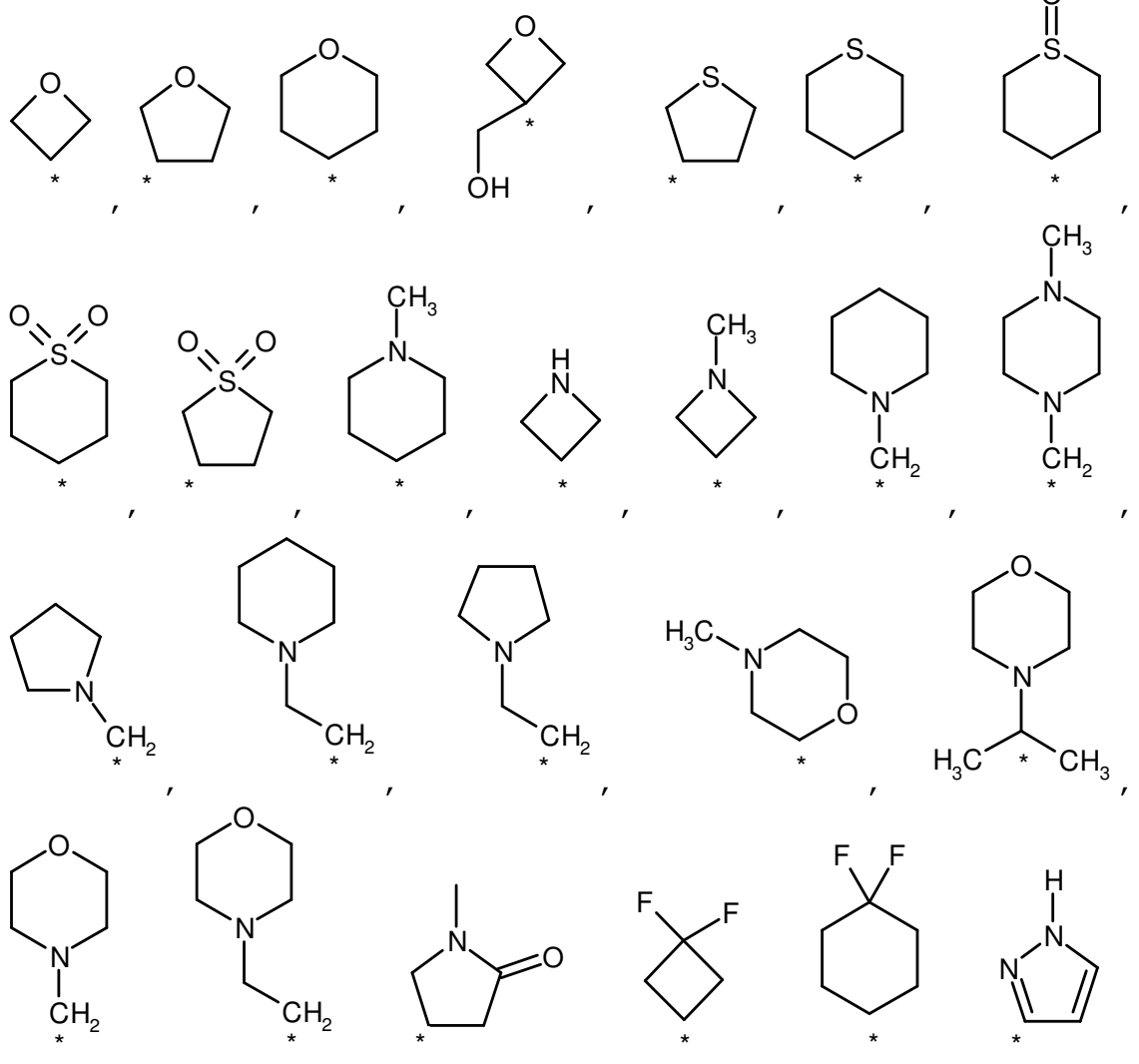
R^5 representa un grupo C_1-C_6-alquilo-, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), arilo- o heteroarilo-;

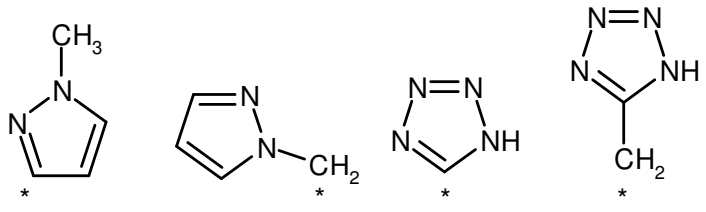
donde dicho grupo C_1-C_6-alquilo-, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros),

arilo-, heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos R^8.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, donde R^5 se selecciona entre el grupo que consiste en:

H, $(CH_3)_2CH-$, CHF2-, CF3-, $CF3-CH_2-$, $CF3-CH_2-CH_2-$, CF3-CH(OH)-, $HO-CH_2-$, $HO-C(CH_3)_2-$, $HO-C(CH_3)_2CH_2-$, $HO-CH_2-CH(OH)-$, $H_3C-O-CH_2-$, $H_2N-CH_2-CH_2-$, $H_2N-C(CH_3)_2-$, $(CH_3)_2N-CH_2-$, $(CH_3)_2N-CH_2-CH_2-$, $(CH_3)_2N-CH_2-CH_2-CH_2-$, $(CH_3)_2N-C(CH_3)_2-$, $H_3C-S(=O)_2-CH_2-$, $H_3C-S(=O)_2-CH_2-CH_2-$, $HO-S(=O)_2-CH_2-$, $HO-S(=O)_2-CH_2-CH_2-$, $NC-CH_2-$, $H_3C-C(=O)-N(H)-CH_2$, $H_3C-C(=O)-N(H)-CH_2-CH_2-$, $H_2N-C(=O)-CH_2-$, $(CH_3)_2N-C(=O)-CH_2-$, $H_3C-N(H)-C(=O)-N(CH3)-CH_2-CH_2-$,





En otra forma de realización preferida, con respecto a los compuestos de fórmula I, como se ha definido,

R^5 representa un grupo 1,1,1-trifluoroetilo.

La invención se relaciona con los compuestos de fórmula I, como se ha definido, donde:

R^6, R^{6a}, R^{6b} y R^{6c}

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, C_2-C_6-alquenilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, aril-C_1-C_6-alquilo- o heteroaril-C_1-C_6-alquilo-.

En una forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, como se ha definido, donde:

R^6, R^{6a}, R^{6b}, R^{6c},

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo- o arilo-.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, donde

R^6, R^{6a}, R^{6b}, y R^{6c} representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-.

La invención se relaciona con los compuestos de fórmula I, como se ha definido, donde:

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$ o $-S(=O)(=NR^{6c})R^6$;

donde dicho grupo C_1-C_6-alcoxi-, arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2 o 3 grupos C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alcoxi-, $-C(=O)O-R^6$ o -OH;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo- o heteroarilo-, donde dichos 2 grupos R^7 juntos forman un puente:

$*O(CH_2)_2O*$, $*O(CH_2)O*$, *NH(C(=O))NH*, donde * representa el punto de unión a dicho anillo arilo- o heteroarilo-.

En una forma de realización preferida, la invención se relaciona

con los compuestos de fórmula I, donde R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, H_2N-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, o $-S(=O)(=NR^{6c})R^6$;

donde dicho grupo C_1-C_6-alcoxi-, arilo-, heterocicloalquilo- o heteroarilo- de entre 3 y 7 miembros está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, o 3 grupos C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alcoxi-, $-C(=O)O-R^6$ o -OH.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, como se ha definido, donde:

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, arilo-, heteroarilo-, $-C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-OR^6$, $-S(=O)R^6$, o $-S(=O)_2R^6$;

donde dicho grupo C_1-C_6-alcoxi- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente,

con un grupo C_1-C_4-alquilo-, halo-C_1-C_6-alcoxi-, -C(=O)O-R^6 o -OH;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo- o heteroarilo-, donde dichos 2 grupos R^7 juntos forman un puente:

O$(CH_2)_2$O, *O(CH_2)O*, *NH(C(=O))NH*, donde * representa el punto de unión a dicho anillo arilo- o heteroarilo-.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, como se ha definido, donde:

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, arilo-, heteroarilo-, -C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -OR^6, -S(=O)R^6, o -S$(=O)_2R^6$;

donde dicho grupo C_1-C_6-alcoxi- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con un grupo C_1-C_4-alquilo-, halo-C_1-C_6-alcoxi-, -C(=O)O-R^6 o -OH.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, como se ha definido, donde:

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, arilo-, heteroarilo-, -C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -OR^6, -S(=O)R^6, o -S$(=O)_2R^6$;

donde dicho heteroarilo- está opcionalmente sustituido con un grupo C_1-C_4-alquilo;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo- o heteroarilo-, donde dichos 2 grupos R^7 juntos forman un puente:

$O(CH_2)_2O$, *$O(CH_2)O$*, *NH(C(=O))NH*, donde * representa el punto de unión a dicho anillo arilo- o heteroarilo-.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, donde R^7 representa un átomo de halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, H_2N-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros, $-C(=O)N(H)R^{6a}$, $-N(R^{6a})R^{6b}$, $-N(H)C(=O)R^6$, o $-SR^6$;

donde dicho grupo C_1-C_6-alcoxi-, o heterocicloalquilo de entre 3 y 7 miembros- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, o 3 grupos C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alcoxi-, $-C(=O)O-R^6$ o -OH.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, donde R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, H_2N-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, -

NO_2, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, o $-S(=O)(=NR^{6c})R^6$;

donde dicho grupo C_1-C_6-alcoxi-, arilo-, heterocicloalquilo o heteroarilo de entre 3 y 7 miembros está opcionalmente sustituido, en forma idéntica o diferente, con un grupo C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alcoxi-, $-C(=O)O-R^6$ o -OH.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, donde R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, H_2N-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros, $-C(=O)N(H)R^{6a}$, $-N(R^{6a})R^{6b}$, $-N(H)C(=O)R^6$ o $-SR^6$;

donde dicho grupo C_1-C_6-alcoxi- o heterocicloalquilo de entre 3 y 7 miembros- está opcionalmente sustituido, en forma idéntica o diferente, con un grupo $-C(=O)O-R^6$ o -OH.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, como se ha definido, donde 2 grupos R^7 están presentes en posición orto entre sí en el anillo arilo- o heteroarilo-de R^3;

donde dichos 2 grupos R^7 juntos forman un puente:

$*O(CH_2)_2O*$, $*O(CH_2)O*$, $*CH_2(CH_2)_2NH*$, $*CH_2CH_2N(R^{6a})CH_2*$, *NH(C(=O))NH*, *C(H)=C(H)-C(=O)-N(H)*,

donde * representa el punto de unión a dicho anillo arilo- o heteroarilo-.

Preferentemente los 2 grupos R^7 juntos forman un puente seleccionado entre:

$CH_2(CH_2)_2NH$, *$CH_2CH_2N(R^{6a})CH_2$*, *C(H)=C(H)-C(=O)-N(H)*.

La invención se relaciona con los compuestos de fórmula I, como se ha definido, donde

R^8 representa un átomo de hidrógeno o halógeno, o un grupo -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ o $-S(=O)_2$-(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho heterocicloalquilo- o heteroarilo- de entre 3 y 7 miembros está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos C_1-C_6 alquilo-.

En una forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, como se ha

definido, donde:

R^8 representa un átomo de halógeno, o un grupo –CN, –OH, C_1–C_6-alcoxi-, C_1–C_6-alquilo-, HO–C_1–C_6-alquilo, –C(=O)N(R^{6a})R^{6b}, –N(R^{6a})R^{6b}, –N(H)C(=O)R^6, –N(R^{6c})C(=O)N(R^{6a})R^{6b}, –S(=O)$_2$$R^6$ o –S(=O)$_2$OH.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, como se ha definido, donde:

R^8 representa un átomo de halógeno, un grupo –CN, –N(R^{6a})R^{6b}, o –OR^6.

Preferentemente, R^8 representa un átomo de halógeno, un grupo –N(R^{6a})R^{6b} o un grupo –OR^6.

La invención se relaciona con los compuestos de fórmula I, donde

m es el entero 0, 1, 2, 3, 4, 5 o 6.

En una forma de realización preferida, con respecto a los compuestos de fórmula I, como se ha definido, m es 0.
En otra forma de realización preferida, con respecto a los compuestos de fórmula I, como se ha definido, m es 1.
La invención se relaciona con los compuestos de fórmula I, donde

n es el entero 0, 1, 2, 3, 4 o 5.

En una forma de realización preferida, con respecto a los compuestos de fórmula I, como se ha definido, n es 1.

La invención se relaciona con los compuestos de fórmula I, donde

X es S, S(=O), S(=O)$_2$, O, NR^6, C$R^{6a}$$R^{6b}$ o C=C$R^{6a}$$R^{6b}$.

En una forma de realización preferida, la invención se relaciona

con los compuestos de fórmula I, donde

X es S.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, donde

X es S(=O).

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, donde

X es $S(=O)_2$.

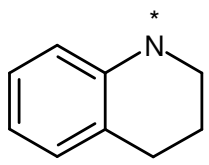
En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, donde

X es O.

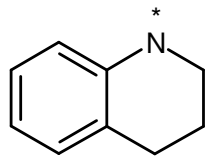
En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, donde

X es NR^6. Preferentemente, X es NH o N(CH3). Con preferencia máxima, X es NH.

Debe notarse que en un grupo por ejemplo de fórmula aril-NR^6- o heteroaril-NR^6- el sustituyente R^6 puede unirse opcionalmente al anillo arilo- o heteroarilo-, formando entonces junto con el átomo de N un anillo heterocíclico fusionado al anillo arilo- o heteroarilo-. Un ejemplo de dicho sistema de anillos fusionados es el grupo:



, en donde * indica el punto de unión de dicho grupo con el resto de la molécula. En otras palabras, un grupo con la fórmula

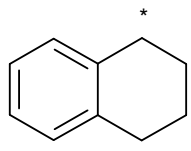


, en donde * indica el punto de unión de dicho grupo con el resto de la molécula, es un ejemplo de un grupo aril-X-.

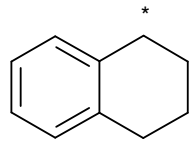
En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, donde

X es $CR^{6a}R^{6b}$. Preferentemente, X es CH_2.

Debe notarse que en un grupo por ejemplo de fórmula aril-$CR^{6a}R^{6b}$- o heteroaril-$CR^{6a}R^{6b}$- los sustituyentes R^{6a} y/o R^{6b} pueden unirse opcionalmente al anillo arilo- o heteroarilo-, formando así uno o más anillos carbocíclicos fusionados al anillo arilo- o heteroarilo-. Un ejemplo de dicho sistema de anillos fusionados es el grupo



, en donde * indica el punto de unión de dicho grupo con el resto de la molécula. En otras palabras, un grupo con la fórmula



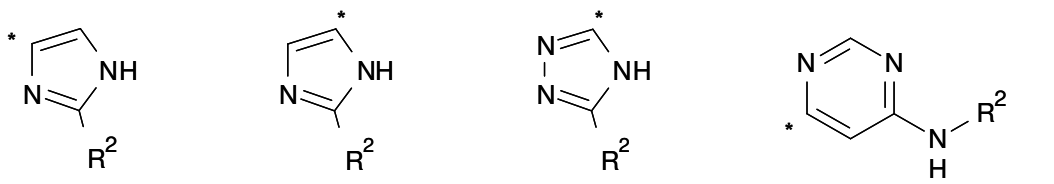
, en donde * indica el punto de unión de dicho grupo con el resto de la molécula, es un ejemplo de un grupo aril-X-.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I, donde

X es $C=CR^{6a}R^{6b}$. Preferentemente, X es $C=CH_2$.

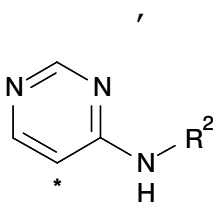
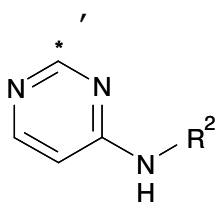
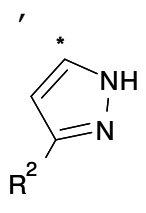
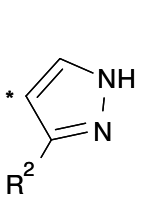
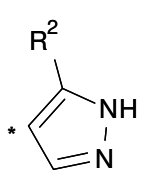
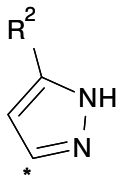
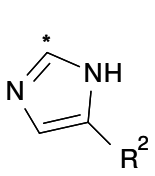
La invención se relaciona con los compuestos de fórmula I, donde

Z representa un grupo $-C(=O)N(H)R^2$ o $-C(=S)N(H)R^2$, o un grupo seleccionado entre


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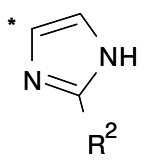
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donde * indica el punto de unión de dichos grupos con el resto de la molécula.

En una forma de realización preferida Z representa un grupo $-C(=O)N(H)R^2$.

En otra forma de realización preferida Z representa un grupo $-C(=S)N(H)R^2$.

En otra forma de realización preferida Z representa un grupo


.

En una forma de realización de los aspectos previamente

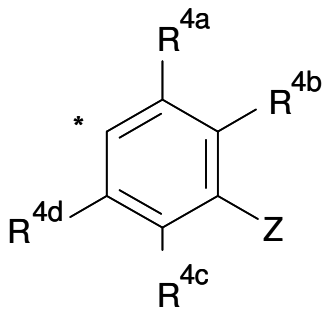
mencionados, la invención se relaciona con los compuestos de fórmula I, de acuerdo con cualquiera de las formas de realización mencionadas, en forma de un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato o una sal de los mismos, o una mezcla de los mismos.

Debe entenderse que la presente invención también se relaciona con cualquier combinación de las formas de realización preferidas que se han descrito.

A continuación se dan algunos ejemplos de combinaciones. Sin embargo, la invención no se limita a dichas combinaciones.

En una forma de realización preferida, la invención se relaciona con los compuestos de fórmula general I, como se ha definido, donde:

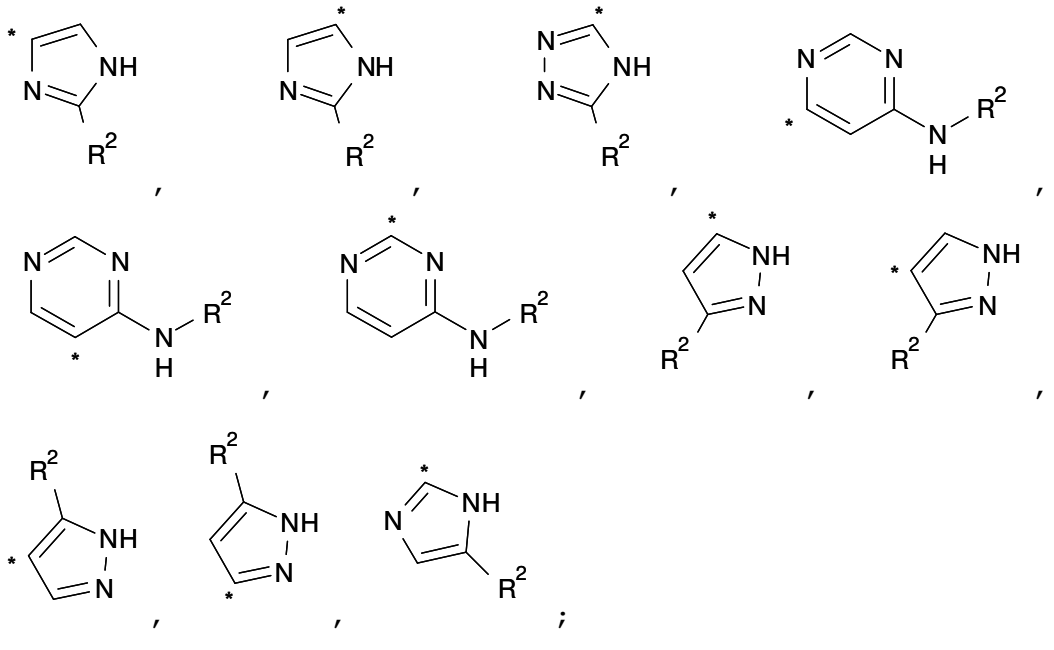
A representa un grupo



–;

donde * indica el punto de unión de dichos grupos con el resto de la molécula;

Z representa un grupo $-C(=O)N(H)R^2$ o $-C(=S)N(H)R^2$, o un grupo seleccionado entre



donde * indica el punto de unión de dichos grupos con el resto de la molécula;

R^2 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, C_2-C_6-alquinilo- o C_3-C_6-cicloalquilo-;

donde dicho grupo C_3-C_6-cicloalquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 - grupos seleccionados entre: halógeno, OH, -CN, C_1-C_6-alquilo, -C_1-C_6-alcoxi, halo-C_1-C_6-alquilo-;

R^3 representa un átomo de hidrógeno o un átomo de halógeno, o un grupo -CN, C_1-C_6-alquilo-, -$(CH_2)_m$-C_2-C_6-alquenilo,, -$(CH_2)_m$-C_4-C_8-cicloalquenilo -$(CH_2)_m$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-,

halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo-, -C_1-C_6-alquil-arilo, -C_1-C_6-alquil-heteroarilo, heteroarilo-, C_1-C_6-alquil-X-, -X-$(CH_2)_m$-C_2-C_6-alquenilo, -X-$(CH_2)_m$-C_4-C_8-cicloalquenilo, -X-$(CH_2)_m$-C_2-C_6-alquinilo, -X-$(CH_2)_m$-C_3-C_6-cicloalquilo, -X-$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -X-$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-X-, heteroaril-X-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)_2R^6$, $-S(=O)(=NR^{6a})R^{6b}$, $-S(=O)_2N(R^{6b})R^{6c}$, -S-$(CH_2)_n$-$N(R^{6a})R^{6b}$, o -S-$(CH_2)_n$-(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho grupo C_1-C_6-alquilo-, -$(CH_2)_m$-C_2-C_6-alquenilo, -$(CH_2)_m$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo-, C_1-C_6-alquil-X-, -X-$(CH_2)_m$-C_2-C_6-alquenilo, -X-$(CH_2)_m$-C_4-C_8-cicloalquenilo, -X-$(CH_2)_m$-C_2-C_6-alquinilo, -X-$(CH_2)_m$-C_3-C_6-cicloalquilo, -X-$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -X-$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-X-, heteroaril-X-, -C_1-C_6-alquil-arilo, -C_1-C_6-alquil-heteroarilo o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos R^7;

R^{4a}, R^{4b}, R^{4c}, R^{4d}

representan, en forma independiente entre sí, un átomo de hidrógeno o halógeno, o un grupo -CN, C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^{6a}$, $-S(=O)_2N(R^{6a})R^{6b}$ o $-S(=O)(=NR^{6c})R^6$.

R^5 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, $-(CH_2)_n$-C_2-C_6-alquenilo, $-(CH_2)_n$-C_2-C_6-alquinilo, $-(CH_2)_m$-C_3-C_6-cicloalquilo, $-(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-,arilo- o heteroarilo;

donde dicho grupo C_1-C_6-alquilo-, $-(CH_2)_n$-C_2-C_6-alquenilo, $-(CH_2)_n$-C_2-C_6-alquinilo, $-(CH_2)_m$-C_3-C_6-cicloalquilo, $-(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-,

C_3–C_6–cicloalquilo–, heterocicloalquilo de entre 3 y 7 miembros–, C_4–C_8–cicloalquenilo–, arilo– o heteroaryl– está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos R^8;

R^6, R^{6a}, R^{6b}, R^{6c},

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1–C_6–alquilo–, HO–C_1–C_6–alquilo–, C_3–C_6–cicloalquilo–, C_2–C_6–alquenilo, heterocicloalquilo de entre 3 y 7 miembros–, arilo–, heteroarilo–, aril–C_1–C_6–alquilo–, o heteroaril–C_1–C_6–alquilo–;

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO–, –CN, C_1–C_6–alcoxi–, C_1–C_6–alquilo–, halo–C_1–C_6–alquilo–, $R^{6a}(R^{6b})N$–C_1–C_6–alquilo–, HO–C_1–C_6–alquilo–, C_1–C_6–alcoxi–C_1–C_6–alquilo–, halo–C_1–C_6–alcoxi–C_1–C_6–alquilo–, C_2–C_6–alquenilo, heterocicloalquilo de entre 3 y 7 miembros, arilo–, heteroarilo–, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$;

donde dicho arilo– o heteroarilo– está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, o 3 grupos C_1–C_6–alquilo;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo, donde dichos 2 grupos R^7 juntos forman un puente:

$O(CH_2)_2O$, *$O(CH_2)O$*, *NH(C(=O))NH*, donde * representa el punto de unión a dicho anillo arilo;

R^8 representa un átomo de hidrógeno o halógeno, o un grupo –CN, C_1–C_6–alcoxi–, C_1–C_6–alquilo–, halo–C_1–C_6–alquilo–, $R^{6a}(R^{6b})N$–C_1–C_6–alquilo–, HO–C_1–C_6–alquilo, C_1–C_6–alcoxi–C_1–C_6–alquilo–, halo–C_1–C_6–alcoxi–C_1–C_6–alquilo–, C_2–C_6–alquenilo, heterocicloalquilo de entre 3 y 7 miembros, arilo–, heteroarilo–, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ o $-S(=O)_2$–(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho heterocicloalquilo– o heteroarilo– de entre 3 y 7 miembros está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos C_1–C_6 alquilo–;

m es el entero 0, 1, 2, 3, 4, 5 o 6;

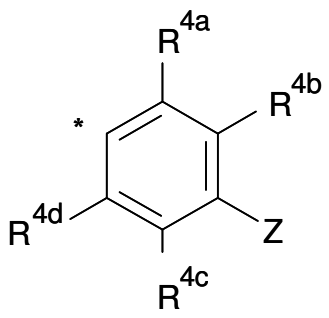
n es el entero 0, 1, 2, 3, 4 o 5;

X es S, S(=O), $S(=O)_2$, O, NR^6;

o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato o una sal de los mismos, o una mezcla de los mismos.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula general I, como se ha definido, donde:

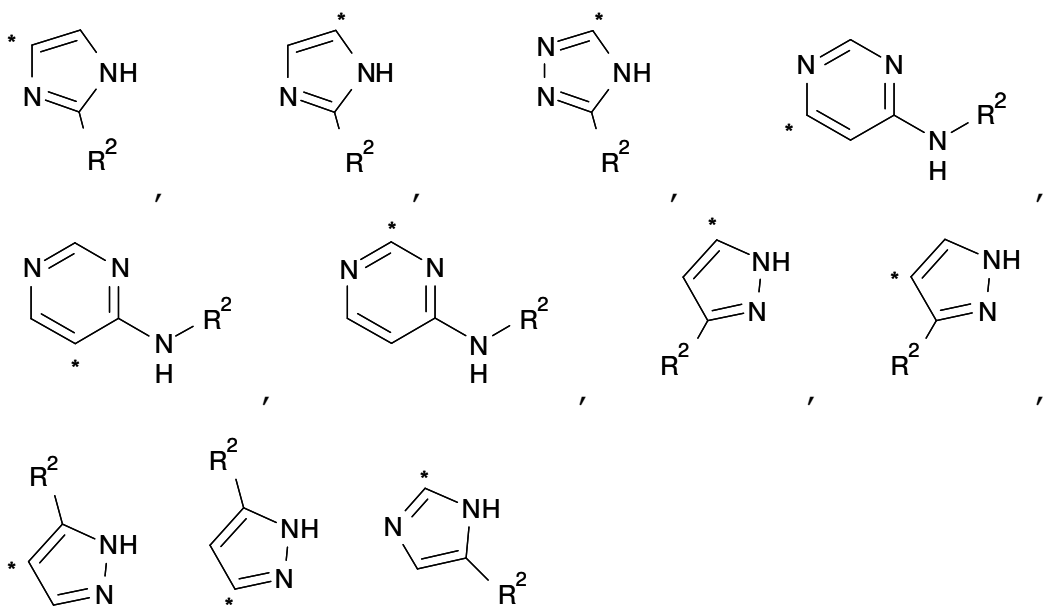
A representa un grupo



-;

donde * indica el punto de unión de dichos grupos con el resto de la molécula;

Z representa un grupo $-C(=O)N(H)R^2$ o $-C(=S)N(H)R^2$, o un grupo seleccionado entre



.

donde * indica el punto de unión de dichos grupos con el resto de la molécula;

R^2 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, C_2-C_6-alquinilo- o C_3-C_6-cicloalquilo-;

donde dicho grupo C_3-C_6-cicloalquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 - grupos seleccionados entre: halógeno, OH, -CN, C_1-C_6-alquilo, -C_1-C_6-alcoxi, halo-C_1-C_6-alquilo-;

R^3 representa un átomo de hidrógeno o un átomo de halógeno, o un grupo -CN, C_1-C_6-alquilo-, -$(CH_2)_m$-C_2-C_6-alquenilo-, -$(CH_2)_m$-C_4-C_8-cicloalquenilo, -$(CH_2)_m$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo-, -C_1-C_6-alquil-arilo, -C_1-C_6-alquil-heteroarilo, heteroarilo-, C_1-C_6-alquil-X-, -X-$(CH_2)_m$-C_2-C_6-alquenilo, -X-$(CH_2)_m$-C_4-C_8-cicloalquenilo, -X-$(CH_2)_m$-C_2-C_6-alquinilo, -X-$(CH_2)_m$-C_3-C_6-cicloalquilo, -X-$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -X-$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-X-, heteroaril-X-, -C(=O)R^6, -C(=O)N(H)R^{6a},

$-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)_2R^6$, $-S(=O)(=NR^{6a})R^{6b}$, $-S(=O)_2N(R^{6b})R^{6c}$, $-S-(CH_2)_n-N(R^{6a})R^{6b}$, o $-S-(CH_2)_n-$(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho grupo C_1-C_6-alquilo-, $-(CH_2)_m-C_2-C_6$-alquenilo, $-(CH_2)_m-C_2-C_6$-alquinilo, $-(CH_2)_m-C_3-C_6$-cicloalquilo, aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo-, C_1-C_6-alquil-X-, $-X-(CH_2)_m-C_2-C_6$-alquenilo, $-X-(CH_2)_m-C_4-C_8$-cicloalquenilo, $-X-(CH_2)_m-C_2-C_6$-alquinilo, $-X-(CH_2)_m-C_3-C_6$-cicloalquilo, $-X-(CH_2)_m-$(heterocicloalquilo de entre 3 y 7 miembros), $-X-(CH_2)_m-$(heterocicloalquenilo de entre 4 y 8 miembros), aril-X-, heteroaril-X-, $-C_1-C_6$-alquil-arilo, $-C_1-C_6$-alquil-heteroarilo, o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos R^7;

R^{4a}, R^{4c}, R^{4d} representan un átomo de hidrógeno, y

R^{4b} representa un átomo de hidrógeno o un átomo de halógeno o un grupo C_1-C_6-alquilo-;

o

R^{4b}, R^{4c}, R^{4d} representan un átomo de hidrógeno, y

R^{4a} representa un átomo de halógeno o un grupo C_1-C_6-alquilo-, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$,

$-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^{6a}$, $-S(=O)_2N(R^{6a})R^{6b}$ o

$-S(=O)(=NR^{6c})R^6$;

R^5 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, $-(CH_2)_n$-C_2-C_6-alquenilo, $-(CH_2)_n$-C_2-C_6-alquinilo, $-(CH_2)_m$-C_3-C_6-cicloalquilo, $-(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-,arilo- o heteroarilo-;

donde dicho grupo C_1-C_6-alquilo-, $-(CH_2)_n$-C_2-C_6-alquenilo, $-(CH_2)_n$-C_2-C_6-alquinilo, $-(CH_2)_m$-C_3-C_6-cicloalquilo, $-(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros, C_4-C_8-cicloalquenilo-, arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos R^8;

R^6, R^{6a}, R^{6b}, R^{6c},

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_3-

C_6-cicloalquilo-, C_2-C_6-alquenilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, aril-C_1-C_6-alquilo-, o heteroaril-C_1-C_6-alquilo-;

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$,

$-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$,

$-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$,

$-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$,

$-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$,

$-S(=O)_2N(R^{6a})R^{6b}$, o $-S(=O)(=NR^{6c})R^6$;

donde dicho arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, o 3 grupos C_1-C_6 alquilo-;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo, donde dichos 2 grupos R^7 juntos

forman un puente:

O(CH_2)$_2$O, *O(CH_2)O*, *NH(C(=O))NH*, donde * representa el punto de unión a dicho anillo arilo;

R^8 representa un átomo de hidrógeno o halógeno, o un grupo -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)$_2$$R^6$, -N($R^{6c}$)S(=O)$_2$$R^6$, -N=S(=O)($R^{6a}$)$R^{6b}$, -O$R^6$, -O(C=O)$R^6$, -O(C=O)N($R^{6a}$)$R^{6b}$, -O(C=O)O$R^6$, -S$R^6$, -S(=O)$R^6$, -S(=O)N(H)$R^6$, -S(=O)N($R^{6a}$)$R^{6b}$, -S(=O)$_2$$R^6$, -S(=O)$_2$N(H)$R^6$, -S(=O)$_2$N($R^{6a}$)$R^{6b}$, -S(=O)(=N$R^{6c}$)$R^6$ o -S(=O)$_2$-(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho heterocicloalquilo- o heteroarilo- de entre 3 y 7 miembros está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos C_1-C_6 alquilo-;

m es el entero 0, 1, 2, 3, 4, 5 o 6;

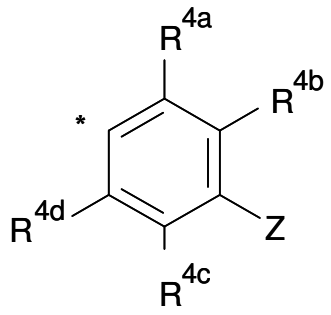
n es el entero 0, 1, 2, 3, 4 o 5;

X es S, S(=O), S(=O)$_2$, O, NR^6;

o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato o una sal de los mismos, o una mezcla de los mismos.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula general I, como se ha definido, donde:

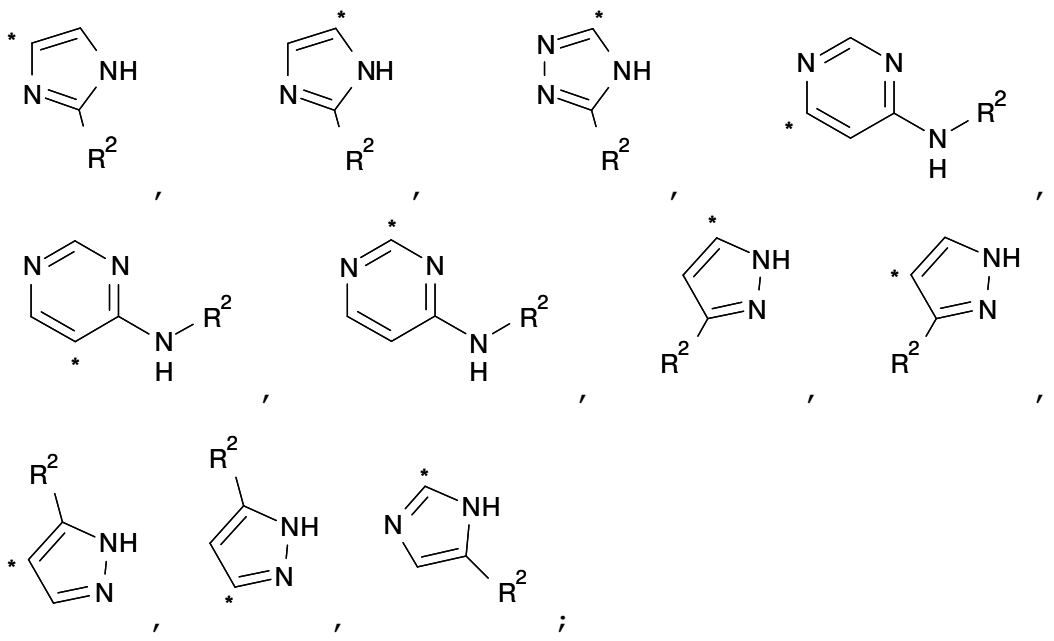
A representa un grupo



–;

donde * indica el punto de unión de dichos grupos con el resto de la molécula;

Z representa un grupo $-C(=O)N(H)R^2$ o $-C(=S)N(H)R^2$, o un grupo seleccionado entre



donde * indica el punto de unión de dichos grupos con el resto de la molécula;

R^2 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, C_2-C_6-alquinilo- o C_3-C_6-cicloalquilo-;

donde dicho grupo C_3-C_6-cicloalquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 - grupos seleccionados entre: halógeno, OH, -CN, C_1-C_6-alquilo, -C_1-C_6-alcoxi, halo-C_1-C_6-alquilo-;

R^3 representa un átomo de hidrógeno o un átomo de halógeno, o un grupo -CN, C_1-C_6-alquilo-, -$(CH_2)_m$-C_2-C_6-alquenilo,, -$(CH_2)_m$-C_4-C_8-cicloalquenilo -$(CH_2)_m$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo-, -C_1-C_6-alquil-arilo, -C_1-C_6-alquil-heteroarilo, heteroarilo-, C_1-C_6-alquil-X-, -X-$(CH_2)_m$-C_2-C_6-alquenilo, -X-$(CH_2)_m$-C_4-C_8-cicloalquenilo, -X-$(CH_2)_m$-C_2-C_6-alquinilo, -X-$(CH_2)_m$-C_3-C_6-cicloalquilo, -X-$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -X-$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-X-, heteroaril-X-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)_2R^6$, $-S(=O)(=NR^{6a})R^{6b}$, $-S(=O)_2N(R^{6b})R^{6c}$, $-S-(CH_2)_n-N(R^{6a})R^{6b}$, o $-S-(CH_2)_n-$

(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho grupo C_1-C_6-alquilo-, -$(CH_2)_m$-C_2-C_6-alquenilo, -$(CH_2)_m$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo-, C_1-C_6-alquil-X-, -X-$(CH_2)_m$-C_2-C_6-alquenilo, -X-$(CH_2)_m$-C_4-C_8-cicloalquenilo, -X-$(CH_2)_m$-C_2-C_6-alquinilo, -X-$(CH_2)_m$-C_3-C_6-cicloalquilo, -X-$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -X-$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-X-, heteroaril-X-, -C_1-C_6-alquil-arilo, -C_1-C_6-alquil-heteroarilo, o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos R^7;

R^{4a}, R^{4c}, R^{4d} representan un átomo de hidrógeno, y

R^{4b} representa un átomo de hidrógeno o un átomo de halógeno o un grupo C_1-C_6-alquilo;

o

R^{4b}, R^{4c}, R^{4d} representan un átomo de hidrógeno, y

R^{4a} representa un átomo de halógeno o un grupo C_1-C_6-alquilo-, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^{6a}$, $-S(=O)_2N(R^{6a})R^{6b}$, o

$-S(=O)(=NR^{6c})R^6$;

R^5 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), arilo- o heteroarilo-;

donde dicho grupo C_1-C_6-alquilo-, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos R^8;

R^6, R^{6a}, R^{6b}, R^{6c}

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, C_2-C_6-alquenilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, aril-C_1-C_6-alquilo-, o heteroaril-C_1-C_6-alquilo-;

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})$N-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6,

-N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2R^6$, -N(R^{6c})S(=O)$_2R^6$, N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -S(=O)$_2R^6$, - S(=O)$_2$N(H)R^6, -S(=O)$_2$N(R^{6a})R^{6b}, -

$S(=O)(=NR^{6c})R^6$;

donde dicho arilo-, heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, o 3 grupos C_1-C_6-alquilo;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo, donde dichos 2 grupos R^7 juntos forman un puente:

$*O(CH_2)_2O*$, $*O(CH_2)O*$, *NH(C(=O))NH*, donde * representa el punto de unión a dicho anillo arilo;

R^8 representa un átomo de hidrógeno o halógeno, o un grupo -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$, $-S(=O)_2$-(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho heterocicloalquilo- o heteroarilo- de entre 3 y 7 miembros está opcionalmente sustituido, en forma idéntica

o diferente, con 1, 2, 3 o 4 grupos C_1-C_6 alquilo-;

m es el entero 0, 1, 2, 3, 4, 5 o 6;

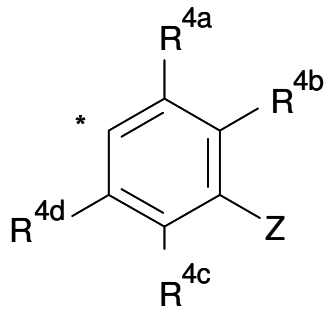
n es el entero 0, 1, 2, 3, 4 o 5;

X es S, S(=O), $S(=O)_2$, O, NR^6;

o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato o una sal de los mismos, o una mezcla de los mismos.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula general I, como se ha definido, donde:

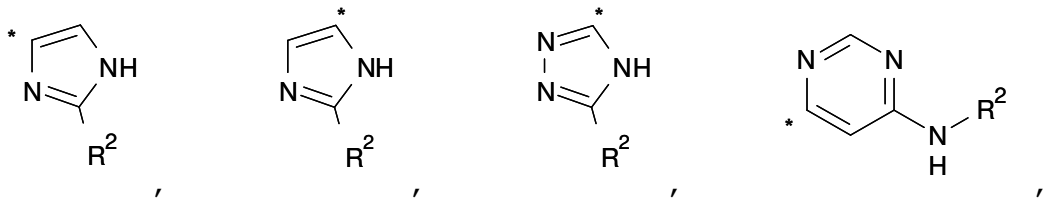
A representa un grupo



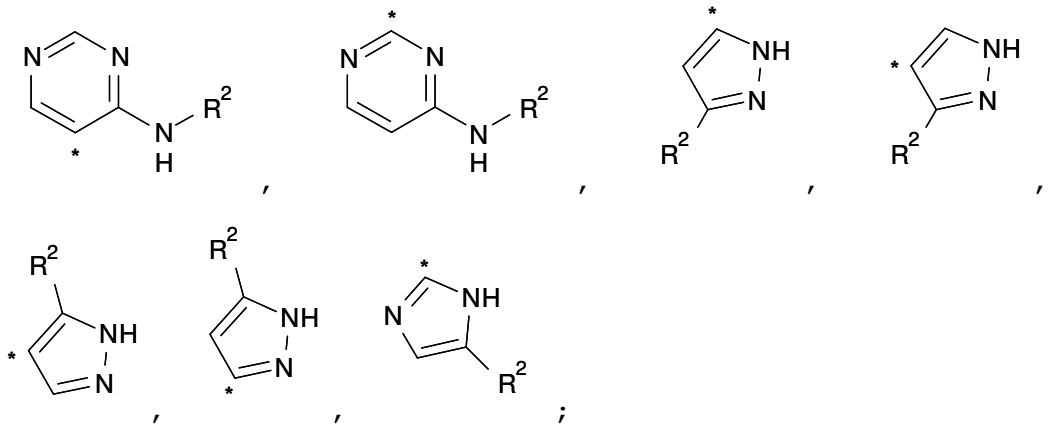
-;

donde * indica el punto de unión de dichos grupos con el resto de la molécula;

Z representa un grupo $-C(=O)N(H)R^2$ o $-C(=S)N(H)R^2$, o un grupo seleccionado entre



, , , ,



donde * indica el punto de unión de dichos grupos con el resto de la molécula;

R^2 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, C_2-C_6-alquinilo- o C_3-C_6-cicloalquilo-;

donde dicho grupo C_3-C_6-cicloalquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos seleccionados entre: halógeno, OH, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi-, halo-C_1-C_6-alquilo-;

R^3 representa un átomo de hidrógeno o un átomo de halógeno, o un grupo -CN, C_1-C_6-alquilo-, -$(CH_2)_m$-C_2-C_6-alquenilo,, -$(CH_2)_m$-C_4-C_8-cicloalquenilo -$(CH_2)_m$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-

alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo-, -C_1-C_6-alquil-arilo, -C_1-C_6-alquil-heteroarilo, heteroarilo-, C_1-C_6-alquil-X-, -X-$(CH_2)_m$-C_2-C_6-alquenilo, -X-$(CH_2)_m$-C_4-C_8-cicloalquenilo, -X-$(CH_2)_m$-C_2-C_6-alquinilo, -X-$(CH_2)_m$-C_3-C_6-cicloalquilo, -X-$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -X-$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-X-, heteroaril-X-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -OR^6, -SR^6, -S(=O)R^6, -S(=O)$_2R^6$, -S(=O)(=NR^{6a})R^{6b}, -S(=O)$_2$N(R^{6b})R^{6c}, -S-$(CH_2)_n$-N(R^{6a})R^{6b}, o -S-$(CH_2)_n$-(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho grupo C_1-C_6-alquilo-, -$(CH_2)_m$-C_2-C_6-alquenilo, -$(CH_2)_m$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo-, C_1-C_6-alquil-X-, -X-$(CH_2)_m$-C_2-C_6-alquenilo, -X-$(CH_2)_m$-C_4-C_8-cicloalquenilo, -X-$(CH_2)_m$-C_2-C_6-alquinilo, -X-$(CH_2)_m$-C_3-C_6-cicloalquilo, -X-$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -X-$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-X-, heteroaril-X-, -C_1-C_6-alquil-arilo, -C_1-C_6-alquil-heteroarilo, o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos R^7;

R^{4a}, R^{4c}, R^{4d} representan un átomo de hidrógeno, y

R^{4b} representa un átomo de hidrógeno o un átomo de

halógeno o un grupo C_1-C_6-alquilo;

o

R^{4b}, R^{4c}, R^{4d} representan un átomo de hidrógeno, y

R^{4a} representa un átomo de halógeno o un grupo C_1-C_6-alquilo-, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^{6a}$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$;

R^5 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, $-(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), arilo- o heteroarilo;

donde dicho C_1-C_6-alquilo-, $-(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos R^8;

R^6, R^{6a}, R^{6b}, R^{6c},

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, C_2-C_6-alquenilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, aril-C_1-C_6-alquilo-, o heteroaril-C_1-C_6-alquilo-;

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-,

$R^{6a}(R^{6b})N-C_1-C_6$-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$;

donde dicho arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, o 3 grupos C_1-C_6-alquilo;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo, donde dichos 2 grupos R^7 juntos forman un puente:

$O(CH_2)_2O$, *$O(CH_2)O$*, *NH(C(=O))NH*, donde * representa el punto de unión a dicho anillo arilo;

R^8 representa un átomo de halógeno, un grupo $-N(R^{6a})R^{6b}$ o $-OR^6$;

m es el entero 0, 1, 2, 3, 4, 5 o 6;

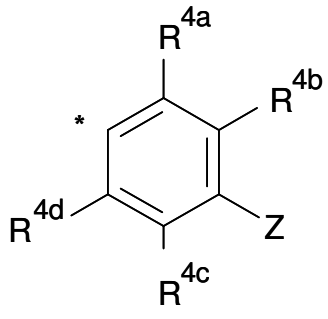
n es el entero 0, 1, 2, 3, 4 o 5;

X es S, S(=O), $S(=O)_2$, O, NR^6;

o un estereoisómero, un tautómero, un N-óxido, un hidrato,

un solvato o una sal de los mismos, o una mezcla de los mismos.

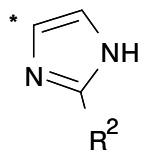
En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula general I, como se ha definido, donde:

A representa un grupo  –;

donde * indica el punto de unión de dichos grupos con el resto de la molécula;

Z representa un grupo $-C(=O)N(H)R^2$ o $-C(=S)N(H)R^2$,

o un grupo



;

donde * indica el punto de unión de dichos grupos con el resto de la molécula;

R^2 representa un átomo de hidrógeno, o un grupo C_1–C_6–alquilo– o C_3–C_6–cicloalquilo–;

R^3 representa un átomo de hidrógeno o un átomo de halógeno, o un grupo $-(CH_2)_m-C_2-C_6$–alquenilo, $-(CH_2)_m-C_4-C_8$–cicloalquenilo $-(CH_2)_m-C_3-C_6$–cicloalquilo, $-(CH_2)_m$–

(heterocicloalquenilo de entre 4 y 8 miembros), arilo-, aril-X-, heteroaril-X-, heteroarilo-, $-C(=O)N(H)R^{6a}$, $-OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)_2R^6$, $-S-(CH_2)_n-N(R^{6a})R^{6b}$, o $-S-(CH_2)_n-$(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho arilo-, aril-X-, heteroaril-X- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos R^7;

R^{4a}, R^{4c}, R^{4d} representan un átomo de hidrógeno, y

R^{4b} representa un átomo de hidrógeno o un átomo de halógeno o un grupo C_1-C_6-alquilo;

o

R^{4b}, R^{4c}, R^{4d} representan un átomo de hidrógeno, y

R^{4a} representa un átomo de halógeno o un grupo C_1-C_6-alquilo-, o $-OR^6$;

R^5 representa un grupo C_1-C_6-alquilo-, $-(CH_2)_m-$(heterocicloalquilo de entre 3 y 7 miembros), arilo- o heteroarilo-;

donde dicho C_1-C_6-alquilo-, $-(CH_2)_m-$(heterocicloalquilo de entre 3 y 7 miembros), arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos R^8;

R^6, R^{6a}, R^{6b}, R^{6c},

representan, en forma independiente entre sí, un átomo de

hidrógeno, o un grupo C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo- o arilo-;

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, arilo-, heteroarilo-, $-C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-OR^6$, $-S(=O)R^6$, o $-S(=O)_2R^6$; donde dicho heteroarilo- está opcionalmente sustituido con un grupo C_1-C_4-alquilo;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo, donde dichos 2 grupos R^7 juntos forman un puente:

$*O(CH_2)_2O*$, $*O(CH_2)O*$, *NH(C(=O))NH*, donde * representa el punto de unión a dicho anillo arilo;

R^8 representa un átomo de halógeno, un grupo $-N(R^{6a})R^{6b}$, o $-OR^6$;

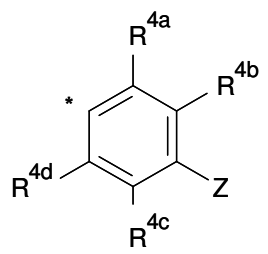
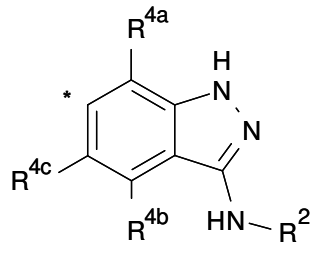
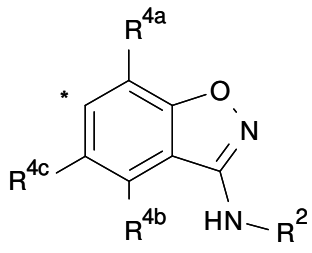
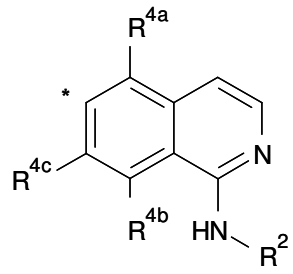
m es el entero 0, 1, 2, 3, 4, 5 o 6;

X es S, S(=O), $S(=O)_2$, O, NR^6;

o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato o una sal de los mismos, o una mezcla de los mismos.

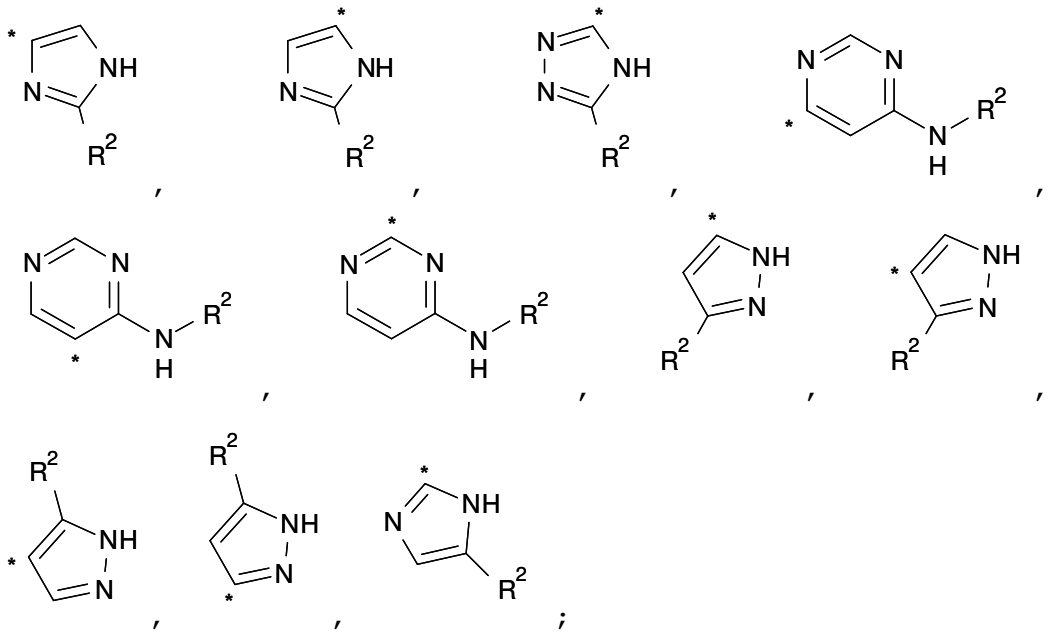
En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula general I, como se ha definido, donde:

A representa un grupo

donde * indica el punto de unión de dichos grupos con el resto de la molécula;

Z representa un grupo $-C(=O)N(H)R^2$ o $-C(=S)N(H)R^2$, o un grupo seleccionado entre



donde * indica el punto de unión de dichos grupos con el resto de la molécula;

R^2 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, C_2-C_6-alquinilo- o C_3-C_6-cicloalquilo-;

donde dicho grupo C_3-C_6-cicloalquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 - grupos seleccionados entre: halógeno, OH, -CN, C_1-C_6-alquilo, -C_1-C_6-alcoxi, halo-C_1-C_6-alquilo-;

R^3 representa un átomo de hidrógeno o un átomo de halógeno, o un grupo -CN, C_1-C_6-alquilo-, -C_1-C_6-alcoxi, -$(CH_2)_m$-C_2-C_6-alquenilo,, -$(CH_2)_m$-C_4-C_8-cicloalquenilo -$(CH_2)_m$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo-, -C_1-C_6-alquil-arilo, -C_1-C_6-alquil-heteroarilo, heteroarilo-, C_1-C_6-alquil-X-, -X-$(CH_2)_m$-C_2-C_6-alquenilo, -X-$(CH_2)_m$-C_4-C_8-cicloalquenilo, -X-$(CH_2)_m$-C_2-C_6-alquinilo, -X-$(CH_2)_m$-C_3-C_6-cicloalquilo, -X-$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -X-$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-X-, heteroaril-X-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)_2R^6$, $-S(=O)(=NR^{6a})R^{6b}$, $-S(=O)_2N(R^{6b})R^{6c}$, -S-

$(CH_2)_n$–$N(R^{6a})R^{6b}$, o –S–$(CH_2)_n$–(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho C_1–C_6–alquilo–, –C_1–C_6–alcoxi, –$(CH_2)_m$–C_2–C_6–alquenilo, –$(CH_2)_m$–C_2–C_6–alquinilo, –$(CH_2)_m$–C_3–C_6–cicloalquilo, aril–C_1–C_6–alquilo–, heteroaril–C_1–C_6–alquilo–, C_3–C_6–cicloalquilo–, heterocicloalquilo de entre 3 y 7 miembros–, C_2–C_6–alquenilo–, C_4–C_8–cicloalquenilo–, C_2–C_6–alquinilo–, arilo–, C_1–C_6–alquil–X–, –X–$(CH_2)_m$–C_2–C_6–alquenilo, –X–$(CH_2)_m$–C_4–C_8–cicloalquenilo, –X–$(CH_2)_m$–C_2–C_6–alquinilo, –X–$(CH_2)_m$–C_3–C_6–cicloalquilo, –X–$(CH_2)_m$–(heterocicloalquilo de entre 3 y 7 miembros), –X–$(CH_2)_m$–(heterocicloalquenilo de entre 4 y 8 miembros), aril–X–, heteroaril–X–, –C_1–C_6–alquil–arilo,

–C_1–C_6–alquil–heteroarilo o heteroarilo– está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, 4 o 5 grupos R^7;

R^{4a}, R^{4b}, R^{4c}, R^{4d}

representan, en forma independiente entre sí, un átomo de hidrógeno o halógeno, o un grupo –CN, C_1–C_6–alquilo–, C_1–C_6–alcoxi–, halo–C_1–C_6–alquilo–, $R^{6a}(R^{6b})N$–C_1–C_6–alquilo–, HO–C_1–C_6–alquilo–, C_1–C_6–alcoxi–C_1–C_6–alquilo–, halo–C_1–C_6–alcoxi–C_1–C_6–alquilo–, –$C(=O)R^6$, –$C(=O)N(H)R^{6a}$, –$C(=O)N(R^{6a})R^{6b}$, –$C(=O)O$–R^6, –$N(R^{6a})R^{6b}$, –NO_2, –$N(H)C(=O)R^6$, –$N(R^{6c})C(=O)R^6$, –$N(H)C(=O)N(R^{6a})R^{6b}$, –$N(R^{6c})C(=O)N(R^{6a})R^{6b}$, –$N(H)C(=O)OR^6$, –$N(R^{6c})C(=O)OR^6$, –$N(H)S(=O)R^6$, –$N(R^{6c})S(=O)R^6$, –$N(H)S(=O)_2R^6$, –$N(R^{6c})S(=O)_2R^6$, –$N=S(=O)(R^{6a})R^{6b}$, –$OR^6$, –$O(C=O)R^6$, –$O(C=O)N(R^{6a})R^{6b}$, –$O(C=O)OR^6$, –$SR^6$, –$S(=O)R^6$, –$S(=O)N(H)R^6$, –

$S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^{6a}$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$;

R^5 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, $-(CH_2)_n$-C_2-C_6-alquenilo, $-(CH_2)_n$-C_2-C_6-alquinilo, $-(CH_2)_m$-C_3-C_6-cicloalquilo, $-(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo- o heteroarilo-;

donde dicho grupo C_1-C_6-alquilo-, $-(CH_2)_n$-C_2-C_6-alquenilo, $-(CH_2)_n$-C_2-C_6-alquinilo, $-(CH_2)_m$-C_3-C_6-cicloalquilo, $-(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros, C_4-C_8-cicloalquenilo-, arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos R^8;

R^6, R^{6a}, R^{6b}, R^{6c},

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, C_2-C_6-alquenilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, aril-C_1-C_6-

alquilo-, o heteroaril-C_1-C_6-alquilo-;

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$,

$-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$,

$-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$;

donde dicho grupo C_1-C_6-alcoxi-, arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, o 3 grupos C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alcoxi-, $-C(=O)O-R^6$ o -OH;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo, donde dichos 2 grupos R^7 juntos forman un puente:

$*O(CH_2)_2O*$, $*O(CH_2)O*$, *NH(C(=O))NH*, donde * representa el punto de unión a dicho anillo arilo;

R^8 representa un átomo de hidrógeno o halógeno, o un grupo -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ o $-S(=O)_2$-(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho heterocicloalquilo- o heteroarilo- de entre 3 y 7 miembros está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos C_1-C_6 alquilo-;

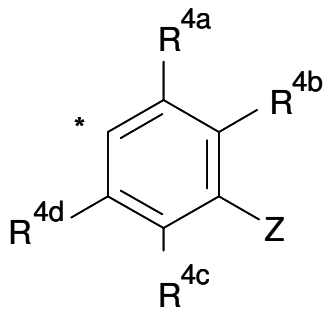
m es el entero 0, 1, 2, 3, 4, 5 o 6;

n es el entero 0, 1, 2, 3, 4 o 5;

X es S, S(=O), $S(=O)_2$, O, NR^6;

o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato o una sal de los mismos, o una mezcla de los mismos.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula general I, como se ha definido, donde:

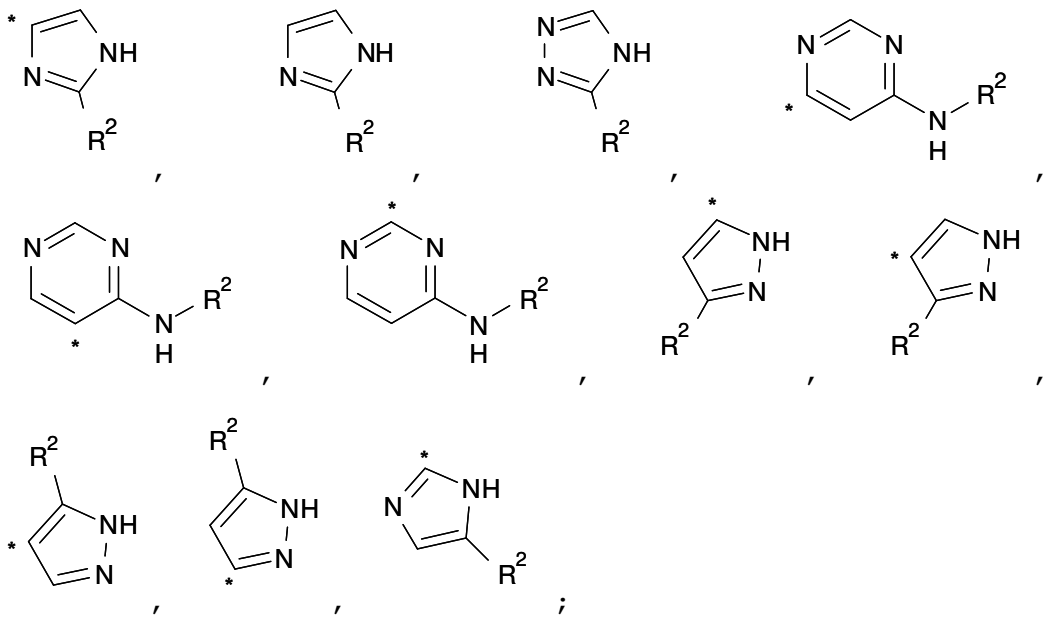


A representa un grupo –;

donde * indica el punto de unión de dichos grupos con el resto de la molécula;

Z representa un grupo $-C(=O)N(H)R^2$ o $-C(=S)N(H)R^2$,

o un grupo seleccionado entre



donde * indica el punto de unión de dichos grupos con el resto de la molécula;

R^2 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, C_2-C_6-

alquinilo- o C_3-C_6-cicloalquilo-;

donde dicho grupo C_3-C_6-cicloalquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 - grupos seleccionados entre: halógeno, OH, -CN, C_1-C_6-alquilo, -C_1-C_6-alcoxi, halo-C_1-C_6-alquilo-;

R^3 representa un átomo de hidrógeno o un átomo de halógeno, o un grupo -CN, C_1-C_6-alquilo-, -C_1-C_6-alcoxi, -$(CH_2)_m$-C_2-C_6-alquenilo, -$(CH_2)_m$-C_4-C_8-cicloalquenilo, -$(CH_2)_m$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo-, -C_1-C_6-alquil-arilo, -C_1-C_6-alquil-heteroarilo, heteroarilo-, C_1-C_6-alquil-X-, -X-$(CH_2)_m$-C_2-C_6-alquenilo, -X-$(CH_2)_m$-C_4-C_8-cicloalquenilo, -X-$(CH_2)_m$-C_2-C_6-alquinilo, -X-$(CH_2)_m$-C_3-C_6-cicloalquilo, -X-$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -X-$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-X-, heteroaril-X-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)_2R^6$, $-S(=O)(=NR^{6a})R^{6b}$, $-S(=O)_2N(R^{6b})R^{6c}$, -S-$(CH_2)_n$-$N(R^{6a})R^{6b}$, o -S-$(CH_2)_n$-(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho grupo C_1-C_6-alquilo-, -C_1-C_6-alcoxi, -$(CH_2)_m$-C_2-

C_6-alquenilo, $-(CH_2)_m-C_2-C_6$-alquinilo, $-(CH_2)_m-C_3-C_6$-cicloalquilo, aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo-, C_1-C_6-alquil-X-, $-X-(CH_2)_m-C_2-C_6$-alquenilo, $-X-(CH_2)_m-C_4-C_8$-cicloalquenilo, $-X-(CH_2)_m-C_2-C_6$-alquinilo, $-X-(CH_2)_m-C_3-C_6$-cicloalquilo, $-X-(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), $-X-(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-X-, heteroaril-X-, $-C_1-C_6$-alquil-arilo, $-C_1-C_6$-alquil-heteroarilo o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, 4 o 5 grupos R^7;

R^{4a}, R^{4b}, R^{4c}, R^{4d}

representan, en forma independiente entre sí, un átomo de hidrógeno o halógeno, o un grupo -CN, C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N-C_1-C_6$-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^{6a}$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$;

R^5 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-,

$-(CH_2)_n-C_2-C_6$-alquenilo, $-(CH_2)_n-C_2-C_6$-alquinilo, $-(CH_2)_m-C_3-C_6$-cicloalquilo, $-(CH_2)_m-$(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N-C_1-C_6$-alquilo-, HO-C_1-C_6-alquilo-, $-C_1-C_6$-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-,arilo- o heteroarilo;

donde dicho grupo C_1-C_6-alquilo-, $-(CH_2)_n-C_2-C_6$-alquenilo, $-(CH_2)_n-C_2-C_6$-alquinilo, $-(CH_2)_m-C_3-C_6$-cicloalquilo, $-(CH_2)_m-$(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N-C_1-C_6$-alquilo-, HO-C_1-C_6-alquilo-, $-C_1-C_6$-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros, C_4-C_8-cicloalquenilo-, arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos R^8;

R^6, R^{6a}, R^{6b}, R^{6c}

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, C_2-C_6-alquenilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, aril-C_1-C_6-alquilo-, o heteroaril-C_1-C_6-alquilo-;

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-,

$R^{6a}(R^{6b})N-C_1-C_6$-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$ o $-S(=O)(=NR^{6c})R^6$;

donde dicho grupo C_1-C_6-alcoxi-, arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, o 3 grupos C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alcoxi-, $-C(=O)O-R^6$ o -OH;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo, donde dichos 2 grupos R^7 juntos forman un puente:

$*O(CH_2)_2O*$, $*O(CH_2)O*$, *NH(C(=O))NH*, donde * representa el punto de unión a dicho arilo;

R^8 representa un átomo de hidrógeno o halógeno, o un grupo -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N-C_1-C_6$-alquilo-, HO-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros-, arilo-,

heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$, $-S(=O)_2$-(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho heterocicloalquilo- o heteroarilo- de entre 3 y 7 miembros, está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos C_1-C_6 alquilo-;

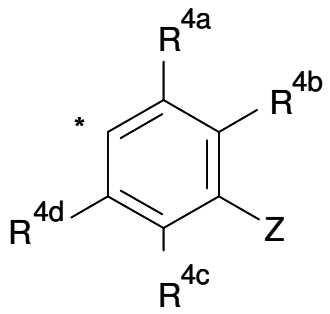
m es el entero 0, 1, 2, 3, 4, 5 o 6;

n es el entero 0, 1, 2, 3, 4 o 5;

X es S, S(=O), $S(=O)_2$, O, NR^6;

o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato o una sal de los mismos, o una mezcla de los mismos.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula general I, como se ha definido, donde:

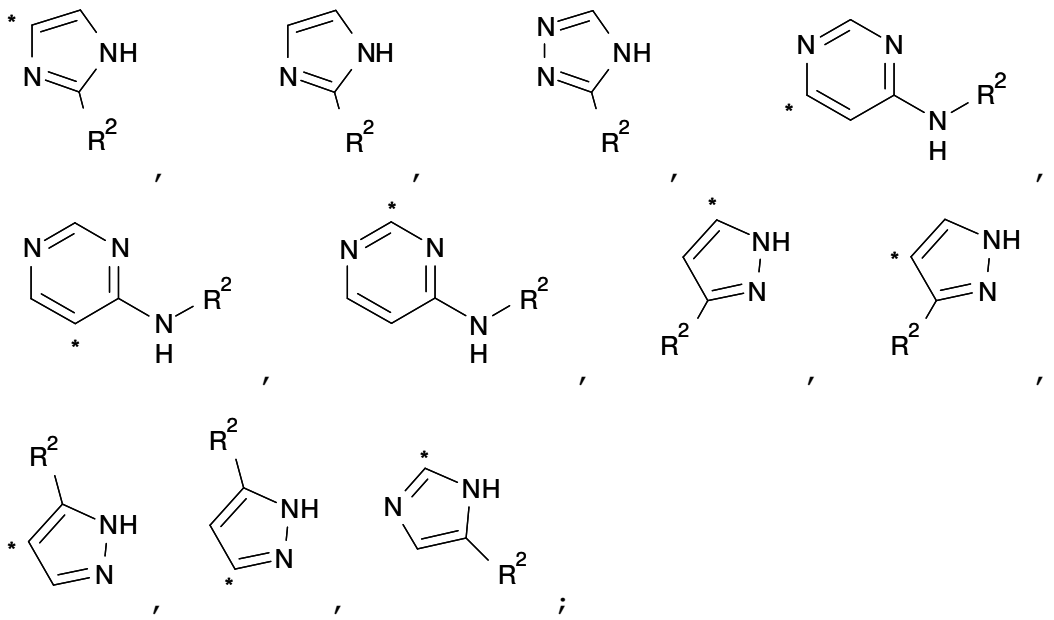


A representa un grupo –;

donde * indica el punto de unión de dichos grupos con el resto de la molécula;

Z representa un grupo $-C(=O)N(H)R^2$ o $-C(=S)N(H)R^2$,

o un grupo seleccionado entre



donde * indica el punto de unión de dichos grupos con el resto de la molécula;

R^2 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, C_2-C_6-

alquinilo- o C_3-C_6-cicloalquilo-;

donde dicho grupo C_3-C_6-cicloalquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 - grupos seleccionados entre: halógeno, OH, -CN, C_1-C_6-alquilo, -C_1-C_6-alcoxi, halo-C_1-C_6-alquilo-;

R^3 representa un átomo de hidrógeno o un átomo de halógeno, o un grupo -CN, C_1-C_6-alquilo-, C_1-C_6-alcoxi-, -$(CH_2)_m$-C_2-C_6-alquenilo, -$(CH_2)_m$-C_4-C_8-cicloalquenilo -$(CH_2)_m$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo-, -C_1-C_6-alquil-arilo, -C_1-C_6-alquil-heteroarilo, heteroarilo-, C_1-C_6-alquil-X-, -X-$(CH_2)_m$-C_2-C_6-alquenilo, -X-$(CH_2)_m$-C_4-C_8-cicloalquenilo, -X-$(CH_2)_m$-C_2-C_6-alquinilo, -X-$(CH_2)_m$-C_3-C_6-cicloalquilo, -X-$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -X-$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-X-, heteroaril-X-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)_2R^6$, $-S(=O)(=NR^{6a})R^{6b}$, $-S(=O)_2N(R^{6b})R^{6c}$, -S-$(CH_2)_n$-$N(R^{6a})R^{6b}$, o -S-$(CH_2)_n$-(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho grupo C_1-C_6-alquilo-, -C_1-C_6-alcoxi, -$(CH_2)_m$-C_2-

C_6-alquenilo, -$(CH_2)_m$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo-, C_1-C_6-alquil-X-, -X-$(CH_2)_m$-C_2-C_6-alquenilo, -X-$(CH_2)_m$-C_4-C_8-cicloalquenilo, -X-$(CH_2)_m$-C_2-C_6-alquinilo, -X-$(CH_2)_m$-C_3-C_6-cicloalquilo, -X-$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -X-$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-X-, heteroaril-X-, -C_1-C_6-alquil-arilo, -C_1-C_6-alquil-heteroarilo o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, 4 o 5 grupos R^7;

R^{4a}, R^{4c}, R^{4d} representan un átomo de hidrógeno, y

R^{4b} representa un átomo de hidrógeno o un átomo de halógeno o un grupo C_1-C_6-alquilo;

o

R^{4b}, R^{4c}, R^{4d} representan un átomo de hidrógeno, y

R^{4a} representa un átomo de halógeno o un grupo C_1-C_6-alquilo-, -OR^6, -$O(C=O)R^6$,

-$O(C=O)N(R^{6a})R^{6b}$, -$O(C=O)OR^6$, -SR^6, -$S(=O)R^6$, -$S(=O)N(H)R^6$,

-$S(=O)N(R^{6a})R^{6b}$, -$S(=O)_2R^6$, -$S(=O)_2N(H)R^{6a}$, -$S(=O)_2N(R^{6a})R^{6b}$,

$-S(=O)(=NR^{6c})R^{6}$;

R^{5} representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, $-(CH_2)_n$-C_2-C_6-alquenilo, $-(CH_2)_n$-C_2-C_6-alquinilo, $-(CH_2)_m$-C_3-C_6-cicloalquilo, $-(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-,arilo- o heteroarilo;

donde dicho grupo C_1-C_6-alquilo-, $-(CH_2)_n$-C_2-C_6-alquenilo, $-(CH_2)_n$-C_2-C_6-alquinilo, $-(CH_2)_m$-C_3-C_6-cicloalquilo, $-(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros, C_4-C_8-cicloalquenilo-, arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos R^{8};

R^{6}, R^{6a}, R^{6b}, R^{6c},

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, C_2-C_6-alquenilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, aril-C_1-C_6-alquilo-, o heteroaril-C_1-C_6-alquilo-;

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO–, –CN, C_1–C_6–alcoxi–, C_1–C_6–alquilo–, halo–C_1–C_6–alquilo–, $R^{6a}(R^{6b})N$–C_1–C_6–alquilo–, HO–C_1–C_6–alquilo–, C_1–C_6–alcoxi–C_1–C_6–alquilo–, halo–C_1–C_6–alcoxi–C_1–C_6–alquilo–, C_2–C_6–alquenilo, heterocicloalquilo de entre 3 y 7 miembros–, arilo–, heteroarilo–, –C(=O)R^6, –C(=O)N(H)R^{6a}, –C(=O)N(R^{6a})R^{6b}, –C(=O)O–R^6, –N(R^{6a})R^{6b}, –NO_2, –N(H)C(=O)R^6, –N(R^{6c})C(=O)R^6, –N(H)C(=O)N(R^{6a})R^{6b}, –N(R^{6c})C(=O)N(R^{6a})R^{6b}, –N(H)C(=O)OR^6, –N(R^{6c})C(=O)OR^6, –N(H)S(=O)R^6, –N(R^{6c})S(=O)R^6, –N(H)S(=O)$_2R^6$, –N(R^{6c})S(=O)$_2R^6$, –N=S(=O)(R^{6a})R^{6b}, –OR^6, –O(C=O)R^6, –O(C=O)N(R^{6a})R^{6b}, –O(C=O)OR^6, –SR^6, –S(=O)R^6, –S(=O)N(H)R^6, –S(=O)N(R^{6a})R^{6b}, –S(=O)$_2R^6$, –S(=O)$_2$N(H)R^6, –S(=O)$_2$N(R^{6a})R^{6b}, –S(=O)(=NR^{6c})R^6;

donde dicho grupo C_1–C_6–alcoxi–, arilo– o heteroarilo– está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2 o 3 grupos C_1–C_6–alquilo–, C_1–C_6–alcoxi–, halo–C_1–C_6–alcoxi–, –C(=O)O–R^6 o –OH;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo, donde dichos 2 grupos R^7 juntos forman un puente:

O(CH_2)$_2$O, *O(CH_2)O*, *NH(C(=O))NH*, donde * representa el punto de unión a dicho anillo arilo;

R^8 representa un átomo de hidrógeno o halógeno, o un grupo –CN, C_1–C_6–alcoxi–, C_1–C_6–alquilo–, halo–C_1–C_6–alquilo–, $R^{6a}(R^{6b})N$–C_1–C_6–alquilo–, HO–C_1–C_6–alquilo, C_1–C_6–alcoxi–C_1–C_6–

alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$, $-S(=O)_2$-(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho heterocicloalquilo- o heteroarilo- de entre 3 y 7 miembros está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos C_1-C_6 alquilo-;

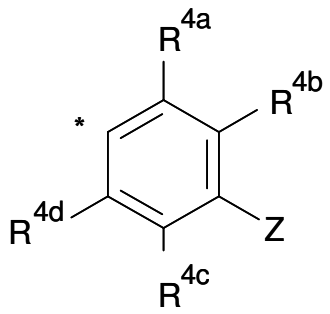
m es el entero 0, 1, 2, 3, 4, 5 o 6;

n es el entero 0, 1, 2, 3, 4 o 5;

X es S, S(=O), $S(=O)_2$, O, NR^6;

o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato o una sal de los mismos, o una mezcla de los mismos.

En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula general I, como se ha definido, donde:

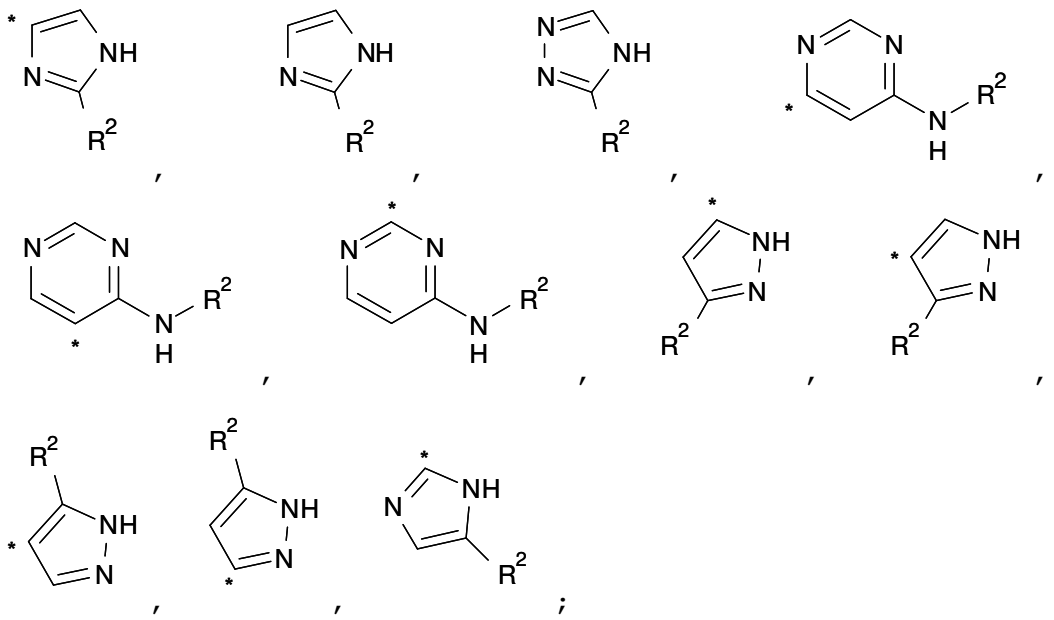


A representa un grupo –;

donde * indica el punto de unión de dichos grupos con el resto de la molécula;

Z representa un grupo $-C(=O)N(H)R^2$ o $-C(=S)N(H)R^2$,

o un grupo seleccionado entre



donde * indica el punto de unión de dichos grupos con el resto de la molécula;

R^2 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, C_2-C_6-

alquinilo– o C_3–C_6–cicloalquilo–;

donde dicho grupo C_3–C_6–cicloalquilo– está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 – grupos seleccionados entre: halógeno, OH, –CN, C_1–C_6–alquilo, –C_1–C_6–alcoxi, halo–C_1–C_6–alquilo–;

R^3 representa un átomo de hidrógeno o un átomo de halógeno, o un grupo –CN, C_1–C_6–alquilo–, –C_1–C_6–alcoxi, –$(CH_2)_m$–C_2–C_6–alquenilo, –$(CH_2)_m$–C_4–C_8–cicloalquenilo –$(CH_2)_m$–C_2–C_6–alquinilo, –$(CH_2)_m$–C_3–C_6–cicloalquilo, –$(CH_2)_m$–(heterocicloalquilo de entre 3 y 7 miembros), –$(CH_2)_m$–(heterocicloalquenilo de entre 4 y 8 miembros), aril–C_1–C_6–alquilo–, heteroaril–C_1–C_6–alquilo–, halo–C_1–C_6–alquilo–, $R^{6a}(R^{6b})N$–C_1–C_6–alquilo–, halo–C_1–C_6–alcoxi–C_1–C_6–alquilo–, C_3–C_6–cicloalquilo–, heterocicloalquilo de entre 3 y 7 miembros–, C_2–C_6–alquenilo–, C_4–C_8–cicloalquenilo–, C_2–C_6–alquinilo–, arilo–, –C_1–C_6–alquil–arilo, –C_1–C_6–alquil–heteroarilo, heteroarilo–, C_1–C_6–alquil–X–, –X–$(CH_2)_m$–C_2–C_6–alquenilo, –X–$(CH_2)_m$–C_4–C_8–cicloalquenilo, –X–$(CH_2)_m$–C_2–C_6–alquinilo, –X–$(CH_2)_m$–C_3–C_6–cicloalquilo, –X–$(CH_2)_m$–(heterocicloalquilo de entre 3 y 7 miembros), –X–$(CH_2)_m$–(heterocicloalquenilo de entre 4 y 8 miembros), aril–X–, heteroaril–X–, $–C(=O)R^6$, $–C(=O)N(H)R^{6a}$, $–C(=O)N(R^{6a})R^{6b}$, $–C(=O)O–R^6$, $–N(R^{6a})R^{6b}$, $–NO_2$, $–N(H)C(=O)R^6$, $–OR^6$, $–SR^6$, $–S(=O)R^6$, $–S(=O)_2R^6$, $–S(=O)(=NR^{6a})R^{6b}$, $–S(=O)_2N(R^{6b})R^{6c}$, –S–$(CH_2)_n$–$N(R^{6a})R^{6b}$, o –S–$(CH_2)_n$–(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho grupo C_1–C_6–alquilo–, –C_1–C_6–alcoxi, –$(CH_2)_m$–C_2–

C_6-alquenilo, $-(CH_2)_m-C_2-C_6$-alquinilo, $-(CH_2)_m-C_3-C_6$-cicloalquilo, aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo-, C_1-C_6-alquil-X-, $-X-(CH_2)_m-C_2-C_6$-alquenilo, $-X-(CH_2)_m-C_4-C_8$-cicloalquenilo, $-X-(CH_2)_m-C_2-C_6$-alquinilo, $-X-(CH_2)_m-C_3-C_6$-cicloalquilo, $-X-(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), $-X-(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-X-, heteroaril-X-, $-C_1-C_6$-alquil-arilo, $-C_1-C_6$-alquil-heteroarilo o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, 4 o 5 grupos R^7;

R^{4a}, R^{4c}, R^{4d} representan un átomo de hidrógeno, y

R^{4b} representa un átomo de hidrógeno o un átomo de halógeno o un grupo C_1-C_6-alquilo;

o

R^{4b}, R^{4c}, R^{4d} representan un átomo de hidrógeno, y

R^{4a} representa un átomo de halógeno o un grupo C_1-C_6-alquilo-, o $-OR^6$ $O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$,

$-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^{6a}$, $-S(=O)_2N(R^{6a})R^{6b}$,

$-S(=O)(=NR^{6c})R^6$;

R^5 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), arilo- o heteroarilo;

donde dicho C_1-C_6-alquilo-, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos R^8;

R^6, R^{6a}, R^{6b}, R^{6c},

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, C_2-C_6-alquenilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, aril-C_1-C_6-alquilo-, o heteroaril-C_1-C_6-alquilo-;

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2R^6$, -N(R^{6c})S(=O)$_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -S(=O)$_2R^6$, -S(=O)$_2$N(H)R^6, -S(=O)$_2$N(R^{6a})R^{6b}, -S(=O)(=NR^{6c})R^6;

donde dicho grupo C_1-C_6-alcoxi-, arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, o 3 grupos C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alcoxi-, -C(=O)O-R^6 o -OH;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo, donde dichos 2 grupos R^7 juntos forman un puente:

O$(CH_2)_2$O, *O(CH_2)O*, *NH(C(=O))NH*, donde * representa el punto de unión a dicho anillo arilo;

R^8 representa un átomo de hidrógeno o halógeno, o un grupo -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})$N-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2R^6$, -N(R^{6c})S(=O)$_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -S(=O)$_2R^6$, -S(=O)$_2$N(H)R^6, -S(=O)$_2$N(R^{6a})R^{6b}, -S(=O)(=NR^{6c})R^6, -S(=O)$_2$-(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho heterocicloalquilo- o heteroarilo- de entre 3 y 7 miembros está opcionalmente sustituido, en forma idéntica

o diferente, con 1, 2, 3, o 4 grupos C_1-C_6 alquilo-;

m es el entero 0, 1, 2, 3, 4, 5 o 6;

n es el entero 0, 1, 2, 3, 4 o 5;

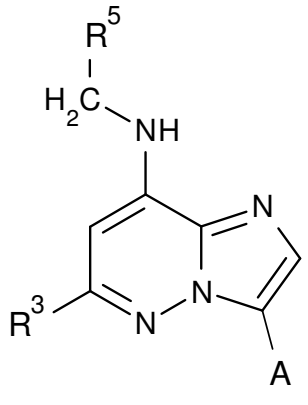
X es S, S(=O), $S(=O)_2$, O, NR^6;

o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato o una sal de los mismos, o una mezcla de los mismos.

WO 2011/013729A1 describe los valores de IC50 values para la inhibición de Mps-1 (TTK) para un par de compuestos de fórmula C1, como se ha definido. Sin embargo, WO 2011/013729A1 no describe ninguna información sobre la estabilidad metabólica de los compuestos.

Los autores de la presente invención han observado en forma sorprendente que los compuestos de fórmula general I, como se ha definido, en donde R^3 es un grupo aril-X- o heteroaril-X-, y en donde al menos uno de los grupos R^{4c} y R^{4b} no es un átomo de hidrógeno muestran una alta actividad inhibitoria así como también una alta estabilidad metabólica.

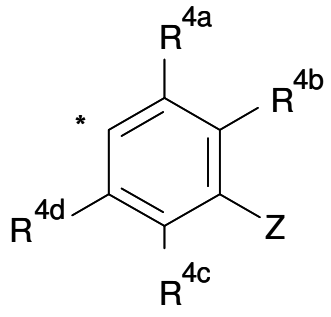
Por lo tanto, en otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula general I:



I

donde:

A representa



;

donde * indica el punto de unión de dichos grupos con el resto de la molécula;

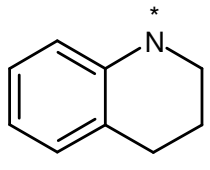
Z representa un grupo $-C(=O)N(H)R^2$ o un grupo $-C(=S)N(H)R^2$;

R^2 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo- o C_3-C_6-cicloalquilo-;

donde dicho grupo C_1-C_6-alquilo- o C_3-C_6-cicloalquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos seleccionados entre:

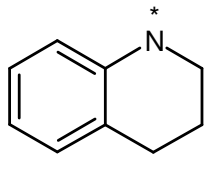
halógeno, -OH, -CN, $-C_1$-C_6-alquilo, $-C_1$-C_6-alcoxi;

R^3 representa un grupo aril–X– o heteroaril–X–, o un grupo



, en donde * indica el punto de unión de dicho grupo con el resto de la molécula;

donde dicho aril–X–, heteroaril–X– o



está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, 4 o 5 grupos R^7;

R^{4a}, R^{4b}, R^{4c}, R^{4d}

representan, en forma independiente entre sí, un átomo de hidrógeno o halógeno, o un grupo –CN, –OH, C_1–C_6–alquilo–, C_1–C_6–alcoxi–, halo–C_1–C_6–alquilo–, halo–C_1–C_6–alcoxi–, $R^{6a}(R^{6b})$N–C_1–C_6–alquilo–, HO–C_1–C_6–alquilo–, NC–C_1–C_6–alquilo–, C_1–C_6–alcoxi–C_1–C_6–alquilo–, halo–C_1–C_6–alcoxi–C_1–C_6–alquilo–;

con la condición de que al menos uno de los grupos R^{4b} y R^{4c} no es un átomo de hidrógeno;

R^5 representa un átomo de hidrógeno, o un grupo C_1–C_6–alquilo–, –$(CH_2)_n$–C_2–C_6–alquenilo, –$(CH_2)_n$–C_2–C_6–alquinilo, –$(CH_2)_m$–C_3–C_6–cicloalquilo, –$(CH_2)_m$–(heterocicloalquilo de entre 3 y 7 miembros), aril–C_1–C_6–alquilo–, heteroaril–C_1–C_6–alquilo–, halo–C_1–C_6–alquilo–, $R^{6a}(R^{6b})$N–C_1–C_6–alquilo–, HO–C_1–C_6–alquilo–, –C_1–C_6–alquil–CN, C_1–C_6–alcoxi–C_1–C_6–alquilo–,

halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo- o heteroarilo-;

donde dicho C_1-C_6-alquilo-, -$(CH_2)_n$-C_2-C_6-alquenilo, -$(CH_2)_n$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros, C_4-C_8-cicloalquenilo-, arilo- o heteroarilo-

está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos R^8;

R^6, R^{6a}, R^{6b}, R^{6c},

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1-C_6-alquilo, HO-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros, arilo, heteroarilo, aril-C_1-C_6-alquilo-, o heteroaril-C_1-C_6-alquilo-;

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, H_2N-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros, arilo-, heteroarilo-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -

$C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, o $-S(=O)(=NR^{6c})R^6$;

donde dicho grupo C_1-C_6-alcoxi-, arilo-, heterocicloalquilo o heteroarilo de entre 3 y 7 miembros está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, o 3 grupos C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alcoxi-, $-C(=O)O-R^6$ o $-OH$;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo o heteroarilo, donde dichos 2 grupos R^7 juntos forman un puente:

$*O(CH_2)_2O*$, $*O(CH_2)O*$, $*CH_2(CH_2)_2NH*$, $*CH_2CH_2N(R^{6a})CH_2*$, *NH(C(=O))NH*, *C(H)=C(H)-C(=O)-N(H)*,

donde * representa el punto de unión a dicho anillo arilo o heteroarilo;

R^8 representa un átomo de hidrógeno o halógeno, o un grupo -CN, $-OH$, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, -

C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2$$R^6$, -N($R^{6c}$)S(=O)$_2$$R^6$, -N=S(=O)($R^{6a}$)$R^{6b}$, -O$R^6$, -O(C=O)$R^6$, -O(C=O)N($R^{6a}$)$R^{6b}$, -O(C=O)O$R^6$, -S$R^6$, -S(=O)$R^6$, -S(=O)N(H)$R^6$, -S(=O)N($R^{6a}$)$R^{6b}$, -S(=O)$_2$$R^6$, -S(=O)$_2$OH, -S(=O)$_2$N(H)$R^6$, -S(=O)$_2$N($R^{6a}$)$R^{6b}$, -S(=O)(=N$R^{6c}$)$R^6$, -S(=O)$_2$-(heterocicloalquilo de entre 3 y 7 miembros);

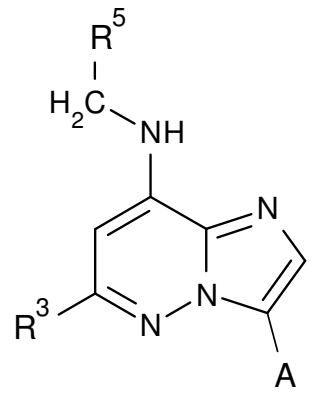
donde dicho heterocicloalquilo- o heteroarilo- de entre 3 y 7 miembros está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos C_1-C_6 alquilo-;

m es el entero 0, 1, 2, 3, 4, 5 o 6;

n es el entero 0, 1, 2, 3, 4 o 5; y

X es S, S(=O), S(=O)$_2$, O, NR^6, C$R^{6a}$$R^{6b}$, C=C$R^{6a}$$R^{6b}$.

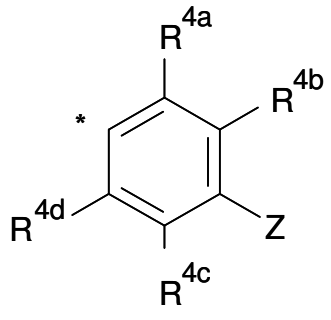
En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I



I

donde:

A representa



;

donde * indica el punto de unión de dichos grupos con el resto de la molécula;

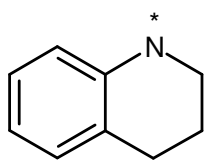
Z representa un grupo $-C(=O)N(H)R^2$ o un grupo $-C(=S)N(H)R^2$;

R^2 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo- o C_3-C_6-cicloalquilo-;

donde dicho grupo C_1-C_6-alquilo- o C_3-C_6-cicloalquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos seleccionados entre:

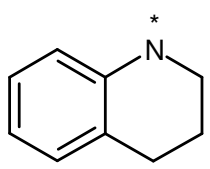
halógeno, -OH, -CN, $-C_1$-C_6-alquilo, $-C_1$-C_6-alcoxi;

R^3 representa un grupo aril-X- o heteroaril-X-, o un grupo



, en donde * indica el punto de unión de dicho grupo con el resto de la molécula;

donde dicho aril-X-, heteroaril-X- o



está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, 4 o 5 grupos R^7;

R^{4a} representa hidrógeno;

R^{4d} representa hidrógeno;

uno de los grupos R^{4b} y R^{4c} representa un átomo de hidrógeno mientras que el otro representa un grupo seleccionado entre: halo-, -CN, -OH, C_1-C_6-alquilo- y C_1-C_6-alcoxi-;

R^5 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, -$(CH_2)_n$-C_2-C_6-alquenilo, -$(CH_2)_n$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})$N-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo- o heteroarilo-;

donde dicho C_1-C_6-alquilo-, -$(CH_2)_n$-C_2-C_6-alquenilo, -$(CH_2)_n$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})$N-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros, C_4-C_8-cicloalquenilo-, arilo- o heteroarilo-

está opcionalmente sustituido, en forma idéntica o

diferente, con 1, 2, 3, o 4 grupos R^8;

R^6, R^{6a}, R^{6b}, R^{6c},

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1-C_6-alquilo, HO-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros, arilo, heteroarilo, aril-C_1-C_6-alquilo-, o heteroaril-C_1-C_6-alquilo-;

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, H_2N-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, o $-S(=O)(=NR^{6c})R^6$;

donde dicho grupo C_1-C_6-alcoxi-, arilo-, heterocicloalquilo o heteroarilo de entre 3 y 7 miembros está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, o 3 grupos C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alcoxi-, $-C(=O)O-R^6$ o -OH;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo o heteroarilo, donde dichos 2 grupos R^7 juntos forman un puente:

O(CH$_2$)$_2$O, *O(CH$_2$)O*, *CH$_2$(CH$_2$)$_2$NH*, *CH$_2$CH$_2$N(R^{6a})CH$_2$*, *NH(C(=O))NH*, *C(H)=C(H)-C(=O)-N(H)*,

donde * representa el punto de unión a dicho anillo arilo o heteroarilo;

R^8 representa un átomo de hidrógeno o halógeno, o un grupo -CN, -OH, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})$N-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros, arilo-, heteroarilo-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2$$R^6$, -N($R^{6c}$)S(=O)$_2$$R^6$, -N=S(=O)($R^{6a}$)$R^{6b}$, -O$R^6$, -O(C=O)$R^6$, -O(C=O)N($R^{6a}$)$R^{6b}$, -O(C=O)O$R^6$, -S$R^6$, -S(=O)$R^6$, -S(=O)N(H)$R^6$, -S(=O)N($R^{6a}$)$R^{6b}$, -S(=O)$_2$$R^6$, -S(=O)$_2$OH, -S(=O)$_2$N(H)$R^6$, -S(=O)$_2$N($R^{6a}$)$R^{6b}$, -S(=O)(=N$R^{6c}$)$R^6$, -S(=O)$_2$-(heterocicloalquilo de entre 3 y 7 miembros);

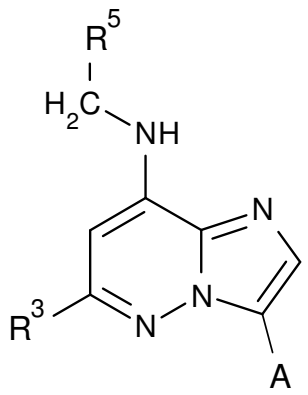
donde dicho heterocicloalquilo- o heteroarilo- de entre 3 y 7 miembros está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos C_1-C_6 alquilo-;

m es el entero 0, 1, 2, 3, 4, 5 o 6;

n es el entero 0, 1, 2, 3, 4 o 5; y

X es S, S(=O), $S(=O)_2$, O, NR^6, $CR^{6a}R^{6b}$, $C=CR^{6a}R^{6b}$.

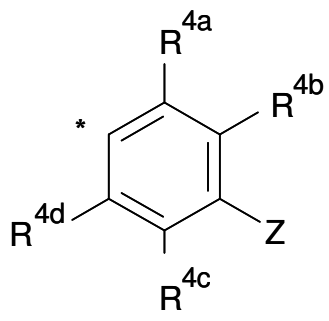
En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I



I

donde:

A representa



;

donde * indica el punto de unión de dichos grupos con el resto de la molécula;

Z representa un grupo $-C(=O)N(H)R^2$ o un grupo $-C(=S)N(H)R^2$;

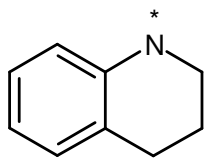
R^2 representa un grupo C_1-C_3-alquilo- o C_3-C_6-cicloalquilo-;

donde dicho grupo C_1-C_3-alquilo- o C_3-C_6-cicloalquilo- está opcionalmente sustituido, en forma idéntica o diferente,

con 1, 2 o 3 grupos seleccionados entre:

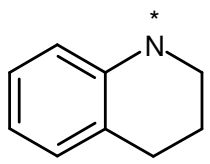
halógeno, –OH, –CN, $-C_1-C_6$-alquilo, $-C_1-C_6$-alcoxi;

R^3 representa un grupo aril–X– o heteroaril–X–, o un grupo



, en donde * indica el punto de unión de dicho grupo con el resto de la molécula;

donde dicho aril–X–, heteroaril–X– o



está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, 4 o 5 grupos R^7;

R^{4a} representa hidrógeno;

R^{4d} representa hidrógeno;

uno de los grupos R^{4b} y R^{4c} representa un átomo de hidrógeno mientras que el otro representa un grupo seleccionado entre: halo–, –CN, –OH, C_1-C_6-alquilo– y C_1-C_6-alcoxi–;

R^5 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo–, $-(CH_2)_n-C_2-C_6$-alquenilo, $-(CH_2)_n-C_2-C_6$-alquinilo, $-(CH_2)_m-C_3-C_6$-cicloalquilo, $-(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril–C_1-C_6-alquilo–, heteroaril–C_1-C_6-alquilo–, halo–C_1-C_6-alquilo–, $R^{6a}(R^{6b})N-C_1-C_6$-alquilo–, HO–C_1-C_6-alquilo–, $-C_1-C_6$-alquil–CN, C_1-C_6-alcoxi–C_1-C_6-alquilo–,

halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo- o heteroarilo-;

donde dicho C_1-C_6-alquilo-, -$(CH_2)_n$-C_2-C_6-alquenilo, -$(CH_2)_n$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros, C_4-C_8-cicloalquenilo-, arilo- o heteroarilo-

está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos R^8;

R^6, R^{6a}, R^{6b}, R^{6c},

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1-C_6-alquilo, HO-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros, arilo, heteroarilo, aril-C_1-C_6-alquilo-, o heteroaril-C_1-C_6-alquilo-;

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, H_2N-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros, arilo-, heteroarilo-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -

$C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, o $-S(=O)(=NR^{6c})R^6$;

donde dicho grupo C_1-C_6-alcoxi-, arilo-, heterocicloalquilo o heteroarilo de entre 3 y 7 miembros está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, o 3 grupos C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alcoxi-, $-C(=O)O-R^6$ o $-OH$;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo o heteroarilo, donde dichos 2 grupos R^7 juntos forman un puente:

$*O(CH_2)_2O*$, $*O(CH_2)O*$, $*CH_2(CH_2)_2NH*$, $*CH_2CH_2N(R^{6a})CH_2*$, $*NH(C(=O))NH*$, $*C(H)=C(H)-C(=O)-N(H)*$,

donde * representa el punto de unión a dicho anillo arilo o heteroarilo;

R^8 representa un átomo de hidrógeno o halógeno, o un grupo -CN, $-OH$, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, -

C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2R^6$, -N(R^{6c})S(=O)$_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -S(=O)$_2R^6$, -S(=O)$_2$OH, -S(=O)$_2$N(H)R^6, -S(=O)$_2$N(R^{6a})R^{6b}, -S(=O)(=NR^{6c})R^6, -S(=O)$_2$-(heterocicloalquilo de entre 3 y 7 miembros);

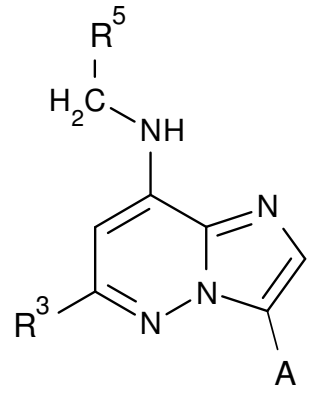
donde dicho heterocicloalquilo- o heteroarilo- de entre 3 y 7 miembros está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos C_1-C_6 alquilo-;

m es el entero 0, 1, 2, 3, 4, 5 o 6;

n es el entero 0, 1, 2, 3, 4 o 5; y

X es S, S(=O), S(=O)$_2$, O, NR^6, C$R^{6a}R^{6b}$, C=C$R^{6a}R^{6b}$.

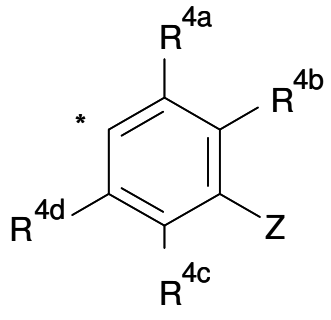
En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I



I

donde:

A representa



;

donde * indica el punto de unión de dichos grupos con el resto de la molécula;

Z representa un grupo $-C(=O)N(H)R^2$ o un grupo $-C(=S)N(H)R^2$;

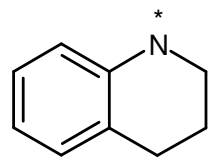
R^2 representa un grupo C_1-C_3-alquilo- o C_3-C_6-cicloalquilo-;

donde dicho grupo C_1-C_3-alquilo- o C_3-C_6-cicloalquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2 o 3 grupos seleccionados entre:

halógeno, -OH, -CN, $-C_1$-C_6-alquilo, $-C_1$-C_6-alcoxi;

R^3 representa un grupo seleccionado entre:

fenil-X, quinolinil-X-, piridil-X-, tienil-X-, pirazinil-X-, imidazil-X-, triazil-X-, pirazil-X- y



;

donde dicho grupo está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, 4 o 5 grupos R^7;

R^{4a} representa hidrógeno;

R^{4d} representa hidrógeno;

uno de los grupos R^{4b} y R^{4c} representa un átomo de hidrógeno mientras que el otro representa halo- o un grupo C_1-C_6-alquilo-;

R^5 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, -$(CH_2)_n$-C_2-C_6-alquenilo, -$(CH_2)_n$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})$N-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo- o heteroarilo-;

donde dicho C_1-C_6-alquilo-, -$(CH_2)_n$-C_2-C_6-alquenilo, -$(CH_2)_n$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})$N-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros, C_4-C_8-cicloalquenilo-, arilo- o heteroarilo-

está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos R^8;

R^6, R^{6a}, R^{6b}, R^{6c}

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1-C_6-alquilo, HO-C_1-C_6-alquilo-, C_3-

C_6-cicloalquilo, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros, arilo, heteroarilo, aril-C_1-C_6-alquilo-, o heteroaril-C_1-C_6-alquilo-;

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, H_2N-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, o $-S(=O)(=NR^{6c})R^6$;

donde dicho grupo C_1-C_6-alcoxi-, arilo-, heterocicloalquilo o heteroarilo de entre 3 y 7 miembros está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, o 3 grupos C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alcoxi-, $-C(=O)O-R^6$ o -OH;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo o heteroarilo, donde dichos 2 grupos R^7 juntos forman un puente:

$*O(CH_2)_2O*$, $*O(CH_2)O*$, $*CH_2(CH_2)_2NH*$, $*CH_2CH_2N(R^{6a})CH_2*$,

NH(C(=O))NH, *C(H)=C(H)-C(=O)-N(H)*,

donde * representa el punto de unión a dicho anillo arilo o heteroarilo;

R^8 representa un átomo de hidrógeno o halógeno, o un grupo -CN, -OH, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2OH$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$, $-S(=O)_2$-(heterocicloalquilo de entre 3 y 7 miembros);

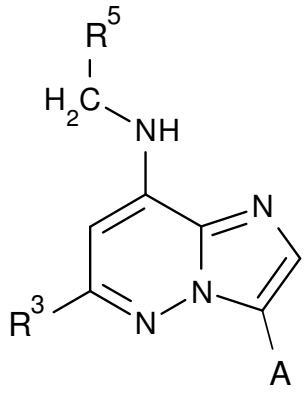
donde dicho heterocicloalquilo- o heteroarilo- de entre 3 y 7 miembros está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos C_1-C_6 alquilo-;

m es el entero 0, 1, 2, 3, 4, 5 o 6;

n es el entero 0, 1, 2, 3, 4 o 5; y

X es S, S(=O), $S(=O)_2$, O, NR^6, $CR^{6a}R^{6b}$, $C=CR^{6a}R^{6b}$.

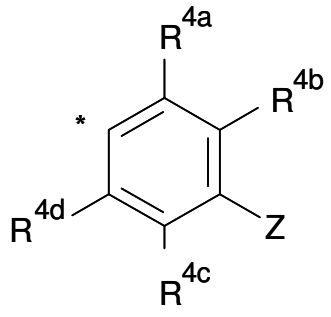
En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I



I

donde:

A representa



;

donde * indica el punto de unión de dichos grupos con el resto de la molécula;

Z representa un grupo $-C(=O)N(H)R^2$ o un grupo $-C(=S)N(H)R^2$;

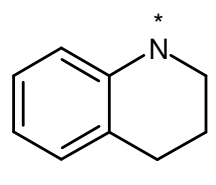
R^2 representa un grupo C_1-C_3-alquilo- o C_3-C_6-cicloalquilo-;

donde dicho grupo C_1-C_3-alquilo- o C_3-C_6-cicloalquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2 o 3 grupos seleccionados entre:

halógeno, -OH, -CN, $-C_1$-C_6-alquilo, $-C_1$-C_6-alcoxi;

R^3 representa un grupo seleccionado entre:

fenil–X, quinolinil–X–, piridil–X–, tienil–X–, pirazinil–X–, imidazil–X–, triazil–X–, pirazil–X– y



;

donde dicho grupo está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, 4 o 5 grupos R^7;

R^{4a} representa hidrógeno;

R^{4d} representa hidrógeno;

uno de los grupos R^{4b} y R^{4c} representa un átomo de hidrógeno mientras que el otro representa un grupo C_1–C_4–alquilo–;

R^5 representa un átomo de hidrógeno, o un grupo C_1–C_6–alquilo–, halo–C_1–C_6–alquilo–, HO–C_1–C_6–alquilo–, C_3–C_6–cicloalquilo–, heterocicloalquilo o heteroarilo de entre 3 y 7 miembros;

donde dicho C_1–C_6–alquilo–, halo–C_1–C_6–alquilo–, HO–C_1–C_6–alquilo–,, C_3–C_6–cicloalquilo–, heterocicloalquilo de entre 3 y 7 miembros, heteroarilo– está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos R^8;

R^6, R^{6a}, R^{6b}, R^{6c},

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1–C_6–alquilo, HO–C_1–C_6–alquilo–, C_3–C_6–cicloalquilo, C_2–C_6–alquenilo, heterocicloalquilo de entre 3 y 7 miembros, arilo, heteroarilo, aril–C_1–C_6–

alquilo-, o heteroaril-C_1-C_6-alquilo-;

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, H_2N-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, o $-S(=O)(=NR^{6c})R^6$;

donde dicho grupo C_1-C_6-alcoxi-, arilo-, heterocicloalquilo o heteroarilo de entre 3 y 7 miembros está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, o 3 grupos C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alcoxi-, $-C(=O)O-R^6$ o -OH;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo o heteroarilo, donde dichos 2 grupos R^7 juntos forman un puente:

$*O(CH_2)_2O*$, $*O(CH_2)O*$, $*CH_2(CH_2)_2NH*$, $*CH_2CH_2N(R^{6a})CH_2*$, *NH(C(=O))NH*, *C(H)=C(H)-C(=O)-N(H)*,

donde * representa el punto de unión a dicho anillo arilo o

heteroarilo;

R^8 representa un átomo de hidrógeno o halógeno, o un grupo -CN, -OH, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2OH$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$, $-S(=O)_2$-(heterocicloalquilo de entre 3 y 7 miembros);

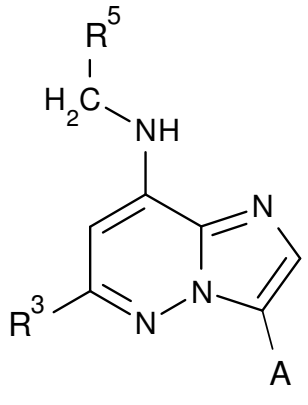
donde dicho heterocicloalquilo- o heteroarilo- de entre 3 y 7 miembros está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos C_1-C_6 alquilo-;

m es el entero 0, 1, 2, 3, 4, 5 o 6;

n es el entero 0, 1, 2, 3, 4 o 5; y

X es S, S(=O), $S(=O)_2$, O, NR^6, $CR^{6a}R^{6b}$, $C=CR^{6a}R^{6b}$.

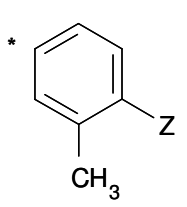
En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I



I

donde:

A representa un grupo



;

donde * indica el punto de unión de dichos grupos con el resto de la molécula;

Z representa un grupo $-C(=O)N(H)R^2$ o un grupo $-C(=S)N(H)R^2$;

R^2 representa un grupo C_1-C_3-alquilo- o C_3-C_6-cicloalquilo-;

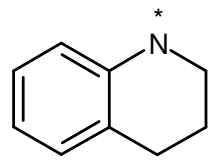
donde dicho grupo C_1-C_3-alquilo- o C_3-C_6-cicloalquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2 o 3 grupos seleccionados entre:

halógeno, -OH, -CN, $-C_1$-C_6-alquilo, $-C_1$-C_6-alcoxi;

R^3 representa un grupo seleccionado entre:

fenil-X, quinolinil-X-, piridil-X-, tienil-X-, pirazinil-X-

, imidazil-X-, triazil-X-, pirazil-X- y



;

donde dicho grupo está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, 4 o 5 grupos R^7;

R^5 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo o heteroarilo de entre 3 y 7 miembros;

donde dicho C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-,, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros, heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos R^8;

R^6, R^{6a}, R^{6b}, R^{6c},

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1-C_6-alquilo, HO-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros, arilo, heteroarilo, aril-C_1-C_6-alquilo-, o heteroaril-C_1-C_6-alquilo-;

R^7 representa un átomo de halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, H_2N-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros, -C(=O)N(H)R^{6a}, -N(R^{6a})R^{6b}, -N(H)C(=O)R^6, o -SR^6;

donde dicho grupo C_1-C_6-alcoxi-, o heterocicloalquilo de

entre 3 y 7 miembros– está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, o 3 grupos C_1–C_6–alquilo–, C_1–C_6–alcoxi–, halo–C_1–C_6–alcoxi–, –C(=O)O–R^6 o –OH;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo o heteroarilo, donde dichos 2 grupos R^7 juntos forman un puente:

$CH_2(CH_2)_2NH$, *$CH_2CH_2N(R^{6a})CH_2$*, *C(H)=C(H)–C(=O)–N(H)*,

donde * representa el punto de unión a dicho anillo arilo o heteroarilo;

R^8 representa un átomo de hidrógeno o halógeno, o un grupo –CN, –OH, C_1–C_6–alcoxi–, C_1–C_6–alquilo–, halo–C_1–C_6–alquilo–, $R^{6a}(R^{6b})N$–C_1–C_6–alquilo–, HO–C_1–C_6–alquilo, C_1–C_6–alcoxi–C_1–C_6–alquilo–, halo–C_1–C_6–alcoxi–C_1–C_6–alquilo–, C_2–C_6–alquenilo, heterocicloalquilo de entre 3 y 7 miembros, arilo–, heteroarilo–, –C(=O)R^6, –C(=O)N(H)R^{6a}, –C(=O)N(R^{6a})R^{6b}, –C(=O)O–R^6, –N(R^{6a})R^{6b}, –NO_2, –N(H)C(=O)R^6, –N(R^{6c})C(=O)R^6, –N(H)C(=O)N(R^{6a})R^{6b}, –N(R^{6c})C(=O)N(R^{6a})R^{6b}, –N(H)C(=O)OR^6, –N(R^{6c})C(=O)OR^6, –N(H)S(=O)R^6, –N(R^{6c})S(=O)R^6, –N(H)$S(=O)_2R^6$, –N(R^{6c})$S(=O)_2R^6$, –N=S(=O)(R^{6a})R^{6b}, –OR^6, –O(C=O)R^6, –O(C=O)N(R^{6a})R^{6b}, –O(C=O)OR^6, –SR^6, –S(=O)R^6, –S(=O)N(H)R^6, –S(=O)N(R^{6a})R^{6b}, –$S(=O)_2R^6$, –$S(=O)_2$OH, –$S(=O)_2$N(H)R^6, –$S(=O)_2$N(R^{6a})R^{6b}, –S(=O)(=NR^{6c})R^6, –$S(=O)_2$–(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho heterocicloalquilo– o heteroarilo– de entre 3 y

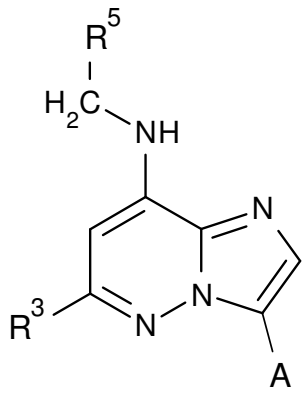
7 miembros está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos C_1-C_6 alquilo-;

m es el entero 0, 1, 2, 3, 4, 5 o 6;

n es el entero 0, 1, 2, 3, 4 o 5; y

X es S, S(=O), $S(=O)_2$, O, NR^6, $CR^{6a}R^{6b}$, $C=CR^{6a}R^{6b}$.

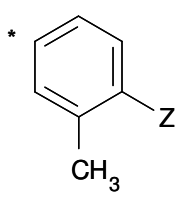
En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I



I

donde:

A representa un grupo



;

donde * indica el punto de unión de dichos grupos con el resto de la molécula;

Z representa un grupo $-C(=O)N(H)R^2$ o un grupo $-C(=S)N(H)R^2$;

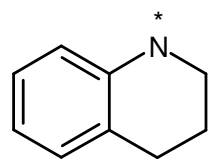
R^2 representa un grupo C_1-C_3-alquilo- o C_3-C_6-cicloalquilo-;

donde dicho grupo C_1-C_3-alquilo- o C_3-C_6-cicloalquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2 o 3 grupos seleccionados entre:

halógeno, -OH, -CN, -C_1-C_6-alquilo, -C_1-C_6-alcoxi;

R^3 representa un grupo seleccionado entre:

fenil-X, quinolinil-X-, piridil-X-, tienil-X-, pirazinil-X-, imidazil-X-, triazil-X-, pirazil-X- y



;

donde dicho grupo está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, 4 o 5 grupos R^7;

R^5 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo o heteroarilo de entre 3 y 7 miembros;

donde dicho C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-,, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros, heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos R^8;

R^6, R^{6a}, R^{6b}, R^{6c},

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-;

R^7 representa un átomo de halógeno, o un grupo HO-, -CN, C_1-C_6-

alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, H_2N-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros, -C(=O)N(H)R^{6a}, -N(R^{6a})R^{6b}, -N(H)C(=O)R^6, o -SR^6;

donde dicho grupo C_1-C_6-alcoxi-, o heterocicloalquilo de entre 3 y 7 miembros- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, o 3 grupos C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alcoxi-, -C(=O)O-R^6 o -OH;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo o heteroarilo, donde dichos 2 grupos R^7 juntos forman un puente:

$CH_2(CH_2)_2NH$, *$CH_2CH_2N(R^{6a})CH_2$*, *C(H)=C(H)-C(=O)-N(H)*,

donde * representa el punto de unión a dicho anillo arilo o heteroarilo;

R^8 representa un átomo de hidrógeno o halógeno, o un grupo -CN, -OH, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros, arilo-, heteroarilo-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2R^6$, -N(R^{6c})S(=O)$_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -

$O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^{6}$, $-SR^{6}$, $-S(=O)R^{6}$, $-S(=O)N(H)R^{6}$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^{6}$, $-S(=O)_2OH$, $-S(=O)_2N(H)R^{6}$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^{6}$, $-S(=O)_2$-(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho heterocicloalquilo- o heteroarilo- de entre 3 y 7 miembros está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos C_1-C_6 alquilo-;

m es el entero 0, 1, 2, 3, 4, 5 o 6;

n es el entero 0, 1, 2, 3, 4 o 5; y

X es S, S(=O), $S(=O)_2$, O, NR^{6}, $CR^{6a}R^{6b}$, $C=CR^{6a}R^{6b}$.

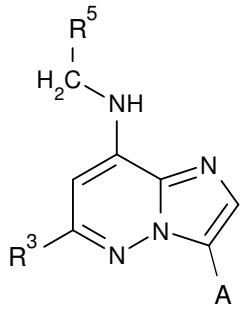
WO 2011/013729 A1 señala que los compuestos de fórmula C1, como se ha definido, en donde R^{8} representa un grupo ciclopropilo, son preferibles porque tienen tendencia a mostrar mayor actividad de inhibición Mps-1 que los compuestos de fórmula C1 en donde R^{8} no representa un grupo ciclopropilo.

Los autores de la presente invención han observado de manera sorprendente que los compuestos de fórmula C1 en donde R^{8} es un grupo no cíclico en lugar de un grupo cicloalquilo muestran una mayor estabilidad metabólica. Los autores de la presente invención han observado de manera soprendente que los compuestos de fórmula C1 muestran un efecto inhibitorio especialmente alto sobre la quinasa Mps-1 si R^{6} representa un grupo aril-X- o heteroaril-X- en donde X se define como para los compuestos de fórmula I, como se ha definido.

Por lo tanto la combinación en la que R^{8} es un grupo no cíclico y R^{6} es un grupo aril-X- o heteroaril-X-, resulta

en compuestos con propiedades inhibitorias y metbólicas superiores.

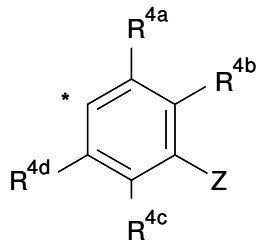
Por lo tanto, en otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula I



I

donde:

A representa



donde * indica el punto de unión de dicho grupo con el resto de la molécula;

Z representa un grupo $-C(=O)N(H)R^2$ o $-C(=S)N(H)R^2$;

R^2 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-;

donde dicho grupo C_1-C_6-alquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos seleccionados entre: halógeno, -OH, -CN, C_1-C_6-alquilo-, C_1-C_6-alcoxi-;

R^3 representa un grupo aril–X– o heteroaril–X–, donde dicho aril–X– o heteroaril–X– está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, 4 o 5 grupos R^7;

R^{4a}, R^{4b}, R^{4c}, R^{4d}

representan, en forma independiente entre sí, un átomo de hidrógeno o halógeno, o un grupo –CN, C_1–C_6–alquilo–, C_1–C_6–alcoxi–, halo–C_1–C_6–alquilo–, halo–C_1–C_6–alcoxi–, $R^{6a}(R^{6b})N$–C_1–C_6–alquilo–, HO–C_1–C_6–alquilo–, NC–C_1–C_6–alquilo–, C_1–C_6–alcoxi–C_1–C_6–alquilo–, halo–C_1–C_6–alcoxi–C_1–C_6–alquilo–;

R^5 representa un átomo de hidrógeno, o un grupo C_1–C_6–alquilo–, $-(CH_2)_n$–C_2–C_6–alquenilo, $-(CH_2)_n$–C_2–C_6–alquinilo, $-(CH_2)_m$–C_3–C_6–cicloalquilo, $-(CH_2)_m$–(heterocicloalquilo de entre 3 y 7 miembros), aril–C_1–C_6–alquilo–, heteroaril–C_1–C_6–alquilo–, halo–C_1–C_6–alquilo–, $R^{6a}(R^{6b})N$–C_1–C_6–alquilo–, HO–C_1–C_6–alquilo–, –C_1–C_6–alquil–CN, C_1–C_6–alcoxi–C_1–C_6–alquilo–, halo–C_1–C_6–alcoxi–C_1–C_6–alquilo–, C_3–C_6–cicloalquilo–, heterocicloalquilo de entre 3 y 7 miembros–, C_4–C_8–cicloalquenilo–, arilo– o heteroarilo–;

donde dicho C_1–C_6–alquilo–, $-(CH_2)_n$–C_2–C_6–alquenilo, $-(CH_2)_n$–C_2–C_6–alquinilo, $-(CH_2)_m$–C_3–C_6–cicloalquilo, $-(CH_2)_m$–(heterocicloalquilo de entre 3 y 7 miembros), aril–C_1–C_6–alquilo–, heteroaril–C_1–C_6–alquilo–, halo–C_1–C_6–alquilo–, $R^{6a}(R^{6b})N$–C_1–C_6–alquilo–, HO–C_1–C_6–alquilo–, –C_1–C_6–alquil–CN, C_1–C_6–alcoxi–C_1–C_6–alquilo–, halo–C_1–C_6–alcoxi–C_1–C_6–alquilo–, C_3–C_6–cicloalquilo–, heterocicloalquilo de entre 3 y 7 miembros–, C_4–C_8–cicloalquenilo–, arilo– o heteroarilo– está opcionalmente sustituido, en forma idéntica o diferente,

con 1, 2, 3, 4 o 5 grupos R^8;

R^6, R^{6a}, R^{6b}, R^{6c},

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, C_2-C_6-alquenilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, aril-C_1-C_6-alquilo- o heteroaril-C_1-C_6-alquilo-;

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, C_2-C_6-alquinilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O2)R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$;

donde dicho arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2 o 3 grupos C_1-C_6 alquilo-;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo- o heteroarilo-, donde dichos 2

grupos R^7 juntos forman un puente:

$O(CH_2)_2O$, *$O(CH_2)O$*, *NH(C(=O))NH*, donde * representa el punto de unión a dicho anillo arilo- o heteroarilo-;

R^8 representa un átomo de hidrógeno o halógeno, o un grupo -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, C_2-C_6-alquinilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O2)R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ o $-S(=O)_2$-(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho heterocicloalquilo- o heteroarilo- de entre 3 y 7 miembros, está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos C_1-C_6 alquilo-

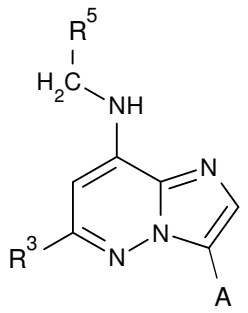
m es el entero 0, 1, 2, 3, 4, 5 o 6;

n es el entero 0, 1, 2, 3, 4 o 5; y

X se selecciona entre: S, S(=O), $S(=O)_2$, O, NR^6, $CR^{6a}R^{6b}$;

o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato o una sal de los mismos, o una mezcla de los mismos.

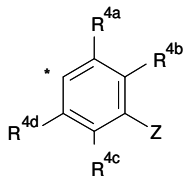
En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula general I:



I

donde:

A representa



donde * indica el punto de unión de dichos grupos con el resto de la molécula;

Z representa un grupo $-C(=O)N(H)R^2$ o $-C(=S)N(H)R^2$;

donde * indica el punto de unión de dichos grupos con el resto de la molécula;

R^2 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-;

donde dicho grupo C_1-C_6-alquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos seleccionados entre: halógeno, OH, -CN, C_1-C_6-alquilo-, C_1-C_6-alcoxi-;

R^3 representa un grupo aril–X– o heteroaril–X–, donde dicho aril–X– o heteroaril–X– está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, 4 o 5 grupos R^7;

R^{4a}, R^{4b}, R^{4c}, R^{4d}

se seleccionan, en forma independiente entre sí, entre hidrógeno, halógeno, –CN, C_1–C_6–alquilo–, C_1–C_6–alcoxi–, halo–C_1–C_6–alquilo–, halo–C_1–C_6–alcoxi–;

R^5 representa un átomo de hidrógeno, o un grupo C_1–C_6–alquilo–, –$(CH_2)_n$–C_2–C_6–alquenilo, –$(CH_2)_n$–C_2–C_6–alquinilo, –$(CH_2)_m$–C_3–C_6–cicloalquilo, –$(CH_2)_m$–(heterocicloalquilo de entre 3 y 7 miembros), aril–C_1–C_6–alquilo–, heteroaril–C_1–C_6–alquilo–, halo–C_1–C_6–alquilo–, $R^{6a}(R^{6b})$N–C_1–C_6–alquilo–, HO–C_1–C_6–alquilo–, –C_1–C_6–alquil–CN, C_1–C_6–alcoxi–C_1–C_6–alquilo–, halo–C_1–C_6–alcoxi–C_1–C_6–alquilo–, C_3–C_6–cicloalquilo–, heterocicloalquilo de entre 3 y 7 miembros–, C_4–C_8–cicloalquenilo–, arilo– o heteroarilo–;

donde dicho C_1–C_6–alquilo–, –$(CH_2)_n$–C_2–C_6–alquenilo, –$(CH_2)_n$–C_2–C_6–alquinilo, –$(CH_2)_m$–C_3–C_6–cicloalquilo, –$(CH_2)_m$–(heterocicloalquilo de entre 3 y 7 miembros), aril–C_1–C_6–alquilo–, heteroaril–C_1–C_6–alquilo–, halo–C_1–C_6–alquilo–, $R^{6a}(R^{6b})$N–C_1–C_6–alquilo–, HO–C_1–C_6–alquilo–, –C_1–C_6–alquil–CN, C_1–C_6–alcoxi–C_1–C_6–alquilo–, halo–C_1–C_6–alcoxi–C_1–C_6–alquilo–, C_3–C_6–cicloalquilo–, heterocicloalquilo de entre 3 y 7 miembros–, C_4–C_8–cicloalquenilo–, arilo– o heteroarilo– está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, 4 o 5 grupos R^8;

R^6, R^{6a}, R^{6b}, R^{6c},

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1–C_6–alquilo–, HO–C_1–C_6–alquilo–, C_3–C_6–cicloalquilo–, C_2–C_6–alquenilo–, heterocicloalquilo de entre 3 y 7 miembros–, arilo–, heteroarilo–, aril–C_1–C_6–alquilo–, o heteroaril–C_1–C_6–alquilo–;

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO–, –CN, C_1–C_6–alcoxi–, C_1–C_6–alquilo–, halo–C_1–C_6–alquilo–, $R^{6a}(R^{6b})$N–C_1–C_6–alquilo–, HO–C_1–C_6–alquilo–, C_1–C_6–alcoxi–C_1–C_6–alquilo–, halo–C_1–C_6–alcoxi–C_1–C_6–alquilo–, C_2–C_6–alquenilo–, C_2–C_6–alquinilo–, heterocicloalquilo de entre 3 y 7 miembros–, arilo–, heteroarilo–, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O2)R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$;

donde dicho arilo– o heteroarilo– está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2 o 3 grupos C_1–C_6 alquilo–;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo– o heteroarilo–, donde dichos 2 grupos R^7 juntos forman un puente:

$O(CH_2)_2O$, *$O(CH_2)O$*, *NH(C(=O))NH*, donde * representa el punto de unión a dicho anillo arilo- o heteroarilo-;

R^8 representa un átomo de hidrógeno o halógeno, o un grupo -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, C_2-C_6-alquinilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$, $-S(=O)_2$-(heterocicloalquilo de entre 3 y 7 miembros);

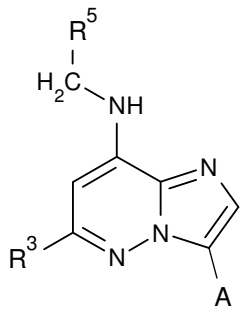
donde dicho heterocicloalquilo- o heteroarilo- de entre 3 y 7 miembros, está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos C_1-C_6 alquilo-;

m es el entero 0, 1, 2, 3, 4, 5 o 6;

n es el entero 0, 1, 2, 3, 4 o 5; y

X es S, S(=O), $S(=O)_2$, O, NR^6 o $CR^{6a}R^{6b}$.

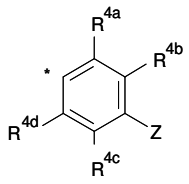
En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula general I:



I

donde:

A representa



donde * indica el punto de unión de dichos grupos con el resto de la molécula;

Z representa un grupo $-C(=O)N(H)R^2$ o $-C(=S)N(H)R^2$;

R^2 representa un grupo C_1-C_4-alquilo-;

donde dicho grupo C_1-C_4-alquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1 o 2 grupos seleccionados entre: halógeno, -OH, -CN, C_1-C_3-alquilo-, C_1-C_4-alcoxi-;

R^3 representa un grupo aril-X- o heteroaril-X-, donde dicho aril-X- o heteroaril-X- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, 4 o 5 grupos R^7;

R^{4a}, R^{4b}, R^{4c}, R^{4d}

se seleccionan, en forma independiente entre sí, entre hidrógeno, halógeno, -CN, C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-;

R^5 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, -$(CH_2)_n$-C_2-C_6-alquenilo, -$(CH_2)_n$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})$N-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_4-C_8-cicloalquenilo-, arilo- o heteroarilo-;

donde dicho C_1-C_6-alquilo-, -$(CH_2)_n$-C_2-C_6-alquenilo, -$(CH_2)_n$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})$N-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_4-C_8-cicloalquenilo-, arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, 4 o 5 grupos R^8;

R^6, R^{6a}, R^{6b}, R^{6c},

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, C_2-C_6-alquenilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, aril-C_1-C_6-

alquilo-, o heteroaril-C_1-C_6-alquilo-;

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, C_2-C_6-alquinilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O2)R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$;

donde dicho arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, o 3 grupos C_1-C_6 alquilo-;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo- o heteroarilo-, donde dichos 2 grupos R^7 juntos forman un puente:

$*O(CH_2)_2O*$, $*O(CH_2)O*$, *NH(C(=O))NH*, donde * representa el punto de unión a dicho anillo arilo- o heteroarilo-;

R^8 representa un átomo de hidrógeno o halógeno, o un grupo -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-

C_6–alquilo–, halo–C_1–C_6–alcoxi–C_1–C_6–alquilo–, C_2–C_6–alquenilo–, C_2–C_6–alquinilo–, heterocicloalquilo de entre 3 y 7 miembros–, arilo–, heteroarilo–, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ o $-S(=O)_2$–(heterocicloalquilo de entre 3 y 7 miembros);

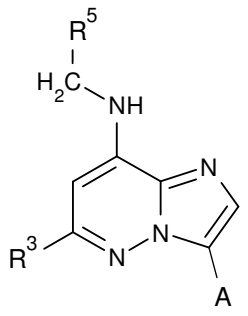
donde dicho heterocicloalquilo– o heteroarilo– de entre 3 y 7 miembros, está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos C_1–C_6 alquilo–;

m es el entero 0, 1, 2, 3, 4, 5 o 6;

n es el entero 0, 1, 2, 3, 4 o 5; y

X es S, S(=O), $S(=O)_2$, O, NR^6 o $CR^{6a}R^{6b}$.

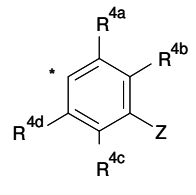
En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula general I:



I

donde:

A representa



donde * indica el punto de unión de dichos grupos con el resto de la molécula;

Z representa un grupo $-C(=O)N(H)R^2$ o $-C(=S)N(H)R^2$;

R^2 representa un grupo metilo- o etilo-;

donde dicho metilo- o etilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1 o 2 grupos seleccionados entre: halógeno, -OH, -CN, C_1-C_3-alcoxi-;

R^3 representa un grupo aril-X- o heteroaril-X-, donde dicho aril-X- o heteroaril-X- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, 4 o 5 grupos R^7;

R^{4a}, R^{4b}, R^{4c}, R^{4d}

se seleccionan, en forma independiente entre sí, entre hidrógeno, halógeno, -CN, C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-;

R^5 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, $-(CH_2)_n$-C_2-C_6-alquenilo, $-(CH_2)_n$-C_2-C_6-alquinilo, $-(CH_2)_m$-C_3-C_6-cicloalquilo, $-(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-

alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_4-C_8-cicloalquenilo-, arilo- o heteroarilo-;

donde dicho C_1-C_6-alquilo-, -$(CH_2)_n$-C_2-C_6-alquenilo, -$(CH_2)_n$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_4-C_8-cicloalquenilo-, arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, 4 o 5 grupos R^8;

R^6, R^{6a}, R^{6b}, R^{6c},

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, C_2-C_6-alquenilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, aril-C_1-C_6-alquilo-, o heteroaril-C_1-C_6-alquilo-;

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, C_2-C_6-alquinilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, -$C(=O)R^6$, -$C(=O)N(H)R^{6a}$, -$C(=O)N(R^{6a})R^{6b}$, -$C(=O)O$-R^6, -$N(R^{6a})R^{6b}$, -NO_2, -

$N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O2)R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$;

donde dicho arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2 o 3 grupos C_1-C_6 alquilo-;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo- o heteroarilo-, donde dichos 2 grupos R^7 juntos forman un puente:

$*O(CH_2)_2O*$, $*O(CH_2)O*$, *NH(C(=O))NH*, donde * representa el punto de unión a dicho anillo arilo- o heteroarilo-;

R^8 representa un átomo de hidrógeno o halógeno, o un grupo -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, C_2-C_6-alquinilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$,

$-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$, $-S(=O)_2-$(heterocicloalquilo de entre 3 y 7 miembros);

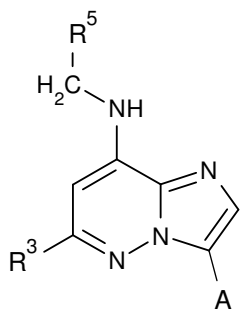
donde dicho heterocicloalquilo- o heteroarilo- de entre 3 y 7 miembros, está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos C_1-C_6 alquilo-;

m es el entero 0, 1, 2, 3, 4, 5 o 6;

n es el entero 0, 1, 2, 3, 4 o 5; y

X es S, S(=O), $S(=O)_2$, O, NR^6 o $CR^{6a}R^{6b}$.

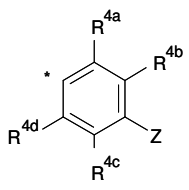
En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula general I:



I

donde:

A representa



donde * indica el punto de unión de dichos grupos con el

resto de la molécula;

Z representa un grupo $-C(=O)N(H)R^2$ o $-C(=S)N(H)R^2$;

R^2 representa un grupo C_1-C_4-alquilo-;

donde dicho grupo C_1-C_4-alquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1 o 2 grupos seleccionados entre: halógeno, OH, -CN, C_1-C_3-alquilo-, C_1-C_4-alcoxi-;

R^3 representa un grupo aril-X- o heteroaril-X-; donde dicho aril-X- o heteroaril-X- está opcionalmente sustituido, en forma idéntica o diferente, con 1 o 2 grupos R^7;

R^{4a}, R^{4b}, R^{4c}, R^{4d}

se seleccionan, en forma independiente entre sí, entre hidrógeno, halógeno, -CN, C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-;

R^5 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, $-(CH_2)_n$-C_2-C_6-alquenilo, $-(CH_2)_n$-C_2-C_6-alquinilo, $-(CH_2)_m$-C_3-C_6-cicloalquilo, $-(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_4-C_8-cicloalquenilo-, arilo- o heteroarilo-;

donde dicho C_1-C_6-alquilo-, $-(CH_2)_n$-C_2-C_6-alquenilo, $-(CH_2)_n$-C_2-C_6-alquinilo, $-(CH_2)_m$-C_3-C_6-cicloalquilo, $-(CH_2)_m$-

(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_4-C_8-cicloalquenilo-, arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, 4 o 5 grupos R^8;

R^6, R^{6a}, R^{6b}, R^{6c},

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, C_2-C_6-alquenilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, aril-C_1-C_6-alquilo-, o heteroaril-C_1-C_6-alquilo-;

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, C_2-C_6-alquinilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O2)R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$;

donde dicho arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2 o 3 grupos C_1-C_6 alquilo-;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo- o heteroarilo-, donde dichos 2 grupos R^7 juntos forman un puente:

$O(CH_2)_2O$, *$O(CH_2)O$*, *NH(C(=O))NH*, donde * representa el punto de unión a dicho anillo arilo- o heteroarilo-;

R^8 representa un átomo de hidrógeno o halógeno, o un grupo -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, C_2-C_6-alquinilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$, $-S(=O)_2$-(heterocicloalquilo de entre 3 y 7 miembros);

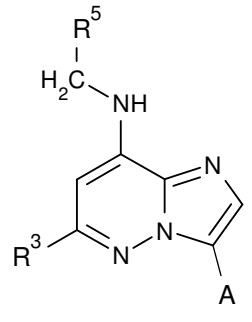
donde dicho heterocicloalquilo- o heteroarilo- de entre 3 y 7 miembros, está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos C_1-C_6 alquilo-;

m es el entero 0, 1, 2, 3, 4, 5 o 6;

n es el entero 0, 1, 2, 3, 4 o 5; y

X es S, S(=O), $S(=O)_2$, O, NR^6 o $CR^{6a}R^{6b}$.

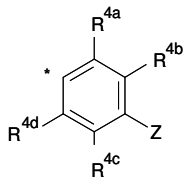
En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula general I:



I

donde:

A representa



donde * indica el punto de unión de dichos grupos con el resto de la molécula;

Z representa un grupo $-C(=O)N(H)R^2$ o $-C(=S)N(H)R^2$;

R^2 representa un grupo C_1-C_4-alquilo-;

donde dicho grupo C_1-C_4-alquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1 o 2 grupos seleccionados entre: halógeno, -OH, -CN, C_1-C_3-alquilo-, C_1-

C_4–alcoxi–;

R^3 se selecciona entre aril–X– o heteroaril–X–; donde dicho aril–X– o heteroaril–X– está opcionalmente sustituido, en forma idéntica o diferente, con 1 o 2 grupos R^7;

R^{4a}, R^{4b}, R^{4c}, R^{4d}

se seleccionan, en forma independiente entre sí, entre hidrógeno, halógeno, –CN, C_1–C_6–alquilo–, C_1–C_6–alcoxi–, halo–C_1–C_6–alquilo–, o halo–C_1–C_6–alcoxi–;

R^5 representa un átomo de hidrógeno, C_1–C_6–alquilo–, –$(CH_2)_m$–(heterocicloalquilo de entre 3 y 7 miembros), arilo– o heteroarilo–;

donde dicho grupo C_1–C_6–alquilo–, –$(CH_2)_m$–(heterocicloalquilo de entre 3 y 7 miembros),

arilo– o heteroarilo– está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos R^8;

R^6, R^{6a}, R^{6b}, R^{6c},

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1–C_6–alquilo–, HO–C_1–C_6–alquilo–, C_3–C_6–cicloalquilo–, C_2–C_6–alquenilo–, heterocicloalquilo de entre 3 y 7 miembros–, arilo–, heteroarilo–, aril–C_1–C_6–alquilo–, o heteroaril–C_1–C_6–alquilo–;

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO–, –CN, C_1–C_6–alcoxi–, C_1–C_6–alquilo–, halo–C_1–C_6–alquilo–, $R^{6a}(R^{6b})$N–C_1–C_6–alquilo–, HO–C_1–C_6–alquilo–, C_1–C_6–alcoxi–C_1–C_6–alquilo–, halo–C_1–C_6–alcoxi–C_1–C_6–alquilo–, C_2–C_6–

alquenilo-, C_2-C_6-alquinilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O2)R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$;

donde dicho arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2 o 3 grupos C_1-C_6 alquilo-;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo- o heteroarilo-, donde dichos 2 grupos R^7 juntos forman un puente:

$*O(CH_2)_2O*$, $*O(CH_2)O*$, *NH(C(=O))NH*, donde * representa el punto de unión a dicho anillo arilo- o heteroarilo-;

R^8 representa un átomo de hidrógeno o halógeno, o un grupo -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, C_2-C_6-alquinilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, -

$N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$, $-S(=O)_2-$(heterocicloalquilo de entre 3 y 7 miembros);

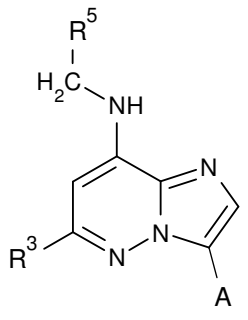
donde dicho heterocicloalquilo- o heteroarilo- de entre 3 y 7 miembros está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos C_1-C_6 alquilo-;

m es el entero 0, 1, 2, 3, 4, 5 o 6;

n es el entero 0, 1, 2, 3, 4 o 5; y

X es S, S(=O), $S(=O)_2$, O, NR^6 o $CR^{6a}R^{6b}$.

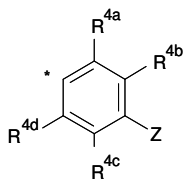
En otra forma de realización preferida, la invención se relaciona con los compuestos de fórmula general I:



I

donde:

A representa



donde * indica el punto de unión de dichos grupos con el resto de la molécula;

Z representa un grupo $-C(=O)N(H)R^2$ o $-C(=S)N(H)R^2$;

R^2 representa un grupo C_1-C_4-alquilo-;

donde dicho grupo C_1-C_4-alquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1 o 2 grupos seleccionados entre: halógeno, OH, -CN, C_1-C_3-alquilo-, C_1-C_4-alcoxi-;

R^3 representan an aril-X- o heteroaril-X-; donde dicho aril-X- o heteroaril-X- está opcionalmente sustituido, en forma idéntica o diferente, con 1 o 2 grupos R^7;

R^{4a}, R^{4b}, R^{4c}, R^{4d}

se seleccionan, en forma independiente entre sí, entre hidrógeno, halógeno, -CN, C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-;

R^5 representa un átomo de hidrógeno, C_1-C_6-alquilo-, $-(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), arilo- o heteroarilo-;

donde dicho grupo C_1-C_6-alquilo-, $-(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros),

arilo- o heteroarilo- está opcionalmente sustituido, en

forma idéntica o diferente, con 1, 2, 3 o 4 grupos R^8;

R^6, R^{6a}, R^{6b}, R^{6c},

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, C_2-C_6-alquenilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, aril-C_1-C_6-alquilo-, o heteroaril-C_1-C_6-alquilo-;

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})$N-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, C_2-C_6-alquinilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2R^6$, -N(R^{6c})S(=O)$_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -S(=O2)R^6, -S(=O)$_2$N(H)R^6, -S(=O)$_2$N(R^{6a})R^{6b}, -S(=O)(=NR^{6c})R^6;

donde dicho arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2 o 3 grupos C_1-C_6 alquilo-;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo- o heteroarilo-, donde dichos 2

grupos R^7 juntos forman un puente:

$O(CH_2)_2O$, *$O(CH_2)O$*, *NH(C(=O))NH*, donde * representa el punto de unión a dicho anillo arilo- o heteroarilo-;

R^8 representa un átomo de halógeno, un grupo –CN, $-N(R^{6a})R^{6b}$, o $-OR^6$;

m es el entero 0, 1, 2, 3, 4, 5 o 6;

n es el entero 0, 1, 2, 3, 4 o 5; y

X es S, S(=O), $S(=O)_2$, O, NR^6 o $CR^{6a}R^{6b}$.

Se debe entender que la presente invención se refiere a cualquier sub-combinación dentro de cualquier forma de realización o aspecto de la presente invención de los anteriores compuestos con la fórmula general **I**.

Aún más en particular, la presente invención abarca a los compuestos con la fórmula general **I** que se divulgan en la Sección Experimental del presente texto, *más adelante*.

Los compuestos de la presente invención pueden contener uno o más centros asimétricos, dependiendo de la localización y la naturaleza de los distintos sustituyentes deseados. Puede haber átomos de carbono asimétricos en la configuración (*R*) o (*S*), lo cual dará como resultado mezclas racémicas en el caso de un solo centro asimétrico, y mezclas diastereoméricas en el caso de múltiples centros asimétricos. En determinados casos, también puede haber asimetría presente debido a la rotación restringida alrededor de un enlace determinado, por ejemplo, el enlace central que une los dos anillos aromáticos sustituidos de

los compuestos especificados.

Los sustituyentes en un anillo también pueden estar presentes en la forma cis o trans. Todas estas configuraciones (incluyendo los enantiómeros y los diastereómeros) han de quedar incluidas dentro del alcance de la presente invención.

Los compuestos preferidos son aquellos que producen la actividad biológica más deseable. Dentro del alcance de la presente invención también se incluyen los isómeros y estereoisómeros o mezclas racémicas o diastereoméricas separados, puros o parcialmente purificados de los compuestos de esta invención. La purificación y la separación de dichos materiales se pueden efectuar usando técnicas estándar conocidas en la técnica.

Los isómeros ópticos se pueden obtener por resolución de las mezclas racémicas de acuerdo con procesos convencionales, por ejemplo, por formación de sales diastereoisoméricas usando un ácido o una base ópticamente activo o por formación de diastereómeros covalentes. Los ejemplos de los ácidos apropiados son el ácido tartárico, diacetiltártarico, ditoluiltartárico y canforsulfónico. Pueden separarse las mezclas de diastereoisómeros en sus diastereómeros individuales sobre la base de sus diferencias físicas y/o químicas, empleando métodos conocidos en la técnica, por ejemplo, por cromatografía o cristalización fraccionada. Las bases o ácidos ópticamente activos entonces se liberan de las sales diastereoméricas separadas. Un proceso diferente para separar isómeros

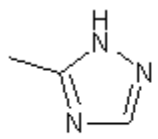
ópticos comprende el uso de cromatografía quiral (por ejemplo, columnas quirales para HPLC), con o sin una derivatización convencional, elegida óptimamente para maximizar la separación de los enantiómeros. Las columnas quirales de HPLC apropiadas son producidas por Diacel, por ejemplo, Chiracel OD y Chiracel OJ, entre muchos otros, todos los cuales se pueden seleccionar de forma rutinaria. También son de utilidad las separaciones enzimáticas, con o sin derivatización. Del mismo modo, pueden obtenerse los compuestos ópticamente activos de la presente invención por síntesis quiral, usando materiales iniciales ópticamente activos.

Con el fin de diferenciar los distintos tipos de isómeros unos de otros, puede usarse la Sección E de las reglas de la IUPAC como referencia (*Pure Appl Chem* **45**, 11-30, 1976).

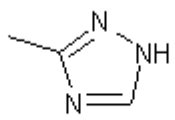
La presente invención abarca todos los estereoisómeros posibles de los compuestos de la presente invención, que pueden tomar la forma de estereoisómeros individuales o de mezclas de dichos estereoisómeros, en cualquier proporción. El aislamiento de un único estereoisómero de un compuesto de la presente invención, por ejemplo, un único enantiómero o un único diastereómero, puede efectuarse con cualquier método conocido en la técnica, tal como la cromatografía, especialmente, por ejemplo, la cromatografía quiral.

Además, los compuestos de la presente invención pueden existir como tautómeros. Por ejemplo, cualquier compuesto de la presente invención que contenga una unidad de pirazol

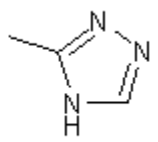
como un grupo heteroarilo, por ejemplo, podrá existir como un tautómero 1H, como un tautómero 2H o incluso como una mezcla de los dos tautómeros en cualquier cantidad. Cualquier compuesto que contenga una unidad de triazol, por ejemplo, podrá existir como un tautómero 1H, como un tautómero 2H, como un tautómero 4H o incluso como una mezcla de dichos tautómeros 1H, 2H y 4H en cualquier cantidad.



tautómero 1H



tautómero 2H



tautómero 4H

La presente invención abarca todos los tautómeros posibles de los compuestos de la presente invención, que pueden tomar la forma de tautómeros individuales o de mezclas de dichos tautómeros, en cualquier proporción.

Además, los compuestos de la presente invención pueden existir como N-óxidos, que se definen como aquellos compuestos de la presente invención que presentan al menos un nitrógeno oxidado. La presente invención abarca todos los N-óxidos posibles.

Además, la presente invención incluye a todas las posibles formas cristalinas, o polimorfos, de los compuestos de la presente invención, ya sea como polimorfos únicos, o como una mezcla de más que un polimorfo, en cualquier proporción.

Cuando los compuestos de la presente invención contengan solventes polares, particularmente agua, metanol o etanol, por ejemplo, como un elemento estructural de su

red cristalina, podrán existir como un hidrato o como un solvato. La cantidad de los solventes polares, particularmente del agua, puede presentan en una relación estequiométrica o no estequiométrica. En el caso de los solvatos estequiométricos, por ejemplo, los hidratos, son posibles los hemi, (semi), mono, sesqui, di, tri, tetra, penta-solvatos o hidratos, respectivamente, etcétera. La presente invención abarca todos estos hidratos o solvatos.

En una forma de realización de los aspectos mencionados anteriormente, la invención se refiere a compuestos de fórmula **I**, de acuerdo con cualquiera de las formas de realización mencionadas anteriormente, en la forma de o como un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato, o una sal de los mismos, o una mezcla de los mismos.

Sorprendentemente, se ha descubierto que los compuestos de la presente invención inhiben efectivamente la Mps-1 quinasa y por lo tanto se pueden utilizar para el tratamiento o la profilaxis de enfermedades de crecimiento, proliferación y/o supervivencia celular descontrolados, respuestas inmunes celulares inapropiadas, o respuestas celulares inflamatorias inapropiadas o enfermedades que acompañadas por un crecimiento, proliferación y/o supervivencia celular descontrolados, respuestas inmunes celulares inapropiadas, o respuestas celulares inflamatorias inapropiadas, en particular en los cuales el crecimiento, proliferación y/o supervivencia celular descontrolados, respuestas inmunes celulares inapropiadas,

o respuestas celulares inflamatorias inapropiadas son mediados por la Mps-1 quinasa, tal como, por ejemplo, tumores hematológicos, tumores sólidos, y/o metástasis de los mismos, *por ejemplo* leucemias y síndrome mielodisplástico, linfomas malignos, tumores de cabeza y cuello que incluyen tumores cerebrales y metástasis en el cerebro, tumores de tórax que incluyen tumores pulmonares de células no pequeñas y de células pequeñas, tumores gastrointestinales, tumores endocrinos, tumores mamarios y otros tumores ginecológicos, tumores urológicos, incluyendo tumores renales, de vejiga y de próstata, tumores de piel, y sarcomas, y/o metástasis de los mismos.

Por lo tanto, se espera que los compuestos de fórmula **I**, citados anteriormente, sean valiosos como agentes terapéuticos.

Por lo tanto, en otra forma de realización, la presente invención tiene como objeto a un compuesto de fórmula general **I**, citado anteriormente, o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato, o una sal de los mismos, en particular una sal farmacéuticamente aceptable de los mismos, o una mezcla de los mismos, para utilizar en el tratamiento o la profilaxis de una enfermedad.

En otra forma de realización, la presente invención provee un método para tratar trastornos asociados con la intensificación de procesos celulares proliferativos descontrolados en un paciente que necesita dicho tratamiento, que comprende administrar al paciente una

cantidad efectiva de un compuesto de fórmula **I**.

El término “tratar” o “tratamiento” según se utiliza a través de todo el presente documento se utiliza de la manera convencional, por ejemplo, la gestión o el cuidado de un sujeto con el propósito de combatir, aliviar, reducir, mejorar la condición de una enfermedad o trastorno, como por ejemplo un carcinoma.

El término “sujeto” o “paciente” incluye organismos que pueden padecer un trastorno proliferativo celular o quienes pueden beneficiarse de otra manera con la administración de un compuesto de la invención, como por ejemplo seres humanos y animales no humanos. Los humanos preferidos incluyen pacientes humanos que padecen o son propensos a padecer un trastorno proliferativo celular o un estado asociado, según se describe aquí. El término “animales no humanos” incluye a los vertebrados, por ejemplo, mamíferos, como por ejemplo primates no humanos, ovejas, vacas, perros, gatos y roedores, por ejemplo, ratones, y no mamíferos, como por ejemplo pollos, anfibios, reptiles, etc.

Las expresiones “trastorno proliferativo celular” o “trastorno asociado con la intensificación de procesos celulares proliferativos descontrolados” incluyen a los trastornos que incluyen la proliferación no deseada o descontrolada de una célula. Los compuestos de la presente invención se pueden utilizar para prevenir, inhibir, bloquear, reducir, disminuir, controlar, etc., la proliferación celular y/o la división celular, y/o producir

su apoptosis. Este método comprende administrar a un sujeto que lo necesita, incluyendo a un mamífero, incluyendo a un humano, una cantidad de un compuesto de la presente invención, o una sal farmacéuticamente aceptable, isómero, polimorfo, metabolito, hidrato o solvato de los mismos que sea efectivo para tratar o prevenir el trastorno.

En otra forma de realización, la presente invención tiene como objeto a un compuesto de fórmula general **I**, o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato, o una sal de los mismos, en particular una sal farmacéuticamente aceptable de los mismos, o una mezcla de los mismos, para utilizar en el tratamiento o la profilaxis de una enfermedad, donde dicha enfermedad es una enfermedad por crecimiento, proliferación y/o supervivencia celular descontrolados, una respuesta celular inmune inapropiada, o una respuesta celular inflamatoria inapropiada, en particular en la cual el crecimiento, proliferación y/o supervivencia celular descontrolados, la respuesta celular inmune inapropiada, o la respuesta celular inflamatoria inapropiada son mediadas por la vía metabólica de la proteína quinasa activada por mitógeno (MEK-ERK), más en particular en las cuales la enfermedad por crecimiento, proliferación y/o supervivencia celular descontrolados, respuesta celular inmune inapropiada, o respuesta celular inflamatoria inapropiada es un tumor hematológico, un tumor sólido y/o una metástasis de los mismos, *por ejemplo* leucemias y síndrome mielodisplástico, linfomas malignos, tumores de cabeza y cuello que incluyen tumores cerebrales

y metástasis en el cerebro, tumores de tórax que incluyen tumores pulmonares de células no pequeñas y de células pequeñas, tumores gastrointestinales, tumores endocrinos, tumores mamarios y otros tumores ginecológicos, tumores urológicos que incluyen tumores renales, de vejiga y de próstata, tumores de piel, y sarcomas, y/o metástasis de los mismos.

La presente invención también se refiere a formas útiles de los compuestos que se divulgan aquí, como por ejemplo metabolitos, hidratos, solvatos, prodrogas, sales, en particular sales farmacéuticamente aceptables, ésteres hidrolizables *in vivo*, y co-precipitados.

El término “sal farmacéuticamente aceptable" hace referencia a una sal de adición ácida inorgánica u orgánica, relativamente no tóxica, de un compuesto de la presente invención. Por ejemplo, véase S. M. Berge, *et al.* “Pharmaceutical Salts,” J. Pharm. Sci. **1977**, 66, 1-19.

Una sal farmacéuticamente aceptable de los compuestos de la presente invención puede ser, por ejemplo, una sal de adición ácida de un compuesto de la presente invención, que contiene un átomo de nitrógeno en una cadena o en un anillo, por ejemplo, que es suficientemente básico, tal como una sal de adición ácida con un ácido inorgánico, tal como el ácido clorhídrico, bromhídrico, iodhídrico, sulfúrico, bisulfúrico, fosfórico o nítrico, por ejemplo, o con un ácido orgánico, tal como el ácido fórmico, acético, acetoacético, pirúvico, trifluoroacético, propiónico,

butírico, hexanoico, heptanoico, undecanoico, láurico, benzoico, salicílico, 2-(4-hidroxibenzoil)-benzoico, canfórico, cinámico, ciclopentanopropiónico, diglucónico, 3-hidroxi-2-naftoico, nicotínico, pamoico, pectínico, persulfúrico, 3-fenilpropiónico, pícrico, piválico, 2-hidroxietanosulfónico, itacónico, sulfámico, trifluorometanosulfónico, dodecilsulfúrico, etanosulfónico, bencenosulfónico, para-toluenosulfónico, metanosulfónico, 2-naftalenosulfónico, naftalenodisulfonico, canforsulfónico, cítrico, tartárico, esteárico, láctico, oxálico, malónico, succínico, málico, adípico, algínico, maleico, fumárico, D-glucónico, mandélico, ascórbico, glucoheptanoico, glicerofosfórico, aspártico, sulfosalicílico, hemisulfúrico, o tiociánico, por ejemplo.

Además, otra sal apropiada farmacéuticamente aceptable de un compuesto de la presente invención es una sal de metal alcalino suficientemente ácida, por ejemplo, una sal de sodio o potasio, una sal de metal alcalino térreo, por ejemplo, una sal de calcio o magnesio, una sal de amonio o una sal con una base orgánica que proporciona un catión aceptable para el uso fisiológico, por ejemplo, una sal con N-metil-glucamina, dimetil-glucamina, etil-glucamina, lisina, diciclohexilamina, 1,6-hexadiamina, etanolamina, glucosamina, sarcosina, serinol, tris-hidroxi-metil-aminometano, aminopropandiol, base sovak, 1-amino-2,3,4-butantriol. Además, los grupos que contienen nitrógeno básico se pueden cuaternizar con agentes tales como haluros de alquilo inferior, tal como metilo, etilo, propilo, y

butilo cloruros, bromuros y ioduros; sulfatos de dialquilo como sulfato de dimetilo, dietilo y dibutilo; y sulfatos de diamilo, haluros de cadena larga, tales como cloruros, bromuros y ioduros de decilo, laurilo, miristilo y estearilo, haluros de aralquilo como bromuros de bencilo y fenetilo y otros.

Aquellos versados en la técnica comprenderán además que las sales de adición ácida de los compuestos reivindicados se pueden preparar por reacción de los compuestos con el ácido inorgánico u orgánico apropiado utilizando cualquiera de los numerosos métodos conocidos. Como alternativa, se pueden preparar sales de metales alcalinos y alcalino-térreos de los compuestos ácidos de la invención por reacción de los compuestos de la invención con la base apropiada utilizando diversos métodos conocidos.

La presente invención incluye todas las sales posibles de los compuestos de la presente invención, que pueden tomar la forma de sales individuales o de mezclas de cualquiera de dichas sales, en cualquier proporción.

Como se lo usa en la presente, el término “éster que puede hidrolizarse *in vivo*” se interpreta como un éster que puede hidrolizarse *in vivo* de un compuesto de la presente invención que contiene un grupo carboxilo o hidroxilo, por ejemplo, un éster farmacéuticamente aceptable que se hidroliza en el cuerpo del ser humano o el animal para producir el ácido o el alcohol original. Los ésteres farmacéuticamente aceptables para carboxi incluyen por ejemplo, alquilo, cicloalquilo y fenilalquilo

opcionalmente sustituido, en particular ésteres de bencilo, ésteres de C_1-C_6 alcoximetilo, por ejemplo, metoximetilo, ésteres de C_1-C_6 alcanoiloximetilo, por ejemplo, pivaloiloximetilo, ésteres de ftalidilo, ésteres de C_3-C_8 cicloalcoxi-carboniloxi-C_1-C_6 alquilo, por ejemplo, 1-ciclohexilcarboniloxietilo; ésteres de 1,3-dioxolen-2-onilmetilo, por ejemplo, 5-metil-1,3-dioxolen-2-onilmetilo; y ésteres de C_1-C_6-alcoxicarboniloxietilo, por ejemplo, 1-metoxicarboniloxietilo, y pueden formarse en cualquier grupo carboxi en los compuestos de esta invención.

Un éster hidrolizable *en vivo* de un compuesto de la presente invención que contiene un grupo hidroxi incluye ésteres inorgánicos tal como ésteres de fosfato y éteres de α-aciloxialquilo y compuestos relacionados que, como resultado de la ruptura del éster por hidrólisis *en vivo* para dar el grupo hidroxi madre. Los ejemplos de ésteres de [alfa] -aciloxialquilo incluyen acetoximetoxilo y 2,2-dimetilpropioniloximetoxilo. Una selección de grupos formadores de ésteres hidrolizables *en vivo* para hidroxi comprende alcanoilo. benzoilo fenilacetilo y benzoilo y fenilacetilo sustituidos, alcoxicarbonilo (para dar ésteres de alquilcarbonato), dialquilcarbamoilo y N-(dialquilaminoetil)-N-alquilcarbamoilo (para dar carbamatos), dialquilaminoacetilo y carboxiacetilo. La presente invención abarca todos estos ésteres.

Los compuestos de fórmula **I** se pueden administrar como el único agente farmacéutico o en combinación con uno o más agentes terapéuticos adicionales donde la combinación no causa efectos adversos inaceptables. Esta terapia de combinación incluye la administración de una única

formulación para dosificación farmacéutica que contiene un compuesto de fórmula **I** y uno o más agentes terapéuticos adicionales, así la como administración del compuesto de fórmula **I** y cada agente terapéutico adicional en su propia formulación para dosificación farmacéutica separada. Por ejemplo, un compuesto de fórmula **I** y un agente terapéutico se pueden administrar juntos al paciente en una única composición para dosificación oral tal como una tableta o cápsula, o cada agente se puede administrar en formulaciones para dosificación separada.

Donde se utilizan formulaciones para dosificación separada, el compuesto de fórmula **I** y uno o más agentes terapéuticos adicionales se pueden administrar esencialmente al mismo tiempo (por ejemplo, de manera concurrente) o por separado a tiempos escalonados (por ejemplo, en forma consecutiva).

En otro aspecto, la invención provee una composición farmacéutica que comprende un compuesto de fórmula general **I**, o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato, o una sal de los mismos, en particular una sal farmacéuticamente aceptable de los mismos, o una mezcla de los mismos, y un diluyente o vehículo farmacéuticamente aceptable.

Preferiblemente, la combinación farmacéutica comprende:

- uno o más compuestos de fórmula general **I**, o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato, o una sal de los mismos, en particular una sal farmacéuticamente aceptable de los mismos, o una mezcla de los mismos; y

– uno o más agentes que se seleccionan entre: un taxano, como por ejemplo Docetaxel, Paclitaxel, o Taxol; un epotilona, como por ejemplo Ixabepilona, Patupilona, o Sagopilona; Mitoxantrona; Predinisolona; Dexametasona; Estramustina; Vinblastina; Vincristina; Doxorrubicina; Adriamicina; Idarrubicina; Daunorrubicina; Bleomicina; Etopósido; Ciclofosfamida; Ifosfamida; Procarbazina; Melfalán; 5-Fluorouracilo; Capecitabina; Fludarabina; Citarabina; Ara-C; 2-Cloro-2´-desoxiadenosina; Tioguanina; un antiandrógeno, como por ejemplo Flutamida, acetato de ciproterona, o Bicalutamida; Bortezomib; un derivado de platino, como por ejemplo Cisplatino, o Carboplatino; Clorambucilo; Metotrexato; y Rituximab.

En aún otro aspecto, la invención provee un proceso para preparar una composición farmacéutica. El proceso incluye el paso de combinar por lo menos un compuesto de fórmula **I** según se definió anteriormente con por lo menos un vehículo farmacéuticamente aceptable, y darle a la combinación que se obtiene como resultado una forma de administración apropiada.

En aún otro aspecto, la invención provee el uso de un compuesto de fórmula **I** según se definió anteriormente para la elaboración de una composición farmacéutica para el tratamiento o la prevención de un trastorno proliferativo celular. En ciertas formas de realización, el trastorno proliferativo celular es cáncer.

El componente activo de la fórmula **I** puede actuar de manera sistémica y/o localmente. Para dicho propósito, se puede

aplicar de una manera apropiada, por ejemplo en forma oral, parenteral, pulmonar, nasal, sublingual, lingual, bucal, rectal, transdérmica, por la conjuntiva, óticamente, o como un implante o stent.

Cuando los compuestos de la presente invención se administran como productos farmacéuticas, a seres humanos y animales, los mismos se pueden suministrar tal cual o como una composición farmacéutica que contiene, por ejemplo, en entre 0,1 y 99,5% (más preferiblemente, entre 0,5 y 90%) de ingrediente activo en combinación con un vehículo farmacéuticamente aceptable.

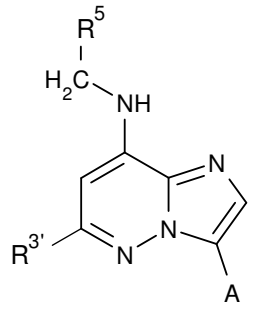
Independientemente de la ruta de administración que se seleccione, los compuestos de la invención, que se pueden utilizar en una forma hidratada apropiada, y/o las composiciones farmacéuticas de la presente invención, se formulan en formas de dosificación farmacéuticamente aceptables usando métodos convencionales conocidos por aquellos con experiencia en el arte.

Los niveles de dosificación y el curso de tiempo de administración reales de los ingredientes activos de las composiciones farmacéuticas de la invención se pueden variar de manera tal de obtener una cantidad del ingrediente activo que sea efectiva para obtener la respuesta terapéutica deseada para un paciente, composición, y modalidad de administración en particular, sin que sea tóxica para el paciente.

De acuerdo con otro aspecto, la presente invención abarca a métodos para preparar los compuestos de la presente

invención.

De acuerdo con una primera forma de realización, la presente invención se refiere a un método para preparar un compuesto de fórmula general **I**, citado anteriormente, donde dicho método comprende el paso de permitir que un compuesto intermediario con la fórmula general **IV**:



IV

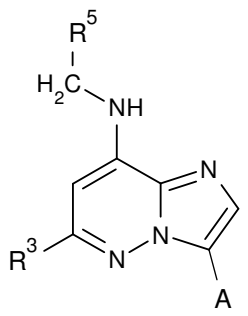
en donde A, y R^5 son según se los definió para la fórmula general **I**, citada anteriormente, y $R^{3'}$ es un grupo saliente; reaccione con un compuesto de fórmula general **IVa**:

R^3–Y

IVa

en donde R^3 es según se definió para la fórmula general **I**, citada anteriormente, e Y es un sustituyente que es desplazado en una reacción de acoplamiento, como por ejemplo un átomo de hidrógeno, o un grupo ácido borónico, o un grupo éster borónico, por ejemplo;

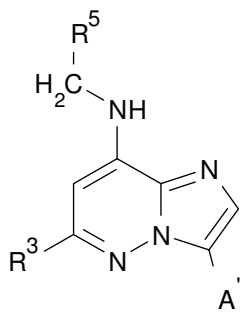
para dar de esa manera un compuesto de fórmula general **I**:



I

en donde A, R^3, y R^5 son según se los definió para la fórmula general **I**, citada anteriormente.

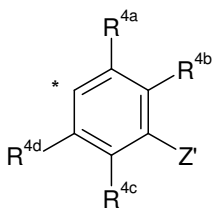
De acuerdo con una segunda forma de realización, la presente invención también se refiere a un método para preparar un compuesto de fórmula general **I**, citado anteriormente, donde dicho método comprende el paso de permitir que un compuesto intermediario con la fórmula general **Ia**:



Ia

en donde R^3 y R^5 son según se los definió para la fórmula general **I**, citada anteriormente;

y A′ es



donde * indica el punto de unión de dicho grupo con el resto de la molécula; R^{4a}, R^{4b}, R^{4c} y R^{4d} son según se los definió para la fórmula general **I**, citada anteriormente, y Z' representa un grupo que se selecciona entre:

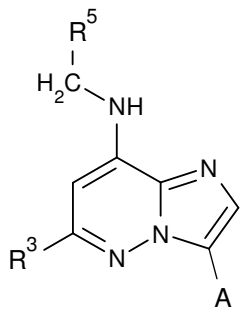
$-C(=O)OH$, $-C(=S)OH$, $-C(=O)O-(C_1-C_6\text{-alquilo})$ o $-C(=S)O-(C_1-C_6\text{-alquilo})$;

reaccione con un compuesto de fórmula general **Ib:**

H_2NR^2

Ib

en donde R^2 es según se definió para la fórmula general **I**, citada anteriormente, para dar de esa manera, tras una desprotección opcional, un compuesto de fórmula general **I:**

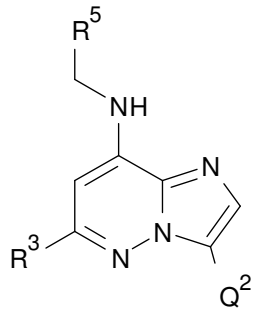


I

en donde R^3, R^5 y A son según se los definió para la fórmula general **I**, citada anteriormente.

De acuerdo con una tercera forma de realización, la presente invención también se refiere a un método para preparar un compuesto de fórmula general **I**, citado anteriormente, donde dicho método comprende el paso de permitir que un compuesto intermediario con la fórmula

general **II:**



II

en donde R^3 y R^5 son según se los definió para la fórmula general **I**, citada anteriormente, y Q^2 es un grupo saliente, preferiblemente Q^2 es un átomo de halógeno;

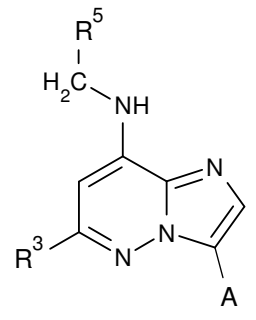
reaccione con un compuesto de fórmula general **IIa:**

A–Y

IIa

en donde A es según se definió para la fórmula general **I**, citada anteriormente, e Y es un sustituyente que es desplazado en una reacción de acoplamiento, como por ejemplo un grupo ácido borónico, o un éster de un grupo ácido borónico, por ejemplo,

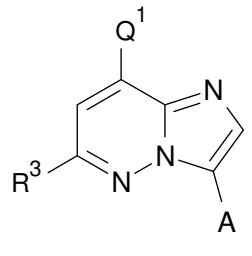
para dar de esa manera, tras una desprotección opcional, un compuesto de fórmula general **I:**



I

en donde R^3, R^5 y A son según se los definió para la fórmula general **I**, citada anteriormente.

De acuerdo con a cuarto forma de realización, la presente invención también se refiere a un método para preparar un compuesto de fórmula general **I**, citado anteriormente, donde dicho método comprende el paso de permitir que un compuesto intermediario con la fórmula general **VII**:



VII

en donde R^3 y A son según se los definió para la fórmula general **I**, citada anteriormente, y Q^1 es un grupo saliente, por ejemplo un átomo de halógeno,

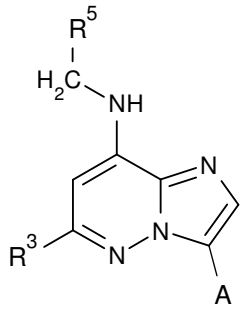
reaccione con un compuesto de fórmula general **VIIa**:

$$R^5\text{–}CH_2\text{–}NH_2$$

VIIa

en donde R^5 es según se definió para la fórmula general **I**, citada anteriormente,

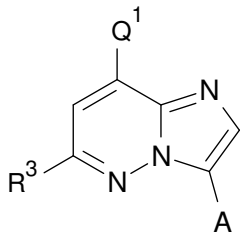
para dar de esa manera, tras una desprotección opcional, un compuesto de fórmula general **I**:



I

en donde R^3, R^5 y A son según se los definió para la fórmula general **I**, citada anteriormente.

De acuerdo con una cuarta forma de realización, la presente invención también se refiere a un método para preparar un compuesto de fórmula general **I**, citado anteriormente, donde dicho método comprende el paso de permitir que un compuesto intermediario con la fórmula general **VII**:



VII

en donde R^3 y A son según se los definió para la fórmula general **I**, citada anteriormente, y Q^1 es un grupo NH_2 opcionalmente protegido

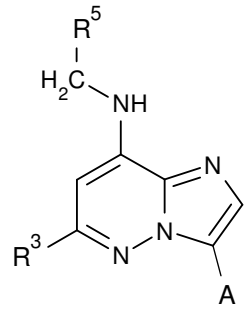
reaccione con un compuesto de fórmula general **VIIb**:

$O=CHR^5$

VIIb

en donde R^5 es según se definió para la fórmula general **I**, citada anteriormente,

para dar de esa manera, tras una desprotección opcional, un compuesto de fórmula general **I:**

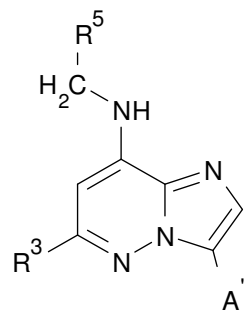


I

en donde R^3, R^5 y A son según se los definió para la fórmula general **I**, citada anteriormente.

De acuerdo con un aspecto adicional, la presente invención abarca a los compuestos intermediarios que son útiles en la preparación de compuestos de la presente invención de fórmula general **I**, en particular en el método descrito aquí.

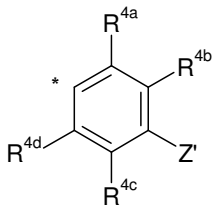
En particular, la presente invención abarca a los compuestos intermediarios de fórmula general **Ia:**



Ia

en donde R^3 y R^5 son según se los definió para la fórmula general **I**, citada anteriormente;

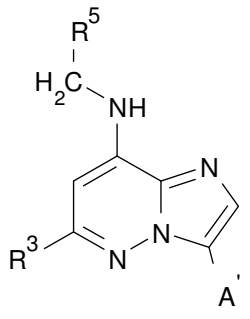
y A´ es



donde * indica el punto de unión de dicho grupo con el resto de la molécula; R^{4a}, R^{4b}, R^{4c} y R^{4d} son según se los definió para la fórmula general **I**, citada anteriormente, y Z' representa un grupo que se selecciona entre:

-C(=O)OH, -C(=S)OH, -C(=O)O-(C_1-C_6-alquilo) o -C(=S)O-(C_1-C_6-alquil).

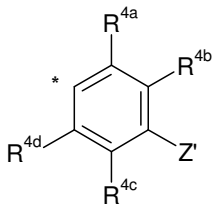
De acuerdo con aún otro aspecto, la presente invención abarca el uso de los compuestos intermediarios de fórmula general **Ia:**



Ia

en donde R^3 y R^5 son según se los definió para la fórmula general **I,** citada anteriormente;

y A´ es



donde * indica el punto de unión de dicho grupo con el resto de la molécula; R^{4a}, R^{4b}, R^{4c} y R^{4d} son según se los

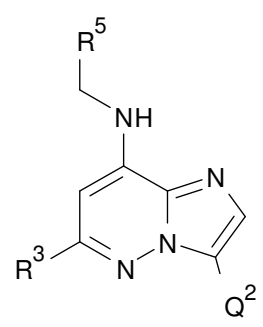
definió para la fórmula general **I**, citada anteriormente, y

Z' representa un grupo que se selecciona entre:

$-C(=O)OH$, $-C(=S)OH$, $-C(=O)O-(C_1-C_6-alquilo)$ o $-C(=S)O-(C_1-C_6-alquilo)$;

para la preparación de un compuesto de fórmula general **I** según se definió anteriormente.

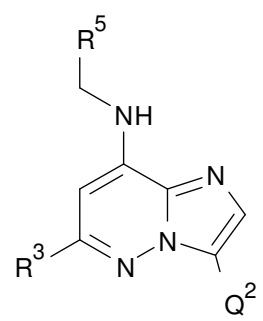
De acuerdo con aún otro aspecto, la presente invención abarca a los compuestos intermediarios de fórmula general **II**:



II

en donde R^3 y R^5 son según se los definió para la fórmula general **I**, citada anteriormente, y Q^2 es un grupo saliente, preferiblemente Q^2 es un átomo de halógeno.

De acuerdo con aún otro aspecto, la presente invención abarca el uso de los compuestos intermediarios de fórmula general **II**:

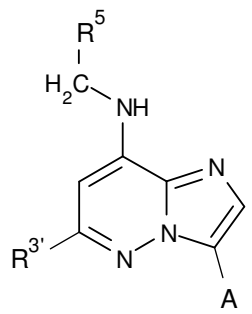


II

en donde R^3 y R^5 son según se los definió para la fórmula general **I**, citada anteriormente, y Q^2 es un grupo saliente, preferiblemente Q^2 es un átomo de halógeno;

para la preparación de un compuesto de fórmula general **I** según se definió anteriormente.

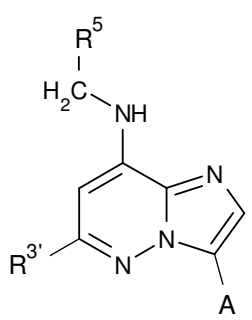
De acuerdo con aún otro aspecto, la presente invención abarca a los compuestos intermediarios de fórmula general **IV:**



IV

en donde A, y R^5 son según se los definió para la fórmula general **I**, citada anteriormente, y $R^{3'}$ es un grupo saliente.

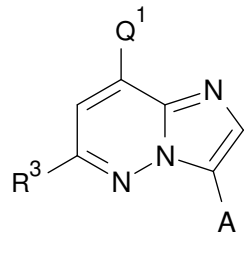
De acuerdo con aún otro aspecto, la presente invención abarca el uso de los compuestos intermediarios de fórmula general **IV:**



IV

en donde A, y R^5 son según se los definió para la fórmula general **I**, citada anteriormente, y $R^{3'}$ es un grupo saliente, para la preparación de un compuesto de fórmula general **I** según se definió anteriormente.

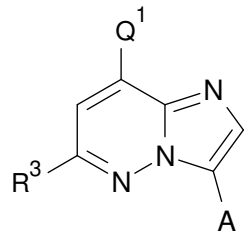
De acuerdo con un aspecto adicional, la presente invención abarca a los compuestos intermediarios de fórmula general **VII**:



VII

en donde A, y R^3 son según se los definió para la fórmula general **I**, citada anteriormente, y Q^1 representa un grupo NH_2 opcionalmente protegido o un grupo saliente.

De acuerdo con aún otro aspecto, la presente invención abarca el uso de los compuestos intermediarios de fórmula general **VII**:



VII

en donde A, y R^3 son según se los definió para la fórmula general **I**, citada anteriormente, y Q^1 representa un grupo NH_2 opcionalmente protegido o un grupo saliente;

para la preparación de un compuesto de fórmula general **I** según se definió anteriormente.

SECCIÓN EXPERIMENTAL

En la siguiente tabla se indican las abreviaturas usadas en este párrafo y en la sección de Ejemplos.

Abreviatura	**Significado**
EDC	1-Etil-3-(3-dimetilaminopropil)carbodiimida
DIPEA	N,N-diisopropiletilamina
DMF	N,N-Dimetilformamida
DMSO	Dimetilsulfóxido
$Pd(dppf)Cl_2$	Dicloro[1,1'-bis(difenilfosfino)ferroceno]paladio(II)
RMN	espectroscopía de resonancia magnética nuclear
Rt	Temperatura ambiente
RT	Tiempo de retención en minutos
MW	Peso molecular
NMP	*N*-metilpirrolidinona
Oxona	peroximonosulfato de potasio
UPLC	cromatografía líquida de rendimiento ultra alto

Síntesis de los compuestos de fórmula general I de la presente invención

Los compuestos de fórmula general **I** se pueden sintetizar según se muestra en el Esquema, donde

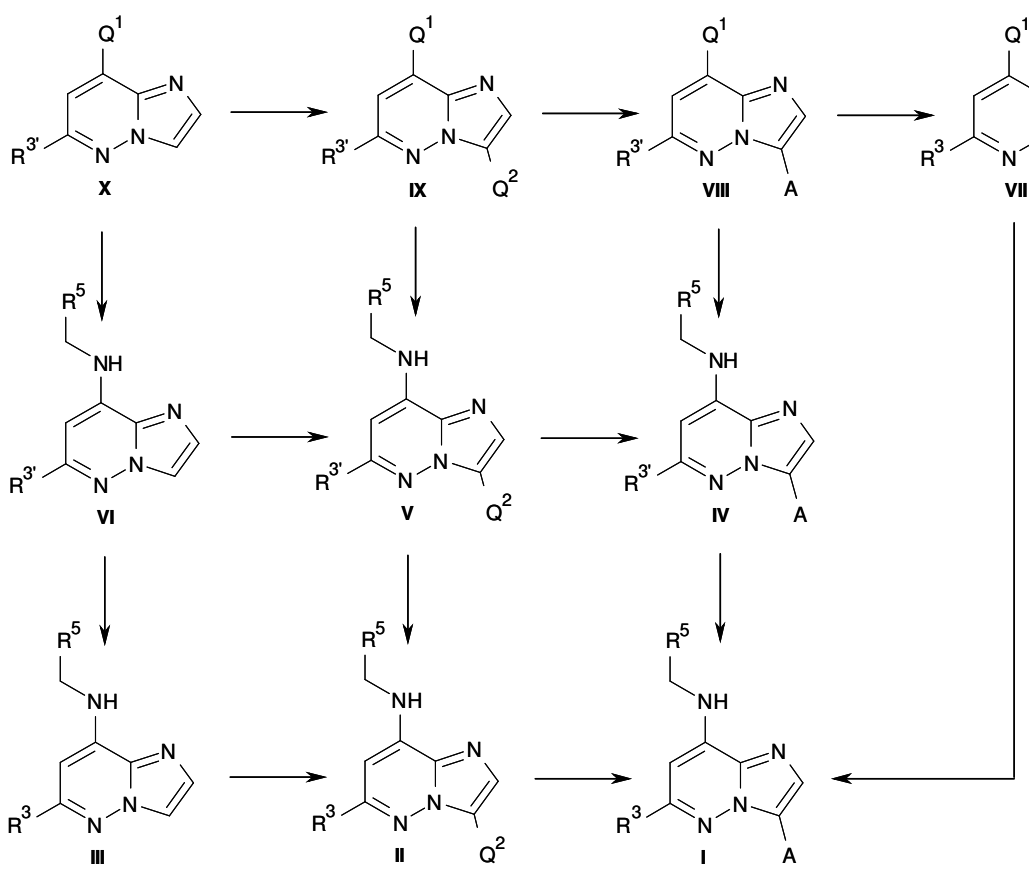
A, R^3, R^5 tienen el significado que se les da para la fórmula general **I**, citada anteriormente;

$R^{3'}$, Q^2 representan grupos salientes; y

Q^1 representa un grupo NH_2 opcionalmente protegido o

un grupo saliente.

Los ejemplos de grupos salientes típicos incluyen pero de manera no taxativa, a los átomos de halógeno como un átomo de cloro, bromo o yodo, o grupos $S(O)_pR^6$- (donde p es 0, 1, o 2, y R^6 es según se definió para la fórmula general **I**, citada anteriormente) como un grupo metilsulfonilo-, o un grupo triflato- o nonaflato-.



Esquema

El Esquema ejemplifica las rutas que permiten obtener variaciones para diferentes R^3, $R^{3'}$, R^5, Q^1, Q^2 y A durante la síntesis. Las unidades funcionales en R^3, $R^{3'}$, R^5, Q^1, Q^2 y A se pueden convertir en cada etapa apropiada de la síntesis.

Sin embargo, para la síntesis de los compuestos objetivo

también se utilizaron otras rutas.

Los compuestos de fórmula **X** se pueden obtener comercialmente o se pueden sintetizar de acuerdo con procedimientos conocidos por las personas con experiencia en el arte, por ejemplo aplicando procedimientos descritos en WO2007/38314A2.

En los compuestos de fórmula general **X**, **VI** o **III** se puede introducir un grupo saliente Q^2 empleando procedimientos conocidos por las personas con experiencia en el arte, para dar los compuestos de fórmula general **IX**, **V** o **II**. Como un ejemplo, se pueden introducir halógenos usando reactivos de halogenación como N-yodosuccinimida (NIS), N-bromosuccinimida (NBS), o N-clorosuccinimida (NCS), en un solvente inerte como la N,N-dimetilformamida o la 1-metilpirrolidin-2-ona, por ejemplo, a temperaturas dentro del rango entre la temperatura ambiente y el punto de ebullición del solvente, por ejemplo.

Los compuestos de fórmula general **I**, **IV** o **VIII** se pueden obtener a partir de los compuestos de fórmula general **II**, **V** o **IX** mediante una reacción de acoplamiento entre un reactivo de fórmula Y-A, en el cual A es como se definió anteriormente e Y representa un grupo funcional apropiado mediante el cual el grupo A se puede transferir al átomo de carbono que porta el grupo Q de los compuestos de fórmula **II**, **V** o **IX**. Los ejemplos de grupos funcionales apropiados para Y en A-Y incluyen ácidos borónicos $A-B(OH)_2$, o ésteres de ácidos borónicos $A-B(OC_1-C_6\text{-alquilo})_2$. Dichas reacciones de acoplamiento se llevan a cabo en presencia de

catalizadores apropiados, tales como, por ejemplo, catalizadores a base de paladio como, por ejemplo, acetato de paladio (II), tetrakis(trifenilfosfina)paladio (0), cloruro de bis(trifenilfosfina)paladio (II) o (1,1-bis(difenilfosfino)ferroceno)dicloropaladio (II) y opcionalmente aditivos apropiados tales como, por ejemplo, fosfinas como, por ejemplo, $P(oTol)_3$ o trifenilfosfina y opcionalmente con una base apropiada, tal como, por ejemplo, carbonato de potasio, 2-metilpropan-2-olato de sodio, fluoruro de tetrabutilamonio o fosfato tribásico de potasio en un solvente apropiado, tal como, por ejemplo, tetrahidrofurano.

Los ejemplos de dichas reacciones de acoplamiento se pueden ver en el libro de texto cuyo título es "Metal-Catalyzed Cross-Coupling Reactions", Armin de Meijere (Editor), François Diederich (Editor) septiembre 2004, Wiley Interscience ISBN: 978-3-527-30518-6.

Los compuestos de fórmula general **I**, **II**, **III** o **VII** se pueden obtener a partir de los compuestos de fórmula general **IV**, **V**, **VI** o **VIII** mediante una reacción de acoplamiento usando un reactivo de fórmula $Y-R^3$ en el cual R^3 es como se definió anteriormente e Y representa un grupo funcional apropiado mediante el cual el grupo R^3 se puede transferir al átomo de carbono que porta al grupo R^3' de los compuestos de fórmula **IV**, **V**, **VI** o **VIII**. Los ejemplos de grupos funcionales apropiados Y para usar en reacciones de acoplamiento se dieron anteriormente para la preparación de compuestos de fórmula general **I**, **IV** o **VIII** a partir de

compuestos de fórmula general **II**, **V** o **IX**.

Las reacciones de acoplamiento incluyen reacciones de acoplamiento catalizadas por metales como las reacciones de acoplamiento de Sonogashira con alquinos para la introducción de alquinos, reacciones de acoplamiento de Heck con alquenos para la introducción de alquenos, reacciones de acoplamiento de Hartwig Buchwald con aminas para la introducción de aminas.

El Y en Y–R^3 también puede representar un hidrógeno ácido que se puede eliminar usando bases apropiadas, por ejemplo hidruro de sodio, en un solvente apropiado, como por ejemplo DMSO o tetrahidrofurano a temperaturas dentro del rango entre la temperatura ambiente y el punto de ebullición. Los nucleófilos que se obtienen como resultado, como, por ejemplo, grupos que portan aminas primarias o secundarias, alcóxidos, tiolatos o anión carbono se pueden utilizar para reemplazar a $R^{3'}$ en los compuestos de fórmula general **IV**, **V**, **VI** o **VIII** para agregar aminas secundarias o terciarias, éteres, tioéteres o grupos unidos a un átomo de carbono para dar compuestos de fórmula general **I**, **II**, **III** o **VII**.

Los compuestos de fórmula general **I**, **II**, **III** o **VII** que contienen aminas primarias o secundarias, éteres o tioéteres también se puede construir por reacciones de acoplamiento del tipo de Ullmann en presencia de catalizadores apropiados, tales como, por ejemplo, catalizadores a base de cobre como diacetato de cobre(II) en presencia de una base apropiada, como por ejemplo,

carbonato de cesio comenzando a partir de compuestos de fórmula general **IV**, **V**, **VI** o **VIII** en los cuales $R^{3'}$ representa un grupo saliente tal como, por ejemplo, un átomo de yodo, bromo o cloro. Opcionalmente, se pueden agregar ligandos apropiados como N,N-dimetilglicina o pirrolidin-2-ilfosfonato ácido de fenilo.

En el caso en que Q^1 representa un grupo saliente, se puede conseguir la introducción de un grupo R^5-CH_2 por sustitución nucleofílica de Q^1 en compuestos de fórmula **VII**, **VIII**, **IX** o **X** es decir por una reacción con aminas $R^5-CH_2-NH_2$ apropiadas en presencia de una base apropiada, tal como, por ejemplo DIPEA en un solvente apropiado tal como N,N-dimetilformamida o 1-metilpirrolidin-2-ona, a temperaturas dentro del rango entre la temperatura ambiente y el punto de ebullición del solvente para dar aminas de fórmula general **I**, **IV**, **V** o **VI**.

En el caso en que Q^1 representa un grupo saliente, la introducción de un grupo R^5-CH_2 también se puede conseguir mediante una reacción de acoplamiento en la cual, los Q^1 en los compuestos de fórmula **VII**, **VIII**, **IX** o **X** se hace reaccionar con aminas $R^5-CH_2-NH_2$ apropiadas opcionalmente en presencia de un catalizador apropiado, como por ejemplo Pd_2dba_3 y BINAP por ejemplo, y opcionalmente con una base apropiada, tal como, por ejemplo, tert-butilato de sodio en un solvente apropiado, tal como, por ejemplo, N,N-dimetilformamida o 1-metilpirrolidin-2-ona para dar aminas de fórmula general **I**, **IV**, **V** o **VI**.

En el caso en que Q^1 representa un grupo NH_2 opcionalmente

protegido la introducción de un grupo R^5–CH_2, luego de la desprotección de un grupo NH_2, se puede conseguir mediante una reacción de aminación reductiva usando un aldehído de fórmula $O=CHR^5$, un agente reductor apropiado, por ejemplo tris(acetato-kappaO)(hidruro)borato de sodio o cianoborohidruro de sodio en un solvente apropiado como, por ejemplo, ácido acético a temperaturas de reacción dentro del rango entre la temperatura ambiente y el punto de ebullición del solvente.

Opcionalmente , los residuos de los compuestos de fórmula **I**, **II**, **III**, **IV**, **V**, **VI**, **VII**, **VIII**, **IX** o **X** se pueden modificar. Por ejemplo, los tioéteres se pueden oxidar usando reactivos de oxidación como ácido 3-clorobencenocarboperoxoico , oxona o dimetildioxirano en solventes inertes como diclorometano o acetona, respectivamente. Dependiendo de la proporción estequiométrica del reactivo de oxidación con los compuestos mencionados anteriormente , se obtendrán sulfóxidos o sulfonas o mezclas de los mismos.

Además, los compuestos de fórmula **I** de la presente invención se pueden convertir en cualquier sal según se describe aquí, por cualquier método conocido por las personas con experiencia en el arte. De manera similar, cualquier sal de un compuesto de fórmula **I** de la presente invención se puede convertir en el compuesto libre, por cualquier método conocido por las personas con experiencia en el arte.

Los compuestos e intermediarios producidos de acuerdo con los métodos de la invención pueden requerir

purificación. La purificación de compuestos orgánicos es conocida para el especialista en la materia y pueden haber diversas formas de purificar el mismo compuesto. En algunos casos, puede no ser necesaria purificación alguna. En algunos casos, los compuestos pueden purificarse por cristalización. En algunos casos, las impurezas pueden separarse utilizando un solvente apropiado. En algunos casos, los compuestos pueden purificarse por cromatografía, particularmente por cromatografía instantánea, usando, por ejemplo, cartuchos de sílice envasados con antelación, por ejemplo, de Separtis, tales como el gel de sílice Isolute® Flash o el sílice Isolute® Flash NH2 , en combinación con un sistema de cromatografía apropiado, tal como un sistema Flashmaster II (Separtis) o un sistema Isolera (Biotage), con eluyentes que pueden incluir, por ejemplo, gradientes de hexano/EtOAc o de DCM/metanol. En algunos casos, los compuestos pueden purificarse por HPLC preparativa utilizando por ejemplo, un autopurificador Aguas equipado con un detector por conjunto de diodos y/o espectrómetro de masa de ionización por electroatomización en línea, en combinación con una columna de fase reversa preparada apropiada y eluyentes como por ejemplo, gradientes de agua y acetonitrilo que pueden contener aditivos como por ejemplo, ácido trifluoroacético, ácido fórmico o amoníaco acuoso.

Ejemplos

La UPLC-MS analítica se llevó a cabo como se describe a continuación.

Método A. Sistema: UPLC Acquity (Waters) con un detector PDA y un espectrómetro de masa Waters ZQ. Columna: Acquity BEH C18, de 1,7 µm 2,1 x 50 mm. Temperatura: 60°C. Solvente A: Agua + 0,1% de ácido fórmico. Solvente B: acetonitrilo. Gradiente: 99% de A → 1% de A (1,6 minutos) → 1% de A (0,4 minutos). Flujo: 0,8 ml/minuto. Volumen de inyección: 1,0 µl (con la muestra en una concentración de 0,1 mg/ml–1 mg/ml). Detección: PDA, con un rango de barrido fijo de 210–400 nm, y ESI (+), con un rango de barrido de 170–800 m/z

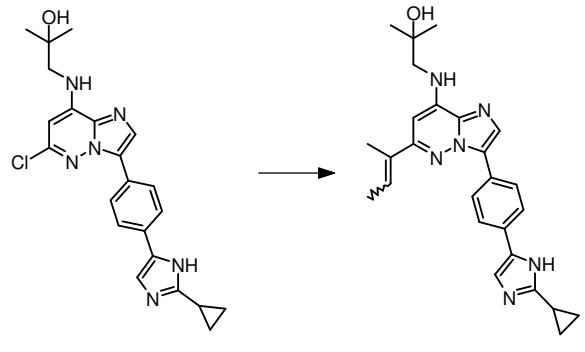
General:

Todas las reacciones se corrieron bajo una atmósfera de argón en solventes desgaseados, a no ser que se especifique otra cosa.

Ejemplo 1

1-({6-[(2E/Z)-But-2-en-2-il]-3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]

imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol



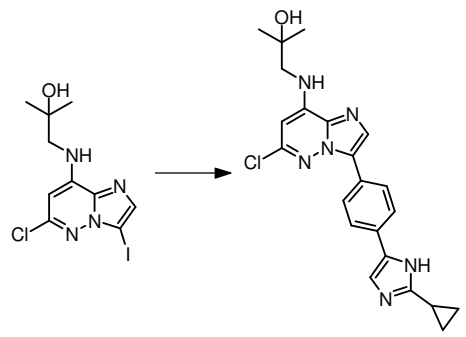
Una mezcla de 47,5 mg (112 µmol) de 1-({6-cloro-3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol, que se preparó de acuerdo con el Ejemplo Intermediario 1a, 47,3 mg de ácido (2E/Z)-but-2-en-2-

ilborónico, 1,6 mL de n-propanol, 228 µL de 1-metilpirrolidin-2-ona, 168 µL de una solución acuosa de carbonato de potasio 2M, 1,47 mg de trifenilfosfina, y 7,9 mg de cloruro de bis(trifenilfosfin)paladio (II) se agitó a 120°C durante 2 horas bajo irradiación de microondas. El solvente se eliminó y el residuo se purificó mediante cromatografía para dar 20,7 mg (40%) de los compuestos del título.

1H-RMN (DMSO-d6): δ= 0,81-0,91 (4H), 1,15 (6H), 1,72 (3H), 1,93 (1H), 2,05 (3H), 3,13+3,26 (2H), 4,75+4,77 (1H), 5,73 (1H), 6,16+6,18 (1H), 6,75 (1H), 7,19+7,45 (1H), 7,65+7,76 (2H), 7,90+7,95 (1H), 8,06+8,14 (2H), 11,79+12,09 (1H) ppm.

Ejemplo Intermediario 1a

1-({6-Cloro-3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol

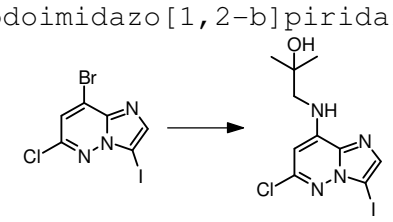


Una mezcla de 700 mg (1,91 mmol) de 1-[(6-cloro-3-yodoimidazo[1,2-b]piridazin-8-il)amino]-2-metilpropan-2-ol, que se preparó de acuerdo con el Ejemplo Intermediario 1b, 610 mg de ácido [4-(2-ciclopropil-1H-imidazol-5-il)fenil]borónico, que se preparó de acuerdo con el Ejemplo Intermediario 1d, 156 mg de (1,1,-bis(difenilfosfino)ferrocen)-dicloropaladio (II), 2,86 mL de solución acuosa de fostato de potasio tribásica 2M y 8,2 mL

de tetrahidrofurano se agitó a 45°C durante 12 horas. Se agregó agua y la mezcla se extrajo con acetato de etilo y metanol. La capa orgánica se lavó con salmuera y se secó sobre sulfato de sodio. Luego de la filtración y la eliminación del solvente el residuo se purificó mediante cromatografía para dar 345 mg (43%) del compuesto del título.

Ejemplo Intermediario 1b

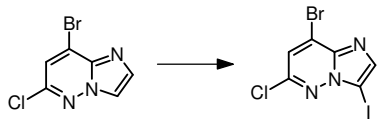
1-[(6-Cloro-3-yodoimidazo[1,2-b]piridazin-8-il)amino]-2-metilpropan-2-ol



A una solución de 1,20 g (3,35 mmol) de 8-bromo-6-cloro-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 1c, en 24 mL de N,N-dimetilformamida, se agregaron 895 mg de 1-amino-2-metilpropan-2-ol y la mezcla se agitó a 40°C durante la noche. Se agregó agua y la mezcla se extrajo con diclorometano y metanol. La fase orgánica se lavó con agua y se secó sobre sulfato de sodio. Luego de la filtración y la eliminación del solvente el residuo se purificó mediante cromatografía para dar 798 mg (65%) del compuesto del título.

Ejemplo Intermediario 1c

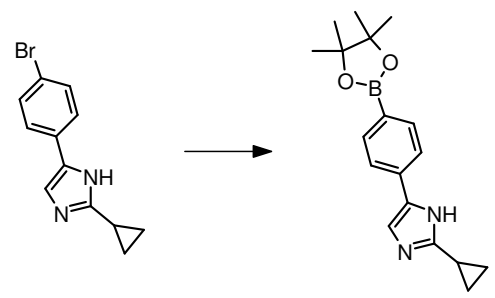
8-Bromo-6-cloro-3-yodoimidazo[1,2-b]piridazina



Una mezcla de 100 g (430 mmol) de 8-bromo-6-cloroimidazo[1,2-b]piridazina, que se preparó de acuerdo con el procedimiento descrito en US2007/78136 (WO2007/38314), 145 g de N-yodosuccinimida, ácido clorhídrico concentrado 5 % en peso y 1 L de triclorometano se calentó a reflujo durante 6 horas., se agregaron 20 g de N-yodosuccinimida y el calentamiento se continuó durante otras 3 horas. El precipitado se retiró y el material filtrado se lavó con solución de hidróxido de sodio 1N, salmuera y se secó sobre sulfato de sodio. Luego de la filtración y la eliminación del solvente se agregó éter diisopropílico y el residuo se agitó a 23°C durante la noche. El precipitado se retiró por filtración y se secó para dar 66,6 g (43%) del compuesto del título.

Ejemplo Intermediario 1d

2-Ciclopropil-5-[4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil]-1H-imidazol

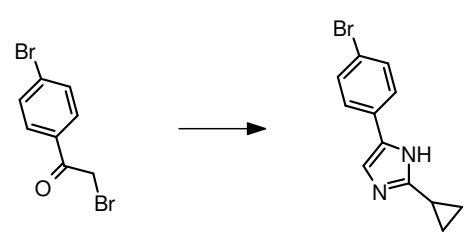


Una mezcla de 42,1 g (160 mmol) de 5-(4-bromofenil)-2-ciclopropil-1H-imidazol, que se preparó de acuerdo con el Ejemplo Intermediario 1e, 60,9 g de 4,4,4',4',5,5,5',5'-octametil-2,2'-bi-1,3,2-dioxaborolano, 3,05 g de diciclohexil(2',4',6'-triisopropilbifenil-2-il)fosfina, 1,46 g de tris-(dibencilidenacetone)-dipaladio(0), 23,5 g de acetato de

potasio y 267 mL de 1,4-dioxano se agitó a 110°C durante 4 horas. Luego de enfriar a 23°C, se agregaron acetato de etilo y ácido clorhídrico 1M y el pH se ajustó a 8,0 agregando solución de hidróxido de sodio 5%. La mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de sodio. Luego de la filtración y la eliminación del solvente el residuo se purificó mediante cristalización para dar 33,5 g (67%) del compuesto del título.

Ejemplo Intermediario 1e

5-(4-Bromofenil)-2-ciclopropil-1H-imidazol



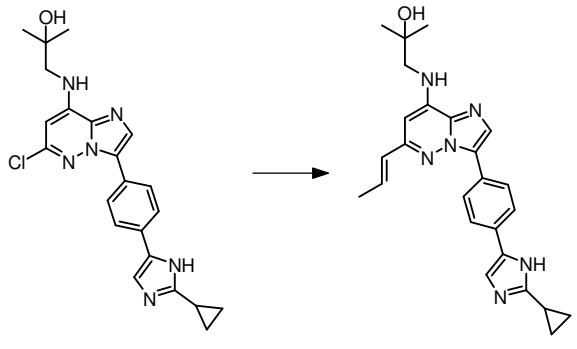
A una solución de 89,0 g (320 mmol) de 2-bromo-1-(4-bromofenil)etanona en 2,0 L de N,N-dimetilformamida, se agregaron clorhidrato de ciclopropancarboximidamida, 132,8 g de carbonato de potasio y la mezcla se agitó a 23°C durante la noche. Luego de la eliminación del solvente, se agregó agua y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de sodio. Luego de la filtración y la eliminación del solvente el residuo se purificó mediante cristalización para dar 42,1 g (50%) del compuesto del título.

Ejemplo 2

1-({3-[4-(2-Ciclopropil-1H-imidazol-5-il)fenil]-6-[(1E/Z)-prop-

1-en-1-il]

imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol



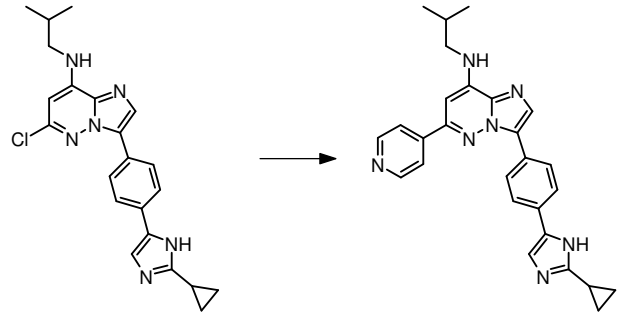
Se trataron 47,5 mg (112 µmol) de 1-({6-cloro-3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol, que se preparó de acuerdo con el Ejemplo Intermediario 1a, de manera análoga al Ejemplo 1 usando ácido (1E/Z) prop-1-en-1-ilborónico para dar, luego del tratamiento posterior y la purificación, 34,1 mg (71%) de los compuestos del título.

1H-RMN (DMSO-d6): δ= 0,81-0,93 (4H), 1,16 (6H), 1,83-1,98 (4H), 3:13+3,26 (2H), 4,76 (1H), 6,34-6,46 (2H), 6,59-6,78 (2H), 7,19+7,45 (1H), 7,66+7,76 (2H), 7,85+7,91 (1H), 8,08+8,15 (2H), 11,79+12,11 (1H) ppm.

Ejemplo 3

3-[4-(2-Ciclopropil-1H-imidazol-5-il)fenil]-N-isobutil-6-(piridin-4-il)

imidazo[1,2-b]piridazin-8-amina

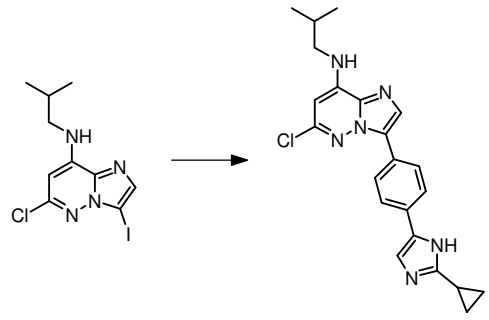


Se trataron 50 mg (123 µmol) de 6-cloro-3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-N-isobutilimidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 3a, de manera análoga al Ejemplo 1 usando ácido piridin-4-ilborónico para dar, luego del tratamiento posterior y la purificación, 10,9 mg (20%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,82-0,91 (4H), 0,94 (6H), 1,94 (1H), 2,04 (1H), 3,26 (2H), 6,74 (1H), 7,49 (1H), 7,68 (1H), 7,82 (2H), 7,98 (1H), 8,05 (2H), 8,16 (2H), 8,72 (2H), 11,82+12,13 (1H) ppm.

Ejemplo Intermediario 3a

6-Cloro-3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-N-isobutilimidazo[1,2-b]piridazin-8-amina

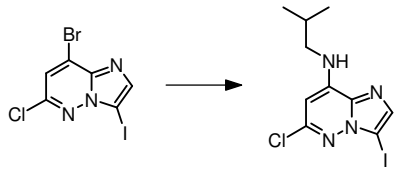


Se trataron 200 mg (570 µmol) de 6-cloro-3-yodo-N-isobutilimidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 3b, de manera análoga al

Ejemplo Intermediario 1a para dar, luego del tratamiento posterior y la purificación, 114 mg (49%) del compuesto del título.

Ejemplo Intermediario 3b

6-Cloro-3-yodo-N-isobutilimidazo[1,2-b]piridazin-8-amina

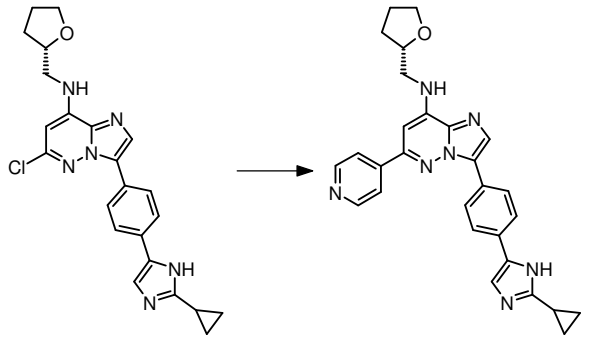


Se trataron 200 mg (558 µmol) de 8-bromo-6-cloro-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 1c, de manera análoga al Ejemplo Intermediario 1b usando 2-metilpropan-1-amina para dar, luego del tratamiento posterior y la purificación, 188 mg (96%) del compuesto del título.

Ejemplo 4

3-[4-(2-Ciclopropil-1H-imidazol-5-il)fenil]-6-(piridin-4-il)-N-[(2S)-

tetrahidrofurano-2-ilmetil]imidazo[1,2-b]piridazin-8-amina



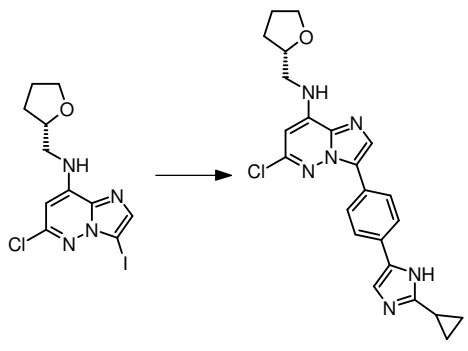
Se trataron 50 mg (115 µmol) de 6-cloro-3-[4-(2-ciclopropil-1H-

imidazol-5-il)fenil]-N-[(2S)-tetrahidrofurano-2-ilmetil]imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 4a, de manera análoga al Ejemplo 1 usando ácido piridin-4-ilborónico para dar, luego del tratamiento posterior y la purificación, 4,4 mg (8%) del compuesto del título.

1H-RMN (CDCl3): δ= 1,01-1,12 (4H), 1,73 (1H), 1,95 (2H), 2,09 (2H), 3,44 (1H), 3,53 (1H), 3,78 (1H), 3,92 (1H), 4,21 (1H), 6,50 (1H), 7,21 (1H), 7,70 (2H), 7,74 (1H), 7,85 (2H), 8,07 (2H), 8,17 (1H), 8,63 (2H) ppm.

Ejemplo Intermediario 4a

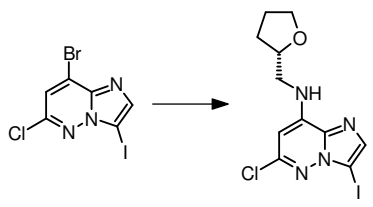
6-Cloro-3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-N-[(2S)-tetrahidrofurano-2-ilmetil]imidazo[1,2-b]piridazin-8-amina



Se trataron 232 mg (613 µmol) de 6-cloro-3-yodo-N-[(2S)-tetrahidrofurano-2-ilmetil]imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 4b, de manera análoga al Ejemplo Intermediario 1a para dar, luego del tratamiento posterior y la purificación, 118 mg (44%) del compuesto del título.

Ejemplo Intermediario 4b

6-Cloro-3-yodo-N-[(2S)-tetrahidrofurano-2-ilmetil]imidazo[1,2-b]piridazin-8-amina

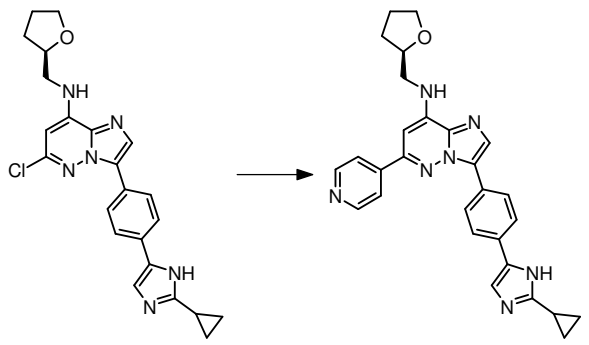


Se trataron 500 mg (1,40 mmol) de 8-bromo-6-cloro-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 1c, de manera análoga al Ejemplo Intermediario 1b usando 1-[(2S)-tetrahidrofurano-2-il]metanamina para dar, luego del tratamiento posterior y la purificación, 497 mg (94%) del compuesto del título.

Ejemplo 5

3-[4-(2-Ciclopropil-1H-imidazol-5-il)fenil]-6-(piridin-4-il)-N-[(2R)-

tetrahidrofurano-2-ilmetil]imidazo[1,2-b]piridazin-8-amina



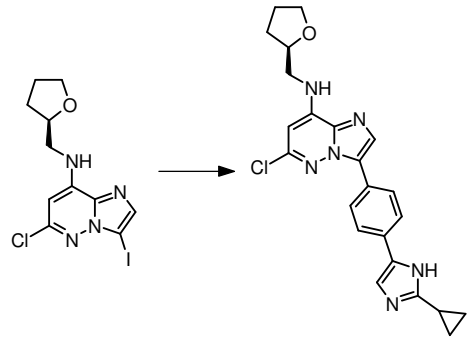
Se trataron 50 mg (115 µmol) de 6-cloro-3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-N-[(2R)-tetrahidrofurano-2-ilmetil]imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 5a, de manera análoga al Ejemplo 1 usando ácido piridin-4-ilborónico para dar, luego del

tratamiento posterior y la purificación, 6,1 mg (11%) del compuesto del título.

1H-RMN (CDCl3): δ= 1,01-1,12 (4H), 1,73 (1H), 1,95 (2H), 2,09 (2H), 3,44 (1H), 3,53 (1H), 3,78 (1H), 3,92 (1H), 4,21 (1H), 6,50 (1H), 7,21 (1H), 7,70 (2H), 7,74 (1H), 7,85 (2H), 8,07 (2H), 8,17 (1H), 8,63 (2H) ppm.

Ejemplo Intermediario 5a

6-Cloro-3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-N-[(2R)-tetrahidrofurano-2-ilmetil]imidazo[1,2-b]piridazin-8-amina

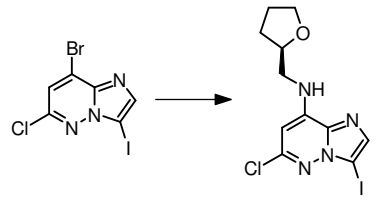


Se trataron 247 mg (652 µmol) de 6-cloro-3-yodo-N-[(2R)-tetrahidrofurano-2-ilmetil]imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 5b, de manera análoga al Ejemplo Intermediario 1a para dar, luego del tratamiento posterior y la purificación, 112 mg (39%) del compuesto del título.

Ejemplo Intermediario 5b

6-Cloro-3-yodo-N-[(2R)-tetrahidrofurano-2-ilmetil]imidazo[1,2-b]piridazin-

8-amina

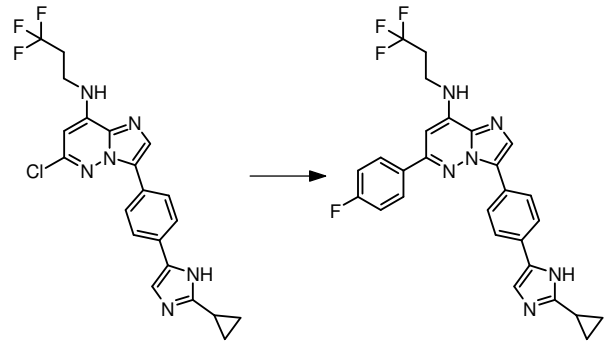


Se trataron 500 mg (1,40 mmol) de 8-bromo-6-cloro-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 1c, de manera análoga al Ejemplo Intermediario 1b usando 1-[(2R)-tetrahidrofurano-2-il]metanamina para dar, luego del tratamiento posterior y la purificación, 513 mg (97%) del compuesto del título.

Ejemplo 6

3-[4-(2-Ciclopropil-1H-imidazol-5-il)fenil]-6-(4-fluorofenil)-N-(3,3,3-

trifluoropropil)imidazo[1,2-b]piridazin-8-amina



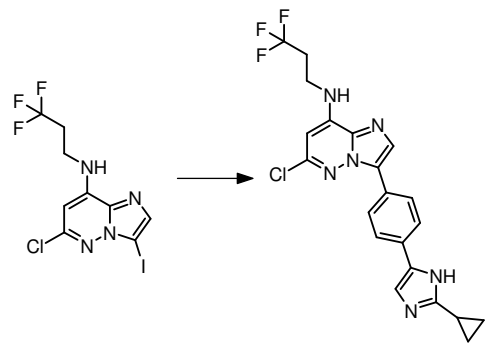
Se trataron 40 mg (90 µmol) de 6-cloro-3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 6a, de manera análoga al Ejemplo 1 usando ácido (4-fluorofenil)borónico para dar, luego del tratamiento posterior y la purificación, 3,6 mg (7%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,97-1,09 (4H), 2,00 (2H), 2,59 (2H), 3,73 (2H), 5,97 (1H), 6,37 (1H), 7,14-7,26 (3H), 7,75-7,84 (3H), 7,96 (2H), 8,13 (2H) ppm.

Ejemplo Intermediario 6a

6-Cloro-3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-N-(3,3,3-trifluoropropil)

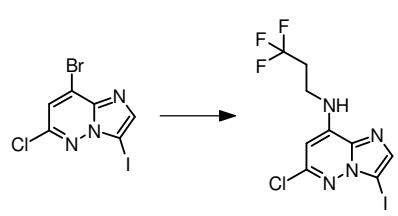
imidazo[1,2-b]piridazin-8-amina



Se trataron 330mg (845 µmol) de 6-cloro-3-yodo-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 6b, de manera análoga al Ejemplo Intermediario 1a para dar, luego del tratamiento posterior y la purificación, 220 mg (58%) del compuesto del título.

Ejemplo Intermediario 6b

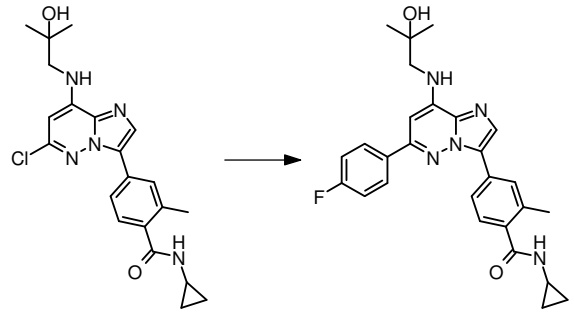
6-Cloro-3-yodo-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina



Se trataron 1,96 g (5,46 mmol) de 8-bromo-6-cloro-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 1c, de manera análoga al Ejemplo Intermediario 1b usando 3,3,3-trifluoropropan-1-amina para dar, luego del tratamiento posterior y la purificación, 1,58 g (74%) del compuesto del título.

Ejemplo 7

N-ciclopropil-4-{6-(4-fluorofenil)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



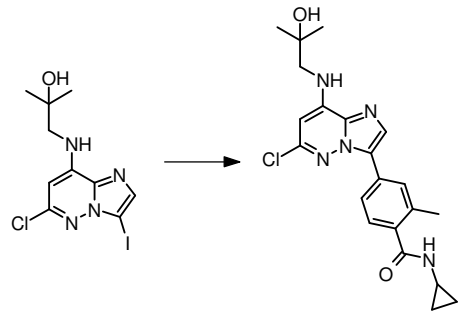
Se trataron 76 mg (184 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 1 usando ácido (4-fluorofenil)borónico para dar, luego del tratamiento posterior y la purificación, 25,7 mg (30%) del compuesto del título.

1H-RMN (CDCl3/CD3OD): δ= 0,61 (2H), 0,86 (2H), 1,37 (6H), 2,47 (3H), 2,88 (1H), 3,33 (2H), 6,38 (1H), 7,13 (2H), 7,39 (1H), 7,69 (1H), 7,83-7,91 (3H), 7,94 (1H) ppm.

Ejemplo Intermediario 7a

4-{6-Cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-

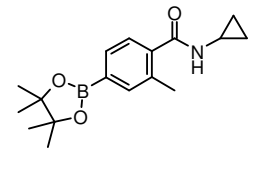
N-ciclopropil-2-metilbenzamida



Se trataron 700 mg (1,91 mmol) de 1-[(6-cloro-3-yodoimidazo[1,2-b]piridazin-8-il)amino]-2-metilpropan-2-ol, que se preparó de acuerdo con el Ejemplo Intermediario 1b, de manera análoga al Ejemplo Intermediario 1a usando N-ciclopropil-2-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7b para dar, luego del tratamiento posterior y la purificación, 360 mg (46%) del compuesto del título.

Ejemplo Intermediario 7b

N-ciclopropil-2-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzamida



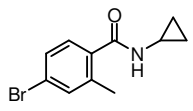
A una solución de 260g (1,02 mol) de 4-bromo-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7c, en 2L de dioxano a 23°C, se agregaron 390g de bis-(pinacolato)-diboro, 19,5g de 2-diciclohexilfosfino-2',4',6'-triisopropilbifenilo, 150 g de

acetato de potasio y 9,37 g de tris-(dibencilidenaceton)-dipaladio(0) y la mezcla se sometió a reflujo durante 6 h. Luego de enfriar a 23°C, se agregaron agua y acetato de etilo y la mezcla se agitó durante 15 min. La fase orgánica se lavó con agua, se secó sobre sulfato de sodio, se filtró y se evaporó. El residuo se purificó mediante cromatografía para dar 308g (56%) del compuesto del título.

1H-RMN (300 MHz, CDCl3): δ = 0,59 (2H), 0,85 (2H), 1,33 (6H), 2,41 (3H), 2,87 (1H), 5,94 (1H), 7,28 (1H), 7,60 (1H), 7,63 (1H) ppm.

Ejemplo Intermediario 7c

4-Bromo-N-ciclopropil-2-metilbenzamida

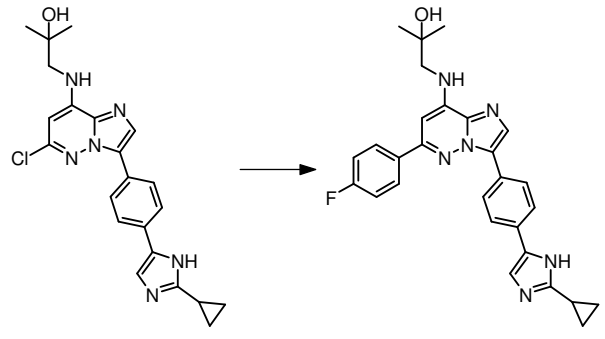


A una solución agitada de 300g (1,4 mol) de ácido 4-bromo-2-metilbenzoico en 8,4L de diclorometano a 23°C, se agregaron 79,6g de ciclopropanamina y 320,9g de EDC. Luego de agitar durante la noche, la solución se lavó con agua y la fase acuosa se extrajo con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato de sodio, se filtró y se evaporó. Los sólidos restantes se trituraron con éter diisopropílico, se filtró, se lavó y se secó al vacío para dar 260g (73%) del compuesto del título.

Ejemplo 8

1-({3-[4-(2-Ciclopropil-1H-imidazol-5-il)fenil]-6-(4-fluorofenil)imidazo

[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol

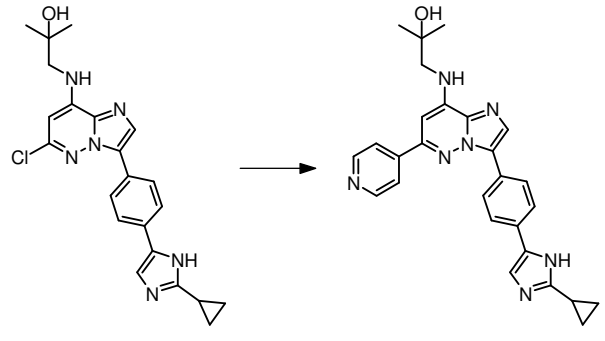


Se trataron 70 mg (166 µmol) de 1-({6-cloro-3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol, que se preparó de acuerdo con el Ejemplo Intermediario 1a, de manera análoga al Ejemplo 1 usando ácido (4-fluorofenil)borónico para dar, luego del tratamiento posterior y la purificación, 4,9 mg (6%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,80-0,94 (4H), 1,18 (6H), 1,93 (1H), 3,39 (2H), 4,79 (1H), 6,77 (1H), 6,86 (1H), 7,21+7,48 (1H), 7,85 (2H), 7,70+7,81 (2H), 7,94+7,99 (1H), 8,06-8,24 (4H), 11,81+12,12 (1H) ppm.

Ejemplo 9

1-({3-[4-(2-Ciclopropil-1H-imidazol-5-il)fenil]-6-(piridin-4-il)imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol



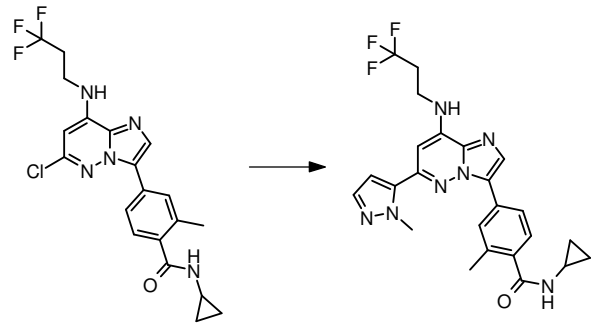
Se trataron 47,5 mg (112 µmol) de 1-({6-cloro-3-[4-(2-

ciclopropil-1H-imidazol-5-il)fenil]imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol, que se preparó de acuerdo con el Ejemplo Intermediario 1a, de manera análoga al Ejemplo 1 usando ácido piridin-4-ilborónico para dar, luego del tratamiento posterior y la purificación, 12,5 mg (23%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,82-0,92 (4H), 1,19 (6H), 1,93 (1H), 3,42 (2H), 4,79 (1H), 6,89 (1H), 7,01 (1H), 7,22+7,49 (1H), 7,72+7,83 (2H), 7,97-8,08 (3H), 8,15+8,23 (2H), 8,73 (2H), 7,82+12,13 (1H) ppm.

Ejemplo 10

N-ciclopropil-2-metil-4-{6-(1-metil-1H-pirazol-5-il)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida



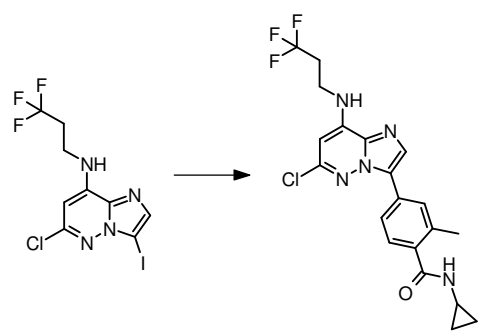
Se trataron 40 mg (91 µmol) de 4-{6-cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 10a, de manera análoga al Ejemplo 1 usando 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol para dar, luego del tratamiento posterior y la purificación, 7,2 mg (16%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,64 (2H), 0,90 (2H), 2,52 (3H), 2,58 (2H), 2,93 (1H), 3,72 (2H), 4,20 (3H), 5,95 (1H), 6,01 (1H), 6,28 (1H), 6,66 (1H), 7,42 (1H), 7,55 (1H), 7,79 (1H), 7,85 (1H), 7,89 (1H) ppm.

Ejemplo Intermediario 10a

4-{6-Cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-

N-ciclopropil-2-metilbenzamida

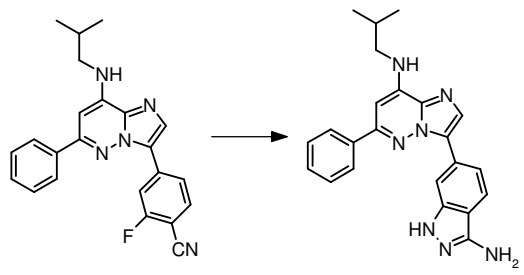


Se trataron 500 mg (1,28 mmol) de 6-cloro-3-yodo-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 6b, de manera análoga al Ejemplo Intermediario 1a usando N-ciclopropil-2-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzamida para dar, luego del tratamiento posterior y la purificación, 139 mg (25%) del compuesto del título.

Ejemplo 11

3-(3-Amino-1H-indazol-6-il)-N-isobutil-6-fenilimidazo[1,2-b]piridazin-

8-amina

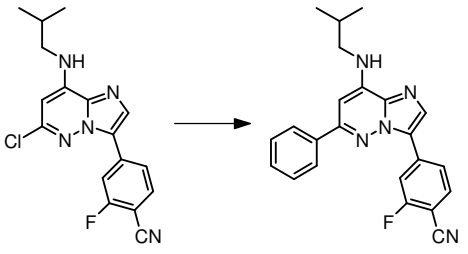


A una solución de 46 mg (119 µmol) de 2-fluoro-4-[8-(isobutilamino)-6-fenilimidazo[1,2-b]piridazin-3-il]benzonitrilo, que se preparó de acuerdo con el Ejemplo Intermediario 11a, en 2,5 mL de n-butanol, se agregaron 232 µL de hidrato de hidrazina y la mezcla se calentó a 120°C durante la noche. El precipitado se filtró, se lavó con 2-propanol y se secó para dar 26,5 mg (53%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,94 (6H), 2,04 (1H), 3,26 (2H), 5,33 (2H), 6,63 (1H), 7,46-7,58 (5H), 7,74 (1H), 8,00 (1H), 8,07 (2H), 8,38 (1H), 11,53 (1H) ppm.

Ejemplo Intermediario 11a

2-Fluoro-4-[8-(isobutilamino)-6-fenilimidazo[1,2-b]piridazin-3-il]benzonitrilo

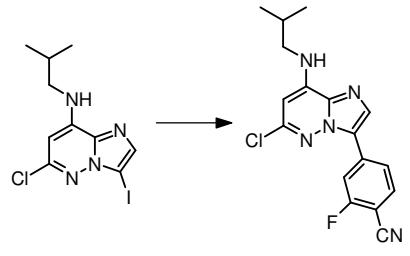


Se trataron 100 mg (291 µmol) de 4-[6-cloro-8-(isobutilamino)imidazo[1,2-b]piridazin-3-il]-2-fluorobenzonitrilo, que se preparó de acuerdo con el Ejemplo Intermediario 11b, de manera análoga al Ejemplo 1 usando ácido fenilborónico para dar, luego del tratamiento posterior y la

purificación, 49 mg (44%) del compuesto del título.

Ejemplo Intermediario 11b

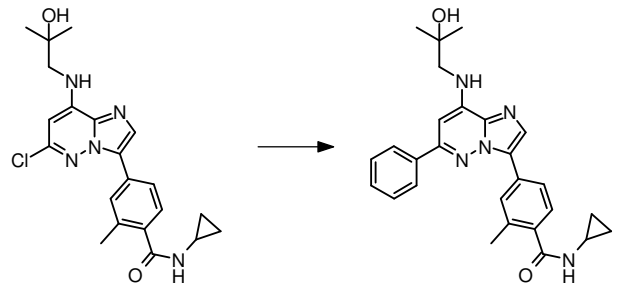
4-[6-Cloro-8-(isobutilamino)imidazo[1,2-b]piridazin-3-il]-2-fluorobenzonitrilo



Se trataron 500 mg (1,43 mmol) de 6-Cloro-3-yodo-N-isobutilimidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 3b, de manera análoga al Ejemplo Intermediario 1a usando ácido (4-ciano-3-fluorofenil)borónico para dar, luego del tratamiento posterior y la purificación, 217 mg (44%) del compuesto del título.

Ejemplo 12

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-fenilimidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



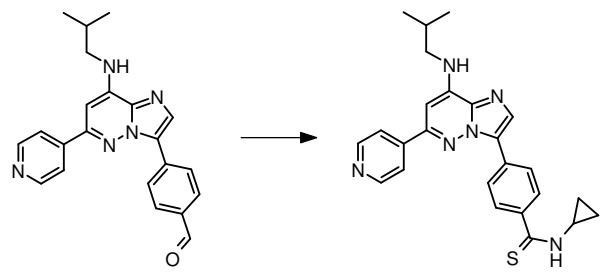
Se trataron 250 mg (604 µmol) de 4-{6-Cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 1 usando ácido

fenilborónico para dar, luego del tratamiento posterior y la purificación, 48 mg (17%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 1,18 (6H), 2,39 (3H), 2,81 (1H), 3,39 (2H), 4,78 (1H), 6,80 (1H), 6,90 (1H), 7,40 (1H), 7,46-7,55 (3H), 8,00-8,07 (4H), 8,13 (1H), 8,30 (1H) ppm.

Ejemplo 13

N-ciclopropil-4-[8-(isobutilamino)-6-(piridin-4-il)imidazo[1,2-b]piridazin-3-il]bencencarbotioamida



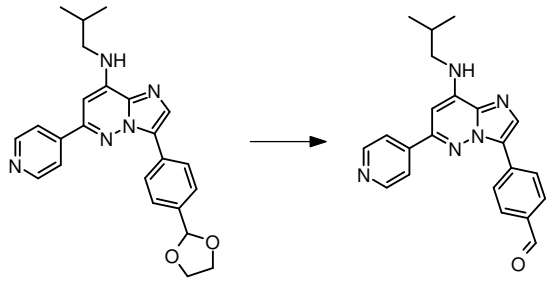
Una mezcla de 40 mg (108 µmol) de 4-[8-(isobutilamino)-6-(piridin-4-il)imidazo[1,2-b]piridazin-3-il]benzaldehído, que se preparó de acuerdo con el Ejemplo Intermediario 13a, 3,45 mg de azufre, 37 µL de ciclopropanamina y 250 µL de dimetilsulfóxido se calentó a 100°C bajo irradiación de microondas durante 4 horas. La mezcla se agitó a 90°C durante la noche, el solvente se evaporó y el residuo se purificó mediante cromatografía para dar 4,8 mg (10%) del compuesto del título.

1H-RMN (CDCl3/CD3OD): δ= 0,80 (2H), 1,03 (2H), 1,08 (6H), 2,08 (1H), 3,21 (2H), 3,40 (1H), 6,40 (1H), 7,78-7,89 (5H), 8,12 (2H), 8,69 (2H) ppm.

Ejemplo Intermediario 13a

4-[8-(Isobutilamino)-6-(piridin-4-il)imidazo[1,2-b]piridazin-3-

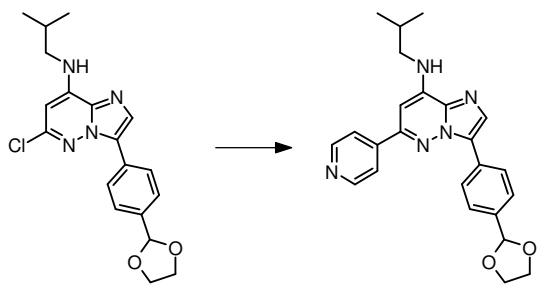
il]benzaldehído



A una solución de 63 mg (152 µmol) de 3-[4-(1,3-dioxolan-2-il)fenil]-N-isobutil-6-(piridin-4-il)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 13b, en 2,8 mL de acetona, se agregaron 190 µL de ácido clorhídrico 4N y la mezcla se agitó a 23°C durante 2 horas. Se agregó solución saturada de carbonato ácido y la mezcla se extrajo con diclorometano. La fase orgánica se secó sobre sulfato de sodio. Luego de la filtración y la eliminación del solvente el residuo se purificó mediante cromatografía para dar 41 mg (73%) del compuesto del título.

Ejemplo Intermediario 13b

3-[4-(1,3-Dioxolan-2-il)fenil]-N-isobutil-6-(piridin-4-il)imidazo[1,2-b]piridazin-8-amina

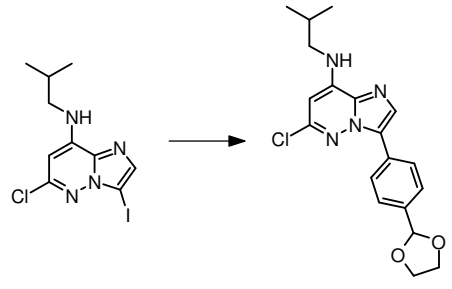


Se trataron 105 mg (282 µmol) de 6-cloro-3-[4-(1,3-dioxolan-2-il)fenil]-N-isobutilimidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 13c, de manera

análoga al Ejemplo 1 usando ácido piridin-4-ilborónico para dar, luego del tratamiento posterior y la purificación, 64 mg (55%) del compuesto del título.

Ejemplo Intermediario 13c

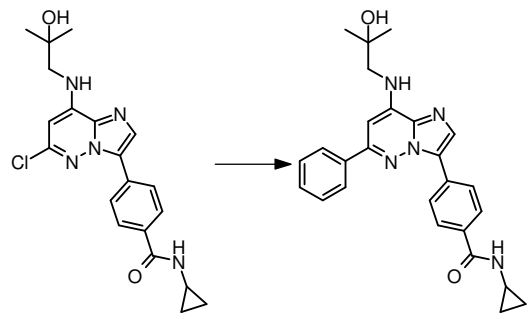
6-Cloro-3-[4-(1,3-dioxolan-2-il)fenil]-N-isobutilimidazo[1,2-b]piridazin-8-amina



Se trataron 500 mg (1,43 mmol) de 6-Cloro-3-yodo-N-isobutilimidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 3b, de manera análoga al Ejemplo Intermediario 1a usando 2-[4-(1,3-dioxolan-2-il)fenil]-4,4,5,5-tetrametil-1,3,2-dioxaborolano para dar, luego del tratamiento posterior y la purificación, 314 mg (47%) del compuesto del título.

Ejemplo 14

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-fenilimidazo[1,2-b]piridazin-3-il}benzamida

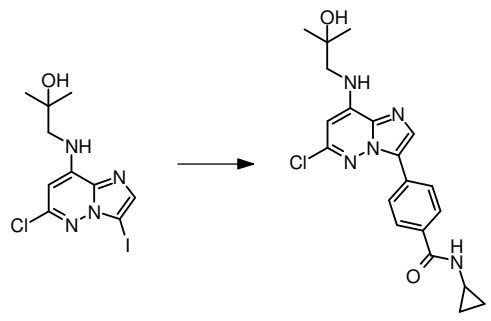


Se trataron 176 mg (440 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida que se preparó de acuerdo con el Ejemplo Intermediario 14a, de manera análoga al Ejemplo 1 usando ácido fenilborónico para dar, luego del tratamiento posterior y la purificación, 42 mg (21%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,56 (2H), 0,67 (2H), 1,19 (6H), 2,85 (1H), 3,40 (2H), 4,78 (1H), 6,82 (1H), 6,93 (1H), 7,46-7,55 (3H), 7,93 (2H), 8,05 (2H), 8,09 (1H), 8,33 (2H), 8,45 (1H) ppm.

Ejemplo Intermediario 14a

4-{6-Cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida



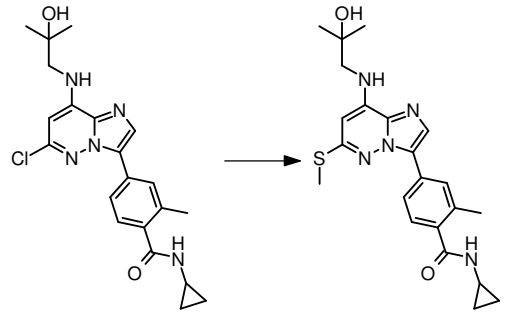
Se trataron 976 mg (2,66 mmol) de 1-[(6-cloro-3-yodoimidazo[1,2-b]piridazin-8-il)amino]-2-metilpropan-2-ol, que se preparó de acuerdo con el Ejemplo Intermediario 1b, de manera análoga al Ejemplo Intermediario 1a usando ácido [4-(ciclopropilcarbamoil)fenil]borónico para dar, luego del tratamiento posterior y la purificación, 602 mg (57%) del compuesto del título.

Ejemplo 15

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-

(metilsulfanil)

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

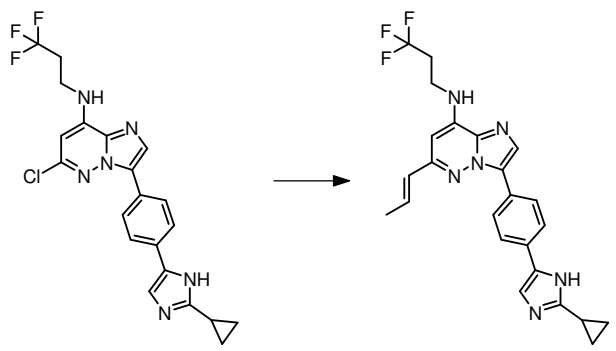


A una solución de 83 mg (201 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, en 1,0 mL de dimetilsulfóxido, se agregaron 70 mg de metantiolato de sodio y la mezcla se calentó bajo radiación de microondas a 70°C durante 1 hora. La mezcla se volcó sobre agua y se extrajo con diclorometano y metanol. La capa orgánica se lavó con salmuera y se secó sobre sulfato de sodio. Luego de la filtración y la eliminación del solvente el residuo se purificó mediante recristalización para dar 46,7 mg (55%) del compuesto del título.

Ejemplo 16

3-[4-(2-Ciclopropil-1H-imidazol-5-il)fenil]-6-[(1E)-prop-1-en-1-il]-

N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina



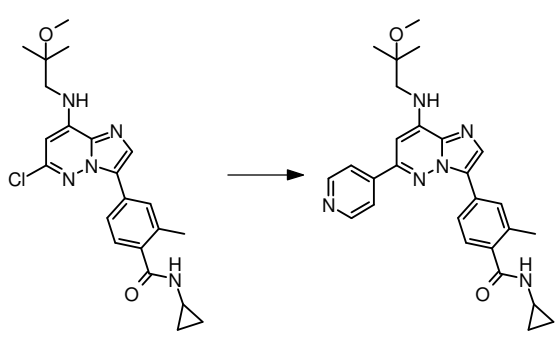
Se trataron 35 mg (78 µmol) de 6-cloro-3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 6a, de manera análoga al Ejemplo 1 usando ácido (1E)-prop-1-en-1-ilborónico para dar, luego del tratamiento posterior y la purificación, 3,6 mg (10%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,95-1,04 (4H), 1,95 (3H), 2,00 (1H), 2,55 (2H), 3,62 (2H), 6,10 (1H), 6,46 (1H), 6,61 (1H), 7,16 (1H), 7,67 (1H), 7,70 (2H), 8,05 (2H) ppm.

Ejemplo 17

N-ciclopropil-4-{8-[(2-metoxi-2-metilpropil)amino]-6-(piridin-4-il)

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



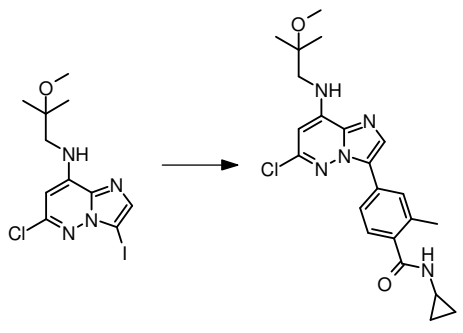
Se trataron 60 mg (140 µmol) de 4-{6-Cloro-8-[(2-metoxi-2-

metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 17a, de manera análoga al Ejemplo 1 usando ácido piridin-4-ilborónico para dar, luego del tratamiento posterior y la purificación, 18,7 mg (28%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,64 (2H), 0,90 (2H), 1,33 (6H), 2,54 (3H), 2,93 (1H), 3,28 (3H), 3,38 (2H), 6,11 (1H), 6,18 (1H), 6,42 (1H), 7,44 (1H), 7,80-7,85 (3H), 7,92 (1H), 8,00 (1H), 8,71 (2H) ppm.

Ejemplo Intermediario 17a

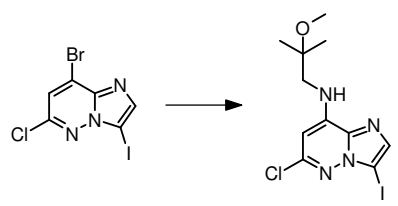
4-{6-Cloro-8-[(2-metoxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



Se trataron 145 mg (380 µmol) de 6-cloro-3-yodo-N-(2-metoxi-2-metilpropil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 17b, de manera análoga al Ejemplo Intermediario 1a usando N-ciclopropil-2-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzamida para dar, luego del tratamiento posterior y la purificación, 131 mg (81%) del compuesto del título.

Ejemplo Intermediario 17b

6-Cloro-3-yodo-N-(2-metoxi-2-metilpropil)imidazo[1,2-b]piridazin-8-amina

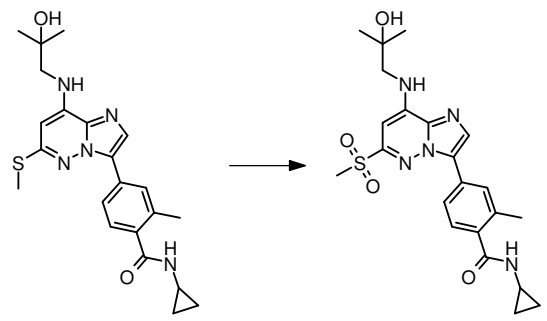


Se trataron 250 mg (698 µmol) de 8-bromo-6-cloro-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 1c, de manera análoga al Ejemplo Intermediario 1b usando 2-metoxi-2-metilpropan-1-amina para dar, luego del tratamiento posterior y la purificación, 260 mg (98%) del compuesto del título.

Ejemplo 18

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(metilsulfonil)

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



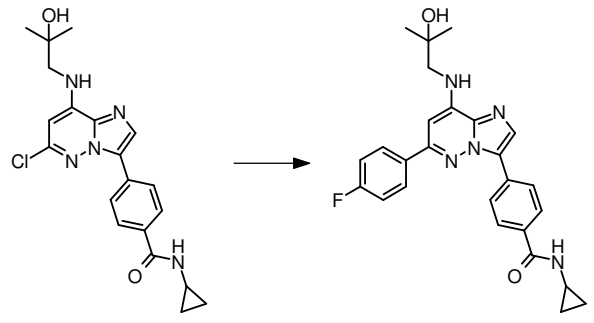
A una solución de 38,7 mg (91 µmol) de N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(metilsulfanil)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 15, en 1,2 mL de N,N-dimetilformamida, se agregaron 168 mg de Oxona y la mezcla se

agitó a 23°C durante 2,5 días. Se agregó agua y la mezcla se extrajo con diclorometano. La fase orgánica se lavó con agua y se secó sobre sulfato de sodio. Luego de la filtración y la eliminación del solvente el residuo se purificó mediante cromatografía para dar 18,5 mg (39%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,65 (2H), 1,15 (6H), 2,37 (3H), 2,80 (1H), 3,34 (2H), 3,38 (3H), 4,79 (1H), 6,76 (1H), 7,40 (1H), 7,71 (1H), 7,95 (1H), 7,99 (1H), 8,16 (1H), 8,32 (1H) ppm.

Ejemplo 19

N-ciclopropil-4-{6-(4-fluorofenil)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida



Se trataron 200 mg (500 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 14a, de manera análoga al Ejemplo 1 usando ácido (4-fluorofenil)borónico para dar, luego del tratamiento posterior y la purificación, 136 mg (59%) del compuesto del título.

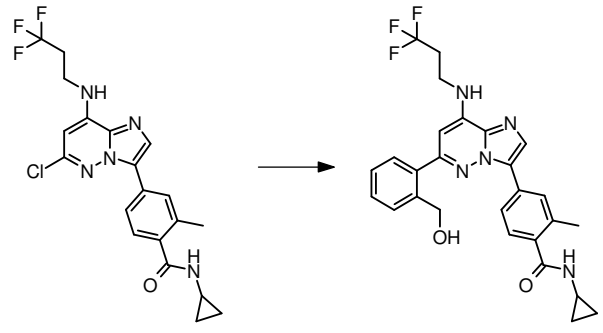
1H-RMN (DMSO-d6): δ= 0,56 (2H), 0,68 (2H), 1,18 (6H), 2,85 (1H), 3,39 (2H), 4,79 (1H), 6,81 (1H), 6,94 (1H), 7,35 (2H), 7,93

(2H), 8,09 (1H), 8,11 (2H), 8,31 (2H), 8,46 (1H) ppm.

Ejemplo 20

N-ciclopropil-4-{6-[2-(hidroximetil)fenil]-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

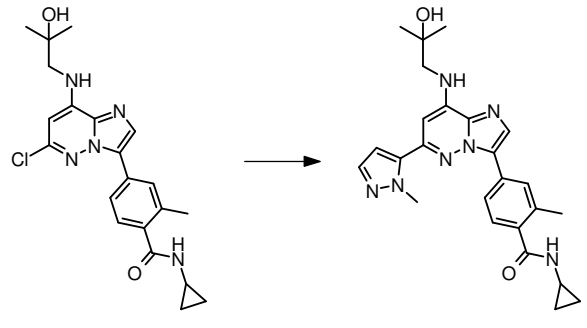


Se trataron 172 mg (393 µmol) de 4-{6-cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 10a, de manera análoga al Ejemplo 1 usando ácido [2-(hidroximetil)fenil] borónico para dar, luego del tratamiento posterior y la purificación, 29,1 mg (14%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,58 (2H), 0,85 (2H), 2,48 (3H), 2,58 (2H), 2,88 (1H), 3,72 (2H), 3,96 (1H), 4,41 (2H), 6,16 (1H), 6,19 (1H), 6,24 (1H), 7,38 (1H), 7,45-7,52 (3H), 7,60 (1H), 7,61 (1H), 7,70 (1H), 7,72 (1H) ppm.

Ejemplo 21

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(1-metil-1H-pirazol-5-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

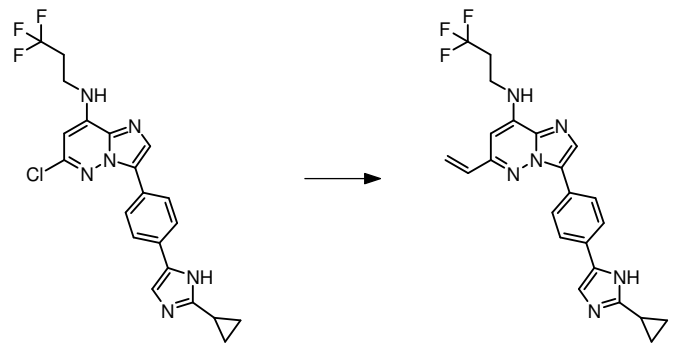


Se trataron 100 mg (242 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 1 usando 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol para dar, luego del tratamiento posterior y la purificación, 35,9 mg (31%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,65 (2H), 1,17 (6H), 2,35 (3H), 2,80 (1H), 3,35 (2H), 4,13 (3H), 4,76 (1H), 6,62 (1H), 6,89 (1H), 7,00 (1H), 7,37 (1H), 7,51 (1H), 7,93 (1H), 7,97 (1H), 7,98 (1H), 8,30 (1H) ppm.

Ejemplo 22

3-[4-(2-Ciclopropil-1H-imidazol-5-il)fenil]-6-etenil-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina



Se trataron 55 mg (123 µmol) de 6-cloro-3-[4-(2-ciclopropil-1H-

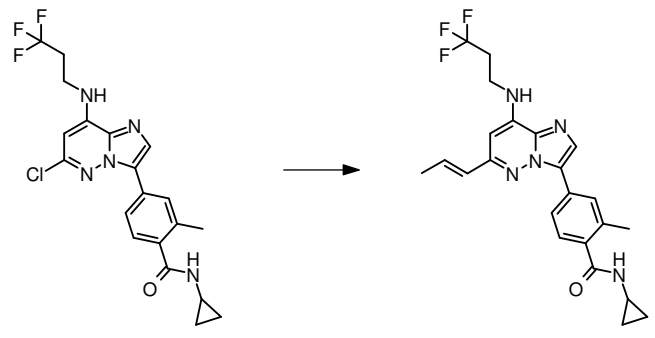
imidazol-5-il)fenil]-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 6a, de manera análoga al Ejemplo 1 usando 4,4,5,5-tetrametil-2-vinil-1,3,2-dioxaborolano para dar, luego del tratamiento posterior y la purificación, 3,2 mg (6%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,95-1,03 (4H), 1,99 (1H), 2,56 (2H), 3,64 (2H), 5,58 (1H), 6,07 (1H), 6,18 (1H), 6,76 (1H), 7,16 (1H), 7,68-7,74 (3H), 8,05 (2H) ppm.

Ejemplo 23

N-ciclopropil-2-metil-4-{6-[(1E/Z)-prop-1-en-1-il]-8-[(3,3,3-trifluoropropil)

amino]imidazo[1,2-b]piridazin-3-il}benzamida

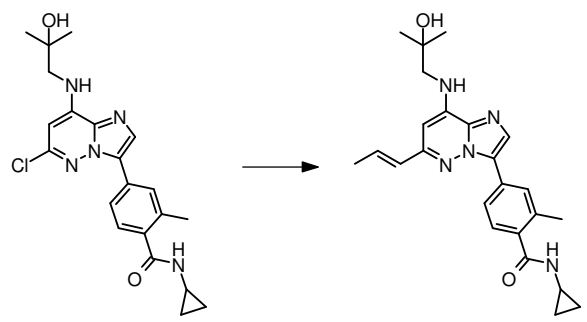


Se trataron 75 mg (171 µmol) de 4-{6-Cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 10a, de manera análoga al Ejemplo 1 usando ácido (1E)-prop-1-en-1-ilborónico para dar, luego del tratamiento posterior y la purificación, 3,0 mg (4%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,63 (2H), 0,90 (2H), 1,98 (3H), 2,47-2,65 (2H), 2,54 (3H), 2,92 (1H), 3,67 (2H), 5,91 (1H), 5,98 (1H), 6,46 (1H), 6,60+6,66 (1H), 7,25 (1H), 7,43 (1H), 7,73 (1H), 7,90 (1H), 7,96 (1H) ppm.

Ejemplo 24

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(1E/Z)-prop-1-en-1-il]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 75 mg (181 µmol) de 4-{6-Cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 1 usando (1E)-prop-1-en-1-ilborónico ácido para dar, luego del tratamiento posterior y la purificación, 22 mg (29%) del compuesto del título.

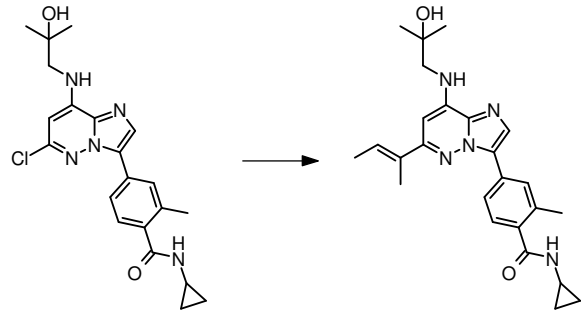
1H-RMN (CDCl3): δ= 0,63 (2H), 0,89 (2H), 1,43 (6H), 1,95+2,16 (3H), 2,51 (3H), 2,92 (1H), 3,32 (2H), 4,33 (1H), 5,99 (1H), 6,07+6,14 (1H), 6,37 (1H), 6,41 (1H), 6,57+6,63 (1H), 7,39 (1H), 7,66+7,70 (1H), 7,84+7,87 (1H), 7,94 (1H) ppm.

Ejemplo 25

4-{6-[(2E)-But-2-en-2-il]-8-[(2-hidroxi-2-

metilpropil)amino]imidazo[1,2-b]

piridazin-3-il}-N-ciclopropil-2-metilbenzamida



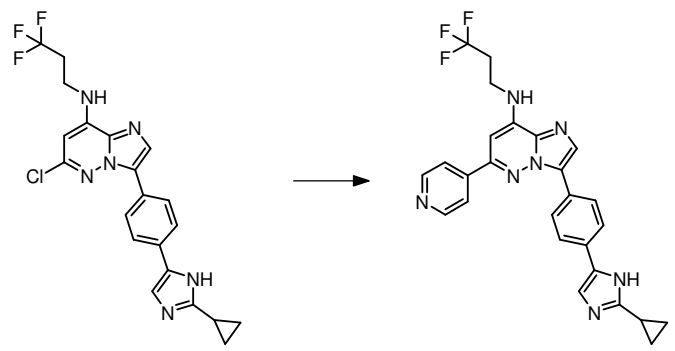
Se trataron 75 mg (181 µmol) de 4-{6-Cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 1 para dar, luego del tratamiento posterior y la purificación, 7,0 mg (8%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,62 (2H), 0,88 (2H), 1,45 (6H), 1,79 (3H), 2,11 (3H), 2,50 (3H), 2,91 (1H), 3,32 (2H), 5,02 (1H), 5,77 (1H), 5,97 (1H), 6,00 (1H), 6,50 (1H), 7,38 (1H), 7,70 (1H), 7,89 (1H), 7,91 (1H) ppm.

Ejemplo 26

3-[4-(2-Ciclopropil-1H-imidazol-5-il)fenil]-6-(piridin-4-il)-N-(3,3,3-

trifluoropropil)imidazo[1,2-b]piridazin-8-amina



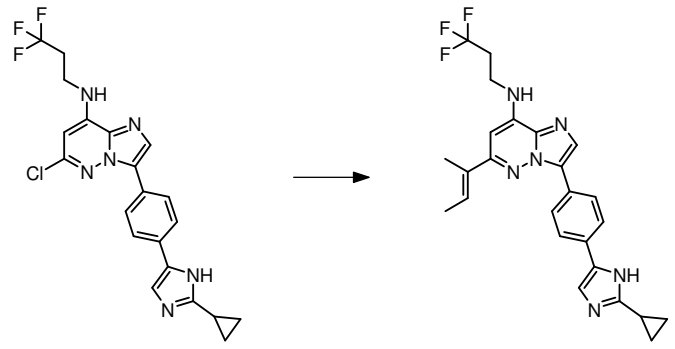
70 mg (157 µmol) de 6-Cloro-3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 6a Se trataron, de manera análoga al Ejemplo 1 usando ácido piridin-4-ilborónico para dar, luego del tratamiento posterior y la purificación, 3,2 mg (4%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,92-0,98 (4H), 1,98 (1H), 2,58 (2H), 3,32 (2H), 3,69 (2H), 6,42 (1H), 7,15 (1H), 7,72 (2H), 7,75 (1H), 7,87 (2H), 8,04 (2H), 8,65 (2H) ppm.

Ejemplo 27

6-[(2E)-But-2-en-2-il]-3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-N-(3,3,3-

trifluoropropil)imidazo[1,2-b]piridazin-8-amina



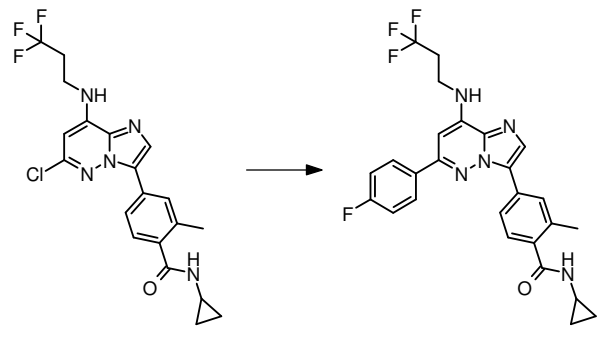
Se trataron 50 mg (112 µmol) de 6-Cloro-3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-N-(3,3,3-trifluoropropil)imidazo[1,2-

b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 6a, de manera análoga al Ejemplo 1 para dar, luego del tratamiento posterior y la purificación, 3,0 mg (5%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,95-1,02 (4H), 1,78 (3H), 1,99 (1H), 2,12 (3H), 2,46-2,63 (2H), 3,62 (2H), 5,78 (1H), 5,96 (1H), 7,16 (1H), 7,69 (2H), 7,73 (1H), 8,05 (2H) ppm.

Ejemplo 28

N-ciclopropil-4-{6-(4-fluorofenil)-8-[(3,3,3-trifluoropropil)amino]imidazo [1,2-b]piridazin-3-il}-2-metilbenzamida



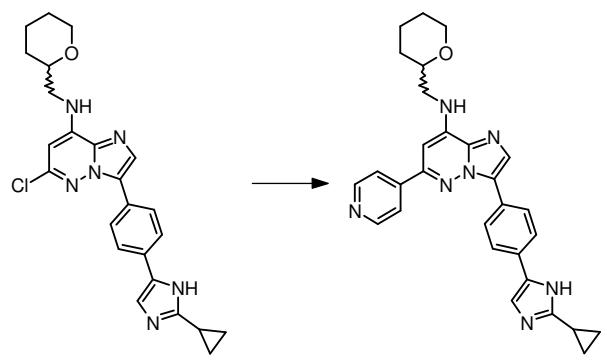
Se trataron 50 mg (114 µmol) de 4-{6-cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 10a, de manera análoga al Ejemplo 1 usando ácido (4-fluorofenil)borónico para dar, luego del tratamiento posterior y la purificación, 5,4 mg (9%) del compuesto del título.

1H-RMN (CDCl3/CD3OD): δ= 0,59 (2H), 0,86 (2H), 2,48 (3H), 2,58 (2H), 2,86 (1H), 3,68 (2H), 6,36 (1H), 7,16 (2H), 7,41 (1H),

7,74 (1H), 7,85-8,03 (4H) ppm.

Ejemplo 29

(RS) 3-[4-(2-Ciclopropil-1H-imidazol-5-il)fenil]-6-(piridin-4-il)-N-(tetrahidro-2H-piran-2-ilmetil)imidazo[1,2-b]piridazin-8-amina

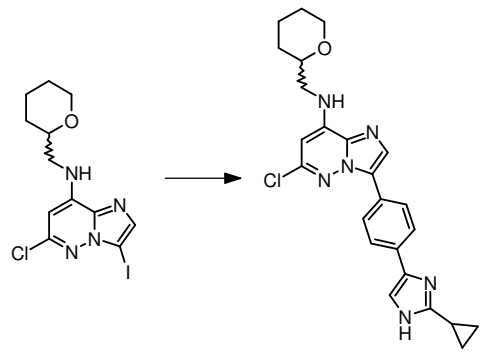


Se trataron 53 mg (118 µmol) de (RS)-6-Cloro-3-[4-(2-ciclopropil-1H-imidazol-4-il)fenil]-N-(tetrahidro-2H-piran-2-ilmetil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 29a, de manera análoga al Ejemplo 1 usando ácido piridin-4-ilborónico para dar, luego del tratamiento posterior y la purificación, 6,2 mg (10%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,99-1,09 (4H), 1,45-2,07 (7H), 3,34-3,55 (3H), 3,67 (1H), 4,06 (1H), 6,26 (1H), 6,44 (1H), 7,24 (1H), 7,79 (2H), 7,83 (1H), 7,88 (2H), 8,13 (2H), 8,74 (2H) ppm.

Ejemplo Intermediario 29a

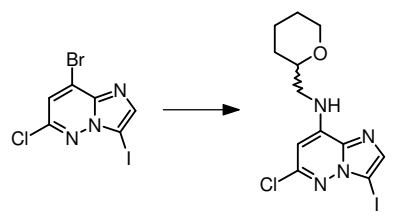
(RS)-6-Cloro-3-[4-(2-ciclopropil-1H-imidazol-4-il)fenil]-N-(tetrahidro-2H-piran-2-ilmetil)imidazo[1,2-b]piridazin-8-amina



Se trataron 105 mg (267 µmol) de (RS)-6-cloro-3-yodo-N-(tetrahidro-2H-piran-2-ilmetil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 29b, de manera análoga al Ejemplo Intermediario 1a para dar, luego del tratamiento posterior y la purificación, 61 mg (51%) del compuesto del título.

Ejemplo Intermediario 29b

(RS)-6-Cloro-3-yodo-N-(tetrahidro-2H-piran-2-ilmetil)imidazo[1,2-b]piridazin-8-amina

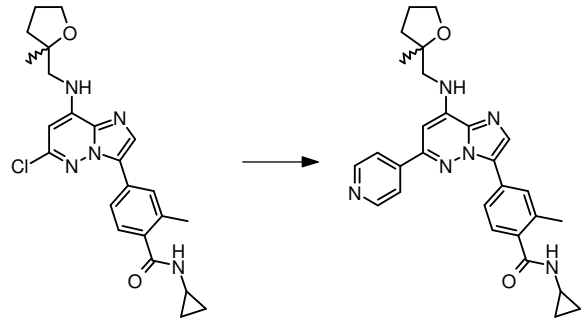


Se trataron 530 mg (1,48 mmol) de 8-bromo-6-cloro-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 1c, de manera análoga al Ejemplo Intermediario 1b usando 1-[(2RS)-tetrahidro-2H-piran-2-il]metanamina para dar, luego del tratamiento posterior y la purificación, 214 mg (37%) del compuesto del título.

Ejemplo 30

(RS)-N-ciclopropil-2-metil-4-[8-{[(2-metiltetrahidrofuran-2-il)metil]

amino}-6-(piridin-4-il)imidazo[1,2-b]piridazin-3-il]benzamida



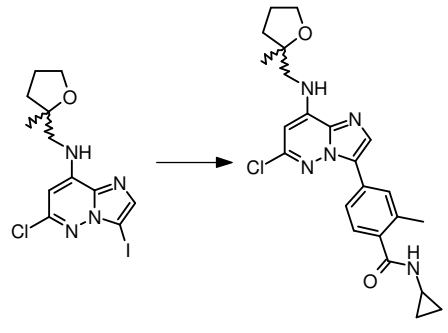
Se trataron 50 mg (114 µmol) de (RS)-4-(6-Cloro-8-{[(2-metiltetrahidrofuran-2-il)metil]amino}imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 30a, de manera análoga al Ejemplo 1 usando ácido piridin-4-ilborónico para dar, luego del tratamiento posterior y la purificación, 12,5 mg (22%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,64 (2H), 0,89 (2H), 1,35 (3H), 1,81 (1H), 1,91-2,10 (3H), 2,54 (3H), 2,93 (1H), 3,45 (2H), 3,93 (2H), 6,10 (1H), 6,20 (1H), 6,50 (1H), 7,44 (1H), 7,79-7,84 (3H), 7,92 (1H), 7,99 (1H), 8,71 (2H) ppm.

Ejemplo Intermediario 30a

(RS)-4-(6-Cloro-8-{[(2-metiltetrahidrofuran-2-il)metil]amino}imidazo[1,2-b]

piridazin-3-il)-N-ciclopropil-2-metilbenzamida

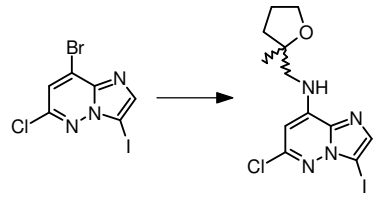


Se trataron 150 mg (382 µmol) de (RS)-6-cloro-3-yodo-N-[(2-metiltetrahidrofuran-2-il)metil]imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 30b, de manera análoga al Ejemplo Intermediario 1a usando N-ciclopropil-2-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzamida para dar, luego del tratamiento posterior y la purificación, 110 mg (65%) del compuesto del título.

Ejemplo Intermediario 30b

(RS) 6-Cloro-3-yodo-N-[(2-metiltetrahidrofuran-2-il)metil]imidazo[1,2-b]piridazin-

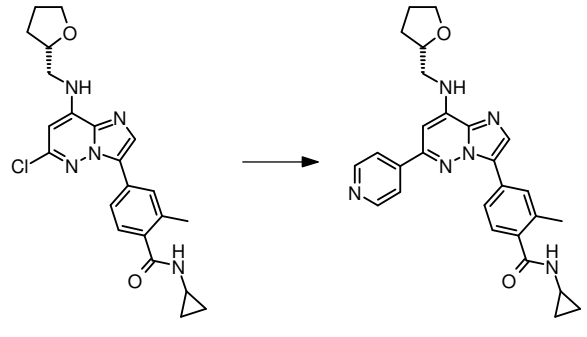
8-amina



Se trataron 250 mg (698 µmol) de 8-bromo-6-cloro-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 1c, de manera análoga al Ejemplo Intermediario 1b usando 1-[(2RS)-2-metiltetrahidrofuran-2-il]metanamina para dar, luego del tratamiento posterior y la purificación, 262 mg (96%) del compuesto del título.

Ejemplo 31

N-ciclopropil-2-metil-4-[6-(piridin-4-il)-8-{[(2S)-tetrahidrofurano-2-ilmetil]amino}imidazo[1,2-b]piridazin-3-il]benzamida

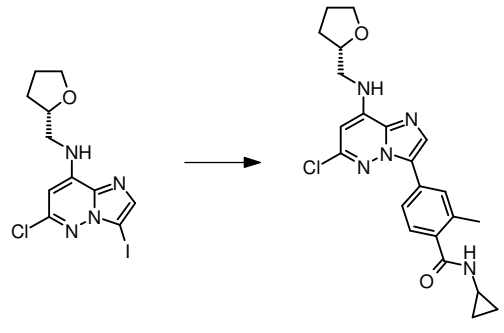


Se trataron 49 mg (115 µmol) de 4-(6-Cloro-8-{[(2S)-tetrahidrofurano-2-ilmetil]amino}imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 31a, de manera análoga al Ejemplo 1 usando ácido piridin-4-ilborónico para dar, luego del tratamiento posterior y la purificación, 3,6 mg (6%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,64 (2H), 0,90 (2H), 1,75 (1H), 1,98 (2H), 2,11 (1H), 2,55 (3H), 2,93 (1H), 3,46 (1H), 3,60 (1H), 3,82 (1H), 3,96 (1H), 4,24 (1H), 6,01 (1H), 6,23 (1H), 6,50 (1H), 7,45 (1H), 7,83 (1H), 7,84 (2H), 7,93 (1H), 8,00 (1H), 8,74 (2H) ppm.

Ejemplo Intermediario 31a

4-(6-Cloro-8-{[(2S)-tetrahidrofurano-2-ilmetil]amino}imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida

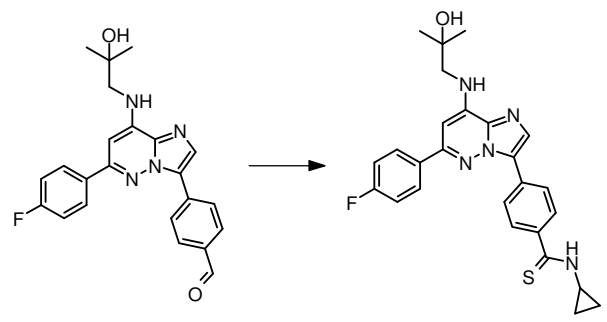


Se trataron 232 mg (613 µmol) de 6-cloro-3-yodo-N-[(2S)-tetrahidrofurano-2-ilmetil]imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 4b, de manera análoga al Ejemplo Intermediario 1a usando N-ciclopropil-2-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzamida para dar, luego del tratamiento posterior y la purificación, 98 mg (38%) del compuesto del título.

Ejemplo 32

N-ciclopropil-4-{6-(4-fluorofenil)-8-[(2-hidroxi-2-metilpropil)amino]

imidazo[1,2-b]piridazin-3-il}bencencarbotioamida



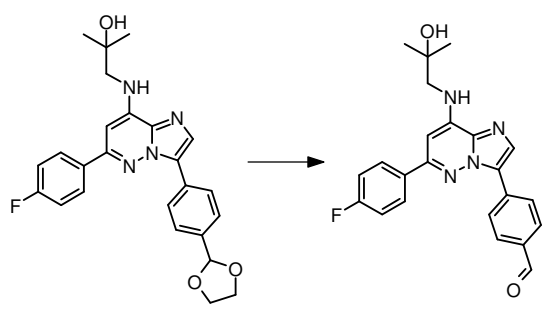
Se trataron 33 mg (82 µmol) de 4-{6-(4-fluorofenil)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzaldehído, que se preparó de acuerdo con el Ejemplo Intermediario 32a, de manera análoga al Ejemplo 13 para dar, luego del tratamiento posterior y la purificación, 3,3 mg (8%)

del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,75-0,88 (4H), 1,18 (6H), 3,40 (2H), 3,47 (1H), 4,78 (1H), 6,81 (1H), 6,95 (1H), 7,35 (2H), 7,84 (2H), 8,07 (1H), 8,11 (2H), 8,26 (2H), 10,16 (1H) ppm.

Ejemplo Intermediario 32a

4-{6-(4-Fluorofenil)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzaldehído

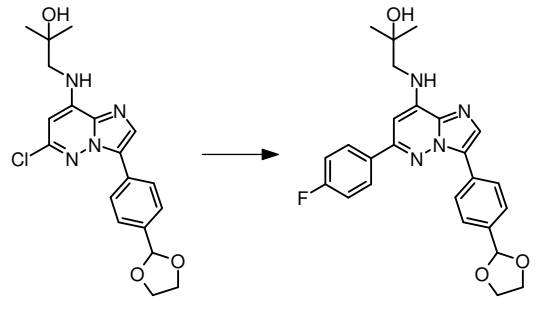


Se trataron 48 mg (107 µmol) de 1-({3-[4-(1,3-dioxolan-2-il)fenil]-6-(4-fluorofenil)imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol, que se preparó de acuerdo con el Ejemplo Intermediario 32b, de manera análoga al Ejemplo Intermediario 13a para dar, luego del tratamiento posterior y la purificación, 34,6 mg (76%) del compuesto del título.

Ejemplo Intermediario 32b

1-({3-[4-(1,3-Dioxolan-2-il)fenil]-6-(4-fluorofenil)imidazo[1,2-b]piridazin-8-il}

amino)-2-metilpropan-2-ol

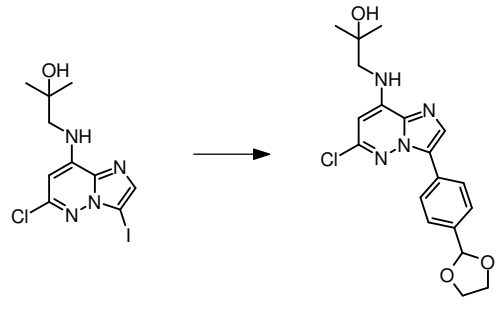


Se trataron 100 mg (257 µmol) de 1-({6-cloro-3-[4-(1,3-dioxolan-2-il)fenil]imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol, que se preparó de acuerdo con el Ejemplo Intermediario 32c, de manera análoga al Ejemplo 1 usando ácido (4-fluorofenil)borónico para dar, luego del tratamiento posterior y la purificación, 50,0 mg (43%) del compuesto del título.

Ejemplo Intermediario 32c

1-({3-[4-(1,3-Dioxolan-2-il)fenil]-6-(4-fluorofenil)imidazo[1,2-b]piridazin-8-il}

amino)-2-metilpropan-2-ol

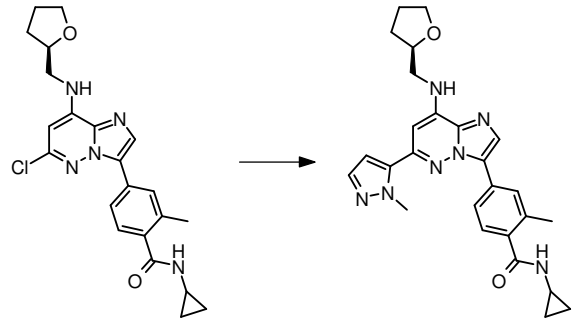


Se trataron 2,65 g (7,2 mmol) de 1-[(6-cloro-3-yodoimidazo[1,2-b]piridazin-8-il)amino]-2-metilpropan-2-ol, que se preparó de acuerdo con el Ejemplo Intermediario 1b, de manera análoga al Ejemplo Intermediario 1a usando 2-[4-(1,3-dioxolan-2-il)fenil]-4,4,5,5-tetrametil-1,3,2-dioxaborolano para dar, luego del tratamiento posterior y la purificación, 1,36 g (48%) del

compuesto del título.

Ejemplo 33

N-ciclopropil-2-metil-4-[6-(1-metil-1H-pirazol-5-il)-8-{[(2R)-tetrahidrofurano-2-ilmetil]amino}imidazo[1,2-b]piridazin-3-il]benzamida



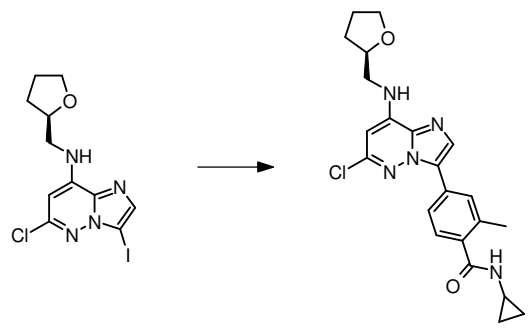
Se trataron 63 mg (148 µmol) de 4-(6-cloro-8-{[(2R)-tetrahidrofurano-2-ilmetil]amino}imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 33a, de manera análoga al Ejemplo 1 usando 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol para dar, luego del tratamiento posterior y la purificación, 10,6 mg (14%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,64 (2H), 0,89 (2H), 1,72 (1H), 1,97 (2H), 2,09 (1H), 2,50 (3H), 2,92 (1H), 3,40 (1H), 3,53 (1H), 3,81 (1H), 3,95 (1H), 4,17 (3H), 4,21 (1H), 6,05 (1H), 6,17 (1H), 6,30 (1H), 6,63 (1H), 7,39 (1H), 7,52 (1H), 7,76 (1H), 7,83 (1H), 7,88 (1H) ppm.

Ejemplo Intermediario 33a

4-(6-Cloro-8-{[(2R)-tetrahidrofurano-2-ilmetil]amino}imidazo[1,2-b]piridazin-3-

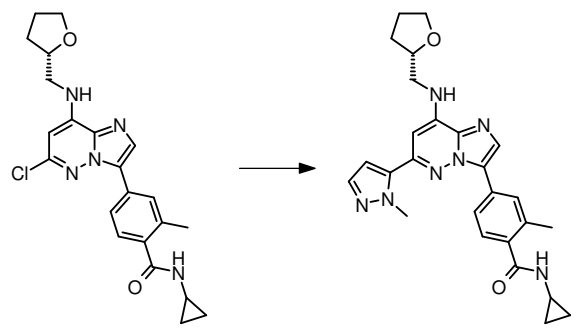
il)-N-ciclopropil-2-metilbenzamida



Se trataron 247 mg (652 µmol) de 6-cloro-3-yodo-N-[(2R)-tetrahidrofurano-2-ilmetil]imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 5b, de manera análoga al Ejemplo Intermediario 1a usando N-ciclopropil-2-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzamida para dar, luego del tratamiento posterior y la purificación, 127 mg (46%) del compuesto del título.

Ejemplo 34

N-ciclopropil-2-metil-4-[6-(1-metil-1H-pirazol-5-il)-8-{[(2S)-tetrahidrofurano-2-ilmetil]amino}imidazo[1,2-b]piridazin-3-il]benzamida



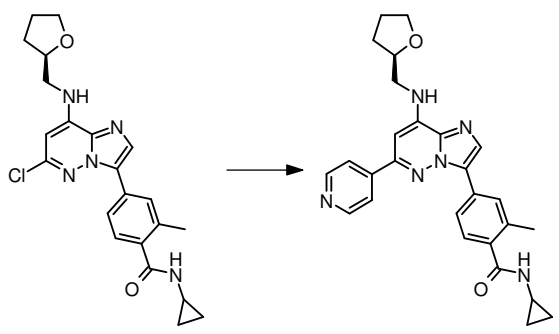
Se trataron 49 mg (115 µmol) de 4-(6-cloro-8-{[(2S)-tetrahidrofurano-2-ilmetil]amino}imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el

Ejemplo Intermediario 31a, de manera análoga al Ejemplo 1 usando 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol para dar, luego del tratamiento posterior y la purificación, 8,5 mg (15%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,64 (2H), 0,89 (2H), 1,72 (1H), 1,97 (2H), 2,09 (1H), 2,50 (3H), 2,92 (1H), 3,40 (1H), 3,53 (1H), 3,81 (1H), 3,95 (1H), 4,17 (3H), 4,21 (1H), 6,05 (1H), 6,17 (1H), 6,30 (1H), 6,63 (1H), 7,39 (1H), 7,52 (1H), 7,76 (1H), 7,83 (1H), 7,88 (1H) ppm.

Ejemplo 35

N-ciclopropil-2-metil-4-[6-(piridin-4-il)-8-{[(2R)-tetrahidrofurano-2-ilmetil]amino}imidazo[1,2-b]piridazin-3-il]benzamida



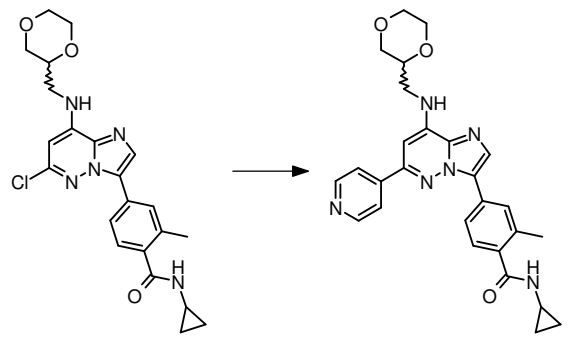
Se trataron 63 mg (148 µmol) de 4-(6-cloro-8-{[(2R)-tetrahidrofurano-2-ilmetil]amino}imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 33a, de manera análoga al Ejemplo 1 usando ácido piridin-4-ilborónico para dar, luego del tratamiento posterior y la purificación, 4,2 mg (6%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,64 (2H), 0,90 (2H), 1,75 (1H), 1,98 (2H),

2,11 (1H), 2,55 (3H), 2,93 (1H), 3,46 (1H), 3,59 (1H), 3,82 (1H), 3,96 (1H), 4,24 (1H), 6,02 (1H), 6,20 (1H), 6,49 (1H), 7,45 (1H), 7,83 (1H), 7,84 (2H), 7,93 (1H), 8,01 (1H), 8,73 (2H) ppm.

Ejemplo 36

(RS)-N-ciclopropil-4-{8-[(1,4-dioxan-2-ilmetil)amino]-6-(piridin-4-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

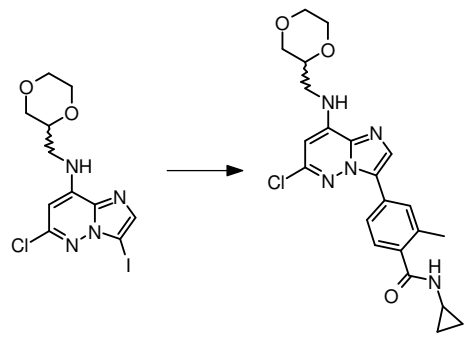


Se trataron 88 mg (199 µmol) de (RS)-4-{6-cloro-8-[(1,4-dioxan-2-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 36a, de manera análoga al Ejemplo 1 usando ácido piridin-4-ilborónico para dar, luego del tratamiento posterior y la purificación, 2,9 mg (3%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,62 (2H), 0,88 (2H), 2,52 (3H), 2,90 (1H), 3,36-4,01 (9H), 6,06 (1H), 6,23 (1H), 6,46 (1H), 7,44 (1H), 7,80 (1H), 7,84 (2H), 7,90 (1H), 7,98 (1H), 8,70 (2H) ppm.

Ejemplo Intermediario 36a

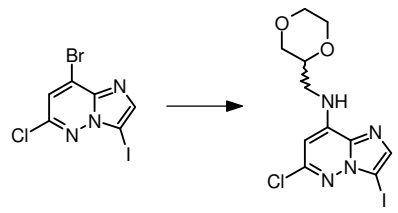
(RS)-4-{6-Cloro-8-[(1,4-dioxan-2-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



Se trataron 200 mg (507 µmol) de (RS)-6-cloro-N-(1,4-dioxan-2-ilmetil)-3-yodoimidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 36b, de manera análoga al Ejemplo Intermediario 1a usando N-ciclopropil-2-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzamida para dar, luego del tratamiento posterior y la purificación, 93,6 mg (42%) del compuesto del título.

Ejemplo Intermediario 36b

(RS)-6-Cloro-N-(1,4-dioxan-2-ilmetil)-3-yodoimidazo[1,2-b]piridazin-8-amina

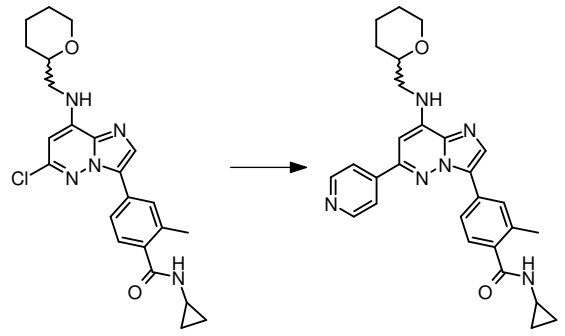


Se trataron 500 mg (1,40 mmol) de 8-bromo-6-cloro-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 1c, de manera análoga al Ejemplo Intermediario 1b usando 1-[(2RS)-1,4-dioxan-2-il]metanamina para dar, luego del tratamiento posterior y la purificación, 520 mg (94%) del compuesto del título.

Ejemplo 37

(RS)-N-ciclopropil-2-metil-4-{6-(piridin-4-il)-8-[(tetrahidro-2H-

piran-2-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}benzamida



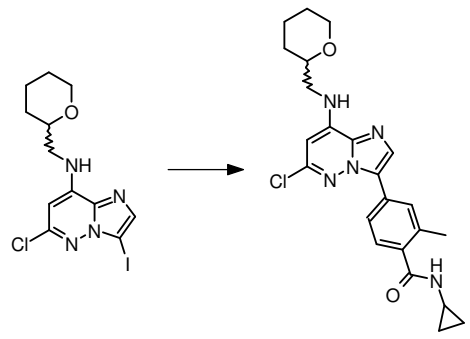
Se trataron 63 mg (143µmol) de (RS)-4-{6-cloro-8-[(tetrahidro-2H-piran-2-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 37a, de manera análoga al Ejemplo 1 usando ácido piridin-4-ilborónico para dar, luego del tratamiento posterior y la purificación, 4,0 mg (5%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,63 (2H), 0,88 (2H), 1,40-2,03 (6H), 2,53 (3H), 2,91 (1H), 3,33-3,55 (3H), 3,66 (1H), 4,05 (1H), 6,18 (1H), 6,43 (1H), 6,47 (1H), 7,44 (1H), 7,80 (1H), 7,83 (2H), 7,91 (1H), 7,98 (1H), 8,70 (2H) ppm.

Ejemplo Intermediario 37a

(RS)-4-{6-Cloro-8-[(tetrahidro-2H-piran-2-ilmetil)amino]imidazo[1,2-b]

piridazin-3-il}-N-ciclopropil-2-metilbenzamida

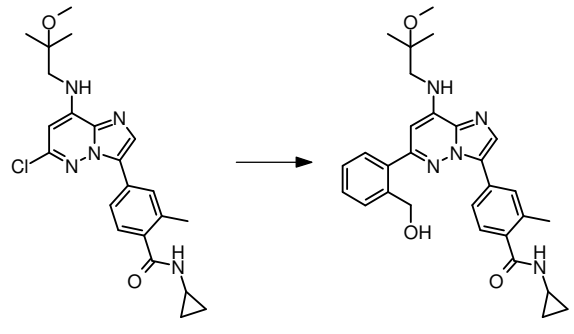


Se trataron 100 mg (255 µmol) de 6-cloro-3-yodo-N-(tetrahidro-2H-piran-2-ilmetil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 29b, de manera análoga al Ejemplo Intermediario 1a usando N-ciclopropil-2-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzamida para dar, luego del tratamiento posterior y la purificación, 68 mg (61%) del compuesto del título.

Ejemplo 38

N-ciclopropil-4-{6-[2-(hidroximetil)fenil]-8-[(2-metoxi-2-metilpropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



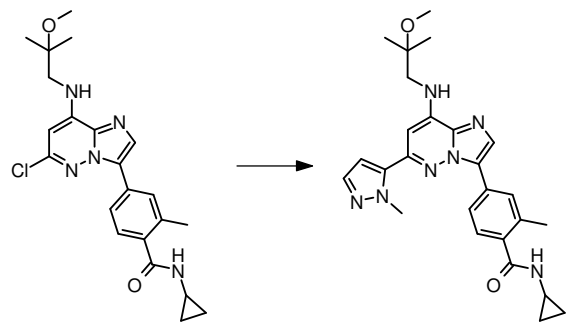
Se trataron 62 mg (145 µmol) de 4-{6-cloro-8-[(2-metoxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 17a, de manera análoga al Ejemplo 1 usando ácido

[2-(hidroximetil)fenil]borónico para dar, luego del tratamiento posterior y la purificación, 24,8 mg (33%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,58 (2H), 0,84 (2H), 1,31 (6H), 2,47 (3H), 2,87 (1H), 3,28 (3H), 3,34 (2H), 4,13 (1H), 4,38 (2H), 6,19 (1H), 6,21 (1H), 6,25 (1H), 7,36 (1H), 7,42-7,49 (3H), 7,59 (1H), 7,61 (1H), 7,70 (1H), 7,72 (1H) ppm.

Ejemplo 39

N-ciclopropil-4-{8-[(2-metoxi-2-metilpropil)amino]-6-(1-metil-1H-pirazol-5-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 70 mg (164 µmol) de 4-{6-cloro-8-[(2-metoxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 17a, de manera análoga al Ejemplo 1 usando 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol para dar, luego del tratamiento posterior y la purificación, 30 mg (37%) del compuesto del título.

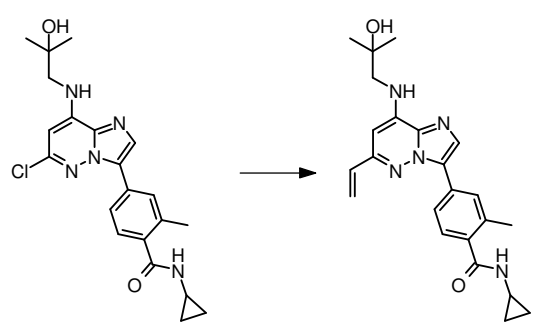
1H-RMN (CDCl3): δ= 0,63 (2H), 0,89 (2H), 1,31 (6H), 2,50 (3H), 2,91 (1H), 3,27 (3H), 3,32 (2H), 4,16 (3H), 6,10 (1H), 6,17

(1H), 6,25 (1H), 6,62 (1H), 7,38 (1H), 7,51 (1H), 7,76 (1H), 7,83 (1H), 7,87 (1H) ppm.

Ejemplo 40

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-vinilimidazo[1,2-b]

piridazin-3-il}-2-metilbenzamida



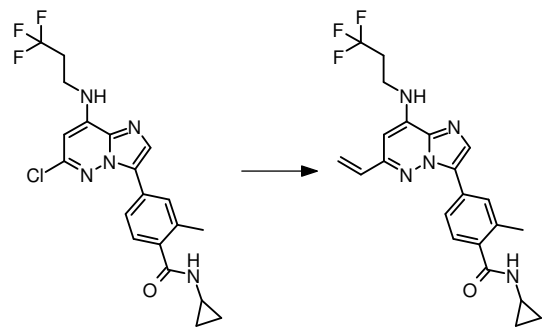
Se trataron 100 mg (242 µmol) de 4-{6-Cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 1 usando 4,4,5,5-tetrametil-2-vinil-1,3,2-dioxaborolano para dar, luego del tratamiento posterior y la purificación, 13 mg (12%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,63 (2H), 0,89 (2H), 1,43 (6H), 2,52 (3H), 2,92 (1H), 3,35 (2H), 5,56 (1H), 5,97 (1H), 6,07 (1H), 6,22 (1H), 6,37 (1H), 6,73 (1H), 7,40 (1H), 7,71 (1H), 7,50 (1H), 7,94 (1H) ppm.

Ejemplo 41

N-ciclopropil-2-metil-4-{8-[(3,3,3-trifluoropropil)amino]-6-vinilimidazo

[1,2-b]piridazin-3-il}benzamida

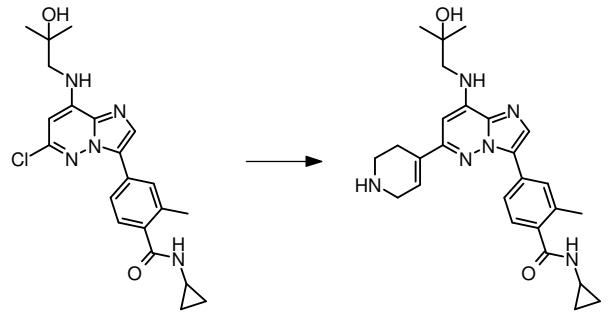


Se trataron 100 mg (228 µmol) de 4-{6-Cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 10a, de manera análoga al Ejemplo 1 usando 4,4,5,5-tetrametil-2-vinil-1,3,2-dioxaborolano para dar, luego del tratamiento posterior y la purificación, 11,4 mg (10%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,62 (2H), 0,89 (2H), 2,52 (3H), 2,56 (2H), 2,92 (1H), 3,69 (2H), 5,60 (1H), 5,92 (1H), 5,95 (1H), 6,09 (1H), 6,20 (1H), 6,77 (1H), 7,42 (1H), 7,75 (1H), 7,91 (1H), 7,95 (1H) ppm.

Ejemplo 42

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(1,2,3,6-tetrahidropiridin-4-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



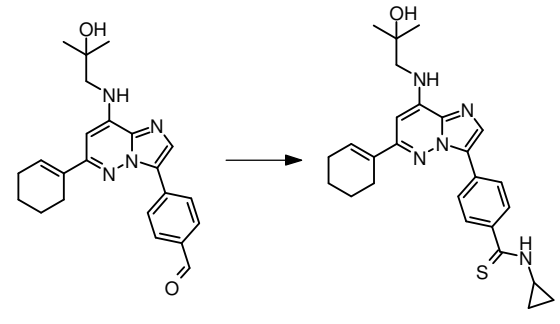
Se trataron 50 mg (121 µmol) de 4-{6-Cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 1 usando 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1,2,3,6-tetrahidropiridina para dar, luego del tratamiento posterior y la purificación, 10,5 mg (18%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,65 (2H), 1,16 (6H), 2,37 (3H), 2,61 (2H), 2,80 (1H), 3,05 (2H), 3,31 (2H), 3,56 (1H), 6,54 (1H), 6,66-6,74 (2H), 7,35 (1H), 7,97 (1H), 8,03 (1H), 8,04 (1H), 8,26 (1H), 8,28 (1H) ppm.

Ejemplo 43

4-{6-(Ciclohex-1-en-1-il)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]

piridazin-3-il}-N-ciclopropilbencencarbotioamida



Se trataron 20,6 mg (53 µmol) de 4-{6-(ciclohex-1-en-1-il)-8-

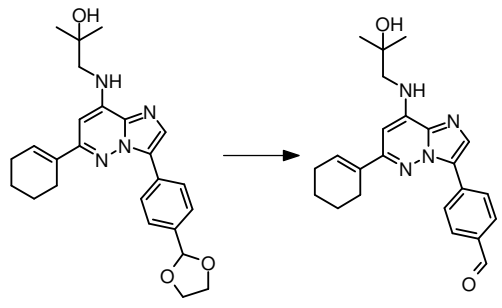
[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzaldehído, que se preparó de acuerdo con el Ejemplo Intermediario 43a, de manera análoga al Ejemplo 13 para dar, luego del tratamiento posterior y la purificación, 3,2 mg (13%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,75-0,85 (4H), 1,15 (6H), 1,61 (2H), 1,71 (2H), 2,22 (2H), 2,52 (2H), 3,13 (2H), 3,49 (1H), 4,77 (1H), 6,51 (1H), 6,63 (1H), 6,68 (1H), 7,83 (2H), 8,01 (1H), 8,21 (2H), 10,12 (1H) ppm.

Ejemplo Intermediario 43a

4-{6-(Ciclohex-1-en-1-il)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]

piridazin-3-il}benzaldehído

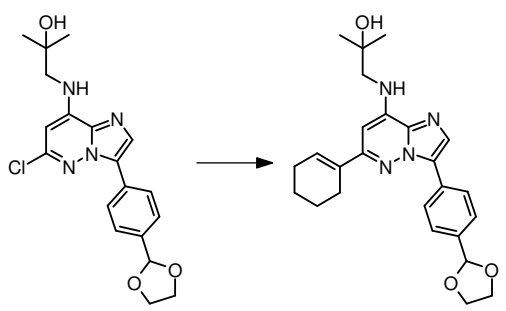


Se trataron 97 mg (223 µmol) de 1-({6-(ciclohex-1-en-1-il)-3-[4-(1,3-dioxolan-2-il)fenil]imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol, que se preparó de acuerdo con el Ejemplo Intermediario 43b, de manera análoga al Ejemplo Intermediario 13a para dar, luego del tratamiento posterior y la purificación, 24 mg (25%) del compuesto del título.

Ejemplo Intermediario 43b

1-({6-(Ciclohex-1-en-1-il)-3-[4-(1,3-dioxolan-2-il)fenil]imidazo[1,2-b]

piridazin-8-il}amino)-2-metilpropan-2-ol

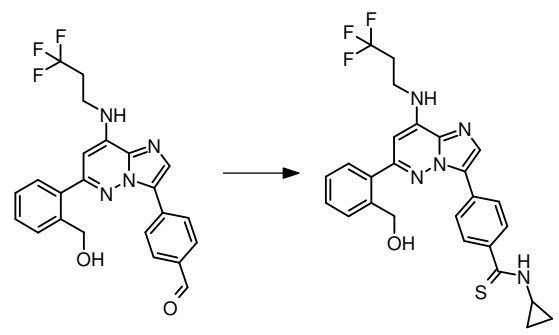


Se trataron 100 mg (257 µmol) de 1-({6-cloro-3-[4-(1,3-dioxolan-2-il)fenil]imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol, que se preparó de acuerdo con el Ejemplo Intermediario 32c, de manera análoga al Ejemplo 1 usando ácido ciclohex-1-en-1-ilborónico para dar, luego del tratamiento posterior y la purificación, 97 mg (87%) del compuesto del título.

Ejemplo 44

N-ciclopropil-4-{6-[2-(hidroximetil)fenil]-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}bencencarbotioamida



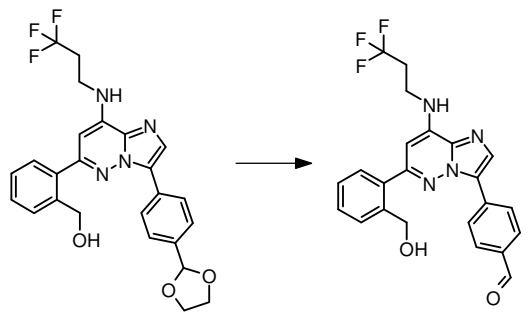
Se trataron 72,3 mg (164 µmol) de 4-{6-[2-(hidroximetil)fenil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-

il}benzaldehído, que se preparó de acuerdo con el Ejemplo Intermediario 44a, de manera análoga al Ejemplo 13 para dar, luego del tratamiento posterior y la purificación, 6,6 mg (7%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,76 (2H), 1,00 (2H), 2,58 (2H), 3,37 (1H), 3,72 (2H), 3,96 (1H), 4,40 (2H), 6,16 (1H), 6,25 (1H), 7,46-7,51 (3H), 7,59 (1H), 7,76 (1H), 7,77 (2H), 7,84 (2H), 7,89 (1H) ppm.

Ejemplo Intermediario 44a

4-{6-[2-(Hidroximetil)fenil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzaldehído

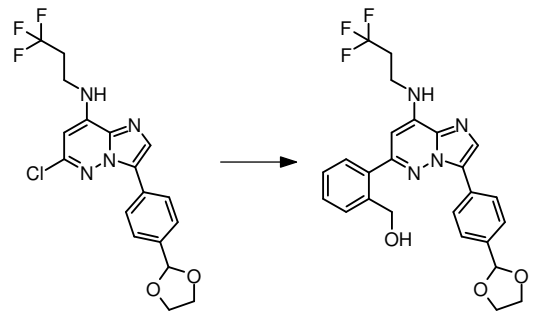


Se trataron 52 mg (107 µmol) de (2-{3-[4-(1,3-dioxolan-2-il)fenil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-6-il}fenil)metanol, que se preparó de acuerdo con el Ejemplo Intermediario 44b, de manera análoga al Ejemplo Intermediario 13a para dar, luego del tratamiento posterior y la purificación, 72,3 mg (76%) del compuesto del título.

Ejemplo Intermediario 44b

(2-{3-[4-(1,3-Dioxolan-2-il)fenil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]

piridazin-6-il}fenil)metanol

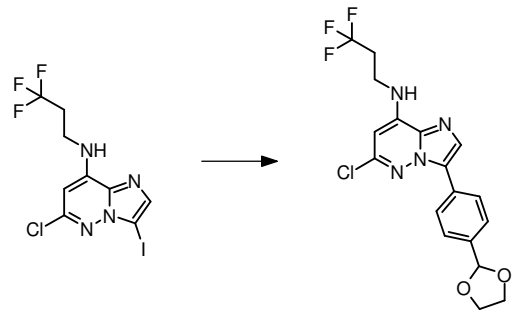


Se trataron 100 mg (242 µmol) de 6-cloro-3-[4-(1,3-dioxolan-2-il)fenil]-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 44c, de manera análoga al Ejemplo 1 usando ácido [2-(hidroximetil)fenil]borónico para dar, luego del tratamiento posterior y la purificación, 52 mg (44%) del compuesto del título.

Ejemplo Intermediario 44c

6-Cloro-3-[4-(1,3-dioxolan-2-il)fenil]-N-(3,3,3-trifluoropropil)imidazo[1,2-b]

piridazin-8-amina



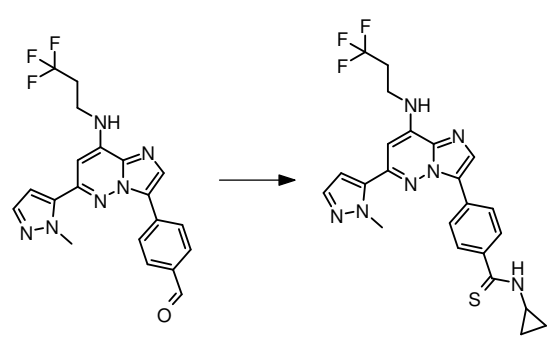
Se trataron 800 mg (2,05 Mmol) de 6-cloro-3-yodo-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 6b, de manera análoga al Ejemplo Intermediario 1a usando 2-[4-(1,3-dioxolan-2-il)fenil]-

4,4,5,5-tetrametil-1,3,2-dioxaborolano para dar, luego del tratamiento posterior y la purificación, 332 mg (35%) del compuesto del título.

Ejemplo 45

N-ciclopropil-4-{6-(1-metil-1H-pirazol-5-il)-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}bencencarbotioamida



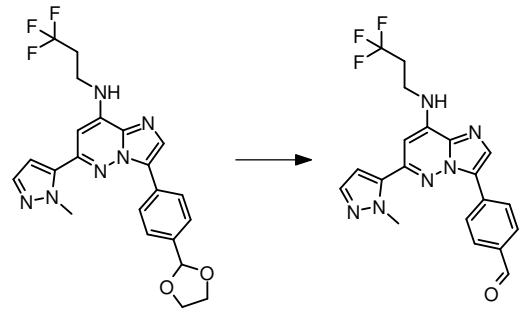
Se trataron 27 mg (65 µmol) de 4-{6-(1-metil-1H-pirazol-5-il)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzaldehído, que se preparó de acuerdo con el Ejemplo Intermediario 45a, de manera análoga al Ejemplo 13 para dar, luego del tratamiento posterior y la purificación, 1,8 mg (5%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,82 (2H), 1,07 (2H), 2,59 (2H), 3,42 (1H), 3,73 (2H), 4,19 (3H), 6,08 (1H), 6,29 (1H), 6,66 (1H), 7,56 (1H), 7,64 (1H), 7,84 (2H), 7,85 (1H), 8,07 (2H) ppm.

Ejemplo Intermediario 45a

4-{6-(1-Metil-1H-pirazol-5-il)-8-[(3,3,3-trifluoropropil)amino]imidazo[12-b]

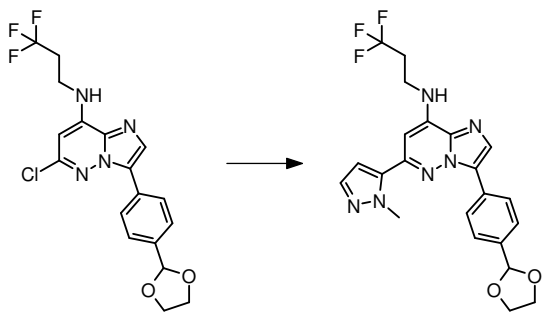
piridazin-3-il}benzaldehído



Se trataron 73 mg (159 µmol) de 3-[4-(1,3-dioxolan-2-il)fenil]-6-(1-metil-1H-pirazol-5-il)-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 45b, de manera análoga al Ejemplo Intermediario 13a para dar, luego del tratamiento posterior y la purificación, 27 mg (41%) del compuesto del título.

Ejemplo Intermediario 45b

3-[4-(1,3-Dioxolan-2-il)fenil]-6-(1-metil-1H-pirazol-5-il)-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina



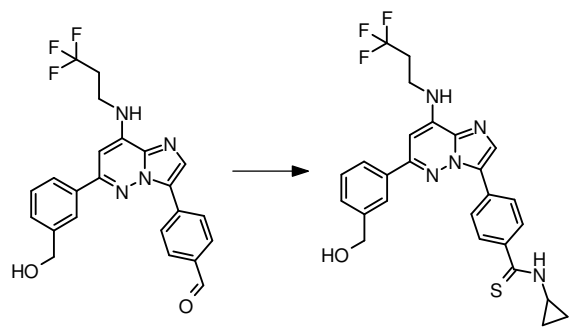
Se trataron 100 mg (242 µmol) de 6-cloro-3-[4-(1,3-dioxolan-2-il)fenil]-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 44c, de manera análoga al Ejemplo 1 usando 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol para dar, luego

del tratamiento posterior y la purificación, 73 mg (66%) del compuesto del título.

Ejemplo 46

N-ciclopropil-4-{6-[3-(hidroximetil)fenil]-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}bencencarbotioamida



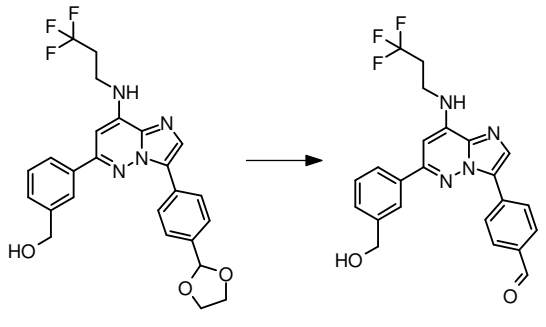
Se trataron 39,1 mg (89 µmol) de 4-{6-[3-(hidroximetil)fenil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzaldehído, que se preparó de acuerdo con el Ejemplo Intermediario 46a, de manera análoga al Ejemplo 13 para dar, luego del tratamiento posterior y la purificación, 2,0 mg (4%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,83 (2H), 1,07 (2H), 2,56 (2H), 3,43 (1H), 3,68 (2H), 4,82 (2H), 6,00 (1H), 6,40 (1H), 7,50 (2H), 7,71 (1H), 7,79-7,90 (5H), 8,15 (2H) ppm.

Ejemplo Intermediario 46a

4-{6-[3-(Hidroximetil)fenil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]

piridazin-3-il}benzaldehído

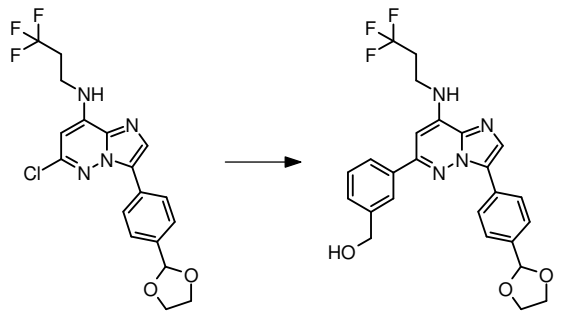


Se trataron 167 mg (µmol) de (3-{3-[4-(1,3-dioxolan-2-il)fenil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-6-il}fenil)metanol, que se preparó de acuerdo con el Ejemplo Intermediario 46b, de manera análoga al Ejemplo Intermediario 13a para dar, luego del tratamiento posterior y la purificación, 39,1 mg (37%) del compuesto del título.

Ejemplo Intermediario 46b

(3-{3-[4-(1,3-Dioxolan-2-il)fenil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]

piridazin-6-il}fenil)metanol

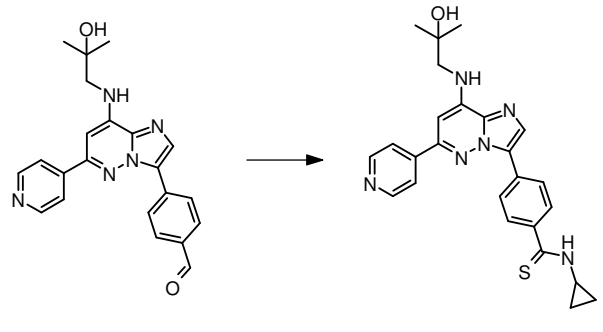


Se trataron 100 mg (242 µmol) de 6-cloro-3-[4-(1,3-dioxolan-2-il)fenil]-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 44c, de manera análoga al Ejemplo 1 usando ácido [3-(hidroximetil)fenil]borónico para dar, luego del tratamiento posterior y la purificación, 83,5 mg (71%) del compuesto del

título.

Ejemplo 47

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(piridin-4-il)imidazo[1,2-b]piridazin-3-il}bencencarbotioamida

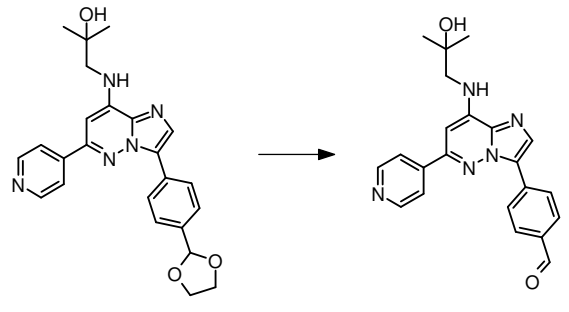


Se trataron 48 mg (124 µmol) de 4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(piridin-4-il)imidazo[1,2-b]piridazin-3-il}benzaldehído, que se preparó de acuerdo con el Ejemplo Intermediario 47a, de manera análoga al Ejemplo 13 para dar, luego del tratamiento posterior y la purificación, 4,7 mg (6%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,76-0,88 (4H), 1,18 (6H), 3,38-3,52 (3H), 4,79 (1H), 6,93 (1H), 7,09 (1H), 7,86 (2H), 8,04 (2H), 8,12 (1H), 8,27 (2H), 8,73 (2H), 10,16 (1H) ppm.

Ejemplo Intermediario 47a

4-{8-[(2-Hidroxi-2-metilpropil)amino]-6-(piridin-4-il)imidazo[1,2-b]piridazin-3-il}benzaldehído

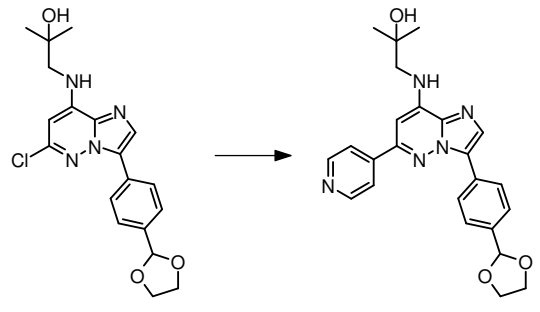


Se trataron 69 mg (160 µmol) de 1-({3-[4-(1,3-dioxolan-2-il)fenil]-6-(piridin-4-il)imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol, que se preparó de acuerdo con el Ejemplo Intermediario 47b, de manera análoga al Ejemplo Intermediario 13a para dar, luego del tratamiento posterior y la purificación, 51,5 mg (83%) del compuesto del título.

Ejemplo Intermediario 47b

1-({3-[4-(1,3-Dioxolan-2-il)fenil]-6-(piridin-4-il)imidazo[1,2-b]piridazin-8-il}

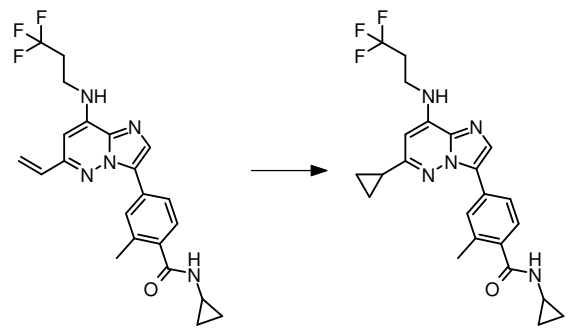
amino)-2-metilpropan-2-ol



Se trataron 200 mg (514 µmol) de 1-({6-cloro-3-[4-(1,3-dioxolan-2-il)fenil]imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol, que se preparó de acuerdo con el Ejemplo Intermediario 32c, de manera análoga al Ejemplo 1 usando ácido piridin-4-ilborónico para dar, luego del tratamiento posterior y la purificación, 51,5 mg (23%) del compuesto del título.

Ejemplo 48

N-ciclopropil-4-{6-ciclopropil-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

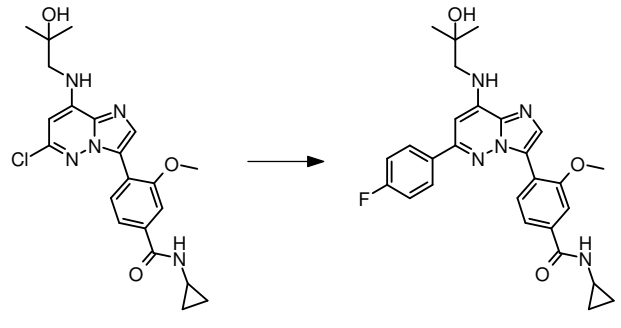


Una solución de 31 mg (72 µmol) de N-ciclopropil-2-metil-4-{8-[(3,3,3-trifluoropropil)amino]-6-vinilimidazo[1,2-b]piridazin-3-il}benzamida, que se preparó de acuerdo con el ejemplo 41, en 3,5 mL de tetrahidrofurano se enfrió a 3°C, se agregaron 5 mL de solución de diazometano en éter dietílico seguidos por 0,81 mg de diacetato de paladio(II) y la mezcla se agitó durante 1 hora. Los solventes se eliminaron y el residuo se purificó mediante cromatografía para dar 5,8 mg (18%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,63 (2H), 0,89 (2H), 1,00-1,11 (4H), 2,00 (1H), 2,53 (3H), 2,47-2,61 (2H), 2,92 (1H), 3,65 (2H), 5,78 (1H), 5,91 (1H), 5,93 (1H), 7,41 (1H), 7,73 (1H), 7,91 (1H), 7,92 (1H) ppm.

Ejemplo 49

N-ciclopropil-4-{6-(4-fluorofenil)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-3-metoxibenzamida



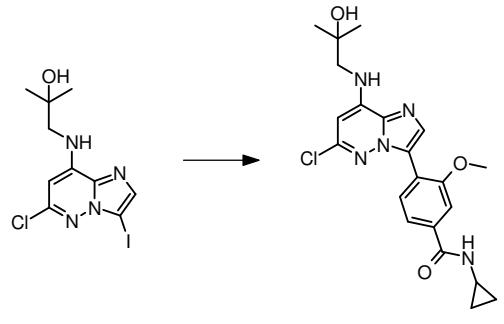
Se trataron 75 mg (174 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-3-metoxibenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 49a, de manera análoga al Ejemplo 1 usando ácido (4-fluorofenil)borónico para dar, luego del tratamiento posterior y la purificación, 18,5 mg (22%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,57 (2H), 0,69 (2H), 1,19 (6H), 2,85 (1H), 3,39 (2H), 3,89 (3H), 4,78 (1H), 6,77 (1H), 6,87 (1H), 7,31 (2H), 7,54 (1H), 7,56 (1H), 7,87 (1H), 8,03 (2H), 8,25 (1H), 8,51 (1H) ppm.

Ejemplo 49a

4-{6-Cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-

N-ciclopropil-3-metoxibenzamida

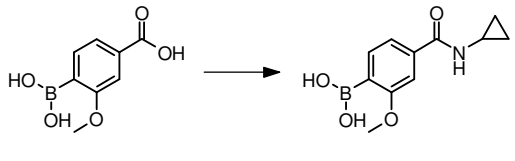


Se trataron 1,0 g (2,73 mmol) de 1-[(6-Cloro-3-yodoimidazo[1,2-

b]piridazin-8-il)amino]-2-metilpropan-2-ol, que se preparó de acuerdo con el Ejemplo Intermediario 1b, de manera análoga al Ejemplo Intermediario 1a usando ácido [4-(ciclopropilcarbamoil)-2-metoxifenil]borónico, que se preparó de acuerdo con el Ejemplo Intermediario 49b para dar, luego del tratamiento posterior y la purificación, 741 mg (60%) del compuesto del título.

Ejemplo 49b

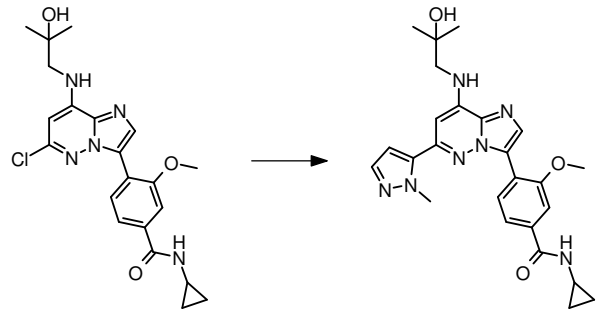
ácido [4-(Ciclopropilcarbamoil)-2-metoxifenil]borónico



Una suspensión de 3,0 g (15,3 mmol) de ácido 4-(dihidroxiboril)-3-metoxibenzoico, 874 mg de ciclopropanamina y 3,5 g de N-[3-(dimetilamino)propil]-N'-etilcarbodiimida en 93 mL de diclorometano se agitó durante la noche a 23°C. Se agregó agua y la mezcla se extrajo con diclorometano. La capa orgánica se lavó con salmuera y se secó sobre sulfato de sodio. Luego de la filtración y la eliminación del solvente el residuo se purificó mediante cromatografía para dar 2,60 g (72%) del compuesto del título.

Ejemplo 50

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(1-metil-1H-pirazol-5-il)imidazo[1,2-b]piridazin-3-il}-3-metoxibenzamida



Se trataron 75 mg (174 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-3-metoxibenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 49a, de manera análoga al Ejemplo 1 usando 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol para dar, luego del tratamiento posterior y la purificación, 14,8 mg (18%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,57 (2H), 0,69 (2H), 1,17 (6H), 2,83 (1H), 3,35 (2H), 3,85 (3H), 4,01 (3H), 4,77 (1H), 6,59 (1H), 6,85 (1H), 6,95 (1H), 7,47 (1H), 7,51 (1H), 7,53 (1H), 7,81 (1H), 8,03 (1H), 8,49 (1H) ppm.

Ejemplo 51

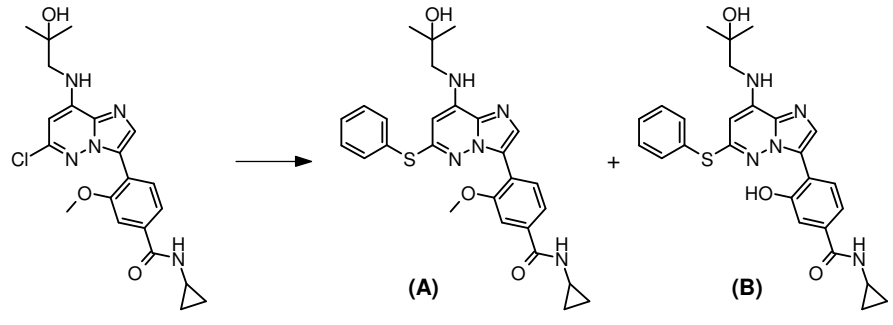
N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(fenilsulfanil)

imidazo[1,2-b]piridazin-3-il}-3-metoxibenzamida (A)

y

N-ciclopropil-3-hidroxi-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-

(fenilsulfanil)imidazo[1,2-b]piridazin-3-il}benzamida (B)



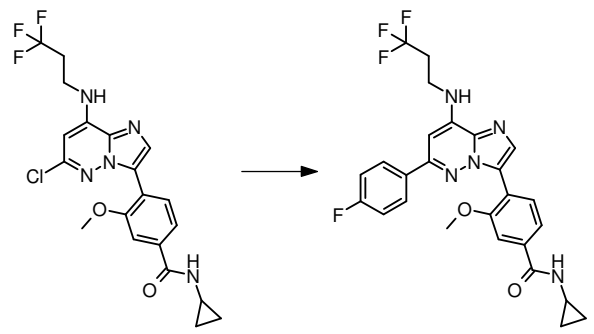
A una solución de 76,9 mg de bencenotiol en 1,0 mL de dimetilsulfóxido, se agregaron 27,9 mg de hidruro de sodio (60%) y la mezcla se agitó a 23°C durante 1 hora. Luego se agregaron 50 mg (116 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-3-metoxibenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 49a, y la mezcla se calentó a 120°C usando irradiación de microondas durante 1 hora. Se agregó agua y la mezcla se extrajo con diclorometano y metanol. La capa orgánica se lavó con salmuera y se secó sobre sulfato de sodio. Luego de la filtración y la eliminación del solvente el residuo se purificó mediante cromatografía para dar 8,0 mg (18%) del compuesto del título A y 15,3 mg (27%) del compuesto del título B.

1H-RMN (DMSO-d6) de A: δ= 0,56 (2H), 0,69 (2H), 1,10 (6H), 2,82 (1H), 3,19 (2H), 3,27 (3H), 4,70 (1H), 6,19 (1H), 6,97 (1H), 7,22 (1H), 7,41-7,47 (4H), 7,53-7,58 (2H), 7,85 (1H), 7,86 (1H), 8,44 (1H) ppm.

1H-RMN (DMSO-d6) de B: δ= 0,54 (2H), 0,66 (2H), 1,10 (6H), 2,80 (1H), 3,18 (2H), 4,70 (1H), 6,17 (1H), 6,98 (1H), 7,04 (1H), 7,33 (1H), 7,42-7,48 (3H), 7,55-7,61 (2H), 7,87 (1H), 7,95 (1H), 8,33 (1H), 10,13 (1H) ppm.

Ejemplo 52

N-ciclopropil-4-{6-(4-fluorofenil)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-3-metoxibenzamida



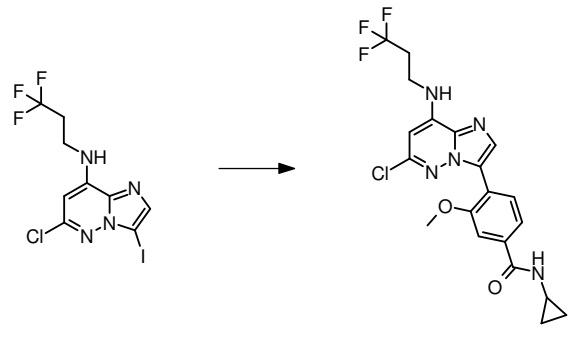
Se trataron 65 mg (143 µmol) de 4-{6-cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-3-metoxibenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 52a, de manera análoga al Ejemplo 1 usando ácido (4-fluorofenil)borónico para dar, luego del tratamiento posterior y la purificación, 14,3 mg (18%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,66 (2H), 0,91 (2H), 2,59 (2H), 2,95 (1H), 3,75 (2H), 3,97 (3H), 6,00 (1H), 6,32 (1H), 6,39 (1H), 7,17 (2H), 7,33 (1H), 7,58 (1H), 7,90 (2H), 8,01 (1H), 8,37 (1H) ppm.

Ejemplo Intermediario 52a

4-{6-Cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-

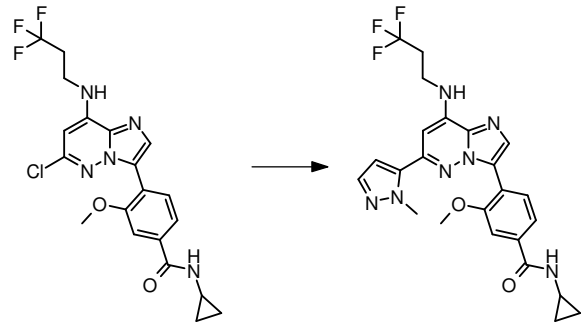
N-ciclopropil-3-metoxibenzamida



Se trataron 484 mg (1,24 mmol) de 6-cloro-3-yodo-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 6b, de manera análoga al Ejemplo Intermediario 1a usando ácido [4-(ciclopropilcarbamoil)-2-metoxifenil]borónico, que se preparó de acuerdo con el Ejemplo Intermediario 49b para dar, luego del tratamiento posterior y la purificación, 163 mg (29%) del compuesto del título.

Ejemplo 53

N-ciclopropil-3-metoxi-4-{6-(1-metil-1H-pirazol-5-il)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida



Se trataron 65 mg (143 µmol) de 4-{6-cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-3-metoxibenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 52a, de manera análoga al Ejemplo 1 usando 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol para dar, luego del tratamiento posterior y la

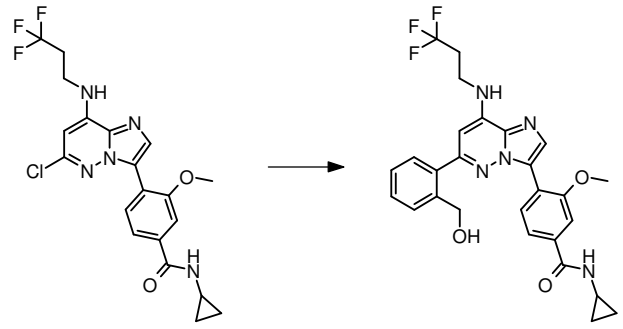
purificación, 3,6 mg (5%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,66 (2H), 0,91 (2H), 2,58 (2H), 2,94 (1H), 3,72 (2H), 3,94 (3H), 4,11 (3H), 6,04 (1H), 6,27 (1H), 6,31 (1H), 6,64 (1H), 7,27 (1H), 7,53 (1H), 7,58 (1H), 7,95 (1H), 8,13 (1H) ppm.

Ejemplo 54

N-ciclopropil-4-{6-[2-(hidroximetil)fenil]-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}-3-metoxibenzamida



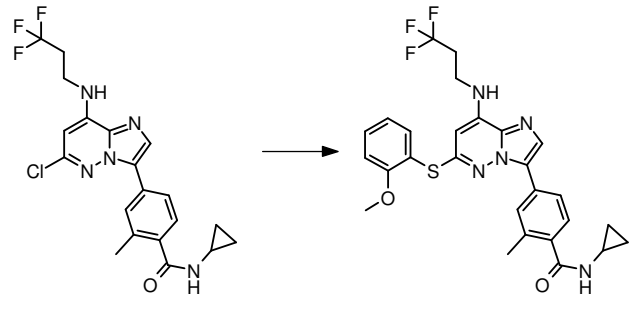
Se trataron 50 mg (110 µmol) de 4-{6-cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-3-metoxibenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 52a, de manera análoga al Ejemplo 1 usando ácido [2-(hidroximetil)fenil]borónico para dar, luego del tratamiento posterior y la purificación, 11,8 mg (18%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,60 (2H), 0,85 (2H), 2,58 (2H), 2,88 (1H), 3,73 (2H), 3,90 (3H), 4,39 (2H), 5,12 (1H), 6,13 (1H), 6,24 (1H), 6,34 (1H), 7,22 (1H), 7,43-7,49 (3H), 7,55 (1H), 7,58 (1H), 7,79 (1H), 7,84 (1H) ppm.

Ejemplo 55

N-ciclopropil-4-{6-[(2-metoxifenil)sulfanil]-8-[(3,3,3-trifluoropropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



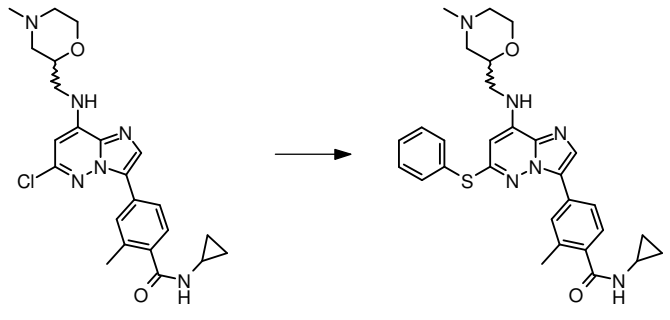
Se trataron 50 mg (114 µmol) de 4-{6-cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 10a, de manera análoga al Ejemplo 51 usando 2-metoxibencenotiol para dar, luego del tratamiento posterior y la purificación, 9,2 mg (14%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,61 (2H), 0,88 (2H), 2,36 (3H), 2,47 (2H), 2,89 (1H), 3,52 (2H), 3,77 (3H), 5,88 (1H), 6,01 (1H), 6,28 (1H), 6,97-7,07 (2H), 7,16 (1H), 7,48 (1H), 7,57-7,65 (3H), 7,67 (1H) ppm.

Ejemplo 56

(RS)-N-ciclopropil-2-metil-4-[8-{[(4-metilmorfolin-2-il)metil]amino}-6-

(fenilsulfanil)imidazo[1,2-b]piridazin-3-il]benzamida

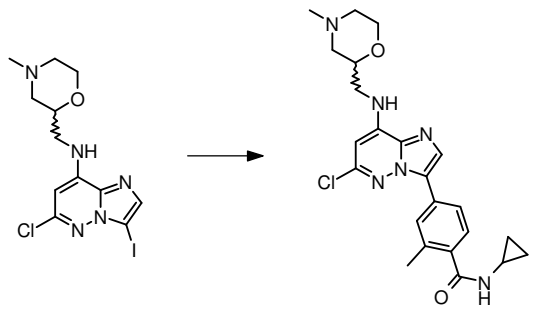


Se trataron 75 mg (165 µmol) de (RS)-4-(6-cloro-8-{[(4-metilmorfolin-2-il)metil]amino}imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 56a, de manera análoga al Ejemplo 51 usando bencenotiol para dar, luego del tratamiento posterior y la purificación, 21,6 mg (25%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,65 (2H), 1,70 (1H), 1,93 (1H), 2,13 (3H), 2,20 (3H), 2,53 (1H), 2,64 (1H), 2,79 (1H), 3,25-3,34 (2H), 3,43 (1H), 3,62 (1H), 3,73 (1H), 6,10 (1H), 7,10 (1H), 7,42 (1H), 7,45-7,51 (3H), 7,59-7,67 (3H), 7,71 (1H), 7,92 (1H), 8,23 (1H) ppm.

Ejemplo Intermediario 56a

(RS)-4-(6-Cloro-8-{[(4-metilmorfolin-2-il)metil]amino}imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida

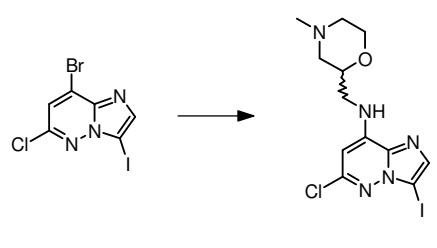


Se trataron 352 mg (864 µmol) de (RS)-6-cloro-3-yodo-N-[(4-

metilmorfolin-2-il)metil]imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 56b, de manera análoga al Ejemplo Intermediario 1a usando N-ciclopropil-2-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzamida para dar, luego del tratamiento posterior y la purificación, 372 mg (95%) del compuesto del título.

Ejemplo Intermediario 56b

(RS)-6-Cloro-3-yodo-N-[(4-metilmorfolin-2-il)metil]imidazo[1,2-b]piridazin-8-amina

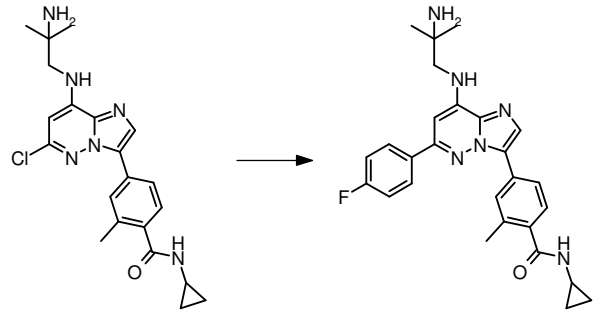


Se trataron 370 mg (1,03 mmol) de 8-bromo-6-cloro-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 1c, de manera análoga al Ejemplo Intermediario 1b usando 1-[(2RS)-4-metilmorfolin-2-il]metanamina para dar, luego del tratamiento posterior y la purificación, 359 mg (85%) del compuesto del título.

Ejemplo 57

4-{8-[(2-Amino-2-metilpropil)amino]-6-(4-fluorofenil)imidazo[1,2-b]

piridazin-3-il}-N-ciclopropil-2-metilbenzamida



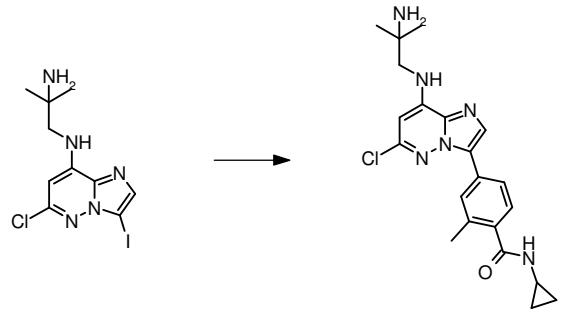
Se trataron 100 mg (242 µmol) de 4-{8-[(2-amino-2-metilpropil)amino]-6-cloroimidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 57a, de manera análoga al Ejemplo 1 usando ácido (4-fluorofenil)borónico para dar, luego del tratamiento posterior y la purificación, 17,9 mg (14%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,63 (2H), 0,90 (2H), 1,25 (2H), 1,29 (6H), 2,55 (3H), 2,93 (1H), 3,27 (2H), 5,94 (1H), 6,34 (1H), 6,41 (1H), 7,17 (2H), 7,45 (1H), 7,81 (1H), 7,91-7,98 (3H), 8,04 (1H) ppm.

Ejemplo Intermediario 57a

4-{8-[(2-Amino-2-metilpropil)amino]-6-cloroimidazo[1,2-b]piridazin-3-il}-

N-ciclopropil-2-metilbenzamida

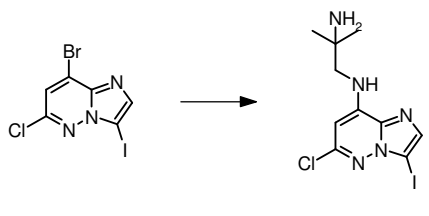


Se trataron 1,07 g (2,93 mmol) de N1-(6-cloro-3-yodoimidazo[1,2-

b]piridazin-8-il)-2-metilpropan-1,2-diamina, que se preparó de acuerdo con el Ejemplo Intermediario 57b, de manera análoga al Ejemplo Intermediario 1a usando N-ciclopropil-2-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzamida para dar, luego del tratamiento posterior y la purificación, 809 mg (64%) del compuesto del título.

Ejemplo Intermediario 57b

N1-(6-cloro-3-yodoimidazo[1,2-b]piridazin-8-il)-2-metilpropan-1,2-diamina

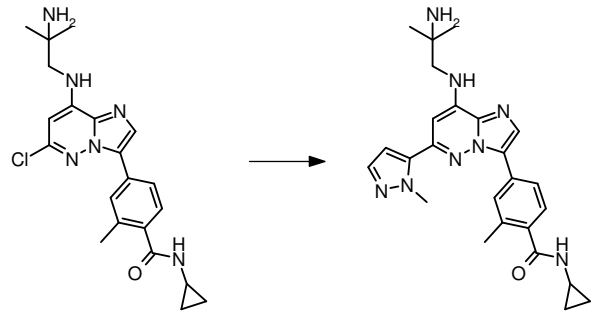


Se trataron 2,00 g (5,58 mmol) de 8-bromo-6-cloro-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 1c, de manera análoga al Ejemplo Intermediario 1b usando 2-metilpropan-1,2-diamina para dar, luego del tratamiento posterior y la purificación, 1,08 g (53%) del compuesto del título.

Ejemplo 58

4-{8-[(2-Amino-2-metilpropil)amino]-6-(1-metil-1H-pirazol-5-il)imidazo

[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



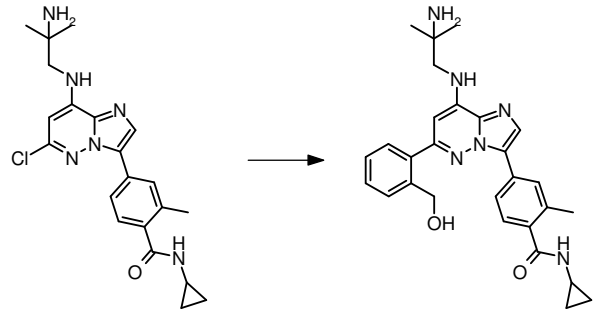
Se trataron 100 mg (242 µmol) de 4-{8-[(2-amino-2-metilpropil)amino]-6-cloroimidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 57a, de manera análoga al Ejemplo 1 usando 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol para dar, luego del tratamiento posterior y la purificación, 27,5 mg (22%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,64 (2H), 0,90 (2H), 1,25 (2H), 1,28 (6H), 2,52 (3H), 2,93 (1H), 3,23 (2H), 4,20 (3H), 5,97 (1H), 6,29 (1H), 6,42 (1H), 6,64 (1H), 7,41 (1H), 7,53 (1H), 7,79 (1H), 7,86 (1H), 7,90 (1H) ppm.

Ejemplo 59

4-{8-[(2-Amino-2-metilpropil)amino]-6-[2-(hidroximetil)fenil]imidazo

[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



Se trataron 100 mg (242 µmol) de 4-{8-[(2-amino-2-

metilpropil)amino]-6-cloroimidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 57a, de manera análoga al Ejemplo 1 usando ácido [2-(hidroximetil)fenil]borónico para dar, luego del tratamiento posterior y la purificación, 30,0 mg (23%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,59 (2H), 0,85 (2H), 1,25 (2H), 1,28 (6H), 2,49 (3H), 2,89 (1H), 3,25 (2H), 4,40 (2H), 5,30 (1H), 6,07 (1H), 6,30 (1H), 6,47 (1H), 7,38 (1H), 7,43-7,50 (3H), 7,60 (1H), 7,64 (1H), 7,73 (1H), 7,74 (1H) ppm.

Ejemplo 60

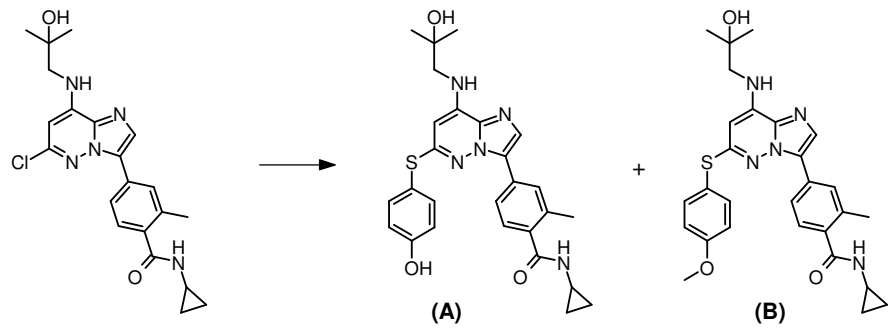
N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(4-hidroxifenil)

sulfanil]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida (A)

y

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(4-metoxifenil)

sulfanil]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida (B)



Se trataron 75 mg (181 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-

metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 4-metoxibencenotiol para dar, luego del tratamiento posterior y la purificación, 50 mg (43%) del compuesto del título A y 8,8 mg (5%) del compuesto del título B.

1H-RMN (DMSO-d6) de A: δ= 0,49 (2H), 0,65 (2H), 1,11 (6H), 2,21 (3H), 2,79 (1H), 3,19 (2H), 4,72 (1H), 6,12 (1H), 6,82-6,91 (3H), 7,12 (1H), 7,42 (2H), 7,65 (1H), 7,70 (1H), 7,91 (1H), 8,22 (1H), 10,04 (1H) ppm.

1H-RMN (CDCl3) de B: δ= 0,64 (2H), 0,90 (2H), 1,39 (6H), 2,37 (3H), 2,92 (1H), 3,24 (2H), 3,88 (3H), 4,09 (1H), 5,30 (1H), 5,92 (1H), 5,97 (1H), 6,36 (1H), 6,96 (2H), 7,12 (1H), 7,50-7,58 (3H), 7,61 (1H) ppm.

Ejemplo 61

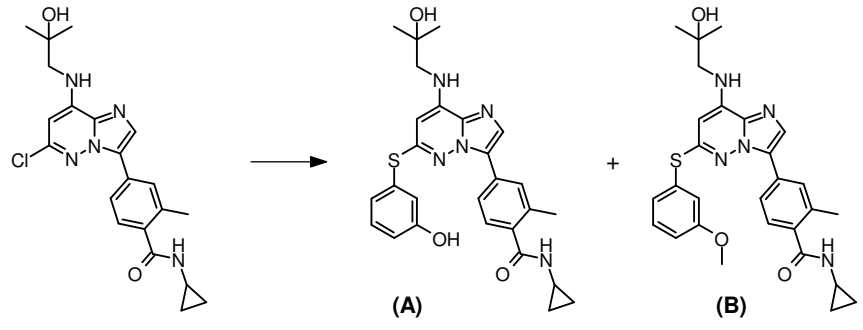
N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(3-hidroxifenil)

sulfanil]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida (A)

y

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(3-metoxifenil)

sulfanil]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida (B)



Se trataron 75 mg (181 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 3-metoxibencenotiol para dar, luego del tratamiento posterior y la purificación, 26,9 mg (21%) del compuesto del título A y 14,9 mg (15%) del compuesto del título B.

1H-RMN (DMSO-d6) de A: δ= 0,49 (2H), 0,65 (2H), 1,11 (6H), 2,22 (3H), 2,79 (1H), 3,20 (2H), 4,71 (1H), 6,21 (1H), 6,85 (1H), 6,94-7,02 (3H), 7,15 (1H), 7,25 (1H), 7,73 (1H), 7,74 (1H), 7,94 (1H), 8,23 (1H), 9,73 (1H) ppm.

1H-RMN (CDCl3) de B: δ= 0,63 (2H), 0,90 (2H), 1,40 (6H), 2,37 (3H), 2,92 (1H), 3,23 (2H), 3,73 (3H), 5,94 (1H), 6,02 (1H), 6,50 (1H), 6,97 (1H), 7,13-7,20 (3H), 7,22 (1H), 7,33 (1H), 7,56-7,63 (3H) ppm.

Ejemplo 62

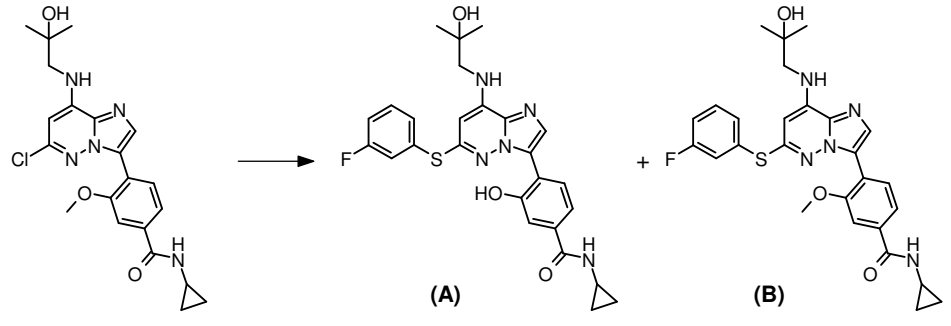
N-ciclopropil-4-{6-[(3-fluorofenil)sulfanil]-8-[(2-hidroxi-2-metilpropil)

amino]imidazo[1,2-b]piridazin-3-il}-3-hidroxibenzamida (A)

y

N-ciclopropil-4-{6-[(3-fluorofenil)sulfanil]-8-[(2-hidroxi-2-metilpropil)

amino]imidazo[1,2-b]piridazin-3-il}-3-metoxibenzamida (B)



Se trataron 150 mg (349 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-3-metoxibenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 49a, de manera análoga al Ejemplo 51 usando 3-fluorobencenotiol para dar, luego del tratamiento posterior y la purificación, 3,3 mg (2%) del compuesto del título A y 2,5 mg (1%) del compuesto del título B.

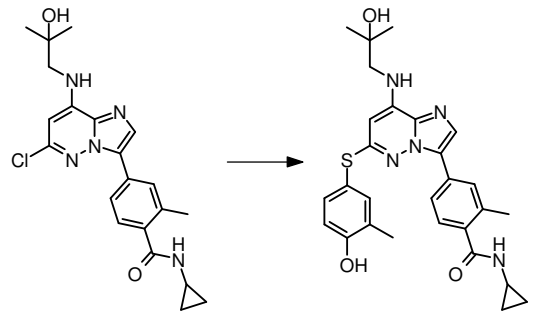
1H-RMN (DMSO-d6) de A: δ= 0,53 (2H), 0,66 (2H), 1,11 (6H), 2,80 (1H), 3,21 (2H), 4,71 (1H), 6,24 (1H), 7,06 (2H), 7,26 (1H), 7,33-7,52 (4H), 7,86 (1H), 7,94 (1H), 8,33 (1H), 10,18 (1H) ppm.

1H-RMN (DMSO-d6) de B: δ= 0,55 (2H), 0,69 (2H), 1,11 (6H), 2,82 (1H), 3,22 (2H), 3,84 (3H), 4,70 (1H), 6,26 (1H), 7,04 (1H), 7,21-7,30 (2H), 7,36 (1H), 7,39-7,49 (3H), 7,84 (1H), 7,85 (1H), 8,44 (1H) ppm.

Ejemplo 63

N-ciclopropil-4-{6-[(4-hidroxi-3-metilfenil)sulfanil]-8-[(2-hidroxi-2-

metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



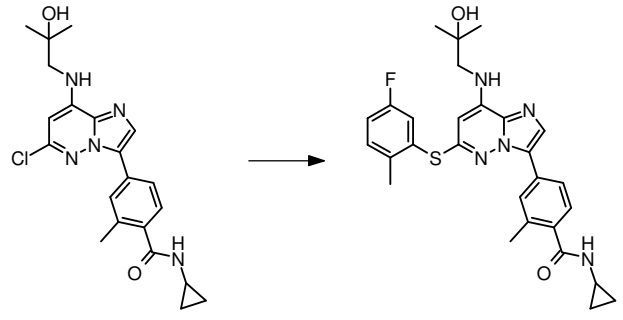
Se trataron 75 mg (181 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 2-metil-4-sulfanilfenol para dar, luego del tratamiento posterior y la purificación, 27,6 mg (28%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,65 (2H), 1,11 (6H), 2,10 (3H), 2,20 (3H), 2,79 (1H), 3,18 (2H), 4,70 (1H), 6,11 (1H), 6,86 (1H), 6,88 (1H), 7,10 (1H), 7,25 (1H), 7,32 (1H), 7,67 (1H), 7,71 (1H), 7,92 (1H), 8,21 (1H), 9,87 (1H) ppm.

Ejemplo 64

N-ciclopropil-4-{6-[(5-fluoro-2-metilfenil)sulfanil]-8-[(2-hidroxi-2-

metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



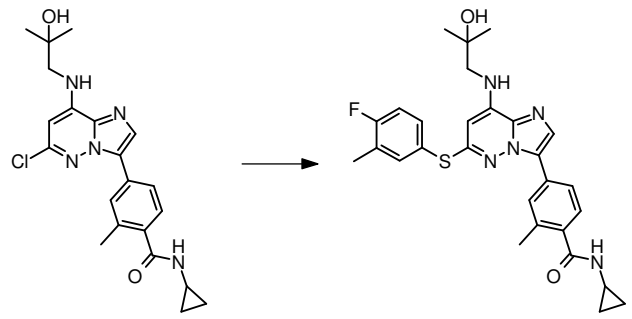
Se trataron 75 mg (181 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 5-fluoro-2-metilbencenotiol para dar, luego del tratamiento posterior y la purificación, 47,7 mg (48%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,65 (2H), 1,12 (6H), 2,19 (3H), 2,31 (3H), 2,79 (1H), 3,23 (2H), 4,71 (1H), 6,27 (1H), 7,01 (1H), 7,06 (1H), 7,29 (1H), 7,42-7,49 (2H), 7,57 (1H), 7,67 (1H), 7,94 (1H), 8,23 (1H) ppm.

Ejemplo 65

N-ciclopropil-4-{6-[(4-fluoro-3-metilfenil)sulfanil]-8-[(2-hidroxi-2-

metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 75 mg (181 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 4-fluoro-3-metilbencenotiol para dar, luego del tratamiento posterior y la purificación, 25,9 mg (26%) del compuesto del

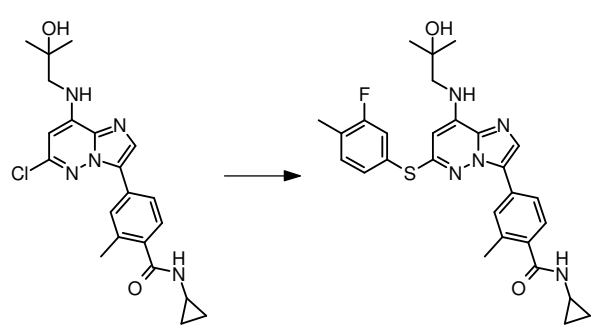
título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,65 (2H), 1,11 (6H), 2,18 (3H), 2,22 (3H), 2,79 (1H), 3,22 (2H), 4,71 (1H), 6,22 (1H), 6,97 (1H), 7,08 (1H), 7,25 (1H), 7,48 (1H), 7,59 (2H), 7,67 (1H), 7,93 (1H), 7,23 (1H) ppm.

Ejemplo 66

N-ciclopropil-4-{6-[(3-fluoro-4-metilfenil)sulfanil]-8-[(2-hidroxi-2-

metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



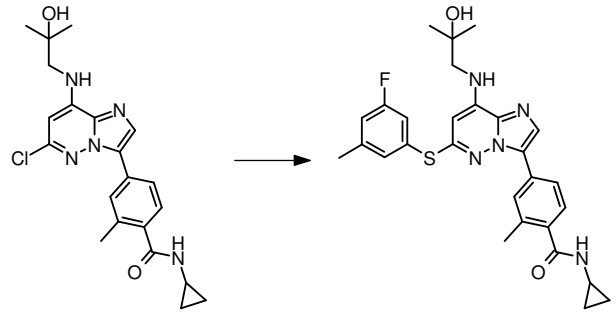
Se trataron 75 mg (181 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 3-fluoro-4-metilbencenotiol para dar, luego del tratamiento posterior y la purificación, 41,7 mg (42%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,65 (2H), 1,12 (6H), 2,19 (3H), 2,28 (3H), 2,79 (1H), 3,23 (2H), 4,72 (1H), 6,27 (1H), 6,99 (1H), 7,07 (1H), 7,34 (1H), 7,39 (1H), 7,44 (1H), 7,63 (1H), 7,69 (1H), 7,94 (1H), 8,25 (1H) ppm.

Ejemplo 67

N-ciclopropil-4-{6-[(3-fluoro-5-metilfenil)sulfanil]-8-[(2-hidroxi-2-

metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



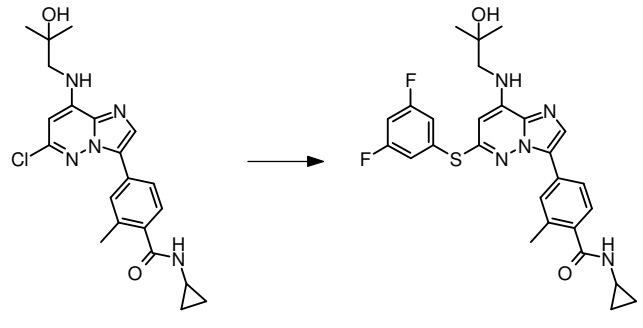
Se trataron 75 mg (181 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 3-fluoro-5-metilbencenotiol para dar, luego del tratamiento posterior y la purificación, 33 mg (33%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,65 (2H), 1,12 (6H), 2,21 (3H), 2,30 (3H), 2,79 (1H), 3,22 (2H), 4,70 (1H), 6,27 (1H), 7,05 (1H), 7,13 (1H), 7,16 (1H), 7,26 (1H), 7,27 (1H), 7,70 (1H), 7,73 (1H), 7,95 (1H), 8,24 (1H) ppm.

Ejemplo 68

N-ciclopropil-4-{6-[(3,5-difluorofenil)sulfanil]-8-[(2-hidroxi-2-

metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



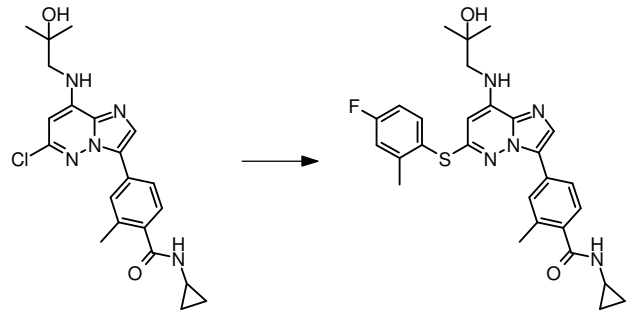
Se trataron 75 mg (181 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 3,5-difluorobencenotiol para dar, luego del tratamiento posterior y la purificación, 5,7 mg (6%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,65 (2H), 1,12 (6H), 2,22 (3H), 2,79 (1H), 3,24 (2H), 4,71 (1H), 6,34 (1H), 7,12 (1H), 7,16 (1H), 7,35-7,40 (3H), 7,71 (1H), 7,74 (1H), 7,96 (1H), 8,25 (1H) ppm.

Ejemplo 69

N-ciclopropil-4-{6-[(4-fluoro-2-metilfenil)sulfanil]-8-[(2-hidroxi-2-

metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 75 mg (181 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-

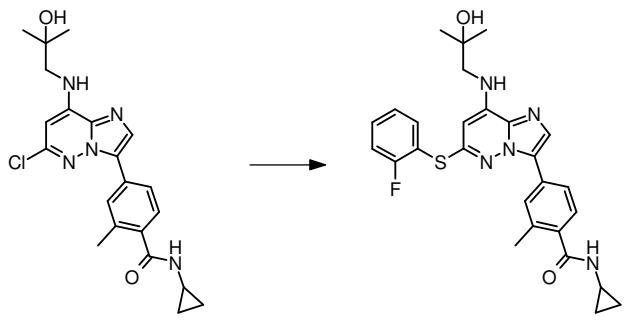
metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 4-fluoro-3-metilbencenotiol para dar, luego del tratamiento posterior y la purificación, 32,1 mg (32%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,65 (2H), 1,12 (6H), 2,18 (3H), 2,35 (3H), 2,79 (1H), 3,22 (2H), 4,72 (1H), 6,23 (1H), 6-95 (1H), 7,05 (1H), 7,15 (1H), 7,34 (1H), 7,53 (1H), 7,63 (1H), 7,65 (1H), 7,92 (1H), 8,23 (1H) ppm.

Ejemplo 70

N-ciclopropil-4-{6-[(2-fluorofenil)sulfanil]-8-[(2-hidroxi-2-metilpropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 75 mg (181 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 2-fluorobencenotiol para dar, luego del tratamiento posterior y la purificación, 36,8 mg (38%) del compuesto del título.

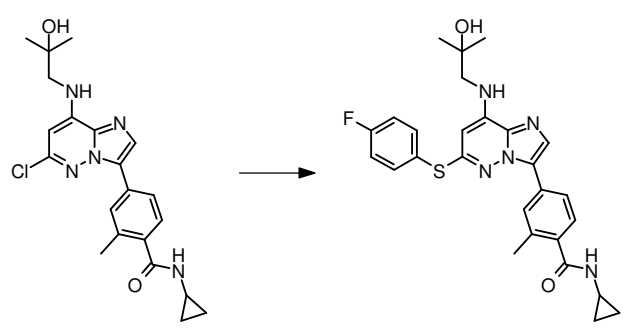
1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,65 (2H), 1,13 (6H), 2,18 (3H), 2,78 (1H), 3,24 (2H), 4,72 (1H), 6,31 (1H), 7,00 (1H), 7,03

(1H), 7,32 (1H), 7,40 (1H), 7,53 (1H), 7,61 (1H), 7,64 (1H), 7,69 (1H), 7,93 (1H), 8,22 (1H) ppm.

Ejemplo 71

N-ciclopropil-4-{6-[(4-fluorofenil)sulfanil]-8-[(2-hidroxi-2-metilpropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



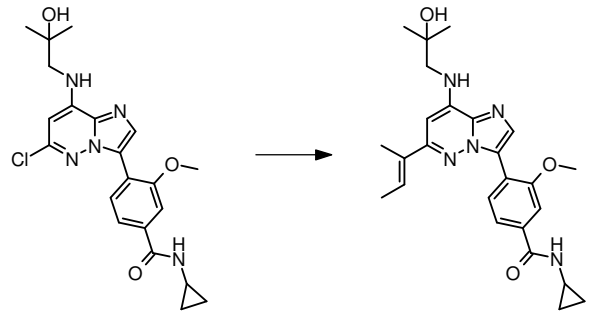
Se trataron 75 mg (181 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 4-fluorobencenotiol para dar, luego del tratamiento posterior y la purificación, 31,6 mg (33%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,65 (2H), 1,12 (6H), 2,19 (3H), 2,79 (1H), 3,22 (2H), 4,72 (1H), 6,24 (1H), 6,97 (1H), 7,08 (1H), 7,33 (2H), 7,58 (1H), 7,64-7,71 (3H), 7,92 (1H), 8,23 (1H) ppm.

Ejemplo 72

4-{6-[(2E)-But-2-en-2-il]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]

piridazin-3-il}-N-ciclopropil-3-metoxibenzamida



Se trataron 75 mg (174 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-3-metoxibenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 49a, de manera análoga al Ejemplo 1 usando ácido (2Z)-but-2-en-2-ilborónico para dar, luego del tratamiento posterior y la purificación, 26,9 mg (33%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,57 (2H), 0,68 (2H), 1,16 (6H), 1,81 (3H), 1,99 (3H), 2,84 (1H), 3,28 (2H), 3,89 (3H), 4,75 (1H), 6,40 (1H), 6,48 (1H), 6,58 (1H), 7,51 (1H), 7,53 (1H), 7,85 (1H), 8,32 (1H), 8,47 (1H) ppm.

Ejemplo 73

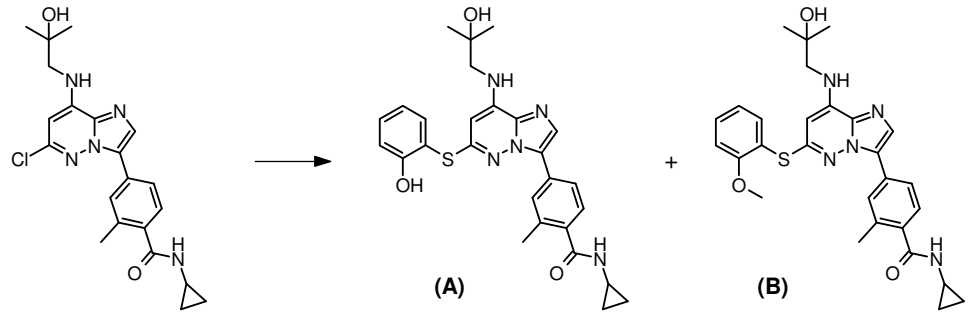
N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(2-hidroxifenil)

sulfanil]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida (A)

y

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(2-metoxifenil)

sulfanil]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida (B)



Se trataron 100 mg (242 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 2-metoxibencenotiol para dar, luego del tratamiento posterior y la purificación, 43,1 mg (35%) del compuesto del título A y 5,8 mg (4%) del compuesto del título B.

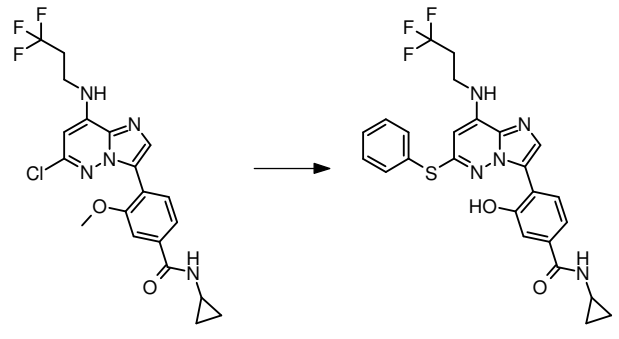
1H-RMN (DMSO-d6) de A: δ= 0,49 (2H), 0,65 (2H), 1,11 (6H), 2,20 (3H), 2,78 (1H), 3,19 (2H), 4,72 (1H), 6,14 (1H), 6,82-6,90 (2H), 6,97 (1H), 7,07 (1H), 7,33 (1H), 7,44 (1H), 7,66 (1H), 7,71 (1H), 7,91 (1H), 8,22 (1H), 9,96 (1H) ppm.

1H-RMN (CDCl3) de B: δ= 0,63 (2H), 0,89 (2H), 1,39 (6H), 2,35 (3H), 2,91 (1H), 3,23 (2H), 3,77 (3H), 4,62 (1H), 5,92 (1H), 5,97 (1H), 6,42 (1H), 6,99 (1H), 7,03 (1H), 7,13 (1H), 7,47 (1H), 7,56-7,64 (4H) ppm.

Ejemplo 74

N-ciclopropil-3-hidroxi-4-{6-(fenilsulfanil)-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}benzamida



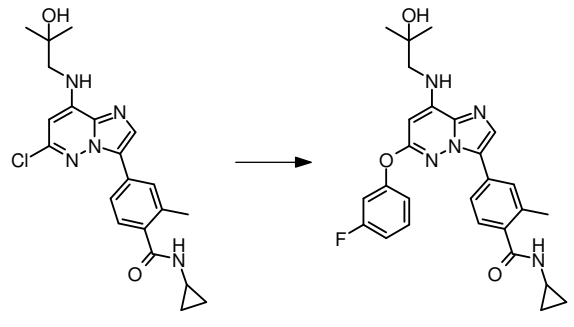
Se trataron 29,5 mg (67 µmol) de 4-{6-cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-3-metoxibenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 52a, de manera análoga al Ejemplo 51 usando bencenotiol para dar, luego del tratamiento posterior y la purificación, 19 mg (52%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,63 (2H), 0,88 (2H), 2,44 (2H), 2,92 (1H), 3,55 (2H), 5,81 (1H), 6,12 (1H), 6,22 (1H), 7,22 (1H), 7,33 (1H), 7,41-7,54 (4H), 7,58-7,66 (3H), 9,01 (1H) ppm.

Ejemplo 75

N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 50 mg (121 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-

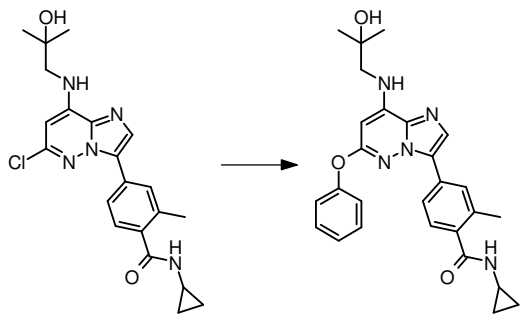
metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 3-fluorofenol para dar, luego del tratamiento posterior y la purificación, 13,9 mg (22%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,47 (2H), 0,63 (2H), 1,16 (6H), 2,14 (3H), 2,76 (1H), 3,27 (2H), 4,74 (1H), 6,18 (1H), 7,02 (1H), 7,08-7,14 (2H), 7,16 (1H), 7,24 (1H), 7,47 (1H), 7,67 (1H), 7,77 (1H), 7,92 (1H), 8,21 (1H) ppm.

Ejemplo 76

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-fenoxiimidazo

[1,2-b]piridazin-3-il}-2-metilbenzamida



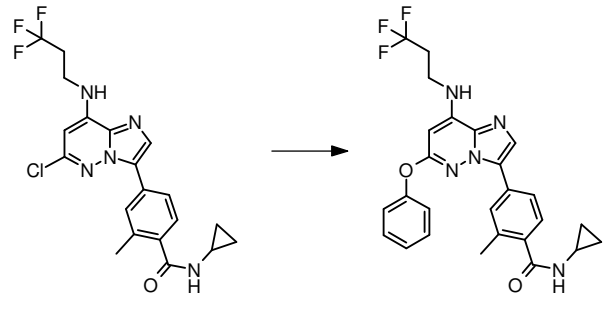
Se trataron 50 mg (121 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando fenol para dar, luego del tratamiento posterior y la purificación, 15,1 mg (25%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,59 (2H), 0,86 (2H), 1,38 (6H), 2,26 (3H), 2,86 (1H), 3,29 (2H), 3,74 (1H), 5,91 (1H), 6,02 (1H), 6,42 (1H), 7,19 (2H), 7,23 (2H), 7,41 (2H), 7,57 (1H), 7,66 (1H),

7,70 (1H) ppm.

Ejemplo 77

N-ciclopropil-2-metil-4-{6-fenoxi-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida

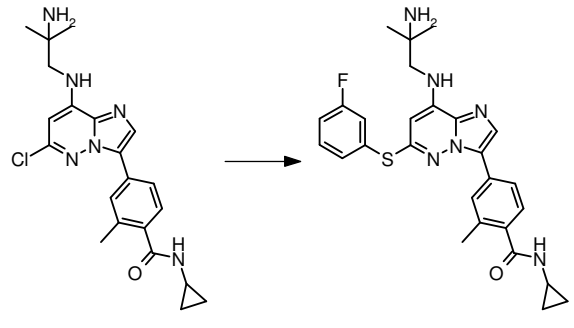


Se trataron 50 mg (114 µmol) de 4-{6-cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 10a, de manera análoga al Ejemplo 51 usando fenol para dar, luego del tratamiento posterior y la purificación, 5,7 mg (9%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,60 (2H), 0,87 (2H), 2,29 (3H), 2,57 (2H), 2,88 (1H), 1,97 (2H), 5,84 (1H), 5,90 (1H), 5,97 (1H), 7,20-7,30 (4H), 7,44 (2H), 7,60 (1H), 7,73 (1H), 7,74 (1H) ppm.

Ejemplo 78

4-{8-[(2-Amino-2-metilpropil)amino]-6-[(3-fluorofenil)sulfanil]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida

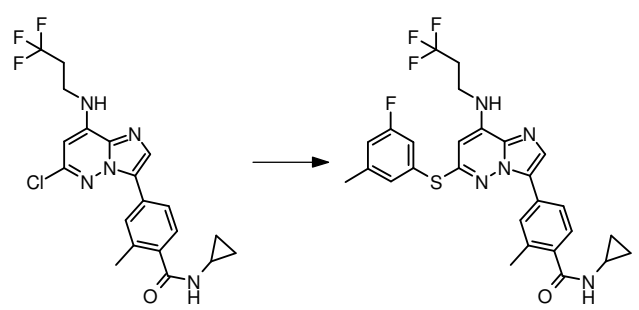


Se trataron 250 mg (605 µmol) de 4-{8-[(2-amino-2-metilpropil)amino]-6-cloroimidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 57a, de manera análoga al Ejemplo 51 usando 3-fluorobencenotiol para dar, luego del tratamiento posterior y la purificación, 9,8 mg (3%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,63 (2H), 0,89 (2H), 1,24 (6H), 1,80 (2H), 2,39 (3H), 2,91 (1H), 3,14 (2H), 5,91 (1H), 5,97 (1H), 6,34 (1H), 7,12 (1H), 7,22 (1H), 7,32-7,42 (3H), 7,62 (1H), 7,64 (1H), 7,69 (1H) ppm.

Ejemplo 79

N-ciclopropil-4-{6-[(3-fluoro-5-metilfenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 50 mg (114 µmol) de 4-{6-cloro-8-[(3,3,3-

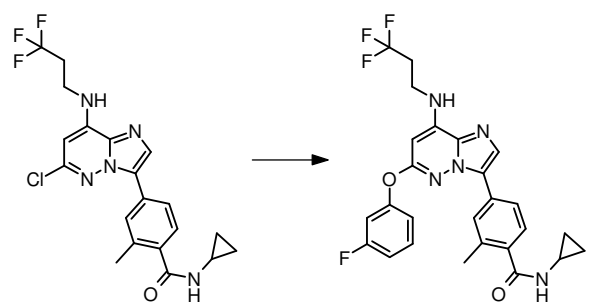
trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 10a, de manera análoga al Ejemplo 51 usando 3-fluoro-5-metilbencenotiol para dar, luego del tratamiento posterior y la purificación, 6,9 mg (11%) del compuesto del título.

1H-RMN (CDCl3 + CD3OD): δ= 0,61 (2H), 0,88 (2H), 2,35 (3H), 2,39 (3H), 2,48 (2H), 2,89 (1H), 3,54 (2H), 5,89 (1H), 6,07 (1H), 6,46 (1H), 6,96 (1H), 7,17 (1H), 7,21 (1H), 7,23 (1H), 7,63 (1H), 7,66 (1H), 7,68 (1H) ppm.

Ejemplo 80

N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo

[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 50 mg (114 µmol) de 4-{6-cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 10a, de manera análoga al Ejemplo 51 usando 3-fluorofenol para dar, luego del tratamiento posterior y la purificación, 9,1 mg (15%) del compuesto del título.

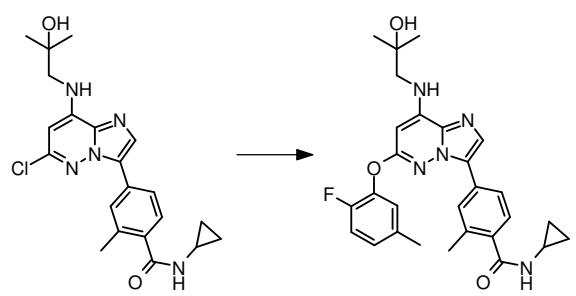
1H-RMN (CDCl3): δ= 0,60 (2H), 0,87 (2H), 2,32 (3H), 2,57 (2H),

2,89 (1H), 3,67 (2H), 5,87 (1H), 5,89 (1H), 6,12 (1H), 6,94-7,08 (3H), 7,25 (1H), 7,39 (1H), 7,60 (1H), 7,72 (2H) ppm.

Ejemplo 81

N-ciclopropil-4-{6-(2-fluoro-5-metilfenoxi)-8-[(2-hidroxi-2-metilpropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



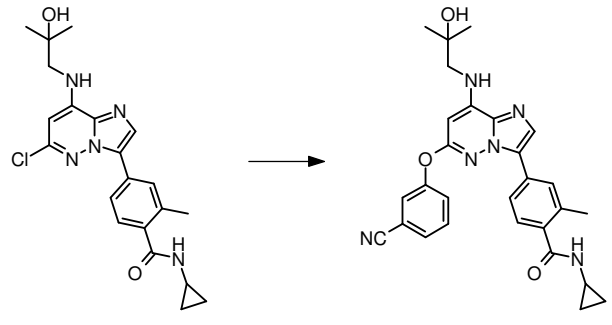
Se trataron 50 mg (121 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 2-fluoro-5-metilfenol para dar, luego del tratamiento posterior y la purificación, 5,2 mg (8%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,46 (2H), 0,63 (2H), 1,17 (6H), 2,09 (3H), 2,29 (3H), 2,76 (1H), 3,29 (2H), 4,75 (1H), 6,23 (1H), 7,02 (1H), 7,10-7,16 (2H), 7,23 (1H), 7,27 (1H), 7,62 (1H), 7,70 (1H), 7,92 (1H), 8,21 (1H) ppm.

Ejemplo 82

4-{6-(3-Cianofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]

piridazin-3-il}-N-ciclopropil-2-metilbenzamida



Se trataron 50 mg (121 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 3-hidroxibenzonitrilo para dar, luego del tratamiento posterior y la purificación, 5,8 mg (9%) del compuesto del título.

1H-RMN (CDCl3 + CD3OD): δ= 0,63 (2H), 0,86 (2H), 1,42 (6H), 2,35 (3H), 2,90 (1H), 3,32 (2H), 5,88 (1H), 6,26 (1H), 6,66 (1H), 7,30 (1H), 7,46 (1H), 7,49-7,60 (4H), 7,65 (1H), 7,72 (1H) ppm.

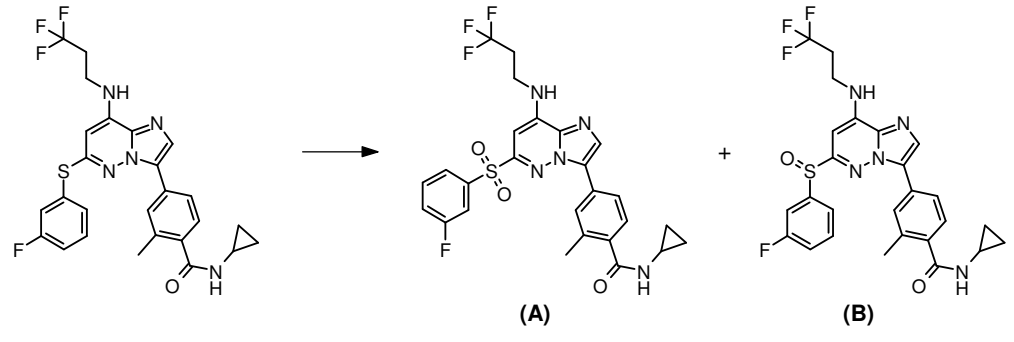
Ejemplo 83

N-ciclopropil-4-{6-[(3-fluorofenil)sulfonil]-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida (A) y

(RS)-N-ciclopropil-4-{6-[(3-fluorofenil)sulfinil]-8-[(3,3,3-trifluoropropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida (B)



A una solución de 50 mg (121 µmol) de N-ciclopropil-4-{6-[(3-fluorofenilo) sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 209, en 1,0 mL de diclorometano, se agregaron 0,71 mg de metil(trioxo)renio, 1,77 mg de isonicotinonitrilo y 58 µL de peróxido de hidrógeno acuoso (30%). La mezcla se agitó durante dos días a 23°C, se volcó sobre solución de tiosulfato de sodio y se extrajo con diclorometano. La fase orgánica se secó sobre sulfato de sodio. Luego de la filtración y la eliminación del solvente el residuo se purificó mediante cromatografía para dar 14,9 mg (53%) del compuesto del título A y 4,5 mg (8%) del compuesto del título B.

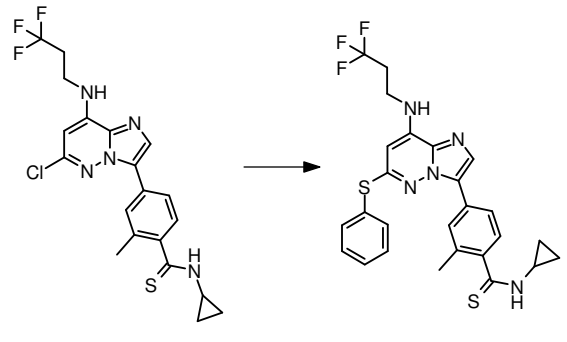
1H-RMN (CDCl3 + CD3OD) de A: δ= 0,65 (2H), 0,90 (2H), 2,47 (3H), 2,59 (2H), 2,92 (1H), 3,75 (2H), 6,08 (1H), 6,76 (1H), 6,77 (1H), 7,33 (1H), 7,38 (1H), 7,53-7,65 (3H), 7,81 (1H), 7,82 (1H), 7,88 (1H) ppm.

1H-RMN (CDCl3) de B: δ= 0,65 (2H), 0,92 (2H), 2,55 (5H), 2,94 (1H), 3,73 (2H), 5,98 (1H), 6,37 (1H), 6,60 (1H), 7,17 (1H), 7,46 (1H), 7,50 (1H), 7,56 (1H), 7,60 (1H), 7,74-7,84 (3H) ppm.

Ejemplo 84

N-ciclopropil-2-metil-4-{6-(fenilsulfanil)-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}bencencarbotioamida



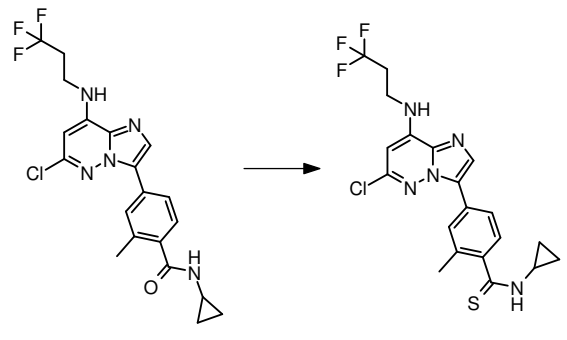
Se trataron 59,1 mg (130 µmol) de 4-{6-cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b] piridazin-3-il}-N-ciclopropil-2-metilbencencarbotioamida, que se preparó de acuerdo con el Ejemplo Intermediario 84a, de manera análoga al Ejemplo 51 usando bencenotiol para dar, luego del tratamiento posterior y la purificación, 7,1 mg (9%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,75 (2H), 1,05 (2H), 2,30 (3H), 2,47 (2H), 3,41 (1H), 3,56 (2H), 5,87 (2H), 7,16 (1H), 7,27 (1H), 7,41-7,50 (3H), 7,57-7,71 (5H) ppm.

Ejemplo Intermediario 84a

4-{6-Cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-

N-ciclopropil-2-metilbencencarbotioamida

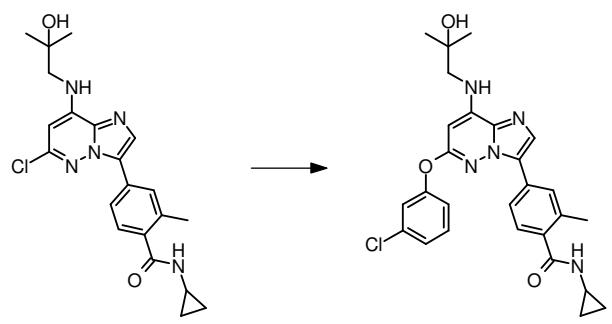


Una mezcla de 100 mg (228 µmol) de 4-{6-cloro-8-[(3,3,3-trifluoropropilo) amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 10a, 25,4 mg de pentasulfuro de fósforo y 0,47 mL de piridina se calentó a 115°C durante 4 horas. Se agregaron agua y salmuera y la mezcla se extrajo varias veces con acetato de etilo. Las capas orgánicas combinadas se secaron sobre sulfato de sodio. Luego de la filtración y la eliminación del solvente el residuo se purificó mediante cromatografía para dar 65,7 mg (63%) del compuesto del título.

Ejemplo 85

4-{6-(3-Clorofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]

piridazin-3-il}-N-ciclopropil-2-metilbenzamida



Se trataron 50 mg (121 µmol) de 4-{6-Cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N- ciclopropil-

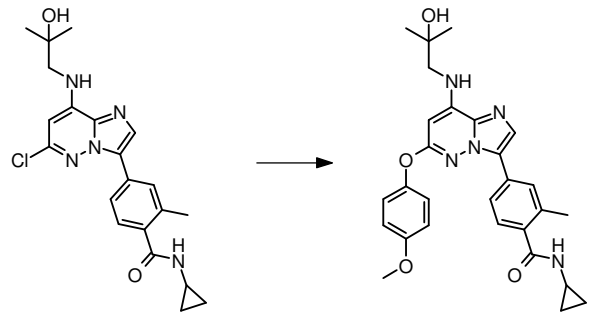
2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 3-clorofenol para dar, luego del tratamiento posterior y la purificación, 9,3 mg (14%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,47 (2H), 0,63 (2H), 1,16 (6H), 2,14 (3H), 2,77 (1H), 3,29 (2H), 4,74 (1H), 6,18 (1H), 7,03 (1H), 7,17 (1H), 7,25 (1H), 7,33 (1H), 7,44 (1H), 7,47 (1H), 7,67 (1H), 7,74 (1H), 7,93 (1H), 8,22 (1H) ppm.

Ejemplo 86

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(4-metoxifenoxi)

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



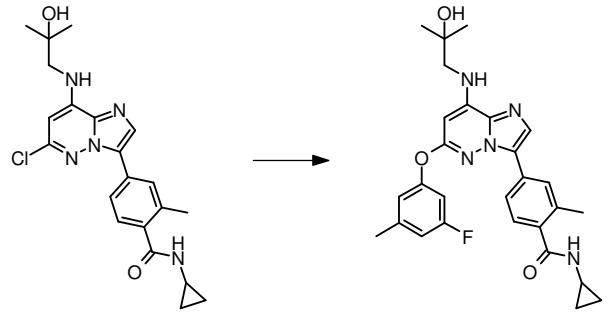
Se trataron 50 mg (121 µmol) de 4-{6-Cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N- ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 4-metoxifenol para dar, luego del tratamiento posterior y la purificación, 22,5 mg (35%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,47 (2H), 0,63 (2H), 1,16 (6H), 2,11 (3H), 2,77 (1H), 3,27 (2H), 3,75 (3H), 4,75 (1H), 6,13 (1H), 6,91 (1H), 6,98 (2H), 7,15 (1H), 7,18 (2H), 7,65 (1H), 7,77 (1H),

7,91 (1H), 8,21 (1H) ppm.

Ejemplo 87

N-ciclopropil-4-{6-(3-fluoro-5-metilfenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

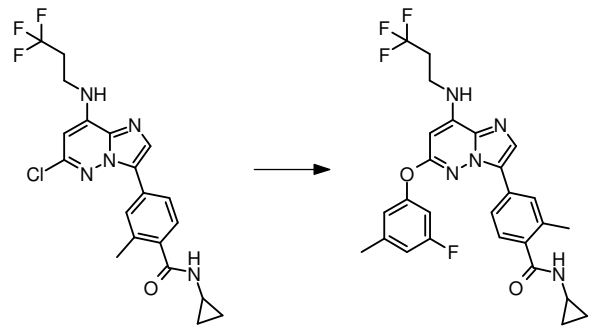


Se trataron 50 mg (121 µmol) de 4-{6-Cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N- ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 3-fluoro-5-metilfenol para dar, luego del tratamiento posterior y la purificación, 12,0 mg (19%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,47 (2H), 0,63 (2H), 1,15 (6H), 2,15 (3H), 2,31 (3H), 2,77 (1H), 3,27 (2H), 4,73 (1H), 6,16 (1H), 6,90-7,06 (4H), 7,17 (1H), 7,69 (1H), 7,78 (1H), 7,92 (1H), 8,22 (1H) ppm.

Ejemplo 88

N-ciclopropil-4-{6-(3-fluoro-5-metilfenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



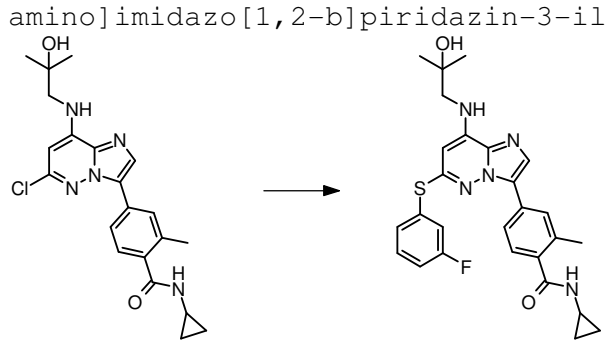
Se trataron 50 mg (114 µmol) de 4-{6-cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 10a, de manera análoga al Ejemplo 51 usando 3-fluoro-5-metilfenol para dar, luego del tratamiento posterior y la purificación, 7,6 mg (12%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,47 (2H), 0,63 (2H), 2,15 (3H), 2,32 (3H), 2,67 (2H), 2,77 (1H), 3,59 (2H), 6,11 (1H), 6,95 (2H), 7,03 (1H), 7,17 (1H), 7,65-7,75 (2H), 7,78 (1H), 7,93 (1H), 8,22 (1H) ppm.

Ejemplo 89

N-ciclopropil-4-{6-[(3-fluorofenil)sulfanil]-8-[(2-hidroxi-2-metilpropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 300 mg (725 µmol) de 4-{6-Cloro-8-[(2-hidroxi-2-

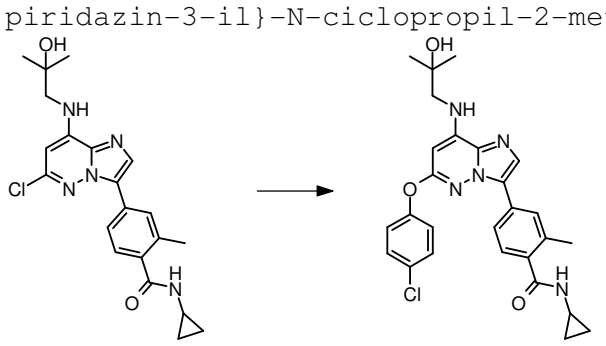
metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N- ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 3-fluorobencenotiol para dar, luego del tratamiento posterior y la purificación, 27,9 mg (7%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,65 (2H), 1,12 (6H), 2,20 (3H), 2,79 (1H), 3,23 (2H), 4,71 (1H), 6,29 (1H), 7,04 (1H), 7,12 (1H), 7,33 (1H), 7,43 (1H), 7,46-7,53 (2H), 7,66 (1H), 7,71 (1H), 7,94 (1H), 8,23 (1H) ppm.

Ejemplo 90

4-{6-(4-Clorofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]

piridazin-3-il}-N-ciclopropil-2-metilbenzamida



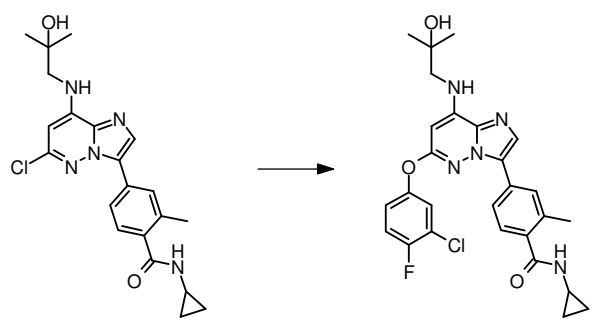
Se trataron 50 mg (121 µmol) de 4-{6-Cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N- ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 4-clorofenol para dar, luego del tratamiento posterior y la purificación, 14,5 mg (23%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,47 (2H), 0,64 (2H), 1,16 (6H), 2,13 (3H), 2,77 (1H), 3,28 (2H), 4,74 (1H), 6,18 (1H), 7,00 (1H), 7,17

(1H), 7,30 (2H), 7,50 (2H), 7,64 (1H), 7,73 (1H), 7,92 (1H), 8,22 (1H) ppm.

Ejemplo 91

4-{6-(3-Cloro-4-fluorofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida

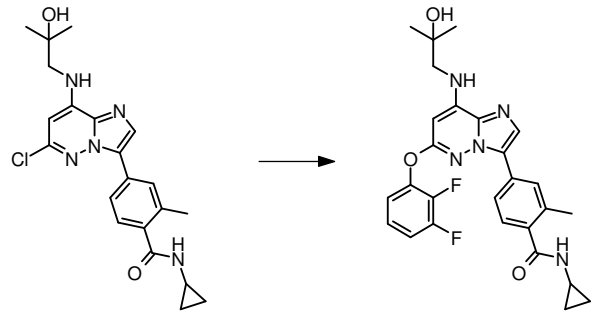


Se trataron 50 mg (121 µmol) de 4-{6-Cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N- ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 3-cloro-4-fluorofenol para dar, luego del tratamiento posterior y la purificación, 16,2 mg (24%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,47 (2H), 0,64 (2H), 1,16 (6H), 2,13 (3H), 2,77 (1H), 3,28 (2H), 4,74 (1H), 6,18 (1H), 7,02 (1H), 7,18 (1H), 7,32 (1H), 7,51 (1H), 7,66 (2H), 7,72 (1H), 7,93 (1H), 8,22 (1H) ppm.

Ejemplo 92

N-ciclopropil-4-{6-(2,3-difluorofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



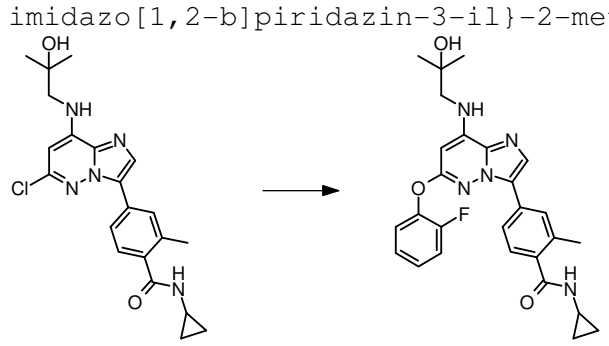
Se trataron 50 mg (121 µmol) de 4-{6-Cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N- ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 2,3-difluorofenol para dar, luego del tratamiento posterior y la purificación, 5,8 mg (9%) del compuesto del título.

1H-RMN (CDCl3 + CD3OD): δ= 0,59 (2H), 0,85 (2H), 1,38 (6H), 2,24 (3H), 2,86 (1H), 3,31 (2H), 5,98 (1H), 6,16 (1H), 6,53 (1H), 7,02-7,14 (3H), 7,17 (1H), 7,47 (1H), 7,61 (2H), ppm.

Ejemplo 93

N-ciclopropil-4-{6-(2-fluorofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



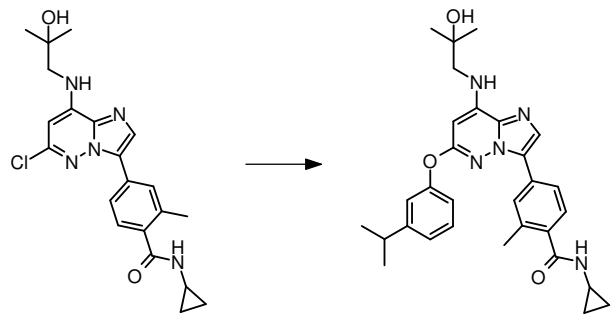
Se trataron 50 mg (121 µmol) de 4-{6-Cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N- ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo

Intermediario 7a, de manera análoga al Ejemplo 51 usando 2-fluorofenol para dar, luego del tratamiento posterior y la purificación, 4,2 mg (7%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,46 (2H), 0,63 (2H), 1,17 (6H), 2,08 (3H), 2,46 (2H), 2,76 (1H), 4,75 (1H), 6,25 (1H), 7,03 (1H), 7,11 (1H), 7,24-7,45 (4H), 7,59 (1H), 7,67 (1H), 7,92 (1H), 8,21 (1H) ppm.

Ejemplo 94

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(3-isopropilfenoxi)
imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

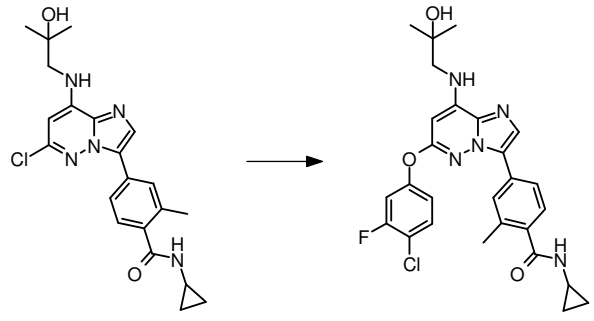


Se trataron 50 mg (121 µmol) de 4-{6-Cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N- ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 3-isopropilfenol para dar, luego del tratamiento posterior y la purificación, 9,0 mg (14%) del compuesto del título.

1H-RMN (CDCl3 + CD3OD): δ= 0,58 (2H), 0,84 (2H), 1,22 (6H), 1,36 (6H), 2,24 (3H), 2,33 (1H), 2,85 (1H), 2,89 (1H), 3,27 (2H), 5,88 (1H), 6,15 (1H), 6,44 (1H), 7,02 (1H), 7,03 (1H), 7,10 (1H), 7,17 (1H), 7,31 (1H), 7,59 (1H), 7,64 (1H), 7,68 (1H) ppm.

Ejemplo 95

4-{6-(4-Cloro-3-fluorofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida

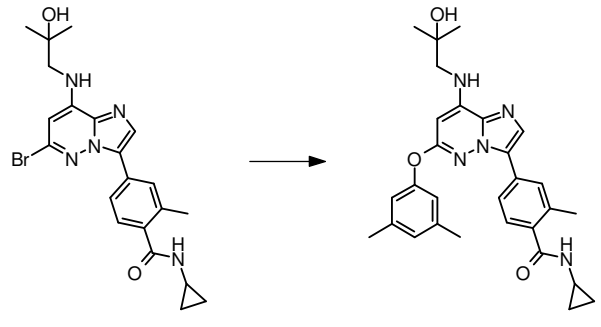


Se trataron 50 mg (121 µmol) de 4-{6-Cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N- ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 4-cloro-3-fluorofenol para dar, luego del tratamiento posterior y la purificación, 4,0 mg (6%) del compuesto del título.

1H-RMN (CDCl3 + CD3OD): δ= 0,60 (2H), 086 (2H), 1,37 (6H), 2,31 (3H), 2,34 (1H), 2,87 (1H), 3,29 (2H), 5,89 (1H), 6,09 (1H), 6,57 (1H), 6,98 (1H), 7,09 (1H), 7,15 (1H), 7,42 (1H), 7,55 (1H), 7,67 (2H) ppm.

Ejemplo 96

N-ciclopropil-4-{6-(3,5-dimetilfenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

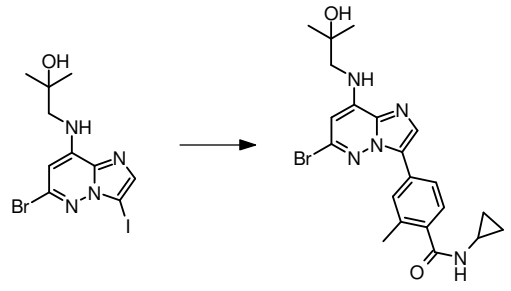


Se trataron 50 mg (109 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N- ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando 3,5-dimetilfenol para dar, luego del tratamiento posterior y la purificación, 14,6 mg (27%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,61 (2H), 0,87 (2H), 1,45 (6H), 2,28 (3H), 2,33 (6H), 2,89 (1H), 3,31 (2H), 3,83 (1H), 5,86 (1H), 5,92 (1H), 6,59 (1H), 6,83 (2H), 6,87 (1H), 7,21 (1H), 7,63 (1H), 7,65 (1H), 7,73 (1H) ppm.

Ejemplo Intermediario 96a

4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N- ciclopropil-2-metilbenzamida

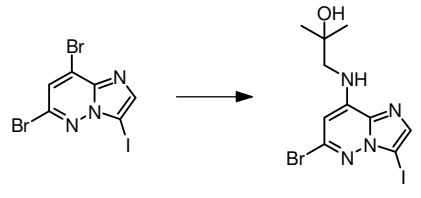


Se trataron 809 mg (1,97 mmol) de 1-[(6-bromo-3-yodoimidazo[1,2-b]piridazin-8-il)amino]-2-metilpropan-2-ol, que se preparó de acuerdo con el Ejemplo Intermediario 96b, de manera análoga al

Ejemplo Intermediario 1a usando N-ciclopropil-2-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzamida para dar, luego del tratamiento posterior y la purificación, 659 mg (73%) del compuesto del título.

Ejemplo Intermediario 96b

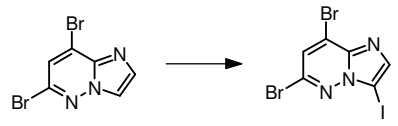
1-[(6-bromo-3-yodoimidazo[1,2-b]piridazin-8-il)amino]-2-metilpropan-2-ol



Se trataron 1,0 g (2,48 mmol) de 6,8-dibromo-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 96c, de manera análoga al Ejemplo Intermediario 1b usando 1-amino-2-metilpropan-2-ol para dar, luego del tratamiento posterior y la purificación, 915 mg (90%) del compuesto del título.

Ejemplo Intermediario 96c

6,8-dibromo-3-yodoimidazo[1,2-b]piridazina

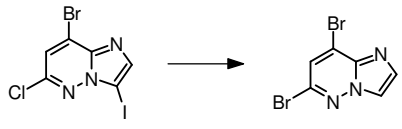


Una mezcla de 3,64 g (10,5 mmol) de 6,8-dibromoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 96d, 2,8 g de N-yodosuccinimida, 72,6 mL de N,N-dimetilformamida se calentó a 60°C durante 3 horas. Se agregaron 1,4 g de N-yodosuccinimida, y el calentamiento se continuó

durante otras 4 horas. La mayor parte del solvente se eliminó, se agregó agua y la mezcla se extrajo con diclorometano. La fase orgánica se lavó con agua, solución de tiosulfato de sodio y se secó sobre sulfato de sodio. Luego de la filtración y la eliminación del solvente el residuo se purificó mediante cromatografía para dar 3,64 g (86%) del compuesto del título.

Ejemplo Intermediario 96d

6,8-dibromoimidazo[1,2-b]piridazina

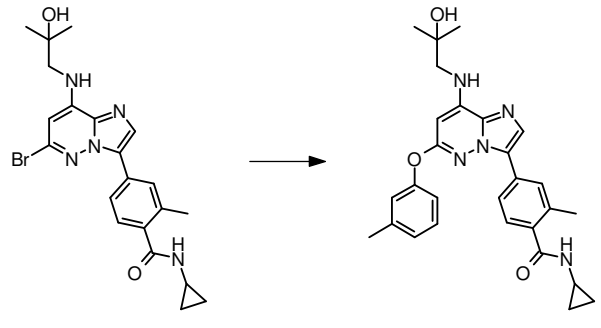


Una mezcla de 5,0 (14,0 mmol) de 8-bromo-6-cloro-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 1c, 30 mL de solución de bromuro de hidrógeno en ácido acético (33%) se agitó a 120°C durante 1 hora bajo irradiación de microondas. La mezcla se volcó sobre agua y se extrajo con diclorometano. La fase orgánica se lavó con tiosulfato de sodio y solución de carbonato ácido de sodio y se secó sobre sulfato de sodio. Luego de la filtración y la eliminación del solvente el residuo se purificó mediante cromatografía para dar 3,0 g (78%) del compuesto del título.

Ejemplo 97

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(3-metilfenoxi)

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



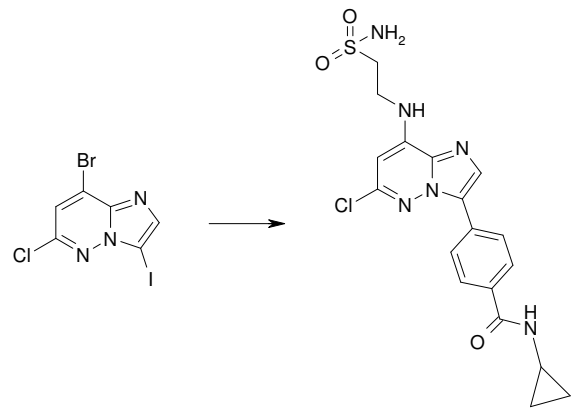
Se trataron 50 mg (109 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N- ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando 3-metilfenol para dar, luego del tratamiento posterior y la purificación, 17,1 mg (32%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,61 (2H), 0,87 (2H), 1,46 (6H), 2,26 (3H), 2,37 (3H), 2,89 (1H), 3,31 (2H), 5,87 (1H), 5,94 (1H), 6,61 (1H), 6,98-7,09 (3H), 7,19 (1H), 7,29 (1H), 7,59 (1H), 7,63 (1H), 7,70 (1H) ppm.

Ejemplo 98

4-{6-Cloro-8-[(2-sulfamoiletil)amino]imidazo[1,2-b]piridazin-3-il}-

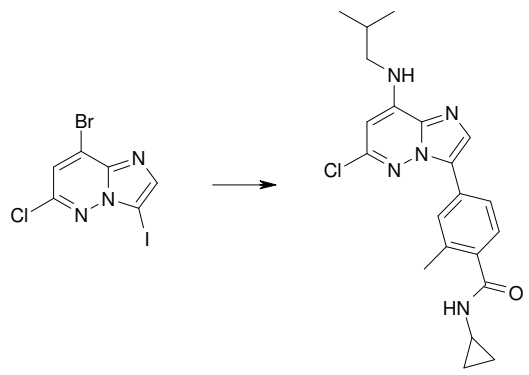
N-ciclopropilbenzamida



Se combinaron 8-Bromo-6-cloro-3-yodoimidazo[1,2-b]piridazina (0,3 mmol) de, que se preparó de acuerdo con el Ejemplo Intermediario 1c, clorhidrato de 2-aminoetansulfonamida (1:1) (0,3 mmol, 1,0 eq)) y DIPEA (3 eq, 157 µL) con 3mL de NMP en un vial sellado y se calentó a 160 °C bajo irradiación de microondas durante 30 min. Luego de enfriar, se agregaron ácido [4-(ciclopropilcarbamoil)fenil]borónico (1,2 eq, 74 mg), Pd(dppf)Cl2 (0,2 eq, 49 mg) y carbonato de potasio (3 eq, 900 µL, 1M en agua), y la mezcla se calentó a 80 °C durante la noche. Luego de enfriar, la solución se filtró y se sometió a HPLC preparativa para dar 4-{6-cloro-8-[(2-sulfamoiletil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida (45 mg, 35 %): UPLC-MS: RT = 0,92 min; m/z (ES+) 435,9 [MH+]; PM requerido = 434,9.

Ejemplo Intermediario 99

4-{6-Cloro-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



Se trataron 6 g (16,7 mmol) de 8-Bromo-6-cloro-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 1c, de manera análoga al Ejemplo 98 usando

2-metilpropan-1-amina y N-ciclopropil-2-metil-4- (4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzamida para dar, luego del tratamiento posterior y la purificación, 1,27 g (19%) del compuesto del título.

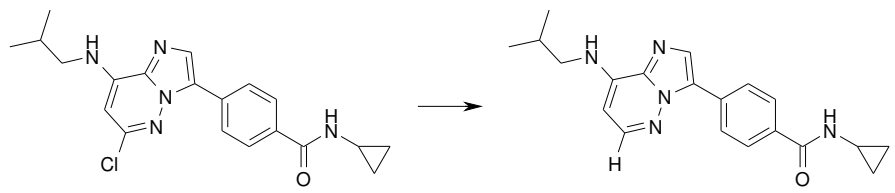
UPLC-MS: RT = 1,32 min; m/z (ES+) 398,9 [MH+]; PM requerido = 397,9.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,65 (2H), 0,90 (6H), 1,96 (1H), 2,35 (3H), 2,80 (1H), 3,12 (2H), 6,29 (1H), 7,36 (1H), 7,84 (1H), 7,91 (1H), 7,96 (1H), 7,99 (1H), 8,29 (1H) ppm.

Ejemplo 100

N-ciclopropil-4-{8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}

benzamida



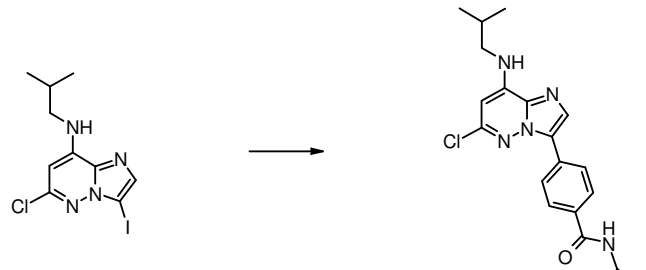
Se disolvieron 100 mg (260 µmol) de 4-{6-cloro-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 100a, en 50 mL de etanol y se sometió a flujo de hidrogenación usando un H-Cube con cartucho de Pd/C 10% CATCART 30 a 30°C, 10 bar y 0,8 mL/min de flujo. La purificación mediante RP-HPLC dio 21,1 mg (23%) del compuesto del título.

UPLC-MS: RT = 1,13 min; m/z (ES+) 350,4 [MH+]; PM requerido = 349,4.

1H-RMN (DMSO-d6): δ= 0,56 (2H), 0,67 (2H), 0,90 (6H), 1,96 (1H), 2,82 (1H), 3,11 (2H), 6,15 (1H), 7,54 (1H), 7,87 (2H), 8,04 (1H), 8,12 (1H),-8,21 (2H), 8,43 (1H) ppm.

Ejemplo Intermediario 100a

4-{6-cloro-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida



Se combinaron 1 mmol de 6-cloro-3-yodo-N-(2-metilpropil)imidazo[1,2-b]piridazin-8-amina (10 mL, 0,1 M en NMP), que se preparó de acuerdo con el Ejemplo Intermediario 100b, 1,5 mmol de ácido [4-(ciclopropilcarbamoil)fenil]borónico, 0,2 mmol de Pd(dppf)Cl2 y 3 mmol de carbonato de potasio (3 mL, 1M en agua, 3 eq) en un vial sellado y se calentó a 150 °C durante 180 min. Luego de enfriar, la mezcla se trató con agua y se extrajo con acetato de etilo, las capas orgánicas combinadas se secaron y se concentró, se purificó mediante flash cromatografía de columna sobre gel de sílice (Acetato de etilo:Éter de petróleo 1:5) para dar 115 mg (30 %) del compuesto del título.

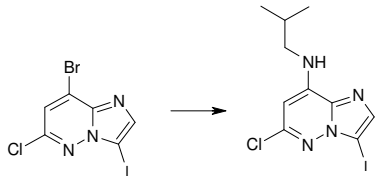
UPLC-MS: RT = 1,29 min; m/z (ES+) 384,9 [MH+]; PM requerido 383,9.

1H-RMN (DMSO-d6): δ= 0,60 (2H), 0,72 (2H), 0,93 (6H), 2,0 (1H),

2,87 (1H), 3,34 (2H), 6,33 (1H), 7,92 (1H), 8,07 (2H), 8,16 (2H), 8,48 (1H) ppm.

Ejemplo Intermediario 100b

6-cloro-3-yodo-N-(2-metilpropil)imidazo[1,2-b]piridazin-8-amina



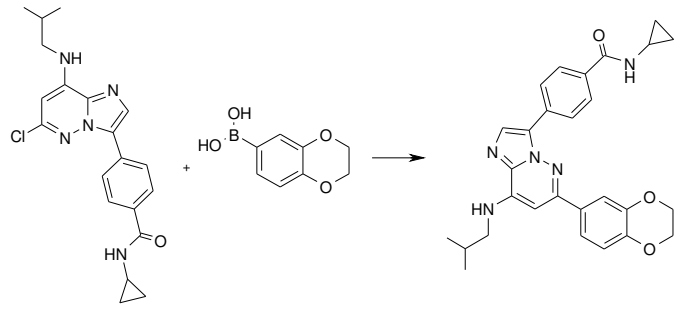
A una solución de 200 mg (0,558 mmol) de 8-bromo-6-cloro-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 1c, en 4 mL de N,N-dimetilformamida, se agregaron 122 mg de 2-metilpropan-1-amina y la mezcla se agitó a temperatura ambiente durante la noche. Se agregó agua y la mezcla se extrajo con diclorometano y metanol. La fase orgánica se lavó con agua y se secó sobre sulfato de sodio. Luego de la filtración y la eliminación del solvente el residuo se purificó mediante cromatografía para dar 188 mg (96%) del compuesto del título.

UPLC-MS: RT = 1,36 min; m/z (ES+) 351,6 [MH+]; PM requerido 350,6.

1H-RMN (DMSO-d6): δ= 1,04 (6H), 2,00 (1H), 3,13 (2H), 6,00 (1H), 7,27 (1H), 7,53 (1H) ppm.

Ejemplo 101

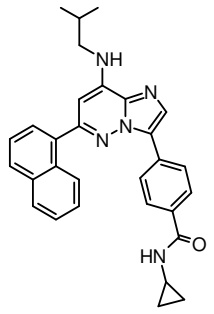
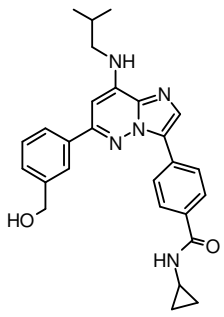
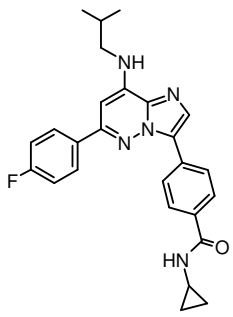
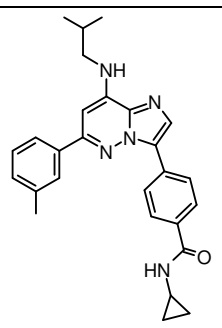
3-[4-(2-Ciclopropil-1H-imidazol-5-il)fenil]-6-etenil-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina

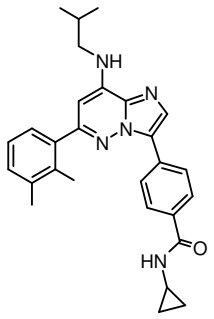
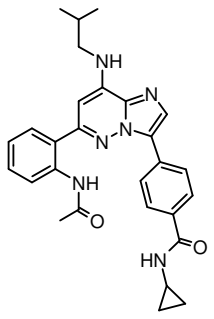
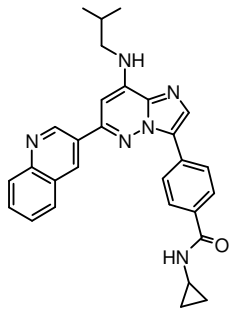
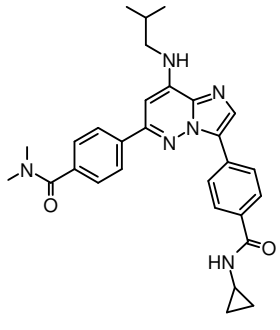


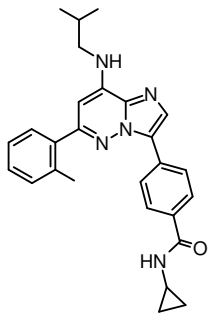
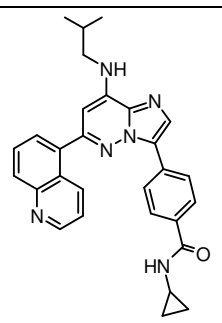
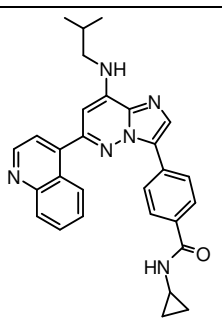
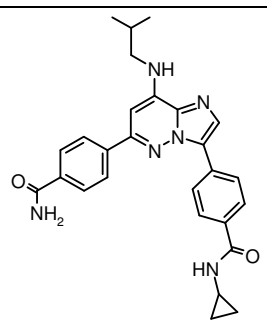
Se combinaron 0,1 mmol de 4-{6-cloro-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida (1 mL, 0,1 M en NMP), que se preparó de acuerdo con el Ejemplo Intermediario 100a, 0,4 mmol de ácido 2,3-dihidro-1,4-benzodioxin-6-ilborónico (0,8 mL, 0,5 M en NMP, 4 eq), 0,02 mmol de Pd(dppf)Cl2 (0,3 eq, 800 µL, 0,0375 M en NMP) y 0,3 mmol de carbonato de potasio (0,3 mL, 1M en agua, 3 eq) en un vial sellado y se calentó a 150 °C bajo irradiación de microondas durante 90 min. Luego de enfriar, la solución se filtró y se sometió a HPLC preparativa para dar 4,2 mg (8 %) del compuesto del título.

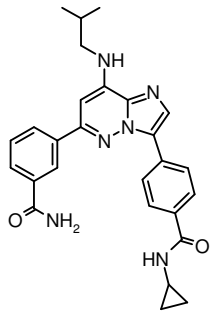
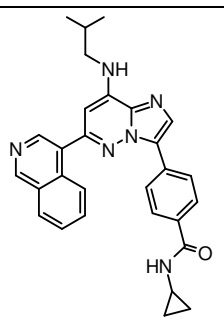
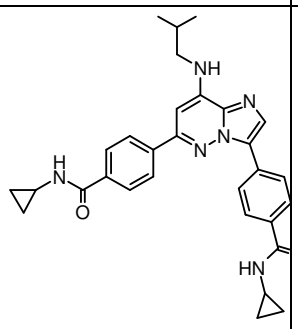
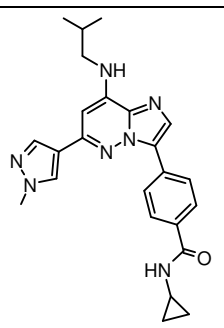
UPLC-MS: RT = 1,34 min; m/z (ES+) 484,6 [MH+]; PM requerido = 483,6.

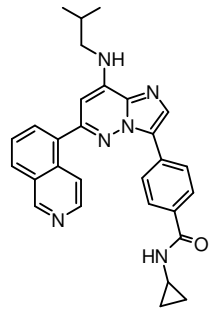
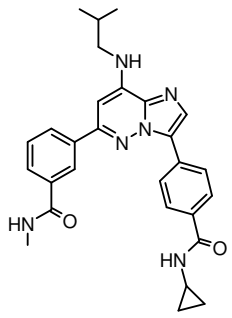
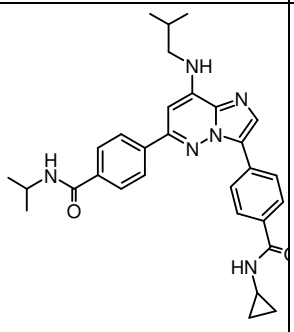
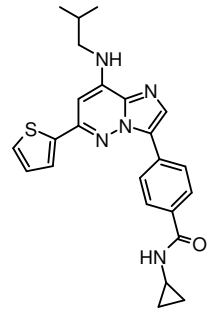
Los siguientes ejemplos de compuestos se prepararon de manera análoga al procedimiento que se ha descrito usando el intermediario apropiado y el bloque molecular ácido borónico apropiado [los datos de LC-MS como por ejemplo tiempo de retención (RT en min) o pico de masa observada se recogieron usando el Método LC-MS A salvo que se especifique lo contrario]:

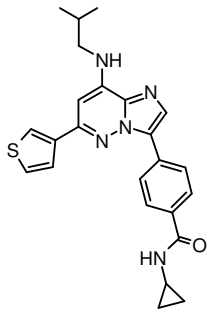
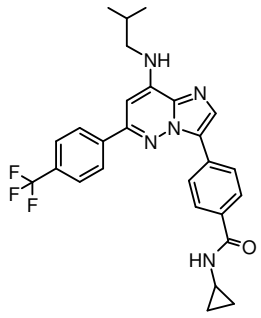
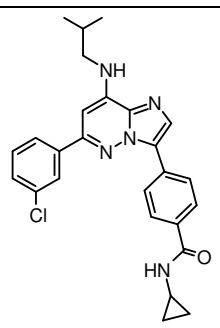
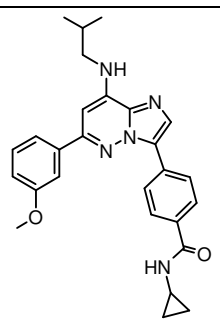
Ejemplo	Estructura	Nombre	Datos analíticos
102		N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(naftalen-1-il)imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,47 PM encontrado = 476,6 PM calculado = 475,6
103		N-ciclopropil-4-{6-[3-(hidroximetil)fenil]-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,18 PM encontrado = 456,6 PM calculado = 455,6
104		N-ciclopropil-4-{6-(4-fluorofenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,39 PM encontrado = 444,5 PM calculado = 443,5
105		N-ciclopropil-4-{6-(3-metilfenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,44 PM encontrado = 440,6 PM calculado = 439,6

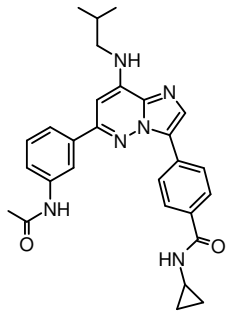
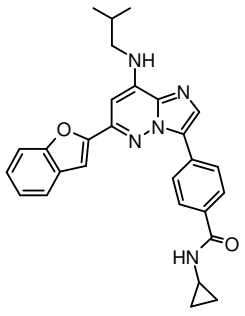
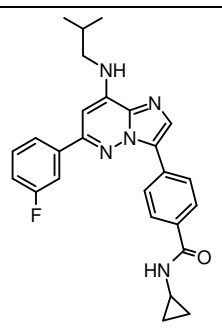
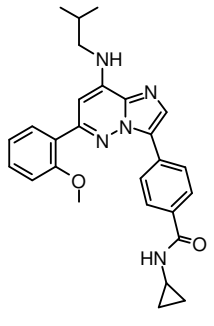
Ejemplo	Estructura	Nombre	Datos analíticos
106		N-ciclopropil-4-{6-(2,3-dimetilfenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,46 PM encontrado = 454,6 PM calculado = 453,6
107		4-{6-[2-(Acetilamino)fenil]-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida	RT = 1,22 PM encontrado = 483,6 PM calculado = 482,6
108		N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(quinolin-3-il)imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,32 PM encontrado = 477,6 PM calculado = 476,6
109		4-{3-[4-(Ciclopropilcarbamoil)fenil]-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-6-il}-N,N-dimetilbenzamida	RT = 1,19 PM encontrado = 497,6 PM calculado = 496,6

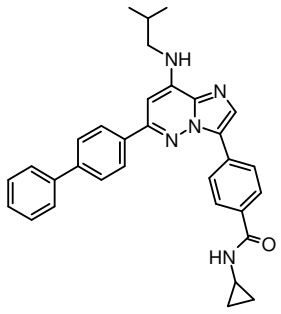
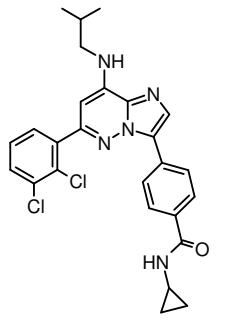
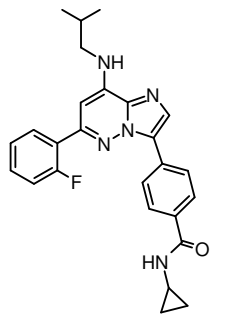
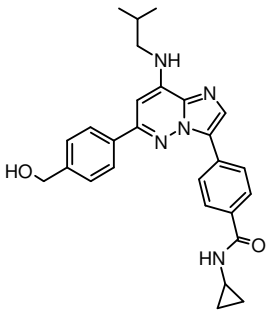
Ejemplo	Estructura	Nombre	Datos analíticos
110		N-ciclopropil-4-{6-(2-metilfenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,41 PM encontrado = 440,6 PM calculado = 439,6
111		N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(quinolin-5-il)imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,18 PM encontrado = 477,6 PM calculado = 476,6
112		N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(quinolin-4-il)imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,23 PM encontrado = 477,6 PM calculado = 476,6
113		4-{6-(4-Carbamoilfenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida	RT = 1,10 PM encontrado = 469,6 PM calculado = 468,6

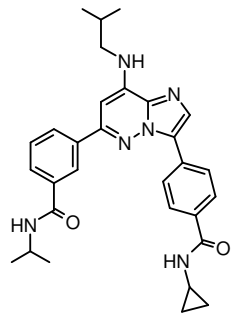
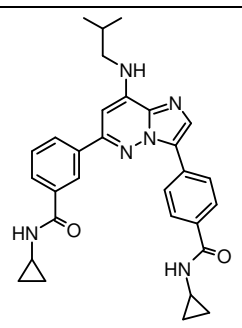
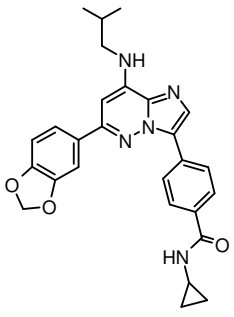
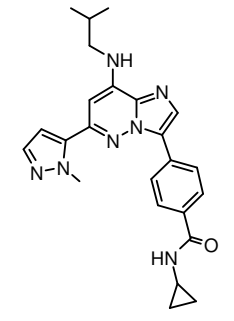
Ejemplo	Estructura	Nombre	Datos analíticos
114		4-{6-(3-Carbamoilfenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida	RT = 1,11 PM encontrado = 469,6 PM calculado = 468,6
115		N-ciclopropil-4-{6-(isoquinolin-4-il)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,21 PM encontrado = 477,6 PM calculado = 476,6
116		4,4'-{8-[(2-Metilpropil)amino]imidazo[1,2-b]piridazin-3,6-diil}bis(N-ciclopropilbenzamida)	RT = 1,21 PM encontrado = 509,6 PM calculado = 508,6
117		N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(1-metil-1H-pirazol-4-il)imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,12 PM encontrado = 430,5 PM calculado = 429,5

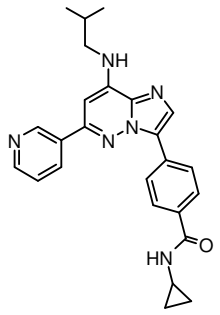
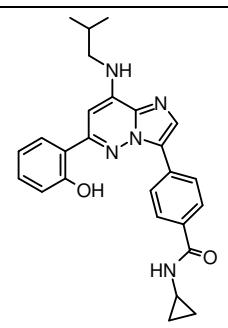
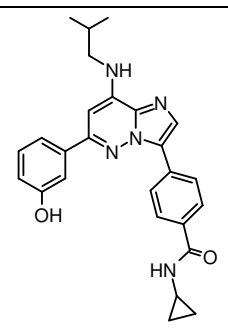
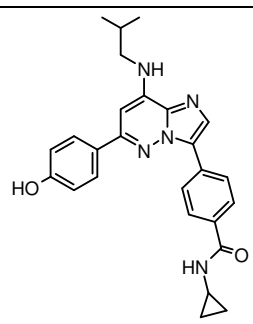
Ejemplo	Estructura	Nombre	Datos analíticos
118		N-ciclopropil-4-{6-(isoquinolin-5-il)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,09 PM encontrado = 477,6 PM calculado = 476,6
119		3-{3-[4-(Ciclopropilcarbamoil)fenil]-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-6-il}-N-metilbenzamida	RT = 1,16 PM encontrado = 483,6 PM calculado = 482,6
120		4-{3-[4-(Ciclopropilcarbamoil)fenil]-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-6-il}-N-(propan-2-il)benzamida	RT = 1,25 PM encontrado = 511,6 PM calculado = 510,6
121		N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(tiofen-2-il)imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,36 PM encontrado = 432,6 PM calculado = 431,6

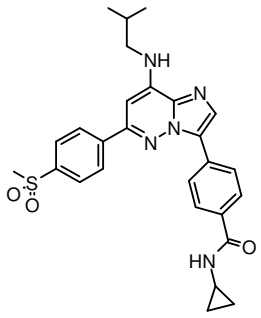
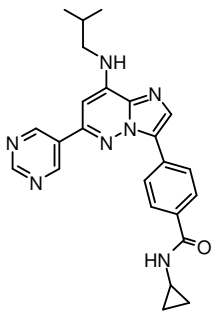
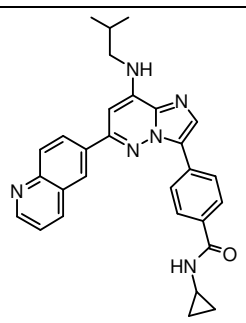
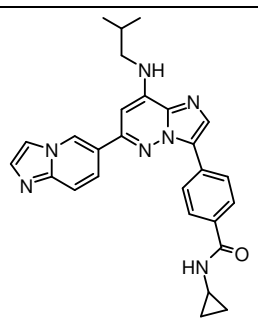
Ejemplo	Estructura	Nombre	Datos analíticos
122		N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(tiofen-3-il)imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,35 PM encontrado = 432,6 PM calculado = 431,6
123		N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-[4-(trifluorometil)fenil]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,49 PM encontrado = 494,5 PM calculado = 493,5
124		4-{6-(3-Clorofenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida	RT = 1,48 PM encontrado = 461,0 PM calculado = 460,0
125		N-ciclopropil-4-{6-(3-metoxifenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,38 PM encontrado = 456,6 PM calculado = 455,6

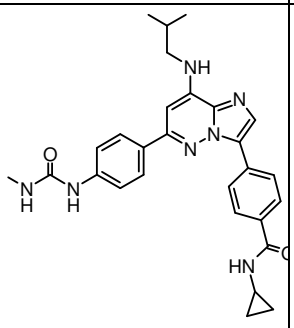
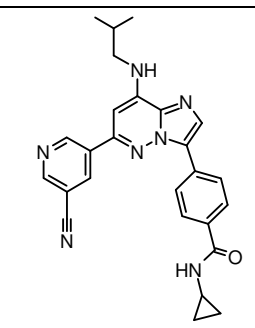
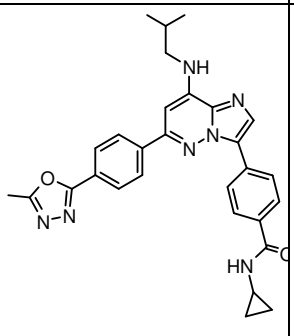
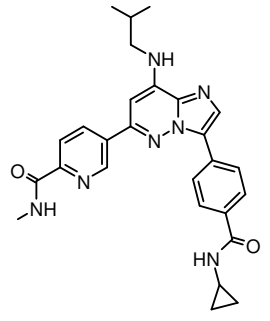
Ejemplo	Estructura	Nombre	Datos analíticos
126		4-{6-[3-(Acetilamino)fenil]-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida	RT = 1,19 PM encontrado = 483,6 PM calculado = 482,6
127		4-{6-(1-Benzofuran-2-il)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida	RT = 1,48 PM encontrado = 466,5 PM calculado = 465,5
128		N-ciclopropil-4-{6-(3-fluorofenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,40 PM encontrado = 444,5 PM calculado = 443,5
129		N-ciclopropil-4-{6-(2-metoxifenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,34 PM encontrado = 456,6 PM calculado = 455,6

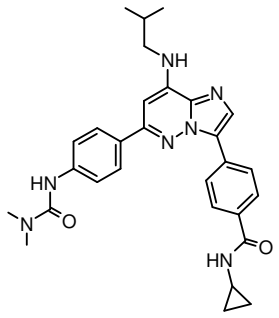
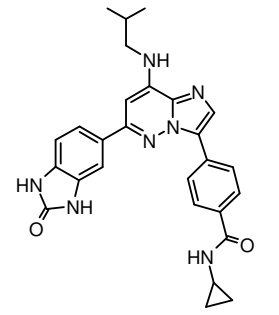
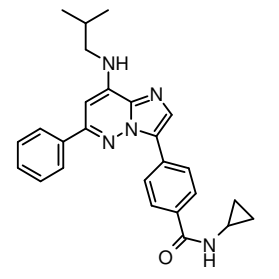
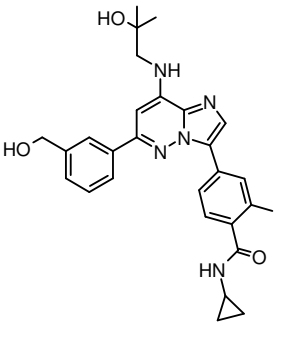
Ejemplo	Estructura	Nombre	Datos analíticos
130		4-{6-(Bifenil-4-il)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida	RT = 1,56 PM encontrado = 502,6 PM calculado = 501,6
131		N-ciclopropil-4-{6-(2,3-diclorofenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,49 PM encontrado = 495,4 PM calculado = 494,4
132		N-ciclopropil-4-{6-(2-fluorofenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,38 PM encontrado = 444,5 PM calculado = 443,5
133		N-ciclopropil-4-{6-[4-(hidroximetil)fenil]-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,17 PM encontrado = 456,6 PM calculado = 455,6

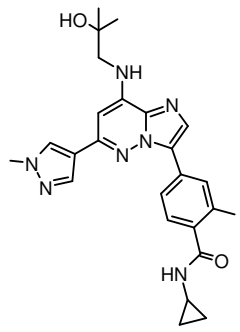
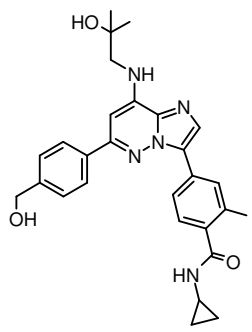
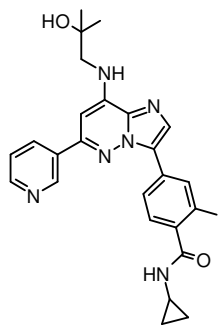
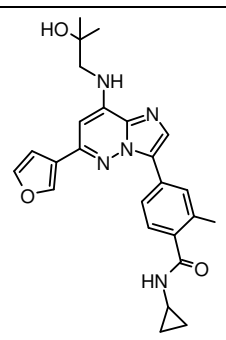
Ejemplo	Estructura	Nombre	Datos analíticos
134		3-{3-[4-(Ciclopropilcarbamoil)fenil]-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-6-il}-N-(propan-2-il)benzamida	RT = 1,26 PM encontrado = 511,6 PM calculado = 510,6
135		N-ciclopropil-3-{3-[4-(ciclopropilcarbamoil)fenil]-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-6-il}benzamida	RT = 1,21 PM encontrado = 509,6 PM calculado = 508,6
136		4-{6-(1,3-Benzodioxol-5-il)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida	RT = 1,34 PM encontrado = 470,5 PM calculado = 469,5
137		N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(1-metil-1H-pirazol-5-il)imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,19 PM encontrado = 430,5 PM calculado = 429,5

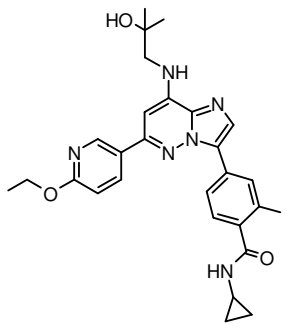
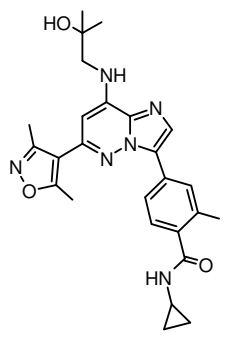
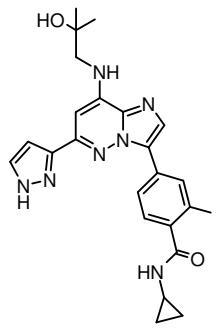
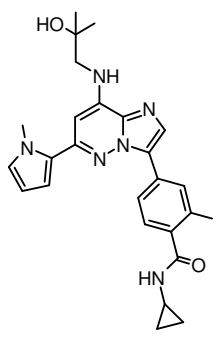
Ejemplo	Estructura	Nombre	Datos analíticos
138		N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(piridin-3-il)imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,11 PM encontrado = 427,5 PM calculado = 426,5
139		N-ciclopropil-4-{6-(2-hidroxifenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,35 PM encontrado = 442,5 PM calculado = 441,5
140		N-ciclopropil-4-{6-(3-hidroxifenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,21 PM encontrado = 442,5 PM calculado = 441,5
141		N-ciclopropil-4-{6-(4-hidroxifenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,18 PM encontrado = 442,5 PM calculado = 441,5

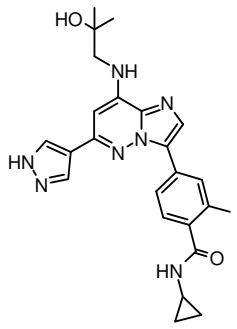
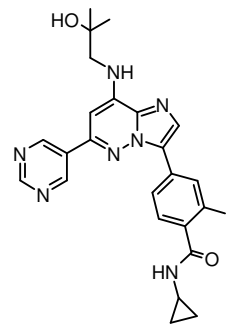
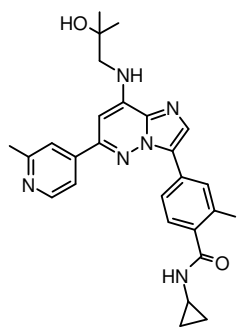
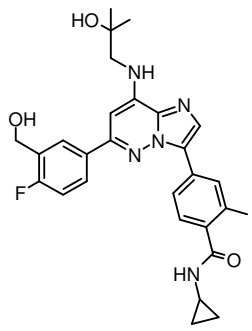
Ejemplo	Estructura	Nombre	Datos analíticos
142		N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-[4-(metilsulfonil)fenil]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,21 PM encontrado = 504,6 PM calculado = 503,6
143		N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(pirimidin-5-il)imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,13 PM encontrado = 428,5 PM calculado = 427,5
144		N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(quinolin-6-il)imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,21 PM encontrado = 477,6 PM calculado = 476,6
145		N-ciclopropil-4-{6-(imidazo[1,2-a]piridin-6-il)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 0,84 PM encontrado = 466,5 PM calculado = 465,5

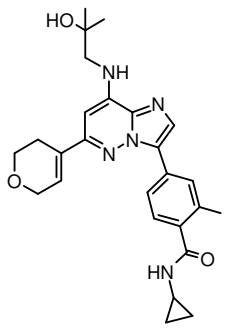
Ejemplo	Estructura	Nombre	Datos analíticos
146		N-ciclopropil-4-(6-{4-[(metilcarbamoil)amino]fenil}-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il)benzamida	RT = 1,13 PM encontrado = 498,6 PM calculado = 497,6
147		4-{6-(5-Cianopiridin-3-il)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida	RT = 1,23 PM encontrado = 452,5 PM calculado = 451,5
148		N-ciclopropil-4-{6-[4-(5-metil-1,3,4-oxadiazol-2-il)fenil]-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,26 PM encontrado = 508,6 PM calculado = 507,6
149		5-{3-[4-(Ciclopropilcarbamoil)fenil]-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-6-il}-N-metilpiridin-2-carboxamida	RT = 1,18 PM encontrado = 484,6 PM calculado = 483,6

Ejemplo	Estructura	Nombre	Datos analíticos
150		N-ciclopropil-4-(6-{4-[(dimetilcarbamoil)amino]fenil}-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il)benzamida	RT = 1,18 PM encontrado = 512,6 PM calculado = 511,6
151		N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(2-oxo-2,3-dihidro-1H-bencimidazol-5-il)imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,07 PM encontrado = 482,5 PM calculado = 481,5
152		N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-fenilimidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,39 PM encontrado = 426,5 PM calculado = 425,5
153		N-ciclopropil-4-{6-[3-(hidroximetil)fenil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,00 PM encontrado = 486,6 PM calculado = 485,6

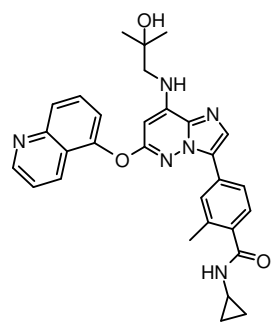
Ejemplo	Estructura	Nombre	Datos analíticos
154		N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(1-metil-1H-pirazol-4-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 0,93 PM encontrado = 460,5 PM calculado = 459,5
155		N-ciclopropil-4-{6-[4-(hidroximetil)fenil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 0,97 PM encontrado = 486,6 PM calculado = 485,6
156		N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(piridin-3-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 0,91 PM encontrado = 457,5 PM calculado = 456,5
157		N-ciclopropil-4-{6-(furan-3-il)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,09 PM encontrado = 446,5 PM calculado = 445,5

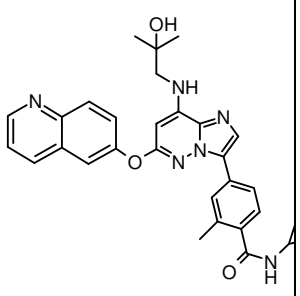
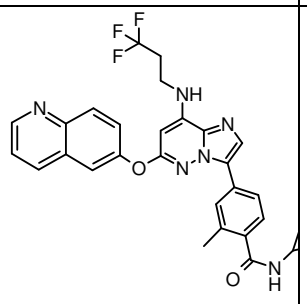
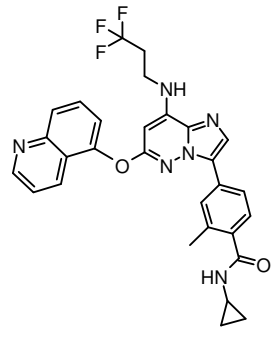
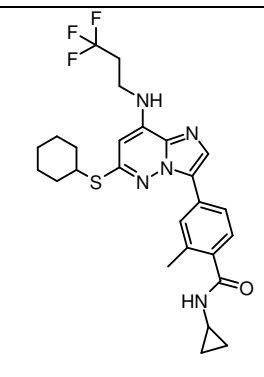
Ejemplo	Estructura	Nombre	Datos analíticos
158		N-ciclopropil-4-{6-(6-etoxipiridin-3-il)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,20 PM encontrado = 501,6 PM calculado = 500,6
159		N-ciclopropil-4-{6-(3,5-dimetil-1,2-oxazol-4-il)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,06 PM encontrado = 475,6 PM calculado = 474,6
160		N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(1H-pirazol-3-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 0,90 PM encontrado = 446,5 PM calculado = 445,5
161		N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(1-metil-1H-pirrol-2-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,12 PM encontrado = 459,6 PM calculado = 458,6

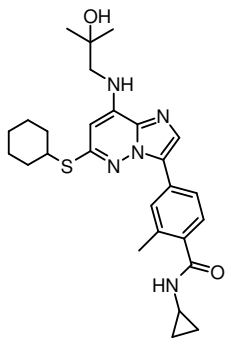
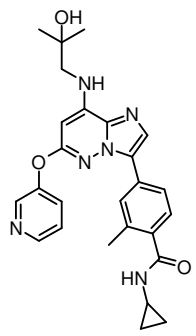
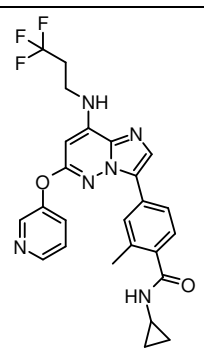
Ejemplo	Estructura	Nombre	Datos analíticos
162		N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(1H-pirazol-4-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 0,84 PM encontrado = 446,5 PM calculado = 445,5
163		N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(pirimidin-5-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 0,94 PM encontrado = 458,5 PM calculado = 457,5
164		N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(2-metilpiridin-4-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 0,80 PM encontrado = 471,6 PM calculado = 470,6
165		N-ciclopropil-4-{6-[4-fluoro-3-(hidroximetil)fenil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,04 PM encontrado = 504,6 PM calculado = 503,6

Ejemplo	Estructura	Nombre	Datos analíticos
166		N-ciclopropil-4-{6-(3,6-dihidro-2H-piran-4-il)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,06 PM encontrado = 462,6 PM calculado = 461,6

Los siguientes ejemplos de compuestos se prepararon de manera análoga al procedimiento descrito para el ejemplo 51 usando el bloque molecular alcohol o tiol apropiado [los datos de LC-MS como por ejemplo tiempo de retención (RT en min) o pico de masa observada se recogieron usando el Método LC-MS A salvo que se especifique lo contrario]:

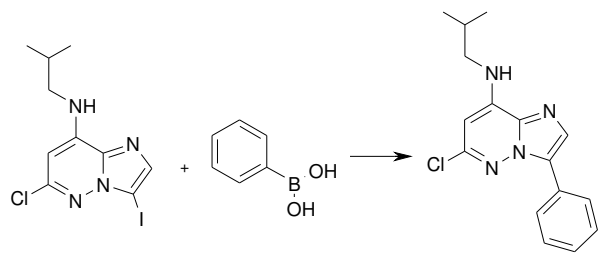
Ejemplo	Estructura	Nombre	Datos analíticos
167		N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(quinolin-5-iloxi)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,03 PM encontrado = 523,6 PM calculado = 522,6

Ejemplo	Estructura	Nombre	Datos analíticos
168		N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(quinolin-6-iloxi)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 0,99 PM encontrado = 523,6 PM calculado = 522,6
169		N-ciclopropil-2-metil-4-{6-(quinolin-6-iloxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,17 PM encontrado = 547,6 PM calculado = 546,6
170		N-ciclopropil-2-metil-4-{6-(quinolin-5-iloxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,20 PM encontrado = 547,6 PM calculado = 546,6
171		4-{6-(ciclohexilsulfanil)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida	RT = 1,51 PM encontrado = 518,6 PM calculado = 517,6

Ejemplo	Estructura	Nombre	Datos analíticos
172		4-{6-(ciclohexilsulfanil)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida	RT = 1,36 PM encontrado = 494,7 PM calculado = 493,7
173		N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(piridin-3-iloxi)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 0,96 PM encontrado = 473,6 PM calculado = 472,6
174		N-ciclopropil-2-metil-4-{6-(piridin-3-iloxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,14 PM encontrado = 497,5 PM calculado = 496,5

Ejemplo 175

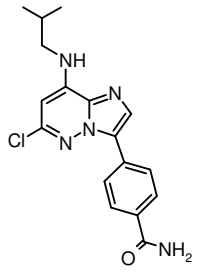
3-[4-(2-Ciclopropil-1H-imidazol-5-il)fenil]-6-etenil-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina

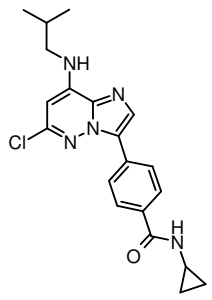
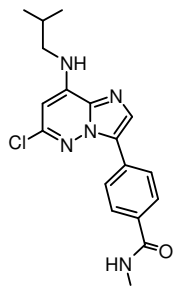
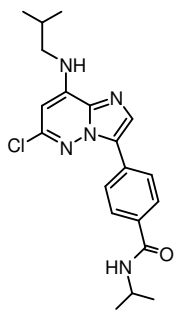
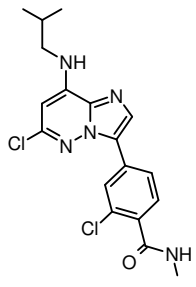
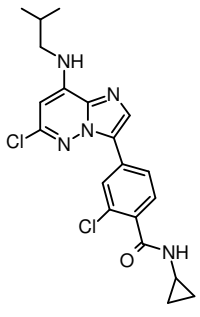


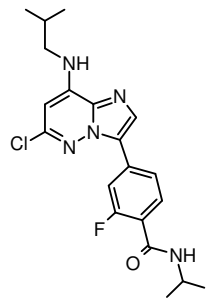
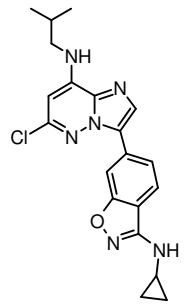
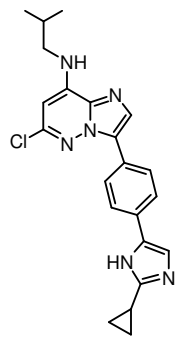
Se trataron 52 mg (150 µmol) de 6-cloro-3-yodo-N-(2-metilpropil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 100b, de manera análoga al Ejemplo Intermediario 1a usando ácido fenilborónico para dar, luego del tratamiento posterior y la purificación, 7,4 mg (17%) del compuesto del título.

UPLC-MS: RT = 1,50 min; m/z (ES+) 301,8 [MH+]; PM requerido = 300,8.

Los siguientes ejemplos de compuestos se prepararon de manera análoga al procedimiento que se ha descrito usando el bloque molecular ácido borónico apropiado [los datos de LC-MS como por ejemplo tiempo de retención (RT en min) o pico de masa observada se recogieron usando el Método LC-MS A salvo que se especifique lo contrario]:

Ejemplo	Estructura	Nombre	Datos analíticos
176		4-{6-Cloro-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,17 PM encontrado = 344,8 PM calculado = 343,8

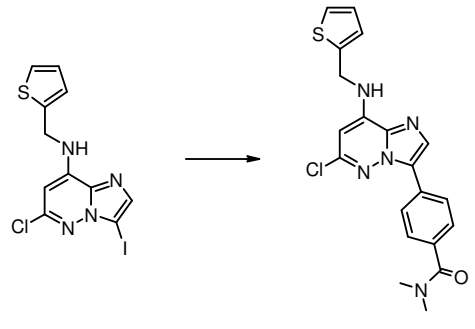
Ejemplo	Estructura	Nombre	Datos analíticos
177		4-{6-Cloro-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida	RT = 1,29 PM encontrado = 384,9 PM calculado = 383,9
178		4-{6-Cloro-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-metilbenzamida	RT = 1,22 PM encontrado = 358,8 PM calculado = 357,8
179		4-{6-Cloro-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-(propan-2-il)benzamida	RT = 1,34 PM encontrado = 386,9 PM calculado = 385,9
180		2-Cloro-4-{6-cloro-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-metilbenzamida	RT = 1,27 PM encontrado = 393,3 PM calculado = 392,3
181		2-Cloro-4-{6-cloro-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida	RT = 1,34 PM encontrado = 419,3 PM calculado = 418,3

Ejemplo	Estructura	Nombre	Datos analíticos
182		4-{6-Cloro-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-fluoro-N-(propan-2-il)benzamida	RT = 1,42 PM encontrado = 404,9 PM calculado = 403,9
183		6-Cloro-3-[3-(ciclopropilamino)-1,2-benzoxazol-6-il]-N-(2-metilpropil)imidazo[1,2-b]piridazin-8-amina	RT = 1,40 PM encontrado = 397,9 PM calculado = 396,9
184		6-Cloro-3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-N-(2-metilpropil)imidazo[1,2-b]piridazin-8-amina	RT = 0,95 PM encontrado = 407,9 PM calculado = 406,9

Ejemplo 185

4-{6-Cloro-8-[(tiofen-2-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-

N,N-dimetilbenzamida

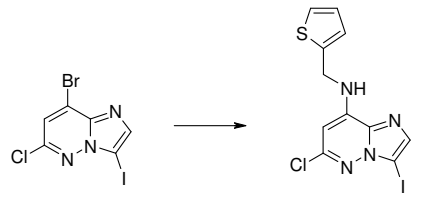


Se trataron 117 mg (300 µmol) de 6-cloro-3-yodo-N-(tiofen-2-ilmetil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 185a, de manera análoga al Ejemplo Intermediario 100a usando ácido [4-(dimetilcarbamoil)fenil]borónico para dar, luego del tratamiento posterior y la purificación, 15 mg (12%) del compuesto del título.

UPLC-MS: RT = 1,25 min; m/z (ES+) 412,9 [MH+]; PM requerido 411,9.

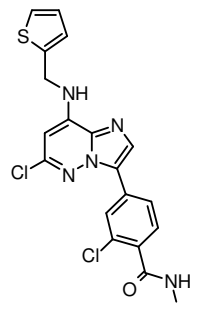
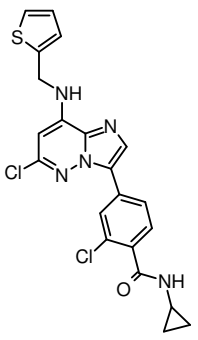
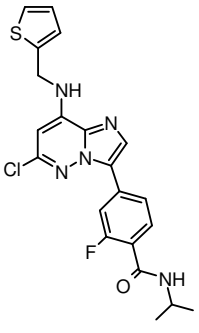
Ejemplo Intermediario 185a

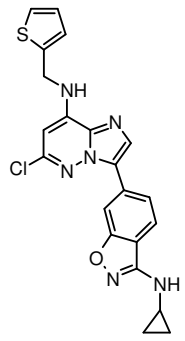
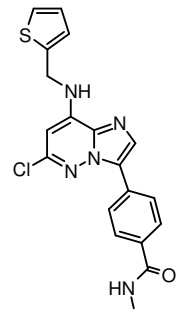
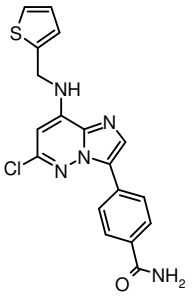
6-cloro-3-yodo-N-(tiofen-2-ilmetil)imidazo[1,2-b]piridazin-8-amina



Se preparó 6-cloro-3-yodo-N-(tiofen-2-ilmetil)imidazo[1,2-b]piridazin-8-amina de manera análoga al Ejemplo 100b usando 1-(tiofen-2-il)metanamina, que se preparó de acuerdo con el Ejemplo Intermediario 1c para dar, luego del tratamiento posterior y la purificación, 80% del compuesto del título.

Los siguientes ejemplos de compuestos se prepararon de manera análoga al procedimiento descrito para el ejemplo 185 usando el bloque molecular ácido borónico apropiado [los datos de LC-MS como por ejemplo tiempo de retención (RT en min) o pico de masa observada se recogieron usando el Método LC-MS A salvo que se especifique lo contrario]:

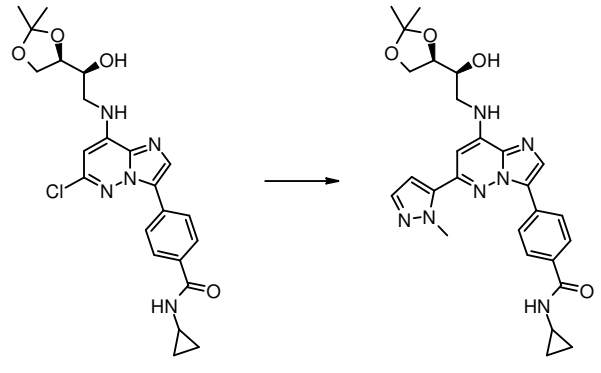
Ejemplo	Estructura	Nombre	Datos analíticos
186		2-Cloro-4-{6-cloro-8-[(tiofen-2-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-metilbenzamida	RT = 1,24 PM encontrado = 433,3 PM calculado = 432,3
187		2-Cloro-4-{6-cloro-8-[(tiofen-2-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida	RT = 1,31 PM encontrado = 459,4 PM calculado = 458,4
188		4-{6-Cloro-8-[(tiofen-2-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-fluoro-N-(propan-2-il)benzamida	RT = 1,40 PM encontrado = 444,9 PM calculado = 443,9

189		6-Cloro-3-[3-(ciclopropilamino)-1,2-benzoxazol-6-il]-N-(tiofen-2-ilmetil)imidazo[1,2-b]piridazin-8-amina	RT = 1,37 PM encontrado = 437,9 PM calculado = 436,9
190		4-{6-Cloro-8-[(tiofen-2-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-metilbenzamida	RT = 1,45 PM encontrado = 398,9 PM calculado = 397,9
191		4-{6-Cloro-8-[(tiofen-2-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,14 PM encontrado = 384,9 PM calculado = 383,9

Ejemplo 192

N-ciclopropil-4-[8-({(2S)-2-[(4R)-2,2-dimetil-1,3-dioxolan-4-il]-2-

hidroxietil}amino)-6-(1-metil-1H-pirazol-5-il)imidazo[1,2-b]piridazin-3-il]benzamida



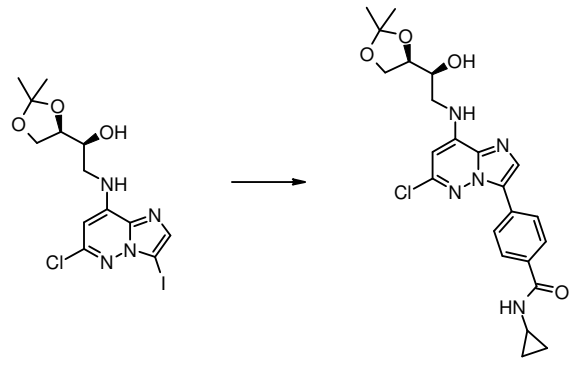
A una mezcla de 52 mg (94 µmol) de 4-[6-cloro-8-({(2S)-2-[(4R)-2,2-dimetil-1,3-dioxolan-4-il]-2-hidroxietil}amino)imidazo[1,2-b]piridazin-3-il]-N-ciclopropilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 192a, 33 mg de ácido (1-metil-1H-pirazol-5-il)borónico, 6,5 mg de tetrakis(trifenilfosfin)paladio en 1 mL de etanol y 1 mL de tolueno se agregó 0,26 mL de una solución acuosa de bicarbonato de sodio 10% y la mezcla se agitó a 120°C durante 2 horas bajo irradiación de microondas. Luego la mezcla se filtró, el solvente se eliminó y el residuo se purificó mediante cromatografía para dar 36 mg de los compuestos del título.

1H-RMN (DMSO-d6): δ= 0,49-0,68 (4H), 1,24 (3H), 1,32 (3H), 2,62 (1H), 3,31 - 3,95 (3H), 3,60 - 4,05 (3H), 4,12 (3H), 6,54 (1H), 6,85 (1H), 7,31 (1H) 7,90 (2H), 8,07 (1H), 8,18 (2H), 8,45 (1H), ppm.

Ejemplo Intermediario 192a

4-[6-cloro-8-({(2S)-2-[(4R)-2,2-dimetil-1,3-dioxolan-4-il]-2-hidroxietil}amino)

imidazo[1,2-b]piridazin-3-il]-N-ciclopropilbenzamida

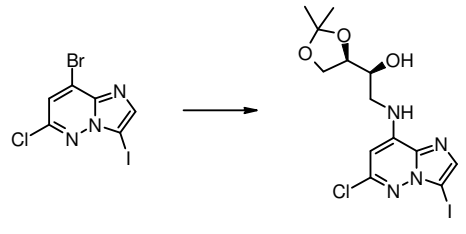


Se trataron 300 mg (684 µmol) de (1S)-2-[(6-cloro-3-yodoimidazo[1,2-b]piridazin-8-il)amino]-1-[(4R)-2,2-dimetil-1,3-dioxolan-4-il]etanol, que se preparó de acuerdo con el Ejemplo Intermediario 192b, de manera análoga al Ejemplo Intermediario 1a usando ácido [4-(ciclopropilcarbamoil)fenil]borónico para dar, luego del tratamiento posterior y la purificación, 17 mg (5%) del compuesto del título.

Ejemplo Intermediario 192b

(1S)-2-[(6-cloro-3-yodoimidazo[1,2-b]piridazin-8-il)amino]-1-[(4R)-2,2-dimetil-

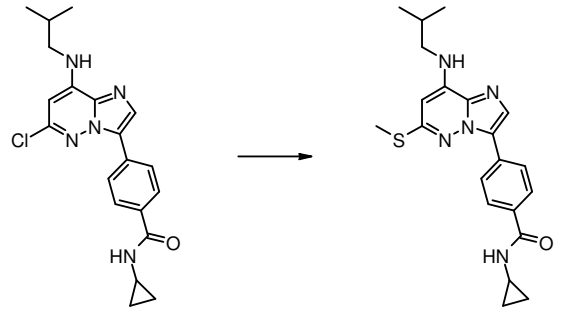
1,3-dioxolan-4-il]etanol



Se trataron 700 mg (1,95 mmol) de 8-bromo-6-cloro-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 1c, de manera análoga al Ejemplo Intermediario 1b usando (1S)-2-amino-1-[(4R)-2,2-dimetil-1,3-dioxolan-4-il]etanol para dar, luego del tratamiento posterior y la purificación, 512 mg (60%) del compuesto del título.

Ejemplo 193

N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(metilsulfanil)imidazo[1,2-b]piridazin-3-il}benzamida

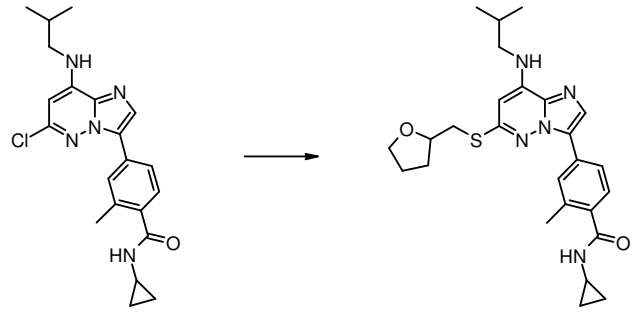


Una solución de 450 mg (1172 µmol) de 4-[6-cloro-8-(isobutilamino)imidazo[1,2-b]piridazin-3-il]-N-ciclopropilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 100a, y 330 mg (4690 µmol) de metilsulfuro de sodio en 8 mL de sulfóxido de dimetilo se calentó durante 60 min a 70°C en el microondas. Luego la mezcla se volcó sobre agua y el precipitado se recogió y se secó bajo vacío para dar 460 mg del compuesto del título como un sólido blanco.

1H-RMN (DMSO-d6): δ= 0,52-0,71 (4H), 0,88 (6H), 1,94 (1H), 2,56 (3H), 2,84 (1H), 3,08 (2H), 6,08 (1H), 7,49 (1H), 7,88 (2H), 7,97 (1H), 8,22 (2H), 8,43 (1H) ppm.

Ejemplo 194

(RS)-N-ciclopropil-2-metil-4-{8-[(2-metilpropil)amino]-6-[(tetrahidrofurano-2-ilmetil)sulfanil]imidazo[1,2-b]piridazin-3-il}benzamida



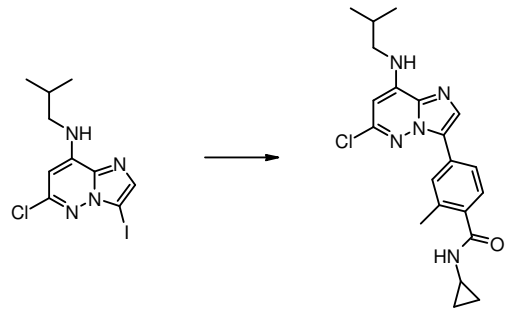
Una solución de 45 mg (377 µmol) de (RS)-tetrahidrofurano-2-ilmetanotiol en 1 mL de sulfóxido de dimetilo se trató con 14 mg (350 µmol) de hidruro de sodio y se agitó a temperatura ambiente durante 2 horas. Luego se agregaron 100 mg (251 µmol) de 4-[6-cloro-8-(isobutilamino)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 194a, y la mezcla se calentó durante 2 horas a 70°C. Luego la mezcla se purificó mediante cromatografía en fase reversa para dar 12 mg del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48-0,68 (4H), 0,88 (6H), 1,63-1,99 (4H), 2,36 (3H), 2,81 (1H), 3,08 (2H), 3,22-3,36 (2H), 3,62 (1H), 3,76 (1H), 4,12 (1H), 6,04 (1H), 7,32 (1H), 7,50 (1H), 7,90 (1H), 7,93 (1H), 8,04 (1H), 8,29 (1H) ppm.

Ejemplo Intermediario 194a

4-[6-cloro-8-(isobutilamino)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-

metilbenzamida

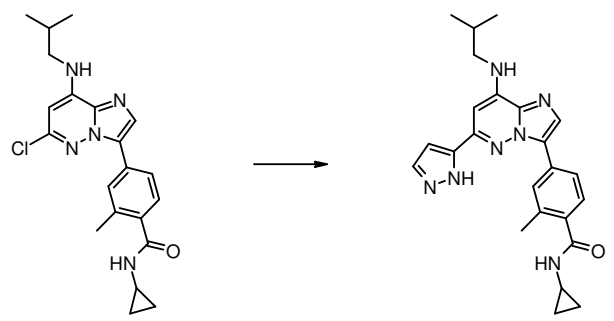


Se trataron 3,54 g (10,1 mmol) de 6-Cloro-3-yodo-N-isobutilimidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 3b, de manera análoga al Ejemplo Intermediario 1a usando ácido [4-(ciclopropilcarbamoil)-3-metilfenil]borónico para dar, luego del tratamiento posterior y la purificación, 1,79 g (45%) del compuesto del título.

Ejemplo 195

N-ciclopropil-2-metil-4-{8-[(2-metilpropil)amino]-6-(1H-pirazol-5-il)

imidazo[1,2-b]piridazin-3-il}benzamida



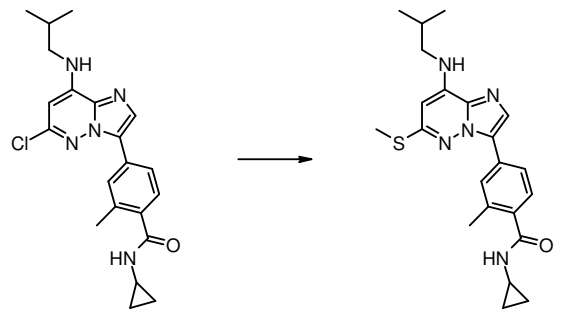
A una mezcla de 125 mg (314 µmol) de 4-[6-cloro-8-(isobutilamino)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el ejemplo 194a, 111 mg (942 µmol) de ácido 1H-pirazol-5-ilborónico, 44 mg de Tetrakis(trifenilfosfin)paladio en 2 mL de etanol y 2 mL de tolueno se agregó 0,63 mL de una solución acuosa de bicarbonato

de sodio 10% y la mezcla se agitó a 120°C durante 2 horas bajo irradiación de microondas. Luego la mezcla se filtró y se concentró y se purificó mediante cromatografía para dar 41 mg del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48-0,69 (4H), 0,91 (6H), 2,02 (1H), 2,39 (3H), 2,82 (1H), 3,17 (2H), 6,72 (1H), 6,78 (1H), 7,39 (1H), 7,85 (1H), 8,00 (1H), 8,10 - 8,17 (2H), 8,29 (1H), ppm.

Ejemplo 196

N-ciclopropil-2-metil-4-{8-[(2-metilpropil)amino]-6-(metilsulfanil) imidazo[1,2-b]piridazin-3-il}benzamida



Una solución de 50 mg (126 µmol) de 4-[6-cloro-8-(isobutilamino)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el ejemplo 194a, y 35 mg (503 µmol) de metilsulfuro de sodio en 1 mL de sulfóxido de dimetilo se calentó durante 30 min a 70°C en el microondas. Luego la mezcla se volcó sobre agua y el precipitado se recogió y se secó bajo vacío para dar 26 mg del compuesto del título como un sólido amarillo.

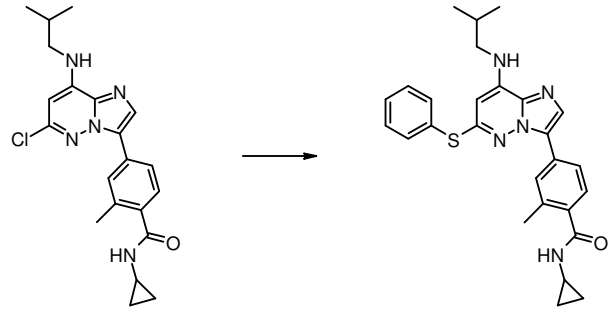
1H-RMN (DMSO-d6): δ= 0,47-0,68 (4H), 0,88 (6H), 1,94 (1H), 2,35 (3H), 2,55 (3H) 2,80 (1H), 3,08 (2H), 6,06 (1H), 7,32 (1H), 7,47

(1H), 7,90 (1H), 7,98 (1H), 8,05 (1H), 8,29 (1H), ppm.

Ejemplo 197

N-ciclopropil-2-metil-4-{8-[(2-metilpropil)amino]-6-(fenilsulfanil)

imidazo[1,2-b]piridazin-3-il}benzamida



Una solución de 180 mg (1634 µmol) de tiofenol en 10 mL de sulfóxido de dimetilo se trató con 64 mg (1608 µmol) de hidruro de sodio y se agitó a temperatura ambiente durante 2 horas. Luego se agregaron 100 mg (251 µmol) de 4-[6-cloro-8-(isobutilamino)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 194a, y la mezcla se calentó durante 1,5 horas a 140°C. Luego la mezcla se volcó sobre agua helada y el precipitado se recogió y a continuación se purificó por cromatografía en fase normal para dar 112 mg del compuesto del título.

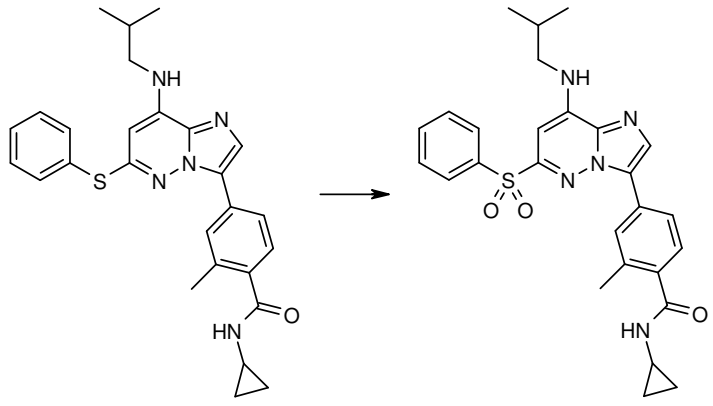
1H-RMN (DMSO-d6): δ= 0,48-0,69 (4H), 0,84 (6H), 1,87 (1H), 2,21 (3H), 2,79 (1H), 3,03 (2H), 5,99 (1H), 7,10 (1H), 7,49 (3H), 7,61-7,71 (5H), 7,92 (1 H), 8,24 (1H), ppm.

Ejemplo 198

N-ciclopropil-2-metil-4-{8-[(2-metilpropil)amino]-6-

(fenilsulfonil)

imidazo[1,2-b]piridazin-3-il}benzamida



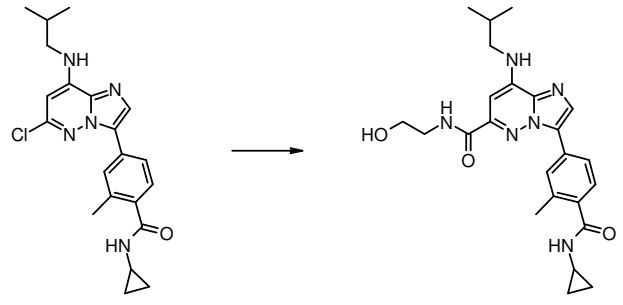
A una solución de 105 mg (223 µmol) de N-ciclopropil-2-metil-4-{8-[(2-metilpropil)amino]-6-(fenilsulfanil)imidazo[1,2-b]piridazin-3-il}benzamida, que se preparó de acuerdo con el ejemplo 197, en 15 mL de DMF, se agregaron 684 mg (1113 µmol) de OXONA (peroximonosulfato de potasio) en pequeñas porciones. La mezcla se agitó durante la noche, luego se enfrió a 0 °C y se volcó sobre 200 mL de agua fría. El precipitado se recogió y se purificó por cromatografía en fase normal para dar 97 mg del compuesto del título como un sólido amarillo.

1H-RMN (DMSO-d6): δ= 0,50-0,69 (4H), 0,91 (6H), 1,99 (1H), 2,30 (3H), 2,56 (1H), 3,41 (2H), 4,31 (1H), 6,71 (1H), 7,28 (1H), 7,66-7,81 (5H), 8,03 (2 H), 8,12 (1H), 8,31 (1H), 8,43 (1H) ppm.

Ejemplo 199

3-[4-(Ciclopropilcarbamoil)-3-metilfenil]-N-(2-hidroxietil)-8-

[(2-metilpropil)amino]imidazo[1,2-b]piridazin-6-carboxamida



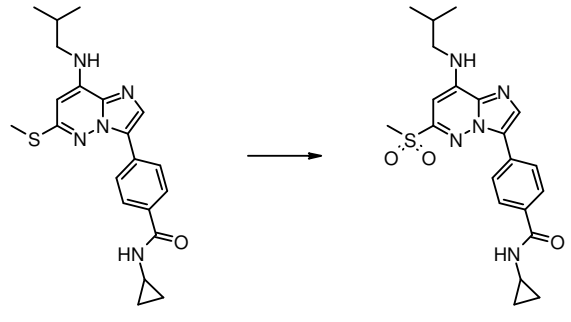
Una solución de 100 mg (251 µmol) de 4-[6-cloro-8-(isobutilamino)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el ejemplo 194a, 46 mg (754 µmol) de aminoetanol, 66 mg (251 µmol) de molibdeno hexacarbonilo, 80 mg (754 µmol) de bicarbonato de sodio, 5,6 mg (25 µmol) de acetato de paladio(II) y 7,3 mg (25 µmol) de tetrafluorborato de tri-tert-butilfosfina en 3 mL de dioxano se calentó en el microondas durante 2 horas a 140 °C. Luego la mezcla se sometió directamente a cromatografía en fase reversa para dar 13 mg del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48-0,69 (4H), 0,91 (6H), 1,99 (1H), 2,38 (3H), 2,81 (1H), 3,17 (2H), 3,38 (3H), 3,53 (2H), 5,99 (1H), 6,61 (1H), 7,36 (1H), 7,84 (1H), 8,00-8,09 (3H), 8,16 (1 H), 8,29 (1H), ppm.

Ejemplo 200

N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(metilsulfonil)imidazo[1,2-b]

piridazin-3-il}benzamida



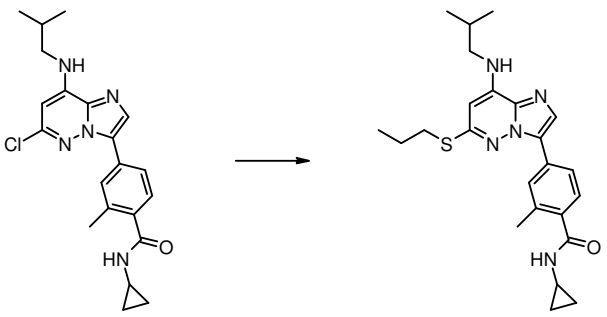
A una solución de 410 mg (1037 µmol) de N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(metilsulfanil)imidazo[1,2-b]piridazin-3-il}benzamida, que se preparó de acuerdo con el ejemplo 193, en 15 mL de DMF, se agregaron 1912 mg (3110 µmol) de OXONA (peroximonosulfato de potasio) en pequeñas porciones. La mezcla se agitó durante la noche, luego se enfrió a 0 °C y se volcó sobre 200 mL de agua fría. El precipitado se recogió y se secó bajo vacío para dar 291 mg del compuesto del título como un sólido amarillo.

1H-RMN (DMSO-d6): δ= 0,53-0,71 (4H), 0,91 (6H), 2,00 (1H), 2,84 (1H), 3,20 (2H), 3,38 (3H), 6,58 (1H), 7,92 (2H), 8,19-8,23 (3H), 8,37 (1 H), 8,46 (1H), ppm.

Ejemplo 201

N-ciclopropil-2-metil-4-{8-[(2-metilpropil)amino]-6-(propilsulfanil)

imidazo[1,2-b]piridazin-3-il}benzamida

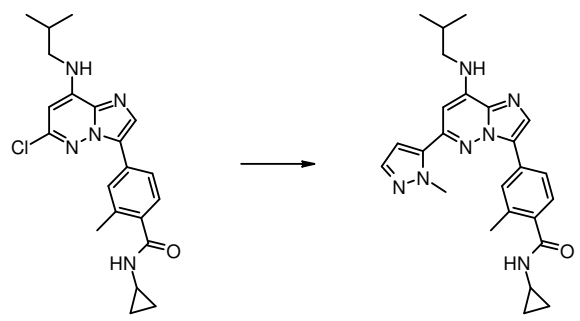


Una solución de 100 mg (251 µmol) de 4-[6-cloro-8-(isobutilamino)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el ejemplo 194a, y 49 mg (503 µmol) de propan-1-tiolato de sodio en 1 mL de sulfóxido de dimetilo se calentó durante 60 min a 70°C en el microondas. Luego la mezcla se purificó mediante cromatografía en fase reversa para dar 18,5 mg del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49-0,66 (4H), 0,88 (6H), 1,00 (3H), 1,74 (2H), 1,94 (1H), 2,36 (3H), 2,79 (1H), 3,05-3,15 (4H), 6,02 (1H), 7,33 (1H), 7,47 (1H), 7,90 (1H), 7,96 (1H), 8,03 (1H), 8,29 (1H) ppm.

Ejemplo 202

N-ciclopropil-2-metil-4-{8-[(2-metilpropil)amino]-6-(1-metil-1H-pirazol-5-il)imidazo[1,2-b]piridazin-3-il}benzamida



A una mezcla de 100 mg (251 µmol) de 4-[6-cloro-8-(isobutilamino)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el ejemplo 194a, 95 mg (750 µmol) de ácido (1-metil-1H-pirazol-5-il)borónico, 35 mg de Tetrakis(trifenilfosfin)paladio en 2 mL de etanol y 2 mL de tolueno se agregó 0,5 mL de una solución acuosa de bicarbonato de sodio 10% y la mezcla se agitó a 120°C durante 2

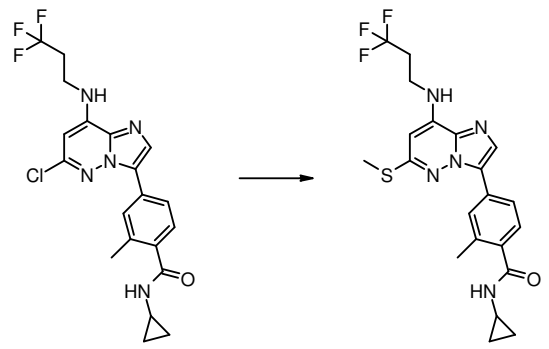
horas bajo irradiación de microondas. Luego se agregó agua y la capa orgánica se lavó con agua y salmuera, se concentró y se purificó mediante cromatografía para dar 99 mg del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49-0,67 (4H), 0,93 (6H), 2,00 (1H), 2,36 (3H), 2,80 (1H), 3,21 (3H), 4,13 (3H), 6,46 (1H), 6,90 (1H), 7,37 (1H), 7,50 (1H), 7,65 (1H), 7,92 - 7,97 (3H), 8,29 (1H) ppm.

Ejemplo 203

N-ciclopropil-2-metil-4-{6-(metilsulfanil)-8-[(3,3,3-trifluoropropil)

amino]imidazo[1,2-b]piridazin-3-il}benzamida



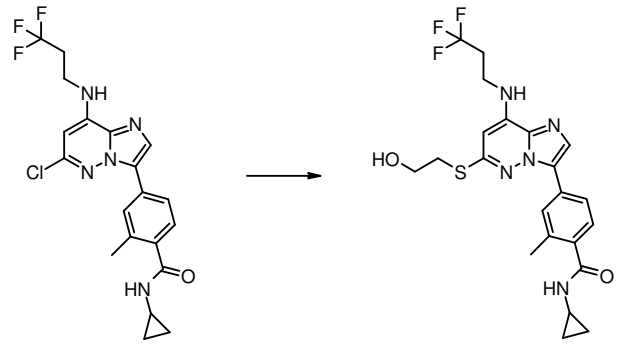
El compuesto del título se preparó de acuerdo con el procedimiento descrito para el ejemplo 193 usando 4-{6-cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 10a.

1H-RMN (DMSO-d6): δ= 0,48-0,70 (4H), 2,36 (3H), 2,54-2,70 (6H), 2,82 (1H), 3,54 (2H), 6,16 (1H), 7,35 (1H), 7,51 (1H), 7,92 (1H), 7,97 (1H), 8,05 (1H), 8,28 (1H), ppm.

Ejemplo 204

N-ciclopropil-4-{6-[(2-hidroxietil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



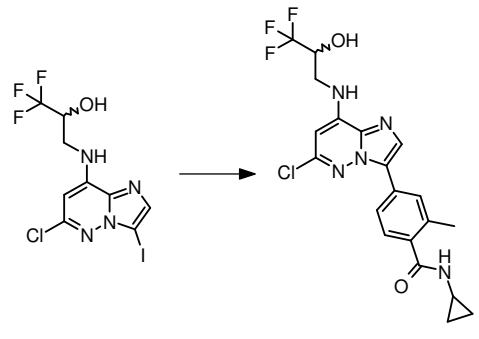
El compuesto del título se preparó de acuerdo con el procedimiento descrito para el ejemplo 194 usando 4-{6-cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 10a.

1H-RMN (DMSO-d6): δ= 0,47-0,70 (4H), 2,36 (3H), 2,53-2,70 (4H), 2,81 (1H), 3,52 (2H), 3,71 (2H), 4,97 (1H), 6,13 (1H), 7,33 (1H), 7,53 (1H), 7,92 (1H), 8,02 (1H), 8,29 (1H), ppm.

Ejemplo Intermediario 205

(RS)-4-{6-Cloro-8-[(3,3,3-trifluoro-2-hidroxipropil)amino]imidazo[1,2-b]

piridazin-3-il}-N-ciclopropil-2-metilbenzamida

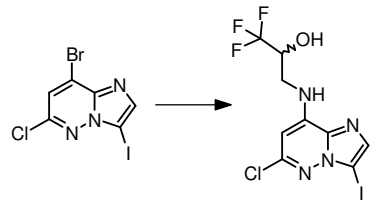


Se trataron 650 mg (1,60 mmol) de (RS)-3-[(6-cloro-3-yodoimidazo[1,2-b]piridazin-8-il)amino]-1,1,1-trifluoropropan-2-ol, que se preparó de acuerdo con el Ejemplo Intermediario 205a, de manera análoga al Ejemplo Intermediario 1a usando N-ciclopropil-2-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7b, para dar, luego del tratamiento posterior y la purificación, 430 mg (59%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48-0,68 (4H), 2,36 (3H), 2,81 (1H), 3,45 -3,62 (2H), 4,31 (1H), 6,40 (2H), 6,58 (1H), 7,37 (1H), 7,81 (1H), 7,85 (1H), 7,90 (1H), 8,00 (1H), 8,29 (1H), ppm.

Ejemplo Intermediario 205a

(RS)-3-[(6-cloro-3-yodoimidazo[1,2-b]piridazin-8-il)amino]-1,1,1-trifluoropropan-2-ol



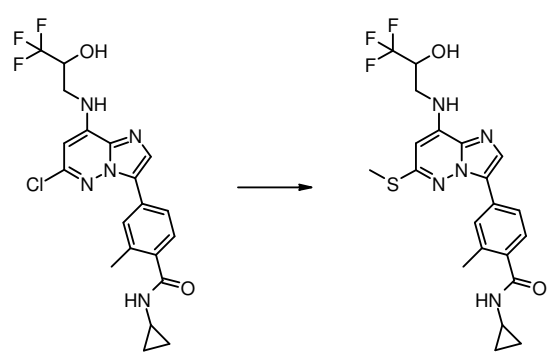
Se trató 8-bromo-6-cloro-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 1c, de manera análoga al Ejemplo Intermediario 1b usando (RS)-(3,3,3-trifluoro-2-hidroxipropil)amina para dar el compuesto del

título.

Ejemplo 206

(RS) N-ciclopropil-2-metil-4-{6-(metilsulfanil)-8-[(3,3,3-trifluoro-2-

hidroxipropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida



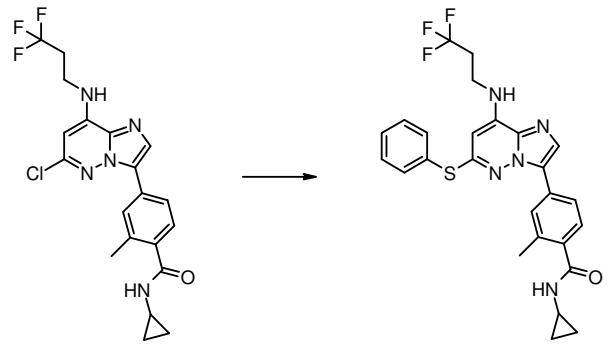
El compuesto del título se preparó de acuerdo con el procedimiento descrito para el ejemplo 193 usando (RS)-4-{6-cloro-8-[(3,3,3-trifluoro-2-hidroxipropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el ejemplo 205.

1H-RMN (DMSO-d6): δ= 0,48-0,70 (4H), 2,36 (3H), 2,56 (3H), 2,80 (1H), 3,47 (1H), 3,58 (1H), 4,30 (1H), 6,19 (1H), 6,56 (1H), 7,29 (1H), 7,35 (1H), 7,93 (1H), 7,97 (1H), 8,06 (1H), 8,28 (1H), ppm.

Ejemplo 207

N-ciclopropil-2-metil-4-{6-(fenilsulfanil)-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}benzamida

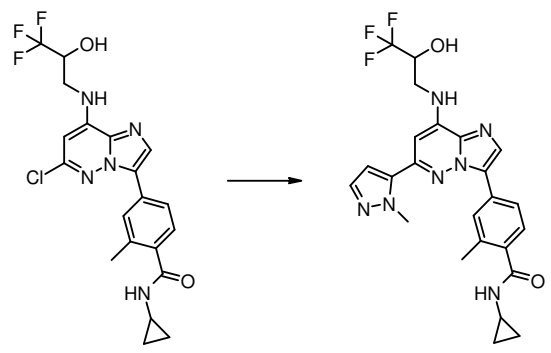


El compuesto del título se preparó de acuerdo con el procedimiento descrito para el ejemplo 197 usando 4-{6-cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 10a.

1H-RMN (DMSO-d6): δ= 0,48-0,70 (4H), 2,20 (3H), 2,54-2,70 (4H), 2,82 (1H), 3,50 (2H), 6,13 (1H), 7,09 (1H), 7,46 - 7,70 (8H), 7,94 (1H), 8,22 (1H), ppm.

Ejemplo 208

(RS)-N-ciclopropil-2-metil-4-{6-(1-metil-1H-pirazol-5-il)-8-[(3,3,3-trifluoro-2-hidroxipropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida



El compuesto del título se preparó de acuerdo con el procedimiento descrito para el ejemplo 211 usando (RS)-4-{6-cloro-8-[(3,3,3-trifluoro-2-hidroxipropil)amino]imidazo[1,2-

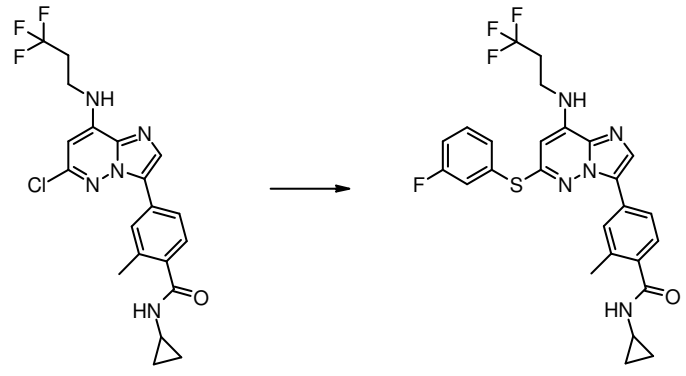
b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el ejemplo 205.

1H-RMN (DMSO-d6): δ= 0,48-0,67 (4H), 2,36 (3H), 2,80 (1H), 3,47 (1H), 3,58 (1H), 4,32 (1H), 6,58 (2H), 6,90 (1H), 7,37 (1H), 7,48 (1H), 7,51 (1H), 7,91-8,00 (3H), 8,29 (1H), ppm.

Ejemplo 209

N-ciclopropil-4-{6-[(3-fluorofenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



El compuesto del título se preparó de acuerdo con el procedimiento descrito para el ejemplo 194 usando 4-{6-cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 10a.

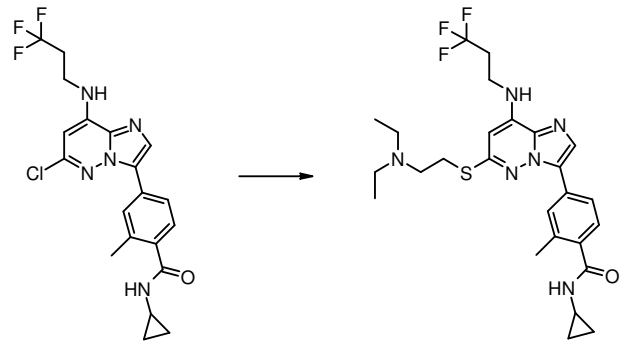
1H-RMN (DMSO-d6): δ= 0,49-0,66 (4H), 2,20 (3H), 2,53-2,70 (4H), 2,78 (1H), 3,54 (2H), 6,20 (1H), 7,12 (1H), 7,34 (1H), 7,43 - 7,71 (6H), 7,95 (1H), 8,23 (1H), ppm.

Ejemplo 210

N-ciclopropil-4-(6-{[2-(dietilamino)etil]sulfanil}-8-[(3,3,3-

trifluoropropil)

amino]imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida



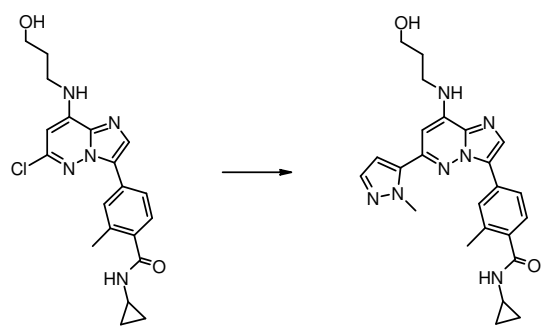
El compuesto del título se preparó de acuerdo con el procedimiento descrito para el ejemplo 194 usando 4-{6-cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 10a.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,65 (2H), 0,86 (6H), 2,36 (3H), 2,59-2,71 (4H), 2,79 (1H), 3,23 - 3,33 (H múltiple, superpuesto con pico de agua), 3,54 (2H), 6,13 (1H), 7,32 (1H), 7,52 (1H), 7,91 (1H), 7,95 (1H), 8,02 (1H) 8,28 (1H), ppm.

Ejemplo 211

N-ciclopropil-4-{8-[(3-hidroxipropil)amino]-6-(1-metil-1H-pirazol-5-il)

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



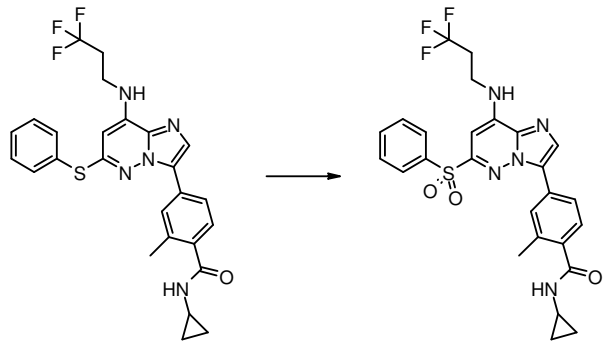
A una mezcla de 51 mg (128 µmol) de 4-{6-cloro-8-[(3-hidroxipropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de manera análoga al Ejemplo 205 usando 3-hidroxi-n-propilamina, 80 mg (380 µmol) de pinacoléster de ácido (1-metil-1H-pirazol-5-il)borónico, 18 mg de Tetrakis(trifenilfosfin)paladio en 1 mL de etanol y 1 mL de tolueno se agregó 0,27 mL de una solución acuosa de bicarbonato de sodio 10% y la mezcla se agitó a 120°C durante 2 horas bajo irradiación de microondas. Luego se agregó agua y acetato de etilo y la capa orgánica se lavó con agua y salmuera, se concentró y se trató con diclorometano. Los sólidos no disueltos restantes dieron 25 mg del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,66 (2H), 1,78 (2H), 2,35 (3H), 2,80 (1H), 3,41 - 3,51 (4H), 6,47 (1H), 6,88 (1H), 7,36 (1H), 7,51 (1H), 7,62 (1H), 7,91 - 7,97 (3H), (1H), 8,29 (1H), ppm.

Ejemplo 212

N-ciclopropil-2-metil-4-{6-(fenilsulfonil)-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}benzamida



Se trataron 50 mg (98 µmol) de N-ciclopropil-2-metil-4-{6-

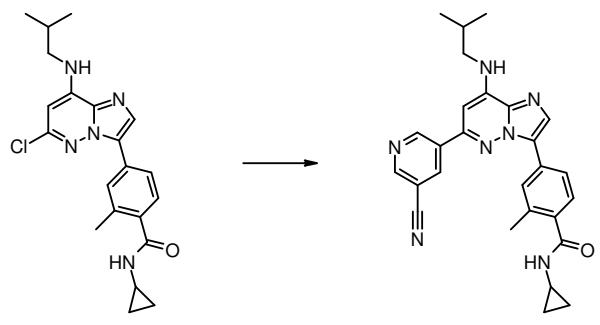
(fenilsulfanil)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida, que se preparó de acuerdo con el ejemplo 207, de manera análoga al Ejemplo 18 para dar, luego del tratamiento posterior y la purificación, 30,2 mg (57%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,67 (2H), 2,31 (3H), 2,70 (2H), 2,81 (1H), 3,29 (2H), 6,81 (1H), 7,28 (1H), 7,65-7,82 (5H), 8,03 (1H), 8,06 (1H), 8,15 (1H), 8,30 (1H), 8,36 (1H) ppm.

Ejemplo 213

4-[6-(5-Cianopiridin-3-il)-8-(isobutilamino)imidazo[1,2-b]piridazin-3-il]-

N-ciclopropil-2-metilbenzamida



Se trataron 200 mg (503 µmol) de 4-[6-cloro-8-(isobutilamino)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 194a, de manera análoga al Ejemplo 202 usando ácido 5-cianopiridin-3-ilborónico para dar, luego del tratamiento posterior y la purificación, 80,9 mg (33%) del compuesto del título.

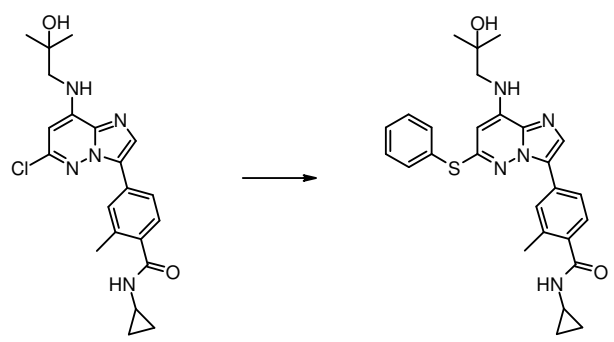
1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,62 (2H), 0,92 (6H), 2,04 (1H), 2,39 (3H), 2,81 (1H), 3,26 (2H), 6,83 (1H), 7,41 (1H), 7,76

(1H), 8,01 – 8,10 (3H), 8,30 (1H), 8,93 (1H), 9,10 (1H), 9,49 (1H), ppm.

Ejemplo 214

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(fenilsulfanil)

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



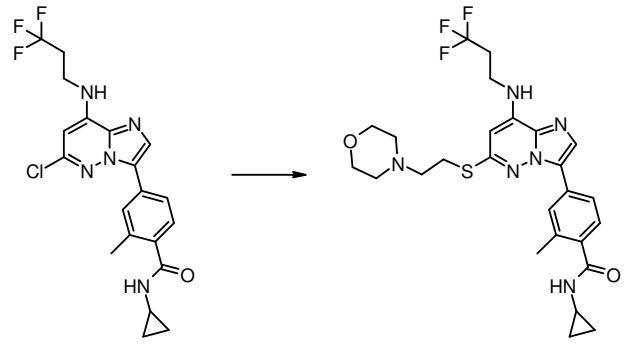
Se trataron 100 mg (242 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 55 usando bencenotiol para dar, luego del tratamiento posterior y la purificación, 113,5 mg (96%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,65 (2H), 1,11 (6H), 2,19 (3H), 2,79 (1H), 3,21 (2H), 4,71 (1H), 6,23 (1H), 6,97 (1H), 7,08 (1H), 7,44-7,52 (3H), 7,58-7,65 (3H), 7,70 (1H), 7,93 (1H), 8,22 (1H) ppm.

Ejemplo 215

N-ciclopropil-2-metil-4-(6-{[2-(morfolin-4-il)etil]sulfanil}-8-[(3,3,3-

trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il)benzamida



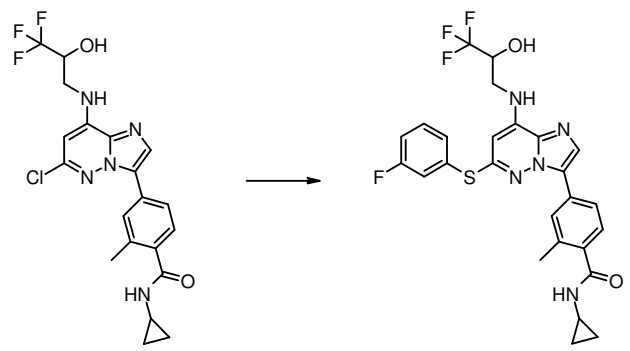
Se trataron 100 mg (228 µmol) de 4-{6-Cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 10a, de manera análoga al Ejemplo 55 usando 2-(morfolin-4-il)etanotiol para dar, luego del tratamiento posterior y la purificación, 78,2 mg (59%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,65 (2H), 2,30-2,39 (4H), 2,37 (3H), 2,57-2,71 (4H), 2,80 (1H), 3,28 (2H), 3,47-3,57 (6H), 6,13 (1H), 7,33 (1H), 7,53 (1H), 7,90 (1H), 7,96 (1H), 7,98 (1H), 8,29 (1H) ppm.

Ejemplo 216

(RS)-N-ciclopropil-4-{6-[(3-fluorofenil)sulfanil]-8-[(3,3,3-trifluoro-2-

hidroxipropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

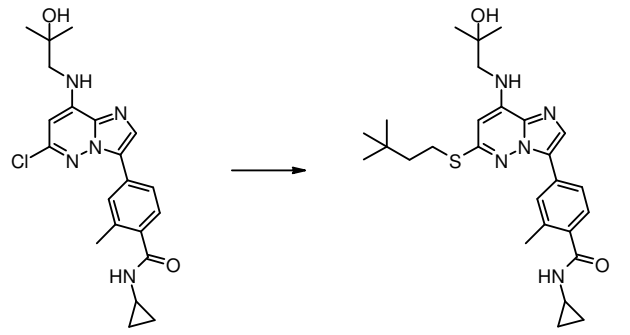


Se trataron 95 mg (191 µmol) de (RS)-4-{6-cloro-8-[(3,3,3-trifluoro-2-hidroxipropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 205, de manera análoga al Ejemplo 194 usando 3-fluorobencenotiol para dar, luego del tratamiento posterior y la purificación, 54 mg (49%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,65 (2H), 2,20 (3H), 2,79 (1H), 3,45 -3,62 (2H), 4,26 (1H), 6,24 (1H), 6,56 (1H), 7,13 (1H), 7,35 (1H), 7,50 (1H), 7,51 - 7,56 (3H), 7,65 (1H), 7,71 (1H), 7,97 (1H), 8,25 (1H), ppm.

Ejemplo 217

N-ciclopropil-4-{6-[(3,3-dimetilbutil)sulfanil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 75 mg (181 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-

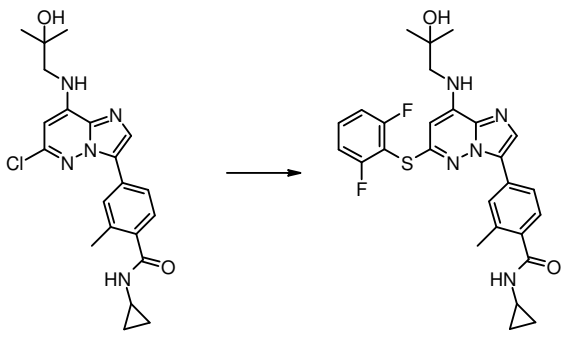
metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 3,3-dimetilbutan-1-tiol para dar, luego del tratamiento posterior y la purificación, 29,2 mg (31%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,65 (2H), 0,89 (9H), 1,13 (6H), 1,54 (2H), 2,35 (3H), 2,79 (1H), 3,13 (2H), 3,21 (2H), 4,72 (1H), 6,17 (1H), 6,81 (1H), 7,29 (1H), 7,91 (1H), 7,98 (1H), 7,99 (1H), 8,28 (1H) ppm.

Ejemplo 218

N-ciclopropil-4-{6-[(2,6-difluorofenil)sulfanil]-8-[(2-hidroxi-2-

metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 75 mg (181 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 2,6-difluorobencenotiol para dar, luego del tratamiento posterior y la purificación, 6,5 mg (6%) del compuesto del título.

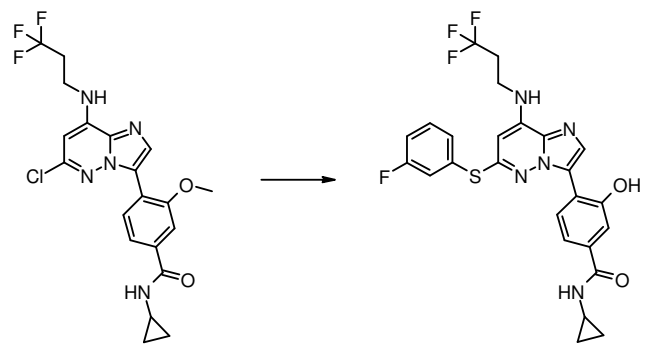
1H-RMN (CDCl3): δ= 0,63 (2H), 0,89 (2H), 1,40 (6H), 2,33 (3H),

2,91 (1H), 3,29 (2H), 5,96 (1H), 6,05 (1H), 6,55 (1H), 7,00-7,11 (3H), 7,41-7,53 (3H), 7,57 (1H) ppm.

Ejemplo 219

N-ciclopropil-4-{6-[(3-fluorofenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}-3-hidroxibenzamida



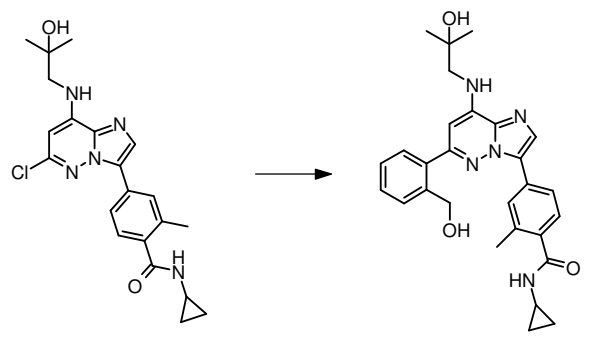
Se trataron 75 mg (165 µmol) de 4-{6-cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-3-metoxibenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 52a, de manera análoga al Ejemplo Intermediario 51 usando 3-fluorobencenotiol para dar, luego del tratamiento posterior y la purificación, 24,0 mg (27%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,54 (2H), 0,66 (2H), 2,60 (2H), 2,80 (1H), 3,52 (2H), 6,13 (1H), 7,07 (1H), 7,28 (1H), 7,34 (1H), 7,38-7,53 (3H), 7,71 (1H), 7,85 (1H), 7,94 (1H), 8,34 (1H), 10,12 (1H) ppm.

Ejemplo 220

N-ciclopropil-4-{6-[2-(hidroximetil)fenil]-8-[(2-hidroxi-2-metilpropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



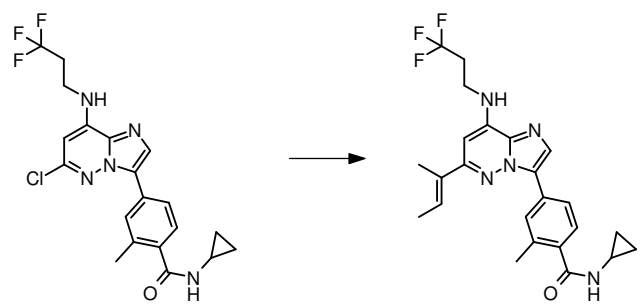
Se trataron 5,25 g (12,7 mmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 1 usando ácido [2-(hidroximetil)fenil]borónico para dar, luego del tratamiento posterior y la purificación, 4,90 g (80%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 1,18 (6H), 2,36 (3H), 2,82 (1H), 3,32 (2H), 4,66 (2H), 4,75 (1H), 5,13 (1H), 6,45 (1H), 6,95 (1H), 7,35 (1H), 7,39 (1H), 7,45-7,52 (2H), 7,66 (1H), 7,95 (1H), 8,00 (1H), 8,01 (1H), 8,26 (1H) ppm.

Ejemplo 221

4-{6-[(2E)-but-2-en-2-il]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]

piridazin-3-il}-N-ciclopropil-2-metilbenzamida



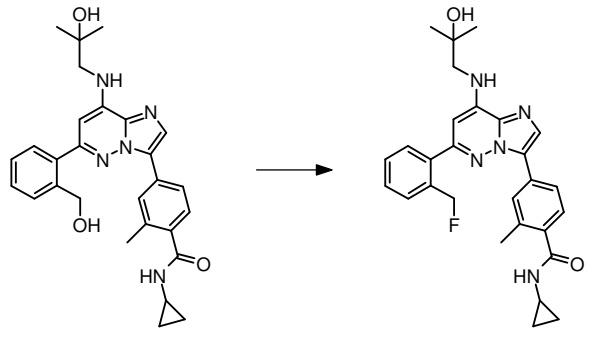
Se trataron 115 mg (262 µmol) de 4-{6-cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 10a, de manera análoga al Ejemplo 1 usando ácido (2Z)-but-2-en-2-ilborónico para dar, luego del tratamiento posterior y la purificación, 7,2 mg (6%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,65 (2H), 1,84 (3H), 2,07 (3H), 2,36 (3H), 2,67 (2H), 2,80 (1H), 3,61 (2H), 6,43 (1H), 6,49 (1H), 7,32 (1H), 7,35 (1H), 7,97 (1H), 8,03 (1H), 8,07 (1H), 8,27 (1H) ppm.

Ejemplo 222

N-ciclopropil-4-{6-[2-(fluorometil)fenil]-8-[(2-hidroxi-2-metilpropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



A una solución de 329 mg (677 µmol) de N-ciclopropil-4-{6-[2-(hidroximetil)fenil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida, que se preparó de acuerdo con el ejemplo 220, en 13 mL de diclorometano a 3°C, se agregaron 98 µL de N-etil-N-(trifluoro-lambda4-sulfanil)etanamina. Luego de agitar durante

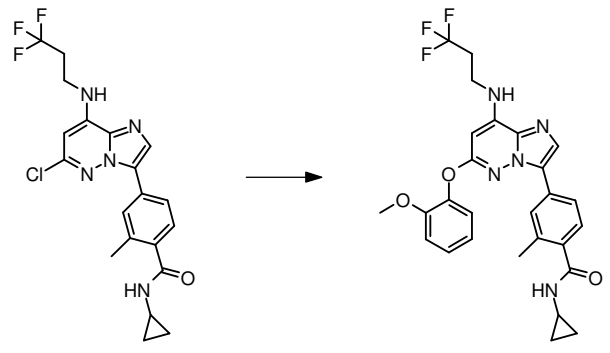
10 minutos, la solución se volcó sobre agua y la fase acuosa se extrajo con diclorometano. Las fases orgánicas combinadas se lavaron con solución de carbonato ácido de sodio y se secó sobre sulfato de sodio. Luego de la filtración y la eliminación del solvente el residuo se purificó mediante cromatografía para dar 28,6 mg (8%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,61 (2H), 0,87 (2H), 1,47 (6H), 2,48 (3H), 2,90 (1H), 3,36 (2H), 5,21 (1H), 5,58 (2H), 5,97 (1H), 6,26 (1H), 6,71 (1H), 7,37 (1H), 7,46 (1H), 7,51 (1H), 7,58 (1H), 7,64 (1H), 7,74 (1H), 7,81 (1H), 7,88 (1H) ppm.

Ejemplo 223

N-ciclopropil-4-{6-(2-metoxifenoxi)-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

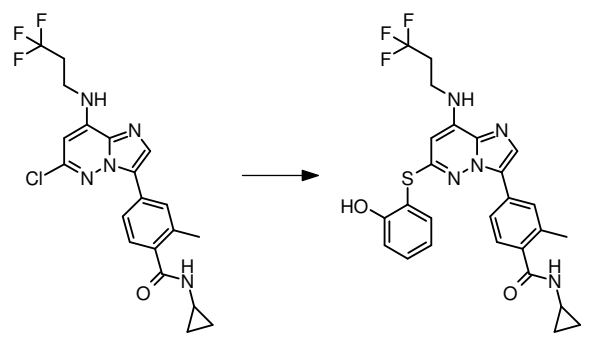


Se trataron 150 mg (343 µmol) de 4-{6-cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 10a, de manera análoga al Ejemplo 51 usando 2-metoxifenol para dar, luego del tratamiento posterior y la purificación, 8,1 mg (5%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,60 (2H), 0,88 (2H), 2,26 (3H), 2,57 (2H), 2,89 (1H), 3,68 (2H), 3,78 (3H), 5,82 (1H), 5,94 (1H), 5,98 (1H), 7,01 (1H), 7,05 (1H), 7,18 (1H), 7,22 (1H), 7,27 (1H), 7,55 (1H), 7,70 (1H), 7,72 (1H) ppm.

Ejemplo 224

N-ciclopropil-4-{6-[(2-hidroxifenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



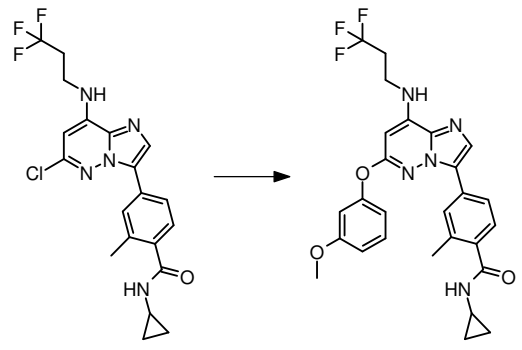
Se trataron 100 mg (228 µmol) de 4-{6-cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 10a, de manera análoga al Ejemplo 51 usando 2-metoxibencenotiol para dar, luego del tratamiento posterior y la purificación, 5,1 mg (4%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,65 (2H), 2,21 (3H), 2,59 (2H), 2,79 (1H), 3,49 (2H), 6,05 (1H), 6,87 (1H), 6,98 (1H), 7,07 (1H), 7,34 (1H), 7,46 (1H), 7,56 (1H), 7,67 (1H), 7,72 (1H), 7,93 (1H), 8,23 (1H), 9,96 (1H) ppm.

Ejemplo 225

N-ciclopropil-4-{6-(3-metoxifenoxi)-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



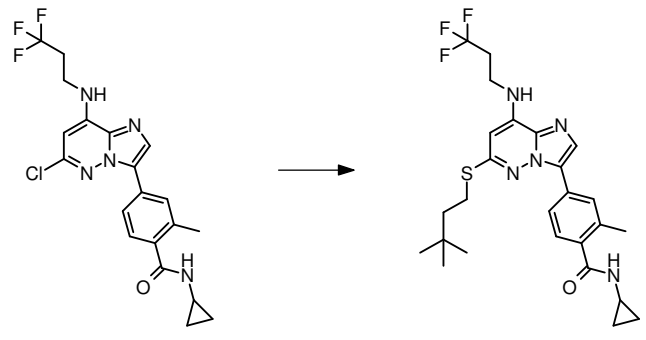
Se trataron 150 mg (343 µmol) de 4-{6-cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 10a, de manera análoga al Ejemplo 51 usando 3-metoxifenol para dar, luego del tratamiento posterior y la purificación, 5,1 mg (3%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,60 (2H), 0,87 (2H), 2,31 (3H), 2,56 (2H), 2,89 (1H), 3,66 (2H), 3,80 (3H), 5,85 (1H), 5,88 (1H), 6,03 (1H), 6,79-6,88 (3H), 7,24 (1H), 7,33 (1H), 7,63 (1H), 7,73 (1H), 7,79 (1H) ppm.

Ejemplo 226

N-ciclopropil-4-{6-[(3,3-dimetilbutil)sulfanil]-8-[(3,3,3-trifluoropropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



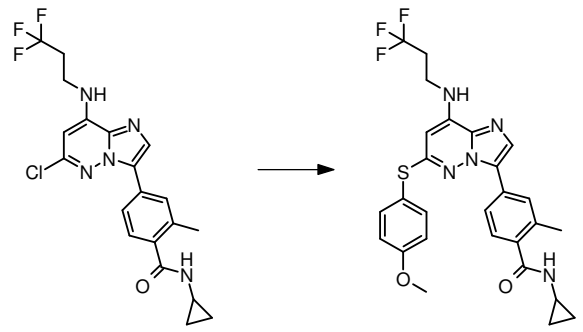
Se trataron 100 mg (228 µmol) de 4-{6-cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 10a, de manera análoga al Ejemplo 51 usando 3,3-dimetilbutan-1-tiol para dar, luego del tratamiento posterior y la purificación, 3,6 mg (3%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,63 (2H), 0,90 (2H), 0,94 (9H), 1,62 (2H), 2,51 (3H), 2,52 (2H), 2,92 (1H), 3,19 (2H), 3,61 (2H), 5,84-5,93 (3H), 7,37 (1H), 7,69 (1H), 7,88 (1H), 7,91 (1H) ppm.

Ejemplo 227

N-ciclopropil-4-{6-[(4-metoxifenil)sulfanil]-8-[(3,3,3-trifluoropropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 100 mg (228 µmol) de 4-{6-cloro-8-[(3,3,3-

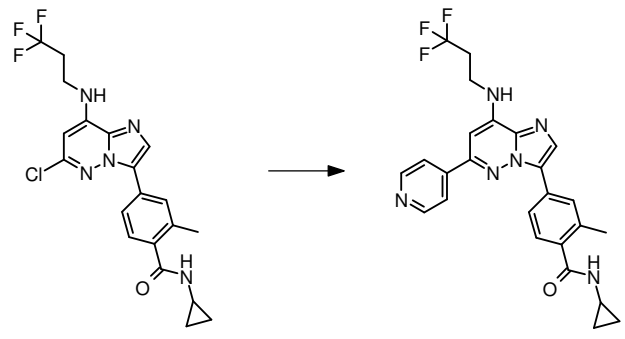
trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 10a, de manera análoga al Ejemplo 51 usando 4-metoxibencenotiol para dar, luego del tratamiento posterior y la purificación, 16,8 mg (13%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,63 (2H), 0,90 (2H), 2,40 (3H), 2,47 (2H), 2,92 (1H), 3,57 (2H), 3,88 (3H), 5,82-5,93 (3H), 6,98 (2H), 7,17 (1H), 7,54-7,63 (4H), 7,69 (1H) ppm.

Ejemplo 228

N-ciclopropil-2-metil-4-{6-(piridin-4-il)-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}benzamida



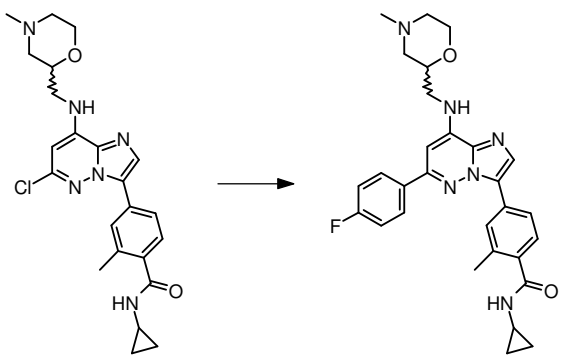
Se trataron 250 mg (571 µmol) de 4-{6-cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 10a, de manera análoga al Ejemplo 1 usando ácido piridin-4-ilborónico para dar, luego del tratamiento posterior y la purificación, 6,7 mg (2%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,63 (2H), 0,89 (2H), 2,53 (3H), 2,61 (2H), 2,91 (1H), 3,72 (2H), 6,20 (1H), 6,43 (1H), 6,67 (1H), 7,44 (1H), 7,80 (1H), 7,82 (2H), 7,89 (1H), 7,96 (1H), 8,72 (2H) ppm.

Ejemplo 229

(RS)-N-ciclopropil-4-[6-(4-fluorofenil)-8-{[(4-metilmorfolin-2-il)metil]

amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida



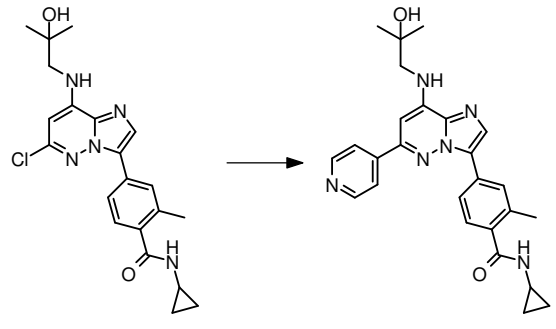
Se trataron 50 mg (110 µmol) de (RS)-4-[6-cloro-8-({[(2S)-4-metilmorfolin-2-il]metil}amino)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 56a, de manera análoga al Ejemplo 1 usando ácido (4-fluorofenil)borónico para dar, luego del tratamiento posterior y la purificación, 12,2 mg (22%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 1,80 (1H), 1,96 (1H), 2,14 (3H), 2,39 (3H), 2,54 (1H), 2,74 (1H), 2,81 (1H), 3,45-3,55 (3H), 3,72-3,80 (2H), 6,72 (1H), 7,34 (2H), 7,39 (2H), 8,00 (1H), 8,03 (1H), 8,06-8,12 (3H), 8,30 (1H), ppm.

Ejemplo 230

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(piridin-4-il)imidazo

[1,2-b]piridazin-3-il}-2-metilbenzamida



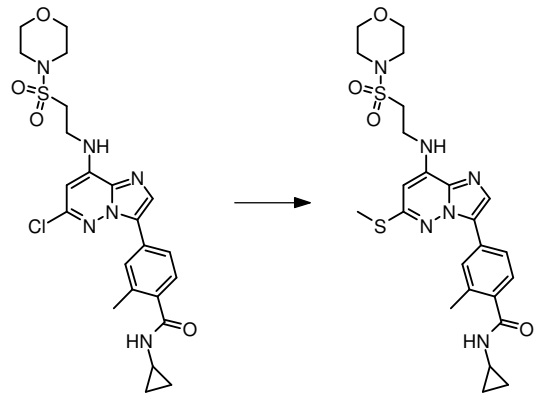
Se trataron 200 mg (483 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 1 usando ácido piridin-4-ilborónico para dar, luego del tratamiento posterior y la purificación, 28,3 mg (12%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,69 (2H), 0,91 (2H), 1,49 (6H), 2,46 (3H), 2,96 (1H), 3,33 (2H), 4,99 (1H), 6,23 (1H), 6,53 (1H), 6,58 (1H), 7,29 (1H), 7,66 (2H), 7,70 (1H), 7,76 (1H), 7,82 (1H), 8,57 (2H) ppm.

Ejemplo 231

N-ciclopropil-2-metil-4-[6-(metilsulfanil)-8-{[2-(morfolin-4-ilsulfonil)

etil]amino}imidazo[1,2-b]piridazin-3-il]benzamida

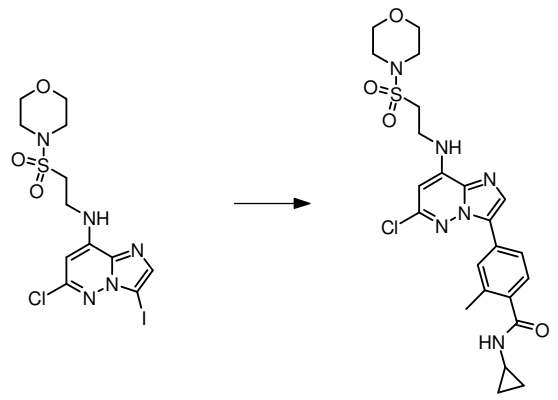


Se trataron 46 mg (89 µmol) de 4-(6-cloro-8-{[2-(morfolin-4-ilsulfonil)etil]amino}imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 231a, de manera análoga al Ejemplo 51 usando metantiolato de sodio para dar, luego del tratamiento posterior y la purificación, 12 mg (25%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,65 (2H), 2,36 (3H), 2,57 (3H), 2,80 (1H), 3,14 (4H), 3,44 (2H), 3,60 (4H), 3,69 (2H), 6,15 (1H), 7,35 (1H), 7,43 (1H), 7,93 (1H), 7,98 (1H), 8,06 (1H), 8,28 (1H) ppm.

Ejemplo Intermediario 231a

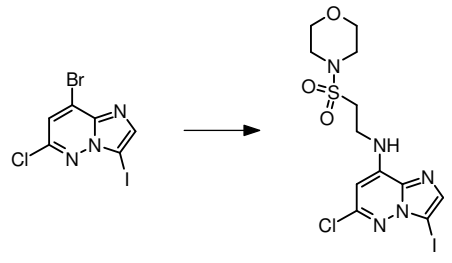
4-(6-cloro-8-{[2-(morfolin-4-ilsulfonil)etil]amino}imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida



Se trataron 650 mg (1,38 mmol) de 6-cloro-3-yodo-N-[2-(morfolin-4-ilsulfonil)etil]imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 231b, de manera análoga al Ejemplo Intermediario 1a usando N-ciclopropil-2-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzamida para dar, luego del tratamiento posterior y la purificación, 102 mg (14%) del compuesto del título.

Ejemplo Intermediario 231b

6-cloro-3-yodo-N-[2-(morfolin-4-ilsulfonil)etil]imidazo[1,2-b]piridazin-8-amina

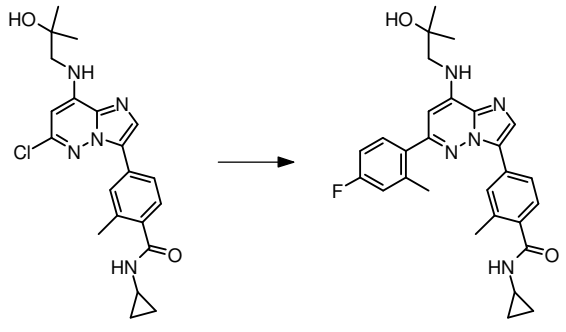


Se trataron 1,00 g (2,79 mmol) de 8-bromo-6-cloro-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 1c, de manera análoga al Ejemplo Intermediario 1b usando 2-(morfolin-4-ilsulfonil)etanamina para dar, luego del tratamiento posterior y la purificación, 650 mg (49%) del compuesto del título.

Ejemplo 232

N-ciclopropil-4-{6-(4-fluoro-2-metilfenil)-8-[(2-hidroxi-2-metilpropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



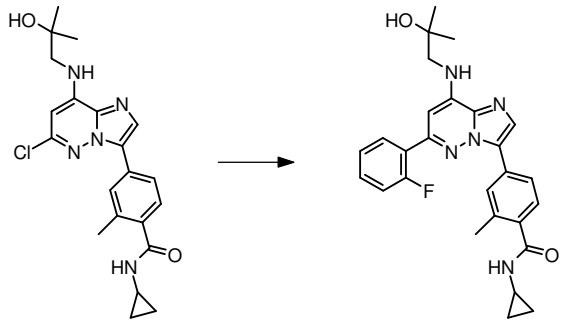
Se trataron 100 mg (242 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 1 usando ácido (4-fluoro-2-metilfenil)borónico para dar, luego del tratamiento posterior y la purificación, 19,0 mg (15%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,47 (2H), 0,64 (2H), 1,15 (6H), 2,33 (3H), 2,38 (3H), 2,78 (1H), 3,31 (2H), 4,71 (1H), 6,36 (1H), 6,95 (1H), 7,12 (1H), 7,19 (1H), 7,32 (1H), 7,47 (1H), 7,92 (1H), 7,98 (1H), 7,99 (1H), 8,24 (1H) ppm.

Ejemplo 233

N-ciclopropil-4-{6-(2-fluorofenil)-8-[(2-hidroxi-2-metilpropil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



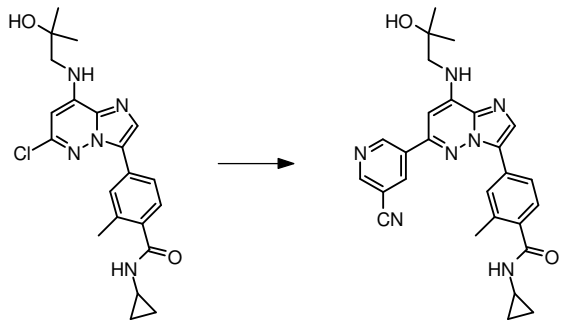
Se trataron 100 mg (242 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 1 usando ácido (2-fluorofenil)borónico para dar, luego del tratamiento posterior y la purificación, 10,0 mg (8%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,64 (2H), 1,16 (6H), 2,36 (3H), 2,79 (1H), 3,31 (2H), 4,74 (1H), 6,57 (1H), 7,00 (1H), 7,31-7,40 (3H), 7,52 (1H), 7,78 (1H), 8,01 (1H), 8,03 (1H), 8,06 (1H), 8,26 (1H) ppm.

Ejemplo 234

4-{6-(5-cianopiridin-3-il)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]

piridazin-3-il}-N-ciclopropil-2-metilbenzamida



Se trataron 200 mg (483 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 1 usando ácido (5-cianopiridin-3-il)borónico para dar, luego del tratamiento posterior y la purificación, 19,0 mg (8%) del compuesto del

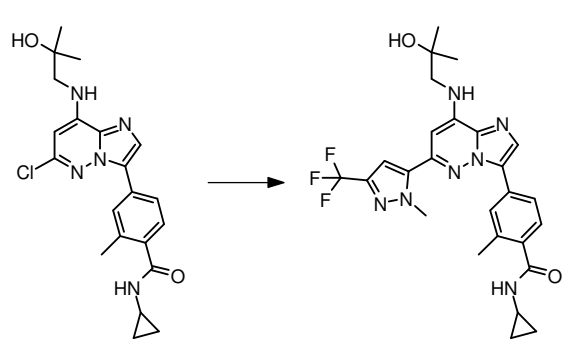
título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 1,19 (6H), 2,39 (3H), 2,81 (1H), 3,42 (2H), 4,79 (1H), 6,96 (1H), 7,08 (1H), 7,41 (1H), 8,01 (1H), 8,04 (1H), 8,10 (1H), 8,31 (1H), 8,91 (1H), 9,11 (1H), 9,50 (1H) ppm.

Ejemplo 235

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[1-metil-3-

(trifluorometil)-1H-pirazol-5-il]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



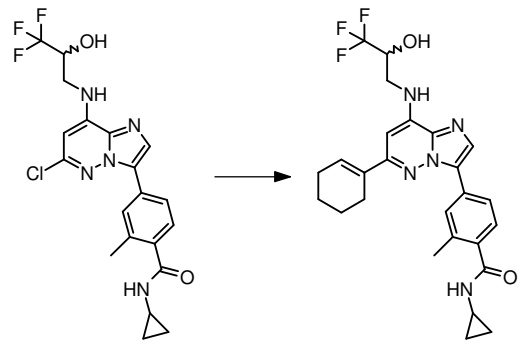
Se trataron 100 mg (242 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 1 usando ácido [1-metil-3-(trifluorometil)-1H-pirazol-5-il]borónico para dar, luego del tratamiento posterior y la purificación, 25 mg (19%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,65 (2H), 1,17 (6H), 2,36 (3H), 2,80 (1H), 3,37 (2H), 4,22 (3H), 4,77 (1H), 6,73 (1H), 7,07 (1H), 7,37 (1H), 7,46 (1H), 7,91 (1H), 7,94 (1H), 8,00 (1H),

8,30 (1H) ppm.

Ejemplo 236

(RS)-4-{6-(ciclohex-1-en-1-il)-8-[(3,3,3-trifluoro-2-hidroxipropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



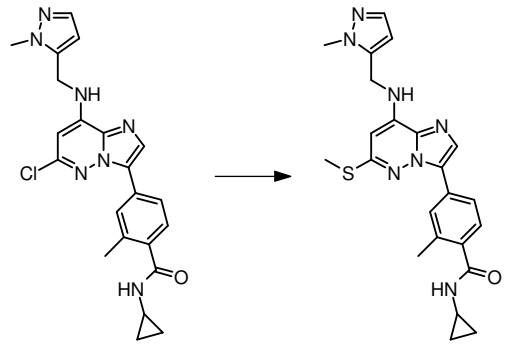
Se trataron 85 mg (187 µmol) de (RS)-4-{6-cloro-8-[(3,3,3-trifluoro-2-hidroxipropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el ejemplo 205, de manera análoga al Ejemplo Intermediario 1 usando ácido ciclohex-1-en-1-ilborónico para dar, luego del tratamiento posterior y la purificación, 4,0 mg (4%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,62 (2H), 1,58 (2H), 1,68 (2H), 2,20 (2H), 2,34 (3H), 2,49 (2H), 2,77 (1H), 3,48 (1H), 3,64 (1H), 4,28 (1H), 6,46 (1H), 6,54 (1H), 6,65 (1H), 7,05 (1H), 7,33 (1H), 7,94 (1H), 8,01 (1H), 8,02 (1H), 8,23 (1H) ppm.

Ejemplo 237

N-ciclopropil-2-metil-4-[8-{[(1-metil-1H-pirazol-5-il)metil]amino}-6-

(metilsulfanil)imidazo[1,2-b]piridazin-3-il]benzamida

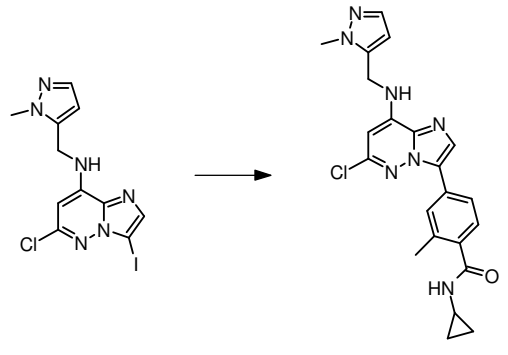


Se trataron 100 mg (229 µmol) de 4-(6-cloro-8-{[(1-metil-1H-pirazol-5-il)metil]amino}imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 237a, de manera análoga al Ejemplo 51 usando metantiolato de sodio para dar, luego del tratamiento posterior y la purificación, 75 mg (72%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,65 (2H), 2,35 (3H), 2,53 (3H), 2,80 (1H), 3,79 (3H), 4,58 (2H), 6,14 (2H), 7,25 (1H), 7,34 (1H), 7,92-8,02 (3H), 8,05 (1H), 8,28 (1H) ppm.

Ejemplo Intermediario 237a

4-(6-cloro-8-{[(1-metil-1H-pirazol-5-il)metil]amino}imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida



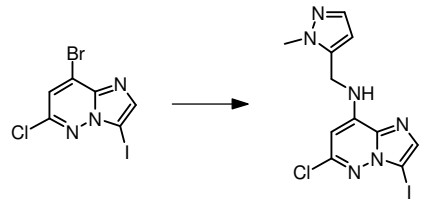
Se trataron 500 mg (1,29 mmol) de 6-cloro-3-yodo-N-[(1-metil-1H-

pirazol-5-il)metil]imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 237b, de manera análoga al Ejemplo Intermediario 1a usando N-ciclopropil-2-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzamida para dar, luego del tratamiento posterior y la purificación, 277 mg (47%) del compuesto del título.

Ejemplo Intermediario 237b

6-cloro-3-yodo-N-[(1-metil-1H-pirazol-5-il)metil]imidazo[1,2-b]piridazin-8-

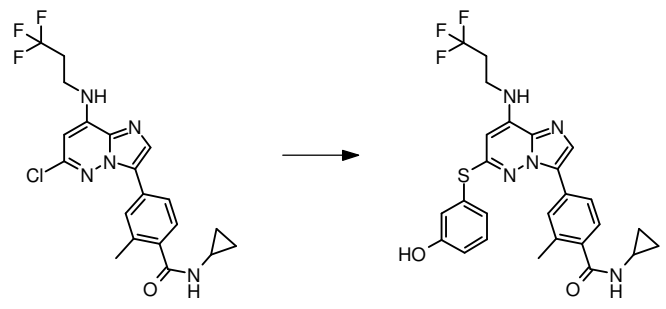
amina



Se trató 1,00 g (2,79 mmol) de 8-bromo-6-cloro-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 1c, de manera análoga al Ejemplo Intermediario 1b usando 1-(1-metil-1H-pirazol-5-il)metanamina para dar, luego del tratamiento posterior y la purificación, 1,00 g (92%) del compuesto del título.

Ejemplo 238

N-ciclopropil-4-{6-[(3-hidroxifenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



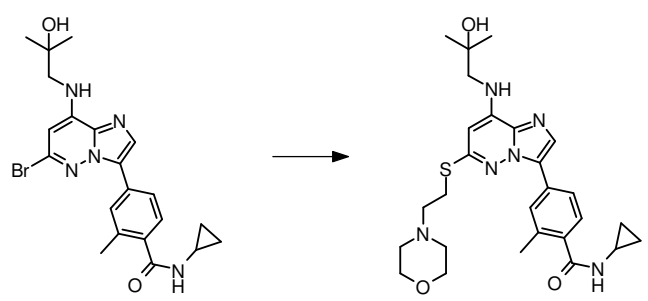
Se trataron 100 mg (228 µmol) de 4-{6-cloro-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 10a, de manera análoga al Ejemplo 51 usando 3-metoxibencenotiol para dar, luego del tratamiento posterior y la purificación, 68 mg (65%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,65 (2H), 2,23 (3H), 2,60 (2H), 2,79 (1H), 3,52 (2H), 6,11 (1H), 6,86 (1H), 6,98 (1H), 7,01 (1H), 7,15 (1H), 7,26 (1H), 7,63 (1H), 7,73 (1H), 7,74 (1H), 7,94 (1H), 8,21 (1H), 9,69 (1H) ppm.

Ejemplo 239

N-ciclopropil-4-(8-[(2-hidroxi-2-metilpropil)amino]-6-{[2-(morfolin-4-il)

etil]sulfanil}imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida



Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-

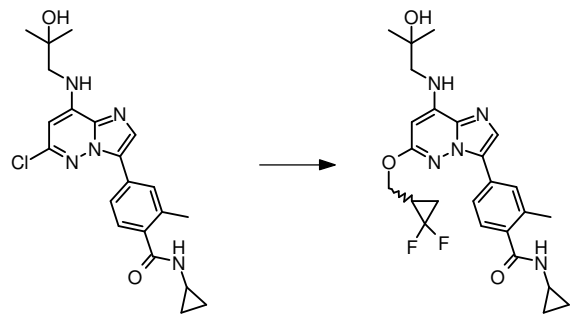
metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando 2-(morfolin-4-il)etanotiol para dar, luego del tratamiento posterior y la purificación, 45,4 mg (50%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,65 (2H), 1,13 (6H), 2,30-2,40 (4H), 2,37 (3H), 2,61 (2H), 2,80 (1H), 3,22 (2H), 3,27 (2H), 3,51 (4H), 4,71 (1H), 6,18 (1H), 6,81 (1H), 7,33 (1H), 7,89 (1H), 7,96 (1H), 7,98 (1H), 8,28 (1H) ppm.

Ejemplo 240

(RS)-N-ciclopropil-4-{6-[(2,2-difluorociclopropil)metoxi]-8-[(2-hidroxi-2-

metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 325 mg (785 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando [(1RS)-2,2-difluorociclopropil]metanol para dar, luego del tratamiento posterior y la purificación, 12,3 mg (3%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,64 (2H), 0,89 (2H), 1,29 (1H), 1,43 (6H), 1,56 (1H), 2,15 (1H), 2,49 (3H), 2,92 (1H), 3,27 (2H), 4,34 (2H), 4,78 (1H), 5,70 (1H), 6,01 (1H), 6,42 (1H), 7,38 (1H), 7,60 (1H), 7,80 (1H), 7,83 (1H) ppm.

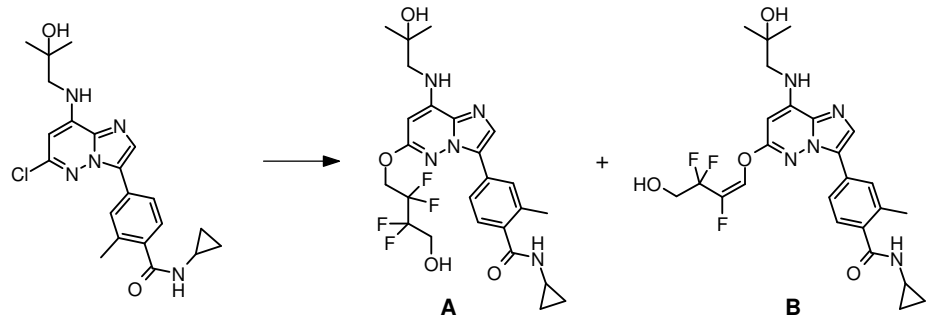
Ejemplo 241

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(2,2,3,3-tetrafluoro-

4-hidroxibutoxi)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida (A)

y

N-ciclopropil-4-(8-[(2-hidroxi-2-metilpropil)amino]-6-{[(1E)-2,3,3-trifluoro-4-hidroxibut-1-en-1-il]oxi}imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida



Se trataron 250 mg (604 µmol) de 4-{6-cloro-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7a, de manera análoga al Ejemplo 51 usando 2,2,3,3-tetrafluorobutan-1,4-diol para dar, luego del tratamiento posterior y la purificación, 38,3 mg (12%) del compuesto del título A y 88,7 mg (28%) del compuesto del título

B.

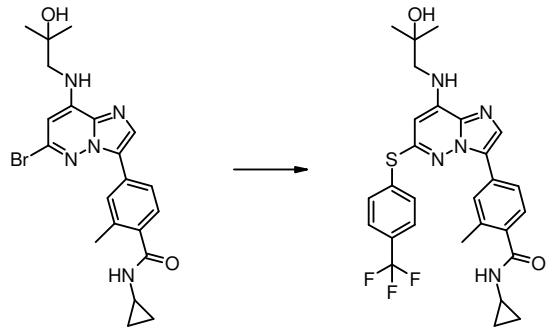
1H-RMN (DMSO-d6) de A: δ= 0,50 (2H), 0,65 (2H), 1,14 (6H), 2,35 (3H), 2,80 (1H), 3,26 (2H), 3,90 (2H), 4,71 (1H), 4,89 (2H), 6,01 (2H), 6,89 (1H), 7,33 (1H), 7,90 (1H), 7,93 (1H), 7,97 (1H), 7,28 (1H) ppm.

1H-RMN (DMSO-d6) de B: δ= 0,50 (2H), 0,65 (2H), 1,14 (6H), 2,35 (3H), 2,80 (1H), 3,26 (2H), 3,85 (2H), 4,70 (1H), 5,93 (1H), 6,18 (1H), 7,17 (1H), 7,33 (1H), 7,70 (1H), 7,89 (1H), 7,96 (1H), 8,02 (1H), 8,29 (1H) ppm.

Ejemplo 242

N-ciclopropil-4-(8-[(2-hidroxi-2-metilpropil)amino]-6-{[4-(trifluorometil)

fenil]sulfanil}imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida

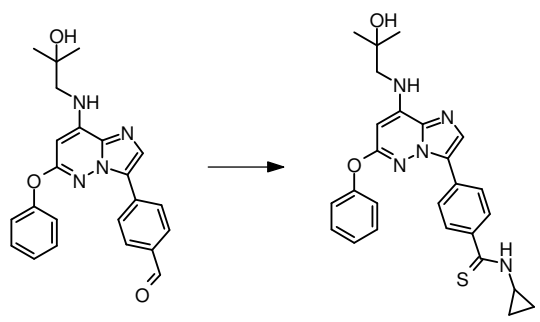


Se trataron 50 mg (109 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando 4-(trifluorometil)bencenotiol para dar, luego del tratamiento posterior y la purificación, 23 mg (36%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,47 (2H), 0,65 (2H), 1,13 (6H), 2,17 (3H), 2,78 (1H), 3,25 (2H), 4,70 (1H), 6,37 (1H), 7,04-7,10 (2H), 7,59 (1H), 7,69 (1H), 7,79 (4H), 7,95 (1H), 8,18 (1H) ppm.

Ejemplo 243

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-fenoxiimidazo[1,2-b]piridazin-3-il}bencencarbotioamida

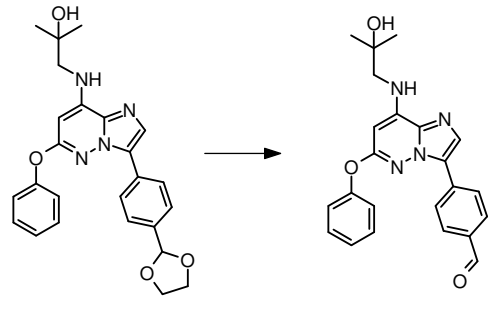


Se trataron 127 mg (316 µmol) de 4-{8-[(2-hidroxi-2-metilpropil)amino]-6-fenoxiimidazo[1,2-b]piridazin-3-il}benzaldehído, que se preparó de acuerdo con el Ejemplo Intermediario 243a, de manera análoga al Ejemplo 13 para dar, luego del tratamiento posterior y la purificación, 47 mg (30%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,71-0,87 (4H), 1,16 (6H), 3,26 (2H), 3,41 (1H), 4,72 (1H), 6,16 (1H), 6,99 (1H), 7,21-7,30 (3H), 7,44 (2H), 7,57 (2H), 7,91 (2H), 7,99 (1H), 10,05 (1H) ppm.

Ejemplo Intermediario 243a

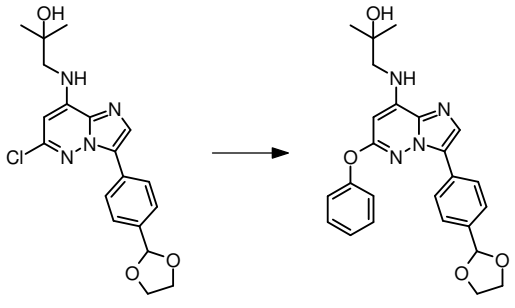
4-{8-[(2-hidroxi-2-metilpropil)amino]-6-fenoxiimidazo[1,2-b]piridazin-3-il}benzaldehído



Se trataron 152 mg (340 µmol) de 1-({3-[4-(1,3-dioxolan-2-il)fenil]-6-fenoxiimidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol, que se preparó de acuerdo con el Ejemplo Intermediario 243b, de manera análoga al Ejemplo Intermediario 13a para dar, luego del tratamiento posterior y la purificación, 132 mg (96%) del compuesto del título.

Ejemplo Intermediario 243b

1-({3-[4-(1,3-dioxolan-2-il)fenil]-6-fenoxiimidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol

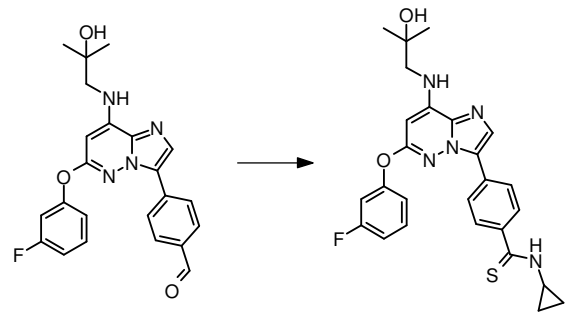


Se trataron 250 mg (643 µmol) de 1-({6-cloro-3-[4-(1,3-dioxolan-2-il)fenil]imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol, que se preparó de acuerdo con el Ejemplo Intermediario 32c, de manera análoga al Ejemplo 51 usando fenol para dar, luego del tratamiento posterior y la purificación, 157 mg (55%) del compuesto del título.

Ejemplo 244

N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]

imidazo[1,2-b]piridazin-3-il}bencencarbotioamida



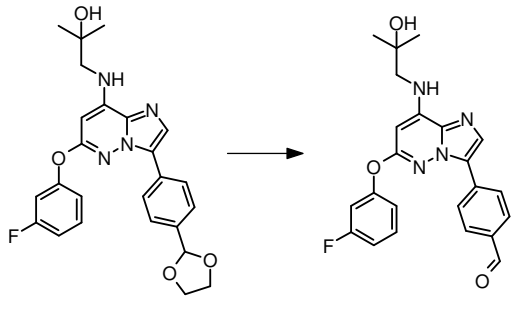
Se trataron 79 mg (188 µmol) de 4-{6-(3-fluorofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzaldehído, que se preparó de acuerdo con el Ejemplo Intermediario 244a, de manera análoga al Ejemplo 13 para dar, luego del tratamiento posterior y la purificación, 22 mg (22%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,72-0,86 (4H), 1,15 (6H), 3,41 (2H), 3,49 (1H), 4,72 (1H), 6,18 (1H), 7,03-7,15 (3H), 7,21 (1H), 7,47 (1H), 7,60 (2H), 7,92 (2H), 8,00 (1H), 10,07 (1H) ppm.

Ejemplo Intermediario 244a

4-{6-(3-fluorofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]

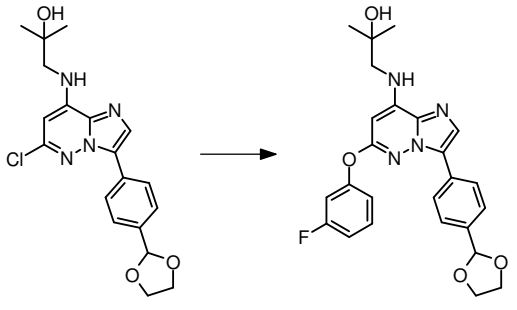
piridazin-3-il}benzaldehído



Se trataron 92 mg (198 µmol) de 1-({3-[4-(1,3-dioxolan-2-il)fenil]-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol, que se preparó de acuerdo con el Ejemplo Intermediario 244b, de manera análoga al Ejemplo Intermediario 13a para dar, luego del tratamiento posterior y la purificación, 80 mg (96%) del compuesto del título.

Ejemplo Intermediario 244b

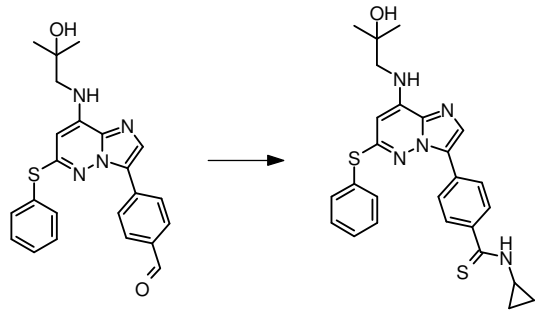
1-({3-[4-(1,3-dioxolan-2-il)fenil]-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol



Se trataron 250 mg (643 µmol) de 1-({6-cloro-3-[4-(1,3-dioxolan-2-il)fenil]imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol, que se preparó de acuerdo con el Ejemplo Intermediario 32c, de manera análoga al Ejemplo 51 usando 3-fluorofenol para dar, luego del tratamiento posterior y la purificación, 94,2 mg (32%) del compuesto del título.

Ejemplo 245

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(fenilsulfanil)imidazo[1,2-b]piridazin-3-il}bencencarbotioamida

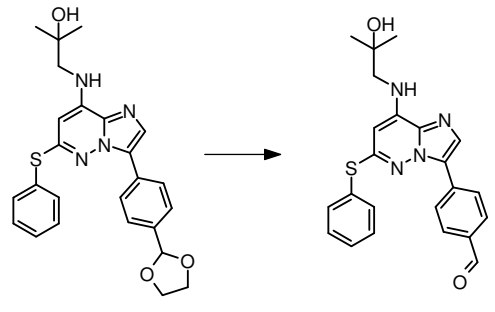


Se trataron 105 mg (251 µmol) de 4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(fenilsulfanil)imidazo[1,2-b]piridazin-3-il}benzaldehído, que se preparó de acuerdo con el Ejemplo Intermediario 245a, de manera análoga al Ejemplo 13 para dar, luego del tratamiento posterior y la purificación, 27,3 mg (21%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,75-0,87 (4H), 1,12 (6H), 3,22 (2H), 3,43 (1H), 4,69 (1H), 6,24 (1H), 6,98 (1H), 7,46-7,59 (5H), 7,63 (2H), 7,82 (2H), 7,99 (1H), 10,07 (1H) ppm.

Ejemplo Intermediario 245a

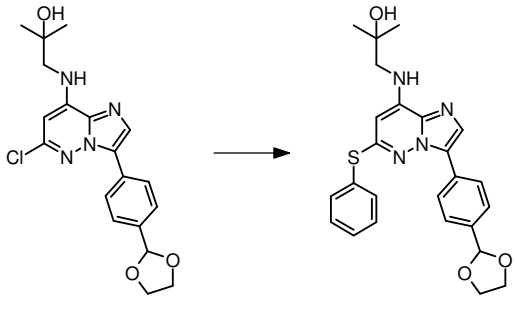
4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(fenilsulfanil)imidazo[1,2-b]piridazin-3-il}benzaldehído



Se trataron 155 mg (335 µmol) de 1-({3-[4-(1,3-dioxolan-2-il)fenil]-6-(fenilsulfanil)imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol, que se preparó de acuerdo con el Ejemplo Intermediario 245b, de manera análoga al Ejemplo Intermediario 13a para dar, luego del tratamiento posterior y la purificación, 109 mg (78%) del compuesto del título.

Ejemplo Intermediario 245b

1-({3-[4-(1,3-dioxolan-2-il)fenil]-6-(fenilsulfanil)imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol

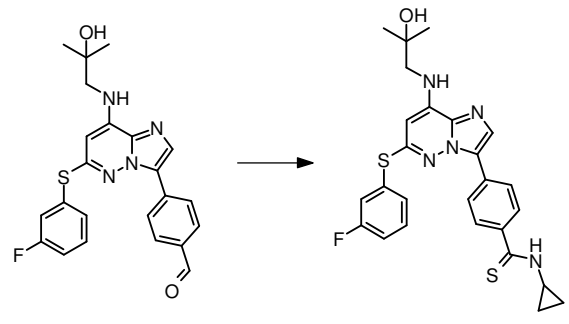


Se trataron 250 mg (643 µmol) de 1-({6-cloro-3-[4-(1,3-dioxolan-2-il)fenil]imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol, que se preparó de acuerdo con el Ejemplo Intermediario 32c, de manera análoga al Ejemplo 51 usando bencenotiol para dar, luego del tratamiento posterior y la purificación, 154 mg (52%) del compuesto del título.

Ejemplo 246

N-ciclopropil-4-{6-[(3-fluorofenil)sulfanil]-8-[(2-hidroxi-2-metilpropil)

amino]imidazo[1,2-b]piridazin-3-il}bencencarbotioamida

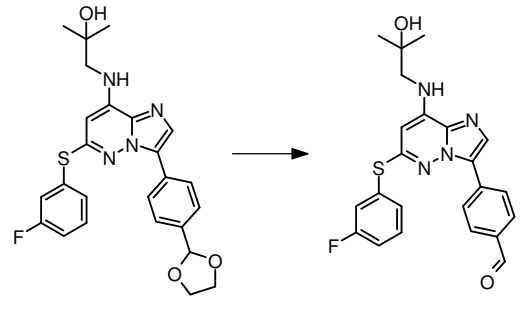


Se trataron 94 mg (215 µmol) de 4-{6-[(3-fluorofenil)sulfanil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzaldehído, que se preparó de acuerdo con el Ejemplo Intermediario 246a, de manera análoga al Ejemplo 13 para dar, luego del tratamiento posterior y la purificación, 9,2 mg (8%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,75-0,87 (4H), 1,12 (6H), 3,23 (2H), 3,44 (1H), 4,71 (1H), 6,31 (1H), 7,07 (1H), 7,35 (1H), 7,44 (1H), 7,48-7,55 (2H), 7,58 (2H), 7,85 (2H), 8,01 (1H), 10,10 (1H) ppm.

Ejemplo Intermediario 246a

4-{6-[(3-fluorofenil)sulfanil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzaldehído

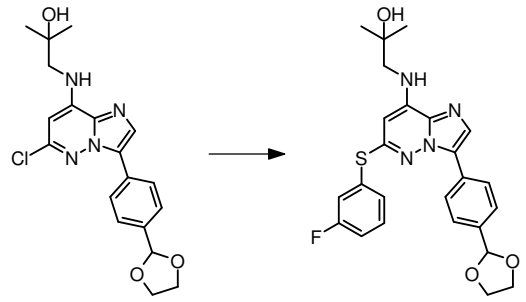


Se trataron 108 mg (225 µmol) de 1-({3-[4-(1,3-dioxolan-2-il)fenil]-6-[(3-fluorofenil)sulfanil]imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol, que se preparó de acuerdo con el Ejemplo Intermediario 246b, de manera análoga al Ejemplo Intermediario 13a para dar, luego del tratamiento posterior y la purificación, 95 mg (97%) del compuesto del título.

Ejemplo Intermediario 246b

1-({3-[4-(1,3-dioxolan-2-il)fenil]-6-[(3-fluorofenil)sulfanil]imidazo[1,2-b]

piridazin-8-il}amino)-2-metilpropan-2-ol



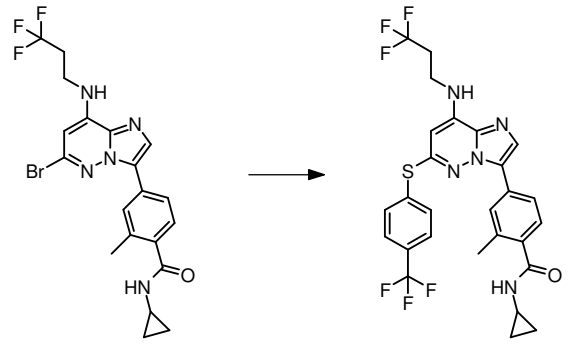
Se trataron 250 mg (643 µmol) de 1-({6-cloro-3-[4-(1,3-dioxolan-2-il)fenil]imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol, que se preparó de acuerdo con el Ejemplo Intermediario 32c, de manera análoga al Ejemplo 51 usando 3-fluorobencenotiol para dar, luego del tratamiento posterior y la purificación, 103,2 mg (33%) del compuesto del título.

Ejemplo 247

N-ciclopropil-2-metil-4-(6-{[4-(trifluorometil)fenil]sulfanil}-8-

[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-

il)benzamida

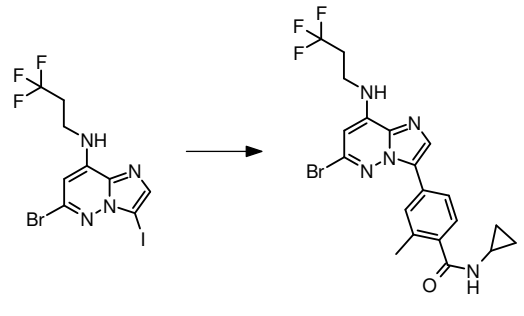


Se trataron 50 mg (104 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 4-(trifluorometil)bencenotiol para dar, luego del tratamiento posterior y la purificación, 20,2 mg (32%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,60 (2H), 0,86 (2H), 2,37 (3H), 2,51 (2H), 2,87 (1H), 3,57 (2H), 5,95 (1H), 6,04 (1H), 6,54 (1H), 7,08 (1H), 7,48 (1H), 7,55 (1H), 7,66 (2H), 7,68 (1H), 7,73 (2H) ppm.

Ejemplo Intermediario 247a

4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida

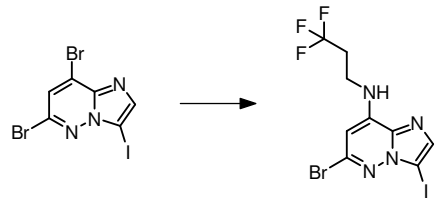


Se trató 1,00 g (2,3 mmol) de 6-bromo-3-yodo-N-(3,3,3-

trifluoropropil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 247b, de manera análoga al Ejemplo Intermediario 1a usando N-ciclopropil-2-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzamida, que se preparó de acuerdo con el Ejemplo Intermediario 7b para dar, luego del tratamiento posterior y la purificación, 580 mg (52%) del compuesto del título.

Ejemplo Intermediario 247b

6-bromo-3-yodo-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina

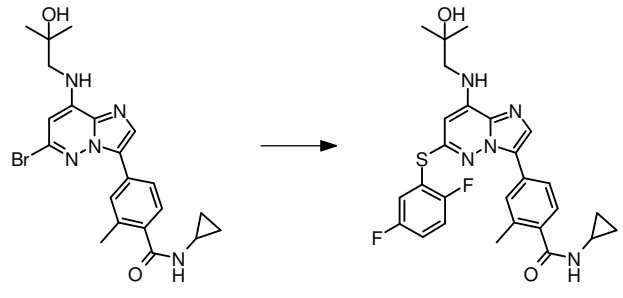


Se trataron 2,30 g (5,71 mmol) de 6,8-dibromo-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 96c, de manera análoga al Ejemplo Intermediario 1b usando 3,3,3-trifluoropropan-1-amina para dar, luego del tratamiento posterior y la purificación, 2,0 g (81%) del compuesto del título.

Ejemplo 248

N-ciclopropil-4-{6-[(2,5-difluorofenil)sulfanil]-8-[(2-hidroxi-2-

metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



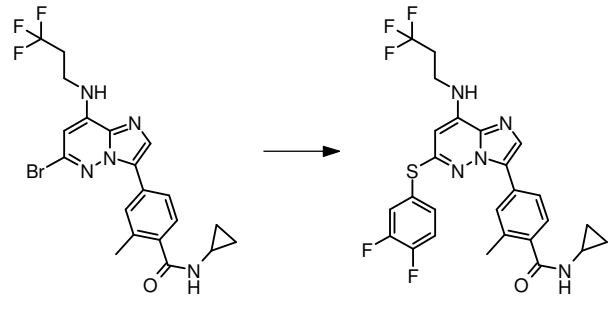
Se trataron 50 mg (109 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando 2,5-difluorobencenotiol para dar, luego del tratamiento posterior y la purificación, 10,4 mg (17%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,65 (2H), 1,14 (6H), 2,20 (3H), 2,79 (1H), 3,25 (2H), 4,71 (1H), 6,35 (1H), 7,04 (1H), 7,08 (1H), 7,42-7,51 (2H), 7,57 (1H), 7,62 (1H), 7,66 (1H), 7,94 (1H), 8,22 (1H) ppm.

Ejemplo 249

N-ciclopropil-4-{6-[(3,4-difluorofenil)sulfanil]-8-[(3,3,3-trifluoropropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 50 mg (104 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-

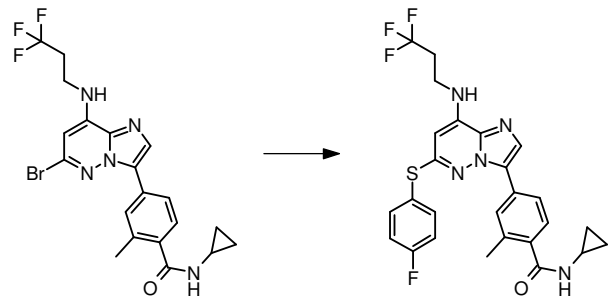
ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 3,4-difluorobencenotiol para dar, luego del tratamiento posterior y la purificación, 5,0 mg (8%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,64 (2H), 0,90 (2H), 2,42 (3H), 2,52 (2H), 2,93 (1H), 3,61 (2H), 5,88 (1H), 8,90 (1H), 5,94 (1H), 7,20-7,28 (2H), 7,39 (1H), 7,51 (1H), 7,56 (1H), 7,57 (1H), 7,70 (1H) ppm.

Ejemplo 250

N-ciclopropil-4-{6-[(4-fluorofenil)sulfanil]-8-[(3,3,3-trifluoropropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 50 mg (104 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 4-fluorobencenotiol para dar, luego del tratamiento posterior y la purificación, 3,8 mg (7%) del compuesto del título.

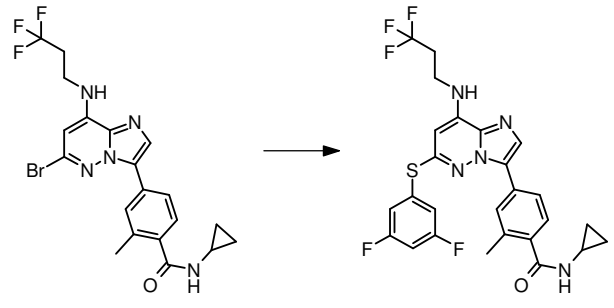
1H-RMN (CDCl3): δ= 0,64 (2H), 0,90 (2H), 2,41 (3H), 2,50 (2H), 2,93 (1H), 3,59 (2H), 5,87 (1H), 5,88 (1H), 5,96 (1H), 7,15

(2H), 7,19 (1H), 7,55 (1H), 7,59 (1H), 7,64 (2H), 7,70 (1H) ppm.

Ejemplo 251

N-ciclopropil-4-{6-[(3,5-difluorofenil)sulfanil]-8-[(3,3,3-trifluoropropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



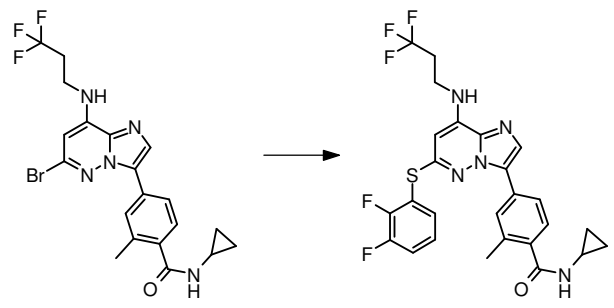
Se trataron 50 mg (104 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 3,5-difluorobencenotiol para dar, luego del tratamiento posterior y la purificación, 2,9 mg (5%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,63 (2H), 0,90 (2H), 2,43 (3H), 2,52 (2H), 2,93 (1H), 3,62 (2H), 5,86 (1H), 5,96 (1H), 6,00 (1H), 6,88 (1H), 7,18 (2H), 7,29 (1H), 7,65 (1H), 7,69 (1H), 7,73 (1H) ppm.

Ejemplo 252

N-ciclopropil-4-{6-[(2,3-difluorofenil)sulfanil]-8-[(3,3,3-trifluoropropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



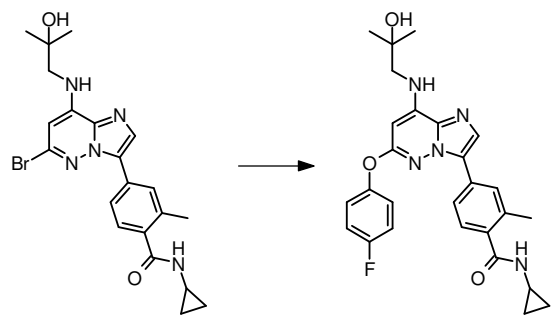
Se trataron 50 mg (104 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 2,3-difluorobencenotiol para dar, luego del tratamiento posterior y la purificación, 1,6 mg (3%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,63 (2H), 0,90 (2H), 2,39 (3H), 2,54 (2H), 2,93 (1H), 3,62 (2H), 5,85 (1H), 5,97 (1H), 6,10 (1H), 7,16 (1H), 7,20 (1H), 7,33 (1H), 7,41 (1H), 7,56 (1H), 7,57 (1H), 7,69 (1H) ppm.

Ejemplo 253

N-ciclopropil-4-{6-(4-fluorofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 50 mg (109 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-

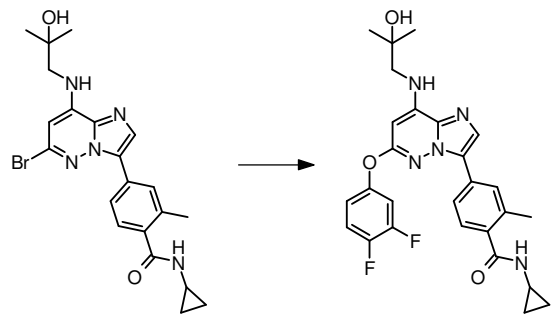
metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando 4-fluorofenol para dar, luego del tratamiento posterior y la purificación, 27,5 mg (49%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,47 (2H), 0,63 (2H), 1,16 (6H), 2,13 (3H), 2,77 (1H), 3,27 (2H), 4,73 (1H), 6,16 (1H), 6,95 (1H), 7,16 (1H), 7,24-7,34 (4H), 7,64 (1H), 7,73 (1H), 7,91 (1H), 8,19 (1H) ppm.

Ejemplo 254

N-ciclopropil-4-{6-(3,4-difluorofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 50 mg (109 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando 3,4-difluorofenol para dar, luego del tratamiento posterior y la purificación, 18,1 mg (31%) del compuesto del título.

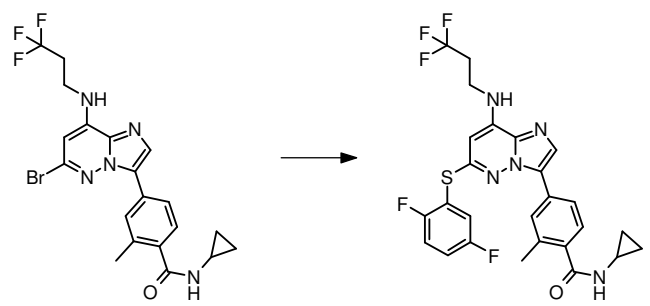
1H-RMN (DMSO-d6): δ= 0,47 (2H), 0,64 (2H), 1,16 (6H), 2,14 (3H), 2,77 (1H), 3,27 (2H), 4,73 (1H), 6,17 (1H), 7,00 (1H), 7,13

(1H), 7,18 (1H), 7,51 (1H), 7,56 (1H), 7,65 (1H), 7,75 (1H), 7,91 (1H), 8,21 (1H) ppm.

Ejemplo 255

N-ciclopropil-4-{6-[(2,5-difluorofenil)sulfanil]-8-[(3,3,3-trifluoropropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

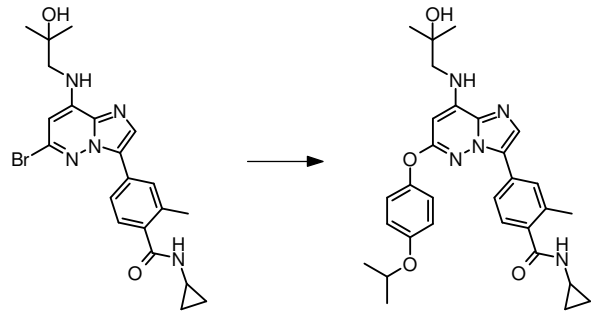


Se trataron 50 mg (104 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 2,5-difluorobencenotiol para dar, luego del tratamiento posterior y la purificación, 13,3 mg (22%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,62 (2H), 0,90 (2H), 2,39 (3H), 2,53 (2H), 2,92 (1H), 3,62 (2H), 5,87 (1H), 5,97 (1H), 6,06 (1H), 7,14-7,23 (3H), 7,39 (1H), 7,57 (1H), 7,59 (1H), 7,70 (1H) ppm.

Ejemplo 256

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(4-isopropoxifenoxi)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



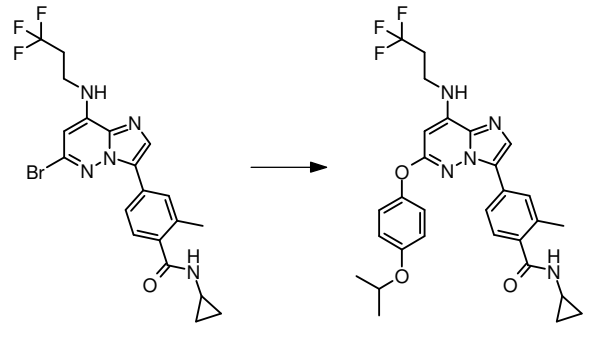
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando 4-isopropoxifenol para dar, luego del tratamiento posterior y la purificación, 13,7 mg (15%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,60 (2H), 0,87 (2H), 1,36 (6H), 1,44 (6H), 2,30 (3H), 2,89 (1H), 3,31 (2H), 4,52 (1H), 5,87 (1H), 5,93 (1H), 6,52 (1H), 6,91 (2H), 7,11 (2H), 7,19 (1H), 7,58 (1H), 7,64 (1H), 7,74 (1H) ppm.

Ejemplo 257

N-ciclopropil-4-{6-(4-isopropoxifenoxi)-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-

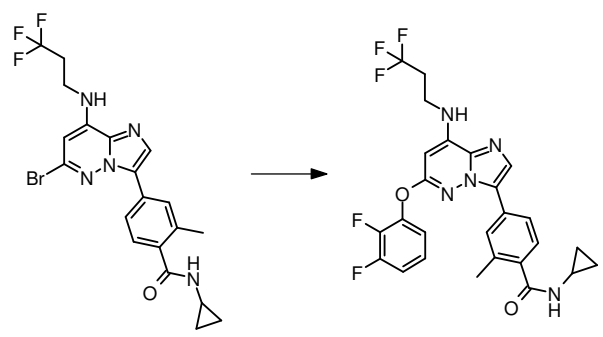
trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 4-isopropoxifenol para dar, luego del tratamiento posterior y la purificación, 9,3 mg (10%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,59 (2H), 0,88 (2H), 1,37 (6H), 2,32 (3H), 2,56 (2H), 2,88 (1H), 3,66 (2H), 4,53 (1H), 5,84 (1H), 5,88 (1H), 5,91 (1H), 6,93 (2H), 7,14 (2H), 7,22 (1H), 7,62 (1H), 7,73 (1H), 7,79 (1H) ppm.

Ejemplo 258

N-ciclopropil-4-{6-(2,3-difluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

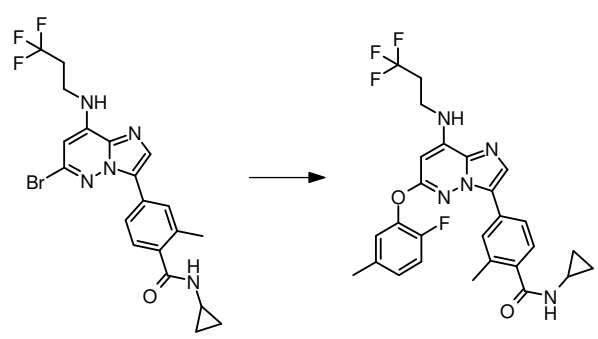


Se trataron 100 mg (207 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 2,3-difluorofenol para dar, luego del tratamiento posterior y la purificación, 22 mg (19%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,60 (2H), 0,88 (2H), 2,29 (3H), 2,58 (2H), 2,89 (1H), 3,70 (2H), 5,86 (1H), 5,96 (1H), 6,07 (1H), 7,06-7,17 (3H), 7,22 (1H), 7,53 (1H), 7,66 (1H), 7,71 (1H) ppm.

Ejemplo 259

N-ciclopropil-4-{6-(2-fluoro-5-metilfenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



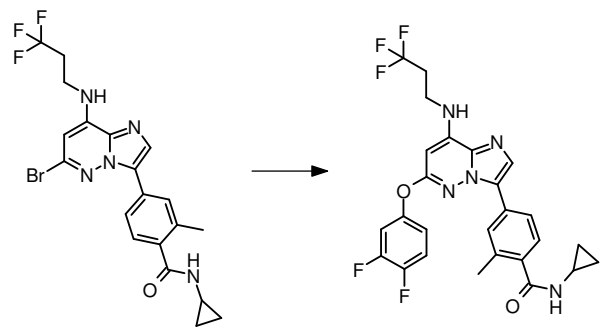
Se trataron 100 mg (207 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 2-fluoro-5-metilfenol para dar, luego del tratamiento posterior y la purificación, 23 mg (20%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,60 (2H), 0,88 (2H), 2,27 (3H), 2,35 (3H), 2,58 (2H), 2,89 (1H), 3,68 (2H), 5,84 (1H), 5,95 (1H), 6,11 (1H), 7,00-7,16 (3H), 7,21 (1H), 7,55 (1H), 7,71 (2H) ppm.

Ejemplo 260

N-ciclopropil-4-{6-(3,4-difluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



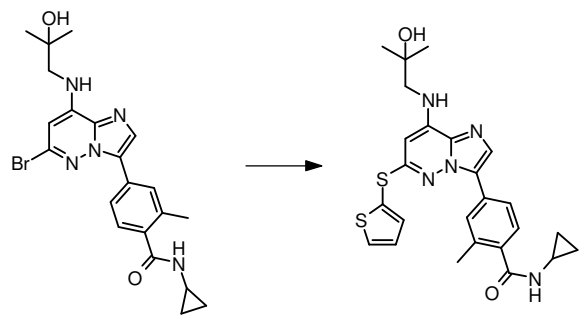
Se trataron 100 mg (207 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 3,4-difluorofenol para dar, luego del tratamiento posterior y la purificación, 36 mg (31%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,61 (2H), 0,88 (2H), 2,34 (3H), 2,57 (2H), 2,90 (1H), 3,68 (2H), 5,86 (1H), 5,87 (1H), 6,04 (1H), 6,99 (1H), 7,11-7,29 (3H), 7,59 (1H), 7,71 (1H), 7,72 (1H) ppm.

Ejemplo 261

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(2-tienilsulfanil)

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



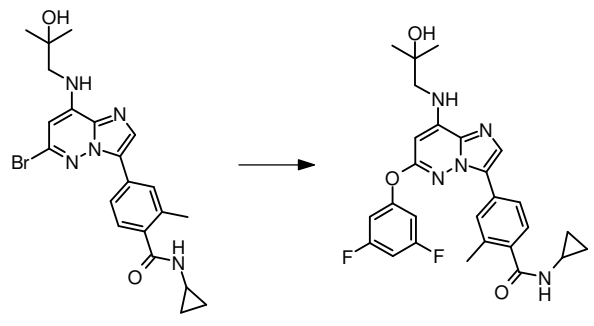
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando tiofen-2-tiol para dar, luego del tratamiento posterior y la purificación, 34 mg (41%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,65 (2H), 1,12 (6H), 2,26 (3H), 2,80 (1H), 1,64 (2H), 4,70 (1H), 6,21 (1H), 7,01 (1H), 7,17 (1H), 7,23 (1H), 7,47 (1H), 7,71 (1H), 7,76 (1H), 7,94 (2H), 8,23 (1H) ppm.

Ejemplo 262

N-ciclopropil-4-{6-(3,5-difluorofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



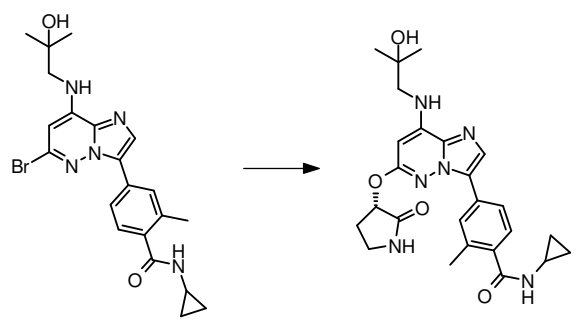
Se trataron 200 mg (436 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando 3,5-difluorofenol para dar, luego del tratamiento posterior y la purificación, 34,6 mg (15%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,47 (2H), 0,63 (2H), 1,15 (6H), 2,17 (3H),

2,77 (1H), 3,27 (2H), 4,74 (1H), 6,19 (1H), 7,08 (1H), 7,12-7,22 (4H), 7,68 (1H), 7,79 (1H), 7,93 (1H), 8,23 (1H) ppm.

Ejemplo 263

N-ciclopropil-4-(8-[(2-hidroxi-2-metilpropil)amino]-6-{[(3S)-2-oxopirrolidin-3-il]oxi}imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida



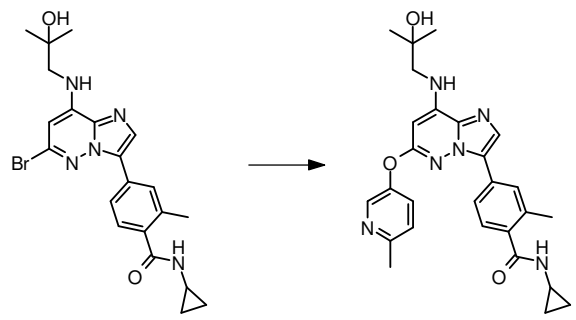
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando (3S)-3-hidroxipirrolidin-2-ona para dar, luego del tratamiento posterior y la purificación, 3,2 mg (4%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,64 (2H), 0,89 (2H), 1,40 (6H), 2,20 (1H), 2,49 (3H), 2,80 (1H), 2,92 (1H), 3,27 (2H), 3,37-3,51 (2H), 4,04 (1H), 5,33 (1H), 5,82 (1H), 6,09 (1H), 6,18 (1H), 6,34 (1H), 7,38 (1H), 7,57 (1H), 7,74 (1H), 7,80 (1H) ppm.

Ejemplo 264

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(6-metilpiridin-3-

il)oxi]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



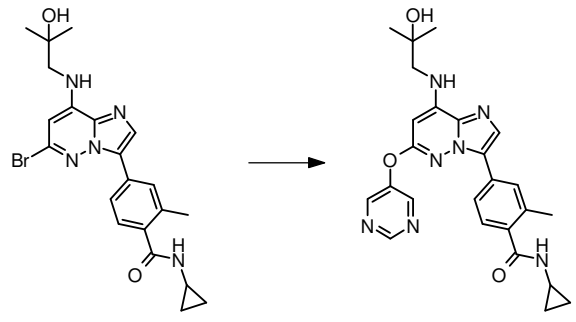
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando 6-metilpiridin-3-ol para dar, luego del tratamiento posterior y la purificación, 24,5 mg (30%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,66 (2H), 1,19 (6H), 2,14 (3H), 2,51 (3H), 2,80 (1H), 3,32 (2H), 4,76 (1H), 6,23 (1H), 7,02 (1H), 7,19 (1H), 7,37 (1H), 7,64 (1H), 7,68 (1H), 7,73 (1H), 7,94 (1H), 8,22 (1H), 8,43 (1H) ppm.

Ejemplo 265

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(pirimidin-5-iloxi)

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

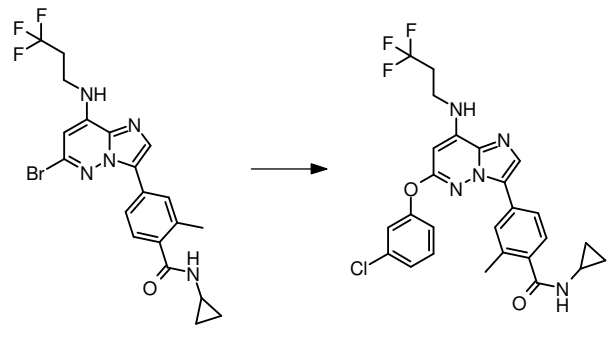


Se trataron 200 mg (436 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando pirimidin-5-ol para dar, luego del tratamiento posterior y la purificación, 34,6 mg (15%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,64 (2H), 0,89 (2H), 1,48 (6H), 2,30 (3H), 2,92 (1H), 3,35 (2H), 4,81 (1H), 5,87 (1H), 6,41 (1H), 6,62 (1H), 7,23 (1H), 7,45 (1H), 7,51 (1H), 7,58 (1H), 8,52 (2H), 9,05 (1H) ppm.

Ejemplo 266

4-{6-(3-clorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida

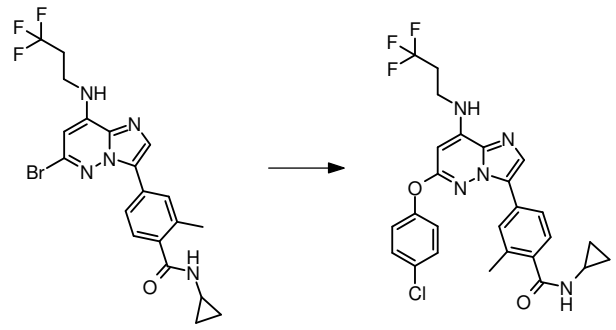


Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 3-clorofenol para dar, luego del tratamiento posterior y la purificación, 13,9 mg (17%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,61 (2H), 0,88 (2H), 2,34 (3H), 2,58 (2H), 2,90 (1H), 3,68 (2H), 5,82 (1H), 5,89 (1H), 5,97 (1H), 7,15 (1H), 7,25 (1H), 7,27 (1H), 7,31 (1H), 7,36 (1H), 7,63 (1H), 7,72 (1H), 7,74 (1H) ppm.

Ejemplo 267

4-{6-(4-clorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



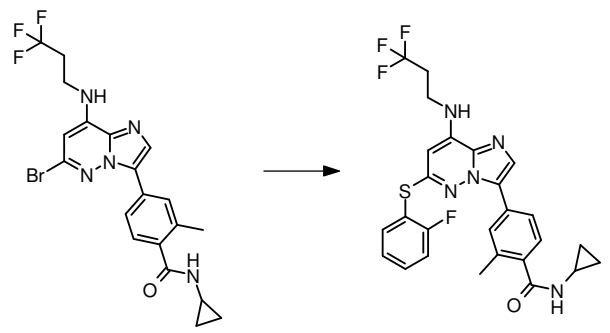
Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 4-clorofenol para dar, luego del tratamiento posterior y la purificación, 12,6 mg (12,6%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,61 (2H), 0,88 (2H), 2,33 (3H), 2,57 (2H), 2,90 (1H), 3,68 (2H), 5,83 (1H), 5,89 (1H), 5,96 (1H), 7,19 (2H), 7,25 (1H), 7,40 (2H), 7,58 (1H), 7,72 (1H), 7,73 (1H) ppm.

Ejemplo 268

N-ciclopropil-4-{6-[(2-fluorofenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

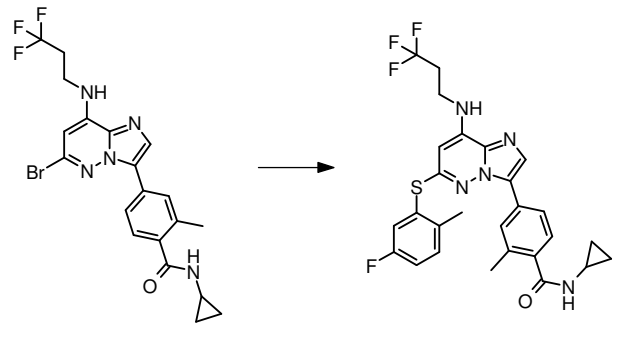


Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 2-fluorobencenotiol para dar, luego del tratamiento posterior y la purificación, 31,8 mg (39%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,62 (2H), 0,90 (2H), 2,37 (3H), 2,51 (2H), 2,92 (1H), 3,60 (2H), 5,83 (1H), 5,89 (1H), 5,94 (1H), 7,16 (1H), 7,20 (1H), 7,25 (1H), 7,51 (1H), 7,56 (1H), 7,59 (1H), 7,66 (1H), 7,70 (1H) ppm.

Ejemplo 269

N-ciclopropil-4-{6-[(5-fluoro-2-metilfenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

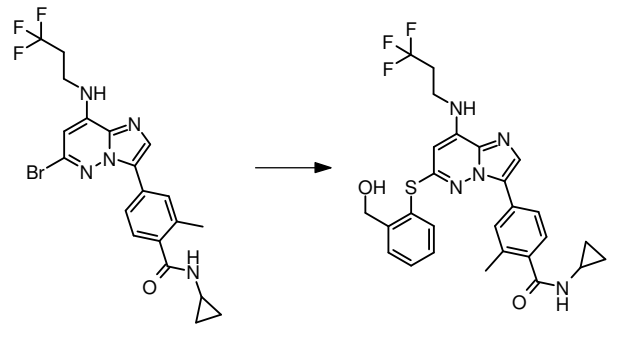


Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 5-fluoro-2-metilbencenotiol para dar, luego del tratamiento posterior y la purificación, 6,1 mg (7%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,63 (2H), 0,90 (2H), 2,39 (3H), 2,40 (3H), 2,50 (2H), 2,92 (1H), 3,59 (2H), 5,86 (1H), 5,89 (1H), 5,93 (1H), 7,10 (1H), 7,19 (1H), 7,31 (1H), 7,38 (1H), 7,57 (1H), 7,60 (1H), 7,71 (1H) ppm.

Ejemplo 270

N-ciclopropil-4-(6-{[2-(hidroximetil)fenil]sulfanil}-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida



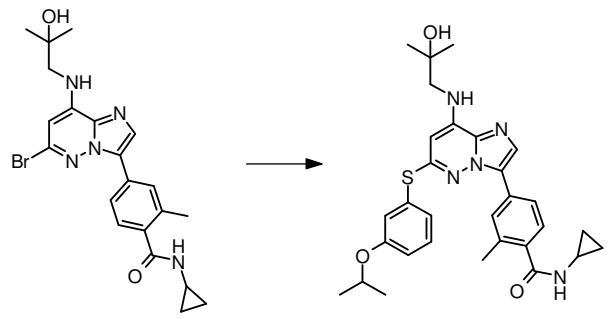
Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando (2-sulfanilfenil)metanol para dar, luego del tratamiento posterior y la purificación, 12,3 mg (15%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,63 (2H), 0,90 (2H), 2,34 (3H), 2,51 (2H), 2,92 (1H), 3,61 (2H), 4,83 (2H), 5,86 (1H), 5,89 (1H), 5,94 (1H), 7,14 (1H), 7,41 (1H), 7,42 (1H), 7,50 (1H), 7,57 (1H), 7,65 (1H), 7,68 (1H), 7,70 (1H) ppm.

Ejemplo 271

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(3-metoxifenil)

sulfanil]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



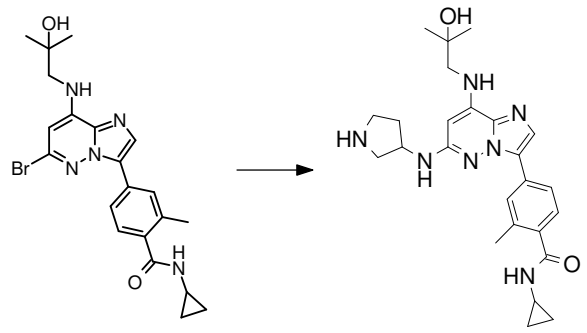
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando 3-isopropoxibencenotiol para dar, luego del tratamiento posterior y la purificación, 18,5 mg (20%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,65 (2H), 1,11 (6H), 1,18 (6H), 2,21 (3H), 2,78 (1H), 3,20 (2H), 4,58 (1H), 4,71 (1H), 6,21 (1H), 6,95-7,05 (2H), 7,08-7,16 (3H), 7,34 (1H), 7,71 (1H), 7,73 (1H), 7,94 (1H), 8,23 (1H) ppm.

Ejemplo 272

(RS)-N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(pirrolidin-3-

ilamino)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



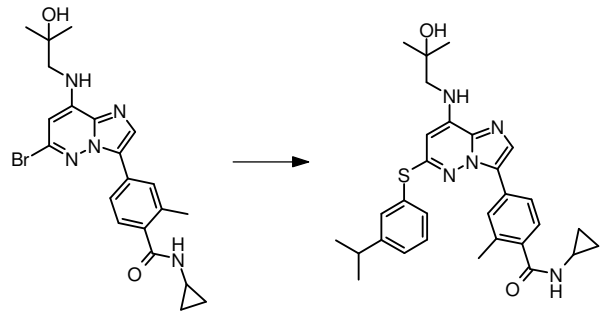
Se trataron 50 mg (109 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando (RS)-pirrolidin-3-amina para dar, luego del tratamiento posterior y la purificación, 18 mg (36%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,65 (2H), 1,16 (6H), 1,86 (1H), 2,15 (1H), 2,36 (3H), 2,80 (1H), 3,21 (2H), 3,28 (1H), 3,45 (1H), 3,53-3,65 (2H), 3,71 (1H), 4,27 (1H), 5,68 (1H), 6,36 (1H), 7,31 (1H), 7,78 (1H), 8,07 (1H), 8,10 (1H), 8,26 (1H), 8,29 (1H) ppm.

Ejemplo 273

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(3-isopropilfenil)

sulfanil]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



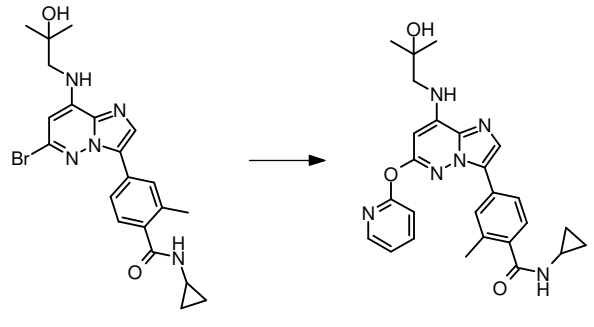
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando 3-isopropilbencenotiol para dar, luego del tratamiento posterior y la purificación, 14,0 mg (15%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,64 (2H), 1,10 (6H), 1,14 (6H), 2,18 (3H), 2,78 (1H), 2,88 (1H), 3,18 (2H), 4,71 (1H), 6,18 (1H), 6,98 (1H), 7,08 (1H), 7,34-7,43 (3H), 7,45 (1H), 7,64 (1H), 7,71 (1H), 7,94 (1H), 8,22 (1H) ppm.

Ejemplo 274

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(piridin-2-iloxi)

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



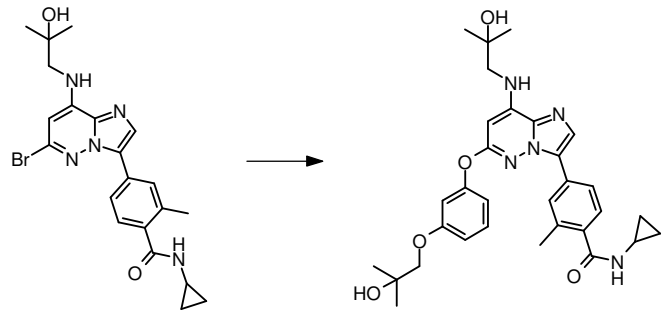
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando piridin-2-ol para dar, luego del tratamiento posterior y la purificación, 11,0 mg (14%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,64 (2H), 1,14 (6H), 2,33 (3H), 2,79 (1H), 3,27 (2H), 4,73 (1H), 6,33 (1H), 6,47 (1H), 6,48 (1H), 7,21 (1H), 7,33 (1H), 7,54 (1H), 7,79 (1H), 7,82 (1H), 7,91 (1H), 8,03 (1H), 8,24 (1H) ppm.

Ejemplo 275

N-ciclopropil-4-{6-[3-(2-hidroxi-2-metilpropoxi)fenoxi]-8-[(2-hidroxi-2-

metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 50 mg (109 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-

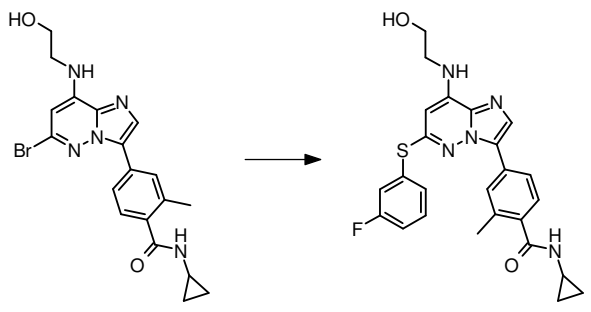
metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando 3-{2-metil-2-[(triisopropilsilil)oxi]propoxi}fenol para dar, luego del tratamiento posterior y la purificación, 2,3 mg (4%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,46 (2H), 0,63 (2H), 1,14 (6H), 1,15 (6H), 2,14 (3H), 2,76 (1H), 3,27 (2H), 3,66 (2H), 4,59 (1H), 4,74 (1H), 6,14 (1H), 6,76-6,86 (3H), 6,97 (1H), 7,16 (1H), 7,31 (1H), 7,70 (1H), 7,79 (1H), 7,92 (1H), 8,21 (1H) ppm.

Ejemplo 276

N-ciclopropil-4-{6-[(3-fluorofenil)sulfanil]-8-[(2-hidroxietil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



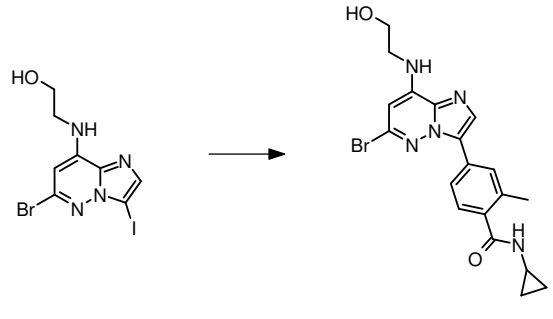
Se trataron 75 mg (174 µmol) de 4-{6-bromo-8-[(2-hidroxietil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 276a, de manera análoga al Ejemplo 51 usando 3-fluorobencenotiol para dar, luego del tratamiento posterior y la purificación, 14,5 mg (17%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,65 (2H), 2,20 (3H), 2,78 (1H), 3,33 (2H), 3,57 (2H), 4,82 (1H), 6,19 (1H), 7,12 (1H), 7,33

(1H), 7,38-7,54 (4H), 7,66 (1H), 7,71 (1H), 7,94 (1H), 8,23 (1H) ppm.

Ejemplo Intermediario 276a

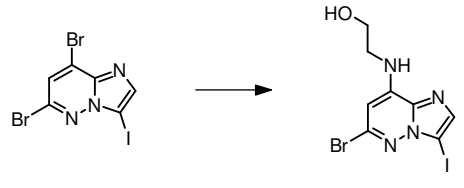
4-{6-bromo-8-[(2-hidroxietil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



Se trataron 1,98 g (5,17 mmol) de 2-[(6-bromo-3-yodoimidazo[1,2-b]piridazin-8-il)amino]etanol, que se preparó de acuerdo con el Ejemplo Intermediario 276b, de manera análoga al Ejemplo Intermediario 1a usando N-ciclopropil-2-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzamida para dar, luego del tratamiento posterior y la purificación, 1,27 g (51%) del compuesto del título.

Ejemplo Intermediario 276b

2-[(6-bromo-3-yodoimidazo[1,2-b]piridazin-8-il)amino]etanol

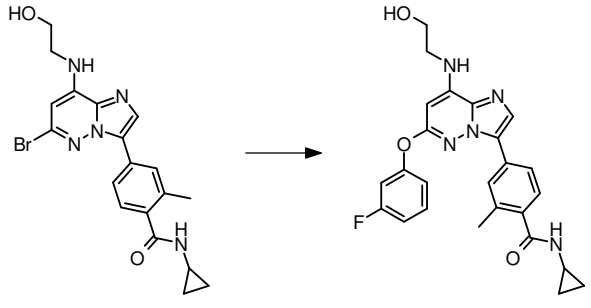


Se trataron 2,50 g (6,21 mmol) de 6,8-dibromo-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 96c, de manera análoga al Ejemplo Intermediario 1b usando 2-aminoetanol para dar, luego del tratamiento posterior y

la purificación, 1,99 g (81%) del compuesto del título.

Ejemplo 277

N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(2-hidroxietil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 75 mg (174 µmol) de 4-{6-bromo-8-[(2-hidroxietil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamid, que se preparó de acuerdo con el Ejemplo Intermediario 276a, de manera análoga al Ejemplo 51 usando 3-fluorofenol para dar, luego del tratamiento posterior y la purificación, 17,2 mg (21%) del compuesto del título.

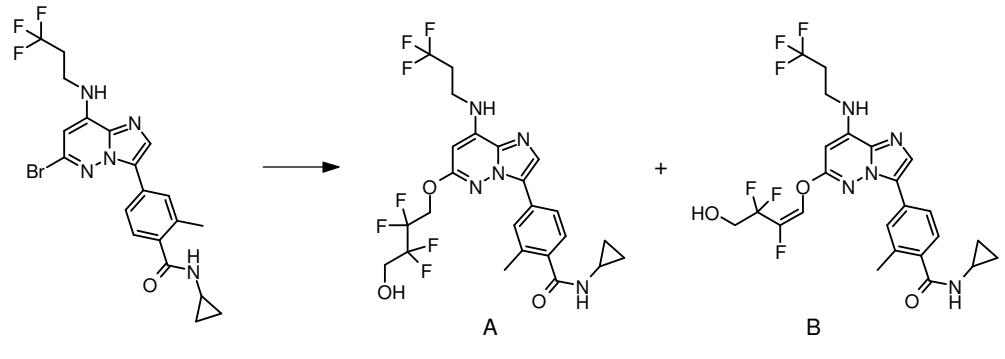
1H-RMN (DMSO-d6): δ= 0,46 (2H), 0,63 (2H), 2,14 (3H), 2,76 (1H), 3,38 (2H), 3,62 (2H), 4,84 (1H), 6,08 (1H), 7,07-7,20 (3H), 7,24 (1H), 7,41 (1H), 7,48 (1H), 7,66 (1H), 7,76 (1H), 7,92 (1H), 8,21 (1H) ppm.

Ejemplo 278

N-ciclopropil-2-metil-4-{6-(2,2,3,3-tetrafluoro-4-hidroxibutoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida (A)

y

N-ciclopropil-2-metil-4-(6-{[(1E)-2,3,3-trifluoro-4-hidroxibut-1-en-1-il]oxi}-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il)benzamida



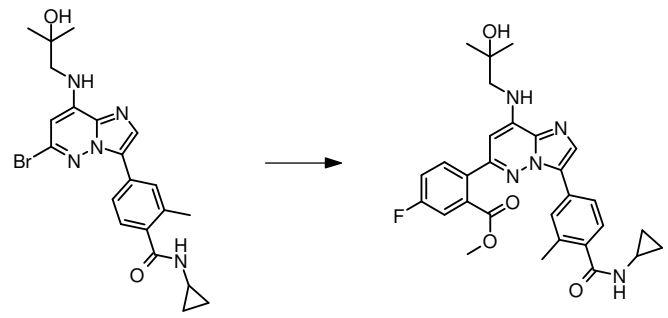
Se trataron 100 mg (207 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 2,2,3,3-tetrafluorobutan-1,4-diol para dar, luego del tratamiento posterior y la purificación, 5,2 mg (4%) del compuesto del título A y 5,3 mg (4%) del compuesto del título B.

1H-RMN (DMSO-d6) de A: δ= 0,50 (2H), 0,65 (2H), 2,35 (3H), 2,65 (2H), 2,80 (1H), 3,56 (2H), 3,91 (2H), 4,91 (2H), 5,97 (1H), 6,00 (1H), 7,33 (1H), 7,60 (1H), 7,90 (1H), 7,92 (1H), 7,97 (1H), 8,27 (1H) ppm.

1H-RMN (DMSO-d6) de B: δ= 0,50 (2H), 0,66 (2H), 2,35 (3H), 2,66 (2H), 2,80 (1H), 3,59 (2H), 3,86 (2H), 5,92 (1H), 6,14 (1H), 7,33 (1H), 7,70 (1H), 7,84 (1H), 7,89 (1H), 7,97 (1H), 8,02 (1H), 8,28 (1H) ppm.

Ejemplo 279

metiléster de ácido 2-{3-[4-(ciclopropilcarbamoil)-3-metilfenil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-6-il}-5-fluoro-benzoico



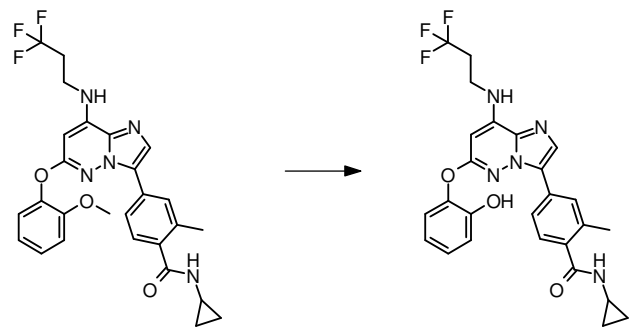
Se trataron 600 mg (1,31 mmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 1 usando ácido [4-fluoro-2-(metoxicarbonil)fenil]borónico. Después del tratamiento posterior, se agregaron 19 mL de tetrahidrofurano al producto crudo y la suspensión se enfrió a 3°C. Se agregaron 21,8 mL de una solución recién preparada de diazometano en éter dietílico en porciones durante 2 horas. El solvente se eliminó y el residuo se purificó mediante cromatografía para dar 52,7 mg (9%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,65 (2H), 1,17 (6H), 2,36 (3H), 2,80 (1H), 3,33 (2H), 3,47 (3H), 4,75 (1H), 6,52 (1H), 6,96 (1H), 7,30 (1H), 7,51-7,59 (2H), 7,78 (1H), 7,92 (1H), 7,97 (1H), 8,04 (1H), 8,23 (1H) ppm.

Ejemplo 280

N-ciclopropil-4-{6-(2-hidroxifenoxi)-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

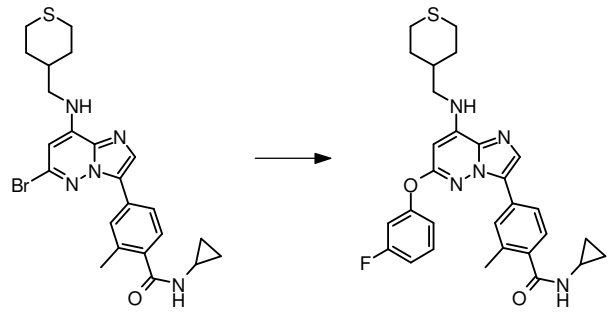


Una mezcla de 28,0 mg (53 µmol) de N-ciclopropil-4-{6-(2-metoxifenoxi)-8- [(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida, que se preparó de acuerdo con el ejemplo 223, 44,8 mg de metantiolato de sodio y 350 µL de N,N-dimetilformamida se calentó bajo irradiación de microondas durante 30 minutos a 120°C. La mezcla se volcó sobre agua, el pH se ajustó entre 7 y 8 mediante la adición de cloruro de amonio y se extrajo con una mezcla de diclorometano y metanol. Las fases orgánicas combinadas se secaron sobre sulfato de sodio. Luego de la filtración y la eliminación del solvente el residuo se purificó mediante cromatografía para dar 11,5 mg (40%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,47 (2H), 0,63 (2H), 2,09 (3H), 2,68 (2H), 2,76 (1H), 3,59 (2H), 6,08 (1H), 6,83 (1H), 6,97 (1H), 7,05-7,17 (3H), 7,55 (1H), 7,62 (1H), 7,75 (1H), 7,90 (1H), 8,18 (1H), 9,53 (1H) ppm.

Ejemplo 281

N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

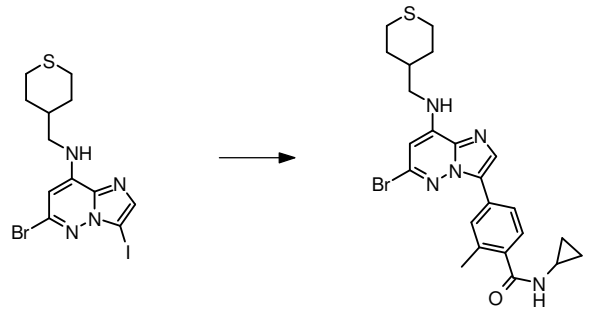


Se trataron 75 mg (150 µmol) de 4-{6-bromo-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 281a, de manera análoga al Ejemplo 51 usando 3-fluorofenol para dar, luego del tratamiento posterior y la purificación, 33,7 mg (40%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,66 (2H), 1,32 (2H), 1,78 (1H), 2,04 (2H), 2,17 (3H), 2,59 (4H), 2,79 (1H), 3,22 (2H), 6,09 (1H), 7,15 (2H), 7,18 (1H), 7,27 (1H), 7,50 (1H), 7,68 (1H), 7,72 (1H), 7,78 (1H), 7,93 (1H), 8,22 (1H) ppm.

Ejemplo Intermediario 281a

4-{6-bromo-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida

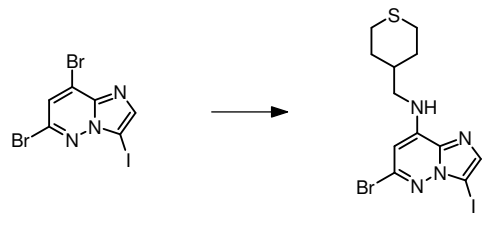


Se trataron 2,22 g (4,90 mmol) de 6-bromo-3-yodo-N-(tetrahidro-2H-tiopiran-4-ilmetil)imidazo[1,2-b]piridazin-8-amina, que se

preparó de acuerdo con el Ejemplo Intermediario 281b, de manera análoga al Ejemplo Intermediario 1a usando N-ciclopropil-2-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzamida para dar, luego del tratamiento posterior y la purificación, 1,49 g (55%) del compuesto del título.

Ejemplo Intermediario 281b

6-bromo-3-yodo-N-(tetrahidro-2H-tiopiran-4-ilmetil)imidazo[1,2-b]piridazin-8-amina

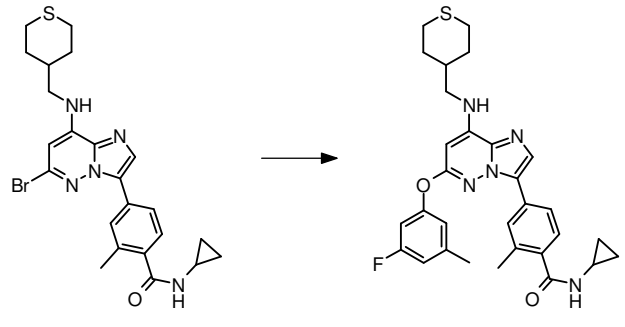


Se trataron 2,31 g (5,75 mmol) de 6,8-dibromo-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 96c, de manera análoga al Ejemplo Intermediario 1b usando 1-(tetrahidro-2H-tiopiran-4-il)metanamina para dar, luego del tratamiento posterior y la purificación, 2,23 g (81%) del compuesto del título.

Ejemplo 282

N-ciclopropil-4-{6-(3-fluoro-5-metilfenoxi)-8-[(tetrahidro-2H-tiopiran-4-

ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



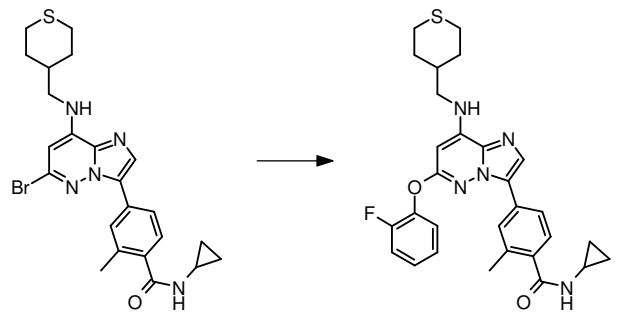
Se trataron 75 mg (150 µmol) de 4-{6-bromo-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 281a, de manera análoga al Ejemplo 51 usando 3-fluoro-5-metilfenol para dar, luego del tratamiento posterior y la purificación, 14,1 mg (16%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,66 (2H), 1,32 (2H), 1,77 (1H), 2,04 (2H), 2,18 (3H), 2,34 (3H), 2,59 (4H), 2,79 (1H), 3,22 (2H), 6,07 (1H), 6,96 (1H), 6,97 (1H), 7,04 (1H), 7,20 (1H), 7,68-7,74 (2H), 7,80 (1H), 7,93 (1H), 8,23 (1H) ppm.

Ejemplo 283

N-ciclopropil-4-{6-(2-fluorofenoxi)-8-[(tetrahidro-2H-tiopiran-4-ilmetil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 75 mg (150 µmol) de 4-{6-bromo-8-[(tetrahidro-2H-

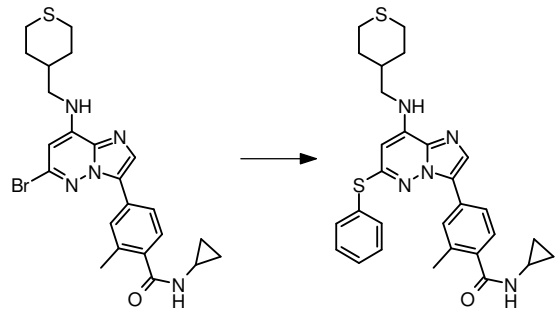
tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 281a, de manera análoga al Ejemplo 51 usando 2-fluorofenol para dar, luego del tratamiento posterior y la purificación, 26,6 mg (32%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,66 (2H), 1,33 (2H), 1,80 (1H), 2,06 (2H), 2,11 (3H), 2,60 (4H), 2,78 (1H), 3,23 (2H), 6,16 (1H), 7,13 (1H), 7,30 (1H), 7,37 (1H), 7,43 (1H), 7,47 (1H), 7,61 (1H), 7,69 (1H), 7,74 (1H), 7,93 (1H), 8,21 (1H) ppm.

Ejemplo 284

N-ciclopropil-2-metil-4-{6-(fenilsulfanil)-8-[(tetrahidro-2H-tiopiran-4-

ilmetil)amino]imidazo[1,2-b]piridazin-3-il}benzamida



Se trataron 75 mg (150 µmol) de 4-{6-bromo-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 281a, de manera análoga al Ejemplo 51 usando bencenotiol para dar, luego del tratamiento posterior y la purificación, 45,3 mg (54%) del compuesto del título.

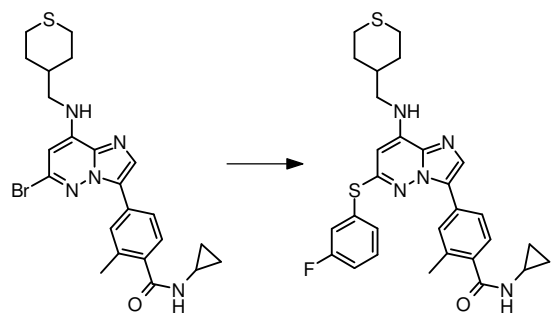
1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,65 (2H), 1,22 (2H), 1,60 (1H), 1,91 (2H), 2,21 (3H), 2,52 (4H), 2,78 (1H), 3,08 (2H), 5,99

(1H), 7,10 (1H), 7,44-7,53 (3H), 7,59-7,73 (5H), 7,91 (1H), 8,24 (1H) ppm.

Ejemplo 285

N-ciclopropil-4-{6-[(3-fluorofenil)sulfanil]-8-[(tetrahidro-2H-tiopiran-4-

ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



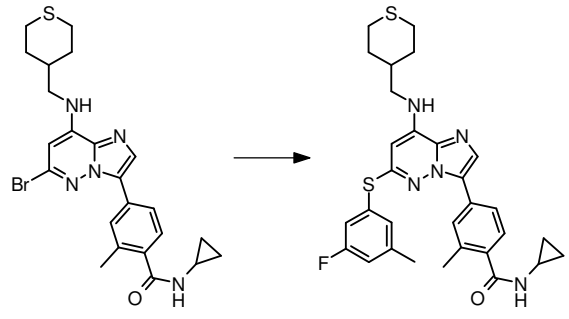
Se trataron 75 mg (150 µmol) de 4-{6-bromo-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 281a, de manera análoga al Ejemplo 51 usando 3-fluorobencenotiol para dar, luego del tratamiento posterior y la purificación, 9,8 mg (11%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,65 (2H), 1,23 (2H), 1,64 (1H), 1,93 (2H), 2,21 (3H), 2,53 (4H), 2,79 (1H), 3,11 (2H), 6,10 (1H), 7,13 (1H), 7,34 (1H), 7,44 (1H), 7,48-7,54 (2H), 7,68 (1H), 7,72 (1H), 7,74 (1H), 7,93 (1H), 8,25 (1H) ppm.

Ejemplo 286

N-ciclopropil-4-{6-[(3-fluoro-5-metilfenil)sulfanil]-8-[(tetrahidro-2H-

tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



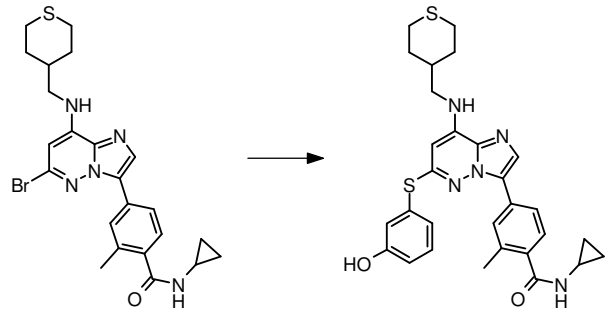
Se trataron 75 mg (150 µmol) de 4-{6-bromo-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 281a, de manera análoga al Ejemplo 51 usando 3-fluoro-5-metilbencenotiol para dar, luego del tratamiento posterior y la purificación, 9,1 mg (10%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,65 (2H), 1,23 (2H), 1,62 (1H), 1,92 (2H), 2,21 (3H), 2,31 (3H), 2,52 (4H), 2,79 (1H), 3,11 (2H), 6,07 (1H), 7,14 (1H), 7,17 (1H), 7,26-7,32 (2H), 7,68-7,76 (3H), 7,93 (1H), 8,25 (1H) ppm.

Ejemplo 287

N-ciclopropil-4-{6-[(3-hidroxifenil)sulfanil]-8-[(tetrahidro-2H-tiopiran-4-

ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



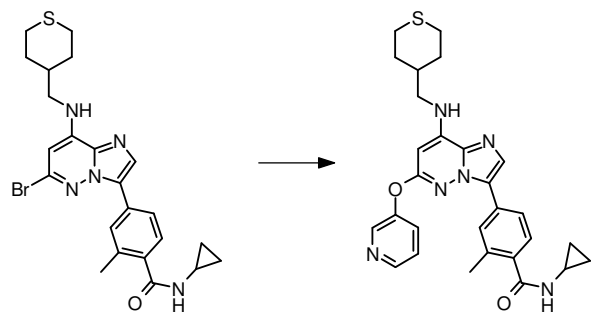
Se trataron 100 mg (200 µmol) de 4-{6-bromo-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 281a, de manera análoga al Ejemplo 51 usando 3-metoxibencenotiol para dar, luego del tratamiento posterior y la purificación, 14 mg (12%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,65 (2H), 1,22 (2H), 1,58 (1H), 1,90 (2H), 2,24 (3H), 2,52 (4H), 2,79 (1H), 3,07 (2H), 5,95 (1H), 6,86 (1H), 6,96 (1H), 7,01 (1H), 7,17 (1H), 7,26 (1H), 7,69 (1H), 7,73-7,80 (2H), 7,92 (1H), 8,24 (1H), 9,76 (1H) ppm.

Ejemplo 288

N-ciclopropil-2-metil-4-{6-(piridin-3-iloxi)-8-[(tetrahidro-2H-tiopiran-4-

ilmetil)amino]imidazo[1,2-b]piridazin-3-il}benzamida



Se trataron 75 mg (150 µmol) de 4-{6-bromo-8-[(tetrahidro-2H-

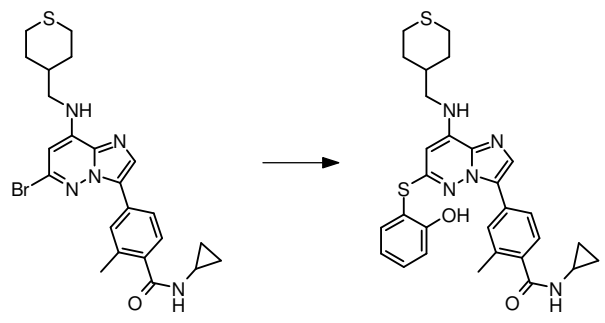
tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 281a, de manera análoga al Ejemplo 51 usando piridin-3-ol para dar, luego del tratamiento posterior y la purificación, 25,2 mg (31%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,46 (2H), 0,63 (2H), 1,30 (2H), 1,76 (1H), 2,02 (2H), 2,12 (3H), 2,57 (4H), 2,76 (1H), 3,20 (2H), 6,13 (1H), 7,13 (1H), 7,51 (1H), 7,60 (1H), 7,68 (1H), 7,76 (1H), 7,80 (1H), 7,90 (1H), 8,21 (1H), 8,48 (1H), 8,57 (1H) ppm.

Ejemplo 289

N-ciclopropil-4-{6-[(2-hidroxifenil)sulfanil]-8-[(tetrahidro-2H-tiopiran-4-

ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 75 mg (150 µmol) de 4-{6-bromo-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 281a, de manera análoga al Ejemplo 51 usando 2-metoxibencenotiol para dar, luego del tratamiento posterior y la purificación, 40,9 mg (48%) del compuesto del título.

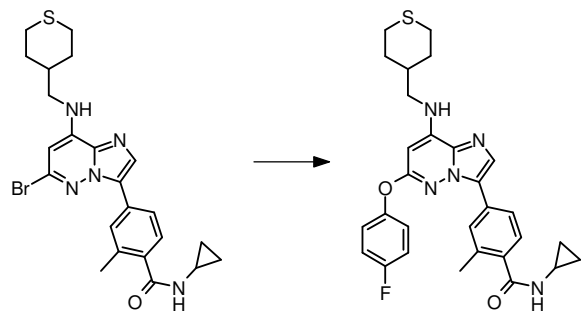
1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,65 (2H), 1,20 (2H), 1,57 (1H),

1,88 (2H), 2,23 (3H), 2,52 (4H), 2,79 (1H), 3,03 (2H), 5,86 (1H), 6,87 (1H), 6,98 (1H), 7,12 (1H), 7,34 (1H), 7,46 (1H), 7,60 (1H), 7,72 (1H), 7,74 (1H), 7,90 (1H), 8,23 (1H), 10,01 (1H) ppm.

Ejemplo 290

N-ciclopropil-4-{6-(4-fluorofenoxi)-8-[(tetrahidro-2H-tiopiran-4-ilmetil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



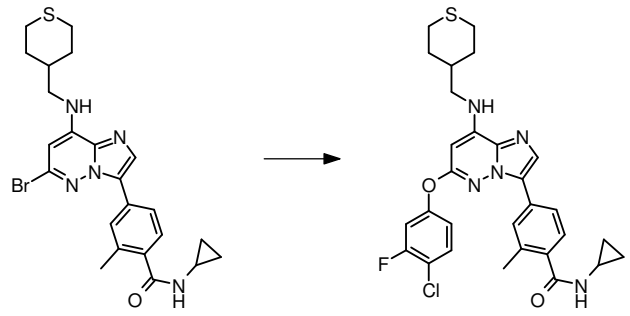
Se trataron 75 mg (150 µmol) de 4-{6-bromo-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 281a, de manera análoga al Ejemplo 51 usando 4-fluorofenol para dar, luego del tratamiento posterior y la purificación, 45,6 mg (54%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,46 (2H), 0,63 (2H), 1,29 (2H), 1,75 (1H), 2,02 (2H), 2,12 (3H), 2,56 (4H), 2,76 (1H), 3,19 (2H), 6,06 (1H), 7,15 (1H), 7,23-7,35 (4H), 7,63 (1H), 7,68 (1H), 7,72 (1H), 7,90 (1H), 8,21 (1H) ppm.

Ejemplo 291

4-{6-(4-cloro-3-fluorofenoxi)-8-[(tetrahidro-2H-tiopiran-4-

ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



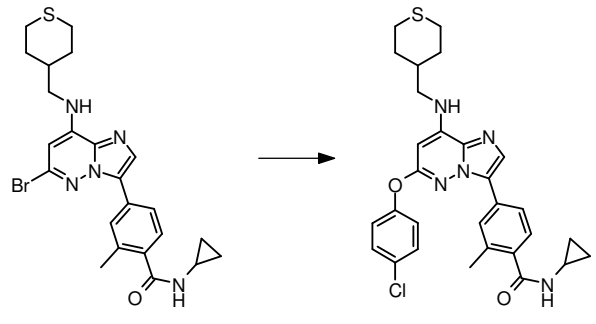
Se trataron 75 mg (150 µmol) de 4-{6-bromo-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 281a, de manera análoga al Ejemplo 51 usando 4-cloro-3-fluorofenol para dar, luego del tratamiento posterior y la purificación, 5,4 mg (6%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,64 (2H), 0,91 (2H), 1,54 (2H), 1,80 (1H), 2,20 (2H), 2,37 (3H), 2,65-2,79 (4H), 2,93 (1H), 3,26 (2H), 5,86 (1H), 5,87 (1H), 5,97 (1H), 7,04 (1H), 7,16 (1H), 7,30 (1H), 7,46 (1H), 7,62 (1H), 7,74 (2H) ppm.

Ejemplo 292

4-{6-(4-clorofenoxi)-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo

[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



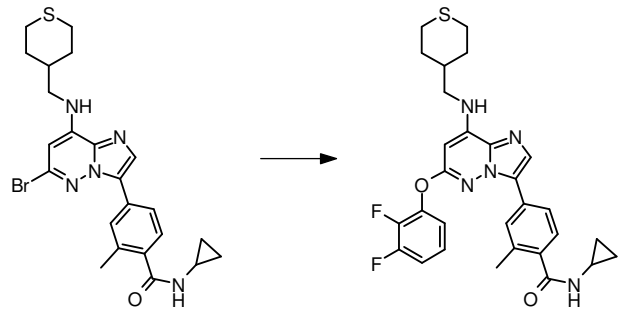
Se trataron 75 mg (150 µmol) de 4-{6-bromo-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 281a, de manera análoga al Ejemplo 51 usando 4-clorofenol para dar, luego del tratamiento posterior y la purificación, 30,7 mg (36%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,46 (2H), 0,63 (2H), 1,29 (2H), 1,75 (1H), 2,02 (2H), 2,12 (3H), 2,56 (4H), 2,77 (1H), 3,19 (2H), 6,07 (1H), 7,16 (1H), 7,31 (2H), 7,50 (2H), 7,62 (1H), 7,72 (2H), 7,90 (1H), 8,21 (1H) ppm.

Ejemplo 293

N-ciclopropil-4-{6-(2,3-difluorofenoxi)-8-[(tetrahidro-2H-tiopiran-4-

ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 75 mg (150 µmol) de 4-{6-bromo-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-

ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 281a de manera análoga al Ejemplo 51 usando 2,3-difluorofenol para dar, luego del tratamiento posterior y la purificación, 19,1 mg (22%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,60 (2H), 0,88 (2H), 1,52 (2H), 1,79 (1H), 2,19 (2H), 2,30 (3H), 2,61-2,79 (4H), 2,89 (1H), 3,25 (2H), 5,82 (1H), 5,92 (2H), 7,05-7,17 (3H), 7,22 (1H), 7,54 (1H), 7,68 (1H), 7,70 (1H) ppm.

Ejemplo 294

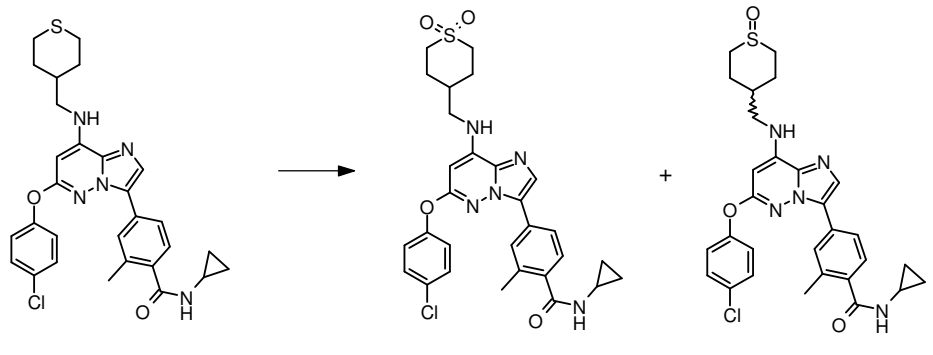
4-[6-(4-clorofenoxi)-8-{[(1,1-dioxidotetrahidro-2H-tiopiran-4-il)metil]

amino}imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida (A)

y

4-[6-(4-clorofenoxi)-8-({[(cis/trans)-1-oxidotetrahidro-2H-tiopiran-4-il]

metil}amino)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida (B)



A B

A una solución de 22,4 mg (41 µmol) de 4-{6-(4-clorofenoxi)-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el ejemplo 292 en 327 µL de triclorometano, se agregaron 13,7 mg de ácido 3-clorobencencarboperoxoico (77%) y la mezcla se agitó a 23°C durante 40 minutos. Se agregó solución saturada de carbonato ácido de sodio y los solventes se eliminaron. El residuo se purificó mediante cromatografía para dar 9,1 mg (38%) del compuesto del título A y 3,1 mg (13%) de una mezcla cis/trans de los compuestos del título B.

1H-RMN (DMSO-d6) de A: δ= 0,47 (2H), 0,63 (2H), 1,66 (2H), 1,98-2,15 (3H), 2,12 (3H), 2,77 (1H), 2,97-3,15 (4H), 3,25 (2H), 6,16 (1H), 7,17 (1H), 7,30 (2H), 7,50 (2H), 7,62 (1H), 7,72 (1H), 7,79 (1H), 7,91 (1H), 8,19 (1H) ppm.

1H-RMN (DMSO-d6) de B: δ= 0,46 (2H), 0,63 (2H), 1,65 (2H), 1,95-2,17 (3H), 2,12 (3H), 2,76 (1H), 2,96-3,16 (4H), 3,27 (2H), 6,17 (1H), 7,16 (1H), 7,30 (2H), 7,50 (2H), 7,62 (1H), 7,72 (1H), 7,82 (1H), 7,91 (1H), 8,22 (1H) ppm.

Ejemplo 295

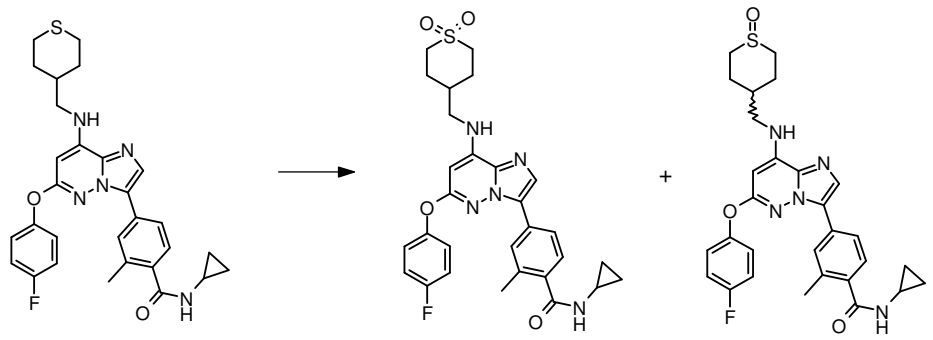
N-ciclopropil-4-[8-{[(1,1-dioxidotetrahidro-2H-tiopiran-4-il)metil]amino}-

6-(4-fluorofenoxi)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida (A)

y

N-ciclopropil-4-[6-(4-fluorofenoxi)-8-({[(cis/trans)-1-oxidotetrahidro-2H-

tiopiran-4-il]metil}amino)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida (B)



A B

Se trataron 37 mg (70 µmol) de N-ciclopropil-4-{6-(4-fluorofenoxi)-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida, que se preparó de acuerdo con el ejemplo 290, de manera análoga al Ejemplo 294 para dar, luego del tratamiento posterior y la purificación, 5,2 mg (13%) del compuesto del título A y 1,7 mg (4%) de una mezcla cis/trans de los compuestos del título B.

1H-RMN (DMSO-d6) de A: δ= 0,47 (2H), 0,63 (2H), 1,66 (2H), 1,95-2,17 (3H), 2,12 (3H), 2,76 (1H), 2,97-3,16 (4H), 3,22 (2H), 6,15 (1H), 7,15 (1H), 7,23-7,36 (4H), 7,63 (1H), 7,72 (1H), 7,76 (1H), 7,90 (1H), 8,19 (1H) ppm.

1H-RMN (DMSO-d6) de B: δ= 0,47 (2H), 0,63 (2H), 1,38 (1H), 1,64-2,26 (5H), 2,12 (3H), 2,57 (2H), 2,67-2,88 (2H), 3,19 (2H), 6,11 (1H), 7,15 (1H), 7,22-7,35 (4H), 7,63 (1H), 7,68-7,77 (2H), 7,90 (1H), 8,19 (1H) ppm.

Ejemplo 296

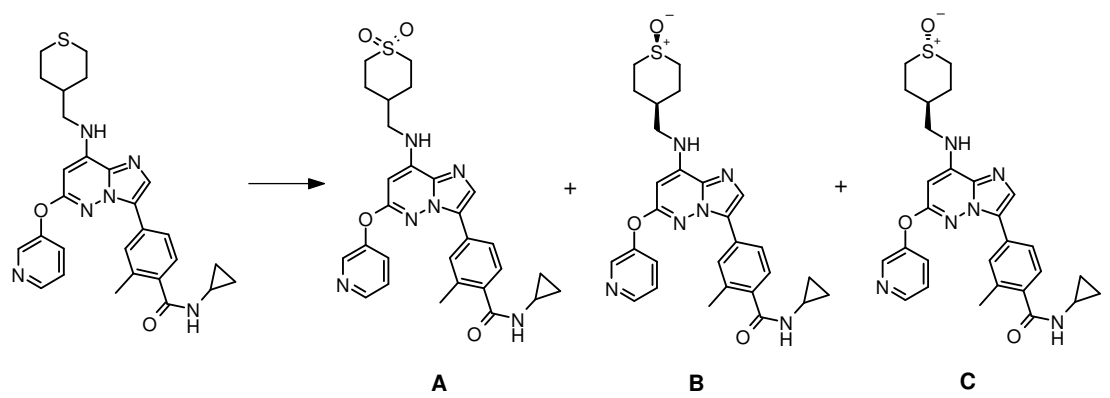
N-ciclopropil-4-[8-{[(1,1-dioxidotetrahidro-2H-tiopiran-4-il)metil]amino}-

6-(piridin-3-iloxi)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida (A)

y

N-ciclopropil-2-metil-4-[8-({[(cis)-1-oxidotetrahidro-2H-tiopiran-4-il]metil}amino)-6-(piridin-3-iloxi)imidazo[1,2-b]piridazin-3-il]benzamida (B) y

N-ciclopropil-2-metil-4-[8-({[(trans)-1-oxidotetrahidro-2H-tiopiran-4-il]metil}amino)-6-(piridin-3-iloxi)imidazo[1,2-b]piridazin-3-il]benzamida (C)



Se trataron 17,1 mg (33 µmol) de N-ciclopropil-2-metil-4-{6-(piridin-3-iloxi)-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}benzamida, que se preparó de acuerdo con el ejemplo 288, de manera análoga al Ejemplo 294 para dar, luego del tratamiento posterior y la purificación, 6,7 mg (37%) del compuesto del título A, 2,4 mg (12%) del compuesto del título B y 3,1 mg (16%) del compuesto del título C.

1H-RMN (CDCl3) de A: δ= 0,61 (2H), 0,88 (2H), 1,96-2,11 (3H), 2,29 (2H), 2,32 (3H), 2,89 (1H), 3,04 (2H), 3,14 (2H), 3,37 (2H), 5,90 (1H), 5,92 (1H), 6,51 (1H), 7,24 (1H), 7,40 (1H), 7,55 (1H), 7,62 (1H), 7,64 (1H), 7,72 (1H), 8,54 (1H), 8,61 (1H) ppm.

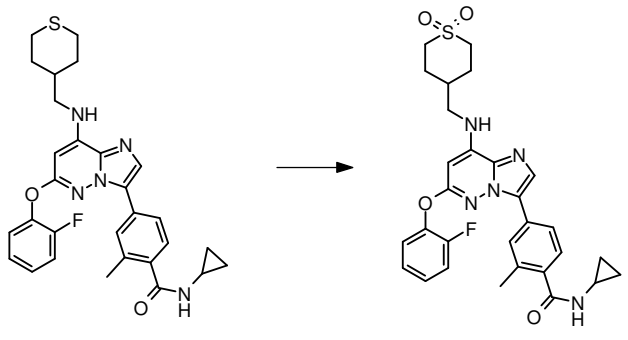
1H-RMN (CDCl3) de B: δ= 0,61 (2H), 0,88 (2H), 1,87-2,01 (3H), 2,24 (2H), 2,32 (3H), 2,48 (2H), 2,89 (1H), 3,10 (2H), 3,33 (2H), 5,89 (1H), 5,92 (1H), 6,02 (1H), 7,24 (1H), 7,39 (1H), 7,56 (1H), 7,62 (1H), 7,66 (1H), 7,71 (1H), 8,53 (1H), 8,60 (1H) ppm.

1H-RMN (CDCl3) de C: δ= 0,61 (2H), 0,88 (2H), 1,57 (2H), 1,99 (1H), 2,29 (2H), 2,31 (3H), 2,68 (2H), 2,89 (1H), 3,30 (2H), 3,40 (2H), 5,87-5,92 (2H), 5,99 (1H), 7,23 (1H), 7,39 (1H), 7,55 (1H), 7,62 (1H), 7,65 (1H), 7,71 (1H), 8,53 (1H), 8,60 (1H) ppm.

Ejemplo 297

N-ciclopropil-4-[8-{[(1,1-dioxidotetrahidro-2H-tiopiran-4-il)metil]amino}-

6-(2-fluorofenoxi)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida



Se trataron 19,7 mg (37 µmol) de N-ciclopropil-4-{6-(2-fluorofenoxi)-8-[(tetrahidro-2H-tiopiran-4-

ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida, que se preparó de acuerdo con el ejemplo 283, de manera análoga al Ejemplo 294 para dar, luego del tratamiento posterior y la purificación, 9,8 mg (47%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,60 (2H), 0,88 (2H), 1,94-2,08 (3H), 2,26 (3H), 2,28 (2H), 2,89 (1H), 3,02 (2H), 3,13 (2H), 3,36 (2H), 5,82 (1H), 5,94 (1H), 5,99 (1H), 7,17-7,33 (5H), 7,53 (1H), 7,68 (1H), 7,71 (1H) ppm.

Ejemplo 298

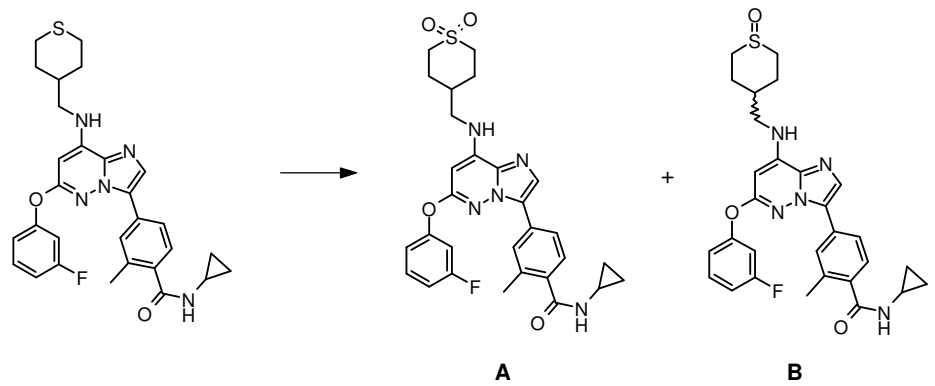
N-ciclopropil-4-[8-{[(1,1-dioxidotetrahidro-2H-tiopiran-4-il)metil]amino}-

6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida (A)

y

N-ciclopropil-4-[6-(3-fluorofenoxi)-8-({[(cis/trans)-1-oxidotetrahidro-2H-

tiopiran-4-il]metil}amino)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida (B)



Se trataron 25,5 mg (48 µmol) de N-ciclopropil-4-{6-(3-

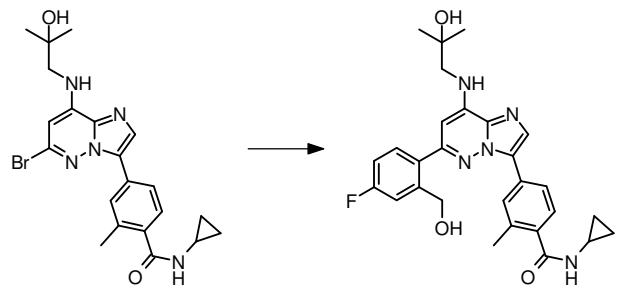
fluorofenoxi)-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida, que se preparó de acuerdo con el ejemplo 281, de manera análoga al Ejemplo 294 para dar, luego del tratamiento posterior y la purificación, 12,3 mg (43%) del compuesto del título A y 5,6 mg (21%) de una mezcla cis/trans de los compuestos del título B.

1H-RMN (CDCl3) de A: δ= 0,61 (2H), 0,88 (2H), 1,93-2,08 (3H), 2,28 (2H), 2,33 (3H), 2,89 (1H), 3,02 (2H), 3,13 (2H), 3,35 (2H), 5,84 (1H), 5,86 (1H), 6,04 (1H), 6,95-7,09 (3H), 7,25 (1H), 7,39 (1H), 7,61 (1H), 7,72 (1H), 7,74 (1H) ppm.

1H-RMN (CDCl3) de B: δ= 0,60 (2H), 0,88 (2H), 1,55 (1H), 1,89 (1H), 1,97 (1H), 2,15-2,31 (2H), 2,32 (3H), 2,47+2,67 (2H), 2,89 (1H), 3,08+3,39 (2H), 3,29 (2H), 5,84+5,87 (1H), 5,89 (1H), 6,13 (1H), 6,95-7,07 (3H), 7,25 (1H), 7,39 (1H), 7,61 (1H), 7,72 (1H), 7,74 (1H) ppm.

Ejemplo 299

N-ciclopropil-4-{6-[4-fluoro-2-(hidroximetil)fenil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



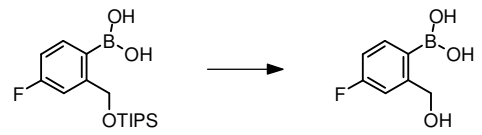
Se trataron 250 mg (545 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-

metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 1 usando ácido [4-fluoro-2-(hidroximetil)fenil]borónico, que se preparó de acuerdo con el Ejemplo Intermediario 299a para dar, luego del tratamiento posterior y la purificación, 239 mg (87%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,64 (2H), 1,15 (6H), 2,34 (3H), 2,79 (1H), 3,28 (2H), 4,65 (2H), 4,73 (1H), 5,31 (1H), 6,41 (1H), 6,97 (1H), 7,19 (1H), 7,32 (1H), 7,40 (1H), 7,53 (1H), 7,91 (1H), 7,95 (1H), 7,99 (1H), 8,26 (1H) ppm.

Ejemplo Intermediario 299a

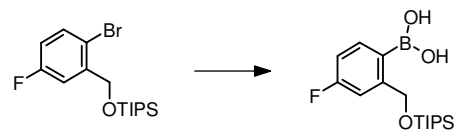
ácido [4-fluoro-2-(hidroximetil)fenil]borónico



A una solución de 2,60 g (7,97 mmol) de ácido (4-fluoro-2-{[(triisopropilsilil)oxi]metil} fenil)borónico, que se preparó de acuerdo con el Ejemplo Intermediario 299b en 10 mL de diclorometano, se agregaron 6,14 mL de ácido trifluoroacético y la mezcla se agitó durante 16 horas a 23°C. El solvente se eliminó y el residuo se cristalizó desde n-hexano para dar 682 mg (50%) del compuesto del título.

Ejemplo Intermediario 299b

ácido (4-fluoro-2-{[(triisopropilsilil)oxi]metil}fenil)borónico



A una solución de 6,00 g (16,6 mmol) de [(2-bromo-5-fluorobencil)oxi](triisopropil)silano, que se preparó de acuerdo con el Ejemplo Intermediario 299c en 60 mL de tetrahidrofurano, se agregaron 7,31 mL de n-butillitio (2,5M en hexano) a -78°C. Luego de 20 minutos de agitación se agregaron 5,58 mL de borato de trimetilo, y la agitación se continuó durante otros 60 minutos. La mezcla se dejó calentar a 23°C, se volcó sobre una solución saturada de cloruro de amonio y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de sodio. Luego de la filtración y la eliminación del solvente el residuo se purificó mediante cromatografía para dar 3,16 g (58%) del compuesto del título.

Ejemplo Intermediario 299c

[(2-bromo-5-fluorobencil)oxi](triisopropil)silano

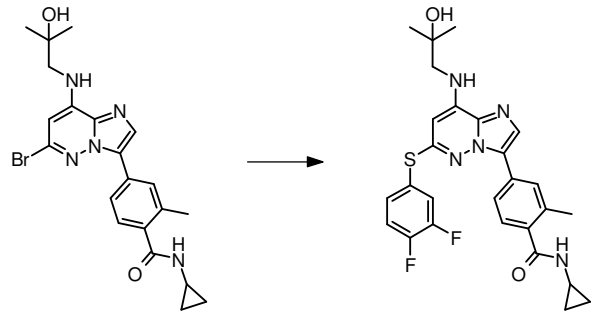


A una solución de 5,00 g (24,4 mmol) de (2-bromo-5-fluorofenil)metanol en 100 mL de N,N-dimetilformamida, se agregaron 2,49 g de imidazol, 6,20 mL de cloro(triisopropil)silano, 1,49 g de N,N-dimetilpiridin-4-amina y la mezcla se agitó a 23°C durante 2 días. Se agregó agua y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de sodio. Luego de la filtración y la eliminación del solvente el residuo se purificó mediante cromatografía para dar 8,17 g (93%) del compuesto del título.

Ejemplo 300

N-ciclopropil-4-{6-[(3,4-difluorofenil)sulfanil]-8-[(2-hidroxi-2-

metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



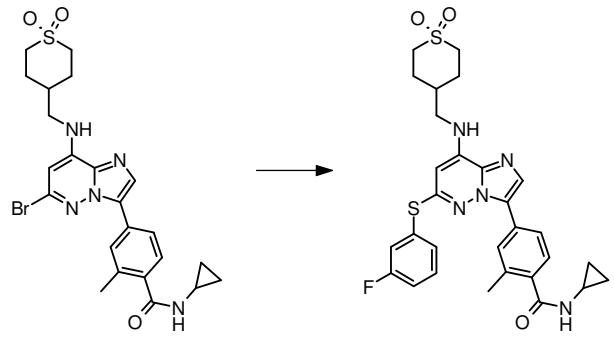
Se trataron 200 mg (436 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando 3,4-difluorobencenotiol para dar, luego del tratamiento posterior y la purificación, 5,8 mg (2%) del compuesto del título.

1H-RMN (CDCl3/CD3OD): δ= 0,62 (2H), 0,88 (2H), 1,33 (6H), 2,37 (3H), 2,89 (1H), 3,22 (2H), 5,95 (1H), 6,13 (1H), 6,42 (1H), 7,17 (1H), 7,21 (1H), 7,35 (1H), 7,47 (1H), 7,51 (1H), 7,52 (1H), 7,62 (1H) ppm.

Ejemplo 301

N-ciclopropil-4-(8-{[(1,1-dioxidotetrahidro-2H-tiopiran-4-il)metil]amino}-

6-[(3-fluorofenil)sulfanil]imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida

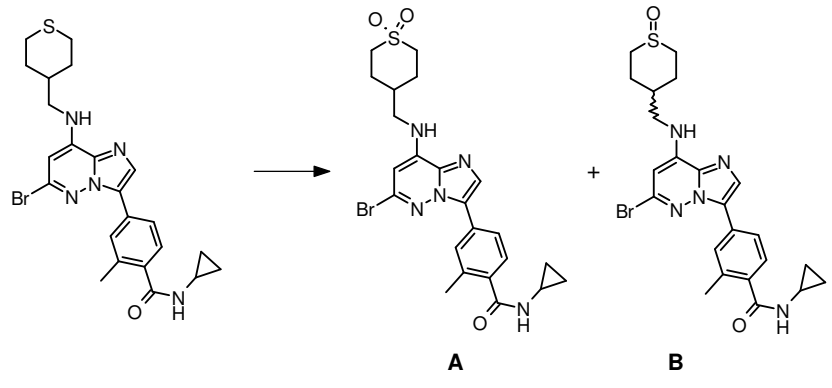


Se trataron 25 mg (47 µmol) de 4-(6-bromo-8-{[(1,1-dioxidotetrahidro-2H-tiopiran-4-il)metil]amino}imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 301a, de manera análoga al Ejemplo 51 usando 3-fluorobencenotiol para dar, luego del tratamiento posterior y la purificación, 13,0 mg (48%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,65 (2H), 1,62 (2H), 1,94 (1H), 2,01 (2H), 2,20 (3H), 2,79 (1H), 2,96-3,11 (4H), 3,23 (2H), 6,25 (1H), 7,11 (1H), 7,34 (1H), 7,44 (1H), 7,49 (1H), 7,54 (1H), 7,65 (1H), 7,70 (1H), 7,82 (1H), 7,94 (1H), 8,24 (1H) ppm.

Ejemplo Intermediario 301a

4-(6-bromo-8-{[(1,1-dioxidotetrahidro-2H-tiopiran-4-il)metil]amino}imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida (A) y 4-(6-bromo-8-({[(cis/trans)-1-oxidotetrahidro-2H-tiopiran-4-il]metil}amino)imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida (B)

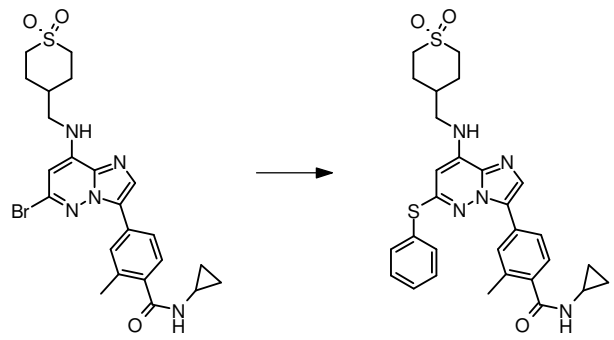


Se trataron 328 mg (655 µmol) de 4-{6-bromo-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 281a, de manera análoga al Ejemplo 294 para dar, luego del tratamiento posterior y la purificación, 167 mg (48%) del compuesto del título A y 128 mg (38%) de los compuestos del título B.

Ejemplo 302

N-ciclopropil-4-[8-{[(1,1-dioxidotetrahidro-2H-tiopiran-4-il)metil]amino}-

6-(fenilsulfanil)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida



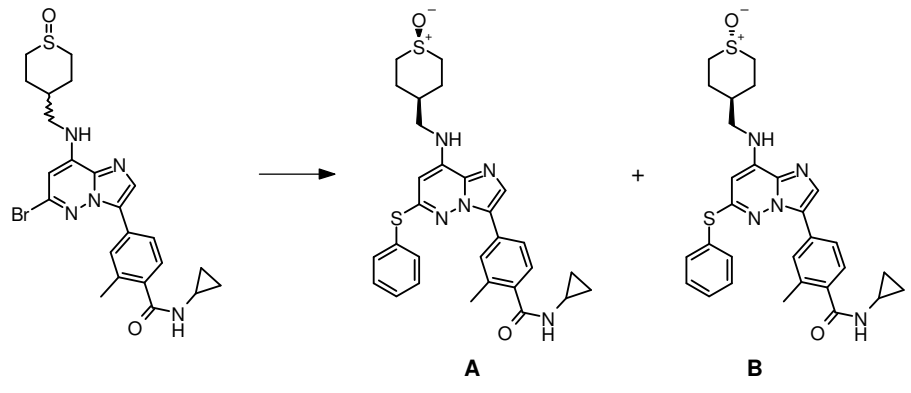
Se trataron 25 mg (47 µmol) de 4-(6-bromo-8-{[(1,1-dioxidotetrahidro-2H-tiopiran-4-il)metil]amino}imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 301a, de manera análoga

al Ejemplo 51 usando bencenotiol para dar, luego del tratamiento posterior y la purificación, 10,1 mg (26%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,65 (2H), 1,61 (2H), 1,91 (1H), 1,99 (2H), 2,19 (3H), 2,78 (1H), 2,96-3,12 (4H), 3,20 (2H), 6,15 (1H), 7,08 (1H), 7,44-7,53 (3H), 7,58-7,65 (3H), 7,69 (1H), 7,77 (1H), 7,93 (1H), 8,23 (1H) ppm.

Ejemplo 303

N-ciclopropil-2-metil-4-[8-({[(cis)-1-oxidotetrahidro-2H-tiopiran-4-il]metil}amino)-6-(fenilsulfanil)imidazo[1,2-b]piridazin-3-il]benzamida (A) y N-ciclopropil-2-metil-4-[8-({[(trans)-1-oxidotetrahidro-2H-tiopiran-4-il]metil}amino)-6-(fenilsulfanil)imidazo[1,2-b]piridazin-3-il]benzamida (B)



Se trataron 25 mg (48 µmol) de 4-(6-bromo-8-({[(cis/trans)-1-oxidotetrahidro-2H-tiopiran-4-il]metil}amino)imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 301a, de manera análoga

al Ejemplo 51 usando bencenotiol para dar, luego del tratamiento posterior y la purificación, 3,7 mg (14%) del compuesto del título A y 2,5 mg (9%) del compuesto del título B.

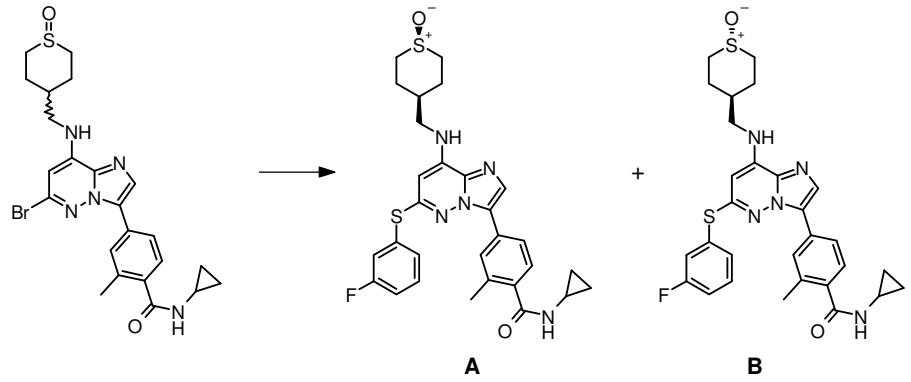
1H-RMN (CDCl3) de A: δ= 0,62 (2H), 0,89 (2H), 1,75-1,88 (3H), 2,15 (2H), 2,38 (3H), 2,42 (2H), 2,91 (1H), 3,05 (2H), 3,19 (2H), 5,87 (1H), 5,89 (1H), 5,97 (1H), 7,20 (1H), 7,41-7,50 (3H), 7,61-7,686 (4H), 7,69 (1H) ppm.

1H-RMN (CDCl3) de B: δ= 0,62 (2H), 0,89 (2H), 1,46 (2H), 1,83 (1H), 2,17 (2H), 2,39 (3H), 2,60 (2H), 2,92 (1H), 3,15 (2H), 3,34 (2H), 5,82 (1H), 5,85 (1H), 5,90 (1H), 7,21 (1H), 7,42-7,51 (3H), 7,61-7,68 (4H), 7,70 (1H) ppm.

Ejemplo 304

N-ciclopropil-4-(6-[(3-fluorofenil)sulfanil]-8-({[(cis)-1-oxidotetrahidro-2H-

tiopiran-4-il]metil}amino)imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida (A) y N-ciclopropil-4-(6-[(3-fluorofenil)sulfanil]-8-({[(trans)-1-oxidotetrahidro-2H-tiopiran-4-il]metil}amino)imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida (B)



Se trataron 25 mg (48 µmol) de 4-(6-bromo-8-({[(cis/trans)-1-oxidotetrahidro-2H-tiopiran-4-il]metil}amino)imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 301a, de manera análoga al Ejemplo 81 usando 3-fluorobencenotiol para dar, luego del tratamiento posterior y la purificación, 7,4 mg (27%) del compuesto del título A y 4,8 mg (18%) del compuesto del título B.

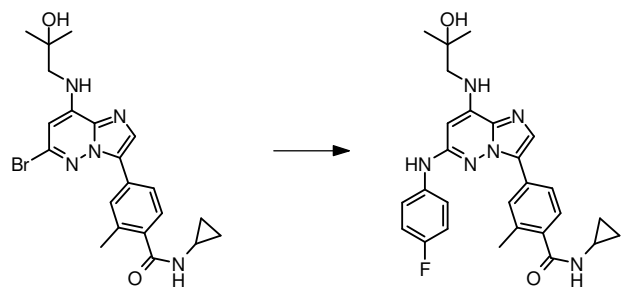
1H-RMN (CDCl3) de A: δ= 0,63 (2H), 0,89 (2H), 1,74-1,89 (3H), 2,17 (2H), 2,40 (3H), 2,43 (2H), 2,92 (1H), 3,06 (2H), 3,22 (2H), 5,90 (1H), 5,92 (1H), 5,98 (1H), 7,15 (1H), 7,23 (1H), 7,35-7,44 (3H), 7,63 (1H), 7,65 (1H), 7,69 (1H) ppm.

1H-RMN (CDCl3) de B: δ= 0,62 (2H), 0,90 (2H), 1,49 (2H), 0,87 (1H), 2,20 (2H), 2,40 (3H), 2,62 (2H), 2,92 (1H), 3,19 (2H), 3,35 (2H), 5,87 (2H), 5,93 (1H), 7,15 (1H), 7,24 (1H), 7,35-7,44 (3H), 7,64 (1H), 7,65 (1H), 7,70 (1H) ppm.

Ejemplo 305

N-ciclopropil-4-{6-[(4-fluorofenil)amino]-8-[(2-hidroxi-2-metilpropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



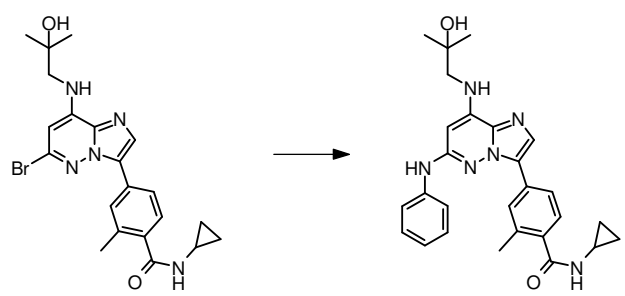
Una mezcla de 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-

metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, 3 mL de dimetilsulfóxido, 61,1 mg de 1,1'-binaftalen-2,2'-diilbis(difenilfosfina), 30,0 mg de tris(dibencilidenacetona)dipaladio (0) y 55 mg de 2-metilpropan-2-olato de sodio se calentó a 160°C bajo irradiación de microondas durante una hora. La mezcla de la reacción se volcó sobre agua y se extrajo con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato de sodio. Luego de la filtración y la eliminación del solvente el residuo se purificó mediante cromatografía para dar 11,3 mg (14%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,52 (2H), 0,66 (2H), 1,18 (6H), 2,37 (3H), 2,81 (1H), 3,15 (2H), 4,81 (1H), 5,85 (1H), 6,55 (1H), 7,10 (2H), 7,35 (1H), 7,65 (2H), 7,76 (1H), 7,84 (1H), 8,04 (1H), 8,29 (1H), 8,94 (1H) ppm.

Ejemplo 306

4-{6-anilino-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



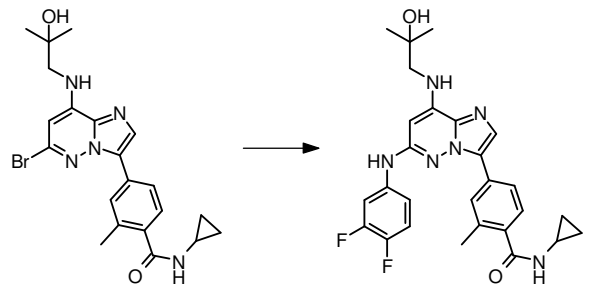
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo

Intermediario 96a, de manera análoga al Ejemplo 305 usando anilina para dar, luego del tratamiento posterior y la purificación, 15,8 mg (21%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 1,18 (6H), 2,38 (3H), 2,81 (1H), 3,16 (2H), 4,81 (1H), 5,89 (1H), 6,53 (1H), 6,90 (1H), 7,27 (2H), 7,34 (1H), 7,66 (2H), 7,77 (1H), 7,85 (1H), 8,12 (1H), 8,30 (1H), 8,92 (1H) ppm.

Ejemplo 307

N-ciclopropil-4-{6-[(3,4-difluorofenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

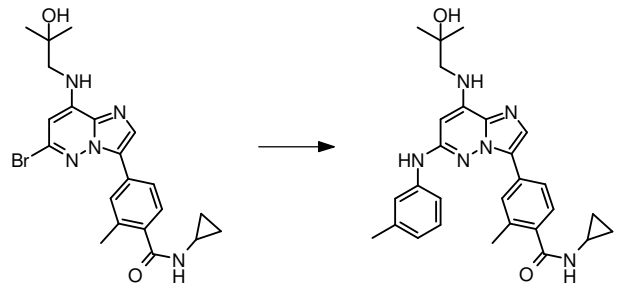


Se trataron 50 mg (109 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando 3,4-difluoroanilina para dar, luego del tratamiento posterior y la purificación, 8,3 mg (14%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 1,18 (6H), 2,36 (3H), 2,81 (1H), 3,16 (2H), 4,80 (1H), 5,85 (1H), 6,65 (1H), 7,22 (1H), 7,31 (1H), 7,34 (1H), 7,76 (1H), 7,82 (1H), 7,91 (1H), 8,00 (1H), 8,30 (1H), 9,17 (1H) ppm.

Ejemplo 308

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(3-metilfenil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



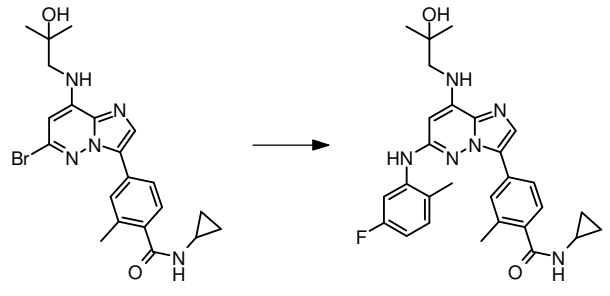
Se trataron 50 mg (109 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando m-toluidina para dar, luego del tratamiento posterior y la purificación, 8,3 mg (16%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,66 (2H), 1,18 (6H), 2,25 (3H), 2,36 (3H), 2,81(1H), 3,15 (2H), 4,81 (1H), 5,89 (1H), 6,51 (1H), 6,71 (1H), 7,14 (1H), 7,33 (1H), 7,40 (1H), 7,51 (1H), 7,77 (1H), 7,95 (1H), 8,01 (1H), 8,29 (1H), 8,83 (1H) ppm.

Ejemplo 309

N-ciclopropil-4-{6-[(5-fluoro-2-metilfenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

e

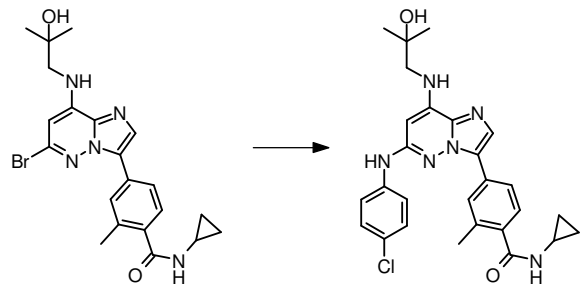


Se trataron 50 mg (109 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando 5-fluoro-2-metilanilina para dar, luego del tratamiento posterior y la purificación, 5,9 mg (11%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,64 (2H), 1,19 (6H), 2,23 (3H), 2,26 (3H), 2,79 (1H), 3,17 (2H), 4,82 (1H), 6,15 (1H), 6,51 (1H), 6,74 (1H), 7,18 (1H), 7,23 (1H), 7,77-7,87 (3H), 7,95 (1H), 8,01 (1H), 8,25 (1H) ppm.

Ejemplo 310

4-{6-[(4-clorofenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida

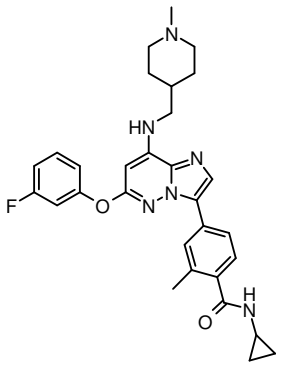


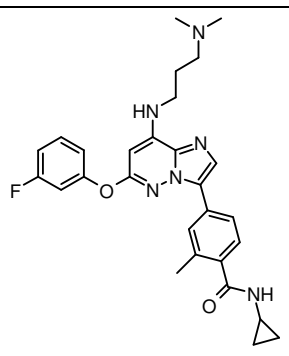
Se trataron 50 mg (109 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo

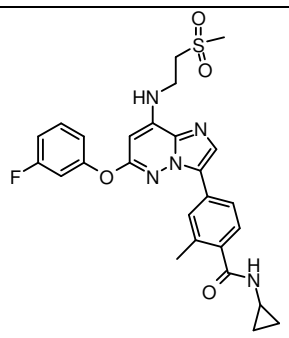
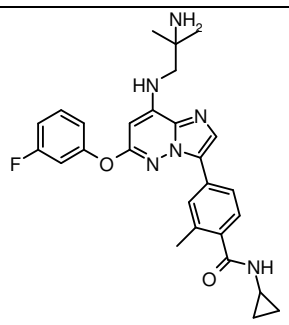
Intermediario 96a, de manera análoga al Ejemplo 305 usando 4-cloroanilina para dar, luego del tratamiento posterior y la purificación, 8,1 mg (15%) del compuesto del título.

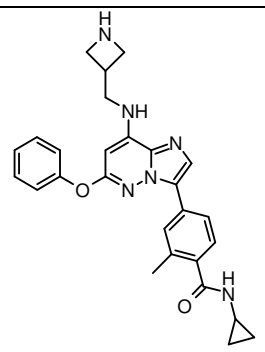
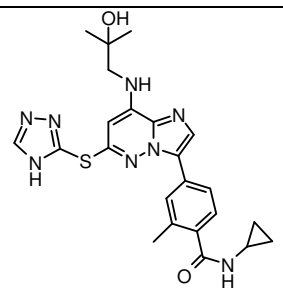
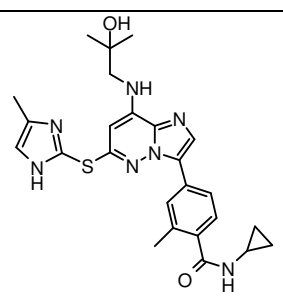
1H-RMN (DMSO-d6): δ= 0,52 (2H), 0,67 (2H), 1,18 (6H), 2,38 (3H), 2,81 (1H), 3,16 (2H), 4,80 (1H), 5,87 (1H), 6,60 (1H), 7,29 (2H), 7,37 (1H), 7,67 (2H), 7,77 (1H), 7,84 (1H), 8,02 (1H), 8,30 (1H), 9,08 (1H) ppm.

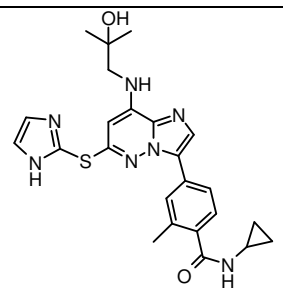
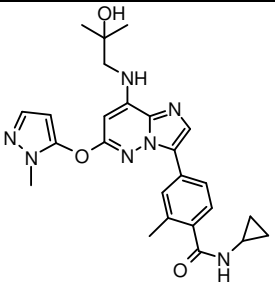
Los siguientes ejemplos de compuestos se prepararon de manera análoga al procedimiento descrito para el ejemplo 51 usando el intermediario apropiado y los alcoholes, tioles, o aminas apropiados [los datos de LC-MS como por ejemplo tiempo de retención (RT en min) o pico de masa observada se recogieron usando el Método LC-MS A salvo que se especifique lo contrario]:

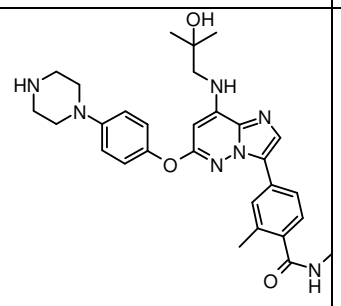
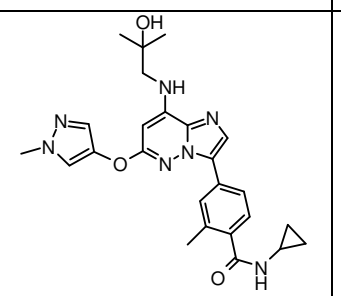
Ejemplo	Estructura	Nombre	Datos analíticos
311		N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[(1-metilpiperidin-4-il)metil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	1H-RMN (DMSO-d6): δ= 0,47 (2H), 0,63 (2H), 1,33 (2H), 1,77 (3H), 2,14 (3H), 2,37 (2H), 2,40 (3H), 2,77 (1H), 3,05 (2H), 3,23 (2H), 6,10 (1H), 7,09 - 7,14 (2H), 7,16 (1H), 7,25 (1H), 7,47

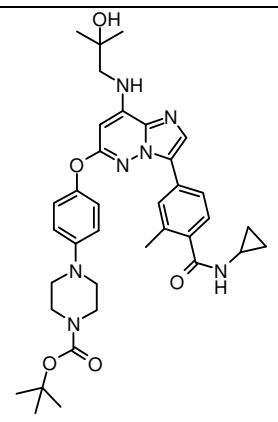
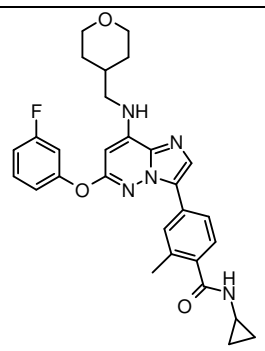
Ejemplo	Estructura	Nombre	Datos analíticos
			(1H), 7,65 (1H), 7,76 (1H), 7,78 (1H), 7,91 (1H), 8,23 (1H), 8,26 (1H) ppm RT = 0,95 PM encontrado = 529,6 PM calculado =528,6
312		N-ciclopropil-4-[8-{[3-(dimetilamino)propil]amino}-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	1H-RMN (DMSO-d6): δ= 0,47 (2H), 0,62 (2H), 1,85 (2H), 2,14 (3H), 2,38 (6H), 2,63 (2H, 2,77 (1H), 3,36 (2H), 6,07 (1H), 7,08 - 7,15 (3H), 7,17 (1H), 7,24 (1H), 7,48 (1H), 7,66 (1H), 7,76 (1H), 7,78 (1H), 7,92 (1H) ppm RT = 0,93 PM encontrado = 503,6 PM calculado =502,6

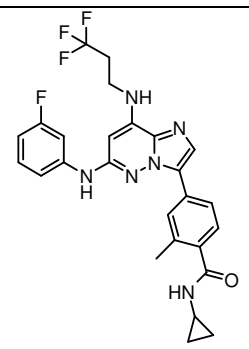
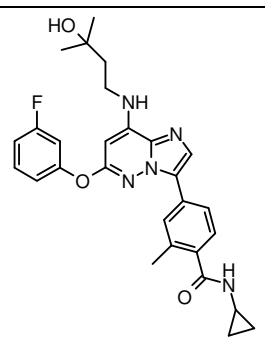
Ejemplo	Estructura	Nombre	Datos analíticos
313		N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[2-(metilsulfonil)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 1,12 PM encontrado = 524,6 PM calculado =523,6
314		4-{8-[(2-amino-2-metilpropil)amino]-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida	1H-RMN (DMSO-d6): δ= 0,47 (2H), 0,63 (2H), 1,25 (6H), 2,14 (3H), 2,76 (1H), 3,50 (2H), 6,31 (1H), 7,12 (2H), 7,17 (1H), 7,24 (1H), 7,48 (1H), 7,67 (1H), 7,77 (1H), 7,95 (1H), 8,24 (1H), 8,36 (1H) ppm RT = 0,94 PM encontrado = 489,6 PM calculado =488,6

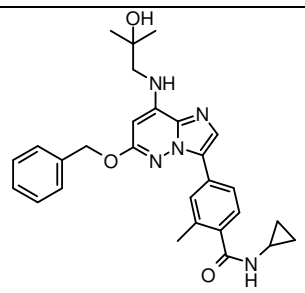
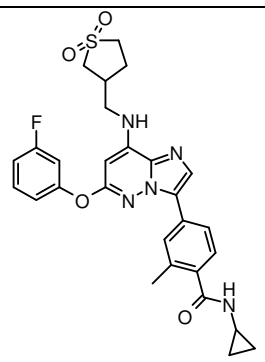
Ejemplo	Estructura	Nombre	Datos analíticos
315		4-{8-[(azetidin-3-ilmetil)amino]-6-fenoxiimidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida	RT = 0,90 PM encontrado = 469,6 PM calculado =468,6
316		N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(4H-1,2,4-triazol-3-ilsulfanil)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,65 (2H), 1,11 (6H), 2,28 (3H), 2,79 (1H), 3,21 (2H), 6,28 (1H), 7,06 (1H), 7,23 (1H), 7,41 - 7,59 (2H), 7,68 (2H), 7,95 (1H), 8,27 (1H), 8,82 (1H) ppm RT = 0,85 PM encontrado = 479,6 PM calculado =478,6
317		N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(4-metil-1H-imidazol-2-il)sulfanil]imidazo[	RT = 0,71 PM encontrado = 492,6 PM calculado =491,6

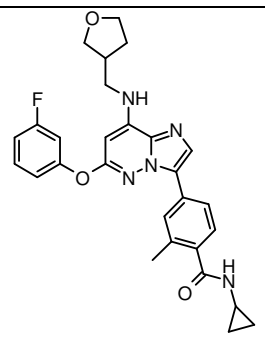
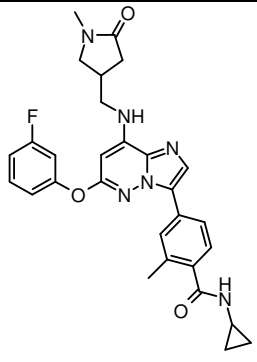
Ejemplo	Estructura	Nombre	Datos analíticos
		1,2-b]piridazin-3-il}-2-metilbenzamida	
318		N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(1H-imidazol-2-ilsulfanil)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,65 (2H), 1,11 (6H), 2,29 (3H), 2,79 (1H), 3,19 (2H), 6,13 (1H), 7,00 (1H), 7,20 (1H), 7,69 (1H), 7,74 (1H), 7,94 (1H), 8,10 (2H), 8,24 (1H) ppm RT = 0,73 PM encontrado = 478,6 PM calculado =477,6
319		N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(1-metil-1H-pirazol-5-il)oxi]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 0,97 PM encontrado = 476,6 PM calculado =475,6

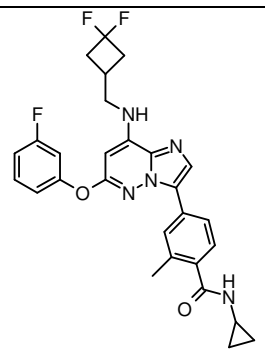
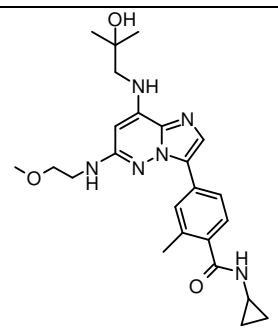
Ejemplo	Estructura	Nombre	Datos analíticos
320		N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[4-(piperazin-1-il)fenoxi]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 0,81 PM encontrado = 556,7 PM calculado =555,7
321		N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(1-metil-1H-pirazol-4-il)oxi]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	1H-RMN (DMSO-d6): δ= 0,55 (2H), 0,78 (2H), 1,30 (6H), 2,28 (3H), 2,82 (1H), 3,19 (2H), 3,75 (3H), 5,73 (1H), 6,36 (1H), 6,78 (1H), 7,18 (2H), 7,33 (2H), 7,44 (2H), 7,58 (1H), 8,06 (1H) ppm RT = 0,96 PM encontrado = 476,6 PM calculado =475,6

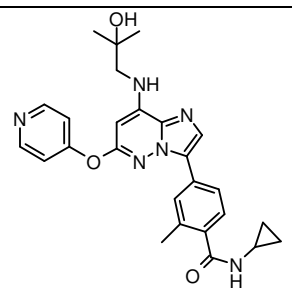
Ejemplo	Estructura	Nombre	Datos analíticos
322		4-[4-({3-[4-(ciclopropilcarbamoil)-3-metilfenil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-6-il}oxi)fenil]piperazin-1-carboxilato de tert-butilo	RT = 1,36 PM encontrado = 666,8 PM calculado =665,8
323		N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	1H-RMN (DMSO-d6): δ= 0,46 (2H), 0,64 (2H), 1,21 (2H), 1,60 (2H), 1,93 (1H), 2,14 (3H), 2,76 (1H), 3,23 (2H), 3,27 (2H), 3,82 (2H), 6,09 (1H), 7,07 - 7,19 (3H), 7,25 (1H), 7,47 (1H), 7,66 (1H), 7,73 (1H), 7,76 (1H), 7,91 (1H), 8,22 (1H) ppm RT = 1,30 PM encontrado = 516,9

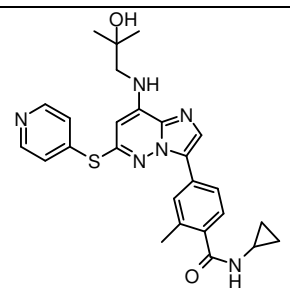
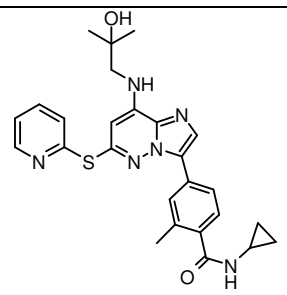
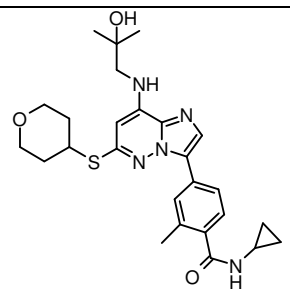
Ejemplo	Estructura	Nombre	Datos analíticos
			PM calculado =515,9
324		N-ciclopropil-4-{6-[(3-fluorofenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,65 (2H), 2,35 (3H), 2,67 (2H), 2,80 (1H), 3,49 325(2H), 5,82 (1H), 6,70 (1H), 7,21 - 7,40 (4H), 7,72 (1H), 7,78 (1H), 7,82 (1H), 8,05 (1H), 8,30 (1H), 9,21 (1H) ppm RT = 1,24 PM encontrado = 513,5 PM calculado =512,5
325		N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(3-hidroxi-3-metilbutil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	1H-RMN (CDCl3): δ= 0,60 (2H), 0,87 (2H), 1,35 (6H), 1,94 (2H), 2,31 (3H), 2,89 (1H), 3,50 (2H), 5,88 (2H), 6,72 (1H), 6,93 - 7,09 (3H), 7,23 (1H), 7,36 (1H), 7,60 (1H),

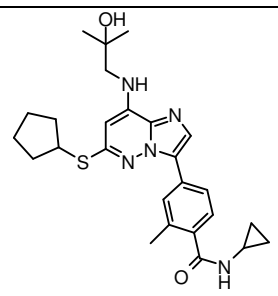
Ejemplo	Estructura	Nombre	Datos analíticos
			7,70 (2H) ppm RT = 1,25 PM encontrado = 504,6 PM calculado =505,6
326		4-{6-(benciloxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida	1H-RMN (CDCl3): δ= 0,63 (2H), 0,88 (2H), 1,39 (2H), 2,50 (3H), 2,93 (1H), 3,27 (2H), 5,35 (2H), 5,78 (1H), 5,95 (1H), 6,33 (1H), 7,32 - 7,51 (6H), 7,63 (1H), 7,84 (2H) ppm RT = 1,19 PM encontrado = 486,6 PM calculado = 485,6
327		N-ciclopropil-4-[8-{[(1,1-dioxidotetrahidrotiofen-3-il)metil]amino}-6-(3-fluorofenoxi)imidazo	RT = 1,16 PM encontrado = 550,6 PM calculado = 549,6

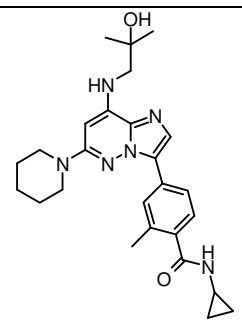
Ejemplo	Estructura	Nombre	Datos analíticos
		[1,2-b]piridazin-3-il]-2-metilbenzamida	
328		N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(tetrahidrofurano-3-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	1H-RMN (CDCl3): δ= 0,61 (2H), 0,88 (2H), 1,69 (1H), 2,12 (1H), 2,32 (3H), 2,68 (1H), 2,90 (1H), 3,32 (2H), 3,72 - 4,00 (4H), ppm RT = 1,25 PM encontrado = 502,6 PM calculado = 501,6
329		N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[(1-metil-5-oxopirrolidin-3-il)metil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 1,12 PM encontrado = 529,6 PM calculado = 528,6

Ejemplo	Estructura	Nombre	Datos analíticos
330		N-ciclopropil-4-[8-{[(3,3-difluorociclobutil)metil]amino}-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	1H-RMN (CDCl3): δ= 0,60 (2H), 0,88 (2H), 2,33 (3H), 2,39 (2H), 2,61 (1H), 2,71 - 2,95 (3H), 3,48 (2H), 5,87 (1H), 5,91 (1H), 6,27 (1H), 6,97 - 7,07 (3H), 7,25 (1H), 7,38 (1H), 7,60 (1H), 7,72 (2H) ppm RT = 1,38 PM encontrado = 522,6 PM calculado = 521,6
331		N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(2-metoxietil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	1H-RMN (DMSO-d6): δ= 0,52 (2H), 0,77 (2H, (2H), 1,28 (6H), 2,38 (3H), 2,81 (1H), 3,11 (2H), 3,28 (3H), 3,41 (2H), 3,51 (2H), 5,37 (1H), 5,92 (1H), 6,28 (1H), 7,15 (2H),

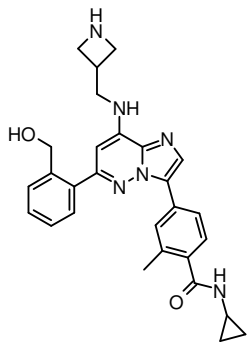
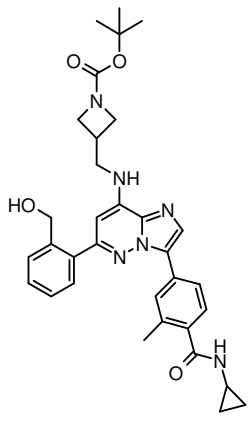
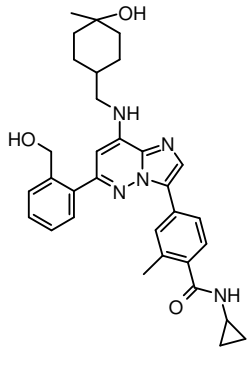
Ejemplo	Estructura	Nombre	Datos analíticos
			7,26 (1H), 7,44 (1H), 7,77 (1H), 7,80 (1H) ppm RT = 0,83 PM encontrado = 453,6 PM calculado = 452,6
332		N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(piridin-4-iloxi)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	1H-RMN (DMSO-d6): δ= 0,56 (2H), 0,70 (2H), 1,22 (6H), 2,42 (3H), 2,85 (1H), 3,41 (2H), 4,82 (1H), 6,32 (2H), 6,69 (1H), 7,40 (1H), 7,42 (1H), 7,93 (1H), 8,01 (1H), 8,05 (1H), 8,32 (2H), 8,34 (1H) ppm RT = 0,82 PM encontrado = 473,6 PM calculado = 472,6

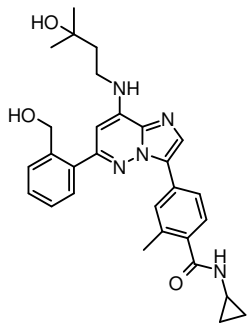
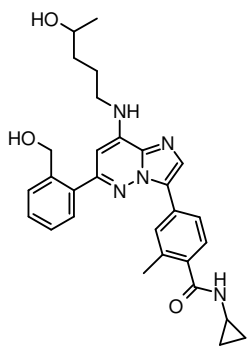
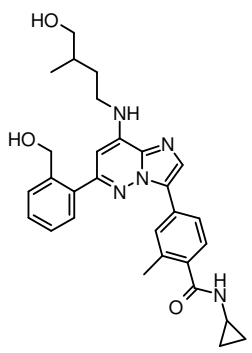
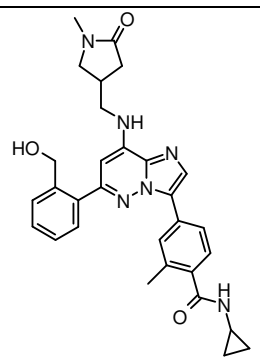
Ejemplo	Estructura	Nombre	Datos analíticos
333		N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(piridin-4-ilsulfanil)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 87 PM encontrado = 489,6 PM calculado = 488,6
334		N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(piridin-2-ilsulfanil)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,05 PM encontrado = 489,6 PM calculado = 488,6
335		N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(tetrahidro-2H-piran-4-ilsulfanil)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,65 (2H), 1,13 (6H), 1,65 (2H), 2,06 (2H), 2,38 (3H), 2,81 (1H), 3,22 (2H), 3,47 (2H), 3,97 (2H), 4,71 (1H), 6,14 (1H), 6,84 (1H)7,35 (1H), 7,92 (2H), 7,97 (1H), 8,28 (1H) ppm

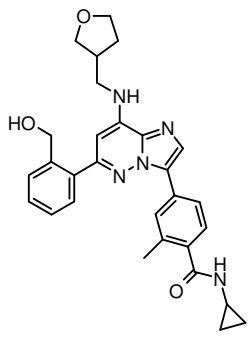
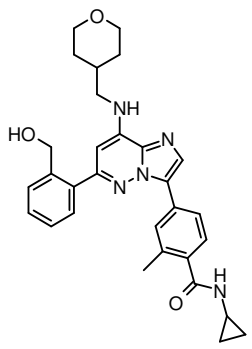
Ejemplo	Estructura	Nombre	Datos analíticos
			RT = 1,09 PM encontrado = 496,7 PM calculado = 495,7
336		4-{6-(ciclopentilsulfanil)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida	1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,65 (2H), 1,13 (6H), 1,52 - 1,76 (6H), 2,20 (2H), 2,35 (3H), 2,80 (1H), 3,21 (2H), 4,00 (1H), 4,71 (1H), 6,13 (1H), 6,78 (1H), 7,33 (1H), 7,90 (1H), 7,95 (1H), 8,05 (1H), 8,28 (1H) ppm RT = 1,31 PM encontrado = 480,7 PM calculado = 479,7

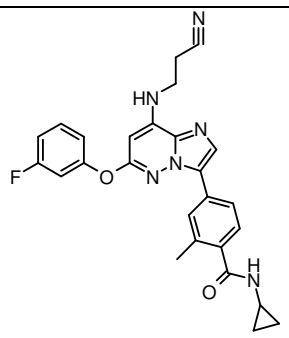
Ejemplo	Estructura	Nombre	Datos analíticos
337		N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(piperidin-1-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,65 (2H), 1,15 (6H), 1,58 (6H), 2,27 (4H), 2,35 (3H), 2,78 (1H), 3,23 (2H), 4,75 (1H), 6,07 (1H), 6,40 (1H), 7,33 (1H), 7,86 (1H), 7,98 (1H), 8,03 (1H), 8,27 (1H) ppm RT = 1,08 PM encontrado = 463,6 PM calculado = 462,6

Los siguientes ejemplos de compuestos se prepararon de manera análoga al procedimiento descrito para el ejemplo 101 usando el intermediario apropiado y el bloque molecular ácido borónico apropiado [los datos de LC-MS como por ejemplo tiempo de retención (RT en min) o pico de masa observada se recogieron usando el Método LC-MS A salvo que se especifique lo contrario]:

Ejemplo	Estructura	Nombre	Datos analíticos
338		4-{8-[(azetidin-3-ilmetil)amino]-6-[2-(hidroximetil)fenil]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida	RT = 0,77 PM encontrado = 483,6 PM calculado = 482,6
339		3-[({3-[4-(ciclopropilcarbamoil)-3-metilfenil]-6-[2-(hidroximetil)fenil]imidazo[1,2-b]piridazin-8-il}amino)metil]azetidin-1-carboxilato de tert-butilo	RT = 1,24 PM encontrado = 583,7 PM calculado = 582,7
340		N-ciclopropil-4-(8-{[(4-hidroxi-4-metilciclohexil)metil]amino}-6-[2-(hidroximetil)fenil]imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida	RT = 1,13 PM encontrado = 540,7 PM calculado = 539,7

Ejemplo	Estructura	Nombre	Datos analíticos
341		N-ciclopropil-4-{8-[(3-hidroxi-3-metilbutil)amino]-6-[2-(hidroximetil)fenil]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,05 PM encontrado = 500,6 PM calculado = 499,6
342		(RS)-N-ciclopropil-4-{6-[2-(hidroximetil)fenil]-8-[(4-hidroxipentil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,03 PM encontrado = 500,6 PM calculado = 499,6
343		(RS)-N-ciclopropil-4-{8-[(4-hidroxi-3-metilbutil)amino]-6-[2-(hidroximetil)fenil]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,04 PM encontrado = 500,6 PM calculado = 499,6
344		N-ciclopropil-4-(6-[2-(hidroximetil)fenil]-8-{[(1-metil-5-oxopirrolidin-3-il)metil]amino}imidazo[1,2-b]piridazin-3-il)-	RT = 0,95 PM encontrado = 525,6 PM calculado = 524,6

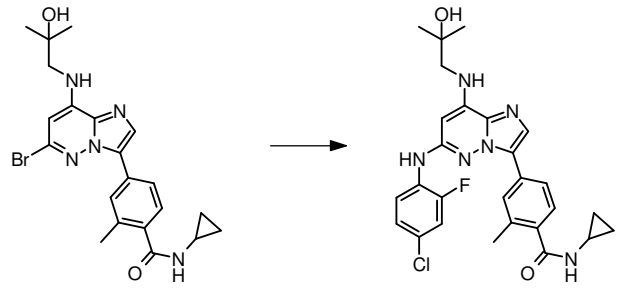
Ejemplo	Estructura	Nombre	Datos analíticos
		2-metilbenzamida	
345		(RS)-N-ciclopropil-4-{6-[2-(hidroximetil)fenil]-8-[(tetrahidrofurano-3-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,06 PM encontrado = 498,6 PM calculado = 497,6
346		N-ciclopropil-4-{6-[2-(hidroximetil)fenil]-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	1H-RMN (DMSO-d6): δ= 0,59 (2H), 0,86 (2H), 1,44 (2H), 1,78 (2H), 2,02 (1H), 2,47 (3H), 2,89 (1H), 3,31 (2H), 3,41 (2H), 4,02 (2H), 4,40 (2H), 6,17 (1H), 6,22 (1H), 6,38 (1H), 7,26 (2H), 7,38 (1H), 7,48 (2H), 7,60 (2H), 7,69 (2H) ppm RT = 1,09 PM encontrado = 512,6

Ejemplo	Estructura	Nombre	Datos analíticos
			PM calculado = 511,6
347		4-{8-[(2-cianoetil)amino]-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida	RT = 1,18 PM encontrado = 471,5 PM calculado =470,5 1H-RMN (DMSO-d6): δ= 0,47 (2H), 0,63 (2H), 2,14 (3H), 2,76 (1H), 2,86 (2H), 3,65 (2H). 6,26 (1H), 7,07 - 7,20 (3H), 7,25 (1H), 7,49 (1H), 7,67 (1H), 7,76 (1H), 7,87 (1H), 7,94 (1H), 8,22 (1H) ppm.

Ejemplo 348

4-{6-[(4-cloro-2-fluorofenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]

imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



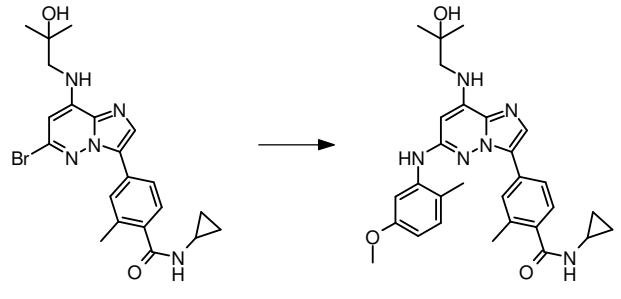
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando 4-cloro-2-fluoroanilina para dar, luego del tratamiento posterior y la purificación, 3,1 mg (3%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,65 (2H), 1,18 (6H), 2,31 (3H), 2,79 (1H), 3,16 (2H), 4,79 (1H), 6,15 (1H), 6,59 (1H), 7,19 (1H), 7,31 (1H), 7,43 (1H), 7,77 (1H), 7,79 (1H), 7,95 (1H), 8,15 (1H), 8,27 (1H), 8,63 (1H) ppm.

Ejemplo 349

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(5-metoxi-2-

metilfenil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



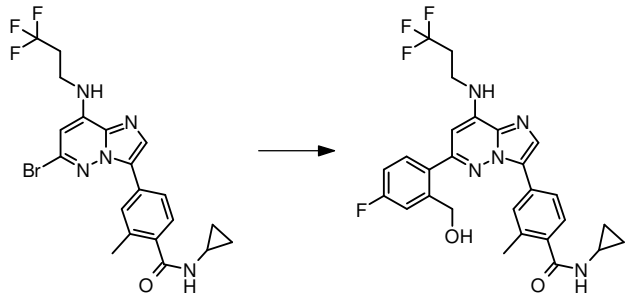
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo

Intermediario 96a, de manera análoga al Ejemplo 305 usando 5-metoxi-2-metilanilina para dar, luego del tratamiento posterior y la purificación, 9,1 mg (10%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,64 (2H), 1,18 (6H), 2,17 (3H), 2,22 (3H), 2,78 (1H), 3,16 (2H), 3,62 (3H), 4,81 (1H), 6,04 (1H), 6,43 (1H), 6,56 (1H), 7,08 (1H), 7,20 (1H), 7,34 (1H), 7,80 (1H), 7,85 (1H), 7,88 (1H), 8,02 (1H), 8,23 (1H) ppm.

Ejemplo 350

N-ciclopropil-4-{6-[4-fluoro-2-(hidroximetil)fenil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



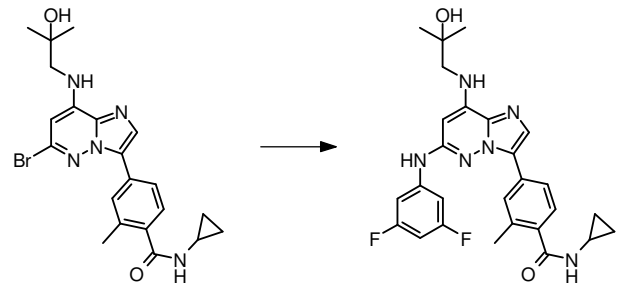
Se trataron 50 mg (104 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 1 usando ácido [4-fluoro-2-(hidroximetil)fenil]borónico para dar, luego del tratamiento posterior y la purificación, 10,4 mg (18%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,64 (2H), 2,34 (3H), 2,67 (2H), 2,79 (1H), 3,61 (2H), 4,65 (2H), 5,34 (1H), 6,36 (1H), 7,20 (1H), 7,33 (1H), 7,41 (1H), 7,59 (1H), 7,67 (1H), 7,91 (1H), 7,95 (1H), 8,01 (1H), 8,27 (1H) ppm.

Ejemplo 351

N-ciclopropil-4-{6-[(3,5-difluorofenil)amino]-8-[(2-hidroxi-2-metilpropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



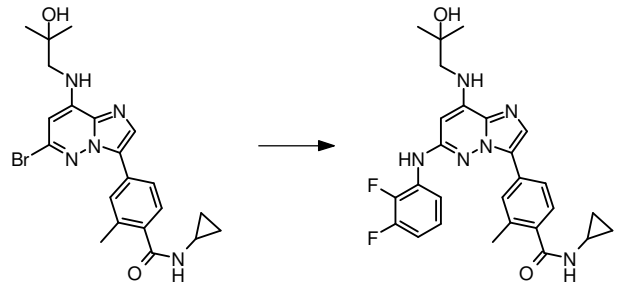
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando 3,5-difluoroanilina para dar, luego del tratamiento posterior y la purificación, 4,9 mg (6%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,66 (2H), 1,18 (6H), 2,35 (3H), 2,81 (1H), 3,17 (2H), 4,80 (1H), 5,87 (1H), 6,67 (1H), 6,73 (1H), 7,30-7,39 (3H), 7,77 (1H), 7,79 (1H), 8,01 (1H), 8,31 (1H), 9,40 (1H) ppm.

Ejemplo 352

N-ciclopropil-4-{6-[(2,3-difluorofenil)amino]-8-[(2-hidroxi-2-metilpropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



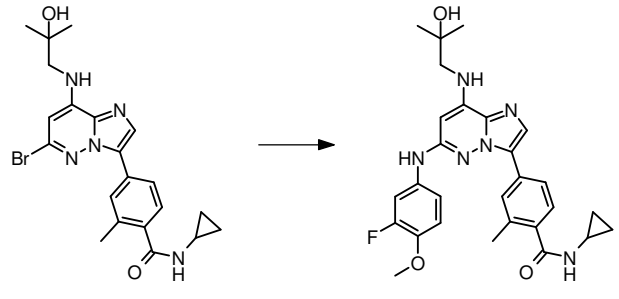
Se trataron 75 mg (164µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando 2,3-difluoroanilina para dar, luego del tratamiento posterior y la purificación, 4,3 mg (5%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,65 (2H), 1,18 (6H), 2,30 (3H), 2,79 (1H), 3,17 (2H), 4,80 (1H), 6,16 (1H), 6,62 (1H), 7,02 (1H), 7,12 (1H), 7,28 (1H), 7,80 (2H), 7,92 (1H), 8,00 (1H), 8,27 (1H), 8,77 (1H) ppm.

Ejemplo 353

N-ciclopropil-4-{6-[(3-fluoro-4-metoxifenil)amino]-8-[(2-hidroxi-2-

metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



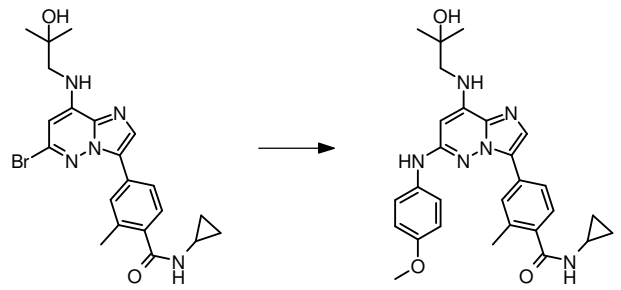
Se trataron 75 mg (164µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo

Intermediario 96a, de manera análoga al Ejemplo 305 usando 3-fluoro-4-metoxianilina para dar, luego del tratamiento posterior y la purificación, 16,8 mg (19%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,66 (2H), 1,18 (6H), 2,35 (3H), 2,81 (1H), 3,15 (2H), 3,77 (3H), 4,80 (1H), 5,82 (1H), 6,55 (1H), 7,06 (1H), 7,21 (1H), 7,32 (1H), 7,70 (1H), 7,75 (1H), 7,83 (1H), 8,04 (1H), 8,29 (1H), 8,91 (1H) ppm.

Ejemplo 354

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(4-metoxifenil)
amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

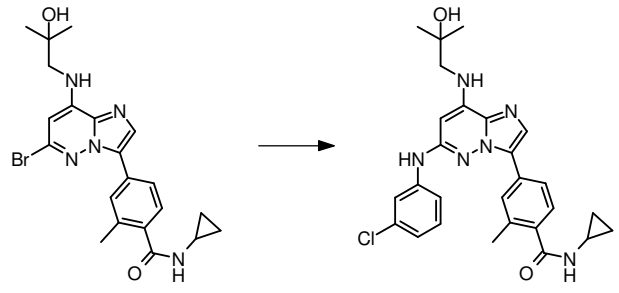


Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando 4-metoxianilina para dar, luego del tratamiento posterior y la purificación, 11,4 mg (13%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 1,18 (6H), 2,37 (3H), 2,81 (1H), 3,14 (2H), 3,70 (3H), 4,80 (1H), 5,83 (1H), 6,46 (1H), 6,86 (2H), 7,33 (1H), 7,55 (2H), 7,75 (1H), 7,85 (1H), 8,10 (1H), 8,29 (1H), 8,71 (1H) ppm.

Ejemplo 355

4-{6-[(3-clorofenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida

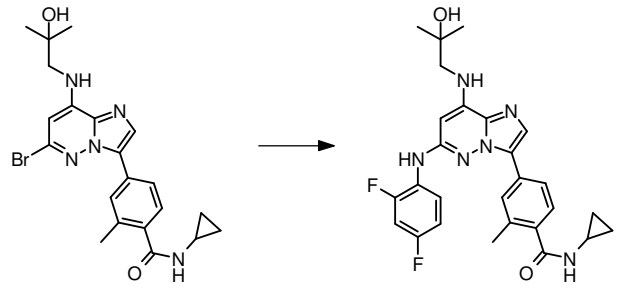


Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando 3-cloroanilina para dar, luego del tratamiento posterior y la purificación, 15,4 mg (18%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,66 (2H), 1,18 (6H), 2,36 (3H), 2,81 (1H), 3,16 (2H), 4,80 (1H), 5,88 (1H), 6,64 (1H), 6,92 (1H), 7,27 (1H), 7,36 (1H), 7,71 (1H), 7,58 (1H), 7,83 (1H), 7,93 (1H), 7,95 (1H), 8,28 (1H), 9,15 (1H) ppm.

Ejemplo 356

N-ciclopropil-4-{6-[(2,4-difluorofenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



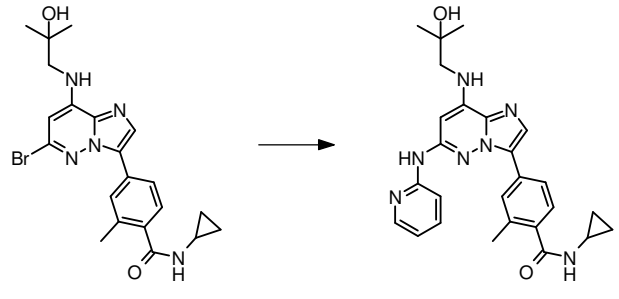
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando 2,4-difluoroanilina para dar, luego del tratamiento posterior y la purificación, 5,0 mg (6%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,65 (2H), 1,18 (6H), 2,28 (3H), 2,79 (1H), 3,14 (2H), 4,80 (1H), 6,06 (1H), 6,54 (1H), 7,04 (1H), 7,27 (1H), 7,30 (1H), 7,78 (1H), 7,79 (1H), 7,94 (1H), 7,99 (1H), 8,25 (1H), 8,48 (1H) ppm.

Ejemplo 357

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(piridin-2-ilamino)

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



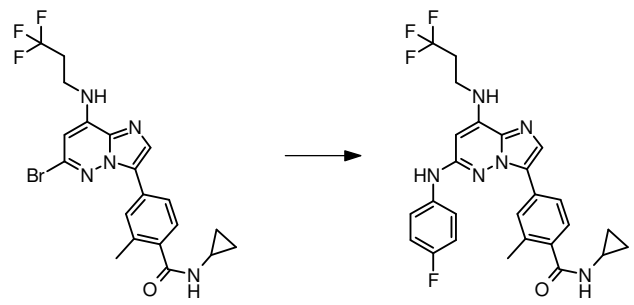
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo

Intermediario 96a, de manera análoga al Ejemplo 305 usando piridin-2-amina para dar, luego del tratamiento posterior y la purificación, 10,1 mg (12%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 1,18 (6H), 2,39 (3H), 2,81 (1H), 3,16 (2H), 4,80 (1H), 6,27 (1H), 6,60 (1H), 6,91 (1H), 7,36 (1H), 7,69 (1H), 7,80 (1H), 7,86 (1H), 8,01 (1H), 8,08 (1H), 8,23 (1H), 8,31 (1H), 9,48 (1H) ppm.

Ejemplo 358

N-ciclopropil-4-{6-[(4-fluorofenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

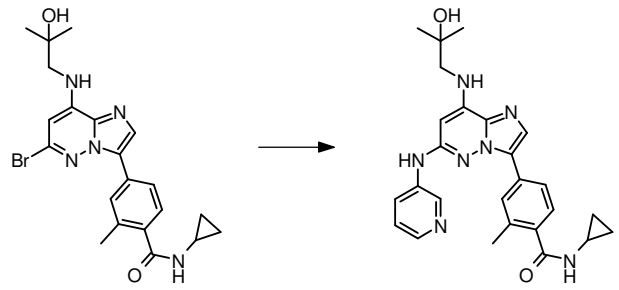


Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando 4-fluoroanilina para dar, luego del tratamiento posterior y la purificación, 20,1 mg (24%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,52 (2H), 0,66 (2H), 2,37 (3H), 2,68 (2H), 2,81 (1H), 3,49 (2H), 5,79 (1H), 7,11 (2H), 7,28 (1H), 7,35 (1H), 7,65 (2H), 7,77 (1H), 7,84 (1H), 8,04 (1H), 8,29 (1H), 8,98 (1H) ppm.

Ejemplo 359

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(piridin-3-ilamino)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

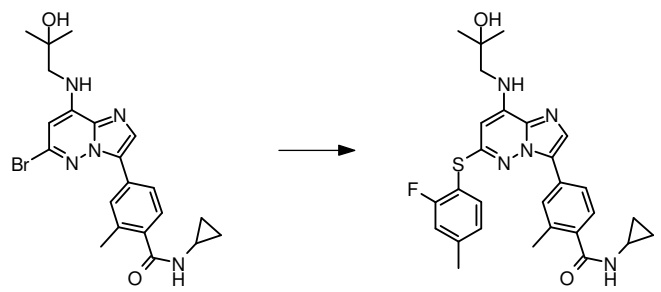


Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando piridin-2-amina para dar, luego del tratamiento posterior y la purificación, 12,6 mg (13%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 1,19 (6H), 2,39 (3H), 2,81 (1H), 3,17 (2H), 4,82 (1H), 5,91 (1H), 6,66 (1H), 7,28 (1H), 7,34 (1H), 7,78 (1H), 7,81 (1H), 8,06 (1H), 8,11 (1H), 8,13 (1H), 8,31 (1H), 8,80 (1H), 9,13 (1H) ppm.

Ejemplo 360

N-ciclopropil-4-{6-[(2-fluoro-4-metilfenil)sulfanil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

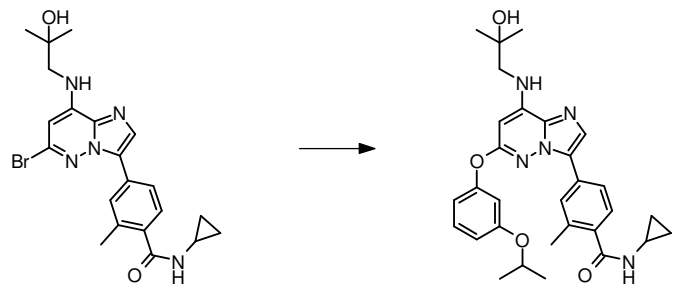


Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando 2-fluoro-4-metilbencenotiol para dar, luego del tratamiento posterior y la purificación, 43,2 mg (48%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,65 (2H), 1,13 (6H), 2,19 (3H), 2,39 (3H), 2,79 (1H), 3,24 (2H), 4,72 (1H), 6,29 (1H), 6,97 (1H), 7,00 (1H), 7,14 (1H), 7,25 (1H), 7,52 (1H), 7,57 (1H), 7,64 (1H), 7,93 (1H), 8,24 (1H) ppm.

Ejemplo 361

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(3-isopropoxifenoxi)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



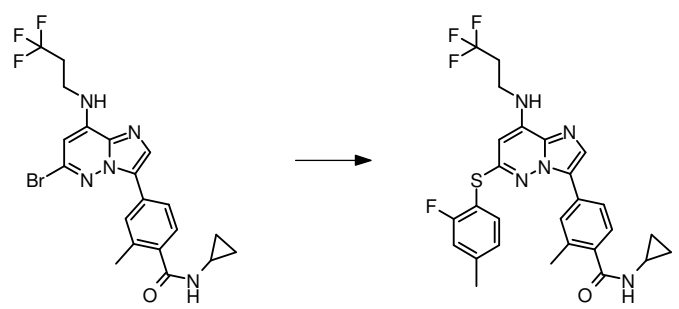
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando 3-isopropoxifenol para dar, luego del tratamiento posterior y la purificación, 33,3 mg (37%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,46 (2H), 0,63 (2H), 1,15 (6H), 1,20 (6H),

2,14 (3H), 2,76 (1H), 3,27 (2H), 4,58 (1H), 4,74 (1H), 6,14 (1H), 6,73-6,83 (3H), 6,96 (1H), 7,15 (1H), 7,30 (1H), 7,70 (1H), 7,80 (1H), 7,92 (1H), 8,21 (1H) ppm.

Ejemplo 362

N-ciclopropil-4-{6-[(2-fluoro-4-metilfenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 75 mg (156µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 2-fluoro-4-metilbencenotiol para dar, luego del tratamiento posterior y la purificación, 30,3 mg (34%) del compuesto del título.

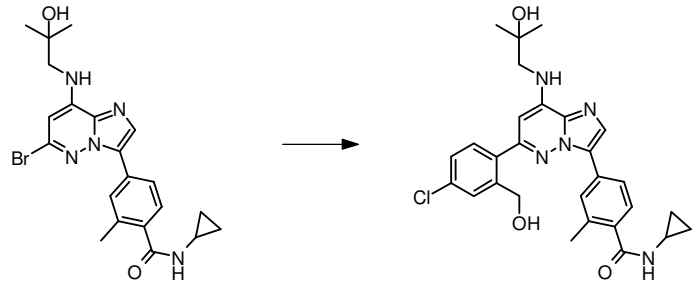
1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,66 (2H), 2,19 (3H), 2,40 (3H), 2,64 (2H), 2,80 (1H), 3,55 (2H), 6,23 (1H), 7,01 (1H), 7,15 (1H), 7,26 (1H), 7,53 (1H), 7,57 (1H), 7,64 (1H), 7,66 (1H), 7,94 (1H), 8,25 (1H) ppm.

Ejemplo 363

4-{6-[4-cloro-2-(hidroximetil)fenil]-8-[(2-hidroxi-2-

metilpropil)amino]

imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



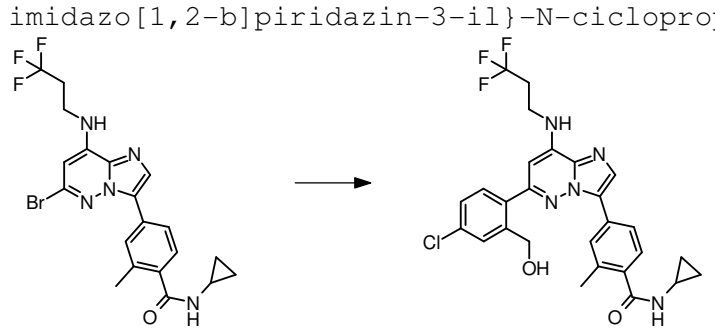
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 1 usando ácido [4-cloro-2-(hidroximetil)fenil]borónico para dar, luego del tratamiento posterior y la purificación, 22,5 mg (26%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,64 (2H), 1,15 (6H), 2,33 (3H), 2,79 (1H), 3,31 (2H), 4,64 (2H), 4,73 (1H), 5,32 (1H), 6,42 (1H), 7,00 (1H), 7,32 (1H), 7,43 (1H), 7,51 (1H), 7,65 (1H), 7,91 (1H), 7,95 (1H), 8,00 (1H), 8,26 (1H) ppm.

Ejemplo 364

4-{6-[4-cloro-2-(hidroximetil)fenil]-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



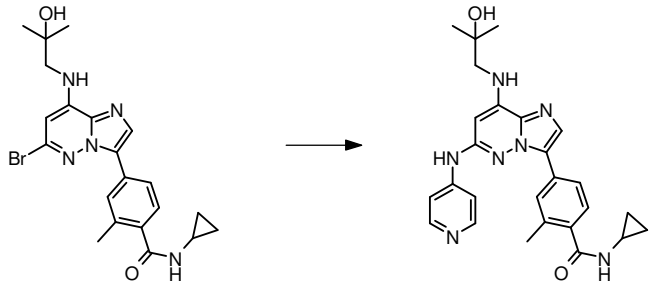
Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 1 usando ácido [4-cloro-2-(hidroximetil)fenil]borónico para dar, luego del tratamiento posterior y la purificación, 15,6 mg (18%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,64 (2H), 2,33 (3H), 2,67 (2H), 2,79 (1H), 3,61 (2H), 4,64 (2H), 5,35 (1H), 6,37 (1H), 7,32 (1H), 7,43 (1H), 7,57 (1H), 7,65 (1H), 7,68 (1H), 7,91 (1H), 7,94 (1H), 8,01 (1H), 8,26 (1H) ppm.

Ejemplo 365

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(piridin-4-ilamino)

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



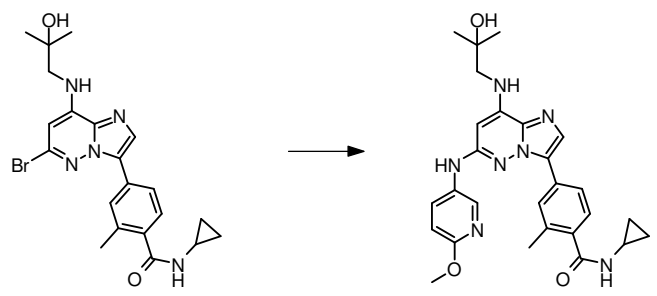
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando piridin-4-amina para dar, luego del tratamiento posterior y la purificación, 10,7 mg (14%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,52 (2H), 0,67 (2H), 1,18 (6H), 2,40 (3H), 2,82 (1H), 3,18 (2H), 4,81 (1H), 5,95 (1H), 6,77 (1H), 7,38 (1H), 7,59 (2H), 7,81 (1H), 7,83 (1H), 8,06 (1H), 8,27-8,35 (3H), 9,45 (1H) ppm.

Ejemplo 366

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(6-metoxipiridin-

3-il)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



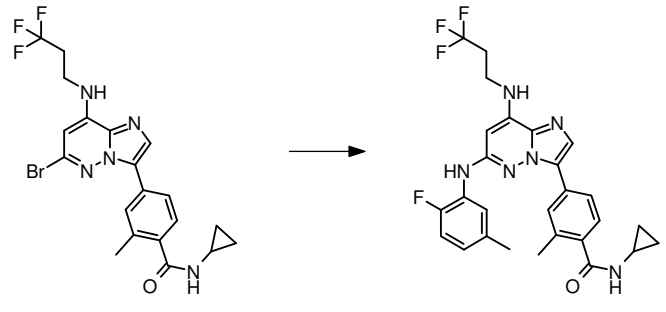
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando 4-metoxianilina para dar, luego del tratamiento posterior y la purificación, 27 mg (33%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,65 (2H), 1,18 (6H), 2,36 (3H), 2,80 (1H), 3,15 (2H), 3,79 (3H), 4,80 (1H), 5,83 (1H), 6,55 (1H), 6,77 (1H), 7,30 (1H), 7,76 (1H), 7,77 (1H), 7,92 (1H), 8,09 (1H), 8,28 (1H), 8,45 (1H), 8,82 (1H) ppm.

Ejemplo 367

N-ciclopropil-4-{6-[(2-fluoro-5-metilfenil)amino]-8-[(3,3,3-

trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



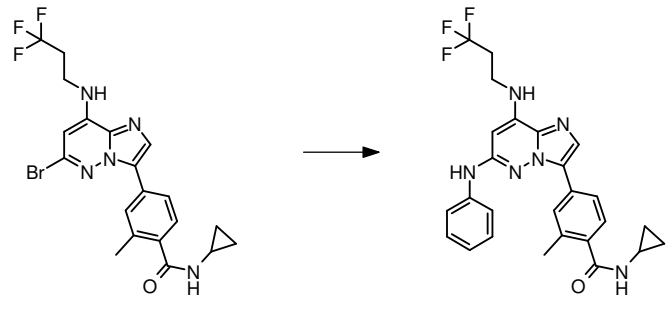
Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando 2-fluoro-5-metilanilina para dar, luego del tratamiento posterior y la purificación, 18,7 mg (22%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,65 (2H), 2,23 (3H), 2,28 (2H), 2,68 (3H), 2,79 (1H), 3,48 (2H), 6,10 (1H), 6,79 (1H), 7,09 (1H), 7,24-7,32 (2H), 7,78 (1H), 7,87 (1H), 7,90 (1H), 7,94 (1H), 8,25 (1H), 8,47 (1H) ppm.

Ejemplo 368

4-{6-anilino-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-

N-ciclopropil-2-metilbenzamida



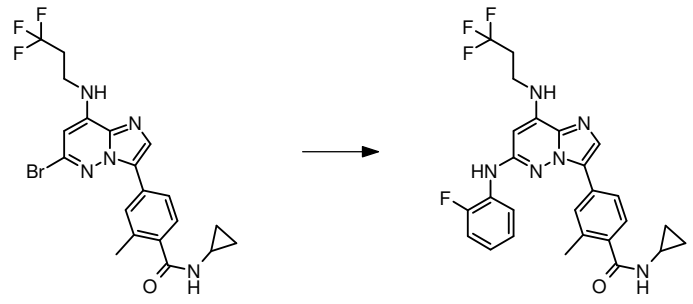
Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando anilina para dar, luego del tratamiento posterior y la purificación, 21,1 mg (26%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 2,38 (3H), 2,68 (2H), 2,81 (1H), 3,49 (2H), 5,84 (1H), 6,90 (1H), 7,23-7,31 (3H), 7,34 (1H), 7,66 (2H), 7,78 (1H), 7,84 (1H), 8,12 (1H), 8,30 (1H), 8,96 (1H) ppm.

Ejemplo 369

N-ciclopropil-4-{6-[(2-fluorofenil)amino]-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



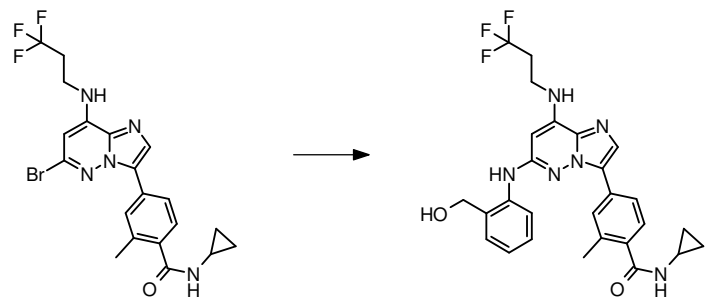
Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-

ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando 2-fluoroanilina para dar, luego del tratamiento posterior y la purificación, 12,0 mg (14%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,65 (2H), 2,32 (3H), 2,68 (2H), 2,80 (1H), 3,49 (2H), 6,14 (1H), 7,00 (1H), 7,14 (1H), 7,23 (1H), 7,26-7,34 (2H), 7,79 (1H), 7,81 (1H), 8,02 (1H), 8,17 (1H), 8,27 (1H), 8,57 (1H) ppm.

Ejemplo 370

N-ciclopropil-4-(6-{[2-(hidroximetil)fenil]amino}-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida



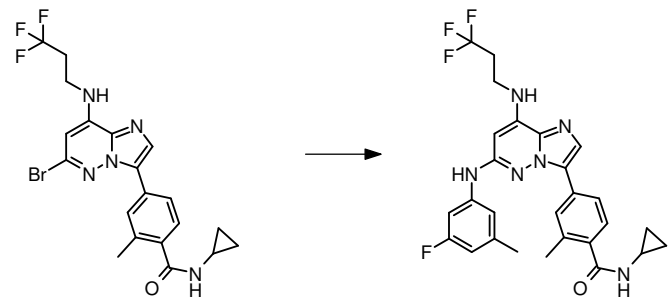
Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando (2-aminofenil)metanol para dar, luego del tratamiento posterior y la purificación, 5,2 mg (6%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,64 (2H), 2,25 (3H), 2,69 (2H), 2,78 (1H), 3,50 (2H), 4,55 (2H), 5,30 (1H), 5,94 (1H), 7,05

(1H), 7,18-7,29 (3H), 7,38 (1H), 7,77-7,87 (3H), 8,01 (1H), 8,07 (1H), 8,24 (1H) ppm.

Ejemplo 371

N-ciclopropil-4-{6-[(3-fluoro-5-metilfenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



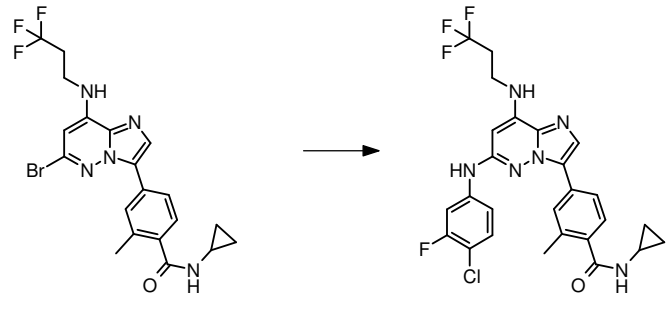
Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando 3-fluoro-5-metilanilina para dar, luego del tratamiento posterior y la purificación, 20,2 mg (23%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,66 (2H), 2,25 (3H), 2,35 (3H), 2,68 (2H), 2,81 (1H), 3,49 (2H), 5,82 (1H), 6,53 (1H), 7,05 (1H), 7,29-7,39 (2H), 7,54 (1H), 7,77 (1H), 7,87 (1H), 7,98 (1H), 8,30 (1H), 9,12 (1H) ppm.

Ejemplo 372

4-{6-[(4-cloro-3-fluorofenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo

[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida

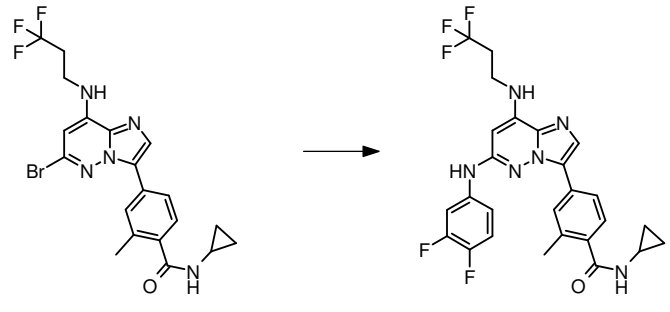


Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando 4-cloro-3-fluoroanilina para dar, luego del tratamiento posterior y la purificación, 16,9 mg (19%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 2,36 (3H), 2,68 (2H), 2,81 (1H), 3,50 (2H), 5,81 (1H), 7,26 (1H), 7,35 (1H), 7,39 (1H), 7,44 (1H), 7,77 (1H), 7,80 (1H), 7,95 (1H), 7,98 (1H), 8,31 (1H), 9,36 (1H) ppm.

Ejemplo 373

N-ciclopropil-4-{6-[(3,4-difluorofenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



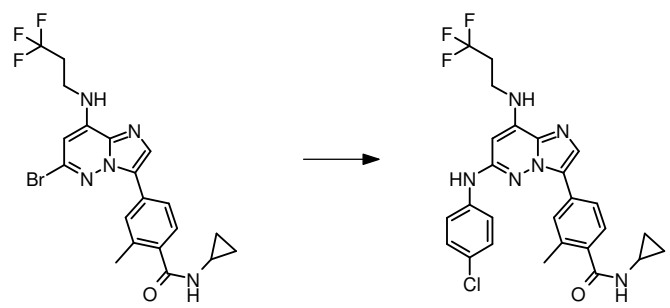
Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando 3,4-difluoroanilina para dar, luego del tratamiento posterior y la purificación, 11,9 mg (14%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 2,36 (3H), 2,68 (2H), 2,81 (1H), 3,50 (2H), 5,79 (1H), 7,22 (1H), 7,28-7,39 (3H), 7,77 (1H), 7,81 (1H), 7,91 (1H), 8,00 (1H), 8,30 (1H), 9,20 (1H) ppm.

Ejemplo 374

4-{6-[(4-clorofenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]

piridazin-3-il}-N-ciclopropil-2-metilbenzamida



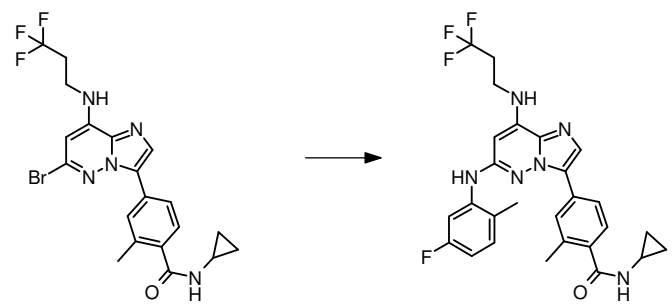
Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando 4-cloroanilina para dar, luego del tratamiento posterior y la purificación, 14,3 mg (17%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,52 (2H), 0,67 (2H), 2,38 (3H), 2,68 (2H),

2,81 (1H), 3,49 (2H), 5,82 (1H), 7,30 (2H), 7,33 (1H), 7,38 (1H), 7,68 (2H), 7,78 (1H), 7,84 (1H), 8,02 (1H), 8,30 (1H), 9,12 (1H) ppm.

Ejemplo 375

N-ciclopropil-4-{6-[(5-fluoro-2-metilfenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



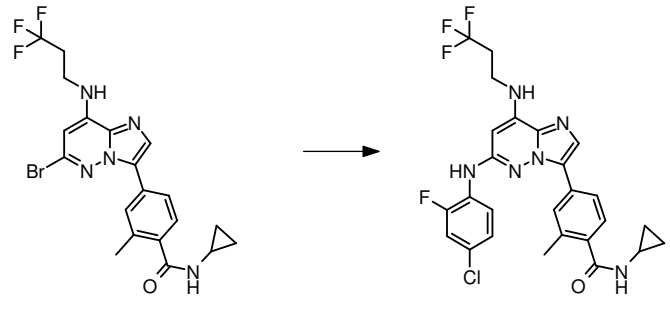
Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando 5-fluoro-2-metilanilina para dar, luego del tratamiento posterior y la purificación, 6,6 mg (8%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,64 (2H), 2,24 (3H), 2,26 (3H), 2,63-2,85 (3H), 3,50 (2H), 6,11 (1H), 6,75 (1H), 7,19 (1H), 7,24 (1H), 7,29 (1H), 7,78-7,86 (3H), 7,96-8,03 (2H), 8,25 (1H) ppm.

Ejemplo 376

4-{6-[(4-cloro-2-fluorofenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo

[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



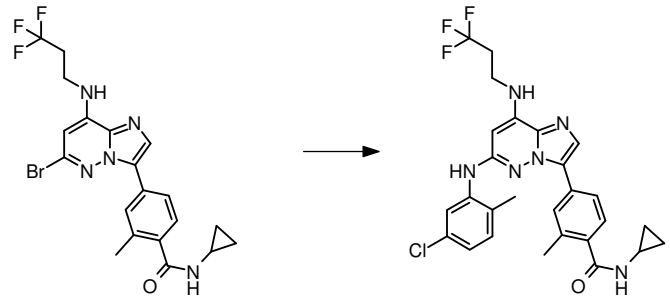
Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando 4-cloro-2-fluoroanilina para dar, luego del tratamiento posterior y la purificación, 10,8 mg (12%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 2,31 (3H), 2,68 (2H), 2,80 (1H), 3,49 (2H), 6,12 (1H), 7,21 (1H), 7,32 (1H), 7,35 (1H), 7,46 (1H), 7,79 (1H), 7,80 (1H), 7,96 (1H), 8,18 (1H), 8,28 (1H), 8,69 (1H) ppm.

Ejemplo 377

4-{6-[(5-cloro-2-metilfenil)amino]-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida

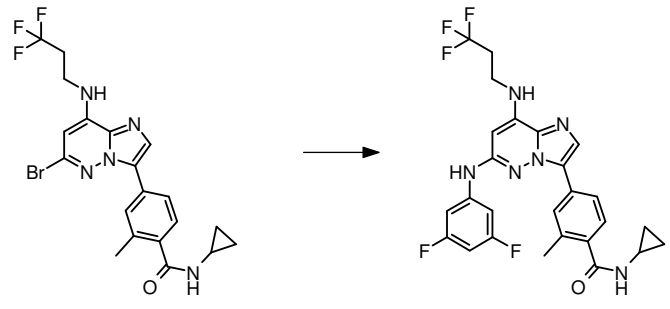


Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando 5-cloro-2-metilanilina para dar, luego del tratamiento posterior y la purificación, 9,7 mg (11%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,64 (2H), 2,24 (3H), 2,26 (3H), 2,70 (2H), 2,78 (1H), 3,50 (2H), 6,06 (1H), 7,00 (1H), 7,21 (1H), 7,26 (1H), 7,29 (1H), 7,83 (1H), 7,89 (1H), 7,91-7,95 (2H), 8,04 (1H), 8,23 (1H) ppm.

Ejemplo 378

N-ciclopropil-4-{6-[(3,5-difluorofenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

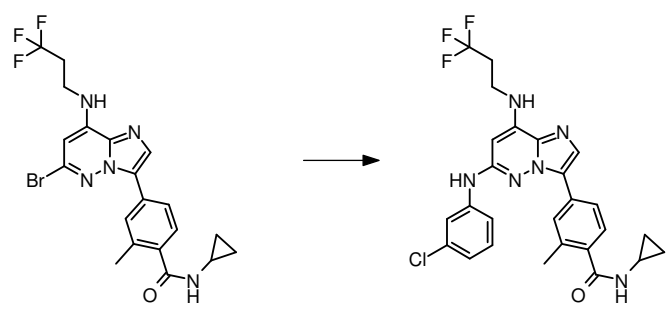


Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando 3,5-difluoroanilina para dar, luego del tratamiento posterior y la purificación, 14,7 mg (17%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,66 (2H), 2,35 (3H), 2,68 (2H), 2,81 (1H), 3,51 (2H), 5,80 (1H), 6,69 (1H), 7,31-7,38 (3H), 7,43 (1H), 7,78 (1H), 7,79 (1H), 8,00 (1H), 8,31 (1H), 9,43 (1H) ppm.

Ejemplo 379

4-{6-[(3-clorofenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



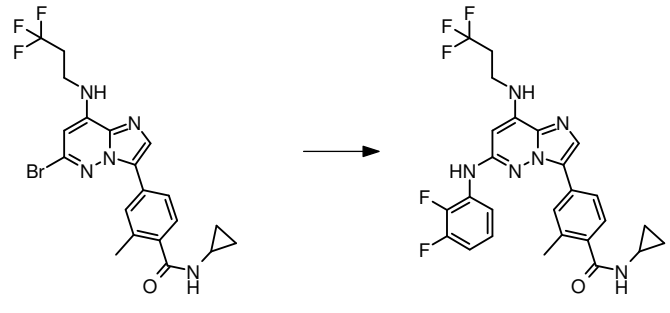
Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando 3-cloroanilina para dar, luego del tratamiento posterior y la purificación, 16,7 mg (19%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,66 (2H), 2,36 (3H), 2,68 (2H), 2,81 (1H), 3,50 (2H), 5,82 (1H), 6,93 (1H), 7,28 (1H), 7,32-7,39 (2H), 7,50 (1H), 7,79 (1H), 7,83 (1H), 7,92 (1H), 7,94 (1H), 8,28 (1H), 9,18 (1H) ppm.

Ejemplo 380

N-ciclopropil-4-{6-[(2,3-difluorofenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-

metilbenzamida

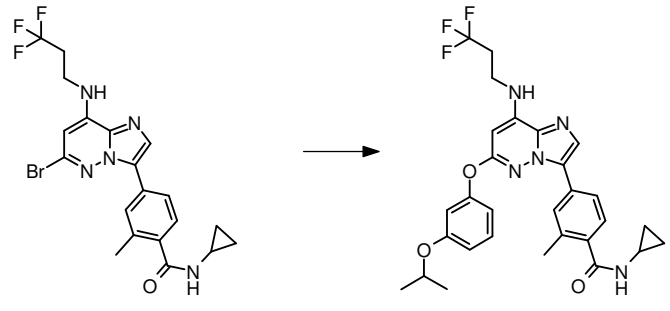


Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando 2,3-difluoroanilina para dar, luego del tratamiento posterior y la purificación, 6,6 mg (8%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,65 (2H), 2,31 (3H), 2,68 (2H), 2,80 (1H), 3,50 (2H), 6,13 (1H), 7,02 (1H), 7,13 (1H), 7,28 (1H), 7,37 (1H), 7,79 (1H), 7,81 (1H), 7,95 (1H), 7,99 (1H), 8,28 (1H), 8,81 (1H) ppm.

Ejemplo 381

N-ciclopropil-2-metil-4-{6-[3-(propan-2-iloxi)fenoxi]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida



Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-

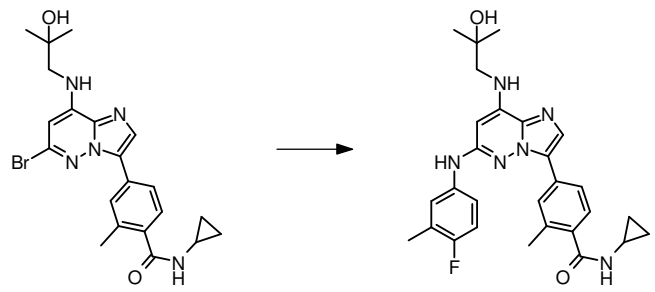
trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 3-isopropoxianilina para dar, luego del tratamiento posterior y la purificación, 4,8 mg (5%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,46 (2H), 0,63 (2H), 1,21 (6H), 2,14 (3H), 2,67 (2H), 2,76 (1H), 3,58 (2H), 4,58 (1H), 6,09 (1H), 6,75-6,84 (3H), 7,15 (1H), 7,31 (1H), 7,66 (1H), 7,70 (1H), 7,79 (1H), 7,93 (1H), 8,21 (1H) ppm.

Ejemplo 382

N-ciclopropil-4-{6-[(4-fluoro-3-metilfenil)amino]-8-[(2-hidroxi-2-

metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando 4-fluoro-3-metilanilina para dar, luego del tratamiento posterior y la purificación, 16,5 mg (19%) del compuesto del título.

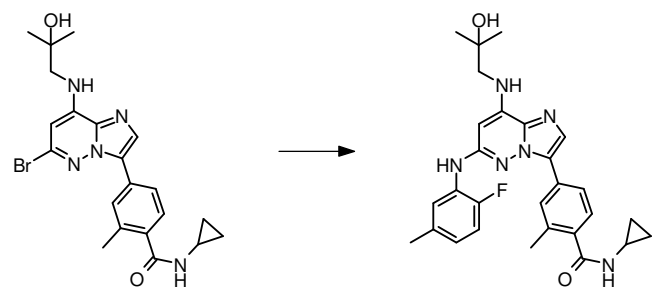
1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,66 (2H), 1,18 (6H), 2,18 (3H),

2,34 (3H), 2,81 (1H), 3,15 (2H), 4,80 (1H), 5,84 (1H), 6,52 (1H), 7,02 (1H), 7,34 (1H), 7,44-7,51 (2H), 7,75 (1H), 7,92 (1H), 7,96 (1H), 8,27 (1H), 8,83 (1H) ppm.

Ejemplo 383

N-ciclopropil-4-{6-[(2-fluoro-5-metilfenil)amino]-8-[(2-hidroxi-2-

metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



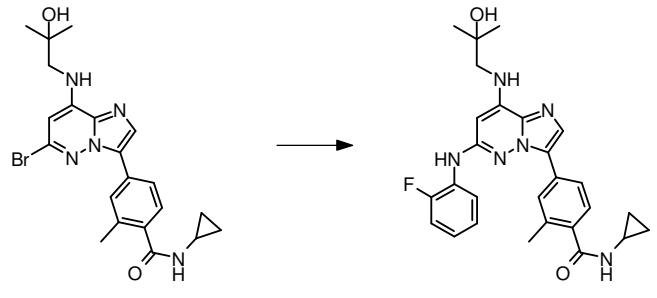
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando 2-fluoro-5-metilanilina para dar, luego del tratamiento posterior y la purificación, 10,5 mg (12%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,65 (2H), 1,18 (6H), 2,23 (3H), 2,28 (3H), 2,79 (1H), 3,15 (2H), 4,79 (1H), 6,13 (1H), 6,52 (1H), 6,79 (1H), 7,09 (1H), 7,27 (1H), 7,78 (1H), 7,86 (1H), 7,88 (1H), 7,95 (1H), 8,25 (1H), 8,42 (1H) ppm.

Ejemplo 384

N-ciclopropil-4-{6-[(2-fluorofenil)amino]-8-[(2-hidroxi-2-metilpropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



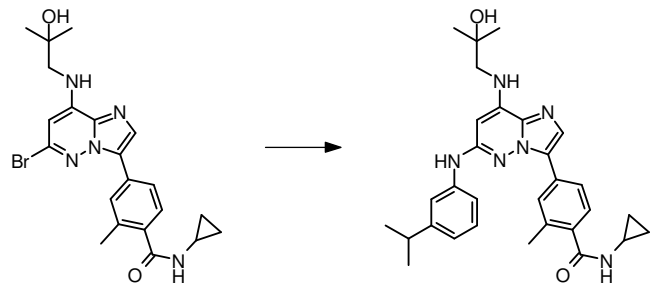
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando 2-fluoroanilina para dar, luego del tratamiento posterior y la purificación, 8,3 mg (10%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,65 (2H), 1,18 (6H), 2,31 (3H), 2,80 (1H), 3,16 (2H), 4,79 (1H), 6,17 (1H), 6,54 (1H), 7,00 (1H), 7,14 (1H), 7,22 (1H), 7,28 (1H), 7,78 (1H), 7,81 (1H), 8,02 (1H), 8,14 (1H), 8,27 (1H), 8,52 (1H) ppm.

Ejemplo 385

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(3-isopropilfenil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-

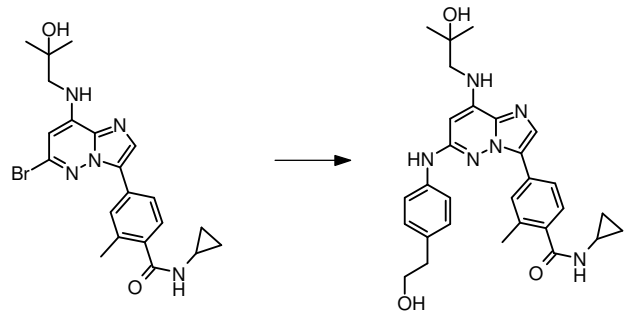
metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando 3-isopropilanilina para dar, luego del tratamiento posterior y la purificación, 11,6 mg (14%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,66 (2H), 1,16 (6H), 1,18 (6H), 2,37 (3H), 2,74-2,87 (2H), 3,15 (2H), 4,79 (1H), 5,89 (1H), 6,51 (1H), 6,79 (1H), 7,18 (1H), 7,26 (1H), 7,32 (1H), 7,68 (1H), 7,76 (1H), 7,93 (1H), 8,02 (1H), 8,28 (1H), 8,84 (1H) ppm.

Ejemplo 386

N-ciclopropil-4-(6-{[4-(2-hidroxietil)fenil]amino}-8-[(2-hidroxi-2-

metilpropil)amino]imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida



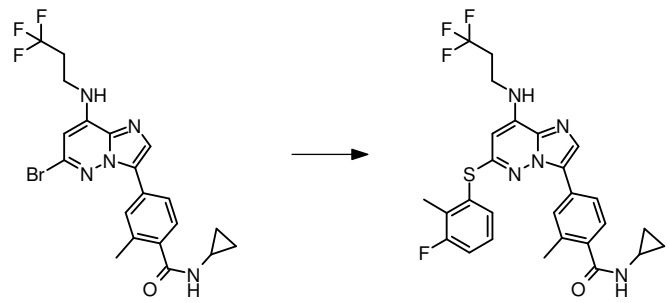
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando 2-(4-aminofenil)etanol para dar, luego del tratamiento posterior y la purificación, 10,6 mg (13%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,52 (2H), 0,66 (2H), 1,18 (6H), 2,38 (3H), 2,64 (2H), 2,81 (1H), 3,15 (2H), 3,54 (2H), 4,57 (1H), 4,80

(1H), 5,87 (1H), 6,49 (1H), 7,10 (2H), 7,34 (1H), 7,55 (2H), 7,76 (1H), 7,84 (1H), 8,12 (1H), 8,31 (1H), 8,82 (1H) ppm.

Ejemplo 387

N-ciclopropil-4-{6-[(3-fluoro-2-metilfenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



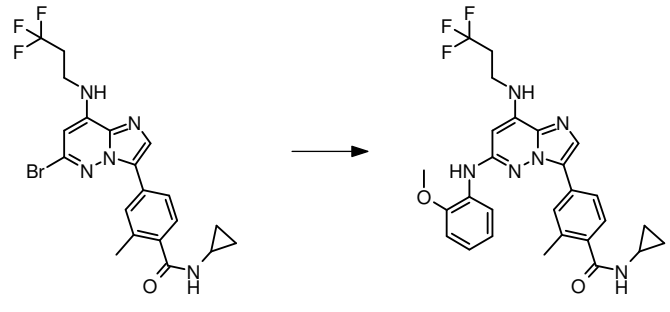
Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 3-fluoro-2-metilbencenotiol para dar, luego del tratamiento posterior y la purificación, 35,3 mg (42%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,65 (2H), 2,18 (3H), 2,27 (3H), 2,62 (2H), 2,79 (1H), 3,54 (2H), 6,19 (1H), 7,06 (1H), 7,30-7,42 (2H), 7,48 (1H), 7,55 (1H), 7,65 (1H), 7,68 (1H), 7,95 (1H), 8,24 (1H) ppm.

Ejemplo 388

N-ciclopropil-4-{6-[(2-metoxifenil)amino]-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

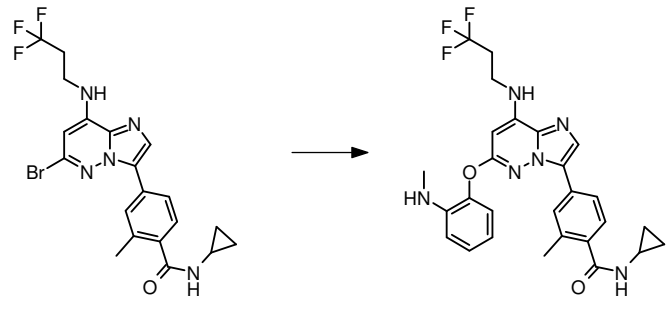


Se trataron 200 mg (415 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando 2-metoxianilina para dar, luego del tratamiento posterior y la purificación, 68,3 mg (31%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,65 (2H), 2,35 (3H), 2,69 (2H), 2,80 (1H), 3,29 (3H), 3,49 (2H), 6,28 (1H), 6,87-7,05 (3H), 7,21 (1H), 7,31 (1H), 7,78 (1H), 7,84 (1H), 8,02 (1H), 8,09 (1H), 8,24-8,32 (2H) ppm.

Ejemplo 389

N-ciclopropil-2-metil-4-{6-[2-(metilamino)fenoxi]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida



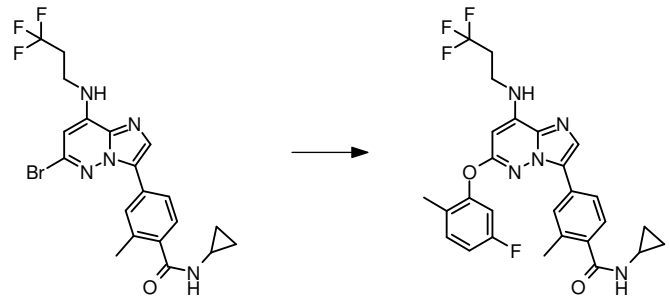
Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-

ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 2-(metilamino)fenol para dar, luego del tratamiento posterior y la purificación, 35,1 mg (43%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,65 (2H), 2,33 (3H), 2,46 (2H), 2,80 (1H), 3,25 (2H), 3,29 (3H), 5,21 (1H), 6,84 (1H), 6,95 (1H), 7,06 (1H), 7,14 (1H), 7,19 (1H), 7,31 (1H), 7,82 (1H), 8,04 (1H), 8,09 (1H), 8,26 (1H), 9,54 (1H) ppm.

Ejemplo 390

N-ciclopropil-4-{6-(5-fluoro-2-metilfenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 5-fluoro-2-metilfenol para dar, luego del tratamiento posterior y la purificación, 31,5 mg (38%) del compuesto del título.

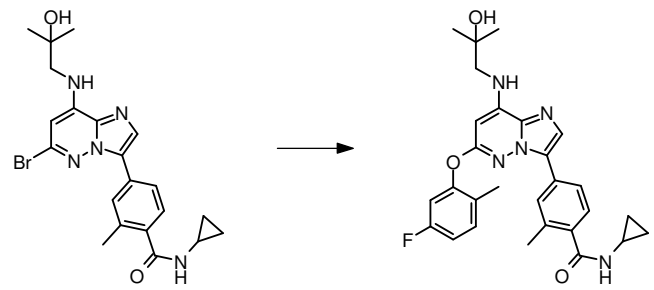
1H-RMN (DMSO-d6): δ= 0,46 (2H), 0,63 (2H), 2,10 (6H), 2,69 (2H),

2,76 (1H), 3,60 (2H), 6,16 (1H), 7,07 (1H), 7,13 (1H), 7,18 (1H), 7,37 (1H), 7,60 (1H), 7,69 (1H), 7,72 (1H), 7,93 (1H), 8,21 (1H) ppm.

Ejemplo 391

N-ciclopropil-4-{6-(5-fluoro-2-metilfenoxi)-8-[(2-hidroxi-2-metilpropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



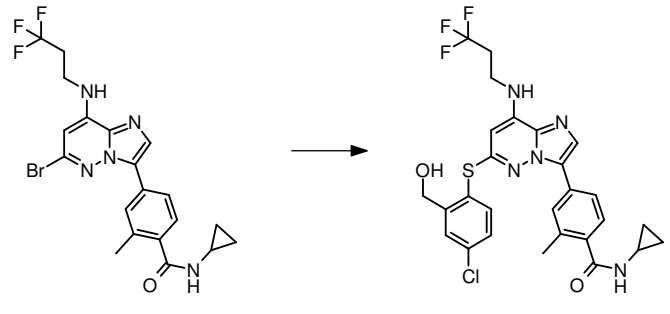
Se trataron 50 mg (109 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando 5-fluoro-2-metilfenol para dar, luego del tratamiento posterior y la purificación, 29,4 mg (54%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,46 (2H), 0,73 (2H), 1,17 (6H), 2,10 (6H), 2,76 (1H), 3,28 (2H), 4,76 (1H), 6,20 (1H), 6,98 (1H), 7,06 (1H), 7,13 (1H), 7,17 (1H), 7,36 (1H), 7,61 (1H), 7,71 (1H), 7,92 (1H), 8,21 (1H) ppm.

Ejemplo 392

4-(6-{[4-cloro-2-(hidroximetil)fenil]sulfanil}-8-[(3,3,3-trifluoropropil)

amino]imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida

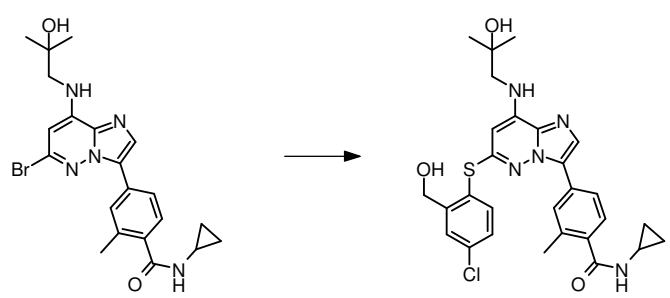


Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando (5-cloro-2-sulfanilfenil)metanol para dar, luego del tratamiento posterior y la purificación, 49,0 mg (55%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,65 (2H), 2,19 (3H), 2,63 (2H), 2,79 (1H), 3,54 (2H), 4,58 (2H), 5,43 (1H), 6,21 (1H), 7,06 (1H), 7,42 (1H), 7,47 (1H), 7,58-7,70 (4H), 7,94 (1H), 8,24 (1H) ppm.

Ejemplo 393

4-(6-{[4-cloro-2-(hidroximetil)fenil]sulfanil}-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida

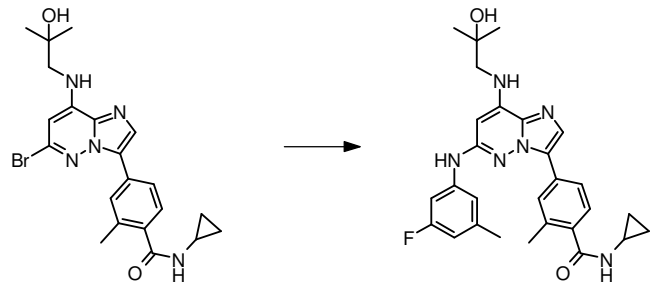


Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando (5-cloro-2-sulfanilfenil)metanol para dar, luego del tratamiento posterior y la purificación, 57,0 mg (63%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,65 (2H), 1,13 (6H), 2,19 (3H), 2,79 (1H), 3,24 (2H), 4,57 (2H), 4,72 (1H), 5,42 (1H), 6,28 (1H), 6-98 (1H), 7,06 (1H), 7,41 (1H), 7,48 (1H), 7,59 (1H), 7,61 (1H), 7,64 (1H), 7,92 (1H), 8,23 (1H) ppm.

Ejemplo 394

N-ciclopropil-4-{6-[(3-fluoro-5-metilfenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

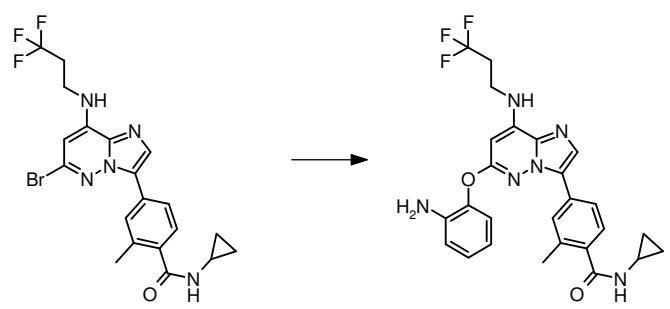


Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando 3-fluoro-5-metilanilina para dar, luego del tratamiento posterior y la purificación, 9,7 mg (11%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,65 (2H), 1,18 (6H), 2,24 (3H), 2,34 (3H), 2,81 (1H), 3,16 (2H), 4,81 (1H), 5,89 (1H), 6,52 (1H), 6,61 (1H), 7,05 (1H), 7,32 (1H), 7,53 (1H), 7,76 (1H), 7,88 (1H), 7,98 (1H), 8,29 (1H), 9,11 (1H) ppm.

Ejemplo 395

4-{6-(2-aminofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 2-aminofenol para dar, luego del tratamiento posterior y la purificación, 25,6 mg (32%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,47 (2H), 0,63 (2H), 2,13 (3H), 2,69 (2H), 2,76 (1H), 3,58 (2H), 4,92 (2H), 6,08 (1H), 6,58 (1H), 6,79 (1H), 6,97 (1H), 7,03 (1H), 7,13 (1H), 7,59 (1H), 7,67 (1H), 7,83 (1H), 7,91 (1H), 8,20 (1H) ppm.

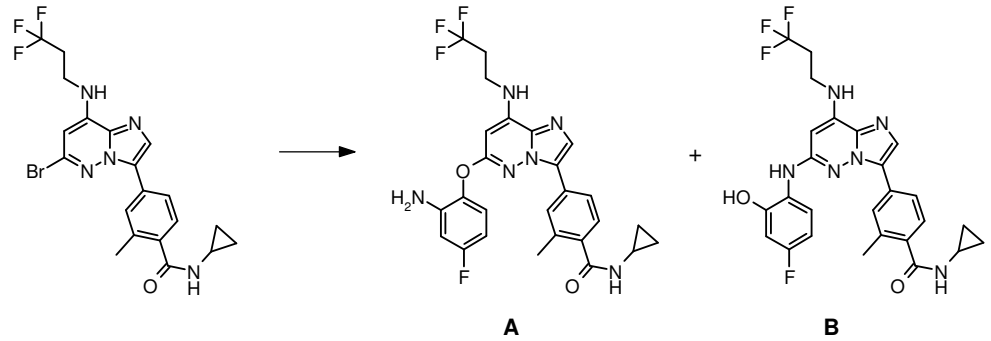
Ejemplo 396

4-{6-(2-amino-4-fluorofenoxi)-8-[(3,3,3-

trifluoropropil)amino]imidazo

[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida (A) y N-ciclopropil-4-{6-[(4-fluoro-2-hidroxifenil)amino]-8-[(3,3,3-

trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida (B)



A B

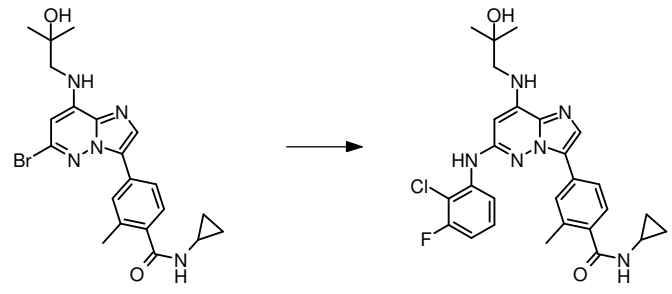
Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 2-amino-5-fluorofenol para dar, luego del tratamiento posterior y la purificación, 14,8 mg (18%) del compuesto del título A y 12,6 mg (15%) del compuesto del título B.

1H-RMN (DMSO-d6) de A: δ= 0,47 (2H), 0,64 (2H), 2,15 (3H), 2,69 (2H), 2,77 (1H), 3,58 (2H), 5,27 (2H), 6,08 (1H), 6,34 (1H), 6,55 (1H), 7,03 (1H), 7,15 (1H), 7,60 (1H), 7,67 (1H), 7,83 (1H), 7,92 (1H), 8,22 (1H) ppm.

1H-RMN (DMSO-d6) de B: δ= 0,50 (2H), 0,66 (2H), 2,34 (3H), 2,68 (2H), 2,81 (1H), 3,49 (2H), 6,38 (1H), 6,55 (1H), 6,79 (1H), 7,26 (1H), 7,30 (1H), 7,76 (1H), 7,82 (1H), 8,04 (1H), 8,09 (1H), 8,14 (1H), 8,29 (1H), 9,86 (1H) ppm.

Ejemplo 397

4-{6-(2-cloro-3-fluorofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida

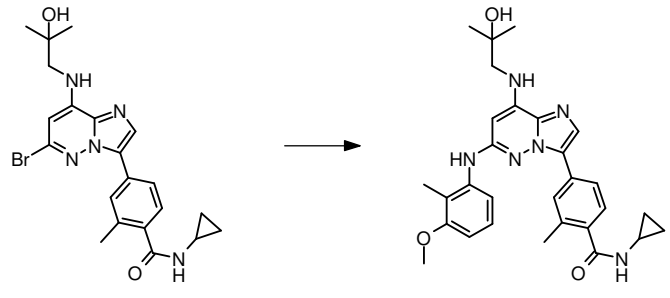


Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando 2-cloro-3-fluoroanilina para dar, luego del tratamiento posterior y la purificación, 6,0 mg (6%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 1,17 (6H), 2,36 (3H), 2,81 (1H), 3,17 (2H), 4,83 (1H), 5,95 (1H), 6,68 (1H), 7,28 (1H), 7,35 (1H), 7,40 (1H), 7,76 (1H), 7,81 (1H), 7,95 (1H), 7,99 (1H), 8,31 (1H), 9,51 (1H) ppm.

Ejemplo 398

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(3-metoxi-2-metilfenil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



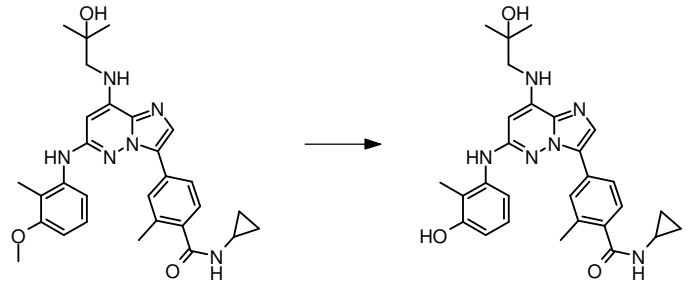
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando 3-metoxi-2-metilanilina para dar, luego del tratamiento posterior y la purificación, 16,7 mg (20%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,64 (2H), 1,18 (6H), 2,06 (3H), 2,21 (3H), 2,78 (1H), 3,15 (2H), 3,77 (3H), 4,81 (1H), 5,97 (1H), 6,40 (1H), 6,73 (1H), 7,13 (1H), 7,18 (1H), 7,24 (1H), 7,79 (2H), 8,01 (2H), 8,22 (1H) ppm.

Ejemplo 399

N-ciclopropil-4-{6-[(2-hidroxifenil)amino]-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



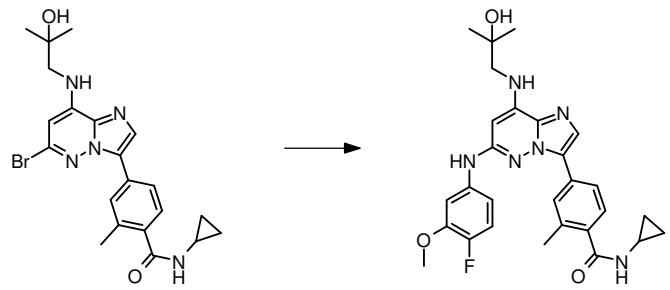
Se trataron 40 mg (76 µmol) de N-ciclopropil-4-{6-[(2-metoxifenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida, que se preparó de acuerdo

con el ejemplo 388, de manera análoga al Ejemplo Intermediario 280 para dar, luego del tratamiento posterior y la purificación, 14,7 mg (36%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 2,35 (3H), 2,68 (2H), 2,80 (1H), 3,48 (2H), 6,28 (1H), 6,73-6,88 (3H), 7,17 (1H), 7,30 (1H), 7,77 (1H), 7,83 (1H), 7,91 (1H), 8,10 (1H), 8,18 (1H), 8,28 (1H), 9,80 (1H) ppm.

Ejemplo 400

N-ciclopropil-4-{6-[(4-fluoro-3-metoxifenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



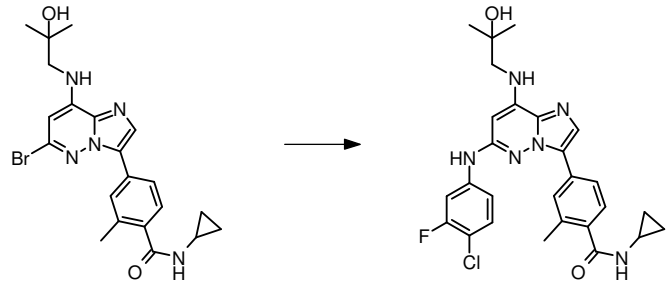
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo Intermediario 305 usando 4-fluoro-3-metoxianilina para dar, luego del tratamiento posterior y la purificación, 20,3 mg (24%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 1,18 (6H), 2,33 (3H), 2,81 (1H), 3,16 (2H), 3,67 (3H), 4,80 (1H), 5,85 (1H), 6,57 (1H), 7,08 (1H), 7,23 (1H), 7,28 (1H), 7,33 (1H), 7,75 (1H),

7,86 (1H), 7,99 (1H), 8,27 (1H), 8,91 (1H) ppm.

Ejemplo 401

4-{6-[(4-cloro-3-fluorofenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



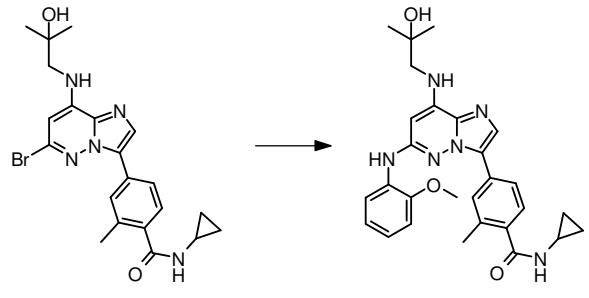
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo Intermediario 305 usando 4-cloro-3-fluoroanilina para dar, luego del tratamiento posterior y la purificación, 5,6 mg (7%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,52 (2H), 0,66 (2H), 1,18 (6H), 2,37 (3H), 2,82 (1H), 3,17 (2H), 4,81 (1H), 5,91 (1H), 6,69 (1H), 7,28 (1H), 7,35 (1H), 7,41 (1H), 7,76 (1H), 7,81 (1H), 7,95 (1H), 7,99 (1H), 8,31 (1H), 9,41 (1H) ppm.

Ejemplo 402

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(2-metoxifenil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



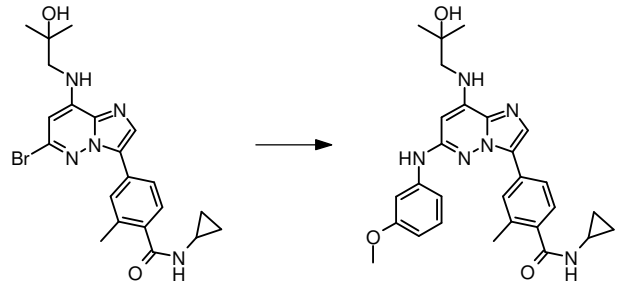
Se trataron 50 mg (109 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando 2-metoxianilina para dar, luego del tratamiento posterior y la purificación, 59,7 mg (35%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 1,18 (6H), 2,35 (3H), 2,80 (1H), 3,17 (2H), 3,84 (3H), 4,78 (1H), 6,29 (1H), 6,43 (1H), 6,88-6,96 (2H), 7,00 (1H), 7,31 (1H), 7,77 (1H), 7,84 (1H), 7,92 (1H), 8,09 (1H), 8,25 (1H), 8,29 (1H) ppm.

Ejemplo 403

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(3-metoxifenil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



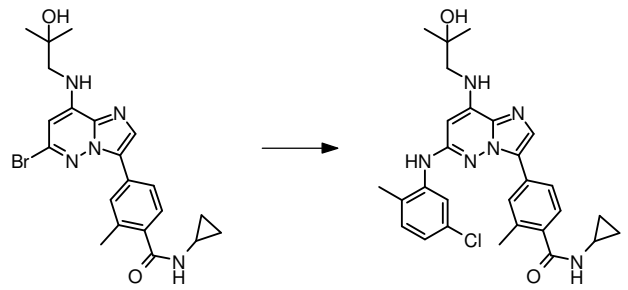
Se trataron 150 mg (327 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo

Intermediario 96a, de manera análoga al Ejemplo 305 usando 3-metoxianilina para dar, luego del tratamiento posterior y la purificación, 44,4 mg (24%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,67 (2H), 1,18 (6H), 2,36 (3H), 2,81 (1H), 3,15 (2H), 3,66 (3H), 4,80 (1H), 5,88 (1H), 6,48 (1H), 6,55 (1H), 7,16 (1H), 7,20-7,28 (2H), 7,32 (1H), 7,77 (1H), 7,86 (1H), 8,08 (1H), 8,29 (1H), 8,90 (1H) ppm.

Ejemplo 404

4-{6-[(5-cloro-2-metilfenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida

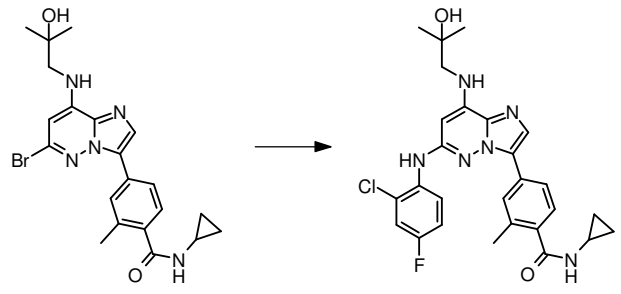


Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando 5-cloro-2-metilanilina para dar, luego del tratamiento posterior y la purificación, 6,2 mg (7%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,64 (2H), 1,19 (6H), 2,23 (3H), 2,26 (3H), 2,78 (1H), 3,17 (2H), 4,82 (1H), 6,10 (1H), 6,52 (1H), 6,99 (1H), 7,20 (1H), 7,26 (1H), 7,82 (1H), 7,88-7,96 (3H), 8,01 (1H), 8,23 (1H) ppm.

Ejemplo 405

4-{6-[(2-cloro-4-fluorofenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida

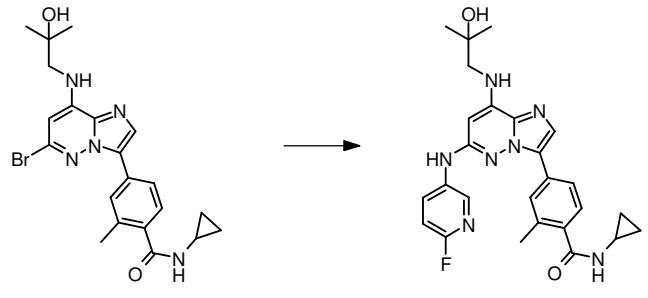


Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando 2-cloro-4-fluoroanilina para dar, luego del tratamiento posterior y la purificación, 7,3 mg (8%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,64 (2H), 1,18 (6H), 2,24 (3H), 2,78 (1H), 3,17 (2H), 4,80 (1H), 5,72 (1H), 6,09 (1H), 6,53 (1H), 7,23 (1H), 7,49 (1H), 7,76 (1H), 7,79 (1H), 7,90 (1H), 7,92 (1H), 8,23 (1H), 8,25 (1H) ppm.

Ejemplo 406

N-ciclopropil-4-{6-[(6-fluoropiridin-3-il)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



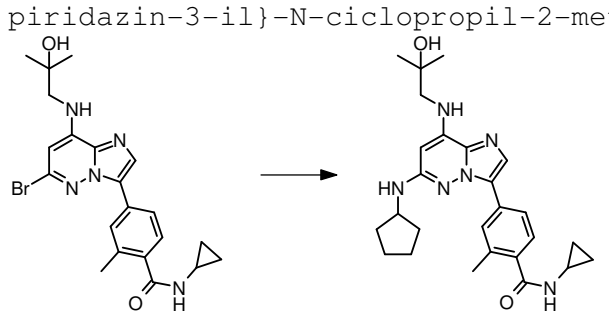
Se trataron 50 mg (109 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando 6-fluoropiridin-3-amina para dar, luego del tratamiento posterior y la purificación, 9,9 mg (18%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 1,18 (6H), 2,37 (3H), 2,81 (1H), 3,17 (2H), 4,80 (1H), 5,87 (1H), 6,67 (1H), 7,10 (1H), 7,34 (1H), 7,76 (1H), 7,78 (1H), 8,00 (1H), 8,16 (1H), 8,29 (1H), 8,50 (1H), 9,17 (1H) ppm.

Ejemplo 407

4-{6-(ciclopentilamino)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]

piridazin-3-il}-N-ciclopropil-2-metilbenzamida



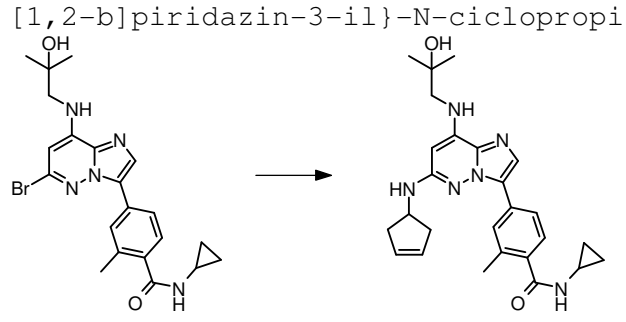
Se trataron 50 mg (109 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo

Intermediario 96a, de manera análoga al Ejemplo 305 usando ciclopentanamina para dar, luego del tratamiento posterior y la purificación, 10,8 mg (20%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,64 (2H), 1,15 (6H), 1,43-1,72 (6H), 1,97 (2H), 2,34 (3H), 2,79 (1H), 3,06 (2H), 3,99 (1H), 4,76 (1H), 5,61 (1H), 6,17 (1H), 6,37 (1H), 7,29 (1H), 7,72 (1H), 7,99 (1H), 8,17 (1H), 8,24 (1H) ppm.

Ejemplo 408

4-{6-(ciclopent-3-en-1-ilamino)-8-[(2-hidroxi-2-metilpropil)amino]imidazo [1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



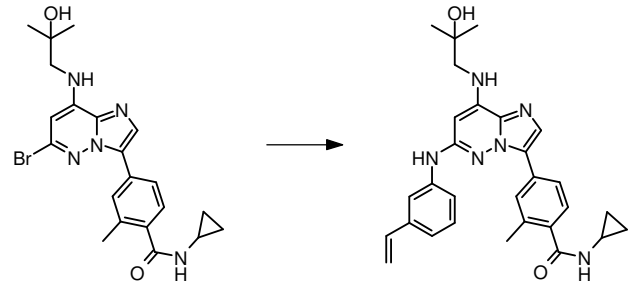
Se trataron 100 mg (218 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando ciclopent-3-en-1-amina para dar, luego del tratamiento posterior y la purificación, 12,8 mg (12%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,64 (2H), 1,15 (6H), 2,25 (1H), 2,28 (1H), 2,34 (3H), 2,73-2,83 (3H), 3,07 (2H), 4,32 (1H), 4,76 (1H), 5,61 (1H), 5,73 (2H), 6,21 (1H), 6,57 (1H), 7,31 (1H), 7,73 (1H), 8,02 (1H), 8,13 (1H), 8,25 (1H) ppm.

Ejemplo 409

N-ciclopropil-4-{6-[(3-etenilfenil)amino]-8-[(2-hidroxi-2-metilpropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



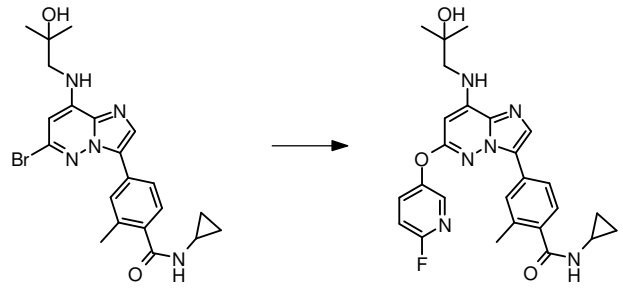
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando 3-vinilanilina para dar, luego del tratamiento posterior y la purificación, 28,0 mg (33%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 1,18 (6H), 2,34 (3H), 2,81 (1H), 3,16 (2H), 4,81 (1H), 5,18 (1H), 5,67 (1H), 5,89 (1H), 6,56 (1H), 6,64 (1H), 7,03 (1H), 7,24 (1H), 7,31 (1H), 7,62 (1H), 7,63 (1H), 7,77 (1H), 7,91 (1H), 8,01 (1H), 8,29 (1H), 8,94 (1H) ppm.

Ejemplo 410

N-ciclopropil-4-{6-[(6-fluoropiridin-3-il)oxi]-8-[(2-hidroxi-2-metilpropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

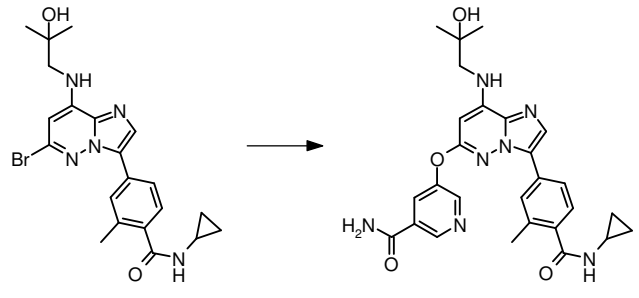


Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando 6-fluoropiridin-3-ol para dar, luego del tratamiento posterior y la purificación, 4,1 mg (5%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,47 (2H), 0,64 (2H), 1,17 (6H), 2,14 (3H), 2,77 (1H), 3,28 (2H), 4,75 (1H), 6,24 (1H), 7,07 (1H), 7,17 (1H), 7,32 (1H), 7,61 (1H), 7,68 (1H), 7,92 (1H), 8,03 (1H), 8,23 (1H), 8,25 (1H) ppm.

Ejemplo 411

5-({3-[4-(ciclopropilcarbamoil)-3-metilfenil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-6-il}oxi)nicotinamida



Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando 5-

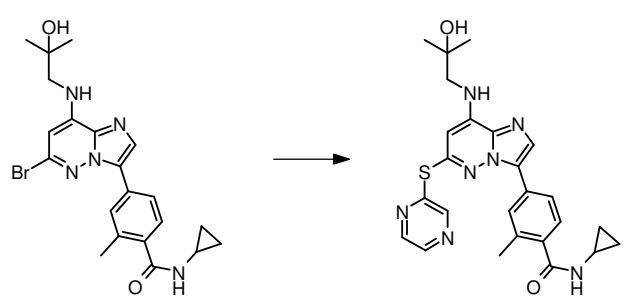
hidroxinicotinamida para dar, luego del tratamiento posterior y la purificación, 22,0 mg (25%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,46 (2H), 0,63 (2H), 1,17 (6H), 2,09 (3H), 2,76 (1H), 3,13 (2H), 4,75 (1H), 6,27 (1H), 7,10 (1H), 7,13 (1H), 7,61 (1H), 7,64 (1H), 7,69 (1H), 7,92 (1H), 8,17-8,22 (3H), 8,72 (1H), 8,96 (1H) ppm.

Ejemplo 412

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(pirazin-2-ilsulfanil)

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



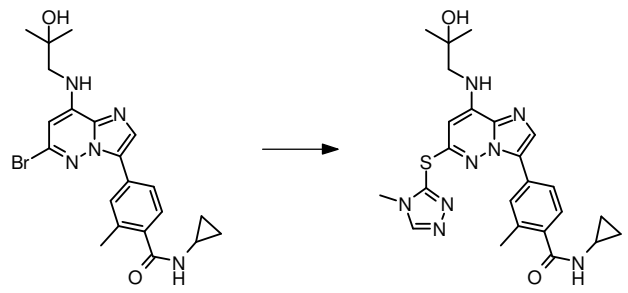
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando pirazin-2-tiol para dar, luego del tratamiento posterior y la purificación, 17,5 mg (21%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,65 (2H), 1,13 (6H), 2,23 (3H), 2,79 (1H), 3,25 (2H), 4,71 (1H), 6,48 (1H), 7,16 (1H), 7,19 (1H), 7,66 (1H), 7,71 (1H), 7,97 (1H), 8,25 (1H), 8,58 (1H), 8,61 (1H), 8,83 (1H) ppm.

Ejemplo 413

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(4-metil-4H-1,2,4-

triazol-3-il)sulfanil]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



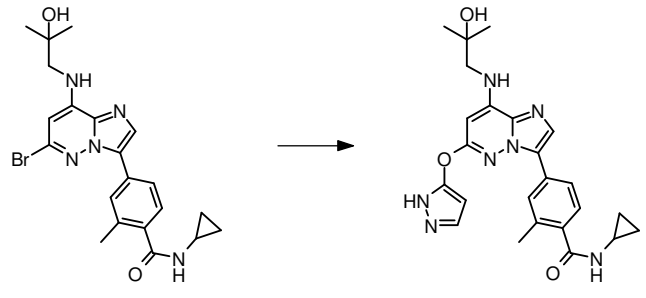
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando 4-metil-4H-1,2,4-triazol-3-tiol para dar, luego del tratamiento posterior y la purificación, 17,5 mg (21%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 1,14 (6H), 2,28 (3H), 2,80 (1H), 3,25 (2H), 3,61 (3H), 4,73 (1H), 6,38 (1H), 7,17 (1H), 7,21 (1H), 7,48 (1H), 7,60 (1H), 7,96 (1H), 8,28 (1H), 8,93 (1H) ppm.

Ejemplo 414

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(1H-pirazol-5-iloxi)

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



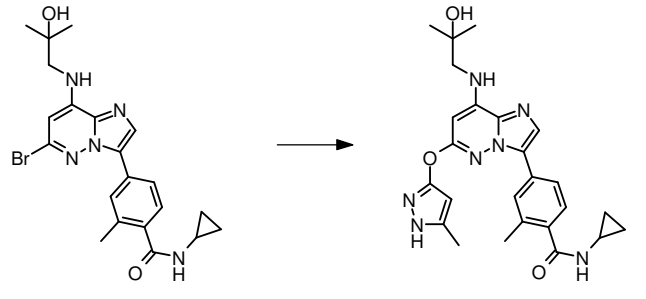
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando 1H-pirazol-5-ol para dar, luego del tratamiento posterior y la purificación, 5,5 mg (7%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,64 (2H), 1,15 (6H), 2,25 (3H), 2,78 (1H), 3,26 (2H), 4,75 (1H), 6,13 (1H), 6,16 (1H), 6,98 (1H), 7,23 (1H), 7,73-7,80 (2H), 7,91 (1H), 7,93 (1H), 8,26 (1H), 12,45 (1H) ppm.

Ejemplo 415

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(5-metil-1H-

pirazol-3-il)oxi]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



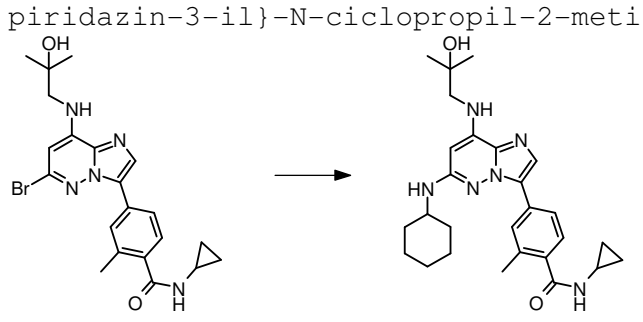
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo

Intermediario 96a, de manera análoga al Ejemplo 51 usando 5-metil-1H-pirazol-3-ol para dar, luego del tratamiento posterior y la purificación, 6,3 mg (8%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,64 (2H), 1,15 (6H), 2,23 (3H), 2,26 (3H), 2,79 (1H), 3,26 (2H), 4,74 (1H), 5,92 (1H), 6,11 (1H), 6,96 (1H), 7,24 (1H), 7,77 (1H), 7,90 (1H), 7,96 (1H), 8,26 (1H), 12,13 (1H) ppm.

Ejemplo 416

4-{6-(ciclohexilamino)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida

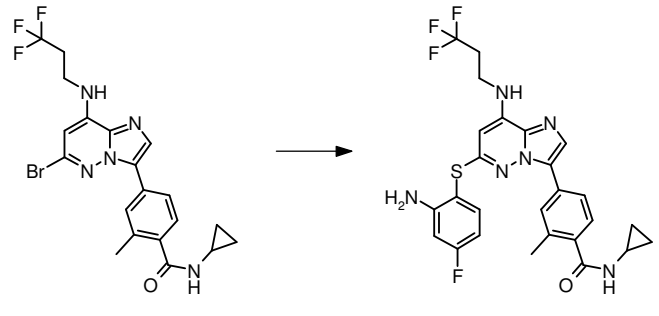


Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando ciclohexanamina para dar, luego del tratamiento posterior y la purificación, 7,8 mg (10%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,64 (2H), 1,11-1,42 (5H), 1,15 (6H), 1,60 (1H), 1,73 (2H), 2,03 (2H), 2,35 (3H), 2,79 (1H), 3,06 (2H), 3,56 (1H), 4,77 (1H), 5,61 (1H), 6,17 (1H), 6,25 (1H), 7,28 (1H), 7,72 (1H), 7,95 (1H), 8,16 (1H), 8,26 (1H) ppm.

Ejemplo 417

4-{6-[(2-amino-4-fluorofenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida

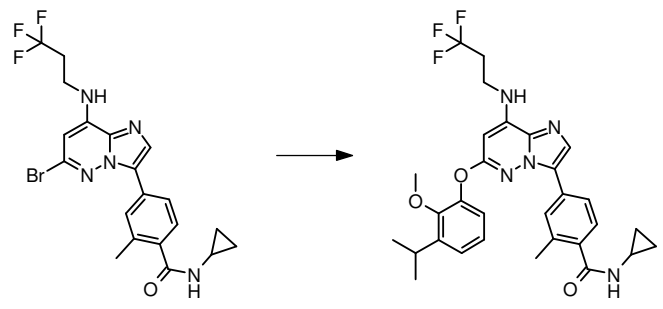


Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 2-amino-4-fluorobencenotiol para dar, luego del tratamiento posterior y la purificación, 23,7 mg (27%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,65 (2H), 2,24 (3H), 2,60 (2H), 2,79 (1H), 3,49 (2H), 5,75 (2H), 6,02 (1H), 6,40 (1H), 6,58 (1H), 7,12 (1H), 7,38 (1H), 7,60 (1H), 7,74 (1H), 7,75 (1H), 7,93 (1H), 8,24 (1H) ppm.

Ejemplo 418

N-ciclopropil-4-{6-[2-metoxi-3-(propan-2-il)fenoxi]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



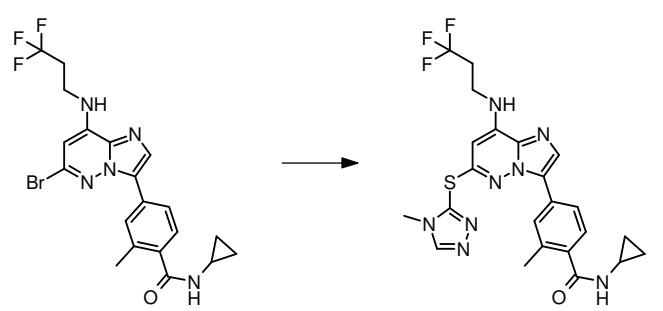
Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 3-isopropil-2-metoxifenol para dar, luego del tratamiento posterior y la purificación, 45 mg (48%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,45 (2H), 0,63 (2H), 1,16 (6H), 2,06 (3H), 2,60-2,80 (3H), 3,17-3,26 (1H), 3,60 (2H), 3,71 (3H), 6,17 (1H), 7,04-7,23 (4H), 7,61 (1H), 7,67 (1H), 7,71 (1H), 7,94 (1H), 8,19 (1H) ppm.

Ejemplo 419

N-ciclopropil-2-metil-4-{6-[(4-metil-4H-1,2,4-triazol-3-il)sulfanil]-8-

[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida



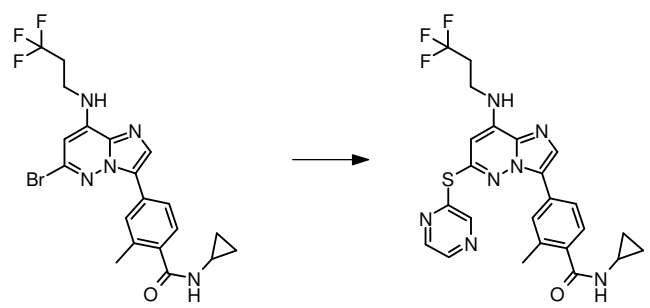
Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 4-metil-4H-1,2,4-triazol-3-tiol para dar, luego del tratamiento posterior y la purificación, 29,4 mg (35%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 2,28 (3H), 2,66 (2H), 2,80 (1H), 3,57 (2H), 3,61 (3H), 6,35 (1H), 7,20 (1H), 7,46 (1H), 7,59 (1H), 7,84 (1H), 7,96 (1H), 8,27 (1H), 8,93 (1H) ppm.

Ejemplo 420

N-ciclopropil-2-metil-4-{6-(pirazin-2-ilsulfanil)-8-[(3,3,3-trifluoropropil)

amino]imidazo[1,2-b]piridazin-3-il}benzamida



Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando pirazin-2-tiol para dar, luego del tratamiento posterior y la purificación, 28,6 mg (34%) del compuesto del título.

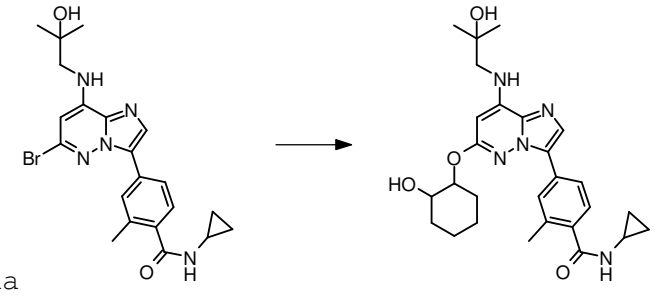
1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,64 (2H), 2,23 (3H), 2,64 (2H),

2,79 (1H), 3,57 (2H), 6,43 (1H), 7,18 (1H), 7,64 (1H), 7,69 (1H), 7,83 (1H), 7,97 (1H), 8,25 (1H), 8,57-8,62 (2H), 8,86 (1H) ppm.

Ejemplo 421

N-ciclopropil-4-(6-{[(1RS,2RS)-2-hidroxiciclohexil]oxi}-8-[(2-hidroxi-2-

metilpropil)amino]imidazo[1,2-b]piridazin-3-il)-2-



metilbenzamida

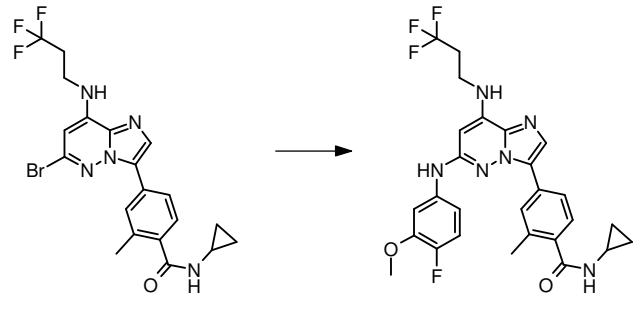
Se trataron 50 mg (109 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando (1RS,2RS)-ciclohexano-1,2-diol para dar, luego del tratamiento posterior y la purificación, 2,8 mg (5%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,65 (2H), 1,13 (6H), 1,23-1,39 (4H), 1,66 (2H), 1,89 (1H), 2,36 (3H), 2,80 (1H), 3,19 (2H), 3,54 (1H), 4,65 (1H), 4,72 (1H), 4,82 (1H), 5,72 (1H), 5,84 (1H), 6,66 (1H), 7,33 (1H), 7,87 (1H), 7,91 (1H), 8,08 (1H), 8,29 (1H) ppm.

Ejemplo 422

N-ciclopropil-4-{6-[(4-fluoro-3-metoxifenil)amino]-8-[(3,3,3-

trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

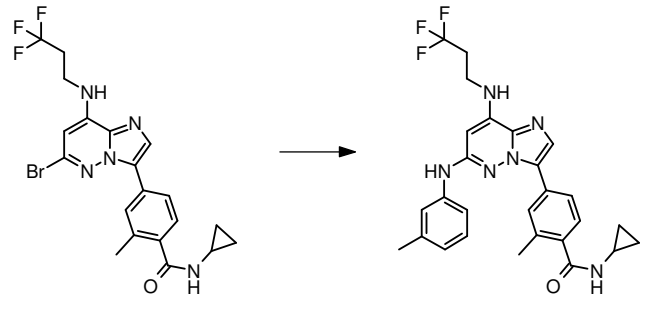


Se trataron 100 mg (207 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando 4-fluoro-3-metoxianilina para dar, luego del tratamiento posterior y la purificación, 43,1 mg (38%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 2,33 (3H), 2,67 (2H), 2,81 (1H), 3,49 (2H), 3,67 (3H), 5,78 (1H), 7,08 (1H), 7,19-7,37 (4H), 7,76 (1H), 7,85 (1H), 7,99 (1H), 8,27 (1H), 8,94 (1H) ppm.

Ejemplo 423

N-ciclopropil-2-metil-4-{6-[(3-metilfenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida



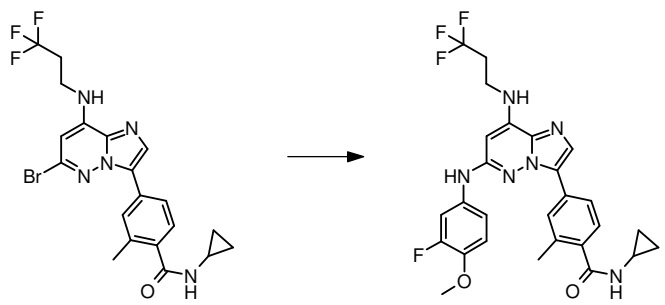
Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-

trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando m-toluidina para dar, luego del tratamiento posterior y la purificación, 14,5 mg (17%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,63 (2H), 0,90 (2H), 2,35 (3H), 2,43-2,58 (2H), 2,51 (3H), 2,61 (1H), 2,92 (1H), 3,59 (2H), 5,64 (1H), 5,78 (1H), 5,91 (1H), 6,25 (1H), 6,89 (1H), 7,22 (1H), 7,35 (1H), 7,40 (1H), 7,65 (1H), 7,90 (1H), 7,92 (1H) ppm.

Ejemplo 424

N-ciclopropil-4-{6-[(3-fluoro-4-metoxifenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando 3-fluoro-4-metoxianilina para dar, luego del tratamiento posterior y la purificación, 21,0 mg (24%) del compuesto del título.

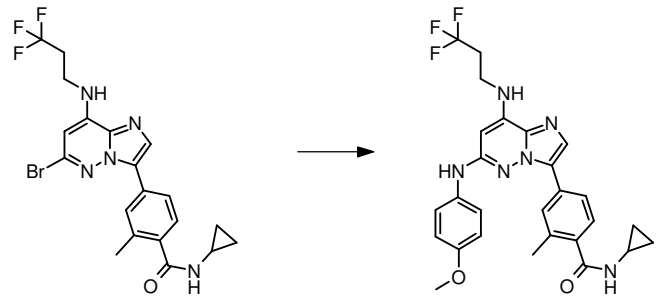
1H-RMN (CDCl3): δ= 0,64 (2H), 0,90 (2H), 2,44-2,60 (2H), 2,51

(3H), 2,92 (1H), 3,59 (2H), 3,89 (3H), 5,55 (1H), 5,78 (1H), 5,94 (1H), 6,20 (1H), 6,92 (1H), 7,06 (1H), 7,41 (1H), 7,55 (1H), 7,64 (1H), 7,83 (1H), 7,92 (1H) ppm.

Ejemplo 425

N-ciclopropil-4-{6-[(4-metoxifenil)amino]-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



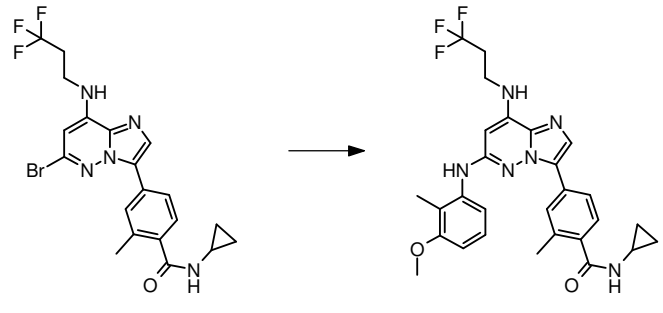
Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando 4-metoxianilina para dar, luego del tratamiento posterior y la purificación, 17,8 mg (21%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,63 (2H), 0,90 (2H), 2,43-2,60 (2H), 2,51 (3H), 2,92 (1H), 3,57 (2H), 3,82 (3H), 5,56 (1H), 5,77 (1H), 5,91 (1H), 6,10 (1H), 6,91 (2H), 7,35-7,42 (3H), 7,64 (1H), 7,83 (1H), 7,98 (1H) ppm.

Ejemplo 426

N-ciclopropil-4-{6-[(3-metoxi-2-metilfenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-

metilbenzamida

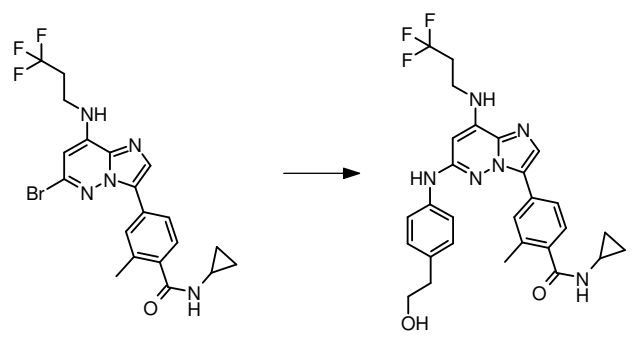


Se trataron 150 mg (311 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando 3-metoxi-2-metilanilina para dar, luego del tratamiento posterior y la purificación, 21,3 mg (12%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,62 (2H), 0,89 (2H), 2,20 (3H), 2,47 (3H), 2,50 (2H), 2,92 (1H), 3,55 (2H), 3,87 (3H), 5,63 (1H), 5,81 (1H), 5,89 (1H), 6,00 (1H), 6,72 (1H), 7,16-7,25 (2H), 7,36 (1H), 7,65 (1H), 7,84 (1H); 7,93 (1H) ppm.

Ejemplo 427

N-ciclopropil-4-(6-{[4-(2-hidroxietil)fenil]amino}-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida

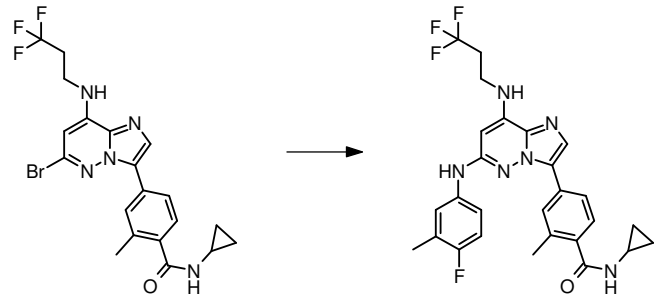


Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando 2-(4-aminofenil)etanol para dar, luego del tratamiento posterior y la purificación, 9,2 mg (10%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,52 (2H), 0,66 (2H), 2,38 (3H), 2,58-2,77 (4H), 2,82 (1H), 3,41-3,59 (4H), 4,59 (1H), 5,82 (1H), 7,11 (2H), 7,24 (1H), 7,34 (1H), 7,56 (2H), 7,77 (1H), 7,83 (1H), 8,12 (1H), 8,32 (1H), 8,86 (1H) ppm.

Ejemplo 428

N-ciclopropil-4-{6-[(4-fluoro-3-metilfenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



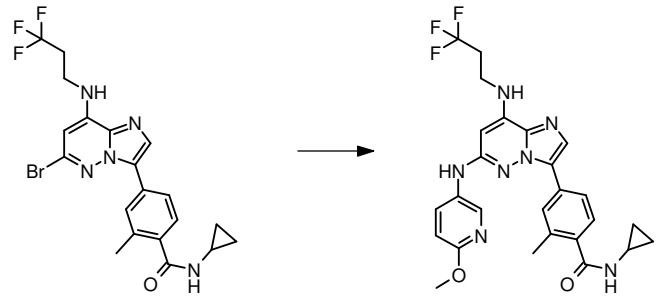
Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando 4-fluoro-3-metilanilina para dar, luego del tratamiento posterior y la purificación, 11,9 mg (14%) del compuesto del

título.

1H-RMN (CDCl3): δ= 0,63 (2H), 0,89 (2H), 2,25 (3H), 2,42-2,56 (2H), 2,48 (3H), 2,92 (1H), 3,53 (2H), 5,57 (1H), 5,87 (1H), 5,99 (1H), 6,39 (1H), 6,95 (1H), 7,21-7,34 (2H), 7,36 (1H), 7,62 (1H), 7,85 (1H), 7,87 (1H) ppm.

Ejemplo 429

N-ciclopropil-4-{6-[(6-metoxipiridin-3-il)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

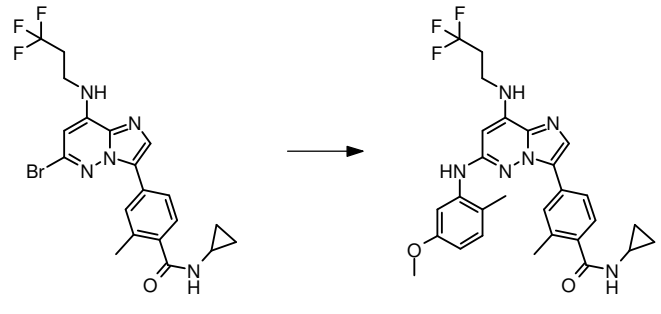


Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando 6-metoxipiridin-3-amina para dar, luego del tratamiento posterior y la purificación, 8,7 mg (10%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,64 (2H), 2,37 (3H), 2,68 (2H), 2,80 (1H), 3,30 (3H), 3,49 (2H), 5,77 (1H), 6,78 (1H), 7,25-7,35 (2H), 7,77 (2H), 7,93 (1H), 8,09 (1H), 8,29 (1H), 8,46 (1H), 8,86 (1H) ppm.

Ejemplo 430

N-ciclopropil-4-{6-[(5-metoxi-2-metilfenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



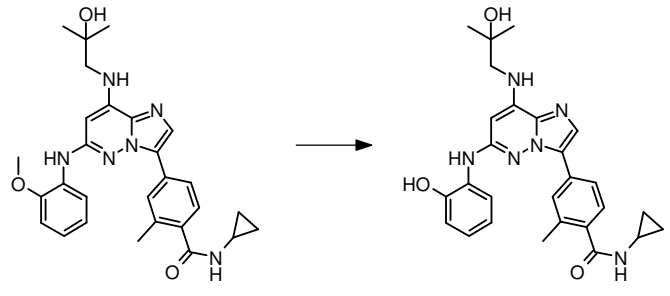
Se trataron 150 mg (311 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando 5-metoxi-2-metilanilina para dar, luego del tratamiento posterior y la purificación, 15,5 mg (9%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,62 (2H), 0,89 (2H), 2,26 (3H), 2,48 (3H), 2,52 (2H), 2,92 (1H), 3,58 (2H), 3,73 (3H), 5,65 (1H), 5,79 (1H), 5,89 (1H), 5,96 (1H), 6,62 (1H), 7,14 (1H), 7,31 (1H), 7,38 (1H), 7,66 (1H), 7,87 (1H), 7,90 (1H) ppm.

Ejemplo 431

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(2-hidroxifenil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



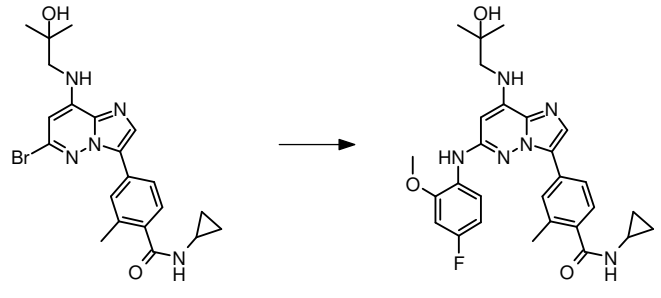
Se trataron 40 mg (80 µmol) de N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(2-metoxifenil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida, que se preparó de acuerdo con el ejemplo 402, de manera análoga al Ejemplo 280 para dar, luego del tratamiento posterior y la purificación, 5,8 mg (13%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 1,17 (6H), 2,36 (3H), 2,81 (1H), 3,17 (2H), 4,76 (1H), 6,28 (1H), 6,40 (1H), 6,71-6,89 (3H), 7,30 (1H), 7,76 (1H), 7,80-7,91 (2H), 8,11 (1H), 8,16 (1H), 8,29 (1H), 9,90 (1H) ppm.

Ejemplo 432

N-ciclopropil-4-{6-[(4-fluoro-2-metoxifenil)amino]-8-[(2-hidroxi-2-

metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



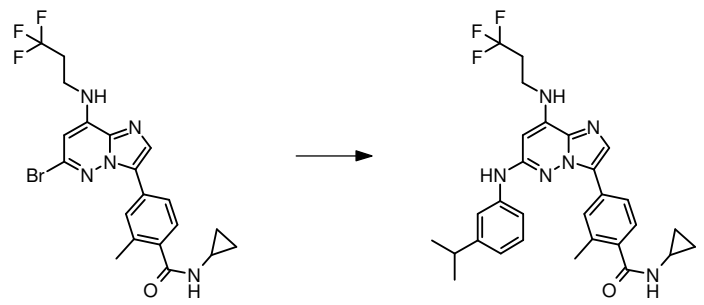
Se trataron 150 mg (327 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo

Intermediario 96a, de manera análoga al Ejemplo 305 usando 4-fluoro-2-metoxianilina para dar, luego del tratamiento posterior y la purificación, 12,2 mg (6%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,65 (2H), 1,18 (6H), 2,32 (3H), 2,80 (1H), 3,15 (2H), 3,84 (3H), 4,79 (1H), 6,21 (1H), 6,42 (1H), 6,72 (1H), 6,96 (1H), 7,30 (1H), 7,76 (1H), 7,82 (1H), 7,91 (1H), 8,01 (1H), 8,10 (1H), 8,27 (1H) ppm.

Ejemplo 433

N-ciclopropil-2-metil-4-(6-{[3-(propan-2-il)fenil]amino}-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il)benzamida



Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando 3-isopropilanilina para dar, luego del tratamiento posterior y la purificación, 22,8 mg (26%) del compuesto del título.

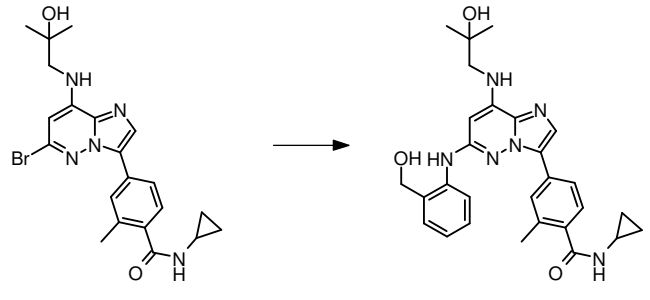
1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,66 (2H), 1,16 (6H), 2,37 (3H), 2,49-2,88 (4H), 3,49 (2H), 5,84 (1H), 6,79 (1H), 7,19 (1H), 7,23-7,29 (2H), 7,33 (1H), 7,70 (1H), 7,77 (1H), 7,92 (1H), 8,02

(1H), 8,29(1H), 8,88 (1H) ppm.

Ejemplo 434

N-ciclopropil-4-(6-{[2-(hidroximetil)fenil]amino}-8-[(2-hidroxi-2-

metilpropil)amino]imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida



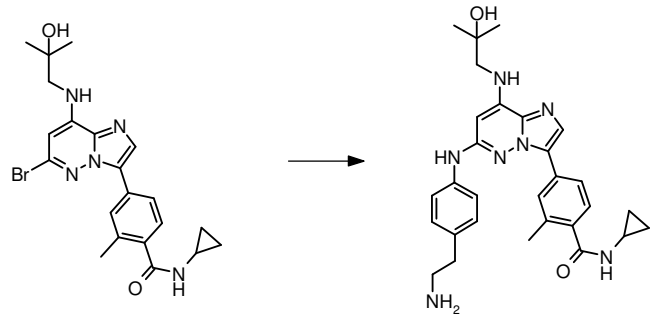
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando (2-aminofenil)metanol para dar, luego del tratamiento posterior y la purificación, 2,0 mg (2%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,49 (2H), 0,64 (2H), 1,18 (6H), 2,26 (3H), 2,78 (1H), 3,18 (2H), 4,54 (2H), 4,80 (1H), 5,35 (1H), 5,96 (1H), 6,46 (1H), 7,03 (1H), 7,24 (2H), 7,36 (1H), 7,77-7,91 (3H), 8,02 (1H), 8,06 (1H), 8,24 (1H) ppm.

Ejemplo 435

4-(6-{[4-(2-aminoetil)fenil]amino}-8-[(2-hidroxi-2-metilpropil)amino]

imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida



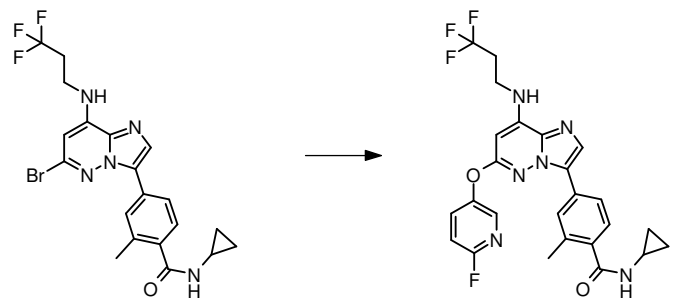
Se trataron 75 mg (164 µmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 305 usando 4-(2-aminoetil)anilina para dar, luego del tratamiento posterior y la purificación, 11 mg (12%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 1,18 (6H), 2,38 (3H), 2,59-2,65 (2H), 2,74-2,85 (3H), 3,15 (2H), 4,82 (1H), 5,88 (1H), 6,51 (1H), 7,10 (2H), 7,34 (1H), 7,58 (2H), 7,76 (1H), 7,84 (1H), 8,12 (1H), 8,32 (1H), 8,87 (1H) ppm.

Ejemplo 436

N-ciclopropil-4-{6-[(6-fluoropiridin-3-il)oxi]-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 200 mg (415 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-

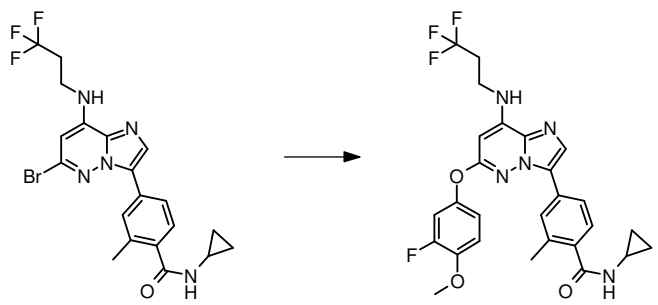
ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 6-fluoropiridin-3-ol para dar, luego del tratamiento posterior y la purificación, 4,8 mg (2%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,47 (2H), 0,64 (2H), 2,13 (3H), 2,60-2,80 (3H), 3,61 (2H), 6,19 (1H), 7,17 (1H), 7,32 (1H), 7,60 (1H), 7,67 (1H), 7,77 (1H), 7,93 (1H), 8,04 (1H), 8,22 (1H), 8,26 (1H) ppm.

Ejemplo 437

N-ciclopropil-4-{6-(2-fluoro-4-metoxifenoxi)-8-[(3,3,3-trifluoropropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 400 mg (829 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 2-fluoro-4-metoxifenol para dar, luego del tratamiento posterior y la purificación, 194 mg (41%) del compuesto del título.

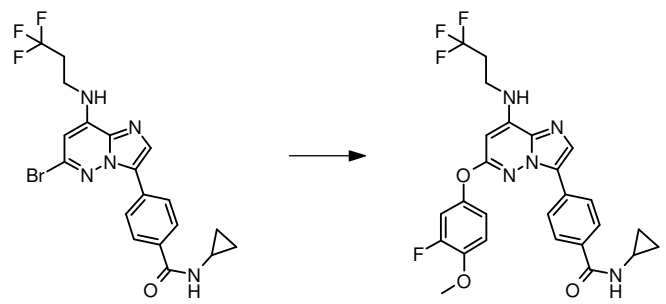
1H-RMN (DMSO-d6): δ= 0,46 (2H), 0,64 (2H), 2,08 (3H), 2,60-2,80

(3H), 3,60 (2H), 3,78 (3H), 6,16 (1H), 6,84 (1H), 7,06 (1H), 7,15 (1H), 7,33 (1H), 7,61 (1H), 7,67-7,74 (2H), 7,94 (1H), 8,21 (1H) ppm.

Ejemplo 438

N-ciclopropil-4-{6-(2-fluoro-4-metoxifenoxi)-8-[(3,3,3-trifluoropropil)

amino]imidazo[1,2-b]piridazin-3-il}benzamida

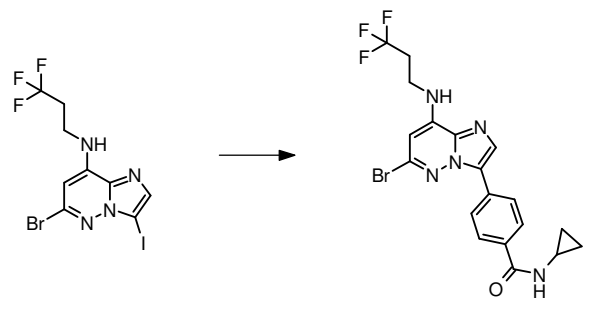


Se trataron 400 mg (854 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 438a, de manera análoga al Ejemplo 51 usando 2-fluoro-4-metoxifenol para dar, luego del tratamiento posterior y la purificación, 219 mg (46%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,53 (2H), 0,66 (2H), 2,69 (2H), 2,79 (1H), 3,60 (2H), 3,81 (3H), 6,17 (1H), 6,85 (1H), 7,08 (1H), 7,34 (1H), 7,65 (2H), 7,74 (1H), 7,89 (2H), 8,01 (1H), 8,40 (1H) ppm.

Ejemplo Intermediario 438a

4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida

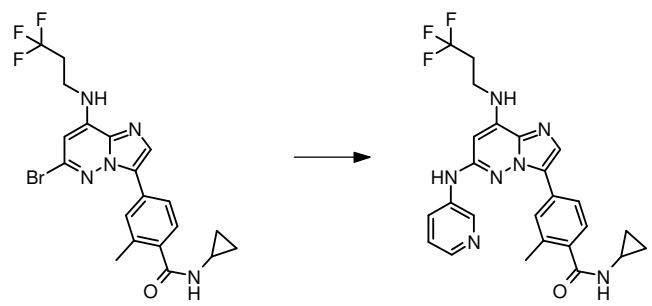


Se trataron 1,50 g (3,45 mmol) de 6-bromo-3-yodo-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 247b, de manera análoga al Ejemplo Intermediario 1a usando ácido [4-(ciclopropilcarbamoil)fenil]borónico para dar, luego del tratamiento posterior y la purificación, 1,05 g (65%) del compuesto del título.

Ejemplo 439

N-ciclopropil-2-metil-4-{6-(piridin-3-ilamino)-8-[(3,3,3-trifluoropropil)

amino]imidazo[1,2-b]piridazin-3-il}benzamida



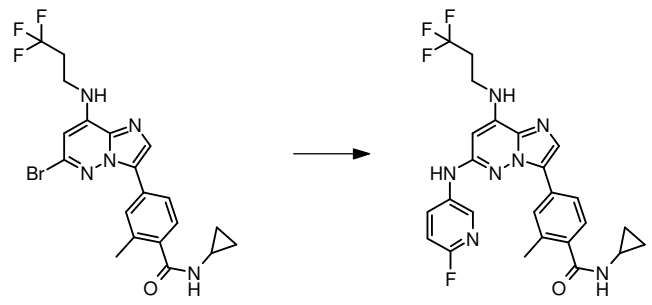
Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando piridin-3-amina para dar, luego del tratamiento posterior y la purificación, 15,5 mg (19%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 2,38 (3H), 2,68 (2H), 2,81 (1H), 3,51 (2H), 5,84 (1H), 7,29 (1H), 7,34 (1H), 7,38 (1H), 7,79 (1H), 7,80 (1H), 8,06 (1H), 8,10-8,16 (2H), 8,32 (1H), 8,80 (1H), 9,18 (1H) ppm.

Ejemplo 440

N-ciclopropil-4-{6-[(6-fluoropiridin-3-il)amino]-8-[(3,3,3-trifluoropropil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

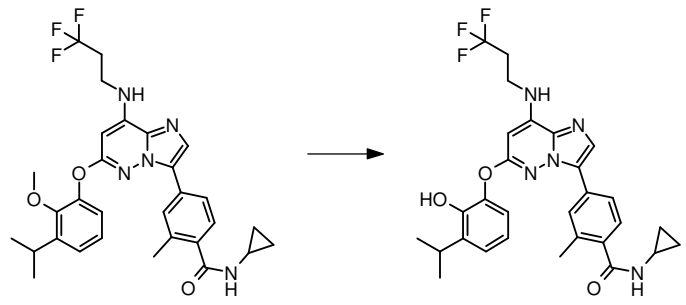


Se trataron 75 mg (156 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 305 usando 6-fluoropiridin-3-amina para dar, luego del tratamiento posterior y la purificación, 25,5 mg (30%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 2,37 (3H), 2,68 (2H), 2,81 (1H), 3,50 (2H), 5,80 (1H), 7,12 (1H), 7,34 (1H), 7,39 (1H), 7,76-7,80 (2H), 8,00 (1H), 8,16 (1H), 8,31 (1H), 8,51 (1H), 9,21 (1H) ppm.

Ejemplo 441

N-ciclopropil-4-{6-[2-hidroxi-3-(propan-2-il)fenoxi]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

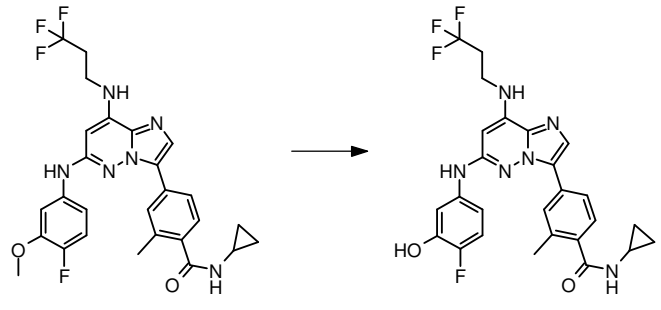


Se trataron 32 mg (56 µmol) de N-ciclopropil-4-{6-[2-metoxi-3-(propan-2-il)fenoxi]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida, que se preparó de acuerdo con el ejemplo 418, de manera análoga al Ejemplo 280 para dar, luego del tratamiento posterior y la purificación, 8,2 mg (25%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,46 (2H), 0,62 (2H), 1,07 (6H), 2,05 (3H), 2,69 (2H), 2,75 (1H), 3,04 (1H), 3,60 (2H), 6,14 (1H), 6,76 (1H), 6,82 (1H), 7,03-7,09 (2H), 7,56 (1H), 7,62 (1H), 7,77 (1H), 7,93 (1H), 8,19 (1H), 9,37 (1H) ppm.

Ejemplo 442

N-ciclopropil-4-{6-[(4-fluoro-3-hidroxifenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

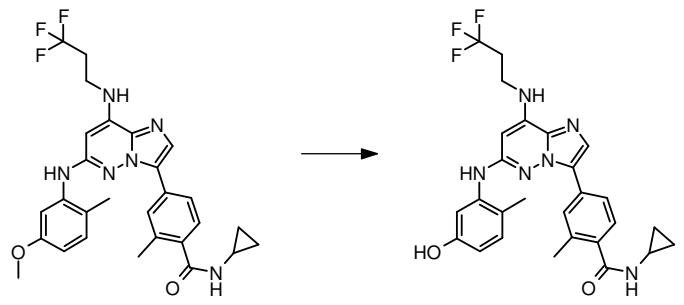


Se trataron 33 mg (61 µmol) de N-ciclopropil-4-{6-[(4-fluoro-3-metoxifenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida, que se preparó de acuerdo con el ejemplo 422, de manera análoga al Ejemplo 280 para dar, luego del tratamiento posterior y la purificación, 9,3 mg (27%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 2,36 (3H), 2,67 (2H), 2,81 (1H), 3,47 (2H), 5,78 (1H), 7,00 (1H), 7,05 (1H), 7,20-7,27 (2H), 7,33 (1H), 7,78 (1H), 7,87 (1H), 8,06 (1H), 8,28 (1H), 8,79 (1H), 9,71 (1H) ppm.

Ejemplo 443

N-ciclopropil-4-{6-[(5-hidroxi-2-metilfenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 10,5 mg (19 µmol) de N-ciclopropil-4-{6-[(5-metoxi-2-metilfenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-

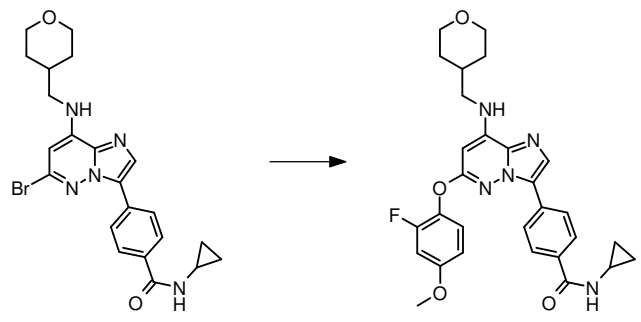
b]piridazin-3-il}-2-metilbenzamida, que se preparó de acuerdo con el ejemplo 430, de manera análoga al Ejemplo 280 para dar, luego del tratamiento posterior y la purificación, 2,0 mg (20%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,47 (2H), 0,64 (2H), 2,11 (3H), 2,24 (3H), 2,69 (2H), 2,77 (1H), 3,48 (2H), 5,94 (1H), 6,42 (1H), 6,95 (1H), 7,10 (1H), 7,16 (1H), 7,20 (1H), 7,65-7,95 (3H), 8,01 (1H), 8,21 (1H), 9,06 (1H) ppm.

Ejemplo 444

N-ciclopropil-4-{6-(2-fluoro-4-metoxifenoxi)-8-[(tetrahidro-2H-piran-4-

ilmetil)amino]imidazo[1,2-b]piridazin-3-il}benzamida



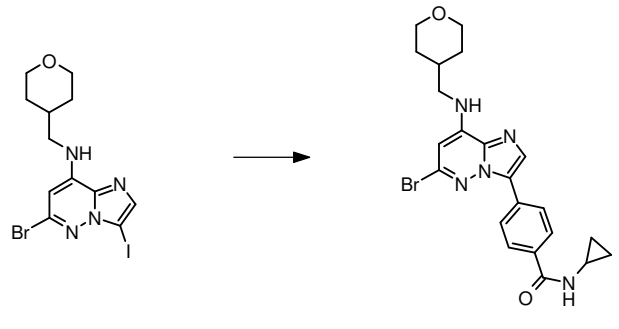
Se trataron 400 mg (850 µmol) de 4-{6-bromo-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 444a, de manera análoga al Ejemplo 51 usando 2-fluoro-4-metoxifenol para dar, luego del tratamiento posterior y la purificación, 257 mg (54%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,53 (2H), 0,66 (2H), 1,22 (2H), 1,62 (2H), 1,94 (1H), 2,80 (1H), 3,17-3,32 (4H), 3,81 (3H), 3,84 (2H), 6,12 (1H), 6,84 (1H), 7,07 (1H), 7,34 (1H), 7,64 (2H), 7,74 (1H),

7,89 (2H), 7,98 (1H), 8,39 (1H) ppm.

Ejemplo Intermediario 444a

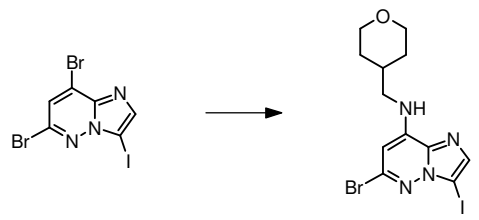
4-{6-bromo-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida



Se trataron 1,20 g (2,75 mmol) de 6-bromo-3-yodo-N-(tetrahidro-2H-piran-4-ilmetil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 444b, de manera análoga al Ejemplo Intermediario 1a usando ácido [4-(ciclopropilcarbamoil)fenil]borónico para dar, luego del tratamiento posterior y la purificación, 1,08 g (84%) del compuesto del título.

Ejemplo Intermediario 444b

6-bromo-3-yodo-N-(tetrahidro-2H-piran-4-ilmetil)imidazo[1,2-b]piridazin-8-amina



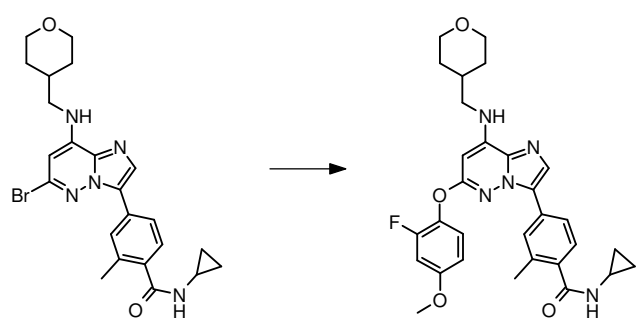
Se trataron 3,00 g (7,45 mmol) de 6,8-dibromo-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 96c, de manera análoga al Ejemplo Intermediario 1b

usando 1-(tetrahidro-2H-piran-4-il)metanamina para dar, luego del tratamiento posterior y la purificación, 2,81 g (81%) del compuesto del título.

Ejemplo 445

N-ciclopropil-4-{6-(2-fluoro-4-metoxifenoxi)-8-[(tetrahidro-2H-piran-

4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 400 mg (826 µmol) de 4-{6-bromo-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 445a, de manera análoga al Ejemplo 51 usando 2-fluoro-4-metoxifenol para dar, luego del tratamiento posterior y la purificación, 295 mg (65%) del compuesto del título.

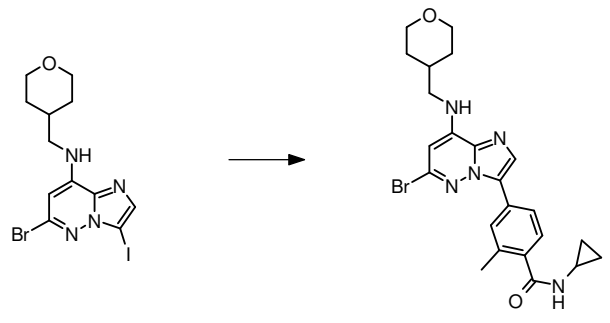
1H-RMN (DMSO-d6): δ= 0,46 (2H), 0,63 (2H), 1,22 (2H), 1,62 (2H), 1,95 (1H), 2,08 (3H), 2,77 (1H), 3,19-3,27 (4H), 3,77 (3H), 3,83 (2H), 6,12 (1H), 6,83 (1H), 7,05 (1H), 7,14 (1H), 7,33 (1H), 7,61 (1H), 7,67-7,74 (2H), 7,91 (1H), 8,21 (1H) ppm.

Ejemplo Intermediario 445a

4-{6-bromo-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-

b]piridazin-

3-il}-N-ciclopropil-2-metilbenzamida

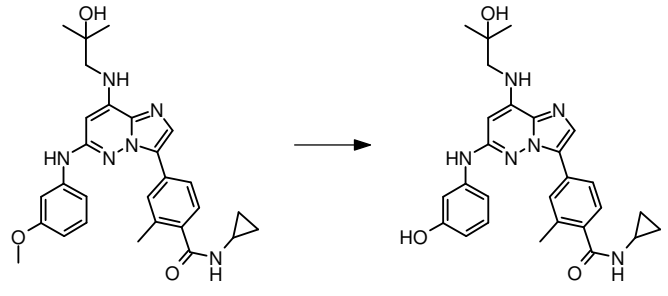


Se trataron 1,58 g (3,62 mmol) de 6-bromo-3-yodo-N-(tetrahidro-2H-piran-4-ilmetil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 444b, de manera análoga al Ejemplo Intermediario 1a usando N-ciclopropil-2-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzamida para dar, luego del tratamiento posterior y la purificación, 1,05 g (57%) del compuesto del título.

Ejemplo 446

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(3-hidroxifenil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



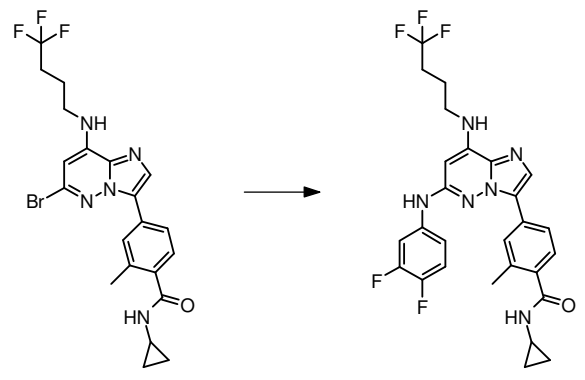
Se trataron 30 mg (60 µmol) de N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(3-metoxifenil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida, que se preparó de acuerdo

con el ejemplo 403, de manera análoga al Ejemplo 280 para dar, luego del tratamiento posterior y la purificación, 9,60 mg (31%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,65 (2H), 1,18 (6H), 2,37 (3H), 2,81 (1H), 3,14 (2H), 4,81 (1H), 5,88 (1H), 6,33 (1H), 6,49 (1H), 6,94 (1H), 7,03 (1H), 7,23 (1H), 7,32 (1H), 7,77 (1H), 7,89 (1H), 8,12 (1H), 8,29 (1H), 8,77 (1H), 9,25 (1H) ppm.

Ejemplo 447

N-ciclopropil-4-{6-[(3,4-difluorofenil)amino]-8-[(4,4,4-trifluorobutil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



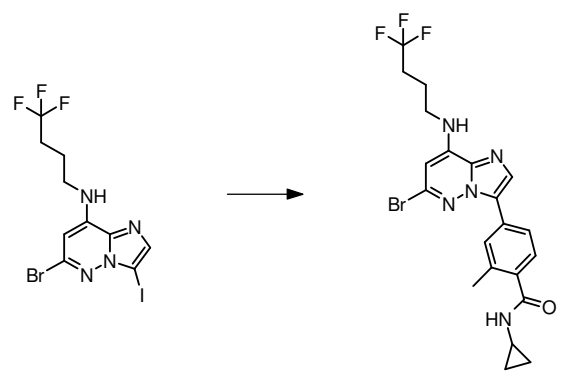
Se trataron 75 mg (151µmol) de 4-{6-bromo-8-[(4,4,4-trifluorobutil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 447a, de manera análoga al Ejemplo 305 usando 3,4-difluoroanilina para dar, luego del tratamiento posterior y la purificación, 6,3 mg (7%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,51 (2H), 0,66 (2H), 1,86 (2H), 2,26-2,43 (2H), 2,36 (3H), 2,81 (1H), 3,32-3,38 (2H), 5,75 (1H), 7,20-7,39

(4H), 7,75 (1H), 7,81 (1H), 7,90 (1H), 7,99 (1H), 8,28 (1H), 9,14 (1H) ppm.

Ejemplo Intermediario 447a

4-{6-bromo-8-[(4,4,4-trifluorobutil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



Se trataron 4,27 g (9,51 mmol) de 6-bromo-3-yodo-N-(4,4,4-trifluorobutil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 447b, de manera análoga al Ejemplo Intermediario 1a usando N-ciclopropil-2-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzamida para dar, luego del tratamiento posterior y la purificación, 2,37 g (50%) del compuesto del título.

Ejemplo Intermediario 447b

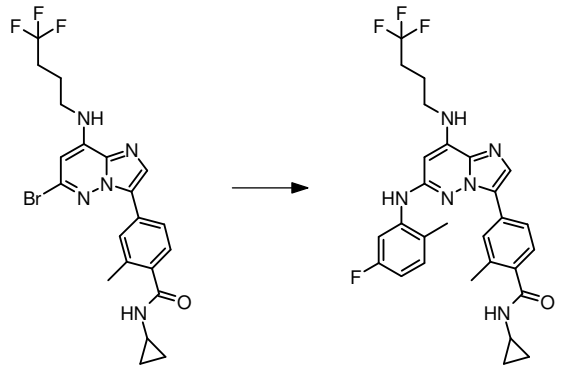
6-bromo-3-yodo-N-(4,4,4-trifluorobutil)imidazo[1,2-b]piridazin-8-amina

Se trataron 3,96 g (9,83 mmol) de 6,8-dibromo-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 96c, de manera análoga al Ejemplo Intermediario 1b usando 4,4,4-trifluorobutan-1-amina para dar, luego del tratamiento posterior y la purificación, 3,43 g (74%) del compuesto del título.

Ejemplo 448

N-ciclopropil-4-{6-[(5-fluoro-2-metilfenil)amino]-8-[(4,4,4-trifluorobutil)

amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



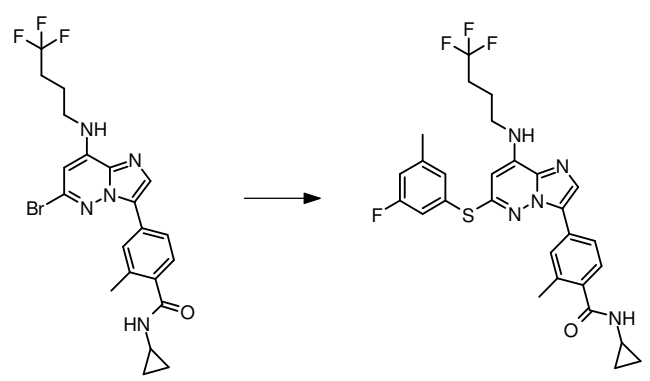
Se trataron 75 mg (151 µmol) de 4-{6-bromo-8-[(4,4,4-trifluorobutil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 447a, de manera análoga al Ejemplo 305 usando 5-fluoro-2-metilanilina para dar, luego del tratamiento posterior y la purificación, 10,5 mg (12%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,63 (2H), 0,89 (2H), 2,00 (2H), 2,20-2,33 (2H), 2,30 (3H), 2,50 (3H), 2,92 (1H), 3,39 (2H), 5,62 (1H), 5,77 (1H), 5,92 (1H), 6,02 (1H), 6,70 (1H), 7,14 (1H), 7,40

(1H), 7,65 (1H), 7,76 (1H), 7,84 (1H), 7,87 (1H) ppm.

Ejemplo 449

N-ciclopropil-4-{6-[(3-fluoro-5-metilfenil)sulfanil]-8-[(4,4,4-trifluorobutil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



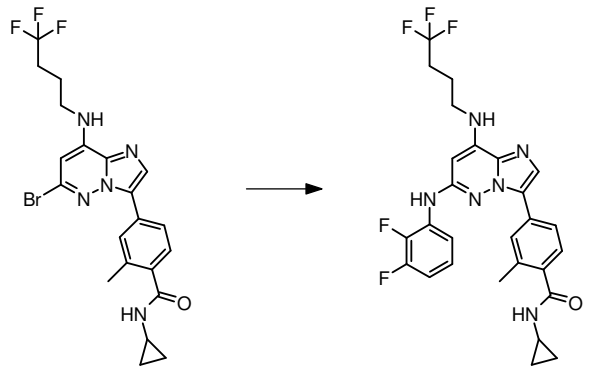
Se trataron 75 mg (151 µmol) de 4-{6-bromo-8-[(4,4,4-trifluorobutil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 447a, de manera análoga al Ejemplo 51 usando 3-fluoro-5-metilbencenotiol para dar, luego del tratamiento posterior y la purificación, 44,6 mg (50%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,63 (2H), 0,90 (2H), 1,97 (2H), 2,23 (2H), 2,36 (3H), 2,41 (3H), 2,92 (1H), 3,38 (2H), 5,79 (1H), 5,87 (1H), 5,91 (1H), 6,96 (1H), 7,17-7,29 (3H), 7,66 (1H), 7,69 (1H), 7,72 (1H) ppm.

Ejemplo 450

N-ciclopropil-4-{6-[(2,3-difluorofenil)amino]-8-[(4,4,4-trifluorobutil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



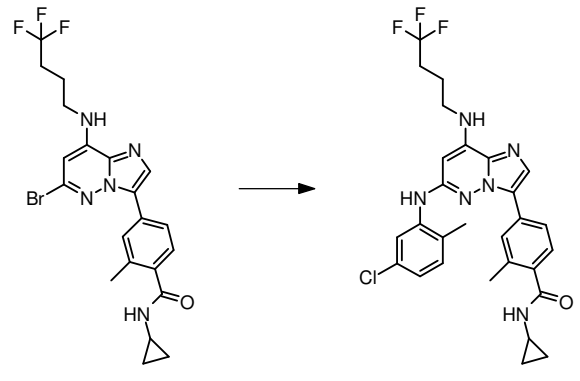
Se trataron 75 mg (151 µmol) de 4-{6-bromo-8-[(4,4,4-trifluorobutil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 447a, de manera análoga al Ejemplo 305 usando 2,3-difluoroanilina para dar, luego del tratamiento posterior y la purificación, 10,6 mg (12%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,63 (2H), 0,90 (2H), 2,03 (2H), 2,28 (2H), 2,52 (3H), 2,93 (1H), 3,43 (2H), 5,64 (1H), 5,75 (1H), 5,91 (1H), 6,40 (1H), 6,81 (1H), 7,03 (1H), 7,40 (1H), 7,66 (1H), 7,78 (1H), 7,98 (1H), 8,07 (1H) ppm.

Ejemplo 451

4-{6-[(5-cloro-2-metilfenil)amino]-8-[(4,4,4-trifluorobutil)amino]imidazo

[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



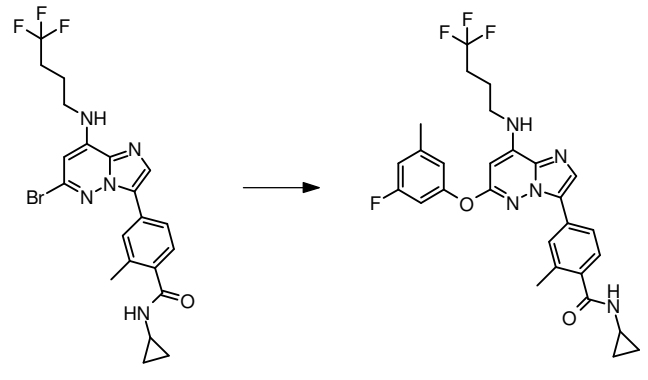
Se trataron 75 mg (151 µmol) de 4-{6-bromo-8-[(4,4,4-trifluorobutil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 447a, de manera análoga al Ejemplo 305 usando 5-cloro-2-metilanilina para dar, luego del tratamiento posterior y la purificación, 12,7 mg (14%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,61 (2H), 0,88 (2H), 1,99 (2H), 2,17-2,38 (2H), 2,29 (3H), 2,48 (3H), 2,92 (1H), 3,38 (2H), 5,60 (1H), 5,73 (1H), 5,90 (1H), 5,98 (1H), 6,99 (1H), 7,13 (1H), 7,43 (1H), 7,65 (1H), 7,76 (1H), 7,91 (1H), 7,93 (1H) ppm.

Ejemplo 452

N-ciclopropil-4-{6-(3-fluoro-5-metilfenoxi)-8-[(4,4,4-trifluorobutil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



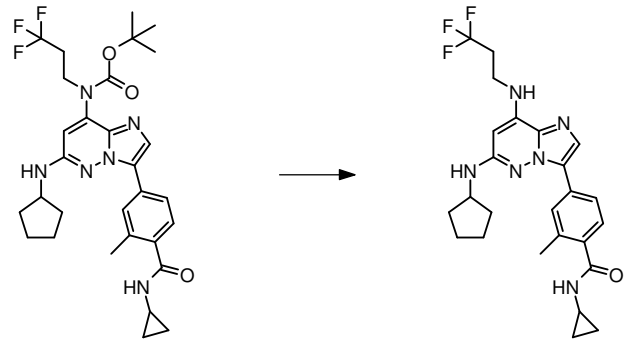
Se trataron 75 mg (151 µmol) de 4-{6-bromo-8-[(4,4,4-trifluorobutil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 447a, de manera análoga al Ejemplo 51 usando 3-fluoro-5-metilfenol para dar, luego del tratamiento posterior y la purificación, 27,7 mg (32%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,60 (2H), 0,88 (2H), 2,04 (2H), 2,28 (2H), 2,34 (3H), 2,37 (3H), 2,90 (1H), 3,46 (2H), 5,81-5,89 (3H), 6,77-6,87 (3H), 7,27 (1H), 7,66 (1H), 7,73 (1H), 7,77 (1H) ppm.

Ejemplo 453

4-{6-(ciclopentilamino)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]

piridazin-3-il}-N-ciclopropil-2-metilbenzamida



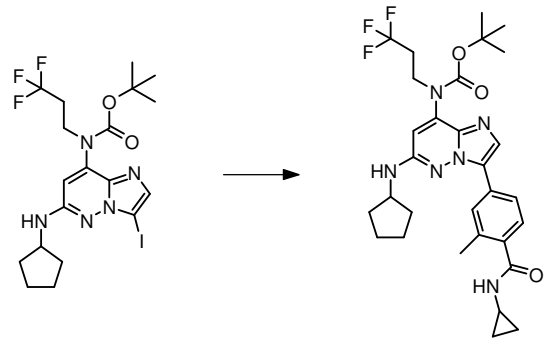
A una solución de 90 mg (153 µmol) de {6-(ciclopentilamino)-3-

[4-(ciclopropilcarbamoil)-3-metilfenil]imidazo[1,2-b]piridazin-8-il}(3,3,3-trifluoropropil)carbamato de tert-butilo, que se preparó de acuerdo con el Ejemplo Intermediario 453a, en 1 mL de diclorometano, se agregaron 177 µL de ácido trifluoroacético y la mezcla se agitó durante 2 horas a 23°C. La mezcla se volcó sobre agua y se extrajo con diclorometano. La fase orgánica se lavó con solución de carbonato ácido de sodio y se secó sobre sulfato de sodio. Luego de la filtración y la eliminación del solvente el residuo se purificó mediante cromatografía para dar 64,1 mg (82%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,64 (2H), 1,44-1,72 (6H), 1,90-2,05 (2H), 2,34 (3H), 2,62 (2H), 2,79 (1H), 3,41 (2H), 3,99 (1H), 5,57 (1H), 6,43 (1H), 6,92 (1H), 7,30 (1H), 7,73 (1H), 7,98 (1H), 8,17 (1H), 8,24 (1H) ppm.

Ejemplo Intermediario 453a

4-{6-(ciclopentilamino)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



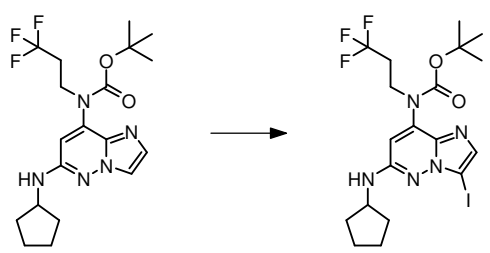
Se trataron 135 mg (250 µmol) de [6-(ciclopentilamino)-3-yodoimidazo[1,2-b]piridazin-8-il](3,3,3-trifluoropropil)carbamato de tert-butilo, que se preparó de

acuerdo con el Ejemplo Intermediario 453b, de manera análoga al Ejemplo Intermediario 1a usando ácido [4-(ciclopropilcarbamoil)-3-metilfenil]borónico para dar, luego del tratamiento posterior y la purificación, 101 mg (65%) del compuesto del título.

Ejemplo Intermediario 453b

[6-(ciclopentilamino)-3-yodoimidazo[1,2-b]piridazin-8-il](3,3,3-trifluoropropil)

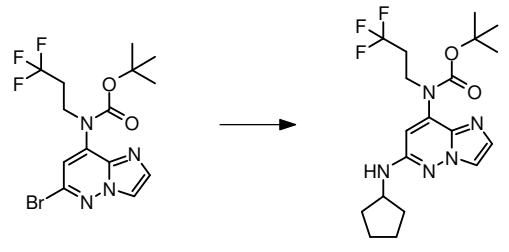
carbamato de tert-butilo



Se trataron 197 mg (405 µmol) de [6-(ciclopentilamino)imidazo[1,2-b]piridazin-8-il](3,3,3-trifluoropropil)carbamato de tert-butilo, que se preparó de acuerdo con el Ejemplo Intermediario 453c, de manera análoga al Ejemplo Intermediario 96c para dar, luego del tratamiento posterior y la purificación, 141 mg (58%) del compuesto del título.

Ejemplo Intermediario 453c

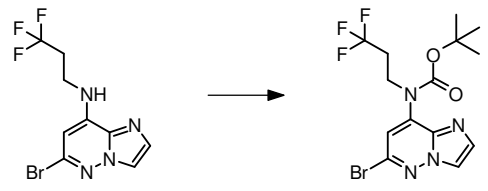
[6-(ciclopentilamino)imidazo[1,2-b]piridazin-8-il](3,3,3-trifluoropropil)carbamato de tert-butilo



Se trataron 200 mg (489 µmol) de (6-bromoimidazo[1,2-b]piridazin-8-il)(3,3,3-trifluoropropil)carbamato de tert-butilo, que se preparó de acuerdo con el Ejemplo Intermediario 453d, de manera análoga al Ejemplo Intermediario 305 usando ciclopentanamina para dar, luego del tratamiento posterior y la purificación, 205 mg (101%) del compuesto del título que contenía algo de reactivo.

Ejemplo Intermediario 453d

(6-bromoimidazo[1,2-b]piridazin-8-il)(3,3,3-trifluoropropil)carbamato de tert-butilo

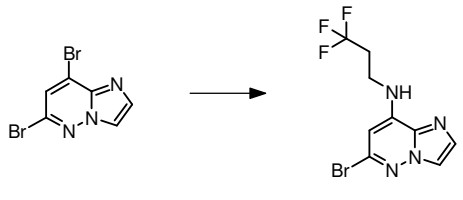


A una solución de 1,88 g (6,08 mmol) de 6-bromo-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 453e, en 7,0 mL de tetrahidrofurano, se agregaron 2,92 g de dicarbonato de di-tert-butilo, 74,3 mg de N,N-dimetilpiridin-4-amina y la mezcla se calentó durante 2 horas a 55°C. se agregó acetato de etilo y la fase orgánica se lavó con solución saturada de carbonato ácido de sodio y se secó sobre sulfato de sodio. Luego de la filtración y la eliminación del solvente el residuo se purificó mediante cromatografía para dar 2,15 g (82%) del compuesto del

título.

Ejemplo Intermediario 453e

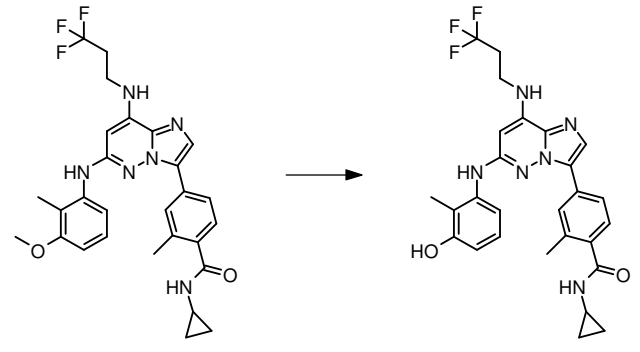
6-bromo-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina



Se trataron 5,00 g (18,06 mmol) de 6,8-dibromoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 96d, de manera análoga al Ejemplo Intermediario 1b usando 3,3,3-trifluoropropan-1-amina para dar, luego del tratamiento posterior y la purificación, 3,04 g (49%) del compuesto del título.

Ejemplo 454

N-ciclopropil-4-{6-[(3-hidroxi-2-metilfenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



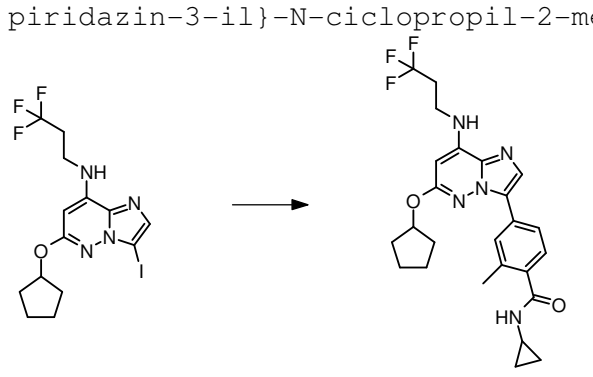
Se trataron 14,1 mg (26 µmol) de N-ciclopropil-4-{6-[(3-metoxi-2-metilfenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida, que se preparó de acuerdo

con el ejemplo 426, de manera análoga al Ejemplo 280 para dar, luego del tratamiento posterior y la purificación, 4,7 mg (33%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,64 (2H), 2,04 (3H), 2,23 (3H), 2,60-2,82 (3H), 3,48 (2H), 5,94 (1H), 6,58 (1H), 6,95 (1H), 7,06-7,29 (3H), 7,79 (1H), 7,81 (1H), 7,93 (1H), 8,03 (1H), 8,22 (1H), 9,24 (1H) ppm.

Ejemplo 455

4-{6-(ciclopentiloxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



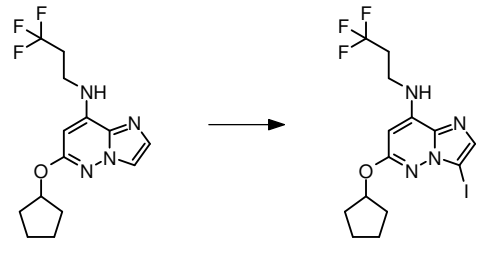
Se trataron 32 mg (73 µmol) de 6-(ciclopentiloxi)-3-yodo-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 455a, de manera análoga al Ejemplo Intermediario 1a usando ácido [4-(ciclopropilcarbamoil)-3-metilfenil]borónico para dar, luego del tratamiento posterior y la purificación, 17,4 mg (47%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,65 (2H), 0,91 (2H), 1,50-1,73 (6H), 1,84 (2H), 2,40 (2H), 2,48 (3H), 2,94 (1H), 4,08 (2H), 4,82 (1H), 5,26 (1H), 5,93 (1H), 7,10 (1H), 7,13 (1H), 7,40 (1H), 7,45

(1H), 7,64 (1H) ppm.

Ejemplo Intermediario 455a

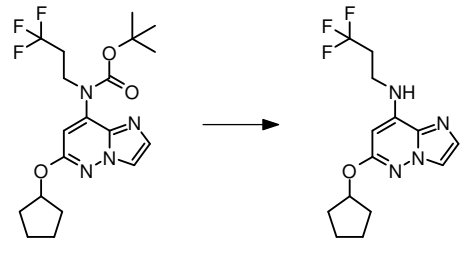
6-(ciclopentiloxi)-3-yodo-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina



Se trataron 42 mg (134 µmol) de 6-(ciclopentiloxi)-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 455b, de manera análoga al Ejemplo Intermediario 96c para dar, luego del tratamiento posterior y la purificación, 33 mg (56%) del compuesto del título.

Ejemplo Intermediario 455b

6-(ciclopentiloxi)-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina

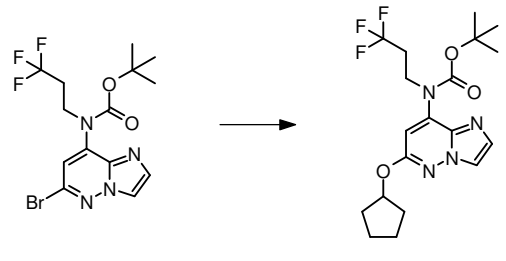


Se trataron 361 mg (max. 784 µmol) de [6-(ciclopentiloxi)imidazo[1,2-b]piridazin-8-il](3,3,3-trifluoropropil)carbamato de tert-butilo, que se preparó de acuerdo con el Ejemplo Intermediario 455c, de manera análoga al

Ejemplo 453 para dar, luego del tratamiento posterior y la purificación, 43 mg (17%) del compuesto del título.

Ejemplo Intermediario 455c

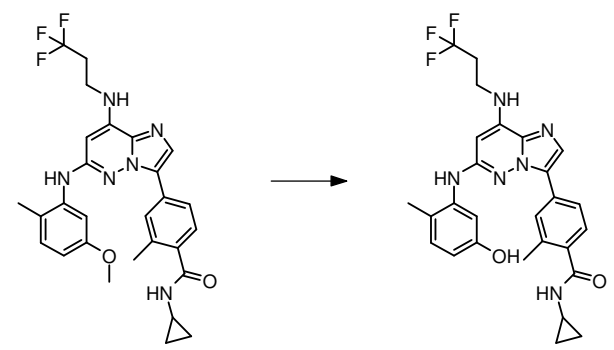
[6-(ciclopentiloxi)imidazo[1,2-b]piridazin-8-il](3,3,3-trifluoropropil)carbamato de tert-butilo



Se trataron 321 mg (784 µmol) de (6-bromoimidazo[1,2-b]piridazin-8-il)(3,3,3-trifluoropropil)carbamato de tert-butilo, que se preparó de acuerdo con el Ejemplo Intermediario 453d, de manera análoga al Ejemplo Intermediario 51 usando ciclopentanol para dar después del tratamiento posterior 361 mg del compuesto del título que contenía material de partida y productos en los que el carbamato se encontraba separado.

Ejemplo 456

N-ciclopropil-4-{6-[(5-hidroxi-2-metilfenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

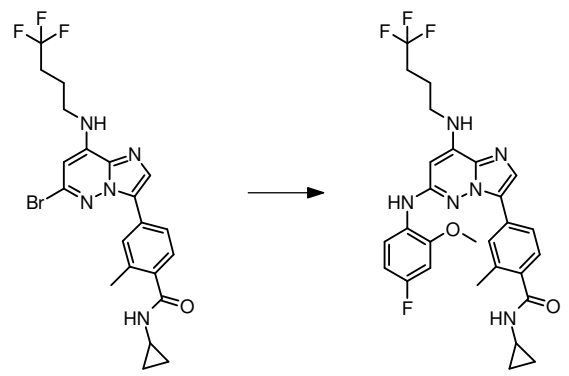


Se trataron 10,5 mg (19 µmol) de N-ciclopropil-4-{6-[(5-metoxi-2-metilfenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida, que se preparó de acuerdo con el ejemplo 430, de manera análoga al Ejemplo 280 para dar, luego del tratamiento posterior y la purificación, 2,0 mg (18%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,48 (2H), 0,64 (2H), 2,21 (3H), 2,24 (3H), 2,60-2,83 (3H), 3,48 (2H), 5,94 (1H), 6,42 (1H), 6,95 (1H), 7,10 (1H), 7,16 (1H), 7,20 (1H), 7,79-7,90 (3H), 8,01 (1H), 8,21 (1H), 9,06 (1H) ppm.

Ejemplo 457

N-ciclopropil-4-{6-[(4-fluoro-2-metoxifenil)amino]-8-[(4,4,4-trifluorobutil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 150 mg (302µmol) de 4-{6-bromo-8-[(4,4,4-trifluorobutil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 447a, de manera análoga al Ejemplo 305 usando 4-fluoro-2-metoxianilina para dar, luego del tratamiento posterior y la purificación, 43,1 mg (24%) del compuesto del

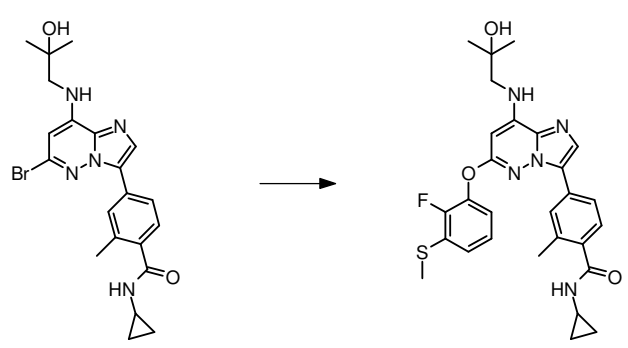
título.

1H-RMN (CDCl3): δ= 0,65 (2H), 0,91 (2H), 2,02 (2H), 2,28 (2H), 2,54 (3H), 2,94 (1H), 3,42 (2H), 3,92 (3H), 5,58 (1H), 5,66 (1H), 5,93 (1H), 6,63-6,71 (3H), 7,41 (1H), 7,63 (1H), 7,81 (1H), 8,01 (1H), 8,28 (1H) ppm.

Ejemplo 458

N-ciclopropil-4-{6-[2-fluoro-3-(metilsulfanil)fenoxi]-8-[(2-hidroxi-2-

metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

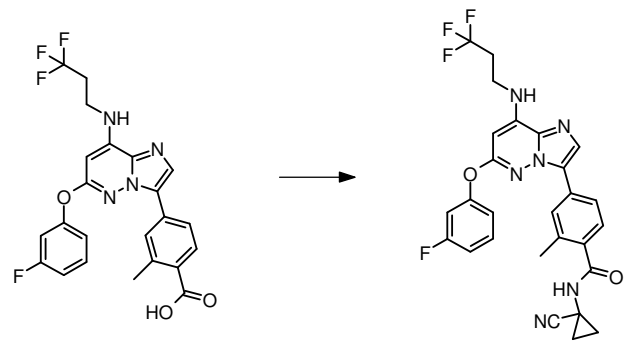


Se trataron 2,00 g (4,36 mmol) de 4-{6-bromo-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 96a, de manera análoga al Ejemplo 51 usando 2,3-difluorofenol para dar, luego del tratamiento posterior y la purificación, 4,6 mg (0,2%) del compuesto del título y 933 mg (42%) del compuesto del título descrito en el ejemplo 92.

1H-RMN (DMSO-d6): δ= 0,50 (2H), 0,67 (2H), 1,21 (6H), 2,14 (3H), 2,52 (3H), 2,80 (1H), 3,33 (2H), 4,78 (1H), 6,27 (1H), 7,05 (1H), 7,17 (1H), 7,26 (1H), 7,28-7,34 (2H), 7,64 (1H), 7,70 (1H), 7,95 (1H), 8,23 (1H) ppm.

Ejemplo 459

4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metil-N-(1-metilciclopropil)benzamida



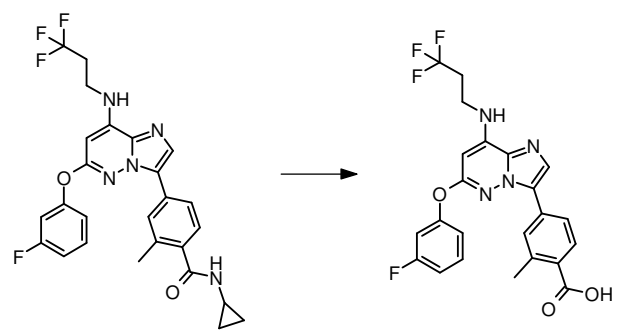
Una mezcla de 10,5 mg (22 µmol) de ácido 4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzoico, que se preparó de acuerdo con el Ejemplo Intermediario 459a, 3,94 mg de cloruro de 1-cianociclopropanaminio, 12,6 mg de hexafluorofosfato de N-[(dimetilamino)(3H-[1,2,3]triazolo[4,5-b]piridin-3-iloxi)metilen]-N-metilmetanaminio, 4,06 mg de N,N-dimetilpiridin-4-amina y 0,5 mL de N,N-dimetilformamida se agitó a 23°C durante la noche. El solvente se eliminó y el residuo se purificó mediante cromatografía para dar 4,5 mg (36%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 1,21 (2H), 1,50 (2H), 2,16 (3H), 2,68 (2H), 3,60 (2H), 6,14 (1H), 7,14 (2H), 7,25 (2H), 7,49 (1H), 7,67-7,76 (2H), 7,81 (1H), 7,97 (1H), 9,09 (1H) ppm.

Ejemplo Intermediario 459a

ácido 4-{6-(3-fluorofenoxi)-8-[(3,3,3-

trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzoico

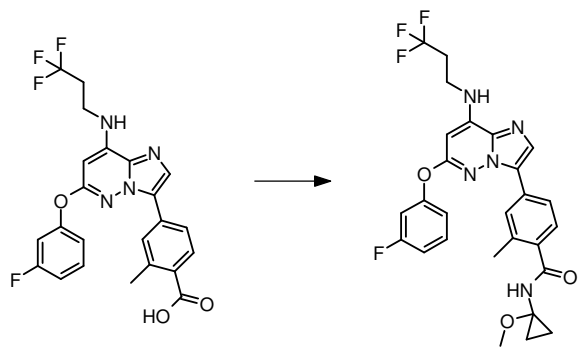


Una mezcla de 231,8 mg (451 µmol) de N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida, que se preparó de acuerdo con el ejemplo 80, y 7,73 mL de ácido bromhídrico se calentó a 120°C durante 10 horas. Se agregó agua, el precipitado se retiró por filtración y se purificó mediante cromatografía para dar 74 mg (24%) de compuesto del título que contenía aproximadamente 30% de 4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida.

Ejemplo 460

4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]

piridazin-3-il}-N-(1-metoxiciclopropil)-2-metilbenzamida

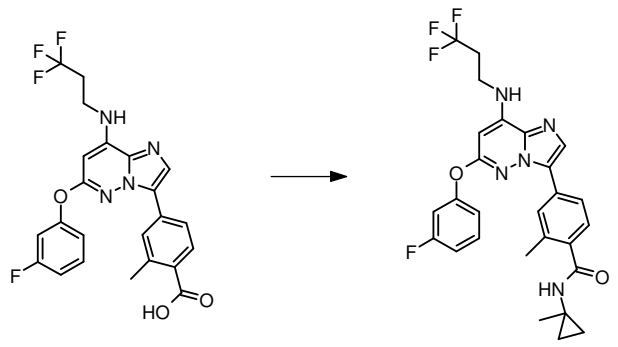


Se trataron 10,5 mg (22 µmol) de ácido 4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzoico, que se preparó de acuerdo con el Ejemplo Intermediario 459a, de manera análoga al Ejemplo 459 usando cloruro de 1-metoxiciclopropanaminio para dar, luego del tratamiento posterior y la purificación, 10,7 mg (85%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 0,84 (2H), 0,97 (2H), 2,15 (3H), 2,68 (2H), 3,24 (3H), 3,60 (2H), 6,13 (1H), 7,09-7,16 (2H), 7,21 (1H), 7,25 (1H), 7,49 (1H), 7,67 (1H), 7,71 (1H), 7,78 (1H), 7,94 (1H), 9,04 (1H) ppm.

Ejemplo 461

4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metil-N-(1-metilciclopropil)benzamida



Se trataron 10,5 mg (22 µmol) de ácido 4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzoico, que se preparó de acuerdo con el Ejemplo Intermediario 459a, de manera análoga al Ejemplo 459 usando cloruro de 1-metilciclopropanaminio para dar, luego del tratamiento posterior y la purificación, 12,0 mg (98%) del compuesto del título.

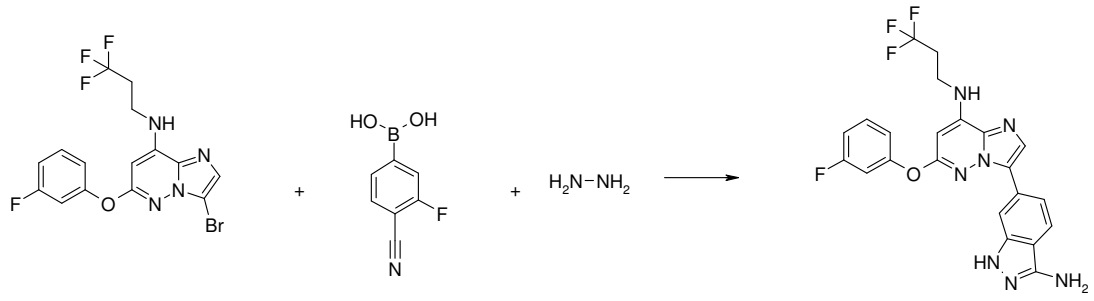
1H-RMN (CDCl3): δ= 0,74 (2H), 0,85 (2H), 1,51 (3H), 2,31 (3H), 2,58 (2H), 3,68 (2H), 5,89 (1H), 5,99 (1H), 6,07 (1H), 6,94-7,09 (3H), 7,23 (1H), 7,39 (1H), 7,61 (1H), 7,73 (2H) ppm.

Ejemplo 462

3-(3-amino-1H-indazol-6-il)-6-(3-fluorofenoxi)-N-(3,3,3-trifluoropropil)

imidazo[1,2-b]piridazin-8-

amina



Se trataron 42 mg (100 µmol) de 3-bromo-6-(3-fluorofenoxi)-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 462a, de manera análoga al Ejemplo 101 usando ácido (4-ciano-3-fluorofenil)borónico para dar 2-fluoro-4-[6-(3-fluoro-fenoxi)-8-(3,3,3-trifluoro-propilamino)-imidazo[1,2-b]piridazin-3-il]-benzonitrilo. Se agregaron 62 µL de (2 mmol) de hidrato de

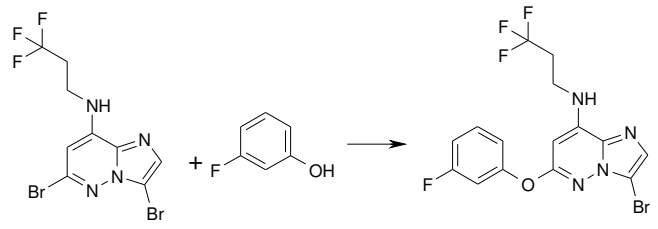
hidrazina y la mezcla se calentó a 80°C durante la noche. Después del tratamiento posterior y la purificación se obtuvieron 5,1 mg (11%) del compuesto del título.

UPLC-MS: RT = 1,14, PM encontrado = 472,4, PM calculado = 471,4.

1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 2,65 (3H), 3,58 (3H), 5,32 (2H), 6,06 (1H), 7,00-7,21 (3H), 7,38 (1H), 7,49 (1H), 7,59 (1H), 7,73 (1H), 7,83 (1H), 7,91 (1H), 11,31 (1H)

Ejemplo Intermediario 462a

3-bromo-6-(3-fluorofenoxi)-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina

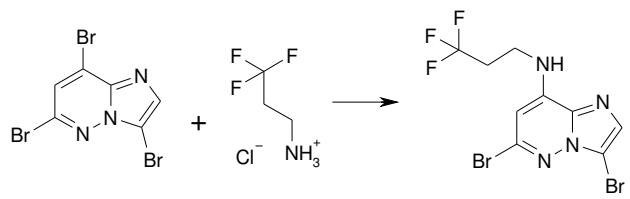


Se trataron 448,9 mg (1,16 mmol) de 3,6-dibromo-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 462b, de manera análoga al Ejemplo 51 usando 3-fluorofenol para dar, luego del tratamiento posterior y la purificación, 105,7 mg (22%) del compuesto del título.

1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 2,55-2,73 (2H), 3,55 (2H), 6,06 (1H), 7,00-7,09 (2H), 7,11-7,22 (1H), 7,33-7,49 (1H), 7,56 (1H), 7,82 (1H)

Ejemplo Intermediario 462b

3,6-dibromo-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina



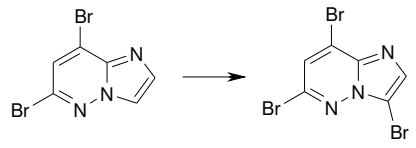
3,6-dibromo-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina

Se trataron 3,00 g (8,43 mmol) de 3,6,8-tribromoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 462c, de manera análoga al Ejemplo Intermediario 1b usando cloruro de 3,3,3-trifluoropropan-1-aminio para dar, luego del tratamiento posterior y la purificación, 2,97 g (91%) del compuesto del título.

1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 2,52-2,73 (2H), 3,56 (2H), 6,45 (1H), 7,61 (1H), 8,01 (1H)

Ejemplo Intermediario 462c

3,6,8-tribromoimidazo[1,2-b]piridazina



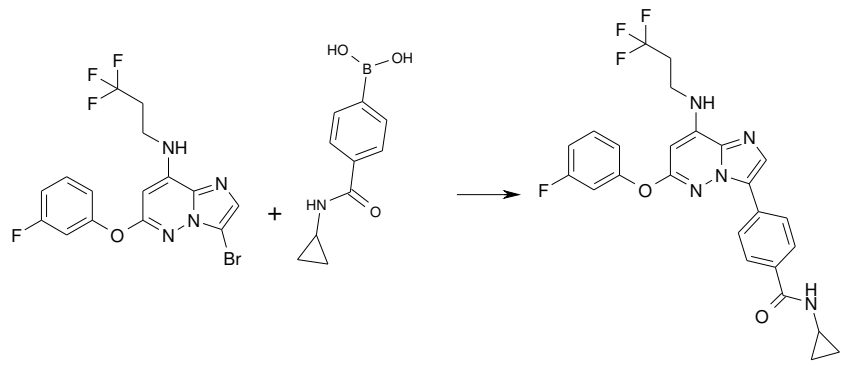
A una suspensión agitada de 100,00 g (361,1 mmol) de 6,8-dibromoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 96d, en 1,6 L de ácido acético, se agregaron 69,2 g (433,3 mmol) de bromo a temperatura ambiente y la mezcla se agitó durante 1 h. El precipitado se filtró, se lavó con agua y se disolvió en 10 L de DCM. La fase orgánica se lavó con solución saturada de carbonato ácido de sodio, se secó sobre sulfato de sodio, se filtró y se evaporó para dar 81,99 g

(64%) del compuesto del título.

1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 7,96 (1H), 8,04 (1H).

Ejemplo 463

N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida



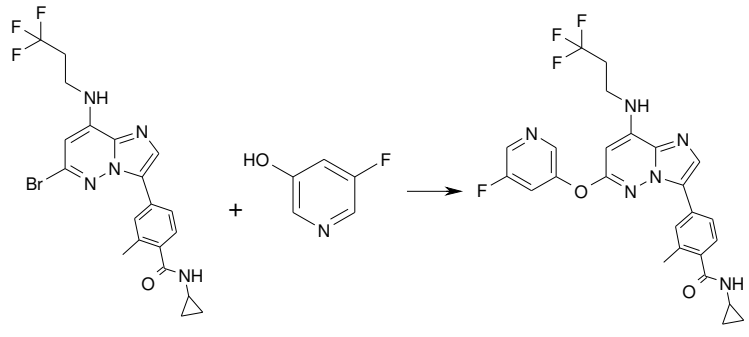
Se trataron 42 mg (100 µmol) de 3-bromo-6-(3-fluorofenoxi)-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina, que se preparó de acuerdo con el Ejemplo Intermediario 462a, de manera análoga al Ejemplo 101 usando ácido [4-(ciclopropilcarbamoil)fenil]borónico para dar, luego del tratamiento posterior y la purificación, 2,9 mg (5%) del compuesto del título.

UPLC-MS: RT = 1,31, PM encontrado = 500,5, PM calculado = 499,5.
1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,52 (2H), 0,66 (2H), 2,67 (2H), 2,79 (1H), 3,59 (2H), 6,14 (1H), 7,08-7,17 (2H), 7,24 (1H), 7,33-7,60 (2H), 7,68 (1H), 7,77 (1H), 7,95 (1H), 8,01 (1H), 8,40 (1H).

Ejemplo 464

N-ciclopropil-4-{6-[(5-fluoropiridin-3-il)oxi]-8-[(3,3,3-trifluoropropil)amino]

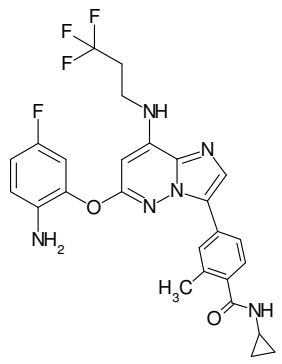
imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

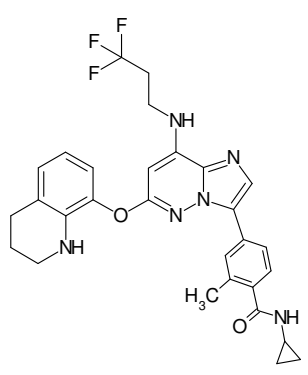


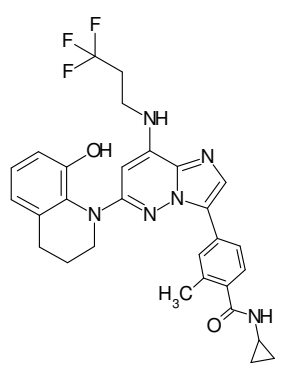
Se trataron 48 mg (100 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida que se preparó de acuerdo con el Ejemplo Intermediario 247a, de manera análoga al Ejemplo 51 usando 5-fluoropiridin-3-ol para dar, luego del tratamiento posterior y la purificación, 8,1 mg (16%) del compuesto del título.

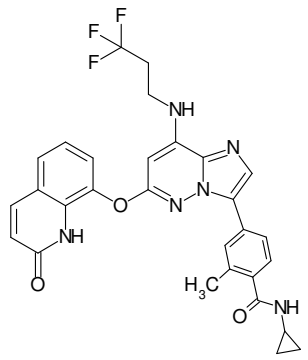
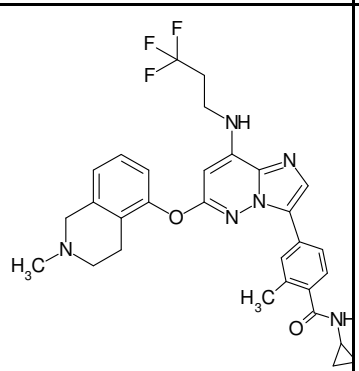
UPLC-MS: RT = 1,19, PM encontrado = 515,5, PM calculado = 514,5. 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,41-0,54 (2H), 0,58-0,71 (2H), 2,14 (3H), 2,59-2,85 (3H), 3,61 (2H), 6,21 (1H), 7,17 (1H), 7,61 (1H), 7,70 (1H), 7,81 (1H), 7,93 (1H), 7,95-8,06 (1H), 8,22 (1H), 8,46-8,63 (2H)

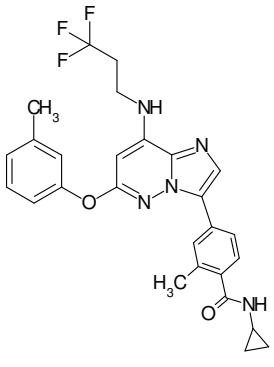
Los siguientes ejemplos de compuestos se prepararon de manera análoga al procedimiento descrito para el ejemplo 51 usando los fenoles o anilinas apropiados [los datos de LC-MS como por ejemplo tiempo de retención (RT en min) o pico de masa observada se recogieron usando el Método LC-MS A salvo que se especifique lo contrario]:

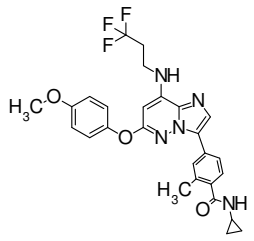
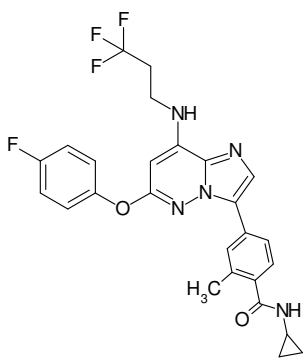
Ejemplo	Estructura	Nombre	Datos analíticos
465		4-{6-(2-amino-5-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida	RT = 1,25 PM encontrado = 529,5 PM calculado = 528,5 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,43-0,51 (2H), 0,58-0,69 (2H), 2,15 (3H), 2,60-2,82 (3H), 3,59 (2H), 4,83 (2H), 6,10 (1H), 6,74-6,82 (1H), 6,85 (1H), 7,03 (1H), 7,15 (1H), 7,61-7,70 (2H), 7,84 (1H), 7,92 (1H), 8,22 (1H)

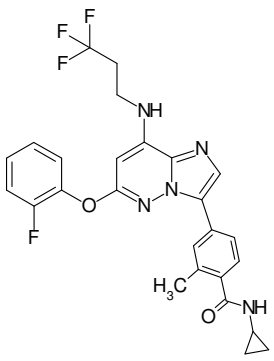
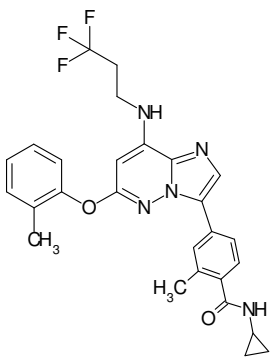
Ejemplo	Estructura	Nombre	Datos analíticos
466		N-ciclopropil-2-metil-4-{6-(1,2,3,4-tetrahidroquinolin-8-iloxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,36 PM encontrado = 551,6 PM calculado = 550,6 1H-RMN (600 MHz,DMSO-d6), δ [ppm]= 0,48-0,54 (2H), 0,63-0,70 (2H), 1,76-1,82 (2H), 2,19 (3H), 2,66-2,78 (4H), 2,80 (1H), 3,12-3,20 (2H), 3,61 (2H), 5,24 (1H), 6,08 (1H), 6,50 (1H), 6,82 (1H), 6,90 (1H), 7,18 (1H), 7,60 (1H), 7,72-7,77 (1H), 7,87 (1H), 7,95 (1H), 8,23 (1H)

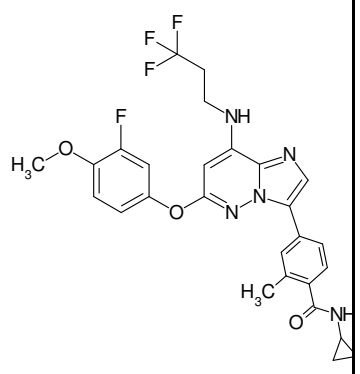
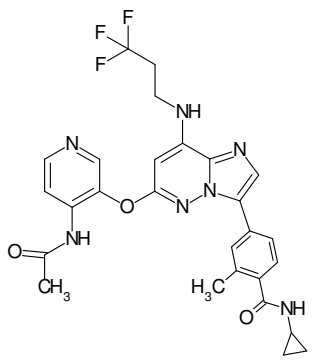
Ejemplo	Estructura	Nombre	Datos analíticos
467		N-ciclopropil-4-{6-(8-hidroxi-3,4-dihidroquinolin-1(2H)-il)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,19 PM encontrado = 551,6 PM calculado = 550,6 1H-RMN (600 MHz,DMSO-d6), δ [ppm]= 0,50-0,56 (2H), 0,64-0,71 (2H), 1,88 (2H), 2,31 (3H), 2,62 (2H), 2,69 (2H), 2,83 (1H), 3,44 (2H), 3,84 (2H), 5,72 (1H), 6,66 (1H), 6,74 (1H), 6,90-6,94 (1H), 7,11 (1H), 7,27 (1H), 7,84 (1H), 7,92 (1H), 7,96 (1H), 8,25 (1H), 9,29 (1H) Isómero!

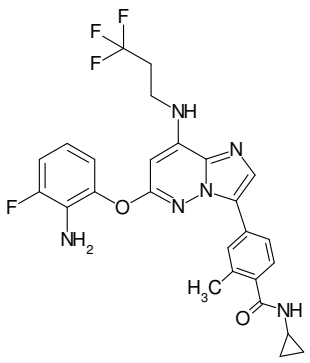
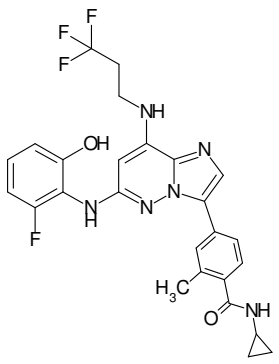
Ejemplo	Estructura	Nombre	Datos analíticos
468		N-ciclopropil-2-metil-4-{6-[(2-oxo-1,2-dihidroquinolin-8-il)oxi]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,01 PM encontrado = 563,5 PM calculado = 562,5 1H-RMN (600 MHz,DMSO-d6), δ [ppm]= 0,47-0,51 (2H), 0,64-0,69 (2H), 2,06 (3H), 2,71-2,82 (3H), 3,66 (2H), 6,25 (1H), 6,55 (1H), 7,08 (1H), 7,26 (1H), 7,54 (1H), 7,57 (1H), 7,62-7,65 (2H), 7,66-7,71 (1H), 7,93 (1H), 8,02 (1H), 8,20 (1H)
469		N-ciclopropil-2-metil-4-{6-[(2-metil-1,2,3,4-tetrahidroisoquinolin-5-il)oxi]-8-[(3,3,3-	RT = 0,95 PM encontrado = 565,6 PM calculado = 564,6 1H-RMN (300

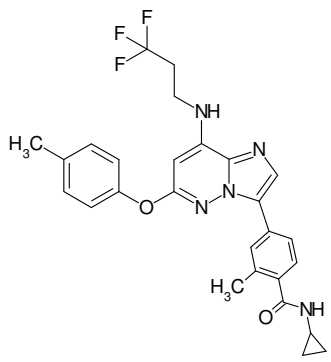
Ejemplo	Estructura	Nombre	Datos analíticos
		trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	MHz,DMSO-d6), δ [ppm]= 0,42-0,50 (2H), 0,58-0,68 (2H), 2,09 (3H), 2,28 (3H), 2,53 (2H), 2,60-2,81 (5H), 3,51 (2H), 3,59 (2H), 6,11 (1H), 6,97-7,06 (2H), 7,12 (1H), 7,16-7,24 (1H), 7,58-7,67 (2H), 7,71 (1H), 7,91 (1H), 8,18 (1H)
470		N-ciclopropil-2-metil-4-{6-(3-metilfenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,42 PM encontrado = 510,5 PM calculado = 509,5

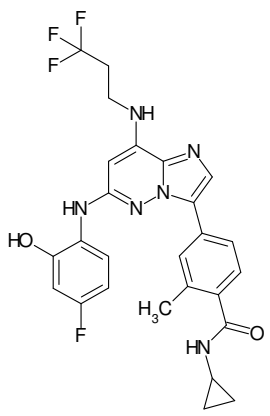
Ejemplo	Estructura	Nombre	Datos analíticos
471		N-ciclopropil-4-{6-(4-metoxifenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,34 PM encontrado = 526,5 PM calculado = 525,5 1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 0,43-0,50 (2H), 0,60-0,68 (2H), 2,11 (3H), 2,60-2,73 (2H), 2,77 (1H), 3,59 (2H), 3,75 (3H), 6,07 (1H), 6,99 (2H), 7,13-7,22 (3H), 7,58-7,67 (2H), 7,77 (1H), 7,91 (1H), 8,19 (1H)
472		N-ciclopropil-4-{6-(4-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,36 PM encontrado = 514,5 PM calculado = 513,5 1H-RMN (400 MHz,DMSO-d6), δ

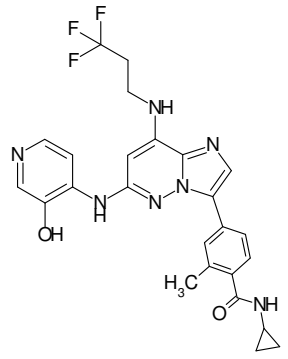
Ejemplo	Estructura	Nombre	Datos analíticos
			[ppm]= 0,47 (2H), 0,63 (2H), 2,13 (3H), 2,60-2,73 (2H), 2,73-2,82 (1H), 3,60 (2H), 6,11 (1H), 7,16 (1H), 7,23-7,36 (4H), 7,60-7,70 (2H), 7,72 (1H), 7,92 (1H), 8,20 (1H)
473		N-ciclopropil-4-{6-(2-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,36 PM encontrado = 514,5 PM calculado = 513,5
474		N-ciclopropil-2-metil-4-{6-(2-metilfenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-	RT = 1,40 PM encontrado = 510,5 PM calculado = 509,5

Ejemplo	Estructura	Nombre	Datos analíticos
		il}benzamida	
475		N-ciclopropil-4-{6-(3-fluoro-4-metoxifenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,35 PM encontrado = 544,5 PM calculado = 543,5
476		4-(6-{[4-(acetilamino)piridin-3-il]oxi}-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida	RT = 0,89 PM encontrado = 554,5 PM calculado = 553,5 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,44-0,55 (2H), 0,60-0,69 (2H), 2,20-2,27 (3H), 2,36 (3H), 2,65-2,85 (3H), 3,69 (2H), 6,76 (1H), 7,38 (1H), 7,84-7,93 (2H), 7,95-8,04 (2H), 8,09 (1H), 8,23-8,34 (3H), 8,36 (1H)

Ejemplo	Estructura	Nombre	Datos analíticos
477		4-{6-(2-amino-3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida	RT = 1,28 PM encontrado = 529,5 PM calculado = 528,5 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,42-0,53 (2H), 0,58-0,69 (2H), 2,13 (3H), 2,59-2,85 (3H), 3,50-3,66 (2H), 4,98 (2H), 6,11 (1H), 6,53-6,63 (1H), 6,93 (1H), 6,96-7,03 (1H), 7,14 (1H), 7,60-7,68 (2H), 7,80 (1H), 7,89-7,95 (1H), 8,22 (1H)
478		N-ciclopropil-4-{6-[(2-fluoro-6-hidroxifenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-	RT = 1,10 PM encontrado = 529,5 PM calculado = 528,5 1H-RMN (300 MHz,DMSO-d6), δ

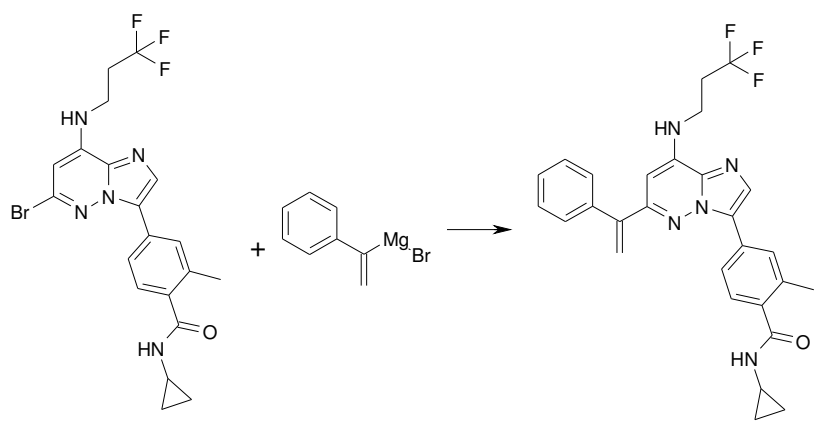
Ejemplo	Estructura	Nombre	Datos analíticos
		metilbenzamida	[ppm]= 0,42-0,52 (2H), 0,59-0,69 (2H), 2,17 (3H), 2,58-2,82 (3H), 3,49 (2H), 5,89 (1H), 6,67-6,77 (2H), 6,99-7,10 (1H), 7,10-7,19 (2H), 7,68-7,75 (1H), 7,77 (1H), 7,92 (1H), 7,87 (1H), 8,21 (1H), 9,78 (1H)Isómero
479		N-ciclopropil-2-metil-4-{6-(4-metilfenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,41 PM encontrado = 510,5 PM calculado = 509,5 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,42-0,50 (2H), 0,59-0,67 (2H), 2,09 (3H), 2,31 (3H), 2,59-2,82 (3H), 3,58 (2H), 6,09 (1H),

Ejemplo	Estructura	Nombre	Datos analíticos
			7,15 (3H), 7,25 (2H), 7,60-7,68 (2H), 7,75 (1H), 7,92 (1H), 8,21 (1H)
480		N-ciclopropil-4-{6-[(4-fluoro-2-hidroxifenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,25 PM encontrado = 529,5 PM calculado = 528,5 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,45-0,55 (2H), 0,60-0,71 (2H), 2,33 (3H), 2,67 (2H), 2,80 (1H), 3,43-3,53 (2H), 6,21 (1H), 6,53-6,63 (1H), 6,67 (1H), 7,18 (1H), 7,30 (1H), 7,76 (1H), 7,78-7,86 (1H), 7,90 (1H), 7,98-8,14 (3H), 8,28 (1H),

Ejemplo	Estructura	Nombre	Datos analíticos
			10,28 (1H)
481		N-ciclopropil-4-{6-[(3-hidroxipiridin-4-il)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 0,84 PM encontrado = 512,5 PM calculado = 511,5 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,47-0,56 (2H), 0,62-0,71 (2H), 2,39 (3H), 2,68 (2H), 2,82 (1H), 3,45-3,56 (2H), 6,46 (1H), 7,32-7,42 (2H), 7,77-7,85 (2H), 7,88 (1H), 8,00 (1H), 8,06 (1H), 8,14 (2H), 8,29 (2H)

Ejemplo 482

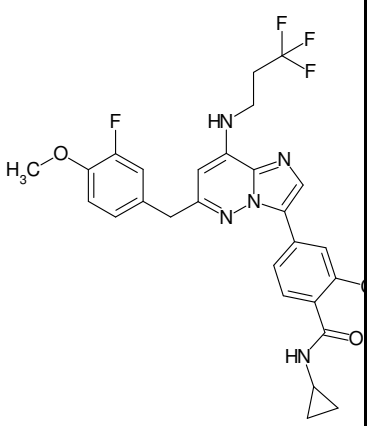
N-ciclopropil-2-metil-4-{6-(1-feniletenil)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida

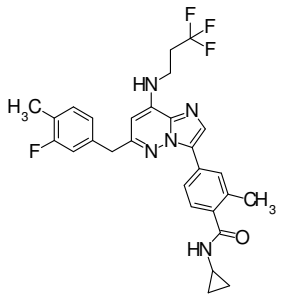
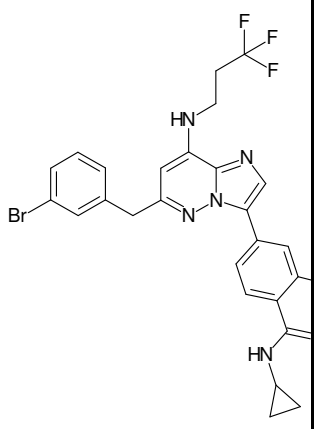


A una solución agitada de 24 mg (50 µmol) de 4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 247a, en 1 mL de THF se agregó 1,0 mL de (0,5 mmol) de una solución de bromo(1-feniletenil)magnesio en THF 0,5 M por goteo a temperatura ambiente. Luego de agitar durante la noche a temperatura ambiente, la mezcla se calentó a 50°C y se agitó durante 3 días más para dar, luego del tratamiento posterior y la purificación, 1,7 mg (5%) del compuesto del título.

UPLC-MS: RT = 1,36, PM encontrado = 506,5, PM calculado = 505,5. 1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 0,42-0,50 (2H), 0,59-0,66 (2H), 2,15 (3H), 2,61-2,71 (2H), 2,77 (1H), 3,60 (2H), 5,74 (1H), 5,99 (1H), 6,36 (1H), 7,16-7,20 (2H), 7,34-7,45 (3H), 7,55 (2H), 7,79-7,84 (1H), 7,86 (1H), 8,01 (1H), 8,22 (1H)

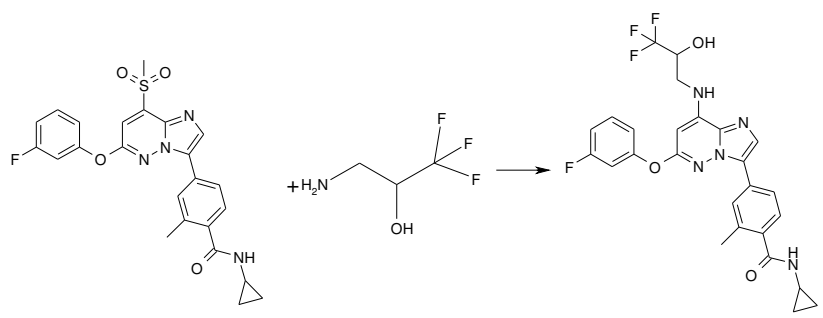
Los siguientes ejemplos de compuestos se prepararon de manera análoga al procedimiento descrito para el ejemplo 482 usando los reactivos de Grignard apropiados [los datos de LC-MS como por ejemplo tiempo de retención (RT en min) o pico de masa observada se recogieron usando el Método LC-MS A salvo que se especifique lo contrario]:

Ejemplo	Estructura	Nombre	Datos analíticos
483		N-ciclopropil-4-{6-(3-fluoro-4-metoxibencil)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,33 PM encontrado = 542,5 PM calculado = 541,5 1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 0,47-0,53 (2H), 0,62-0,69 (2H), 2,32 (3H), 2,64 (2H), 2,77-2,84 (1H), 3,53 (2H), 3,76 (3H), 3,96 (2H), 6,20 (1H), 7,04-7,12 (2H), 7,17-7,23 (1H), 7,30 (1H), 7,47 (1H), 7,93-7,98 (3H), 8,27 (1H)

Ejemplo	Estructura	Nombre	Datos analíticos
484		N-ciclopropil-4-{6-(3-fluoro-4-metilbencil)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,25 PM encontrado = 526,5 PM calculado = 525,5 1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 0,47-0,53 (2H), 0,62-0,68 (2H), 2,14-2,17 (3H), 2,31 (3H), 2,59-2,71 (2H), 2,80 (1H), 3,53 (2H), 3,99 (2H), 6,21 (1H), 7,06 (1H), 7,13 (1H), 7,16-7,22 (1H), 7,30 (1H), 7,47 (1H), 7,92-7,99 (3H), 8,27 (1H)
485		4-{6-(3-bromobencil)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida	RT = 1,44 PM encontrado = 573,4 PM calculado = 572,4 1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 0,47-0,53 (2H), 0,62-0,68 (2H), 2,33 (3H), 2,58-2,70 (2H), 2,80 (1H), 3,54 (2H), 4,03 (2H), 6,24 (1H), 7,27 (1H), 7,31 (1H), 7,36 (1H), 7,39-7,44 (1H), 7,47-7,53 (1H), 7,57-7,61 (1H), 7,95 (3H), 8,27 (1H)

Ejemplo 486

N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoro-2-hidroxipropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



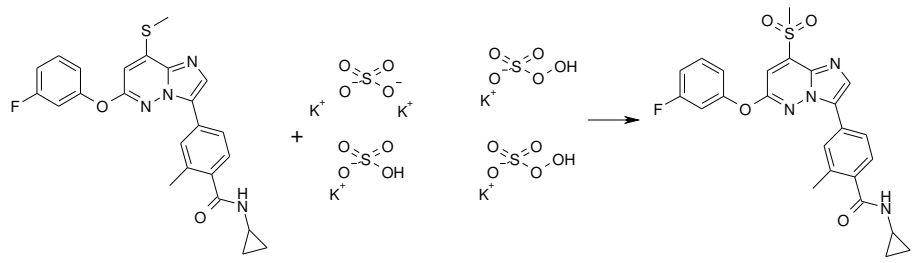
A una solución agitada de 96 mg (200 µmol) de N-ciclopropil-4-[6-(3-fluorofenoxi)-8-(metilsulfonil)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 486a, en 2 mL de NMP se agregaron 77,5 mg (0,6 mmol) de 3-amino-1,1,1-trifluoropropan-2-ol y 77,5 mg (0,6 mmol) de DIPEA y la mezcla se calentó a 160°C durante 30 min en un horno de microondas. Después del tratamiento posterior y la purificación se obtuvieron 10,5 mg (9%) del compuesto del título.

UPLC-MS: RT = 1,23, PM encontrado = 530,5, PM calculado = 529,5)

Ejemplo Intermediario 486a

N-ciclopropil-4-[6-(3-fluorofenoxi)-8-(metilsulfonil)imidazo[1,2-b]piridazin-

3-il]-2-metilbenzamida

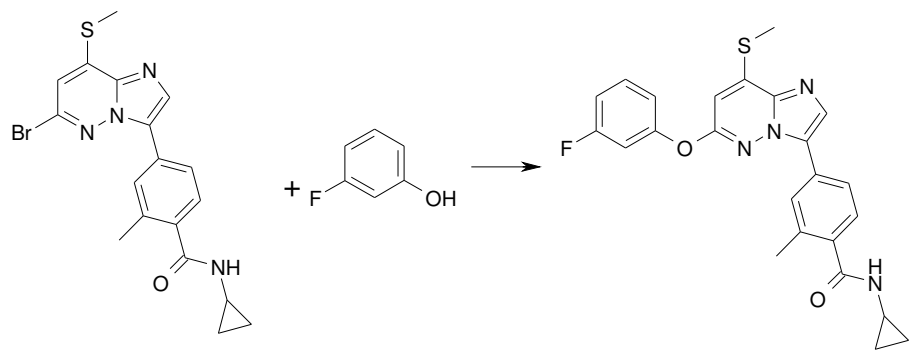


A una solución agitada de 4,96 g (11,06 mmol) de N-ciclopropil-4-[6-(3-fluorofenoxi)-8-(metilsulfanil)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 486b en DMF (250 mL), se agregaron 20,4 g (33,18 mmol) de oxona en una porción a temperatura ambiente. Después de dejarse reaccionar durante 72 h, se agregaron otros 30 g (55 mmol) de oxona y la mezcla se calentó a 70°C durante una hora. La extracción con acetato de etilo / agua, el filtrado de la fase orgánica a través de un filtro Whatman y la evaporación de la fase orgánica dieron el producto crudo (4,96 g, 93%) que se usó sin purificación adicional.

1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 0,44-0,50 (2H), 0,64 (2H), 2,73-2,82 (1H), 3,65 (3H), 7,19-7,24 (2H), 7,24-7,29 (1H), 7,39-7,45 (1H), 7,53-7,61 (2H), 7,68 (1H), 7,72 (1H), 8,28 (1H), 8,37 (1H)

Ejemplo Intermediario 486b

N-ciclopropil-4-[6-(3-fluorofenoxi)-8-(metilsulfanil)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida



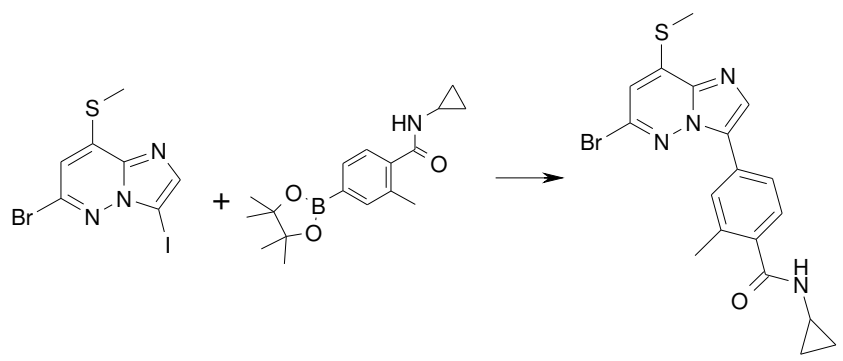
Se trataron 8 g (19,2 mmol) de 4-[6-bromo-8-(metilsulfanil)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 486c, de manera análoga al Ejemplo 51 usando 3-fluorofenol para dar, luego del tratamiento posterior y la purificación, 4,96 g (46%) del compuesto del título.

1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 0,44-0,50 (2H), 0,60-0,67 (2H), 2,13 (3H), 2,65 (3H), 2,76 (1H), 6,99 (1H), 7,15-7,25 (3H), 7,37 (1H), 7,49-7,56 (1H), 7,65 (1H), 7,73 (1H), 8,06 (1H), 8,24 (1H)

Ejemplo Intermediario 486c

4-[6-bromo-8-(metilsulfanil)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-

2-metilbenzamida

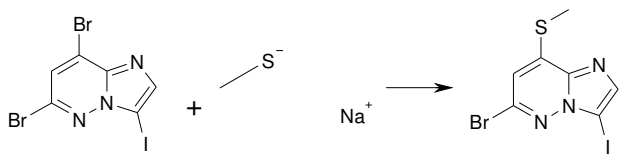


Se trataron 42,1 g (113,9 mmol) de 6-bromo-3-yodo-8-(metilsulfanil)imidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 486d, de manera análoga al Ejemplo 1a usando N-ciclopropil-2-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzamida para dar, luego del tratamiento posterior y la purificación, 17,78 g (34%) del compuesto del título.

1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,47-0,53 (2H), 0,62-0,70 (2H), 2,36 (4H), 2,64 (3H), 2,81 (1H), 7,19 (1H), 7,40 (1H), 7,86 (1H), 7,90 (1H), 8,12 (1H), 8,31 (1H)

Ejemplo Intermediario 486d

6-bromo-3-yodo-8-(metilsulfanil)imidazo[1,2-b]piridazina

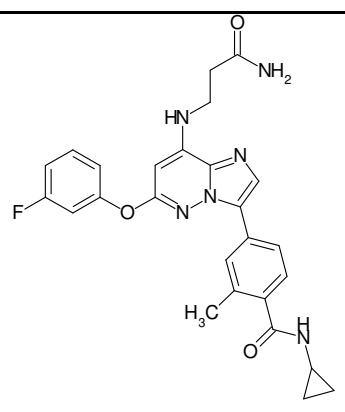
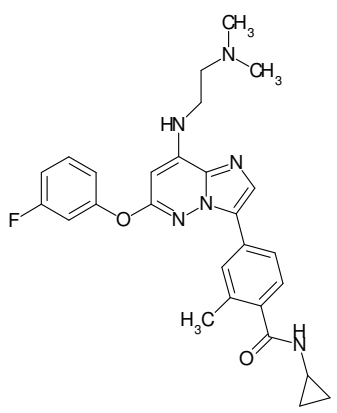


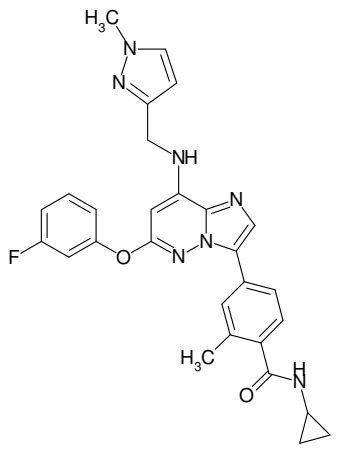
A una solución agitada de 51,2 g (146,8 mmol) de 6,8-dibromo-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 96c, en NMP (450 mL) se agregaron 12,35 g (176,2 mmol) de metantiolato de sodio en una porción a 0° C. Después de dejarse reaccionar durante 15 min, se agregaron 700 mL de agua y el precipitado se retiró por filtración y se secó. La trituración con éter, el filtrado y el secado al vacío dieron 44,3 g (65%) del compuesto del título

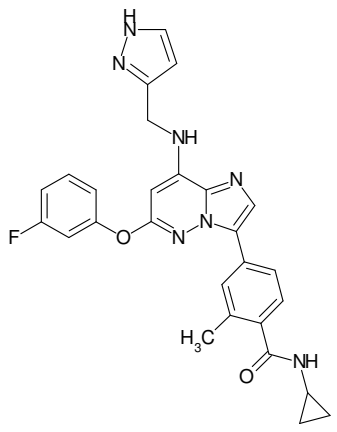
1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 2,62 (4H), 7,15 (1H), 7,75 (1H)

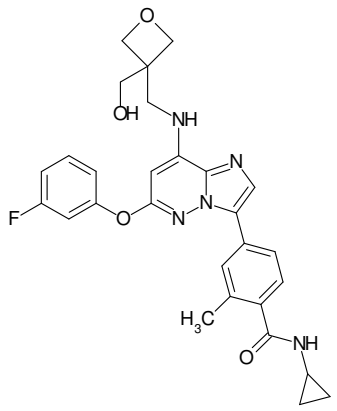
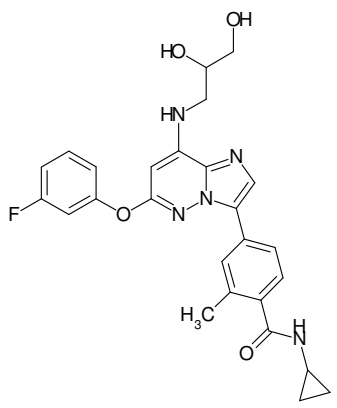
Los siguientes ejemplos de compuestos se prepararon de manera

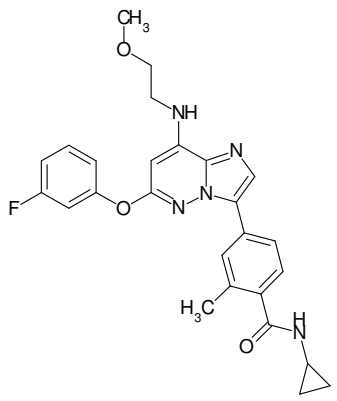
análoga al procedimiento descrito para el ejemplo 486 usando la amina apropiada [los datos de LC-MS como por ejemplo tiempo de retención (RT en min) o pico de masa observada se recogieron usando el Método LC-MS A salvo que se especifique lo contrario]:

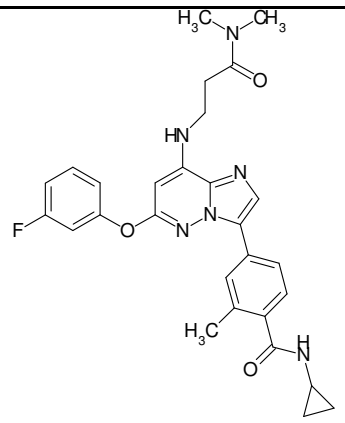
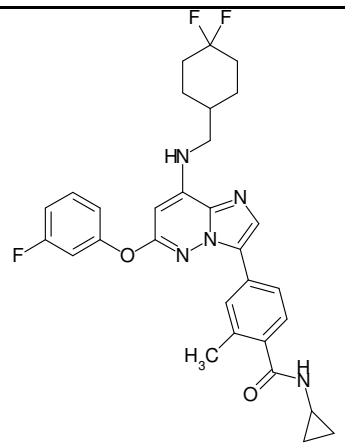
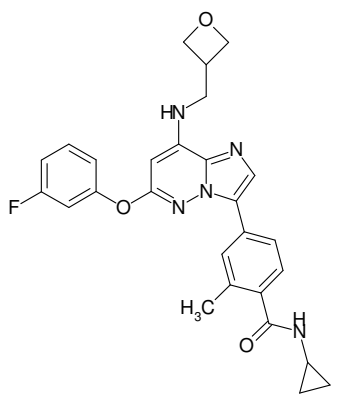
Ejemplo	Estructura	Nombre	Datos analíticos
549		4-{8-[(3-amino-3-oxopropil)amino]-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida	RT = 1,01 PM encontrado = 489,5 PM calculado = 488,5
487		N-ciclopropil-4-[8-{[2-(dimetilamino)etil]amino}-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 0,88 PM encontrado = 489,6 PM calculado = 488,6 1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 0,46 (2H), 0,63 (2H), 2,14 (3H), 2,19 (6H), 2,52 (2H), 2,76 (1H), 3,39 (2H), 6,06 (1H), 7,09-7,19 (4H), 7,24 (2H), 7,48 (1H),

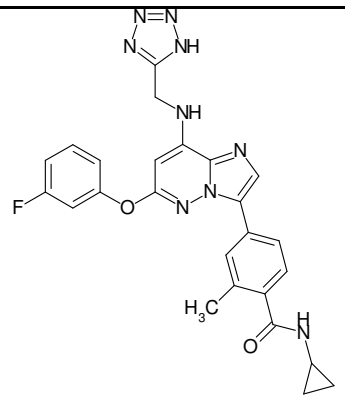
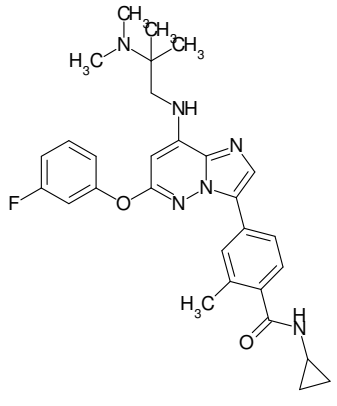
Ejemplo	Estructura	Nombre	Datos analíticos
			7,66 (1H), 7,76 (1H), 7,90 (1H), 8,21 (1H)
488		N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[(1-metil-1H-pirazol-3-il)metil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 1,17 PM encontrado = 512,6 PM calculado = 511,6 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,42-0,51 (2H), 0,58-0,68 (2H), 2,14 (3H), 2,76 (1H), 3,76 (3H), 4,45 (2H), 6,00 (1H), 6,15 (1H), 7,06-7,26 (5H), 7,46 (1H), 7,58 (1H), 7,66 (1H), 7,75 (1H), 7,92 (1H), 7,93-8,01 (1H), 8,21 (1H)

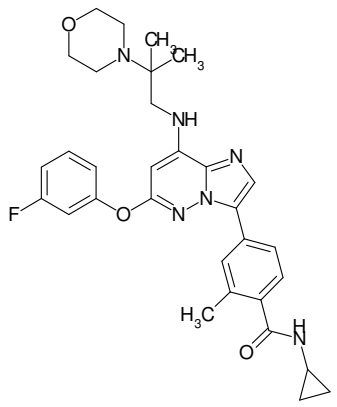
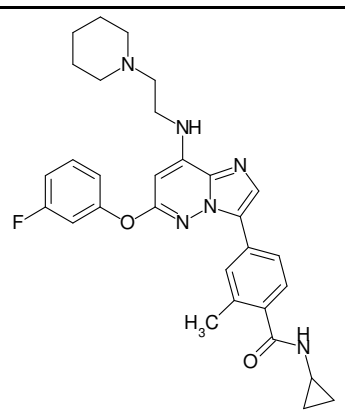
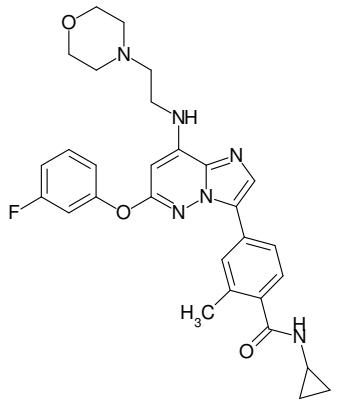
Ejemplo	Estructura	Nombre	Datos analíticos
489		N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(1H-pirazol-3-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,14 PM encontrado = 498,5 PM calculado = 497,5 1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 0,43-0,50 (2H), 0,59-0,66 (2H), 2,13 (3H), 2,76 (1H), 4,51 (2H), 6,06 (1H), 6,19 (1H), 7,07-7,19 (4H), 7,23 (1H), 7,42-7,51 (2H), 7,65 (2H), 7,75 (1H), 7,87-7,95 (1H), 7,95-8,05 (1H), 8,21 (2H)

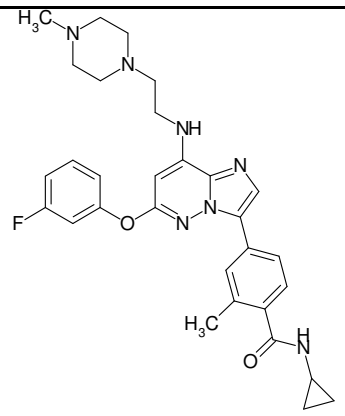
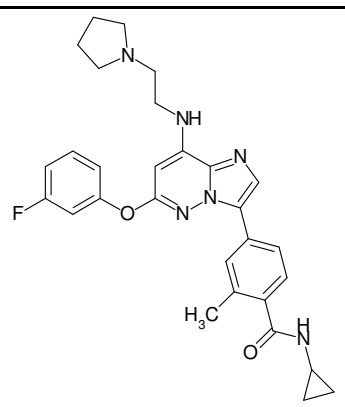
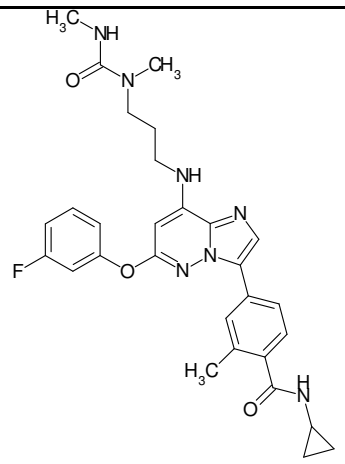
Ejemplo	Estructura	Nombre	Datos analíticos
490		N-ciclopropil-4-[6-(3-fluorofenoxi)-8-({[3-(hidroximetil)oxetan-3-il]metil}amino)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 1,08 PM encontrado = 518,6 PM calculado = 517,6
491		N-ciclopropil-4-{8-[(2,3-dihidroxipropil)amino]-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,04 PM encontrado = 492,5 PM calculado = 491,5 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,39-0,51 (2H), 0,58-0,69 (2H), 2,14 (3H), 2,76 (1H), 3,39 (3H), 3,73 (1H), 4,70 (1H), 4,98 (1H), 6,08 (1H), 7,02-7,20 (3H), 7,20-7,37 (2H), 7,41-7,55 (1H), 7,66 (1H), 7,76 (1H), 7,91 (1H), 8,21 (1H)

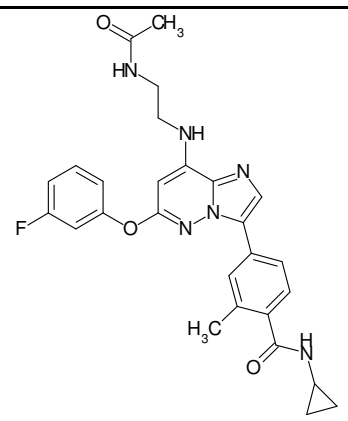
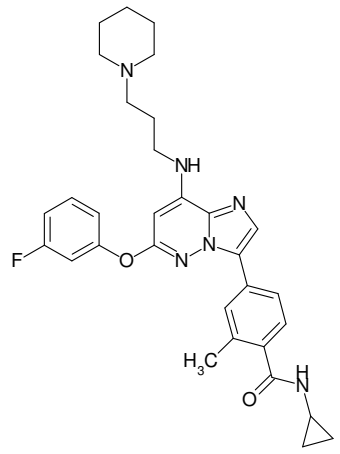
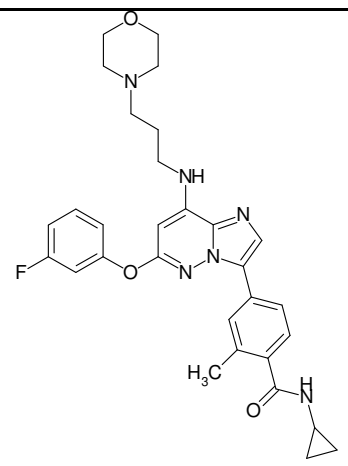
Ejemplo	Estructura	Nombre	Datos analíticos
492		N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(2-metoxietil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,26 PM encontrado = 476,5 PM calculado = 475,5 1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 0,42-0,50 (2H), 0,60-0,67 (2H), 2,14 (3H), 2,77 (1H), 3,26 (3H), 3,51 (2H), 3,53-3,58 (2H), 6,10 (1H), 7,08-7,19 (3H), 7,25 (1H), 7,43-7,52 (2H), 7,66 (1H), 7,76 (1H), 7,92 (1H), 8,21 (1H)

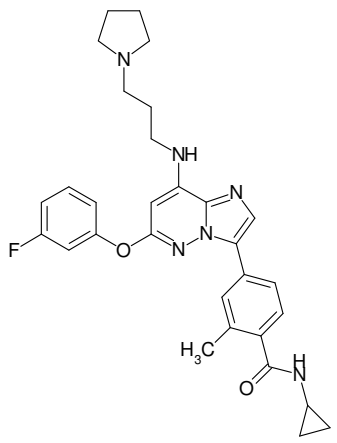
Ejemplo	Estructura	Nombre	Datos analíticos
493		N-ciclopropil-4-[8-{[3-(dimetilamino)-3-oxopropil]amino}-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 1,26 PM encontrado = 517,6 PM calculado = 516,6
494		N-ciclopropil-4-[8-{[(4,4-difluorociclohexil)metil]amino}-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 1,45 PM encontrado = 550,6 PM calculado = 549,6
495		N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(oxetan-3-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,17 PM encontrado = 488,5 PM calculado = 487,5 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,40-0,51 (2H), 0,56-0,69 (2H), 0,75-0,89 (1H), 2,13 (3H), 2,76 (1H), 3,61 (2H), 4,34 (2H),

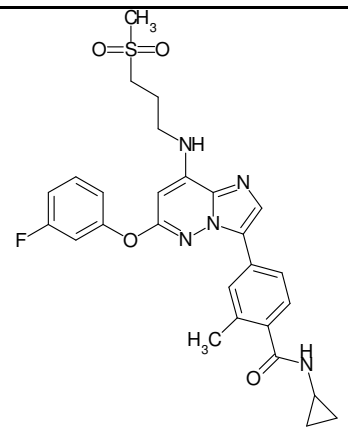
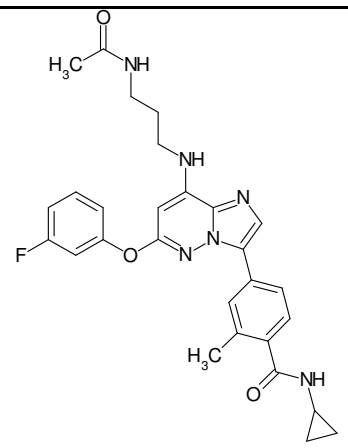
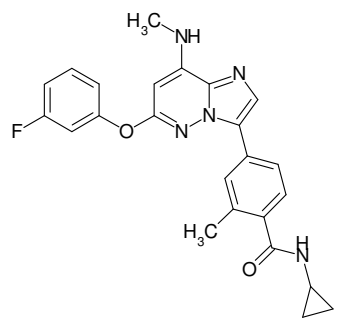
Ejemplo	Estructura	Nombre	Datos analíticos
			4,63 (2H), 6,13 (1H), 7,05-7,20 (3H), 7,25 (1H), 7,41-7,54 (1H), 7,65 (1H), 7,75 (1H), 7,85-7,96 (2H), 8,21 (1H)
496		N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(1H-tetrazol-5-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,03 PM encontrado = 500,5 PM calculado = 499,5
497		N-ciclopropil-4-[8-{[2-(dimetilamino)-2-metilpropil]amino}-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 0,97 PM encontrado = 517,6 PM calculado = 516,6

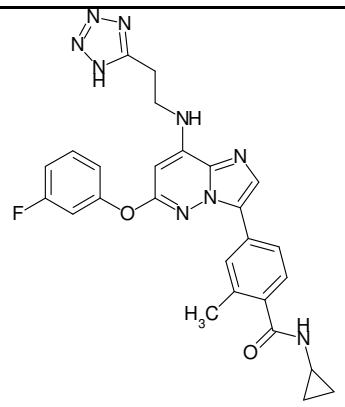
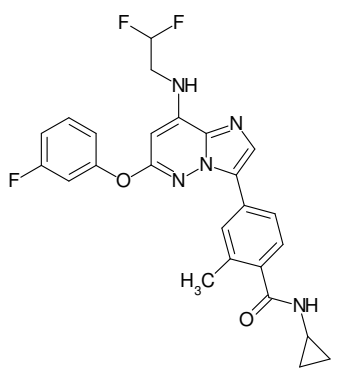
Ejemplo	Estructura	Nombre	Datos analíticos
498		N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[2-metil-2-(morfolin-4-il)propil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 0,99 PM encontrado = 559,6 PM calculado = 558,6
499		N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[2-(piperidin-1-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 0,98 PM encontrado = 529,6 PM calculado = 528,6
500		N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 0,93 PM encontrado = 531,6 PM calculado = 530,6

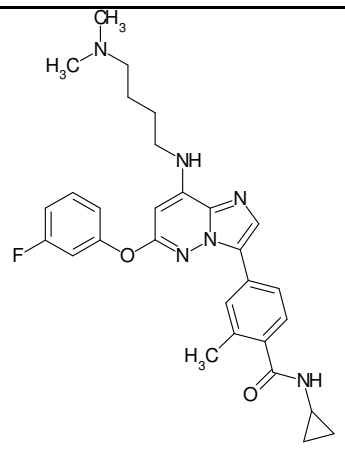
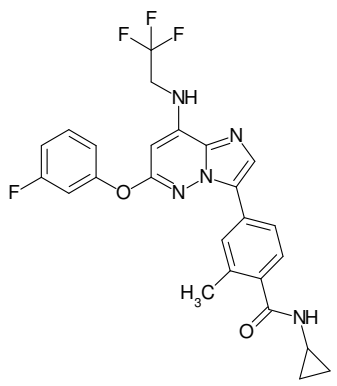
Ejemplo	Estructura	Nombre	Datos analíticos
501		N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[2-(4-metilpiperazin-1-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 0,96 PM encontrado = 544,6 PM calculado = 543,6
502		N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[2-(pirrolidin-1-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 0,96 PM encontrado = 515,6 PM calculado = 514,6
503		N-ciclopropil-4-[6-(3-fluorofenoxi)-8-({3-[metil(metilcarbamoil)amino]propil}amino)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 1,17 PM encontrado = 546,6 PM calculado = 545,6

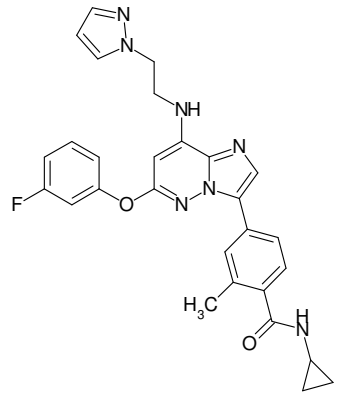
Ejemplo	Estructura	Nombre	Datos analíticos
504		4-[8-{[2-(acetilamino)etil]amino}-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida	RT = 1,10 PM encontrado = 503,5 PM calculado = 502,5
505		N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[3-(piperidin-1-il)propil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 1,01 PM encontrado = 543,6 PM calculado = 542,6
506		N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[3-(morfolin-4-il)propil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 0,96 PM encontrado = 545,6 PM calculado = 544,6

Ejemplo	Estructura	Nombre	Datos analíticos
507		N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[3-(pirrolidin-1-il)propil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 0,98 PM encontrado = 529,6 PM calculado = 528,6 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,43-0,50 (2H), 0,58-0,67 (2H), 1,68 (4H), 1,78 (2H), 2,14 (3H), 2,48-2,54 (2H), 2,76 (1H), 3,36 (6H), 6,04 (1H), 7,06-7,19 (4H), 7,23 (1H), 7,42-7,52 (1H), 7,62-7,70 (1H), 7,76 (1H), 7,82-7,92 (2H), 8,17-8,24 (1H)

Ejemplo	Estructura	Nombre	Datos analíticos
508		N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[3-(metilsulfonil)propil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 1,15 PM encontrado = 538,6 PM calculado = 537,6
509		4-[8-{[3-(acetilamino)propil]amino}-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida	RT = 1,12 PM encontrado = 517,6 PM calculado = 516,6
510		N-ciclopropil-4-[6-(3-fluorofenoxi)-8-(metilamino)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 1,26 PM encontrado = 432,5 PM calculado = 431,5 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,40-0,52 (2H), 0,57-0,73 (2H), 2,20 (3H), 2,69-2,82 (1H), 2,90 (3H), 5,95 (1H), 7,04-7,20

Ejemplo	Estructura	Nombre	Datos analíticos
			(3H), 7,24 (1H), 7,41-7,55 (1H), 7,59-7,73 (2H), 7,76 (1H), 7,90 (1H), 8,21 (1H)
511		N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[2-(1H-tetrazol-5-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 1,10 PM encontrado = 514,5 PM calculado = 513,5
512		N-ciclopropil-4-{8-[(2,2-difluoroetil)amino]-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,28 PM encontrado = 482,5 PM calculado = 481,5

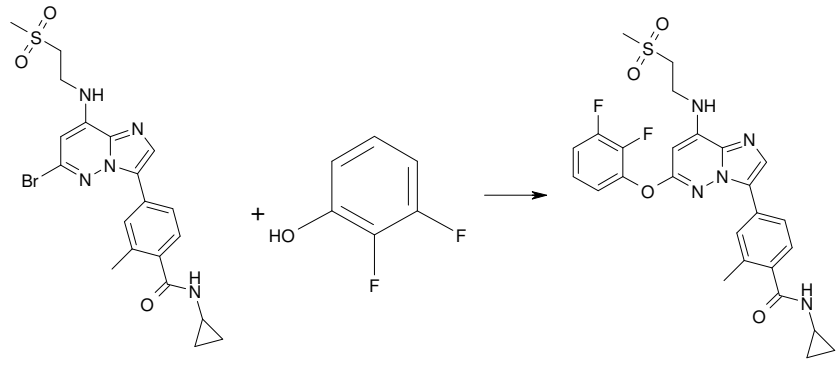
Ejemplo	Estructura	Nombre	Datos analíticos
513		N-ciclopropil-4-[8-{[4-(dimetilamino)butil]amino}-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 0,99 PM encontrado = 517,6 PM calculado = 516,6
514		N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(2,2,2-trifluoroetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,06 PM encontrado = 500,5 PM calculado = 499,5 1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 0,43-0,51 (2H), 0,59-0,69 (2H), 2,14 (3H), 2,72-2,81 (1H), 5,20 (2H), 6,96 (1H), 7,15-7,27 (4H), 7,39 (1H), 7,54 (1H), 7,67 (1H), 7,74 (1H), 8,17 (1H), 8,25 (1H)

Ejemplo	Estructura	Nombre	Datos analíticos
515		N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[2-(1H-pirazol-1-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 1,22 PM encontrado = 512,6 PM calculado = 511,6

Ejemplo 516

N-ciclopropil-4-[6-(2,3-difluorofenoxi)-8-{[2-(metilsulfonil)etil]amino}

imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida

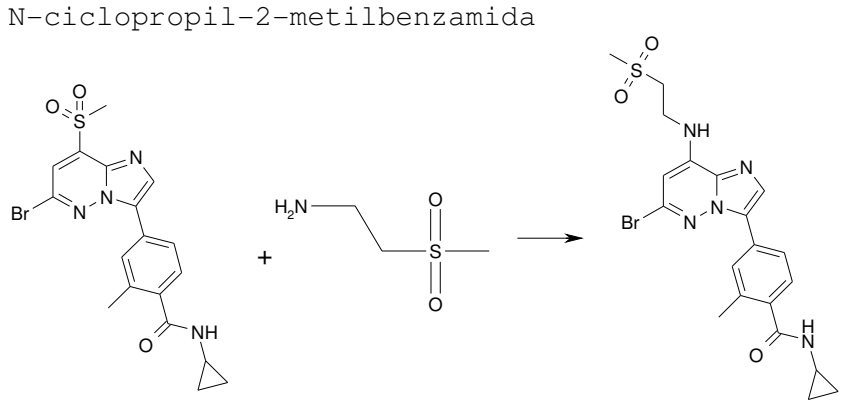


Se trataron 147 mg (300 µmol) de 4-(6-bromo-8-{[2-(metilsulfonil)etil]amino}imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 516a, de manera análoga al Ejemplo 51 usando 2,3-difluorofenol para dar, luego del tratamiento posterior y la purificación, 38 mg (21%) del compuesto del título.

UPLC-MS: RT = 1,14, PM encontrado = 542,6, PM calculado = 541,6

Ejemplo Intermediario 516a

4-(6-bromo-8-{[2-(metilsulfonil)etil]amino}imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida

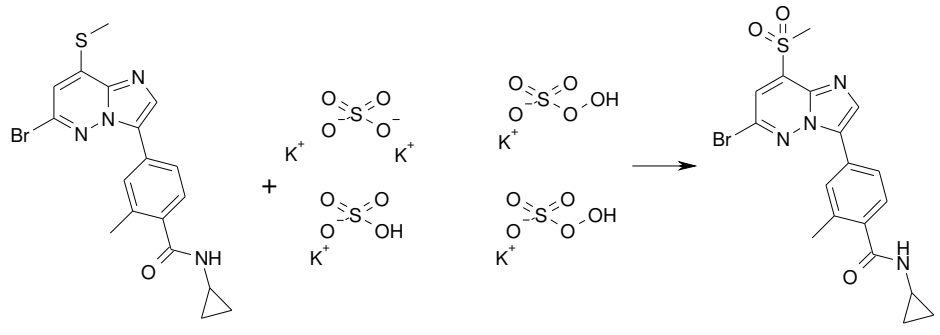


A una solución agitada de 1,12 g (2,5 mmol) de 4-[6-bromo-8-(metilsulfonil)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 516b, en 15 mL de NMP se agregaron 924 mg (7,5 mmol) de 2-(metilsulfonil)etanamina y 1,94 g (15 mmol) de DIPEA y la mezcla se calentó a 160°C durante 4 h en un bloque de calentamiento. Después del tratamiento posterior y sin purificación adicional se obtuvieron 1,18 g (96%) del compuesto del título.

UPLC-MS: RT = 0,95, PM encontrado = 493,4, PM calculado = 492,4

Ejemplo Intermediario 516b

4-[6-bromo-8-(metilsulfonil)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida

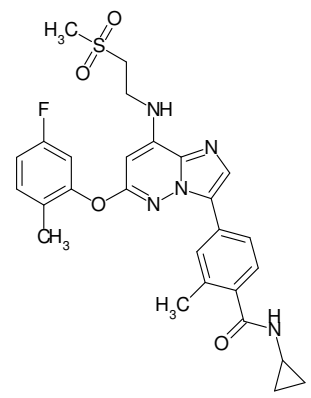
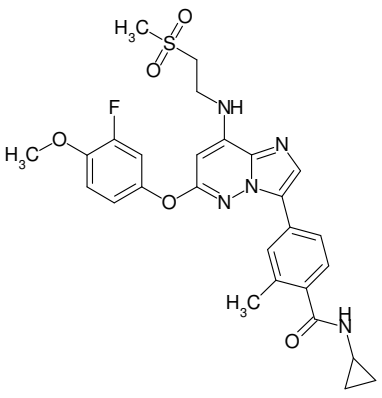


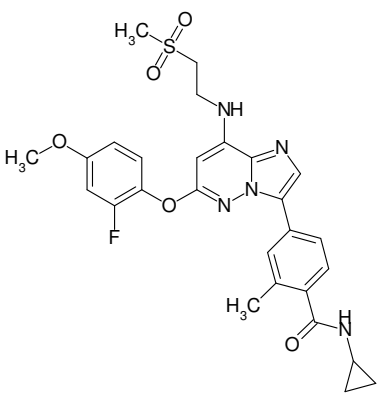
Se trataron 12 g (28,8 mmol) de 4-[6-bromo-8-(metilsulfanil)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 486b, de manera análoga al Ejemplo Intermediario 486a para dar, luego del tratamiento posterior y la purificación, 8,61 g (59%) del compuesto del título.

UPLC-MS: RT = 0,98, PM encontrado = 450,4, PM calculado = 449,4

Los siguientes ejemplos de compuestos se prepararon de manera análoga al procedimiento descrito para el ejemplo 516 usando el bloque molecular fenol o anilina apropiado [los datos de LC-MS como por ejemplo tiempo de retención (RT en min) o pico de masa observada se recogieron usando el Método LC-MS A salvo que se especifique lo contrario]:

Ejemplo	Estructura	Nombre	Datos analíticos

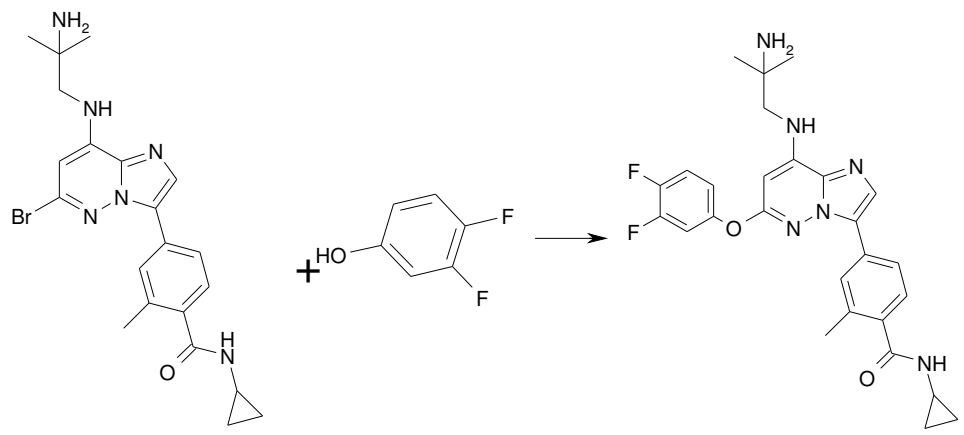
Ejemplo	Estructura	Nombre	Datos analíticos
517		N-ciclopropil-4-[6-(5-fluoro-2-metilfenoxi)-8-{[2-(metilsulfonil)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 1,17 PM encontrado = 538,6 PM calculado = 537,6
518		N-ciclopropil-4-[6-(3-fluoro-4-metoxifenoxi)-8-{[2-(metilsulfonil)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 1,33 PM encontrado = 554,6 PM calculado = 553,6 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,43-0,51 (2H), 0,59-0,68 (2H), 2,12 (3H), 2,77 (1H), 3,05 (3H), 3,49 (2H), 3,73-3,81 (2H), 3,84 (3H), 6,13 (1H), 7,07

Ejemplo	Estructura	Nombre	Datos analíticos
			(1H), 7,17 (1H), 7,19-7,26 (1H), 7,30 (1H), 7,49-7,69 (2H), 7,77 (1H), 7,92 (1H), 8,20 (1H)
519		N-ciclopropil-4-[6-(2-fluoro-4-metoxifenoxi)-8-{[2-(metilsulfonil)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 1,12 PM encontrado = 554,6 PM calculado = 553,6 1H-RMN (500 MHz,DMSO-d6), δ [ppm]= 0,49-0,53 (2H), 0,66-0,71 (2H), 2,13 (3H), 2,81 (1H), 3,11 (3H), 3,55 (2H), 3,82 (5H), 6,25 (1H), 6,89 (1H), 7,11 (1H), 7,19

Ejemplo	Estructura	Nombre	Datos analíticos
			(1H), 7,38 (1H), 7,66 (1H), 7,74-7,79 (2H), 7,99 (1H), 8,26 (1H)

Ejemplo 520

4-{8-[(2-amino-2-metilpropil)amino]-6-(3,4-difluorofenoxi)imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida

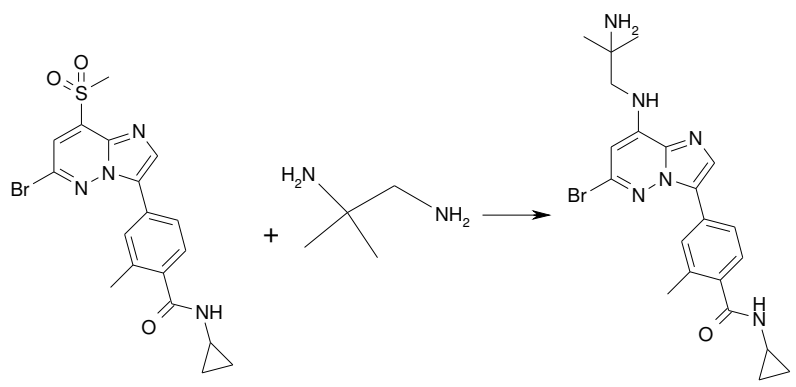


Se trataron 78 mg (171 µmol) de 4-{8-[(2-amino-2-metilpropil)amino]-6-bromoimidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 520a, de manera análoga al Ejemplo 51 usando 2,3-difluorofenol para dar, luego del tratamiento posterior y la purificación, 8 mg (8%) del compuesto del título.

UPLC-MS: RT = 0,97 PM encontrado = 507,5 PM calculado = 506,5

Ejemplo Intermediario 520a

4-{8-[(2-amino-2-metilpropil)amino]-6-bromoimidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida

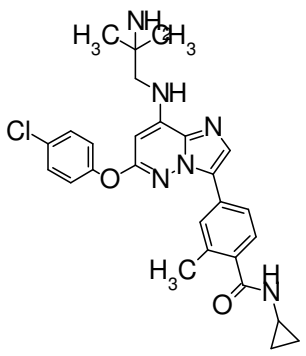


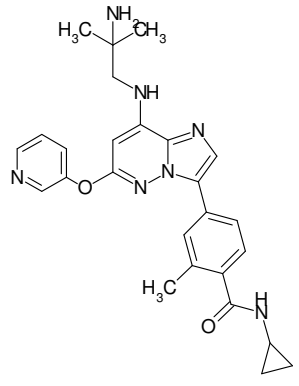
Se trataron 449 mg (1 mmol) de 4-[6-bromo-8-(metilsulfonil)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 516b, de manera análoga al Ejemplo Intermediario 516a usando 2-metilpropan-1,2-diamina para dar, luego del tratamiento posterior y la purificación, 395 mg (86%) del compuesto del título.

UPLC-MS: RT = 0,75, PM encontrado = 458,4, PM calculado = 457,4. 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,46-0,53 (2H), 0,62-0,69 (2H), 1,07 (6H), 2,35 (3H), 2,80 (1H), 3,16 (2H), 6,50 (1H), 7,36 (1H), 7,85 (1H), 7,91 (1H), 7,93-7,96 (1H), 8,29 (1H)

Los siguientes ejemplos de compuestos se prepararon de manera análoga al procedimiento descrito para el ejemplo 520 usando el bloque molecular fenol o anilina apropiado [los datos de LC-MS como por ejemplo tiempo de retención (RT en min) o pico de masa

observada se recogieron usando el Método LC-MS A salvo que se especifique lo contrario]:

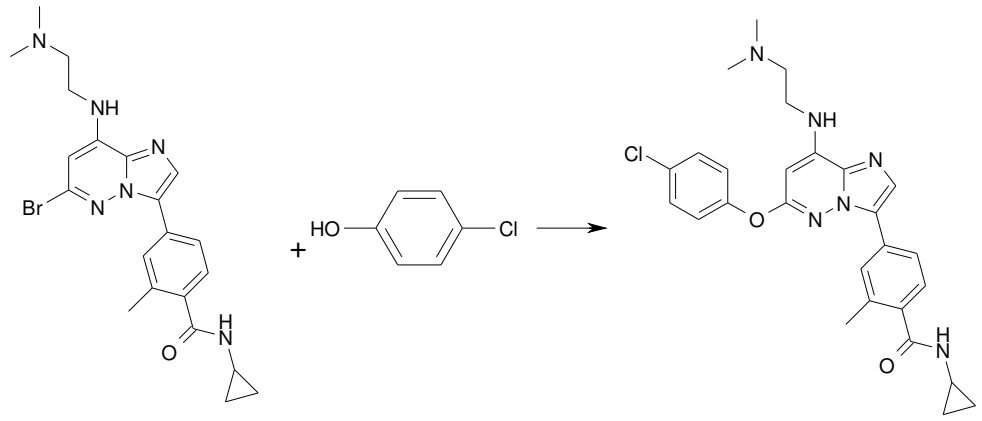
Ejemplo	Estructura	Nombre	Datos analíticos
521		4-{8-[(2-amino-2-metilpropil)amino]-6-(4-clorofenoxi)imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida	RT = 0,97 PM encontrado = 506,0 PM calculado = 505,0 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,44-0,52 (2H), 0,59-0,68 (2H), 1,12 (6H), 2,14 (3H), 2,77 (1H), 3,27 (3H), 6,20 (1H), 7,11-7,22 (3H), 7,34 (1H), 7,46-7,61 (2H), 7,62-7,68 (1H), 7,74 (1H), 7,92 (1H), 8,23 (1H)

Ejemplo	Estructura	Nombre	Datos analíticos
522		4-{8-[(2-amino-2-metilpropil)amino]-6-(piridin-3-iloxi)imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida	RT = 0,76 PM encontrado = 472,6 PM calculado = 471,6 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,43-0,50 (2H), 0,59-0,68 (2H), 1,14 (6H), 2,12 (3H), 2,76 (1H), 3,30 (3H), 6,27 (1H), 7,14 (1H), 7,40 (1H), 7,51 (1H), 7,58-7,64 (1H), 7,69 (1H), 7,76-7,82 (1H), 7,92 (1H), 8,21 (1H), 8,49 (1H), 8,57 (1H)

Ejemplo 523

4-[6-(4-clorofenoxi)-8-{[2-(dimetilamino)etil]amino}imidazo[1,2-b]

piridazin-3-il]-N-ciclopropil-2-metilbenzamida



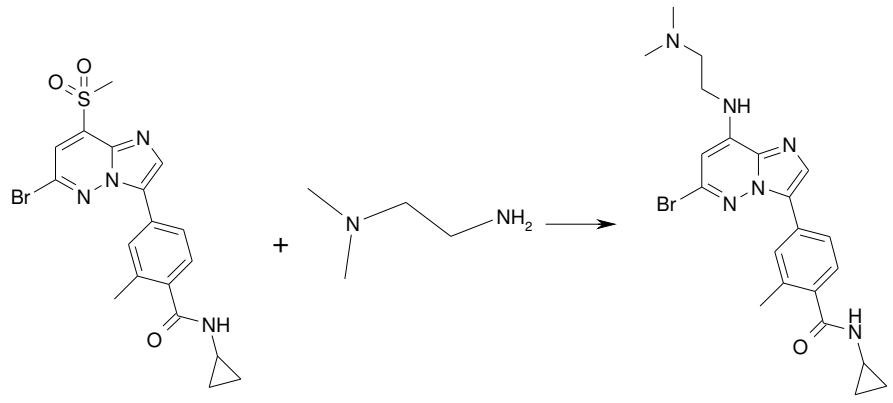
Se trataron 68 mg (150 µmol) de 4-(6-bromo-8-{[2-(dimetilamino)etil]amino}imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 523a, de manera análoga al Ejemplo 51 usando 4-clorofenol para dar, luego del tratamiento posterior y la purificación, 20 mg (27%) del compuesto del título.

UPLC-MS: RT = 0,97, PM encontrado = 506,0, PM calculado = 505,0.
1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,47 (2H), 0,59-0,68 (2H), 2,12 (3H), 2,18 (6H), 2,52 (2H), 2,76 (1H), 3,39 (2H), 6,06 (1H), 7,13-7,25 (2H), 7,27-7,35 (2H), 7,46-7,54 (2H), 7,63 (1H), 7,72 (1H), 7,90 (1H), 8,22 (1H)

Ejemplo Intermediario 523a

4-(6-bromo-8-{[2-(dimetilamino)etil]amino}imidazo[1,2-b]piridazin-3-il)-

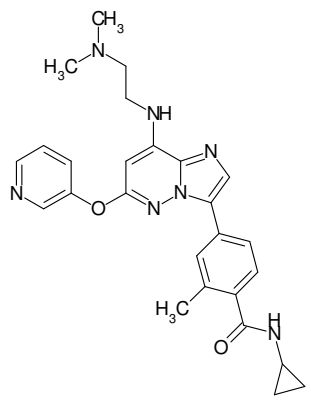
N-ciclopropil-2-metilbenzamida

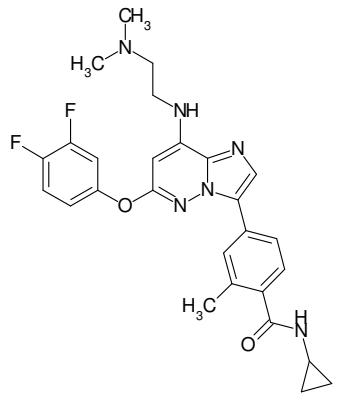


Se trataron 449 mg (1 mmol) de 4-[6-bromo-8-(metilsulfonil)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 516b, de manera análoga al Ejemplo Intermediario 516a usando N,N-dimetiletan-1,2-diamina para dar, luego del tratamiento posterior y la purificación, 367 mg (80%) del compuesto del título.

UPLC-MS: RT = 0,70, PM encontrado = 458,4, PM calculado = 457,4. 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,50 (2H), 0,65 (2H), 2,17 (6H), 2,35 (3H), 2,51 (2H), 2,80 (1H), 3,39 (2H), 6,38 (1H), 7,36 (1H), 7,44-7,50 (1H), 7,84 (1H), 7,91 (1H), 7,94 (1H), 8,28 (1H)

Los siguientes ejemplos de compuestos se prepararon de manera análoga al procedimiento descrito para el ejemplo 523 usando el bloque molecular fenol o anilina apropiado [los datos de LC-MS como por ejemplo tiempo de retención (RT en min) o pico de masa observada se recogieron usando el Método LC-MS A salvo que se especifique lo contrario]:

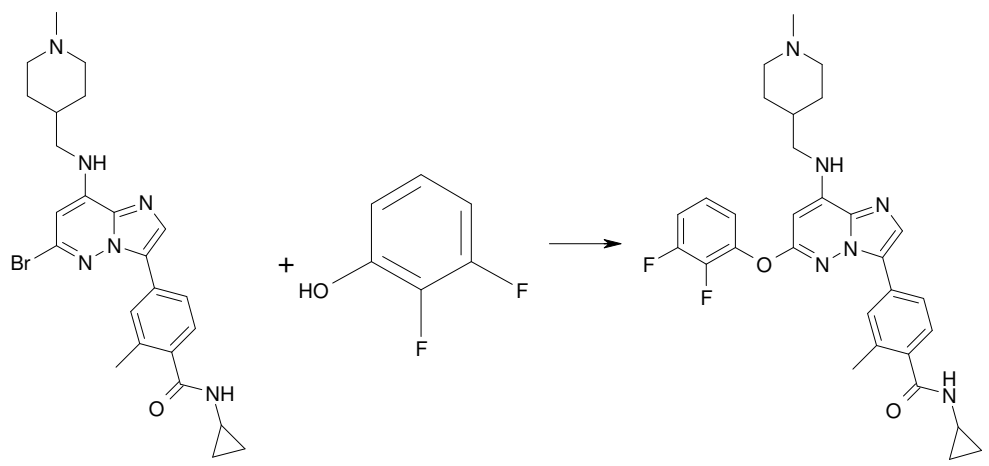
Ejemplo	Estructura	Nombre	Datos analíticos
524		N-ciclopropil-4-[8-{[2-(dimetilamino)etil]amino}-6-(piridin-3-iloxi)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 0,74 PM encontrado = 472,6 PM calculado = 471,6 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,43-0,50 (2H), 0,59-0,67 (2H), 2,12 (3H), 2,20 (6H), 2,49-2,59 (2H), 2,76 (1H), 3,37-3,47 (2H), 6,11 (1H), 7,13 (1H), 7,26 (1H), 7,51 (1H), 7,57-7,64 (1H), 7,68 (1H), 7,80 (1H), 7,88-7,92 (1H), 8,21 (1H), 8,49 (1H), 8,57 (1H)

Ejemplo	Estructura	Nombre	Datos analíticos
525		N-ciclopropil-4-[6-(3,4-difluorofenoxi)-8-{[2-(dimetilamino)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 0,95 PM encontrado = 507,5 PM calculado = 506,5

Ejemplo 526

N-ciclopropil-4-[6-(2,3-difluorofenoxi)-8-{[(1-metilpiperidin-4-il)metil]

amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida



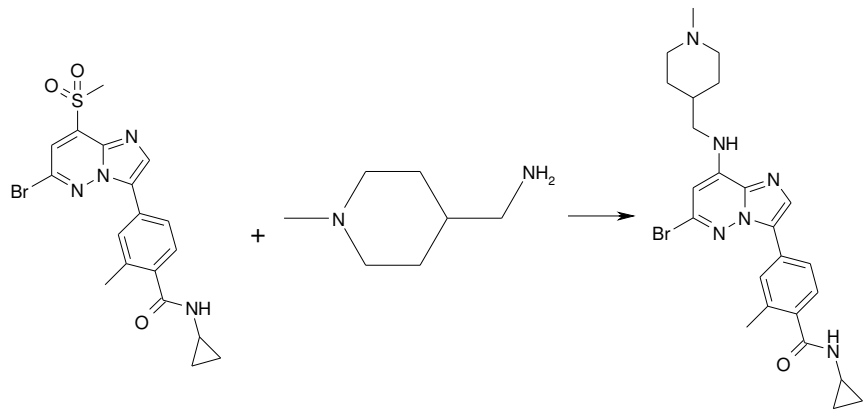
Se trataron 90 mg (181 µmol) de 4-(6-bromo-8-{[(1-metilpiperidin-4-il)metil]amino}imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 526a, de manera análoga al Ejemplo 51

usando 2,3-difluorofenol para dar, luego del tratamiento posterior y la purificación, 16 mg (15%) del compuesto del título.

UPLC-MS: RT = 0,97,PM encontrado = 547,6, PM calculado = 546,6. 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,41-0,52 (2H), 0,58-0,69 (2H), 1,20 (2H), 1,67 (3H), 1,80 (2H), 2,11 (6H), 2,67-2,82 (3H), 3,22 (2H), 6,16 (1H), 6,69-6,81 (1H), 7,13 (1H), 7,26-7,34 (2H), 7,42 (1H), 7,59 (1H), 7,67 (1H), 7,79 (1H), 7,92 (1H), 8,22 (1H).

Ejemplo Intermediario 526a

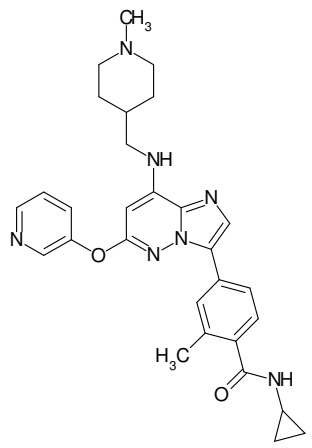
4-(6-bromo-8-{[(1-metilpiperidin-4-il)metil]amino}imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida



Se trataron 449 mg (1 mmol) de 4-[6-bromo-8-(metilsulfonil)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 516b, de manera análoga al Ejemplo Intermediario 516a usando 1-(1-metilpiperidin-4-il)metanamina para dar, luego del tratamiento posterior y la purificación, 460 mg (92%) del compuesto del título.

UPLC-MS: RT = 0,76, PM encontrado = 498,5, PM calculado = 497,5. 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,46-0,53 (2H), 0,61-0,70 (2H), 1,18 (2H), 1,53-1,68 (3H), 1,75 (2H), 2,08 (3H), 2,34 (3H), 2,63-2,76 (2H), 2,80 (1H), 3,18 (2H), 6,38 (1H), 7,36 (1H), 7,84 (1H), 7,87-7,98 (3H), 8,28 (1H)

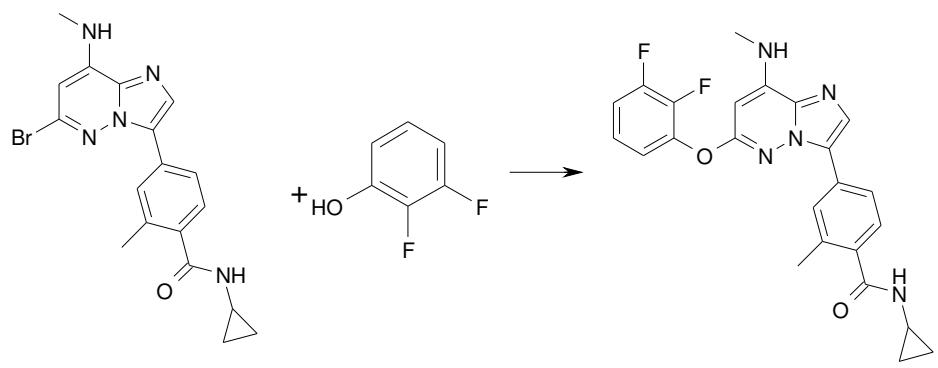
Los siguientes ejemplos de compuestos se prepararon de manera análoga al procedimiento descrito para el ejemplo 526 usando el bloque molecular fenol o anilina apropiado [los datos de LC-MS como por ejemplo tiempo de retención (RT en min) o pico de masa observada se recogieron usando el Método LC-MS A salvo que se especifique lo contrario]:

Ejemplo	Estructura	Nombre	Datos analíticos
527		N-ciclopropil-2-metil-4-[8-{[(1-metilpiperidin-4-il)metil]amino}-6-(piridin-3-iloxi)imidazo[1,2-b]piridazin-3-il]benzamida	RT = 0,77 PM encontrado = 512,6 PM calculado = 511,6 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,43-0,50 (2H), 0,59-0,68 (2H), 1,21 (2H), 1,67 (3H), 1,85 (2H), 2,12 (3H), 2,14 (3H), 2,70-2,81 (3H), 3,22

Ejemplo	Estructura	Nombre	Datos analíticos
			(2H), 6,11 (1H), 7,13 (1H), 7,51 (1H), 7,56-7,62 (1H), 7,68 (1H), 7,74 (1H), 7,78-7,83 (1H), 7,90 (1H), 8,18-8,23 (1H), 8,48 (1H), 8,57 (1H)

Ejemplo 528

N-ciclopropil-4-[6-(2,3-difluorofenoxi)-8-(metilamino)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida



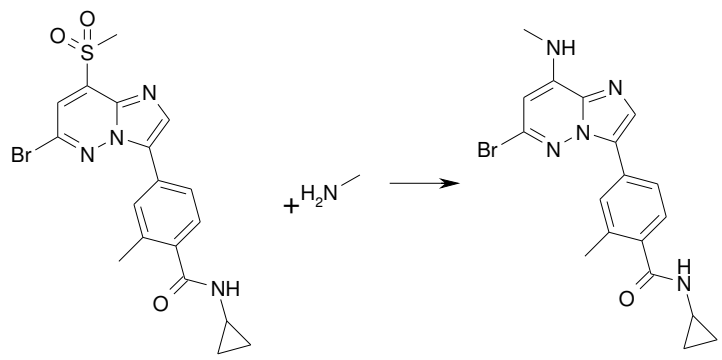
Se trataron 80 mg (200 µmol) de 4-[6-bromo-8-(metilamino)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo

Intermediario 528a, de manera análoga al Ejemplo 51 usando 2,3-difluorofenol para dar, luego del tratamiento posterior y la purificación, 18 mg (14%) del compuesto del título.

UPLC-MS: RT = 1,27, PM encontrado = 450,5, PM calculado = 449.

Ejemplo Intermediario 528a

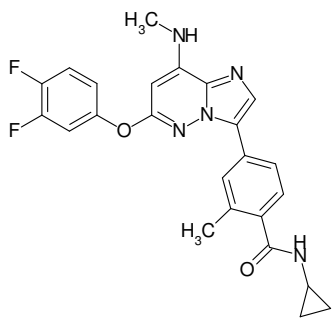
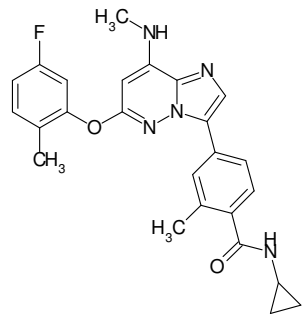
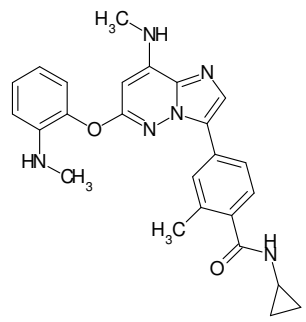
4-[6-bromo-8-(metilamino)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida

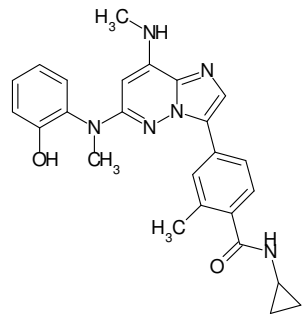
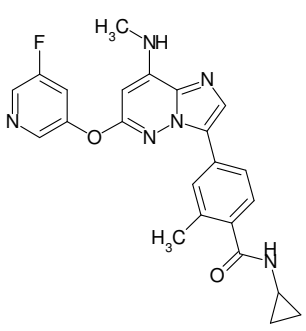


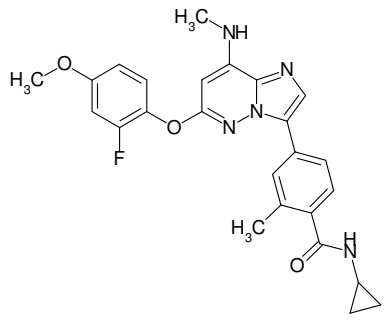
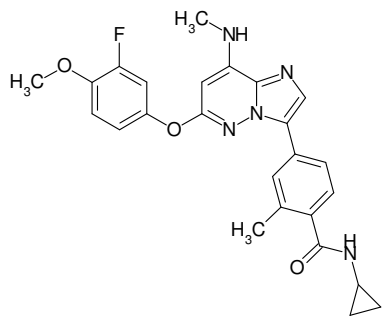
Se trataron 1123 mg (2,5 mmol) de 4-[6-bromo-8-(metilsulfonil)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 516b, de manera análoga al Ejemplo Intermediario 516a usando metanamina para dar, luego del tratamiento posterior y la purificación, 1000 mg (100%) del compuesto del título.

UPLC-MS: RT = 1,08, PM encontrado = 401,3, PM calculado = 400,3.

Los siguientes ejemplos de compuestos se prepararon de manera análoga al procedimiento descrito para el ejemplo 528 usando el bloque molecular fenol o anilina apropiado [los datos de LC-MS como por ejemplo tiempo de retención (RT en min) o pico de masa observada se recogieron usando el Método LC-MS A salvo que se especifique lo contrario]:

Ejemplo	Estructura	Nombre	Datos analíticos
529		N-ciclopropil-4-[6-(3,4-difluorofenoxi)-8-(metilamino)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 1,27 PM encontrado = 450,5 PM calculado = 449,5
530		N-ciclopropil-4-[6-(5-fluoro-2-metilfenoxi)-8-(metilamino)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 1,31 PM encontrado = 446,5 PM calculado = 445,5
531		N-ciclopropil-2-metil-4-{8-(metilamino)-6-[2-(metilamino)fenoxi]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 0,97 PM encontrado = 443,5 PM calculado = 442,5 1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 0,51-0,56 (2H), 0,65-0,70 (2H), 2,36 (3H), 2,61 (3H), 2,83

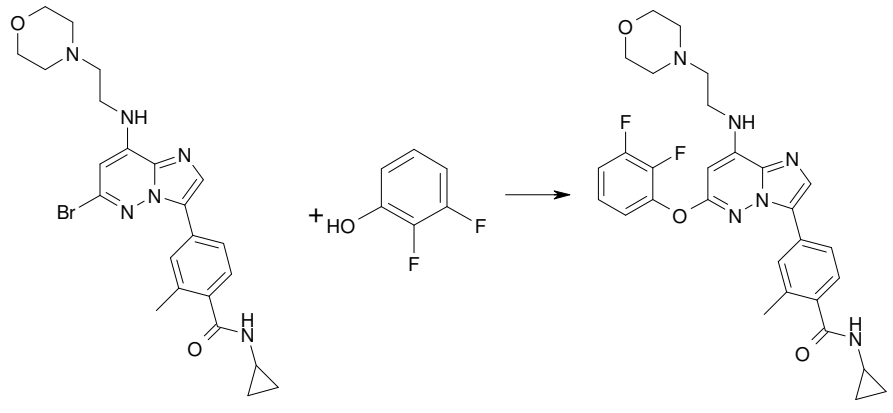
Ejemplo	Estructura	Nombre	Datos analíticos
			(1H), 3,29 (3H), 5,16 (1H), 6,84-6,90 (1H), 6,99 (2H), 7,15-7,23 (2H), 7,33 (1H), 7,82 (1H), 8,06 (1H), 8,12 (1H), 8,26 (1H)
532		N-ciclopropil-4-{6-[(2-hidroxifenil)(metil)amino]-8-(metilamino)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,21 PM encontrado = 443,5 PM calculado = 442,5
533		N-ciclopropil-4-{6-[(5-fluoropiridin-3-il)oxi]-8-(metilamino)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,06 PM encontrado = 433,5 PM calculado = 432,5

Ejemplo	Estructura	Nombre	Datos analíticos
534		N-ciclopropil-4-[6-(2-fluoro-4-metoxifenoxi)-8-(metilamino)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 1,24 PM encontrado = 462,5 PM calculado = 461,5
535		N-ciclopropil-4-[6-(3-fluoro-4-metoxifenoxi)-8-(metilamino)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 1,23 PM encontrado = 462,5 PM calculado = 461,5 1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 0,44-0,50 (2H), 0,61-0,67 (2H), 2,12 (3H), 2,74-2,81 (1H), 2,90 (3H), 3,84 (3H), 5,91 (1H), 7,03-7,08 (1H), 7,17 (1H), 7,19-7,25 (1H), 7,29 (1H), 7,61 (1H), 7,65 (1H), 7,78 (1H), 7,89 (1H),

Ejemplo	Estructura	Nombre	Datos analíticos
			8,20 (1H)

Ejemplo 536

N-ciclopropil-4-[6-(2,3-difluorofenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida



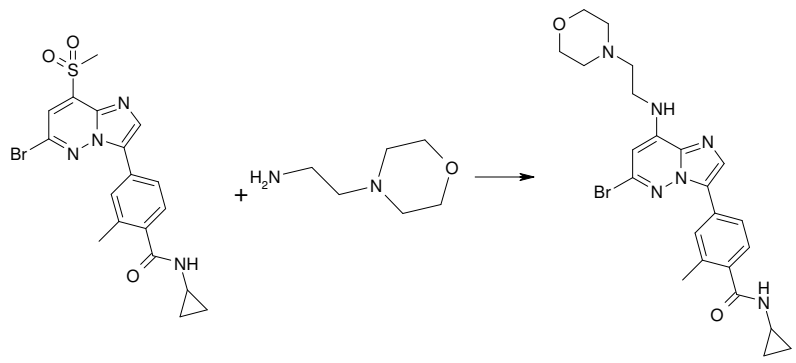
Se trataron 100 mg (200 µmol) de 4-(6-bromo-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 536a, de manera análoga al Ejemplo 51 usando 2,3-difluorofenol para dar, luego del tratamiento posterior y la purificación, 25 mg (21%) del compuesto del título.

UPLC-MS: RT = 0,93, PM encontrado = 549,6, PM calculado = 548,6. 1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 0,44-0,50 (2H), 0,60-0,67 (2H), 2,11 (3H), 2,46 (4H), 2,61 (2H), 2,77 (1H), 3,46 (2H), 3,57 (4H), 6,17 (1H), 7,14 (1H), 7,27-7,34 (2H), 7,39-7,46 (2H),

7,59 (1H), 7,67 (1H), 7,93 (1H), 8,11 (1H), 8,23 (1H)

Ejemplo Intermediario 536a

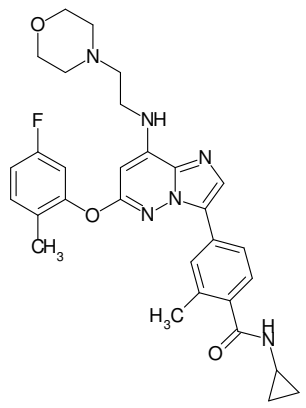
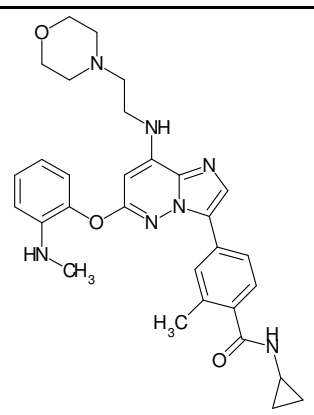
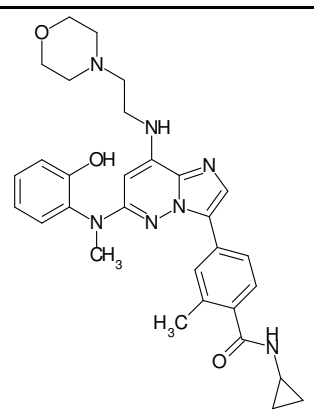
4-(6-bromo-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida

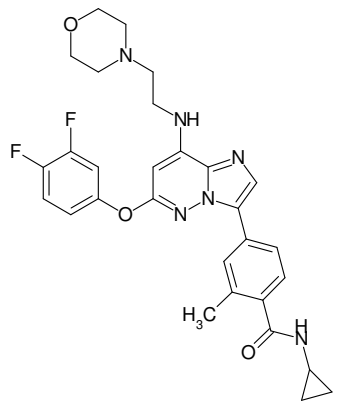
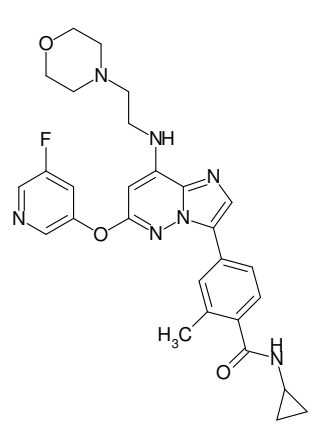


Se trataron 1123 mg (2,5 mmol) de 4-[6-bromo-8-(metilsulfonil)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 516b, de manera análoga al Ejemplo Intermediario 516a usando 2-(morfolin-4-il)etanamina para dar, luego del tratamiento posterior y la purificación, 1360 mg (108%) del compuesto del título.

UPLC-MS: RT = 0,74, PM encontrado = 500,4, PM calculado = 499,4.

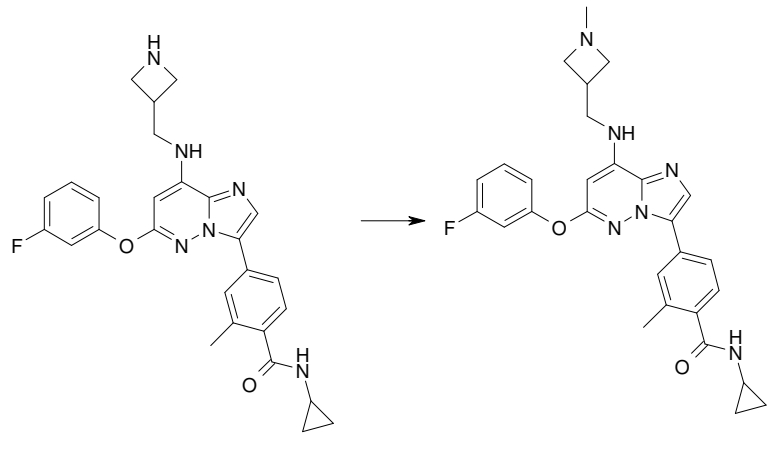
Los siguientes ejemplos de compuestos se prepararon de manera análoga al procedimiento descrito para el ejemplo 536 usando el bloque molecular fenol o anilina apropiado [los datos de LC-MS como por ejemplo tiempo de retención (RT en min) o pico de masa observada se recogieron usando el Método LC-MS A salvo que se especifique lo contrario]:

Ejemplo	Estructura	Nombre	Datos analíticos
537		N-ciclopropil-4-[6-(5-fluoro-2-metilfenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 0,95 PM encontrado = 545,6 PM calculado = 544,6 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,44-0,51 (2H), 0,60-0,67 (2H), 2,11 (6H), 2,40-2,49 (4H), 2,59 (2H), 2,77 (1H), 3,38-3,49 (2H), 3,53-3,60 (4H), 6,09 (1H), 7,06 (1H), 7,11-7,20 (2H), 7,27 (1H), 7,32-7,39 (1H), 7,58-7,64 (1H), 7,71 (1H), 7,91 (1H), 8,20 (1H)
538		N-ciclopropil-2-metil-4-(6-[2-(metilamino)fenoxi]-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il)benzamida	RT = 0,85 PM encontrado = 542,6 PM calculado = 541,6
539		N-ciclopropil-4-(6-[(2-hidroxifenil)(metil)amino]-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida	RT = 0,81 PM encontrado = 542,6 PM calculado = 541,6 1H-RMN (300 MHz,CDCl3), δ [ppm]= 0,70 (2H), 0,89 (2H), 2,38 (7H), 2,52 (2H), 2,98 (3H), 3,30 (2H), 3,71 (4H), 5,06 (1H), 5,92 (1H), 6,42 (1H), 6,89-6,99 (1H), 7,10 (2H), 7,22 (3H), 7,65 (1H), 7,78 (1H), 7,90 (1H)

540		N-ciclopropil-4-[6-(3,4-difluorofenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 0,94 PM encontrado = 549,6 PM calculado = 548,6
541		N-ciclopropil-4-(6-[(5-fluoropiridin-3-il)oxi]-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida	RT = 1,06 PM encontrado = 532,6 PM calculado = 531,6 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,44-0,52 (2H), 0,59-0,68 (2H), 2,14 (3H), 2,39-2,44 (4H), 2,58 (2H), 2,73-2,81 (1H), 3,45 (2H), 3,51-3,59 (4H), 6,14 (1H), 7,17 (1H), 7,41 (1H), 7,59-7,64 (1H), 7,70 (1H), 7,91 (1H), 7,98 (1H), 8,22 (1H), 8,50 (1H), 8,54 (1H)

Ejemplo 542

3-[({3-[4-(ciclopropilcarbamoil)-3-metilfenil]-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-8-il}amino)metil]azetidin-1-carboxilato de tert-butilo



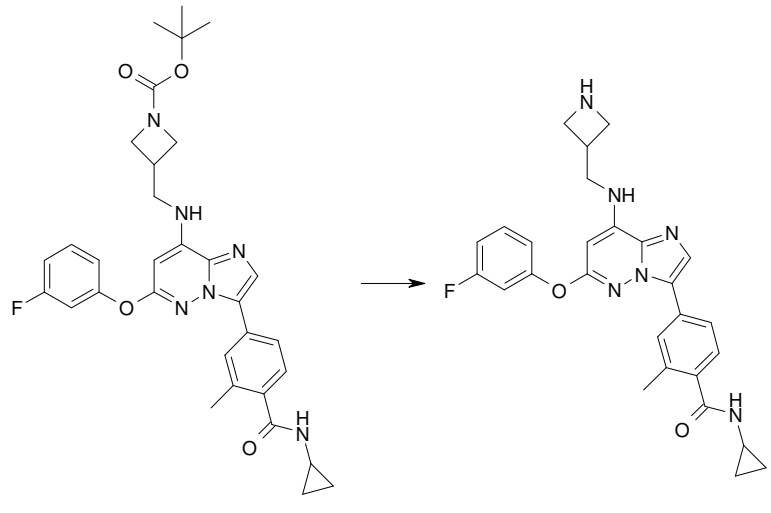
A una solución agitada de 10 mg (21 µmol) de 4-{8-[(azetidin-3-ilmetil)amino]-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 542a, en 1 mL de DCE se agregaron 1,2 mg (42 µmol) de formaldehído, 44 mg (204 µmol) de triacetoxiborhidruro de sodio y 24 µL de (411 µmol) de HOAc a temperatura ambiente. Después de 72h la mezcla se sometió a tratamiento posterior y se purificó para dar 2 mg (18%) del compuesto del título.

UPLC-MS: RT = 0,93, PM encontrado = 501,6, PM calculado = 500,6. 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,43-0,50 (2H), 0,59-0,67 (2H), 2,14 (3H), 2,30 (3H), 2,77 (1H), 3,15 (3H), 3,40 (2H), 3,51 (2H), 6,08 (1H), 7,07-7,19 (2H), 7,24 (1H), 7,47 (1H), 7,66 (1H), 7,76 (1H), 7,82 (1H), 7,91 (1H), 8,18-8,26 (2H)

Ejemplo Intermediario 542a

3-[({3-[4-(ciclopropilcarbamoil)-3-metilfenil]-6-(3-fluorofenoxi)imidazo

[1,2-b]piridazin-8-il}amino)metil]azetidin-1-carboxilato de tert-butilo



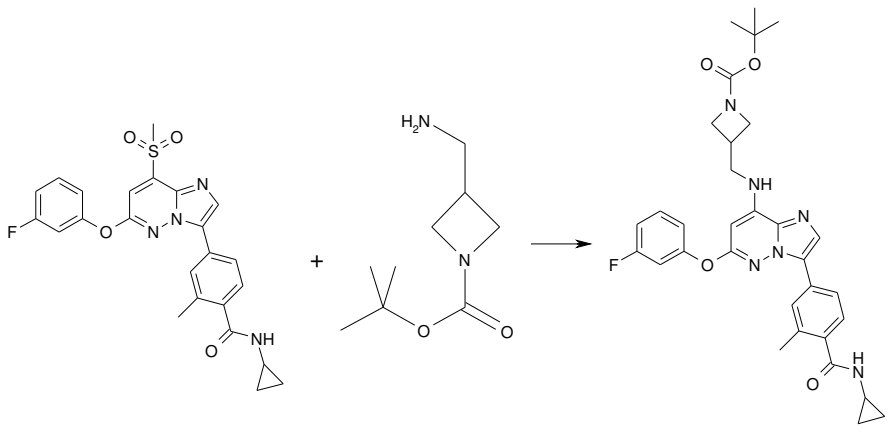
A una solución agitada de 43 mg (74 µmol) de 3-[({3-[4-(ciclopropilcarbamoil)-3-metilfenil]-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-8-il}amino)metil]azetidin-1-carboxilato de tert-butilo, que se preparó de acuerdo con el Ejemplo Intermediario 542b, en 3 mL de DCM se agregó 1mL de TFA y dos gotas de agua a temperatura ambiente. Luego de 1h la mezcla se sometió a tratamiento posterior para dar 34 mg (93%) del compuesto del título.

UPLC-MS: RT = 0,82, PM encontrado = 487,5, PM calculado = 486,5.

Ejemplo Intermediario 542b

3-[({3-[4-(ciclopropilcarbamoil)-3-metilfenil]-6-(3-fluorofenoxi)

imidazo[1,2-b]piridazin-8-il}amino)metil]azetidin-1-carboxilato de tert-butilo



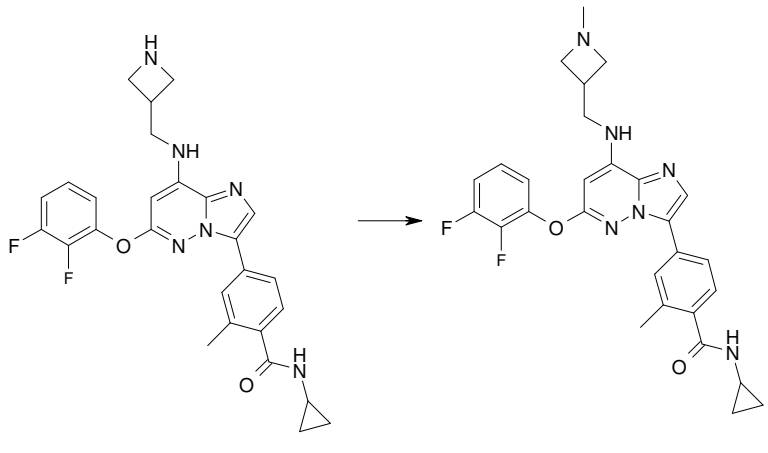
Se trataron 192 mg (400 µmol) de N-ciclopropil-4-[6-(3-fluorofenoxi)-8-(metilsulfonil)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 486a, de manera análoga al Ejemplo 486 usando 3-(aminometil)azetidin-1-carboxilato de tert-butilo para dar, luego del tratamiento posterior y la purificación, 43 mg (18%) del compuesto del título.

UPLC-MS: RT = 1,36, PM encontrado = 587,7, PM calculado = 586,7.

Ejemplo 543

N-ciclopropil-4-[6-(2,3-difluorofenoxi)-8-{[(1-metilazetidin-3-il)metil]

amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida

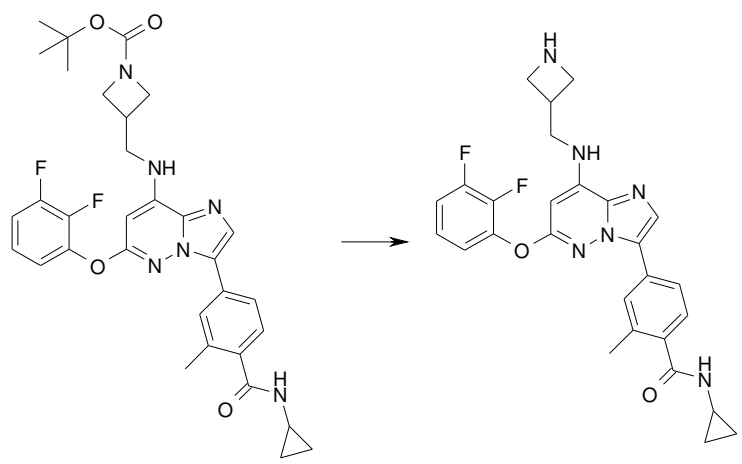


Se trataron 10 mg (21 µmol) de 4-{8-[(azetidin-3-ilmetil)amino]-6-(2,3-difluorofenoxi)imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 543a, de manera análoga al Ejemplo 542 para dar, luego del tratamiento posterior y la purificación, 0,8 mg (6%) del compuesto del título.

UPLC-MS: RT = 0,94, PM encontrado = 519,6, PM calculado = 518,6.

Ejemplo Intermediario 543a

4-{8-[(azetidin-3-ilmetil)amino]-6-(2,3-difluorofenoxi)imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



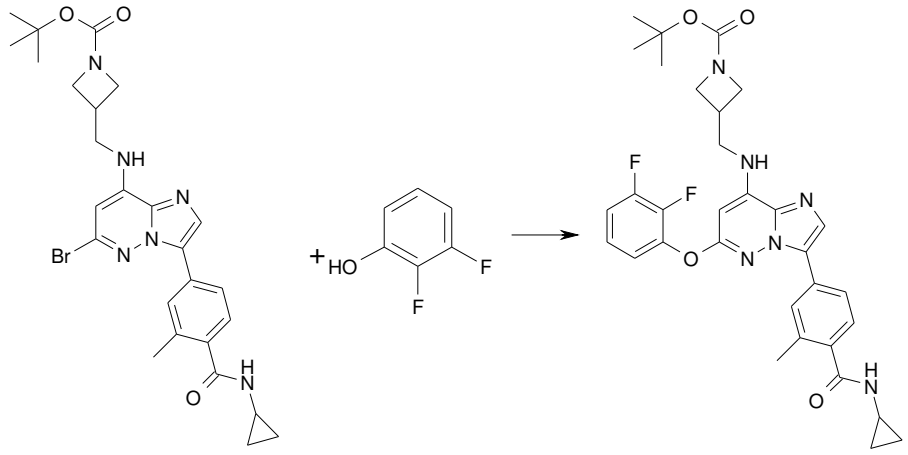
Se trataron 120 mg (200 µmol) de 3-[({3-[4-(ciclopropilcarbamoil)-3-metilfenil]-6-(2,3-difluorofenoxi)imidazo[1,2-b]piridazin-8-il}amino)metil]azetidin-1-carboxilato de tert-butilo, que se preparó de acuerdo con el Ejemplo Intermediario 543b, de manera análoga al Ejemplo Intermediario 542a para dar, luego del tratamiento posterior y la purificación, 13 mg (13%) del compuesto del título.

UPLC-MS: RT = 0,92, PM encontrado = 505,5, PM calculado = 504,5.

1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 0,44-0,50 (2H), 0,60-0,68 (2H), 2,11 (3H), 2,72-2,81 (1H), 3,08-3,18 (1H), 3,59 (2H), 3,66-3,74 (2H), 3,91 (2H), 6,26 (1H), 6,74 (2H), 6,93 (1H), 7,14 (1H), 7,26-7,34 (1H), 7,43 (1H), 7,59 (1H), 7,67 (1H), 7,94 (1H), 7,99 (1H), 8,21 (1H)

Ejemplo Intermediario 543b

3-[({3-[4-(ciclopropilcarbamoil)-3-metilfenil]-6-(2,3-difluorofenoxi)imidazo[1,2-b]piridazin-8-il}amino)metil]azetidin-1-carboxilato de tert-butilo

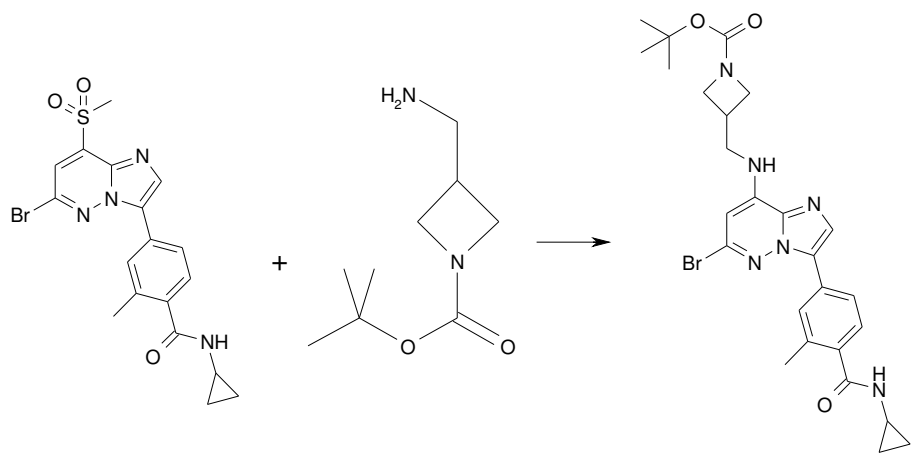


Se trataron 195 mg (200 µmol) de 3-[({6-bromo-3-[4-(ciclopropilcarbamoil)-3-metilfenil]imidazo[1,2-b]piridazin-8-il}amino)metil]azetidin-1-carboxilato de tert-butilo, que se preparó de acuerdo con el Ejemplo Intermediario 543c, de manera análoga al Ejemplo 51 usando 2,3-difluorofenol y el producto se usó sin someterse a tratamiento posterior en el siguiente paso.

UPLC-MS: RT = 0,1,37, PM encontrado = 605,7, PM calculado = 605,7.

Ejemplo Intermediario 543c

3-[({6-bromo-3-[4-(ciclopropilcarbamoil)-3-metilfenil]imidazo[1,2-b]piridazin-8-il}amino)metil]azetidin-1-carboxilato de tert-butilo



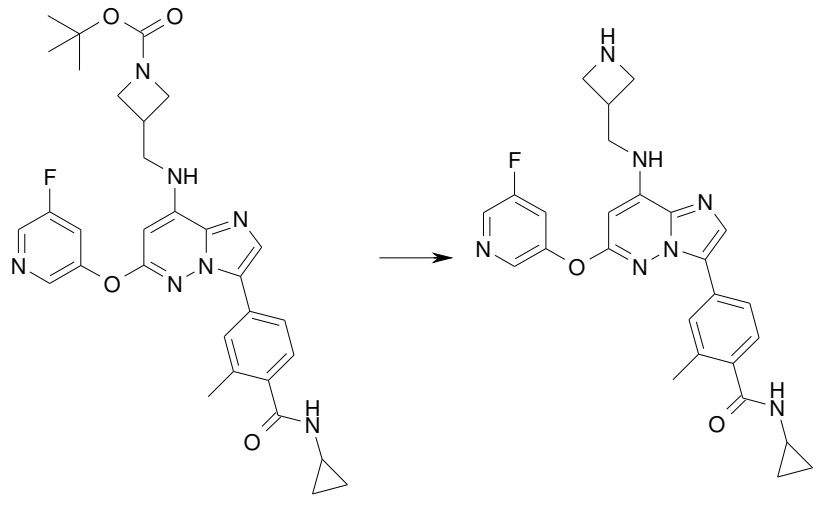
Se trataron 1348 mg (3 mmol) de 4-[6-bromo-8-(metilsulfonil)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 516a, de manera análoga al Ejemplo 516 para dar, luego del tratamiento posterior y la purificación, 1,67 g (100%) del compuesto del título.

UPLC-MS: RT = 1,28, PM encontrado = 556,5, PM calculado = 555,5

Ejemplo 544

4-{8-[(azetidin-3-ilmetil)amino]-6-[(5-fluoropiridin-3-il)oxi]imidazo

[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



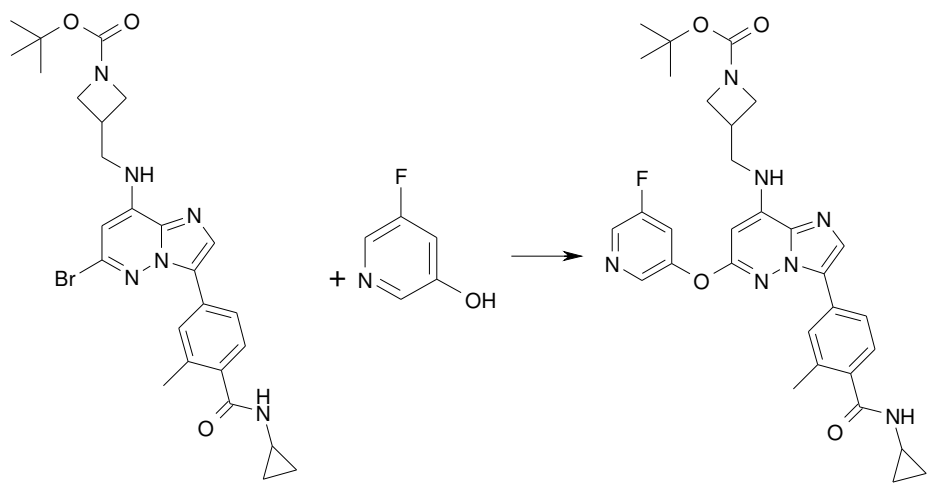
Se trataron 5 mg (8 µmol) de 3-[({3-[4-(ciclopropilcarbamoil)-3-metilfenil]-6-[(5-fluoropiridin-3-il)oxi]imidazo[1,2-b]piridazin-8-il}amino)metil]azetidin-1-carboxilato de tert-butilo, que se preparó de acuerdo con el Ejemplo Intermediario 544a, de manera análoga al Ejemplo Intermediario 542a para dar, luego del tratamiento posterior y la purificación, 3,7 mg (99%) del compuesto del título.

RT = 0,80, PM encontrado = 488,5, PM calculado = 487,5. 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,43-0,51 (2H), 0,59-0,69 (2H), 2,15 (3H), 2,77 (1H), 3,17 (1H), 3,59 (2H), 3,73-3,85 (2H), 3,92-4,04 (2H), 6,21-6,26 (1H), 7,17 (1H), 7,64 (1H), 7,70 (1H), 7,73 (1H), 7,92-8,01 (2H), 8,20 (1H), 8,33 (1H), 8,39 (1H), 8,55 (1H).

Ejemplo Intermediario 544a

3-[({3-[4-(ciclopropilcarbamoil)-3-metilfenil]-6-[(5-fluoropiridin-3-il)oxi]

imidazo[1,2-b]piridazin-8-il}amino)metil]azetidin-1-carboxilato de tert-butilo

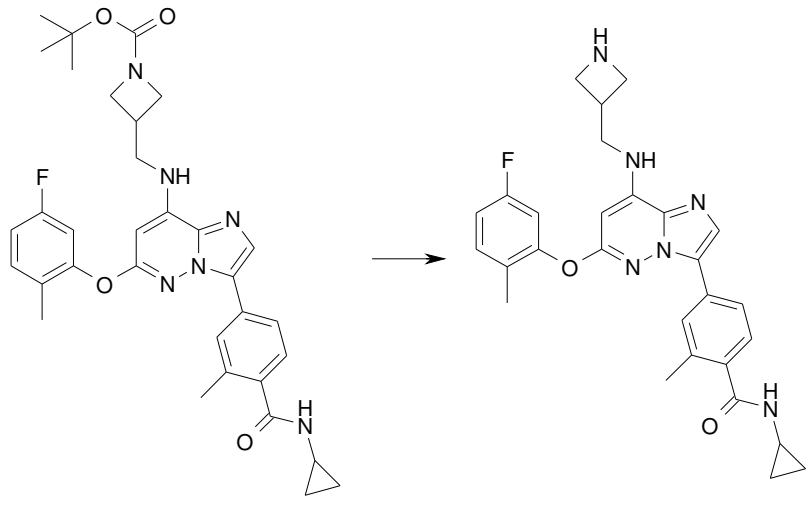


Se trataron 111 mg (200 µmol) de 3-[({6-bromo-3-[4-(ciclopropilcarbamoil)-3-metilfenil]imidazo[1,2-b]piridazin-8-il}amino)metil]azetidin-1-carboxilato de tert-butilo, que se preparó de acuerdo con el Ejemplo Intermediario 543c, de manera análoga al Ejemplo 51 usando 5-fluoropiridin-3-ol para dar, luego del tratamiento posterior y la purificación, 5 mg (4%) del compuesto del título.

UPLC-MS: RT = 1,25, PM encontrado = 588,7, PM calculado = 587,7.

Ejemplo 545

4-{8-[(azetidin-3-ilmetil)amino]-6-(5-fluoro-2-metilfenoxi)imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



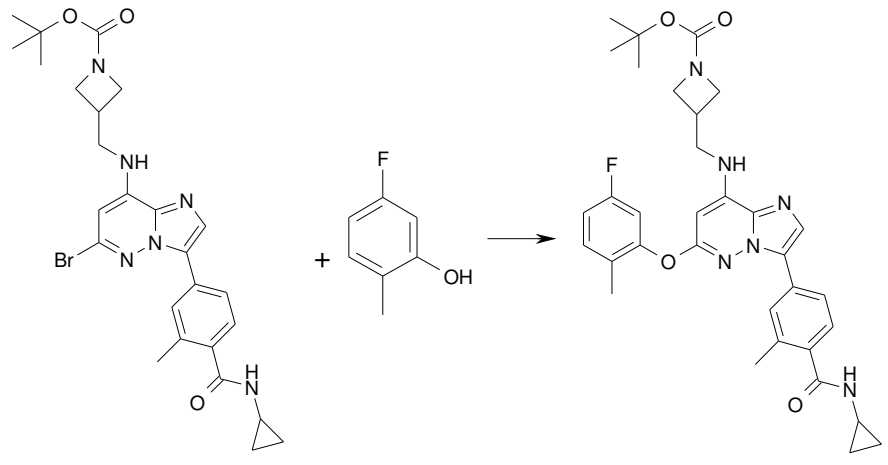
Se trataron 120 mg (200 µmol) de 3-[({3-[4-(ciclopropilcarbamoil)-3-metilfenil]-6-(5-fluoro-2-metilfenoxi)imidazo[1,2-b]piridazin-8-il}amino)metil]azetidin-1-carboxilato de tert-butilo, que se preparó de acuerdo con el Ejemplo Intermediario 545a, de manera análoga al Ejemplo Intermediario 542a para dar, luego del tratamiento posterior y la purificación, 13 mg (13%) del compuesto del título.

UPLC-MS: RT = 0,94 PM encontrado = 501,6 PM calculado = 500,6

Ejemplo Intermediario 545a

3-[({3-[4-(ciclopropilcarbamoil)-3-metilfenil]-6-(5-fluoro-2-metilfenoxi)

imidazo[1,2-b]piridazin-8-il}amino)metil]azetidin-1-carboxilato de tert-butilo

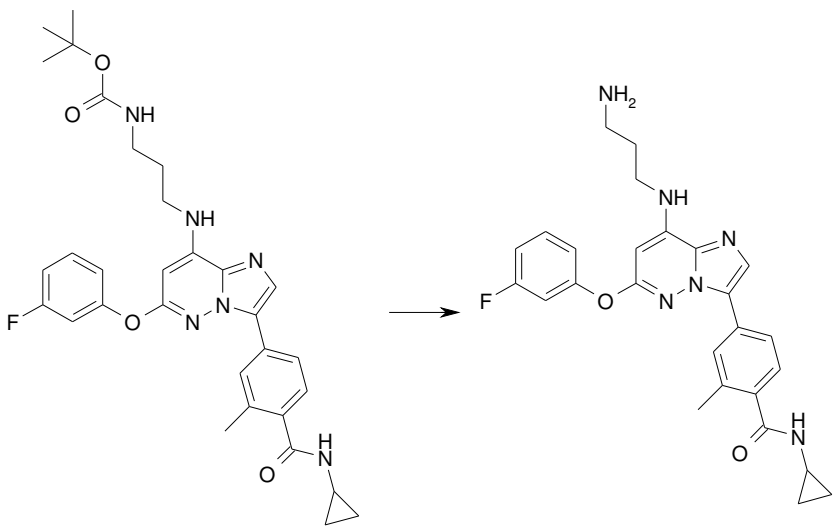


Se trataron 111 mg (200 µmol) de 3-[({6-bromo-3-[4-(ciclopropilcarbamoil)-3-metilfenil]imidazo[1,2-b]piridazin-8-il}amino)metil]azetidin-1-carboxilato de tert-butilo, que se preparó de acuerdo con el Ejemplo Intermediario 543c, de manera análoga al Ejemplo 51 usando 2,3-difluorofenol y el producto se usó sin someterse a tratamiento posterior en el siguiente paso.

UPLC-MS: RT = 0,1,43, PM encontrado = 601,7, PM calculado = 600,7.

Ejemplo 546

4-{8-[(3-aminopropil)amino]-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida



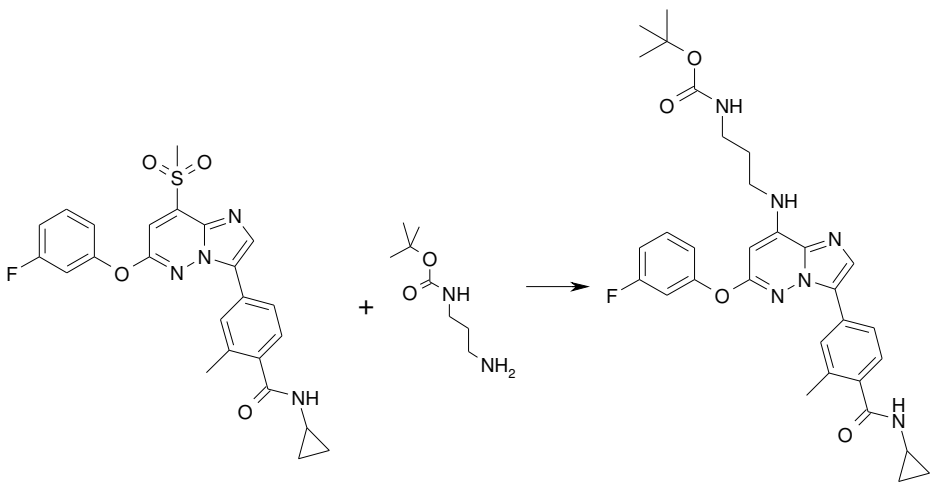
Se trataron 23 mg (40 µmol) de [3-({3-[4-(ciclopropilcarbamoil)-3-metilfenil]-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-8-il}amino)propil]carbamato de tert-butilo, que se preparó de acuerdo con el Ejemplo Intermediario 546a, de manera análoga al Ejemplo Intermediario 542a para dar, luego del tratamiento posterior y la purificación, 7 mg (36%) del compuesto del título.

UPLC-MS: RT = 0,94, PM encontrado = 475,5, PM calculado = 474,5. 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,43-0,51 (2H), 0,59-0,68 (2H), 1,81-1,97 (2H), 2,14 (3H), 2,76 (1H), 2,87 (2H), 3,41 (2H), 6,14 (1H), 7,08-7,19 (4H), 7,19-7,28 (1H), 7,49 (1H), 7,60-7,73 (3H), 7,73-7,82 (2H), 7,93 (1H), 8,21 (1H)

Ejemplo Intermediario 546a

N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoro-2-hidroxipropil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 67 mg (140 µmol) de N-ciclopropil-4-[6-(3-fluorofenoxi)-8-(metilsulfonil)imidazo[1,2-b]piridazin-3-il]-2-

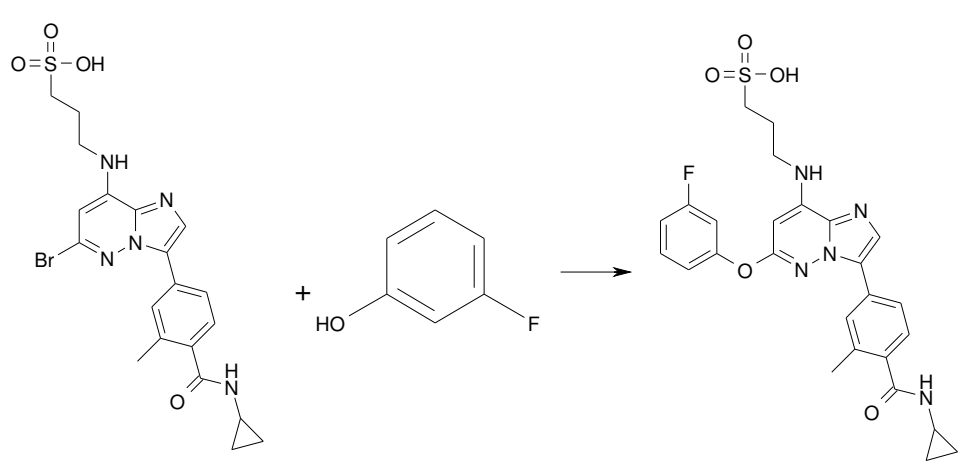
metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 486a, de manera análoga al Ejemplo 486 para dar, luego del tratamiento posterior y la purificación, 23 mg (29%) del compuesto del título.

UPLC-MS: RT = 1,38, PM encontrado = 575,7, PM calculado = 574,7.

Ejemplo 547

ácido 3-({3-[4-(ciclopropilcarbamoil)-3-metilfenil]-6-(3-fluorofenoxi)imidazo

[1,2-b]piridazin-8-il}amino)propan-1-sulfónico



Se trataron 101 mg (200 µmol) de ácido 3-({6-bromo-3-[4-(ciclopropilcarbamoil)-3-metilfenil]imidazo[1,2-b]piridazin-8-il}amino)propan-1-sulfónico, que se preparó de acuerdo con el Ejemplo Intermediario 547a, de manera análoga al Ejemplo 51 para dar, luego del tratamiento posterior y la purificación, 12 mg (9%) del compuesto del título.

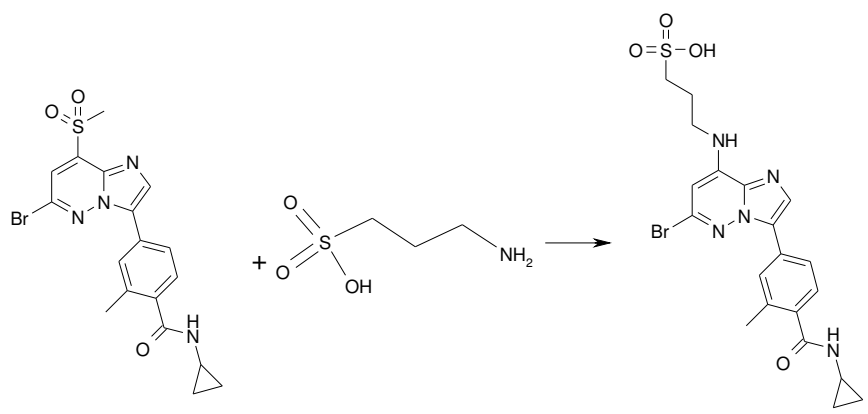
UPLC-MS: RT = 0,98, PM encontrado = 540,6, PM calculado = 539,6.

1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 0,40-0,54 (2H), 0,58-0,70 (2H), 1,81-1,99 (2H), 2,14 (3H), 2,49-2,62 (2H), 2,77 (1H), 3,46

(2H), 6,29 (1H), 7,11-7,21 (3H), 7,27 (1H), 7,42-7,55 (1H), 7,64 (2H), 7,74 (2H), 8,11 (1H), 8,22 (1H)

Ejemplo Intermediario 547a

ácido 3-({6-bromo-3-[4-(ciclopropilcarbamoil)-3-metilfenil]imidazo[1,2-b]piridazin-8-il}amino)propan-1-sulfónico



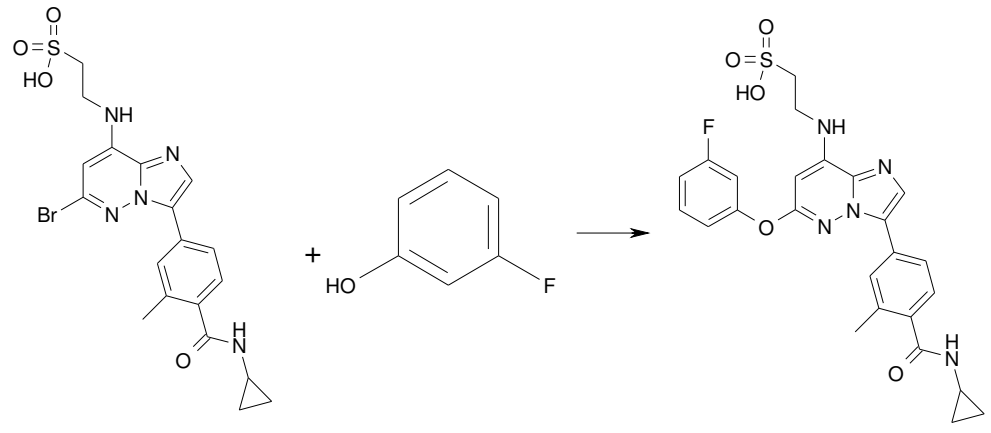
A una solución agitada de 41 mg (300 µmol) de ácido 3-aminopropan-1-sulfónico en 2 mL de DMSO se agregaron 24 mg (600 µmol) de hidruro de sodio a temperatura ambiente. Luego de 30 min, se agregaron 90 mg (200 µmol) de 4-[6-bromo-8-(metilsulfonil)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 516b, para dar, luego de agitar durante 2 h, el compuesto del título crudo que se usó luego de la evaporación del solvente sin someterse a tratamiento posterior.

UPLC-MS: RT = 0,82, PM encontrado = 509,4, PM calculado = 508,4.

Ejemplo 548

ácido 2-({3-[4-(ciclopropilcarbamoil)-3-metilfenil]-6-(3-fluorofenoxi)imidazo

[1,2-b]piridazin-8-il}amino)etansulfónico

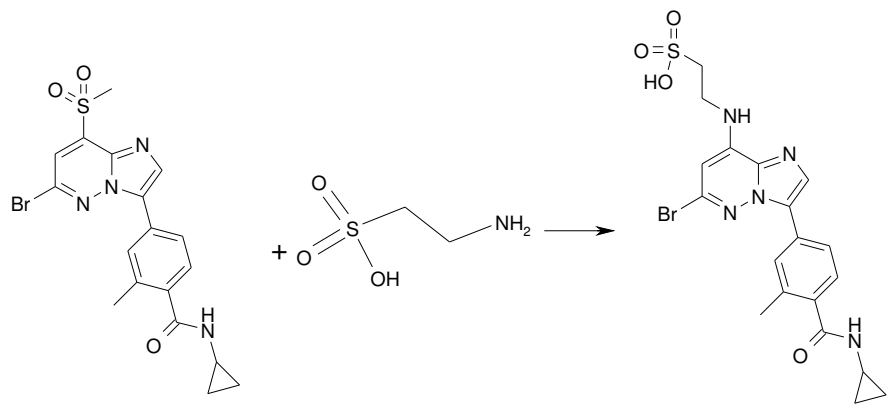


Se trataron 99 mg (200 µmol) de ácido 2-({6-bromo-3-[4-(ciclopropilcarbamoil)-3-metilfenil]imidazo[1,2-b]piridazin-8-il}amino)etansulfónico, que se preparó de acuerdo con el Ejemplo Intermediario 548a, de manera análoga al Ejemplo 51 para dar, luego del tratamiento posterior y la purificación, 9 mg (7%) del compuesto del título.

UPLC-MS: RT = 0,97, PM encontrado = 526,6, PM calculado = 525,6. 1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 0,44-0,54 (2H), 0,59-0,70 (2H), 2,14 (3H), 2,71-2,84 (3H), 3,59 (2H), 6,22 (1H), 7,09-7,21 (4H), 7,27 (1H), 7,49 (1H), 7,61-7,67 (1H), 7,73 (2H), 8,12 (1H), 8,23 (1H)

Ejemplo Intermediario 548a

ácido 2-({6-bromo-3-[4-(ciclopropilcarbamoil)-3-metilfenil]imidazo[1,2-b]piridazin-8-il}amino)etansulfónico

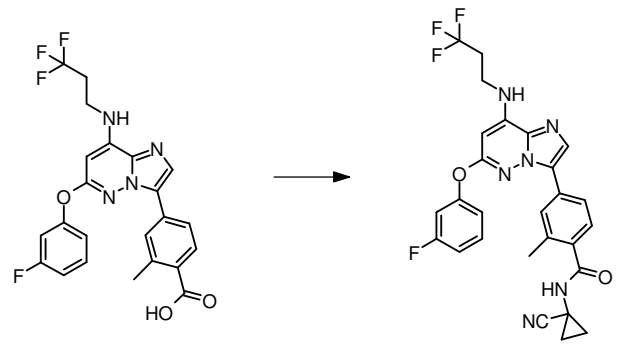


Se trataron 89 mg (200 µmol) de 4-[6-bromo-8-(metilsulfonil)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 516b, de manera análoga al Ejemplo 547a para dar el compuesto del título crudo que se usó en el siguiente paso sin purificación adicional.

UPLC-MS: RT = 0,84, PM encontrado = 495,4, PM calculado = 494,4.

Ejemplo 549

N-(1-cianociclopropil)-4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 10,5 mg (22 µmol) de ácido 4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzoico, que se preparó de acuerdo con el Ejemplo

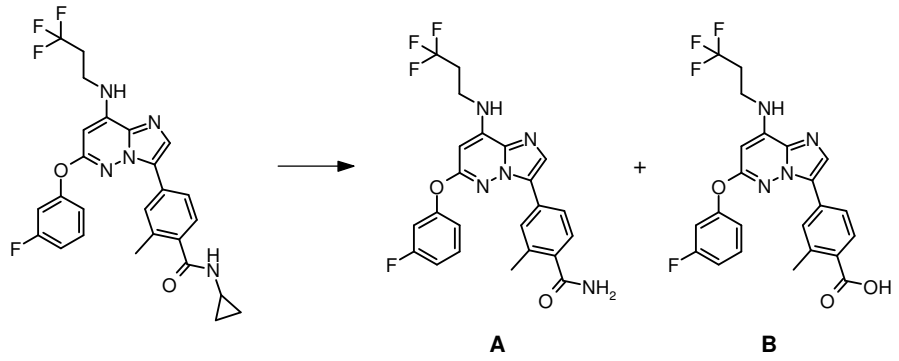
Intermediario 459a, de manera análoga al Ejemplo 459 usando cloruro de 1-cianociclopropanaminio para dar, luego del tratamiento posterior y la purificación, 4,5 mg (36%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 1,21 (2H), 1,50 (2H), 2,16 (3H), 2,61-2,76 (2H), 3,60 (2H), 6,14 (1H), 7,14 (2H), 7,25 (2H), 7,49 (1H), 7,66-7,76 (2H), 7,81 (1H), 7,97 (1H), 9,09 (1H) ppm.

Ejemplo 550

4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b] piridazin-3-il}-2-metilbenzamida (A) y

ácido 4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b] piridazin-3-il}-2-metilbenzoico (B)



A B

Una mezcla de 50 mg (97 µmol) de N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida y 0,5 mL de ácido bromhídrico se calentó a 120°C durante 10 minutos bajo irradiación de microondas. Se agregó agua, el precipitado se retiró por

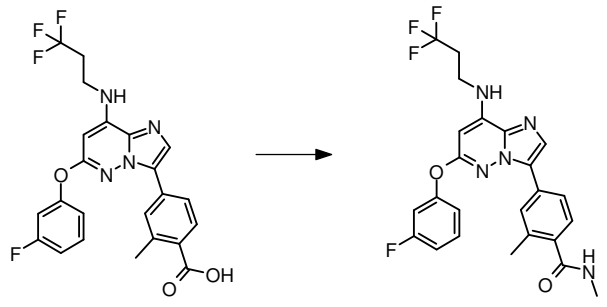
filtración y se purificó mediante cromatografía para dar 30,0 mg (62%) de compuesto del título A y 4,1 mg (9%) de compuesto del título B.

1H-RMN (DMSO-d6) de A: δ= 2,20 (3H), 2,68 (2H), 3,60 (2H), 6,13 (1H), 7,13 (2H), 7,22-7,30 (3H), 7,48 (1H), 7,60-7,78 (4H), 7,93 (1H) ppm.

1H-RMN (DMSO-d6) de B: δ= 2,35 (3H), 2,68 (2H), 3,59 (2H), 6,15 (1H), 7,14 (2H), 7,26 (1H), 7,49 (1H), 7,64-7,77 (3H), 7,82 (1H), 7,99 (1H), 8,20 (1H) ppm.

Ejemplo 551

4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida



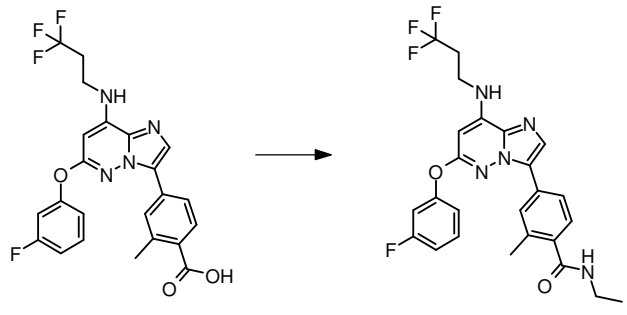
Una mezcla de 30 mg (63 µmol) de ácido 4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzoico, que se preparó de acuerdo con el ejemplo 550, 2,94 mg de metanamina, 36,1 mg de hexafluorofosfato de N-[(dimetilamino)(3H-[1,2,3]triazolo[4,5-b]piridin-3-iloxi)metilen]-N-metilmetanaminio, 11,6 mg de N,N-dimetilpiridin-4-amina y 1,5 mL de N,N-dimetilformamida se agitó a 23°C durante la noche. El solvente se eliminó y el residuo se

purificó mediante cromatografía para dar 30,0 mg (92%) de compuesto del título.

1H-RMN (DMSO-d6): δ= 2,16 (3H), 2,49-2,76 (2H), 2,69 (3H), 3,60 (2H), 6,13 (1H), 7,13 (2H), 7,20 (1H), 7,25 (1H), 7,48 (1H), 7,63-7,74 (2H), 7,76 (1H), 7,93 (1H), 8,08 (1H) ppm.

Ejemplo 552

N-etil-4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



Se trataron 30 mg (63 µmol) de ácido 4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzoico, que se preparó de acuerdo con el ejemplo 550, de manera análoga al Ejemplo 2 usando etanamina para dar, luego del tratamiento posterior y la purificación, 29,7 mg (89%) del compuesto del título.

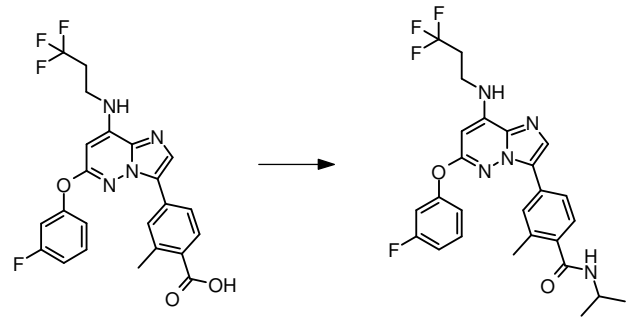
1H-RMN (DMSO-d6): δ= 1,06 (3H), 2,16 (3H), 2,68 (2H), 3,19 (2H), 3,60 (2H), 6,13 (1H), 7,13 (2H), 7,19 (1H), 7,25 (1H), 7,48 (1H), 7,64-7,74 (2H), 7,76 (1H), 7,93 (1H), 8,15 (1H) ppm.

Ejemplo 553

4-{6-(3-fluorofenoxi)-8-[(3,3,3-

trifluoropropil)amino]imidazo[1,2-b]

piridazin-3-il}-N-isopropil-2-metilbenzamida



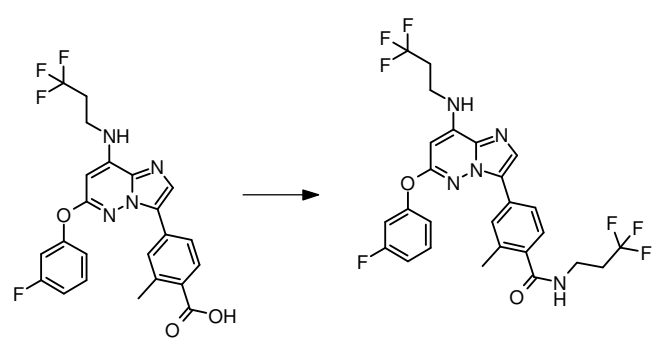
Se trataron 30 mg (63 µmol) de ácido 4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzoico, que se preparó de acuerdo con el ejemplo 550, de manera análoga al Ejemplo 2 usando propan-2-amina para dar, luego del tratamiento posterior y la purificación, 13,4 mg (39%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 1,09 (6H), 2,14 (3H), 2,68 (2H), 3,60 (2H), 3,99 (1H), 6,13 (1H), 7,08-7,19 (3H), 7,26 (1H), 7,48 (1H), 7,66 (1H), 7,72 (1H), 7,77 (1H), 7,92 (1H), 8,03 (1H) ppm.

Ejemplo 554

4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]

piridazin-3-il}-2-metil-N-(3,3,3-trifluoropropil)benzamida



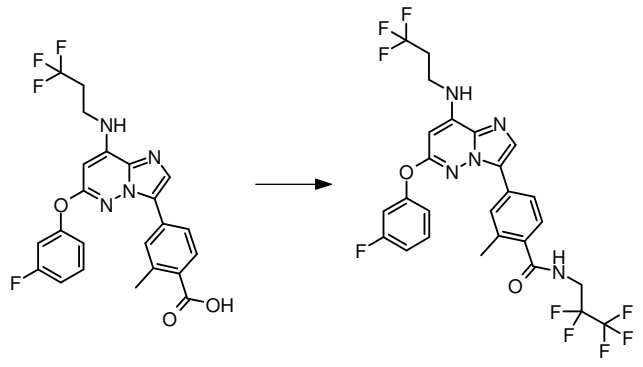
Se trataron 11,8 mg (25 µmol) de ácido 4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzoico, que se preparó de acuerdo con el ejemplo 550, de manera análoga al Ejemplo 2 usando 3,3,3-trifluoropropan-1-amina para dar, luego del tratamiento posterior y la purificación, 12,0 mg (83%) del compuesto del título.

1H-RMN (CDCl3): δ= 2,34 (3H), 2,41-2,65 (4H), 3,69 (4H), 5,90 (1H), 5,97 (2H), 6,94-7,08 (3H), 7,28 (1H), 7,39 (1H), 7,65 (1H), 7,75 (1H), 7,77 (1H) ppm.

Ejemplo 555

4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]

piridazin-3-il}-2-metil-N-(2,2,3,3,3-pentafluoropropil)benzamida



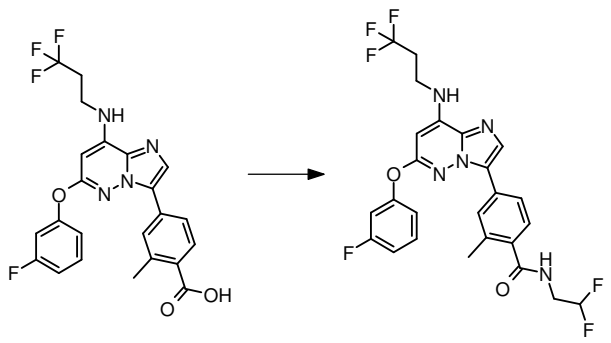
Se trataron 11,8 mg (25 µmol) de ácido 4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzoico, que se preparó de acuerdo con el ejemplo 550, de manera análoga al Ejemplo 552 usando 2,2,3,3,3-pentafluoropropan-1-amina para dar, luego del tratamiento posterior y la purificación, 12,5 mg (82%) del compuesto del título.

1H-RMN (CDCl3): δ= 2,34 (3H), 2,50-2,65 (2H), 3,69 (2H), 4,16 (2H), 5,91 (1H), 5,96 (2H), 6,93-7,08 (3H), 7,32 (1H), 7,40 (1H), 7,67 (1H), 7,76 (1H), 7,80 (1H) ppm.

Ejemplo 556

N-(2,2-difluoroetil)-4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



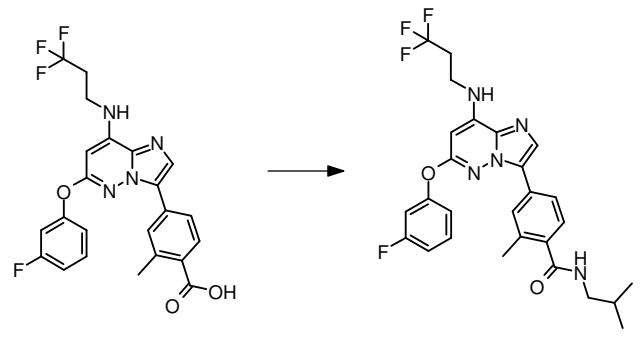
Se trataron 11,8 mg (25 µmol) de ácido 4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzoico, que se preparó de acuerdo con el ejemplo 550, de manera análoga al Ejemplo 551 usando 2,2-difluoroetanamina para dar, luego del tratamiento posterior y la purificación, 13,4 mg (93%) del compuesto del título.

1H-RMN (CDCl3): δ= 2,35 (3H), 2,58 (2H), 3,69 (2H), 3,82 (2H), 5,90 (1H), 5,93-6,02 (2H), 5,99 (1H) 6,95-7,08 (3H), 7,33 (1H), 7,40 (1H), 7,66 (1H), 7,76 (1H), 7,79 (1H) ppm.

Ejemplo 557

4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]

piridazin-3-il}-N-isobutil-2-metilbenzamida



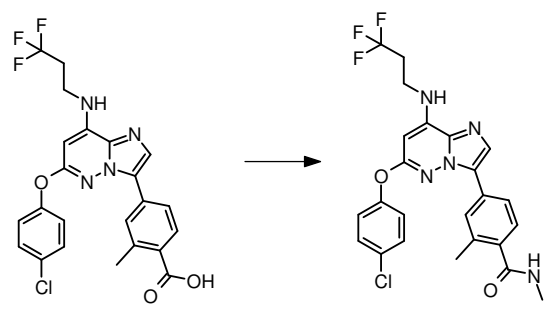
Se trataron 11,8 mg (25 µmol) de ácido 4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzoico, que se preparó de acuerdo con el ejemplo 550, de manera análoga al Ejemplo 551 usando 2-metilpropan-1-amina para dar, luego del tratamiento posterior y la purificación, 12,8 mg (96%) del compuesto del título.

1H-RMN (CDCl3): δ= 0,99 (6H), 1,89 (1H), 2,35 (3H), 2,58 (2H), 3,28 (2H), 3,68 (2H), 5,74 (1H), 5,89 (1H), 5,97 (1H), 6,92-7,08 (3H), 7,30 (1H), 7,39 (1H), 7,64 (1H), 7,74 (1H), 7,76 (1H) ppm.

Ejemplo 558

4-{6-(4-clorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]

piridazin-3-il}-N,2-dimetilbenzamida



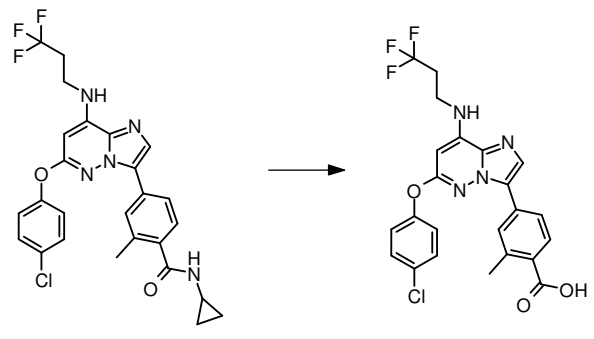
Se trataron 25 mg (51µmol) de ácido 4-{6-(4-clorofenoxi)-8-

[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzoico, que se preparó de acuerdo con el Ejemplo Intermediario 558a, de manera análoga al Ejemplo 551 para dar, luego del tratamiento posterior y la purificación, 11,1 mg (43%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 2,15 (3H), 2,61-2,75 (2H), 2,70 (3H), 3,60 (2H), 6,13 (1H), 7,21 (1H), 7,32 (2H), 7,51 (2H), 7,64 (1H), 7,69 (1H), 7,74 (1H), 7,93 (1H), 8,09 (1H) ppm.

Ejemplo Intermediario 558a

ácido 4-{6-(4-clorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzoico



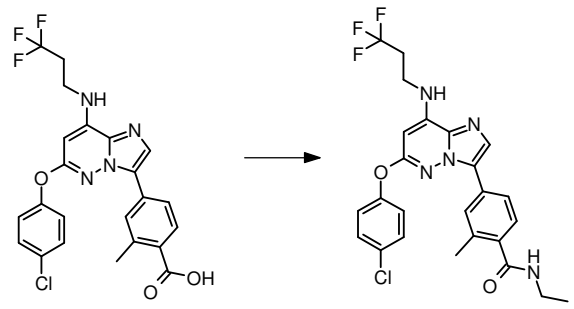
Una mezcla de 300 mg (566 µmol) de 4-{6-(4-clorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida y 13,4 mL de ácido bromhídrico se calentó a 120°C durante 2,5 días. Se agregó agua, el precipitado se retiró por filtración para dar el compuesto del título crudo que se usó sin purificación adicional.

Ejemplo 559

4-{6-(4-clorofenoxi)-8-[(3,3,3-

trifluoropropil)amino]imidazo[1,2-b]

piridazin-3-il}-N-etil-2-metilbenzamida



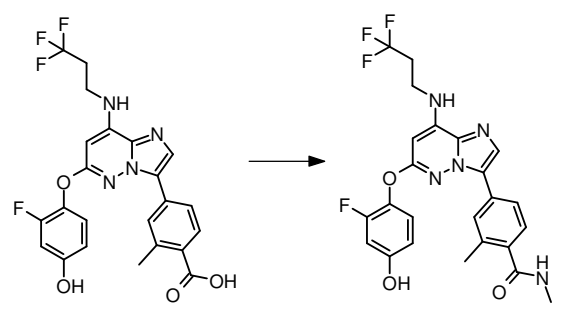
Se trataron 25 mg (51 µmol) de ácido 4-{6-(4-clorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzoico, que se preparó de acuerdo con el Ejemplo Intermediario 558a, de manera análoga al Ejemplo 2 usando etanamina para dar, luego del tratamiento posterior y la purificación, 10,4 mg (37%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 1,07 (3H), 2,14 (3H), 2,62-2,75 (2H), 3,20 (2H), 3,60 (2H), 6,13 (1H), 7,20 (1H), 7,32 (2H), 7,51 (2H), 7,64 (1H), 7,69 (1H), 7,74 (1H), 7,93 (1H), 8,15 (1H) ppm.

Ejemplo 560

4-{6-(2-fluoro-4-hidroxifenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo

[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida



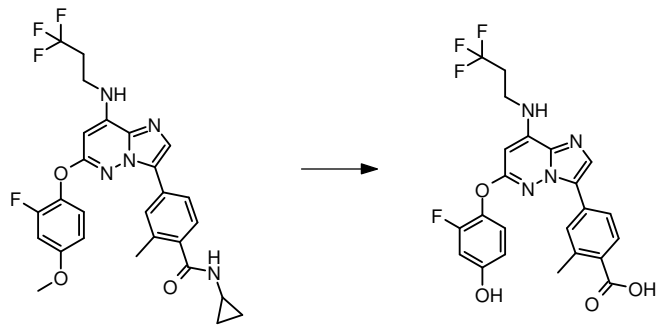
Se trataron 12,8 mg (26 µmol) de ácido 4-{6-(2-fluoro-4-hidroxifenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzoico, que se preparó de acuerdo con el Ejemplo Intermediario 560a, de manera análoga al Ejemplo 551 para dar, luego del tratamiento posterior y la purificación, 5,6 mg (43%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 2,15 (3H), 2,61-2,79 (2H), 2,70 (3H), 3,60 (2H), 6,13 (1H), 6,64 (1H), 6,73 (1H), 7,13-7,25 (2H), 7,58-7,70 (2H), 7,75 (1H), 7,93 (1H), 8,09 (1H), 9,87 (1H) ppm.

Ejemplo 560a

ácido 4-{6-(2-fluoro-4-hidroxifenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]

piridazin-3-il}-2-metilbenzoico

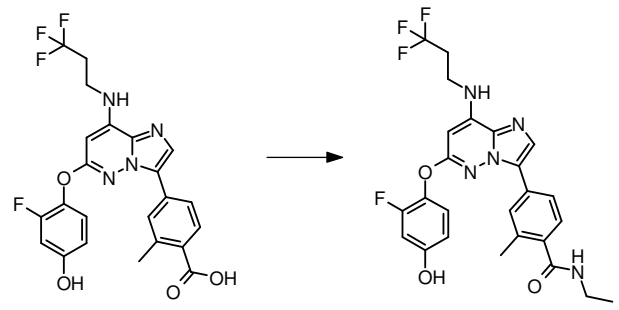


Se trataron 75 mg (138µmol) de N-ciclopropil-4-{6-(2-fluoro-4-metoxifenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida, de manera análoga al Ejemplo Intermediario 558a para dar después del tratamiento posterior 76,6 mg del compuesto del título con una pureza de 85% que se usó sin purificación adicional.

Ejemplo 561

N-etil-4-{6-(2-fluoro-4-hidroxifenoxi)-8-[(3,3,3-trifluoropropil)amino]

imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida



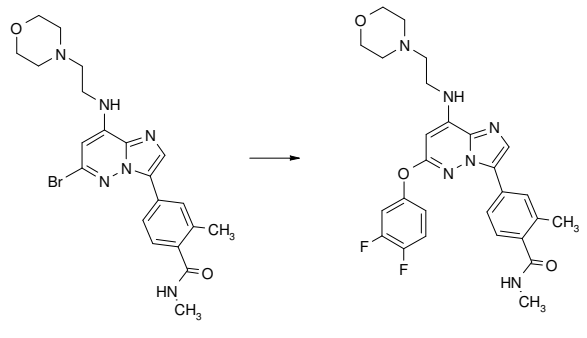
Se trataron 12,8 mg (26 µmol) de ácido 4-{6-(2-fluoro-4-hidroxifenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzoico, que se preparó de acuerdo con el Ejemplo Intermediario 560a, de manera análoga al Ejemplo 551 usando etanamina para dar, luego del tratamiento posterior y la purificación, 9,6 mg (713%) del compuesto del título.

1H-RMN (DMSO-d6): δ= 1,07 (3H), 2,15 (3H), 2,68 (2H), 3,20 (2H), 3,60 (2H), 6,13 (1H), 6,64 (1H), 6,74 (1H), 7,14-7,23 (2H), 7,60-7,70 (2H), 7,75 (1H), 7,92 (1H), 8,16 (1H), 9,86 (1H) ppm.

Ejemplo 562

4-[6-(3,4-difluorofenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo

[1,2-b]piridazin-3-il]-N,2-dimetilbenzamida

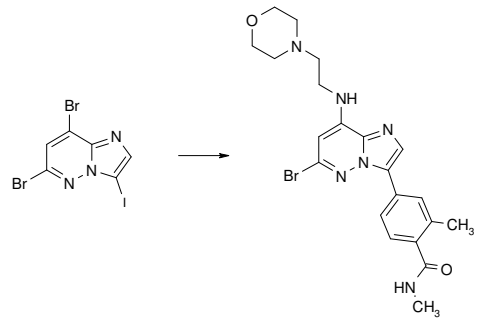


A una solución agitada de 48 mg (1200 µmol) de hidruro de sodio en 1,2 mL de DMSO, se agregaron 156 mg (1200 µmol) de 3,4-difluorofenol en una porción a temperatura ambiente. Luego de 1 h, se agregaron 95 mg (200 µmol) de 4-(6-bromo-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il)-N,2-dimetilbenzamida, que se preparó de acuerdo con el Ejemplo Intermediario 562a, en 1 mL de DMSO, y la mezcla se calentó durante 8 h a 140°C en un horno de microondas. Después del tratamiento posterior y la purificación se obtuvieron 7,42 mg (7%) del compuesto del título.

UPLC-MS: RT = 0,82, PM encontrado = 523,5, PM calculado = 522,5.
1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 2,16 (3H), 2,45-2,47 (3H), 2,59 (2H), 2,67-2,75 (4H), 3,44 (2H), 3,53-3,60 (4H), 6,07 (1H), 7,12-7,19 (1H), 7,22 (1H), 7,31 (1H), 7,47-7,60 (2H), 7,66 (1H), 7,74 (1H), 7,91 (1H), 8,09 (1H).

Ejemplo Intermediario 562a

4-(6-bromo-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il)-
N,2-dimetilbenzamida

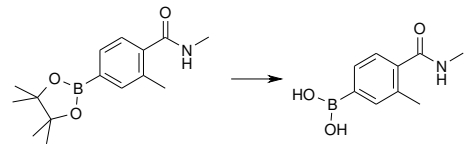


A una solución agitada de 2,01 g (5 mmol) de 6,8-dibromo-3-yodoimidazo[1,2-b]piridazina, que se preparó de acuerdo con el Ejemplo Intermediario 96c en NMP (15 mL), se agregaron 1,94 g (15 mmol) de DIPEA y 1,30 g (10 mmol) de 2-(morfolin-4-il)etanamina en una porción a temperatura ambiente. Después de calentar durante 2 h a 70°C, se agregaron 100 mL de DCM, y la mezcla se lavó con agua (3 x 100 mL). La fase orgánica se secó sobre sulfato de sodio y se evaporó para dar un sólido marrón que se usó sin purificación adicional en el siguiente paso. A una solución agitada de los sólidos restantes en 20 mL de THF, se agregaron 1,16 g (6 mmol) de ácido [3-metil-4-(metilcarbamoil)fenil]borónico, que se preparó de acuerdo con el Ejemplo Intermediario 562b, 15 mL de solución acuosa de carbonato de potasio (15 mmol, 1M), 816 mg de Pd(dppf)Cl2 (1 mmol) y la mezcla se calentó durante 41 h a 70°C, para dar, luego del tratamiento posterior y la purificación, 2,35 g (99%) del compuesto del título.

UPLC-MS: RT = 0,71, PM encontrado = 474,4, PM calculado = 473,4.
1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 2,37 (3H), 2,42 (4H), 2,54 (2H), 2,73 (3H), 3,26 (2H), 3,49-3,59 (4H), 6,42 (1H), 7,40 (2H), 7,56-7,63 (1H), 7,86 (1H), 7,92 (1H), 7,96 (1H), 8,18 (1H)

Ejemplo Intermediario 562b

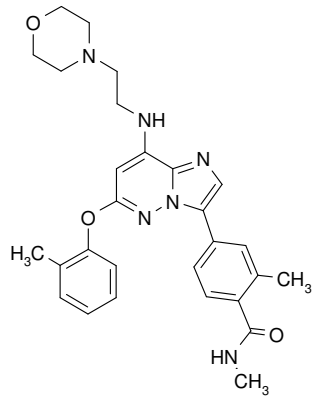
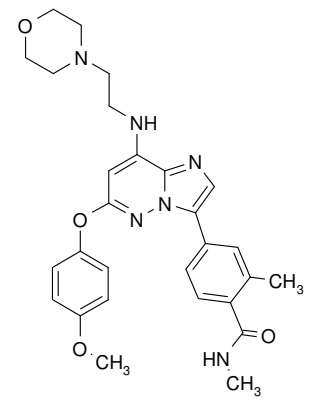
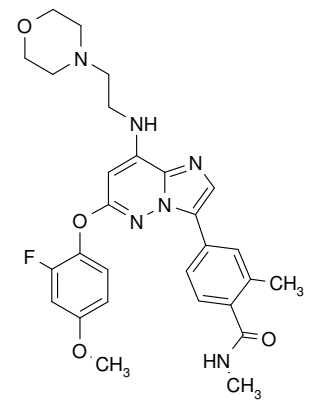
ácido [3-metil-4-(metilcarbamoil)fenil]borónico

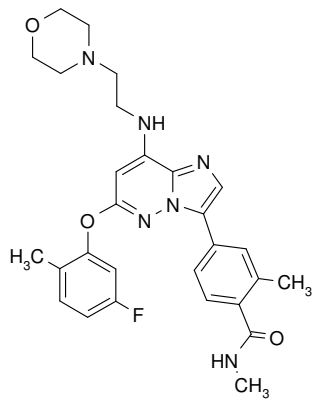
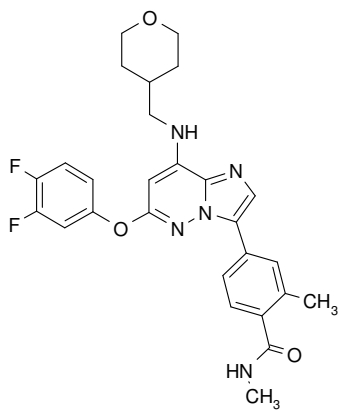
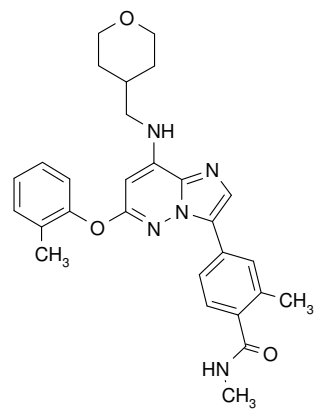


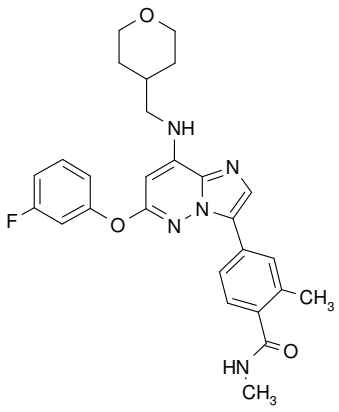
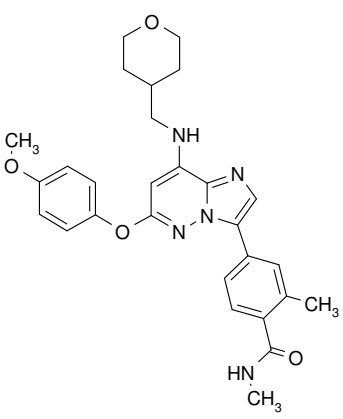
A una solución agitada de 20,22 g (67 mmol) de N-ciclopropil-2-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzamida en acetona (300 mL), se agregaron 43,08 g (201 mmol) de periodato de sodio, 134 mL de acetato de amonio (134 mmol, 1M en agua) y la mezcla se agitó durante 3 h a temperatura ambiente y 2 h a 40°C. Se agregó HCl 4 N (32 mL) y la fase orgánica se retiró al vacío. La mezcla se extrajo con acetato de etilo, y la fase orgánica se lavó con agua, se secó y se eliminó al vacío para dar 14,59 g (94,2 %) del compuesto del título. 1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 0,44-0,52 (2H), 0,59-0,67 (2H), 2,26 (3H), 2,78 (1H), 7,18 (1H), 7,53-7,61 (2H), 8,01 (2H), 8,19 (1H).

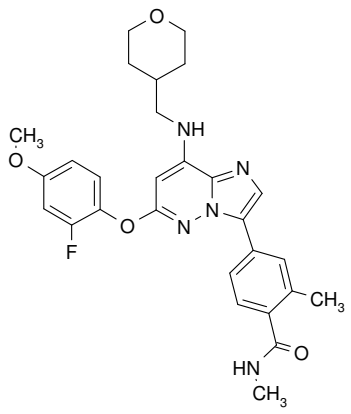
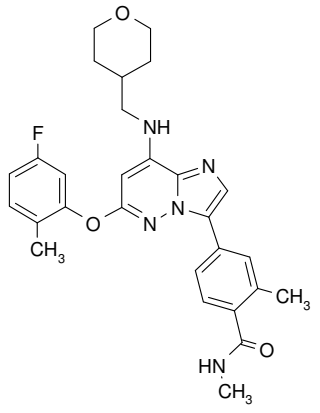
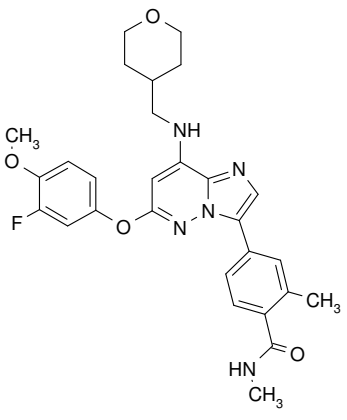
Los siguientes ejemplos de compuestos se prepararon de manera análoga al procedimiento que se ha descrito para el ejemplo 562 usando el Ejemplo Intermediario apropiado y el fenol apropiado [los datos de LC-MS como por ejemplo tiempo de retención (RT en min) o pico de masa observada se recogieron usando el Método LC-MS A salvo que se especifique lo contrario]:

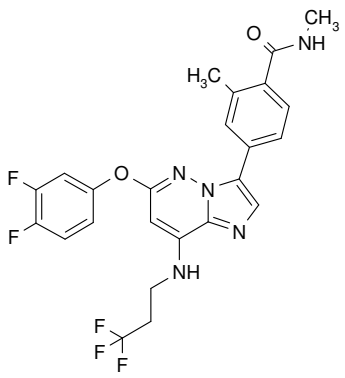
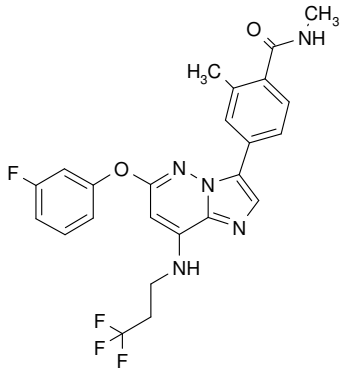
Ejemplo	Estructura	Nombre	Datos analíticos

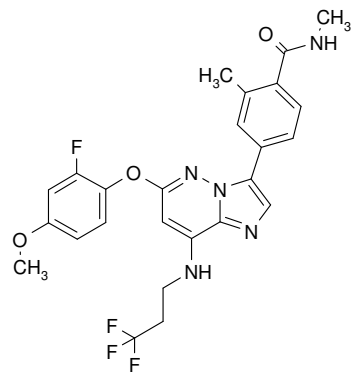
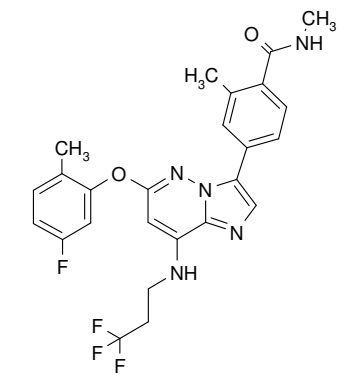
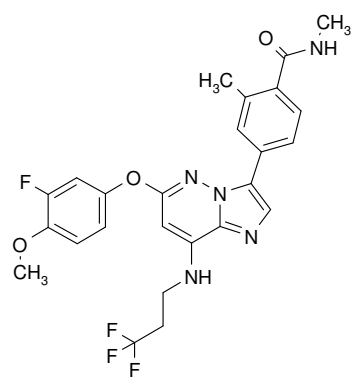
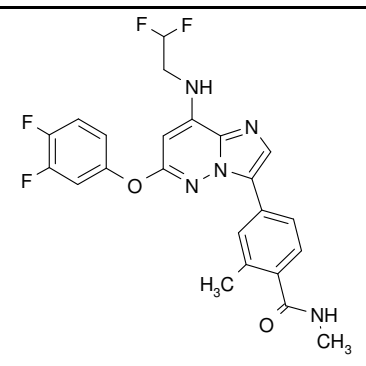
Ejemplo	Estructura	Nombre	Datos analíticos
563		N,2-dimetil-4-[6-(2-metilfenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il]benzamida	RT = 0,82 PM encontrado = 501,6 PM calculado = 500,6
564		4-[6-(4-metoxifenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-N,2-dimetilbenzamida	RT = 0,78 PM encontrado = 517,6 PM calculado = 516,6
565		4-[6-(2-fluoro-4-metoxifenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-N,2-dimetilbenzamida	RT = 0,80 PM encontrado = 535,6 PM calculado = 534,6

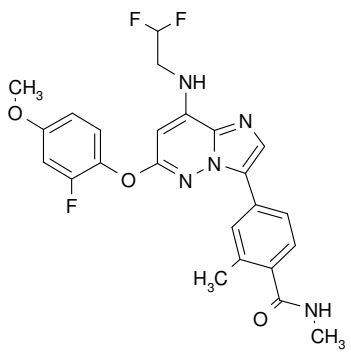
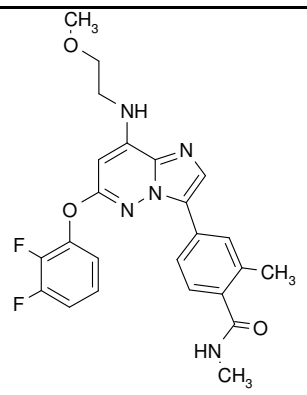
Ejemplo	Estructura	Nombre	Datos analíticos
566		4-[6-(5-fluoro-2-metilfenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-N,2-dimetilbenzamida	RT = 0,84 PM encontrado = 519,6 PM calculado = 518,6
567		4-{6-(3,4-difluorofenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida	RT = 1,22 PM encontrado = 508,5 PM calculado = 507,5
568		N,2-dimetil-4-{6-(2-metilfenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,22 PM encontrado = 486,6 PM calculado = 485,6 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 1,14-1,32 (2H), 1,63 (2H), 1,86-2,03 (1H), 2,50 (6H), 2,68 (3H), 3,22 (4H),

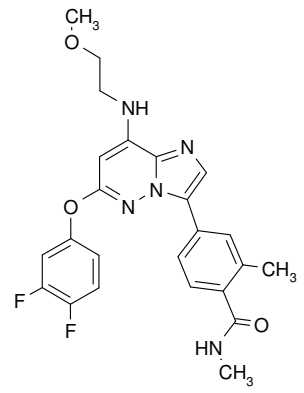
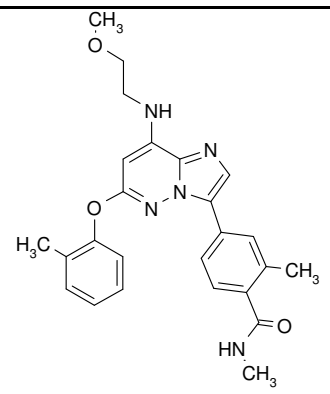
Ejemplo	Estructura	Nombre	Datos analíticos
			3,83 (2H), 6,08 (1H), 7,13 (1H), 7,15-7,23 (2H), 7,23-7,28 (1H), 7,33 (1H), 7,57-7,65 (2H), 7,69 (1H), 7,89 (1H), 8,05 (1H)
569		4-{6-(3-fluorofenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida	RT = 1,20 PM encontrado = 490,5 PM calculado = 489,5
570		4-{6-(4-metoxifenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida	RT = 1,16 PM encontrado = 502,6 PM calculado = 501,6

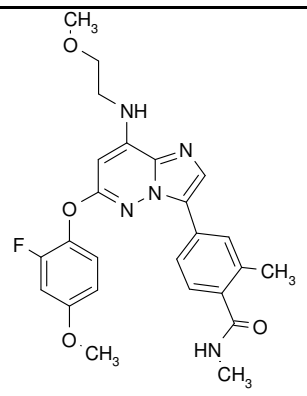
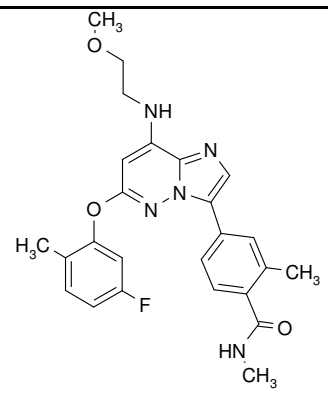
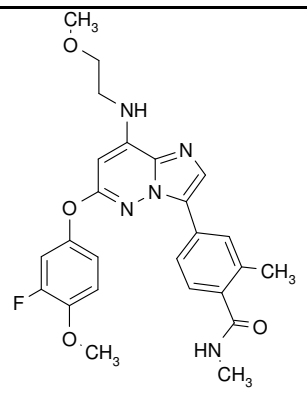
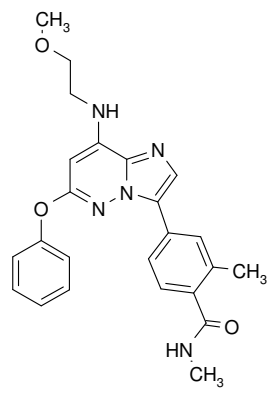
Ejemplo	Estructura	Nombre	Datos analíticos
571		4-{6-(2-fluoro-4-metoxifenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida	RT = 1,19 PM encontrado = 520,6 PM calculado = 519,6
572		4-{6-(5-fluoro-2-metilfenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida	RT = 1,24 PM encontrado = 504,6 PM calculado = 503,6
573		4-{6-(3-fluoro-4-metoxifenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida	RT = 1,17 PM encontrado = 520,6 PM calculado = 519,6

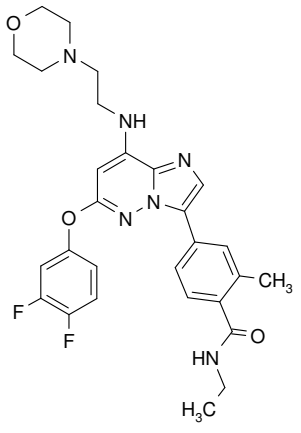
Ejemplo	Estructura	Nombre	Datos analíticos
574		4-{6-(3,4-difluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida	RT = 1,29 PM encontrado = 506,4 PM calculado = 505,4
575		4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida	RT = 1,29 PM encontrado = 488,5 PM calculado = 487,5 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 2,16 (3H), 2,59-2,76 (5H), 3,54-3,66 (2H), 6,13 (1H), 7,13 (2H), 7,20 (1H), 7,25 (1H), 7,43-7,53 (1H), 7,64-7,74 (2H), 7,76 (1H), 7,93 (1H), 8,08 (1H)

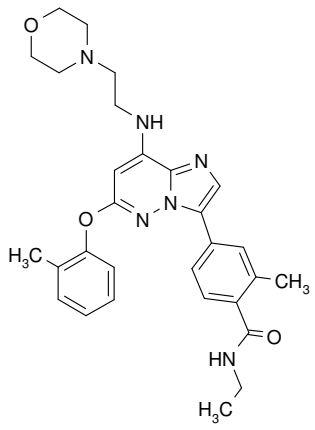
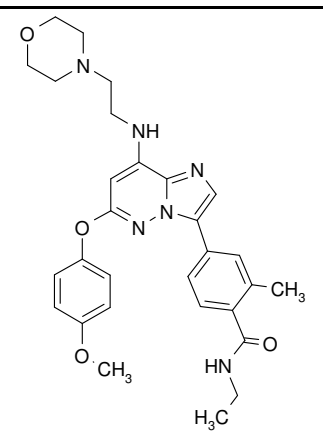
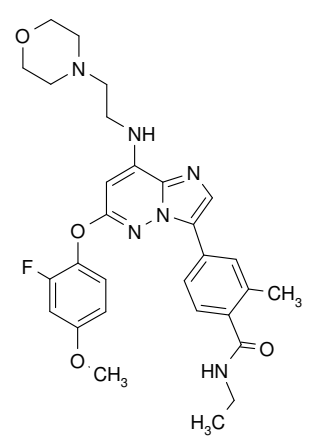
Ejemplo	Estructura	Nombre	Datos analíticos
576		4-{6-(2-fluoro-4-metoxifenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida	RT = 1,26 PM encontrado = 518,5 PM calculado = 517,5
577		4-{6-(5-fluoro-2-metilfenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida	RT = 1,32 PM encontrado = 502,5 PM calculado = 501,5
578		4-{6-(3-fluoro-4-metoxifenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida	RT = 1,25 PM encontrado = 518,5 PM calculado = 517,5
579		4-{8-[(2,2-difluoroetil)amino]-6-(3,4-difluorofenoxi)imidazo[1,2-b]piridazin-3-il}-N,2-	RT = 1,17 PM encontrado = 474,4 PM calculado = 473,4

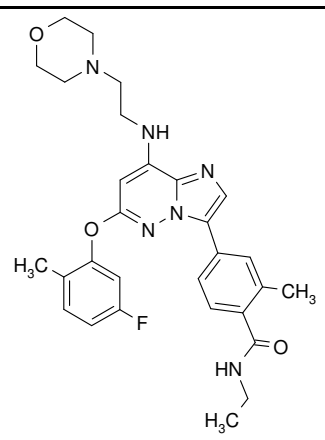
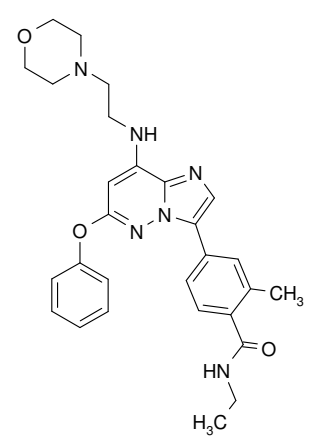
Ejemplo	Estructura	Nombre	Datos analíticos
		dimetilbenzamida	
580		4-{8-[(2,2-difluoroetil)amino]-6-(2-fluoro-4-metoxifenoxi)imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida	RT = 1,16 PM encontrado = 486,5 PM calculado = 485,5 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 2,10 (3H), 2,70 (3H), 3,78 (3H), 3,86 (3H), 6,23 (1H), 6,32 (1H), 6,84 (1H), 7,05 (1H), 7,19 (1H), 7,34 (1H), 7,62 (1H), 7,70-7,79 (1H), 7,97 (1H), 8,08 (1H)
581		4-{6-(2,3-difluorofenoxi)-8-[(2-metoxietil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-	RT = 1,17 PM encontrado = 468,5 PM calculado = 467,5

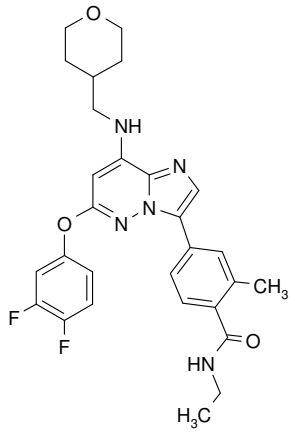
Ejemplo	Estructura	Nombre	Datos analíticos
		dimetilbenzamida	
582		4-{6-(3,4-difluorofenoxi)-8-[(2-metoxietil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida	RT = 1,18 PM encontrado = 468,5 PM calculado = 467,5 1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 2,16 (3H), 2,70 (3H), 3,27 (3H), 3,52 (2H), 3,54-3,59 (2H), 6,10 (1H), 7,13-7,19 (1H), 7,22 (1H), 7,45 (1H), 7,50-7,60 (2H), 7,66 (1H), 7,75 (1H), 7,92 (1H), 8,09 (1H)
583		4-{8-[(2-metoxietil)amino]-6-(2-metilfenoxi)imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida	RT = 1,18 PM encontrado = 446,5 PM calculado = 445,5

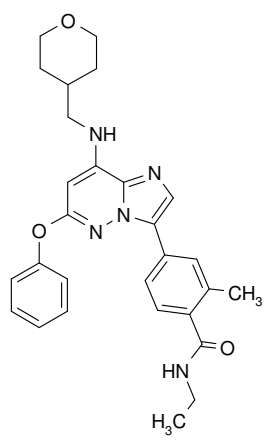
Ejemplo	Estructura	Nombre	Datos analíticos
584		4-{6-(2-fluoro-4-metoxifenoxi)-8-[(2-metoxietil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida	RT = 1,15 PM encontrado = 480,5 PM calculado = 479,5
585		4-{6-(5-fluoro-2-metilfenoxi)-8-[(2-metoxietil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida	RT = 1,20 PM encontrado = 464,5 PM calculado = 463,5
586		4-{6-(3-fluoro-4-metoxifenoxi)-8-[(2-metoxietil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida	RT = 1,13 PM encontrado = 480,5 PM calculado = 479,5
587		4-{8-[(2-metoxietil)amino]-6-fenoxiimidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida	RT = 1,14 PM encontrado = 432,5 PM calculado = 431,5 1H-RMN (400 MHz,DMSO-d6), δ

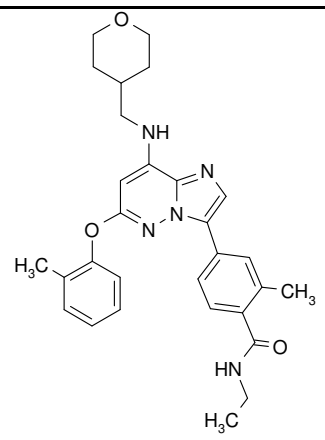
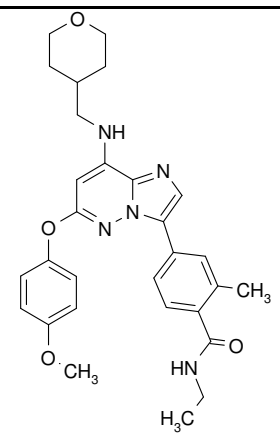
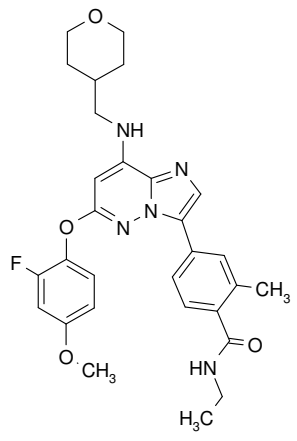
Ejemplo	Estructura	Nombre	Datos analíticos
			[ppm]= 2,14 (3H), 2,69 (3H), 3,17-3,29 (3H), 3,51 (2H), 3,53-3,59 (2H), 6,08 (1H), 7,18 (1H), 7,24-7,29 (3H), 7,38 (1H), 7,41-7,48 (2H), 7,67 (1H), 7,75 (1H), 7,91 (1H), 8,09 (1H)
588		4-[6-(3,4-difluorofenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-N-etil-2-metilbenzamida	RT = 0,88 PM encontrado = 537,6 PM calculado = 536,6

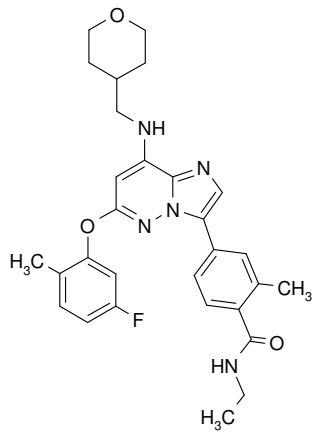
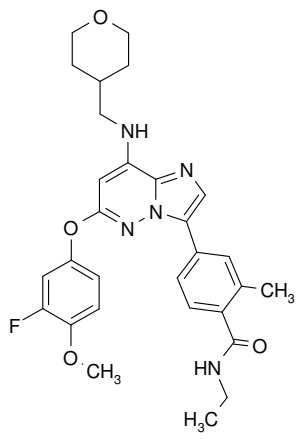
Ejemplo	Estructura	Nombre	Datos analíticos
589		N-etil-2-metil-4-[6-(2-metilfenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il]benzamida	RT = 0,88 PM encontrado = 515,6 PM calculado = 514,6
590		N-etil-4-[6-(4-metoxifenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 0,83 PM encontrado = 531,6 PM calculado = 530,6
591		N-etil-4-[6-(2-fluoro-4-metoxifenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 0,86 PM encontrado = 549,6 PM calculado = 548,6 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 1,06 (3H), 2,10 (3H), 2,42 (4H), 2,59 (2H), 3,14-3,24 (2H), 3,44 (2H),

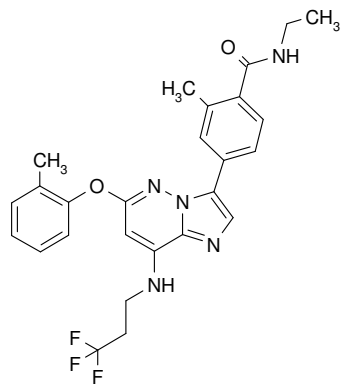
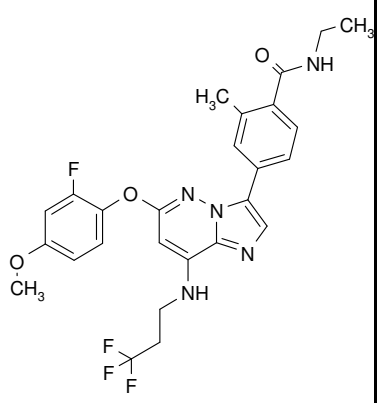
Ejemplo	Estructura	Nombre	Datos analíticos
			3,53-3,59 (4H), 3,77 (3H), 6,10 (1H), 6,54 (1H), 6,67-6,88 (1H), 7,05 (1H), 7,17 (1H), 7,25-7,32 (1H), 7,62 (1H), 7,72 (1H), 7,92 (1H), 8,16 (1H)
592		N-etil-4-[6-(5-fluoro-2-metilfenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida	RT = 0,89 PM encontrado = 533,6 PM calculado = 532,6
593		N-etil-2-metil-4-(8-{[2-(morfolin-4-il)etil]amino}-6-fenoxiimidazo[1,2-b]piridazin-3-il)benzamida	RT = 0,89 PM encontrado = 501,6 PM calculado = 500,6 1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 1,06 (3H), 2,14 (3H),

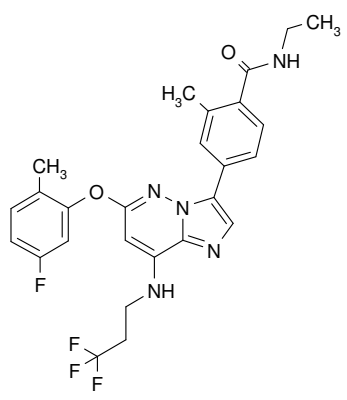
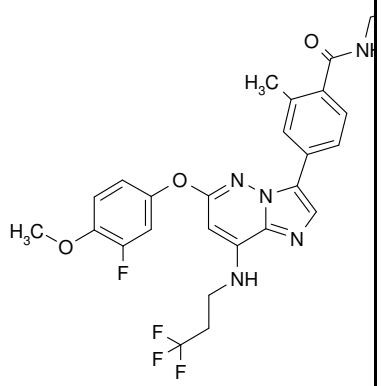
Ejemplo	Estructura	Nombre	Datos analíticos
			2,59 (2H), 3,19 (4H), 3,43 (3H), 3,56 (5H), 6,05 (1H), 7,17 (1H), 7,26 (5H), 7,41-7,50 (2H), 7,66 (1H), 7,75 (1H), 7,90 (1H), 8,13 (2H)
594		4-{6-(3,4-difluorofenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-etil-2-metilbenzamida	RT = 1,28 PM encontrado = 522,6 PM calculado = 521,6 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 1,07 (3H), 1,14-1,32 (2H), 1,62 (2H), 1,86-2,01 (1H), 2,16 (3H), 3,14-3,25 (6H), 3,83 (2H), 6,09 (1H), 7,11-7,23 (2H), 7,46-7,60 (2H),

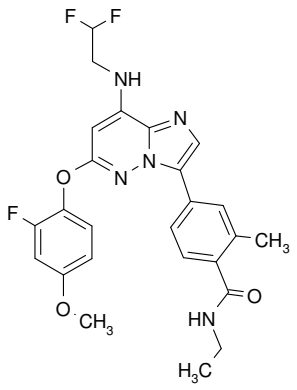
Ejemplo	Estructura	Nombre	Datos analíticos
			7,61-7,68 (1H), 7,68-7,77 (2H), 7,90 (1H), 8,15 (1H)
595		N-etil-2-metil-4-{6-fenoxi-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,26 PM encontrado = 486,6 PM calculado = 485,6 485,6 1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 1,06 (3H), 1,15-1,29 (4H), 1,62 (2H), 1,89-2,00 (1H), 2,13 (3H), 3,15-3,29 (4H), 3,83 (2H), 6,07 (1H), 7,16 (1H), 7,27 (3H), 7,41-7,48 (2H), 7,62-7,68 (2H), 7,75 (1H), 7,90 (1H), 8,10-8,18 (1H)

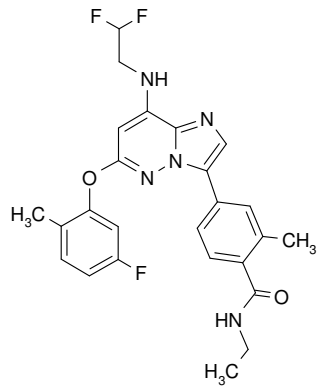
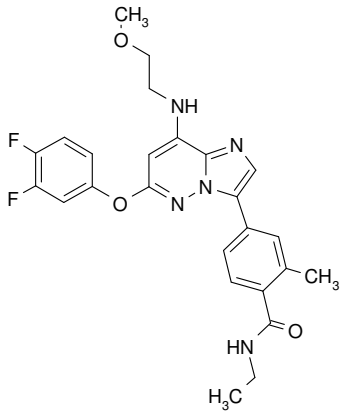
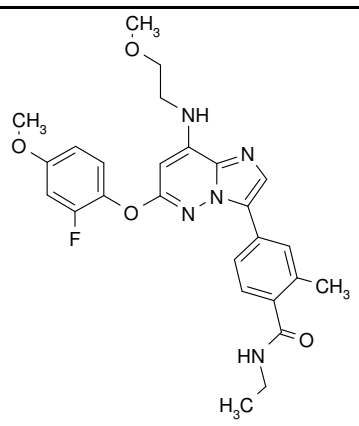
Ejemplo	Estructura	Nombre	Datos analíticos
596		N-etil-2-metil-4-{6-(2-metilfenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,29 PM encontrado = 500,6 PM calculado = 499,6
597		N-etil-4-{6-(4-metoxifenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,22 PM encontrado = 516,6 PM calculado = 515,6
598		N-etil-4-{6-(2-fluoro-4-metoxifenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,24 PM encontrado = 534,6 PM calculado = 533,6

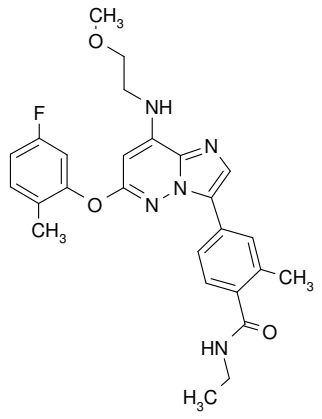
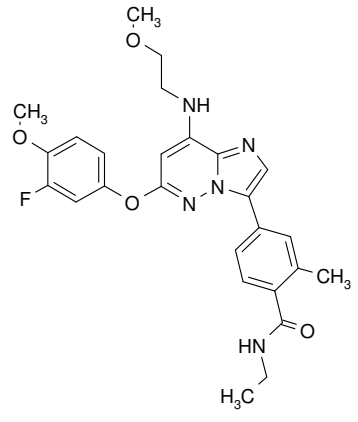
Ejemplo	Estructura	Nombre	Datos analíticos
599		N-etil-4-{6-(5-fluoro-2-metilfenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,31 PM encontrado = 518,6 PM calculado = 517,6
600		N-etil-4-{6-(3-fluoro-4-metoxifenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,25 PM encontrado = 534,6 PM calculado = 533,6 1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 1,07 (3H), 1,15-1,29 (2H), 1,62 (2H), 1,94 (1H), 2,13 (3H), 3,15-3,26 (6H), 3,78-3,83 (2H), 3,84 (3H), 6,05 (1H), 7,03-7,09 (1H), 7,16-7,25 (2H), 7,30 (1H), 7,62-7,69 (2H), 7,78 (1H),

Ejemplo	Estructura	Nombre	Datos analíticos
			7,90 (1H), 8,15 (1H)
601		N-etil-2-metil-4-{6-(2-metilfenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida	RT = 1,36 PM encontrado = 498,5 PM calculado = 497,5
602		N-etil-4-{6-(2-fluoro-4-metoxifenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,31 PM encontrado = 532,5 PM calculado = 531,5 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 1,06 (3H), 2,10 (3H), 2,69 (2H), 3,13-3,24 (2H), 3,61 (2H), 3,77 (3H), 6,16 (1H), 6,84 (1H), 7,06 (1H), 7,17 (1H), 7,34 (1H), 7,58-7,65

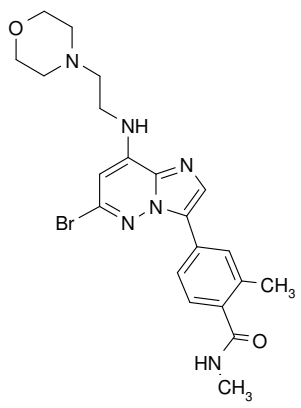
Ejemplo	Estructura	Nombre	Datos analíticos
			(1H), 7,68 (1H), 7,72 (1H), 7,93 (1H), 8,15 (1H)
603		N-etil-4-{6-(5-fluoro-2-metilfenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,37 PM encontrado = 516,5 PM calculado = 515,5
604		N-etil-4-{6-(3-fluoro-4-metoxifenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,32 PM encontrado = 532,5 PM calculado = 531,5 1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 1,07 (3H), 2,13 (3H), 2,61-2,74 (2H), 3,20 (2H), 3,59 (2H), 3,84 (3H), 6,09 (1H), 7,04-7,09 (1H), 7,17-

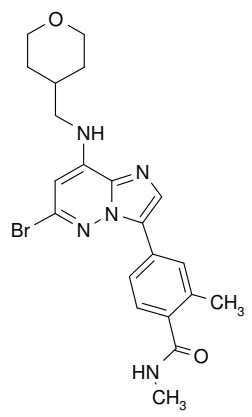
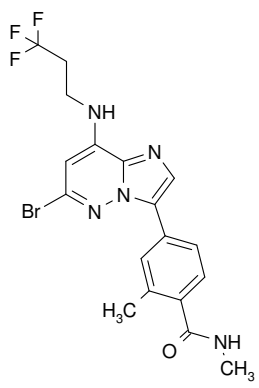
Ejemplo	Estructura	Nombre	Datos analíticos
			7,20 (1H), 7,20-7,25 (1H), 7,31 (1H), 7,63-7,68 (2H), 7,78 (1H), 7,93 (1H), 8,15 (1H)
605		4-{8-[(2,2-difluoroetil)amino]-6-(2-fluoro-4-metoxifenoxi)imidazo[1,2-b]piridazin-3-il}-N-etil-2-metilbenzamida	RT = 1,22 PM encontrado = 500,5 PM calculado = 499,5 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 1,06 (3H), 2,10 (3H), 3,19 (2H), 3,77 (2H), 3,86 (1H), 6,32 (1H), 6,84 (1H), 7,06 (1H), 7,17 (1H), 7,34 (1H), 7,59-7,65 (1H), 7,69-7,79 (2H), 7,96 (1H), 8,15 (1H)

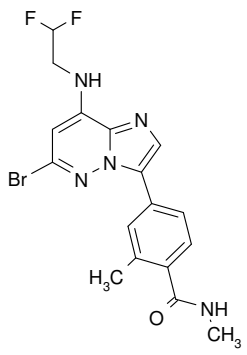
Ejemplo	Estructura	Nombre	Datos analíticos
606		4-{8-[(2,2-difluoroetil)amino]-6-(5-fluoro-2-metilfenoxi)imidazo[1,2-b]piridazin-3-il}-N-etil-2-metilbenzamida	RT = 1,28 PM encontrado = 484,5 PM calculado = 483,5
607		4-{6-(3,4-difluorofenoxi)-8-[(2-metoxietil)amino]imidazo[1,2-b]piridazin-3-il}-N-etil-2-metilbenzamida	RT = 1,24 PM encontrado = 482,5 PM calculado = 481,5
608		N-etil-4-{6-(2-fluoro-4-metoxifenoxi)-8-[(2-metoxietil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,21 PM encontrado = 494,5 PM calculado = 493,5

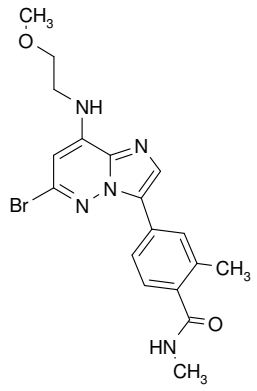
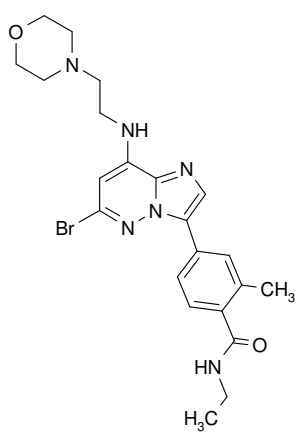
Ejemplo	Estructura	Nombre	Datos analíticos
609		N-etil-4-{6-(5-fluoro-2-metilfenoxi)-8-[(2-metoxietil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,27 PM encontrado = 478,5 PM calculado = 477,5 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 1,06 (3H), 2,11 (3H), 2,12 (3H), 3,19 (4H), 3,46-3,61 (5H), 6,12 (1H), 7,06 (1H), 7,12-7,21 (2H), 7,32-7,44 (2H), 7,62 (1H), 7,71 (1H), 7,91 (1H), 8,14 (1H)
610		N-etil-4-{6-(3-fluoro-4-metoxifenoxi)-8-[(2-metoxietil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida	RT = 1,19 PM encontrado = 494,5 PM calculado = 493,5

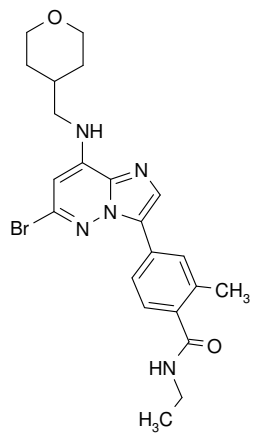
Los siguientes Ejemplos Intermediarios se prepararon de manera análoga al procedimiento que se ha descrito para el ejemplo 562a usando la amina apropiada y el ácido borónico apropiado [los datos de LC-MS como por ejemplo tiempo de retención (RT en min) o pico de masa observada se recogieron usando el Método LC-MS A salvo que se especifique lo contrario]:

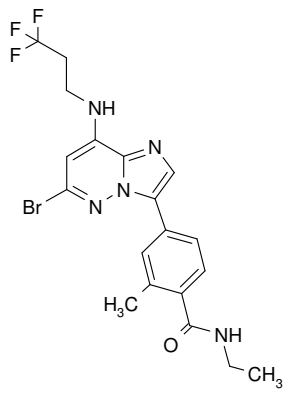
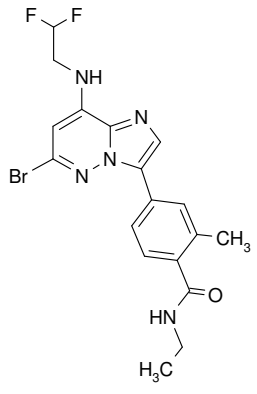
Ejemplo Intermediario	Estructura	Nombre	Datos analíticos
562a		4-(6-bromo-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il)-N,2-dimetilbenzamida	RT = 0,71 PM encontrado = 474,4 PM calculado = 473,4 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 2,37 (3H), 2,42 (4H), 2,54 (2H), 2,73 (3H), 3,26 (2H), 3,49-3,59 (4H), 6,42 (1H), 7,40 (2H), 7,56-7,63 (1H), 7,86 (1H), 7,92 (1H), 7,96 (1H), 8,18 (1H)

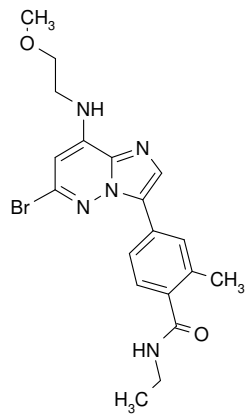
Ejemplo Intermediario	Estructura	Nombre	Datos analíticos
567a		4-{6-bromo-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida	RT = 1,09 PM encontrado = 459,4 PM calculado = 458,4 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 1,11-1,31 (2H), 1,59 (2H), 1,83-1,98 (1H), 2,37 (3H), 2,69-2,78 (3H), 3,15-3,27 (4H), 3,81 (2H), 6,42 (1H), 7,40 (1H), 7,86 (1H), 7,89-8,00 (3H), 8,18 (1H)
574a		4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida	RT = 1,18 PM encontrado = 457,3 PM calculado = 456,3 1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 2,37 (3H),

Ejemplo Intermediario	Estructura	Nombre	Datos analíticos
			2,59-2,71 (2H), 2,73 (3H), 3,59 (2H), 6,46 (1H), 7,41 (1H), 7,86 (1H), 7,89-7,96 (2H), 7,97 (1H), 8,17 (1H)
579a		4-{6-bromo-8-[(2,2-difluoroetil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida	RT = 1,03 PM encontrado = 425,3 PM calculado = 424,3 1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 2,37 (3H), 2,73 (3H), 3,25 (1H), 3,85 (2H), 6,62 (1H), 7,41 (1H), 7,87 (1H), 7,92 (1H), 7,97-8,03 (2H), 8,17 (1H)

Ejemplo Intermediario	Estructura	Nombre	Datos analíticos
581a		4-{6-bromo-8-[(2-metoxietil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida	RT = 1,02 PM encontrado = 419,3 PM calculado = 418,3 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 2,37 (3H), 2,73 (3H), 3,25 (3H), 3,53 (4H), 6,42 (1H), 7,41 (1H), 7,71 (1H), 7,86 (1H), 7,89-7,94 (1H), 7,95 (1H), 8,16 (1H)
588a		4-(6-bromo-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il)-N-etil-2-metilbenzamida	RT = 0,75 PM encontrado = 488,4 PM calculado = 487,4 1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 1,06-1,12 (3H), 2,37 (3H), 2,42 (4H), 2,56 (2H), 3,18-3,26

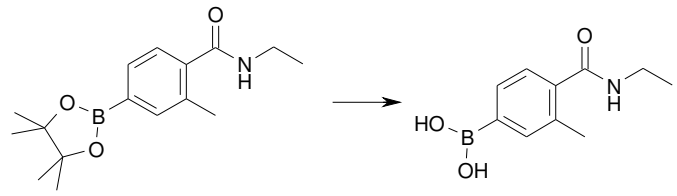
Ejemplo Intermediario	Estructura	Nombre	Datos analíticos
			(2H), 3,43 (2H), 3,52-3,58 (4H), 6,41 (1H), 7,39 (1H), 7,57 (1H), 7,85 (1H), 7,91 (1H), 7,95 (1H), 8,22 (1H)
594a		4-{6-bromo-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-etil-2-metilbenzamida	RT = 1,1,17 PM encontrado = 473,4 PM calculado = 472,4 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 1,05-1,12 (3H), 1,13-1,31 (2H), 1,59 (2H), 1,89 (1H), 2,37 (3H), 3,16-3,25 (6H), 3,81 (2H), 6,42 (1H), 7,39 (1H), 7,85 (1H), 7,88-7,98 (3H), 8,22 (1H)

Ejemplo Intermediario	Estructura	Nombre	Datos analíticos
601a		4-{6-bromo-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-etil-2-metilbenzamida	RT = 1,25 PM encontrado = 471,3 PM calculado = 470,3 1H-RMN (400 MHz,DMSO-d6), δ [ppm]= 1,09 (3H), 2,37 (3H), 2,66 (2H), 3,18-3,26 (2H), 3,59 (2H), 6,46 (1H), 7,40 (1H), 7,85 (1H), 7,89-7,96 (2H), 7,96 (1H), 8,23 (1H)
605a		4-{6-bromo-8-[(2,2-difluoroetil)amino]imidazo[1,2-b]piridazin-3-il}-N-etil-2-metilbenzamida	RT = 1,10 PM encontrado = 439,3 PM calculado = 438,3 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 1,09 (3H), 2,37 (3H), 3,18-3,26 (3H), 3,86

Ejemplo Intermediario	Estructura	Nombre	Datos analíticos
			(2H), 6,61 (1H), 7,40 (1H), 7,86 (1H), 7,89-7,95 (1H), 7,99 (2H), 8,23 (1H)
607a		4-{6-bromo-8-[(2-metoxietil)amino]imidazo[1,2-b]piridazin-3-il}-N-etil-2-metilbenzamida	RT = 1,09 PM encontrado = 433,3 PM calculado = 432,3 1H-RMN (300 MHz,DMSO-d6), δ [ppm]= 1,09 (3H), 2,37 (3H), 3,18-3,27 (4H), 3,43-3,59 (5H), 6,43 (1H), 7,39 (2H), 7,75 (1H), 7,86 (1H), 7,92 (1H), 7,95 (1H), 8,24 (1H)

Ejemplo Intermediario 582b

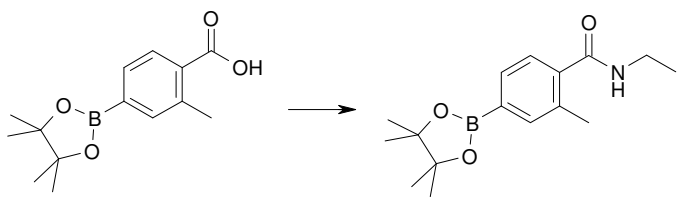
ácido [4-(etilcarbamoil)-3-metilfenil]borónico



Se trataron 17,72 g (61,27 mmol) de N-etil-2-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzamida, que se preparó de acuerdo con el Ejemplo Intermediario 582c, de manera análoga al Ejemplo Intermediario 562b para dar, luego del tratamiento posterior y la purificación, 8,75 g (70%) del compuesto del título.

Ejemplo Intermediario 582c

N-etil-2-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzamida



A una solución agitada de 15 g (57 mmol) de ácido 2-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)benzoico en NMP (20 mL), se agregaron 85,84 mL de (171,68 mmol) de etilamina y 72,8 mL de 2,4,6-trióxido de 2,4,6-tripropil-1,3,5,2,4,6-trioxatrifosfinano (114,45 mmol, 2M en THF) y la mezcla se agitó durante 2 h a temperatura ambiente para dar, luego del tratamiento posterior y la purificación, 16,00 g (96,7 %) del compuesto del título.

Composiciones farmacéuticas de los compuestos de la invención

Esta invención también se relaciona con composiciones farmacéuticas que contienen uno o más de los compuestos de la presente invención. Estas composiciones pueden utilizarse para obtener un efecto farmacológico deseado al administrarse a un paciente que las necesita. Un paciente, para el propósito de esta invención, es un mamífero, incluyendo un humano, que necesita el tratamiento para una condición o enfermedad particular. Por ello, la presente invención incluye composiciones farmacéuticas compuestas por un vehículo farmacéuticamente aceptable y una cantidad eficaz para uso farmacéutico de un compuesto, o una sal de éste, de la presente invención. Un vehículo farmacéuticamente aceptable es preferiblemente un vehículo que es relativamente no tóxico e inocuo para un paciente, a concentraciones consistentes con la actividad efectiva del ingrediente activo, de modo que los efectos colaterales que pueden adjudicarse al vehículo no perjudican los efectos beneficiosos del ingrediente activo. Una cantidad efectiva para el uso farmacéutico del compuesto es preferiblemente una cantidad que produce un resultado o ejerce una influencia sobre la condición particular a tratar. Los compuestos de la presente invención pueden administrarse con vehículos farmacéuticamente aceptables bien conocidos en la técnica, usando cualquier forma de dosificación convencional efectiva, incluyendo preparaciones de liberación inmediata, lenta y demorada, de administración oral, parenteral, tópica, nasal, oftálmica, óptica, sublingual, rectal, vaginal y semejantes.

Para administración oral, pueden formularse los compuestos

en preparaciones sólidas o líquidas, tales como cápsulas, píldoras, comprimidos, pastillas, grageas, líquidos fundidos, polvos, soluciones, suspensiones o emulsiones, y puede preparárselos de acuerdo con métodos conocidos en la técnica para la fabricación de composiciones farmacéuticas. Las formas de dosificación sólidas pueden comprender una cápsula, que puede ser del tipo de las cápsulas de gelatina convencionales, duras o blandas, que contienen, por ejemplo, agentes tensioactivos, lubricantes y rellenos inertes, tales como lactosa, sacarosa, fosfato de calcio y almidón de maíz.

En otra realización, pueden colocarse los compuestos de esta invención en comprimidos con bases para comprimidos convencionales, tales como lactosa, sacarosa y almidón de maíz, en combinación con aglutinantes, tales como acacia, almidón de maíz o gelatina, agentes desintegradores dirigidos a contribuir a la degradación y la disolución de el comprimido una vez administrado, tal como almidón de papa, ácido algínico, almidón de maíz y goma guar, goma tragacanto, acacia, lubricantes dirigidos a mejorar el flujo de granulación del comprimido y a evitar la adhesión del material del comprimido a las superficies de los colorantes del comprimido y los envases, por ejemplo, talco, ácido esteárico o estearato de magnesio, calcio o cinc, tinturas, agentes colorantes y agentes saborizantes, tales como menta salvaje, aceite de té del Canadá o sabor a cereza, dirigidos a mejorar las cualidades estéticas de los comprimidos y tornarlos más aceptables para el paciente. Los excipientes apropiados para usar en formas líquidas de dosificación oral incluyen fosfato de dicalcio y diluyentes, tales como agua y

alcoholes, por ejemplo, etanol, alcohol bencílico y polietilen alcoholes, con o sin la adición de un agente tensioactivo, un agente de suspensión o un agente emulsificante farmacéuticamente aceptable. Puede contener diversos materiales adicionales, tales como recubrimientos o para modificar la forma física de la unidad de dosificación. Por ejemplo, pueden recubrirse comprimidos, píldoras o cápsulas con shellac, azúcar o ambos.

Los polvos dispersables y los gránulos son apropiados para la preparación de una suspensión acuosa. Proveen el ingrediente activo en combinación con un agente dispersante o humectante, un agente de suspensión y uno o más preservadores. Los ejemplos de agentes dispersantes o humectantes y de suspensión apropiados son aquellos que se mencionaron con anterioridad. También puede haber excipientes adicionales presentes, por ejemplo, aquellos agentes edulcorantes, saborizantes y colorantes descriptos previamente.

Las composiciones farmacéuticas de esta invención también pueden tomar la forma de emulsiones de aceite en agua. La fase oleosa puede ser un aceite vegetal, tal como parafina líquida o una mezcla de aceites vegetales. Los agentes emulsionantes apropiados pueden ser (1) gomas de ocurrencia natural, tales como goma acacia y goma tragacanto, (2) fosfátidos de ocurrencia natural, tales como soja y lecitina, (3) ésteres o ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo, monooleato de sorbitano, (4) productos de la condensación de dichos ésteres parciales con óxido de etileno, por ejemplo, monooleato de polioxietilen sorbitano. Las emulsiones también pueden contener agentes edulcorantes y

saborizantes.

Pueden formularse suspensiones oleosas suspendiendo el ingrediente activo en un aceite vegetal, tal como, por ejemplo, aceite de araquís, aceite de oliva, aceite de sésamo o aceite de coco, o en un aceite mineral, tal como parafina líquida. Las suspensiones oleosas pueden contener un agente espesante, tal como, por ejemplo, cera de abeja, parafina dura o alcohol cetílico. Las suspensiones pueden contener uno o más preservadores, por ejemplo, p-hidroxibenzoato de etilo o *n*-propilo; uno o más agentes colorantes; uno o más agentes saborizantes; y uno o más agentes saborizantes, tales como sacarosa o sacarina.

Pueden formularse jarabes y elíxires con agentes edulcorantes, por ejemplo, glicerol, propilenglicol, sorbitol o sacarosa. Dichas formulaciones pueden contener un demulcente y un preservador, tal como metil y propil paraben, y agentes saborizantes y colorantes.

Los compuestos de esta invención también pueden administrarse por vía parenteral, es decir, por vía subcutánea, intravenosa, intraocular, intrasinovial, intramuscular o interperitoneal, como dosificaciones inyectables del compuesto, preferiblemente en un diluyente aceptable para el uso fisiológico, con un vehículo farmacéutico que puede ser un líquido estéril o una mezcla de líquidos, tales como agua, solución salina, dextrosa acuosa y soluciones de azúcares relacionados, un alcohol, tal como etanol, isopropanol o alcohol hexadecílico, glicoles, tal como propilenglicol o

polietilenglicol, cetales de glicerol, tales como 2,2-dimetil-1,1-dioxolan-4-metanol, éteres, tales como poli(etilenglicol) 400, un aceite, un ácido graso, un éster de ácido graso, un glicérido de ácido graso o un glicérido acetilado de ácido graso, con o sin la adición de un agente tensioactivo farmacéuticamente aceptable, tal como un jabón o un detergente, un agente de suspensión, tal como pectina, carbómeros, meticelulosa, hidroxipropilmetilcelulosa o carboximetilcelulosa, o un agente emulsionantes, y otros coadyuvantes farmacéuticos.

Los ejemplos de aceites que pueden usarse en las formulaciones parenterales de esta invención son los aceites de petróleo de origen animal, vegetal o sintético, por ejemplo, aceite de maní, aceite de soja, aceite de sésamo, aceite de semilla de algodón, aceite de maíz, aceite de oliva, aceite de vaselina y aceite mineral. Los ácidos grasos apropiados incluyen ácido oleico, ácido esteárico, ácido isoesteárico y ácido mirístico. Los ésteres de ácidos grasos apropiados son, por ejemplo, oleato de etilo y miristato de isopropilo. Los jabones apropiados incluyen sales de ácidos grasos con metales alcalinos, amonio y trietanolamina, los detergentes apropiados incluyen detergentes catiónicos, por ejemplo, haluros de dimetil dialquil amonio, haluros de alquil piridinio y acetatos de alquilamina; detergentes aniónicos, por ejemplo, sulfonatos y sulfosuccinatos de alquilo, arilo y olefina, sulfatos de alquilo, olefina, éter y monoglicéridos; detergentes no iónicos, por ejemplo, óxidos de aminas grasas, alcanolamidas de ácidos grasos, y poli(oxietilen-oxipropileno), o copolímeros de óxido de etileno y óxido de propileno; y detergentes anfotéricos, por

ejemplo, alquil-beta-aminopropionatos, y sales de amonio cuaternario de 2-alquilimidazolina, así como mezclas.

Las composiciones parenterales de esta invención típicamente contendrán entre aproximadamente 0,5% y aproximadamente 25% en peso de ingrediente activo en solución. También pueden usarse ventajosamente preservadores y amortiguadores. Con el fin de minimizar o eliminar la irritación en el sitio de inyección, dichas composiciones pueden contener un agente tensioactivo no iónico que tenga un balance hidrófilo-lipófilo (HLB) preferiblemente de entre aproximadamente 12 y aproximadamente 17. La cantidad de agente tensioactivo en dicha formulación preferiblemente varía entre aproximadamente 5% y aproximadamente 15% en peso. El agente tensioactivo puede ser un único componente con el HLB indicado previamente, o puede ser una mezcla de dos o más componentes con el HLB deseado.

Los agentes tensioactivos ilustrativos usados en las formulaciones parenterales son aquellos de la clase de los ésteres de ácidos grasos de polioxietilen sorbitano, por ejemplo, monooleato de sorbitano, y los aductos de alto peso molecular de óxido de etileno con a una base hidrofóbica, formados por la condensación de óxido de propileno con propilenglicol.

Las composiciones farmacéuticas pueden tomar la forma de suspensiones acuosas estériles inyectables. Dichas suspensiones pueden formularse de acuerdo con métodos conocidos, usando agentes dispersantes o humectantes, y agentes de suspensión apropiados, tales como, por ejemplo, carboximetilcelulosa de

sodio, metilcelulosa, hidroxipropilmetil-celulosa, alginato de sodio, polivinilpirrolidona, goma tragacanto y goma acacia; agentes dispersantes o humectantes, que pueden ser un fosfátido de ocurrencia natural, tal como la lecitina, un producto de condensación de un óxido de alquileno con un ácido graso, por ejemplo, estearato de polioxietileno, un producto de condensación de un óxido de etileno con un alcohol alifático de cadena larga, por ejemplo, heptadeca-etilenoxietanol, un producto de condensación de un óxido de etileno con un éster parcial derivado de un ácido graso y un hexitol, tal como monooleato de polioxietilen sorbitol, o un producto de condensación de un óxido de etileno con un éster parcial derivado de un ácido graso y un anhídrido de hexitol, por ejemplo, monooleato de polioxietilen sorbitano.

La preparación inyectable estéril también puede ser una solución o una suspensión inyectable estéril en un diluyente o solvente no tóxico aceptable para el uso parenteral. Los diluyentes y los solventes que pueden emplearse son, por ejemplo, agua, solución de Ringer, soluciones isotónicas de cloruro de sodio y soluciones isotónicas de glucosa. Además, pueden emplearse comúnmente aceites fijos estériles como solventes o medios de suspensión. Con este propósito, puede emplearse cualquier aceite blando fijo, incluyendo mono o diglicéridos sintéticos. Además, pueden usarse ácidos grasos, tales como ácido oleico, en la preparación de soluciones inyectables.

También puede administrarse una composición de la invención, bajo la forma de supositorios, para la administración

rectal de la droga. Pueden prepararse estas composiciones mezclando la droga con un excipiente no irritante apropiado, que sea sólido a temperaturas ordinarias, pero líquido a la temperatura del recto, y, de este modo, se funda en el recto para liberar la droga. Dichos materiales son, por ejemplo, manteca de cacao y polietilenglicol.

Otra formulación empleada en los métodos de la presente invención utiliza dispositivos de administración transdérmica ("parches"). Pueden usarse dichos parches transdérmicos para obtener una infusión continua o discontinua de los compuestos de la presente invención en cantidades controladas. La construcción y el uso de parches transdérmicos para la administración de agentes farmacéuticos es bien conocida en la técnica (véase, por ejemplo, la Patente de los EEUU Nº 5023252, publicada el 11 de Junio de 1991, incorporada en la presente documentación a modo de referencia). Pueden construirse dichos parches para lograr una administración continua, pulsátil o basada en la demanda de los agentes farmacéuticos.

Las formulaciones de liberación controlada para administración parenteral incluyen formulaciones liposomales, formulaciones de microesferas poliméricas y formulaciones de geles poliméricos, que son conocidas en la técnica.

Puede ser deseable o necesario introducir la composición farmacéutica en el paciente mediante un dispositivo de administración mecánica. La construcción y el uso de dispositivos de administración mecánica para la administración de agentes farmacéuticos son bien conocidos en la técnica. Las

técnicas directas, por ejemplo, para administrar una droga directamente al cerebro, comprenden comúnmente la colocación de un catéter de administración de la droga en el sistema ventricular del paciente para superar la barrera hematoencefálica. Se describe uno de estos sistemas de administración por implantación, usado para transportar los agentes a regiones anatómicas específicas en el cuerpo, en la Patente de los EEUU N° 5011472, publicada el 30 de Abril de 1991.

Las composiciones de la invención también pueden contener otros ingredientes de composición convencionales farmacéuticamente aceptables, generalmente conocidos como vehículos o diluyentes, según sea necesario o se lo desee. Pueden usarse procedimientos convencionales para preparar dichas composiciones en formas de dosificación apropiadas. Dichos ingredientes y procedimientos incluyen aquellos que se describen en las siguientes referencias, cada una de las cuales se incorpora en la presente documentación a modo de referencia: Powell, M.F. *et al,* "Compendium of Excipients for Parenteral Formulations" *PDA Journal of Pharmaceutical Science & Technology* **1998**, 52(5), 238-311; Strickley, R.G "Parenteral Formulations of Small Molecule Therapeutics Marketed in the United States (1999)-Part-1" *PDA Journal of Pharmaceutical Science & Technology* **1999**, 53(6), 324-349; y Nema, S. *et al*, "Excipients and Their Use in Injectable Products" *PDA Journal of Pharmaceutical Science & Technology* **1997**, 51(4), 166-171.

Los ingredientes farmacéuticos de uso común que pueden emplearse, según sea apropiado, para formular la composición

destinada a una ruta de administración determinada, incluyen:

agentes acidificantes (los ejemplos incluyen, sin limitaciones, ácido acético, ácido cítrico, ácido fumárico, ácido clorhídrico, ácido nítrico);

agentes alcalinizantes (los ejemplos incluyen, sin limitaciones, soluciones de amonio, carbonato de amonio, dietanolamina, monoetanolamina, hidróxido de potasio, borato de sodio, carbonato de sodio, hidróxido de sodio, trietanolamina, trolamina);

adsorbentes (los ejemplos incluyen, sin limitaciones, celulosa en polvo y carbón activado);

propelentes de aerosol (los ejemplos incluyen, sin limitaciones, dióxido de carbono, CCl_2F_2, $F_2ClC-CClF_2$ y $CClF_3$);

agentes de desplazamiento aéreo (los ejemplos incluyen, sin limitaciones, nitrógeno y argón);

preservadores antifúngicos (los ejemplos incluyen, sin limitaciones, ácido benzoico, butilparaben, etilparaben, metilparaben, propilparaben, benzoato de sodio);

preservadores antimicrobianos (los ejemplos incluyen, sin limitaciones, cloruro de benzalconio, cloruro de benzetonio, alcohol bencílico, cloruro de cetilpiridinio, clorobutanol, fenol, alcohol feniletílico, nitrato fenilmercúrico y timerosal);

antioxidantes (los ejemplos incluyen, sin limitaciones, ácido ascórbico, palmitato de asrcobilo, hidroxianisol butilado,

hidroxitolueno butilado, ácido hipofosforoso, monotioglicerol, galato de propilo, ascorbato de sodio, bisulfito de sodio, sulfoxilato de formaldehído de sodio, metabisulfito de sodio);

materiales aglutinantes (los ejemplos incluyen, sin limitaciones, polímeros de bloque, goma natural y sintética, poliacrilatos, poliuretanos, siliconas, polisiloxanos y copolímeros de estireno-butadieno);

agentes amortiguadores (los ejemplos incluyen, sin limitaciones, metafosfato de potasio, fosfato de dipotasio, acetato de sodio, citrato de sodio anhidro y citrato de dihidrato de sodio);

agentes de transporte (los ejemplos incluyen, sin limitaciones, jarabe de acacia, jarabe aromático, elixir aromático, jarabe de cereza, jarabe de cacao, jarabe de naranja, jarabe, aceite de maíz, aceite mineral, aceite de maní, aceite de sésamo, inyecciones bacteriostáticas de cloruro de sodio y agua bacteriostática para inyección);

agentes quelantes (los ejemplos incluyen, sin limitaciones, edetato disódico y ácido edético);

colorantes (los ejemplos incluyen, sin limitaciones, FD&C Rojo N° 3, FD&C Rojo N° 20, FD&C Yellow N° 6, FD&C Azul N° 2, D&C Verde N° 5, D&C Orange N° 5, D&C Rojo N° 8, caramelo y óxido férrico rojo);

agentes de transparentado (los ejemplos incluyen, sin limitaciones, bentonita);

agentes emulsionantes (los ejemplos incluyen, sin limitaciones, acacia, cetomacrogol, alcohol cetílico, monoestearato de

glicerilo, lecitina, monooleato de sorbitano, monostearato de polioxietileno 50);

agentes de encapsulamiento (los ejemplos incluyen, sin limitaciones, gelatina y acetato de ftalato de celulosa);

saborizantes (los ejemplos incluyen, sin limitaciones, aceite de anís, aceite de canela, cacao, mentol, aceite de naranja, aceite de menta salvaje y vainillina);

humectantes (los ejemplos incluyen, sin limitaciones, glicerol, propilenglicol y sorbitol);

agentes levigantes (los ejemplos incluyen, sin limitaciones, aceite mineral y glicerina);

aceites (los ejemplos incluyen, sin limitaciones, aceite de araquís, aceite mineral, aceite de oliva, aceite de maní, aceite de sésamo y aceite vegetal);

bases de ungüentos (los ejemplos incluyen, sin limitaciones, lanolina, ungüentos hidrofílicos, ungüentos de polietilenglicol, vaselina, vaselina hidrofílica, ungüento blanco, ungüento amarillo y ungüento de agua de rosa);

potenciadores de la penetración (administración transdérmica) (los ejemplos incluyen, sin limitaciones, alcoholes monohidroxilados o polihidroxilados, alcoholes mono o polivalentes, alcoholes grasos saturados o no saturados, ésteres grasos saturados o no saturados, ácidos dicarboxílicos saturados o no saturados, aceites esenciales, derivados de fosfatidilo, cefalina, terpenos, amidas, éteres, cetonas y ureas);

plastificadores (los ejemplos incluyen, sin limitaciones, ftalato de dietilo y glicerol);

solventes (los ejemplos incluyen, sin limitaciones, etanol, aceite de maíz, aceite de semilla de algodón, glicerol, isopropanol, aceite mineral, ácido oleico, aceite de maní, agua purificada, agua para inyección, agua estéril para inyección y agua estéril para irrigación);

agentes endurecedores (los ejemplos incluyen, sin limitaciones, alcohol cetílico, ceras de ésteres cetílicos, cera microcristalina, parafina, alcohol estearílico, cera blanca y cera amarilla);

bases para supositorios (los ejemplos incluyen, sin limitaciones, manteca de cacao y polietilenglicoles (mezclas));

agentes tensioactivos (los ejemplos incluyen, sin limitaciones, cloruro de benzalconio, nonoxinol 10, oxtoxinol 9, polisorbato 80, lauril sulfato de sodio y mono-palmitato de sorbitano);

agentes de suspensión (los ejemplos incluyen, sin limitaciones, agar, bentonita, carbómeros, carboximetilcelulosa de sodio, hidroxietil celulosa, hidroxipropil celulosa, hidroxipropil metilcelulosa, kaolina, metilcelulosa, tragacanto y goma vee);

agentes edulcorantes (los ejemplos incluyen, sin limitaciones, aspartame, dextrosa, glicerol, manitol, propilenglicol, sacarina de sodio, sorbitol y sacarosa);

anti-adherentes para comprimidos (los ejemplos incluyen, sin limitaciones, estearato de magnesio y talco);

aglutinantes para comprimidos (los ejemplos incluyen, sin limitaciones, acacia, ácido algínico, carboximetilcelulosa de sodio, azúcar compresible, etilcelulosa, gelatina, glucosa líquida, metilcelulosa, polivinil pirrolidona no reticulada y almidón pregelificado);

diluyentes para comprimidos y cápsulas (los ejemplos incluyen, sin limitaciones, fosfato de calcio dibásico, kaolina, lactosa, manitol, celulosa microcristalina, celulosa en polvo, carbonato de calcio precipitado, carbonato de sodio, fosfato de sodio, sorbitol y almidón);

agentes de recubrimiento para comprimidos (los ejemplos incluyen, sin limitaciones, glucosa líquida, hidroxietil celulosa, hidroxipropil celulosa, hidroxipropil metilcelulosa, metilcelulosa, etilcelulosa, acetato de ftalato de celulosa y shellac);

excipientes para la compresión directa de comprimidos (los ejemplos incluyen, sin limitaciones, fosfato de calcio dibásico);

desintegradores para comprimidos (los ejemplos incluyen, sin limitaciones, ácido algínico, carboximetilcelulosa de calcio, celulosa microcristalina, poloacrilina de potasio, polivinilpirrolidona reticulada, alginato de sodio, glicolato de almidón de sodio y almidón);

deslizantes para comprimidos (los ejemplos incluyen, sin limitaciones, sílice coloidal, almidón de maíz y talco);

lubricantes para comprimidos (los ejemplos incluyen, sin

limitaciones, estearato de calcio, estearato de magnesio, aceite mineral, ácido esteárico y estearato de cinc);

opacantes para comprimidos/cápsulas (los ejemplos incluyen, sin limitaciones, dióxido de titanio);

agentes de acabado de comprimidos (los ejemplos incluyen, sin limitaciones, cera de carnuba y cera blanca);

agentes espesantes (los ejemplos incluyen, sin limitaciones, cera de abeja, alcohol cetílico y parafina);

agentes para proporcionar tonicidad (los ejemplos incluyen, sin limitaciones, dextrosa y cloruro de sodio);

agentes para incrementar la viscosidad (los ejemplos incluyen, sin limitaciones, ácido algínico, bentonita, carbómeros, carboximetilcelulosa de sodio, metilcelulosa, polivinil pirrolidona, alginato de sodio y tragacanto); y

agentes humectantes (los ejemplos incluyen, sin limitaciones, heptadecaetilen oxicetanol, lecitinas, monooleato de sorbitol, monooleato de polioxietilen sorbitol, y estearato de polioxietileno).

Pueden ilustrarse las composiciones farmacéuticas de acuerdo con la presente invención como se indica a continuación:

Solución estéril IV: Puede prepararse una solución de 5 mg/ml del compuesto deseado de esta invención usando agua estéril para inyección, y puede ajustarse el pH según sea necesario. La solución se diluye para la administración a 1 – 2 mg/ml con dextrosa estéril 5% y se administra como una

infusión IV sobre un período de 60 minutos aproximadamente.

Polvo liofilizado para una administración IV: Se puede preparar una preparación estéril con (i) 100 – 1000 mg del compuesto deseado de esta invención como un polvo liofilizado, (ii) citrato de sodio 32– 327 mg/ml, y (iii) 300 – 3000 mg de Dextran 40. La formulación se reconstituye con salina o dextrosa 5% estéril, inyectable hasta una concentración de entre 10 y 20 mg/ml, que se diluye aún más con salina o dextrosa 5% hasta 0,2 – 0,4 mg/ml, y luego es administrada ya sea como un bolo IV o por infusión IV sobre un período de 15 – 60 minutos.

Suspensión intramuscular: Puede prepararse la siguiente solución o suspensión para inyección intramuscular:

50 mg/ml del compuesto insoluble en agua deseado de esta invención

5 mg/ml de carboximetilcelulosa de sodio

4 mg/ml de TWEEN 80

9 mg/ml de cloruro de sodio

9 mg/ml de alcohol bencílico

Cápsulas con recubrimiento duro: Se prepara una gran cantidad de cápsulas rellenando cápsulas de gelatina convencionales de dos piezas con 100 mg de ingrediente activo en polvo, 150 mg de lactosa, 50 mg de celulosa y 6 mg de estearato de magnesio cada una.

Cápsulas de gelatina blanda: Se prepara una mezcla de ingrediente activo en un aceite digerible, tal como aceite

de soja, aceite de semilla de algodón o aceite de oliva, y se la inyecta por medio de una bomba de desplazamiento positivo en gelatina fundida, de modo de formar cápsulas de gelatina blandas que contienen 100 mg de ingrediente activo. Las cápsulas se lavan y secan. Puede disolverse el ingrediente activo en una mezcla de polietilenglicol, glicerina y sorbitol para preparar una mezcla medicinal miscible con agua.

Comprimidos: Se prepara una gran cantidad de comprimidos empleando procedimientos convencionales, de modo que la unidad de dosificación comprende 100 mg de ingrediente activo, 0,2 mg de dióxido de silicio coloidal, 5 mg de estearato de magnesio, 275 mg de celulosa microcristalina, 11 mg de almidón y 98,8 mg de lactosa. Pueden aplicarse recubrimientos acuosos y no acuosos apropiados para incrementar la palatabilidad, mejorar la elegancia y la estabilidad o demorar la absorción.

Comprimidos/cápsulas de liberación inmediata: Son formas de dosificación sólidas orales elaboradas mediante procesos convencionales y novedosos. Estas unidades se toman por vía oral sin agua para una disolución y una administración inmediata de la medicación. Se mezcla el ingrediente activo en un líquido que contiene un ingrediente, tal como azúcar, gelatina, pectina y edulcorantes. Estos líquidos se solidifican en comprimidos o cápsulas sólidas mediante técnicas de secado por congelamiento y extracción en estado sólido. Los compuestos de droga pueden comprimirse con azúcares y polímeros viscoelásticos y termoelásticos para producir matrices porosas de liberación

inmediata que no requieren de agua.

Terapias de combinación

Los compuestos de esta invención pueden administrarse como el único agente farmacéutico o en combinación con uno o más agentes farmacéuticos adicionales, donde la combinación no posee efectos adversos inaceptables. La presente invención también se relaciona con estas combinaciones. Por ejemplo, pueden combinarse los compuestos de esta invención con agentes anti-hiperproliferativos conocidos o con agentes para tratar otras indicaciones, y semejantes, así como con mezclas y combinaciones de éstos. Otros agentes que se pueden indicar incluyen, pero en un sentido no limitativo, agentes anti-angiogénicos, inhibidores mitóticos, agentes alquilantes, antimetabolitos, antibióticos intercaladores de ADN, inhibidores de factores de crecimiento, inhibidores del ciclo celular, inhibidores de enzimas, inhibidores de topoisomerasa, modificadores de la respuesta biológica o antihormonas.

El agente farmacéutico adicional puede ser afinitor, aldesleuquina, ácido alendrónico, alfaferona, alitretinoína, alopurinol, aloprim, aloxi, altretamina, aminoglutetimida, amifostina, amrubicina, amsacrina, anastrozol, anzmet, aranesp, arglabina, trióxido de arsénico, aromasina, 5-azacitidina, azatioprina, BCG o *tice* BCG, bestatina, acetato de betametasona, fosfato de betametasona sódica, bexaroteno, sulfato de bleomicina, broxuridina, bortezomib, busulfán, calcitonina, campat, capecitabina, carboplatino, casodex, cefesona, celmoleuquina, cerubidina, clorambucilo, cisplatino, cladribina,

cladribina, ácido clodrónico, ciclofosfamida, citarabina, dacarbazina, dactinomicina, DaunoXome, decadrón, fosfato de decadrón, delestrógeno, denileuquina diftitox, depo-medrol, deslorelina, dexrazoxano, dietilestilbestrol, diflucan, docetaxel, doxifluridina, doxorubicina, dronabinol, DW-166HC, eligard, elitek, ellence, emend, epirubicina, epoetina alfa, epógeno, eptaplatino, ergamisol, estrace, estradiol, fosfato de estramustina sódica, etinilestradiol, etiol, ácido etidrónico, etopofos, etopósido, fadrozol, farstón, filgrastim, finasteride, fligrastim, floxuridina, fluconazol, fludarabina, monofosfato de 5-fluorodeoxiuridina, 5-fluorouracilo (5-FU), fluoximesterona, flutamida, formestane, fosteabine, fotemustina, fulvestrant, gammagard, gemcitabine, gemtuzumab, gleevec, gliadel, goserelina, granisetrón HCl, histrelina, hicamtina, hidrocortona, eritro-hidroxinoniladenina, hidroxiurea, ibritumomab tiuxetan, idarubicina, ifosfamida, interferón alfa, interferón-alfa 2, interferón alfa-2A, interferón alfa-2B, interferón alfa-n1, interferón alfa-n3, interferón beta, interferón gamma-1a, interleuquina-2, intrón A, iressa, irinotecan, kitrilo, lapatinib, sulfato de lentinan, letrozol, leucovorina, leuprolida, acetato de leuprolida, levamisol, sal de calcio del ácido levofolínico, levotroide, levoxilo, lomustine, lonidamina, marinol, mecloretamina, mecobalamina, acetato de medroxiprogesterona, acetato de megestrol, melfalán, menest, 6-mercaptopurina, Mesna, metotrexato, metvix, miltefosina, minociclina, mitomicina C, mitotano, mitoxantrona, Modrenal, Miocet, nedaplatino, neulasta, neumega, neupogen, nilutamida, nolvadex, NSC-631570, OCT-43, octreotida,

ondansetrón HCl, orapred, oxaliplatino, paclitaxel, pediapred, pegaspargase, Pegasis, pentostatina, picibanilo, pilocarpina HCl, pirarubicina, plicamicina, porfímero sódico, prednimustina, prednisolona, prednisona, premarina, procarbazina, procrit, raltitrexed, rebif, etidronato de renio-186, rituximab, roferón-A, romurtida, salagen, sandostatina, sargramostim, semustina, sizofiran, sobuzoxano, solu-medrol, ácido esparfósico, terapia con células madre, estreptozocina, cloruro de estroncio-89, sunitinib, sintroide, tamoxifeno, tamsulosina, tasonermin, tastolactona, taxotere, teceleuquina, temozolomida, tenipósido, propionato de testosterona, testred, tioguanina, tiotepa, tirotropina, ácido tiludrónico, topotecan, toremifeno, tositumomab, trastuzumab, treosulfán, tretinoína, trexal, trimetilmelamina, trimetrexato, acetato de triptorelina, pamoato de triptorelina, UFT, uridina, valrubicina, vesnarinona, vinblastina, vincristina, vindesina, vinorelbina, virulizina, zinecard, estimalamer zinostatina, zofrán, ABI-007, acolbifeno, actinmune, afinitak, aminopterina, arzoxifeno, asoprisnilo, atamestano, atrasentán, BAY 43-9006 (sorafenib), avastina, CCI-779, CDC-501, celebrex, cetuximab, crisnatol, acetato de ciproterona, decitabina, DN-101, doxorubicina-MTC, dSLIM, dutasterida, edotecarina, eflornitina, exatecan, fenretinide, diclorhidrato de histamina, implantae de hidrogel de histrelina, holmio-166 DOTMP, ácido ibandrónico, interferón gamma, intrón-PEG, ixabepilona, hemocianina de lapa, L-651582, lanreotide, lasofoxifeno, libra, lonafarnib, miproxifeno, minodronato, MS-209, MTP-PE liposómico, MX-6, nafarelina, nemorubicina, neovastat, nolatrexed, oblimersen, onco-TCS, osidem, paclitaxel

poliglutamato, pamidronato disódico, PN-401, QS-21, quazepam, R-1549, raloxifeno, ranpirnase, ácido 13-cis-retinoico, satraplatino, seocalcitol, T-138067, tarceva, taxoprexina, timosina alfa 1, tiazofurina, tipifarnib, tirapazamina, TLK-286, toremifeno, TransMID-107R, valspodar, vapreotide, vatalanib, verteporfina, vinflunina, Z-100, ácido zoledrónico o combinaciones de éstos.

Los agentes anti-hiperproliferativos opcionales que pueden agregarse a la composición incluyen, sin limitaciones, los compuestos indicados para los regímenes de quimioterapia del cáncer en la 11ª edición de *Merck Index*, (1996), que se incorpora en la presente documentación a modo de referencia, tales como asparraginasa, bleomicina, carboplatina, carmustina, clorambucilo, cisplatina, colaspasa, ciclofosfamida, citarabina, dacarbazina, dactinomicina, daunorubicina, doxorrubicina (adriamicina), epirrubicina, epotilona, un derivado de epotilona , etopósido, 5-fluorouracilo, hexametilmelamina, hidroxiurea, ifosfamida, irinotecan, leucovorina, lomustina, mecloretamina, 6-mercaptopurina, mesna, metotrexato, mitomicina C, mitoxantrona, prednisolona, prednisona, procarbazina, raloxifen, estreptozocina, tamoxifeno, tioguanina, topotecan, vinblastina, vincristina y vindesina.

Otros agentes anti-hiperproliferativos apropiados para usar con la composición de la invención incluyen, sin limitaciones, aquellos compuestos que pueden usarse en el tratamiento de enfermedades neoplásticas, según se indica en *Goodman y Gilman's: The Pharmacological Basis de Therapeutics* (novena edición), editado por Molinoff et al., publicado por McGraw-

Hill, páginas 1225-1287, (1996), que se incorpora en la presente documentación a modo de referencia, tales como aminoglutetimida, L-asparraginasa, azatioprina, 5-azacitidina, cladribina, busulfan, dietilstilbestrol, 2'0,2'-difluorodeoxicitidina, docetaxel, eritroidroxinoniladenina, etinil estradiol, 5-fluorodesoxiuridina, monofosfato de 5-fluorodeoxiuridina, fosfato de fludarabina, fluoximesterona, flutamida, caproato de hidroxiprogesterona, idarrubicina, interferón, acetato de medroxiprogesterona, acetato de megestrol, melfalan, mitotano, paclitaxel, pentostatina, N-fosfonoacetil-L-aspartato (PALA), plicamicina, semustina, tenipósido, propionato de testosterona, tiotepa, trimetilmelamina, uridina y vinorelbina.

Otros agentes anti-hiperproliferativos apropiados para usar con la composición de la invención incluyen, sin limitaciones, otros agentes anti-cáncer, tales como epotilona y sus derivados, irinotecan, raloxifeno y topotecan.

Los compuestos de la invención también se pueden administrar en combinación con compuestos terapéuticos de proteínas. Dichos compuestos terapéuticos de proteínas apropiados para el tratamiento de cáncer u otros trastornos angiogénicos y para su uso con las composiciones de la invención incluyen, pero en un sentido no limitativo, un interferón (por ejemplo, interferón.alfa.,.beta., o.gamma.) anticuerpos monoclonales supraagonista, Tuebingen, vacuna de la proteína TRP-1, Colostrinina, anticuerpo anti-FAP, YH-16, gemtuzumab, infliximab, cetuximab, trastuzumab, denileuquina diftitox, rituximab, timosina alfa 1, bevacizumab, mecasermina, mecasermina rinfabato, oprelvequina, natalizumab, rhMBL, MFE-CP1

+ ZD-2767-P, ABT-828, inmunotoxina específica de ErbB2, SGN-35, MT-103, rinfabato, AS-1402, B43-genisteína, compuestos radioinmunoterapéuticos basados en L-19, AC-9301, vacuna NY-ESO-1, IMC-1C11, CT-322, rhCC10, r(m)CRP, MORAb-009, aviscumina, MDX-1307, vacuna Her-2, APC-8024, NGR-hTNF, rhH1,3, IGN-311, Endostatina, volociximab, PRO-1762, lexatumumab, SGN-40, pertuzumab, EMD-273063, proteína de fusión L19-IL-2, PRX-321, CNTO-328, MDX-214, tigapotide, CAT-3888, labetuzumab, lintuzumab ligado a radioisótopos emisores de partículas alfa, EM-1421, vacuna HiperAcute, tucotuzumab celmoleuquina, galiximab, HPV-16-E7, Javelin: cáncer de próstata, Javelin: melanoma, vacuna NY-ESO-1, vacuna EGF, CYT-004-MelQbG10, péptido WT1, oregovomab, ofatumumab, zalutumumab, cintredequina besudotox, WX-G250, Albuferón, aflibercept, denosumab, vacuna, CTP-37, efungumab o 131I-chTNT-1/B. Los anticuerpos monoclonales de utilidad como compuestos terapéuticos de proteínas incluyen, pero en un sentido no limitativo, muromonab-CD3, abciximab, edrecolomab, daclizumab, gentuzumab, alemtuzumab, ibritumomab, cetuximab, bevicizumab, efalizumab, adalimumab, omalizumab, muromomab-CD3, rituximab, daclizumab, trastuzumab, palivizumab, basiliximab e infliximab.

Los compuestos de la invención también se pueden combinar con agentes terapéuticos biológicos, como por ejemplo anticuerpos (por ejemplo avastina, rituxan, erbitux, herceptina), o proteínas recombinantes.

Los compuestos de la invención también se pueden combinar con agentes antiangiogénesis , tales como, por ejemplo, avastina, axitinib, DAST, recentin, sorafenib o sunitinib.

También son posibles las combinaciones con inhibidores de proteasomas o inhibidores de mTOR , o antihormonas o inhibidores de enzimas metabólicas esteroides.

En general, el uso de agentes citotóxicos y/o citostáticos en combinación con un compuesto o una composición de la presente invención contribuirá a:

(1) obtener una mayor eficacia en la reducción del crecimiento de un tumor, o aún permitirá eliminar el tumor, en comparación con la administración de cada agente por separado,

(2) poder administrar menores cantidades de los agentes quimioterapéuticos empleados,

(3) proporcionar un tratamiento quimioterapéutico que sea bien tolerado en el paciente, con menos complicaciones farmacológicas perjudiciales que las observadas con quimioterapias con agentes individuales y otras terapias de combinación,

(4) poder tratar un espectro más amplio de distintos tipos de cáncer en mamíferos, especialmente humanos,

(5) obtener una tasa de respuesta más elevada entre los pacientes tratados,

(6) obtener un tiempo de supervivencia más largo entre los pacientes tratados, en comparación con los tratamientos quimioterapéuticos convencionales,

(7) lograr un tiempo de progresión tumoral más prolongado, y/u

(8) obtener resultados de eficacia y tolerabilidad al menos tan buenos como los obtenidos con el uso de los agentes por

separado, en comparación con las instancias conocidas donde otras combinaciones de agentes anti-cáncer produzcan efectos de antagonismo.

Métodos para sensibilizar células a la radiación

En una forma de realización distinta de la presente invención, se puede usar un compuesto de la presente invención para sensibilizar una célula a la radiación. Es decir, el tratamiento de una célula con un compuesto de la presente invención antes de tratar la célula con radiación vuelve a la célula más susceptible a los daños del ADN y a la muerte celular de lo que sería en ausencia de cualquier tratamiento con un compuesto de la invención. En un aspecto, la célula es tratada con al menos un compuesto de la invención.

Por consiguiente, la presente invención también provee un método para matar una célula, donde a dicha célula se le administra uno o más compuestos de la invención en combinación con una terapia convencional de radiación.

La presente invención también provee un método para volver una célula más susceptible a la muerte celular, donde la célula es tratada con uno o más compuestos de la invención antes de tratar la célula para causar o inducir muerte celular. En un aspecto, después de tratar la célula con uno o más compuestos de la invención, la célula es tratada con al menos un compuesto, o mediante al menos un método, o una combinación de ambos, con el fin de causar daño en el ADN con el propósito de inhibir la función de la célula normal o de matar la célula.

En una forma de realización, se mata una célula mediante tratamiento de dicha célula con al menos un agente perjudicial para el ADN. Es decir, después de tratar una célula con uno o más compuestos de la invención para sensibilizar la célula a la muerte celular, la célula es tratada con al menos un agente perjudicial para el ADN para matar a la célula. Los agentes perjudiciales para el ADN de utilidad en la presente invención incluyen, pero en un sentido no limitativo, agentes quimioterapéuticos (por ejemplo, cisplatino), radiación ionizante (rayos X, radiación ultravioleta), agentes carcinogénicos y agentes mutagénicos.

En otra realización, se mata una célula mediante tratamiento de la célula con al menos un método que causa o induce daño en el ADN. Dichos métodos incluyen, pero en un sentido no limitativo, activación de una vía de señalización celular que da como resultado daños en el ADN cuando la vía es activada, inhibición de una vía de señalización celular que da como resultado daños en el ADN cuando la vía es inhibida e inducción de un cambio bioquímico en una célula, donde dicho cambio da como resultado daños en el ADN. A modo de ejemplo no limitativo, se puede inhibir una vía de reparación de ADN en una célula, impidiendo de esa manera la reparación del daño en el ADN y dando como resultado una acumulación anormal de daños en el ADN en una célula.

En un aspecto de la invención, se administra un compuesto de la invención a una célula antes de aplicar radiación u otra inducción de daño del ADN en la célula. En otro aspecto de la invención, se administra un compuesto de la invención a una

célula de manera concomitante con una radiación u otra inducción de daño del ADN en la célula. En aún otro aspecto de la invención, se administra un compuesto de la invención a una célula de manera inmediatamente después que ha comenzado una radiación u otra inducción de daño del ADN en la célula.

En otro aspecto, la célula es *in vitro*. En otra realización, la célula es *in vivo*.

Como se mencionó con anterioridad, sorprendentemente se ha descubierto que los compuestos de la presente invención inhiben Mps-1, por lo que pueden usarse para el tratamiento o la profilaxis de enfermedades relacionadas con un crecimiento, una proliferación y/o una supervivencia celular descontrolada, con una respuesta inmune celular inapropiada o con una respuesta inflamatoria celular inapropiada, o de enfermedades que están acompañadas por un crecimiento, una proliferación y/o una supervivencia celular descontrolada, por una respuesta inmune celular inapropiada o por una respuesta inflamatoria celular inapropiada, particularmente donde el crecimiento, la proliferación y/o la supervivencia celular descontrolada, la respuesta inmune celular inapropiada o la respuesta inflamatoria celular inapropiada están mediados por Mps-1, por ejemplo, los tumores hematológicos, los tumores sólidos y/o sus metástasis, por ejemplo, las leucemias y el síndrome mielodisplástico, los linfomas malignos, los tumores de la cabeza y el cuello, incluyendo los tumores cerebrales y las metástasis cerebrales, los tumores del tórax, incluyendo los tumores de las células pulmonares no

pequeñas y de las células pulmonares pequeñas, los tumores gastrointestinales, los tumores endocrinos, los tumores mamarios y otros tumores ginecológicos, los tumores del tracto urinario, incluyendo los tumores renales, vesicales y prostáticos, los tumores en la piel y los sarcomas, y/o sus metástasis.

Por consiguiente, de acuerdo con otro aspecto, la presente invención abarca un compuesto de la fórmula general (I), o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato o una sal de éste, particularmente una sal farmacéuticamente aceptable de éste, o una mezcla que lo contiene, como se describe y se define en la presente, para usarlo en el tratamiento o la profilaxis de una enfermedad, como se mencionó con anterioridad.

En consecuencia, otro aspecto particular de la presente invención es el uso de un compuesto de la fórmula general (I), como se describió con anterioridad, o de un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato o una sal de éste, particularmente de una sal farmacéuticamente aceptable de éste, o de una mezcla que lo contiene, para la profilaxis o el tratamiento de una enfermedad.

Entonces, otro aspecto particular de la presente invención es el uso de un compuesto de la fórmula general (I) como se describió con anterioridad para preparar una composición farmacéutica para el tratamiento o la profilaxis de una enfermedad.

Las enfermedades mencionadas en los dos párrafos

precedentes son enfermedades relacionadas con un crecimiento, una proliferación y/o una supervivencia celular descontrolada, con una respuesta inmune celular inapropiada o con una respuesta inflamatoria celular inapropiada, o enfermedades que están acompañadas por un crecimiento, una proliferación y/o una supervivencia celular descontrolada, por una respuesta inmune celular inapropiada o por una respuesta inflamatoria celular inapropiada, particularmente donde el crecimiento, la proliferación y/o la supervivencia celular descontrolada, la respuesta inmune celular inapropiada o la respuesta inflamatoria celular inapropiada están mediados por Mps-1, por ejemplo, los tumores hematológicos, los tumores sólidos y/o sus metástasis, por ejemplo, las leucemias y el síndrome mielodisplástico, los linfomas malignos, los tumores de la cabeza y el cuello, incluyendo los tumores cerebrales y las metástasis cerebrales, los tumores del tórax, incluyendo los tumores de las células pulmonares no pequeñas y de las células pulmonares pequeñas, los tumores gastrointestinales, los tumores endocrinos, los tumores mamarios y otros tumores ginecológicos, los tumores del tracto urinario, incluyendo los tumores renales, vesicales y prostáticos, los tumores en la piel y los sarcomas, y/o sus metástasis.

En el contexto de la presente invención y en función del uso que se le da en la presente, el término “inapropiado”, particularmente en el contexto de “las respuestas inmunes celulares inapropiadas o las respuestas

inflamatorias celulares inapropiadas", ha de hacer referencia a una respuesta que es menor o mayor que la normal y que está asociada a la patología de dichas enfermedades, que es responsable de dicha patología o que es el resultado de dicha patología.

Preferiblemente, el uso es en el tratamiento o la profilaxis de enfermedades, donde las enfermedades son los tumores hematológicos, los tumores sólidos y/o sus metástasis.

Método para tratar trastornos de hiperproliferación

La presente invención se relaciona con un método para usar los compuestos de la presente invención y composiciones con los mismos, en el tratamiento de trastornos hiperproliferativos de mamífero. Los compuestos se pueden utilizar para inhibir, bloquear, reducir, disminuir, etc., la proliferación celular y/o división celular y/o produce apoptosis. Este método comprende administrarle a un mamífero que lo necesita, incluyendo un ser humano, una cantidad de un compuesto de esta invención, o una sal farmacéuticamente aceptable, isómero, forma polimórfica, metabolito, hidrato, solvato o éster de ésta; etc. que sea eficaz para tratar el trastorno. Los trastornos hiperproliferativos incluyen, pero sin limitaciones, por ejemplo, psoriasis, queloides y otras hiperplasias que afectan a la piel, hiperplasia de próstata benigna (BPH), tumores sólidos, tales como cáncer de mama, del tracto respiratorio, cerebro, órganos reproductores, tracto digestivo, tracto urinario, ojos, hígado, piel, cabeza y cuello, tiroides, paratiroides y sus metástasis distantes. Estos trastornos también incluyen linfoma,

sarcomas y leucemias.

Los ejemplos de cáncer de mama incluyen, sin limitaciones, carcinoma ductal invasivo, carcinoma lobular invasivo, carcinoma ductal in situ y carcinoma lobular in situ.

Los ejemplos de cánceres del tracto respiratorio incluyen, sin limitaciones, carcinomas de las células pulmonares pequeñas y no pequeñas, así como adenomas bronquiales y blastomas pleuropulmonares.

Los ejemplos de cánceres de cerebro incluyen, sin limitaciones gliomas del tallo cerebral y el hipotálamo, astrocitoma cerebelar y cerebral, meduloblastoma, ependimoma, así como tumores neuroectodermales y pineales.

Los tumores de los órganos reproductivos masculinos incluyen, sin limitaciones, cáncer de próstata y testicular. Los tumores de los órganos reproductivos femeninos incluyen, sin limitaciones, cáncer del endometrio, cervical, ovárico, vaginal y vulvar, así como sarcoma de útero.

Los tumores del tracto digestivo incluyen, sin limitaciones, cánceres anales, de colon, colorrectales, esofágico, de vejiga, gástricos, pancreáticos, rectales, del intestino delgado y de las glándulas salivales.

Los tumores del tracto urinario incluyen, pero en un sentido no limitativo, cáncer de vejiga, pene, riñón, pelvis renal, uréter, uretral y papilar renal humano.

Los cánceres oculares incluyen, sin limitaciones, melanoma intraocular y retinoblastoma.

Los ejemplos de cánceres hepáticos incluyen, sin limitaciones, carcinoma hepatocelular (carcinomas de células hepáticas con o sin variantes fibrolamelares), colangiocarcinoma (carcinoma del conducto biliar intrahepático) y colangiocarcinoma hepatocelular mixto.

Los cánceres de piel incluyen, sin limitaciones, carcinoma de células escamosas, sarcoma de Kaposi, melanoma maligno, cáncer de células cutáneas de Merkel y cáncer cutáneo distinto del melanoma.

Los distintos tipos de cáncer de cabeza y cuello incluyen, pero en un sentido no limitativo, de laringe, de hipofaringe, nasofaringeo, orofaringeo, labio y de la cavidad oral y de células escamosas. Los linfomas incluyen, pero en un sentido no limitativo, linfoma relacionado con SIDA, linfoma no Hodgkin, linfoma de linfocitos T cutáneo, linfoma de Burkitt, enfermedad de Hodgkin y linfoma del sistema nervioso central.

Los sarcomas incluyen, sin limitaciones, sarcoma de los tejidos blandos, osteosarcoma, histiocitoma fibroso maligno, linfosarcoma y rabdomiosarcoma.

Las leucemias incluyen, sin limitaciones, leucemia mieloide aguda, leucemia linfoblástica aguda, leucemia linfocítica crónica, leucemia mielógena crónica y leucemia de las células pilosas.

Estos trastornos han sido todos bien caracterizados en humanos, pero también existen con una etiología similar en otros mamíferos, y pueden tratarse administrando las composiciones

farmacéuticas de la presente invención.

El término “tratando” o “tratamiento”, según se estableció en todo este documento de usa de la manera convencional, por ejemplo, el manejo o cuidado de un sujeto con el propósito de combatir, aminorar, reducir, aliviar, mejorar la condición, etc., de una enfermedad o trastorno, tal como un carcinoma.

Métodos de tratamiento de trastornos por quinasas

La presente invención también provee métodos para el tratamiento de los trastornos asociados con una actividad de quinasa extracelular regulada por mitógenos aberrante, incluyendo, pero sin limitaciones, accidente cerebrovascular, insuficiencia cardíaca, hepatomegalia, cardiomegalia, diabetes, mal de Alzheimer, fibrosis quística, síntomas de rechazo de xenoinjerto, shock séptico o asma.

Las cantidades eficaces de los compuestos de la presente invención se pueden usar para tratar dichos trastornos, incluyendo las enfermedades (por ejemplo, cáncer) mencionadas antes en la sección de Antecedentes. Sin embargo, dichos tipos de cáncer y otras enfermedades se pueden tratar con los compuestos de la presente invención, en forma independiente del mecanismo de acción y/o la relación entre la quinasa y el trastorno.

La frase “actividad de quinasa aberrante” o “actividad tirosina quinasa aberrante” incluye cualquier expresión o actividad anormal del gen que codifica la quinasa o del polipéptido codificado por el mismo. Los ejemplos de dicha

actividad aberrante incluyen, pero en un sentido no limitativo, la sobreexpresión del gen o polipéptido; la amplificación del gen; mutaciones que producen una actividad de quinasa constitutivamente activa o hiperactiva; mutaciones de genes, supresiones, sustituciones, adiciones, etc.

La presente invención también provee métodos para inhibir una actividad de quinasa, en especial de una quinasa extracelular regulada por mitógenos, que comprende administrar una cantidad eficaz de un compuesto de la presente invención, incluyendo sales, formas polimórficas, metabolitos, hidratos, solvatos, prodrogas (por ejemplo: ésteres) de éste, y formas diaestereoisoméricas de éste. La actividad de quinasa se puede inhibir en células (por ejemplo, *in vitro*), o en las células de un sujeto mamífero, en especial un paciente humano que necesita de dicho tratamiento.

Métodos de tratamiento de trastornos angiogénicos

La presente invención también provee métodos de tratamiento de trastornos y enfermedades asociados con una angiogénesis excesiva y/o anormal.

Una expresión inapropiada y ectópica de la angiogénesis puede ser perjudicial para un organismo. Hay un número de condiciones patológicas asociadas con el crecimiento de los vasos sanguíneos extraños. Estas incluyen, por ejemplo, retinopatía diabética, oclusión isquémica de la vena retinal y retinopatía de premadurez (Aiello et al. *New Engl. J. Med.* **1994**, *331*, 1480; Peer et al. *Lab. Invest.* **1995**, *72*, 638), degeneración macular relacionada con la edad (AMD; véase, Lopez et al.

Invest. Opthalmol. Vis. Sci. **1996**, *37*, 855), glaucoma neovascular, psoriasis, fibroplasias retrolentales, angiofibroma, inflamación, artritis reumatoide (RA), restenosis, restenosis *in-stent*, restenosis de injertos vasculares, etc. Además, el mayor suministro de sangre asociado con el tejido canceroso y neoplásico, estimula el crecimiento, lo que conduce a un agrandamiento rápido de tumores y metástasis. Más aún, el crecimiento de nuevos vasos sanguíneos y linfáticos en un tumor provee una ruta de escape para las células renegadas, estimula la metástasis y en consecuencia la dispersión del cáncer. Por consiguiente, los compuestos de la presente invención se pueden utilizar para tratar y/o prevenir cualquiera de los trastornos debido a una angiogénesis mencionados previamente, por ejemplo, por inhibición y/o reducción de la formación de vasos sanguíneos; por inhibición, bloqueo, reducción, disminución, etc. de la proliferación celular endotelial u otros tipos relacionados con la angiogénesis, así como para causar la muerte celular o apoptosis de dichos tipos celulares.

Dosis y administración

Sobre la base de las técnicas de laboratorio estándar conocidas para evaluar los compuestos de utilidad en el tratamiento de trastornos hiperproliferativos y trastornos angiogénicos, mediante pruebas de toxicidad estándar y mediante ensayos farmacológicos estándar para determinar el tratamiento de las condiciones identificadas previamente en mamíferos, y por comparación de estos resultados con los resultados de los medicamentos conocidos que se usan para tratar estas condiciones, la dosificación eficaz de los compuestos de esta

invención puede determinarse fácilmente para el tratamiento de cada indicación deseada. La cantidad de ingrediente activo a administrar en el tratamiento de una de estas condiciones puede variar ampliamente de acuerdo con dichas consideraciones, tales como el compuesto particular y la unidad de dosificación empleada, el modo de administración, el período de tratamiento, la edad y el sexo del paciente tratado, y la naturaleza y la extensión de la condición a tratar.

La cantidad total de ingrediente activo que será administrada varía en general en el rango entre aproximadamente 0,001 mg/kg y aproximadamente 200 mg/kg de peso corporal por día y preferentemente entre aproximadamente 0,01 mg/kg y aproximadamente 20 mg/kg de peso corporal por día. Los programas de dosificación clínicamente útiles varían en un rango entre una dosificación de una a tres veces por día y una dosificación una vez cada cuatro semanas. Además, el "descanso de la droga" durante el cual un paciente no recibe dosis de la droga por un período de tiempo determinado, puede ser beneficioso para el balance global entre efecto farmacológico y la capacidad de tolerancia. Una dosificación unitaria puede contener entre aproximadamente 0,5 mg y aproximadamente 1500 mg de ingrediente activo, y puede ser administrada una o más veces por día o menos que una vez por día. La dosificación diaria promedio para una administración por inyección, incluyendo inyecciones intravenosas, intramusculares, subcutáneas y parenterales, y el uso de técnicas de infusión, será preferiblemente de entre 0,01 y 200 mg/kg de peso corporal total. El régimen de dosificación diaria rectal promedio será preferiblemente de entre 0,01 y 200

mg/kg de peso corporal total. El régimen de dosificación diaria vaginal promedio será preferiblemente de entre 0,01 y 200 mg/kg de peso corporal total. El régimen de dosificación diaria tópica promedio será preferiblemente de entre 0,1 y 200 mg, donde las dosis se administran entre una y cuatro veces por día. La concentración transdérmica será preferentemente la que se requiere para mantener una dosis diaria entre 0,01 y 200 mg/kg. El régimen de dosificación diaria promedio por inhalación comprenderá preferentemente entre 0,01 y 100 mg/kg de peso corporal total.

Por supuesto, el régimen de dosificación inicial y continuo específico para cada paciente varía de acuerdo con la naturaleza y severidad de la afección como lo podrá determinar el médico a cargo del paciente, con la actividad del compuesto específico empleado, la edad y condición general del paciente, el tiempo de administración, la ruta de administración, la velocidad de excreción de la droga, las combinaciones de droga y semejantes. El modo de tratamiento deseado y la cantidad de dosis de un compuesto de la presente invención, o una sal, un éster o una composición farmacéuticamente aceptable de éste, pueden ser evaluados por aquellos versados en la técnica, usando pruebas de tratamiento convencionales.

Preferiblemente, las enfermedades relacionadas con dicho método son los tumores hematológicos, los tumores sólidos y/o sus metástasis.

Los compuestos de la presente invención se pueden usar en particular en terapias y prevención, es decir, profilaxis, del crecimiento y metástasis de tumores,

especialmente de los tumores sólidos de todas las indicaciones y etapas con o sin pretratamiento del crecimiento tumoral.

Los métodos para evaluar una propiedad farmacológica o farmacéutica particular son bien conocidos por aquellos versados en la técnica.

Los experimentos de ensayo de ejemplos descritos en la presente sirven para ilustrar la presente invención y la invención no está limitada a los ejemplos dados.

Ensayo biológico: ensayo de proliferación

Se sembraron células tumorales cultivadas (MCF7, células de un carcinoma mamario humano dependiente de hormonas, ATCC HTB22; NCI-H460, células de un carcinoma de células pulmonares no pequeñas humanas, ATCC HTB-177; DU 145, células de un carcinoma de próstata humano independiente de hormonas, ATCC HTB-81; HeLa-MaTu, células de un carcinoma cervical humano, EPO-GmbH, Berlín; HeLa-MaTu-ADR, células de un carcinoma cervical humano resistente a múltiples drogas, EPO-GmbH, Berlín; HeLa, células de tumores cervicales humanos, ATCC CCL-2; B16F10, células de melanoma de ratón, ATCC CRL-6475), en una densidad de 5000 células/cavidad (MCF7, DU145, HeLa-MaTu-ADR), de 3000 células/cavidad (NCI-H460, HeLa-MaTu, HeLa) o de 1000 células/cavidad (B16F10), en una placa de multititulación de 96 cavidades, en 200 µl del medio de cultivo respectivo, con la adición de 10% de suero fetal bovino. Después de 24 horas, las células de una placa (la placa del punto cero) se colorearon con violeta cristal (véase la descripción más adelante), mientras que el medio de las otras placas fue reemplazado por un medio de

cultivo fresco (200 µl), al cual se le agregaron las sustancias de prueba en diversas concentraciones (0 µM, así como en el rango de entre 0,01 y 30 µM; la concentración final del solvente dimetil sulfóxido fue de 0,5%). Las células se incubaron durante 4 días en presencia de las sustancias de prueba. La proliferación celular se determinó coloreando las células con violeta cristal: las células se fijaron agregando 20 µl/punto de medición de una solución de aldehído glutárico al 11%, durante 15 minutos a temperatura ambiente. Después someter las células fijadas a tres ciclos de lavado con agua, se secaron las placas a temperatura ambiente. Las células se colorearon agregando 100 µl/punto de medición de una solución de violeta cristal al 0,1% (pH 3,0). Después someter las células fijadas a tres ciclos de lavado con agua, se secaron las placas a temperatura ambiente. El colorante se disolvió agregando 100 µl/punto de medición de una solución de ácido acético al 10%. La extinción se determinó por fotometría, con una longitud de onda de 595 nm. Se calculó el cambio porcentual en la cantidad de células normalizando los valores medidos en función de los valores de extinción obtenidos de la placa del punto cero (=0%) y de la extinción de las células sin tratar (0 µm) (=100%). Los valores de la IC50 se determinaron a través de un ajuste de los parámetros, que se realizó con el software propio de la compañía.

Ensayo de la quinasa Mps-1

La quinasa humana Mps-1 fosforila un sustrato peptídico biotinilado. La detección del producto fosforilado se efectúa a través de una transferencia de energía de resonancia por fluorescencia con resolución temporal (TR-FRET), a partir de un

anticuerpo anti-fosfo-serina/treonina marcado con europio, que hace de las veces de donante, y con estreptavidina marcada con alofcocianina entrecruzada (SA-XLent) como aceptor. Se evalúa la actividad de inhibición de la quinasa de los compuestos.

Se usó una quinasa Mps-1 recombinante humana completa, con una marca de GST en el extremo N (que se adquirió en Invitrogen, Karslruhe, Alemania, cat. N° PV4071). Como sustrato para la reacción de la quinasa, se usó un péptido biotinilado con la siguiente secuencia de aminoácidos: PWDPDDADITEILG (con el extremo C en forma de amida, que se adquirió en Biosynthan GmbH, Berlín).

Para el ensayo, se pipetearon 50 nl de una solución concentrada 100 veces del compuesto de prueba en DMSO en una placa de microtitulación de 384 cavidades de volumen bajo (Greiner Bio-One, Frickenhausen, Alemania), se agregaron 2 µl de una solución de Mps-1 en el amortiguador de ensayo [orto-vanadato de sodio 0,1 mM, $MgCl_2$ 10 mM, DTT 2 mM, Hepes 25 mM, pH 7,7, 0,05% de BSA, 0,001% de Pluronic F-127] y se incubó la mezcla durante 15 minutos a 22°C, con el propósito de permitir que tuviera lugar la unión preliminar entre los compuestos de prueba y Mps-1, antes de comenzar con la reacción de la quinasa. Luego se comenzó la reacción de la quinasa agregando 3 µl de una solución de tri-fosfato de adenosina (ATP 16,7 µM, la concentración final en el volumen del ensayo, 5 µl, fue de 10 µM) y el sustrato peptídico (1,67 µM, la concentración final en el volumen del ensayo, 5 µl, fue de 1 µM) en el amortiguador del ensayo. La mezcla se incubó durante un período de 60 minutos a 22°C. La concentración de Mps-1 en el ensayo se ajustó en

función de la actividad del lote de la enzima, y se la seleccionó de manera que fuera apropiada para mantener un rango lineal en el ensayo. Las concentraciones típicas de las enzima fueron de aproximadamente 1 nM (la concentración final en el volumen del ensayo, 5 µl). La reacción se detuvo agregando 3 µl de una solución de los reactivos de detección de HTRF (Hepes 100 mM, pH 7,4, 0,1% de BSA, EDTA 40 mM, etreptavidina-XLent 140 nM [N° 61GSTXLB, Fa. Cis Biointernational, Marcoule, Francia], así como un anticuerpo anti-fosfo(Ser/Thr) marcado con europio 1,5 nM [N° AD0180, PerkinElmer LAS, Rodgau-Jügesheim, Alemania].

La mezcla resultante se incubó durante 1 hora a 22°C para permitir que tuviera lugar la unión entre el péptido fosforilado y el anticuerpo anti-fosfo(Ser/Thr) marcado con europio. Luego se evaluó la cantidad de sustrato fosforilado midiendo la transferencia de energía de resonancia por fluorescencia desde el anticuerpo anti-fosfo(Ser/Thr) marcado con europio hasta la estreptavidina-XLent. Entonces, se midieron las emisiones de fluorescencia a 620 nm y a 665 nm después de una excitación a 350 nm en un lector Viewlux TR-FRET (PerkinElmer LAS, Rodgau-Jügesheim, Alemania). Se usó la “proporción normalizada con una corrección en función del blanco” (una lectura específica en Viewlux, similar a la proporción tradicional de las emisiones a 665 nm y a 622 nm, donde las lecturas del blanco y del donante marcado con Eu se sustraen de la señal a 665 nm antes de calcular la proporción) como medida de la cantidad de sustrato fosforilado. Se normalizaron los datos (la reacción de la enzima sin el inhibidor = 0% de inhibición, la reacción con todos los otros componentes del ensayo pero sin la enzima = 100% de

inhibición). Los compuestos de prueba se evaluaron en la misma placa de microtitulación en la que se evaluaron 10 concentraciones diferentes en el rango de entre 20 µM y 1 nM (20 µM, 6,7 µM, 2,2 µM, 0,74 µM, 0,25 µM, 82 nM, 27 nM, 9,2 nM, 3,1 nM y 1 nM; se trata de una serie de diluciones preparada antes de poner en práctica el ensayo con las soluciones madre concentradas 100 veces; se realizaron diluciones de 1:3 en serie), en valores por duplicado para cada concentración. Los valores de IC_{50} se calcularon a partir de un ajuste de 4 parámetros, usando un software propio.

Sorprendentemente, se descubrió que el hecho de que R^3 sea un grupo arilo-X- o heteroarilo-X- puede influir positivamente sobre la actividad inhibitoria de los compuestos de fórmula general **I** .

Por lo tanto, los compuestos de fórmula general **I**, citados anteriormente, en los cuales R^3 representa un grupo arilo-X- o heteroarilo-X- son los preferidos.

Tabla 1

Ejemplo	Mps1 IC50 [nM]
1	61,1
2	90,5
3	13,7

Ejemplo	Mps1 IC50 [nM]
26	4,1
27	33,2
28	<1,0

4	20,6
5	13,3
6	43,6
7	1,2
8	111,0
9	25,0
10	<1,0
11	2,4
12	3,2
13	1,8
14	1,2
15	21,5
16	27,3
17	3,2
18	228,0
19	1,6
20	1,2
21	3,7
22	35,7
23	2,4

29	80,2
30	2,1
31	1,1
32	4,3
33	1,5
34	2,4
35	2,5
36	3,0
37	<1,0
38	10,3
39	3,7
40	111,0
41	7,1
42	7,8
43	21,1
44	2,6
45	1,1
46	1,1
47	2,0
48	1,4

24	23,8
25	13,1

49	11,9
50	84,8

Tabla 1 (cont.)

Ejemplo	Mps1 IC50 [nM]
51A	58,0
51B	1,2
52	3,2
53	7,1
54	7,6
55	1,2
56	< 1,0
57	4,4
58	20,5
59	32,5
60A	0,2
60B	< 0,1

Ejemplo	Mps1 IC50 [nM]
72	44,4
73A	< 0,7
73B	3,8
74	< 0,7
75	< 0,7
76	< 0,7
77	< 0,7
78	0,2
79	0,7
80	0,2
81	0,2
82	0,3

61A	0,2
61B	0,3
62A	0,2
62B	11,5
63	< 0,1
64	0,1
65	0,7
66	0,2
67	0,1
68	< 0,1
69	1,0
70	0,3
71	0,8

83A	0,2
83B	0,8
84	0,3
85	0,2
86	0,1
87	0,2
88	0,4
89	0,2
90	0,5
91	0,5
92	0,2
93	0,3
94	0,3

Tabla 1 (cont.)

Ejemplo	Mps1 IC50 [nM]
95	0,3

Ejemplo	Mps1 IC50 [nM]
121	1,8

96	0,8
97	0,2
98	52,3
99	29,5
100	7,6
101	6,3
102	24,6
103	<1,0
104	<1,0
105	3,5
106	8,9
107	35,5
108	7,0
109	2,1
110	1,3
111	6,3
112	5,1
113	2,0
114	<1,0
115	27,5

122	2,9
123	7,6
124	4,7
125	3,8
126	2,0
127	40,0
128	2,7
129	3,3
130	5,9
131	10,0
132	1,5
133	<1,0
134	<1,0
135	<1,0
136	4,0
137	<1,0
138	2,0
139	3,7
140	3,9
141	2,4

116	4,0
117	3,3
118	4,3
119	<1,0
120	2,5

142	1,4
143	4,7
144	2,3
145	<1,0
146	3,8

Tabla 1 (cont.)

Ejemplo	Mps1 IC50 [nM]
147	2,2
148	1,5
149	2,2
150	3,7
151	3,1
152	3,3
153	3,6
154	25,0
155	3,6

Ejemplo	Mps1 IC50 [nM]
172	0,8
173	0,4
174	< 0,1
175	7280,0
176	465,0
177	32,2
178	172,0
179	601,0
180	327,0

156	5,1
157	12,0
158	6,4
159	14,8
160	13,6
161	6,2
162	64,9
163	30,5
164	6,3
165	1,8
166	5,3
167	2,3
168	0,3
169	0,1
170	0,7
171	0,8

181	39,9
182	Ne
183	290,0
184	101,0
185	Ne
186	338,0
187	49,8
188	Ne
189	Ne
190	660,0
191	20000,0
192	21,5
193	1,3
194	2,5
195	3,2
196	2,7

Tabla 1 (cont.)

Ejemplo	Mps1

Ejemplo	Mps1

	IC50 [nM]
197	< 1,0
198	2,6
199	6,9
200	Ne
201	2,3
202	1,5
203	1,4
204	< 1,0
205	72,7
206	6,2
207	< 1,0
208	2,0
209	0,6
210	6,9
211	5,8
212	< 1,0
213	< 1,0
214	< 1,0

	IC50 [nM]
225	0,2
226	1,3
227	0,2
228	0,6
229	2,6
230	2,7
231	14,3
232	1,0
233	1,7
234	6,1
235	6,2
236	Ne
237	5,6
238	< 0,1
239	25,5
240	1,2
241A	Ne
241B	3,4

215	1,7		242	3,7
216	< 1,0		243	0,9
217	3,6		244	0,3
218	3,7		245	0,7
219	Ne		246	0,6
220	Ne		247	1,7
221	1,2		248	0,5
222	2,1		249	0,2
223	0,2		250	0,3
224	< 0,1		251	0,2

Tabla 1 (cont.)

Ejemplo	Mps1 IC50 [nM]		Ejemplo	Mps1 IC50 [nM]
252	0,2		278B	1,0
253	0,3		279	148,0
254	0,1		280	0,1

255	0,2
256	0,2
257	0,4
258	0,2
259	0,3
260	0,2
261	0,5
262	0,2
263	32,4
264	2,0
265	0,9
266	0,3
267	0,3
268	0,2
269	0,3
270	0,1
271	1,0
272	21,1
273	0,5
274	73,8

281	0,3
282	0,4
283	0,3
284	0,4
285	0,4
286	0,4
287	0,3
288	0,1
289	0,2
290	0,3
291	0,6
292	0,5
293	0,4
294A	0,3
294B	0,2
295A	0,4
295B	0,2
296A	0,5
296B	0,5
296C	0,2

275	5,4
276	0,1
277	< 0,1
278A	0,4

297	0,1
298A	< 0,1
298B	0,1
299	6,9

Tabla 1 (cont.)

300	0,8
301	0,2
302	0,3
303A	Ne
303B	0,2
304A	< 0,1
304B	0,1
305	0,6
306	0,6
307	0,5
308	1,0
309	Ne

323	0,2
324	0,3
325	0,1
326	1,9
327	0,3
328	0,3
329	< 0,1
330	0,2
331	12,6
332	26,8
333	9,5
334	30,0

310	Ne
311	0,2
312	0,2
313	0,1
314	0,2
315	0,3
316	118,0
317	7,4
318	64,3
319	121,0
320	3,3
321	0,6
322	70,6

335	3,6
336	1,0
337	3,9
338	83,9
339	95,9
340	3,3
341	10,6
342	6,9
343	4,3
344	23,0
345	3,0
346	1,6
347	0,1

Tabla 1 (cont.)

348	1,5
349	0,4
351	1,0

380	0,1
381	0,6
382	1,2

352	0,2
353	0,4
354	0,4
355	0,9
356	0,6
357	4,4
358	0,1
359	1,2
360	0,9
361	0,3
362	0,2
365	4,4
366	1,1
367	0,1
368	0,1
369	0,1
370	0,1
371	0,2
372	0,2
373	0,2

383	0,3
384	0,4
385	0,9
386	1,5
387	0,3
388	0,4
389	0,1
390	0,1
391	0,1
392	0,4
393	2,3
394	0,2
395	0,3
396	0,1
396	0,3
397	1,0
398	0,4
399	0,1
400	3,1
401	1,0

374	0,3
375	0,1
376	0,2
377	0,3
378	0,2
379	0,2

402	3,4
403	1,0
404	0,3
405	0,2
406	0,4
409	0,7

Tabla 1 (cont.)

410	0,5
411	4,8
412	19,2
413	45,7
414	6,7
415	8,2
417	0,2
418	1,2
419	3,5
420	2,8

442	0,1
443	0,1
445	0,2
446	0,4
447	1,1
448	0,6
449	0,6
450	0,3
451	1,3
452	0,8

422	0,4
423	0,3
424	0,2
425	0,1
426	0,2
427	0,2
428	0,4
429	0,1
430	0,3
431	0,1
432	4,6
433	0,6
434	1,3
435	1,6
436	0,1
437	0,4
439	0,2
440	0,1
441	0,5

454	0,1
456	nt
457	5,4
458	1,1
459	0,4
460	0,3
461	0,2
464	0,1
465	nt
466	4,8
467	1,6
468	7,5
469	1,7
470	0,4
471	0,2
472	0,2
473	0,4
474	0,3
475	0,2

Tabla 1 (cont.)

476	10,3		505	0,2
477	0,3		506	0,1
478	0,3		507	0,2
479	0,2		508	0,2
480	nt		509	0,1
481	3,1		510	0,1
482	0,6		511	0,3
483	0,1		512	0,1
484	0,3		513	0,2
485	0,4		514	8,0
486	0,1		515	0,4
487	0,1		516	0,3
488	0,1		517	0,2
489	0,2		518	0,1
490	1,5		519	0,1
491	0,1		520	0,2
492	0,1		521	0,3

493	0,3
494	0,3
495	0,1
496	8,9
497	0,2
498	0,3
499	0,2
500	0,1
501	0,1
502	0,2
503	0,2
504	0,2

522	1,8
523	0,7
524	2,3
525	0,7
526	0,1
527	0,6
528	0,7
529	0,4
530	0,6
531	14,8
532	0,2
533	1,2

Tabla 1 (cont.)

534	0,1
535	0,1
536	0,3
537	0,2

550	0,5
551	0,2
552	0,2
553	0,7

538	0,8
539	0,2
540	0,1
541	0,4
542	0,1
543	0,2
544	1,1
545	0,1
546	0,1
547	0,2
548	0,7
549	0,2

554	1,6
555	9,4
556	0,3
557	2,2
558	0,3
559	0,6
560	0,1
561	0,6

Ejemplo	Mps1 IC50 [nM]
562	2,7
563	4,3
564	Ne

Ejemplo	Mps1 IC50 [nM]
587	3,2
588	2,2
589	4,3

565	3,5
566	1,7
567	< 1,0
568	< 1,0
569	< 1,0
570	< 1,0
571	< 1,0
572	< 1,0
573	< 1,0
574	Ne
575	< 1,0
576	< 1,0
577	1,4
578	Ne
579	Ne
580	< 1,0
581	< 1,0
582	3,8
583	6,9
584	2,3

590	Ne
591	2,5
592	1,5
593	9,0
594	< 1,0
596	1,1
597	1,1
598	< 1,0
599	1,0
600	< 1,0
601	< 1,0
602	< 1,0
603	< 1,0
604	< 1,0
605	1,2
606	Ne
607	3,7
608	3,9
609	2,9
610	< 1,0

585	5,4
586	1,0

En la Tabla anterior, Ne = no evaluado

Ensayo del punto de verificación del ensamblaje del huso

Con el ensayo del punto de verificación del ensamblaje del huso, puede asegurarse la segregación apropiada de los cromosomas durante la mitosis. Una vez que comienza la mitosis, los cromosomas comienzan a condensarse, lo que está acompañado por la fosforilación de la serina 10 en la histona H3. La desfosforilación de la serina 10 en la histona H3 comienza en la anafase y termina prácticamente en la telofase. Por consiguiente, la fosforilación de de la serina 10 en la histona H3 puede utilizarse como marcador de las células en mitosis. El nocodazol es una sustancia que desestabiliza los microtúbulos. Por lo tanto, el nocodazol interfiere con la dinámica de los microtúbulos y moviliza el punto de verificación del ensamblaje del huso. En las células, la mitosis se interrumpe en la transición G2/M. Las células presentan la histona H3 fosforilada en la serina 10. La inhibición del punto de verificación del ensamblaje del huso con inhibidores de Mps-1 anula el bloqueo de la mitosis en presencia de nocodazol, por lo que las células completan la mitosis de manera prematura. Esta alteración se detecta a través de la disminución en las células que presentan la histona H3 fosforilada en la serina 10. Esta declinación se usa como marcador para determinar la capacidad de los compuestos

de la presente invención de inducir una alteración en la mitosis.

Se sembraron células cultivadas de la línea de células de tumores cervicales humanos HeLa (ATCC CCL-2), en una densidad de 2500 células/cavidad, en una placa de 384 cavidades, en 20 µl del medio de Dulbeco (sin rojo fenol o piruvato de sodio, con 1000 mg/ml de glucosa y piridoxina) con la adición de 1% (v/v) de glutamina, 1% (v/v) de penicilina, 1% (v/v) de estreptomicina y 10% (v/v) de suero fetal bovino. Después de incubar durante la noche a 37°C, a las células se les agregaron 10 µl/cavidad de nocodazol, en una concentración final de 0,1 µg/ml. Después de incubar durante 24 horas, el progreso del ciclo celular en estas células se detuvo en la fase G2/M. Se agregaron los compuestos de prueba solubilizados en dimetil sulfóxido (DMSO) en diversas concentraciones (0 µM, así como en el rango de entre 0,005 µM y 10 µM; la concentración final del solvente DMSO fue de 0,5% (v/v)). Las células se incubaron durante 4 horas a 37°C, en presencia de los compuestos de prueba. Posteriormente, las células se fijaron en paraformaldehído al 4% (v/v) en solución salina amortiguada con fosfato (PBS), a 4°C durante la noche, después de lo cual se las permeabilizó en Triton X™ 100 al 0,1% (v/v) en PBS, a temperatura ambiente durante 20 minutos, y se las bloqueó en albúmina de suero bovino (BSA) al 0,5% (v/v) en PBS, a temperatura ambiente durante 15 minutos. Después de lavar con PBS, a las células se les agregaron 20 µl/cavidad de la solución del anticuerpo (el clon de anti-fosfo-histona H3 3H10, FITC, Upstate, Cat N° 16-222, en una dilución de 1:200). Luego se incubó durante 2 horas a temperatura ambiente. Seguidamente,

las células se lavaron con PBS y se les agregaron 20 µl/cavidad de la solución colorante HOECHST 33342 (5 µg/ml), después de lo cual se las incubó durante 12 minutos a temperatura ambiente en la oscuridad. Las células se lavaron dos veces con PBS, luego se las cubrió con PBS y se las almacenó a 4°C hasta analizarlas. Las imágenes se adquirieron con un lector de análisis de alto contenido Perkin Elmer OPERA™. Las imágenes se analizaron con el software de análisis de imágenes MetaXpress™, de Molecular Devices, usando el módulo de aplicación para el ciclo celular. En este ensayo, se midieron las marcas de HOECHST 33342 y de la histona H3 fosforilada en la serina 10. HOECHST 33342 marca el ADN y se usa para determinar la cantidad de células. La coloración de la histona H3 fosforilada en la serina 10 permite determinar la cantidad de células en mitosis. Mediante la inhibición de Mps-1, puede reducirse la cantidad de células en mitosis en presencia de nocodazol, lo que refleja un progreso inapropiado de la mitosis. Los datos en bruto del ensayo se sometieron a un análisis adicional con una regresión logística de cuatro parámetros, con el objeto de determinar el valor de la IC_{50} para cada compuesto evaluado.

Para aquellos versados en la técnica, ha de ser evidente que pueden ponerse en práctica ensayos para otras quinasas Mps de manera análoga, mediante el uso de los reactivos apropiados.

Por lo tanto, los compuestos de la presente invención inhiben de manera efectiva una o más quinasas Mps-1, por lo que son apropiados para el tratamiento o la profilaxis de enfermedades relacionadas con un crecimiento, una

proliferación y/o una supervivencia celular descontrolada, con una respuesta inmune celular inapropiada o con una respuesta inflamatoria celular inapropiada, particularmente donde el crecimiento, la proliferación y/o la supervivencia celular descontrolada, la respuesta inmune celular inapropiada o la respuesta inflamatoria celular inapropiada están mediados por Mps-1, más particularmente donde las enfermedades relacionadas con un crecimiento, una proliferación y/o una supervivencia celular descontrolada, con una respuesta inmune celular inapropiada o con una respuesta inflamatoria celular inapropiada son los tumores hematológicos, los tumores sólidos y/o sus metástasis, por ejemplo, las leucemias y el síndrome mielodisplástico, los linfomas malignos, los tumores de la cabeza y el cuello, incluyendo los tumores cerebrales y las metástasis cerebrales, los tumores del tórax, incluyendo los tumores de las células pulmonares no pequeñas y de las células pulmonares pequeñas, los tumores gastrointestinales, los tumores endocrinos, los tumores mamarios y otros tumores ginecológicos, los tumores del tracto urinario, incluyendo los tumores renales, vesicales y prostáticos, los tumores en la piel y los sarcomas, y/o sus metástasis.

Investigación de la estabilidad metabólica *in vitro* en hepatocitos de rata (incluyendo cálculos de la depuración hepática *in vivo* (CL))

Se aislaron hepatocitos de ratas Han Wistar mediante un método de perfusión en 2 pasos. Luego de la perfusión, se extrajo cuidadosamente el hígado de la rata: se abrió la cápsula

hepática y los hepatocitos se extrajeron sacudiendo suavemente sobre una placa de Petri con WME enfriada con hielo. La suspensión de células que se obtuvo como resultado se filtró a través de una gasa estéril en tubos tipo Falcon de 50 ml y se centrifugó a 50 × *g* durante 3 min a la temperatura ambiente. El pellet de células se resuspendió en 30 ml de WME y se centrifugó a través de un gradiente de Percoll® 2 veces a 100 × *g*. Los hepatocitos se lavaron nuevamente con medio E de Williams (WME) y se resuspendieron en un medio que contenía 5% de FCS. La viabilidad de las células se determinó por exclusión con azul trypan.

Para el ensayo de estabilidad metabólica , las células hepáticas se distribuyeron en WME que contenía 5% de FCS a ampolletas de vidrio con una densidad de $1,0 \times 10^6$ células vivas/ml. El compuesto de prueba se agregó hasta una concentración final 1 µM. Durante la incubación, las suspensiones de hepatocitos se sacudieron continuamennte y se tomaron alícuotas a los 2, 8, 16, 30, 45 y 90 min, agregándoles inmediatamente un volumen igual de metanol frío. Las muestras se congelaron a −20°C durante toda la noche, luego , subsiguientemente se centrifugó durante 15 minutos a 3000 rpm y se analizó el sobrenadante con un sistema de HPLC Agilent 1200 con detección por LCMS/MS.

La vida media de los compuestos de prueba se determinó a partir del gráfico concentración-tiempo. A partir de la vida media , se calcularon las depuraciones intrínsecas. Junto con los parámetros adicionales de flujo sanguíneo hepático, cantidad de células hepáticas *in vivo* e *in vitro.* Se calculó la depuración hepática *in vivo* (CL) y la máxima biodisponibilidad oral

(F_{max}). Para los parámetros, se utilizaron los siguientes valores: Flujo sanguíneo hepático – 4,2 L/h/kg rata; peso específico del hígado – 32 g/kg de peso corporal de la rata ; células hepáticas *in vivo*– 1,1 x 10^8 células/g de hígado, células hepáticas *in vitro* – 0,5 x 10^6/ml.

Sorprendentemente, se descubrió que el hecho de que por lo menos uno de los grupos R^{4b} y R^{4c} sea(n) diferente(s) de un átomo de hidrógeno puede influir positivamente sobre la estabilidad metabólica de los compuestos de fórmula general **I**.

Por ejemplo, el reemplazo por un grupo metilo de uno de R^{4c} o R^{4b} cuando es un átomo de hidrógeno , incrementa la estabilidad metabólica en un 700% (Tabla 2a) o en 177% (Tabla 2b), respectivamente.

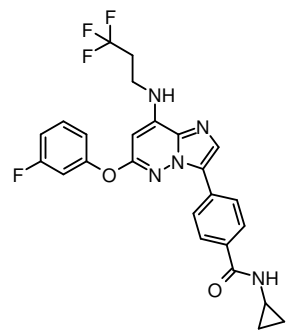
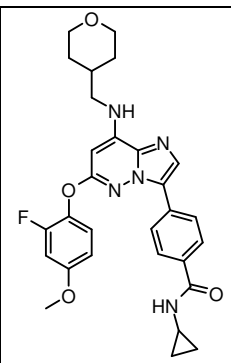
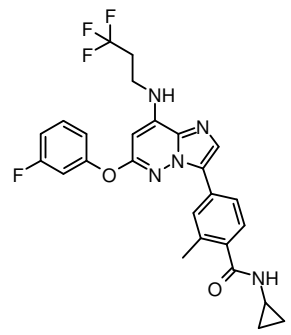
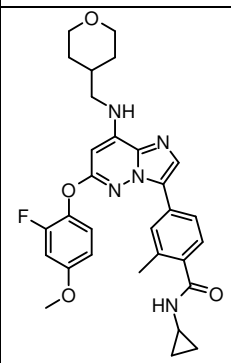
Por lo tanto, en una forma de realización preferida , R^{4a}, R^{4b}, R^{4c} y R^{4d} representan, independientemente entre sí, un átomo de hidrógeno o de halógeno, o un grupo –CN, C_1–C_6–alquilo–, C_1–C_6–alcoxi–, halo–C_1–C_6–alquilo–, halo–C_1–C_6–alcoxi–, $R^{6a}(R^{6b})N$–C_1–C_6–alquilo–, HO–C_1–C_6–alquilo–, NC–C_1–C_6–alquilo–, C_1–C_6–alcoxi–C_1–C_6–alquilo–, halo–C_1–C_6–alcoxi–C_1–C_6–alquilo–; con la condición de que por lo menos uno de los grupos R^{4b} y R^{4c} no sea un átomo de hidrógeno.

Tabla 2a:

Ejemplo	Estructura	Fmax [%]

Tabla 2b:

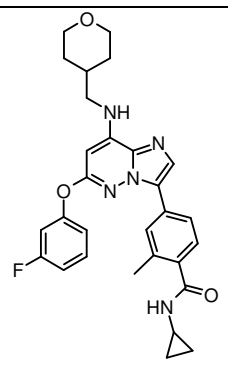
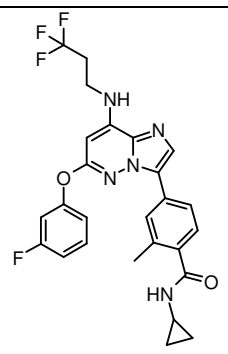
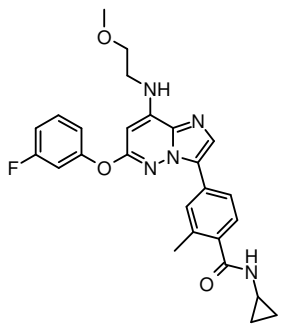
Ejemplo	Estructura	Fmax [%]

463		7	444		22
80		56	445		61

Sorprendentemente, se descubrió que R^5 puede influir positivamente sobre la estabilidad metabólica de los compuestos de fórmula general **I** (Tablas 3a, 3b, y 3c). Por ejemplo, el reemplazo de R^5 , cuando es un grupo 4-tetrahidropiranilo- , (compuesto de ejemplo 323) por un grupo 1,1,1-trifluoroetilo (compuesto de ejemplo 80) incrementa la estabilidad metabólica en un 81% (Tabla 3a).

Tabla 3a

Ejemplo	Estructura	Fmax [%]	Ejemplo	Estructura	Fmax [%]

323		31
80		56
492		42

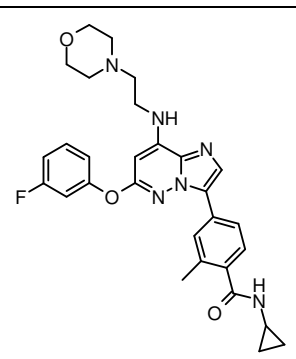
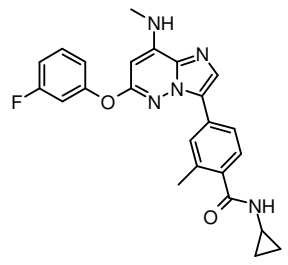
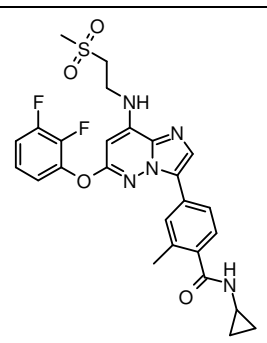
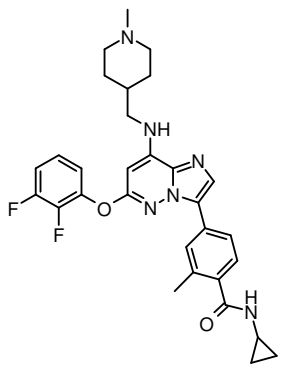
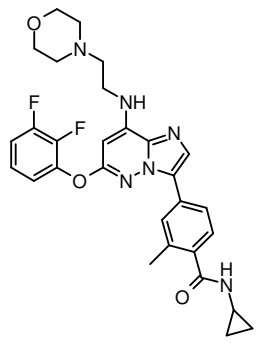
500		40
510		39

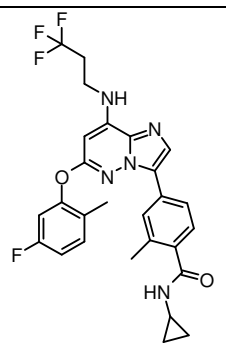
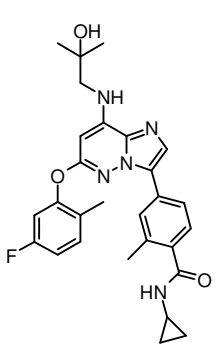
Tabla 3b

Ejemplo	Estructura	Fmax [%]

Tabla 3c

Ejemplo	Estructura	Fmax [%]

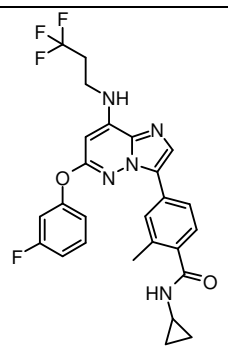
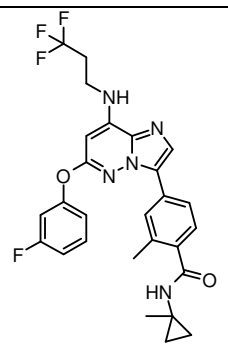
516		69
526		50
536		37

390		55
391		47

Sorprendentemente, se descubrió que R^2 puede influir positivamente sobre la estabilidad metabólica de los compuestos de fórmula general **I**.

Por ejemplo, el reemplazo de R^2 cuando es un grupo ciclopropilo-, por un grupo ciclopropilo- sustituido tal como un grupo 1-metilciclopropilo , incrementa la estabilidad metabólica en un 34% (Tabla 4).

Tabla 4

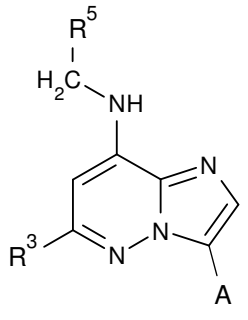
Ejemplo	Estructura	Fmax [%]
80		56
461		75

Sorprendentemente, se descubrió que R^2 puede influir positivamente sobre la estabilidad metabólica de los compuestos de fórmula general **I**.

Por ejemplo, el reemplazo de R^2 , cuando es un grupo ciclopropilo–, por un grupo alquilo– no cíclico incrementa la estabilidad metabólica significativamente.

REIVINDICACIONES

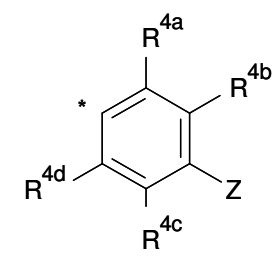
1. Un compuesto de fórmula general I:



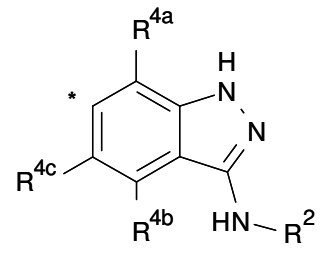
I

donde:

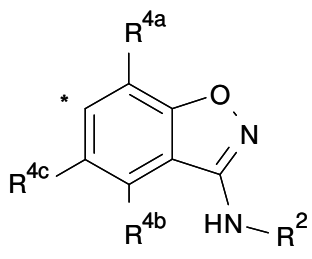
A representa un grupo



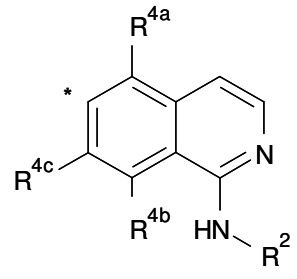
o



o



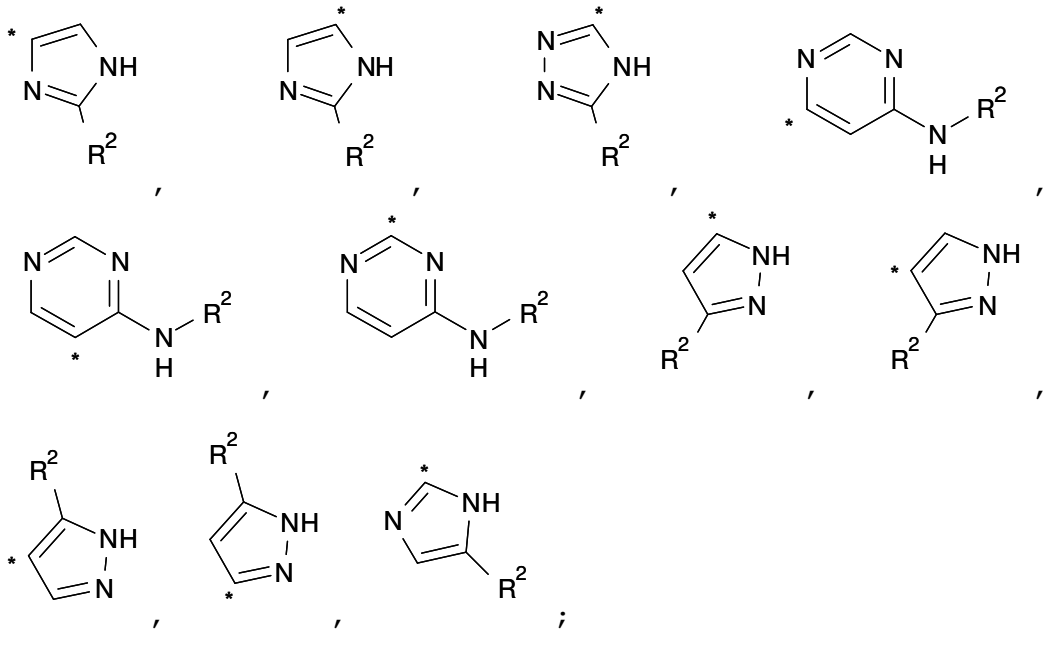
o



–;

donde * indica el punto de unión de dichos grupos con el resto de la molécula;

Z representa un grupo $-C(=O)N(H)R^2$ o $-C(=S)N(H)R^2$, o un grupo seleccionado entre



donde * indica el punto de unión de dichos grupos con el resto de la molécula;

R^2 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, C_2-C_6-alquinilo- o C_3-C_6-cicloalquilo-;

donde dicho grupo C_3-C_6-cicloalquilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos seleccionados entre: halógeno, -OH, -CN, C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alquilo-;

R^3 representa un átomo de hidrógeno o un átomo de halógeno, o un grupo -CN, C_1-C_6-alquilo-, C_1-C_6-alcoxi-, -$(CH_2)_m$-C_2-C_6-alquenilo, -$(CH_2)_m$-C_4-C_8-cicloalquenilo, -$(CH_2)_m$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, -$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-C_1-C_6-

alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo-, -C_1-C_6-alquil-arilo, -C_1-C_6-alquil-heteroarilo, heteroarilo-, C_1-C_6-alquil-X-, -X-$(CH_2)_m$-C_2-C_6-alquenilo, -X-$(CH_2)_m$-C_4-C_8-cicloalquenilo, -X-$(CH_2)_m$-C_2-C_6-alquinilo, -X-$(CH_2)_m$-C_3-C_6-cicloalquilo, -X-$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -X-$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-X-, heteroaril-X-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)_2R^6$, $-S(=O)(=NR^{6a})R^{6b}$, $-S(=O)_2N(R^{6b})R^{6c}$, -S-$(CH_2)_n$-$N(R^{6a})R^{6b}$ o -S-$(CH_2)_n$-(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho grupo C_1-C_6-alquilo-, C_1-C_6-alcoxi-, -$(CH_2)_m$-C_2-C_6-alquenilo, -$(CH_2)_m$-C_2-C_6-alquinilo, -$(CH_2)_m$-C_3-C_6-cicloalquilo, aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-, arilo-, C_1-C_6-alquil-X-, -X-$(CH_2)_m$-C_2-C_6-alquenilo, -X-$(CH_2)_m$-C_4-C_8-cicloalquenilo, -X-$(CH_2)_m$-C_2-C_6-alquinilo, -X-$(CH_2)_m$-C_3-C_6-cicloalquilo, -X-$(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), -X-$(CH_2)_m$-(heterocicloalquenilo de entre 4 y 8 miembros), aril-X-, heteroaril-X-, -C_1-C_6-alquil-arilo, -C_1-C_6-alquil-heteroarilo o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, 4 o 5 grupos

R^7;

R^{4a}, R^{4b}, R^{4c}, R^{4d}

representan, en forma independiente entre sí, un átomo de hidrógeno o halógeno, o un grupo -CN, C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, $-NO_2$, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)$S(=O)_2R^6$, -N(R^{6c})$S(=O)_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^{6a}$, $-S(=O)_2N(R^{6a})R^{6b}$, -S(=O)(=NR^{6c})R^6;

R^5 representa un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, $-(CH_2)_n$-C_2-C_6-alquenilo, $-(CH_2)_n$-C_2-C_6-alquinilo, $-(CH_2)_m$-C_3-C_6-cicloalquilo, $-(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_2-C_6-alquenilo-, C_4-C_8-cicloalquenilo-, C_2-C_6-alquinilo-,arilo- o heteroarilo-;

donde dicho grupo C_1-C_6-alquilo-, $-(CH_2)_n$-C_2-C_6-alquenilo, $-(CH_2)_n$-C_2-C_6-alquinilo, $-(CH_2)_m$-C_3-C_6-cicloalquilo, $-(CH_2)_m$-(heterocicloalquilo de entre 3 y 7 miembros), aril-C_1-C_6-

alquilo-, heteroaril-C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, heterocicloalquilo de entre 3 y 7 miembros-, C_4-C_8-cicloalquenilo-, arilo- o heteroarilo- está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos R^8;

R^6, R^{6a}, R^{6b}, R^{6c},

representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_3-C_6-cicloalquilo-, C_2-C_6-alquenilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, aril-C_1-C_6-alquilo- o heteroaril-C_1-C_6-alquilo-;

R^7 representa un átomo de hidrógeno o halógeno, o un grupo HO-, -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, -$C(=O)R^6$, -$C(=O)N(H)R^{6a}$, -$C(=O)N(R^{6a})R^{6b}$, -$C(=O)O$-R^6, -$N(R^{6a})R^{6b}$, -NO_2, -$N(H)C(=O)R^6$, -$N(R^{6c})C(=O)R^6$, -$N(H)C(=O)N(R^{6a})R^{6b}$, -$N(R^{6c})C(=O)N(R^{6a})R^{6b}$, -$N(H)C(=O)OR^6$, -$N(R^{6c})C(=O)OR^6$, -$N(H)S(=O)R^6$, -$N(R^{6c})S(=O)R^6$, -$N(H)S(=O)_2R^6$, -$N(R^{6c})S(=O)_2R^6$, -$N=S(=O)(R^{6a})R^{6b}$, -$OR^6$, -$O(C=O)R^6$, -$O(C=O)N(R^{6a})R^{6b}$, -$O(C=O)OR^6$, -$SR^6$, -$S(=O)R^6$, -$S(=O)N(H)R^6$, -$S(=O)N(R^{6a})R^{6b}$, -$S(=O)_2R^6$, -$S(=O)_2N(H)R^6$, -$S(=O)_2N(R^{6a})R^{6b}$ o -$S(=O)(=NR^{6c})R^6$;

donde dicho grupo C_1-C_6-alcoxi-, arilo- o heteroarilo- está

opcionalmente sustituido, en forma idéntica o diferente, con 1, 2 o 3 grupos C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alcoxi-, -C(=O)O-R^6 o -OH;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo- o heteroarilo-, donde dichos 2 grupos R^7 juntos forman un puente:

O$(CH_2)_2$O, *O(CH_2)O*, *NH(C(=O))NH*, donde * representa el punto de unión a dicho anillo arilo- o heteroarilo-;

R^8 representa un átomo de hidrógeno o halógeno, o un grupo -CN, C_1-C_6-alcoxi-, C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})$N-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, heterocicloalquilo de entre 3 y 7 miembros-, arilo-, heteroarilo-, -C(=O)R^6, -C(=O)N(H)R^{6a}, -C(=O)N(R^{6a})R^{6b}, -C(=O)O-R^6, -N(R^{6a})R^{6b}, -NO_2, -N(H)C(=O)R^6, -N(R^{6c})C(=O)R^6, -N(H)C(=O)N(R^{6a})R^{6b}, -N(R^{6c})C(=O)N(R^{6a})R^{6b}, -N(H)C(=O)OR^6, -N(R^{6c})C(=O)OR^6, -N(H)S(=O)R^6, -N(R^{6c})S(=O)R^6, -N(H)S(=O)$_2R^6$, -N(R^{6c})S(=O)$_2R^6$, -N=S(=O)(R^{6a})R^{6b}, -OR^6, -O(C=O)R^6, -O(C=O)N(R^{6a})R^{6b}, -O(C=O)OR^6, -SR^6, -S(=O)R^6, -S(=O)N(H)R^6, -S(=O)N(R^{6a})R^{6b}, -S(=O)$_2R^6$, -S(=O)$_2$N(H)R^6, -S(=O)$_2$N(R^{6a})R^{6b}, -S(=O)(=NR^{6c})R^6 o -S(=O)$_2$-(heterocicloalquilo de entre 3 y 7 miembros);

donde dicho heterocicloalquilo- o heteroarilo- de entre 3 y 7 miembros está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3 o 4 grupos C_1-C_6 alquilo-;

m es el entero 0, 1, 2, 3, 4, 5 o 6;

n es el entero 0, 1, 2, 3, 4 o 5;

X representa $S(=O)_p$, O, NR^6, $CR^{6a}R^{6b}$ o $C=CR^{6a}R^{6b}$;

p es el entero 0, 1 o 2;

o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato o una sal del mismo, o una mezcla de los mismos.

2. Un compuesto de acuerdo con la reivindicación 1, en donde

R^{4a} representa hidrógeno;

R^{4d} representa hidrógeno; y

uno de los grupos R^{4b} y R^{4c} representa un átomo de hidrógeno mientras que el otro representa un grupo seleccionado entre: halo-, -CN, -OH, C_1-C_6-alquilo- y C_1-C_6-alcoxi-;

o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato o una sal del mismo, o una mezcla de los mismos.

3. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 2, en donde

R^2 se selecciona entre los siguientes grupos:

C_1-C_6-alquilo-, halo-C_1-C_6-alquilo-, $R^{6a}(R^{6b})N$-C_1-C_6-alquilo-, HO-C_1-C_6-alquilo-, -C_1-C_6-alquil-CN, C_1-C_6-alcoxi-C_1-C_6-alquilo-, halo-C_1-C_6-alcoxi-C_1-C_6-alquilo-, C_2-C_6-alquenilo-, C_2-C_6-alquinilo-;

o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato o una sal del mismo, o una mezcla de los mismos.

4. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 3, en donde

R^3 representa un grupo aril–X– o heteroaril–X–;

donde dicho aril–X– o heteroaril–X– está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, 4 o 5 grupos R^7;

o un estereoisómero, un tautómero, un N–óxido, un hidrato, un solvato o una sal del mismo, o una mezcla de los mismos.

5. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 4, en donde

R^5 representa un átomo de hidrógeno, o un grupo C_1–C_6–alquilo–, halo–C_1–C_6–alquilo–, HO–C_1–C_6–alquilo–, C_3–C_6–cicloalquilo–, heterocicloalquilo o heteroarilo de entre 3 y 7 miembros;

donde dicho C_1–C_6–alquilo–, halo–C_1–C_6–alquilo–, HO–C_1–C_6–alquilo–,, C_3–C_6–cicloalquilo–, heterocicloalquilo de entre 3 y 7 miembros, heteroarilo– está opcionalmente sustituido, en forma idéntica o diferente, con 1, 2, 3, o 4 grupos R^8;

o un estereoisómero, un tautómero, un N–óxido, un hidrato, un solvato o una sal del mismo, o una mezcla de los mismos.

6. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 5, en donde

R^7 representa un átomo de halógeno, o un grupo HO–, –CN, C_1–C_6–alcoxi–, C_1–C_6–alquilo–, halo–C_1–C_6–alquilo–, HO–C_1–C_6–alquilo–, H_2N–C_1–C_6–alquilo–, C_2–C_6–alquenilo, heterocicloalquilo de entre 3 y 7 miembros, –C(=O)N(H)R^{6a}, –N(R^{6a})R^{6b}, –N(H)C(=O)R^6, o –SR^6;

donde dicho grupo C_1–C_6–alcoxi–, o heterocicloalquilo de entre 3 y 7 miembros– está opcionalmente sustituido, en

forma idéntica o diferente, con 1, 2, o 3 grupos C_1-C_6-alquilo-, C_1-C_6-alcoxi-, halo-C_1-C_6-alcoxi-, -C(=O)O-R^6 o -OH;

o

cuando 2 grupos R^7 están presentes en posición orto entre sí en un anillo arilo o heteroarilo, donde dichos 2 grupos R^7 juntos forman un puente:

$CH_2(CH_2)_2NH$, *$CH_2CH_2N(R^{6a})CH_2$*, *C(H)=C(H)-C(=O)-N(H)*, donde * representa el punto de unión a dicho anillo arilo o heteroarilo;

o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato o una sal del mismo, o una mezcla de los mismos.

7. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 6, en donde

R^6, R^{6a}, R^{6b}, y R^{6c} representan, en forma independiente entre sí, un átomo de hidrógeno, o un grupo C_1-C_6-alquilo-;

o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato o una sal del mismo, o una mezcla de los mismos.

8. Un compuesto de acuerdo con la reivindicación 1, que se selecciona entre el grupo que consiste en:

1-({6-[(2E/Z)-but-2-en-2-il]-3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol,

1-({3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-6-[(1E/Z)-prop-1-en-1-il]imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol,

3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-N-isobutil-6-(piridin-4-il)imidazo[1,2-b]piridazin-8-amina,

3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-6-(piridin-4-il)-N-[(2S)-tetrahidrofurano-2-ilmetil]imidazo[1,2-b]piridazin-8-amina,

3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-6-(piridin-4-il)-N-[(2R)-tetrahidrofurano-2-ilmetil]imidazo[1,2-b]piridazin-8-amina,

3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-6-(4-fluorofenil)-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina,

N-ciclopropil-4-{6-(4-fluorofenil)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

1-({3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-6-(4-fluorofenil)imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol,

1-({3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-6-(piridin-4-il)imidazo[1,2-b]piridazin-8-il}amino)-2-metilpropan-2-ol,

N-ciclopropil-2-metil-4-{6-(1-metil-1H-pirazol-5-il)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

3-(3-amino-1H-indazol-6-il)-N-isobutil-6-fenilimidazo[1,2-b]piridazin-8-amina,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-fenilimidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-[8-(isobutilamino)-6-(piridin-4-il)imidazo[1,2-b]piridazin-3-il]bencencarbotioamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-fenilimidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(metilsulfanil)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-6-[(1E)-prop-1-en-1-il]-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina,

N-ciclopropil-4-{8-[(2-metoxi-2-metilpropil)amino]-6-(piridin-4-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(metilsulfonil)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(4-fluorofenil)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-[2-(hidroximetil)fenil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(1-metil-1H-pirazol-5-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-6-etenil-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina,

N-ciclopropil-2-metil-4-{6-[(1E)-prop-1-en-1-il]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(1E)-prop-1-en-1-il]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-[(2E)-but-2-en-2-il]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-

metilbenzamida,

3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-6-(piridin-4-il)-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina,

6-[(2E)-but-2-en-2-il]-3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina,

N-ciclopropil-4-{6-(4-fluorofenil)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-6-(piridin-4-il)-N-(tetrahidro-2H-piran-2-ilmetil)imidazo[1,2-b]piridazin-8-amina,

(RS)-N-ciclopropil-2-metil-4-[8-{[(2-metiltetrahidrofuran-2-il)metil]amino}-6-(piridin-4-il)imidazo[1,2-b]piridazin-3-il]benzamida,

N-ciclopropil-2-metil-4-[6-(piridin-4-il)-8-{[(2S)-tetrahidrofurano-2-ilmetil]amino}imidazo[1,2-b]piridazin-3-il]benzamida,

N-ciclopropil-4-{6-(4-fluorofenil)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}bencencarbotioamida,

N-ciclopropil-2-metil-4-[6-(1-metil-1H-pirazol-5-il)-8-{[(2R)-tetrahidrofurano-2-ilmetil]amino}imidazo[1,2-b]piridazin-3-il]benzamida,

N-ciclopropil-2-metil-4-[6-(1-metil-1H-pirazol-5-il)-8-{[(2S)-tetrahidrofurano-2-ilmetil]amino}imidazo[1,2-b]piridazin-3-il]benzamida,

N-ciclopropil-2-metil-4-[6-(piridin-4-il)-8-{[(2R)-tetrahidrofurano-2-ilmetil]amino}imidazo[1,2-b]piridazin-3-il]benzamida,

N-ciclopropil-4-{8-[(1,4-dioxan-2-ilmetil)amino]-6-(piridin-4-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-2-metil-4-{6-(piridin-4-il)-8-[(tetrahidro-2H-piran-2-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-[2-(hidroximetil)fenil]-8-[(2-metoxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-metoxi-2-metilpropil)amino]-6-(1-metil-1H-pirazol-5-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-vinilimidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-2-metil-4-{8-[(3,3,3-trifluoropropil)amino]-6-vinilimidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(1,2,3,6-tetrahidropiridin-4-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-(ciclohex-1-en-1-il)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbencencarbotioamida,

N-ciclopropil-4-{6-[2-(hidroximetil)fenil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}bencencarbotioamida,

N-ciclopropil-4-{6-(1-metil-1H-pirazol-5-il)-8-[(3,3,3-

trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}bencencarbotioamida,

N-ciclopropil-4-{6-[3-(hidroximetil)fenil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}bencencarbotioamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(piridin-4-il)imidazo[1,2-b]piridazin-3-il}bencencarbotioamida,

N-ciclopropil-4-{6-ciclopropil-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(4-fluorofenil)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-3-metoxibenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(1-metil-1H-pirazol-5-il)imidazo[1,2-b]piridazin-3-il}-3-metoxibenzamida,

N-ciclopropil-3-hidroxi-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(fenilsulfanil)imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(fenilsulfanil)imidazo[1,2-b]piridazin-3-il}-3-metoxibenzamida,

N-ciclopropil-4-{6-(4-fluorofenil)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-3-metoxibenzamida,

N-ciclopropil-3-metoxi-4-{6-(1-metil-1H-pirazol-5-il)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-[2-(hidroximetil)fenil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-3-

metoxibenzamida,

N-ciclopropil-4-{6-[(2-metoxifenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

(RS)-N-ciclopropil-2-metil-4-[8-{[(4-metilmorfolin-2-il)metil]amino}-6-(fenilsulfanil)imidazo[1,2-b]piridazin-3-il]benzamida,

4-{8-[(2-amino-2-metilpropil)amino]-6-(4-fluorofenil)imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

4-{8-[(2-amino-2-metilpropil)amino]-6-(1-metil-1H-pirazol-5-il)imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

4-{8-[(2-amino-2-metilpropil)amino]-6-[2-(hidroximetil)fenil]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(4-hidroxifenil)sulfanil]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(4-metoxifenil)sulfanil]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(3-hidroxifenil)sulfanil]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(3-metoxifenil)sulfanil]imidazo[1,2-b]piridazin-3-il}-2-

metilbenzamida,

N-ciclopropil-4-{6-[(3-fluorofenil)sulfanil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-3-hidroxibenzamida,

N-ciclopropil-4-{6-[(3-fluorofenil)sulfanil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-3-metoxibenzamida

N-ciclopropil-4-{6-[(4-hidroxi-3-metilfenil)sulfanil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(5-fluoro-2-metilfenil)sulfanil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(4-fluoro-3-metilfenil)sulfanil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(3-fluoro-4-metilfenil)sulfanil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(3-fluoro-5-metilfenil)sulfanil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(3,5-difluorofenil)sulfanil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(4-fluoro-2-metilfenil)sulfanil]-8-[(2-

hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(2-fluorofenil)sulfanil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(4-fluorofenil)sulfanil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-[(2E)-but-2-en-2-il]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-3-metoxibenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(2-hidroxifenil)sulfanil]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(2-metoxifenil)sulfanil]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-3-hidroxi-4-{6-(fenilsulfanil)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-fenoxiimidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-2-metil-4-{6-fenoxi-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

4-{8-[(2-amino-2-metilpropil)amino]-6-[(3-fluorofenil)sulfanil]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{6-[(3-fluoro-5-metilfenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(2-fluoro-5-metilfenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-(3-cianofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

(RS)-N-ciclopropil-4-{6-[(3-fluorofenil)sulfinil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(3-fluorofenil)sulfonil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-2-metil-4-{6-(fenilsulfanil)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}bencencarbotioamida,

4-{6-(3-clorofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-

metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(4-metoxifenoxi)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(3-fluoro-5-metilfenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(3-fluoro-5-metilfenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(3-fluorofenil)sulfanil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

4-{6-(4-clorofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

4-{6-(3-cloro-4-fluorofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{6-(2,3-difluorofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(2-fluorofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(3-isopropilfenoxi)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-(4-cloro-3-fluorofenoxi)-8-[(2-hidroxi-2-

metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{6-(3,5-dimetilfenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(3-metilfenoxi)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-cloro-8-[(2-sulfamoiletil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida,

4-{6-cloro-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-(2,3-dihidro-1,4-benzodioxin-6-il)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(naftalen-1-il)imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-[3-(hidroximetil)fenil]-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-(4-fluorofenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-(3-metilfenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-(2,3-dimetilfenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

4-{6-[2-(acetilamino)fenil]-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida,

N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(quinolin-3-il)imidazo[1,2-b]piridazin-3-il}benzamida,

4-{3-[4-(ciclopropilcarbamoil)fenil]-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-6-il}-N,N-dimetilbenzamida,

N-ciclopropil-4-{6-(2-metilfenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(quinolin-5-il)imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(quinolin-4-il)imidazo[1,2-b]piridazin-3-il}benzamida,

4-{6-(4-carbamoilfenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida,

4-{6-(3-carbamoilfenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida,

N-ciclopropil-4-{6-(isoquinolin-4-il)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

4,4'-{8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3,6-diil}bis(N-ciclopropilbenzamida),

N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(1-metil-1H-pirazol-4-il)imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-(isoquinolin-5-il)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

3-{3-[4-(ciclopropilcarbamoil)fenil]-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-6-il}-N-metilbenzamida,

4-{3-[4-(ciclopropilcarbamoil)fenil]-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-6-il}-N-(propan-2-il)benzamida,

N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(tiofen-2-il)imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(tiofen-3-il)imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-[4-(trifluorometil)fenil]imidazo[1,2-b]piridazin-3-il}benzamida,

4-[6-(3-clorofenil)-8-(isobutilamino)imidazo[1,2-b]piridazin-3-il]-N-ciclopropilbenzamida,

N-ciclopropil-4-{6-(3-metoxifenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

4-{6-[3-(acetilamino)fenil]-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida,

4-{6-(1-benzofuran-2-il)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida,

N-ciclopropil-4-{6-(3-fluorofenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-(2-metoxifenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

4-{6-(bifenil-4-il)-8-[(2-metilpropil)amino]imidazo[1,2-

b]piridazin-3-il}-N-ciclopropilbenzamida,

N-ciclopropil-4-{6-(2,3-diclorofenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-(2-fluorofenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-[4-(hidroximetil)fenil]-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

3-{3-[4-(ciclopropilcarbamoil)fenil]-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-6-il}-N-(propan-2-il)benzamida,

N-ciclopropil-3-{3-[4-(ciclopropilcarbamoil)fenil]-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-6-il}benzamida,

4-{6-(1,3-benzodioxol-5-il)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida,

N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(1-metil-1H-pirazol-5-il)imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(piridin-3-il)imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-(2-hidroxifenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-(3-hidroxifenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-(4-hidroxifenil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-[4-

(metilsulfonil)fenil]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(pirimidin-5-il)imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(quinolin-6-il)imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-(imidazo[1,2-a]piridin-6-il)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-(6-{4-[(metilcarbamoil)amino]fenil}-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il)benzamida,

4-{6-(5-cianopiridin-3-il)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida,

N-ciclopropil-4-{6-[4-(5-metil-1,3,4-oxadiazol-2-il)fenil]-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

5-{3-[4-(ciclopropilcarbamoil)fenil]-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-6-il}-N-metilpiridin-2-carboxamida,

N-ciclopropil-4-(6-{4-[(dimetilcarbamoil)amino]fenil}-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il)benzamida,

N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(2-oxo-2,3-dihidro-1H-bencimidazol-5-il)imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-fenilimidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-[3-(hidroximetil)fenil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(1-metil-1H-pirazol-4-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[4-(hidroximetil)fenil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(piridin-3-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(furan-3-il)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(6-etoxipiridin-3-il)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(3,5-dimetil-1,2-oxazol-4-il)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(1H-pirazol-3-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(1-metil-1H-pirrol-2-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(1H-pirazol-4-il)imidazo[1,2-b]piridazin-3-il}-2-

metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(pirimidin-5-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(2-metilpiridin-4-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[4-fluoro-3-(hidroximetil)fenil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(3,6-dihidro-2H-piran-4-il)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(quinolin-5-iloxi)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(quinolin-6-iloxi)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-2-metil-4-{6-(quinolin-6-iloxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-2-metil-4-{6-(quinolin-5-iloxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

4-{6-(ciclohexilsulfanil)-8-[(3,3,3-

trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

4-{6-(ciclohexilsulfanil)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(piridin-3-iloxi)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-2-metil-4-{6-(piridin-3-iloxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-6-etenil-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina,

4-{6-cloro-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

4-{6-cloro-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida,

4-{6-cloro-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-metilbenzamida,

4-{6-cloro-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-(propan-2-il)benzamida,

2-cloro-4-{6-cloro-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-metilbenzamida,

2-cloro-4-{6-cloro-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida,

4-{6-cloro-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-

3-il}-2-fluoro-N-(propan-2-il)benzamida,

6-cloro-3-[3-(ciclopropilamino)-1,2-benzoxazol-6-il]-N-(2-metilpropil)imidazo[1,2-b]piridazin-8-amina,

6-cloro-3-[4-(2-ciclopropil-1H-imidazol-5-il)fenil]-N-(2-metilpropil)imidazo[1,2-b]piridazin-8-amina,

4-{6-cloro-8-[(tiofen-2-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N,N-dimetilbenzamida,

2-cloro-4-{6-cloro-8-[(tiofen-2-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-metilbenzamida,

2-cloro-4-{6-cloro-8-[(tiofen-2-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropilbenzamida,

4-{6-cloro-8-[(tiofen-2-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-fluoro-N-(propan-2-il)benzamida,

6-cloro-3-[3-(ciclopropilamino)-1,2-benzoxazol-6-il]-N-(tiofen-2-ilmetil)imidazo[1,2-b]piridazin-8-amina,

4-{6-cloro-8-[(tiofen-2-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-metilbenzamida,

4-{6-cloro-8-[(tiofen-2-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-[8-({(2S)-2-[(4R)-2,2-dimetil-1,3-dioxolan-4-il]-2-hidroxietil}amino)-6-(1-metil-1H-pirazol-5-il)imidazo[1,2-b]piridazin-3-il]benzamida,

N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(metilsulfanil)imidazo[1,2-b]piridazin-3-il}benzamida,

(RS)-N-ciclopropil-2-metil-4-{8-[(2-metilpropil)amino]-6-

[(tetrahidrofurano-2-ilmetil)sulfanil]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-2-metil-4-{8-[(2-metilpropil)amino]-6-(1H-pirazol-5-il)imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-2-metil-4-{8-[(2-metilpropil)amino]-6-(metilsulfanil)imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-2-metil-4-{8-[(2-metilpropil)amino]-6-(fenilsulfanil)imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-2-metil-4-{8-[(2-metilpropil)amino]-6-(fenilsulfonil)imidazo[1,2-b]piridazin-3-il}benzamida,

3-[4-(ciclopropilcarbamoil)-3-metilfenil]-N-(2-hidroxietil)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-6-carboxamida,

N-ciclopropil-4-{8-[(2-metilpropil)amino]-6-(metilsulfonil)imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-2-metil-4-{8-[(2-metilpropil)amino]-6-(propilsulfanil)imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-2-metil-4-{8-[(2-metilpropil)amino]-6-(1-metil-1H-pirazol-5-il)imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-2-metil-4-{6-(metilsulfanil)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-[(2-hidroxietil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-cloro-8-[(3,3,3-trifluoro-2-hidroxipropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-

2-metilbenzamida,

N-ciclopropil-2-metil-4-{6-(metilsulfanil)-8-[(3,3,3-trifluoro-2-hidroxipropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-2-metil-4-{6-(fenilsulfanil)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-2-metil-4-{6-(1-metil-1H-pirazol-5-il)-8-[(3,3,3-trifluoro-2-hidroxipropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-[(3-fluorofenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-(6-{[2-(dietilamino)etil]sulfanil}-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida,

N-ciclopropil-4-{8-[(3-hidroxipropil)amino]-6-(1-metil-1H-pirazol-5-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-2-metil-4-{6-(fenilsulfonil)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

4-{6-(5-cianopiridin-3-il)-8-[(2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(fenilsulfanil)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-2-metil-4-(6-{[2-(morfolin-4-il)etil]sulfanil}-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il)benzamida,

N-ciclopropil-4-{6-[(3-fluorofenil)sulfanil]-8-[(3,3,3-

trifluoro-2-hidroxipropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(3,3-dimetilbutil)sulfanil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(2,6-difluorofenil)sulfanil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(3-fluorofenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-3-hidroxibenzamida,

N-ciclopropil-4-{6-[2-(hidroximetil)fenil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-[(2E)-but-2-en-2-il]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{6-[2-(fluorometil)fenil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(2-metoxifenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(2-hidroxifenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(3-metoxifenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(3,3-dimetilbutil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(4-metoxifenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-2-metil-4-{6-(piridin-4-il)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

(RS)-N-ciclopropil-4-[6-(4-fluorofenil)-8-{[(4-metilmorfolin-2-il)metil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(piridin-4-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-2-metil-4-[6-(metilsulfanil)-8-{[2-(morfolin-4-ilsulfonil)etil]amino}imidazo[1,2-b]piridazin-3-il]benzamida,

N-ciclopropil-4-{6-(4-fluoro-2-metilfenil)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(2-fluorofenil)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-(5-cianopiridin-3-il)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[1-metil-3-(trifluorometil)-1H-pirazol-5-il]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

(RS)-4-{6-(ciclohex-1-en-1-il)-8-[(3,3,3-trifluoro-2-hidroxipropil)amino] imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-2-metil-4-[8-{[(1-metil-1H-pirazol-5-il)metil]amino}-6-(metilsulfanil)imidazo[1,2-b]piridazin-3-il]benzamida,

N-ciclopropil-4-{6-[(3-hidroxifenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-(8-[(2-hidroxi-2-metilpropil)amino]-6-{[2-(morfolin-4-il)etil]sulfanil}imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida,

(RS)-N-ciclopropil-4-{6-[(2,2-difluorociclopropil)metoxi]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-(8-[(2-hidroxi-2-metilpropil)amino]-6-{[(1E)-2,3,3-trifluoro-4-hidroxibut-1-en-1-il]oxi}imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(2,2,3,3-tetrafluoro-4-hidroxibutoxi)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-(8-[(2-hidroxi-2-metilpropil)amino]-6-{[4-(trifluorometil)fenil]sulfanil}imidazo[1,2-b]piridazin-3-il)-2-

metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-fenoxiimidazo[1,2-b]piridazin-3-il}bencencarbotioamida,

N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(2-hidroxi-2-metilpropilo) amino]imidazo[1,2-b]piridazin-3-il}bencencarbotioamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(fenilsulfanil)imidazo[1,2-b]piridazin-3-il}bencencarbotioamida,

N-ciclopropil-4-{6-[(3-fluorofenil)sulfanil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}bencencarbotioamida,

N-ciclopropil-2-metil-4-(6-{[4-(trifluorometil)fenil]sulfanil}-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il)benzamida,

N-ciclopropil-4-{6-[(2,5-difluorofenil)sulfanil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(3,4-difluorofenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(4-fluorofenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(3,5-difluorofenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(2,3-difluorofenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(4-fluorofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(3,4-difluorofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(2,5-difluorofenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(4-isopropoxifenoxi)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(4-isopropoxifenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(2,3-difluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(2-fluoro-5-metilfenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(3,4-difluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(2-tienilsulfanil)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(3,5-difluorofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-(8-[(2-hidroxi-2-metilpropil)amino]-6-{[(3S)-2-oxopirrolidin-3-il]oxi}imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(6-metilpiridin-3-il)oxi]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(pirimidin-5-iloxi)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-(3-clorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

4-{6-(4-clorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{6-[(2-fluorofenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(5-fluoro-2-metilfenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-(6-{[2-(hidroximetil)fenil]sulfanil}-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(3-metoxi-fenil)sulfanil]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

(RS)-N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(pirrolidin-3-ilamino)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(3-isopropil-fenil)sulfanil]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(piridin-2-iloxi)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[3-(2-hidroxi-2-metilpropoxi)fenoxi]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(3-fluorofenil)sulfanil]-8-[(2-hidroxi-etil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(2-hidroxietil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-2-metil-4-(6-{[(1E)-2,3,3-trifluoro-4-hidroxibut-1-en-1-il]oxi}-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il)benzamida,

N-ciclopropil-2-metil-4-{6-(2,2,3,3-tetrafluoro-4-

hidroxibutoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

metiléster de ácido 2-{3-[4-(ciclopropilcarbamoil)-3-metilfenil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-6-il}-5-fluoro-benzoico,

N-ciclopropil-4-{6-(2-hidroxifenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(3-fluoro-5-metilfenoxi)-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(2-fluorofenoxi)-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-2-metil-4-{6-(fenilsulfanil)-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-[(3-fluorofenil)sulfanil]-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(3-fluoro-5-metilfenil)sulfanil]-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(3-hidroxifenil)sulfanil]-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-2-metil-4-{6-(piridin-3-iloxi)-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-[(2-hidroxifenil)sulfanil]-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(4-fluorofenoxi)-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

4-{6-(4-cloro-3-fluorofenoxi)-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

4-{6-(4-clorofenoxi)-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{6-(2,3-difluorofenoxi)-8-[(tetrahidro-2H-tiopiran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-[6-(4-clorofenoxi)-8-({[(cis/trans)-1-oxidotetrahidro-2H-tiopiran-4-il]metil}amino)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida,

4-[6-(4-clorofenoxi)-8-{[(1,1-dioxidotetrahidro-2H-tiopiran-4-il)metil]amino}imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-[6-(4-fluorofenoxi)-8-({[(cis/trans)-1-oxidotetrahidro-2H-tiopiran-4-il]metil}amino)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[8-{[(1,1-dioxidotetrahidro-2H-tiopiran-4-

il)metil]amino}-6-(4-fluorofenoxi)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-2-metil-4-[8-({[(cis)-1-oxidotetrahidro-2H-tiopiran-4-il]metil}amino)-6-(piridin-3-iloxi)imidazo[1,2-b]piridazin-3-il]benzamida,

N-ciclopropil-2-metil-4-[8-({[(trans)-1-oxidotetrahidro-2H-tiopiran-4-il]metil}amino)-6-(piridin-3-iloxi)imidazo[1,2-b]piridazin-3-il]benzamida,

N-ciclopropil-4-[8-{[(1,1-dioxidotetrahidro-2H-tiopiran-4-il)metil]amino}-6-(piridin-3-iloxi)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[8-{[(1,1-dioxidotetrahidro-2H-tiopiran-4-il)metil]amino}-6-(2-fluorofenoxi)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[6-(3-fluorofenoxi)-8-({[(cis/trans)-1-oxidotetrahidro-2H-tiopiran-4-il]metil}amino)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[8-{[(1,1-dioxidotetrahidro-2H-tiopiran-4-il)metil]amino}-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-{6-[4-fluoro-2-(hidroximetil)fenil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(3,4-difluorofenil)sulfanil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-(8-{[(1,1-dioxidotetrahidro-2H-tiopiran-4-il)metil]amino}-6-[(3-fluorofenil)sulfanil]imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida,

N-ciclopropil-4-[8-{[(1,1-dioxidotetrahidro-2H-tiopiran-4-il)metil]amino}-6-(fenilsulfanil)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-2-metil-4-[8-({[(cis)-1-oxidotetrahidro-2H-tiopiran-4-il]metil}amino)-6-(fenilsulfanil)imidazo[1,2-b]piridazin-3-il]benzamida,

N-ciclopropil-2-metil-4-[8-({[(trans)-1-oxidotetrahidro-2H-tiopiran-4-il]metil}amino)-6-(fenilsulfanil)imidazo[1,2-b]piridazin-3-il]benzamida,

N-ciclopropil-4-(6-[(3-fluorofenil)sulfanil]-8-({[(cis)-1-oxidotetrahidro-2H-tiopiran-4-il]metil}amino)imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida,

N-ciclopropil-4-(6-[(3-fluorofenil)sulfanil]-8-({[(trans)-1-oxidotetrahidro-2H-tiopiran-4-il]metil}amino)imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida,

N-ciclopropil-4-{6-[(4-fluorofenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-anilino-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{6-[(3,4-difluorofenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(3-metilfenil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(5-fluoro-2-metilfenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-[(4-clorofenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[(1-metilpiperidin-4-il)metil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[8-{[3-(dimetilamino)propil]amino}-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[2-(metilsulfonil)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

4-{8-[(2-amino-2-metilpropil)amino]-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

4-{8-[(azetidin-3-ilmetil)amino]-6-fenoxiimidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(4H-1,2,4-triazol-3-ilsulfanil)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(4-metil-1H-imidazol-2-il)sulfanil]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(1H-imidazol-2-ilsulfanil)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(1-metil-1H-pirazol-5-il)oxi]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[4-(piperazin-1-il)fenoxi]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(1-metil-1H-pirazol-4-il)oxi]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-[4-({3-[4-(ciclopropilcarbamoil)-3-metilfenil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-6-il}oxi)fenil]piperazin-1-carboxilato de tert-butilo,

N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(3-fluorofenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(3-hidroxi-3-metilbutil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-(benciloxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-[8-{[(1,1-dioxidotetrahidrotiofen-3-il)metil]amino}-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il]-

2-metilbenzamida,

N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(tetrahidrofurano-3-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[(1-metil-5-oxopirrolidin-3-il)metil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[8-{[(3,3-difluorociclobutil)metil]amino}-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(2-metoxietil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(piridin-4-iloxi)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(piridin-4-ilsulfanil)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(piridin-2-ilsulfanil)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(tetrahidro-2H-piran-4-ilsulfanil)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-(ciclopentilsulfanil)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(piperidin-1-il)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{8-[(azetidin-3-ilmetil)amino]-6-[2-(hidroximetil)fenil]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

3-[({3-[4-(ciclopropilcarbamoil)-3-metilfenil]-6-[2-(hidroximetil)fenil]imidazo[1,2-b]piridazin-8-il}amino)metil]azetidin-1-carboxilato de tert-butilo,

N-ciclopropil-4-(8-{[(4-hidroxi-4-metilciclohexil)metil]amino}-6-[2-(hidroximetil)fenil]imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida,

N-ciclopropil-4-{8-[(3-hidroxi-3-metilbutil)amino]-6-[2-(hidroximetil)fenil]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

(RS)-N-ciclopropil-4-{6-[2-(hidroximetil)fenil]-8-[(4-hidroxipentil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

(RS)-N-ciclopropil-4-{8-[(4-hidroxi-3-metilbutil)amino]-6-[2-(hidroximetil)fenil]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-(6-[2-(hidroximetil)fenil]-8-{[(1-metil-5-oxopirrolidin-3-il)metil]amino}imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida,

(RS)-N-ciclopropil-4-{6-[2-(hidroximetil)fenil]-8-[(tetrahidrofurano-3-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[2-(hidroximetil)fenil]-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{8-[(2-cianoetil)amino]-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

4-{6-[(4-cloro-2-fluorofenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(5-metoxi-2-metilfenil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[4-fluoro-2-(hidroximetil)fenil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(3,5-difluorofenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(2,3-difluorofenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(3-fluoro-4-metoxifenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(4-metoxifenil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-[(3-clorofenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{6-[(2,4-difluorofenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-

metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(piridin-2-ilamino)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(4-fluorofenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(piridin-3-ilamino)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(2-fluoro-4-metilfenil)sulfanil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(3-isopropoxifenoxi)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(2-fluoro-4-metilfenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-[4-cloro-2-(hidroximetil)fenil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

4-{6-[4-cloro-2-(hidroximetil)fenil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(piridin-4-ilamino)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(6-metoxipiridin-3-il)amino]imidazo[1,2-b]piridazin-3-il}-2-

metilbenzamida,

N-ciclopropil-4-{6-[(2-fluoro-5-metilfenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-anilino-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{6-[(2-fluorofenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-(6-{[2-(hidroximetil)fenil]amino}-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida,

N-ciclopropil-4-{6-[(3-fluoro-5-metilfenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-[(4-cloro-3-fluorofenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{6-[(3,4-difluorofenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-[(4-clorofenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{6-[(5-fluoro-2-metilfenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-

metilbenzamida,

4-{6-[(4-cloro-2-fluorofenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

4-{6-[(5-cloro-2-metilfenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{6-[(3,5-difluorofenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-[(3-clorofenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{6-[(2,3-difluorofenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-2-metil-4-{6-[3-(propan-2-iloxi)fenoxi]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-[(4-fluoro-3-metilfenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(2-fluoro-5-metilfenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(2-fluorofenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-

metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(3-isopropilfenil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-(6-{[4-(2-hidroxietil)fenil]amino}-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida,

N-ciclopropil-4-{6-[(3-fluoro-2-metilfenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(2-metoxifenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-2-metil-4-{6-[2-(metilamino)fenoxi]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-(5-fluoro-2-metilfenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(5-fluoro-2-metilfenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-(6-{[4-cloro-2-(hidroximetil)fenil]sulfanil}-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida,

4-(6-{[4-cloro-2-(hidroximetil)fenil]sulfanil}-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-

metilbenzamida,

N-ciclopropil-4-{6-[(3-fluoro-5-metilfenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-(2-aminofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

4-{6-(2-amino-4-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{6-[(4-fluoro-2-hidroxifenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-(2-cloro-3-fluorofenoxi)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(3-metoxi-2-metilfenil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(2-hidroxifenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(4-fluoro-3-metoxifenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-[(4-cloro-3-fluorofenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(2-metoxifenil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(3-metoxifenil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-[(5-cloro-2-metilfenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

4-{6-[(2-cloro-4-fluorofenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{6-[(6-fluoropiridin-3-il)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-(ciclopentilamino)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

4-{6-(ciclopent-3-en-1-ilamino)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{6-[(3-etenilfenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(6-fluoropiridin-3-il)oxi]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

5-({3-[4-(ciclopropilcarbamoil)-3-metilfenil]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-6-il}oxi)nicotinamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(pirazin-2-ilsulfanil)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(4-metil-4H-1,2,4-triazol-3-il)sulfanil]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-(1H-pirazol-5-iloxi)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(5-metil-1H-pirazol-3-il)oxi]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-(ciclohexilamino)-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

4-{6-[(2-amino-4-fluorofenil)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{6-[2-metoxi-3-(propan-2-il)fenoxi]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-2-metil-4-{6-[(4-metil-4H-1,2,4-triazol-3-il)sulfanil]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-2-metil-4-{6-(pirazin-2-ilsulfanil)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-(6-{[(1RS,2RS)-2-hidroxiciclohexil]oxi}-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida,

N-ciclopropil-4-{6-[(4-fluoro-3-metoxifenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-2-metil-4-{6-[(3-metilfenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-[(3-fluoro-4-metoxifenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(4-metoxifenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(3-metoxi-2-metilfenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-(6-{[4-(2-hidroxietil)fenil]amino}-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida,

N-ciclopropil-4-{6-[(4-fluoro-3-metilfenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(6-metoxipiridin-3-il)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(5-metoxi-2-metilfenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(2-hidroxifenil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(4-fluoro-2-metoxifenil)amino]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-2-metil-4-(6-{[3-(propan-2-il)fenil]amino}-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il)benzamida,

N-ciclopropil-4-(6-{[2-(hidroximetil)fenil]amino}-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida,

4-(6-{[4-(2-aminoetil)fenil]amino}-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{6-[(6-fluoropiridin-3-il)oxi]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(2-fluoro-4-metoxifenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(2-fluoro-4-metoxifenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-2-metil-4-{6-(piridin-3-ilamino)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-[(6-fluoropiridin-3-il)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[2-hidroxi-3-(propan-2-il)fenoxi]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(4-fluoro-3-hidroxifenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(5-hidroxi-2-metilfenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(2-fluoro-4-metoxifenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-(2-fluoro-4-metoxifenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{8-[(2-hidroxi-2-metilpropil)amino]-6-[(3-hidroxifenil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(3,4-difluorofenil)amino]-8-[(4,4,4-trifluorobutil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(5-fluoro-2-metilfenil)amino]-8-[(4,4,4-

trifluorobutil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(3-fluoro-5-metilfenil)sulfanil]-8-[(4,4,4-trifluorobutil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(2,3-difluorofenil)amino]-8-[(4,4,4-trifluorobutil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-[(5-cloro-2-metilfenil)amino]-8-[(4,4,4-trifluorobutil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{6-(3-fluoro-5-metilfenoxi)-8-[(4,4,4-trifluorobutil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-(ciclopentilamino)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{6-[(3-hidroxi-2-metilfenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-(ciclopentiloxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{6-[(5-hidroxi-2-metilfenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(4-fluoro-2-metoxifenil)amino]-8-[(4,4,4-trifluorobutil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[2-fluoro-3-(metilsulfanil)fenoxi]-8-[(2-hidroxi-2-metilpropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metil-N-(1-metilciclopropil)benzamida,

4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-(1-metoxiciclopropil)-2-metilbenzamida,

N-(1-cianociclopropil)-4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

3-(3-amino-1H-indazol-6-il)-6-(3-fluorofenoxi)-N-(3,3,3-trifluoropropil)imidazo[1,2-b]piridazin-8-amina,

N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-[(5-fluoropiridin-3-il)oxi]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-(2-amino-5-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-2-metil-4-{6-(1,2,3,4-tetrahidroquinolin-8-iloxi)-

8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-(8-hidroxi-3,4-dihidroquinolin-1(2H)-il)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-2-metil-4-{6-[(2-oxo-1,2-dihidroquinolin-8-il)oxi]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-2-metil-4-{6-[(2-metil-1,2,3,4-tetrahidroisoquinolin-5-il)oxi]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-2-metil-4-{6-(3-metilfenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-(4-metoxifenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(4-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(2-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-2-metil-4-{6-(2-metilfenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-(3-fluoro-4-metoxifenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-

metilbenzamida,

4-(6-{[4-(acetilamino)piridin-3-il]oxi}-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il)-N-ciclopropil-2-metilbenzamida,

4-{6-(2-amino-3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{6-[(2-fluoro-6-hidroxifenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-2-metil-4-{6-(4-metilfenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-[(4-fluoro-2-hidroxifenil)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(3-hidroxipiridin-4-il)amino]-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-2-metil-4-{6-(1-feniletenil)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-(3-fluoro-4-metoxibencil)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(3-fluoro-4-metilbencil)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-(3-bromobencil)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoro-2-hidroxipropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-[8-{[2-(dimetilamino)etil]amino}-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[(1-metil-1H-pirazol-3-il)metil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(1H-pirazol-3-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-[6-(3-fluorofenoxi)-8-({[3-(hidroximetil)oxetan-3-il]metil}amino)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-{8-[(2,3-dihidroxipropil)amino]-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(2-metoxietil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-[8-{[3-(dimetilamino)-3-oxopropil]amino}-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[8-{[(4,4-difluorociclohexil)metil]amino}-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(oxetan-3-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(1H-tetrazol-5-

ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-[8-{[2-(dimetilamino)-2-metilpropil]amino}-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[2-metil-2-(morfolin-4-il)propil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[2-(piperidin-1-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[2-(4-metilpiperazin-1-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[2-(pirrolidin-1-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[6-(3-fluorofenoxi)-8-({3-[metil(metilcarbamoil)amino]propil}amino)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

4-[8-{[2-(acetilamino)etil]amino}-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[3-(piperidin-1-il)propil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[3-(morfolin-4-il)propil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[3-(pirrolidin-1-il)propil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[3-

(metilsulfonil)propil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

4-[8-{[3-(acetilamino)propil]amino}-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-[6-(3-fluorofenoxi)-8-(metilamino)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[2-(1H-tetrazol-5-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-{8-[(2,2-difluoroetil)amino]-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-[8-{[4-(dimetilamino)butil]amino}-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-{6-(3-fluorofenoxi)-8-[(2,2,2-trifluoroetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[2-(1H-pirazol-1-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[6-(2,3-difluorofenoxi)-8-{[2-(metilsulfonil)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[6-(5-fluoro-2-metilfenoxi)-8-{[2-(metilsulfonil)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[6-(3-fluoro-4-metoxifenoxi)-8-{[2-(metilsulfonil)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-

metilbenzamida,

N-ciclopropil-4-[6-(2-fluoro-4-metoxifenoxi)-8-{[2-(metilsulfonil)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

4-{8-[(2-amino-2-metilpropil)amino]-6-(3,4-difluorofenoxi)imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

4-{8-[(2-amino-2-metilpropil)amino]-6-(4-clorofenoxi)imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

4-{8-[(2-amino-2-metilpropil)amino]-6-(piridin-3-iloxi)imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

4-[6-(4-clorofenoxi)-8-{[2-(dimetilamino)etil]amino}imidazo[1,2-b]piridazin-3-il]-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-[8-{[2-(dimetilamino)etil]amino}-6-(piridin-3-iloxi)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[6-(3,4-difluorofenoxi)-8-{[2-(dimetilamino)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[6-(2,3-difluorofenoxi)-8-{[(1-metilpiperidin-4-il)metil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-2-metil-4-[8-{[(1-metilpiperidin-4-il)metil]amino}-6-(piridin-3-iloxi)imidazo[1,2-b]piridazin-3-il]benzamida,

N-ciclopropil-4-[6-(2,3-difluorofenoxi)-8-

(metilamino)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[6-(3,4-difluorofenoxi)-8-
(metilamino)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[6-(5-fluoro-2-metilfenoxi)-8-
(metilamino)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-2-metil-4-{8-(metilamino)-6-[2-
(metilamino)fenoxi]imidazo[1,2-b]piridazin-3-il}benzamida,

N-ciclopropil-4-{6-[(2-hidroxifenil)(metil)amino]-8-
(metilamino)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-{6-[(5-fluoropiridin-3-il)oxi]-8-
(metilamino)imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-ciclopropil-4-[6-(2-fluoro-4-metoxifenoxi)-8-
(metilamino)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[6-(3-fluoro-4-metoxifenoxi)-8-
(metilamino)imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[6-(2,3-difluorofenoxi)-8-{[2-(morfolin-4-
il)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-[6-(5-fluoro-2-metilfenoxi)-8-{[2-(morfolin-4-
il)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-2-metil-4-(6-[2-(metilamino)fenoxi]-8-{[2-
(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-
il)benzamida,

N-ciclopropil-4-(6-[(2-hidroxifenil)(metil)amino]-8-{[2-
(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il)-2-
metilbenzamida,

N-ciclopropil-4-[6-(3,4-difluorofenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-ciclopropil-4-(6-[(5-fluoropiridin-3-il)oxi]-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il)-2-metilbenzamida,

N-ciclopropil-4-[6-(3-fluorofenoxi)-8-{[(1-metilazetidin-3-il)metil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

4-{8-[(azetidin-3-ilmetil)amino]-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

N-ciclopropil-4-[6-(2,3-difluorofenoxi)-8-{[(1-metilazetidin-3-il)metil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

4-{8-[(azetidin-3-ilmetil)amino]-6-(2,3-difluorofenoxi)imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

4-{8-[(azetidin-3-ilmetil)amino]-6-[(5-fluoropiridin-3-il)oxi]imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

4-{8-[(azetidin-3-ilmetil)amino]-6-(5-fluoro-2-metilfenoxi)imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

4-{8-[(3-aminopropil)amino]-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-3-il}-N-ciclopropil-2-metilbenzamida,

ácido 3-({3-[4-(ciclopropilcarbamoil)-3-metilfenil]-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-8-il}amino)propan-1-sulfónico,

ácido 2-({3-[4-(ciclopropilcarbamoil)-3-metilfenil]-6-(3-fluorofenoxi)imidazo[1,2-b]piridazin-8-il}amino)etansulfónico,

N-(1-cianociclopropil)-4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida,

N-etil-4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-isopropil-2-metilbenzamida,

4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metil-N-(3,3,3-trifluoropropil)benzamida,

4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metil-N-(2,2,3,3,3-pentafluoropropil)benzamida,

N-(2,2-difluoroetil)-4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-isobutil-

2-metilbenzamida,

4-{6-(4-clorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida,

4-{6-(4-clorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N-etil-2-metilbenzamida,

4-{6-(2-fluoro-4-hidroxifenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida,

N-etil-4-{6-(2-fluoro-4-hidroxifenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-[6-(3,4-difluorofenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-N,2-dimetilbenzamida,

N,2-dimetil-4-[6-(2-metilfenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il]benzamida,

4-[6-(4-metoxifenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-N,2-dimetilbenzamida,

4-[6-(2-fluoro-4-metoxifenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-N,2-dimetilbenzamida,

4-[6-(5-fluoro-2-metilfenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-N,2-

dimetilbenzamida,

4-{6-(3,4-difluorofenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida,

N,2-dimetil-4-{6-(2-metilfenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

4-{6-(3-fluorofenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida,

4-{6-(4-metoxifenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida,

4-{6-(2-fluoro-4-metoxifenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida,

4-{6-(5-fluoro-2-metilfenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida,

4-{6-(3-fluoro-4-metoxifenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida,

4-{6-(3,4-difluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida,

4-{6-(3-fluorofenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-

dimetilbenzamida,

4-{6-(2-fluoro-4-metoxifenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida,

4-{6-(5-fluoro-2-metilfenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida,

4-{6-(3-fluoro-4-metoxifenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida,

4-{8-[(2,2-difluoroetil)amino]-6-(3,4-difluorofenoxi)imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida,

4-{8-[(2,2-difluoroetil)amino]-6-(2-fluoro-4-metoxifenoxi)imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida,

4-{6-(2,3-difluorofenoxi)-8-[(2-metoxietil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida,

4-{6-(3,4-difluorofenoxi)-8-[(2-metoxietil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida,

4-{8-[(2-metoxietil)amino]-6-(2-metilfenoxi)imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida,

4-{6-(2-fluoro-4-metoxifenoxi)-8-[(2-metoxietil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida,

4-{6-(5-fluoro-2-metilfenoxi)-8-[(2-metoxietil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-

dimetilbenzamida,

4-{6-(3-fluoro-4-metoxifenoxi)-8-[(2-metoxietil)amino]imidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida,

4-{8-[(2-metoxietil)amino]-6-fenoxiimidazo[1,2-b]piridazin-3-il}-N,2-dimetilbenzamida,

4-[6-(3,4-difluorofenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-N-etil-2-metilbenzamida,

N-etil-2-metil-4-[6-(2-metilfenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il]benzamida,

N-etil-4-[6-(4-metoxifenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-etil-4-[6-(2-fluoro-4-metoxifenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-etil-4-[6-(5-fluoro-2-metilfenoxi)-8-{[2-(morfolin-4-il)etil]amino}imidazo[1,2-b]piridazin-3-il]-2-metilbenzamida,

N-etil-2-metil-4-(8-{[2-(morfolin-4-il)etil]amino}-6-fenoxiimidazo[1,2-b]piridazin-3-il)benzamida,

4-{6-(3,4-difluorofenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-N-etil-2-metilbenzamida,

N-etil-2-metil-4-{6-(2-metilfenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-etil-4-{6-(4-metoxifenoxi)-8-[(tetrahidro-2H-piran-4-

ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-etil-4-{6-(2-fluoro-4-metoxifenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-etil-4-{6-(5-fluoro-2-metilfenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-etil-4-{6-(3-fluoro-4-metoxifenoxi)-8-[(tetrahidro-2H-piran-4-ilmetil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-etil-2-metil-4-{6-(2-metilfenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}benzamida,

N-etil-4-{6-(2-fluoro-4-metoxifenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-etil-4-{6-(5-fluoro-2-metilfenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-etil-4-{6-(3-fluoro-4-metoxifenoxi)-8-[(3,3,3-trifluoropropil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

4-{8-[(2,2-difluoroetil)amino]-6-(2-fluoro-4-metoxifenoxi)imidazo[1,2-b]piridazin-3-il}-N-etil-2-metilbenzamida,

4-{8-[(2,2-difluoroetil)amino]-6-(5-fluoro-2-metilfenoxi)imidazo[1,2-b]piridazin-3-il}-N-etil-2-metilbenzamida,

4-{6-(3,4-difluorofenoxi)-8-[(2-metoxietil)amino]imidazo[1,2-b]piridazin-3-il}-N-etil-2-metilbenzamida,

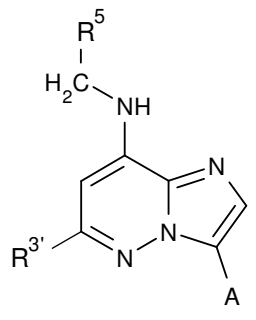
N-etil-4-{6-(2-fluoro-4-metoxifenoxi)-8-[(2-metoxietil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-etil-4-{6-(5-fluoro-2-metilfenoxi)-8-[(2-metoxietil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

N-etil-4-{6-(3-fluoro-4-metoxifenoxi)-8-[(2-metoxietil)amino]imidazo[1,2-b]piridazin-3-il}-2-metilbenzamida,

o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato o una sal del mismo, o una mezcla de los mismos.

9. Un método para preparar un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 8, en donde dicho método comprende el paso de permitir que un compuesto intermediario con la fórmula general **IV**:



IV

en donde A, y R^5 son según se los definió para la fórmula general **I** en cualquiera de las reivindicaciones 1 a 8, y $R^{3'}$ es un grupo saliente;

reaccione con un compuesto de fórmula general **IVa**:

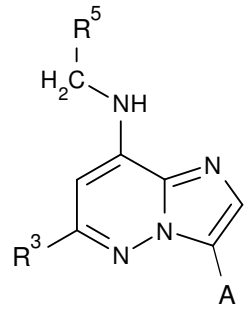
R^3–Y

IVa

en donde R^3 es según se definió para la fórmula general **I** en cualquiera de las reivindicaciones 1 a 8, e Y es un

sustituyente que es desplazado en una reacción de acoplamiento, como por ejemplo un átomo de hidrógeno, o un grupo ácido borónico, o un grupo éster borónico, por ejemplo,

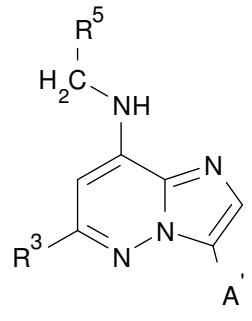
para dar de esa manera un compuesto de fórmula general **I**:



I

en donde A, R^3, y R^5 son según se los definió para la fórmula general **I** en cualquiera de las reivindicaciones 1 a 8.

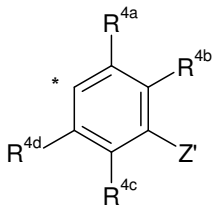
10. Un método para preparar un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 8, en donde dicho método comprende el paso de permitir que un compuesto intermediario con la fórmula general **Ia**:



Ia

en donde R^3 y R^5 son según se los definió para la fórmula general **I** en cualquiera de las reivindicaciones 1 a 8;

y A' es



donde * indica el punto de unión de dicho grupo con el resto de la molécula; R^{4a}, R^{4b}, R^{4c} y R^{4d} son según se los definió para la fórmula general **I** en cualquiera de las reivindicaciones 1 a 8, y Z' representa un grupo que se selecciona entre:

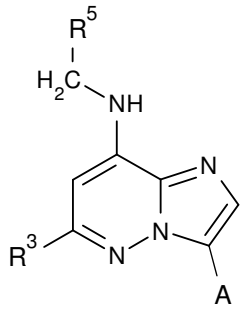
-C(=O)OH, -C(=S)OH, -C(=O)O-(C_1-C_6-alquilo) o -C(=S)O-(C_1-C_6-alquilo);

reaccione con un compuesto de fórmula general **Ib:**

H_2NR^2

Ib

en donde R^2 es según se definió para la fórmula general **I** en cualquiera de las reivindicaciones 1 a 8, para dar de esa manera, tras una desprotección opcional, un compuesto de fórmula general **I:**

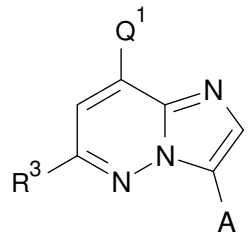


I

en donde R^3, R^5 y A son según se los definió para la fórmula

general **I** en cualquiera de las reivindicaciones 1 a 8.

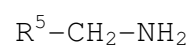
11. Un método para preparar un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 8, en donde dicho método comprende el paso de permitir que un compuesto intermediario con la fórmula general **VII:**



VII

en donde R^3 y A son según se los definió para la fórmula general **I** en cualquiera de las reivindicaciones 1 a 8, y Q^1 es un grupo saliente,

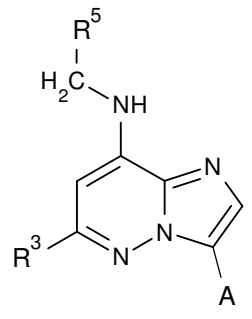
reaccione con un compuesto de fórmula general **VIIa:**



VIIa

en donde R^5 es según se definió para la fórmula general **I**, en cualquiera de las reivindicaciones 1 a 8,

para dar de esa manera, tras una desprotección opcional, un compuesto de fórmula general **I:**



I

en donde R^3, R^5 y A son según se los definió para la fórmula general **I** en cualquiera de las reivindicaciones 1 a 8.

12. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 8, o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato, o una sal de los mismos, en particular una sal farmacéuticamente aceptable de los mismos, o una mezcla de los mismos, para utilizar en el tratamiento o la profilaxis de una enfermedad.

13. Una composición farmacéutica que comprende un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 8, o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato, o una sal de los mismos, en particular una sal farmacéuticamente aceptable de los mismos, o una mezcla de los mismos, y un diluyente o vehículo farmacéuticamente aceptable.

14. Una combinación farmacéutica que comprende:

- uno o más compuestos de acuerdo con cualquiera de las reivindicaciones 1 a 8, o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato, o una sal de los mismos, en particular una sal farmacéuticamente aceptable de los mismos, o una mezcla de los mismos;

y

- uno o más agentes que se seleccionan entre: un taxano, como por ejemplo Docetaxel, Paclitaxel, o Taxol; un epotilona, como por ejemplo Ixabepilona, Patupilona, o Sagopilona; Mitoxantrona; Predinisolona; Dexametasona; Estramustina; Vinblastina; Vincristina; Doxorrubicina;

Adriamicina; Idarrubicina; Daunorrubicina; Bleomicina; Etopósido; Ciclofosfamida; Ifosfamida; Procarbazina; Melphalan; 5-Fluorouracilo; Capecitabina; Fludarabina; Citarabina; Ara-C; 2-Cloro-2´-desoxiadenosina; Tioguanina; un antiandrógeno, como por ejemplo Flutamida, acetato de ciproterona , o Bicalutamida; Bortezomib; un derivado de platino, como por ejemplo Cisplatino, o Carboplatino; Clorambucilo; Metotrexato; y Rituximab.

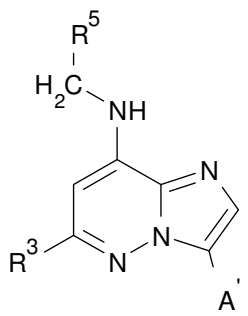
15. El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 8, o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato, o una sal de los mismos, en particular una sal farmacéuticamente aceptable de los mismos, o una mezcla de los mismos, para la profilaxis o el tratamiento de una enfermedad.

16. El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 8, o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato, o una sal de los mismos, en particular una sal farmacéuticamente aceptable de los mismos, o una mezcla de los mismos, para la preparación de un medicamento para la profilaxis o el tratamiento de una enfermedad.

17. El uso de acuerdo con la reivindicación 12, 15 o 16, en donde dicha enfermedad es una enfermedad por crecimiento, proliferación y/o supervivencia celular descontrolados, una respuesta celular inmune inapropiada, o una respuesta celular inflamatoria inapropiada, en particular en la cual el crecimiento, la proliferación y/o la supervivencia celular descontrolados, la respuesta celular inmune

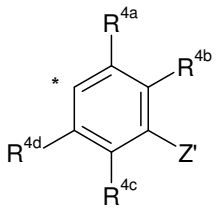
inapropiada, o la respuesta celular inflamatoria inapropiada son mediados por la vía metabólica de la proteína quinasa activada por mitógeno (MEK-ERK), más en particular en la cual la enfermedad por crecimiento, proliferación y/o supervivencia celular descontrolados, respuesta celular inmune inapropiada, o respuesta celular inflamatoria inapropiada es un tumor hematológico, un tumor sólido y/o una metástasis de los mismos, *por ejemplo* leucemias y síndrome mielodisplástico, linfomas malignos, tumores de cabeza y cuello , incluyendo tumores cerebrales y metástasis en el cerebro, tumores de tórax , incluyendo tumores pulmonares de células no pequeñas y de células pequeñas, tumores gastrointestinales, tumores endocrinos, tumores mamarios y otros tumores ginecológicos, tumores urológicos que incluyen tumores renales, de vejiga y de próstata, tumores de piel, y sarcomas, y/o metástasis de los mismos.

18. Un compuesto que se puede representar por la fórmula general **Ia:**



Ia

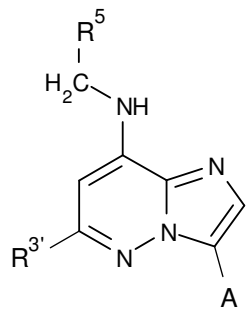
en donde R^3 y R^5 son según se los definió para los compuestos con la fórmula general **I** en cualquiera de las reivindicaciones 1 a 8, y A' es



donde * indica el punto de unión de dicho grupo con el resto de la molécula; R^{4a}, R^{4b}, R^{4c} y R^{4d} son según se los definió para los compuestos con la fórmula general **I** en cualquiera de las reivindicaciones 1 a 8, y Z' representa un grupo que se selecciona entre:

-C(=O)OH, -C(=S)OH, -C(=O)O-(C_1-C_6-alquilo) o -C(=S)O-(C_1-C_6-alquil).

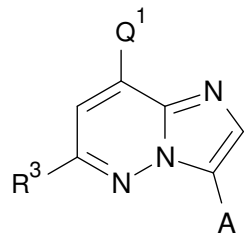
19. Un compuesto que se puede representar por la fórmula general **IV:**



IV

en donde A, y R^5 son según se los definió para los compuestos con la fórmula general **I** en cualquiera de las reivindicaciones 1 a 8, y $R^{3'}$ es un grupo saliente.

20. Un compuesto que se puede representar por la fórmula general **VII:**



VII

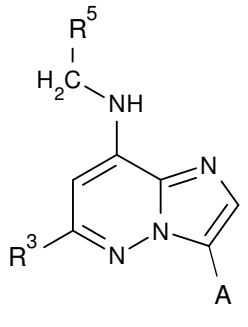
en donde A, y R^3 son según se los definió para los compuestos con la fórmula general **I** en cualquiera de las reivindicaciones 1 a 8, y Q^1 representa un grupo NH_2 opcionalmente protegido o un grupo saliente.

21. El uso de un compuesto de cualquiera de las reivindicaciones 18, 19 ó 20 para la preparación de un compuesto de fórmula general **I**.

IMIDAZOPIRIDAZINAS SUSTITUIDAS

RESUMEN

Compuestos de imidazopiridazina sustituida de la fórmula general I



I

donde R^3, R^5 y A son como se definen en la descripción y en las reivindicaciones. Métodos para preparar dichos compuestos. Composiciones y combinaciones farmacéuticas que comprenden dichos compuestos. Uso de dichos compuestos para preparar una composición farmacéutica para el tratamiento o la profilaxis de una enfermedad, en particular de un trastorno hiperproliferativo y/o angiogenésis, como un único agente o en combinación con otros ingredientes activos.

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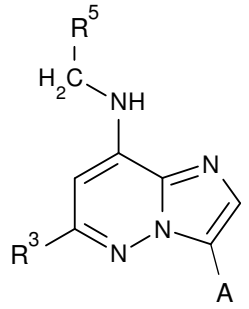
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(54) Título: IMIDAZOPIRIDAZINAS SUSTITUIDAS

57) Resumen: (I)



La presente invención se relaciona con compuestos de imidazopiridazina sustituida de la fórmula general I, que son inhibidores de la quinasa Mps –1 (del huso monopolar 1) (también conocidos como quinasa de tirosina y treonina, TTK)
donde R^3, R^5 y A son como se definen en la descripción y en las reivindicaciones. Métodos para preparar dichos compuestos. Composiciones y combinaciones farmacéuticas que comprenden dichos compuestos. Uso de dichos compuestos para preparar una composición farmacéutica para el tratamiento o la profilaxis de una enfermedad, en particular de un trastorno hiperproliferativo y/o angiogenésis, como un único agente o en combinación con otros ingredientes activos.

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06 September 2011 (06.09.2011)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address
BAYER PHARMA AKTIENGESELLSCHAFT
Müllerstrasse 178
13353 Berlin
Germany

State of Nationality: DE
State of Residence: DE
Telephone No.:
Facsimile No.:
E-mail address:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address
BAYER INTELLECTUAL PROPERTY GMBH
Alfred-Nobel-Strasse 10
40789 Monheim
Germany

State of Nationality: DE
State of Residence: DE
Telephone No.:
Facsimile No.:
E-mail address:
☐ Notifications by e-mail authorized

3. Further observations, if necessary:
The common representative has also changed, as indicated in the addressee box at the top of this form.

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Authorized officer
Nissen Diana
e-mail diana.nissen@wipo.int
Telephone No. +4122 338 8054

TRATADO DE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES

ADELANTO POR E_MAIL

De la OFICINA INTERNACIONAL

PCT

Notificación de registro de una modificación

(regla PCT 92bis.1 e Instrucciones Administrativas , sección 422)

A:

BAYER INTELLECTUAL PROPERTY GMBH
Creativ Campus Monheim
Alfred-Nobel-Straße 10
40789 Monheim
ALEMANIA

Fecha de envío (*día/mes/año*):
01 de octubre de 2012 (01.10.2012)

Referencia del solicitante o del agente:
BHC103048-WO

NOTIFICACIÓN IMPORTANTE

Solicitud Internacional Nº:
PCT/EP 2011/065368

Fecha de presentación internacional (*día/mes/año*):
06 de septiembre de 2011 (06.09.2011)

1. Las siguientes indicaciones aparecen en los registros concernientes a:

☒ el solicitante ☐ el inventor ☐ el agente ☐ el representante común

Nombre y dirección:

BAYER PHARMA AKTIENGESELLSCHAFT
Müllerstrasse 178
13353 Berl{in
ALEMANIA

País de Nacionalidad: *DE*
País de Residencia: *DE*

Teléfono Nº:

Facsímil Nº:

Dirección de E-mail

2. La Oficina Internacional notifica por este medio al solicitante que se registró la siguiente modificación, concerniente a:

☒ la persona ☐ el nombre ☐ el domicilio ☐ la nacionalidad ☐ la residencia

Nombre y dirección:

BAYER INTELLECTUAL PROPERTY GMBH
Alfred-Nobel-Straße 10
40789 Monheim
ALEMANIA

País de Nacionalidad: *DE*
País de Residencia: *DE*

Teléfono Nº:

Facsímil Nº:

Dirección de E-mail

☐ Se autoriza notificar por E-mail

3. Otras observaciones, si son necesarias:

El representante común también ha cambiado, como lo indica el campo de la dirección en el encabezamiento de este formulario

4. Se envía una copia de esta notificación a:

☒ la Oficina receptora
☐ el Organismo de Búsqueda Internacional
☐ el Organismo especificado para búsquedas suplementarias
☐ el Organismo de Examen Preliminar Internacional
☒ las Oficinas designadas concernientes
☐ las Oficinas seleccionadas concernientes
☐ otros:

La Oficina Internacional de WIPO
34, chemin des Colombettes
1211 Geneva 20, Suiza

Facsímil Nº: +41 22 338 82 70

Funcionario autorizado:
Nissen Diana
e-mail: *diana.nissen@wipo.int*
Teléfono Nº: *+41 22 338 8054*

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
BHC103048-WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2011/065368	06/09/2011	10/09/2010
Applicant		
BAYER PHARMA AKTIENGESELLSCHAFT		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

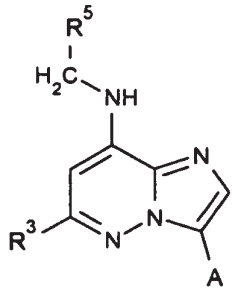
4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

ABSTRACT

The present invention relates to substituted imidazopyridazine compounds of general formula I:



I

in which R^3, R^5, and A are as defined in the claims, to methods of preparing said compounds, to pharmaceutical compositions and combinations comprising said compounds and to the use of said compounds for manufacturing a pharmaceutical composition for the treatment or prophylaxis of a disease, in particular of a hyper-proliferative and/or angiogenesis disorder, as a sole agent or in combination with other active ingredients.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/065368

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/5025 A61P35/00
ADD.

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.
X,P	WO 2011/013729 A1 (ONCOTHERAPY SCIENCE INC [JP]; KUSAKABE KEN-ICHI [JP]; YOSHIDA HIROSHI) 3 February 2011 (2011-02-03) cited in the application pages 66-68,15; claim 1	1-21
A	WO 2007/038314 A2 (SQUIBB BRISTOL MYERS CO [US]; VACCARO WAYNE [US]; CHEN ZHONG [US]; DOD) 5 April 2007 (2007-04-05) cited in the application page 44, line 4; claim 1	1-21

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 November 2011	18/11/2011

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

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2011/065368

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011013729 A1	03-02-2011	TW 201107329 A	01-03-2011
WO 2007038314 A2	05-04-2007	AR 055177 A1	08-08-2007
		AU 2006295439 A1	05-04-2007
		BR PI0616393 A2	21-06-2011
		CA 2623369 A1	05-04-2007
		EA 200800873 A1	29-08-2008
		EP 1928879 A2	11-06-2008
		JP 2009509961 A	12-03-2009
		KR 20080063344 A	03-07-2008
		NZ 566663 A	31-03-2011
		PE 05202007 A1	29-08-2007
		TW 200804385 A	16-01-2008
		US 2007078136 A1	05-04-2007
		US 2008045536 A1	21-02-2008
		US 2010204212 A1	12-08-2010

TRATADO DE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES

PCT

Informe de Búsqueda Internacional

(Artículo PCT 18, así como reglas PCT 43 y 44)

Referencia del solicitante o del agente	**PROCEDER**	Ver notificación formulario PCT/ISA/220, así como, en tanto corresponda, el punto 5.abajo
BHC103048-WO		
Solicitud Internacional Nº:	Fecha de presentación Internacional (*día/mes/año*)	Fecha de prioridad (la más antigua) (*día/mes/año*)
PCT/EP/ 2011/065368	*06/09/2011*	*10/09/2010*
Solicitante		
BAYER PHARMA AKTIENGESELLSCHAFT		

Este Informe de Búsqueda Internacional fue elaborado por el Organismo de Búsqueda Internacional y, de acuerdo con el artículo 18, es enviado al solicitante. Se envía una copia a la Oficina Internacional.

Este informe de búsqueda Internacional comprende, en total, 4 hojas.

☒ Además se adjunta una copia de cada uno de los documentos del estado de la técnica mencionados en este informe

1. **Fundamentos del Informe**

   a. Con respecto al idioma, la búsqueda internacional fue llevada a cabo sobre la base de:

      ☒ la solicitud internacional en el idioma en que fue presentada
      ☐ una traducción de la solicitud internacional al , que es el idioma de una traducción suministrada a los fines de la búsqueda internacional (reglas 12.3(a) y 23.1 (b)).

   b. ☐ Este informe de búsqueda internacional ha sido confeccionado teniendo en consideración la **rectificación de un error obvio**, autorizada por o notificada a este organismo según la regla 91 (regla 43.6*bis*(b))

   c. ☐ Con respecto a los **nucleótidos y/o aminoácidos** revelados en la solicitud internacional, ver campo Nº 1

2. ☐ **Determinadas reivindicaciones no eran investigables** (ver campo II)**.**

3. ☐ **La invención carece de unidad** (ver campo III)**.**

4. Con respecto **al título**,

   ☒ se aprueba el texto presentado por el solicitante.

   ☐ el texto fue establecido por el organismo como sigue:

5. Con respecto al **resumen**,

   ☐ se aprueba el texto presentado por el solicitante.

   ☒ el texto fue establecido por el organismo, de acuerdo con la regla 38.2 b), en la versión indicada en el campo IV. El solicitante puede presentar una posición ante el organismo durante el transcurso de un mes a partir de la fecha de envío de este Informe de Búsqueda Internacional.

6. Con respecto a las **ilustraciones**

   a. Con el resumen se debe publicar la siguiente figura de Las **ilustraciones**: figura Nº --.

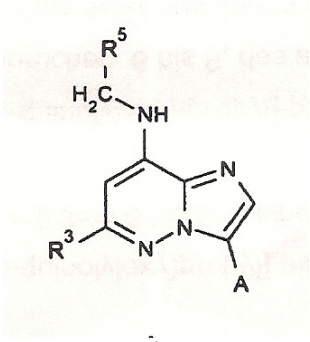
      ☐ sugerida por el solicitante.

      ☐ seleccionada por el organismo, dado que el mismo solicitante no sugiere ninguna figura.

      ☐ seleccionada por el organismo, dado que esta figura caracteriza mejor la invención.

   b. ☐ con el resumen no se publica ninguna de las ilustraciones

La presente invención se refiere a compuestos de imidazopiridazinas sustituidos que responden a la fórmula general I:



I

en la cual R^3, R^5 y A son como están definidas en las reivindicaciones, a métodos de preparación de tales compuestos, a composiciones y combinaciones farmacéuticas que comprenden tales compuestos y al uso de tales compuestos en la elaboración de una composición farmacéutica para el tratamiento o profilaxis de una enfermedad, en particular, de un trastorno hiperproliferativo y/o angiogenético, como agente individual o en combinación con otros ingredientes activos.

los que son inhibidores de la quinasa Mps = 1 (Monopolar spindle 1) (también conocidos como quinasa tirosina treonina, TTK)

INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud Internacional Nº:
PCT/EP 2011/065368

A. CLASIFICACIÓN DEL OBJETO DE LA SOLICITUD
INV. C07D487/04 A61K31/5025 A61P35/00
ADD.

Según la clasificación internacional de patentes (IPC) o las clasificaciones nacional e IPC

B. ÁMBITOS INVESTIGADOS

Documentación mínima investigada (Sistema de clasificación y símbolos de clasificación)

C07D

Publicaciones investigadas pero no pertenecientes al material mínimo investigado, en tanto pertenezcan al ámbito investigado

Base de datos electrónica consultada durante la búsqueda internacional (nombre de la base de datos y expresiones de búsqueda eventualmente empleadas)

EPO-Internal, CHEM ABS Data

C. ANTECEDENTES CONSIDERADOS RELEVANTES

Categoría°	Denominación de la publicación, así como, de ser apropiado, indicación de los pasajes relevantes	Relevante para reivindicación Nº:
X, P	*WO 2011/013729 A1 (ONCOTHERAPY SCIENCE INC [JP]; KUSAKABE KEN-ICHI [JP]; YOSHIDA HIROSHI) 3 de febrero de 2011 (2011-02-03) mencionado en la solicitud pp. 66-68, 15; reivindicación 1*	*1-21*
A	*WO 2007/038314 A2 (SQUIBB BRISTOL MEYERS CO[US]; VACCARO WAYNE [US]; CHEN ZONG [US]; DOD) 5 de abril de 2007 (2007-04-05) mencionado en la solicitud pp. 44, renglón 4; reivindicación 1*	*1-21*

☐ Otras publicaciones están listadas en la continuación del campo C

☒ Ver familia de patentes en el anexo

° Categorías particulares indicadas en publicaciones
"A" publicación que define el estado general de la técnica pero no considerada como particularmente importante
"B" documento anterior pero publicado recién o después de la de la fecha de presentación internacional
"L" publicación adecuada para hacer aparecer como dudosa una reivindicación de prioridad, o mediante la cual debe ser considerada la fecha de divulgación de otra publicación mencionada en el informe de búsqueda o que es indicada por otra razón particular (como realizada)
"O" publicación que se refiere a una revelación oral, a una utilización, a una exposición o a otras disposiciones
"P" publicación realizada antes de la fecha de presentación internacional pero luego de la fecha de prioridad reivindicada
"T" publicaciones posteriores a las difundidas en la fecha de presentación internacional o de la fecha de prioridad y que no colisionan con la solicitud, sino que solo están indicadas para mayor entendimiento del principio fundamental de la invención o de la teoría sobre la cual se basa
"X" publicación de particular importancia: la invención reivindicada no puede ser considerada, solo como consecuencia de esta publicación, como novedosa o apoyarse en una actividad inventiva
"Y" publicación de particular importancia: la invención reivindicada no puede ser considerada como apoyada en una actividad inventiva cuando puede ser relacionada con una o varias otras publicaciones de esta categoría y tal relación es notoria para un especialista
"&" publicación que es miembro de la misma familia

Fecha de finalización de la búsqueda internacional	Fecha de envío del Informe de Búsqueda Internacional
8 de noviembre de 2011	*18/11/2011*
Nombre y Dirección Postal del ISA/ Oficina de Patentes Europea NL – 2280 HV Rijswijk Tel (+31-70) 340-2040. Fax Nº (+31-70) 340-3016	Funcionario Apoderado *Grassi, Damian*

INFORME DE BÚSQUEDA INTERNACIONAL
Información de miembros de la familia de patentes

Solicitud Internacional Nº:
PCT/EP 2011/065368

Documentos de Patente citados en el Informe de Búsqueda	Fecha de publicación	Miembros de la familia de patentes	Fecha de publicación
WO 2011013729 A1	03-02-2011	TW 2011107329 A	01-03-2011
WO 2007038374 A2	05-04-2007	AR 055177 A1	08-08-2007
		AU 2006295439 A1	05-04-2007
		BR PI0616393 A2	21-06-2011
		CA 2326369 A1	05-04-2007
		EA 200800873 A1	29-08-2008
		EP 1928879 A2	11-06-2008
		JP 2009509961 A	12-03-2009
		KR 20080063344 A	03-07-2008
		NZ 566663 A	31-03-2011
		PE 05202007 A1	29-08-2007
		TW 200804385 A	16-01-2008
		US 2007078136 A1	05-04-2007
		US 2008045536 A1	21-02-2008
		US 2010204212 A1	12-08-2010