SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 14-073129- -00000-0000
Fecha: 2014-04-04 17:17:24 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 87

Industria y Comercio
SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DIVISIONAL DE PATENTE DE INVENCIÓN

TITULO: BENZILINDAZOLES SUSTITUIDOS PARA USO COMO INHIBIDORES DE LA QUINASA BUB1 EN EL TRATAMIENTO DE ENFERMEDADES HIPERPROLIFERATIVAS

SOLICITANTE: Bayer Intellectual Property GmbH y Bayer Pharma Aktiengesellschaft

DIRECCIÓN: (1) Alfred-Nobel-Str. 10, 40789 Monheim, Alemania
(2) Müllerstrasse 178, 13353 Berlin, Alemania.

APODERADO: CARLOS R. OLARTE

BOGOTÁ: 04 de abril de 2014

P2014/000053

OLARTEMOURE

OLARTE MOURE & ASOCIA

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 14-073129- -00000-0000

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PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2014/000053**

SOLICITUD DE:

(1)

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

[X] Capítulo I. [ ] Capítulo II.

(2)

SOLICITANTE (71)

Nombres: **Bayer Intellectual Property GmbH y Bayer Pharma Aktiengesellschaft**
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C.C. [ ] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual
Número

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C.E. [ ] **Otro** [ ]
Cual
Número 79.782.747Bta
TP 74.295

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA
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NACIONALIDAD O DOMICILIO: VER PAGINA ADJUNTA

(5)

PCT (86)
Solicitud Internacional No. PCT/EP2012/069562 Fecha Octubre 4, 2012
Publicación Internacional No. WO 2013/050438 Fecha Abril 11, 2013

(6)

Título (54) **BENZILINDAZOLES SUSTITUIDOS PARA USO COMO INHIBIDORES DE LA QUINASA BUB1 EN EL TRATAMIENTO DE ENFERMEDADES HIPERPROLIFERATIVAS**

Clasificación Internacional (51) C07D 401/14, C07D 405/14, C07D 413/14, C07D 498/04, A61K 31/506, A61P 35/00.

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
EP	Octubre 06, 2011	11184061.7

(9)

Comprobante de pago No. 14- **Fecha**

(10) **ANEXOS**

X	Comprobante de pago de la tasa de presentación de la solicitud.
	Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
X	Poderes, si fuere el caso.
	Documento de cesión del inventor al solicitante o a su causante.
X	Declaraciones. Declaración 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.
X	Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

LISTA DE INVENTORES

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Nacionalidad: Alemana

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 14 - 0029539

Bogotá D.C., Marzo 17 de 2014 - 13:53:00

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	609953573	14/03/2014	17.818.250.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	515.000.00	515.000.00
				$515.000.00

SON: **QUINIENTOSQUINCE MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-********-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 14-073129- -00000-0000
Fecha: 2014-04-04 17:17:24 Dep. 2020 DIR.NUEVASCR
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7
6

Industria y Comercio
SUPERINTENDENCIA

PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA
RELACIÓN DE ANEXOS

Dependencia: 2020	Fecha: 14 / 04 / 04 (AAAA / MM / DD)	Recorrido: 4
Tipo de Radicación: Entrada: X Salida: ☐ Traslado: ☐ Convenio: ☐		
Radicador:		Planilla:

ID	No. Radicación	Consecutivo	Item
1	14-73129	0	7
2			
3			
4			
5			
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***
X	CD
8	Disquete
9	DVD
10	Folleto
11	Foto
12	Periódico
13	Plano
14	Publicación Periódica
15	USB
16	Otro

Observaciones:

EL CD ANEXO CONTIENE UN TOTAL DE 9 ARCHIVOS:

9 EN FORMATO PDF, LOS CUALES FUERON PROCESADOS

EL CD SE ENCUENTRA EN EL FOLIO (6)

Industria y Comercio
SUPERINTENDENCIA

LISTA DE CHEQUEO
ADMISIÓN A TRÁMITE – NUEVAS CREACIONES

PATENTE DE INVENCIÓN ☐ MODELO DE UTILIDAD ☐ Art 33 Decisión 486/00

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

Completa ☐ Incompleta ☐

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

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

Completa ☐ Incompleta ☐

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

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

Completa ☐ Incompleta ☐

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

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

Completa ☐ Incompleta ☐

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 14-073129- -00000-0000

Fecha: 2014-04-04 17:17:24 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 8

OLARTEMOURE

OLARTE MOURE & ASOCIADOS LTDA.

Industria y Comercio
SUPERINTENDENCIA

Espacio reservado para el adhesivo de radicación.

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2014/000053**

SOLICITUD DE:

1

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

[X] Capítulo I. [ ] Capítulo II.

2

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E-mail:

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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
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Cual
Número 79.782.747Bta
TP 74.295

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA
DIRECCIÓN VER PAGINA ADJUNTA
NACIONALIDAD O DOMICILIO: VER PAGINA ADJUNTA

5

PCT (86)
Solicitud Internacional No. PCT/EP2012/069562 Fecha Octubre 4, 2012
Publicación Internacional No. WO 2013/050438 Fecha Abril 11, 2013

6

Título (54) **BENZILINDAZOLES SUSTITUIDOS PARA USO COMO INHIBIDORES DE LA QUINASA BUB1 EN EL TRATAMIENTO DE ENFERMEDADES HIPERPROLIFERATIVAS**

Clasificación Internacional (51) C07D 401/14, C07D 405/14, C07D 413/14, C07D 498/04, A61K 31/506, A61P 35/00.

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
EP	Octubre 06, 2011	11184061.7

9

Comprobante de pago No. 14- **Fecha**

10 ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso.
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- [x] Declaraciones. Bajo la Regla 4.17 (ii) del PCT.
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- [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

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Nacionalidad: Alemana

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"**,

N 015080567

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

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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

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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

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

ACTUACION NOTARIAL

LEY 404

ESCRIBANA MARIA SILVINA LASARTE

Pco 911316.

N 014090248

FOLIO 444.- PRIMERA COPIA.- ESCRITURA NÚMERO: CIENTO DIECISÉIS.- SUSTITUCIÓN PARCIAL DE PODER: MESSERER, Dagmar a favor de OLARTE, Carlos Reinaldo y otro del Poder otorgado por BAYER PHARMA AKTIENGESELLS-CHAFT.- ----------

En la Ciudad Autónoma de Buenos Aires, Capital de la República Argentina, el día **CINCO** de **SEPTIEMBRE** del año **DOS MIL ONCE**, ante mí María Silvina Lasarte, Escribana Autorizante, titular del Registro Notarial número 1788, **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, Clave Única de Identificación Tributaria número 27-20383892-27, domiciliada legalmente en la Avenida Leandro N. Alem 1.134, Piso 10°, 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 PHARMA AKTIENGESELLSCHAFT"**, con domicilio en Muellerstrasse 178, 13353, Berlín, Alemania, le confirió con fecha 1° de Agosto de 2011 en dicho país, un Poder, el cual mediante Escritura número 115, del día de la fecha otorgada ante mí, al folio 441, protocolo corriente de este Registro Notarial 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 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 **Carlos Reinaldo OLARTE** y/o **Juan Guillermo MOURE PÉREZ,** al sólo y único objeto de que en nombre y representación de la Sociedad **"BAYER PHARMA AKTIENGESELLS-CHAFT"**, y actuando en forma individual, indistinta y/o alternadamente, se presente exclusivamente ante las autoridades de **COLOMBIA** que correspondan y realicen los actos enume-

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rados en el citado poder y con las facultades que surgen del mismo, el que transcripto en lo pertinente dice: "FOLIO 441.- PRIMERA COPIA.- ESCRITURA NÚMERO: CIENTO QUINCE.- ...- En la Ciudad Autónoma de Buenos Aires, ..., el día CINCO de SEPTIEMBRE del año DOS MIL ONCE, ante mí ..., Escribana Autorizante, titular del Registro Notarial número 1788, 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, ..., domiciliada legalmente en la Avenida Leandro N. Alem 1.134, Piso 10°, 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 Berlín, Alemania, el 1° de Agosto de 2011, por la Sociedad "BAYER PHARMA AKTIENGESELLSCHAFT", con domicilio en Muellerstrasse 178, 13353, Berlín, 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 idioma 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 Liliana Carlota Spitzer de Córdoba.- 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 Pharma Aktiengesellschaft domiciliados en Muellerstrasse 178 13353 Berlín - 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 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

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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:) ppa Dr. Walter Klose (Sigue texto en idioma inglés). Sigue otra firma ilegible (Aclarado:) Dr. Noeske-Jungblut (Sigue texto en idioma inglés)".- ES COPIA FIEL, doy fe.- En hojas adjuntas constan: a) La certificación notarial de las firmas obrantes en el poder en idioma alemán, efectuada por el Abogado Stefan Röhnisch, representante legal del Escribano de Berlín, Alemania, Dimitri Rempen; y b) La respectiva legalización de la firma y sello del nombrado Abogado (Sello de Apostilla de la Convención de La Haya del 5 de octubre de 1961), en idioma alemán, efectuada por el Presidente del Tribunal Regional de Berlín, Alemania, Doctor Gerwing.- En hojas adjuntas sigue la referida traducción al idioma nacional la que transcripta textualmente, dice: "TRADUCCIÓN PÚBLICA.- Adjunto a un Poder redactado en idioma español consta: Registro Notarial Nº R 333/2011.- He aclarado la prohibición de colaboración en el sentido del art. 3 inc. 1 Nº 7 de la ley alemana de certificaciones. Los interesados han contestado por la negativa a la pregunta en cuanto a una actuación previa en el sentido de dicha ley.- Certifico la autenticidad de las firmas estampadas en mi presencia de: a) Sr. Dr. Walter Klose, nacido el 26.12.1952, y b) Sra. Dra. Christiane Noeske-Jungblut, nacida el 26.06.1957, - ambos de mi conocimiento y con domicilio comercial en 13353 Berlín, Müllerstraße 178 - Al mismo tiempo certifico que, habiendo visto en el día de la fecha el registro electrónico de comercio, del Juzgado de Primera Instancia de Charlottenburg respecto del número inscripción HR B 283, que la empresa Bayer Pharma Aktiengesellschaft, con sede en Berlín, está inscripta con el citado número ante el Registro de Comercio y que la precitada Sra. Dra. Noeske-Jungblut y el precitado Sr. Dr. Klose están autorizados a firmar en forma conjunta en calidad de apoderados para representar a la empresa Bayer Pharma Aktiengesellschaft, Berlín.- Firmado en Berlín el 1.08.2011 por el representante del Escribano. Consta un

sello adherido - ... - Firmado en Berlín el 1.08.2011 por el representante del Escribano.- Adjunto: Apostilla (Convention de La Haye du 5 octobre 1961).- 1. País: República Federal Alemana.- El presente documento – 2. Está firmado por el abogado Stefan Röhnisch – 3. En su calidad de representante legal del Escribano en Berlín Dimitri Rempen – 4. Estando provisto con el sello del Escribano – Confirmado – 5. En Berlín 6. El 5.08.2011 - 7. por el Presidente del Juzgado Regional en Berlín - 8. bajo el número 9101a E-F 6352/11 - 9. Sello – Consta un sello adherido.- 10. Firma – Consta firma (aclarada) del Juez del Juzgado Regional, Dr. Gerwing.- ES TRADUCCIÓN FIEL al idioma español de la parte pertinente del documento adjunto en idioma alemán que he tenido a la vista, la que sello y firmo en Buenos Aires el 29.08.2011.- Hay una firma ilegible.- Hay un sello que dice: "Liliana C. Spitzer – Mat. 502 – Traductora Pública – Inglés - Alemán – Mac. F. 233 – T. IV – Nac. F. 232 - T. IV – Prov. F. 177 – T. V – Roque s. Peña 1690 – Tel. 4790-8588 - Olivos".- 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 Nº 70221/11. Sigue una firma ilegible: Sergio Alejandro Iervasi".- ES COPIA FIEL, doy fe.- ...- A continuación sigue la legalización de la firma de la nombrada traductora, ...- En este estado la compareciente DICE: que en la forma expresada deja INCORPORADO y TRANSCRIPTO en este Protocolo el Poder que agrego a la presente, solicitando de mí, la Escribana Autorizante, expida primera copia de la presente para Gerardo MESSERER y/o Dagmar MESSERER y/o Karen MESSERER y/o MOELLER & CO. S.A.- 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. ...-".- **ES COPIA**

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CECBA - LEY404 GCBA
LEGALIZACION
110906 477202
06/09/2011 10:29:15

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

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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.- **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 444 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 014090248 al presente inclusive, que sello y firmo en la fecha y lugar de su otorgamiento, doy fe.-

ESCRIBANA NACIONAL
MARIA SILVINA LASARTE

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

LEGALIZACION

LEY 404

L 010347255

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 N°** 110906477202/0 **La presente legalización no juzga sobre el contenido y forma del documento.**

Buenos Aires, Martes 6 de Septiembre de 2011

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

ESC. MARIA CRISTINA ESTER MOORE
COLEGIO DE ESCRIBANOS
CONSEJERA

SERIE A 0037952

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 MARIA CRISTINA ESTER MOORE
3. Quien actúa en calidad de CONSEJERA
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 06/09/2011
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: 110906116556
9. Sello/Timbre: COLEGIO DE ESCRIBANOS APOSTILLA
10. Firma

Esc. MARIA BELEN OVIEDO
COLEGIO DE ESCRIBANOS
CONSEJERA

PCT REQUEST

Print Out (Original in Electronic Form)

VIII-2-1	**Declaration: Entitlement to apply for and be granted a patent** Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	In relation to this international application Bayer Intellectual Property GmbH is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(ii)		Bayer Pharma Aktiengesellschaft is entitled as employer of the inventor, HITCHCOCK, Marion
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VIII-2-1(iii)		Bayer Pharma Aktiengesellschaft is entitled as employer of the inventor, GNOTH, Mark Jean
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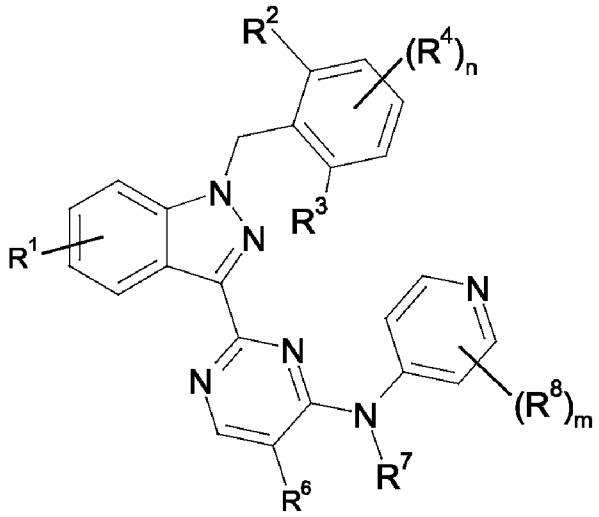
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(54) Title: SUBSTITUTED BENZYLINDAZOLES FOR USE AS BUB1 KINASE INHIBITORS IN THE TREATMENT OF HYPERPROLIFERATIVE DISEASES.

(57) Abstract: Compounds of formula (I) which are inhibitors of Bub1 kinase, processes for their production and their use as pharmaceuticals.



(I)

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

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SUBSTITUTED BENZYLINDAZOLES FOR USE AS BUB1 KINASE INHIBITORS IN THE TREATMENT OF HYPERPROLIFERATIVE DISEASES.

Field of application of the invention

The invention relates to substituted benzylindazole compounds, a process for their production and the use thereof.

BACKGROUND OF THE INVENTION

One of the most fundamental characteristics of cancer cells is their ability to sustain chronic proliferation whereas in normal tissues the entry into and progression through the cell divison cycle is tightly controlled to ensure a homeostasis of cell number and maintenance of normal tissue function. Loss of proliferation control was emphasized as one of the six hallmarks of cancer [Hanahan D and Weinberg RA, Cell 100, 57, 2000; Hanahan D and Weinberg RA, Cell 144, 646, 2011].

The eukaryotic cell division cycle (or cell cycle) ensures the duplication of the genome and its distribution to the daughter cells by passing through a coordinated and regulated sequence of events. The cell cycle is divided into four successive phases:

1. The G1 phase represents the time before the DNA replication, in which the cell grows and is sensitive to external stimuli.
2. In the S phase the cell replicates its DNA, and
3. in the G2 phase preparations are made for entry into mitosis.
4. In mitosis (M phase), the duplicated chromosomes get separated supported by a spindle device built from microtubules, and cell division into two daughter cells is completed.

To ensure the extraordinary high fidelity required for an accurate distribution of the chromosomes to the daughter cells, the passage through the cell cycle is strictly regulated and controlled. The enzymes that are necessary for the progression through the cycle must be activated at the correct time and are also turned off

again as soon as the corresponding phase is passed. Corresponding control points ("checkpoints") stop or delay the progression through the cell cycle if DNA damage is detected, or the DNA replication or the creation of the spindle device is not yet completed. The mitotic checkpoint (also known as spindle checkpoint or spindle assembly checkpoint) controls the accurate attachment of mircrotubules of the spindle device to the kinetochors (the attachment site for microtubules) of the duplicated chromosomes. The mitotic checkpoint is active as long as unattached kinetochores are present and generates a wait-signal to give the dividing cell the time to ensure that each kinetochore is attached to a spindle pole, and to correct attachment errors. Thus the mitotic checkpoint prevents a mitotic cell from completing cell division with unattached or erroneously attached chromosomes [Suijkerbuijk SJ and Kops GJ, Biochem. Biophys. Acta 1786, 24, 2008; Musacchio A and Salmon ED, Nat. Rev. Mol. Cell. Biol. 8, 379, 2007]. Once all kinetochores are attached with the mitotic spindle poles in a correct bipolar (amphitelic) fashion, the checkpoint is satisfied and the cell enters anaphase and proceeds through mitosis.

The mitotic checkpoint is established by a 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, Mps1 kinase, cdc20, as well as other components [reviewed in Bolanos-Garcia VM and Blundell TL, Trends Biochem. Sci. 36, 141, 2010], many of these being over-expressed in proliferating cells (*e.g.* cancer cells) and tissues [Yuan B *et al.*, Clin. Cancer Res. 12, 405, 2006]. The major function of an unsatisfied mitotic checkpoint is to keep the anaphase-promoting complex/cyclosome (APC/C) in an inactive state. As soon as the checkpoint gets satisfied the APC/C ubiquitin-ligase targets cyclin B and securin for proteolytic degradation leading to separation of the paired chromosomes and exit from mitosis.

Inactive mutations of the Ser/Thr kinase Bub1 prevented the delay in progression through mitosis upon treatment of cells of the yeast *S. cerevisiae* with microtubule-destabilizing drugs, which led to the identification of Bub1 as a mitotic checkpoint protein [Roberts BT *et al.*, Mol. Cell Biol., 14, 8282, 1994]. A number of recent publications provide evidence that Bub1 plays multiple roles during mitosis which,

have been reviewed by Elowe [Elowe S, Mol. Cell. Biol. 31, 3085, 2011. In particular, Bub1 is one of the first mitotic checkpoint proteins that binds to the kinetochores of duplicated chromosomes and probably acts as a scaffolding protein to constitute the mitotic checkpoint complex. Furthermore, via phosphorylation of histone H2A, Bub1 localizes the protein shugoshin to the centromeric region of the chromosomes to prevent premature segregation of the paired chromosomes [Kawashima *et al.* Science 327, 172, 2010]. In addition, together with a Thr-3 phosphorylated Histone H3 the shugoshin protein functions as a binding site for the chromosomal passenger complex which includes the proteins survivin, borealin, INCENP and Aurora B. The chromosomal passenger complex is seen as a tension sensor within the mitotic checkpoint mechanism, which dissolves erroneously formed microtubule-kinetochor attachments such as syntelic (both sister kinetochors are attached to one spindle pole) or merotelic (one kinetochor is attached to two spindle poles) attachments [Watanabe Y, Cold Spring Harb. Symp. Quant. Biol. 75, 419, 2010].

Incomplete mitotic checkpoint function has been linked with aneuploidy and tumourigenesis [Weaver BA and Cleveland DW, Cancer Res. 67, 10103, 2007; King RW, Biochim Biophys Acta 1786, 4, 2008]. 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 Rev. Cancer 5, 773, 2005; Schmidt M and Medema RH, Cell Cycle 5, 159, 2006; Schmidt M and Bastians H, Drug Res. Updates 10, 162, 2007]. Thus, mitotic checkpoint abrogation through pharmacological inhibition of components of the mitotic checkpoint, such as Bub1 kinase, represents a new approach for the treatment of proliferative disorders, including solid tumours such as carcinomas, sarcomas, leukaemias and lymphoid malignancies or other disorders, associated with uncontrolled cellular proliferation.

The present invention relates to chemical compounds that inhibit Bub1 kinase.

Established anti-mitotic drugs such as vinca alkaloids, taxanes or epothilones activate the mitotic checkpoint, inducing a mitotic arrest either by stabilising or desta-

bilising microtubule dynamics. This arrest prevents separation of the duplicated chromosomes to form the two daughter cells. Prolonged arrest in mitosis forces a cell either into mitotic exit without cytokinesis (mitotic slippage or adaption) or into mitotic catastrophe leading to cell death [Rieder CL and Maiato H, Dev. Cell 7, 637, 2004]. In contrast, inhibitors of Bub1 prevent the establishment and/or functionality of the mitotic checkpoint, which finally results in severe chromosomal missegregation, induction of apoptosis and cell death.

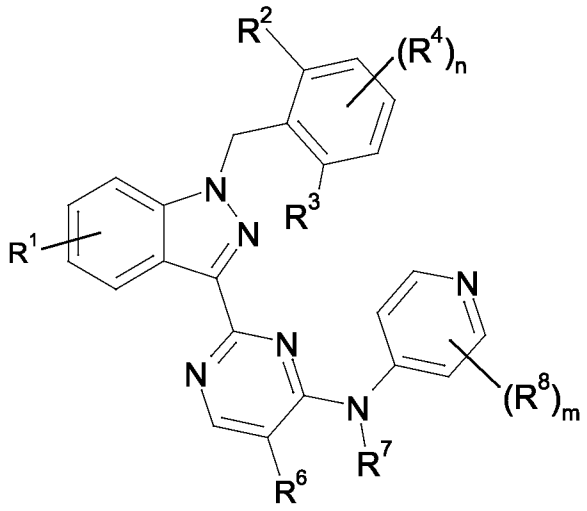
These findings suggest that Bub1 inhibitors should be of therapeutic value for the treatment of proliferative disorders associated with enhanced uncontrolled proliferative cellular processes such as, for example, cancer, inflammation, arthritis, viral diseases, cardiovascular diseases, or fungal diseases in a warm-blooded animal such as man.

Due to the fact that especially cancer disease as being expressed by uncontrolled proliferative cellular processes in tissues of different organs of the human- or animal body still is not considered to be a controlled disease in that sufficient drug therapies already exist, there is a strong need to provide further new therapeutically useful drugs, preferably inhibiting new targets and providing new therapeutic options.

Description of the invention

Therefore, inhibitors of Bub1 represent valuable compounds that should complement therapeutic options either as single agents or in combination with other drugs.

In accordance with a first aspect, the invention relates to compounds of formula (I)



(I)

in which

R^1 is hydrogen, halogen, 1-3C-alkyl,

R^2/R^3 are independently from each other hydrogen, halogen, cyano, hydroxy 1-6C-haloalkyl, 1-6C-haloalkoxy, 1-6C-alkoxy,

R^4 is independently hydrogen, hydroxy, halogen, cyano, NO_2, 1-6C-alkyl, 2-6C-alkenyl, 2-6C-alkynyl, 1-6C-haloalkyl, 1-6C-hydroxyalkyl, 1-6C-alkoxy, -O-(2-6Calkylen)-O-C(O)-(1-6C-alkyl), 1-6C-haloalkoxy, $-C(O)OR^9$, -(1-6C-alkylen)-$C(O)OR^9$, -C(O)-(1-6C-alkyl), $-C(O)NR^{10}R^{11}$, 3-7C-cycloalkyl, -S-(1-6C-haloalkyl), SF_5, $-SO_2NH$-(3-7C-cycloalkyl), $-SO_2NR^{10}R^{11}$, $NR^{10}R^{11}$, heteroaryl which optionally is substituted independently one or more times with cyano, 1-4C-alkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,

whereby two of R^2, R^3 $(R^4)_n$, when positioned ortho to each other, may form together with the two carbon atoms to which they are attached, a heterocyclic 5-, 6- or 7-membered ring containing 1 or 2 heteroatoms selected from O or N, and optionally containing an additional double bond and/or optionally substituted by an oxo (=O) group and/or an 1-4C-alkyl group,

n 0 - 3

R^6 is (a) hydrogen;

(b) hydroxy;

(c) cyano;

(d) 1-6C-alkoxy optionally substituted independently one or more times with

(d1) OH,

(d2) –O-(1-6C-alkyl)

(d3) $C(O)OR^9$,

(d4) $C(O)NR^{10}R^{11}$,

(d5) $NR^{10}R^{11}$,

(d6) –S-(1-6C-alkyl),

(d7) –S(O)-(1-6C-alkyl),

(d8) $–SO_2$-(1-6C-alkyl)

(d9) $SO_2NR^{10}R^{11}$,

(d10) heterocyclyl, which is optionally substituted with $C(O)OR^9$, or oxo (=O),

(d11) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-4C-alkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, (1-6C-alkylen)-O-(1-6C-alkyl),

(e) $SO_2NR^{10}R^{11}$,

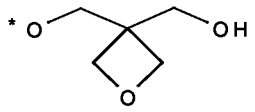
(f) 3-7C-cycloalkoxy,

(g) 1-6C-haloalkoxy,

(h) $COOR^9$,

(i) $-C(O)NR^{10}R^{11}$,

(j) -O-heteroaryl opt. subst. with CN

(k) 

, whereby the * is the point of attachment,

(l) –O-(2-6C-alkylen)-O-(1-6C-alkyl) which is optionally substituted with hydroxy, $NH(CO)OR^9$,

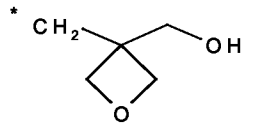
R^7 is

(a) hydrogen,

(b)1-6C-alkyl, which is optionally substituted with heteroaryl

(c) 1-6C-haloalkyl,

(d) 1-6C-hydroxyalkyl,

(e) 

, whereby the * is the point of attachment,

(f) -C(O)-(1-6C-alkyl)

(g) –C(O)-(1-6C-alkylen)-O-(1-6C-alkyl)

(h) –C(O)-(1-6C-alkylen)-O-(2-6C-alkylen)-O-(1-6C-alkyl)

(i) –C(O)-heterocyclyl,

(j) benzyl whereby the phenyl ring is opt. subst with 1-5 substituents independently selected from the group consisting of hydrogen, halogen, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-alkoxy, 1-4C-haloalkoxy, cyano, $C(O)OR^9$,

(k) heteroaryl

or

optionally, R^6 and R^7 together with the nitrogen atom to which R^7 is attached form a 6-membered ring which may contain one further heteroatom selected from the group consisting of O, S, N,

and which is optionally substituted by (1-6C-alkyl)-OH, (1-6C-alkyl)-$NR^{10}R^{11}$,

R^8 is hydrogen, halogen, hydroxy, cyano, 1-6C-alkyl, 1-6C-hydroxyalkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,

m is 0-4

R^9 is (a) hydrogen,

(b) 1-6C-alkyl which optionally is substituted with hydroxy,

R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl, 1-4C-hydroxyalkyl, 1-4C-alkoxy, -(CO)-(1-6C-alkyl), CHO, $COOR^9$, or together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, and which is optionally substituted with 1-2 fluorine atoms or $COOR^9$,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

According to a further aspect of the invention, the invention relates to compounds of formula (I)

wherein

R^1 is hydrogen, halogen, 1-3C-alkyl,

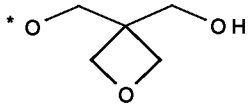
R^2/R^3 are independently from each other hydrogen, halogen, cyano, 1-6C-haloalkyl,
1-6C-haloalkoxy,

R^4 is independently hydrogen, halogen, cyano, 1-6C-alkyl, 2-6C-alkenyl, 1-6C-haloalkyl, 1-6C-hydroxyalkyl, 1-6C-alkoxy, 1-6C-haloalkoxy, $-C(O)OR^9$, -(1-6C-alkylen)-$C(O)OR^9$, $-C(O)$-(1-6C-alkyl), $-C(O)NR^{10}R^{11}$, 3-7C-cycloalkyl, -S-(1-6C-haloalkyl), SF_5, $-SO_2NH$-(3-7-cycloalkyl), $-SO_2NR^{10}R^{11}$,
heteroaryl which optionally is substituted independently one or more times with cyano, 1-4C-alkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,
whereby two of R^2, R^3 $(R^4)_n$, when positioned ortho to each other, may form together with the two carbon atoms to which they are attached, a heterocyclic 5-, 6- or 7-membered ring containing 1 or 2 heteroatoms selected from O or N, and optionally an additional double bond and/or a carbonyl group and/or an 1-4C-alkyl group,

n 0 - 3

R^6 is (a) hydrogen;
(b) hydroxy;
(c) cyano;
(d) 1-6C-alkoxy opt. subst. with
(d1) 1-2 OH,
(d2) $NR^{10}R^{11}$,
(d3) SO2$NR^{10}R^{11}$,
(d4) heterocyclyl,
(d5) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-4Calkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,
(e) $SO_2NR^{10}R^{11}$,
(f) 3-7C-cycloalkoxy,
(g) 1-6C-haloalkoxy,
(h) $-C(O)NR^{10}R^{11}$,

(i) -O-heteroaryl opt. subst. with CN



(j) , whereby the * is the point of attachment,

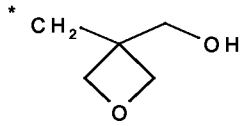
R^7 is

(a) hydrogen,

(b)1-6C-alkyl, which is optionally substituted with heteroaryl

(c) 1-6C-haloalkyl,

(d) 1-6C-hydroxyalkyl,



(e) , whereby the * is the point of attachment,

(f) -C(O)-(1-6C-alkyl)

(g) –C(O)-(1-6C-alkylen)-O-(1-6C-alkyl)

(h) –C(O)-(1-6C-alkylen)-O-(1-6C-alkylen)-O-(1-6C-alkyl)

(i) –C(O)-heterocyclyl,

(j) benzyl whereby the phenyl ring is opt. subst with 1-5 substituents independently selected from the group consisting of

hydrogen, halogen, 1-4Calkyl, 1-4C-haloalkyl, 1-4C-alkoxy,

1-4C-haloalkoxy, cyano,

$C(O)OR^9$,

(k) heteroaryl

or

optionally R^6 and R^7 together with the nitrogen atom to which they are attached form a 6-membered ring which may contain one further heteroatom selected from the group consisting of O, S, N,

and which is optionally substituted by hydroxy-(1-6alkyl),

R^8 is hydrogen, halogen, cyano, 1-6C-haloalkyl, 1-6C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,

m is 0-4

R^9 is (a) hydrogen,

(b) 1-6C-alkyl which optionally may be substituted with hydroxy,

R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl, 1-4C-hydroxyalkyl, 1-4C-alkoxy, or
together with the nitrogen atom to which they are attached form a 5-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

Another aspect of the invention are compounds of formula (I) according to claim 1, wherein

R^1 is hydrogen, halogen, 1-3C-alkyl,

R^2/R^3 are independently from each other hydrogen, halogen, cyano, hydroxy, 1-3C-haloalkyl, 1-3C-haloalkoxy, 1-3C-alkoxy,

R^4 is independently hydrogen, hydroxy, halogen, cyano, NO_2, 1-3C-alkyl, 2-3C-alkenyl, 2-3C-alkynyl, 1-3C-haloalkyl, 1-3C-hydroxyalkyl, 1-3C-alkoxy, -O-(2-3C-alkylen)-O-C(O)-(1-3C-alkyl), 1-3C-haloalkoxy, -C(O)OR^9, -(1-3C-alkylen)-C(O)OR^9, -C(O)-(1-3C-alkyl), -C(O)$NR^{10}R^{11}$, 3-7C-cycloalkyl, -S-(1-3C-haloalkyl), SF_5, -SO_2NH-(3-7C-cycloalkyl), -$SO_2NR^{10}R^{11}$, $NR^{10}R^{11}$, heteroaryl which optionally is substituted independently one or more times with cyano, 1-3C-alkyl, 1-3C-haloalkyl, 1-3C-haloalkoxy, C(O)OR^9, C(O)$NR^{10}R^{11}$,
whereby two of R^2, R^3 $(R^4)_n$, when positioned ortho to each other, may form together with the two carbon atoms to which they are attached, a heterocyclic 5-, 6- or 7-membered ring containing 1 or 2 heteroatoms selected from O or N, and optionally containing an additional double bond and/or optionally substituted by an oxo (=O) group and/or an 1-3C-alkyl group,

n 0 - 3

R^6 is (a) hydrogen;
(b) hydroxy;
(c) cyano;
(d) 1-6C-alkoxy optionally substituted independently one or more times with
(d1) OH,
(d2) –O-(1-3C-alkyl)

(d3) $C(O)OR^9$,

(d4) $C(O)NR^{10}R^{11}$,

(d5) $NR^{10}R^{11}$,

(d6) –S-(1-3C-alkyl),

(d7) –S(O)-(1-3C-alkyl),

(d8) $–SO_2$-(1-3C-alkyl)

(d9) $SO_2NR^{10}R^{11}$,

(d10) heterocyclyl, which is optionally substituted with $C(O)OR^9$, or oxo (=O),

(d11) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-3C-alkyl, 1-3C-haloalkyl, 1-3C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, (1-3C-alkylen)-O-(1-3C-alkyl),

(e) $SO_2NR^{10}R^{11}$,

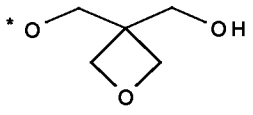
(f) 3-7C-cycloalkoxy,

(g) 1-6C-haloalkoxy,

(h) $COOR^9$,

(i) $-C(O)NR^{10}R^{11}$,

(j) -O-heteroaryl opt. subst. with CN

(k) 

, whereby the * is the point of attachment,

(l) –O-(2-3C-alkylen)-O-(1-3C-alkyl) which is optionally substituted with hydroxy, $NH(CO)OR^9$,

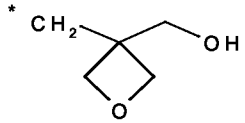
R^7 is

(a) hydrogen,

(b)1-3C-alkyl, which is optionally substituted with heteroaryl

(c) 1-3C-haloalkyl,

(d) 1-3C-hydroxyalkyl,

(e) 

, whereby the * is the point of attachment,

(f) -C(O)-(1-3C-alkyl)

(g) –C(O)-(1-3C-alkylen)-O-(1-3C-alkyl)

(h) –C(O)-(1-3C-alkylen)-O-(2-3C-alkylen)-O-(1-3C-alkyl)

(i) –C(O)-heterocyclyl,

(j) benzyl whereby the phenyl ring is opt. subst with 1-5 substituents independently selected from the group consisting of hydrogen, halogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-haloalkoxy, cyano, $C(O)OR^9$,

(k) heteroaryl

or

optionally, R^6 and R^7 together with the nitrogen atom to which R^7 is attached form a 6-membered ring which may contain one further heteroatom selected from the group consisting of O, S, N,

and which is optionally substituted by (1-3C-alkyl)-OH, (1-3C-alkyl)-$NR^{10}R^{11}$,

R^8 is hydrogen, halogen, hydroxy, cyano, 1-3C-alkyl, 1-3C-hydroxyalkyl, 1-3C-haloalkyl, 1-3C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,

m is 0-4

R^9 is (a) hydrogen,

(b) 1-3C-alkyl which optionally is substituted with hydroxy,

R^{10}, R^{11} are independently from each other hydrogen, 1-3C-alkyl, 1-3C-hydroxyalkyl, 1-3C-alkoxy, -(CO)-(1-3C-alkyl), CHO, $COOR^9$ or together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, which is optionally substituted with 1-2 fluorine atoms or $COOR^9$,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

A further aspect of the invention are compounds of formula (I) according to claim 1, wherein

R^1 is hydrogen, halogen, 1-4C-alkyl,

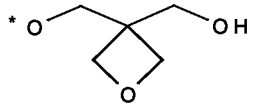
R^2/R^3 are independently from each other hydrogen, halogen, cyano, 1-4C-haloalkyl,
1-4C-haloalkoxy,

R^4 is independently hydrogen, halogen, cyano, 1-4C-alkyl, 2-4C-alkenyl, 1-4C-haloalkyl, 1-4C-hydroxyalkyl, 1-4C-alkoxy, 1-4C-haloalkoxy, $-C(O)OR^9$, -(1-4C-alkylen)-$C(O)OR^9$, $-C(O)$-(1-4C-alkyl), $-C(O)NR^{10}R^{11}$, 3-6C-cycloalkyl, -S-(1-6C-haloalkyl), SF_5, $-SO_2NH$-(3-6-cycloalkyl), $-SO_2NR^{10}R^{11}$, heteroaryl which optionally is substituted independently one or more times with cyano, 1-4C-alkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,
whereby two of R^2, R^3 $(R^4)_n$, when positioned ortho to each other, may form together with the two carbon atoms to which they are attached, a heterocyclic 5-, 6- or 7-membered ring containing 1 or 2 heteroatoms selected from O or N, and optionally an additional double bond and/or a carbonyl group and/or an 1-4C-alkyl group,

n 0 - 3

R^6 is (a) hydrogen;
(b) hydroxy;
(c) cyano;
(d) 1-4C-alkoxy opt. subst. with
(d1) 1-2 OH,
(d2) $NR^{10}R^{11}$,
(d3) SO2$NR^{10}R^{11}$,
(d4) heterocyclyl,
(d5) heteroaryl, which is optionally independently one or more times substituted with cyano, 1-4C-alkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,
(e) SO2$NR^{10}R^{11}$, ;
(f) 3-6C-cycloalkoxy,
(g) 1-4C-haloalkoxy,
(h) $-C(O)NR^{10}R^{11}$,

(i) O-heteroaryl opt. subst. with CN



(j) , whereby the * is the point of attachment,

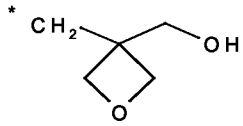
R^7 is

(a) hydrogen,

(b)1-4C-alkyl, which is optionally substituted with heteroaryl

(c) 1-4C-haloalkyl,

(d) 1-4C-hydroxyalkyl,



(e) , whereby the * is the point of attachment,

(f) -C(O)-(1-4C-alkyl)

(g) –C(O)-(1-4C-alkylen)-O-(1-4C-alkyl)

(h) –C(O)-(1-4C-alkylen)-O-(1-4C-alkylen)-O-(1-4C-alkyl)

(i) –C(O)-heterocyclyl,

(j) benzyl whereby the phenyl ring is opt. subst with 1-5 substituents independently selected from the group consisting of

hydrogen, halogen, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-alkoxy, 1-4C-haloalkoxy, cyano,

C(O)OR9,

(k) heteroaryl

or

optionally R^6 and R^7 together with the nitrogen atom to which they are attached form a 6-membered ring which may contain one further heteroatom selected from the group consisting of O, S, N,

and which is optionally substituted by hydroxy-(1-4-alkyl),

R^8 is hydrogen, halogen, $C(O)NR^{10}R^{11}$, $C(O)OR^9$, 1-4C-haloalkyl, 1-4C-haloalkoxy, cyano,

m is 0-4

R^9 is (a) hydrogen,

(b) 1-4C-alkyl which optionally may be substituted with hydroxy,

R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl, 1-4C-hydroxyalkyl, 1-4C-alkoxy, or
together with the nitrogen atom to which they are attached form a 5-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

Another aspect of the invention are compounds of formula (I) according to claim 1, wherein

R^1 is hydrogen, 1-3C-alkyl,

R^2/R^3 are independently from each other hydrogen, halogen, cyano, hydroxy, 1-4C-haloalkyl, 1-4C-alkoxy,

R^4 is independently hydrogen, hydroxy, halogen, cyano, 1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl, 1-4C-haloalkyl, 1-4C-hydroxyalkyl, 1-4C-alkoxy, -O-(2-4C-alkylen)-O-C(O)-(1-4C-alkyl), 1-4C-haloalkoxy, -C(O)OR^9, -(1-4C-alkylen)-C(O)OR^9, -C(O)-(1-4C-alkyl), -C(O)$NR^{10}R^{11}$, 3-7C-cycloalkyl, -S-(1-4C-haloalkyl), SF_5, -SO_2NH-(3-7C-cycloalkyl), -$SO_2NR^{10}R^{11}$, $NR^{10}R^{11}$, heteroaryl which optionally is substituted independently one or more times with cyano, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy, C(O)OR^9, C(O)$NR^{10}R^{11}$,
whereby two of R^2, R^3 $(R^4)_n$, when positioned ortho to each other, may form together with the two carbon atoms to which they are attached, a heterocyclic 5-, 6- or 7-membered ring containing 1 or 2 heteroatoms selected from O or N, and optionally containing an additional double bond and/or optionally substituted by an oxo (=O) group and/or an 1-4C-alkyl group,

n 0 - 3

R^6 is (a) hydrogen;
(b) hydroxy;
(d) 1-4C-alkoxy optionally substituted independently one or more times with
(d1) OH,
(d2) –O-(1-4C-alkyl)
(d3) C(O)OR^9,

(d4) $C(O)NR^{10}R^{11}$,

(d5) $NR^{10}R^{11}$,

(d6) –S-(1-4C-alkyl),

(d7) –S(O)-(1-4C-alkyl),

(d8) $–SO_2$-(1-4C-alkyl)

(d9) $SO_2NR^{10}R^{11}$,

(d10) heterocyclyl, which is optionally substituted with $C(O)OR^9$, or oxo (=O),

(d11) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, (1-4C-alkylen)-O-(1-4C-alkyl),

(e) $SO_2NR^{10}R^{11}$,

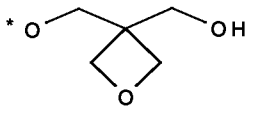
(f) 3-7C-cycloalkoxy,

(g) 1-6C-haloalkoxy,

(h) $COOR^9$,

(i) $-C(O)NR^{10}R^{11}$,

(j) -O-heteroaryl opt. subst. with CN

(k) 

, whereby the * is the point of attachment,

(l) –O-(2-4C-alkylen)-O-(1-4C-alkyl) which is optionally substituted with hydroxy, $NH(CO)OR^9$,

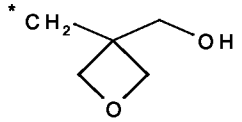
R^7 is

(a) hydrogen,

(b) (1-4C-alkyl)-heteroaryl

(c) 1-4C-haloalkyl,

(d) 1-4C-hydroxyalkyl,

(e) 

, whereby * is the point of attachment,

(f) -C(O)-(1-4C-alkyl)

(g) –C(O)-(1-4C-alkylen)-O-(1-4C-alkyl)

(h) –C(O)-(1-4C-alkylen)-O-(2-4C-alkylen)-O-(1-4C-alkyl)

(i) –C(O)-heterocyclyl,

(j) benzyl whereby the phenyl ring is opt. subst with 1-5 substituents independently selected from the group consisting of

hydrogen, halogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-haloalkoxy, cyano, $C(O)OR^9$,

(k) heteroaryl

or

optionally, R^6 and R^7 together with the nitrogen atom to which R^7 is attached form a 6-membered ring which may contain one further heteroatom selected from the group consisting of O, S, N,

and which is optionally substituted by (1-4C-alkyl)-OH, (1-4C-alkyl)-$NR^{10}R^{11}$,

R^8 is hydrogen, halogen, hydroxy, cyano, $C(O)NR^{10}R^{11}$, 1-4C-alkyl, 1-4C-hydroxyalkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy,

m is 0-2,

R^9 is hydrogen, 1-4C-alkyl which optionally is substituted with hydroxy,

R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl, 1-4C-hydroxyalkyl, 1-4C-alkoxy, -C(O)-(1-4C-alkyl), or $COOR^9$ or

together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, which is optionally substituted with 1-2 fluorine atoms or $COOR^9$,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

A further aspect of the invention are compounds of formula (I) according to claim 1, wherein

R^1 is hydrogen, halogen,

R^2/R^3 are independently from each other hydrogen, halogen, cyano, 1-4C-haloalkyl,

R^4 is independently hydrogen, halogen, cyano, 1-4C-alkyl, 2-4C-alkenyl, 1-4C-haloalkyl, 1-4C-hydroxyalkyl, 1-4C-alkoxy, 1-4C-haloalkoxy, $-C(O)OR^9$, -(1-4C-alkylen)-$C(O)OR^9$, -C(O)-(1-4C-alkyl), -C(O)NR10R11, 3-7C-cycloalkyl,

-S-(1-4C-haloalkyl), SF_5, $-SO_2NH$-(3-7-cycloalkyl), $-SO_2NR^{10}R^{11}$, heteroaryl which optionally is substituted independently one or more times with cyano, 1-4C-alkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,

whereby two of R^2, R^3 $(R^4)_n$, when positioned ortho to each other, may form together with the two carbon atoms to which they are attached, a heterocyclic 5-, 6- or 7-membered ring containing 1 or 2 heteroatoms selected from O or N, and optionally an additional double bond and/or a carbonyl group and/or an 1-4C.alkyl group,

n 0 - 3

R^6 is (a) hydrogen;

(b) hydroxy;

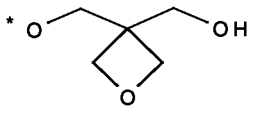
(d) 1-6C-alkoxy opt. subst. with

(d1) 1-2 OH,

(d2) $NR^{10}R^{11}$,

(d3) $SO_2NR^{10}R^{11}$,

(g) 1-6C-haloalkoxy,

(k) 

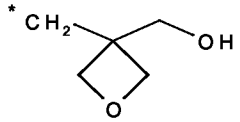
, whereby * is the point of attachment,

R^7 is

(a) hydrogen,

(c) 1-6C-haloalkyl,

(d) 1-4C-hydroxyalkyl,

(e) 

, whereby * is the point of attachment,

(f) -C(O)-(1-4C-alkyl)

(g) –C(O)-(1-4C-alkylen)-O-(1-4C-alkyl)

(h) –C(O)-(1-4C-alkylen)-O-(1-4C-alkylen)-O-(1-4C-alkyl)

(i) –C(O)-heterocyclyl,

(j) benzyl whereby the phenyl ring is opt. subst with 1-5 substituents independently selected from the group consisting of

hydrogen, halogen, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-alkoxy, 1-4C-haloalkoxy, cyano,

$C(O)OR^9$,

or

optionally R^6 and R^7 together with the nitrogen atom to which they are attached form a 6-membered ring which may contain one further heteroatom selected from the group consisting of O, S, N,

and which is optionally substituted by hydroxy-(1-4alkyl),

R^8 is hydrogen, halogen, $C(O)NR^{10}R^{11}$, 1-4C-haloalkyl, 1-4C-haloalkoxy, cyano,

m is 0-2,

R^9 is 1-4C-alkyl which optionally may be substituted with hydroxy,

R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl, 1-4C-hydroxyalkyl, 1-4C-alkoxy, or

together with the nitrogen atom to which they are attached form a 5-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

A further aspect of the invention are compounds of formula (I) according to claim 1, wherein

R^1 is hydrogen,

R^2/R^3 are independently from each other hydrogen, halogen,

R^4 is independently hydrogen, 1-3C-alkyl, 2-3C-alkenyl, 1-3C-haloalkyl, 1-3C-hydroxyalkyl, 1-3C-alkoxy, 1-3C-haloalkoxy, $-C(O)OR^9$, -C(O)-(1-3C-alkyl), $-C(O)NR^{10}R^{11}$, 3-4C-cycloalkyl, $-SO_2NR^{10}R^{11}$,

n 0 - 3

R^6 is (a) hydrogen;

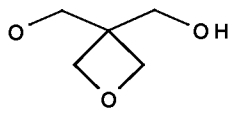
(b) hydroxy;

(d) 1-3C-alkoxy opt. subst. with

(d1) 1-2 OH,

(d2) $NR^{10}R^{11}$,

(g) 1-3C-haloalkoxy,

(k)  ,

R^7 is hydrogen,

R^8 is hydrogen, $C(O)NR^{10}R^{11}$, 1-3C-haloalkyl,

m is 0 - 2,

R^9 is 1-3C-alkyl which optionally may be substituted with hydroxy,

R^{10}, R^{11} are independently from each other hydrogen, 1-3C-alkyl, 1-3C-hydroxyalkyl, 1-3C-alkoxy, or

together with the nitrogen atom to which they are attached form a 5-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

A further aspect of the invention are compounds of formula (I) according to claim 1, compounds of formula (I) according to claim 1,

wherein,

R^1 is hydrogen, ,

R^2/R^3 is independently halogen, cyano, hydroxy, 1-3C-haloalkyl, 1-4C-alkoxy or 1-3C-haloalkoxy,

R^4 is independently of each other hydrogen, halogen, cyano, NO_2, hydroxy, -1-4C-alkyl, 2-3C-alkenyl, 2-3C-alkynyl, 1-3C-haloalkyl, (1-4C-alkyl)-OH, 1-3C-alkoxy, 1-3C-haloalkoxy, -O-(2-3C-alkylen)-O-C(O)-(1-3C-alkyl), -C(O)(1-3C-alkyl), -COOH, -C(O)O(1-4C-alkyl), (1-3C-alkyl)-COOH, -(1-4C-alkyl)-C(O)O(1-3C-alkyl), $-C(O)NR^{10}R^{11}$, $-SO_2$-NH-(3-6C-cycloalkyl), $-SO_2-NR^{10}R^{11}$, $NR^{10}R^{11}$, heteroaryl, $-S-CF_3$, SF_5,

whereby two of R^2, R^3 $(R^4)_n$, when positioned ortho to each other may form together

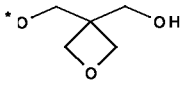
$-O-CH_2-CH_2-CH_2-O-$, $-O-CH_2-CH_2-$, $-(CH_3)C=CH-(C=O)-O-$,

$-CH_2-(C=O)-O-$, $-(CH_2)_2-(C=O)-NH-$, which in addition together with the two carbon atoms to which they are attached form a 5-7-membered ring,

n is 0, 1, 2, 3,

R^6 is hydroxy, cyano, -O-cyclopropyl, 1-3C-alkyoxy, 1-3C-haloalkoxy, -O-(2-3C-alkyl)-OH, -O-(2-3C-alkyl)-NH_2, -O-(2-3C-alkyl)-O(1-3C-alkyl), -O-(2-3C-alkyl)-O-(2-3C-alkyl)-OH, $-O-CH_2-CH(OH)-CH_2OH$, -O-(1-3C-alkyl)-COOH, -O-(1-3C-alkyl)C(O)-O-(1-3C-alkyl), -O-(2-3C-alkyl)-O-(2-3C-alkyl)-NH-C(O)-O-(1-4C-alkyl), $C(O)-NH_2$, $-O-CH_2-C(O)-$(3-fluoro-N-azetidine), $-O-CH_2-C(O)-$(3,3-difluoro-N-azetidine), -O(1-3C-alkyl) $-NR^{10}R^{11}$, $-O-CH_2-CH(OH)-CH_2-$N-piperidinyl,

-O-(2-3C-alkyl)-S-(2-3C-alkyl), -O-(2-3C-alkyl)-SO_2NH_2, -O-(2-3C-alkyl)-SO_2-(1-3C-alkyl),

-O-(2-3C-alkyl)-SO-(1-3C-alkyl),  , whereby * is the point of attachment,

-O-(1-3C-alkyl)heteroaryl,

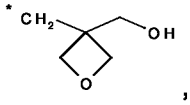
-O-heteroaryl which is optionally substituted one or more times with cyano,

-O-(1-3C-alkyl)-(heterocyclyl, having 1-2 heteroatoms selected from the group consisting of N, O and which is optionally substituted with oxo (=O)),

-O-(1-3C-alkyl)-(heteroaryl)-(1-3C-alkyl)-O-(1-3C-alkyl),

-O-(1-3C-alkyl)- heterocyclyl which is optionally substituted with -C(O)-O-(1-4C-alkyl), $C(O)NH_2$, or

R^6 together with R^7 is a 6-membered ring including the nitrogen atom of the R^7 bearing amino group which may contain one further heteroatom selected from O, S or N and which in addition may be substituted with oxo (=O), $-CH_2-NH-CHO$ or (1-3C-alkyl)-OH,

R^7 is hydrogen, 1-3C-alkyl, 1-3C-haloalkyl, 1-3C-hydroxyalkyl,  , whereby * is the point of attachment,

-(1-3C-alkyl)heteroaryl, heteroaryl, -C(O)-heterocyclyl, -C(O)-(1-3C-alkyl)-O-(1-3C-alkyl), -C(O)-(1-3C-alkyl), -C(O)(1-3C-alkyl)-O-(2-3C-alkyl)-O-(1-3C-alkyl), or benzyl which is optionally substituted one or more times with halo-

gen, cyano, methyl, difluoromethyl, 1-3C-alkoxy, 1-3C-haloalkoxy, -C(O)O(1-3C-alkyl),

R^8 is hydrogen, fluorine, cyano, CF_3, $C(O)NH_2$, $C(O)NHCH_3$, C(O)OH, C(O)O(1-3Calkyl), C(O)(1-3C-alkyl)-OH,

m is 0, 1 or 2

R^{10}/R^{11} hydrogen, 1-3C-alkyl, (1-3C-alkyl)-OH, C(O)(1-3Calkyl),

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

A further aspect of the invention are compounds of formula (I) according to claim 1, wherein

R^1 is hydrogen, ,

R^2/R^3 is independently fluorine, chlorine, bromine, cyano, CF_3, or -O-CH2-CF3,

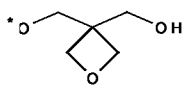
R^4 is independently of each other hydrogen, fluorine, chlorine, bromine or iodine, cyano, -CH3, -C3H9, cyclopropyl, 1-propenyl, -CF3, -CH2-OH, -CH2-CH2-OH, -C(CH3)2-OH, -CH2-C(CH3)2-OH, -C(CH3)2-CH2-OH, -OCH3, -OCF3, -OCF2H, -OCH2CF3, -C(O)CH3, -COOH, -C(O)OCH3, -C(O)OC2H5, -C(O)OC(CH3)3, -CH2-COOC2H5, -CH2-COOH, -C(CH3)2-COOC2H5, -C(O)NH2, -C(O)NH(CH3), -C(O)N(CH3)2, -C(O)NH-(CH2)2-OH, -C(O)-(N-morpholino), -SO2-NH-cyclopropyl, -SO2-(N-morpholino), 5-methyl-oxa-diazol-3-yl, $-S-CF_3$, SF_5,

whereby two of R^2, R^3 $(R^4)_n$, when positioned ortho to each other, form together with the two carbon atoms to which they are attached,

-O-CH2-CH2-CH2-O-, -O-CH2-CH2-, -(CH3)C=CH-(C=O)-O-, -CH2-(C=O)-O-, -(CH2)2-(C=O)-NH-,

n is 0, 1, 2, 3,

R^6 is hydrogen, hydroxy, cyano, -O-cyclopropyl, -OCH3, -OCF3, -OCF2H, -OCH2CF3, -O-(CH2)2-OH, -O(CH2)2-N(CH3)2, -O-CH2-SO2NH2,

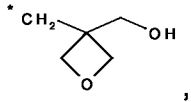


, whereby * is the point of attachment,

-O-(CH2)2-tetrazolyl, -O-CH2-tetrazolyl, -O-pyridine-4-yl, -O-(3-cyano-pyridine-4-yl), -C(O)NH2, or

R^6 together with R^7 is a 6-membered ring including the nitrogen atom of the

R^7 bearing amino group which may contain one further heteroatom selected from O, S or N and which in addition may be substituted with a carbonyl group or -CH2-OH,

R^7 is hydrogen, methyl, difluoromethyl, hydroxyethyl,  , whereby * is the point of attachment,

-(CH2)2-tetrazolyl, pyridine-4-yl, -C(O)-tetrahydropyran-4-yl, -C(O)-CH2-O-CH3, -C(O)-CH3, -C(O)CH2-O-(CH2)2-O-CH3 or benzyl which is optionally substituted one or more times with fluorine, chlorine, cyano, methyl, difluoromethyl, methoxy, ethoxy, difluormethoxy, trifluoromethoxy, -O-CH2-CF3, -C(O)OCH3,

R^8 is hydrogen, fluorine, cyano, CF3, C(O)NH2, C(O)OH, C(O)OC2H5, C(O)(CH2)2-OH,

m is 0, 1 or 2

R^9 is hydrogen, methyl, ethyl, tert.-butyl, hydroxyethyl,

R^{10}/R^{11} is independently from each other hydrogen, methyl, hydroxyethyl,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

A further aspect of the invention are compounds of formula (I) according to claim 1, wherein

R^1 is hydrogen,

R^2/R^3 is independently fluorine, chlorine, bromine, cyano, CF_3, or $-O-CH_2-CF_3$,

R^4 is independently of each other hydrogen, fluorine, chlorine, bromine or iodine, cyano, $-CH_3$, $-C_3H_9$,

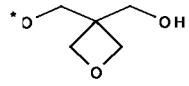
cyclopropyl, 1-propenyl, $-CF_3$, $-CH_2-OH$, $-CH_2-CH_2-OH$, $-C(CH_3)_2-OH$, $-CH_2-C(CH_3)_2-OH$, $-C(CH_3)_2-CH_2-OH$, $-OCH_3$, $-OCF_3$, $-OCF_2H$, $-OCH_2CF_3$, $-C(O)CH_3$, -COOH, $-C(O)OCH_3$, $-C(O)OC_2H_5$, $-C(O)OC(CH_3)_3$, $-CH_2-COOC_2H_5$, $-CH_2-COOH$, $-C(CH_3)_2-COOC_2H_5$, $-C(O)NH_2$, $-C(O)NH(CH_3)$, $-C(O)N(CH_3)_2$, $-C(O)NH-(CH_2)_2-OH$, -C(O)-(N-morpholino), $-SO_2-NH$-cyclopropyl, $-SO_2-$(N-morpholino), 5-methyl-oxa-diazol-3-yl,

whereby two of R^2, R^3 $(R^4)_n$, when positioned ortho to each other, form together with the two carbon atoms to which they are attached,

-O-CH_2-CH_2-CH_2-O-, -O-CH_2-CH_2-, -(CH_3)C=CH-(C=O)-O-,
-CH_2-(C=O)-O-, -$(CH_2)_2$-(C=O)-NH-,

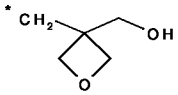
n 0, 1, 2, or 3,

R^6 is hydrogen, hydroxy, -OCH_3, -OCF_3, -OCF_2H, -OCH_2CF_3, -O-$(CH_2)_2$-OH, -O$(CH_2)_2$-N$(CH_3)_2$, -O-CH_2-SO_2NH_2,



, whereby * is the point of attachment,

R^7 is hydrogen, methyl, difluoromethyl, hydroxyethyl,



, whereby * is the point of attachment,

-C(O)-tetrahydropyran-4-yl, -C(O)-CH_2-O-CH_3, -C(O)-CH_3, -C(O)CH_2-O-$(CH_2)_2$-O-CH_3 or benzyl which is optionally substituted one or more times with fluorine, chlorine, cyano, methyl, difluoromethyl, methoxy, ethoxy, difluormethoxy, trifluoromethoxy, -O-CH_2-CF_3, -C(O)OCH_3,

R^8 is hydrogen, fluorine, cyano, C(O)NH_2,

m is 0, 1 or 2

R^9 is hydrogen, methyl, ethyl, tert.-butyl, hydroxyethyl,

R^{10}/R^{11} is independently from each other hydrogen, methyl, hydroxyethyl,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

A further aspect of the invention are compounds of formula (I) according to claim 1,

wherein,

R^1 is hydrogen, ,

R^2/R^3 is independently hydrogen, fluorine, chlorine, bromine, cyano, hydroxy, CF_3, -O-CH_3 or -O-CH_2-CF_3,

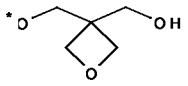
R^4 is independently of each other hydrogen, fluorine, chlorine, bromine or iodine, cyano, NO_2, hydroxy, -CH_3, -C_3H_7, cyclopropyl, 1-propenyl, -C≡CH, -CF_3, -CH_2-OH, -CH_2-CH_2-OH, -C$(CH_3)_2$-OH, -CH_2-C$(CH_3)_2$-OH, -C$(CH_3)_2$-CH_2-OH, -OCH_3, -O-CH_2-CH_3, -OCF_3, -OCF_2H, -OCH_2CF_3, -O-(CH_2)-O-C(O)-CH3, -C(O)CH_3, -COOH, -C(O)OCH_3, -C(O)OC_2H_5, -C(O)OC$(CH_3)_3$, -CH_2-COOH, -CH_2-COOC_2H_5, -C$(CH_3)_2$-COOC_2H_5, -C(O)NH_2,

-C(O)NH(CH_3), -C(O)N(CH_3)$_2$, -C(O)NH-(CH_2)$_2$-OH, -C(O)-(N-morpholinyl), -SO_2-NH-cyclopropyl, -SO_2-(N-morpholinyl), NH_2, NH-C(O)(CH_3), 5-methyl-oxa-diazol-3-yl, N-pyrrolyl, N-pyrazolyl, -S-CF_3, SF_5,

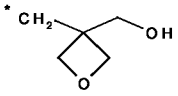
whereby two of R^2, R^3 $(R^4)_n$, when positioned ortho to each other, form together

-O-CH_2-CH_2-CH_2-O-, -O-CH_2-CH_2-, -(CH_3)C=CH-(C=O)-O-, -CH_2-(C=O)-O-, -(CH_2)$_2$-(C=O)-NH-, which together with the two carbon atoms to which they are attached form a 5-, 6- or 7-membered ring,

n is 0, 1, 2, 3,

R^6 is hydrogen, hydroxy, cyano, -O-cyclopropyl, -OCH_3, -OCF_3, -OCF_2H, -OCH_2CF_3, -O-(CH_2)$_2$-OH, -O-(CH_2)$_2$-NH_2, -O(CH_2)$_2$-N(CH_3)$_2$, -O-(CH_2)$_2$-O-CH_3, -O-(CH_2)$_2$-O-(CH_2)$_2$-OH, -O-CH_2-CH(OH)-CH_2OH, -O-CH_2-CH(OH)-CH_2-NH-C(O)OC(CH_3)$_3$, -O-CH_2-COOH, -O-CH_2-$COOC_2H_5$, C(O)NH_2, -O-CH_2-C(O)-(3-fluoro-N-azetidine), -O-CH_2-C(O)-(3,3-difluoro-N-azetidine), -O-CH_2-CH(OH)-CH_2-N-piperidinyl, -O-(CH_2)$_2$(morpholine-4-yl), -O-CH_2-(morpholine-2-yl), -O-CH_2-(morpholine-2-yl-4-tert.-butoxycarboxylate), -O-CH_2-(pyrrolidin-2-one-5-yl), -O-(CH_2)$_2$-S-CH_3, -O-(CH_2)$_2$-SO-CH_3, -O-(CH_2)$_2$-SO_2-CH_2, -O-CH_2-SO_2NH_2, -SO_2-CH(CH_3)$_2$,  , whereby * is the point of attachment,

-O-(CH_2)$_2$-tetrazolyl, -O-CH_2-tetrazolyl, -O-pyridine-4-yl, -O-(3-cyano-pyridine-4-yl), or -O-CH_2-(oxadiazole)-CH_2-O-CH_3,

R^7 is hydrogen, methyl, difluoromethyl, hydroxyethyl,  , whereby * is the point of attachment,

-(CH_2)$_2$-tetrazolyl, pyridine-4-yl, -C(O)-tetrahydropyran-4-yl, -C(O)-CH_2-O-CH_3, -C(O)-CH_3, -C(O)CH_2-O-(CH_2)$_2$-O-CH_3, or benzyl which is optionally substituted one or more times with fluorine, chlorine, bromine, cyano, methyl, difluoromethyl, methoxy, ethoxy, difluormethoxy, trifluoromethoxy, -O-CH_2-CF_3, -C(O)OCH_3, or

optionally, when R^6 is in position 5 of the pyrimidine ring system, R^6 and R^7 together with the nitrogen atom to which R^7 is attached form a 6-membered

ring which may contain one further heteroatom selected from O, S or N and which in addition is optionally substituted by -CH_2-OH or -CH_2-NH-CHO

R^8 is hydrogen, fluorine, hydroxy, cyano, CH_3, CF_3, CH_2-OH, OCH_3, C(O)OH, $C(O)OCH_3$, $C(O)OC_2H_5$, $C(O)O(CH_2)_2$-OH, $C(O)NH_2$, $C(O)NHCH_3$,

m is 0, 1 or 2

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

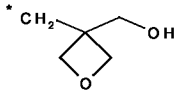
A further aspect of the invention are compounds of formula (I) according to claim 1, wherein

wherein

R^1 is hydrogen or methyl,

R^2/R^3 is independently hydrogen, fluorine, chlorine, methyl,

R^4 is hydrogen, cyclopropyl, CH_2-OH, $-C(CH_3)_2$-OH, -O-CHF_2, -O-CH_2-CH_3, -CH=CH-CH_3,

R^6 is hydrogen, OCH_3, $OCHF_2$, O-CH_2-CF_3, -O-$(CH_2)_2$-OH, -O-$(CH_2)_2$-NH_2, -O-CH_2-CH(OH)CH_2-OH, 

, -O-$(CH_2)_2$-SO-CH_3, -O-$(CH_2)_2$-SO_2-CH_3,

-O-CH_2-SO_2NH_2, -O-CH_2-(pyrrolidin-2-on-5-yl),

-O-CH_2-CH(OH)-CH_2-(piperidin-4-yl), -O-CH_2-(morpholin-2-yl),

R^7 is hydrogen

R^8 is hydrogen, CH_2-OH, $C(O)NH_2$, $C(O)NHCH_3$,

A further aspect of the invention are compounds of formula (I) according to claim 1, wherein

R^1 is hydrogen or methyl

R^2 /R^3 is hydrogen, fluorine, chlorine, hydroxy, methyl, methoxy,

R^4 is cyano, hydroxy, nitro, methyl, tert.-butoxy, CF_3, methoxy, ethoxy, propoxy, NH_2, NH-C(O)-CH_3, -O-$(CH_2)_2$-OC(O)CH_3, $C(O)NH_2$,

n is 1

R^6 is OCH_3, -O-CH_2-C(O)OH, -O-$(CH_2)_2$-S-CH_3, O-$(CH_2)_2$-SO-CH_3, -O-$(CH_2)_2$-SO_2-CH_2, -O-$(CH_2)_2$-NH_2, -O-$(CH_2)_2$-O-CH_3, -O-$(CH_2)_2$-O-$(CH_2)_2$-OH, ,-O-$(CH_2)_2$-O-$(CH_2)_2$-NH-C(O)$OC(CH_3)_3$, -O-CH_2-[morpholin-2-yl-(4-C(O)$OC(CH_3)_3$)], -O-$(CHy)_2$-morpholin-4-yl, -O-CH_2-(3-methoxymethyl-oxadiazol-5-yl), -O-CH_2-C(O)OC_2H_2, -O-CH_2-C(O)-(3,3-difluoroazetidin), -O-CH_2-C(O)-(3-fluoroazetidin), -O-CH_2-(pyrrolidin-2-on-5-yl), -O-CH_2-CH(OH)-CH_2-(1-piperidin), SO_2-$CH(CH_2)_2$, C(O)OC_2H_5,

R^7 is NH-C(O)$OC(CH_3)_3$,

R^8 is fluorine, cyano, hydroxy, methyl, ,C(O)NH_2, C(O)OC_2H_5, CH_2-OH, and

m is 1, 2

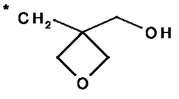
or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

Yet another aspect of the invention are compounds of formula (I) according to claim 1, wherein

R^1 is hydrogen,

R^2/R^3 is independently from each other hydrogen, fluorine, chlorine,

R^4 is –O-(1-4C-alkyl), (2-4C-alkyl)-OH, 3-5C-cycloalkyl, 2-3C-alkenyl,

R^6 is 

, whereby * is the point of attachment,

-O-(2-3C-alkyl)-NH_2, -O-(CH_2)heterocyclyl (which optionally is substituted with oxo (=O) or C(O)OR^9),

-O-(1-3C-alkyl), -O-(2-3C-alkyl)-OH, -O-(2-3C-alkyl)-SO-(2-3C-alkyl), -O-(2-3C-alkyl)-SO_2-(2-3C-alkyl), -O-(2-3Calkyl)-SO_2NH_2, -O-(CH_2)-CH(OH)-(CH_2)-heterocyclyl, -O-(CH_2)-CH(OH)-(CH_2)-OH, -O-(CH_2)-C(O)$NR^{10}R^{11}$,

R^7 is hydrogen

R^8 is hydrogen, C(O)$NR^{10}R^{11}$,

R^9 is hydrogen, 1-4C-alkyl which optionally is substituted with hydroxy,

R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl, 1-4C-hydroxyalkyl, 1-4C-alkoxy, -C(O)-(1-4C-alkyl), or $COOR^9$ or

together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the

group consisting of O, S or N, which is optionally substituted with 1-2 fluorine atoms or $COOR^9$,

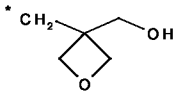
or a salt thereof.

A further aspect of the invention are compounds of formula (I) according to claim 1, wherein

R^1 is hydrogen,

R^2/R^3 is independently from each other hydrogen, fluorine, chlorine,

R^4 is $-O-CH_2-CH_3$, CH_2-OH, $C(CH_3)_3-OH$, cyclopropyl, propenyl, $-O-C(CH_3)_3$,

R^6 is 

, whereby * is the point of attachment, $-O(CH_2)_2-NH_2$, $-O-(CH_2)$heterocyclyl (which optionally is substituted with oxo (=O)), $-O-CH_3$, $-O-(CH_2)_2-OH$, $-O-(CH_2)_2-SO-CH_3$, $-O-(CH_2)_2-SO_2-CH_3$, $-O-(CH_2)_2-SO_2NH_2$, $-O-(CH_2)-CH(OH)-(CH_2)$-heterocyclyl, $-O-(CH_2)-CH(OH)-(CH_2)-OH$, $-O-(CH_2)-C(O)NR^{10}R^{11}$,

R^7 is hydrogen

R^8 is hydrogen, $C(O)NR^{10}R^{11}$,

R^9 is hydrogen, 1-4C-alkyl which optionally is substituted with hydroxy,

R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl, 1-4C-hydroxyalkyl, 1-4C-alkoxy, -C(O)-(1-4C-alkyl), or $COOR^9$ or

together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, which is optionally substituted with 1-2 fluorine atoms or $COOR^9$,

or a salt thereof.

In one aspect of the invention compounds of formula (I) as described above are selected from the group consisting of:

2-[1-(6-chloro-2-fluoro-3-methylbenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(6-chloro-2-fluoro-3-methoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

5-methoxy-2-{1-[3-(5-methyl-1,2,4-oxadiazol-3-yl)benzyl]-1H-indazol-3-yl}-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-chloro-4,5-dimethylbenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

5-methoxy-2-{1-[4-(pentafluoro-λ^6-sulfanyl)benzyl]-1H-indazol-3-yl}-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2,6-difluoro-3-methoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-(2,6-difluoro-3-methoxybenzyl)-2-[1-(2,6-difluoro-3-methoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-{1-[(6-bromo-1,3-benzodioxol-5-yl)methyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-(4-ethoxy-2,6-difluorobenzyl)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzonitrile,

2-[1-(2-chloro-4-methoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(3,4-dihydro-2H-1,5-benzodioxepin-6-ylmethyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-(2,6-difluorobenzyl)-2-[1-(2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

5-methoxy-N-(pyridin-4-yl)-2-(1-{3-[(trifluoromethyl)sulfanyl]benzyl}-1H-indazol-3-yl)pyrimidin-4-amine,

2-[1-(2,3-difluoro-4-methylbenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-(2,3-difluoro-4-methylbenzyl)-2-[1-(2,3-difluoro-4-methylbenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

5-methoxy-2-{1-[4-(1H-pyrazol-1-yl)benzyl]-1H-indazol-3-yl}-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2,6-dichlorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-(2,6-dichlorobenzyl)-2-[1-(2,6-dichlorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

5-methoxy-N-(pyridin-4-yl)-2-(1-{4-[(trifluoromethyl)sulfanyl]benzyl}-1H-indazol-3-yl)pyrimidin-4-amine,

2-[1-(2-chlorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-(2-chlorobenzyl)-2-[1-(2-chlorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

methyl 3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzoate,

methyl 3-chloro-4-{[(2-{1-[2-chloro-4-(methoxycarbonyl)benzyl]-1H-indazol-3-yl}-5-methoxypyrimidin-4-yl)(pyridin-4-yl)amino]methyl}benzoate,

2-[1-(4-bromo-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-chloro-4-fluoro-3-methoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-ethoxy-2,3-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-(4-ethoxy-2,3-difluorobenzyl)-2-[1-(4-ethoxy-2,3-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

5-methoxy-N-(pyridin-4-yl)-2-{1-[2,3,5,6-tetrafluoro-4-(2,2,2-trifluoroethoxy)benzyl]-1H-indazol-3-yl}pyrimidin-4-amine,

5-methoxy-N-(pyridin-4-yl)-N-[2,3,5,6-tetrafluoro-4-(2,2,2-trifluoroethoxy)benzyl]-2-{1-[2,3,5,6-tetrafluoro-4-(2,2,2-trifluoroethoxy)benzyl]-1H-indazol-3-yl}pyrimidin-4-amine,

methyl 2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzoate,

5-methoxy-N-(pyridin-4-yl)-2-[1-(2,4,6-trifluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-amine,

5-methoxy-N-(pyridin-4-yl)-N-(2,4,6-trifluorobenzyl)-2-[1-(2,4,6-trifluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-amine,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2,4-dichlorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-fluoro-4-iodobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-bromobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-(2-bromobenzyl)-2-[1-(2-bromobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

[3-fluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]acetic acid,

5-methoxy-N-(pyridin-4-yl)-2-[1-(2,3,5,6-tetrafluoro-4-methoxybenzyl)-1H-indazol-3-yl]pyrimidin-4-amine

5-methoxy-2-[1-(4-propylbenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-{1-[2,6-dichloro-4-(trifluoromethoxy)benzyl]-1H-indazol-3-yl}-5-

methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-[2,6-dichloro-4-(trifluoromethoxy)benzyl]-2-{1-[2,6-dichloro-4-(trifluoromethoxy)benzyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

7-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)-3,4-dihydroquinolin-2(1H)-one,,

2-[1-(2-chloro-4-iodobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(3,5-dimethoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-{1-[2-chloro-6-(trifluoromethyl)benzyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-chloro-5-fluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

7-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)-4-methyl-2H-chromen-2-one,

3-fluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzonitrile,

4-{[{2-[1-(4-cyano-2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}(pyridin-4-yl)amino]methyl}-3-fluorobenzonitrile,

2-{1-[2,6-dichloro-3-(trifluoromethyl)benzyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

ethyl [3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]acetate,

2-[1-(4-fluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-cyclopropyl-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzenesulfonamide,

6-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)-1-benzofuran-2(3H)-one,

2-{1-[4-(difluoromethoxy)-2,6-difluorobenzyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

tert-butyl 3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzoate,

ethyl 2-[3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]-2-methylpropanoate,,

4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzonitrile,

5-methoxy-2-{1-[4-(morpholin-4-ylsulfonyl)benzyl]-1H-indazol-3-yl}-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2,6-dichloro-3-nitrobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-

4-yl)pyrimidin-4-amine,

3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzonitrile,

N-[4-(difluoromethoxy)-2,6-difluorobenzyl]-2-{1-[4-(difluoromethoxy)-2,6-difluorobenzyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

5-methoxy-N-(pyridin-4-yl)-2-{1-[3-(1H-pyrrol-1-yl)benzyl]-1H-indazol-3-yl}pyrimidin-4-amine,

3,5-difluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzonitrile,

5-methoxy-2-{1-[2-methoxy-4-(trifluoromethyl)benzyl]-1H-indazol-3-yl}-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2,6-difluoro-3-methylbenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-fluoro-6-methoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

3,5-difluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzamide,

2-[3,5-difluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenoxy]ethyl acetate,

2-[1-(2,6-difluoro-4-propoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-ethoxy-2-fluoro-6-methoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol,

2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol,

2-[1-(4-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol,

{3-[({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methyl]oxetan-3-yl}methanol,

{3-[({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methyl]oxetan-3-yl}methanol,

(3-{[(2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-{[3-(hydroxymethyl)oxetan-3-yl]methoxy}pyrimidin-4-yl)(pyridin-4-yl)amino]methyl}oxetan-3-yl)methanol,

1-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methanesulfonamide,

5-[2-(dimethylamino)ethoxy]-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)-5-[2-(1H-tetrazol-5-yl)ethoxy]pyrimidin-4-amine,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)-5-[2-(1H-tetrazol-5-yl)ethoxy]-N-[2-(1H-tetrazol-5-yl)ethyl]pyrimidin-4-amine,

5-[2-(dimethylamino)ethoxy]-2-[1-(4-fluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)-5-(1H-tetrazol-5-ylmethoxy)pyrimidin-4-amine,

5-[2-(dimethylamino)ethoxy]-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine

1-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)-3-(piperidin-1-yl)propan-2-ol,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-(2-methoxyethoxy)-N-(pyridin-4-yl)pyrimidin-4-amine,

tert-butyl 2-[({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methyl]morpholine-4-carboxylate,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(morpholin-4-yl)ethoxy]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-{[3-(methoxymethyl)-1,2,4-oxadiazol-5-yl]methoxy}-N-(pyridin-4-yl)pyrimidin-4-amine,

ethyl ({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)acetate,

1-(3,3-difluoroazetidin-1-yl)-2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanone,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(methylsulfanyl)ethoxy]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethoxy]ethanol,

formic acid - (5S)-5-[({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methyl]pyrrolidin-2-one (1:1),

(5R)-5-[({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methyl]pyrrolidin-2-one,

tert-butyl {2-[2-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethoxy]ethyl}carbamate,

2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)-1-(3-fluoroazetidin-1-yl)ethanone,

(5S)-5-[({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methyl]pyrrolidin-2-one,

tert-butyl [2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethyl]carbamate,

N-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-8-(pyridin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-7-yl}methyl)formamide,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-cyclopropyl-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-(1-{2,6-difluoro-4-[(1E)-prop-1-en-1-yl]benzyl}-1H-indazol-3-yl)-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

1-[3,5-difluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]ethanone,

[2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]methanol,

2-[3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]ethanol,

2-[3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]-2-methylpropan-1-ol,

[4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridin-3-yl]methanol,

2-[3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]propan-2-ol,

1-[3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]-2-methylpropan-2-ol,

2-[2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]propan-2-ol

5-(difluoromethoxy)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

5-(difluoromethoxy)-N-(difluoromethyl)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

4-[(difluoromethyl)(pyridin-4-yl)amino]-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]pyrimidin-5-ol,

2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)-5-(2,2,2-trifluoroethoxy)pyrimidin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)-5-(2,2,2-trifluoroethoxy)pyrimidin-4-amine,

3-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)propane-1,2-diol,

(2S)-3-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)propane-1,2-diol,

(2R)-3-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)propane-1,2-diol,

2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanol,

2-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanol,

ethyl 4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)pyridine-3-carboxylate,

4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)-N-methylpyridine-3-carboxamide,

4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)pyridine-3-carboxamide,

2-hydroxyethyl 4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)pyridine-3-carboxylate,

5-(cyclopropyloxy)-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine hydrochloride (1:1),

(2S)-3-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)propane-1,2-diol hydrochloride (1:1),

2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanol hydrochloride (1:1),

2-[1-(2,6-dichlorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine hydrochloride (1:1),

[2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]methanol hydrochloride (1:1),

(2R)-3-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)propane-1,2-diol hydrochloride (1:1),

N-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}-N-(pyridin-4-yl)acetamide,

N-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}-2-methoxy-N-(pyridin-4-yl)acetamide,

N-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}-N-(pyridin-4-yl)tetrahydro-2H-pyran-4-carboxamide,

N-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}-2-(2-methoxyethoxy)-N-(pyridin-4-yl)acetamide,

2-[{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}(pyridin-4-yl)amino]ethanol,

(3-{[{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}(pyridin-4-yl)amino]methyl}oxetan-3-yl)methanol,

2-{1-[4-bromo-2-fluoro-6-(2,2,2-trifluoroethoxy)benzyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-{1-[4-bromo-2,6-bis(2,2,2-trifluoroethoxy)benzyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzoic acid,

({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)acetic acid,

2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)-N-methylbenzamide,

2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzamide,

2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)-N,N-dimethylbenzamide,

2,4-dichloro-N-(2-hydroxyethyl)-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzamide,

[2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl](morpholin-4-yl)methanone,

3,5-difluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)-N-methylbenzamide,

2-[1-(4-ethynyl-2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

{2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-8-(pyridin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-7-yl}methanol,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-methyl-N-(pyridin-4-yl)pyrimidin-4-amine,

4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carbonitrile,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N,N-di(pyridin-4-yl)pyrimidin-4-amine,

methyl 4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carboxylate,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carbonitrile,

2-[(3-{4-[(2,6-dimethylpyridin-4-yl)amino]-5-methoxypyrimidin-2-yl}-1H-indazol-1-yl)methyl]-5-ethoxy-3-fluorophenol,

4-({5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}amino)pyridin-2(1H)-one,

4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridin-2(1H)-one,

4-({5-methoxy-2-[1-(4-propylbenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}amino)nicotinonitrile,

4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carboxamide,

4-({5-methoxy-2-[1-(4-propylbenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}amino)pyridine-3-carboxamide,

4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carboxamide,

4-({2-[1-(2,6-difluoro-4-hydroxybenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carboxamide,

4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)pyridine-3-carbonitrile,

4-({4-[(3-cyanopyridin-4-yl)amino]-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]pyrimidin-5-yl}oxy)pyridine-3-carbonitrile,

5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]-N-[3-(trifluoromethyl)pyridin-4-yl]pyrimidin-4-amine,

3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzoic acid,

formic acid - 3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)-N-methylbenzamide (1:1),

3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)-N-methylbenzamide,

4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)pyridine-3-carboxamide,

4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)pyridine-3-carboxylic acid,

ethyl 4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)pyridine-3-carboxylate,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidine-5-carbonitrile,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidine-5-carboxamide,

4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)pyridine-3-carboxylic acid hydrochloride (1:1),

N-(2-fluoropyridin-4-yl)-5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]pyrimidin-4-amine,

N-(2,6-difluoropyridin-4-yl)-5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]pyrimidin-4-amine,

N-(3-fluoropyridin-4-yl)-5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]pyrimidin-4-amine,

5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]-N-(2-methylpyridin-4-yl)pyrimidin-4-amine,

N-(difluoromethyl)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(methylsulfinyl)ethoxy]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(methylsulfinyl)ethoxy]-N-(pyridin-4-yl)pyrimidin-4-amine (Enantiomer 1),

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(methylsulfinyl)ethoxy]-N-(pyridin-4-yl)pyrimidin-4-amine (Enantiomer 2),

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(methylsulfonyl)ethoxy]-N-(pyridin-4-yl)pyrimidin-4-amine,

5-(2-aminoethoxy)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-(morpholin-2-ylmethoxy)-N-(pyridin-4-yl)pyrimidin-4-amine,

Preparation of ethyl 4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carboxylate,

N-(3,5-difluoropyridin-4-yl)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-amine,

2-[1-(3-amino-2,6-dichlorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-[2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]acetamide,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

One aspect of the invention are all compounds being named in the list below.

2-[1-(2,6-dichloro-3-nitrobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-

4-yl)pyrimidin-4-amine,

3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzonitrile,

3,5-difluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzonitrile,

5-methoxy-2-{1-[2-methoxy-4-(trifluoromethyl)benzyl]-1H-indazol-3-yl}-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2,6-difluoro-3-methylbenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-fluoro-6-methoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

3,5-difluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzamide,

2-[3,5-difluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenoxy]ethyl acetate,

2-[1-(2,6-difluoro-4-propoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-ethoxy-2-fluoro-6-methoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

1-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)-3-(piperidin-1-yl)propan-2-ol,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-(2-methoxyethoxy)-N-(pyridin-4-yl)pyrimidin-4-amine,

tert-butyl 2-[({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methyl]morpholine-4-carboxylate,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(morpholin-4-yl)ethoxy]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-{[3-(methoxymethyl)-1,2,4-oxadiazol-5-yl]methoxy}-N-(pyridin-4-yl)pyrimidin-4-amine,

ethyl ({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)acetate,

1-(3,3-difluoroazetidin-1-yl)-2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanone,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(methylsulfanyl)ethoxy]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethoxy]ethanol,

formic acid - (5S)-5-[({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methyl]pyrrolidin-2-one (1:1),

(5R)-5-[({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-

4-ylamino)pyrimidin-5-yl}oxy)methyl]pyrrolidin-2-one,

tert-butyl {2-[2-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethoxy]ethyl}carbamate,

2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)-1-(3-fluoroazetidin-1-yl)ethanone,

(5S)-5-[({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methyl]pyrrolidin-2-one,

N-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-8-(pyridin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-7-yl}methyl)formamide,

[4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridin-3-yl]methanol,

({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)acetic acid,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carbonitrile,

2-[(3-{4-[(2,6-dimethylpyridin-4-yl)amino]-5-methoxypyrimidin-2-yl}-1H-indazol-1-yl)methyl]-5-ethoxy-3-fluorophenol,

4-({5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}amino)pyridin-2(1H)-one,

4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridin-2(1H)-one,

4-({5-methoxy-2-[1-(4-propylbenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}amino)nicotinonitrile,

4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carboxamide,

4-({2-[1-(2,6-difluoro-4-hydroxybenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carboxamide,

5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]-N-(2-methylpyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(methylsulfinyl)ethoxy]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(methylsulfinyl)ethoxy]-N-(pyridin-4-yl)pyrimidin-4-amine (Enantiomer 1),

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(methylsulfinyl)ethoxy]-N-(pyridin-4-yl)pyrimidin-4-amine (Enantiomer 2),

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(methylsulfonyl)ethoxy]-N-(pyridin-4-yl)pyrimidin-4-amine,

5-(2-aminoethoxy)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-(morpholin-2-ylmethoxy)-N-(pyridin-4-yl)pyrimidin-4-amine,

Preparation of ethyl 4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carboxylate,

N-(3,5-difluoropyridin-4-yl)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-amine,

2-[1-(3-amino-2,6-dichlorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-[2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]acetamide,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine
or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

In one aspect of the invention compounds of formula (I) as described above are selected from the group consisting of:

2-[1-(6-chloro-2-fluoro-3-methylbenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(6-chloro-2-fluoro-3-methoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

5-methoxy-2-{1-[3-(5-methyl-1,2,4-oxadiazol-3-yl)benzyl]-1H-indazol-3-yl}-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-chloro-4,5-dimethylbenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

5-methoxy-2-{1-[4-(pentafluoro-lambda⁶-sulfanyl)benzyl]-1H-indazol-3-yl}-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2,6-difluoro-3-methoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-(2,6-difluoro-3-methoxybenzyl)-2-[1-(2,6-difluoro-3-methoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-{1-[(6-bromo-1,3-benzodioxol-5-yl)methyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-(4-ethoxy-2,6-difluorobenzyl)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzonitrile,

2-[1-(2-chloro-4-methoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(3,4-dihydro-2H-1,5-benzodioxepin-6-ylmethyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-(2,6-difluorobenzyl)-2-[1-(2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

5-methoxy-N-(pyridin-4-yl)-2-(1-{3-[(trifluoromethyl)sulfanyl]benzyl}-1H-indazol-3-yl)pyrimidin-4-amine,

2-[1-(2,3-difluoro-4-methylbenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-(2,3-difluoro-4-methylbenzyl)-2-[1-(2,3-difluoro-4-methylbenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

5-methoxy-2-{1-[4-(1H-pyrazol-1-yl)benzyl]-1H-indazol-3-yl}-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2,6-dichlorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-(2,6-dichlorobenzyl)-2-[1-(2,6-dichlorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

5-methoxy-N-(pyridin-4-yl)-2-(1-{4-[(trifluoromethyl)sulfanyl]benzyl}-1H-indazol-3-yl)pyrimidin-4-amine,

2-[1-(2-chlorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-(2-chlorobenzyl)-2-[1-(2-chlorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

methyl 3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzoate,

methyl 3-chloro-4-{[(2-{1-[2-chloro-4-(methoxycarbonyl)benzyl]-1H-indazol-3-yl}-5-methoxypyrimidin-4-yl)(pyridin-4-yl)amino]methyl}benzoate,

2-[1-(4-bromo-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-chloro-4-fluoro-3-methoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-ethoxy-2,3-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-(4-ethoxy-2,3-difluorobenzyl)-2-[1-(4-ethoxy-2,3-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

5-methoxy-N-(pyridin-4-yl)-2-{1-[2,3,5,6-tetrafluoro-4-(2,2,2-trifluoroethoxy)benzyl]-1H-indazol-3-yl}pyrimidin-4-amine,

5-methoxy-N-(pyridin-4-yl)-N-[2,3,5,6-tetrafluoro-4-(2,2,2-trifluoroethoxy)benzyl]-2-{1-[2,3,5,6-tetrafluoro-4-(2,2,2-trifluoroethoxy)benzyl]-1H-indazol-3-yl}pyrimidin-4-amine,

methyl 2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzoate,

5-methoxy-N-(pyridin-4-yl)-2-[1-(2,4,6-trifluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-amine,

5-methoxy-N-(pyridin-4-yl)-N-(2,4,6-trifluorobenzyl)-2-[1-(2,4,6-trifluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-amine,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2,4-dichlorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-fluoro-4-iodobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-bromobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-(2-bromobenzyl)-2-[1-(2-bromobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

[3-fluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]acetic acid,

5-methoxy-N-(pyridin-4-yl)-2-[1-(2,3,5,6-tetrafluoro-4-methoxybenzyl)-1H-indazol-3-yl]pyrimidin-4-amine,

5-methoxy-2-[1-(4-propylbenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-{1-[2,6-dichloro-4-(trifluoromethoxy)benzyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-[2,6-dichloro-4-(trifluoromethoxy)benzyl]-2-{1-[2,6-dichloro-4-(trifluoromethoxy)benzyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine

7-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)-3,4-dihydroquinolin-2(1H)-one,

2-[1-(2-chloro-4-iodobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(3,5-dimethoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-{1-[2-chloro-6-(trifluoromethyl)benzyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-chloro-5-fluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-

yl)pyrimidin-4-amine,

7-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)-4-methyl-2H-chromen-2-one,

3-fluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzonitrile,

4-{[{2-[1-(4-cyano-2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}(pyridin-4-yl)amino]methyl}-3-fluorobenzonitrile,

2-{1-[2,6-dichloro-3-(trifluoromethyl)benzyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

ethyl [3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]acetate,

2-[1-(4-fluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-cyclopropyl-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzenesulfonamide,

6-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)-1-benzofuran-2(3H)-one,

2-{1-[4-(difluoromethoxy)-2,6-difluorobenzyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

tert-butyl 3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzoate,

ethyl 2-[3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]-2-methylpropanoate,

4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzonitrile

5-methoxy-2-{1-[4-(morpholin-4-ylsulfonyl)benzyl]-1H-indazol-3-yl}-N-(pyridin-4-yl)pyrimidin-4-amine

N-[4-(difluoromethoxy)-2,6-difluorobenzyl]-2-{1-[4-(difluoromethoxy)-2,6-difluorobenzyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

5-methoxy-N-(pyridin-4-yl)-2-{1-[3-(1H-pyrrol-1-yl)benzyl]-1H-indazol-3-yl}pyrimidin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol,

2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol,

2-[1-(4-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol,

{3-[({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-

ylamino)pyrimidin-5-yl}oxy)methyl]oxetan-3-yl}methanol,

{3-[({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methyl]oxetan-3-yl}methanol,

(3-{[(2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-{[3-(hydroxymethyl)oxetan-3-yl]methoxy}pyrimidin-4-yl)(pyridin-4-yl)amino]methyl}oxetan-3-yl)methanol,

1-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methanesulfonamide,

5-[2-(dimethylamino)ethoxy]-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)-5-[2-(1H-tetrazol-5-yl)ethoxy]pyrimidin-4-amine,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)-5-[2-(1H-tetrazol-5-yl)ethoxy]-N-[2-(1H-tetrazol-5-yl)ethyl]pyrimidin-4-amine,

5-[2-(dimethylamino)ethoxy]-2-[1-(4-fluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)-5-(1H-tetrazol-5-ylmethoxy)pyrimidin-4-amine,

5-[2-(dimethylamino)ethoxy]-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-cyclopropyl-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-(1-{2,6-difluoro-4-[(1E)-prop-1-en-1-yl]benzyl}-1H-indazol-3-yl)-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

1-[3,5-difluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]ethanone,

[2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]methanol,

2-[3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]ethanol,

2-[3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]-2-methylpropan-1-ol,

2-[3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]propan-2-ol,

1-[3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-

yl}methyl)phenyl]-2-methylpropan-2-ol,

2-[2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]propan-2-ol,

5-(difluoromethoxy)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

5-(difluoromethoxy)-N-(difluoromethyl)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

4-[(difluoromethyl)(pyridin-4-yl)amino]-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]pyrimidin-5-ol,

2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)-5-(2,2,2-trifluoroethoxy)pyrimidin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)-5-(2,2,2-trifluoroethoxy)pyrimidin-4-amine,

3-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)propane-1,2-diol,

(2S)-3-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)propane-1,2-diol,

(2R)-3-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)propane-1,2-diol,

2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanol,

2-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanol,

ethyl 4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)pyridine-3-carboxylate,

4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)-N-methylpyridine-3-carboxamide,

4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)pyridine-3-carboxamide,

2-hydroxyethyl 4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)pyridine-3-carboxylate,

5-(cyclopropyloxy)-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine hydrochloride (1:1),

(2S)-3-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)propane-1,2-diol hydrochloride (1:1),

2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanol hydrochloride (1:1),

2-[1-(2,6-dichlorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine hydrochloride (1:1),

[2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]methanol hydrochloride (1:1),

(2R)-3-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)propane-1,2-diol hydrochloride (1:1),

N-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}-N-(pyridin-4-yl)acetamide,

N-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}-2-methoxy-N-(pyridin-4-yl)acetamide,

N-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}-N-(pyridin-4-yl)tetrahydro-2H-pyran-4-carboxamide,

N-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}-2-(2-methoxyethoxy)-N-(pyridin-4-yl)acetamide,

2-[{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}(pyridin-4-yl)amino]ethanol,

(3-{[{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}(pyridin-4-yl)amino]methyl}oxetan-3-yl)methanol,

2-{1-[4-bromo-2-fluoro-6-(2,2,2-trifluoroethoxy)benzyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-{1-[4-bromo-2,6-bis(2,2,2-trifluoroethoxy)benzyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzoic acid,

2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)-N-methylbenzamide,

2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzamide,

2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)-N,N-dimethylbenzamide,

2,4-dichloro-N-(2-hydroxyethyl)-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzamide,

[2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl](morpholin-4-yl)methanone,

3,5-difluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)-N-methylbenzamide,

2-[1-(4-ethynyl-2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

{2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-8-(pyridin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-7-yl}methanol,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-methyl-N-(pyridin-4-yl)pyrimidin-4-amine,

4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carbonitrile,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N,N-di(pyridin-4-yl)pyrimidin-4-amine,

methyl 4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carboxylate,

4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carboxamide,

4-({5-methoxy-2-[1-(4-propylbenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}amino)pyridine-3-carboxamide,

4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)pyridine-3-carbonitrile,

4-({4-[(3-cyanopyridin-4-yl)amino]-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]pyrimidin-5-yl}oxy)pyridine-3-carbonitrile,

5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]-N-[3-(trifluoromethyl)pyridin-4-yl]pyrimidin-4-amine,

3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzoic acid,

formic acid - 3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)-N-methylbenzamide (1:1),

3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)-N-methylbenzamide,

4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)pyridine-3-carboxamide,

4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)pyridine-3-carboxylic acid,

ethyl 4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)pyridine-3-carboxylate,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidine-5-carbonitrile,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidine-5-carboxamide,

4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)pyridine-3-carboxylic acid hydrochloride (1:1),

N-(2-fluoropyridin-4-yl)-5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]pyrimidin-4-amine,

N-(2,6-difluoropyridin-4-yl)-5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]pyrimidin-4-amine,

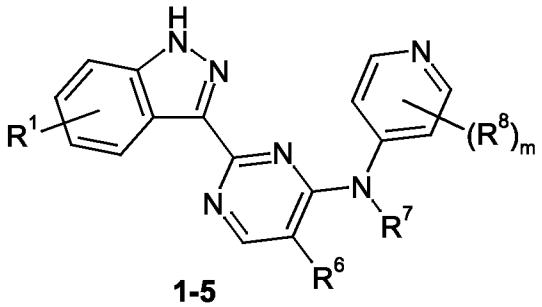
N-(3-fluoropyridin-4-yl)-5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]pyrimidin-4-amine,

N-(difluoromethyl)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine
or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

One aspect of the invention are compounds of formula (I) as described in the examples as characterized by their names in the title as claimed in claim 5 and their structures as well as the subcombinations of all residues specifically disclosed in the compounds of the examples.

Another aspect of the present invention are the intermediates as used for their synthesis.

One special aspect of the invention is intermediate (1-5) wherein ,



1-5

whereby R^1, R^6, R^7 R^8 and m have the meaning according to claim 1.

If embodiments of the invention as disclosed herein relate to compounds of formula (I), it is understood that those embodiments refer to the compounds of formula (I) as disclosed in the claims and the examples.

Another aspect of the invention are compounds of formula (I), wherein

R^1 is hydrogen, halogen, 1-3C-alkyl,

Another aspect of the invention are compounds of formula (I), wherein

R^1 is halogen.

Another aspect of the invention are compounds of formula (I), wherein
R^1 is 1-3C-alkyl.

A further aspect of the invention are compounds of formula (I), wherein
R^1 is hydrogen, 1-3C-alkyl.

Yet another aspect of the invention are compounds of formula (I) according to claims 1, 2, 3, 4, 5 or 6, wherein R^1 is hydrogen.

A further aspect of the invention are compounds of formula (I), wherein
R^2/R^3 are independently from each other hydrogen, halogen, cyano, hydroxy 1-6C-haloalkyl, 1-6C-haloalkoxy, 1-6C-alkoxy,

A further aspect of the invention are compounds of formula (I) according to claim 1, wherein R^2 and/or R^3 are independently from each other hydrogen, halogen, cyano, 1-6C-haloalkyl, 1-6C-haloalkoxy.

Another aspect of the invention are compounds of formula (I), wherein
R^2 and/or R^3 is halogen, especially fluorine, chlorine or bromine, preferably fluorine or chlorine.

Another aspect of the invention are compounds of formula (I), wherein
R^2 and/or R^3 is 1-3C-haloalkyl, especially CF_3.

Another aspect of the invention are compounds of formula (I), wherein
R^2 and/or R^3 is 1-3C-haloalkoxy, especially -O-CH_2-CF_3.

Another aspect of the invention are compounds of formula (I), wherein
R^2 and/or R^3 is fluorine, chlorine, bromine, CF_3, or -O-CH_2-CF_3.

Another aspect of the invention are compounds of formula (I), wherein
R^2 and/or R^3 is fluorine, chlorine, bromine, hydroxy, methoxy, CF_3, or -O-CH_2-CF_3.

Yet another aspect of the invention are compounds of formula (I), wherein R^2 and R^3 are halogen or 1-3C-haloalkoxy, especially fluorine, chlorine, or -O-CH_2-CF_3.

Another aspect of the invention are compounds of formula (I), wherein R^2 and/or R^3 are hydroxy, (1-6C-alkoxy).

A further aspect of the invention are compounds of formula (I), wherein R^2 and R^3 are different.

Another aspect of the invention are compounds of formula (I), wherein one position of R^2 and R^3 is hydrogen and the other is halogen, 1-3C-haloalkyl, 1-3C-haloalkoxy or especially fluorine, chlorine, bromine, CF_3, or -O-CH2-CF3.

Another aspect of the invention are compounds of formula (I), wherein

R^4 is independently hydrogen, hydroxy, halogen, cyano, NO_2, 1-6C-alkyl, 2-6C-alkenyl, 2-6C-alkynyl, 1-6C-haloalkyl, 1-6C-hydroxyalkyl, 1-6C-alkoxy, -O-(2-6Calkylen)-O-C(O)-(1-6C-alkyl), 1-6C-haloalkoxy, -C(O)OR^9, -(1-6C-alkylen)-C(O)OR^9, -C(O)-(1-6C-alkyl), -C(O)$NR^{10}R^{11}$, 3-7C-cycloalkyl, -S-(1-6C-haloalkyl), SF_5, -SO_2NH-(3-7C-cycloalkyl), -$SO_2NR^{10}R^{11}$, $NR^{10}R^{11}$, heteroaryl which optionally is substituted independently one or more times with cyano, 1-4C-alkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, C(O)OR^9, C(O)$NR^{10}R^{11}$, whereby two of R^2, R^3 $(R^4)_n$, when positioned ortho to each other, may form together with the two carbon atoms to which they are attached, a heterocyclic 5-, 6- or 7-membered ring containing 1 or 2 heteroatoms selected from O or N, and optionally containing an additional double bond and/or optionally substituted by an oxo (=O) group and/or an 1-4C-alkyl group,

Another aspect of the invention are compounds of formula (I), wherein R^4 is hydrogen.

Another aspect of the invention are compounds of formula (I), wherein R^4 is hydrogen or halogen, especially hydrogen or fluorine.

Another aspect of the invention are compounds of formula (I), wherein
R^4 is selected from the group consisting of hydroxy, NO_2 or $NR^{10}R^{11}$.

Another aspect of the invention are compounds of formula (I), wherein
R^4 is selected from the group consisting of is independently hydrogen, halogen, cyano, 1-6C-alkyl, 2-6C-alkenyl, 1-6C-haloalkyl, 1-6C-hydroxyalkyl, 1-6C-alkoxy, 1-6C-haloalkoxy, -C(O)OR^9, -(1-6C-alkylen)-C(O)OR^9, -C(O)-(1-6C-alkyl), -C(O)$NR^{10}R^{11}$, 3-7C-cycloalkyl, -S-(1-6C-haloalkyl), SF_5, -SO_2NH-(3-7C-cycloalkyl), -$SO_2NR^{10}R^{11}$,
heteroaryl which optionally is substituted independently one or more times with cyano, 1-4C-alkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, C(O)OR^9, C(O)$NR^{10}R^{11}$, whereby two of R^2, R^3 $(R^4)_n$, when positioned ortho to each other, may form together with the two carbon atoms to which they are attached, a heterocyclic 5-, 6- or 7-membered ring containing 1 or 2 heteroatoms selected from O or N, and optionally an additional double bond and/or a carbonyl group and/or an 1-4C-alkyl group.

Another aspect of the invention are compounds of formula (I), wherein
R^4 is selected from the group consisting of hydrogen, halogen, cyano, 1-3C-alkyl, 3-6C-cycloalkyl, 2-3C-alkenyl, 1-3C-haloalkyl, 1-3C-hydroxyalkyl, 1-3C-alkoxy, 1-3C-haloalkoxy, -C(O)-(1-3C-alkyl), COOH, (1-3C-alkylen)-COOH, -(1-3C-alkylen)-COO-(1-3C-alkyl), -COO-(1-4C-alkyl), -C(O)NH_2, -C(O)NH(1-3C-alkyl), -C(O)N(1-3C-alkyl)$_2$, -C(O)NH-(1-3C-alkyl)-OH, -C(O)-(N-heterocyclyl), -SO_2-NH-(3-6C-cycloalkyl), -SO_2-(N-heterocyclyl),

Yet another aspect of the invention are compounds of formula (I), wherein
R^4 is selected from the group consisting of hydrogen, hydroxy, fluorine, chlorine, bromine or iodine, cyano, nitro, -CH_3, -C_3H_9, cyclopropyl, 1-propenyl, -CF_3, -CH_2-OH, -CH_2-CH_2-OH, -C(CH_3)$_2$-OH, -CH_2-C(CH_3)$_2$-OH, -C(CH_3)$_2$-CH_2-OH, -OCH3, -OCF_3, -OCF_2H, -OCH_2CF_3, -C(O)CH_3, -COOH, -C(O)OCH_3, -C(O)OC_2H_5, -C(O)OC(CH_3)$_3$, -CH_2-$COOC_2H_5$, -CH_2-COOH, -C(CH_3)$_2$-$COOC_2H_5$, -C(O)NH2,

-C(O)NH(CH_3), -C(O)N(CH_3)$_2$, -C(O)NH-(CH_2)$_2$-OH, -C(O)-(N-morpholino), -SO_2-NH-cyclopropyl, -SO_2-(N-morpholino), NH_2.

Yet another aspect of the invention are compounds of formula (I), wherein
R^4 is selected from the group consisting of hydrogen, fluorine, chlorine, bromine or iodine, cyano, -CH_3, -C_3H_9, cyclopropyl, 1-propenyl, -CF_3, -CH_2-OH, -CH_2-CH_2-OH, -C(CH_3)$_2$-OH, -CH_2-C(CH_3)$_2$-OH, -C(CH_3)$_2$-CH_2-OH, -OCH_3, -OCF_3, -OCF_2H, -OCH_2CF_3, -C(O)CH_3, -COOH, -C(O)OCH_3, -C(O)OC_2H_5, -C(O)OC(CH_3)3, -CH2-$COOC_2H_5$, -CH_2-COOH, -C(CH_3)$_2$-$COOC_2H_5$, -C(O)NH_2, -C(O)NH(CH_3), -C(O)N(CH_3)$_2$, -C(O)NH-(CH_2)$_2$-OH, -C(O)-(N-morpholino), -SO_2-NH-cyclopropyl, -SO_2-(N-morpholino).

A further aspect of the invention are compounds of formula (I), wherein whereby two of R^2, R^3 $(R^4)_n$, when positioned ortho to each other, may form together with the two carbon atoms to which they are attached, a heterocyclic 5-, 6- or 7-membered ring containing 1 or 2 heteroatoms selected from O or N, and optionally an additional double bond and/or a carbonyl group and/or an 1-4C-alkyl group, especially whereby two of R^2, R^3 $(R^4)_n$, when positioned ortho to each other, form together with the two carbon atoms to which they are attached, -O-CH2-CH2-CH2-O-, -O-CH2-CH2-, -(CH3)C=CH-(C=O)-O-, -CH2-(C=O)-O-, -(CH2)2-(C=O)-NH-.

In another embodiment of the above-mentioned aspects, the invention relates to compounds of formula (I), wherein n is 0, 1 or 2.

Another aspect of the invention are compounds of formula (I), wherein n is at least 1.

Another aspect of the invention are compounds of formula (I), wherein n is 1.

Another aspect of the invention are compounds of formula (I), wherein
R^6 is (a) hydrogen;

(b) hydroxy;

(c) cyano;

(d) 1-6C-alkoxy optionally substituted independently one or more times with

(d1) OH,

(d2) –O-(1-6C-alkyl)

(d3) $C(O)OR^9$,

(d4) $C(O)NR^{10}R^{11}$,

(d5) $NR^{10}R^{11}$,

(d6) –S-(1-6C-alkyl),

(d7) –S(O)-(1-6C-alkyl),

(d8) $–SO_2$-(1-6C-alkyl)

(d9) $SO_2NR^{10}R^{11}$,

(d10) heterocyclyl, which is optionally substituted with $C(O)OR^9$, or oxo (=O),

(d11) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-4C-alkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, (1-6C-alkylen)-O-(1-6C-alkyl),

(e) $SO_2NR^{10}R^{11}$,

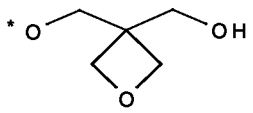
(f) 3-7C-cycloalkoxy,

(g) 1-6C-haloalkoxy,

(h) $COOR^9$,

(i) $-C(O)NR^{10}R^{11}$,

(j) -O-heteroaryl opt. subst. with CN

(k) 

, whereby the * is the point of attachment,

(l) –O-(2-6C-alkylen)-O-(1-6C-alkyl) which is optionally substituted with hydroxy, $NH(CO)OR^9$,

A further aspect of the invention are compounds of formula (I), wherein

R^6 is 1-6C-alkoxy which is optionally substituted independently one or more times.

A further aspect of the invention are compounds of formula (I), wherein

R^6 is heteroaryl, which is optionally substituted independently one or more times with cyano, 1-4C-alkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, (1-6C-alkyl)-O-(1-6C-alkyl). Another aspect of the invention are compounds of formula (I), wherein

R^6 is –O-(2-6Calkyl)-O-(1-6C-alkyl) which is optionally substituted with hydroxy or NH-$C(O)OR^9$.

Another aspect of the invention are compounds of formula (I), wherein

R^6 is 1-6C-alkoxy which is optionally substituted independently one or more times with

(d1) OH,

(d2) –O-(1-6C-alkyl)

(d3) $C(O)OR^9$,

(d4) $C(O)NR^{10}R^{11}$,

(d5) $NR^{10}R^{11}$,

(d6) –S-(1-6C-alkyl),

(d7) –S(O)-(1-6C-alkyl),

(d8) $–SO_2$-(1-6C-alkyl)

(d9) $SO_2NR^{10}R^{11}$,

(d10) heterocyclyl, which is optionally substituted with $C(O)OR^9$, or oxo (=O),

(d11) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-4C-alkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, (2-6C-alkylen)-O-(1-6C-alkyl),

Another aspect of the invention are compounds of formula (I), wherein

R^6 is 1-6C-alkoxy which is optionally substituted independently one or more times with

(d2) $C(O)OR^9$,

(d3) $C(O)NR^{10}R^{11}$,

(d4) –S-(1-6C-alkyl),

(d6) –S(O)-(1-6C-alkyl),

(d7) –SO_2-(1-6C-alkyl),

(d9) heterocyclyl, which is optionally substituted with C(O)OR^9,

oxo (=O).

Another aspect of the invention are compounds of formula (I), wherein

R^6 is (a) hydrogen;

(b) hydroxy;

(c) cyano;

(d) 1-6C-alkoxy opt. subst. with

(d1) 1-2 OH,

(d2) $NR^{10}R^{11}$,

(d3) $SO_2NR^{10}R^{11}$,

(d4) heterocyclyl,

(d5) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-4Calkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, C(O)OR^9, C(O)$NR^{10}R^{11}$,

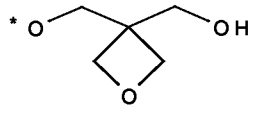
(e) $SO_2NR^{10}R^{11}$, ;

(f) 3-7C-cycloalkoxy,

(g) 1-6C-haloalkoxy,

(h) -C(O)$NR^{10}R^{11}$,

(i) -O-heteroaryl opt. subst. with CN

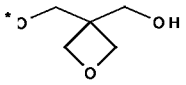
(j) 

, whereby the * is the point of attachment,

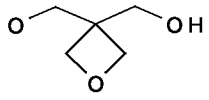
Another aspect of the invention are compounds of formula (I), wherein

R^6 is hydrogen, hydroxy, cyano, -O-(3-6C-cycloalkyl), 1-3C-alkoxy, 1-3C-haloalkoxy, -O-(1-3C-alkylen)-OH, -O-(1-3C-alkylen)-NH2, -O-(1-3C-alkylen)-NH(1-3C-alkyl), -O-(1-3C-alkylen)-N(1-3C-alkyl)2, -O-(1-3C-alkylen)-SO2NH2, -O-(1-3C-alkylen)-SO2N(1-3C-alkyl)2, -O-(1-3C-alkylen)-(optionally substituted heteroaryl), -C(O)NH2, -C(O)N(1-3C-alkyl)2.

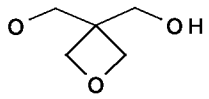
Another aspect of the invention are compounds of formula (I), wherein .

R^6 is hydrogen, hydroxy, cyano, -O-cyclopropyl, $-OCH_3$, $-OCF_3$, $-OCF_2H$, $-OCH_2CF_3$, $-O-(CH_2)_2-OH$, $-O-(CH_2)_2-NH_2$, $-O(CH_2)_2-N(CH_3)_2$, $-O-(CH_2)_2-O-CH_3$, $-O-(CH_2)_2-O-(CH_2)_2-OH$, $-O-CH_2-CH(OH)-CH_2OH$, $-O-CH_2-CH(OH)-CH_2-NH-C(O)OC(CH_3)_3$, $-O-CH_2-COOH$, $-O-CH_2-COOC_2H_5$, $C(O)NH_2$, $-O-CH_2-C(O)-$(3-fluoro-N-azetidine), $-O-CH_2-C(O)-$(3,3-difluoro-N-azetidine), $-O-CH_2-CH(OH)-CH_2-$N-piperidinyl, $-O-(CH_2)_2$(morpholine-4-yl), $-O-CH_2-$(morpholine-2-yl), $-O-CH_2-$(morpholine-2-yl-4-tert.-butoxycarboxylate), $-O-CH_2-$(pyrrolidin-2-one-5-yl), $-O-(CH_2)_2-S-CH_3$, $-O-(CH_2)_2-SO-CH_3$, $-O-(CH_2)_2-SO_2-CH_2$, $-O-CH_2-SO_2NH_2$, $-SO_2-CH(CH_3)_2$,  , whereby * is the point of attachment, $-O-(CH_2)_2-$tetrazolyl, $-O-CH_2-$tetrazolyl, -O-pyridine-4-yl, -O-(3-cyano-pyridine-4-yl), or - $O-CH_2-$(oxadiazole)-CH_2-O-CH_3,

Another aspect of the invention are compounds of formula (I), wherein

R^6 is hydrogen, hydroxy, cyano, -O-cyclopropyl, $-OCH_3$, $-OCF_3$, $-OCF_2H$, $-OCH_2CF_3$, $-O-(CH_2)_2-OH$, $-O(CH_2)_2-N(CH_3)_2$, $-O-CH_2-SO_2NH_2$,  , -O-(CH2)2-tetrazolyl, $-O-CH_2-$tetrazolyl, -O-pyridine-4-yl, -O-(3-cyano-pyridine-4-yl), $-C(O)NH_2$.

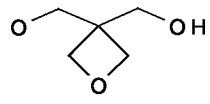
Another aspect of the invention are compounds of formula (I), wherein

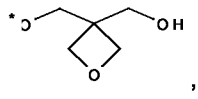
R^6 is hydrogen, hydroxy, cyano, -O-cyclopropyl, $-OCH_3$, $-OCF_3$, $-OCF_2H$, $-OCH_2CF_3$, $-O-(CH_2)_2-OH$, $-O(CH_2)_2-N(CH_3)_2$, $-O-CH_2-SO_2NH_2$,  , $-O-(CH_2)_2-$tetrazolyl, $-O-CH_2-$tetrazolyl, -O-pyridine-4-yl, -O-(3-cyano-pyridine-4-yl), $-C(O)NH_2$.

Another aspect of the invention are compounds of formula (I), wherein if R^6 is in the 5-position of the pyrimidine ring directly neighbouring the R^7 bearing amino substituent, R^6 together with R^7 is a 5 or 6-membered ring including the nitrogen atom of the amino substituent which may contain one further heteroatom selected

from O, S or N and which in addition may be substituted with a carbonyl group or -CH_2-OH.

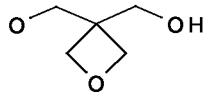
Another aspect of the invention are compounds of formula (I), wherein if R^6 is in the 5-position of the pyrimidine ring directly neighbouring the R^7 bearing amino substituent, R^6 together with R^7 is a 5 or 6-membered ring including the nitrogen atom of the amino substituent which may contain one further heteroatom selected from O, S or N and which in addition may be substituted with a carbonyl group or -CH2-OH or –NH-CHO.

Another preferred aspect of the invention are compounds of formula (I), wherein R^6 is-O-(3-6C-cycloalkyl), 1-3C-alkoxy, 1-3C-haloalkoxy, -O-(1-3C-alkylen)-OH, -O-(1-3C-alkylen)-NH2, -O-(1-3C-alkylen)-NH(1-3C-alkyl), -O-(1-3C-alkylen)-N(1-3C-alkyl)2, -O-(1-3C-alkylen)-SO2NH2, -O-(1-3C-alkylen)-SO2N(1-3C-alkyl)2, -O-(1-3C-alkylen)-(optionally substituted heteroaryl), especially -O-cyclopropyl, -OCH3, -OCF3, -OCF2H, -OCH2CF3, -O-(CH2)2-OH, -O(CH2)2-N(CH3)2, -O-CH2-SO2NH2,  , -O-(CH2)2-tetrazolyl, -O-CH2-tetrazolyl, -O-pyridine-4-yl, -O-(3-cyano-pyridine-4-yl).

Another preferred aspect of the invention are compounds of formula (I), wherein R^6 is hydrogen, hydroxy, cyano, -O-cyclopropyl, -O(1-3C-alkyl), -O-(1-3C-haloalkyl), -O-(1-3C-alkylen optionally substituted by a hydroxy group)-OH, -O(1-3C-alkylen optionally substituted by a hydroxy group)-$NR^{10}R^{11}$, -O-(1-3-alkylen)-O-(1-3C-alkyl), -O-(1-3C-alkylen)-O-(1-3C-alkyl)-OH, -O-(1-3C-alkylen)-$COOR^9$, $C(O)NR^{10}R^{11}$, -O-(1-3C-alkylen)-C(O)-(heterocycyl optionally substituted 1 or two times by fluorine), -O-(1-3-alkylen)-(heterocyclyl optionally substituted by an oxo (=O) group and/or $COOR^9$ or a hydroxy group), -O-(1-3C-alkylen)-S-CH_3, -O-(1-3C-alkylen)-SO-CH_3, -O-(1-3C-alkylen)$_2$-SO_2-CH_3, -O-(1-3C-alkylen)-SO_2NH_2, -SO_2-(1-3C-alkyl),  , whereby * is the point of attachment,

-O-(1-3-alkylen)-[heteroaryl optionally substituted by CN or (1-3C-alkylen)-O-(1-3C-alkyl)],

Another preferred aspect of the invention are compounds of formula (I), wherein

R^6 is-O-(3-6C-cycloalkyl), 1-3C-alkoxy, 1-3C-haloalkoxy, -O-(1-3C-alkylen)-OH, -O-(1-3C-alkylen)-NH_2, -O-(1-3C-alkylen)-NH(1-3C-alkyl), -O-(1-3C-alkylen)-N(1-3C-alkyl)$_2$, -O-(1-3C-alkylen)-SO_2NH_2, -O-(1-3C-alkylen)-SO_2N(1-3C-alkyl)$_2$, -O-(1-3C-alkylen)-(optionally substituted heteroaryl), especially -O-cyclopropyl, $-OCH_3$, $-OCF_3$, $-OCF_2H$, $-OCH_2CF_3$, -O-$(CH_2)_2$-OH, -O$(CH_2)_2$-N$(CH_3)_2$, -O-CH_2-SO_2NH_2,  , -O-$(CH_2)_2$-tetrazolyl, -O-CH_2-tetrazolyl, -O-pyridine-4-yl, -O-(3-cyano-pyridine-4-yl).

A further aspect of the invention are compounds of formula (I), wherein

R^6 is1-6C-alkoxy which is substituted by –S-(1-6C-alkyl), -SO-(1-6C-alkyl) or –SO_2-(1-6C-alkyl).

A further aspect of the invention are compounds of formula (I), wherein

R^6 is $SO_2NR^{10}R^{11}$.

Another aspect of the invention are compounds of formula (I), wherein

R^6 is -C(O)NH_2, -C(O)N(1-3C-alkyl)$_2$ or cyano especially -C(O)NH_2.

Another aspect of the invention are compounds of formula (I), wherein

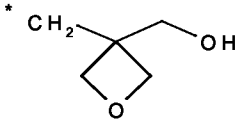
R^7 is

(a) hydrogen,

(b)1-6C-alkyl, which is optionally substituted with heteroaryl

(c) 1-6C-haloalkyl,

(d) 1-6C-hydroxyalkyl,

(e)  , whereby the * is the point of attachment,

(f) -C(O)-(1-6C-alkyl)

(g) –C(O)-(1-6C-alkylen)-O-(1-6C-alkyl)

(h) –C(O)-(1-6C-alkylen)-O-(2-6C-alkylen)-O-(1-6C-alkyl)

(i) –C(O)-heterocyclyl,

(j) benzyl whereby the phenyl ring is opt. subst with 1-5 substituents independently selected from the group consisting of hydrogen, halogen, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-alkoxy, 1-4C-haloalkoxy, cyano, $C(O)OR^9$,

(k) heteroaryl

or

optionally, R^6 and R^7 together with the nitrogen atom to which R^7 is attached form a 6-membered ring which may contain one further heteroatom selected from the group consisting of O, S, N,

and which is optionally substituted by (1-6C-alkyl)-OH, (1-6C-alkyl)-$NR^{10}R^{11}$,

Another aspect of the invention are compounds of formula (I), wherein

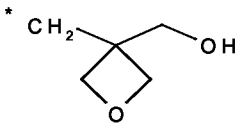
R^7 is

(a) hydrogen,

(b)1-6C-alkyl, which is optionally substituted with heteroaryl

(c) 1-6C-haloalkyl,

(d) 1-6C-hydroxyalkyl,

(e) 

, whereby the * is the point of attachment,

(f) -C(O)-(1-6C-alkyl)

(g) –C(O)-(1-6C-alkylen)-O-(1-6C-alkyl)

(h) –C(O)-(1-6C-alkylen)-O-(2-6C-alkylen)-O-(1-6C-alkyl)

(i) –C(O)-heterocyclyl,

(j) benzyl whereby the phenyl ring is opt. subst with 1-5 substituents independently selected from the group consisting of hydrogen, halogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-haloalkoxy, cyano, $C(O)OR^9$,

(k) heteroaryl

or

optionally, R^6 and R^7 together with the nitrogen atom to which R^7 is attached form a 6-membered ring which may contain one further heteroatom selected from the group consisting of O, S, N,

and which is optionally substituted by (1-6C-alkyl)-OH,

(1-6C-alkyl)-$NR^{10}R^{11}$,

Another aspect of the invention are compounds of formula (I), wherein

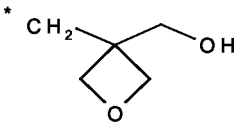
R^7 is

(a) hydrogen,

(b)1-3C-alkyl, which is optionally substituted with heteroaryl

(c) 1-3C-haloalkyl,

(d) 1-3C-hydroxyalkyl,

(e) 

, whereby the * is the point of attachment,

(f) -C(O)-(1-3C-alkyl)

(g) –C(O)-(1-3C-alkylen)-O-(1-3C-alkyl)

(h) –C(O)-(1-3C-alkylen)-O-(2-3C-alkylen)-O-(1-3C-alkyl)

(i) –C(O)-heterocyclyl,

(j) benzyl whereby the phenyl ring is opt. subst with 1-5 substituents independently selected from the group consisting of hydrogen, halogen, 1-3C-alkyl, 1-3C-alkoxy, 1-3C-haloalkoxy, cyano, $C(O)OR^9$,

(k) heteroaryl

or

optionally, R^6 and R^7 together with the nitrogen atom to which R^7 is attached form a 6-membered ring which may contain one further heteroatom selected from the group consisting of O, S, N,

and which is optionally substituted by (1-3C-alkyl)-OH,

(1-3C-alkyl)-$NR^{10}R^{11}$.

Another aspect of the invention are compounds of formula (I), wherein

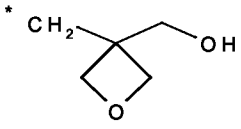
R^7 is

(a) hydrogen,

(b)1-6C-alkyl, which is optionally substituted with heteroaryl

(c) 1-6C-haloalkyl,

(d) 1-6C-hydroxyalkyl,

(e)  , whereby the * is the point of attachment,

(f) -C(O)-(1-6C-alkyl)

(g) –C(O)-(1-6C-alkylen)-O-(1-6C-alkyl)

(h) –C(O)-(1-6C-alkylen)-O-(1-6C-alkylen)-O-(1-6C-alkyl)

(i) –C(O)-heterocyclyl,

(j) benzyl whereby the phenyl ring is opt. subst with 1-5 substituents independently selected from the group consisting of

hydrogen, halogen, 1-4Calkyl, 1-4C-haloalkyl, 1-4C-alkoxy,

1-4C-haloalkoxy, cyano,

$C(O)OR^9$,

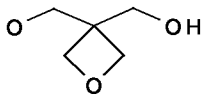
(k) heteroaryl

or

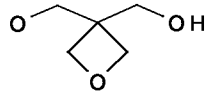
optionally R^6 and R^7 together with the nitrogen atom to which they are attached form a 6-membered ring which may contain one further heteroatom selected from the group consisting of O, S, N,

and which is optionally substituted by hydroxy-(1-6alkyl),

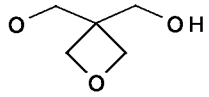
Another aspect of the invention are compounds of formula (I), wherein

R^7 is hydrogen, 1-3C-alkyl, 1-3C-haloalkyl, -(1-3C-alkylen)-OH,  , (1-3C-alkylen)-aryl, -(1-3C-alkylen)-heteroaryl, heteroaryl, -C(O)-(1-3C-alkyl), -C(O)-(1-3C-alkylen)-O-(1-3C-alkyl), -C(O)-(1-3C-alkylen)-O-(1-3C-alkylen)-O-(1-3C-alkyl), -C(O)-heterocyclyl.

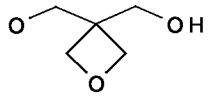
Another aspect of the invention are compounds of formula (I), wherein

R^7 is hydrogen, 1-3C-alkyl, 1-3C-haloalkyl, 1-3C-hydroxyalkyl,  ,
whereby * is the point of attachment,
Heteroaryl, -(1-3C-alkylen)-heteroaryl, , -C(O)-heterocyclyl, -C(O)-(1-3C-alkylen)-O-(1-3C-alkyl), -C(O)-(1-3C-alkyl), $-C(O)CH_2$-O-(1-3C-alkylen)-O-(1-3C-alkyl), or benzyl which is optionally substituted one or more times with halogen, cyano, 1-3C-alkyl, 1-3C-haloalkyl, 1-3C-alkoxy, 1-3C-haloalkoxy, -C(O)O(1-3-alkyl), or optionally, when R^6 is in position 5 of the pyrimidine ring system, R^6 and R^7 together with the nitrogen atom to which R^7 is attached form a 6-membered ring which may contain one further heteroatom selected from O, S or N and which in addition is optionally substituted by CH_2-OH or $-CH_2$-NH-CHO

Another aspect of the invention are compounds of formula (I), wherein

R^7 is hydrogen, methyl, difluoromethyl, hydroxyethyl,  , $-(CH_2)_2$-tetrazolyl, pyridine-4-yl, -C(O)-tetrahydropyran-4-yl, $-C(O)-CH_2-O-CH_3$, $-C(O)-CH_3$, $-C(O)CH_2-O-(CH_2)_2-O-CH_3$ or benzyl which is optionally substituted one or more times with fluorine, chlorine, bromine, cyano, methyl, methoxy, ethoxy, difluormethoxy, trifluoromethoxy, $-O-CH_2-CF_3$, $-C(O)OCH_3$.

Still another aspect of the invention are compounds of formula (I), wherein

R^7 is hydrogen, methyl, difluoromethyl, hydroxyethyl,  , $-(CH_2)_2$-tetrazolyl, pyridine-4-yl, -C(O)-tetrahydropyran-4-yl, $-C(O)-CH_2-O-CH_3$, $-C(O)-CH_3$, $-C(O)CH_2-O-(CH_2)_2-O-CH_3$ or benzyl which is optionally substituted one or more times with fluorine, chlorine, cyano, methyl, methoxy, ethoxy, difluormethoxy, trifluoromethoxy, $-O-CH_2-CF_3$, $-C(O)OCH_3$.

Another aspect of the invention are compounds of formula (I), wherein
R^7 is optionally one or more times substituted benzyl, the substitutents selected from the group consisting of halogen (especially fluorine, chlorine), cyano, 1-3C-

alkoxy (especially methoxy, ethoxy), 1-3C-haloalkoxy (especially -OCF_3, -O-CF_2H, -O-CH_2-CF_3).
In another aspect the benzyl group is substituted 1-, 2-, 3- or 4 times.

Another aspect of the invention are compounds of formula (I), wherein
R^8 is hydrogen, halogen, hydroxy, cyano, 1-6C-alkyl, 1-6C-hydroxyalkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,

Another aspect of the invention are compounds of formula (I), wherein
R^8 is hydrogen, halogen, cyano, 1-6C-haloalkyl, 1-6C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,

Another aspect of the invention are compounds of formula (I), wherein
R^8 is hydrogen, cyano, 1-3C-haloalkyl, -$C(O)NH_2$, -C(O)N(1-3C-alkyl), C(O)OH, -C(O)-O(1-4C-alkyl), -C(O)-(1-3C-alkylen)-OH, especially hydrogen, cyano, CF_3, $C(O)NH_2$, C(O)OH, $C(O)OC_2H_5$, $C(O)O(CH_2)_2$-OH.

Another aspect of the invention are compounds of formula (I), wherein
R^8 is hydroxy-(1-6C-alkyl).

Another aspect of the invention are compounds of formula (I), wherein
R^8 is hydrogen, fluorine, hydroxy, cyano, 1-3C-alkyl, 1-3C-haloalkyl, 1-3C-hydoxyalkyl, 1-3C-alkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, especially hydrogen, fluorine, hydroxy, cyano, methyl, CF_3, methoxy, hydroxymethyl, COOH, $COOCH_3$, $COOC_2H_5$, $C(O)NH_2$, $C(O)NHCH_3$.

Still another aspect of the invention are compounds of formula (I), wherein m is 0.

Another aspect of the invention are compounds of formula (I), wherein m is 0 or 1.

Another aspect of the invention are compounds of formula (I), wherein m is selected from 0, 1 or 2.

Another aspect of the invention are compounds of formula (I), wherein
R^9 is (a) hydrogen,
(b) 1-6C-alkyl which optionally is substituted with hydroxy,

Another aspect of the invention are compounds of formula (I), wherein
R^9 is hydrogen, 1-4C-alkyl, 1-3C-hydroxyalkyl, especially hydrogen, methyl, ethyl, tert.-butyl, hydroxyethyl.

Another aspect of the invention are compounds of formula (I), wherein
R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl, 1-4C-hydroxyalkyl, 1-4C-alkoxy, -(CO)-(1-6C-alkyl), CHO, $COOR^9$, or
together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, and which is optionally substituted with 1-2 fluorine atoms or $COOR^9$,

Another aspect of the invention are compounds of formula (I), wherein
R^{10}/R^{11} is independently from each other hydrogen, 1-3C-alkyl, 1-3C-hydroxyalkyl, especially hydrogen, methyl, hydroxyethyl,

Another aspect of the invention are compounds of formula (I), wherein
R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl, 1-4C-hydroxyalkyl, 1-4C-alkoxy, -(CO)-(1-6C-alkyl) or
together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, which is optionally with 1-2 halogen atoms, especially fluorine atoms.

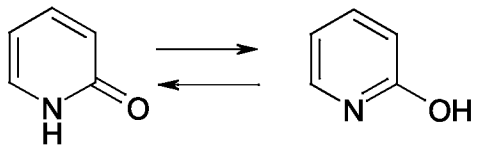
In another aspectof the invention are compounds of formula (I), wherein
R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl, 1-4C-hydroxyalkyl, 1-4C-alkoxy, or

together with the nitrogen atom to which they are attached form a 5-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N.

Another aspect of the invention are compounds of formula (I), wherein R^{10}, R^{11} form together with the nitrogen atom to which they are attached a 4-membered heterocyclic ring, which is optionally with 1-2 halogen atoms, especially fluorine atoms.

A further aspect of the invention are compounds of formula (I), which are present as their salts, especially as their hydrochlorides.

Another embodiment of the invention are the tautomeric forms of a hydroxypyridine which are defined to be encompassed by the claim, should the compound of formula I include such a hydroxypyridine:



Another embodiment of the invention are compounds according to the claims as disclosed in the Claims section wherein the definitions are limited according to the preferred or more preferred definitions as disclosed below or specifically disclosed residues of the exemplified compounds and subcombinations thereof.

Definitions

Constituents which are optionally substituted as stated herein, may be substituted, unless otherwise noted, one or more times, independently from one another at any possible position. When any variable occurs more than one time in any constituent, each definition is independent.

Unless defined otherwise in the claims and in the description, the constituents defined below can optionally be substituted, one or more times, identically or differently, with a substituent selected from:
hydroxy, halogen, cyano, 1-6C-alkyl, 1-4C-haloalkyl, 1-6C-alkoxy, $-NR^{10}R^{11}$, cyano, (=O), $-C(O)NR^{10}R^{11}$, $-C(O)OR^{9}$, $-NHC(O)R^{11}$, $-NHS(O)_2R^{11}$. An alkyl constituent being multiply substituted by halogen includes also a completely halogenated alkyl moiety such as e.g. CF_3.

Should a constituent be composed of more than one part, e.g. –O-(1-6Calkyl)-(3-7C-cycloalkyl), the position of a possible substituent can be at any of these parts at any suitable position. A hyphen at the beginning of the constituent marks the point of attachment to the rest of the molecule. Should a ring be substituted the substitutent could be at any suitable position of the ring, also on a ring nitrogen atom if suitable.

The term “comprising” when used in the specification includes “consisting of”.

If it is referred to “as mentioned above” or “mentioned above” within the description it is referred to any of the disclosures made within the specification in any of the preceding pages.

“suitable” within the sense of the invention means chemically possible to be made by methods within the knowledge of a skilled person.

“1-6C-alkyl” is a straight-chain or branched alkyl group having 1 to 6 carbon atoms. Examples are methyl, ethyl, n propyl, iso-propyl, n butyl, iso-butyl, sec-butyl and *tert*-butyl, pentyl, hexyl, preferably 1-4 carbon atoms (1-4C-alkyl), more preferably 1-3 carbon atoms (1-3C-alkyl). Other alkyl constituents mentioned herein having another number of carbon atoms shall be defined as mentioned above taking into account the different length of their chain. Those parts of constituents containing an alkyl chain as a bridging moiety between two other parts of the constituent which usually is called an “alkylene” moiety is defined in line with the definition

for alkyl above including the preferred length of the chain e.g. methylen, ethylene, n-propylen, iso-propylen, n-butylen, isobutylene, *tert*-butylen.

"2-6C-Alkenyl" is a straight chain or branched alkenyl radical having 2 to 6 carbon atoms. Examples are the but-2-enyl, but-3-enyl (homoallyl), prop-1-enyl, prop-2-enyl (allyl) and the ethenyl (vinyl) radicals.

"Mono- or di-1-4C-alkylamino" radicals contain in addition to the nitrogen atom, independently one or two of the above mentioned 1-4C-alkyl radicals. Examples are the methylamino, the ethylamino, the isopropylamino, the dimethylamino, the diethylamino and the diisopropylamino radical.

"Halogen" within the meaning of the present invention is iodine, bromine, chlorine or fluorine, preferably "halogen" within the meaning of the present invention is chlorine or fluorine.

"1-6C-Haloalkyl" is a straight-chain or branched alkyl group having 1 to 6 carbon atoms in which at least one hydrogen is substituted by a halogen atom. Examples are chloromethyl or 2-bromoethyl. For a partially or completely fluorinated C1-C4-alkyl group, the following partially or completely fluorinated groups are considered, for example: fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, 1,1-difluoroethyl, 1,2-difluoroethyl, 1,1,1-trifluoroethyl, tetrafluoroethyl, and pentafluoroethyl, whereby difluoromethyl, trifluoromethyl, or 1,1,1-trifluoroethyl are preferred. All possible partially or completely fluorinated 1-6C-alkyl groups are considered to be encompassed by the term 1-6C-haloalkyl.

"1-6C-Hydroxyalkyl" is a straight-chain or branched alkyl group having 1 to 6 carbon atoms in which at least one hydrogen atom is substituted by a hydroxy group. Examples are hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1,2-dihydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl, 2,3-dihydroxypropyl, 3-hydroxy-2-methyl-propyl, 2-hydroxy-2-methyl-propyl, 1-hydroxy-2-methyl-propyl.

"1-6C-Alkoxy" represents radicals, which in addition to the oxygen atom, contain a straight-chain or branched alkyl radical having 1 to 6 carbon atoms. Examples which may be mentioned are the hexoxy, pentoxy, butoxy, isobutoxy, sec-butoxy, *tert*-butoxy, propoxy, isopropoxy, ethoxy and methoxy radicals, preferred are methoxy, ethoxy, propoxy, isopropoxy.

"1-6C-Haloalkoxy" represents radicals, which in addition to the oxygen atom, contain a straight-chain or branched alkyl radical having 1 to 6 carbon atoms in which at least one hydrogen is substituted by a halogen atom. Examples are –O-CFH2, –O-CF2H, -O-CF3, -O-CH2-CFH2, -O-CH2-CF2H, -O-CH2-CF3. Preferred are –O-CF2H, -O-CF3, -O-CH2-CF3.

"3-7C-Cycloalkyl" stands for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, preferably cyclopropyl.

"3-7C-Cycloalkyloxy" or "–O-(3-7C-cycloalkyl)" stands for e.g. cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy or cycloheptyloxy, preferably cyclopropyloxy.

"3-7C-Heterocyclyl", or "heterocyclyl" represents a mono- or polycyclic, preferably mono- or bicyclic, more preferably monocyclic, nonaromatic heterocyclic radical containing, 4 to 10, preferably 4 to 7, more preferably 5 to 6 ring atoms, and 1,2 or 3, preferably 1 or 2, hetero atoms and/or hetero groups independently selected from the series consisting of N, O, S, SO, SO_2. The heterocyclyl radicals can be saturated or partially unsaturated and, unless stated otherwise, may be optionally substituted, one or more times, identically or differently, with a substituent selected from: 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-alkoxy, hydroxy, fluorine or (=O) whereby the 1-4C-alkyl may be optionally further substituted with hydroxy and the double bonded oxygen atom leads to a carbonyl group together with the carbon atom of the heterocyclyl ring at any suitable position. Particularly preferred heterocyclic radicals are 4- to 7-membered monocyclic saturated heterocyclyl radicals having up to two hetero atoms from the series consisting of O, N and S, more preferred 5-6-membered heterocyclic radicals. The following may be mentioned by way of ex-

ample and by preference: oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, azetidinyl, 3-hydroxyazetidinyl, 3-fluoroazetidinyl, 3,3-difluoroazetidinyl, pyrrolidinyl, 3-hydroxypyrrolidinyl, pyrrolinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, 3-hydroxypiperidinyl, 4-hydroxypiperidinyl, 3-fluoropiperidinyl, 3,3-difluoropiperidinyl, 4-fluoropiperidinyl, 4,4-difluoropiperidinyl, piperazinyl, N-methyl-piperazinyl, N-(2-hydroxyethyl)-piperazinyl, morpholinyl, thiomorpholinyl, azepanyl, homopiperazinyl, N-methyl-homopiperazinyl.

"N-heterocyclyl" represents a heterocyclic radical which is connected to the remaining molecule via its nitrogen atom contained in the heterocyclic ring.

The term "heteroaryl" represents a monocyclic 5- or 6-membered aromatic heterocycle or a fused bicyclic aromatice moiety comprising without being restricted thereto, the 5-membered heteroaryl radicals furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, triazolyl (1,2,4-triazolyl, 1,3,4-triazolyl or 1,2,3-triazolyl), thiadiazolyl (1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,3-thiadiazolyl or 1,2,4-thiadiazolyl) and oxadiazolyl (1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,3-oxadiazolyl or 1,2,4-oxadiazolyl), as well as the 6-membered heteroaryl radicals pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl as well as the fused ring systems such as e.g. phthalidyl-, thiophthalidyl-, indolyl-, isoindolyl-, dihydroindolyl-, dihydroisoindolyl-, indazolyl-, benzothiazolyl-, benzofuranyl-, benzimidazolyl-, benzoxazinonyl-, chinolinyl-, isochinolinyl-, chinazolinyl-, chinoxalinyl-, cinnolinyl-, phthalazinyl-, 1,7- or 1,8-naphthyridinyl-. cumarinyl-, isocumarinyl-, indolizinyl-, isobenzofuranyl-, azaindolyl-, azaisoindolyl-, furanopyridyl-, furanopyrimidinyl-, furanopyrazinyl-, furanopyidazinyl-, preferred fused ring system is indazolyl. Preferred 5- or 6-membered heteroaryl radicals are furanyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl. More preferred 5- or 6-membered heteroaryl radicals are furan-2-yl, thien-2-yl, pyrrol-2-yl, thiazolyl, oxazolyl, 1,3,4-thiadiazolyl, 1,3,4-oxadiazolyl, pyridin-2-yl, pyridin-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrazin-2-yl or pyridazin-3-yl.

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 heteroarylic, heteroarylenic, or heterocyclic groups mentioned herein may be substituted by their given substituents or parent molecular groups, unless otherwise noted, at any possible position, such as e.g. at any substitutable ring carbon or ring nitrogen atom. Analogously it is being understood that it is possible for any heteroaryl or heterocyclyl group to be attached to the rest of the molecule via any suitable atom if chemically suitable. Unless otherwise noted, any heteroatom of a heteroarylic or heteroarylenic ring with unsatisfied valences mentioned herein is assumed to have the hydrogen atom(s) to satisfy the valences. Unless otherwise noted, rings containing quaternizable amino- or imino-type ring nitrogen atoms (-N=) may be preferably not quaternized on these amino- or imino-type ring nitrogen atoms by the mentioned substituents or parent molecular groups.

The $NR^{10}R^{11}$ group includes, for example, NH_2, $N(H)CH_3$, $N(CH_3)_2$, $N(H)CH_2CH_3$ and $N(CH_3)CH_2CH_3$. In the case of $-NR^{10}R^{11}$, when R^{10} and R^{11} together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, the term “heterocyclic ring” is defined above. Especially preferred is morpholinyl.

The $C(O)NR^{10}R^{11}$ group includes, for example, $C(O)NH_2$, $C(O)N(H)CH_3$, $C(O)N(CH_3)_2$, $C(O)N(H)CH_2CH_3$, $C(O)N(CH_3)CH_2CH_3$ or $C(O)N(CH_2CH_3)_2$. If R^{10} or R^{11} are not hydrogen, they may be substituted by hydroxy, In the case of $-NR^{10}R^{11}$, when R^{10} and R^{11} together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic, the term “heterocyclic ring” is defined above and can be used analogously for $C(O)NR^{10}R^{11}$.

The $C(O)OR^9$ group includes for example C(O)OH, $C(O)OCH_3$, $C(O)OC_2H_5$, $C(O)C_3H_7$, $C(O)CH(CH_3)_2$, $C(O)OC_4H_9$, $C(O)OC_5H_{11}$, $C(O)OC_6H_{13}$; for C(O)O(1-6Calkyl), the alkyl part may be straight or branched and may be substituted.

In the context of the properties of the compounds of the present invention the term "pharmacokinetic profile" means one single parameter or a combination thereof including permeability, bioavailability, exposure, and pharmacodynamic parameters such as duration, or magnitude of pharmacological effect, as measured in a suitable experiment. Compounds with improved pharmacokinetic profiles can, for example, be used in lower doses to achieve the same effect, may achieve a longer duration of action, or a may achieve a combination of both effects.

Salts of the compounds according to the invention include all inorganic and organic acid addition salts and salts with bases, especially all pharmaceutically acceptable inorganic and organic acid addition salts and salts with bases, particularly all pharmaceutically acceptable inorganic and organic acid addition salts and salts with bases customarily used in pharmacy.

One aspect of the invention are salts of the compounds according to the invention including all inorganic and organic acid addition salts, especially all pharmaceutically acceptable inorganic and organic acid addition salts, particularly all pharmaceutically acceptable inorganic and organic acid addition salts customarily used in pharmacy. Another aspect of the invention are the salts with di- and tricarboxylic acids.

Examples of acid addition salts include, but are not limited to, hydrochlorides, hydrobromides, phosphates, nitrates, sulfates, salts of sulfamic acid, formates, acetates, propionates, citrates, D-gluconates, benzoates, 2-(4-hydroxybenzoyl)-benzoates, butyrates, salicylates, sulfosalicylates, lactates, maleates, laurates, malates, fumarates, succinates, oxalates, malonates,pyruvates, acetoacetates, tartarates, stearates, benzensulfonates, toluenesulfonates, methanesulfonates,

trifluoromethansulfonates, 3-hydroxy-2-naphthoates, benzenesulfonates, naphthalinedisulfonates and trifluoroacetates.

Examples of salts with bases include, but are not limited to, lithium, sodium, potassium, calcium, aluminum, magnesium, titanium, meglumine, ammonium, salts optionally derived from NH_3 or organic amines having from 1 to 16 C-atoms such as e.g. ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, N-methylmorpholine, arginine, lysine, ethylendiamine, N-methylpiperindine and and guanidinium salts.

The salts include water-insoluble and, particularly, water-soluble salts.

According to the person skilled in the art the compounds of formula (I) according to this invention as well as their salts may contain, e.g. when isolated in crystalline form, varying amounts of solvents. Included within the scope of the invention are therefore all solvates and in particular all hydrates of the compounds of formula (I) according to this invention as well as all solvates and in particular all hydrates of the salts of the compounds of formula (I) according to this invention.

The term “combination” in the present invention is used as known to persons skilled in the art and may be present as a fixed combination, a non-fixed combination or kit-of-parts.

A “fixed combination” in the present invention is used as known to persons skilled in the art and is defined as a combination wherein the said first active ingredient and the said second active ingredient are present together in one unit dosage or in a single entity. One example of a “fixed combination” is a pharmaceutical composition wherein the said first active ingredient and the said second active ingredient are present in admixture for simultaneous administration, such as in a formulation. Another example of a “fixed combination” is a pharmaceutical combination wherein the said first active ingredient and the said second active ingredient are present in one unit without being in admixture.

A non-fixed combination or "kit-of-parts" in the present invention is used as known to persons skilled in the art and is defined as a combination wherein the said first active ingredient and the said second active ingredient are present in more than one unit. One example of a non-fixed combination or kit-of-parts is a combination wherein the said first active ingredient and the said second active ingredient are present separately. The components of the non-fixed combination or kit-of-parts may be administered separately, sequentially, simultaneously, concurrently or chronologically staggered.

The term "(chemotherapeutic) anti-cancer agents", includes but is not limited to 131I-chTNT, abarelix, abiraterone, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, aminoglutethimide, amrubicin, amsacrine, anastrozole, arglabin, arsenic trioxide, asparaginase, azacitidine, basiliximab, BAY 80-6946, BAY 1000394, belotecan, bendamustine, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin, bortezomib, buserelin, busulfan, cabazitaxel, calcium folinate, calcium levofolinate, capecitabine, carboplatin, carmofur, carmustine, catumaxomab, celecoxib, celmoleukin, cetuximab, chlorambucil, chlormadinone, chlormethine, cisplatin, cladribine, clodronic acid, clofarabine, crisantaspase, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, darbepoetin alfa, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftitox, denosumab, deslorelin, dibrospidium chloride, docetaxel, doxifluridine, doxorubicin, doxorubicin + estrone, eculizumab, edrecolomab, elliptinium acetate, eltrombopag, endostatin, enocitabine, epirubicin, epitiostanol, epoetin alfa, epoetin beta, eptaplatin, eribulin, erlotinib, estradiol, estramustine, etoposide, everolimus, exemestane, fadrozole, filgrastim, fludarabine, fluorouracil, flutamide, formestane, fotemustine, fulvestrant, gallium nitrate, ganirelix, gefitinib, gemcitabine, gemtuzumab, glutoxim, goserelin, histamine dihydrochloride, histrelin, hydroxycarbamide, I-125 seeds, ibandronic acid, ibritumomab tiuxetan, idarubicin, ifosfamide, imatinib, imiquimod, improsulfan, interferon alfa, interferon beta, interferon gamma, ipilimumab, irinotecan, ixabepilone, lanreotide, lapatinib, lenalidomide, lenograstim, lentinan, letrozole, leuprorelin, levamisole, lisuride, lobaplatin, lomustine, lonidamine, masoprocol, medroxyprogesterone, megestrol, melphalan, mepitiostane, mercaptopurine,

methotrexate, methoxsalen, Methyl aminolevulinate, methyltestosterone, mifamurtide, miltefosine, miriplatin, mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane, mitoxantrone, nedaplatin, nelarabine, nilotinib, nilutamide, nimotuzumab, nimustine, nitracrine, ofatumumab, omeprazole, oprelvekin, oxaliplatin, p53 gene therapy, paclitaxel, palifermin, palladium-103 seed, pamidronic acid, panitumumab, pazopanib, pegaspargase, PEG-epoetin beta (methoxy PEG-epoetin beta), pegfilgrastim, peginterferon alfa-2b, pemetrexed, pentazocine, pentostatin, peplomycin, perfosfamide, picibanil, pirarubicin, plerixafor, plicamycin, poliglusam, polyestradiol phosphate, polysaccharide-K, porfimer sodium, pralatrexate, prednimustine, procarbazine, quinagolide, radium-223 chloride, raloxifene, raltitrexed, ranimustine, razoxane, refametinib , regorafenib, risedronic acid, rituximab, romidepsin, romiplostim, sargramostim, sipuleucel-T, sizofiran, sobuzoxane, sodium glycididazole, sorafenib, streptozocin, sunitinib, talaporfin, tamibarotene, tamoxifen, tasonermin, teceleukin, tegafur, tegafur + gimeracil + oteracil, temoporfin, temozolomide, temsirolimus, teniposide, testosterone, tetrofosmin, thalidomide, thiotepa, thymalfasin, tioguanine, tocilizumab, topotecan, toremifene, tositumomab, trabectedin, trastuzumab, treosulfan, tretinoin, trilostane, triptorelin, trofosfamide, tryptophan, ubenimex, valrubicin, vandetanib, vapreotide, vemurafenib, vinblastine, vincristine, vindesine, vinflunine, vinorelbine, vorinostat, vorozole, yttrium-90 glass microspheres, zinostatin, zinostatin stimalamer, zoledronic acid, zorubicin.

The compounds according to the invention and their salts can exist in the form of tautomers which are included in the embodiments of the invention.

The compounds of the invention may, depending on their structure, exist in different stereoisomeric forms. These forms include configurational isomers or optionally conformational isomers (enantiomers and/or diastereoisomers including those of atropisomers). The present invention therefore includes enantiomers, diastereoisomers as well as mixtures thereof. From those mixtures of enantiomers and/or disastereoisomers pure stereoisomeric forms can be isolated with methods known in the art, preferably methods of chromatography, especially high pressure liquid chromatography (HPLC) using achiral or chiral phase. The invention further

includes all mixtures of the stereoisomers mentioned above independent of the ratio, including the racemates.

Some of the compounds and salts according to the invention may exist in different crystalline forms (polymorphs) which are within the scope of the invention.

Furthermore, derivatives of the compounds of formula (I) and the salts thereof which are converted into a compound of formula (I) or a salt thereof in a biological system (bioprecursors or pro-drugs) are covered by the invention. Said biological system is e.g. a mammalian organism, particularly a human subject. The bioprecursor is, for example, converted into the compound of formula (I) or a salt thereof by metabolic processes.

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 Bub1 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 Bub1 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.

The intermediates used for the synthesis of the compounds of claims 1-6 as described below, as well as their use for the synthesis of the compounds of claims 1-6, are one further aspect of the present invention. Preferred intermediates are the Intermediate Examples as disclosed below.

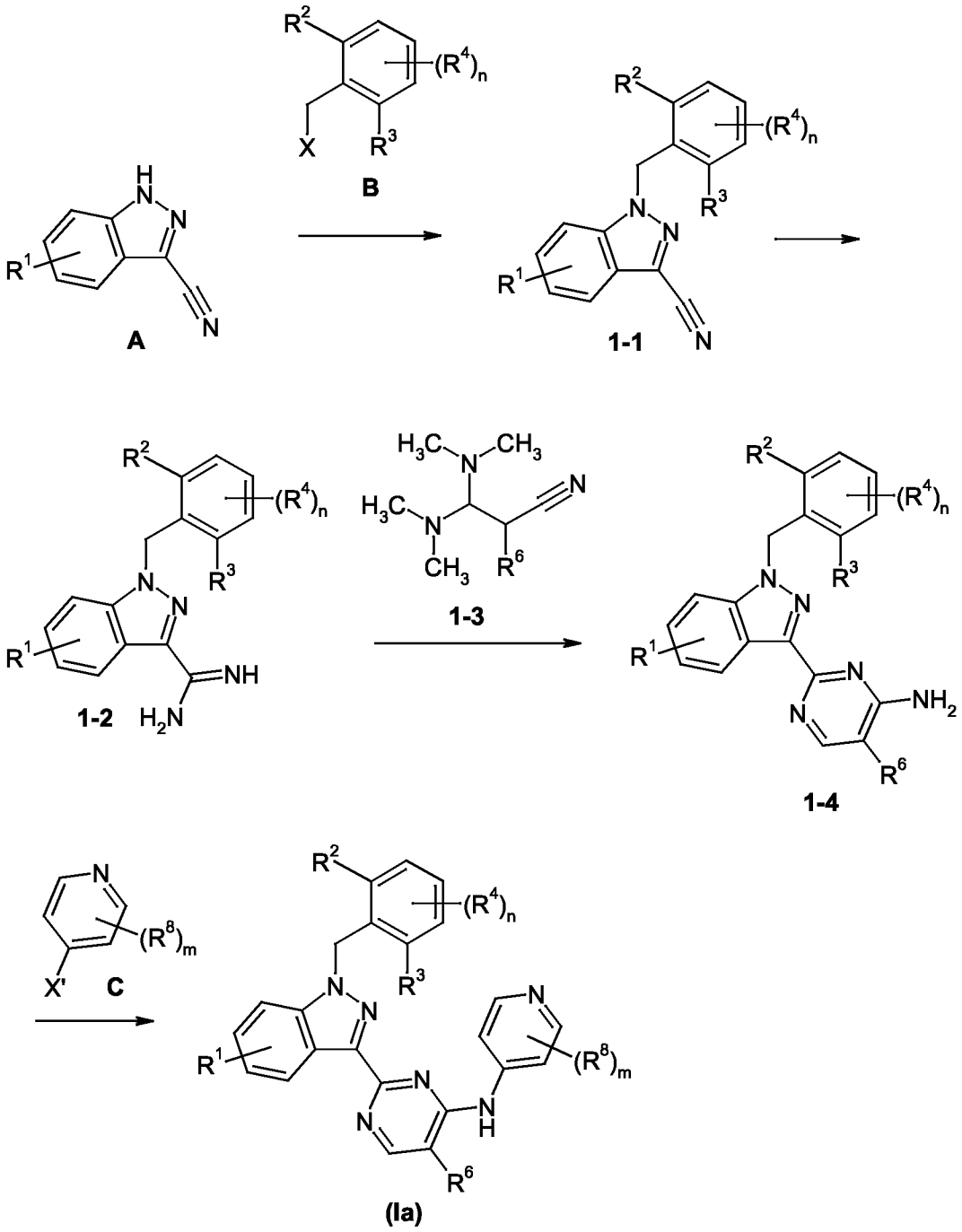
General Procedures

The compounds according to the invention can be prepared according to the following schemes 1 through 6,

The schemes and procedures described below illustrate synthetic routes to the compounds of general formula (I) of the invention and are not intended to be limiting. It is obvious to the person skilled in the art that the order of transformations as exemplified in the Schemes can be modified in various ways. The order of transformations exemplified in the Schemes is therefore not intended to be limiting. In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^4, R^6, R^7 or R^8 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.

One route for the preparation of compounds of general formula (Ia) is described in Scheme 1. In instances where this route is not feasible, scheme 2 can be applied.

Scheme 1



Scheme 1 Route for the preparation of compounds of general formula (Ia), wherein R^1, R^2, R^3, R^4, R^6, R^8, m and n have the meaning as given for general formula (I), supra. In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^4, R^6 or R^8 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of

protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in Protective Groups in Organic Synthesis, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.

Compounds A, B, and C are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art. Specific examples are described in the subsequent paragraphs. X represents a leaving group such as for example a Cl, Br or I, or X stands for an aryl sulfonate such as for example p-toluene sulfonate, or for an alkyl sulfonate such as for example methane sulfonate or trifluoromethane sufonate. X' represents F, Cl, Br, I, boronic acid or a boronic acid ester, such as for example 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (boronic acid pinacole ester).

A suitably substituted 1*H*-indazole-3-carbonitrile (A) can be reacted with a suitably substituted benzyl halide or benzyl sulfonate of general formula (B), such as, for example, a benzyl bromide, in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in the presence of a suitable base, such as, for example, cesium carbonate at temperatures ranging from -78℃ to room temperature, preferably the reaction is carried out at room temperature, to furnish 1-benzyl-1*H*-indazole-3-carbonitrile intermediates of general formula (1-1).

Intermediates of general formula (1-1) can be converted to intermediates of general formula (1-2) by reaction with a suitable alcoholate, such as, for example sodium methanolate, in a suitable solvent system, such as, for example, the corresponding alcohol, e.g. methanol, at a temperature between room temperature and the boiling point of the respective solvent, preferably the reaction is carried out at room temperature, and subsequent treatment with a suitable source of ammonium, such as for example, ammonium chloride in the presence of a suitable acid, such as for example acetic acid in a temperature range from room temperature to

the boiling point of the respective solvent, preferably the reaction is carried out at 50℃.

Intermediates of general formula (1-2) are reacted with a suitably substituted 3,3-bis(dimethylamino)propanenitrile of the general formula (1-3), such as, for example 3,3-bis(dimethylamino)-2-methoxypropanenitrile, in the presence of a suitable base, such as, for example piperidine, in a suitable solvent system, such as, for example, 3-methylbutan-1-ol, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 100℃, to furnish intermediates of general formula (1-4).

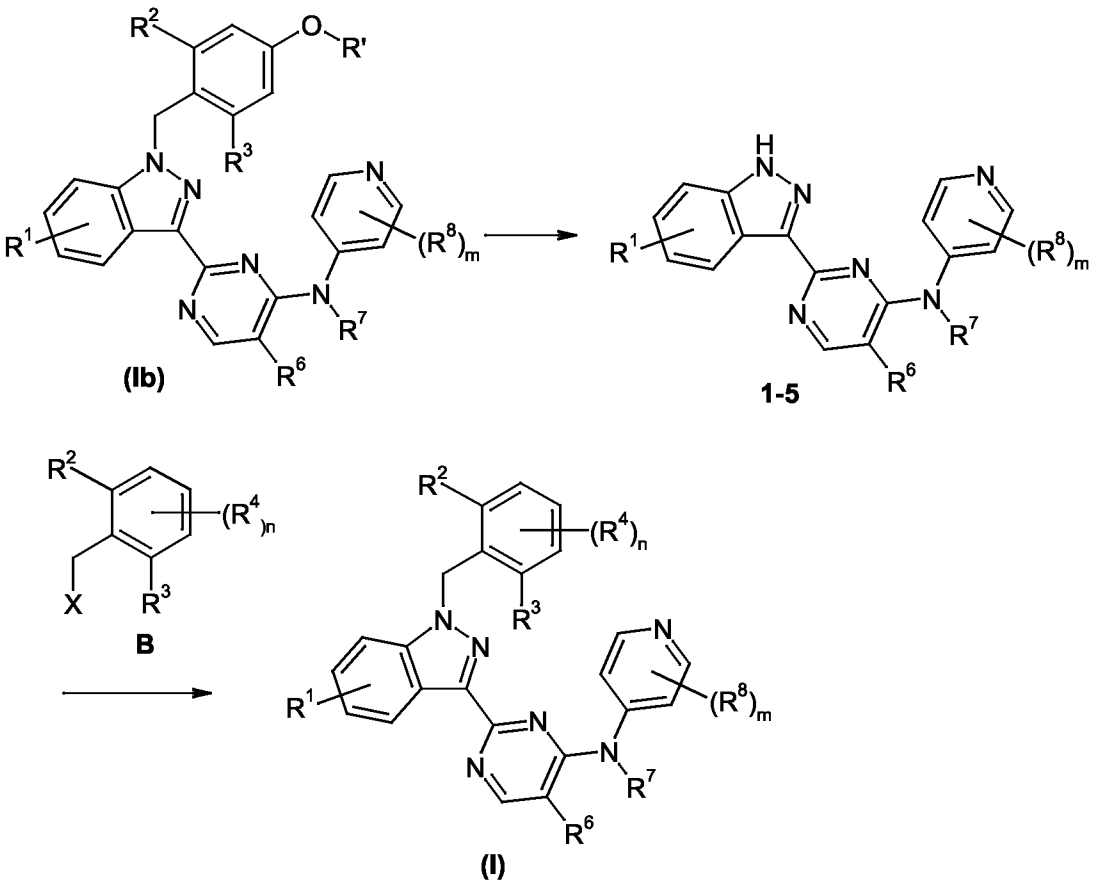
Intermediates of general formula (1-4) can be reacted with a suitable 4-halopyridine of the general formula (C), such as, for example 4-bromopyridine, in the presence of a suitable base, such as, for example sodium 2-methylpropan-2-olate or potassium carbonate. Optionally, a suitable palladium catalyst, such as for example (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one–palladium, and a suitable ligand, such as for example 1'-binaphthalene-2,2'-diylbis(diphenylphosphane), can be added. The reaction is carried out in a suitable solvent system, such as, for example, *N,N*-dimethylformamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 100℃ to furnish compounds of general formula (Ia). Alternatively, the following palladium catalysts can be used:
Allylpalladium chloride dimer, Dichlorobis(benzonitrile)palladium (II), Palladium (II) acetate, Palladium (II) chloride, Tetrakis(triphenylphosphine)palladium (0), Tris(dibenzylideneacetone)dipalladium (0), optionally with addition of the following ligands:
racemic-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl, rac-BINAP, 1,1'-Bis(diphenylphosphino)ferrocene, Bis(2-diphenylphosphinophenyl)ether, Di-t-butylmethylphosphonium tetrafluoroborate, 2-(Di-t-butylphosphino)biphenyl, Tri-t-butylphosphonium tetrafluoroborate, Tri-2-furylphosphine, Tris(2,4-di-t-butylphenyl)phosphite, Tri-o-tolylphosphine, or, favourably, (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine).

Alternatively, intermediates of general formula (1-4) can be reacted with a suitable boronic acid or boronic acid pinacole ester of general formula (C), such as, for example (2-fluoropyridin-4-yl)boronic acid, in the presence of a suitable base, such as, for example triethylamine, a suitable activating agent such as for example N,N-dimethylpyridin-4-amine and a suitable copper salt, such as for example copper (II) acetate, in a suitable solvent system, such as, for example, trichloromethane, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature to furnish compounds of general formula (Ia).

Alternatively, intermediates of general formula (1-4) can be reacted with a suitable pyridyl fluoride of general formula (C, with X' being F), such as, for example 4-fluoro pyridine hydrochloride, in the presence of a suitable base, such as, for example sodium hydride, in a suitable solvent system, such as, for example, dimethyl formamide, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 90℃ to furnish compounds of general formula (Ia).

Compounds of general formula (I) can also be synthesised according to the procedure depicted in Scheme 2.

Scheme 2



Scheme 2 Alternative route for the preparation of compounds of general formula (I), wherein R^1, R^2, R^3, R^4, R^6, R^7, R^8, m and n have the meaning as given for general formula (I), supra. R' is for example alkyl or benzyl, preferably methyl or ethyl. In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^4, R^6, R^7 or R^8 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for fur-ther interconversion of substituents. Appropriate protecting groups and their intro-

duction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in Protective Groups in Organic Synthesis, 3rd edition, Wiley 1999). Further specific examples are described in the subsequent paragraphs.

Compounds of the formula (Ib) can be prepared using the synthetic methods described in context of Scheme 1; the introduction of R^7 different from hydrogen may be accomplished *inter alia* by the methods described in Scheme 5. Compounds B are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art as referred to below scheme 1 above.

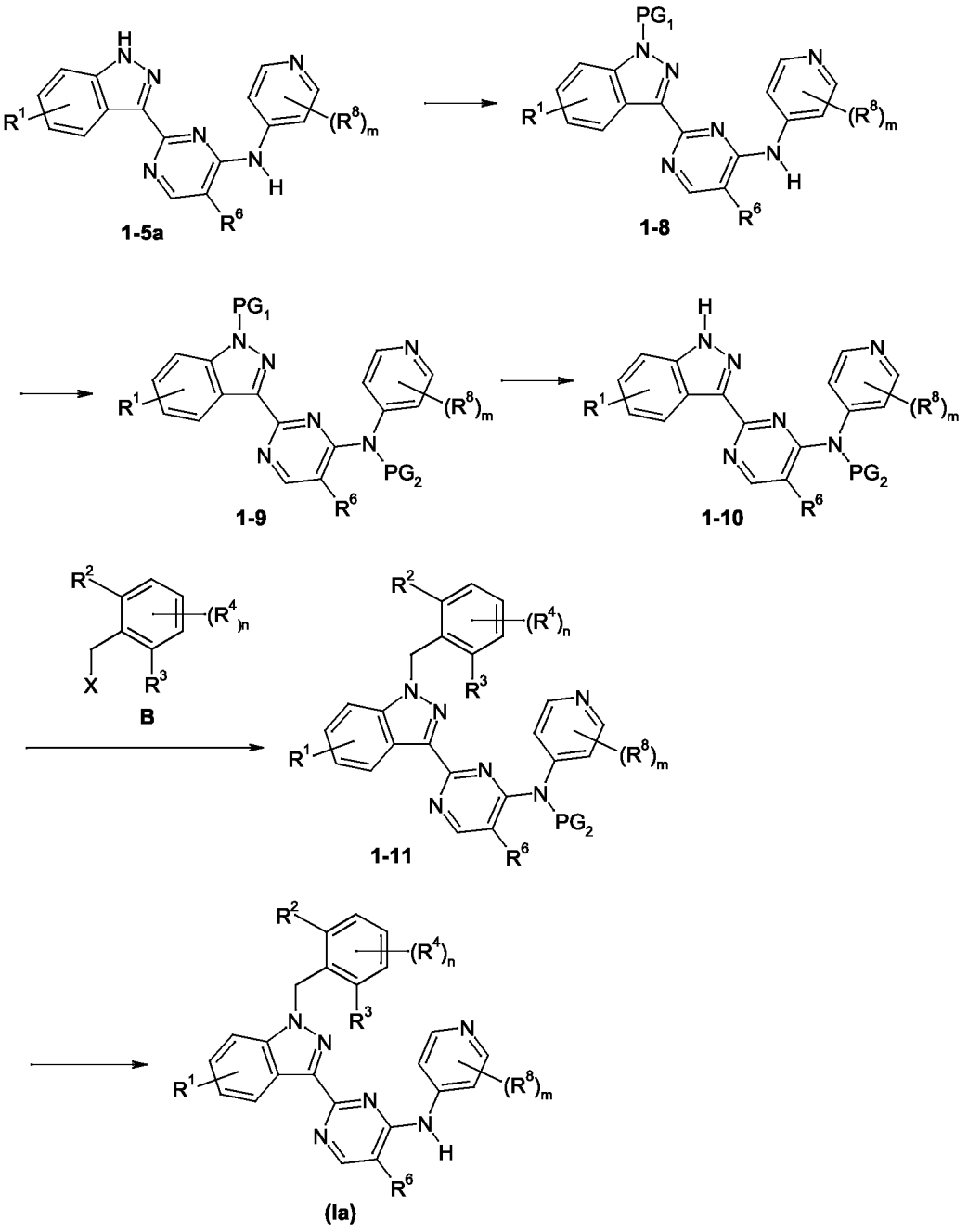
Compounds of general formula (Ib) are converted to intermediates of general formula (1-5) by treatment with a suitable acid system, such as, for example a mixture of trifluoroacetic acid and trifluoromethanesulfonic acid, in a suitable solvent, such as, for example, dichloroethan, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature.

Intermediates of general formula (1-5) can be reacted with a suitably substituted benzyl halide or benzyl sulfonate of general formula (B), such as, for example, a benzyl bromide, in a suitable solvent system, such as, for example, tetrahydrofuran, in the presence of a suitable base, such as, for example, sodium hydride in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature, to furnish compounds of general formula (I). Said reaction can also result in double conversion of intermediate (1-5) if R^7 is hydrogen, giving rise to compounds formed alongside the target compounds, in which R^7 is a benzylic group identical with the benzylic moiety attached to the indazole nitrogen.

Compounds of general formula (Ia) in some instances can be advantageously prepared via a route that utilizes additional protecting groups, according to the procedure depicted in Scheme 2a, in order to avoid the aforementioned bisben-

zylation. Preferably, examples 2-1-3, 2-2-3, 2-3-3, 2-4-3, 2-5-3, 2-6-3, 2-7-3, 2-8-3, 2-9-3 were prepared via this route.

Scheme 2a



Scheme 2a Modified route for the preparation of compounds of general formula (Ia), wherein R^1, R^2, R^3, R^4, R^6, R^8, m and n have the meaning as given for gen-

eral formula (I), supra. PG_1 and PG_2 are independently from each other a protecting group, for example t-butoxycarbonyl (boc), allyloxycarbonyl (alloc) or benzoyl. In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^4, R^6 or R^8 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in Protective Groups in Organic Synthesis, 3rd edition, Wiley 1999). Further specific examples are described in the subsequent paragraphs.

Compounds B are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art as referred to below scheme 1 above.

Intermediates of general formula (1-5a), accessible in analogy to Scheme 2, can be protected by a suitable protecting group such as, for example, tert-butoxycarbonyl with a suitable reagent, such as, for example, di-tert-butyldicarbonate, in the presence of a suitable base, such as, for example, sodium hydroxide in water, in a suitable solvent system, such as, for example, methanol in a temperature range from 0 °C to room temperature, preferable the reaction is carried out at room temperature, to furnish compounds of general formula (1-8).

Intermediates of general formula (1-8) can be protected with a suitable protection group such as, for example, allyloxycarbonyl or benzoyl with a suitable reagent, such as, for example, allyl chloroformate or benzoyl chloride, in a suitable solvent system, such as, for example, pyridine, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature, to furnish compounds of general formula (1-9).

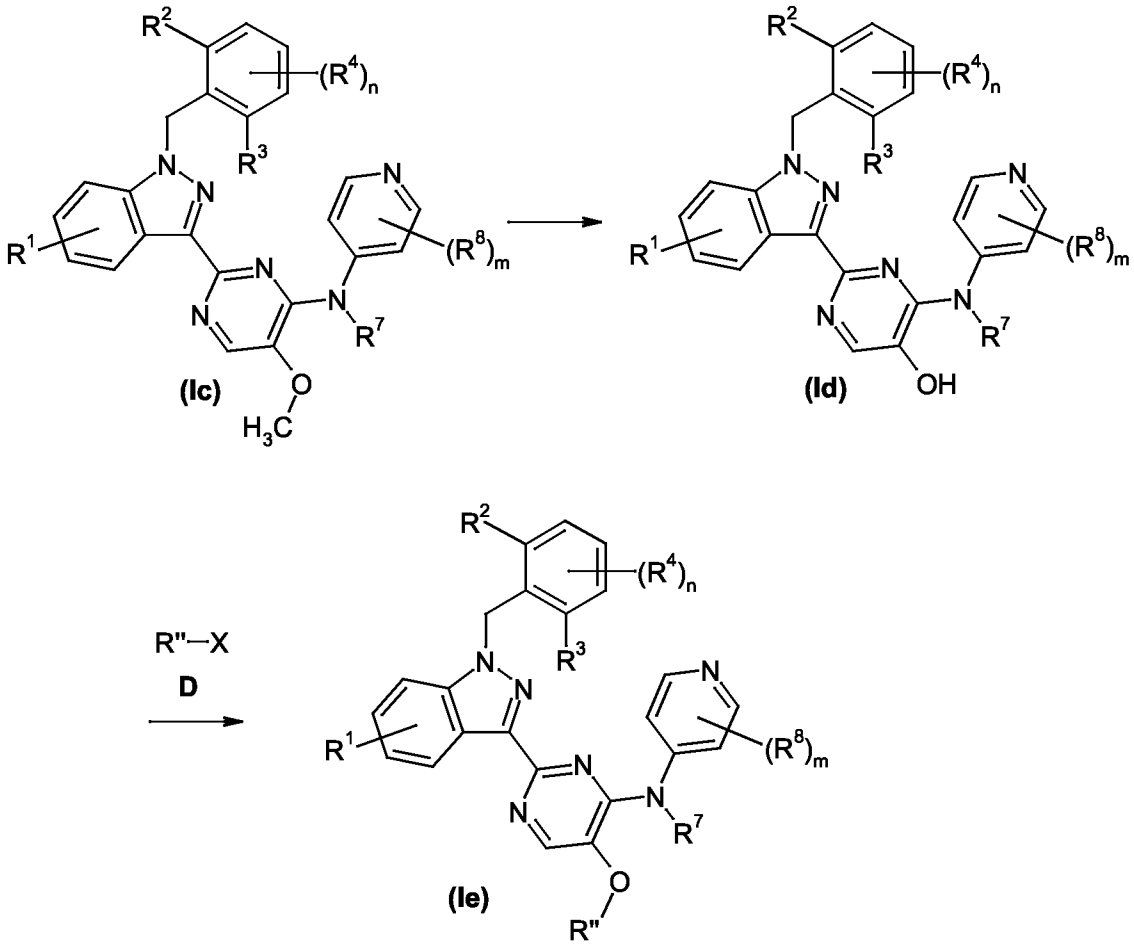
Intermediates of general formula (1-9) can be deprotected under suitable conditions such as, for example, hydrochloric acid or trifluoroacetic acid, in a suitable solvent system, such as, for example, dioxane or dichloromethane, in a temperature range from 0 ℃ to room temperature, to furnis h compounds of general formula (1-10)

Intermediates of general formula (1-10) can be reacted with a suitably substituted benzyl halide or benzyl sulfonate of general formula (B), such as, for example, a benzyl bromide, in a suitable solvent system, such as, for example, tetrahydrofuran, in the presence of a suitable base, such as, for example, sodium hydride in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature, to furnish compounds of general formula (1-11).

Intermediates of general formula (1-11) can be deprotected under suitable conditions such as, for example, pyrrolidine, tetrakis(triphenylphosphin)palladium or sodium hydride, or potassium hydroxide, in a suitable solvent system, such as, for example, dioxane, water, tetrahydrofuran oder ethanol, in a temperature range from 0 ℃ to room temperature to furnish compounds of general formula (Ia).

Compounds of general formula (Ie) and (Id) can be synthesised from compounds of general formula (Ic), according to the procedure depicted in Scheme 3.

Scheme 3

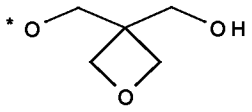


Scheme 3 Process for the preparation of compounds of general formula (Id) via de-methylation of compounds of general formula (Ic) and subsequent etherification to furnish compounds of general formula (Ie), wherein R^1, R^2, R^3, R^4, R^7, R^8, m and n have the meaning as given for general formula (I), supra. In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^4, R^7 or R^8 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion

of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in Protective Groups in Organic Synthesis, 3rd edition, Wiley 1999).

Compounds of the formula (Ic) can be prepared using the synthetic methods described in context of Scheme 1; the introduction of R^7 different from hydrogen may be accomplished *inter alia* by the methods described in Scheme 5.

Compounds of general formula D are commercially available, wherein X represents leaving group such as for example a Cl, Br or I, or X stands for an aryl sulfonate such as for example p-toluene sulfonate, or for an alkyl sulfonate such as for example methane sulfonate or trifluoromethane sulfonate (triflate group). R'' = 1-6C-alkyl (independently one or more times optionally substituted with hydroxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{10}R^{11}$, -S-(1-6C-alkyl), -S(O)-(1-6C-alkyl), $-S(O)_2$-(1-6C-alkyl), $SO_2NR^{10}R^{11}$, heterocyclyl (which itself is optionally substituted with $C(O)OR^9$ or oxo (=O)), heteroaryl (which itself is optionally substituted one or more times with cyano, 1-4C-alkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, -(2-6C-alkyl)-O-1-6C-alkyl), 3-7C-cycloalkyl, halogen, or



, whereby the * is the point of attachment.

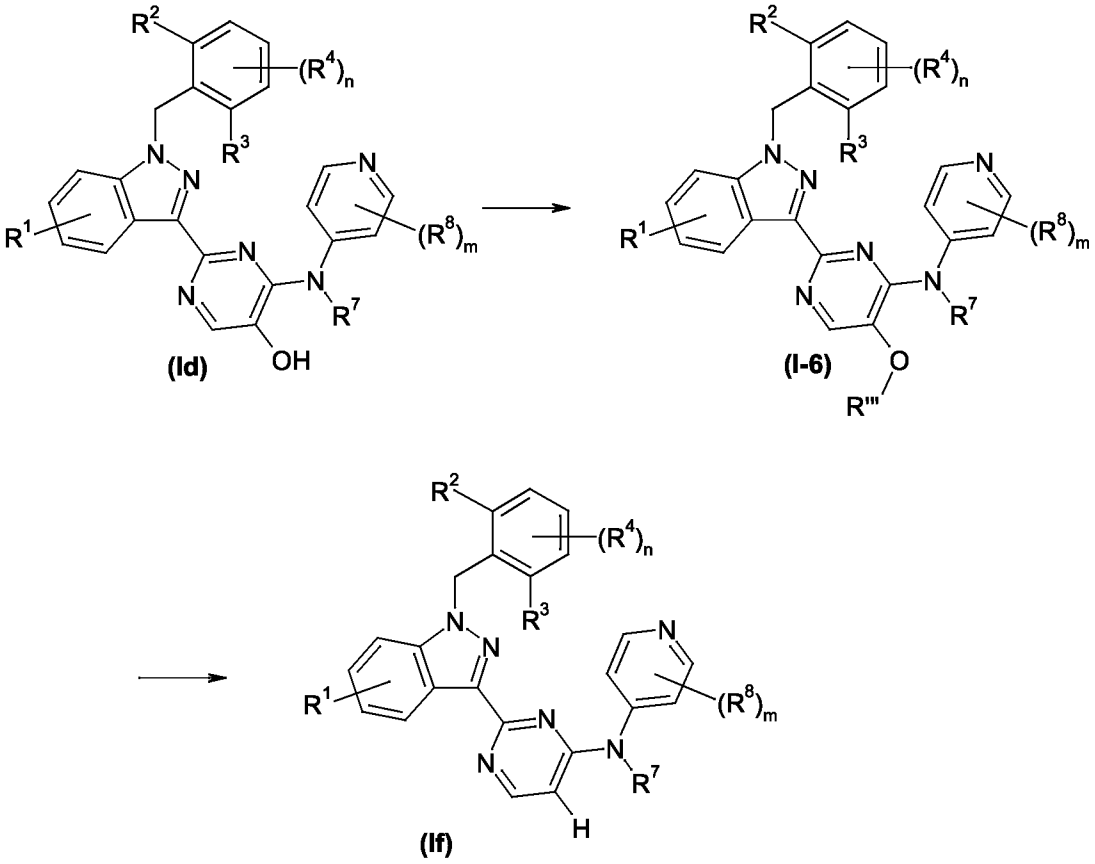
Compounds of general formula (Ic) are converted to compounds of general formula (Id) by treatment with a suitable demethylating agent, such as for example benzenethiol, in a suitable solvent, such as, for example, 1-methylpyrrolidin-2-one, in the presence of a suitable base, such as, for example potassium carbonate, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 190°C.

Compounds of general formula (Id) are then reacted with a compound of general formula (D) as mentioned above, in a suitable solvent, such as, for example, *N,N*-dimethylformamide, in the presence of a suitable base, such as, for example, potassium carbonate in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature, to furnish compounds of general formula (Ie).

Compounds of general formula (Id) can be converted into compounds of general formula (If) according to the procedure depicted in Scheme 4.

Scheme 4

During step 2 of this sequence the residues might potentially undergo a modification, e.g. reduction.



Scheme 4. Process for the transformation of compounds of general formula (Id) into compounds of general formula (If), via an intermediate of the general formula (I-6), wherein R^1, R^2, R^3, R^4, R^7, R^8, m and n have the meaning as given for general formula (I), supra. In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^4, R^7 or R^8 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups,

cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in Protective Groups in Organic Synthesis, 3rd edition, Wiley 1999).

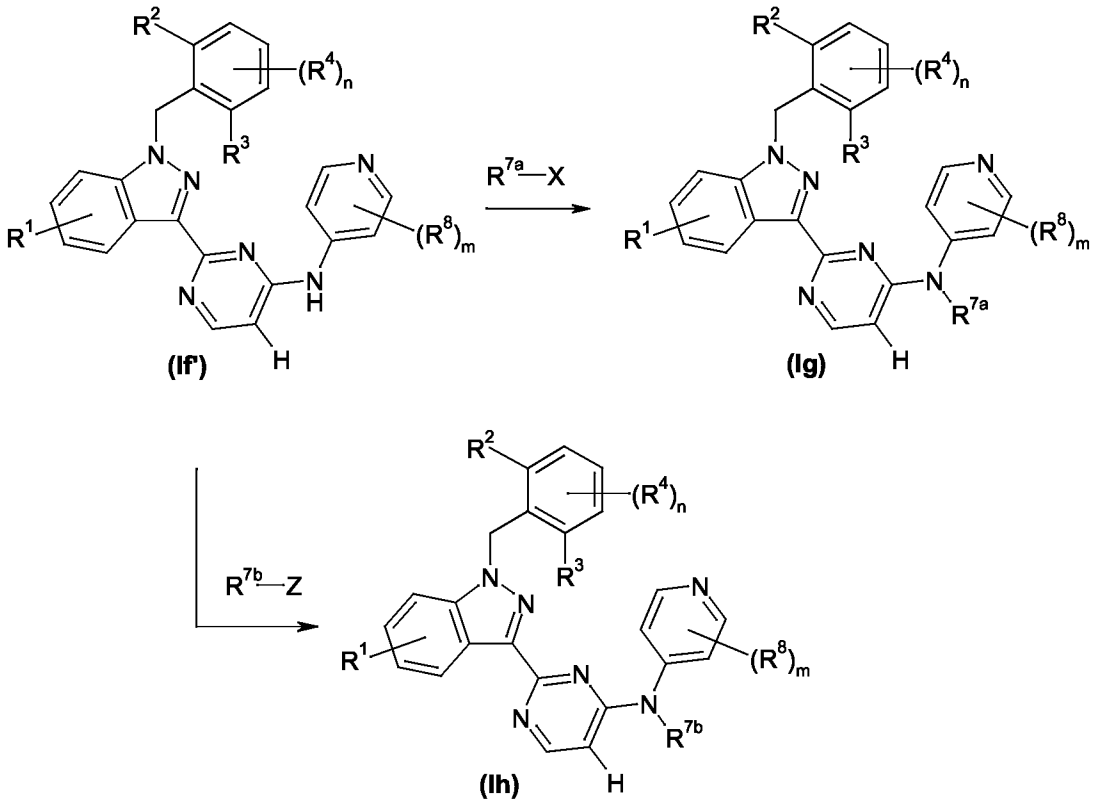
O-$R^{'''}$ represents a suitable leaving group, e.g. a triflate group, nonaflate group.

Compounds of general formula (Id) can be converted to intermediates of general formula (I-6) by reaction with a suitable sulfonic acid derivative, such as, for example trifluoromethanesulfonic anhydride or 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonyl fluoride, in a suitable solvent, such as, for example, dichloromethane, in the presence of a suitable base, such as, for example pyridine, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature.

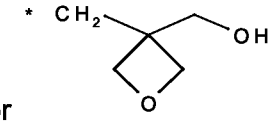
Intermediates of general formula (I-6) are then reacted with a suitable hydride source, such as, for example, triethylsilane, in a suitable solvent such as, for example, *N,N*-dimethyl formamide (DMF), in the presence of a suitable Pd-catalyst, such as, for example, palladium (II) acetate together with a suitable ligand, such as, for example, propane-1,3-diylbis(diphenylphosphane) in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 60℃, to furnish compoun ds of general formula (If).

Compounds of general formula (If ') which is a compound of formula (If) wherein R^7 = hydrogen, can be converted into compounds of general formula (Ig and Ih) according to the procedure depicted in Scheme 5.

Scheme 5



Scheme 5. Process for the transformation of compounds of general formula (If') into compounds of general formula (Ig) and (Ih), wherein R^1, R^2, R^3, R^4, R^8, m and n have the meaning as given for general formula (I), supra. In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^4, R^{7a}, R^{7b} or R^8 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in Protective Groups in Organic Synthesis, 3rd edition, Wiley 1999).

R^{7a} represents 1-6C-alkyl, independently one or more times optionally substituted with heteroaryl, halogen, hydroxy, or R^{7a} stands for 

, whereby the * is the point of attachment, or R^{7a} represents benzyl, whereby the phenyl ring is opt. subst with 1-5 substituents independently selected from the group consisting of hydrogen, halogen, 1-4Calkyl, 1-4C-haloalkyl, 1-4C-alkoxy, 1-4C-haloalkoxy, cyano, $C(O)OR^9$. X as defined below scheme 1, supra, or for example 1,3,2-dioxathiolane 2-oxide.

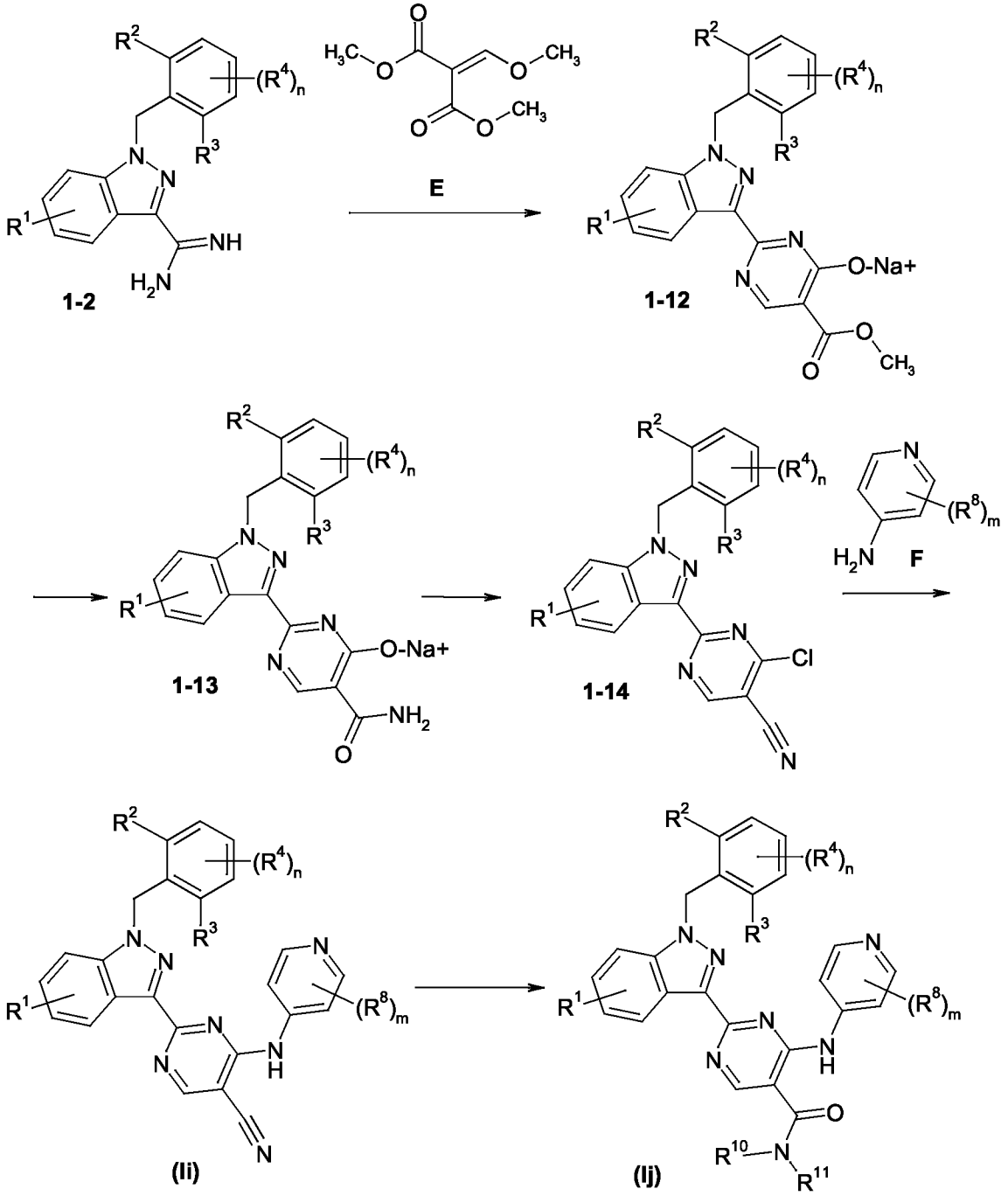
R^{7b} represents an acyl moiety, such as -C(O)-(1-6C-alkyl), –C(O)-(1-6C-alkylen)-O-(1-6C-alkyl), –C(O)-(1-6C-alkylen)-O-(2-6C-alkylen)-O-(1-6C-alkyl), –C(O)-heterocyclyl and Z represents a halogen, hydroxy or -O-R^{7b}.

Compounds of general formula (If') are converted into compounds of general formula (Ig) by reaction with a suitable haloalkyl or dioxathiolane 2-oxide, such as, for example 1,3,2-dioxathiolane 2-oxide, in a suitable solvent system, such as, for example, N,N-dimethyl formamide, in the presence of a suitable base, such as, for example cesium carbonate, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at 60℃.

Compounds of general formula (If') are converted into compounds of general formula (Ih) by reaction with a suitable carboxylic acid derivative, such as for example a carboxylic acid halogenide e.g. carboxylic acid choride, or a carboxylic acid anhydride, in a suitable solvent, such as, for example, dichloromethane, in the presence of a suitable base, such as, for example *N,N*-diethylethanamine, in a temperature range from room temperature to the boiling point of the respective solvent, preferably the reaction is carried out at room temperature.

Compounds of general formula (Ii) and (Ij) can be synthesised according to the procedure depicted in Scheme 6.

Scheme 6



Scheme 6 Route for the preparation of compounds of general formula (Ii) and (Ij), wherein R^1, R^2, R^3, R^4, R^8, m and n have the meaning as given for general formula (I), supra. In addition, interconversion of any of the substituents, R^1, R^2, R^3, R^4 or

R^8 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution or other reactions known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further interconversion of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in Protective Groups in Organic Synthesis, 3rd edition, Wiley 1999).

Compounds E and F are commercially available. R^{10} and R^{11} have the meaning as given for general formula (I), supra.

A suitably substituted carboximidamide or its respective hydrochloride of general formula (1-2), such as for example, 1-(2-fluorobenzyl)-1H-indazole-3-carboximidamide hydrochloride (1:1), can be reacted with dimethyl (methoxymethylidene)-propanedioate (E), in a suitable solvent system, such as, for example, methanol, in the presence of a suitable base, such as, for example, sodium methanolate at temperatures ranging from room temperature to the boiling point of the solvent, preferably the reaction is carried out at 60℃, to furnish intermediates of general formula (1-12).

Intermediates of general formula (1-12) can be converted to intermediates of general formula (1-13) by reaction with a suitable source of ammonia, such as, for example 7N ammonia, in a suitable solvent system, such as, for example methanol, at temperatures ranging from room temperature to the boiling point of the solvent, preferably the reaction is carried out at 60℃, to furnish intermediates of general formula (1-13).

Intermediates of general formula (1-13) can be converted to intermediates of general formula (1-14) by reaction with a suitable source of chloride, such as, for example phosphoric trichloride, neat, in the presence of a suitable base, such as, for example, N,N-diethylaniline, at temperatures ranging from room temperature to

the boiling point of the solvent, preferably the reaction is carried out at 90℃, to furnish intermediates of general formula (1-14).

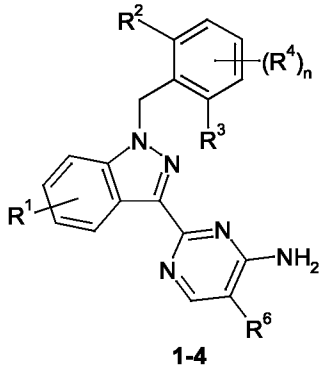
Intermediates of general formula (1-14) can be converted to intermediates of general formula (Ii) by reaction with a suitably substituted pyridin-4-amine, such as, for example pyridin-4-amine, in a suitable solvent system, such as, for example N,N-dimethylformamide, at temperatures ranging from room temperature to the boiling point of the solvent, preferably the reaction is carried out at room temperature, to furnish compounds of general formula (Ii).

Compounds of general formula (Ii) can be converted into compounds of general formula (Ij) by treatment with a suitable acid, such as, for example concentrated sulfuric acid, at temperatures ranging from 0℃ to room temperature, preferably the reaction is carried out at room temperature, to furnish compounds of general formula (Ij).

One preferred aspect of the invention is the process for the preparation of the compounds of claims 1-6 according to the Examples.

A special aspect of the present invention are the following two process steps:

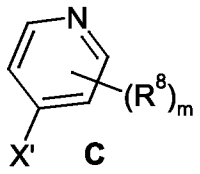
1. Process for the manufacture of compounds of general formula (I) according to claim 1, wherein R^7 is hydrogen as reflected in formula (Ia), characterized in that a compound of formula (1-4)



1-4

whereby R^1, R^2, R^3, R^4, R^6 and n have the meaning according to claim 1,

is reacted with a compound of formula (C)

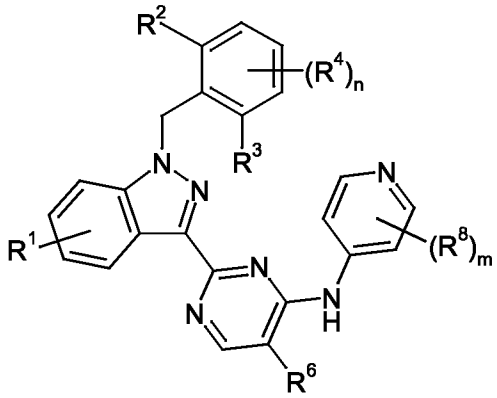


C

whereby R^8 and m have the meaning according to claim 1, and X' represents F, Cl, Br, I, boronic acid or a boronic acid ester,

in the presence of a suitable base, and a suitable palladium catalyst, optionally in the presence of a suitable ligand,

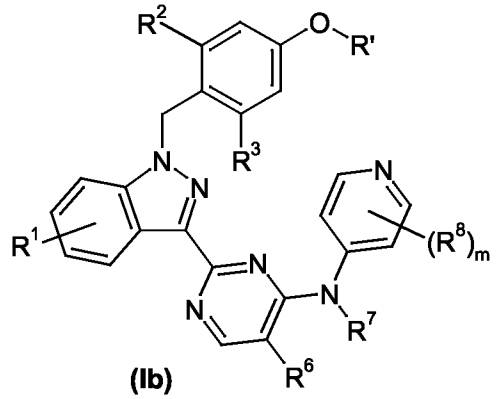
forming a compound of formula (Ia)



(Ia)

which is optionally subsequently deprotected to form a compound of general formula (I) wherein R^7 is hydrogen and R^1, R^2, R^3, R^4, R^6, R^8 and n and m have the meaning as defined in claim 1.

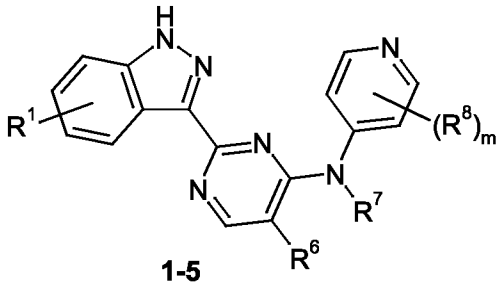
2. Process for the manufacture of compounds of general formula (I) according to claim 1, wherein a compound of formula (Ib)



(Ib)

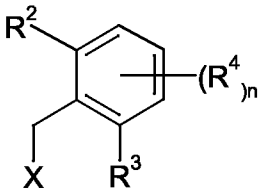
whereby R^1, R^2, R^3, R^6, R^7 R^8 and m have the meaning according to claim 1 and R' is 1-6C-alkyl or benzyl,

is treated with a suitable acid system to cleave the benzylic group in order to obtain a compound of formula 1-5



1-5

followed by reacting the compound of formula 1-5 with a compound of general formula (B),



B

wherein R^2, R^3, R^4 and n have the meaning according to claim 1, and wherein X represents a leaving group, in a suitable solvent system, in the presence of a suitable base, in a temperature range from room temperature to the boiling point of the respective solvent, to furnish compounds of general formula (I).

Another aspect of the invention is the intermediate of general formula (1-5).

It is known to the person skilled in the art that, if there are a number of reactive centers on a starting or intermediate compound, it may be necessary to block one or more reactive centers temporarily by protective groups in order to allow a reaction to proceed specifically at the desired reaction center. A detailed description for the use of a large number of proven protective groups is found, for example, in T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, 1999, 3rd Ed., or in P. Kocienski, Protecting Groups, Thieme Medical Publishers, 2000.

The compounds according to the invention are isolated and purified in a manner known per se, e.g. by distilling off the solvent *in vacuo* and recrystallizing the

residue obtained from a suitable solvent or subjecting it to one of the customary purification methods, such as chromatography on a suitable support material. Furthermore, reverse phase preparative HPLC of compounds of the present invention which possess a sufficiently basic or acidic functionality, may result in the formation of a salt, such as, in the case of a compound of the present invention which is sufficiently basic, a trifluoroacetate or formate salt for example, or, in the case of a compound of the present invention which is sufficiently acidic, an ammonium salt for example. Salts of this type can either be transformed into its free base or free acid form, respectively, by various methods known to the person skilled in the art, or be used as salts in subsequent biological assays. Additionally, the drying process during the isolation of compounds of the present invention may not fully remove traces of cosolvents, especially such as formic acid or trifluoroacetic acid, to give solvates or inclusion complexes. The person skilled in the art will recognise which solvates or inclusion complexes are acceptable to be used in subsequent biological assays. It is to be understood that the specific form (e.g. salt, free base, solvate, inclusion complex) of a compound of the present invention as isolated as described herein is not necessarily the only form in which said compound can be applied to a biological assay in order to quantify the specific biological activity.

Salts of the compounds of formula (I) according to the invention can be obtained by dissolving the free compound in a suitable solvent (for example a ketone such as acetone, methylethylketone or methylisobutylketone, an ether such as diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol such as methanol, ethanol or isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The acid or base can be employed in salt preparation, depending on whether a mono- or polybasic acid or base is concerned and depending on which salt is desired, in an equimolar quantitative ratio or one differing therefrom. The salts are obtained by filtering, reprecipitating, precipitating with a non-solvent for the salt or by evaporating the solvent. Salts obtained can be converted into the free compounds which, in turn, can be converted into salts. In this manner, pharmaceutically unacceptable salts, which

can be obtained, for example, as process products in the manufacturing on an industrial scale, can be converted into pharmaceutically acceptable salts by processes known to the person skilled in the art. Especially preferred are hydrochlorides and the process used in the example section.

Pure diastereomers and pure enantiomers of the compounds and salts according to the invention can be obtained e.g. by asymmetric synthesis, by using chiral starting compounds in synthesis and by splitting up enantiomeric and diasteriomeric mixtures obtained in synthesis.

Enantiomeric and diastereomeric mixtures can be split up into the pure enantiomers and pure diastereomers by methods known to a person skilled in the art. Preferably, diastereomeric mixtures are separated by crystallization, in particular fractional crystallization, or chromatography. Enantiomeric mixtures can be separated e.g. by forming diastereomers with a chiral auxiliary agent, resolving the diastereomers obtained and removing the chiral auxiliary agent. As chiral auxiliary agents, for example, chiral acids can be used to separate enantiomeric bases such as e.g. mandelic acid and chiral bases can be used to separate enantiomeric acids via formation of diastereomeric salts. Furthermore, diastereomeric derivatives such as diastereomeric esters can be formed from enantiomeric mixtures of alcohols or enantiomeric mixtures of acids, respectively, using chiral acids or chiral alcohols, respectively, as chiral auxiliary agents. Additionally, diastereomeric complexes or diastereomeric clathrates may be used for separating enantiomeric mixtures. Alternatively, enantiomeric mixtures can be split up using chiral separating columns in chromatography. Another suitable method for the isolation of enantiomers is the enzymatic separation.

One preferred aspect of the invention is the process for the preparation of the compounds of claims 1-5 according to the examples.

Optionally, compounds of the formula (I) can be converted into their salts, or, optionally, salts of the compounds of the formula (I) can be converted into the free compounds. Corresponding processes are customary for the skilled person.

Optionally, compounds of the formula (I) can be converted into their N-oxides. The N-oxide may also be introduced by way of an intermediate. N-oxides may be prepared by treating an appropriate precursor with an oxidizing agent, such as meta-chloroperbenzoic acid, in an appropriate solvent, such as dichloromethane, at suitable temperatures, such as from 0 °C to 40 °C, whereby room temperature is generally preferred. Further corresponding processes for forming N-oxides are customary for the skilled person.

Commercial utility

As mentioned supra, the compounds of the present invention have surprisingly been found to effectively inhibit Bub1 finally resulting in apoptosis and cell death 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 Bub1, such as, for example, benign and malignant neoplasia, more specifically 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,

especially haematological tumours, solid tumours, and/or metastases of breast, bladder, bone, brain, central and peripheral nervous system, cervix, colon, endocrine glands (e.g. thyroid and adrenal cortex), endocrine tumours, endometrium, esophagus, gastrointestinal tumours, germ cells, kidney, liver, lung, larynx and hypopharynx, mesothelioma, ovary, pancreas, prostate, rectum, renal, small intes-

tine, soft tissue, stomach, skin, testis, ureter, vagina and vulva as well as malignant neoplasias including primary tumors in said organs and corresponding secondary tumors in distant organs ("tumor metastases"). Haematological tumors can e.g be exemplified by aggressive and indolent forms of leukemia and lymphoma, namely non-Hodgkins disease, chronic and acute myeloid leukemia (CML / AML), acute lymphoblastic leukemia (ALL), Hodgkins disease, multiple myeloma and T-cell lymphoma. Also included are myelodysplastic syndrome, plasma cell neoplasia, paraneoplastic syndromes, and cancers of unknown primary site as well as AIDS related malignancies.

A further aspect of the invention is the use of the compounds according to formula (I) for the treatment of cer-vical -, breast -, non-small cell lung -, prostate -, colon – and melanoma tumors and/or metastases thereof, especially preferred for the treatment thereof as well as a method of treatment of cervical -, breast -, non-small cell lung -, prostate -, colon – and melanoma tumors and/or metastases thereof comprising administering an effective amount of a compound of formula (I).

One aspect of the invention is the use of the compounds according to formula (I) for the treatment of cervix tumors as well as a method of treatment of cervix tumors comprising administering an effective amount of a compound of formula (I).

In accordance with an aspect of the present invention therefore the invention relates to a compound of general formula I, or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer 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, especially for use in the treatment of a disease.

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 hyperproliferative disorders or disorders responsive to induction of apoptosis,

especially for the treatment of hyperproliferative disorders or disorders responsive to induction of apoptosis .

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, especially the treatment, wherein the diseases are haemotological tumours, solid tumours and/or metastases thereof. A preferred aspect is the use of a compound of formula (I) for the prophylaxis and/or treatment of cervical -, breast -, non-small cell lung -, prostate -, colon – and/or melanoma tumors, especially preferred for the treatment thereof.

Another aspect is the use of a compound of formula (I) is for the treatment of cervical -, breast -, non-small cell lung -, prostate -, colon – and melanoma tumors and/or metastases thereof, especially preferred for the treatment 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, thy-

roid, 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.

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, especially in therapy of tumour growth and metastases, especially in solid tumours of all indications and stages with or without pretreatment of the tumour growth.

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 or auxiliary and a pharmaceutically effective amount of a compound, or salt thereof, of the present invention.

Another aspect of the invention is a pharmaceutical composition comprising a pharmaceutically effective amount of a compound of formula (I) and a pharmaceutically acceptable auxiliary for the treatment of a disease mentioned supra, especially for the treatment of haemotological tumours, solid tumours and/or metastases thereof.

A pharmaceutically acceptable carrier or auxiliary is preferably a carrier that is 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. Carriers and auxiliaries are all kinds of additives assisting to the composition to be suitable for administration.

A pharmaceutically effective amount of compound is preferably that amount which produces a result or exerts the intended influence on the particular condition being treated.

The compounds of the present invention can be administered with pharmaceutically-acceptable carriers or auxiliaries 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 auxiliaries, 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, hydroxypropylmethylcellulose, 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 rec-

tum to release the drug. Such materials are, for example, cocoa butter and polyethylene glycol.

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 administration, 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 charcoa)l ;

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 monopalmitate) ;

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 i.v. 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 i.v. infusion over about 60 minutes.

Lyophilised powder for i.v. 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.

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.

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. Those combined pharma-

ceutical agents can be other agents having antiproliferative effects such as for example for the treatment of haemotological tumours, solid tumours and/or metastases thereof and/or agents for the treatment of undesired side effects.The present invention relates also to such combinations.

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, especially (chemotherapeutic) anti-cancer agents as defined supra. The combination can be a non-fixed combination or a fixed-dose combination as the case may be.

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.

As will be appreciated by persons skilled in the art, the invention is not limited to the particular embodiments described herein, but covers all modifications of said embodiments that are within the spirit and scope of the invention as defined by the appended claims.

The following examples illustrate the invention in greater detail, without restricting it. Further compounds according to the invention, of which the preparation is not explicitly described, can be prepared in an analogous way.

The compounds, which are mentioned in the examples and the salts thereof represent preferred embodiments of the invention as well as a claim covering all subcombinations of the residues of the compound of formula (I) as disclosed by the specific examples.

The term “according to” within the experimental section is used in the sense that the procedure referred to is to be used “analogously to”.

EXPERIMENTAL PART

The following table lists the abbreviations used in this paragraph and in the Intermediate Examples and Examples section as far as they are not explained within the text body.

Abbreviation	**Meaning**
aq.	aqueous
alloc	allyloxycarbonyl
boc	t-butoxycarbonyl
br	broad
CI	chemical ionisation
d	doublet
dd	doublet of doublet
DAD	diode array detector
DCM	dichloromethane
DMF	*N,N*-dimethylformamide
ELSD	Evaporative Light Scattering Detector
EtOAc	ethyl acetate
Eq.	equivalent
ESI	electrospray (ES) ionisation
HATU	2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (CAS number 148893-10-1)
HPLC	high performance liquid chromatography
LC-MS	liquid chromatography mass spectrometry
m	multiplet
MS	mass spectrometry
n-BuLi	n-butyllithium
NMR	nuclear magnetic resonance spectroscopy : chemical shifts (δ) are given in ppm. The chemical shifts were corrected by setting the DMSO signal to 2.50

	ppm using unless otherwise stated.
PDA	Photo Diode Array
PoraPak™;	a HPLC column obtainable from Waters
q	quartet
r.t. or rt	room temperature
RT	retention time (as measured either with HPLC or UPLC) in minutes
s	singlet
SM	starting material
SQD	Single-Quadrupol-Detector
t	triplet
THF	tetrahydrofuran
UPLC	ultra performance liquid chromatography

Other abbreviations have their meanings customary per se to the skilled person. The various aspects of the invention described in this application are illustrated by the following examples which are not meant to limit the invention in any way.

Specific Experimental Descriptions

NMR peak forms in the following specific experimental descriptions are stated as they appear in the spectra, possible higher order effects have not been considered. Reactions employing microwave irradiation may be run with a Biotage Initator® microwave oven optionally equipped with a robotic unit. The reported reaction times employing microwave heating are intended to be understood as fixed reaction times after reaching the indicated reaction temperature. 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 crystallization. In some cases, impurities may be stirred out using a suitable solvent. In some cases, the compounds may be purified by chromatography, particularly flash column chromatography, using for example pre-

packed silica gel cartridges, *e.g.* from Separtis such as Isolute® Flash silica gel or Isolute® Flash NH_2 silica gel in combination with a Isolera® autopurifier (Biotage) and eluents such as gradients of e.g. hexane/ethyl acetate 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 ionization mass spectrometer in combination with a suitable prepacked reverse phase column and eluents such as gradients of water and acetonitrile which may contain additives such as trifluoroacetic acid, formic acid or aqueous ammonia. In some cases, purification methods as described above can provide those compounds of the present invention which possess a sufficiently basic or acidic functionality in the form of a salt, such as, in the case of a compound of the present invention which is sufficiently basic, a trifluoroacetate or formate salt for example, or, in the case of a compound of the present invention which is sufficiently acidic, an ammonium salt for example. A salt of this type can either be transformed into its free base or free acid form, respectively, by various methods known to the person skilled in the art, or be used as salts in subsequent biological assays. It is to be understood that the specific form (*e.g.* salt, free base etc) of a compound of the present invention as isolated as described herein is not necessarily the only form in which said compound can be applied to a biological assay in order to quantify the specific biological activity.

The percentage yields reported in the following examples are based on the starting component that was used in the lowest molar amount. Air and moisture sensitive liquids and solutions were transferred via syringe or cannula, and introduced into reaction vessels through rubber septa. Commercial grade reagents and solvents were used without further purification. The term “concentrated in vacuo” refers to use of a Buchi rotary evaporator at a minimum pressure of approximately 15 mm of Hg. All temperatures are reported uncorrected in degrees Celsius (℃).

In order that this invention may be better understood, the following examples are set forth. These examples are for the purpose of illustration only, and are not to be construed as limiting the scope of the invention in any manner. All publications mentioned herein are incorporated by reference in their entirety.

Analytical LC-MS conditions

LC-MS-data given in the subsequent specific experimental descriptions refer (unless otherwise noted) to the following conditions:

System:	Waters Acquity UPLC-MS: Binary Solvent Manager, Sample Manager/Organizer, Column Manager, PDA, ELSD, SQD 3001 or ZQ4000
Column:	Acquity UPLC BEH C18 1.7 50x2.1mm
Solvent:	A1 = water + 0.1% vol. formic acid (99%) A2 = water + 0.2% vol. ammonia (32%)
	B1 = acetonitrile
Gradient:	0-1.6 min 1-99% B, 1.6-2.0 min 99% B
Flow:	0.8 mL/min
Temperature:	60℃
Injection:	2.0 µl
Detection:	DAD scan range 210-400 nm -> Peaktable
	ELSD
Methods:	MS ESI+, ESI- Switch -> various scan ranges (Report Header) **Method 1:** A1 + B1 = C:\MassLynx**Mass_100_1000**.flp **Method 2:** A1 + B1 = C:\MassLynx**Mass_160_1000**.flp **Method 3:** A1 + B1 = C:\MassLynx**Mass_160_2000**.flp **Method 4:** A1 + B1 = C:\MassLynx**Mass_160_1000_BasicReport**.flp **Method 5:** A2 + B1 = C:\MassLynx**NH_3_Mass_100_1000**.flp **Method 6:** A2 + B1 = C:\MassLynx**NH_3_Mass_160-_1000_BasicReport**.flp

Preparative HPLC conditions

"Purification by preparative HPLC" in the subsequent specific experimental descriptions refers to (unless otherwise noted) the following conditions:

Analytics (pre- and post analytics: Method B):

System:	Waters Aqcuity UPLC-MS: Binary Solvent Manager, Sample Manager/Organizer, Column Manager, PDA, ELSD, SQD 3001
Column:	Aqcuity BEH C18 1.7 50x2.1mm
Solvent:	A = water + 0.1% vol. formic acid (99%)
	B = acetonitrile
Gradient:	0-1.6 min 1-99% B, 1.6-2.0 min 99% B
Flow:	0.8 mL/min
Temperature:	60℃
Injection:	2.0 µl
Detection:	DAD scan range 210-400 nm MS ESI+, ESI-, scan range 160-1000 m/z ELSD
Methods:	Purify_pre.flp Purify_post.flp

Preparation:

System:	Waters Autopurificationsystem: Pump 2545, Sample Manager 2767, CFO, DAD 2996, ELSD 2424, SQD 3001
Column:	XBrigde C18 5µm 100x30 mm
Solvent:	A = water + 0.1% vol. formic acid (99%)
	B = acetonitrile
Gradient:	0–1 min 1% B, 1-8 min 1-99% B, 8-10 min 99% B

Flow:	50 mL/min
Temperature:	RT
Solution:	max. 250 mg / 2.5 mL dimethyl sufoxide or DMF
Injection:	1 x 2.5 mL
Detection:	DAD scan range 210–400 nm
	MS ESI+, ESI-, scan range 160-1000 m/z

Chiral HPLC conditions

If not specified otherwise, chiral HPLC-data given in the subsequent specific experimental descriptions refer to the following conditions:

Analytics:

System:	Dionex: Pump 680, ASI 100, Waters: UV-Detektor 2487
Column:	Chiralpak IC 5µm 150x4.6 mm
Solvent:	hexane / ethanol 80:20 + 0.1% diethylamine
Flow:	1.0 mL/min
Temperature:	25℃
Solution:	1.0 mg/mL ethanol/methanol 1:1
Injection:	5.0 µl
Detection:	UV 280 nm

Preparation:

System:	Agilent: Prep 1200, 2xPrep Pump, DLA, MWD, Prep FC, ESA: Corona
Column:	Chiralpak IC 5µm 250x30 mm
Solvent:	hexane / ethanol 80:20 + 0.1% diethylamine
Flow:	40 mL/min
Temperature:	RT

Solution:	660 mg / 5.6 mL ethanol
Injection:	8 x 0.7 mL
Detection:	UV 280 nm

Flash column chromatography conditions

"Purification by (flash) column chromatography" as stated in the subsequent specific experimental descriptions refers to the use of a Biotage Isolera purification system. For technical specifications see "Biotage product catalogue" on www.biotage.com.

Determination of optical rotation conditions

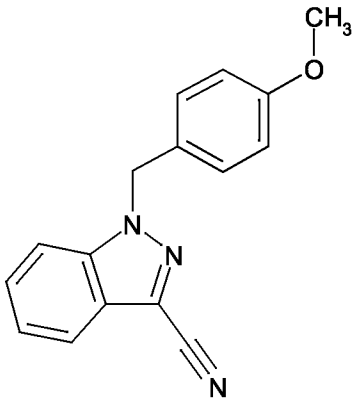
Optical rotations were measured in dimethyl sulfoxide at 589 nm wavelength, 20℃, concentration 1.0000 g/100ml, integration time 10 s, film thickness 100.00 mm.

EXAMPLES

Synthetic Intermediates

Intermediate 1-1-1

Preparation of 1-(4-methoxybenzyl)-1*H*-indazole-3-carbonitrile

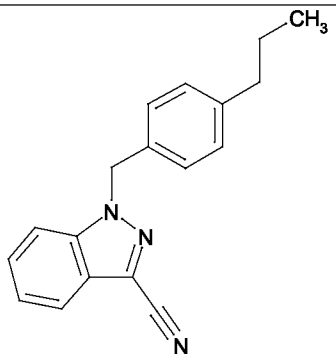
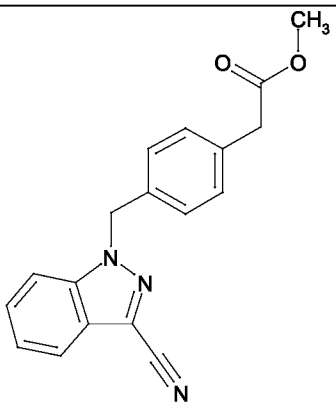


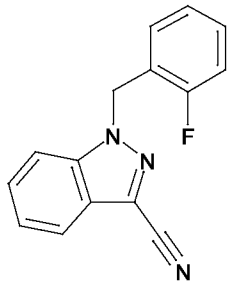
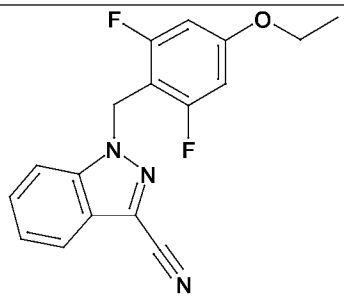
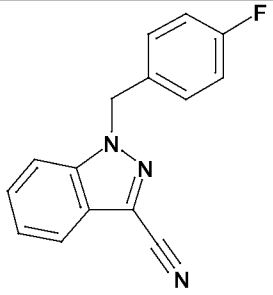
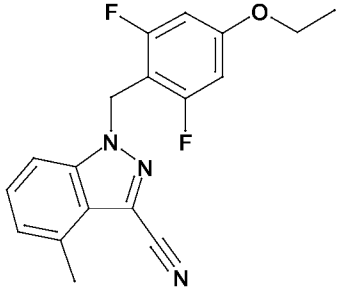
6,47 g of 1*H*-indazole-3-carbonitrile (45,2 mmol, 1 eq.) were dissolved in 65 ml of dry DMF. 10 g of 1-(bromomethyl)-4-methoxybenzene (49,7 mmol, 1,1 eq.) and 17,7 g of cesium carbonate (54,2 mmol, 1,2 eq.) were added. The mixture was stirred at room temperature for 18 hours under nitrogen atmosphere. Then the reaction mixture was partitioned between water and *tert*-butyl methyl ether. The separated aqueous layer was extracted twice with *tert*-butyl methyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated in vacuo. The crystallization from methanol provided 9,25 g (35,1 mmol, 77,7%) of analytically pure target compound.

^{1}H NMR (300 MHz, DMSO-d6) δ [ppm]= 3.64 - 3.71 (s, 3 H), 5.70 (s, 2 H) 6.81 - 6.89 (m, 2 H), 7.22 - 7.29 (m, 2 H), 7.38 (ddd, 1 H), 7.55 (ddd, 1 H), 7.85 (dt, 1 H) 7.97 (dt, 1 H)

LC-MS:
retention time: 1.27 min
MS ES$^+$: 264.31 [M+H]$^+$

The following intermediates were prepared according to the same procedure using the respective commercially available starting materials:

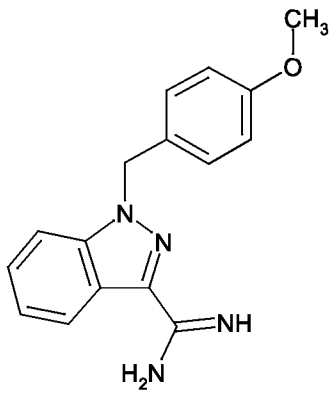
1-1-2		1-(4-propylbenzyl)-1*H*-indazole-3-carbonitrile	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 0.75 - 0.86 (m, 3H), 1.41 - 1.56 (m, 2H), 2.41 - 2.51 (t, 2H), 5.74 (s, 2H), 7.08 - 7.13 (d, 2H), 7.16 - 7.22 (d, 2H), 7.38 (ddd, 1H), 7.55 (ddd, 1H), 7.85 (dt, 1H), 7.92 - 7.98 (dt, 1H). LC-MS: retention time: 1,50 min MS ES$^+$: 276.0 [M+H]$^+$ Method B
1-1-3		methyl {4-[(3-cyano-1*H*-indazol-1-yl)methyl]phenyl}acetate	^{1}H-NMR (500MHz, DMSO-d$_6$): δ [ppm]= 3.58 (s, 3H), 3.64 (s, 2H), 5.81 (s, 2H), 7.21 - 7.25 (m, 2H), 7.25 - 7.29 (m, 2H), 7.43 (td, 1H), 7.59 (ddd, 1H), 7.89 - 7.92 (m, 1H), 8.00 (d, 1H). LC-MS: retention time: 1,24 min MS ES$^+$: 306.0 [M+H]$^+$ Method B

1-1-4		1-(2-fluoroben-zyl)-1H-indazole-3-carbonitrile	^{1}H-NMR (300MHz, DMSO-d6): δ [ppm]= 5.84 (s, 2H), 7.11 - 7.45 (m, 5H), 7.58 (ddd, 1H), 7.87 (d, 1H), 7.96 (d, 1H). LC-MS: retention time: 1.29 min MS ES$^+$: 251.9 [M+H]$^+$ Method B
1-1-5		1-(4-ethoxy-2,6-difluoroben-zyl)-1H-indazole-3-carbonitrile	^{1}H-NMR (300MHz, DMSO-d6): δ [ppm]= 1.26 (t, 3H), 4.01 (q, 2H), 5.72 (s, 2H), 6.70 - 6.76 (m, 2H), 7.34 - 7.47 (m, 1H), 7.56 - 7.67 (m, 1H), 7.80 - 7.88 (m, 1H), 7.91 - 8.01 (m, 1H). LC-MS: retention time: 1.44 min MS ES$^+$: 314.2 [M+H]$^+$
1-1-6		1-(4-fluoroben-zyl)-1H-indazole-3-carbonitrile	^{1}H-NMR (500MHz, DMSO-d$_6$): δ [ppm]= 5.79 (s, 2H), 7.14 (m, 2H), 7.31 - 7.43 (m, 3H), 7.56 (ddd, 1H), 7.87 (d, 1H), 7.98 (d, 1H).
1-1-7		1-(4-ethoxy-2,6-difluoroben-zyl)-4-methyl-1H-indazole-3-	H-NMR (400MHz, DMSO-d6): δ [ppm]= 1.26 (t, 3H), 2.64 (s, 3H), 4.01 (q, 2H), 5.68 (s, 2H), 6.70 - 6.76 (m, 2H), 7.13 (d, 1H), 7.46 (dd, 1H), 7.74 (d,

		carbonitrile	1H).

Intermediate 1-2-1

Preparation of 1-(4-methoxybenzyl)-1*H*-indazole-3-carboximidamide



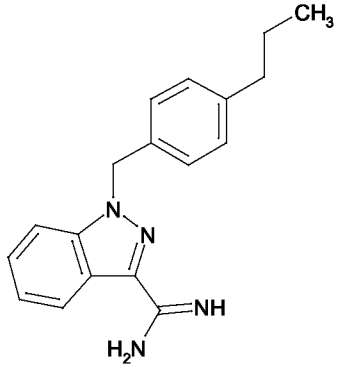
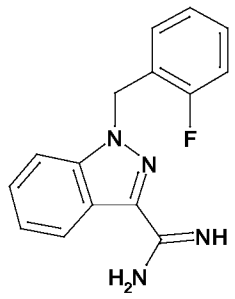
9,25 g of 1-(4-methoxybenzyl)-1*H*-indazole-3-carbonitrile (1-1-1, 35,1 mmol, 1 eq.) were suspended in 128 ml of dry methanol under a nitrogen atmosphere. 0,949 g (17,6 mmol, 0.5 eq.) of sodium methanolate were added. The reaction mixture was stirred for 18 hours at room temperature. To the resulting mixture were added 2,82 g (52,7 mmol, 1.5 eq.) of ammonium chloride and 1,0 ml (17,6 mmol, 0.5 eq.) of 100% acetic acid and stirred for 5 hours at 50°C. After cooling down at room temperature the mixture was concentrated in vacuo. The residue was partitioned between aq. half saturated sodium hydrogen carbonate solution and dichloromethane/isopropanol 4:1. The aqueous layer was extracted three times with dichloromethane/isopropanol 4:1. The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated in vacuo. The residue was

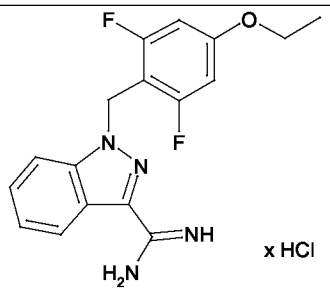
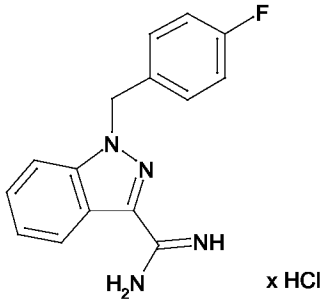
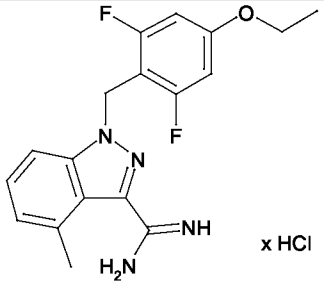
purified by flash chromatography to yield 6,45 g (23 mmol, 65,5%) of the analytically pure target compound.

^{1}H NMR (300 MHz, DMSO-d6) δ [ppm]= 3.62 - 3.70 (s, 3 H), 5.57 (s, 2 H), 6.37 (br. s., 3 H), 6.78 - 6.88 (m, 2 H), 7.10 - 7.23 (m, 3 H), 7.35 (ddd, 1 H), 7.68 (d, 1 H), 8.27 (d, 1 H)

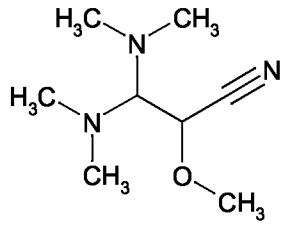
LC-MS:
retention time: 0.75 min
MS ES$^+$: 281.34 $[M+H]^+$

The following intermediates were prepared according to the same procedure from the indicated starting materials (SM = starting material):

1-2-2 SM = 1-1-2		1-(4-propylbenzyl)-1*H*-indazole-3-carboximidamide	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 0.80 (t, 3H), 1.38 - 1.56 (m, 2H), 2.41 - 2.49 (t, 2H), 5.61 (s, 2H), 6.41 (br. s., 3H), 7.04 - 7.19 (m, 5H), 7.36 (ddd, 1H), 7.67 (d, 1H), 8.28 (d, 1H). LC-MS: retention time: 0,94 min MS ES$^+$: 293.0 $[M+H]^+$ Method B
1-2-3 SM = 1-1-4		1-(2-fluorobenzyl)-1H-indazole-3-carboximidamide	^{1}H-NMR (300MHz, DMSO-d6): δ [ppm]= 5.72 (s, 2H), 6.73 (br. s., 3H), 7.01 - 7.13 (m, 2H), 7.15 - 7.23 (m, 2H), 7.27 - 7.36 (m, 1H), 7.40 (ddd, 1H), 7.69 (d, 1H), 8.27 (d, 1H). LC-MS: retention time: 0.75 min

			MS ES+: 268.9 [M+H]+ Method B
1-2-4 SM = 1-1-5		1-(4-ethoxy-2,6-difluoro-benzyl)-1H-indazole-3-carboximid-amide hydrochloride (1:1)	1H-NMR (400MHz, DMSO-d6): δ [ppm]= 1.26 (t, 3H), 4.01 (q, 2H), 5.73 (s, 2H), 6.70 -6.76 (m, 2H), 7.33 - 7.41 (m, 1H), 7.52 - 7.63 (m, 1H), 7.88 (d, 1H), 7.97 (d, 1H), 9.26 (br. s., 3H). LC-MS: retention time: 0.87 min MS ES+: 332.2 [M+H]+
1-2-5 SM = 1-1-6		1-(4-fluoroben-zyl)-1H-indazole-3-carboximid-amide hydrochloride (1:1)	1H-NMR (400MHz, DMSO-d6): δ [ppm]= 5.81 (s, 2H), 7.10 - 7.17 (m, 2H), 7.35 - 7.42 (m, 3H), 7.51 - 7.57 (m, 1H), 7.93 (d, 1H), 8.00 (d, 1H), 9.34 (br. s., 3H). LC-MS: retention time: 0.71 min MS ES+: 269.0 [M+H]+ Method B
1-2-6 SM = 1-1-7		1-(4-ethoxy-2,6-difluoro-benzyl)-4-methyl-1H-indazole-3-carboximid-amide hydrochloride (1:1)	1H-NMR (400MHz, DMSO-d6): δ [ppm]= 1.26 (t, 3H), 2.49 (s, 3H), 3.99 (q, 2H), 5.66 (s, 2H), 6.69 - 6.79 (m, 2H), 7.10 (d, 1H), 7.46 (t, 1H), 7.74 (d, 1H), 7.77 (br. s., 3H). LC-MS (Method 1): retention time: 0.93 min MS ES+: 345.0 [M+H]+

Intermediate 1-3-1 Preparation of 3,3-bis(dimethylamino)-2-methoxypropanenitrile



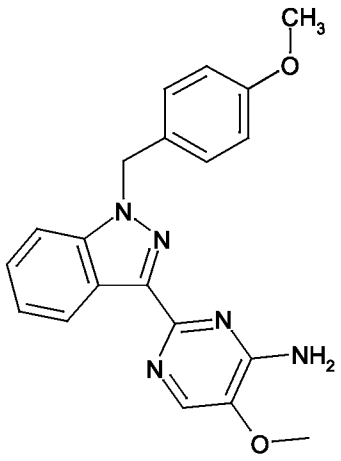
360,4 g of 1-*tert*-butoxy-*N,N,N',N'*-tetramethylmethanediamine (Bredereck's reagent) (2068 mmol, 1 eq.) and 150,0 g of methoxyacetonitrile (2068 mmol, 1 eq.) were stirred for 18 hours at 80°C. The reaction mixture was concentrated in vacuo. The residue was purified by vacuum distillation to yield 117 g (687 mmol, 33,0%) of the analytical pure target compound as a yellowish liquid.

1H-NMR (400 MHz, DMSO-d6): δ [ppm]= 2.23 (s, 6H), 2.29 (s, 6H), 3.23 (d, 1H), 3.36 - 3.41 (s, 3H), 4.73 (d, 1H).

LC-MS:
retention time: 0.79 min
MS ES+: 172.09 $[M+H]^+$

Intermediate 1-4-1

Preparation of 5-methoxy-2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]pyrimidin-4-amine

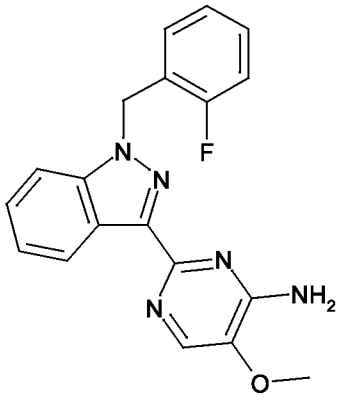


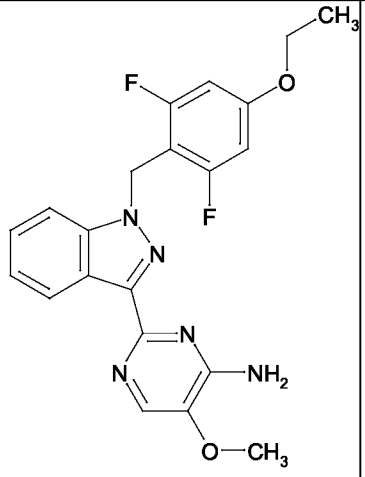
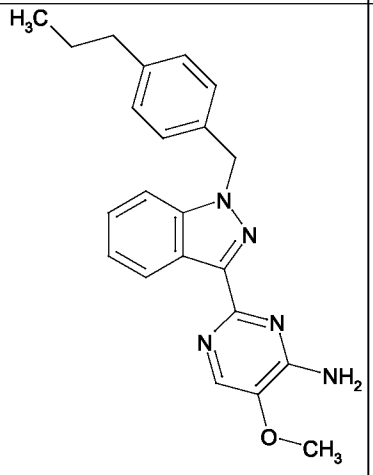
6,45 g of 1-(4-methoxybenzyl)-1*H*-indazole-3-carboximidamide (23,0 mmol, 1 eq.), 5,40 g of 3,3-bis(dimethylamino)-2-methoxypropanenitrile (1-2-1, 31,5 mmol, 1,37 eq.) and 0,455 ml of piperidine (4,60 mmol, 0,2 eq.) were dissolved in 82,7 ml of dry 3-methylbutan-1-ol, put under a nitrogen atmosphere and stirred at 100℃ for 3 days. The mixture was cooled down at room temperature and stirred for 18 hours for crystallization. The resulting suspension was filtered off. The crystals were washed with cold methanol and dried in vacuo at 50°C. The crystallization was repeated twice with cold methanol to recieve 2 further filter cakes and a combined yield of 6,87 g (19 mmol, 82,5%) of the analytically pure target compound.
^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 3.62 - 3.69 (s, 3H), 3.85 (s, 3H), 5.59 (s, 2H), 6.78 - 6.90 (m, 4H), 7.11 - 7.23 (m, 3H), 7.35 (ddd, 1H), 7.68 (d, 1H), 7.95 (s, 1H), 8.53 (d, 1H).

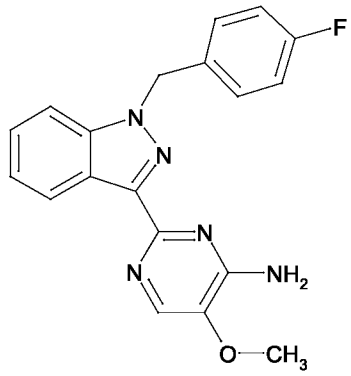
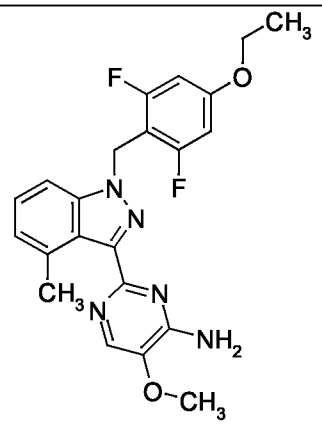
LC-MS: Method B
retention time: 0.87 min

MS ES$^+$: 362.0 $[M+H]^+$

The following intermediates were prepared according to the same procedure from the indicated starting materials (SM = starting material):

1-4-2 SM = 1-2-3		2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrim-idin-4-amine	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 3.85 (s, 3H), 5.73 (s, 2H), 6.85 (br. s., 2H), 7.01 - 7.13 (m, 2H), 7.15 - 7.24 (m, 2H), 7.27 - 7.42 (m, 2H), 7.69 (d, 1H), 7.95 (s, 1H), 8.55 (d, 1H). LC-MS: retention time: 0.88 min MS ES$^+$: 350.0 $[M+H]^+$

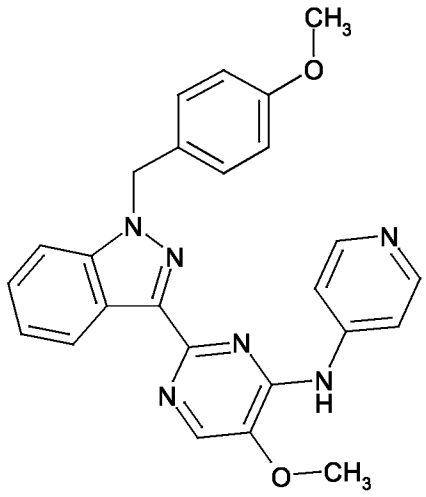
			Method B
1-4-3 SM = 1-2-4		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-amine	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.26 (t, 3H), 3.84 (s, 3H), 3.96 - 4.05 (m, 2H), 5.59 (s, 2H), 6.72 (d, 2H), 6.77 - 6.86 (br. s, 2H), 7.15 - 7.21 (m, 1H), 7.40 (ddd, 1H), 7.69 (d, 1H), 7.93 (s, 1H), 8.52 (d, 1H). LC-MS: retention time: 1.03 min MS ES$^+$: 412.2 $[M+H]^+$
1-4-4 SM = 1-2-2		5-methoxy-2-[1-(4-propylbenzyl)-1*H*-indazol-3-yl]pyrimidin-4-amine	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 0.80 (t, 3H), 1.40 - 1.54 (m, 2H), 2.42 – 2.46 (t, 2H), 3.85 (s, 3H), 5.62 (s, 2H), 6.83 (br. s., 2H), 7.06 - 7.20 (m, 5H), 7.35 (ddd, 1H), 7.68 (d, 1H), 7.95 (s, 1H), 8.54 (d, 1H). LC-MS: retention time: 1.06 min MS ES$^+$: 374.0 $[M+H]^+$ Method B

1-4-5 SM = 1-2-5		2-[1-(4-fluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 3.85 (s, 3H), 5.67 (s, 2H), 6.84 (br. s., 2H), 7.06 - 7.21 (m, 3H), 7.23 - 7.31 (m, 2H), 7.36 (td, 1H), 7.70 (d, 1H), 7.95 (s, 1H), 8.54 (d, 1H). LC-MS: retention time: 0.87 min MS ES$^+$: 350.0 [M+H]$^+$ Method B
1-4-6 SM = 1-2-6		2-[1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1H-indazol-3-yl]-5-methoxypyrimidin-4-amine	^{1}H-NMR (400MHz, DMSO-d6): δ [ppm]= 1.26 (t, 3H), 2.34 (s, 3H), 3.85 (s, 3H), 4.00 (q, 2H), 5.52 (s, 2H), 6.63 - 6.74 (m, 2H),6.78 (br s, 2H), 6.87 (d, 1H), 7.27 (dd, 1H), 7.54 (d, 1H), 7.90 (s, 1H). LC-MS: retention time: 1.32 min MS ES+: 427.08 [M+H]+

Intermediate 1-5-1

Preparation of 5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine

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205 mg of 5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]pyrimidin-4-amine (1-4-1, 0,568 mmol, 1 eq.), 121,6 mg of 4-bromopyridine hydrochloride (1:1) (0,625 mmol. 1,1 eq.), 136,5 mg of sodium 2-methylpropan-2-olate (1,42 mmol, 2,5 eq.), 106,2 mg of 1'-binaphthalene-2,2'-diylbis(diphenylphosphane) (0,171 mmol, 0,3 eq.) and 52,0 mg of (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one - palladium (3:2) (0,057 mmol, 0,1 eq.) were suspended in 3 ml of dry DMF under nitrogen atmosphere. The reaction mixture was stirred for two days at 100℃. 122 mg of 4-bromopyridine hydrochloride (1:1) (0,625 mmol. 1,1 eq.), 137 mg of sodium 2-methylpropan-2-olate (1,42 mmol, 2,5 eq.), 106 mg of 1'-binaphthalene-2,2'-diylbis(diphenylphosphane) (0,171 mmol, 0,3 eq.) and 52,0 mg of (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one - palladium (3:2) (0,057 mmol, 0,1 eq.) were added and stirred for further 24 hours. The mixture was cooled down to room temperature, diluted with 10 ml dichloromethane and filtered off. The filtrate was concentrated in vacuo. The residue was purified by flash chromatography to yield 126 mg (0,23 mmol, 81%) of the analytically pure target compound.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 3.66 (s, 3H), 4.02 (s, 3H), 5.65 (s, 2H), 6.86 (d, 2H), 7.15 - 7.25 (m, 1H), 7.27 - 7.44 (m, 3H), 7.78 (d, 1H), 8.08 - 8.17 (m, 2H), 8.31 - 8.46 (m, 4H), 9.42 (s, 1H).

LC-MS:

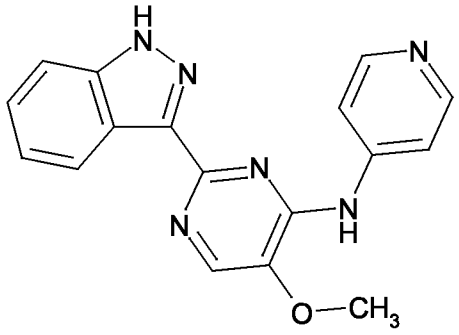
retention time: 0.95 min

MS ES$^+$: 439.31 $[M+H]^+$

Method B

Intermediate 1-6-1

Preparation of 2-(1*H*-indazol-3-yl)-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine



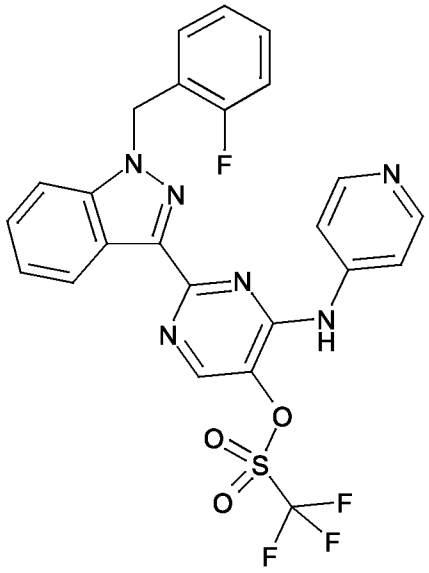
13,4 g of 5-methoxy-2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-4-yl)-pyrimidin-4-amine (1-5-1, 30,6 mmol, 1 eq.) was suspended in 121 ml of 1,2-dichloroethan. First 71 ml of trifluoroacetic acid (918 mmol, 30 eq.) were added dropwise, followed by 27 ml of trifluoromethanesulfonic acid (306 mmol, 10 eq.). The reaction mixture was stirred for three days under nitrogen atmosphere. The mixture was cooled with an ice bath to + 3℃, upon which 2M aq. sodium hydroxide solution was added until pH = 12. The resulting brown suspension was stirred for 18 hours at room temperature and then the precipitate was filtered off and dried under vacuo at 70℃ to yield 9,74g (27,7 mmol, 90,3 %) of the analytically pure target compound as a light brown solid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 4.02 (s, 3H), 7.11 - 7.26 (m, 1H), 7.37 (t, 1H), 7.56 (d, 1H), 8.17 (d, 2H), 8.32 - 8.53 (m, 4H), 9.39 (s, 1H), 13.39 (s, 1H).

LC-MS:
retention time: 0.68 min
MS ES$^+$: 319.0 $[M+H]^+$
Method B

Intermediate 1-7-1

Preparation of 2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)-pyrimidin-5-yl trifluoromethanesulfonate



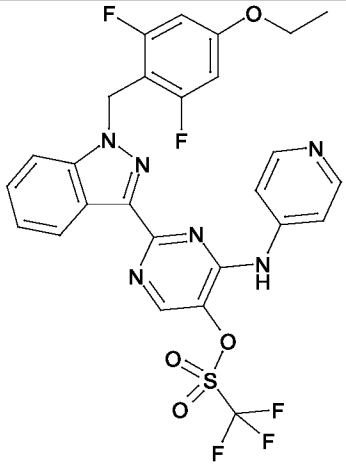
120 mg of 2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol (3-3, 0,291 mmol, 1 eq.) was suspended in 1,9 ml of dry dichloromethane and 0,059 ml of pyridine (0,73 mmol, 2,5 eq.) were added under nitrogen atmosphere. The mixture was cooled with an ice bath to +3℃ and 0,061ml of trifluoro-methanesulfonic anhydride (0,364 mmol, 1,25 eq.) were added dropwise. Upon completion of addition the ice bath was removed and the reaction mixture was stirred for 18 hours. The reaction mixture was cooled again with an ice bath and 0,059 ml of pyridine (0,727 mmol, 2,5 eq.) and 0,061 ml of trifluoromethanesulfonic anhydride (0,364 mmol, 1,25 eq.) were added and stirred for 3 hours. This procedure was repeated and stirred for further 24 hours. The reaction mixture was filtered off a short silica column and diluted with dichloromethane. The filtrate was concentrated in vacuo. The liquid residue was dissolved with toluene and again concentrated in vacuo. Yield = 106,1 mg with 37% purity (0,07 mmol, 24,78%)

LC-MS:

retention time: 1.18 min

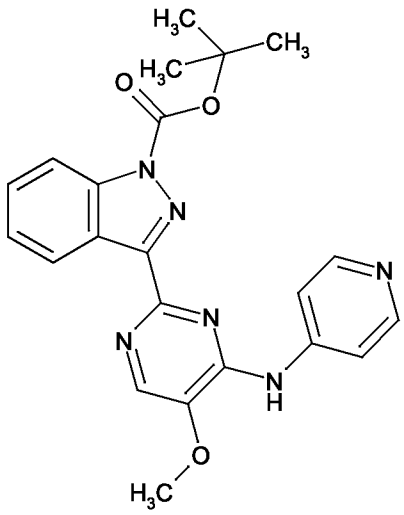
MS ES+: 545.08 [M+H]+

The following intermediate was prepared according to the same procedure using the indicated starting materials (SM = starting material):

1-7-2 SM = 3-1		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-yla-mino)pyrimidin-5-yl trifluoro-methanesul-fonate	(1H-NMR (300MHz, DMSO-d6): δ [ppm]= 1.20 - 1.30 (m, 3H), 4.00 (q, 2H), 5.68 - 5.78 (m, 2H), 6.78 (d,2H), 7.26 - 7.36 (m, 1H), 7.52 (t, 1H), 7.89 (d, 1H), 8.30 - 8.45 (m, 3H), 8.66 (d, 2H), 9.05 (s, 1H), 11.15 - 11.43 (m, 1H).) LC-MS: retention time: 1.03 min MS ES+: 475.1 [M+H]+ Method B

Intermediate 1-8-1

Preparation of tert-butyl 3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazole-1-carboxylate



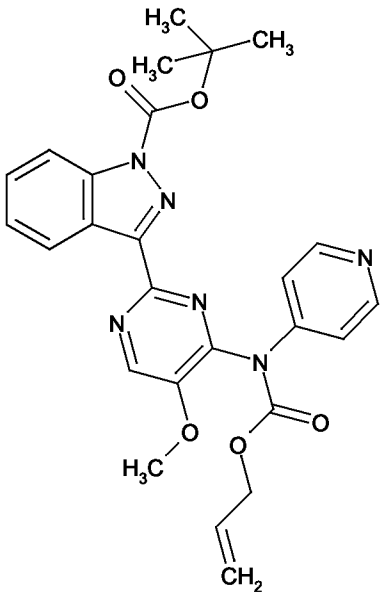
100 mg of [2-(1H-Indazol-3-yl)-5-methoxy-pyrimidin-4-yl]-pyridin-4-yl-amine (1-6-1, 0,314 mmol, 1 eq.) was dissolved in 2 ml of acetonitrile and 0,131 ml of triethylamine (0,942 mmol, 3 eq.). 3,83 mg of 4-Dimethylaminopyridin (0,031 mmol, 0,1 eq.) and 89,1 mg of di-tert-butyl dicarbonate (0,408 mmol, 1.3 eq.) dissolved in 0,5 ml of acetonitrile were added. The solution was stirred for 24 hours at room temperature under nitrogen atmosphere. The resulting suspension was filtered off and the filter cake was washed with acetonitrile to yield 100 mg (0,24 mmol, 76,1%) of the analytically pure target compound.

^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.68 (br. s., 9H), 4.05 (br. s., 3H), 7.43 (br. s., 1H), 7.62 (br. s., 1H), 8.18 (br. s., 3H), 8.33 - 8.45 (m, 3H), 8.57 (d, 1H), 9.53 (br. s., 1H).

LC-MS:
retention time: 0.97 min
MS ES$^+$: 419.1 $[M+H]^+$

Intermediate 1-9-1

Preparation of tert-butyl 3-(5-methoxy-4-{[(prop-2-en-1-yloxy)carbonyl](pyridin-4-yl)amino}pyrimidin-2-yl)-1H-indazole-1-carboxylate



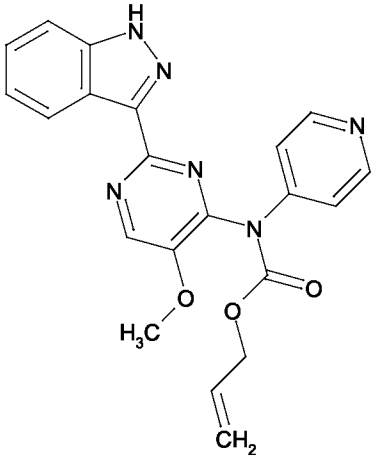
96,3 mg of tert-butyl 3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazole-1-carboxylate (1-8-1, 0,23 mmol, 1 eq.) was suspended in 7 ml of pyridine. 27.7 mg of prop-2-en-1-yl carbonochloridate (0,23 mmol, 1 eq.) were added and stirred for two hours at room temperature. Twice 27.7 mg of prop-2-en-1-yl carbonochloridate (0,23 mmol, 1 eq.) were added again and stirred the first time for 24 hours and the second time for three days at room temperature. The reaction mixture was concentrated in vacuo. To the residue was added water and acidified with 1M aq. hydrogen chloride solution. This aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over a silicone filter and concentrated under vacuo. Purification by flash chromatography (ethyl acetate/ methanol 0-50%) provided 50,8 mg (0,09 mmol, 39,97%) of the analytically pure target compound.

^{1}H-NMR (300MHz, CHLOROFORM-d): δ [ppm]= 1.74 (s, 9H), 4.01 (s, 3H), 4.71 (d, 2H), 5.14 - 5.29 (m, 2H), 5.76 - 5.95 (m, 1H), 7.20 - 7.25 (m, 2H), 7.28 - 7.36 (m, 1H), 7.50 - 7.59 (m, 1H), 8.25 (t, 2H), 8.50 - 8.61 (m, 2H), 8.71 (s, 1H)

LC-MS:
retention time: 1.21 min
MS ES$^+$: 503,3 $[M+H]^+$

Intermediate 1-10-1

Preparation of prop-2-en-1-yl [2-(1H-indazol-3-yl)-5-methoxypyrimidin-4-yl]pyridin-4-ylcarbamate



1.22 g of tert-butyl 3-(5-methoxy-4-{[(prop-2-en-1-yloxy)carbonyl](pyridin-4-yl)amino}pyrimidin-2-yl)-1H-indazole-1-carboxylate (1-9-1, 2,43 mmol, 1 eq.) was suspended in 1,4-dioxane. 2,43 ml of hydrogen acid 4M in 1,4-dioxane (9,711 mmol, 4 eq.) were added dropwise. The reaction mixture was stirred for 24 hours at room temperature. 2,43 ml of hydrogen acid 4M in 1,4-dioxane (9,711 mmol, 4 eq.) were added dropwise again and stirred for further two hours. The reaction mixture was concentrated under vacuo. The residue was extracted with saturated aq. sodium hydrogen carbonate – solution and ethyl acetate. The aqueous layer was reextracted twice by ethyl acetate. The combined organic layers were dried over a silicone filter and concentrated under vacuo. Purification by flash chromatography (ethyl acetate/ methanol 0-25%) provided 877 mg (1,96 mmol, 80.8%) of the analytically pure target compound.

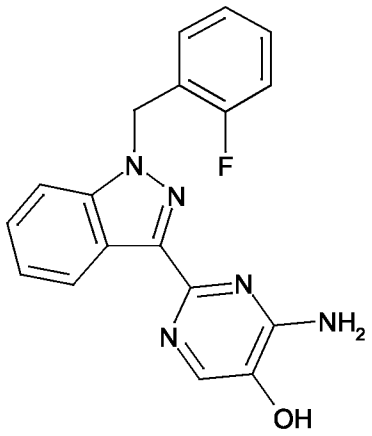
^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 4.00 (s, 3H), 4.71 - 4.81 (m, 2H), 5.12 - 5.23 (m, 2H), 5.79 - 5.93 (m, 1H), 7.13 - 7.23 (m, 1H), 7.33 - 7.41 (m, 1H), 7.54 - 7.62 (m, 1H), 7.82 - 7.91 (m, 2H), 8.25 - 8.31 (m, 1H), 8.71 - 8.79 (m, 2H), 9.09 (s, 1H)

LC-MS:
retention time: 0.84 min
MS ES$^+$: 403,3 $[M+H]^+$

Intermediate 1-11-1

Preparation of 4-amino-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]pyrimidin-5-ol

145



558 mg of 2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-amine (1-4-2, 1,60mmol, 1 eq.) was suspended in 10 ml of 1-methyl-2-pyrrolidon. 623 mg of sodium sulfidosodium (7,99 mmol, 5 eq.) were added and stirred for an hour at 140℃. The reaction mixture was extracted with half-saturated aq. ammonium chloride – solution and ethyl acetate. The aqueous layer was reextracted twice by ethyl acetate. The aqueous layer gave a precipitate, which was filtered off and first purified by flash chromatography (hexane/ dichloro methane/ methanol), followed by a HPLC purification. This provided 23,4 mg (0,07 mmol, 4,37%) of the analytically pure target compound.

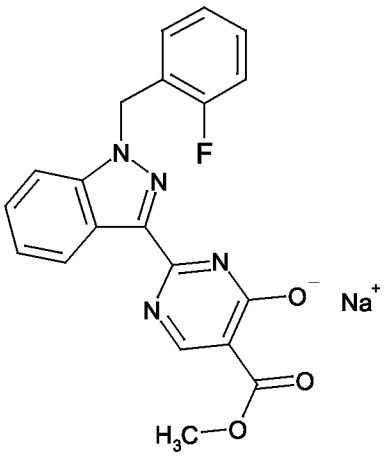
^{1}H-NMR (400MHz, DMSO-d6): δ [ppm]= 5.68 - 5.74 (s, 2H), 6.61 - 6.67 (d, 1H), 7.01 - 7.13 (m, 2H), 7.14 - 7.23 (m, 2H), 7.25 - 7.33 (m, 2H), 7.34 - 7.42 (t, 1H), 7.64 - 7.71 (d, 1H), 7.74 - 7.80 (s, 1H), 8.51 - 8.56 (d, 1H), 9.74 - 9.87 (s, 1H).

LC-MS:
retention time: 0.92 min
MS ES$^+$: 336.1 $[M+H]^+$

Intermediate 1-12-1

Preparation of sodium 2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-(methoxycarbonyl)pyrimidin-4-olate

146



2,5 g of 1-(2-fluorobenzyl)-1H-indazole-3-carboximidamide hydrochloride (1:1) (1-2-3 x HCl, 8,20 mmol, 1 eq.), 1,43 g of dimethyl (methoxymethylidene)propanedioate (8,20 mmol, 1 eq.) and 50 ml of methanol and 443 mg of sodium methanolate were stirred under nitrogen atmosphere at 60℃ bath temperature for 24 hours. The clear yellowish solution turned into a suspension which was filtered off. The crystals were washed with cold methanol to yield 1,64 g (4,1 mmol, 50%) of the analytically pure target compound.

^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 3.67 (s, 3H), 5.76 (s, 2H), 7.05 - 7.36 (m, 5H), 7.42 (ddd, 1H), 7.71 (d, 1H), 8.44 - 8.55 (m, 2H).

LC-MS:

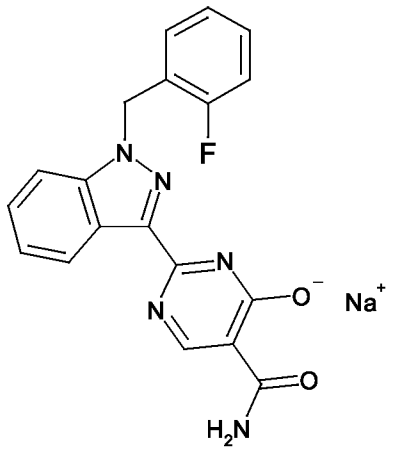
retention time: 1.16 min

MS ES$^+$: 379.1 $[M+H]^+$

Intermediate 1-13-1

Preparation of sodium 5-carbamoyl-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-olate

147



100 mg of sodium 2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-(methoxycarbonyl)pyrimidin-4-olate (1-12-1, 0,25 mmol, 1 eq.) were dissolved in 26,8 ml of 7N ammonia in methanol (187 mmol, 750 eq.) and stirred under a nitrogen atmosphere at 60℃ bath temperature for 24 hours, then at 65℃ ba th temperature for six hours and further 24 hours at 70℃ bath temperature. The reaction mixture was concentrated in vacuo to yield 96 mg (0,22 mmol, 89,8%) of the analytically pure target compound.

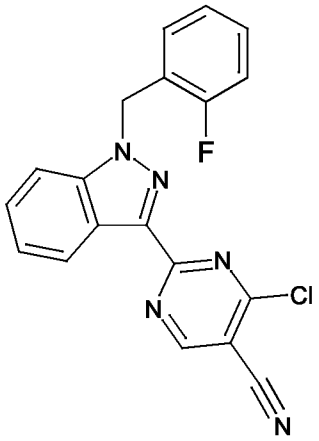
^{1}H-NMR (400MHz, DMSO-d6): δ [ppm]= 5.82 (s, 2H), 7.07 - 7.26 (m, 3H), 7.27 - 7.42 (m, 3H), 7.47 (t, 1H), 7.77 (d, 1H), 8.47 (d, 1H), 8.58 (br. s., 1H), 9.07 - 9.32 (m, 1H).

LC-MS:
retention time: 1.10 min

MS ES$^+$: 364.12 $[M+H]^+$

Intermediate 1-14-1

Preparation of 4-chloro-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]pyrimidine-5-carbonitrile



88 mg of sodium 5-carbamoyl-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-olate (1-13-1, 0,228 mmol, 1 eq.) were suspended in 0,915 ml of phosphoric trichloride (9,82 mmol, 43 eq.) and 69 µl of N,N-diethylaniline (0,457 mmol, 2 eq.). The suspension was stirred at 90℃ bath temperature for 24 hours and then dropped to an ice cooled saturated aqueous sodium hydrogen carbonate solution. The resulting suspension was filtered off and dried in vacuo to yield 82 mg (0,21 mmol, 93.77%) of the analytically pure target compound.

^{1}H-NMR (400MHz, DMSO-d6): δ [ppm]= 5.87 - 5.91 (m, 2H), 7.08 - 7.26 (m, 3H), 7.30 - 7.44 (m, 2H), 7.53 (td, 1H), 7.88 (d, 1H), 8.45 (d, 1H), 9.39 (s, 1H).

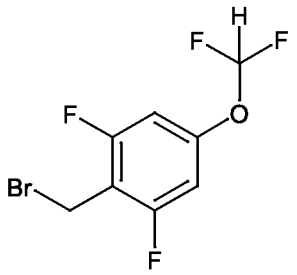
LC-MS: Method B
retention time: 1.38 min

MS ES$^+$: 364.0 $[M+H]^+$

Intermediate 1-15-1

Preparation of 2-(bromomethyl)-5-(difluoromethoxy)-1,3-difluorobenzene

149



Step 1: [4-(difluoromethoxy)-2,6-difluorophenyl]methanol

1 g of 3,5-difluoro-4-(hydroxymethyl)phenol (6,245 mmol, 1 eq.) were dissolved in 16 ml of DMF 1,047 g of sodium chloro(difluoro)acetate (6,87 mmol, 1,1 eq.), 2,442 g of cesium carbonate (7,494 mmol, 1,2 eq.) and 400 µl of water were added. The mixture was stirred at 100 ℃ bath temperat ure for 2 hours under nitrogen atmosphere. Then the reaction mixture was partitioned between water and ethyl acetate. The separated aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over a silicone filter and concentrated in vacuo. The residue was purified by flash chromatography to yield 763,3 mg (3,63 mmol, 58,2%) of the analytically pure target compound.

^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 4.42 (d, 2H), 5.21 (t, 1H), 6.99 (d, 2H), 7.09 - 7.50 (t, 1H).

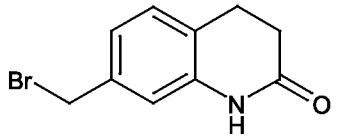
Step 2: 2-(bromomethyl)-5-(difluoromethoxy)-1,3-difluorobenzene

0,76 g of [4-(difluoromethoxy)-2,6-difluorophenyl]methanol (3,62 mmol, 1 eq.) were dissolved in 1,72 ml of 33% hydrogen bromide in glacial acetic acid (9,97 mmol, 2,75 eq.) and stirred at room temperature for 2 hours. 25 ml of diethyl ether were added and the mixture was stirred at room temperature for 15 min. The reaction mixture was added dropwise to 80 ml of aqueous saturated sodium hydrogen carbonate solution and stirred again at room temperature for 15 min. The separated aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over a silicone filter and concentrated in vacuo to yield 991 mg (3,56 mmol, 98,4%) of the analytically pure target compound.

^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 4.60 (s, 2H), 7.08 - 7.14 (d, 2H), 7.08 - 7.59 (t, 1H).

Intermediate 1-16-1

Preparation of 7-bromomethyl-3,4-dihydro-1H-quinolin-2-one

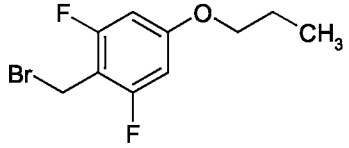


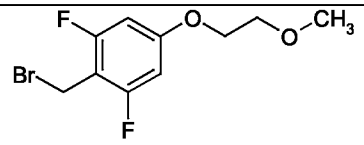
500 mg of 7-(hydroxymethyl)-3,4-dihydroquinolin-2(1*H*)-one (2,82 mmol, 1 eq.) were dissolved in 1,77 ml of 33% hydrogen bromide in glacial acetic acid (31,0 mmol, 11 eq.) under nitrogen atmosphere and stirred at room temperature for 30 minutes. The reaction mixture was partitioned between aq. saturated sodium hydrogen carbonate solution and dichloromethane/ isopropanol 4+1. The aqueous layer was extracted three times with dichloromethane/ isopropanol 4+1. The combined organic layers were washed with brine, dried over a silicone filter and concentrated in vacuo. The crude product was purified by flash chromatography to yield 175 mg (0,66 mmol, 23,3%) of the analytically pure target compound.

^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 2.40 (dd, 2H), 2.82 (t, 2H), 4.60 (s, 2H), 6.87 (d, 1H), 6.94 (dd, 1H), 7.10 (d, 1H).

LC-MS:
retention time: 0,91 min
MS ES$^+$: 240.2 $[M+H]^+$

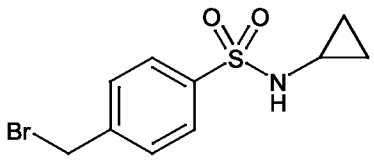
The following compounds were prepared according to the same procedure from the indicated starting materials (SM = starting material):

1-16-2 SM = 1-18-1		2-(bromomethyl)-1,3-difluoro-5-propoxybenzene	

1-16-3 SM = 1-18-2		2-(bromomethyl)-1,3-difluoro-5-(2-methoxyeth-oxy)benzene	

Intermediate 1-17-1

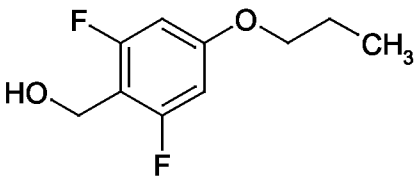
Preparation of 4-(bromomethyl)-N-cyclopropylbenzenesulfonamide



5 g of 4-(bromomethyl)benzenesulfonyl chloride (18.6 mmol, 1 eq.) were dissolved under argon atmosphere in 82,5 ml of dichloromethane and cooled down at -10℃ internal temperature. A solution of 1.29 ml cyclopropanamine (18.6 mmol, 1 eq.) and 2.59 ml of triethylamine (18.6 mmol, 1 eq.) in 82,5 ml of dichloromethane were added dropwise at – 10℃ internal temperature and stirred at this temperature for one hour. The reaction mixture was washed once with 1 M aqueous hydrogene solution and twice with distilled water. The organic layer was dried over sodium sulfate and concentrated in vacuo. The crude product contained a mixture of bromomethyl- and chloromethyl- substituents.

Intermediate 1-18-1

Preparation of (2,6-difluoro-4-propoxyphenyl)methanol

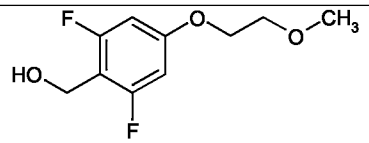


200 mg of 3,5-difluoro-4-(hydroxymethyl)phenol (1.25 mmol, 1.0 eq.) and 184 mg 1-bromopropane (1.50 mmol, 1.2 eq.) were dissolved in 17 ml N,N-

dimethylformamide. 863 mg potassium (6.25 mmol, 5.0 eq.) were added and the reaction mixture was stirred at 0 °C over night. Th e reaction mixture was separated between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate twice. The combined organic layers were dried over a silicone filter and concentrated in vacuo. to yield 283 mg (1.19 mmol, 95 %) of the crude product which was used without further purification.

^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 0.92 (t, 3H), 1.54 - 1.78 (m, 2H), 3.90 (t, 2H), 4.36 (s, 2H), 5.06 (br. s., 1H), 6.53 - 6.79 (m, 2H).

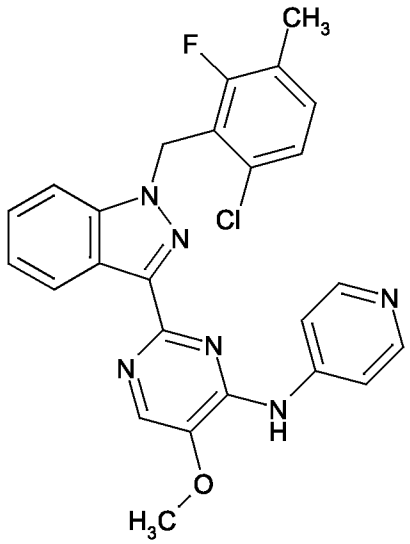
The following intermediate was prepared according to the same procedure from commercial (2-Bromethyl)-methylether and 3,5-difluoro-4-(hydroxymethyl)phenol:

1-18-2		[2,6-difluoro-4-(2-methoxyeth-oxy)phenyl]methanol	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 3.25 (s, 3H), 3.50 - 3.65 (m, 2H), 3.99 - 4.14 (m, 2H), 4.37 (br. s., 2H), 5.07 (br. s., 1H), 6.52 - 6.75 (m, 2H)

EXAMPLE COMPOUNDS

Example 2-1-1

Preparation of 2-[1-(6-chloro-2-fluoro-3-methylbenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine



80 mg of 2-(1H-indazol-3-yl)-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine (1-6-1, 0.251 mmol, 1. eq.) were suspended in dry tetrahydrofuran under a nitrogen atmosphere. 30,2 mg of sodium hydride (60% purity) were added and stirred at room temperature for 10 minutes. Then 59,7 mg of 2-(bromomethyl)-1-chloro-3-fluoro-4-methylbenzene were added. The reaction mixture was stirred for 18 hours at room temperature. Then the mixture was partitioned between half saturated aq. ammonium chloride solution and dichloromethane/ isopropanol 4:1. The phases were separated and the aqueous layer was extracted twice with dichloromethane/isopropanol 4:1. The combined organic layers were washed with brine, dried over a silicone filter and concentrated in vacuo. Preparative HPLC purification provided 29 mg (0,06 mmol, 24,1%) of the analytically pure target compound.

1H-NMR (300 MHz, DMSO-d6): δ [ppm]= 2.19 (d, 3H), 4.00 (s, 3H), 5.80 (d, 2H), 7.17 - 7.37 (m, 3H), 7.42 - 7.53 (m, 1H), 7.89 (d, 1H), 8.13 - 8.22 (m, 2H), 8.29 - 8.40 (m, 3H), 8.46 (d, 1H), 9.39 (s, 1H).

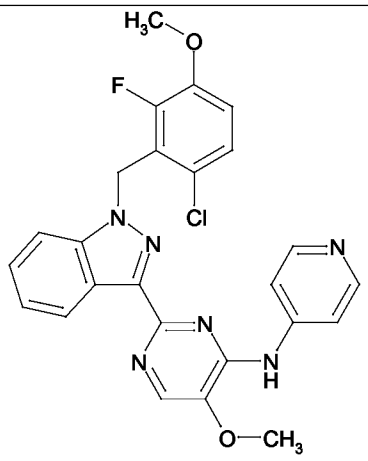
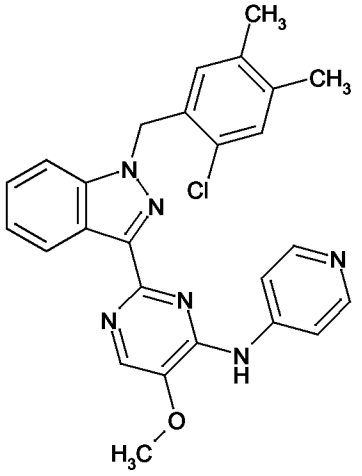
LC-MS:

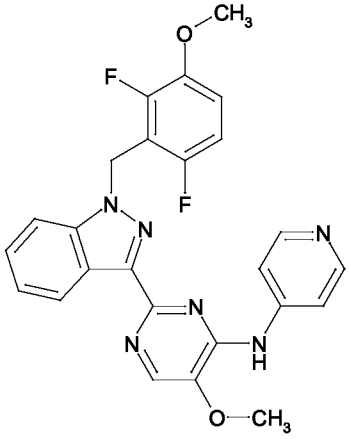
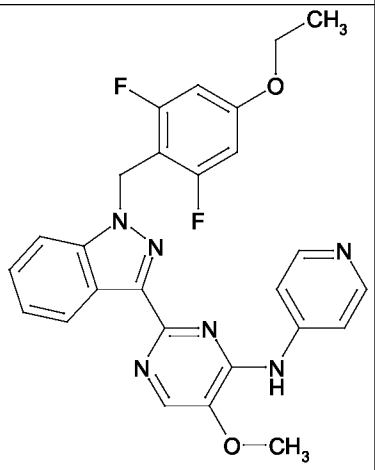
retention time: 1.01 min

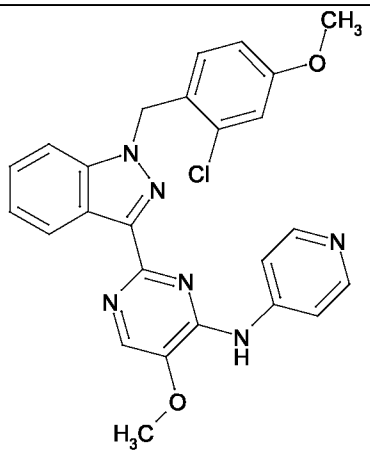
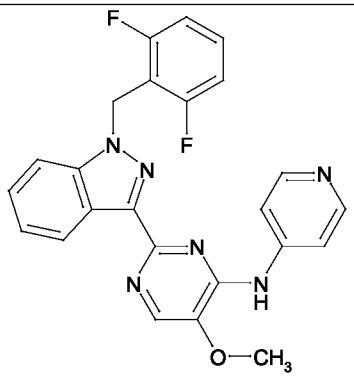
MS ES+: 475.4 $[M+H]^+$

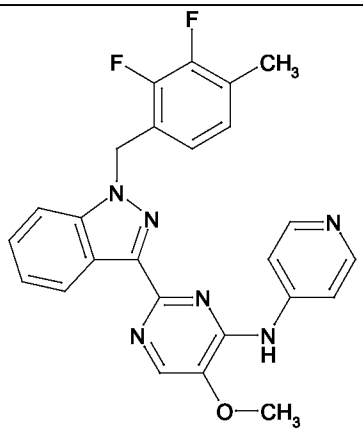
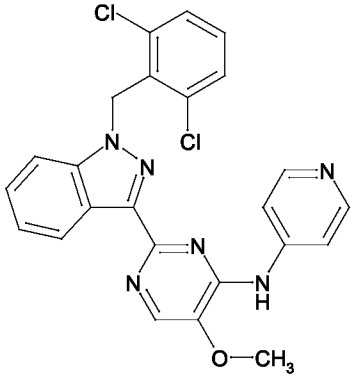
Method B

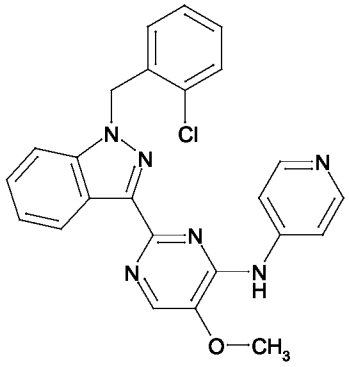
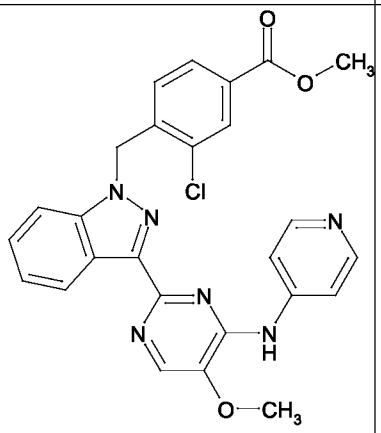
The following compounds were prepared according to the same procedure from the indicated starting materials (SM = starting material):

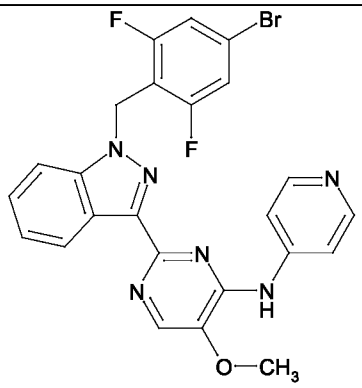
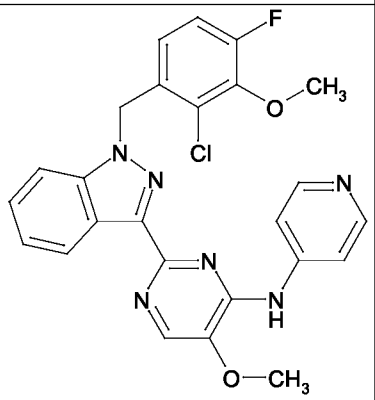
2-2-1 SM = 1-6-1		2-[1-(6-chloro-2-fluoro-3-methoxybenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 3.82 (s, 3H), 4.00 (s, 3H), 5.77 (d, 2H), 7.17 - 7.36 (m, 3H), 7.47 (ddd, 1H), 7.89 (d, 1H), 8.13 - 8.20 (m, 2H), 8.29 - 8.40 (m, 3H), 8.46 (d, 1H), 9.39 (s, 1H). LC-MS: retention time: 0.99 min MS ES$^+$: 491.3 $[M+H]^+$ Method B
2-3-1 SM = 1-6-1		2-[1-(2-chloro-4,5-dimethylbenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 2.09 (s, 3H), 2.15 (s, 3H), 3.96 - 4.05 (m, 3H), 5.71 (s, 2H), 7.09 (s, 1H), 7.19 - 7.31 (m, 2H), 7.43 (s, 1H), 7.78 (d, 1H), 8.11 - 8.17 (m, 2H), 8.30 - 8.40 (m, 3H), 8.46 (d, 1H), 9.44 (s, 1H). LC-MS: retention time: 1.04 min

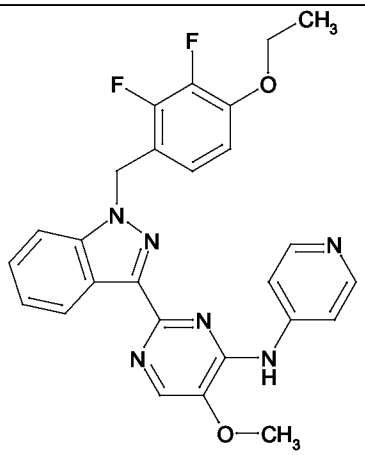
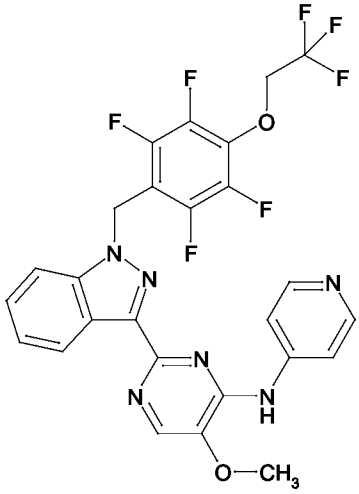
			MS ES+: 471.4 [M+H]+ Method B
2-4-1 SM = 1-6-1		2-[1-(2,6-difluoro-3-methoxybenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 3.78 (s, 3H), 4.00 (s, 3H), 5.74 (s, 2H), 7.02 - 7.30 (m, 3H), 7.42 - 7.52 (m, 1H), 7.84 (d, 1H), 8.10 - 8.19 (m, 2H), 8.28 - 8.48 (m, 4H), 9.38 (s, 1H). LC-MS: retention time: 0.95 min MS ES+: 475.0 [M+H]+ Method B
2-5-1 SM = 1-6-1		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.25 (t, 3H), 3.93 - 4.09 (m, 5H), 5.64 (s, 2H), 6.68 - 6.82 (m, 2H), 7.23 (t, 1H), 7.40 - 7.51 (m, 1H), 7.81 (d, 1H), 8.11 - 8.20 (m, 2H), 8.29 - 8.48 (m, 4H), 9.37 (s, 1H). LC-MS: retention time: 1.05 min MS ES+: 489.0 [M+H]+ Method B

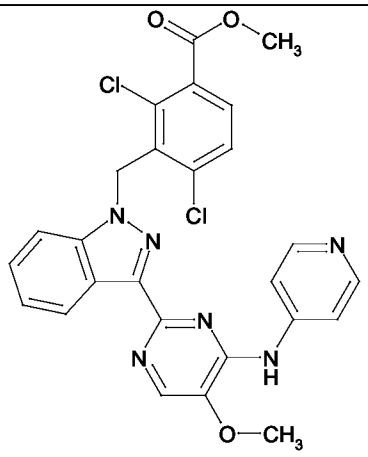
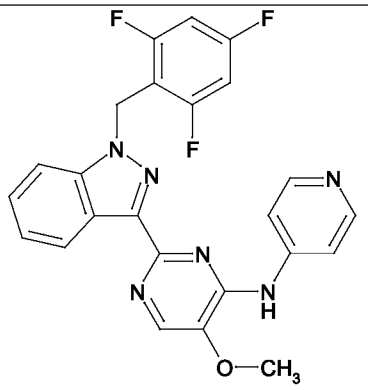
2-6-1 SM = 1-6-1		2-[1-(2-chloro-4-methoxybenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 3.72 (s, 3H), 4.01 (s, 3H), 5.72 (s, 2H), 6.90 (dd, 1H), 7.07 (d, 1H), 7.19 - 7.28 (m, 2H), 7.43 (t, 1H), 7.79 (d, 1H), 8.08 - 8.16 (m, 2H), 8.30 - 8.41 (m, 3H), 8.45 (d, 1H), 9.40 (s, 1H). LC-MS: retention time: 0.99 min MS ES$^+$: 473.4 $[M+H]^+$ Method B
2-7-1 SM = 1-6-1		2-[1-(2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 4.00 (s, 3H), 5.75 (s, 2H), 7.15 (t, 1H), 7.24 (t, 1H), 7.38 - 7.52 (m, 2H), 7.81 - 7.89 (m, 1H), 7.85 (d, 1H), 8.09 - 8.18 (m, 2H), 8.29 - 8.39 (m, 3H), 8.41 - 8.47 (m, 1H), 9.38 (s, 1H). LC-MS: retention time: 0.97 min MS ES$^+$: 445.0 $[M+H]^+$ Method B

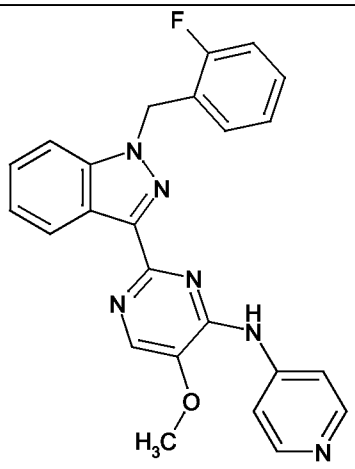
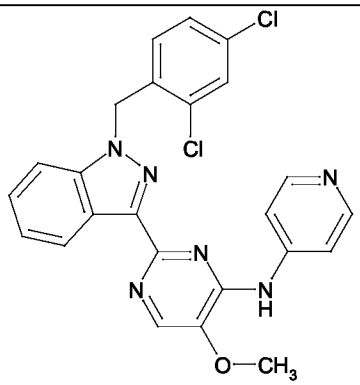
2-8-1 SM = 1-6-1		2-[1-(2,3-difluoro-4-methylbenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 2.21 (d, 3H), 4.01 (s, 3H), 5.77 (s, 2H), 7.00 - 7.09 (m, 2H), 7.24 (t, 1H), 7.44 (t, 1H), 7.81 (d, 1H), 8.08 - 8.17 (m, 2H), 8.30 - 8.50 (m, 4H), 9.39 (s, 1H). LC-MS: retention time: 1.01 min MS ES$^+$: 459.0 $[M+H]^+$ Method B
2-9-1 SM = 1-6-1		2-[1-(2,6-dichlorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 3.99 (s, 3H), 5.87 (s, 2H), 7.25 (t, 1H), 7.39 - 7.53 (m, 2H), 7.55 - 7.62 (m, 2H), 7.90 (d, 1H), 8.13 (d, 2H), 8.28 - 8.40 (m, 3H), 8.48 (d, 1H), 9.32 (s, 1H). LC-MS: retention time: 1.13min MS ES$^+$: 477.22 $[M+H]^+$

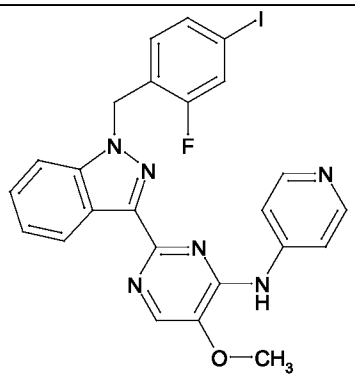
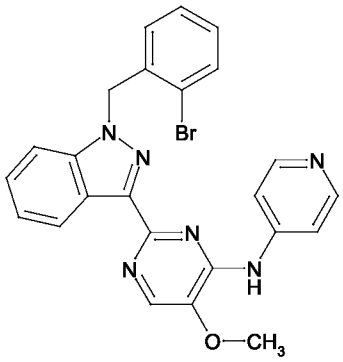
2-10-1 SM = 1-6-1		2-[1-(2-chlorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 4.01 (s, 3H), 5.81 (s, 2H), 7.15 (dd, 1H), 7.20 - 7.38 (m, 3H), 7.39 - 7.54 (m, 2H), 7.78 (d, 1H), 8.05 - 8.15 (m, 2H), 8.29 - 8.40 (m, 3H), 8.47 (d, 1H), 9.38 (s, 1H). LC-MS: retention time: 1.00 min MS ES$^+$: 443.0 $[M+H]^+$ Method B
2-11-1 SM = 1-6-1		methyl 3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)benzoate	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 3.81 (s, 3H), 4.01 (s, 3H), 5.89 (s, 2H), 7.18 - 7.31 (m, 2H), 7.45 (t, 1H), 7.79 (d, 1H), 7.85 (dd, 1H), 7.98 (d, 1H), 8.06 - 8.13 (m, 2H), 8.30 - 8.39 (m, 3H), 8.48 (d, 1H), 9.40 (s, 1H). LC-MS: retention time: 0.96 min MS ES$^+$: 501.1 $[M+H]^+$ Method B

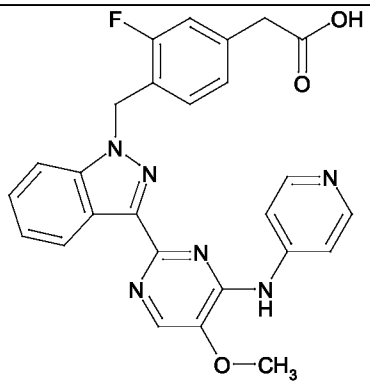
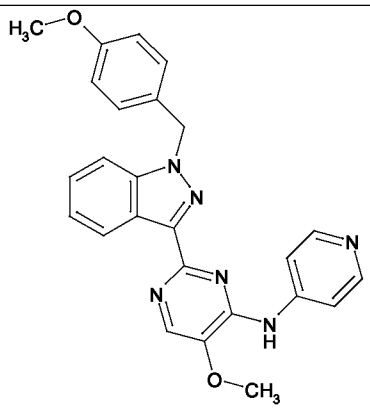
2-12-1 SM = 1-6-1		2-[1-(4-bromo-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 4.00 (s, 3H), 5.72 (s, 2H), 7.25 (t, 1H), 7.44 - 7.52 (m, 1H), 7.54 - 7.61 (m, 2H), 7.85 (d, 1H), 8.12 - 8.18 (m, 2H), 8.32 (s, 1H), 8.35 - 8.40 (m, 2H), 8.44 (d, 1H), 9.40 (s, 1H). LC-MS: retention time: 0.99 min MS ES$^+$: 525.3 $[M+H]^+$ Method B
2-13-1 SM = 1-6-1		2-[1-(2-chloro-4-fluoro-3-methoxybenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 3.85 (d, 3H), 4.01 (s, 3H), 5.79 (s, 2H), 6.91 (dd, 1H), 7.21 - 7.32 (m, 2H), 7.44 (td, 1H), 7.80 (d, 1H), 8.08 - 8.13 (m, 2H), 8.33 (s, 1H), 8.35 - 8.39 (m, 2H), 8.47 (d, 1H), 9.42 (s, 1H). LC-MS: retention time: 0.98 min MS ES$^+$: 491.3 $[M+H]^+$ Method B

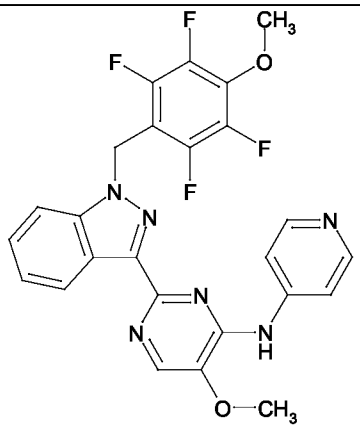
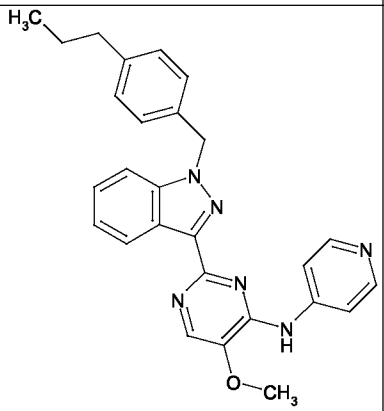
2-14-1 SM = 1-6-1		2-[1-(4-ethoxy-2,3-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.28 (t, 3H), 3.94 - 4.13 (m, 5H), 5.73 (s, 2H), 6.92 - 7.03 (m, 1H), 7.08 - 7.18 (m, 1H), 7.23 (t, 1H), 7.44 (t, 1H), 7.83 (d, 1H), 8.10 - 8.16 (m, 2H), 8.33 (s, 1H), 8.36 - 8.40 (m, 2H), 8.43 (d, 1H), 9.41 (s, 1H). LC-MS: retention time: 1.03 min MS ES$^+$: 489.0 $[M+H]^+$ Method B
2-15-1 SM = 1-6-1		5-methoxy-*N*-(pyridin-4-yl)-2-{1-[2,3,5,6-tetrafluoro-4-(2,2,2-trifluoroethoxy)benzyl]-1*H*-indazol-3-yl}pyrimidin-4-amine	^{1}H-NMR (500MHz, DMSO-d_6): δ [ppm]= 4.04 - 4.07 (s, 3H), 4.99 (q, 2H), 5.90 (s, 2H), 7.31 (t, 1H), 7.55 (t, 1H), 7.93 (d, 1H), 8.23 (d, 2H), 8.38 (s, 1H), 8.42 (d, 2H), 8.49 (d, 1H), 9.46 (s, 1H). LC-MS: retention time: 1.21 min MS ES$^+$: 579.1 $[M+H]^+$ Method B

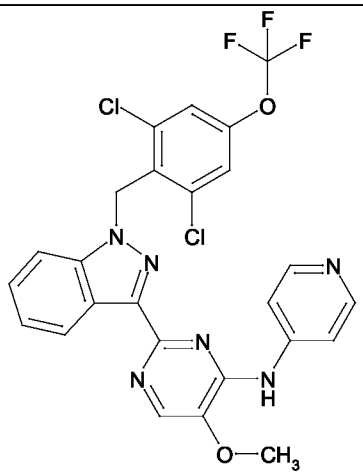
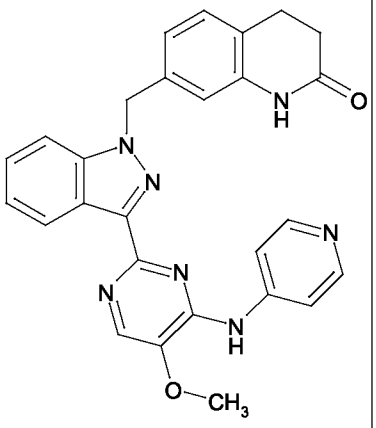
2-16-1 SM = 1-6-1		methyl 2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-yla-mino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)benzoate	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 3.85 (s, 3H), 4.02 (s, 3H), 5.96 (s, 2H), 7.29 (t, 1H), 7.48 - 7.55 (m, 1H), 7.73 - 7.78 (m, 1H), 7.80 - 7.84 (m, 1H), 7.94 (d, 1H), 8.11 - 8.16 (m, 2H), 8.34 (s, 1H), 8.38 (d, 2H), 8.52 (d, 1H), 9.34 (s, 1H). LC-MS: retention time: 1.08 min MS ES$^+$: 535.22 [M+H]$^+$
2-17-1 SM = 1-6-1		5-methoxy-*N*-(pyridin-4-yl)-2-[1-(2,4,6-trifluorobenzyl)-1*H*-indazol-3-yl]pyrimidin-4-amine	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 4.00 (s, 3H), 5.68 - 5.76 (m, 2H), 7.20 - 7.34 (m, 3H), 7.43 - 7.51 (m, 1H), 7.84 (d, 1H), 8.12 - 8.18 (m, 2H), 8.32 (s, 1H), 8.37 (d, 2H), 8.44 (d, 1H), 9.35 - 9.40 (m, 1H). LC-MS: retention time: 1.03 min MS ES$^+$: 463.31 [M+H]$^+$

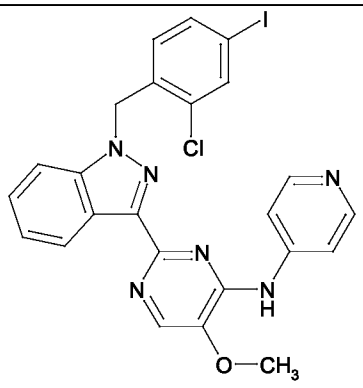
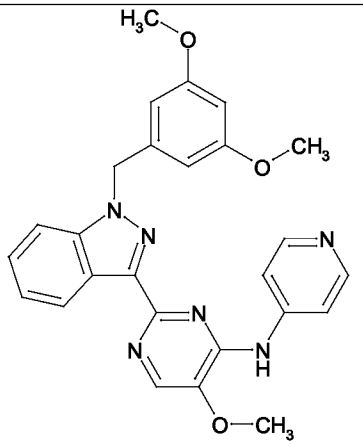
2-18-1 SM = 1-6-1		2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine	1H-NMR (300MHz, DMSO-d6): δ [ppm]= 4.01 (s, 3H), 5.77 (s, 2H), 7.10 - 7.49 (m, 6H), 7.75 - 7.84 (m, 1H), 8.07 - 8.17 (m, 2H), 8.33 (s, 1H), 8.35 - 8.40 (m, 2H), 8.40 - 8.48 (m, 1H), 9.35 - 9.45 (m, 1H). LC-MS: retention time: 1.01 min MS ES+: 427.19 [M+H]+
2-19-1 SM = 1-6-1		2-[1-(2,4-dichlorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 4.01 (s, 3H), 5.80 (s, 2H), 7.15 - 7.29 (m, 2H), 7.38 - 7.49 (m, 2H), 7.68 (d, 1H), 7.79 (d, 1H), 8.05 - 8.13 (m, 2H), 8.31 - 8.40 (m, 3H), 8.47 (d, 1H), 9.40 (s, 1H). LC-MS: retention time: 1.07 min MS ES+: 477.35 [M+H]+

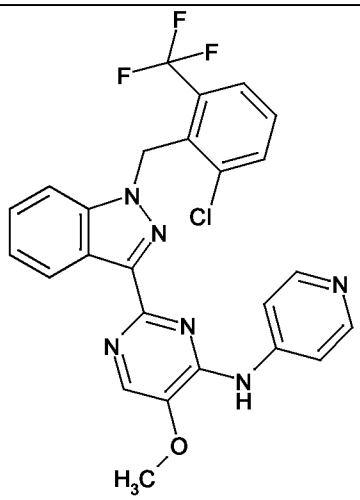
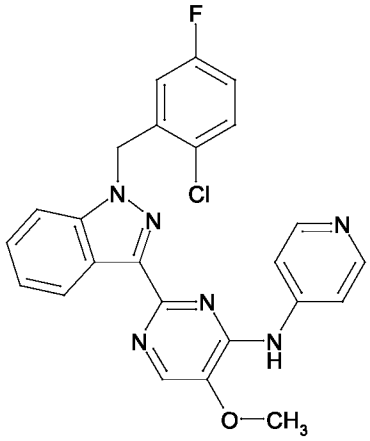
2-20-1 SM = 1-6-1		2-[1-(2-fluoro-4-iodobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 4.01 (s, 3H), 5.73 (s, 2H), 7.07 (t, 1H), 7.24 (t, 1H), 7.44 (ddd, 1H), 7.55 (dd, 1H), 7.67 (dd, 1H), 7.79 (d, 1H), 8.08 - 8.13 (m, 2H), 8.33 (s, 1H), 8.36 - 8.40 (m, 2H), 8.44 (d, 1H), 9.42 (s, 1H). LC-MS: retention time: 1.00 min MS ES$^+$: 553.3 $[M+H]^+$ Method B
2-21-1 SM = 1-6-1		2-[1-(2-bromobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 4.01 (s, 3H), 5.79 (s, 2H), 7.08 (dd, 1H), 7.22 - 7.28 (m, 2H), 7.30 - 7.36 (m, 1H), 7.44 (ddd, 1H), 7.67 (dd, 1H), 7.78 (d, 1H), 8.08 - 8.13 (m, 2H), 8.32 - 8.39 (m, 3H), 8.48 (d, 1H), 9.38 (s, 1H). LC-MS: retention time: 1.02 min MS ES$^+$: 486.9 $[M+H]^+$ Method B

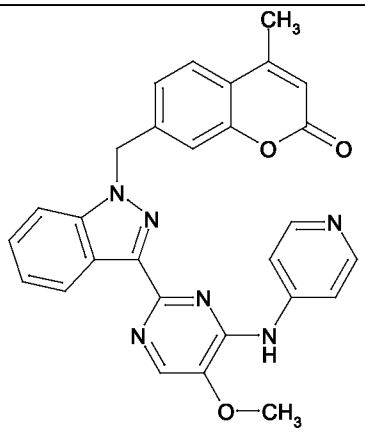
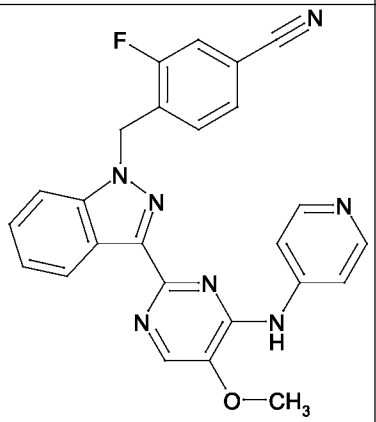
2-22-1 SM = 1-6-1		[3-fluoro-4-({3-[5-methoxy-4-(pyridin-4-yla-mino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)phenyl] acetic acid	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 3.54 (s, 2H), 4.01 (s, 3H), 5.74 (s, 2H), 7.01 - 7.07 (m, 1H), 7.12 (d, 1H), 7.19 - 7.29 (m, 2H), 7.38 - 7.47 (m, 1H), 7.79 (d, 1H), 8.08 - 8.16 (m, 2H), 8.33 (s, 1H), 8.36 - 8.48 (m, 3H), 9.39 (s, 1H). LC-MS: retention time: 0.86 min MS ES$^+$: 485.1 $[M+H]^+$ Method B
2-23-1 SM = 1-6-1		5-methoxy-2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 3.66 (s, 3H), 4.02 (s, 3H), 5.65 (s, 2H), 6.86 (d, 2H), 7.15 - 7.25 (m, 1H), 7.27 - 7.44 (m, 3H), 7.78 (d, 1H), 8.08 - 8.17 (m, 2H), 8.31 - 8.46 (m, 4H), 9.42 (s, 1H). LC-MS: retention time: 0.95 min MS ES$^+$: 439.31 $[M+H]^+$ Method B

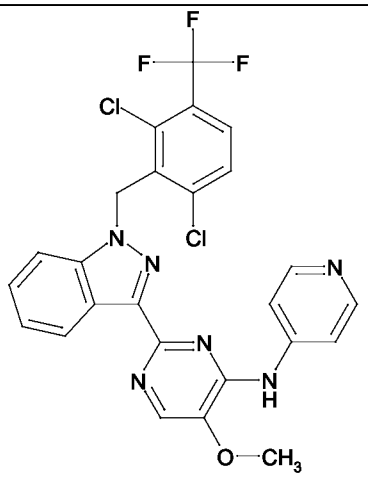
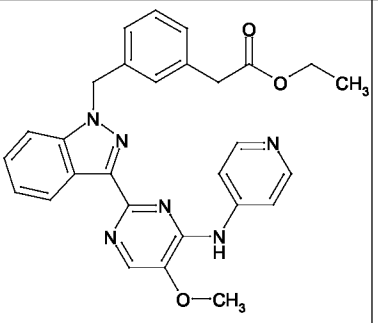
2-24-1 SM = 1-6-1		5-methoxy-*N*-(pyridin-4-yl)-2-[1-(2,3,5,6-tetrafluoro-4-methoxybenzyl)-1*H*-indazol-3-yl]pyrimidin-4-amine	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 4.00 (s, 3H), 4.01 (s, 3H), 5.81 (s, 2H), 7.26 (t, 1H), 7.49 (t, 1H), 7.87 (d, 1H), 8.14 - 8.22 (m, 2H), 8.31 - 8.40 (m, 3H), 8.45 (d, 1H), 9.40 - 9.45 (m, 1H). LC-MS: retention time: 1.09 min MS ES$^+$: 511.17 $[M+H]^+$
2-25-1 SM = 1-6-1		5-methoxy-2-[1-(4-propylbenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 0.80 (t, 3H), 1.20 (br. s., 2H), 1.40 - 1.57 (m, 2H), 4.02 (s, 3H), 5.68 (s, 2H), 7.12 (d, 2H), 7.17 - 7.30 (m, 2H), 7.40 (t, 1H), 7.78 (d, 1H), 8.12 (d, 2H), 8.21 (s, 1H), 8.32 - 8.46 (m, 4H), 9.42 (s, 1H). LC-MS: retention time: 1.15 min MS ES$^+$: 451.3 $[M+H]^+$

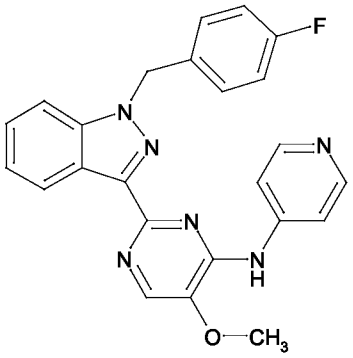
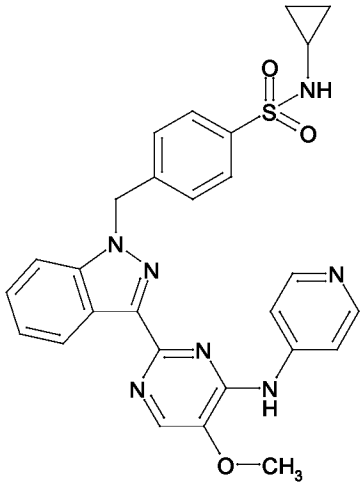
2-26-1 SM = 1-6-1		2-{1-[2,6-dichloro-4-(trifluoromethoxy)benzyl]-1*H*-indazol-3-yl}-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 4.02 (s, 3H), 5.90 (s, 2H), 7.29 (t, 1H), 7.52 (ddd, 1H), 7.83 (d, 2H), 7.94 (d, 1H), 8.12 - 8.18 (m, 2H), 8.35 (s, 1H), 8.37 - 8.40 (m, 2H), 8.51 (d, 1H), 9.35 (s, 1H). LC-MS: retention time: 1.15 min MS ES$^+$: 561.0 $[M+H]^+$ Method B
2-27-1 SM = 1-6-1		7-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)-3,4-dihydroquinolin-2(1*H*)-one	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 2.35 (t, 2H), 2.77 (t, 2H), 4.02 (s, 3H), 5.65 (s, 2H), 6.77 (s, 1H), 6.88 (d, 1H), 7.09 (d, 1H), 7.22 (t, 1H), 7.40 (t, 1H), 7.71 (d, 1H), 8.11 (d, 2H), 8.28 - 8.51 (m, 4H), 9.42 (s, 1H), 10.01 (s, 1H). LC-MS: retention time: 1.04 min MS ES$^+$: 478.1 $[M+H]^+$ Method B

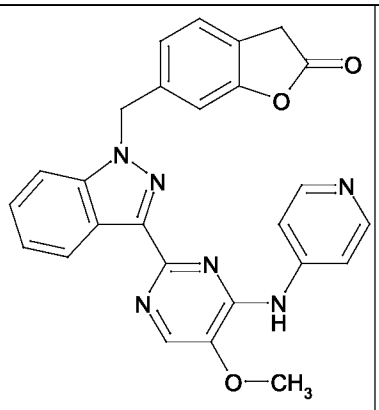
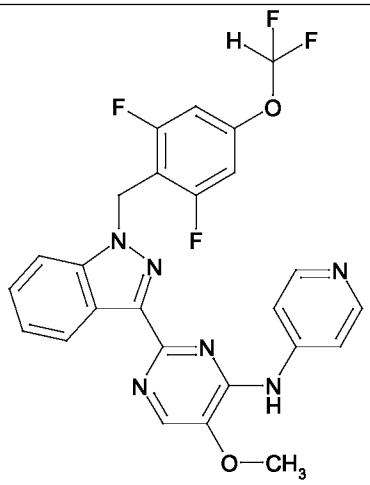
2-28-1 SM = 1-6-1		2-[1-(2-chloro-4-iodobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 4.01 (s, 3H), 5.76 (s, 2H), 6.93 (d, 1H), 7.25 (t, 1H), 7.44 (ddd, 1H), 7.68 (dd, 1H), 7.78 (d, 1H), 7.89 (d, 1H), 8.07 - 8.12 (m, 2H), 8.31 - 8.40 (m, 3H), 8.47 (d, 1H), 9.39 (s, 1H). LC-MS: retention time: 1.08 min MS ES$^+$: 568.9 $[M+H]^+$ Method B
2-29-1 SM = 1-6-1		2-[1-(3,5-dimethoxybenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 3.64 (s, 6H), 4.02 (s, 3H), 5.65 (s, 2H), 6.38 (s, 1H), 6.48 (d, 2H), 7.22 (t, 1H), 7.36 - 7.45 (m, 1H), 7.77 (d, 1H), 8.09 - 8.17 (m, 2H), 8.31 - 8.47 (m, 4H), 9.42 (s, 1H). LC-MS: retention time: 0.89 min MS ES$^+$: 469.4 $[M+H]^+$ Method B

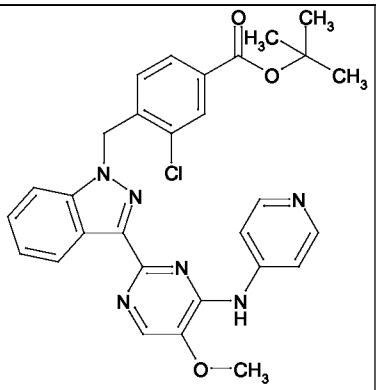
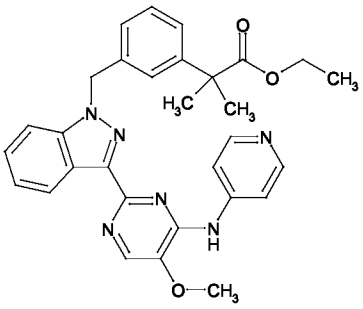
2-30-1 SM = 1-6-1		2-{1-[2-chloro-6-(trifluorome-thyl)benzyl]-1*H*-indazol-3-yl}-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 3.98 (s, 3H), 5.83 (s, 2H), 7.26 (t, 1H), 7.44 - 7.53 (m, 1H), 7.63 - 7.71 (m, 1H), 7.83 - 7.97 (m, 3H), 8.02 - 8.10 (m, 2H), 8.22 - 8.33 (m, 3H), 8.48 (d, 1H), 9.32 (s, 1H). LC-MS: retention time: 1.12 min MS ES$^+$: 511.36 [M+H]$^+$
2-31-1 SM = 1-6-1		2-[1-(2-chloro-5-fluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 4.01 (s, 3H), 5.80 (s, 2H), 7.11 (dd, 1H), 7.20 - 7.29 (m, 2H), 7.42 - 7.50 (m, 1H), 7.56 (dd, 1H), 7.83 (d, 1H), 8.07 - 8.15 (m, 2H), 8.31 - 8.40 (m, 3H), 8.47 (d, 1H), 9.42 (s, 1H). LC-MS: retention time: 1.02 min MS ES$^+$: 461.0 [M+H]$^+$ Method B

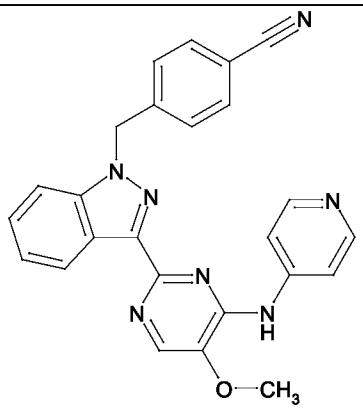
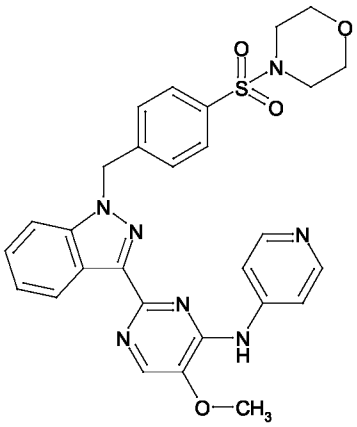
2-32-1 SM = 1-6-1		7-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)-4-methyl-2*H*-chromen-2-one	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 2.34 (d, 3H), 4.02 (s, 3H), 5.86 (s, 2H), 6.32 (d, 1H), 7.19 - 7.31 (m, 2H), 7.34 (s, 1H), 7.42 (t, 1H), 7.71 (d, 1H), 7.81 (d, 1H), 8.07 - 8.15 (m, 2H), 8.31 - 8.48 (m, 4H), 9.41 (s, 1H). LC-MS: retention time: 0.89 min MS ES$^+$: 491.0 $[M+H]^+$ Method B
2-33-1 SM = 1-6-1		3-fluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)benzonitrile	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 4.01 (s, 3H), 5.87 (s, 2H), 7.21 - 7.30 (m, 1H), 7.38 (t, 1H), 7.42 - 7.50 (m, 1H), 7.67 (dd, 1H), 7.81 (d, 1H), 7.90 (dd, 1H), 8.04 - 8.12 (m, 2H), 8.33 (s, 1H), 8.37 (d, 2H), 8.45 (d, 1H), 9.37 - 9.43 (m, 1H). LC-MS: retention time: 0.92 min MS ES$^+$: 452.0 $[M+H]^+$ Method B

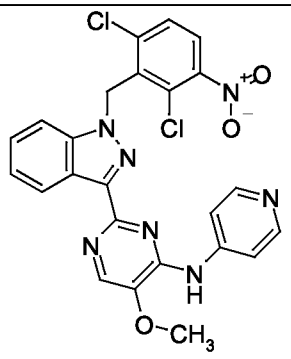
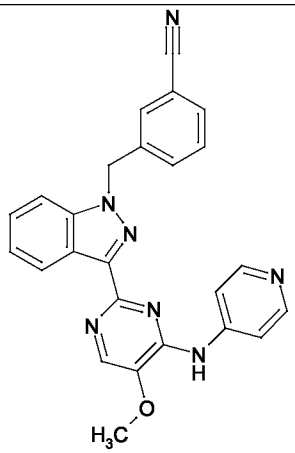
2-34-1 SM = 1-6-1		2-{1-[2,6-dichloro-3-(trifluorome-thyl)benzyl]-1*H*-indazol-3-yl}-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 3.99 (s, 3H), 5.97 (s, 2H), 7.27 (t, 1H), 7.48 - 7.54 (m, 1H), 7.83 - 7.89 (m, 1H), 7.93 (d, 2H), 8.08 - 8.13 (m, 2H), 8.31 - 8.36 (m, 3H), 8.49 (d, 1H), 9.35 (s, 1H). LC-MS: retention time: 1.17 min MS ES$^+$: 545.0 $[M+H]^+$ Method B
2-35-1 SM = 1-6-1		ethyl [3-({3-[5-methoxy-4-(pyridin-4-yla-mino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)phenyl] acetate	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 0.28 (t, 3H), 2.72 - 2.77 (m, 2H), 3.20 (q, 2H), 4.05 (s, 3H), 4.92 (s, 2H), 6.30 - 6.49 (m, 5H), 6.54 - 6.63 (m, 1H), 6.69 - 6.77 (m, 1H), 7.21 - 7.27 (m, 2H), 7.45 (s, 1H), 7.53 - 7.61 (m, 2H), 7.65 (d, 1H). LC-MS: retention time: 0.97 min MS ES$^+$: 495.39 $[M+H]^+$

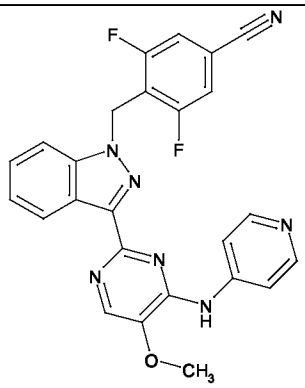
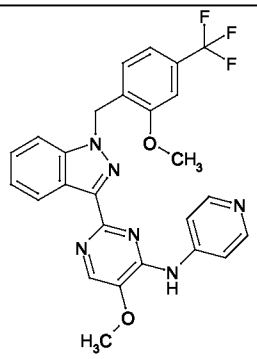
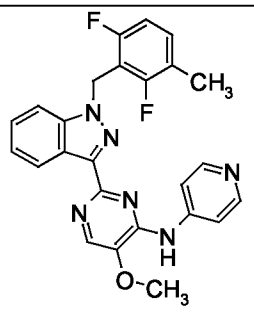
2-36-1 SM = 1-6-1		2-[1-(4-fluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 4.02 (s, 3H), 5.73 (s, 2H), 7.10 - 7.18 (m, 2H), 7.19 - 7.27 (m, 1H), 7.35 - 7.46 (m, 3H), 7.80 (d, 1H), 8.08 - 8.14 (m, 2H), 8.34 (s, 1H), 8.37 - 8.44 (m, 3H), 9.43 (s, 1H). LC-MS: retention time: 0.92 min MS ES$^+$: 427.0 $[M+H]^+$ Method B
2-37-1 SM = 1-6-1		*N*-cyclopropyl-4-({3-[5-methoxy-4-(pyridin-4-yla-mino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)benzenesulfonamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 0.31 (d, 2H), 0.38 (d, 2H), 1.91 - 2.06 (m, 1H), 4.02 (s, 3H), 5.86 (s, 2H), 7.24 (t, 1H), 7.37 - 7.46 (m, 1H), 7.51 (d, 2H), 7.68 - 7.81 (m, 3H), 7.84 (br. s., 1H), 8.10 (d, 2H), 8.32 - 8.41 (m, 3H), 8.45 (d, 1H), 9.37 - 9.44 (m, 1H). LC-MS: retention time: 0.90 min MS ES$^+$: 528.24 $[M+H]^+$

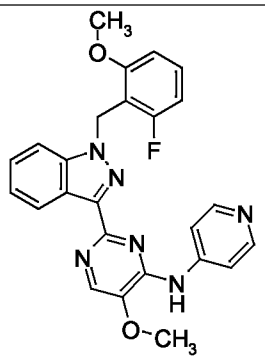
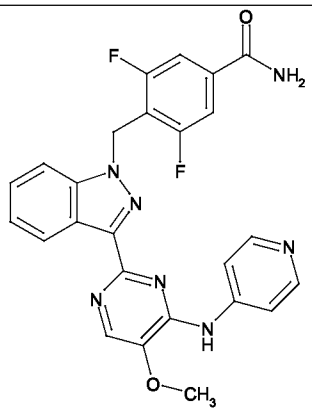
2-38-1 SM = 1-6-1		6-({3-[5-methoxy-4-(pyridin-4-yla-mino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)-1-benzofuran-2(3H)-one	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 4.05 (s, 3H), 5.34 (s, 2H), 5.95 (s, 2H), 7.26 (t, 1H), 7.45 (t, 1H), 7.52 - 7.58 (m, 2H), 7.83 (t, 2H), 8.10 - 8.15 (m, 2H), 8.37 (s, 1H), 8.39 - 8.43 (m, 2H), 8.48 (d, 1H), 9.43 (s, 1H). LC-MS: retention time: 0.81 min MS ES$^+$: 465.0 $[M+H]^+$ Method B
2-39-1 SM = 1-6-1		2-{1-[4-(difluorometh-oxy)-2,6-difluorobenzyl]-1*H*-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d6): δ [ppm]= 3.93 - 4.05 (s, 3H), 5.73 (s, 2H), 7.13 (d, 2H), 7.20 - 7.28 (m, 1H), 7.30 (t, 1H), 7.47 (t, 1H), 7.84 (d, 1H), 8.15 (d, 2H), 8.32 (s, 1H), 8.38 (d, 2H), 8.44 (d, 1H), 9.38 (s, 1H). LC-MS: retention time: 1.01 min MS ES$^+$: 511.0 $[M+H]^+$ Method B

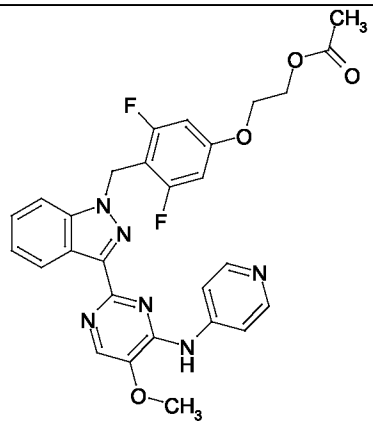
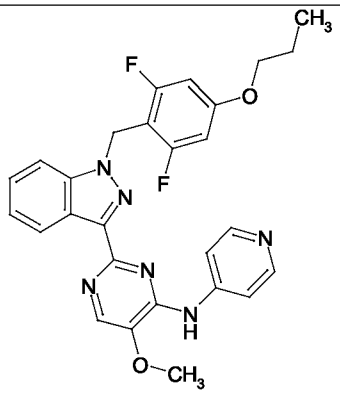
2-40-1 SM = 1-6-1		*tert*-butyl 3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)benzoate	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.52 (s, 9H), 4.04 (s, 3H), 5.90 (s, 2H), 7.25 - 7.33 (m, 2H), 7.44 - 7.51 (m, 1H), 7.78 - 7.86 (m, 2H), 7.93 (d, 1H), 8.07 - 8.12 (m, 2H), 8.33 - 8.40 (m, 3H), 8.47 - 8.52 (m, 1H), 9.40 (s, 1H). LC-MS: retention time: 1.18 min MS ES$^+$: 543.1 $[M+H]^+$ Method B
2-41-1 SM = 1-6-1		ethyl 2-[3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)phenyl]-2-methylpropanoate	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 0.89 (t, 3H), 1.39 (s, 6H), 3.87 (d, 2H), 4.02 (s, 3H), 5.74 (s, 2H), 7.14 - 7.31 (m, 5H), 7.40 (t, 1H), 7.77 (d, 1H), 8.08 - 8.16 (m, 2H), 8.31 - 8.47 (m, 4H), 9.41 (s, 1H). LC-MS: retention time: 1.04 min MS ES$^+$: 523.88 $[M+H]^+$

2-42-1 SM = 1-6-1		4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)benzonitrile	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 4.02 (s, 3H), 5.86 (s, 2H), 7.20 - 7.28 (m, 1H), 7.41 - 7.48 (m, 3H), 7.73 - 7.83 (m, 3H), 8.06 - 8.12 (m, 2H), 8.31 - 8.49 (m, 4H), 9.42 (s, 1H). LC-MS: retention time: 0.82 min MS ES$^+$: 434.4 $[M+H]^+$ Method B
2-43-1 SM = 1-6-1		5-methoxy-2-{1-[4-(morpholin-4-ylsulfonyl)benzyl]-1*H*-indazol-3-yl}-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 2.73 - 2.83 (m, 4H), 3.50 - 3.59 (m, 4H), 4.02 (s, 3H), 5.89 (s, 2H), 7.20 - 7.28 (m, 1H), 7.43 (t, 1H), 7.54 (d, 2H), 7.70 (d, 2H), 7.79 (d, 1H), 8.06 - 8.14 (m, 2H), 8.32 - 8.49 (m, 4H), 9.39 - 9.43 (m, 1H). LC-MS: retention time: 0.90 min MS ES$^+$: 558.23 $[M+H]^+$

2-44-1 SM = 1-6-1		2-[1-(2,6-dichloro-3-nitrobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 3.99 (s, 3H), 5.96 (s, 2H), 7.20 - 7.34 (m, 1H), 7.46 - 7.56 (m, 1H), 7.86 - 7.99 (m, 2H), 8.06 - 8.16 (m, 3H), 8.29 - 8.39 (m, 3H), 8.50 (d, 1H), 9.36 (s, 1H). LC-MS: retention time: 1.03 min MS ES$^+$: 522.1 [M+H]$^+$
2-45-1 SM = 1-6-1		3-({3-[5-methoxy-4-(pyridin-4-yla-mino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzonitrile	^{1}H-NMR (400MHz, METHANOL-d_4): δ [ppm]= 4.08 (s, 3H), 5.79 (s, 2H), 7.20 - 7.28 (m, 1H), 7.41 - 7.50 (m, 2H), 7.55 - 7.63 (m, 3H), 7.70 (s, 1H), 8.06 (d, 2H), 8.27 (s, 1H), 8.36 - 8.42 (m, 2H), 8.47 (s, 1H). LC-MS: retention time: 0.94 min MS ES$^+$: 434.44 [M+H]$^+$

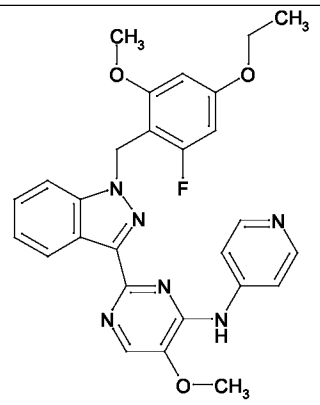
2-46-1 SM = 1-6-1		3,5-difluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzonitrile	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 4.00 (s, 3H), 5.82 (s, 2H), 7.25 (t, 1H), 7.49 (t, 1H), 7.85 - 7.94 (m, 3H), 8.08 - 8.20 (m, 2H), 8.32 (s, 1H), 8.37 - 8.46 (m, 3H), 9.41 (s, 1H). LC-MS: retention time: 0.99 min MS ES$^+$: 470.35 $[M+H]^+$
2-47-1 SM = 1-6-1		5-methoxy-2-{1-[2-methoxy-4-(trifluoromethyl)benzyl]-1H-indazol-3-yl}-N-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 3.93 (s, 3H), 4.12 (s, 3H), 5.61 (s, 2H), 7.17 - 7.26 (m, 1H), 7.34-7.45 (m, 3H), 7.58 (d, 1H), 7.63 - 7.70 (m, 1H), 8.42 - 8.50 (m, 1H), 8.51 - 8.68 (m, 6H). LC-MS: retention time: 1.03 min MS ES$^+$: 507.42 $[M+H]^+$
2-48-1 SM = 1-6-1		2-[1-(2,6-difluoro-3-methylbenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 2.16 (s, 3H), 4.00 (s, 3H), 5.74 (s, 2H), 7.06 (t, 1H), 7.21 - 7.34 (m, 2H), 7.47 (t, 1H), 7.85 (d, 1H), 8.07 - 8.20 (m, 2H), 8.28 - 8.50 (m, 4H),

			9.40 (br. s, 1H). LC-MS: retention time: 1.03 min MS ES+: 459.2 [M+H]+
2-49-1 SM = 1-6-1		2-[1-(2-fluoro-6-methoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine	1H-NMR (400MHz, DMSO-d6): δ [ppm]= 3.80 (s, 3H), 3.85 (s, 3H), 5.09 (s, 2H), 6.85 - 6.99 (m, 4H), 7.06 (t, 1H), 7.31 (t, 1H), 7.36 - 7.48 (m, 1H), 7.51 (d, 1H), 7.62 (d, 2H), 8.16 (s, 1H), 8.39 (d, 1H), 13.15 (br.s., 1H). LC-MS: retention time: 0.90 min MS ES+: 457.2 [M+H]+
2-50-1 SM = 1-6-1		3,5-difluoro-4-({3-[5-methoxy-4-(pyridin-4-yla-mino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzamide	1H-NMR (400MHz, Methanol-d4): δ [ppm]= 4.07 (s, 3H), 5.81 (s, 2H), 7.25 (t, 1H), 7.47 (t, 1H), 7.50 - 7.58 (m, 2H), 7.72 (d, 1H), 8.18 (s, 1H), 8.27 - 8.38 (m, 3H), 8.39 - 8.49 (m, 3H) LC-MS: retention time: 0.87 min MS ES+:488.39 [M+H]+

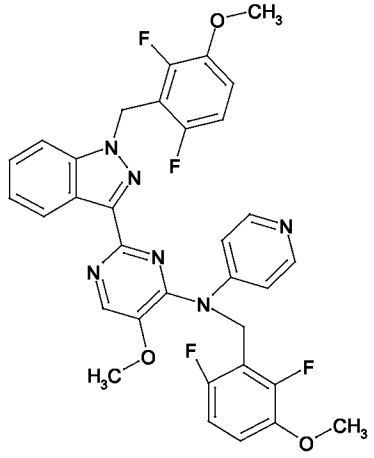
2-51-1 SM = 1-6-1		2-[3,5-difluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenoxy]ethyl acetate	^{1}H-NMR (600MHz, DMSO-d_6): δ [ppm]= 2.00 (s, 3H), 4.04 (s, 3H), 4.21 (t, 2H), 4.29 (t, 2H), 5.69 (s, 2H), 6.80 - 6.94 (m, 2H), 7.19 - 7.34 (m, 1H), 7.42 - 7.55 (m, 1H), 7.79 - 7.90 (m, 1H), 8.10 - 8.25 (m, 2H), 8.35 (s, 1H), 8.39 - 8.44 (m, 2H), 8.44 - 8.51 (m, 1H), 9.41 (s, 1H). LC-MS (Method 5): retention time: 1.22 min MS ES$^+$: 547.3 $[M+H]^+$
2-52-1 SM = 1-6-1		2-[1-(2,6-difluoro-4-propoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 0.93 (t, 3H), 1.59 - 1.79 (m, 2H), 3.94 (t, 2H), 4.04 (s, 3H), 5.68 (s, 2H), 6.74 - 6.94 (m, 2H), 7.21 - 7.35 (m, 1H), 7.42 - 7.62 (m, 1H), 7.80 - 7.90 (m, 1H), 8.15 - 8.26 (m, 2H), 8.36 (s, 1H), 8.37 - 8.43 (m, 2H), 8.43 - 8.51 (m, 1H), 9.44 (s, 1H). LC-MS: retention time: 1.14 min

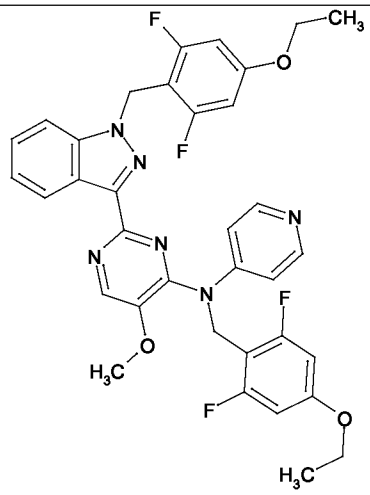
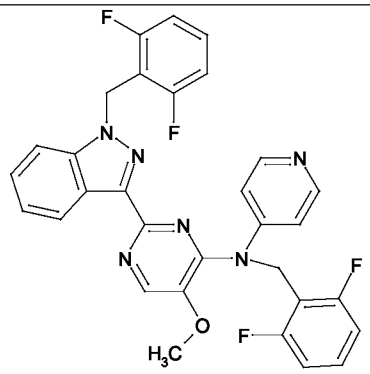
			MS ES+: 503.37 [M+H]+

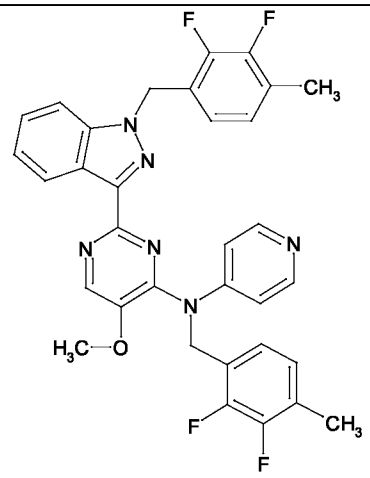
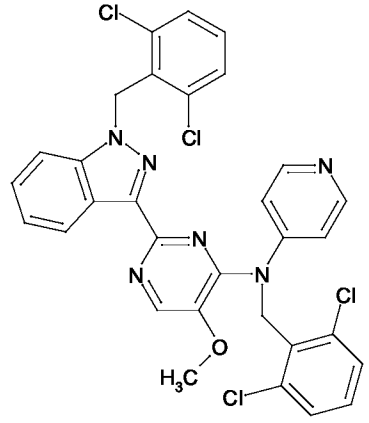
The following compound was also isolated from the reaction leading to 2-5-1:

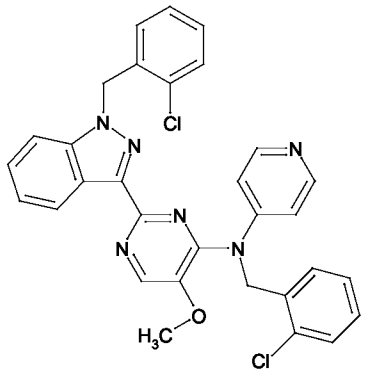
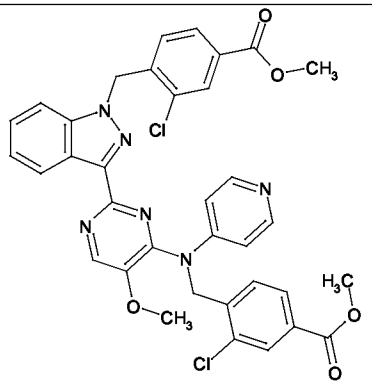
2-53-1 SM = 1-6-1		2-[1-(4-ethoxy-2-fluoro-6-methoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 1.26 (t, 3H), 3.72 (s, 3H), 3.92 - 4.10 (m, 5H), 5.54 (s, 2H), 6.40 (s, 1H), 6.50 (dd, 1H), 7.13 - 7.27 (m, 1H), 7.37 - 7.49 (m, 1H), 7.79 (d, 1H), 8.16 (d, 2H), 8.31 (s, 1H), 8.35 - 8.47 (m, 3H), 9.38 (s, 1H).

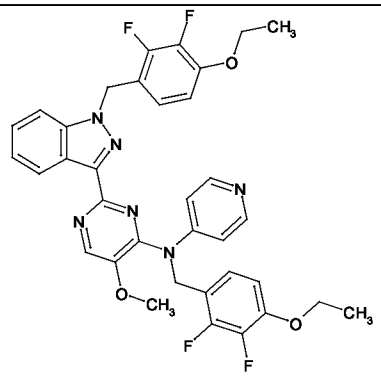
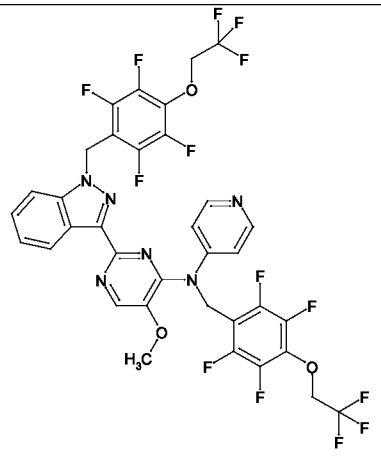
The following bis-benzyl compounds were also formed during the above described procedure using the indicated starting materials (SM = starting material):

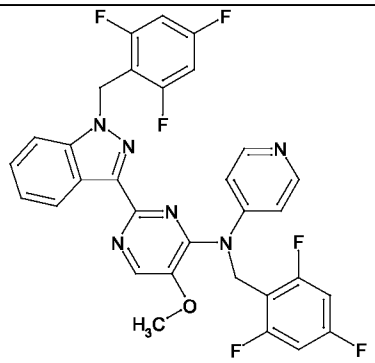
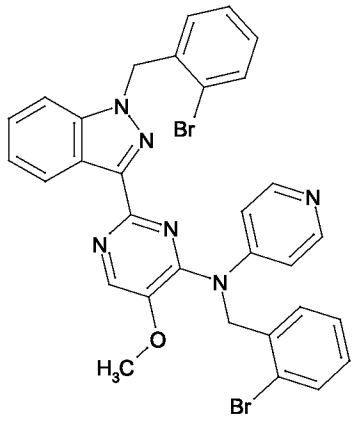
2-4-2 SM = 1-6-1		*N*-(2,6-difluoro-3-methoxybenzyl)-2-[1-(2,6-difluoro-3-methoxybenzyl)-1*H*-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 3.77 (d, 6H), 3.82 (s, 3H), 5.22 (s, 2H), 5.69 (s, 2H), 6.86 (d, 2H), 6.97 - 7.06 (m, 1H), 7.06 - 7.19 (m, 3H), 7.21 - 7.30 (m, 1H), 7.41 (t, 1H), 7.57 (d, 2H), 7.74 (d, 1H), 8.12 (s, 1H), 8.37 (d, 1H).

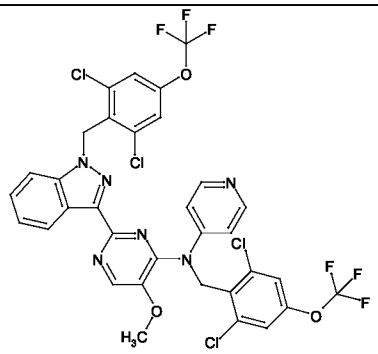
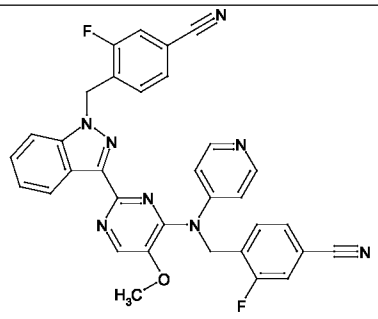
			LC-MS: retention time: 1.16 min MS ES+: 631.24 [M+H]+
2-5-2 SM = 1-6-1		*N*-(4-ethoxy-2,6-difluorobenzyl)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 1.21 - 1.32 (m, 6H), 3.78 (s, 3H), 4.02 (dq, 4H), 5.13 (s, 2H), 5.59 (s, 2H), 6.69 (d, 2H), 6.78 - 6.93 (m, 4H), 7.09 (t, 1H), 7.39 (t, 1H), 7.56 (d, 2H), 7.71 (d, 1H), 8.12 (s, 1H), 8.37 (d, 1H). LC-MS: retention time: 1.26 min MS ES+: 659.0 [M+H]+ Method B
2-7-2 SM = 1-6-1		*N*-(2,6-difluorobenzyl)-2-[1-(2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 3.77 (s, 3H), 5.24 (s, 2H), 5.69 (s, 2H), 6.89 (d, 2H), 7.03 - 7.15 (m, 3H), 7.22 (t, 3H), 7.36 - 7.46 (m, 2H), 7.58 (d, 2H), 7.75 (d, 1H), 8.12 (s, 1H), 8.38 (d, 1H). LC-MS: retention time: 1.13 min MS ES+: 571.18 [M+H]+

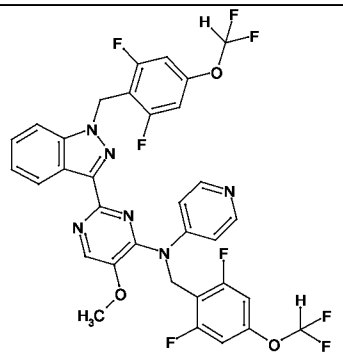
2-8-2 SM = 1-6-1		*N*-(2,3-difluoro-4-methylbenzyl)-2-[1-(2,3-difluoro-4-methylbenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 2.19 (d, 3H), 2.25 (d, 3H), 3.79 (s, 3H), 5.19 (s, 2H), 5.68 - 5.77 (s, 2H), 6.77 - 6.87 (m, 3H), 6.98 (t, 1H), 7.03 - 7.19 (m, 3H), 7.38 (t, 1H), 7.61 - 7.74 (m, 3H), 8.11 - 8.17 (m, 1H), 8.37 - 8.45 (m, 1H). LC-MS: retention time: 1.20 min MS ES$^+$: 599.25 [M+H]$^+$
2-9-2 SM = 1-6-1		*N*-(2,6-dichlorobenzyl)-2-[1-(2,6-dichlorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm]= 3.78 (s, 3H), 5.43 (s, 2H), 5.79 (s, 2H), 7.09 - 7.18 (m, 3H), 7.30 - 7.45 (m, 4H), 7.50 - 7.60 (m, 3H), 7.63 - 7.68 (d, 2H), 7.77 (d, 1H), 8.12 (s, 1H), 8.42 (d, 1H). LC-MS: retention time: 1.26 min MS ES$^+$: 637.09 [M+H]$^+$

2-10-2 SM = 1-6-1		*N*-(2-chlorobenzyl)-2-[1-(2-chlorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm]= 3.81 (s, 3H), 5.23 (s, 2H), 5.76 (s, 2H), 6.81 - 6.89 (m, 3H), 7.12 (t, 1H), 7.19 (td, 1H), 7.23 - 7.30 (m, 2H), 7.34 - 7.42 (m, 3H), 7.47 (dd, 1H), 7.54 (dd, 1H), 7.63 - 7.69 (m, 3H), 8.15 (s, 1H), 8.47 (d, 1H). LC-MS: retention time: 1.12 min MS ES$^+$: 567.2 [M+H]$^+$
2-11-2 SM = 1-6-1		methyl 3-chloro-4-{[(2-{1-[2-chloro-4-(methoxycarbonyl)benzyl]-1*H*-indazol-3-yl}-5-methoxypyrimidin-4-yl)(pyridin-4-yl)amino]methyl}benzoate	^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm]= 3.79 (s, 3H), 3.85 (s, 3H), 3.97 (s, 3H), 5.60 (s, 2H), 5.87 (s, 2H), 7.00 (d, 1H), 7.23 (t, 1H), 7.33 (d, 1H), 7.40 - 7.46 (m, 1H), 7.71 - 7.80 (m, 2H), 7.90 - 7.97 (m, 3H), 8.01 (d, 1H), 8.25 (s, 1H), 8.29 (d, 2H), 8.42 - 8.50 (m, 2H). LC-MS: retention time: 1.17 min MS ES$^+$: 683.1 [M+H]$^+$ Method B

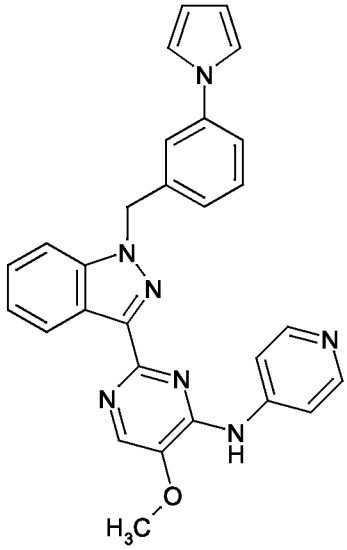
2-14-2 SM = 1-6-1		*N*-(4-ethoxy-2,3-difluorobenzyl)-2-[1-(4-ethoxy-2,3-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 1.22 - 1.36 (m, 6H), 3.79 (s, 3H), 3.99 - 4.18 (m, 4H), 5.14 (s, 2H), 5.68 (s, 2H), 6.81 (d, 2H), 6.92 (d, 2H), 7.00 - 7.22 (m, 3H), 7.38 (t, 1H), 7.61 - 7.74 (m, 3H), 8.14 (s, 1H), 8.40 (d, 1H). LC-MS: retention time: 1.22 min MS ES$^+$: 659.0 [M+H]$^+$ Method B
2-15-2 SM = 1-6-1		5-methoxy-*N*-(pyridin-4-yl)-*N*-[2,3,5,6-tetrafluoro-4-(2,2,2-trifluoroethoxy)benzyl]-2-{1-[2,3,5,6-tetrafluoro-4-(2,2,2-trifluoroethoxy)benzyl]-1*H*-indazol-3-yl}pyrimidin-4-amine	^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm]= 4.00 (s, 3H), 4.93 (qd, 4H), 5.31 (s, 2H), 5.63 (s, 2H), 7.21 (t, 1H), 7.36 (ddd, 1H), 7.64 (d, 1H), 8.04 - 8.11 (m, 2H), 8.27 - 8.33 (m, 2H), 8.43 (d, 1H), 9.35 (s, 1H). LC-MS: retention time: 1.42 min MS ES$^+$: 837.1 [M+H]$^+$ Method B

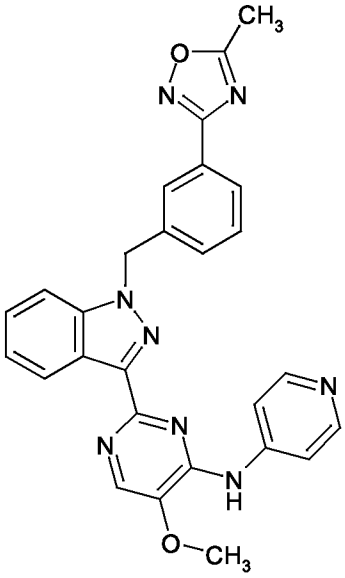
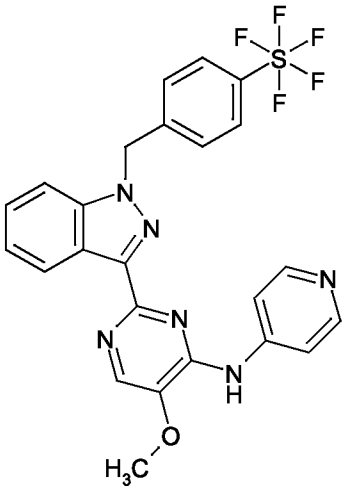
2-17-2 SM = 1-6-1		5-methoxy-*N*-(pyridin-4-yl)-*N*-(2,4,6-trifluorobenzyl)-2-[1-(2,4,6-trifluorobenzyl)-1*H*-indazol-3-yl]pyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 3.78 (s, 3H), 5.20 (s, 2H), 5.66 (s, 2H), 6.86 (d, 2H), 7.07 - 7.26 (m, 3H), 7.29 - 7.46 (m, 3H), 7.58 (d, 2H), 7.75 (d, 1H), 8.13 (s, 1H), 8.38 (d, 1H). LC-MS: retention time: 1.12 min MS ES$^+$: 608.17 [M+H]$^+$
2-21-2 SM = 1-6-1		*N*-(2-bromobenzyl)-2-[1-(2-bromobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 3.81 (s, 3H), 5.20 (s, 2H), 5.73 (s, 2H), 6.69 - 6.76 (m, 1H), 6.87 (d, 2H), 7.08 - 7.26 (m, 4H), 7.28 - 7.48 (m, 3H), 7.60 - 7.73 (m, 5H), 8.15 (s, 1H), 8.48 (d, 1H). LC-MS: retention time: 1.30 min MS ES$^+$: 657.04 [M+H]$^+$

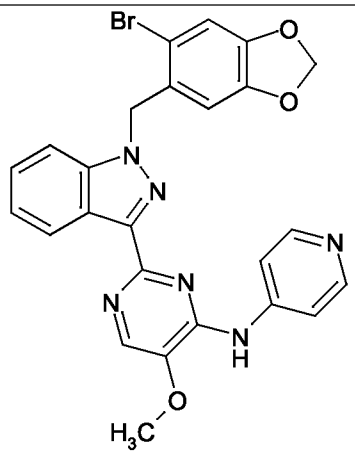
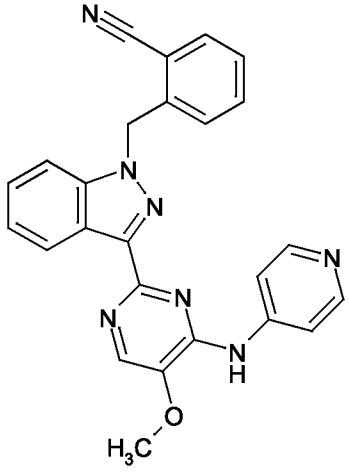
2-26-2 SM = 1-6-1		*N*-[2,6-dichloro-4-(trifluoromethoxy)benzyl]-2-{1-[2,6-dichloro-4-(trifluoromethoxy)benzyl]-1*H*-indazol-3-yl}-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 3.78 (s, 3H), 5.40 (s, 2H), 5.81 (s, 2H), 6.99 (d, 2H), 7.12 (t, 1H), 7.42 (t, 1H), 7.55 (d, 2H), 7.64 (s, 2H), 7.76 - 7.85 (m, 3H), 8.12 (s, 1H), 8.42 (d, 1H). LC-MS: retention time: 1.39 min MS ES$^+$: 804.9 [M+H]$^+$ Method B
2-33-2 SM = 1-6-1		4-{[{2-[1-(4-cyano-2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}(pyridin-4-yl)amino]methyl}-3-fluorobenzonitrile	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 3.80 (s, 3H), 5.28 (s, 2H), 5.84 (s, 2H), 6.83 (d, 2H), 7.09 - 7.19 (m, 2H), 7.43 (dt, 2H), 7.56 - 7.79 (m, 5H), 7.84 - 7.98 (m, 2H), 8.17 (s, 1H), 8.44 (d, 1H). LC-MS: retention time: 1.01 min MS ES$^+$: 586.2 [M+H]$^+$

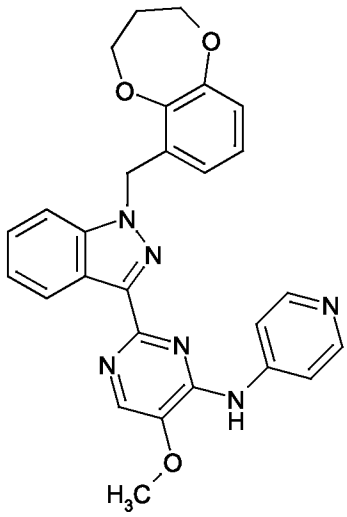
2-39-2 SM = 1-6-1		*N*-[4-(difluoromethoxy)-2,6-difluorobenzyl]-2-{1-[4-(difluoromethoxy)-2,6-difluorobenzyl]-1*H*-indazol-3-yl}-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 3.78 (s, 3H), 5.20 (s, 2H), 5.67 (s, 2H), 6.84 (d, 2H), 7.01 - 7.21 (m, 5H), 7.31 (d, 1H), 7.41 (t, 1H), 7.51 - 7.60 (m, 3H), 7.75 (d, 1H), 8.13 (s, 1H), 8.38 (d, 1H). LC-MS: retention time: 1.17 min MS ES$^+$: 703.1 $[M+H]^+$ Method B

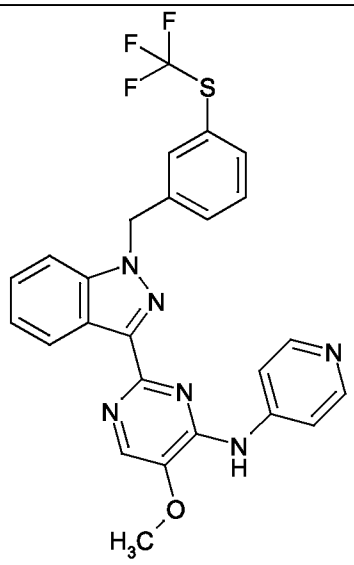
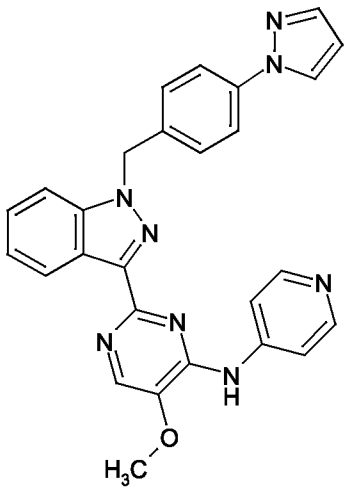
The following compounds were prepared following the procedure described in scheme 2a using the indicated starting materials (SM = starting material):

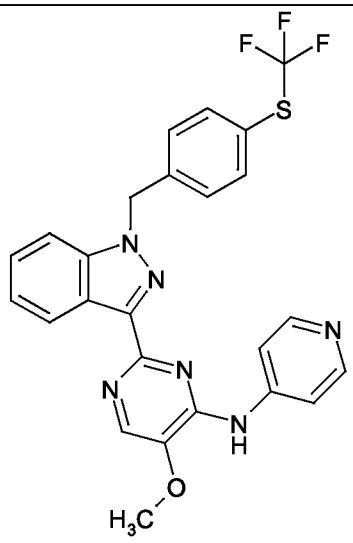
2-1-3 SM = 1-10-1		5-methoxy-N-(pyridin-4-yl)-2-{1-[3-(1H-pyrrol-1-yl)benzyl]-1H-indazol-3-yl}pyrimidin-4-amine	H-NMR (300MHz, METHANOL-d4): δ [ppm]= 4.06 (s, 3H), 5.77 (s, 2H), 6.16 - 6.25 (m, 2H), 7.09 (s, 3H), 7.18 - 7.27 (m, 1H), 7.30 - 7.37 (m, 2H), 7.37 - 7.49 (m, 2H), 7.57 - 7.64 (m, 1H), 8.05 - 8.14 (m, 2H), 8.24 - 8.41 (m, 3H), 8.42 - 8.51 (m, 1H)

			LC-MS: retention time: 1.07 min MS ES+: 474.4 [M+H]+ Method B
2-2-3 SM = 1-10-1		5-methoxy-2-{1-[3-(5-methyl-1,2,4-oxadiazol-3-yl)benzyl]-1H-indazol-3-yl}-N-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (400MHz, CHLOROFORM-d): δ [ppm]= 2.64 (s, 3H), 4.08 (s, 3H), 5.82 (s, 2H), 7.35 - 7.45 (m, 5H), 7.82 - 7.90 (m, 2H), 7.94 - 8.01 (m, 1H), 8.12 (s, 1H), 8.25 (s, 1H), 8.52 - 8.63 (m, 3H) LC-MS: retention time: 0.95 min MS ES+: 491.3 [M+H]+
2-3-3 SM = 1-10-1		5-methoxy-2-{1-[4-(pentafluoro-λ6-sulfa-nyl)benzyl]-1H-indazol-3-yl}-N-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300MHz, CHLOROFORM-d): δ [ppm]= 4.08 (s, 3H), 5.79 (s, 2H), 7.28 - 7.50 (m, 5H), 7.68 (d, 2H), 7.80 - 7.89 (m, 2H), 8.24 (s, 1H), 8.53 - 8.66 (m, 3H) LC-MS:

			retention time: 1.07 min MS ES+: 535.2 [M+H]+
2-4-3 1-10-1		2-{1-[(6-bromo-1,3-benzodioxol-5-yl)methyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine	1H-NMR (300MHz, CHLOROFORM-d): δ [ppm]= 4.08 (s, 3H), 5.76 (s, 2H), 5.89 (s, 2H), 6.45 (s, 1H), 7.04 (s, 1H), 7.41 - 7.43 (m, 3H), 7.79 - 7.90 (m, 2H), 8.24 (s, 1H), 8.47 - 8.65 (m, 3H) LC-MS: retention time: 1.09 min MS ES+: 509.1 [M+H]+ Method B
2-5-3 SM = 1-10-1		2-({3-[5-methoxy-4-(pyridin-4-yla-mino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzonitrile	1H-NMR (300MHz, CHLOROFORM-d): δ [ppm]= 4.08 (s, 3H), 5.98 (s, 2H), 7.13 - 7.22 (m, 1H), 7.30 - 7.53 (m, 5H), 7.67 - 7.77 (m, 1H), 7.79 - 7.94 (m, 2H), 8.25 (s, 1H), 8.51 - 8.70 (m, 3H)

			LC-MS: retention time: 0.90 min MS ES+: 434.2 [M+H]+
2-6-3 SM = 1-10-1		2-[1-(3,4-dihydro-2H-1,5-benzodiox-epin-6-ylmethyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine	1H-NMR (300MHz, CHLOROFORM-d): δ [ppm]= 2.20 (quint, 2H), 4.06 (s, 3H), 4.14 (t, 2H), 4.19 (t, 2H), 5.76 (s, 2H), 6.73 - 6.83 (m, 2H), 6.87 - 6.96 (m, 1H), 7.33 - 7.54 (m, 3H), 7.80 - 7.91 (m, 2H), 8.23 (s, 1H), 8.54 - 8.58 (m, 3H) LC-MS: retention time: 0.95 min MS ES+: 481.3 [M+H]+

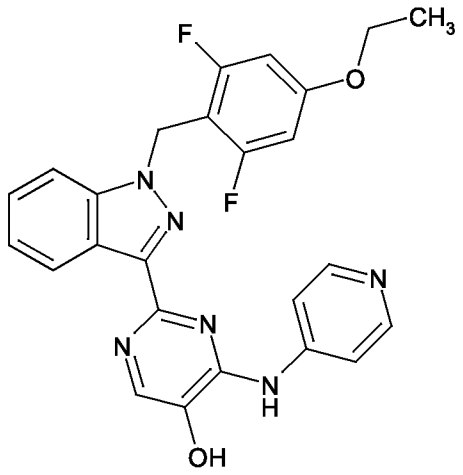
2-7-3 SM = 1-10-1		5-methoxy-N-(pyridin-4-yl)-2-(1-{3-[(trifluoromethyl)sulfanyl]benzyl}-1H-indazol-3-yl)pyrimidin-4-amine	1H-NMR (300MHz, CHLOROFORM-d): δ [ppm]= 4.08 (s, 3H), 5.77 (s, 2H), 7.30 -7.42 (m, 5H), 7.51 - 7.66 (m, 2H), 7.83 (d, 2H), 8.24 (s, 1H), 8.55 - 8.61 (m, 3H) LC-MS: retention time: 1.08 min MS ES+: 509.2 [M+H]+
2-8-3 SM = 1-10-1		5-methoxy-2-{1-[4-(1H-pyrazol-1-yl)benzyl]-1H-indazol-3-yl}-N-(pyridin-4-yl)pyrimidin-4-amine	LC-MS: retention time: 0.98 min MS ES+: 475.42 [M+H]+

2-9-3 SM = 1-10-1		5-methoxy-N-(pyridin-4-yl)-2-(1-{4-[(trifluoromethyl)sulfanyl]benzyl}-1H-indazol-3-yl)pyrimidin-4-amine	H-NMR (300MHz, METHANOL-d4): δ [ppm]= 4.09 (s, 3H), 5.82 (s, 2H), 7.21 - 7.30 (m, 1H), 7.34 - 7.49 (m, 2H), 7.49 - 7.73 (m, 4H), 8.01 - 8.09 (m, 2H), 8.28 (s, 1H), 8.35 - 8.43 (m, 2H), 8.50 (d, 1H) LC-MS: retention time: 1.16 min MS ES$^+$: 509.39 $[M+H]^+$

Example 3-1

Preparation of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol

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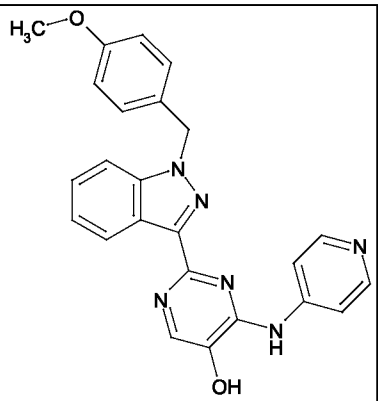
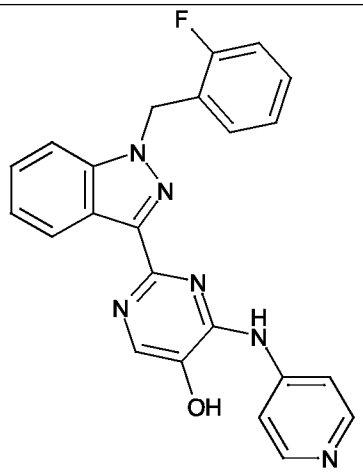


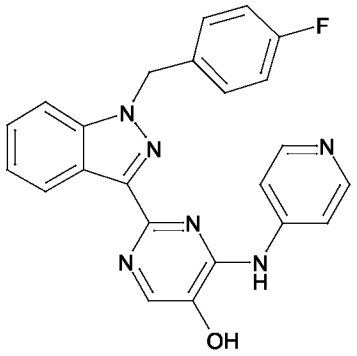
1,32 g of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine (2-5-1, 2,70 mmol, 1. eq.) were dissolved in 117 ml of dry 1-methylpyrrolidin-2-one. 142 mg of potassium carbonate were added under nitrogen atmosphere. Then 0,42 ml of benzenethiol were added dropwise. The reaction mixture was stirred for an hour at 190℃ and c ooled over the weekend at room temperature. Then the mixture was portioned between half saturated aq. ammonium chloride solution and dichloromethane/ isopropanol 4:1. The phases were separated and the aqueous layer was extracted twice with dichloromethane/ isopropanol 4:1. The combined organic layers were washed with brine, dried over a silicone filter and concentrated in vacuo. The residue was purified by flash chromatography to yield 781 mg (1,65 mmol, 60,9%) of the analytically pure target compound.

^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 1.25 (t, 3H), 4.00 (q, 2H), 5.63 (s, 2H), 6.71 - 6.81 (m, 2H), 7.21 (t, 1H), 7.44 (td, 1H), 7.80 (d, 1H), 8.09 - 8.18 (m, 3H), 8.33 - 8.38 (m, 2H), 8.42 (d, 1H), 9.28 (s, 1H), 10.78 (br. s., 1H).

LC-MS:
retention time: 0.97 min
MS ES$^+$: 475.59 [M+H]$^+$

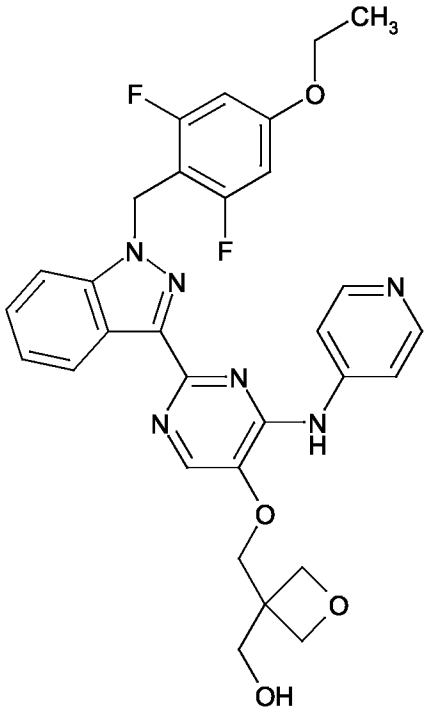
The following compounds were prepared according to the same procedure using the indicated starting materials (SM = starting material):

3-2 SM = 1-5-1		2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 3.66 (s, 3H), 5.64 (s, 2H), 6.83 - 6.88 (m, 2H), 7.19 (t, 1H), 7.27 - 7.33 (m, 2H), 7.38 (ddd, 1H), 7.76 (d, 1H), 8.10 - 8.15 (m, 3H), 8.34 - 8.43 (m, 2H), 9.31 (s, 1H). LC-MS: retention time: 0.83 min MS ES$^+$: 425.1 $[M+H]^+$ Method B
3-3 SM = 2-18-1		2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 5.76 (s, 2H), 7.12 - 7.18 (m, 1H), 7.19 - 7.38 (m, 4H), 7.43 (ddd, 1H), 7.78 (d, 1H), 8.09 - 8.14 (m, 3H), 8.33 - 8.37 (m, 2H), 8.43 (d, 1H), 9.30 (s, 1H), 10.71 - 10.92 (s, 1H). LC-MS: retention time: 0.86 min MS ES$^+$: 413.2 $[M+H]^+$

3-4 SM = 2-36-1		2-[1-(4-fluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-yla-mino)pyrimidin-5-ol	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 5.70 - 5.73 (m, 2H), 7.10 - 7.23 (m, 3H), 7.34 - 7.44 (m, 3H), 7.78 (d, 1H), 8.07 - 8.14 (m, 3H), 8.34 - 8.39 (m, 2H), 8.42 (d, 1H), 9.31 (s, 1H), 10.83 - 11.18 (m, 1H). LC-MS: retention time: 0.85 min MS ES$^+$: 413.0 $[M+H]^+$ Method B

Example 4-1

Preparation of {3-[({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methyl]oxetan-3-yl}methanol



100 mg of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol (3-1, 0.21 mmol, 1. eq.) were dissolved in 1,6 ml of DMF under a nitrogen atmosphere, then 87 mg of potassium carbonate (0.63 mmol, 3 eq.) and 40 mg of [3-(bromomethyl)oxetan-3-yl]methanol (0.21 mmol, 1 eq.) were added. The resulting mixture was stirred at room temperature for 18 hours. 6,0mg of [3-(bromomethyl)oxetan-3-yl]methanol (0,032 mmol, 0,15 eq.) were added and stirred again for 24 hours. Then the mixture was partitioned between half saturated aq. ammonium chloride solution and dichloromethane/ isopropanol 4:1. The phases were separated and the aqueous layer was extracted twice with dichloromethane/isopropanol 4:1. The combined organic layers were washed with brine, dried over a silicone filter and concentrated in vacuo. The residue was purified by flash chromatography to yield 75 mg (0.13 mmol, 61,9%) of the analytically pure target compound.

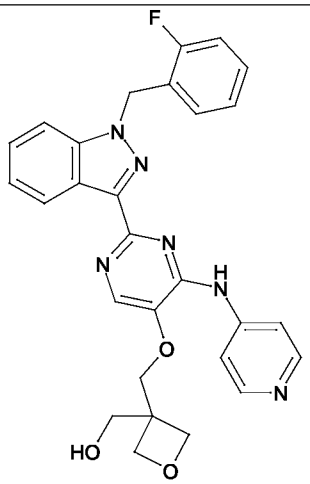
^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.26 (t, 3H), 3.83 (d, 2H), 4.01 (q, 2H), 4.39 - 4.50 (m, 6H), 5.06 (t, 1H), 5.65 (s, 2H), 6.72 - 6.81 (m, 2H), 7.23 (t, 1H), 7.46 (ddd, 1H), 7.82 (d, 1H), 8.01 - 8.09 (m, 2H), 8.38 - 8.46 (m, 4H), 8.90 (s, 1H).

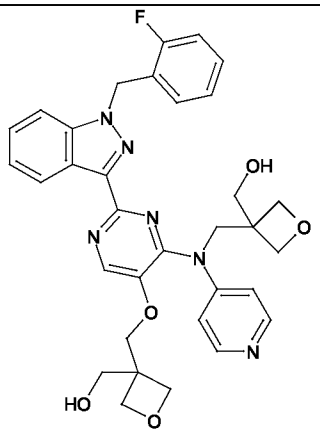
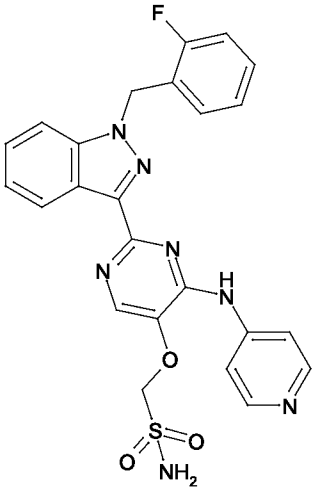
LC-MS:

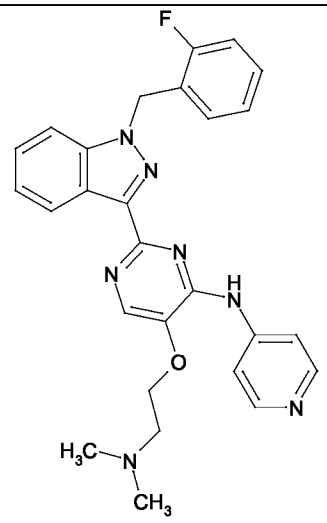
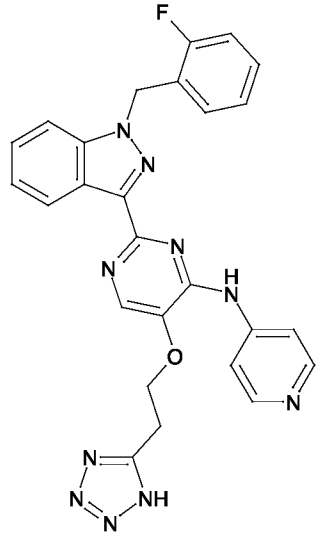
retention time: 1.00 min

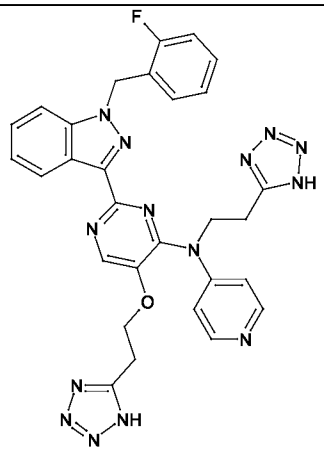
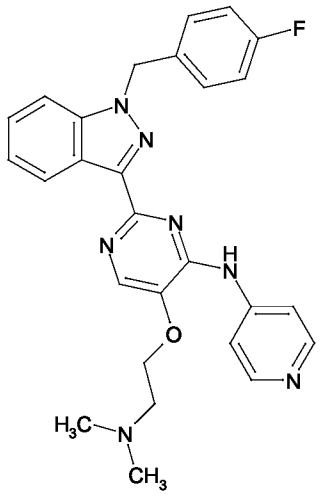
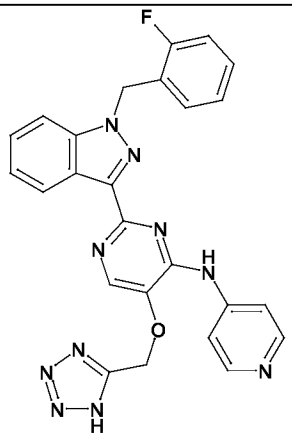
MS ES$^+$: 574.82 $[M+H]^+$

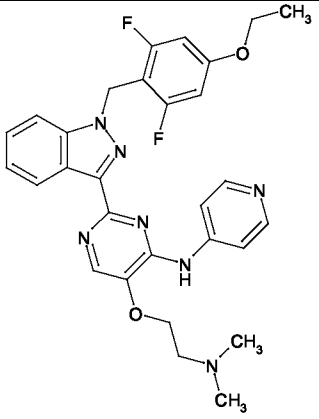
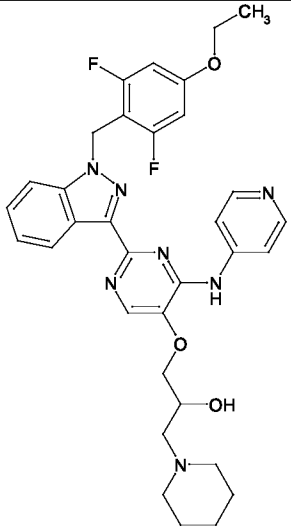
The following compounds were prepared according to the same procedure using the indicated starting materials (SM = starting material):

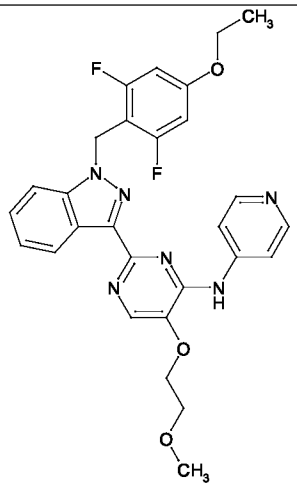
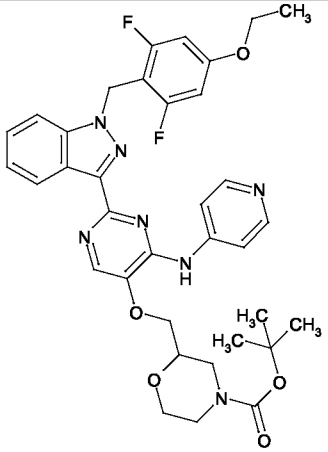
4-2-1 SM = 3-3		{3-[({2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methyl]oxetan-3-	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 3.83 (br. s., 2H), 4.39 - 4.48 (m, 6H), 5.06 (br. s., 1H), 5.78 (s, 2H), 7.11 - 7.38 (m, 5H), 7.40 - 7.49 (m, 1H), 7.80 (d, 1H), 8.00 (d, 2H), 8.37 - 8.46 (m,

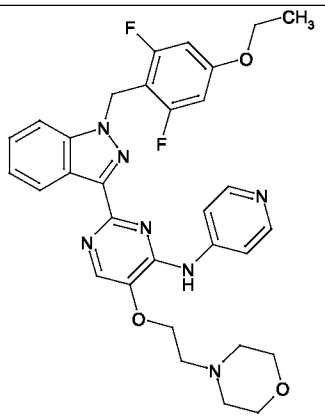
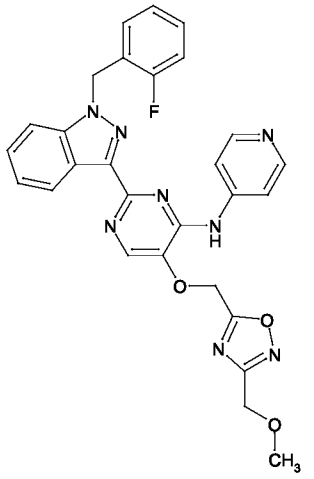
		yl}methanol	4H), 8.92 (br. s., 1H). LC-MS: retention time: 0.92 min MS ES+: 513.25 [M+H]+
4-2-2 SM = 3-3		(3-{[(2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-{[3-(hydroxymethyl)oxetan-3-yl]methoxy}pyrimidin-4-yl)(pyridin-4-yl)amino]methyl}oxetan-3-yl)methanol	LC-MS: retention time: 0.93 min MS ES+: 613.26 [M+H]+
4-3 SM = 3-3		1-({2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methanesulfonamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 5.30 (s, 2H), 5.79 (s, 2H), 7.12 - 7.38 (m, 5H), 7.41 - 7.48 (m, 3H), 7.82 (d, 1H), 8.03 - 8.09 (m, 2H), 8.39 - 8.45 (m, 3H), 8.56 (s, 1H), 9.18 - 9.22 (m, 1H). LC-MS (Method 2): retention time: 1.32 min MS ES+: 506.00 [M+H]+

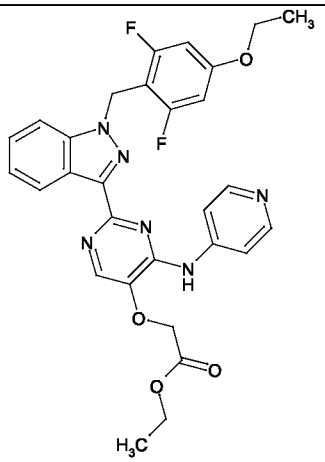
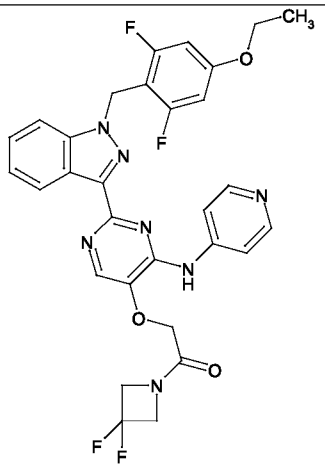
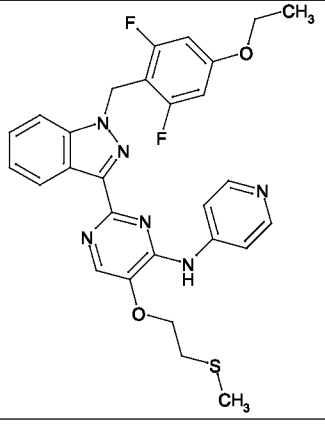
4-4 SM = 3-3		5-[2-(dimethylamino)ethoxy]-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 2.25 (s, 6H), 2.68 - 2.75 (m, 2H), 4.29 (t, 2H), 5.78 (s, 2H), 7.12 - 7.38 (m, 5H), 7.44 (ddd, 1H), 7.80 (d, 1H), 8.01 - 8.06 (m, 2H), 8.37 - 8.46 (m, 4H), 9.42 (s, 1H). LC-MS: retention time: 0.77 min MS ES$^+$: 484.3 $[M+H]^+$
4-5-1 SM = 3-3		2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-4-yl)-5-[2-(1*H*-tetrazol-5-yl)ethoxy]pyrimidin-4-amine	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 3.17 - 3.24 (m, 4H), 4.41 (t, 2H), 5.79 (s, 2H), 7.12 - 7.39 (m, 5H), 7.40 - 7.49 (m, 1H), 7.80 (d, 1H), 8.39 - 8.49 (m, 6H). LC-MS: retention time: 0.91 min MS ES$^+$: 509.36 $[M+H]^+$

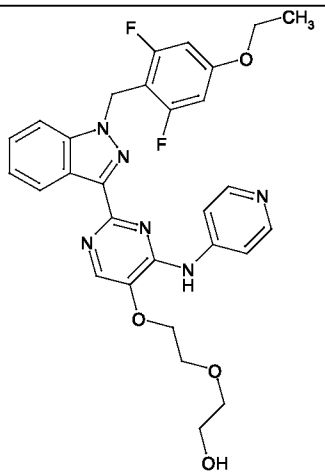
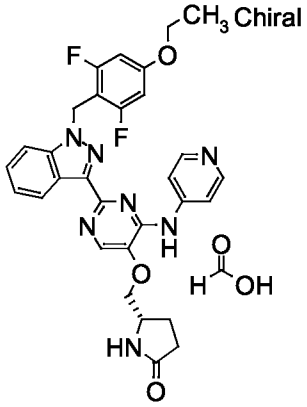
4-5-2 SM = 3-3		2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)-5-[2-(1H-tetrazol-5-yl)ethoxy]-N-[2-(1H-tetrazol-5-yl)ethyl]pyrimidin-4-amine	LC-MS: retention time: 0.95 min MS ES$^+$: 605.32 [M+H]$^+$
4-6 SM = 3-4		5-[2-(dimethylamino)ethoxy]-2-[1-(4-fluorobenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 2.24 (s, 6H), 2.65 - 2.75 (m, 2H), 4.29 (s, 2H), 5.73 (s, 2H), 7.09 - 7.30 (m, 4H), 7.35 - 7.45 (m, 2H), 7.74 - 7.83 (m, 1H), 8.03 (d, 2H), 8.36 - 8.46 (m, 4H), 9.41 - 9.47 (m, 1H). LC-MS: retention time: 0.88 min MS ES$^+$: 484.0 [M+H]$^+$ Method B
4-7 SM = 3-3		2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-4-yl)-5-(1*H*-tetrazol-5-ylmethoxy)pyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 5.70 (s, 2H), 5.79 (s, 2H), 7.11 - 7.39 (m, 5H), 7.45 (t, 1H), 7.81 (d, 1H), 8.19 (d, 2H), 8.39 - 8.50 (m, 3H), 8.59 (s, 1H), 9.61 (br.s.,

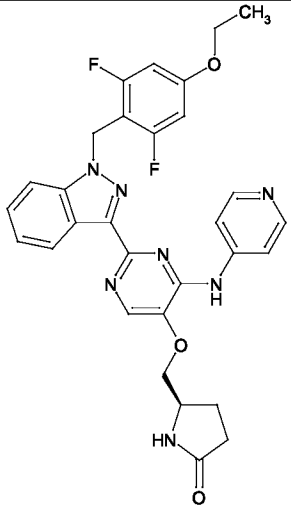
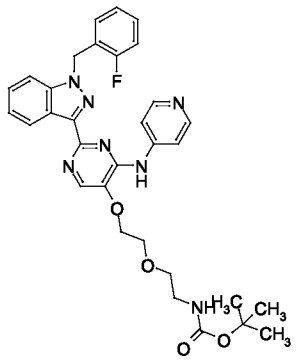
			1H). LC-MS: retention time: 0.92 min MS ES+: 495.2 [M+H]+
4-8 SM = 3-1		5-[2-(dimethylamino)ethoxy]-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine	1H-NMR (400 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 2.24 (s, 6H), 2.69 (t, 2H), 4.01 (q, 2H), 4.20 (t, 2H), 5.56 (s, 2H), 6.76 (d, 2H), 7.23 (t, 1H), 7.46 (td, 1H), 7.82 (d, 1H), 8.07 (dd, 2H), 8.36 - 8.45 (m, 4H), 9.38 (s, 1H). LC-MS: retention time: 0.80 min MS ES+: 546.2 [M+H]+
4-9 SM = 3-1		1-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)-3-(piperidin-1-yl)propan-2-ol	1H-NMR (500 MHz, DMSO-d6): δ [ppm]= 1.30 (t, 3H), 1.38 (m, 2H), 1.50 (m, 4H), 2.37 (m, 1H), 2.38-2.54 (m, 4H), 2.65 (m, 1H), 4.06 (q, 2H), 4.09 (br. d, 1H), 4.11 (br. s, 1H), 4.29 (br. d, 1H), 5.19 (br. d, 1H), 5.70 (s, 2H),

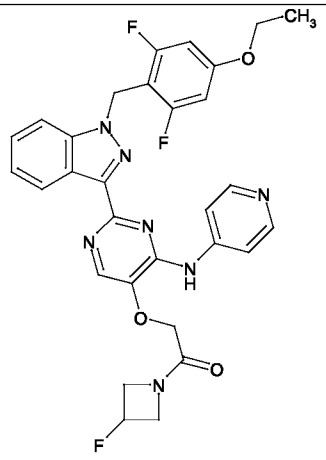
			6.81 (d, 2H), 7.28 (t, 1H), 7.50 (br. t, 1H), 7.86 (d, 1H), 8.12 (br. d, 2H), 8.38 (s, 1H), 8.45 - 8.48 (m, 3H), 9.14 (s, 1H). LC-MS (Method 5): retention time: 1.45 min MS ES+: 616.3 [M+H]+
4-10 SM = 3-1		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-(2-methoxyethoxy)-N-(pyridin-4-yl)pyrimidin-4-amine	1H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 3.32 (s, 3H), 3.76 (m, 2H), 4.01 (q, 2H), 4.36 (m, 2H), 5.65 (s, 2H), 6.76 (m, 2H), 7.23 (t, 1H), 7.46 (br. t, 1H), 7.82 (d, 1H), 8.12 (br. d, 2H), 8.35 - 8.45 (m, 4H), 9.13 (s, 1H).
4-11 SM = 3-1		tert-butyl 2-[({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methyl]morpholine-4-	1H-NMR (300 MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 1.37 (s, 9H), 2.91 (m, 2H), 3.45 (br. t, 1H), 3.70 (br. d, 1H), 3.80 - 4.06 (m, 5H), 4.27 (d, 2H), 5.65 (s, 2H), 6.76 (m, 2H), 7.23 (t, 1H), 7.46 (t, 1H), 7.82 (d, 1H), 8.11

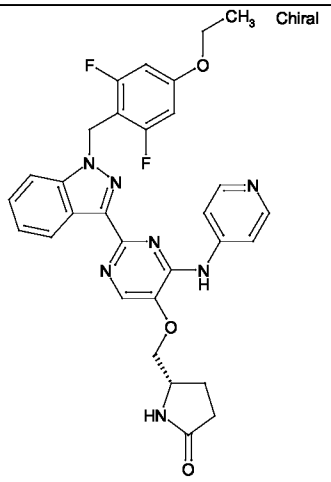
		carboxylate	(br. d, 2H), 8.35 - 8.45 (m, 4H), 9.10 (s, 1H).
4-12 SM = 3-1		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(morpholin-4-yl)ethoxy]-N-(pyridin-4-yl)pyrimidin-4-amine	1H-NMR (300MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 2.79 (t, 2H), 3.51(m, 4H), 3.70 (br. d, 1H), 4.01 (q, 2H), 4.34 (t, 2H), 5.65 (s, 2H), 6.76 (m, 2H), 7.23 (t, 1H), 7.46 (t, 1H), 7.82 (d, 1H), 8.12 (br. d, 2H), 8.35 - 8.45 (m, 4H), 9.08 (s, 1H). LC-MS (Method 5): retention time: 1.14 min MS ES+: 588.2 [M+H]+
4-13 SM = 3-3		2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-{[3-(methoxymethyl)-1,2,4-oxadiazol-5-yl]methoxy}-N-(pyridin-4-yl)pyrimidin-4-amine	1H-NMR (300MHz, DMSO-d6): δ [ppm]= 3.30 (s, 3H), 4.55 (s, 2H), 5.78 (s, 4H), 7.12-7.39 (m, 5H), 7.44 (br. t, 1H), 7.81 (d, 1H), 8.12 (br. d, 2H), 8.37 - 8.47 (m, 4H), 9.50 (s, 1H). LC-MS (Method 5): retention time: 1.20 min MS ES+: 539.3 [M+H]+

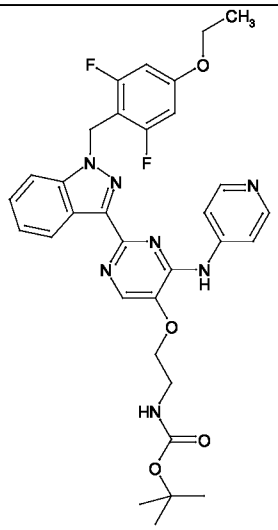
4-14 SM = 3-1		ethyl ({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-yla-mino)pyrimidin-5-yl}oxy)acetate	LC-MS (Method 5): retention time: 1.38 min MS ES+: 561.2 [M+H]+
4-15 SM = 3-1		1-(3,3-difluoroazetidin-1-yl)-2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-yla-mino)pyrimidin-5-yl}oxy)ethanone	1H-NMR (300MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 4.01 (q, 2H), 4.39 (br. t, 2H), 4.73 (br. t, 2H), 4.98 (s, 2H), 5.66 (s, 2H), 6.76 (m, 2H), 7.23 (t, 1H), 7.46 (t, 1H), 7.82 (d, 1H), 8.17 (d, 2H), 8.30 (s, 1H), 8.38 - 8.45 (m, 3H), 9.56 (s, 1H). LC-MS (Method 5): retention time: 1.31 min MS ES+: 608.2 [M+H]+
4-16 SM = 3-1		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(methylsulfa-nyl)ethoxy]-N-(pyridin-4-	1H-NMR (300MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 2.15 (s, 3H), 2.96 (t, 2H), 4.01 (q, 2H), 4.39 (t, 2H), 5.56 (s, 2H), 6.76 (m, 2H), 7.23 (t, 1H), 7.46 (t, 1H), 7.82 (d, 1H),

		yl)pyrimidin-4-amine	8.12 (d, 2H), 8.37 - 8.45 (m, 4H), 9.11 (s, 1H). LC-MS (Method 5): retention time: 1.42 min MS ES+: 550.5 [M+H]+
4-17 SM = 3-1		2-[2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-yla-mino)pyrimidin-5-yl}oxy)ethoxy]ethanol	1H-NMR (300MHz, DMSO-d6): δ [ppm]= 1.26 (t, 3H), 3.52 (s, 4H), 3.85 (m, 2H), 4.01 (q, 2H), 4.36 (m, 2H), 4.63 (m, 1H), 5.56 (s, 2H), 6.76 (m, 2H), 7.23 (t, 1H), 7.46 (t, 1H), 7.82 (d, 1H), 8.12 (d, 2H), 8.35 - 8.45 (m, 4H), 9.10 (s, 1H). LC-MS (Method 5): retention time: 1.24 min MS ES+: 561.4 [M+H]+
4-18 SM = 3-1		formic acid - (5S)-5-[({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-yla-mino)pyrimidin-5-yl}oxy)methyl]py	1H-NMR (400MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 1.64 - 1.85 (m, 1H), 2.13 - 2.29 (m, 3H), 3.86 - 4.09 (m, 4H), 4.28 - 4.38 (m, 1H), 5.65 (s, 2H), 6.71 – 6.88 (m, 2H), 7.23 (t, 1H), 7.43 – 7.48 (m,

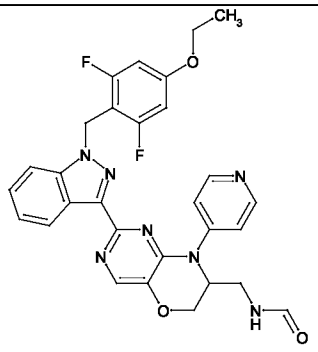
		rrolidin-2-one (1:1)	1H), 7.81 (d, 1H), 8.00 - 8.15 (m, 3H), 8.23 - 8.35 (m, 2H), 8.37 - 8.50 (m, 3H), 8.90 (s, 1H). LC-MS: retention time: 0.96 min MS ES+: 572.3 [M+H]+
4-19 SM = 3-1	 Chiral	(5R)-5-[({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-yla-mino)pyrimidin-5-yl}oxy)methyl]pyrrolidin-2-one	1H-NMR (300MHz, DMSO-d6): δ [ppm]= 1.26 (t, 3H), 2.14-2.28 (m, 4H), 3.88-4.06 (m, 2H), 4.01 (q, 2H), 4.32 (br. d, 1H), 5. 65 (s, 2H), 6.76 (m, 2H), 7.23 (t, 1H), 7.46 (t, 1H), 7.82 (d, 1H), 8.07 (d, 2H), 8.26-8.33 (m, 2H), 8.39-8.46 (m, 3H), 8.90 (s, 1H). LC-MS (Method 5): retention time: 1.22 min MS ES+: 572.3 [M+H]+
4-20 SM = 3-3		tert-butyl {2-[2-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-	1H-NMR (400MHz, DMSO-d6): δ [ppm]= 1.31 (s, 9H), 3.03 - 3.13 (m, 2H), 3.46 (t, 2H), 3.77 - 3.87 (m, 2H), 4.31 - 4.42 (m, 2H), 5.78 (s, 2H), 6.76 - 6.85

		yl}oxy)ethoxy]ethyl}carbamate	(m, 1H), 7.12 - 7.38 (m, 5H), 7.40 - 7.48 (m, 1H), 7.80 (d, 1H), 8.08 – 8.12 (m, 2H), 8.35 - 8.47 (m, 4H), 9.18 (s, 1H) LC-MS: retention time: 1.07 min MS ES+: 600.3 [M+H]+
4-21 SM = 3-1		2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-yla-mino)pyrimidin-5-yl}oxy)-1-(3-fluoroazetidin-1-yl)ethanone	1H-NMR (300MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 3.90 - 3.97 (m, 1 H), 4.01 (q, 2H), 4.29 (m, 2H), 4.56 (m, 1H), 4.91 (s, 2H), 5.29 - 5.54 (m, 1H), 5.66 (s, 2H), 6.76 (m, 2H), 7.24 (t, 1H), 7.46 (t, 1H), 7.82 (d, 1H), 8.16 (d, 2H), 8.26 (s, 1H), 8.38 - 8.45 (m, 3H), 9.61 (s, 1H). LC-MS (Method 5): retention time: 1.29 min MS ES+: 590.4 [M+H]+

4-22 SM = 3-1		(5S)-5-[({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-yla-mino)pyrimidin-5-yl}oxy)methyl]pyrrolidin-2-one	1H-NMR (300MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 1.64 - 1.88 (m, 1H), 2.15 – 2.28 (m, 3H), 3.84 - 4.09 (m, 4H), 4.32 (dd, 1H), 5.65 (s, 2H), 6.73 – 6.81 (m, 2H), 7.24 (t, 1H), 7.46 (t, 1H), 7.82 (d, 1H), 8.07 (d, 2H), 8.24 - 8.50 (m, 5H), 8.94 (s, 1H). LC-MS: retention time: 1.21 min MS ES+: 572.3 [M+H]+

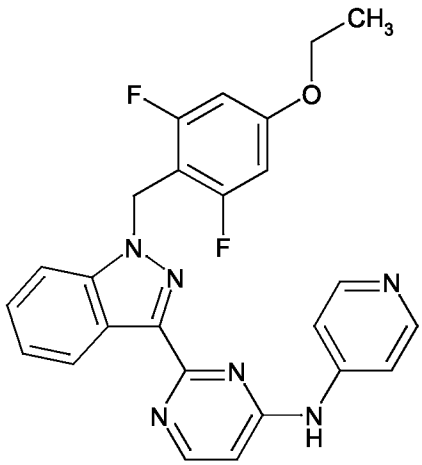
4-23 SM = 3-1		tert-butyl [2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-yla-mino)pyrimidin-5-yl}oxy)ethyl]carbamate	LC-MS (Method 5): retention time: 1.43 min MS ES+: 618.3 [M+H]+

The following compound was formed according to the same procedure using 5-chloromethyl-2-oxazolidinone and the indicated starting material (SM = starting material):

4-24 SM = 3-1		N-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-8-(pyridin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-7-yl}methyl)formamide	

Example 5-1

Preparation of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-N-(pyridin-4-yl)-pyrimidin-4-amine



100 mg of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl trifluoromethanesulfonate (1-7-2, 0.165 mmol, 1. eq.), 0,74 mg of palladium (II) acetate (0,003 mmol, 0,02 eq.) and 1,36 mg of propane-1,3-diylbis(diphenylphosphane) were dissolved in 1 ml of DMF under a nitrogen atmosphere. The mixture was heated to 60℃ bath tempe rature. Then 0,66 ml of triethylsilane (0.41 mmol, 2,5 eq.) were added. The resulting mixture was stirred at 60 ℃ bath temperature for 18 hours. Then the mixtu re was partitioned between

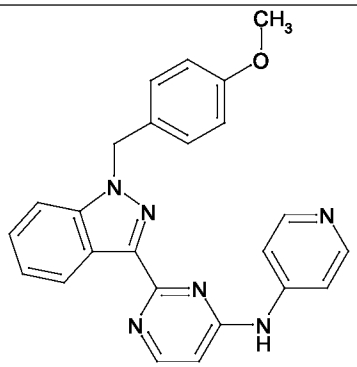
saturated aq. sodium hydrogen carbonate solution and dichloromethane. The phases were separated and the aqueous layer was extracted twice with dichloromethane. The combined organic layers were washed with brine, dried over a silicone filter and concentrated in vacuo. Preparative HPLC purification provided 16 mg (0.03 mmol, 20,1%) of the analytically pure target compound.

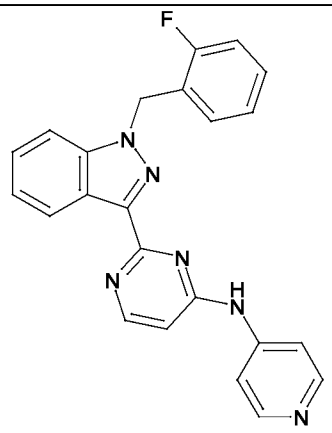
^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.25 (t, 3H), 4.00 (q, 2H), 5.68 (s, 2H), 6.70 - 6.86 (m, 3H), 7.26 (t, 1H), 7.42 - 7.53 (m, 1H), 7.78 - 7.97 (m, 2H), 8.11 (s, 1H), 8.38 (br. s., 2H), 8.44 - 8.57 (m, 2H), 10.07 (s, 1H).

LC-MS:
retention time: 0.97 min
MS ES$^+$: 459.1 $[M+H]^+$

Method B

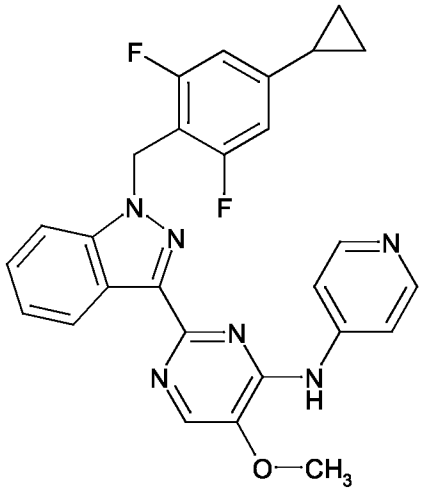
The following compounds were prepared according to the same procedure using the indicated starting materials (SM = starting material):

5-2		2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 3.70 (s, 3H), 5.72 (s, 2H), 6.90 (d, 3H), 7.28 (t, 1H), 7.35 (d, 2H), 7.45 (t, 1H), 7.83 (d, 1H), 7.92 (br. s., 2H), 8.37 - 8.55 (m, 3H), 8.58 (d, 1H), 10.13 (s, 1H). LC-MS: retention time: 0.86 min MS ES$^+$: 409.1 $[M+H]^+$ Method B

5-3 SM = 1-7-1		2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 5.81 (s, 2H), 6.84 (d, 1H), 7.13 - 7.39 (m, 5H), 7.43 - 7.49 (m, 1H), 7.79 - 7.89 (m, 3H), 8.38 (d, 2H), 8.49 (d, 1H), 8.53 (d, 1H), 10.07 (s, 1H). LC-MS: retention time: 0.93 min MS ES$^+$: 397.25 $[M+H]^+$

Example 6-1

Preparation of 2-[1-(4-cyclopropyl-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine



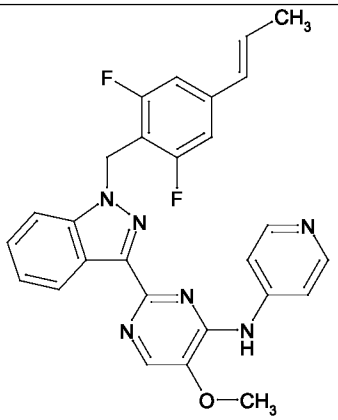
100 mg of 2-[1-(4-bromo-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine (2-12-1, 0.191 mmol, 1. eq.) were suspended in 3 ml of dry toluene. 21,3 mg of cyclopropylboronic acid (0,248 mmol, 1,3 eq.) 5,36 mg of tricyclohexylphosphane (0,019 mmol, 0,1 eq.), 142 mg of potassium phosphate (0,669 mmol, 3,5 eq.) and 50 µl of water were added. Then 2,15 mg of pal-

ladium (II) acetate (0,01 mmol, 0,05 eq.) were added under a nitrogen atmosphere. The mixture was stirred at 100 °C bath temperature for 5 hours. Upon the mixture was cooled to room temperature it was partitioned between water and dichloromethane/ isopropanol 4:1. The phases were separated and the aqueous layer was extracted twice with dichloromethane/ isopropanol 4:1. The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. Preparative HPLC purification provided 28,7 mg (0.06 mmol, 31%) of the analytically pure target compound.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 0.66-0.74 (m, 2H), 0.89-0.98 (m, 2H), 1.93 (m, 1H), 4.00 (s, 3H), 5.67 (s, 2H), 6.85 - 6.92 (m, 2H), 7.23 (t, 1H), 7.46 (t, 1H), 7.83 (d, 1H), 8.13 - 8.20 (m, 2H), 8.32 (s, 1H), 8.34 - 8.40 (m, 2H), 8.43 (d, 1H), 9.41 (s, 1H).

LC-MS:
retention time: 1.06 min
MS ES$^+$: 485.1 $[M+H]^+$
Method B

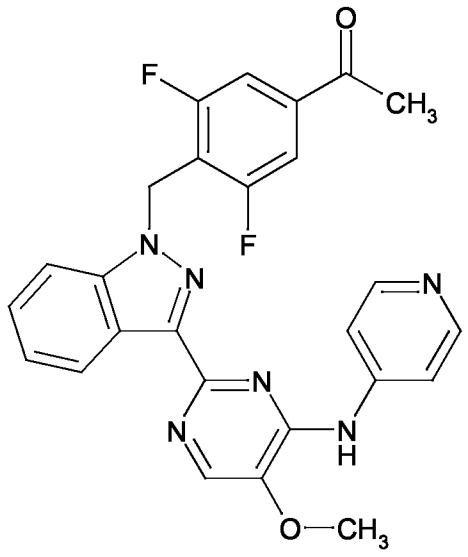
The following compounds were prepared according to the same procedure using the indicated starting materials (SM = starting material):

6-2 SM = 2-12-1		2-(1-{2,6-difluoro-4-[(1*E*)-prop-1-en-1-yl]benzyl}-1*H*-indazol-3-yl)-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.82 (d, 3H), 4.03 (s, 3H), 5.73 (s, 2H), 6.33 - 6.55 (m, 2H), 7.17 - 7.30 (m, 3H), 7.45 - 7.53 (m, 1H), 7.86 (d, 1H), 8.14 - 8.22 (m, 2H), 8.34 (s, 1H), 8.37 - 8.42 (m, 2H), 8.46 (d, 1H),

			9.40 (s, 1H). LC-MS: retention time: 8.67 min MS ES+: 485.1 [M+H]+

Example 7-1

Preparation of 1-[3,5-difluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)phenyl]ethanone



Step 1: 2-{1-[4-(1-ethoxyethenyl)-2,6-difluorobenzyl]-1*H*-indazol-3-yl}-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine

100mg of 2-[1-(4-bromo-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine (2-12-1, 0,191 mmol, 1 eq.) was suspended in dry toluol. 1,34 mg of dichloropalladium - triphenylphosphane (1:2) (0,002 mmol, 0,01 eq.) and 71 µl of tributyl(1-ethoxyethenyl)stannane (0,21 mmol, 1,2 eq.) were added. The mixture was stirred for 5 hours at 100°C bath temperature and for 18 hours at 120°C bath temperature. 5 mg of dichloropalladium - triphenylphosphane (1:2) (0,007 mmol, 0,035 eq.) and 140 µl of tributyl(1-ethoxyethenyl)stannane (0,42

mmol, 2,4 eq.) and 1 ml of 1-methylpyrrolidin-2-one were added. The solution was stirred for 3 days at 100℃ bath temperature. 5 mg of dichloropalladium - triphenylphosphane (1:2) (0,007 mmol, 0,035 eq.) and 140 µl of tributyl(1-ethoxyethenyl)stannane (0,42 mmol, 2,4 eq.) were added and stirred at 100 ℃ again for 22 hours. The reaction mixture was concentrated in vacuo and purified by flash chromatography to yield 119 mg (0.2 mmol, 107%) of the analytically pure target compound.

^{1}H-NMR (300MHz, DMSO-d6): δ [ppm]= 1.25 - 1.33 (t, 3H), 3.78 - 3.89 (m, 2H), 4.00 (s, 3H), 4.34 - 4.41 (d, 1H), 4.91 - 4.97 (d, 1H), 5.74 (s, 2H), 7.24 (t, 1H), 7.37 (d, 1H), 7.43 - 7.64 (m, 2H), 7.84 (d, 1H), 8.09 - 8.18 (dd, 2H), 8.32 (s, 1H), 8.34 - 8.39 (dd, 2H), 8.44 (d, 1H), 9.32 - 9.41 (s, 1H).

LC-MS:

retention time: 1.09 min
MS ES$^+$: 515.1 $[M+H]^+$

Method B

Step 2: 1-[3,5-difluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)phenyl]ethanone

119 mg of 2-{1-[4-(1-ethoxyethenyl)-2,6-difluorobenzyl]-1*H*-indazol-3-yl}-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine (0,231 mmol, 1 eq.) and 66 mg of 4-methylbenzenesulfonic acid hydrate (1:1) (0,347 mmol, 1,5 eq.) were dissolved in 2,4 ml of ethanol and 0,6 ml of water. The mixture was stirred for one hour at 80℃ bath temperature. The reaction mixture was concentrated in vacuo. The residue was partitioned between ethyl acetate and saturated sodium hydrogen carbonate solution. The phases were separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash chromatography and preparative HPLC purification to yield 26 mg (0.05 mmol, 22,7%) of the analytically pure target compound.

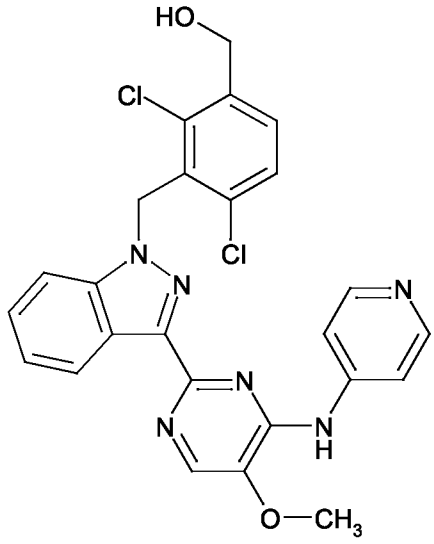
^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 2.54 (s, 3H), 4.00 (s, 3H), 5.82 (s, 2H), 7.25 (t, 1H), 7.49 (t, 1H), 7.69 (d, 2H), 7.87 (d, 1H), 8.14 (d, 2H), 8.31 (s, 1H), 8.37 (d, 2H), 8.44 (d, 1H), 9.38 (s, 1H).

LC-MS:
retention time: 0.95 min
MS ES$^+$: 487.1 $[M+H]^+$

Method B

Example 8-1

Preparation of [2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)phenyl]methanol



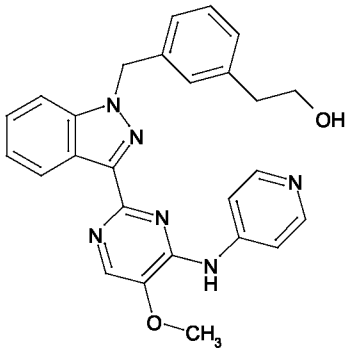
80 mg of methyl 2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)benzoate (2-16-1, 0.149 mmol, 1. eq.) was suspended in 2,4 ml of dry tetrahydrofuran under nitrogen atmosphere. The suspension was cooled with an ice bath to +3 ℃, upon which 254 µl of a 1 M lithium aluminium hydride solution in tetrahydrofuran (0,254 mmol, 1,7 eq.) were added dropwise. The ice bath was remove and the mixture was stirred at room temperature for 30 minutes. Then the mixture was acidified by 2 M sulfuric acid. The mixture formed a

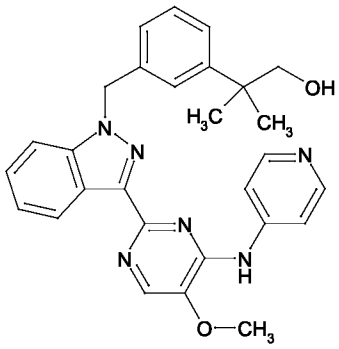
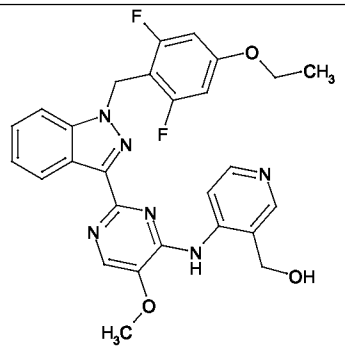
suspension which was filtered off and washed with water. The precipitate was dried in vacuo at 60 ℃ for 18 hours to yield 60 mg (0.11 mmol, 74,4%) of the analytically pure target compound.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 4.02 (s, 3H), 4.51 (s, 2H), 5.47 - 5.57 (m, 1H), 5.90 (s, 2H), 7.26 (t, 1H), 7.49 (t, 1H), 7.54 - 7.67 (m, 2H), 7.91 (d, 1H), 8.34 - 8.41 (m, 2H), 8.42 - 8.49 (m, 4H), 9.98 (s, 1H).

LC-MS:
retention time: 0.91 min
MS ES$^+$: 507.3 $[M+H]^+$
Method B

The following compounds were prepared according to the same procedure using the indicated starting materials (SM = starting material):

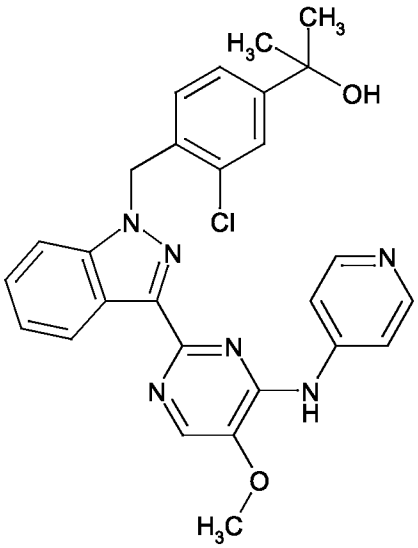
8-2 SM = 2-35-1		2-[3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)phenyl]ethanol	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 2.59 - 2.67 (m, 2H), 3.51 (d, 2H), 4.02 (s, 3H), 4.58 (s, 1H), 5.69 (s, 2H), 7.06 - 7.14 (m, 2H), 7.16 - 7.26 (m, 3H), 7.40 (t, 1H), 7.77 (d, 1H), 8.12 (dd, 2H), 8.31 - 8.46 (m, 4H), 9.42 (s, 1H). LC-MS: retention time:

			0.87 min MS ES+: 453.22 [M+H]+
8-3 SM = 2-41-1		2-[3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)phenyl]-2-methylpropan-1-ol	1H-NMR (300MHz, DMSO-d6): δ [ppm]= 1.13 (s, 6H), 4.05 (s, 3H), 4.57 - 4.66 (m, 1H), 5.69 - 5.76 (m, 4H), 7.03 (d, 1H), 7.15 - 7.27 (m, 3H), 7.37 - 7.48 (m, 2H), 7.79 (d, 1H), 8.32 - 8.54 (m, 6H), 9.97 - 10.04 (m, 1H). LC-MS: retention time: 0.87 min MS ES+: 481.4 [M+H]+ Method B
8-4 SM = 39-1		[4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridin-3-yl]methanol	1H-NMR (300MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H),3.99 (s, 3H), 4.01 (q, 2H), 4.67 (d, 2H), 5. 64 (s, 2H), 5. 96 (t, 1H), 6.76 (m, 2H), 7.23 (t,

			1H), 7.45 (t, 1H), 7.81 (d, 1H), 8.32-8.44 (m, 4H), 8.82 (d, 1H), 9.52 (s, 1H). LC-MS (Method 1): retention time: 1.03 min MS ES+: 481.4 [M+H]+

Example 9-1

Preparation of 2-[3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)phenyl]propan-2-ol



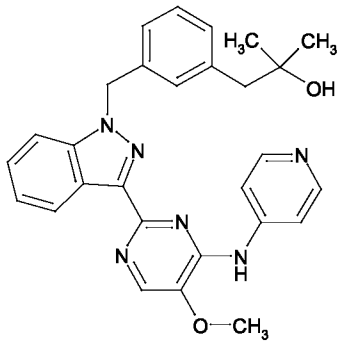
36 mg of methyl 3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)benzoate (2-11-1, 0.072 mmol, 1. eq.) were suspended in 583 µl of dry tetrahydrofuran under nitrogen atmosphere. The suspension was cooled with a freezing mixture to -75 °C. Then 90 µl of 1,6 M methyllithium solution in di-

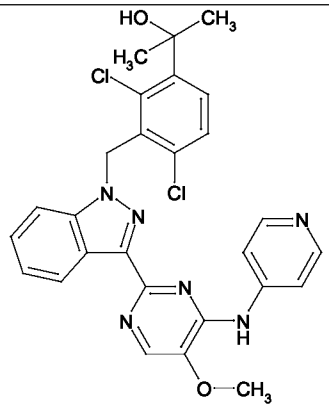
ethyl ether (0,144 mmol, 2 eq.) were added dropwise. The freezing mixture was removed and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was cooled with a freezing mixture to -75 °C. 90 µl of 1,6 M methyllithium solution in diethyl ether (0,144 mmol, 2 eq.) were added dropwise again. The freezing mixture was removed and the reaction mixture was stirred at room temperature for further 24 hours. Then the mixture was partitioned between water and dichloromethane/ isopropanol 4:1. The phases were separated and the aqueous layer was extracted twice with dichloromethane/ isopropanol 4:1. The combined organic layers were washed with brine, dried over a silicone filter and concentrated in vacuo. The residue was purified by preparative TLC to yield 3,5 mg (0.01 mmol, 9,3%) of the analytically pure target compound.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.34 (s, 6H), 4.01 (s, 3H), 5.11 (s, 1H), 5.77 (s, 2H), 7.13 (d, 1H), 7.21 - 7.27 (m, 1H), 7.34 (dd, 1H), 7.44 (ddd, 1H), 7.54 (d, 1H), 7.79 (d, 1H), 8.10 - 8.15 (m, 2H), 8.34 (s, 1H), 8.35 - 8.40 (m, 2H), 8.46 (d, 1H), 9.41 (s, 1H).

LC-MS:
retention time: 0.99 min
MS ES$^+$: 501.2 $[M+H]^+$

The following compounds were prepared according to the same procedure using the indicated starting materials (SM = starting material):

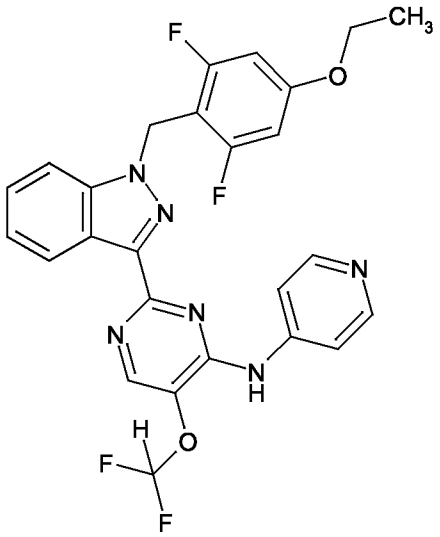
9-2 SM = 2-35-1		1-[3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)phenyl]-2-methylpropan-2-ol	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 0.94 (s, 6H), 1.18 - 1.22 (m, 2H), 4.02 (s, 3H), 4.24 (s, 1H), 5.70 (s, 2H), 7.03 - 7.25 (m, 5H), 7.38 (t, 1H), 7.74 (d, 1H), 8.12 (dd, 2H), 8.32 -

			8.46 (m, 4H), 9.40 - 9.45 (m, 1H). LC-MS: retention time: 0.95 min MS ES+: 481.26 [M+H]+
9-3 SM = 2-16-1		2-[2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)phenyl]propan-2-ol	^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm]= 1.51 (s, 6H), 4.00 (s, 3H), 5.37 (s, 1H), 5.91 (s, 2H), 7.22 - 7.28 (t, 1H), 7.45 - 7.50 (m, 1H), 7.62 (d, 1H), 7.86 - 7.91 (m, 2H), 8.14 (d, 2H), 8.32 (s, 1H), 8.37 (d, 2H), 8.48 (d, 1H), 9.35 (s, 1H). LC-MS: retention time: 1.09 min MS ES+: 535.2 [M+H]+

Example 10-1

Preparation of 5-(difluoromethoxy)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine

220

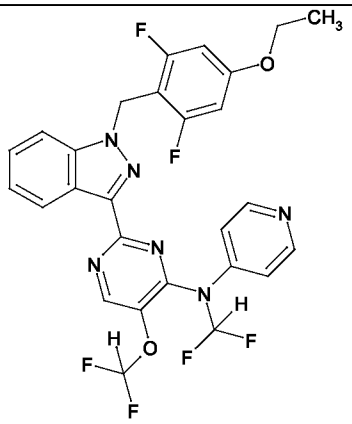
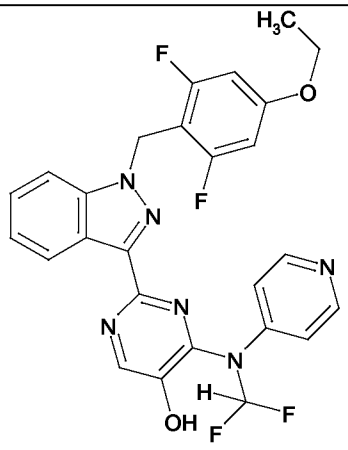


100 mg of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol (3-1, 0.211 mmol, 1. eq.) were suspended in 843 µl of 30% aq. potassium hydroxide solution (5,72 mmol, 27 eq.) and 843µl of acetonitrile. The suspension was cooled with a freezing mixture to -75 °C. 93 µl of 2-chloro-2,2-difluoro-1-phenylethanone (0,632 mmol, 3 eq.) were added dropwise. The freezing mixture was removed. The reaction mixture was stirred at 80 °C bath temperature for 4 hours. Then the mixture was partitioned between water and dichloromethane/ isopropanol 4:1. The phases were separated and the aqueous layer was extracted twice with dichloromethane/ isopropanol 4:1. The combined organic layers were washed with brine, dried over a silicone filter and concentrated in vacuo. Preparative HPLC purification provided 4 mg (0.01 mmol, 3,2%) of the analytically pure target compound.

^{1}H-NMR (500 MHz, DMSO-d_6): δ [ppm]= 1.30 (t, 3H), 4.05 (q, 2H), 5.73 (s, 2H), 6.81 (d, 2H), 7.16 - 7.48 (m, 2H), 7.50 - 7.57 (m, 1H), 7.90 (d, 1H), 8.12 - 8.17 (m, 2H), 8.44 - 8.49 (m, 3H), 8.54 (s, 1H), 9.71 (s, 1H).

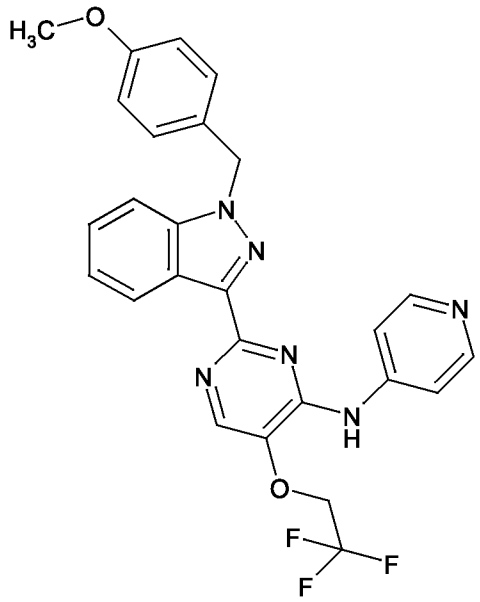
LC-MS:
retention time: 1.65 min
MS ES$^+$: 525.02 $[M+H]^+$

The following compounds were also formed during the same procedure:

10-2 SM = 3-1		5-(difluoromethoxy)-*N*-(difluoromethyl)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 1.25 (t, 3H), 4.00 (q, 2H), 5.65 (s, 2H), 6.72 (d, 2H), 6.91 (d, 1H), 7.16 - 7.25 (m, 1H), 6.97 - 7.47 (t, 2H), 7.34 - 7.60 (m, 2H), 7.76 (d, 1H), 7.91 (d, 2H), 8.36 (d, 1H), 8.46 (s, 1H). LC-MS: retention time: 1.15 min MS ES$^+$: 575.1 $[M+H]^+$
10-3 SM = 3-1		4-[(difluoromethyl)(pyridin-4-yl)amino]-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]pyrimidin-5-ol	1H-NMR (600MHz, DMSO-d6): δ [ppm]= 1.29 (t, 4H), 4.04 (q, 3H), 5.63 (s, 2H), 6.71 - 6.79 (m, 2H), 7.04 (br. s., 1H), 7.20 (t, 1H), 7.44 (td, 1H), 7.49 - 7.71 (m, 1H), 7.74 (d, 1H), 7.91 (d, 2H), 8.15 (s, 1H), 8.41 (d, 1H). LC-MS: retention time: 1.10 min MS ES+: 525.0 [M+H]+

Example 11-1

Preparation of 2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]-N-(pyridin-4-yl)-5-(2,2,2-trifluoroethoxy)pyrimidin-4-amine



143 mg of 2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol (3-2, 0.337 mmol, 1. eq.) were dissolved in 500 µl of dry DMF. Then 117 mg of 2,2,2-trifluoroethyl trifluoromethanesulfonate (0,505 mmol, 1,5 eq.), 93,1 mg of potassium carbonate (0,674 mmol, 2 eq.) and 24 µl of acetonitrile were added. The resulting mixture was stirred at 150 °C for 30 minutes in a microwave. Then the mixture was partitioned between water and dichloromethane/ isopropanol 4:1. The phases were separated and the aqueous layer was extracted twice with dichloromethane/ isopropanol 4:1. The combined organic layers were washed with brine, dried over a silicone filter and concentrated in vacuo. The residue was purified by flash chromatography and preparative TLC to yield 7,7 mg (0.01 mmol, 3,9%) of the analytically pure target compound.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 3.66 (s, 3H), 4.95 - 5.08 (m, 2H), 5.65 (s, 2H), 6.83 - 6.90 (m, 2H), 7.16 - 7.24 (m, 1H), 7.30 (d, 2H), 7.36 - 7.45 (m, 1H), 7.78 (d, 1H), 8.00 - 8.11 (m, 2H), 8.35 - 8.52 (m, 4H), 9.32 (s, 1H).

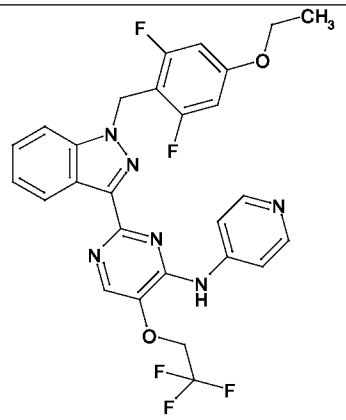
LC-MS:

retention time: 1.03 min

MS ES+: 507.1 [M+H]+

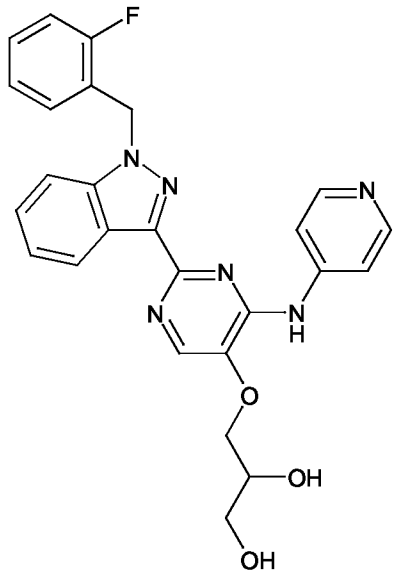
Method B

The following compounds were prepared according to the same procedure using the indicated starting materials (SM = starting material):

11-2 SM = 3-1		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-4-yl)-5-(2,2,2-trifluoroeth-oxy)pyrimidin-4-amine	^{1}H-NMR (400MHz, DMSO-d$_6$): δ [ppm]= 1.28 (t, 3H), 4.04 (q, 2H), 5.03 (q, 2H), 5.69 (s, 2H), 6.79 (d, 2H), 7.22 - 7.30 (m, 1H), 7.49 (ddd, 1H), 7.85 (d, 1H), 8.10 - 8.16 (m, 2H), 8.40 - 8.46 (m, 3H), 8.50 (s, 1H), 9.32 (s, 1H). LC-MS: retention time: 1.11 min MS ES+: 557.1 [M+H]+ Method B

Example 12-1

Preparation of 3-({2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)-pyrimidin-5-yl}oxy)propane-1,2-diol



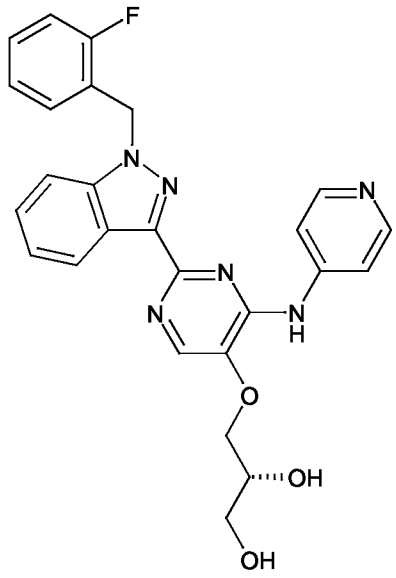
25,0 mg of 2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol (3-3, 0,06 mmol, 1 eq.), 28,2 mg of 3-bromo-propane-1,2-diol (0,18 mmol, 3 eq.) and 41,9 mg of potassium carbonate (0,30 mmol, 5 eq.) were suspended in 466 µl of dry DMF. The reaction mixture was stirred at 100 °C oil bath temperature for 18 hours. Then the mixture was partitioned between half saturated aq. sodium chloride solution and ethyl acetate. The phases were separated and the aqueouse layer was extracted once more with ethyl acetate and once with dichloromethane/isopropanol 4:1. The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The residue was purified by preparative thin layer chromatography to yield 2,60 mg (5.34 µmol, 9%) of the analytically pure target compound.

LC-MS:
retention time: 1.00 min
MS ES$^+$: 487.41 $[M+H]^+$

Example 12-2

Preparation of (2*R*)-3-({2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)propane-1,2-diol

225



Step 1: 5-{[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-4-yl)pyrimidin-4-amine

200 mg of 2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol (3-3, 0,49 mmol, 1 eq.), 94,6 mg of 2,2-dimethyl-4(R)-4-bromomethyl-1,3-dioxalane (0,49 mmol, 1 eq.) and 134 mg of potassium carbonate (0,97 mmol, 2 eq.) were suspended in 3,7 ml of dry DMF. The reaction mixture was stirred at 50 °C oil bath temperature for 18 hours. 201 mg of pot assium carbonate (1,46 mmol, 3 eq.) were added and the mixture was stirred at 90 °C oil bath temperature for further 24 hours. Then the mixture was partitioned between half saturated aq. ammonium chloride solution and dichloromethane/isopropanol 4:1. The phases were separated and the aqueous layer was extracted twice with dichloro-methane/isopropanol 4:1. The combined organic layers were washed with brine, dried over a silicone filter and concentrated in vacuo. The residue was purified by flash chromatography to yield 126 mg (0.27 mmol, 44%) of the analytically pure target compound.

^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.29 (s, 3H), 1.34 (s, 3H), 3.86 (dd, 1H), 4.15 (dd, 1H), 4.27 (dd, 2H), 4.54 (m, 1H), 5.78 (s, 2H), 7.12 - 7.38 (m, 5H), 7.40 - 7.47 (m, 1H), 7.80 (d, 1H), 8.04 - 8.09 (m, 2H), 8.38 - 8.46 (m, 4H), 9.11 (s, 1H).

LC-MS:
retention time: 1.00 min

MS ES+: 527.39 [M+H]+

Step 2: (2*R*)-3-({2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)-pyrimidin-5-yl}oxy)propane-1,2-diol hydrochloride (1:1)

124 mg of 5-{[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-4-yl)pyrimidin-4-amine (0.24 mmol, 1. eq.) were dissolved in 12 ml of acetonitrile. 515 µl of conc. hydrogen chloride (6,00 mmol, 20,8 eq.) were added dropwise. The reaction mixture was stirred at room temperature for 18 hours. The suspension was filtered off and washed with acetonitrile. The precipitate was dried at 45 °C under vacuo to yield 119 mg (0.23 mmol, 97%) of the analytically pure target compound.

^{1}H-NMR (600MHz, DMSO d_6): δ [ppm]= 3.49 (m, 2H), 3.94 (m, 1H), 4.14 (dd, 1H), 4.34 (dd, 1H), 4.73 (br. s, 2H), 5.82 (s, 2H), 7.15 (td, 1H), 7.19 - 7.30 (m, 2H), 7.34 (m, 1H), 7.46 (td, 1H), 7.49 (ddd, 1H), 7.80 (d, 1H), 8.41 (d, 1H), 8.58 (s, 1H), 8.65 (d, 2H), 8.75 (d, 2H), 10.72 (s, 1H), 14.82 (br. s., 1H).

LC-MS:
retention time: 0.86 min
MS ES+: 487.34 [M+H]+

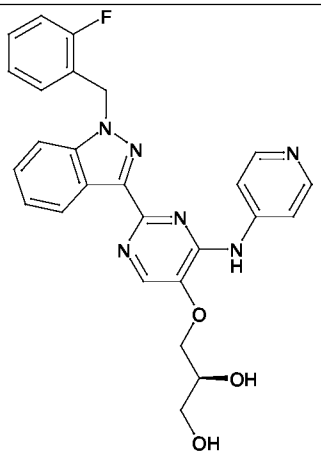
Step 3: (2*R*)-3-({2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)propane-1,2-diol

84,5 mg of (2*R*)-3-({2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)-pyrimidin-5-yl}oxy)propane-1,2-diol hydrochloride (1:1) was dissolved in water. 2M aq. sodium hydroxide solution was added. The mixture was stirred at room temperature for 3 hours. The resulting suspension was filtered off and washed with water to yield 52,9 mg (0,11 mmol, 67%) of the analytically pure target compound.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 3.50 (d, 2H), 3.85 - 3.97 (m, 1H), 4.01 - 4.13 (m, 1H), 4.23 - 4.30 (m, 1H), 4.79 (s, 1H), 5.20 - 5.27 (m, 1H), 5.78 (s, 2H), 7.11 - 7.39 (m, 5H), 7.44 (t, 1H), 7.80 (d, 1H), 7.99 - 8.07 (m, 2H), 8.33 (s, 1H), 8.39 - 8.46 (m, 3H), 9.14 (s, 1H).

LC-MS (chiral):
retention time: 0.85 min
MS ES+: 487.35 [M+H]+

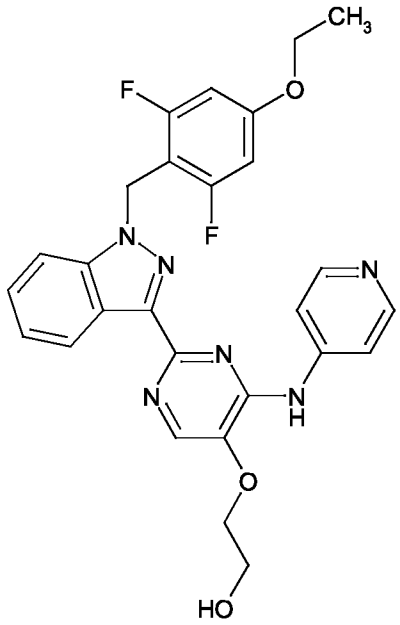
The following enatiomer was prepared according to the same procedure using the indicated starting material (SM = starting material) and 2,2-dimethyl-4(S)-4-bromomethyl-1,3-dioxalane:

12-3 SM = 3-3		(2*S*)-3-({2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)propane-1,2-diol	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 3.50 (d, 2H), 3.86 - 3.98 (m, 1H), 4.08 (s, 1H), 4.19 - 4.30 (m, 1H), 4.79 (s, 1H), 5.25 (d, 1H), 5.78 (s, 2H), 7.11 - 7.39 (m, 5H), 7.44 (t, 1H), 7.80 (d, 1H), 8.01 - 8.07 (m, 2H), 8.33 (s, 1H), 8.39 - 8.47 (m, 3H), 9.14 (s, 1H). LC-MS (chiral): retention time: 0.90 min MS ES+: 487.21 [M+H]+

Example 13-1

Preparation of 2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanol

228



Step 1:

182 mg of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol (3-1, 0,383 mmol, 1 eq.), 110 mg of (2-bromoethoxy)(*tert*-butyl)dimethylsilane (0,459 mmol, 1,2 eq.) and 159 mg of potassium carbonate were suspended in 3 ml of dry DMF under nitrogen atmosphere and stirred for 3 days at room temperature. Then the mixture was partitioned between water and dichloromethane. The phases were separated and the aqueous layer was extracted twice with dichloromethane. The combined organic layers were washed with half saturated aq. sodium chloride solution, dried over a silicone filter and concentrated in vacuo to yield 224 mg (0.32 mmol, 82,3%) of the analytically pure target compound.

^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 0.00 (s, 6H), 0.79 (s, 9H), 1.25 (t, 3H), 4.01 (d, 4H), 4.30 - 4.39 (m, 2H), 5.65 (s, 2H), 6.77 (d, 2H), 7.23 (t, 1H), 7.46 (t, 1H), 7.82 (d, 1H), 8.07 - 8.14 (m, 2H), 8.34 - 8.45 (m, 4H), 9.07 - 9.14 (m, 1H).

LC-MS:
retention time: 1.70 min
MS ES$^+$: 633.4 $[M+H]^+$

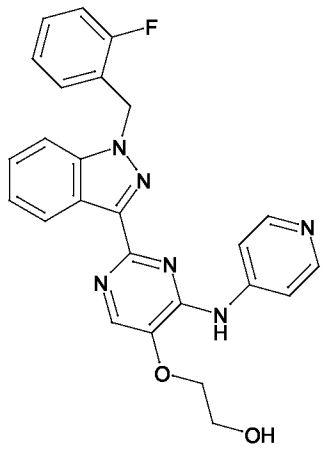
Step 2:

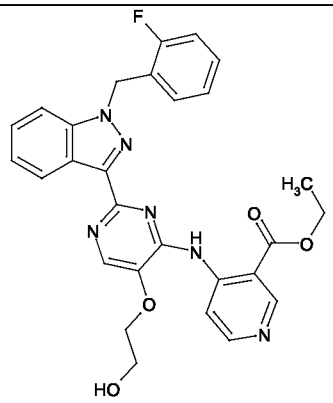
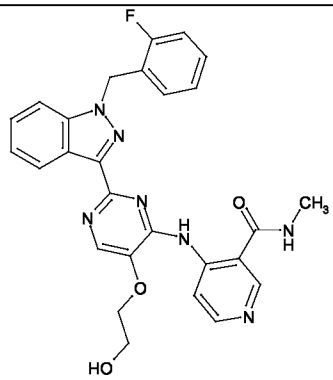
224 mg of 5-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethoxy)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-4-yl)pyrimidin-4-amine (0.337 mmol, 1. eq.) were dissolved in 3 ml of dry dioxane under nitrogen atmosphere. 442 µl of 4 M hydrogen chloride solution in dioxane were added and gave immediately a suspension. This suspension was stirred for 30 minutes. Then 10 ml of a aq. saturated sodium hydrogen carbonate solution were added. The suspension was filtered off and washed with water to yield 210 mg (0.34 mmol, 97,0%) of the analytically pure target compound.

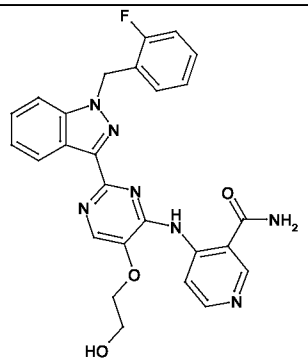
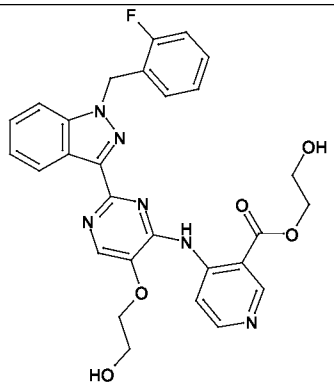
^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.28 (t, 3H), 3.83 (d, 2H), 4.04 (q, 2H), 4.24 (t, 2H), 5.11 (br. s., 1H), 5.68 (s, 2H), 6.75 - 6.84 (m, 2H), 7.26 (t, 1H), 7.45 - 7.52 (m, 1H), 7.85 (d, 1H), 8.09 - 8.14 (m, 2H), 8.36 (s, 1H), 8.41 - 8.48 (m, 3H), 9.12 (s, 1H).

LC-MS:
retention time: 0.95 min
MS ES$^+$: 519.4 $[M+H]^+$
Method B

The following compounds were prepared according to the same two-step procedure using the indicated starting materials (SM = starting material):

13-2 SM = 3-3		2-({2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanol	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 3.77 - 3.85 (m, 2H), 4.22 (t, 2H), 5.10 (t, 1H), 5.78 (s, 2H), 7.12 - 7.39 (m, 5H), 7.44 (td, 1H), 7.80 (d, 1H), 8.04 - 8.09 (m, 2H), 8.35 (s, 1H), 8.40 - 8.46 (m, 3H), 9.17 (s, 1H). LC-MS: retention time: 0.95 min MS ES$^+$: 457.32 $[M+H]^+$

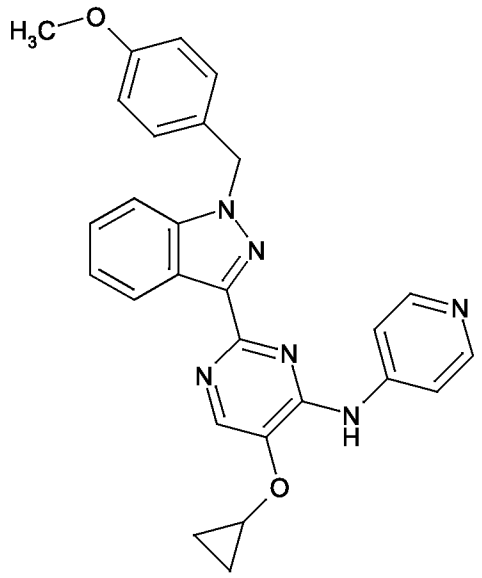
13-3 SM = 30-3		ethyl 4-({2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)pyridine-3-carboxylate	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.35 (t, 3H), 3.83 (q, 2H), 4.33 (t, 2H), 4.40 (q, 2H), 4.90 (t, 1H), 5.79 (s, 2H), 7.12 - 7.39 (m, 5H), 7.46 (t, 1H), 7.82 (d, 1H), 8.45 (d, 1H), 8.50 (s, 1H), 8.58 (d, 1H), 9.02 - 9.09 (m, 1H), 9.29 (d, 1H), 11.23 (s, 1H). LC-MS: retention time: 1.12 min MS ES$^+$: 529.0 $[M+H]^+$ Method B
13-4 SM = 13-3	 (derived from 13-3 via amidation and subsequent desilylation)	4-({2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)-*N*-methylpyridine-3-carboxamide	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 2.81 (d, 3H), 3.83 (q, 2H), 4.29 (t, 2H), 4.83 (t, 1H), 5.79 (s, 2H), 7.12 - 7.38 (m, 5H), 7.41 - 7.49 (m, 1H), 7.81 (d, 1H), 8.42 - 8.47 (m, 2H), 8.50 (d, 1H), 8.84 (s, 1H), 8.91 (d, 1H), 9.15 (d, 1H), 11.91 (s, 1H). LC-MS: retention time: 0.93 min MS ES$^+$: 514.4 $[M+H]^+$ Method B

13-5 SM = 30-1		4-({2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-(2-hydroxyeth-oxy)pyrimidin-4-yl}amino)pyridine-3-carboxamide	LC-MS: retention time: 0.96 min MS ES$^+$: 500.1 $[M+H]^+$ Method B
13-6 SM = 30-2		2-hydroxyethyl 4-({2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-(2-hydroxyeth-oxy)pyrimidin-4-yl}amino)pyridine-3-carboxylate	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 3.69 - 3.77 (m, 2H), 3.79 - 3.88 (m, 2H), 4.28 - 4.40 (m, 4H), 4.86 - 4.94 (m, 1H), 4.96 - 5.04 (m, 1H), 5.76 - 5.83 (m, 2H), 7.13 - 7.40 (m, 5H), 7.46 (t, 1H), 7.82 (d, 1H), 8.45 (d, 1H), 8.51 (s, 1H), 8.59 (d, 1H), 9.15 (s, 1H), 9.30 (d, 1H), 11.22 - 11.27 (m, 1H). LC-MS: retention time: 1.15 min MS ES$^+$: 545.0 $[M+H]^+$ Method B

Example 14-1

Preparation of 5-(cyclopropyloxy)-2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-4-yl)pyrimidin-4-amine

232



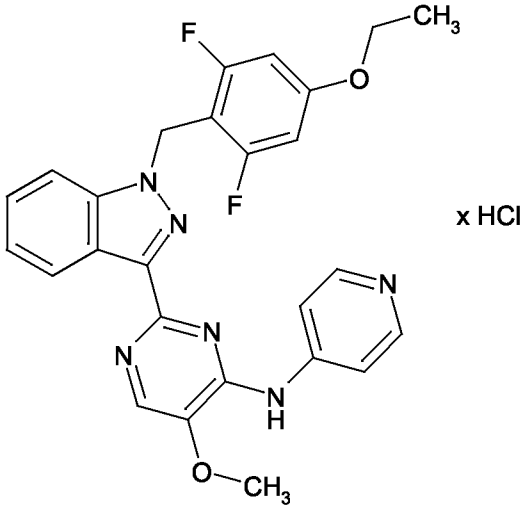
100 mg of 2-[1-(4-methoxybenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol (3-2, 0.236 mmol, 1. eq.), 34,2 mg of bromocyclopropane (0,283 mmol, 1,2 eq.), 44,9 mg of copper (I) chloride (0,236 mmol, 1 eq.) and 154 mg of cesium carbonate (0,471 mmol, 2 eq.) were suspended in 3 ml of dry DMF. The reaction mixture was stirred at 60 °C bath temperature for 18 hours. Then the mixture was partitioned between half saturated aq. ammonium chloride solution and dichloromethane/ isopropanol 4:1. The phases were separated and the aqueous layer was extracted twice with dichloromethane/ isopropanol 4:1. The combined organic layers were washed with brine including a precipitate which was separated with filtering it off. The precipitate was purified by preparative HPLC to yield 2,58 mg (0.047 mmol, 2%) of the analytically pure target compound.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 3.65 (s, 3H), 4.90 (d, 2H), 5.19 - 5.40 (m, 2H), 5.60 (s, 2H), 6.01 - 6.18 (m, 1H), 6.85 (d, 2H), 7.09 - 7.18 (m, 1H), 7.26 (d, 2H), 7.34 (t, 1H), 7.65 (d, 1H), 7.94 (s, 1H), 8.28 (br. s., 1H), 8.43 (dd, 3H), 8.57 (br. s., 2H).

LC-MS:
retention time: 0.95 min
MS ES$^+$: 465.1 [M+H]$^+$Method B

Example 15-1

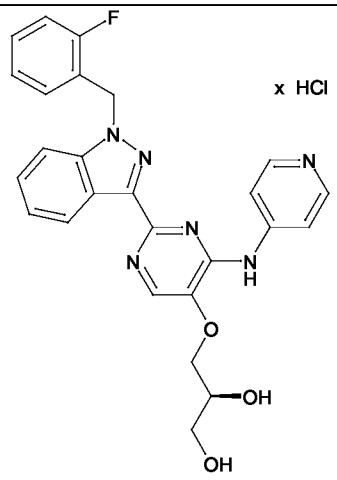
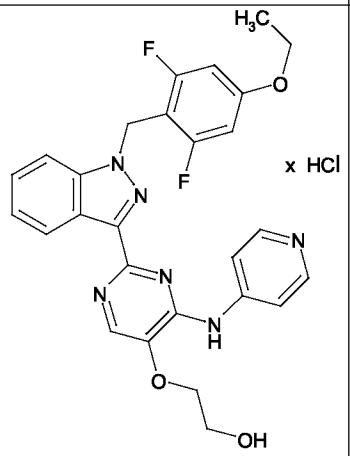
Preparation of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine hydrochloride (1:1)

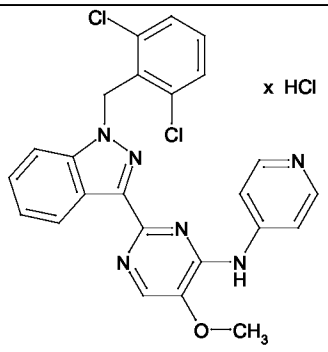
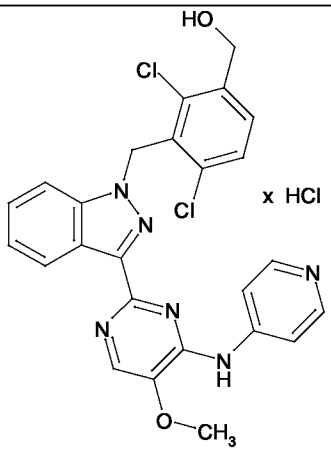


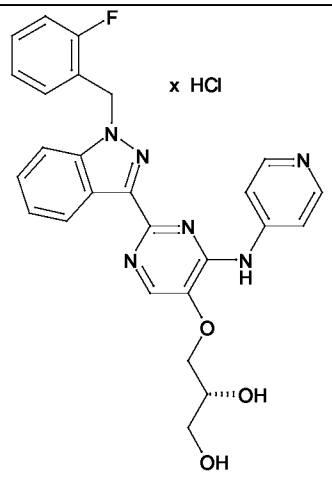
150 mg of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine (2-5-1, 0.307 mmol, 1. eq.) were dissolved in a mixture of 5,9 ml of dry dichloromethane and 2,5 ml of dry methanol. 0,25 ml of 1,25 M hydrogen chloride solution in methanol were added. The mixture was stirred at room temperature for 1 hour. Then the mixture was concentrated in vacuo to yield 161 mg (0.29 mmol, 95,9%) of the analytically pure target compound.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.25 (t, 3H), 3.93 - 4.08 (m, 5H), 5.66 (s, 2H), 6.72 - 6.82 (m, 2H), 7.24 (t, 1H), 7.42 - 7.51 (m, 1H), 7.82 (d, 1H), 8.34 (d, 2H), 8.39 - 8.48 (m, 4H), 9.85 (s, 1H).

LC-MS:
retention time: 1.08 min
MS ES$^+$: 489.1 $[M+H]^+$
Method B

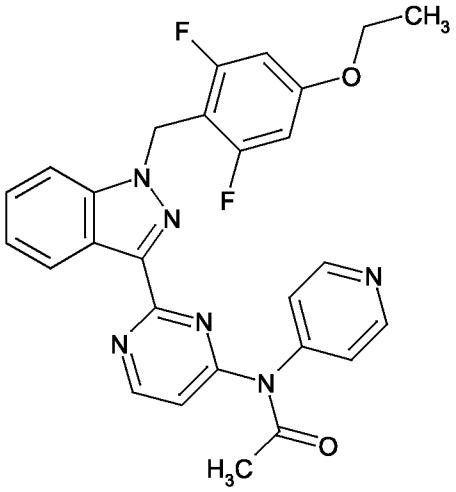
15-2 SM = 12-2		(2*S*)-3-({2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)propane-1,2-diol hydrochloride (1:1)	^{1}H-NMR (600MHz, DMSO d_6): δ [ppm]= 3.50 - 3.58 (m, 2H), 3.95 - 4.01 (m, 1H), 4.18 (dd, 1H), 4.38 (dd, 1H), 5.85 (s, 2H), 7.18 (td, 1H), 7.24 - 7.28 (m, 1H), 7.28 - 7.33 (m, 2H), 7.35 - 7.40 (m, 1H), 7.49 (ddd, 1H), 7.83 (d, 1H), 8.45 (d, 1H), 8.62 (s, 1H), 8.68 (d, 2H), 8.76 (d, 2H), 10.69 (s, 1H), 14.79 (br. s., 1H). LC-MS: retention time: 0.87 min MS ES$^+$: 487.45 $[M+H]^+$
15-3 SM = 13-1		2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanol hydrochloride (1:1)	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.25 (t, 3H), 3.81 (d, 2H), 4.01 (q, 2H), 4.26 (t, 2H), 5.09 (br. s., 1H), 5.66 (s, 2H), 6.73 - 6.81 (m, 2H), 7.25 (t, 1H), 7.47 (t, 1H), 7.82 (d, 1H), 8.33 - 8.44 (m, 3H), 8.45 - 8.54 (m, 3H), 9.74 (br. s., 1H). LC-MS: retention time: 1.04 min MS ES$^+$: 519.1 $[M+H]^+$ Method B

15-4 SM = 2-9-1		2-[1-(2,6-dichlorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine hydrochloride (1:1)	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 4.01 (s, 3H), 5.88 (s, 2H), 7.26 (t, 1H), 7.39 - 7.53 (m, 2H), 7.56 - 7.62 (m, 2H), 7.91 (d, 1H), 8.27 (d, 2H), 8.37 - 8.43 (m, 3H), 8.47 (d, 1H), 9.69 (s, 1H). LC-MS: retention time: 1.05 min MS ES$^+$: 476.9 [M+H]$^+$
15-5 SM = 8-1		[2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)phenyl]methanol hydrochloride (1:1)	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 3.96 - 4.02 (m, 3H), 4.52 (s, 2H), 5.47 - 5.55 (m, 1H), 5.89 (s, 2H), 7.25 (t, 1H), 7.48 (t, 1H), 7.55 - 7.66 (m, 2H), 7.90 (d, 1H), 8.09 - 8.15 (m, 2H), 8.31 (s, 1H), 8.34 - 8.39 (m, 2H), 8.48 (d, 1H), 9.32 (s, 1H). LC-MS: retention time: 0.99 min MS ES$^+$: 507.0 [M+H]$^+$ Method B

15-6 SM = 12-3		(2*R*)-3-({2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)propane-1,2-diol hydrochloride (1:1)	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 3.43 - 3.54 (m, 2H), 3.90 - 3.98 (m, 1H), 4.14 (dd, 1H), 4.34 (dd, 1H), 5.82 (s, 2H), 7.11 - 7.18 (m, 1H), 7.19 - 7.38 (m, 4H), 7.46 (ddd, 1H), 7.80 (d, 1H), 8.41 (d, 1H), 8.58 (s, 1H), 8.65 (d, 2H), 8.74 (d, 2H), 10.72 (s, 1H). LC-MS: retention time: 0.86 min MS ES$^+$: 487.34 $[M+H]^+$

Example 16-1

Preparation of *N*-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]pyrimidin-4-yl}-*N*-(pyridin-4-yl)acetamide

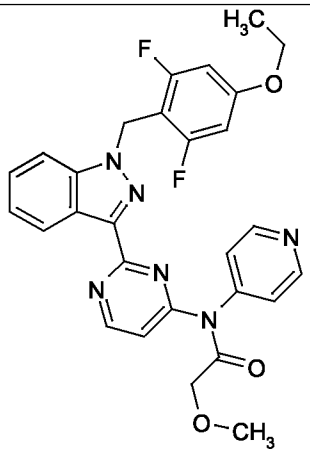


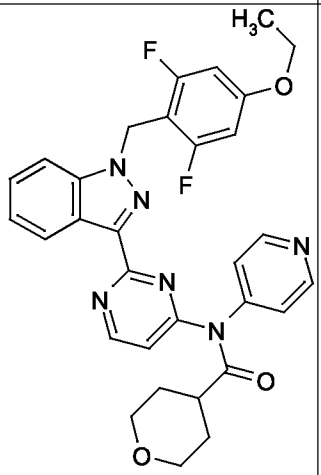
100 mg of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-4-yl)-pyrimidin-4-amine (5-1-1, 0.218 mmol, 1. eq.) was dissolved in 2 ml of dry dichloromethane. First 94 µl of dry *N,N*-diethylethanamine (0.676 mmol, 3,1 eq.) and then 23 µl of acetyl chloride (0,327 mmol, 1,5 eq,) were added under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 18 hours. Then the mixture was partitioned between water and dichloromethane. The phases were separated and the aqueous layer was extracted twice with dichloromethane. The combined organic layers were washed with brine, dried over a silicon filter and concentrated in vacuo. The residue was purified by flash chromatography and preparative TLC to yield 29,8 mg (0.06 mmol, 26,8%) of the analytically pure target compound.

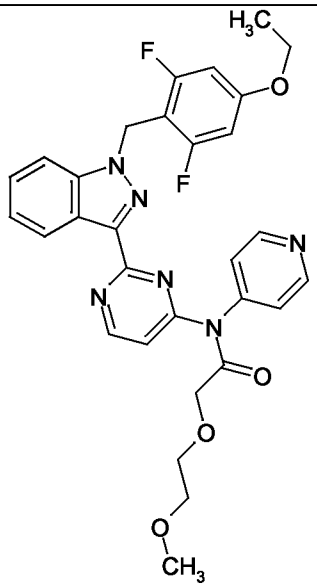
^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 1.25 (t, 3H), 2.08 (s, 3H), 4.00 (q, 2H), 5.61 (s, 2H), 6.63 - 6.75 (m, 2H), 6.85 - 6.93 (m, 1H), 7.09 (d, 1H), 7.36 (ddd, 1H), 7.52 - 7.57 (m, 2H), 7.70 (d, 1H), 7.93 (d, 1H), 8.73 - 8.83 (m, 3H).

LC-MS:
retention time: 1.21 min
MS ES$^+$: 501.1 $[M+H]^+$
Method B

The following compounds were prepared according to the same procedure using the indicated starting materials (SM = starting material):

16-2 SM = 5-1-1		*N*-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]pyrimidin-4-yl}-2-methoxy-*N*-(pyridin-4-yl)acetamide	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 1.25 (s, 3H), 3.94 - 4.05 (m, 2H), 4.11 (s, 3H), 5.62 (s, 2H), 5.72 (s, 2H), 6.71 (d, 2H), 6.90 - 7.00 (m, 1H), 7.28 (d, 1H), 7.38 (t, 1H), 7.52 - 7.58 (m, 2H), 7.70 - 7.77 (m, 2H), 8.72 -

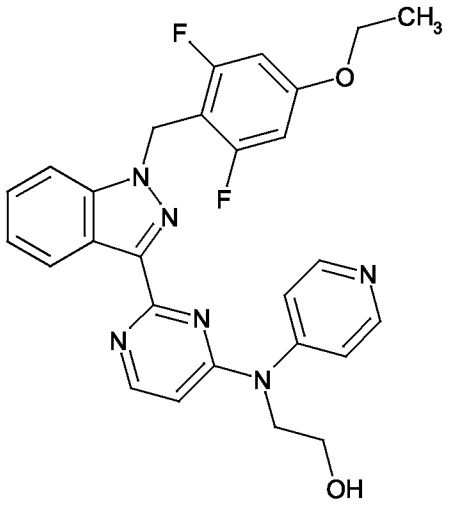
			8.84 (m, 3H). LC-MS: retention time: 1.22 min MS ES+: 531.1 [M+H]+ Method B
16-3 SM = 5-1-1		*N*-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]pyrimidin-4-yl}-*N*-(pyridin-4-yl)tetrahydro-2*H*-pyran-4-carboxamide	^{1}H-NMR (300MHz, DMSO-d$_6$): δ [ppm]= 1.25 (t, 3H), 1.59 - 1.83 (m, 4H), 2.71 - 2.84 (m, 1H), 3.00 - 3.13 (m, 2H), 3.76 (d, 2H), 3.95 - 4.04 (m, 2H), 5.62 (s, 2H), 6.67 - 6.75 (m, 2H), 6.99 (t, 1H), 7.36 - 7.44 (m, 2H), 7.49 - 7.53 (m, 2H), 7.62 (d, 1H), 7.74 (d, 1H), 8.71 - 8.76 (m, 2H), 8.80 (d, 1H). LC-MS: retention time: 1.25 min MS ES+: 571.2 [M+H]+ Method B

16-4 SM = 5-1-1		*N*-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]pyrimidin-4-yl}-2-(2-methoxyeth-oxy)-*N*-(pyridin-4-yl)acetamide	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 1.18 - 1.31 (m, 3H), 3.12 - 3.16 (m, 3H), 3.34 (dd, 2H), 3.51 (dd, 2H), 4.00 (d, 2H), 4.19 (s, 2H), 5.62 (s, 2H), 6.71 (d, 2H), 6.95 (t, 1H), 7.28 (d, 1H), 7.34 - 7.42 (m, 1H), 7.51 - 7.56 (m, 2H), 7.69 - 7.77 (m, 2H), 8.74 - 8.77 (m, 2H), 8.80 (d, 1H). LC-MS: retention time: 1.22 min MS ES$^+$: 575.2 [M+H]$^+$ Method B

Example 17-1

Preparation of 2-[{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]pyrimidin-4-yl}(pyridin-4-yl)amino]ethanol

240



120 mg of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-*N*-(pyridin-4-yl)-pyrimidin-4-amine (5-1-1, 0.262 mmol, 1. eq.) were suspended in 12 ml of dry DMF. 426 mg of cesium carbonate (1.31 mmol, 5 eq.) and 142 mg of 1,3,2-dioxathiolane 2-oxide (1,31 mmol, 5 eq.) were added under nitrogen atmosphere. The reaction mixture was stirred at 60 °C bath temperature for 18 hours. 142 mg of 1,3,2-dioxathiolane 2-oxide (1,31 mmol, 5 eq.) were added and the mixture was stirred at 60 °C bath temperature for further 22 hours. Then the mixture was partitioned between water and dichloromethane/ isopropanol 4:1. The phases were separated and the aqueous layer was extracted twice with dichloromethane/ isopropanol 4:1. The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash chromatography and preparative TLC to yield 14,2 mg (0.03 mmol, 10,5%) of the analytically pure target compound.

^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 1.26 (t, 3H), 3.64 - 3.76 (m, 2H), 4.01 (q, 2H), 4.11 (t, 2H), 4.91 (t, 1H), 5.64 (s, 2H), 6.66 - 6.80 (m, 3H), 7.13 (t, 1H), 7.42 (t, 1H), 7.47 - 7.53 (m, 2H), 7.75 (d, 1H), 8.16 (d, 1H), 8.37 (d, 1H), 8.54 - 8.62 (m, 2H).

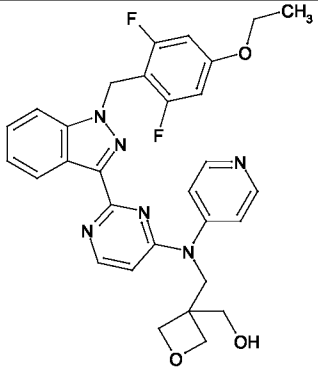
LC-MS:

retention time: 0.96 min

MS ES$^+$: 503.1 $[M+H]^+$

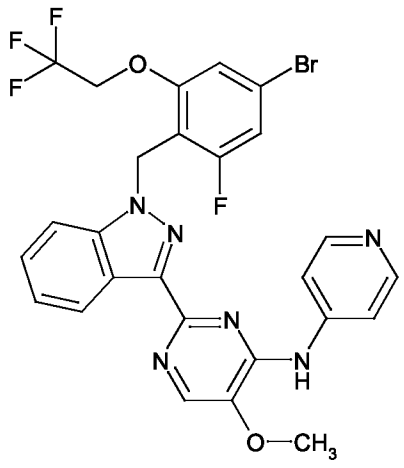
Method B

The following compounds were prepared according to the same procedure using the indicated starting materials (SM = starting material):

17-2 SM = 5-1-1		(3-{[{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}(pyridin-4-yl)amino]methyl} oxetan-3-yl)methanol	^{1}H-NMR (500MHz, DMSO-d6): δ [ppm]= 1.29 (t, 3H), 3.65 (d, 2H), 4.03 (q, 2H), 4.35 (d, 2H), 4.57 (d, 2H), 4.83 (s, 2H), 5.39 (t, 1H), 5.75 (s, 2H), 6.79 - 6.86 (m, 2H), 7.08 (d, 1H), 7.33 (t, 1H), 7.54 (ddd, 1H), 7.90 (d, 1H), 8.38 - 8.55 (m, 3H), 8.63 (d, 2H), 8.81 (d, 1H), 11.45 (br. s., 1H).

Example 18-1

Preparation of 2-{1-[4-bromo-2-fluoro-6-(2,2,2-trifluoroethoxy)benzyl]-1*H*-indazol-3-yl}-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine



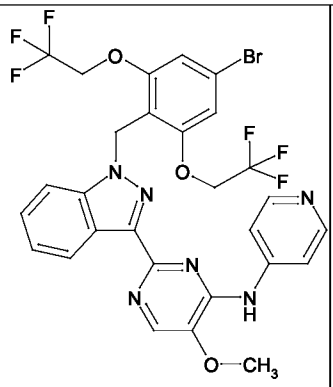
38,2 mg of 2,2,2-trifluoroethanol (0.382 mmol, 2 eq.) were dissolved in 1,5 ml of dry DMF under nitrogen atmosphere. 16,8 mg of 60% sodium hydrid in paraffin oil

(0.42 mmol, 2.2 eq.) were added. The suspension was stirred at room temperature for 15 minutes. 100 mg of 2-[1-(4-bromo-2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine (2-12-1, 0,191 mmol, 1 eq.) were added. The reaction mixture was stirred at room temperature for 18 hours. Water was added dropwise. The suspension was filtered off. The precipitate was dried at 50 °C under vacuo. The precipitate was purified by pre parative HPLC to yield 34 mg (0.05 mmol, 28%) of the analytically pure target compound.

^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 4.00 (s, 3H), 4.82 (q, 2H), 5.60 (s, 2H), 7.22 (t, 1H), 7.30 (s, 1H), 7.39 - 7.46 (m, 1H), 7.74 (d, 1H), 8.10 - 8.16 (m, 3H), 8.32 (s, 1H), 8.35 - 8.39 (m, 2H), 8.42 (d, 1H), 9.38 (s, 1H).

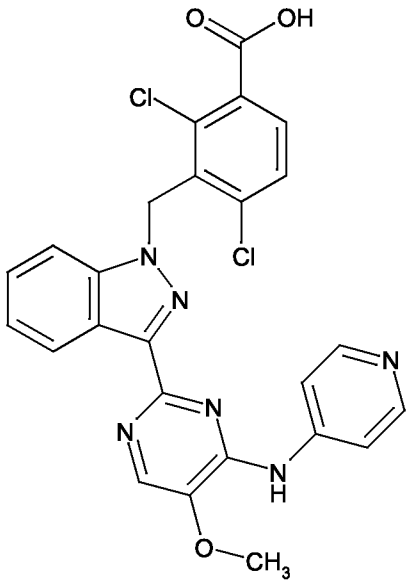
LC-MS:
retention time: 1.05 min
MS ES$^+$: 605.0 $[M+H]^+$

As a second product the following compound was obtained:

18-2 SM = 2-12-1		2-{1-[4-bromo-2,6-bis(2,2,2-trifluoroethoxy)benzyl]-1*H*-indazol-3-yl}-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 4.00 (s, 3H), 4.82 (q, 4H), 5.55 (s, 2H), 7.16 - 7.22 (t, 1H), 7.26 (s, 2H), 7.38 (ddd, 1H), 7.68 (d, 1H), 8.02 - 8.06 (m, 2H), 8.29 - 8.34 (m, 3H), 8.41 (d, 1H), 9.33 (s, 1H). LC-MS: retention time: 1.12 min MS ES$^+$: 685.0 $[M+H]^+$ Method B

Example 19-1

Preparation of 2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzoic acid



1 g of methyl 2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzoate (2-16-1, 1.868 mmol, 1. eq.) were dissolved in 19 ml of dry THF and 2.2 ml of methanol. 4.67 ml of 2 M aqueous sodium hydroxide solution (9.34 mmol, 5 eq.) were added. The mixture was stirred for three hours at room temperature. The reaction mixture was partitioned between citric acid (pH 3) and ethyl acetate. This process dropped out a white precipitate which was filtered off and dried for three days to yield 992 mg (1.86 mmol, 99,8%) of the analytically pure target compound.

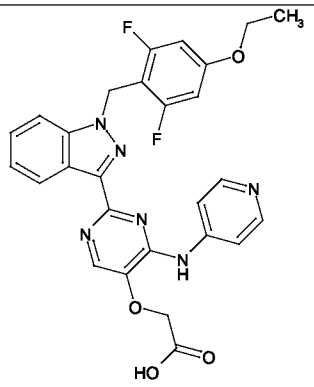
^{1}H-NMR (400MHz, DMSO-d6): δ [ppm]= 3.99 (s, 3H), 5.91 (s, 2H), 7.26 (t, 1H), 7.44 - 7.54 (m, 1H), 7.62 - 7.66 (m, 2H), 7.84 - 7.94 (m, 1H), 8.07 - 8.16 (m, 2H), 8.32 (s, 1H), 8.35 - 8.42 (m, 2H), 8.49 (d, 1H), 9.33 (s, 1H)

LC-MS:

retention time: 0.96 min

MS ES$^+$: 521.1 $[M+H]^+$

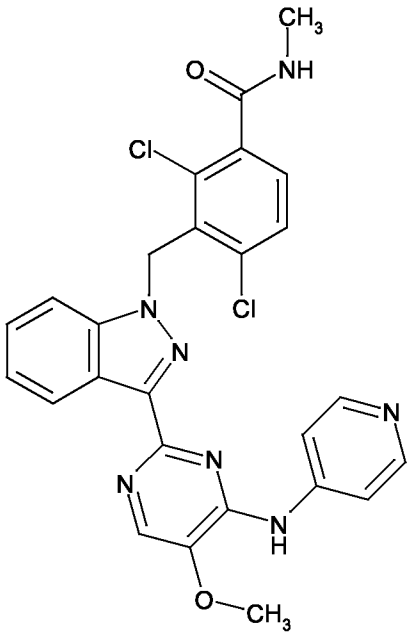
The following compound was obtained according to the same procedure using the indicated starting material (SM):

19-2 SM = 4-14		({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-yla-mino)pyrimidin-5-yl}oxy)acetic acid	1H-NMR (300MHz, DMSO-d6): δ [ppm]= 1.24 (t, 3H), 4.00 (q, 2H), 5.04 (d, 2H), 5. 68 (s, 2H), 6. 78 (m, 2H), 7.26 (t, 1H), 7.48 (t, 1H), 7.83 (d, 1H), 8.39 (d, 1H), 8.51 (s, 1H), 8.53-8.63 (m, 4H), 10.58 (s, 1H), 14.33 (br. s, 1H). LC-MS (Method 1): retention time: 1.03 min MS ES+: 481.4 [

Example 20-1

Preparation of 2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)-*N*-methylbenzamide

245



100 mg of 2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)benzoic acid (19-1, 0.192 mmol, 1. eq.) were dissolved in 0,953 ml of dry dimethyl sulfoxide. 80,2 mg of *N*-[(dimethylamino)(3*H*-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy)methylidene]-*N*-methylmethanaminium hexafluorophosphate (0.211 mmol, 1,1 eq.), 67 µl of *N*-ethyl-*N*-(propan-2-yl)propan-2-amine (0,384 mmol, 2 eq.) and 96 µl of 2 N methyl amine in tetrahydrofuran were added in this sequence. The reaction mixture was stirred at room temperature for 18 hours. 80,2 mg of *N*-[(dimethylamino)(3*H*-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy)-methylidene]-*N*-methylmethanaminium hexafluorophosphate (0.211 mmol, 1,1 eq.), 67 µl of *N*-ethyl-*N*-(propan-2-yl)propan-2-amine (0,384 mmol, 2 eq.) and 96 µl of 2 N methyl amine in tetrahydrofuran were added in this sequence again twice and stirred each time at room temperature for 24 hours. The reaction mixture was stirred at 50 °C bath temperature for further 2 hou rs. Then the mixture was filtered off purified by preparative HPLC to yield 15 mg (0.03 mmol, 14,3%) of the analytically pure target compound.

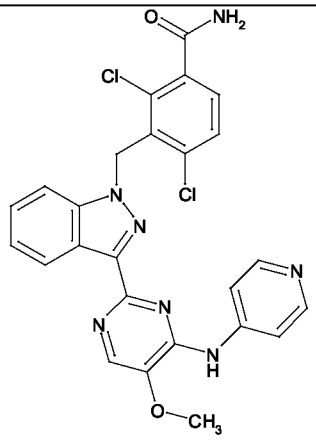
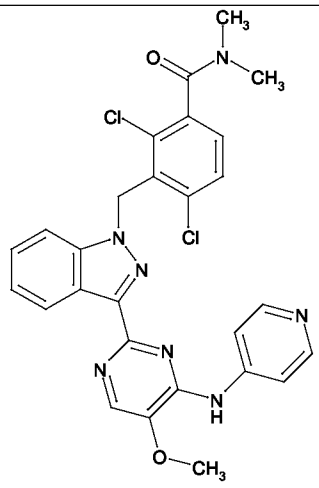
^{1}H-NMR (300MHz, DMSO-d6): δ [ppm]= 2.68 (d, 3H), 3.99 (s, 3H), 5.91 (s, 2H), 7.19 - 7.32 (m, 1H), 7.42 - 7.51 (m, 2H), 7.63 - 7.72 (m, 1H), 7.87 - 7.98 (m, 1H), 8.07 - 8.23 (m, 2H), 8.32 - 8.50 (m, 5H), 9.33 (s, 1H)

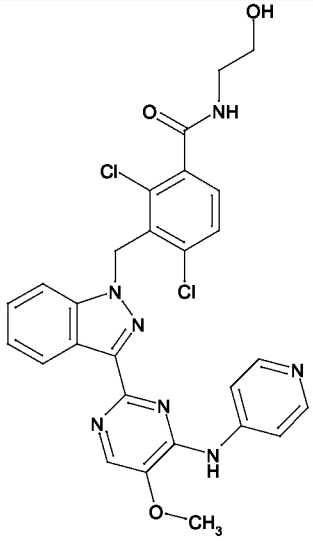
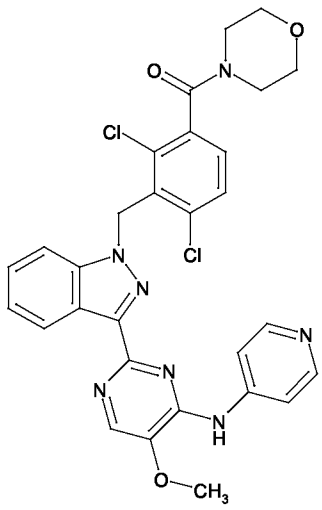
LC-MS:

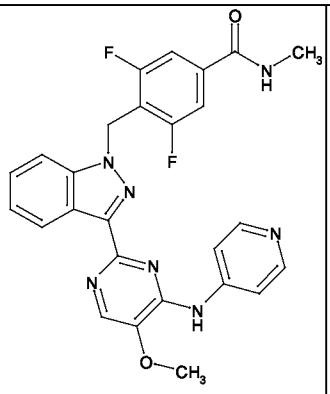
retention time: 0.92 min

MS ES$^+$: 534.2 $[M+H]^+$

The following compounds were obtained according to the same procedure using the indicated starting materials (SM):

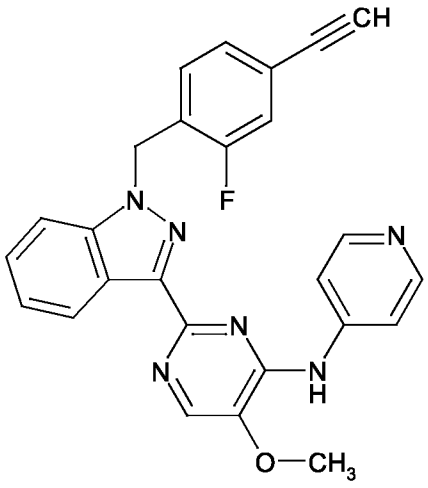
20-2 SM = 19-1		2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)benzamide	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 4.00 (s, 3H), 5.91 (s, 2H), 7.19 - 7.33 (m, 1H), 7.39 - 7.54 (m, 2H), 7.56 - 7.63 (m, 1H), 7.63 - 7.71 (m, 1H), 7.85 - 7.97 (m, 2H), 8.06 - 8.22 (m, 2H), 8.32 (s, 4H), 9.23 - 9.42 (m, 1H) LC-MS: retention time: 0.91 min MS ES$^+$: 520.1 $[M+H]^+$
20-3 SM = 19-1		2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)-*N,N*-dimethylbenzamide	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 2.64 (s, 3H), 2.92 (s, 3H), 3.99 (s, 3H), 5.77 - 6.01 (m, 2H), 7.25 (t, 1H), 7.40 (d, 1H), 7.44 - 7.53 (m, 1H), 7.68 (d, 1H), 7.84 - 7.96 (m, 1H), 8.06 - 8.18 (m, 2H), 8.26 - 8.41 (m, 3H), 8.49 (d, 1H), 9.31 (s, 1H) LC-MS: retention time: 0.98min

			MS ES+: 548.2 [M+H]+
20-4 SM = 19-1		2,4-dichloro-*N*-(2-hydroxyethyl)-3-({3-[5-methoxy-4-(pyridin-4-yla-mino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)benza mide	^{1}H-NMR (400MHz, Chloroform-d): δ [ppm]= 3.62 - 3.73 (m, 2H), 3.81 - 3.91 (m, 2H), 4.03 (s, 3H), 5.90 (s, 2H), 6.69 - 6.81 (m, 1H), 7.31 (t, 1H), 7.37 - 7.45 (m, 2H), 7.45 - 7.56 (m, 2H), 7.66 (d, 1H), 7.97 (d, 2H), 8.18 (s, 1H), 8.48 (d, 2H), 8.64 (d, 1H) LC-MS: retention time: 0.89 min MS ES+: 564.2 [M+H]+
20-5 SM = 19-1		[2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-yla-mino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)phenyl] (morpholin-4-yl)methanone	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 2.99 - 3.11 (m, 2H), 3.37 - 3.45 (m, 2H), 3.56 - 3.64 (m, 4H), 4.03 (s, 3H), 5.91 (s, 2H), 7.28 (t, 1H), 7.45 (d, 1H), 7.47 - 7.55 (m, 1H), 7.69 (d, 1H), 7.92 (d, 1H), 8.36 - 8.44 (m, 2H), 8.46 - 8.50 (m, 4H), 10.08 (br. s., 1H) LC-MS: retention time: 0.95 min MS ES+: 590.1 [M+H]+

20-6 SM = 19-1		3,5-difluoro-4-({3-[5-methoxy-4-(pyridin-4-yla-mino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)-*N*-methylbenzamide	^{1}H-NMR (300MHz, METHANOL-d_4): δ [ppm]= 2.91 (s, 3H), 4.13 (s, 3H), 5.77 - 5.82 (m, 2H), 7.20 - 7.28 (m, 1H), 7.44 (td, 1H), 7.60 (d, 3H), 8.47 (d, 1H), 8.56 (s, 1H), 8.59 - 8.67 (m, 4H). LC-MS: retention time: 0.80 min MS ES$^+$: 502.1 $[M+H]^+$

Example 21-1

Preparation of 2-[1-(4-ethynyl-2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine



Step 1: 2-(1-{2-fluoro-4-[(trimethylsilyl)ethynyl]benzyl}-1*H*-indazol-3-yl)-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine

144,7 mg of 2-[1-(2-fluoro-4-iodobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine (2-201, 0,262 mmol, 1 eq.), 6,02 mg of (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one - palladium (2:1) (0,01 mmol, 0,04 eq.), 2,0 mg of

copper (I) iodide (0,01 mmol, 0,04 eq.), and 13,7 mg of triphenylphosphane (0,052 mmol, 0,2 mmol) were suspended in 2,6 ml of dry *N,N*-diethylethanamine and purged with nitrogen. Then 3,86 ml of ethynyl(trimethyl)silane (1,57 mmol, 6 eq.) were added and the reaction mixture was stirred at 60 °C for 18 hours. The mixture was concentrated under vacuo. The crude product was used without further purification in step 2.

LC-MS:
retention time: 1,14 min
MS ES$^+$: 523,4 $[M+H]^+$
Method B

Step 2: 2-[1-(4-ethynyl-2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine

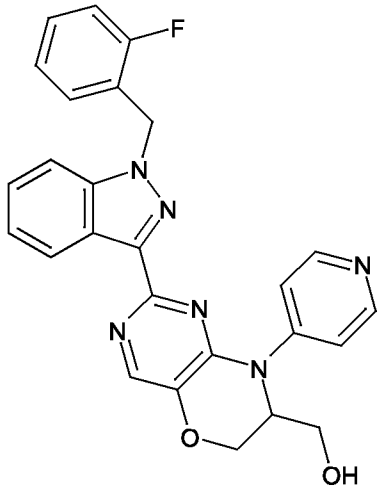
37,3 mg of 2-(1-{2-fluoro-4-[(trimethylsilyl)ethynyl]benzyl}-1*H*-indazol-3-yl)-5-methoxy-*N*-(pyridin-4-yl)pyrimidin-4-amine (0.071 mmol, 1. eq.) were dissolved in 1,0 ml of dry tetrahydrofuran. 71 µl of a 1 M *N,N,N*-tributylbutan-1-ammonium fluoride in tetrahydrofuran (0,071 mmol, 1 eq.) were added under nitrogen atmosphere and stirred at room temperature for 18 hours. Then the mixture was partitioned between a aqueous half saturated sodium hydrogen carbonate solution and dichloromethane/ isopropanol 4:1. The phases were separated and the aqueous layer was extracted twice with dichloromethane/ isopropanol 4:1. The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The residue was purified by preparative TLC in ethyl acetate/ methanol 7:3 to yield 23,2 mg (0.05 mmol, 68,4%) of the analytically pure target compound.

^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 4.01 (s, 3H), 4.28 (s, 1H), 5.79 (s, 2H), 7.20 - 7.31 (m, 3H), 7.34 - 7.48 (m, 2H), 7.80 (d, 1H), 8.07 - 8.13 (m, 2H), 8.33 (s, 1H), 8.35 - 8.40 (m, 2H), 8.44 (d, 1H), 9.41 (s, 1H).

LC-MS:
retention time: 0.91 min
MS ES$^+$: 451.4 $[M+H]^+$
Method B

Example 22-1

Preparation of {2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-8-(pyridin-4-yl)-7,8-dihydro-6*H*-pyrimido[5,4-b][1,4]oxazin-7-yl}methanol



25 mg of 2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol (3-3, 0.061 mmol, 1. eq.), 28,2 mg of 3-bromopropane-1,2-diol (0,182 mmol, 3 eq.) and 41,9 mg of potassium carbonate (0,303 mmol, 5 eq.) were suspended in 470 µl of dry DMF under nitrogen atmosphere. The reaction mixture was stirred at 100 °C bath temperature for 18 hours. Then the mixture was partitioned between aqueous half saturated sodium chloride solution and ethyl acetate. The phases were separated and the aqueous layer was extracted once with ethyl acetate and once with dichloromethane/ isopropanol 4:1. The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The residue was purified by preparative TLC in dichloromethane/ methanol 9:1 to yield 6,26 mg (0.01 mmol, 19,8%) of the analytically pure target compound.

^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 3.53 - 3.67 (m, 2H), 4.14 - 4.23 (m, 1H), 4.25 - 4.32 (m, 1H), 4.53 - 4.61 (m, 1H), 5.26 - 5.33 (m, 1H), 5.73 (s, 2H), 7.01 - 7.24 (m, 4H), 7.27 - 7.42 (m, 2H), 7.68 - 7.78 (m, 3H), 8.13 (d, 1H), 8.26 (s, 1H), 8.50 - 8.57 (m, 2H).

LC-MS:

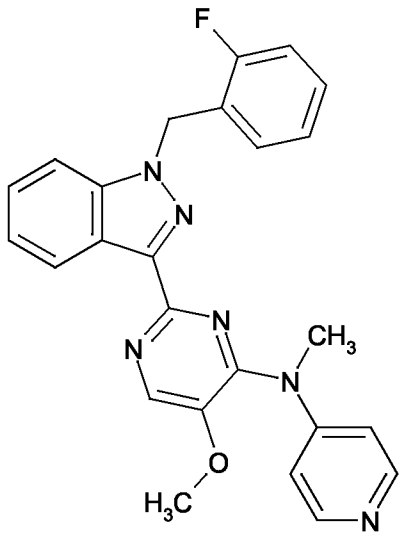
retention time: 0.89 min

MS ES$^+$: 469.0 $[M+H]^+$

Method B

Example 23-1

Preparation of 2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-methyl-*N*-(pyridin-4-yl)pyrimidin-4-amine



135 mg of 2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methoxy-*N*-(pyridin-4-yl)-pyrimidin-4-amine (2-18-1, 0.316 mmol, 1. eq.) were dissolved in 3 ml of 1-methyl-pyrrolidin-2-one and 514 mg of cesium carbonate (1.58 mmol, 5 eq.) were added. The reaction mixture was stirred at 190 °C bath tem perature for 18 hours. After cooling at room temperature the mixture was partitioned between water and butan-2-one. The phases were separated and the aqueous layer was extracted twice with butan-2-one. The combined organic layers were washed with brine and dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash chromatography and preparative TLC to yield 10,9 mg (0.02 mmol, 7,2%) of the analytically pure target compound.

^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 3.77 (s, 3H), 3.89 (s, 3H), 5.80 (s, 2H), 7.15 - 7.19 (m, 3H), 7.21 - 7.29 (m, 3H), 7.34 - 7.41 (m, 2H), 7.44 (ddd, 1H), 7.75 (d, 1H), 7.79 (br. s., 1H), 8.23 (s, 1H), 8.50 (d, 1H).

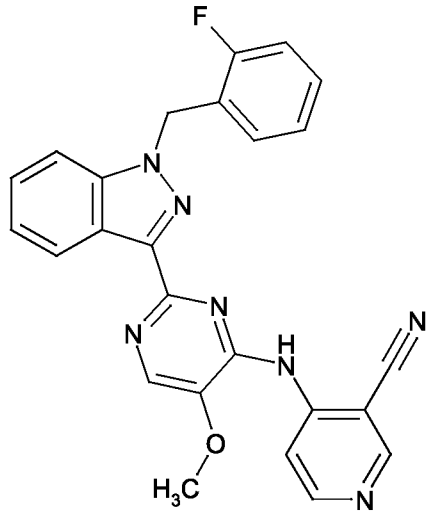
LC-MS:

retention time: 1,02 min

MS ES+: 441.53 $[M+H]^+$

Example 24-1

Preparation of 4-({2-[1-(2-fluorobenzyl)-*1H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carbonitrile



175 mg of 2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-amine (1-11-1, 0.501 mmol, 1. eq.), 101 mg of 4-bromopyridine-3-carbonitrile (0.551 mmol, 1.1 eq.), 115 mg of Tris(dibenzylideneacetone)dipalladium (0) (0.125 mmol, 0.25 eq.), 156 mg of 1,1'-binaphthalene-2,2'-diylbis(diphenylphosphane) (0.25 mmol, 0.5 eq), 144 mg of sodium 2-methylpropan-2-olate (97%) (1.503 mmol, 3 eq.) and 52 ml of N,N-dimethylformamide were stirred under nitrogen atmosphere for 30 minutes at 100 °C and 300 W in a CEM microwave. The reaction mixture was washed with half-saturated aqueous sodium chloride solution. The organic layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography (hexane/ dichloromethane/ methanol) and preparative HPLC. A crystallisation from dichloromethane/methanol gave 5.8 mg (0.01 mmol, 2,6%) of the analytically pure target compound.

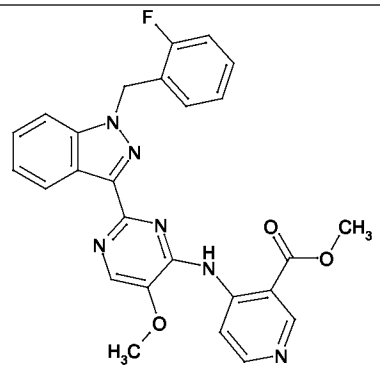
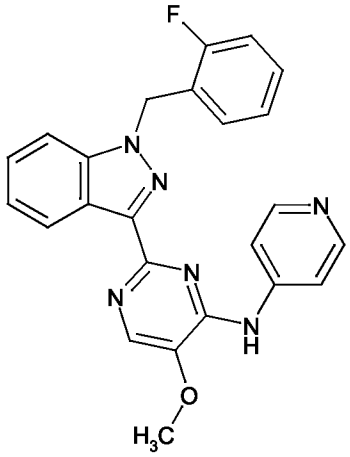
^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 4.04 (s, 3H), 5.76 (s, 2H), 7.08 - 7.26 (m, 4H), 7.28 - 7.46 (m, 2H), 7.75 (d, 1H), 8.20 - 8.31 (m, 2H), 8.45 (s, 1H), 8.68 (d, 1H), 8.88 (s, 1H), 9.23 (s, 1H).

LC-MS:

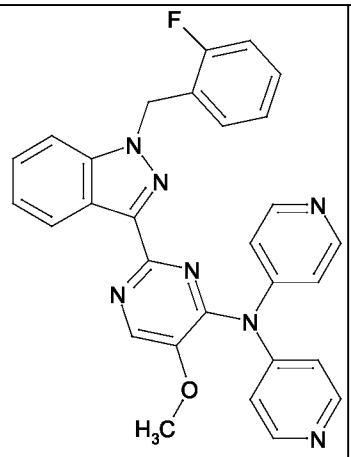
retention time: 1.28 min

MS ES$^+$: 452.33 $[M+H]^+$

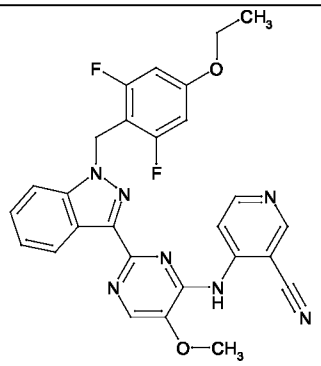
The following compounds were prepared according to the same procedure using the indicated starting materials (SM = starting material), and the respective halopyridines:

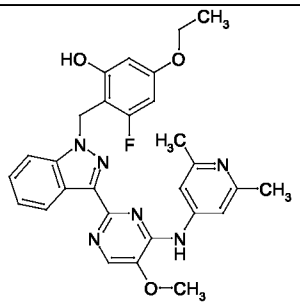
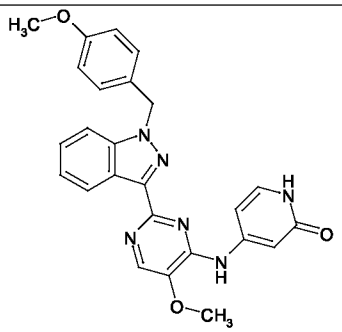
24-2 SM = 1-4-2		methyl 4-({2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carboxylate	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 4.05 (s, 3H), 4.11 (s, 3H), 5.80 - 5.85 (m, 2H), 7.10 - 7.40 (m, 6H), 7.49 - 7.59 (m, 2H), 7.86 (d, 1H), 8.06 (d, 1H), 8.39 (dd, 1H), 8.95 - 9.06 (m, 2H). LC-MS: retention time: 0.91 min MS ES$^+$: 485.11 $[M+H]^+$
24-3 SM = 1-4-2		2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine	1H-NMR (300MHz, DMSO-d6): δ [ppm]= 4.01 (s, 3H), 5.77 (s, 2H), 7.10 - 7.49 (m, 6H), 7.75 - 7.84 (m, 1H), 8.07 - 8.17 (m, 2H), 8.33 (s, 1H), 8.35 - 8.40 (m, 2H), 8.40 - 8.48 (m, 1H), 9.35 - 9.45 (m, 1H). LC-MS: retention time: 1.01 min MS ES$^+$: 427.19 $[M+H]^+$ Method B

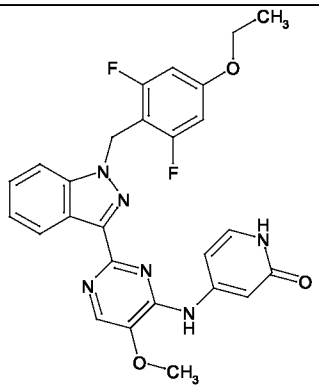
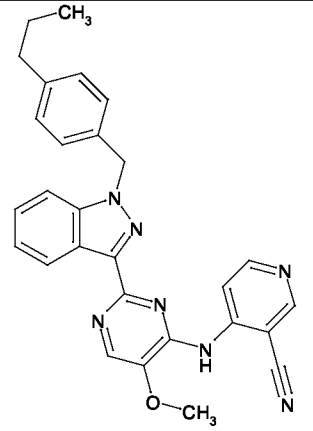
The following compound was also formed during the reaction leading to 24-3:

24-4 SM = 1-4-2		2-[1-(2-fluorobenzyl)-*1H*-indazol-3-yl]-5-methoxy-*N,N*-di(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 3.74 (s, 3H), 5.75 (s, 2H), 6.92 (t, 1H), 6.99 - 7.12 (m, 6H), 7.13 - 7.23 (m, 1H), 7.26 - 7.38 (m, 2H), 7.65 (dd, 2H), 8.41 - 8.50 (m, 4H), 8.71 (s, 1H). LC-MS: retention time: 0.90 min MS ES$^+$: 504.57 $[M+H]^+$

The following compounds were prepared according to the same procedure using the indicated starting materials (SM = starting material), and the respective halopyridines / halopyridones:

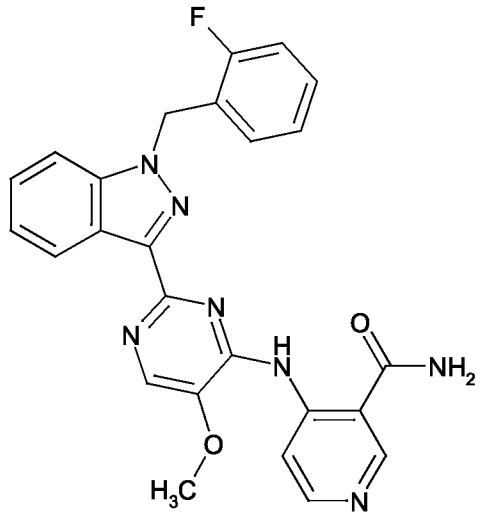
24-5 SM = 1-4-3		4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carbonitrile	1H-NMR (500MHz, DMSO-d6): δ [ppm]= 1.30 (t, 3H), 4.05 (q, 2H), 4.07 (s, 3H), 5. 67 (s, 2H), 6. 80 (m, 2H), 7.22 (t, 1H), 7.48 (t, 1H), 7.83 (d, 1H), 8.32 (d, 1H), 8.45 (br. s, 1H), 8.68 (br. s, 1H), 8.90 (br. s, 1H), 9.15 (br. s, 1H). Ein H fehlt LC-MS (Method 5): retention time: 1.43 min MS ES$^+$: 514.2 [^{5}

24-6 SM = 1-4-3		2-[(3-{4-[(2,6-dimethylpyridin-4-yl)amino]-5-methoxypyrimidin-2-yl}-1H-indazol-1-yl)methyl]-5-ethoxy-3-fluorophenol	1H-NMR (400MHz, DMSO-d6): δ [ppm]= 1.24 (t, 3H), 2.36 (s, 6H), 3.90 (q, 2H), 3.99 (s, 3H), 5. 54 (s, 2H), 6. 20 (br. s, 1H), 6. 24 (br. d, 1H), 7.18 (t, 1H), 7.39 (t, 1H), 7.78 (s, 1H), 7.78 (d, 1H), 8.28 (s, 1H), 8.44 (d, 1H), , 9.09 (s, 1H), 10.26 (br. s, 1H). LC-MS (Method 5): retention time: 0.68 min MS ES+: 515.2
24-7 SM = 1-4-1		4-({5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}amino)pyridin-2(1H)-one	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 3.65 (s, 3H), 4.00 (s, 3H), 5.62 (s, 2H), 6.79 - 6.87 (m, 3H), 7.13 - 7.27 (m, 2H), 7.27 - 7.45 (m, 4H), 7.76 (d, 1H), 8.33 (s, 1H), 8.42 (d, 1H), 9.06 (s, 1H), 11.03 (br. s., 1H). LC-MS: retention time: 0.97 min MS ES+: 455.2 [M+H]+

24-8 SM = 1-4-3		4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridin-2(1H)-one	1H-NMR (300MHz, DMSO-d6): δ [ppm]= 1.25 (t, 3H), 3.98 (s, 3H), 4.00 (q, 2H), 5. 63 (s, 2H), 6. 72 (m, 2H), 6. 97 (br. s, 1H), 7. 05 (br. d, 1H), 7.20 (m, 1H), 7.44 (t, 1H), 7.75 (m, 2H), 8.31 (s, 1H), 8.41 (d, 1H), 9.06 (s, 1H), 11.02 (br. s, 1H). LC-MS (Method 2): retention time: 0.94 min MS ES+: 505.0
24-9 SM = 1-4-4		4-({5-methoxy-2-[1-(4-propylbenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}amino)nicotinonitrile	LC-MS: retention time: 1.51min MS ES+: 476.27 [M+H]+

Example 25-1

Preparation of 4-({2-[1-(2-fluorobenzyl)-*1H*-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carboxamide



54 mg of 4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carbonitrile (24-1, 0.12 mmol, 1. eq.) were dissolved in 1.6 ml of dimethyl sulfoxide under nitrogene atmosphere. 42 µl of 3 M aqueous sodium hydroxide solution (0.126 mmol, 1.05 eq.) were added. The mixture was oilbath heated to 63 ℃ bath temperature. At this temperatu re 302µl hydrogen peroxide (30% in water) (9.87 mmol, 82.2 eq.) were added dropwise. The reaction mixture was stirred at 65 ℃ bath temperature for 3 hours a nd at room temperature for 24 hours. After stirring the mixture one hour with ice-water it was extracted three times with dichloromethane/ isopropanol 4:1. The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The residue was purified by preparative TLC (dichloromethane/ methanol 9:1) to yield 12.0 mg (0.02 mmol, 20.5%) of the analytically pure target compound.

^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 4.01 (s, 3H), 5.79 (s, 2H), 7.10 - 7.39 (m, 5H), 7.45 (t, 1H), 7.81 (d, 2H), 8.34 - 8.55 (m, 4H), 8.91 (s, 1H), 9.22 (d, 1H), 12.10 - 12.19 (m, 1H).

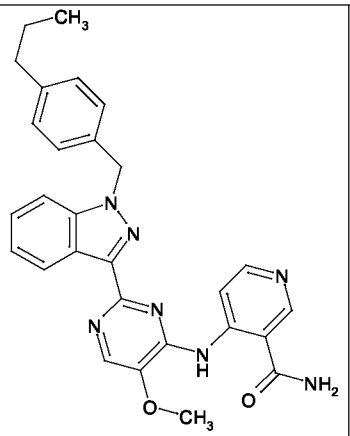
LC-MS:

retention time: 1.01 min

MS ES$^+$: 470.1 $[M+H]^+$

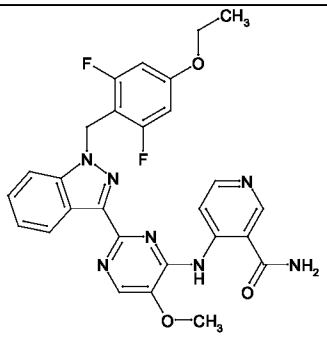
Method B

The following compounds were obtained according to the same procedure using the indicated starting materials (SM = starting material):

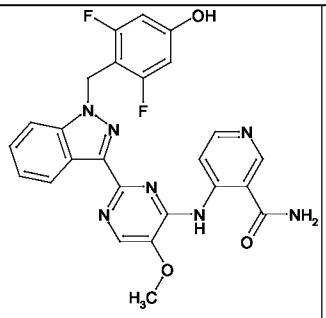
25-2 SM = 24-9		4-({5-methoxy-2-[1-(4-propylbenzyl)-*1H*-indazol-3-yl]pyrimidin-4-yl}amino)pyridine-3-carboxamide	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 0.81 (t, 3H), 1.43 - 1.55 (m, 2H), 2.44 – 2.56 (m, 2H), 4.02 (s, 3H), 5.70 (s, 2H), 7.12 (d, 2H), 7.21 - 7.29 (m, 3H), 7.41 (ddd, 1H), 7.78 (d, 1H), 7.86 (br. s., 1H), 8.38 - 8.46 (m, 3H), 8.54 (d, 1H), 8.92 (s, 1H), 9.25 (d, 1H), 12.19 (s, 1H). LC-MS: retention time: 1.24 min MS ES$^+$: 494.3 $[M+H]^+$

The following compound was prepared according to the following alternative method:

105 mg of 4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carbonitrile (24-5, 0,204 mmol) was dissolved in 311 µl conc. sulphuric acid (5,83 mmol) and stirred at room temperature for 18 hours. The mixture was poured in ice water and then 2M sodium hydroxid was added until a basic pH was reached. The aqueous phase was extracted 3 times with CH2Cl2/isopropanol 4:1, dried over magnesium sulphate, filtered off and concentrated in vacuo. The residue was purified by preparative TLC (dichloromethane/ methanol 9:1) to yield 6.9 mg (0.01 mmol, 6.3%) of the analytically pure target compound.

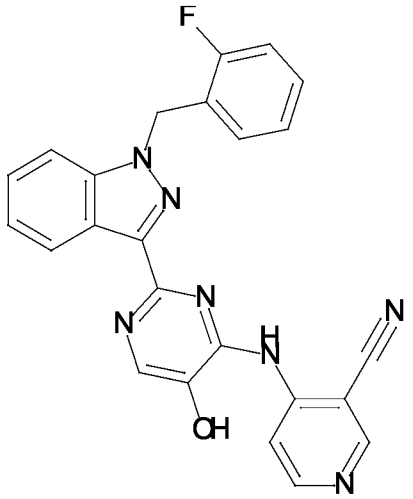
25-3 SM = 24-5		4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carboxamide	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.26 (t, 3H), 3.94 - 4.08 (m, 5H), 5.65 (s, 2H), 6.77 (d, 2H), 7.19 - 7.32 (m, 1H), 7.40 - 7.53 (m, 1H), 7.74 - 7.87 (m, 2H), 8.29 - 8.55 (m, 4H), 8.92 (s, 1H), 9.20 - 9.30 (m, 1H), 12.17 (s, 1H). LC-MS: retention time: 1.13 min MS ES$^+$: 532.3 $[M+H]^+$

The following compound was also formed during the same reaction:

25-4 SM = 24-5		4-({2-[1-(2,6-difluoro-4-hydroxybenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carboxamide	^{1}H-NMR (500MHz, DMSO-d_6): δ [ppm]= 4.05 (s, 3H), 5.66 (s, 2H), 6.54 (m, 2H), 7.30 (t, 1H), 7.51 (t, 1H), 7.85-7.88 (m, 2H), 8.42 (s, 1H), 8.46 (br. s, 1H), 8.48 (s, 1H), 8.49 (s, 1H), 8.53 (d, 1H), 8.96 (s, 1H), 9.33 (d, 1H), 10.56 (br. s, 1H). LC-MS (Method 5): retention time: 0.75 min MS ES$^+$: 504.2 $[M+H]^+$

Example 26-1

Preparation of 4-({2-[1-(2-fluorobenzyl)-*1H*-indazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)pyridine-3-carbonitrile



50 mg of 4-amino-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]pyrimidin-5-ol (1-11-1, 0.149 mmol, 1. eq.) were dissolved in 3 ml of N,N-dimethylformamide. 103 mg of potassium carbonate (0.746 mmol, 5 eq.) and 32.8 mg of 4-bromopyridine-3-carbonitrile (0.179 mmol, 1.2 eq.) were added. The reaction mixture was stirred at 100 °C bath temperature for 18 hours. After cooling at room temperature the mixture was filtered off and washed with dichloromethane. The filtrate was concentrated in vacuo. The residue was purified by preparative HPLC and preparative TLC to yield 4.21 mg (0.01 mmol, 6.1%) of the analytically pure target compound.

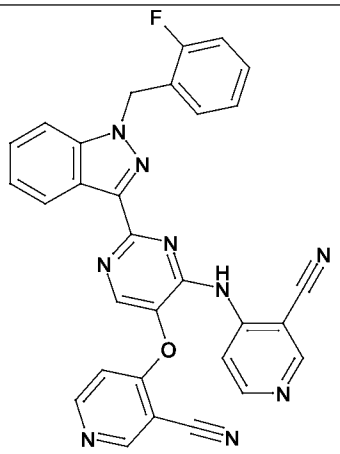
^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 5.75 (s, 2H), 7.10 - 7.25 (m, 4H), 7.29 - 7.37 (m, 1H), 7.41 (ddd, 1H), 7.76 (d, 1H), 8.21 (s, 1H), 8.30 (d, 1H), 8.48 (d, 1H), 8.65 (d, 1H), 8.86 (s, 1H), 8.90 - 9.03 (m, 1H), 11.09 - 11.44 (m, 1H).

LC-MS:

retention time: 1.13 min

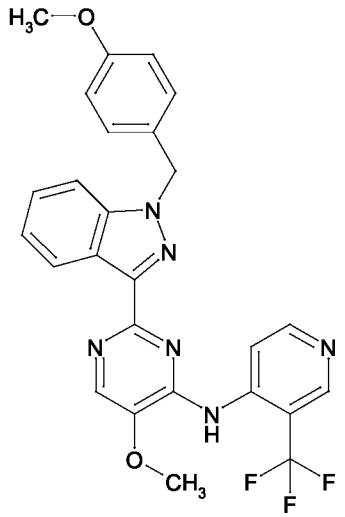
MS ES$^+$: 438.32 $[M+H]^+$

The following compound was formed during the same procedure using the indicated starting material (SM = starting material):

26-2 SM = 1-11-1		4-({4-[(3-cyanopyridin-4-yl)amino]-2-[1-(2-fluorobenzyl)-*1H*-indazol-3-yl]pyrimidin-5-yl}oxy)pyridine-3-carbonitrile	LC-MS: retention time: 1.10 min MS ES$^+$: 540.30 [M+H]$^+$

Example 27-1

Preparation of 5-methoxy-2-[1-(4-methoxybenzyl)-*1H*-indazol-3-yl]-N-[3-(trifluoromethyl)pyridin-4-yl]pyrimidin-4-amine



1 g of 5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]pyrimidin-4-amine (1-4-1, 2.77 mmol, 1. eq.), 938 mg of 4-bromo-3-(trifluoromethyl)pyridine (4.15 mmol, 1.5 eq.), 127 mg of Tris(dibenzylideneacetone)dipalladium (0) (0.138 mmol, 0.05 eq.),

345 mg of 1,1'-binaphthalene-2,2'-diylbis(diphenylphosphane) (0.553 mmol, 0.2 eq), 1.06 g of sodium 2-methylpropan-2-olate (97%) (11.1 mmol, 4 eq.) and 15 ml of N,N-dimethylformamide were stirred under nitrogen atmosphere for 24 hours at 100 ℃ bath temperature in a pressure pipe. The rea ction mixture was washed with half-saturated aqueous ammonium chloride solution. The organic layer was extracted three times with dichloromethane. The combined organic layers were washed with brine and dried over magnesium sulfate and concentrated in vacuo. The residue was purified twice by flash chromatography (hexane/ ethyl acetate/ methanol) and preparative TLC. A crystallisation gave 56.9 mg (0.1 mmol, 3.73%) of the analytically pure target compound.

^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 3.66 (s, 3H), 4.05 (s, 3H), 5.65 (s, 2H), 6.81 - 6.89 (m, 2H), 7.17 (t, 1H), 7.28 (d, 2H), 7.34 - 7.42 (m, 1H), 7.76 (d, 1H), 8.18 - 8.28 (m, 2H), 8.45 (s, 1H), 8.76 - 8.89 (m, 3H).

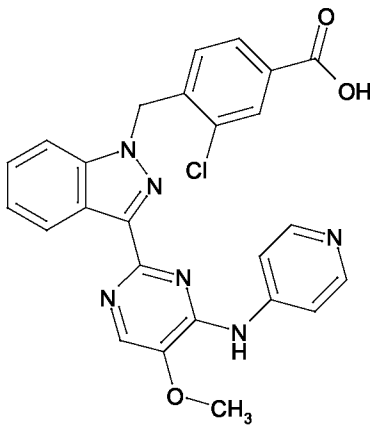
LC-MS:

retention time: 1.39 min

MS ES$^+$: 507.0 $[M+H]^+$

Example 28-1

Preparation of 3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)benzoic acid



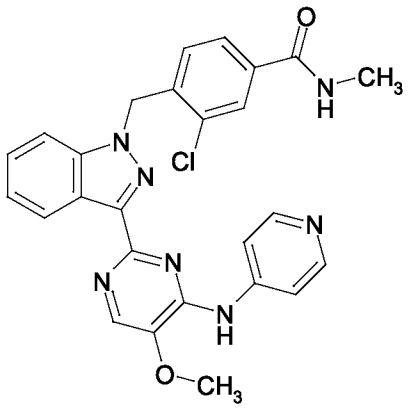
150 mg of methyl 3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzoate (2-11-1, 0.299 mmol, 1. eq.) were dissolved in 0,364 ml of methanol. 60 mg of sodium hydroxid (1.50 mmol, 5 eq.) were added. The reaction mixture was stirred at room temperature for 3 hours. The resulting suspension was neutralised with acetic acid. The solution was diluted with ethyl acetate. The occurred precipitate was filtered off and washed with ethyl acetate and was dried in vacuo at 50 °C to yield 138 mg (0. 28 mmol, 92,8%) of the analytically pure target compound.

^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 4.01 (s, 3H), 5.88 (s, 2H), 7.20 (d, 1H), 7.26 (t, 1H), 7.45 (td, 1H), 7.76 - 7.85 (m, 2H), 7.95 (d, 1H), 8.07 - 8.11 (m, 2H), 8.32 - 8.37 (m, 3H), 8.48 (d, 1H), 9.39 (s, 1H).

LC-MS:
retention time: 0.93 min
MS ES$^+$: 487.2 $[M+H]^+$

Example 29-1

Preparation of formic acid - 3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1*H*-indazol-1-yl}methyl)-*N*-methylbenzamide (1:1)



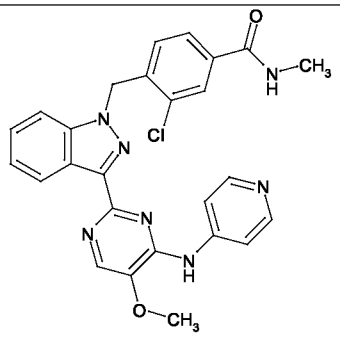
x HCOOH

130.9 mg of 3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzoic acid (28-1, 0.269 mmol, 1. eq.), 1,1 ml of dimethyl-

sulfoxide, 269 µl of 2 M methanamine in tetrahydrofuran (0.538 mmol, 2 eq.), 225 mg of N-[(dimethylamino)(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy)methylidene]-N-methylmethanaminium hexafluorophosphate (HATU; 0.591 mmol, 2.2 eq.) and 140 µl of N-ethyl-N-(propan-2-yl)propan-2-amine (0.806 mmol, 3eq.) were stirred at 50 °C bath temperature for 5 hours. The reaction mixture was filtered off and purified by preparative HPLC to yield 91 mg (0.17 mmol, 62%) of the analytically pure target compound.

^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 2.72 (d, 3H), 4.01 (s, 3H), 5.85 (s, 2H), 7.19 - 7.29 (m, 2H), 7.40 - 7.48 (m, 1H), 7.73 (dd, 1H), 7.79 (d, 1H), 7.92 (d, 1H), 8.06 - 8.13 (m, 3H), 8.31 - 8.39 (m, 3H), 8.44 - 8.54 (m, 2H), 9.39 (s, 1H).
LC-MS:
retention time: 0.82 min
MS ES$^+$: 500.1 $[M+H]^+$
Method B

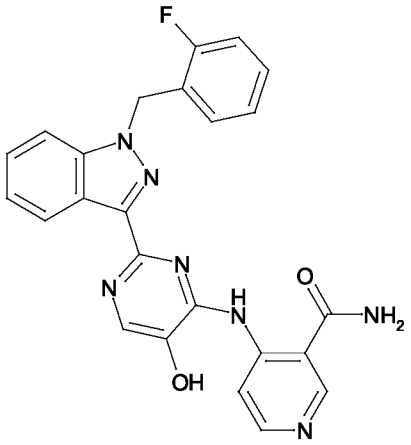
The compound was treated with base to form the salt free analogon:

29-2 SM = 28-1		3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)-N-methylbenzamide	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 2.72 (d, 3H), 4.01 (s, 3H), 5.85 (s, 2H), 7.20 - 7.28 (m, 2H), 7.44 (td, 1H), 7.73 (dd, 1H), 7.79 (d, 1H), 7.92 (d, 1H), 8.10 (dd, 2H), 8.32 - 8.39 (m, 3H), 8.45 - 8.54 (m, 2H), 9.38 (s, 1H).

Example 30-1

Preparation of 4-({2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)pyridine-3-carboxamide

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25 mg of 4-amino-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]pyrimidin-5-ol (1-11-1, 0.075 mmol, 1. eq.) were dissolved in 1.5 ml of N,N-dimethylformamide. 51.52 mg of potassium carbonate (0.373 mmol, 5 eq.) and 23.35 mg of 4-chloropyridine-3-carboxamide (0.149 mmol, 2 eq.) were added. The reaction mixture was stirred at 100 ℃ bath temperature in a pressure pipe for 48 h ours. The reaction mixture was filtered off. The residue was purified by preparative HPLC to yield 2.07 mg (0.004 mmol, 5.6%) of the analytically pure target compound.

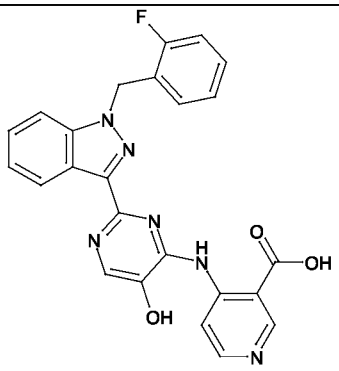
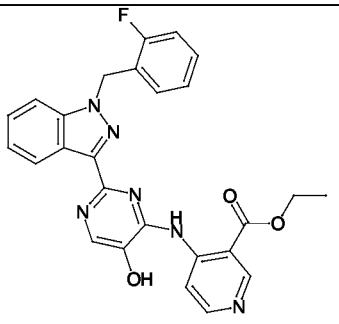
^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 5.77 (s, 2H), 7.11 - 7.37 (m, 5H), 7.40 - 7.48 (m, 1H), 7.74 - 7.83 (m, 2H), 8.18 (s, 1H), 8.38 (br. s., 1H), 8.41 - 8.50 (m, 2H), 8.89 (s, 1H), 9.20 (d, 1H), 10.90 (br. s., 1H), 11.94 (s, 1H).

LC-MS:

retention time: 0.94 min

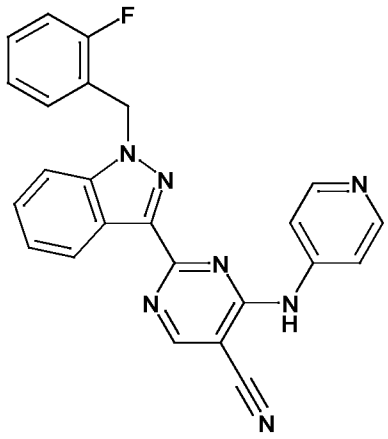
MS ES$^+$: 456.2 $[M+H]^+$

The following compound was formed during the same procedure using the indicated starting material (SM = starting material):

30-2 SM = 1-11-1		4-({2-[1-(2-fluorobenzyl)-*1H*-indazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)pyridine-3-carboxylic acid	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 5.78 (s, 2H), 7.12 - 7.39 (m, 6H), 7.44 (t, 1H), 7.79 (d, 1H), 8.23 (s, 1H), 8.44 (d, 1H), 8.50 (d, 1H), 8.98 (s, 1H), 9.33 (d, 1H), 11.02 (br. s., 1H), 13.66 - 14.11 (br. s., 1H). LC-MS: retention time: 0.95 min MS ES$^+$: 456.9 [M+H]$^+$ Method B
30-3 SM = 1-11-1		ethyl 4-({2-[1-(2-fluorobenzyl)-*1H*-indazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)pyridine-3-carboxylate	^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 1.36 (t, 3H), 4.35 (q, 2H), 5.68 (s, 2H), 7.07 - 7.38 (m, 7H), 7.47 (s, 1H), 7.63 (d, 1H), 8.32 - 8.42 (m, 1H), 8.43 - 8.53 (m, 1H), 8.90 (s, 1H), 9.43 (d, 1H), 11.26 (s, 1H). LC-MS: retention time: 1.09 min MS ES$^+$: 485.21 [M+H]$^+$

Example 31-1

Preparation of 2-[1-(2-fluorobenzyl)-*1H*-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidine-5-carbonitrile



73 mg of 4-chloro-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]pyrimidine-5-carbonitrile (1-14-1, 0.201 mmol, 1. eq.), 22.66 mg of pyridin-4-amine (0.241 mmol, 1.2 eq.), 42 µl of N-ethyl-N-(propan-2-yl)propan-2-amine (0.241 mmol, 1.2 eq.) and 1 ml of N,N-dimethylformamide were stirred at room temperature for 24 hours. The reaction mixture was partitioned between half-saturated aqueous sodium hydrogen carbonate solution and dichloromethane/ isopropanol 4:1. The aqueous layer was extracted twice with dichloromethane/ isopropanol 4:1. The combined organic layers were washed with brine, dried over a silicon filter and concentrated in vacuo. The residue was purified by flash chromatography and preparative HPLC to yield 24.4 mg (0.06 mmol, 28.9%) of the analytically pure target compound.

^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 5.83 (s, 2H), 7.08 - 7.40 (m, 5H), 7.47 (td, 1H), 7.82 - 7.92 (m, 3H), 8.34 (d, 1H), 8.46 (d, 2H), 8.99 (s, 1H), 10.16 - 10.37 (m, 1H).

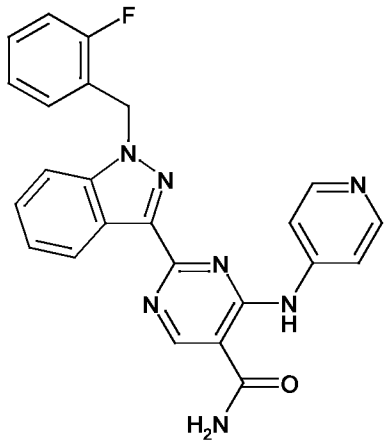
LC-MS:

retention time: 1.00 min

MS ES$^+$: 422.2 $[M+H]^+$

Example 32-1

Preparation of 2-[1-(2-fluorobenzyl)-*1H*-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidine-5-carboxamide



20,7 mg of 2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidine-5-carbonitrile (31-1, 0.049 mmol, 1 eq.) were added to ice bath cooled conc. sulfuric acid (1.84 mmol, 37.5 eq.) and stirred for five minutes at 5 °C and further 24 hours at room temperature. Ice was added to the suspension. The suspension was filtered off, washed with water and the filter cake was dried under vacuo at 50 °C to yield 23.0 mg (0.05 mmol, 106%) of the analyt ically pure target compound.

^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 5.86 (s, 2H), 7.13 - 7.27 (m, 2H), 7.29 - 7.41 (m, 3H), 7.46 - 7.55 (m, 1H), 7.88 (d, 1H), 8.07 (br. s., 1H), 8.28 (d, 2H), 8.46 (d, 1H), 8.57 (d, 3H), 9.19 (s, 1H), 12.07 (s, 1H).

LC-MS:

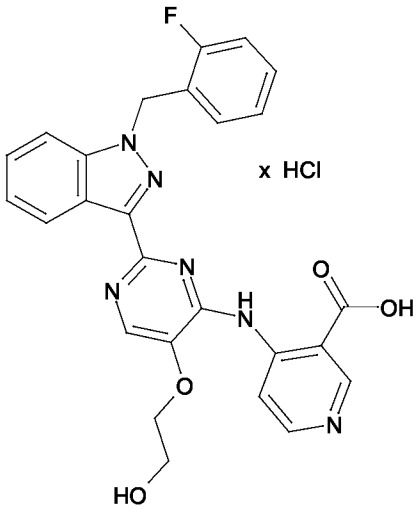
retention time: 1.02 min

MS ES$^+$: 440.37 $[M+H]^+$

Example 33-1

Preparation of 4-({2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)pyridine-3-carboxylic acid hydrochloride (1:1)

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183 mg of 4-({5-(2-{[tert-butyl(dimethyl)silyl]oxy}ethoxy)-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}amino)pyridine-3-carboxylic acid (derived from 30-3 as SM via step 1 of the procedure described in 13-1 and subsequent ester hydrolysis) 0.297 mmol, 1. eq.) were dissolved in 10 ml of 4 M hydrogen chloride solution in dioxane and stirred at room temperature for 24 hours. The precipitate was filtered off, washed with dichloromethane and the filter cake was dried under vacuo to yield 157 mg (0.26 mmol, 88.4%) of the analytically pure target compound.

^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 3.52 (s, 2H), 3.79 - 3.88 (m, 2H), 4.35 (t, 2H), 5.82 (s, 2H), 7.08 - 7.38 (m, 5H), 7.46 (t, 1H), 7.81 (d, 1H), 8.43 (d, 1H), 8.65 - 8.70 (m, 1H), 8.76 (d, 1H), 9.11 (s, 1H), 9.66 (d, 1H), 12.53 (s, 1H).

LC-MS:

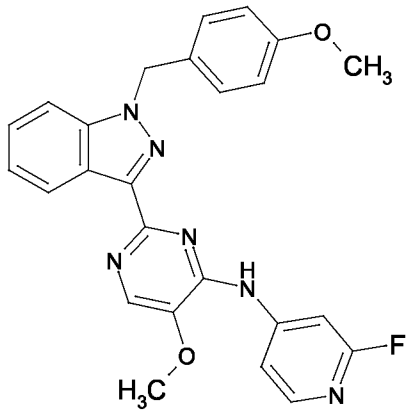
retention time: 0.98 min

MS ES$^+$: 501.33 $[M+H]^+$

Example 34-1

Preparation of N-(2-fluoropyridin-4-yl)-5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]pyrimidin-4-amine

271

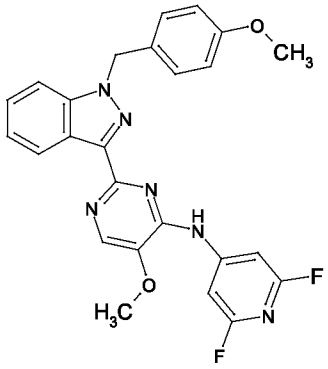
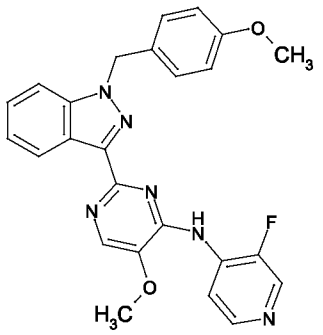
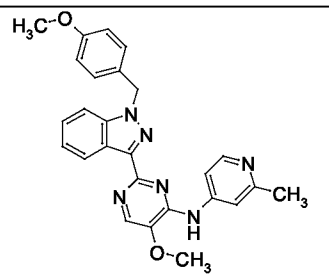


100 mg of 5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]pyrimidin-4-amine (1-4-1, 0.277 mmol, 1. eq.), 78.0 mg of (2-fluoropyridin-4-yl)boronic acid (0.553 mmol, 2 eq.) and 205 mg of copper (II) acetate were suspended in 4 ml of trichloromethane. 154 µl of triethylamine (1.11 mmol, 4 eq.) and 16.9 mg of N,N-dimethylpyridin-4-amine (138 mmol, 0.5 eq.) were added. The reaction mixture was stirred at room temperature for 24 hours.The reaction mixture was filtered off over Celite 545 and washed with dichloromethane. The filtrate was concentrated in vacuo. The residue was purified by flash chromatography and preparative HPLC to yield 13 mg (0.03 mmol, 10.9%) of the analytically pure target compound.

^{1}H-NMR (300MHz, DMSO-d6): δ [ppm]= 3.66 (s, 3H), 4.03 (s, 3H), 5.63 (br. s., 2H), 6.85 (d, 2H), 7.23 (d, 1H), 7.29 - 7.48 (m, 3H), 7.75 - 7.92 (m, 2H), 8.05 (d, 1H), 8.26 (s, 1H), 8.42 (d, 2H), 9.75 (s, 1H).

LC-MS:
retention time: 1.25 min
MS ES$^+$: 457.2 $[M+H]^+$

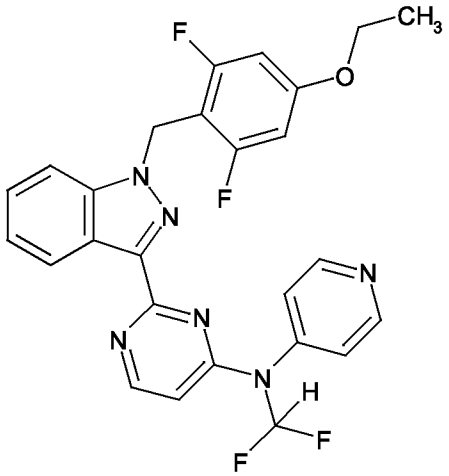
The following compound was formed according to the same procedure using the indicated starting material (SM):

34-2 SM = 1-4-1		N-(2,6-difluoropyridin-4-yl)-5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]pyrimidin-4-amine	^{1}H-NMR (400MHz, DMSO-d6): δ [ppm]= 3.66 (s, 3H), 4.04 (s, 3H), 5.63 (s, 2H), 6.84 (d, 2H), 7.22 (t, 1H), 7.36 (d, 2H), 7.40 (d, 1H), 7.83 (d, 1H), 7.98 (s, 2H), 8.38 - 8.49 (m, 2H), 10.04 (s, 1H). LC-MS: retention time: 1.40 min MS ES$^+$: 475.3 [M+H]$^+$ Method B
34-3 SM = 1-4-1		N-(3-fluoropyridin-4-yl)-5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]pyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d6): δ [ppm]= 3.65 (s, 3H), 4.02 (s, 3H), 5.62 (br. s., 2H), 6.83 (d, 2H), 7.07 - 7.18 (m, 1H), 7.24 (br. s., 2H), 7.38 (t, 1H), 7.74 (d, 1H), 8.22 (d, 1H), 8.29 - 8.79 (m, 5H). LC-MS: retention time: 1.17 min MS ES$^+$: 457.43 [M+H]$^+$ Method B
34-4 SM = 1-4-1		5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]-N-(2-methylpyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (300MHz, DMSO-d6): δ [ppm]= 2.41 (s, 3H), 3.66 (s, 3H), 4.01 (s, 3H), 5.65 (br. s., 2H), 6.85 (d, 2H), 7.20 (t, 1H), 7.31 (d, 2H), 7.40 (t, 1H), 7.72 (br. d, 1H), 7.79 (d,

			1H), 8.23-8.27 (m, 2H), 8.32 (s, 1H) 8.44 (d, 1H), 9.30 (m, 1H). LC-MS (Method 2): retention time: 0.96min MS ES+: 453.1 [M+H]+

Example 35-1

Preparation of N-(difluoromethyl)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine



119.176 mg of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine (5-1, 0.260 mmol, 1. eq.) were dissolved in 2 ml of dry N,N-dimethylformamide. 254.09 mg of cesium carbonate and 39.63 mg of sodium chloro(difluoro)acetate were added and stirred for two hours at 100 ℃ bath temperature under nitrogen atmosphere. Then the mixture was portioned between water and dichloromethane/ isopropanol 4:1. The phases were separated and the aqueous layer (slightly brown) was extracted twice with dichloromethane/ isopropanol 4:1. The combined organic layers were washed with brine, dried over a silicone filter and concentrated in vacuo. The residue was purified by flash chromatography to yield 9 mg (0.02 mmol, 6.13%) of the analytically pure target compound.

^{1}H-NMR (500MHz, DMSO-d 6): δ [ppm]= 1.27 - 1.31 (t, 3H), 4.04 (q, 2H), 5.69 (s, 2H), 6.70 - 6.82 (m, 5H), 7.24 (t, 1H), 7.42 - 7.68 (m, 1H), 7.47 (ddd, 1H), 7.79 (dd, 3H), 8.47 (d, 1H), 8.60 (d, 1H).

LC-MS:

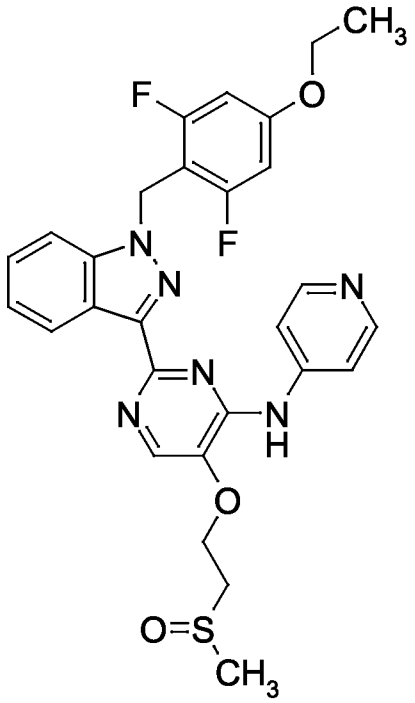
retention time: 1.09 min

MS ES$^+$: 509.1 $[M+H]^+$

Method B

Example 36-1

Preparation of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(methylsulfinyl)ethoxy]-N-(pyridin-4-yl)pyrimidin-4-amine



To a solution of 1.24 g 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(methylsulfanyl) ethoxy]-N-(pyridin-4-yl)pyrimidin-4-amine (4-16, 2.26 mmol, 1. eq.) in 2.15 ml of dry chloroform, was added slowly at 0 ℃ a solution of 557 mg 2-chlorobenzenecarboperoxoic acid (77%, 2.49 mmol, 1.1 eq.) in 2.15 ml chloroform. After 30 min dichloromethane and sodium thiosulfate-solution (10 %) were

added. The slurry was stirred for 5 min.. After separating the solid (product) the aqueous layer was washed with dichloromethane twice. The organic layers were dried with sodium sulphate and concentrated in vacuo. The residue was purified by flash chromatography and combined the former isolated solid to yield 1.22 g (2.05 mmol, 91%) of the analytically pure target compound.

^{1}H-NMR (400MHz, DMSO-d 6): δ [ppm]= 1.29 (t, 3H), 2.72 (s, 3H), 3.18 - 3.28 (m, 1H), 3.34 - 3.47 (m, 1H), 4.04 (q, 2H), 4.58 - 4.78 (m, 2H), 5.69 (s, 2H), 6.73 - 6.87 (m, 2H), 7.21 - 7.34 (m, 1H), 7.43 - 7.56 (m, 1H), 7.80 - 7.92 (m, 1H), 8.08 - 8.17 (m, 2H), 8.39 - 8.52 (m, 4H), 9.40 (s, 1H)

LC-MS:

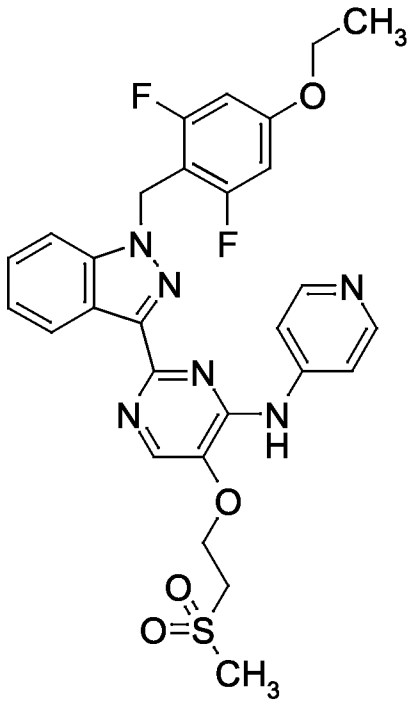
retention time: 0.98 min
MS ES$^+$: 564.0 $[M+H]^+$

Example 36-1 was separated into its enantiomers via chiral HPLC separation (Method:
Column: Chiralpak AD-H 5µ 150x4,6 Channel: UV_VIS_3
Solvent: A:Hexan C:EtOH Wavelength (nm): 280
Puffer: 0.1% DEA Flow (ml/min): 1,000
Gradient: Iso_70%A+30%C Run Time (min): 15,00
Solution: 1 mg/mL EtOH/MeOH 2:1 Vial Number: 6
Comment: 25℃ Injection Volume: 10,0)

36-2 SM = 36-1		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(methylsulfi-nyl)ethoxy]-N-(pyridin-4-yl)pyrimidin-4-amine (Enantiomer 1)	^{1}H-NMR (400MHz, DMSO-d 6): δ [ppm]= 1.29 (t, 3H), 2.72 (s, 3H), 3.18 - 3.28 (m, 1H), 3.34 - 3.47 (m, 1H), 4.04 (q, 2H), 4.58 - 4.78 (m, 2H), 5.69 (s, 2H), 6.73 - 6.87 (m, 2H), 7.21 - 7.34 (m, 1H), 7.43 - 7.56 (m, 1H), 7.80 - 7.92 (m, 1H), 8.08

			- 8.17 (m, 2H), 8.39 - 8.52 (m, 4H), 9.40 (s, 1H). retention time: 10.08 min specific rotation: 18.5° +/- 0.08°
36-3 SM = 36-1		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(methylsulfi-nyl)ethoxy]-N-(pyridin-4-yl)pyrimidin-4-amine (Enantiomer 2)	^{1}H-NMR (400MHz, DMSO-d 6): δ [ppm]= 1.29 (t, 3H), 2.72 (s, 3H), 3.18 - 3.28 (m, 1H), 3.34 - 3.47 (m, 1H), 4.04 (q, 2H), 4.58 - 4.78 (m, 2H), 5.69 (s, 2H), 6.73 - 6.87 (m, 2H), 7.21 - 7.34 (m, 1H), 7.43 - 7.56 (m, 1H), 7.80 - 7.92 (m, 1H), 8.08 - 8.17 (m, 2H), 8.39 - 8.52 (m, 4H), 9.40 (s, 1H) retention time: 12.87 min specific rotation: -14.7° +/- 0.15°

Example 37-1 Preparation of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(methylsulfonyl)ethoxy]-N-(pyridin-4-yl)pyrimidin-4-amine



100 mg of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(methylsulfinyl)ethoxy]-N-(pyridin-4-yl)pyrimidin-4-amine (36-1, 0.177 mmol, 1.0 eq.) were dissolved in 0.9 ml of anhydrous tetrahydrofuran. 0.09 ml of aqueous hydrogen peroxide (30 %, 0.886 mmol, 5.0 eq.) and 37.0 mg Diethylazodicarboxylate were added. The reaction mixture was stirred at 50 °C for 2 h. A white precipitate was filtered off and purified by flash chromatography to yield 18.1 mg (0.03 mmol, 17.6%) of the analytically pure target compound.

^{1}H-NMR (300MHz, DMSO-d 6): δ [ppm]= 1.28 (t, 3H), 3.14 (s, 3H), 3.78 (t, 2H), 4.03 (q, 2H), 4.66 (t, 2H), 5.69 (s, 2H), 6.72 - 6.95 (m, 2H), 7.27 (t, 1H), 7.49 (t, 1H), 7.86 (d, 1H), 8.05 - 8.13 (m, 2H), 8.36 - 8.55 (m, 4H), 9.06 (s, 1H).

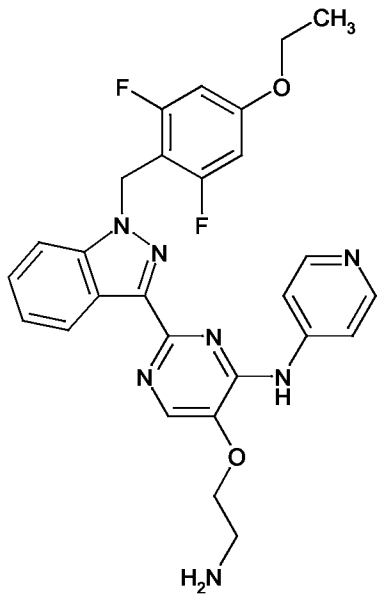
LC-MS (Method 1):

retention time: 1.03 min

MS ES$^+$: 581.2 $[M+H]^+$

Example 38-1

Preparation of 5-(2-aminoethoxy)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine



28.6 mg of tert-butyl [2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethyl]carbamate (4-23, 0.046 mmol, 1.0 eq.) were dissolved in 2 ml of dry dichloromethane. 0.071 ml of trifluoroacetic acid (0.926 mmol, 20.0 eq.) were added at 0 °C. The reaction mixture was stirred over night at room temperature. Then a mixture 2 N sodium carbonate and dichloromethane/ isopropanol 4:1 was added and the mixture was stirred for 30 min. The phases were separated and the aqueous layer (slightly brown) was extracted twice with dichloromethane/ isopropanol 4:1. The combined organic layers were dried over a magnesium sulfate and concentrated in vacuo. The residue was purified by crystallization from ethylacetate to yield 6.8 mg (0.01 mmol, 27.0 %) of the analytically pure target compound.

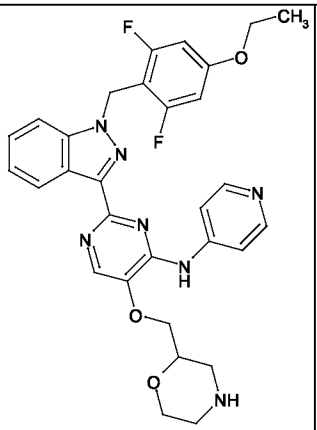
^{1}H-NMR (600MHz, DMSO-d 6): δ [ppm]= 1.29 (t, 3H), 2.98 (t, 2H), 4.05 (q, 2H), 4.15 (t, 2H), 5.68 (s, 2H), 6.75 - 6.82 (m, 2H), 7.23 - 7.29 (m, 1H), 7.47 – 7.50 (m, 1H), 7.85 (d, 1H), 8.13 - 8.17 (m, 2H), 8.31 (s, 1H), 8.35 (s, 1H), 8.42 - 8.45 (m, 2H), 8.46 (d, 1H).

LC-MS (Method 5):

retention time: 1.24 min

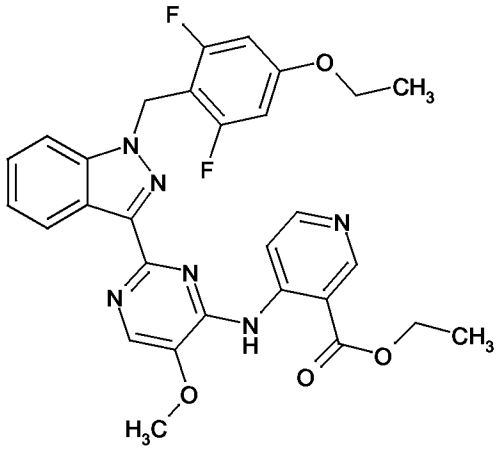
MS ES$^+$: 518.2 $[M+H]^+$

The following compounds were prepared according to the same procedure using the indicated starting materials (SM = starting material):

38-2 SM = 4-11		2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-(morpholin-2-ylmethoxy)-N-(pyridin-4-yl)pyrimidin-4-amine	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.28 (t, 3H), 2.51 - 2.57 (m, 1H), 2.64 - 2.71 (m, 2H), 2.94 - 3.02 (m, 1H), 3.45 - 3.56 (m, 1H), 3.74 - 3.81 (m, 1H), 3.83 - 3.92 (m, 1H), 4.02 (q, 2H), 4.12 - 4.27 (m, 2H), 5.67 (s, 2H), 6.73 - 6.84 (m, 2H), 7.20 - 7.30 (m, 1H), 7.43 - 7.53 (m, 1H), 7.80 - 7.87 (m, 1H), 8.10 - 8.17 (m, 2H), 8.38 (s, 1H), 8.39 - 8.47 (m, 3H), 9.14 (s, 1H). LC-MS (Method 5): retention time: 1.24 min MS ES$^+$: 574.5 $[M+H]^+$

Example 39-1

Preparation of ethyl 4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carboxylate



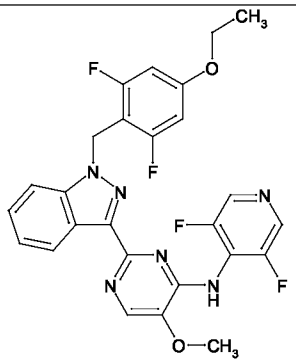
150 mg of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-amine (1-4-3, 0.365 mmol, 1.0 eq.), 89 mg of commercial ethyl 4-chloronicotinate (0.401 mmol, 1.1 eq.), 31.6 mg of (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine) (0.055 mmol, 0.15 eq.), 356 mg of caesium carbonate (1.09 mmol, 3.0 eq.) and 8.2 mg of palladium diacetate (0.036 mmol, 0.1 eq.) were suspended in 4.7 mL of dry dioxane and stirred under nitrogen atmosphere at 105℃ bath temperature for 3 h. Solids were filtere d off, washed with dioxane and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography yielding 77 mg from which only 15.7 mg were further purified by crystallization from THF to yield 3.1 mg (0.01 mmol, 1.44 %) of analytically pure target compound.

^{1}H-NMR (300MHz, DMSO-d 6): δ [ppm]= 1.26 (t, 3H), 1.36 (t, 3H), 3.95 – 4.10 (m, 5H), 4.37 (q, 2H), 5.68 (s, 2H), 6.71 - 6.87 (m, 2H), 7.19 - 7.33 (m, 1H), 7.41 - 7.54 (m, 1H), 7.83 (d, 1H), 8.37 - 8.48 (m, 2H), 8.59 (d, 1H), 9.07 (s, 1H), 9.39 (d, 1H), 11.29 (s, 1H).

LC-MS:

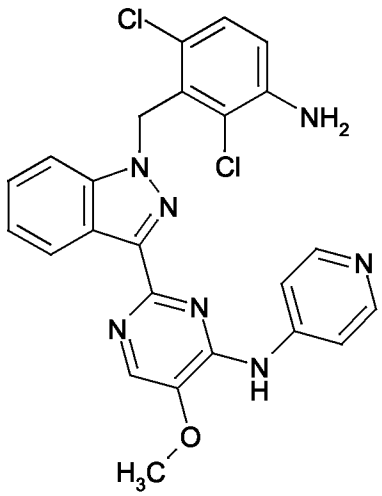
retention time: 1.55min
MS ES$^+$: 560.0 $[M+H]^+$

The following compounds were prepared according to the same procedure using the indicated starting materials (SM = starting material):

39-2 SM = 1-4-3		N-(3,5-difluoropyridin-4-yl)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-amine	^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.26 (t, 3H), 3.90 - 4.12 (m, 5H), 5.58 (s, 2H), 6.62 - 6.79 (m, 2H), 6.94 - 7.04 (m, 1H), 7.25 - 7.40 (m, 1H), 7.65 - 7.74 (m, 1H), 7.76 - 7.85 (m, 1H), 8.24 (s, 1H), 8.59 (s, 2H), 9.36 (s, 1H). LC-MS (Method 5): retention time: 1.34 min MS ES$^+$: 525.2 $[M+H]^+$

Example 40-1

Preparation of 2-[1-(3-amino-2,6-dichlorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine



52 mg of 2-[1-(2,6-dichloro-3-nitrobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine (2-44-1, 0.10 mmol, 1.0 eq.) were dissolved in 5.2 ml of dry methanol. 23.4 mg raney nickel (50 %, 0.199 mmol, 2.0 eq.) and 0.045 ml hydrazine (35 %, 0.498 mmol, 5.0 eq) were added. The reaction mixture was stirred at room temperature vigorously over night. The slurry was filtered over celite and washed with methanol twice. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography to yield 19.2 mg (0.04 mmol, 38%) of the analytically pure target compound.

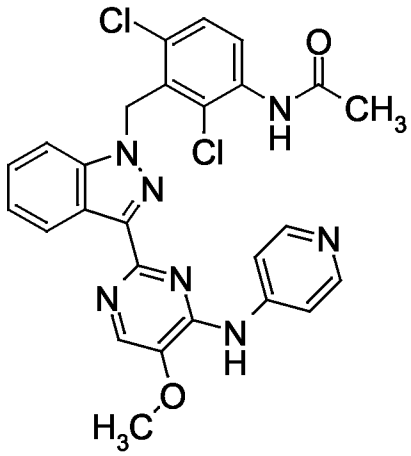
^{1}H-NMR (300MHz, DMSO-d 6): δ [ppm]= 4.00 (s, 3H), 5.62 (s, 2H), 5.78 (s, 2H), 6.82 (d, 1H), 7.22 (t, 2H), 7.46 (t, 1H), 7.86 (d, 1H), 8.14 (d, 2H), 8.32 (s, 1H), 8.38 (d, 2H), 8.47 (d, 1H), 9.34 (s, 1H).

LC-MS:

retention time: 0.97 min
MS ES$^+$: 492.1 $[M+H]^+$

Example 41-1

Preparation of N-[2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]acetamide



50 mg of 2-[1-(3-amino-2,6-dichlorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine (40-1, 0.102 mmol, 1.0 eq.) were dissolved in 0.6 ml of dry

N,N-dimethylformamide. 0.014 ml N,N-diethylethanamine (0.102 mmol, 1.0 eq.) and 0.010 ml acetic anhydride (0.102 mmol, 1.0 eq.) were added at 0 °C and stirred for 3.5 h Then again 0.014 ml N,N-diethylethanamine (0.102 mmol, 1.0 eq.) and 0.010 ml acetic anhydride (0.102 mmol, 1.0 eq.) were added at 0 °C and stirred over night at room temperature. Saturated sodium hydrogen carbonate solution and ethyl acetate were added and the reaction mixture was stirred for 30 min. The organic layer was washed with ethyl acetate twice. The combined organic layers were dried over a silicone filter and concentrated in vacuum. The residue was purified by flash chromatography to yield 17.3 mg (0.03 mmol, 30%) of the analytically pure target compound.

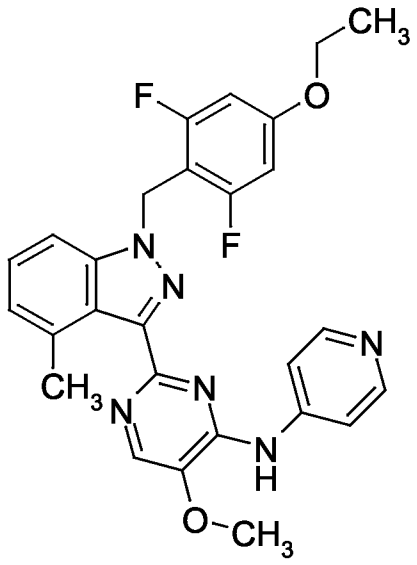
^{1}H-NMR (400MHz, DMSO-d 6): δ [ppm]= 2.07 (s, 3H), 3.99 (s, 3H), 5.89 (s, 2H), 7.22 - 7.29 (m, 1H), 7.44 - 7.52 (m, 1H), 7.58 (d, 1H), 7.79 (d, 1H), 7.90 (d, 1H), 8.09 - 8.16 (m, 2H), 8.31 (s, 1H), 8.34 - 8.39 (m, 2H), 8.48 (d, 1H), 9.32 (s, 1H), 9.60 (s, 1H).

LC-MS (Method 1):

retention time: 0.97 min
MS ES$^+$: 534.1 $[M+H]^+$

Example 42-1

Preparation of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine



100 mg of 2-[1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1H-indazol-3-yl]-5-methoxypyrimidin-4-amine (1-4-6, 0.236 mmol, 1.0 eq.) and 94.2 mg 4-Fluoropyridin hydrochloride (0.705 mmol, 3.0 eq.) were dissolved in 1.1 ml of dry N,N-dimethylformamide. 113 mg sodium hydride (60 %, 2.82 mmol, 12 eq.) were added. The reaction mixture was stirred at 90 °C for 2 h. Water and ethyl acetate were added and the aqueous layer was washed with ethyl acetate twice. The combined organic layers were dried over a silicone filter and concentrated in vacuum. The residue was purified by HPLC to yield 46 mg (0.09 mmol, 38%) of the analytically pure target compound.

^{1}H-NMR (300MHz, DMSO-d 6): δ [ppm]= 1.26 (t, 3H), 2.42 (s, 3H), 3.93 - 4.07 (m, 5H), 5.59 (s, 2H), 6.68 - 6.78 (m, 2H), 6.94 (d, 1H), 7.32 (t, 1H), 7.59 (d, 1H), 7.91 - 8.02 (m, 2H), 8.22 - 8.36 (m, 3H), 9.36 (s, 1H).

LC-MS (Method B):

retention time: 1.32 min

MS ES$^+$: 503.03 $[M+H]^+$

Biological investigations

The following assays can be used to illustrate the commercial utility of the compounds according to the present invention.

Examples were tested in selected biological assays one or more times. When tested more than once, data are reported as either average values or as median values, wherein

- the average value, also referred to as the arithmetic mean value, represents the sum of the values obtained divided by the number of times tested, and
- the median value represents the middle number of the group of values when ranked in ascending or descending order. If the number of values in the data set is odd, the median is the middle value. If the number of values in the data set is even, the median is the arithmetic mean of the two middle values.

Examples were synthesized one or more times. When synthesized more than once, data from biological assays represent average values calculated utilizing data sets obtained from testing of one or more synthetic batch.

Biological Assay 1.0:

Bub1 kinase assay

Bub1-inhibitory activities of compounds described in the present invention were quantified using a time-resolved fluorescence energy transfer (TR-FRET) kinase assay which measures phosphorylation of the synthetic peptide Biotin-Ahx-VLLPKKSFAEPG (C-terminus in amide form), purchased from e.g. Biosyntan (Berlin, Germany) by the (recombinant) catalytic domain of human Bub1 (amino acids 704-1085), expressed in Hi5 insect cells with an N-terminal His6-tag and purified by affinity- (Ni-NTA) and size exclusion chromatography.

In a typical assay 11 different concentrations of each compound (0.1 nM, 0.33 nM, 1.1 nM, 3.8 nM, 13 nM, 44 nM, 0.15 µM, 0.51 µM, 1.7 µM, 5.9 µM and 20 µM)

were tested in duplicate within the same microtiter plate. To this end, 100-fold concentrated compound solutions (in DMSO) were previously prepared by serial dilution (1:3.4) of 2 mM stocks in a clear low volume 384-well source microtiter plate (Greiner Bio-One, Frickenhausen, Germany), from which 50 nl of compounds were transferred into a black low volume test microtiter plate from the same supplier. Subsequently, 2 µl of Bub1 (the final concentration of Bub1 was adjusted depending on the activity of the enzyme lot in order to be within the linear dynamic range of the assay: typically ~ 200 µg/ml were used) in aqueous assay buffer [50 mM Tris/HCl pH 7.5, 10 mM magnesium chloride (MgCl2), 200 mM potassium chloride (KCl), 1.0 mM dithiothreitol (DTT), 0.1 mM sodium ortho-vanadate, 1% (v/v) glycerol, 0.01 % (w/v) bovine serum albumine (BSA), 0.005% (v/v) Trition X-100 (Sigma), 1x Complete EDTA-free protease inhibitor mixture (Roche)] were added to the compounds in the test plate and the mixture was incubated for 15 min at 22℃ to allow pre-equilibration of the putat ive enzyme-inhibitor complexes before the start of the kinase reaction, which was initiated by the addition of 3 µl 1.67-fold concentrated solution (in assay buffer) of adenosine-tri-phosphate (ATP, 10 µM final concentration) and peptide substrate (1 µM final concentration). The resulting mixture (5 µl final volume) was incubated at 22℃ during 60 min., and the reaction was stopped by the addition of 5 µl of an aqueous EDTA-solution (50 mM EDTA, in 100 mM HEPES pH 7.5 and 0.2 % (w/v) bovine serum albumin) which also contained the TR-FRET detection reagents (0.2 µM streptavidin-XL665 [Cisbio Bioassays, Codolet, France] and 1 nM anti-phosho-Serine antibody [Merck Millipore, cat. # 35-001] and 0.4 nM LANCE EU-W1024 labeled anti-mouse IgG antibody [Perkin-Elmer, product no. AD0077, alternatively a Terbium-cryptate-labeled anti-mouse IgG antibody from Cisbio Bioassays can be used]). The stopped reaction mixture was further incubated 1 h at 22℃ in order to allow the formation of complexes between peptides and detection reagents. Subsequently, the amount of product was evaluated by measurement of the resonance energy transfer from the Eu-chelate-antibody complex recognizing the Phosphoserine residue to the streptavidin-XL665 bound to the biotin moiety of the peptide. To this end, the fluorescence emissions at 620 nm and 665 nm after excitation at 330-350 nm were measured in a TR-FRET plate reader, e.g. a Rubystar or Pherastar (both from BMG Labtechnologies, Offenburg, Germany) or a Viewlux (Perkin-Elmer) and

the ratio of the emissions (665 nm/622 nm) was taken as indicator for the amount of phosphorylated substrate. The data were normalised using two sets of (typically 32-) control wells for high- (= enzyme reaction without inhibitor = 0 % = Minimum inhibition) and low- (= all assay components without enzyme = 100 % = Maximum inhibition) Bub1 activity. IC50 values were calculated by fitting the normalized inhibition data to a 4-parameter logistic equation (Minimum, Maximum, IC50, Hill; Y = Max + (Min - Max) / (1 + (X/IC50)Hill)) using a Bayer-proprietary analysis software.

Biological Assay 2.0:

Proliferation Assay:

Cultivated tumor cells (cells were ordered from ATCC, except HeLa-MaTu and HeLa-MaTu-ADR, which were ordered from EPO-GmbH, Berlin) were plated at a density of 1000 to 5000 cells/well, depending on the growth rate of the respective cell line, 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 0.001-10 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. Absorbtion 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 aborbtion values of the zero-point plate (=0%) and the ab-

sorbtion 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.

Tab.1. Compounds had been evaluated in the following cell lines, which examplify the sub-indications listed

Tumor indication	**Cell line**
Cervical cancer	HeLa HeLa-MaTu-ADR
Breast cancer	MDA-MB 453 HCC-70 MCF7 MDA MB231 MDA-MB-468
Ovarian cancer	SKBR-3 A2780 COLO-704 Caov-3 ES-2 SK-OV-3 IGROV-1 OVCAR8
Non-small cell lung cancer (NSCLC)	A549 NCI-H460 NCI-H1299
Prostate cancer	DU145
Colon cancer	Caco2 HCT15 HT29
Pancreas cancer	MIAPaCa2
Osteo sacroma	U2OS
Acute myelogenous leucemia	KG1 MOLM-13 MV-4-11
Burkitt lymphoma	RAMOS
Multiple myeloma	OPM-2
Melanoma	B16F10

The following table gives the data regarding Bub1 kinase inhibition, and inhibition of HeLa cell proliferation, for the examples of the present invention for the biological assays 1 and 2:

Example Nr.	Biological Assay 1: Bub1 kinase assay median IC50 [mol/l]	Biological Assay 2: Proliferation assay (HeLa cell line) median IC50 [mol/l]
2-1-1	2.6e-009	3.8e-006
2-1-3	1.2e-007	not tested
2-10-1	6.7e-009	≥1.0e-005
2-10-2	1.2e-006	not tested
2-11-1	7.1e-009	2.9e-007
2-11-2	5.4e-007	3.4e-006
2-12-1	7.3e-009	1.6e-006
2-13-1	8.0e-009	3.8e-006
2-14-1	8.3e-009	4.7e-006
2-14-2	7.3e-007	not tested
2-15-1	3.8e-008	4.7e-006
2-15-2	3.2e-006	not tested
2-16-1	8.4e-009	1.6e-006
2-17-1	8.8e-009	≥1.0e-005
2-17-2	8.9e-007	not tested
2-18-1	1.3e-008	9.3e-006
2-19-1	1.0e-008	3.4e-006
2-2-1	2.6e-009	3.4e-006
2-2-3	2.5e-008	not tested
2-20-1	1.1e-008	7.3e-006
2-21-1	1.2e-008	≥1.0e-005

Example Nr.	Biological Assay 1: Bub1 kinase assay median IC50 [mol/l]	Biological Assay 2: Proliferation assay (HeLa cell line) median IC50 [mol/l]
2-21-2	2.0e-005	not tested
2-22-1	3.2e-006	not tested
2-23-1	1.3e-008	9.3e-006
2-24-1	1.4e-008	3.1e-006
2-25-1	1.5e-008	9.8e-006
2-26-1	1.6e-008	5.6e-007
2-26-2	8.4e-007	2.9e-006
2-27-1	2.0e-008	≥1.0e-005
2-28-1	2.2e-008	8.1e-006
2-29-1	2.3e-008	9.0e-006
2-3-1	4.4e-009	3.0e-006
2-3-3	3.6e-007	8.5e-006
2-30-1	2.3e-008	2.2e-006
2-31-1	2.8e-008	≥1.0e-005
2-32-1	2.9e-008	4.2e-006
2-33-1	3.8e-008	≥1.0e-005
2-33-2	1.1e-006	not tested
2-34-1	3.8e-008	1.6e-006
2-35-1	5.2e-008	≥1.0e-005
2-36-1	5.8e-008	≥1.0e-005
2-37-1	7.1e-008	≥1.0e-005
2-38-1	7.6e-008	≥1.0e-005
2-39-1	5.6e-009	3.6e-006
2-39-2	6.9e-006	not tested
2-4-1	4.5e-009	3.5e-006

Example Nr.	Biological Assay 1: Bub1 kinase assay median IC50 [mol/l]	Biological Assay 2: Proliferation assay (HeLa cell line) median IC50 [mol/l]
2-4-2	3.5e-006	not tested
2-4-3	1.4e-008	3.9e-006
2-40-1	1.2e-007	5.6e-006
2-41-1	1.5e-007	7.9e-006
2-42-1	1.9e-007	≥1.0e-005
2-43-1	1.2e-006	≥1.0e-005
2-44-1	4.1E-8	not tested
2-45-1	1.1E-7	not tested
2-46-1	1.6e-008	1.4e-006
2-47-1	2.4E-6	not tested
2-48-1	5.5E-9	≥1.0e-005
2-49-1	1.5E-6	not tested
2-5-1	4.6e-009	2.1e-006
2-5-2	9.3e-006	not tested
2-5-3	2.1e-008	≥1.0e-005
2-50-1	1.1e-008	≥1.0e-005
2-51-1	1.0E-8	2.7E-6
2-52-1	1.1E-8	2.1E-6
2-53-1	8.3e-008	3.4e-006
2-6-1	4.7e-009	3.8e-006
2-6-3	5.9e-008	≥1.0e-005
2-7-1	4.8e-009	≥1.0e-005
2-7-2	2.1e-007	not tested
2-7-3	4.3e-007	≥1.0e-005

Example Nr.	Biological Assay 1: Bub1 kinase assay median IC50 [mol/l]	Biological Assay 2: Proliferation assay (HeLa cell line) median IC50 [mol/l]
2-8-1	6.7e-009	≥1.0e-005
2-8-2	2.9e-007	not tested
2-8-3	5.7e-008	1.0e-005
2-9-1	6.7e-009	≥1.0e-005
2-9-2	2.4e-007	not tested
2-9-3	2.0e-005	not tested
3-1	4.7e-009	≥1.0e-005
3-2	9.8e-009	≥1.0e-005
3-3	1.5e-008	≥1.0e-005
3-4	4.8e-008	≥1.0e-005
4-1	2.4e-009	3.5e-006
4-10	9.0e-009	4.4e-006
4-11	2.4e-008	not tested
4-12	7.8e-009	9.0e-006
4-13	7.6e-009	8.0e-006
4-14	1.2e-008	≥1.0e-005
4-15	8.0e-009	3.9e-006
4-16	1.4e-008	4.4e-006
4-17	7.4E-9	4.8E-6
4-18	1.2E-8	not tested
4-19	1.0E-8	1.2E-6
4-2-1	3.3e-009	8.7e-006
4-2-2	4.3e-007	not tested
4-2-3	9.3E-9	4.9E-6

Example Nr.	Biological Assay 1: Bub1 kinase assay median IC50 [mol/l]	Biological Assay 2: Proliferation assay (HeLa cell line) median IC50 [mol/l]
4-20	2.1E-7	not tested
4-21	7.8E-9	3.8E-6
4-22	5.8E-9	1.9E-6
4-23	not tested	not tested
4-3	7.5e-009	1.4e-005
4-4	1.4e-008	3.4e-006
4-5	1.8e-008	≥1.0e-005
4-5-2	3.3e-007	not tested
4-6	2.9e-008	3.6e-006
4-7	3.5e-008	≥1.0e-005
4-8	8.0e-009	1.3E-6
4-9	5.4E-9	1.7E-6
4-10	9.0E-9	4.4E-6
4-11	2.4E-8	not tested
4-12	7.8E-9	9.0E-6
4-13	7.6E-8	8.0E-6
4-14	1.2E-8	≥1.0e-005
4-15	8.0E-9	3.9E-6
4-16	1.4E-8	4.4E-6
4-17	7.4E-9	4.8E-6
4-18	1.2E-8	not tested
4-19	1.0E-8	1.2E-6
4-20	2.1E-7	not tested
4-21	7.8E-9	3.8E-6
4-22	5.8E-9	1.9E-6

Example Nr.	Biological Assay 1: Bub1 kinase assay median IC50 [mol/l]	Biological Assay 2: Proliferation assay (HeLa cell line) median IC50 [mol/l]
4-23	9.3E-9	4.9E-6
5-1	5.2e-009	1.4e-006
5-2	2.7e-008	7.1e-007
5-3	2.8e-008	7.4e-006
6-1	3.9e-009	3.1e-006
6-2	7.4e-009	1.4e-006
7-1	3.0e-009	4.4e-006
8-1	7.4e-009	3.2e-006
8-2	2.1e-008	5.5e-006
8-3	2.4e-007	≥1.0e-005
8-4	1.3E-8	5.0E-6
9-1	9.8e-009	not tested
9-2	2.1e-008	≥1.0e-005
9-3	2.3e-008	7.0e-006
10-1	1.2e-008	2.0e-006
10-2	4.2e-007	1.7e-006
10-3	3.6e-007	9.6e-006
11-1	1.8e-008	8.1e-006
11-2	1.0e-008	≥1.0e-005
12-1	1.1e-008	≥1.0e-005
12-2	4.6e-009	≥1.0e-005
12-3	4.8e-009	≥1.0e-005
13-1	3.3e-009	1.5e-006
13-2	7.2e-009	9.6e-006
13-3	1.7e-008	≥1.0e-005

Example Nr.	Biological Assay 1: Bub1 kinase assay median IC50 [mol/l]	Biological Assay 2: Proliferation assay (HeLa cell line) median IC50 [mol/l]
13-4	4.7e-009	8.0e-006
13-5	6.5e-009	≥1.0e-005
13-6	8.6e-009	≥1.0e-005
14-1	3.3e-006	≥1.0e-005
15-1	5.2e-009	1.4e-006
15-2	5.5e-009	≥1.0e-005
15-3	5.7e-009	1.7e-006
15-4	7.3e-009	≥1.0e-005
15-5	1.2e-008	9.9e-006
15-6	4.6e-009	≥1.0e-005
16-1	1.7e-007	2.8e-006
16-2	2.3e-008	3.5e-006
16-3	2.1e-007	4.1e-006
16-4	2.0e-008	2.7e-006
17-1	1.7e-007	≥1.0e-005
17-2	2.4e-006	≥1.0e-005
18-1	1.6e-008	1.4e-006
18-2	2.8e-006	3.5e-006
19-1	2.0e-005	not tested
19-2	6.3E-9	≥1.0E-5
20-1	2.0e-007	1.9e-007
20-2	4.0e-008	3.3e-006
20-3	1.2e-006	4.1e-006
20-4	7.5e-007	≥1.0e-005
20-5	8.8e-006	5.9e-006

Example Nr.	Biological Assay 1: Bub1 kinase assay median IC50 [mol/l]	Biological Assay 2: Proliferation assay (HeLa cell line) median IC50 [mol/l]
20-6	6.7e-006	not tested
21-1	2.8e-008	3.8e-006
22-1	7.7e-007	not tested
23-1	1.4e-006	≥1.0e-005
24-1	6.2e-008	≥1.0e-005
24-2	2.0e-005	not tested
24-3	1.3e-008	9.3e-006
24-4	4.28e-006	not tested
24-5	1.1E-8	not tested
24-6	9.4E-7	not tested
24-7	1.2E-6	1.0e-005
24-8	2.6E-8	1.0e-005
24-9	not tested	not tested
25-1	1.3e-008	≥1.0e-005
25-2	5.4e-009	≥1.0e-005
25-3	8.8E-9	4.4E-6
25-4	5.03E-9	1.0e-005
26-1	1.7e-008	9.2e-006
26-2	2.4e-006	not tested
27-1	5.5e-008	3.9e-006
28-1	3.7e-006	not tested
29-1	1.1e-008	≥1.0e-005
29-2	8.9e-009	≥1.0e-005
30-1	1.7e-008	≥1.0e-005
30-2	2.0e-008	≥1.0e-005

Example Nr.	Biological Assay 1: Bub1 kinase assay median IC50 [mol/l]	Biological Assay 2: Proliferation assay (HeLa cell line) median IC50 [mol/l]
30-3	8.4e-009	≥1.0e-005
31-1	4.7e-006	not tested
32-1	1.2e-007	≥1.0e-005
33-1	1.1e-008	≥1.0e-005
34-1	2.3e-007	≥1.0e-005
34-2	6.2E-6	≥1.0e-005
34-3	2.8e-008	8.7e-006
34-4	1.2E-7	not tested
35-1	1.3e-006	not tested
36-1	4.91E-9	3.3E-6
36-2	6.2E-9	4.4E-7
36-3	6.3E-9	4.3E-7
37-1	5.7E-9	4.2E-6
38-1	3.4E-9	1.4E-6
38-2	3.8E-9	1.2E-6
39-1	under evaluation	under evaluation
39-2	6.7E-7	≥1.0e-005
40-1	3.9E-8	not tested
41-1	1.9E-8	6.0E-6
42-1	6.7E-9	3.6E-6

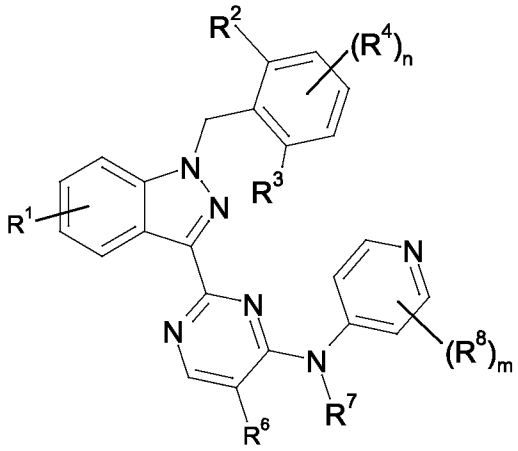
Inhibition of proliferation of HeLa-MaTu-ADR, NCI-H460, DU145, Caco-2 and B16F10 cells by compounds according to the present invention, determined as described under Biological Assays 2.0. All IC_{50} (inhibitory concentration at 50% of maximal effect) values are indicated in [mol/L].

Example Nr.	Biological Assay 2: Proliferation assay (HeLa-MaTu-ADR cell line) median IC50 [mol/l]	Biological Assay 2: Proliferation assay (MCF7 cell line) median IC50 [mol/l]	Biological Assay 2: Proliferation assay (H460 cell line) median IC50 [mol/l]	Biological Assay 2: Proliferation assay (DU145 cell line) median IC50 [mol/l]	Biological Assay 2: Proliferation assay (Caco2 cell line) median IC50 [mol/l]	Biological Assay 2: Proliferation assay (B16F10 cell line) median IC50 [mol/l]
2-4-1	1,3E-06	not tested	4,2E-06	3,3E-06	1,4E-06	1,2E-06
2-5-1	1,2E-06	3,1E-06	1,4E-06	1,7E-06	1,2E-06	1,1E-06
2-9-1	8,1E-06	not tested	1,0E-05	1,0E-05	1,0E-05	9,5E-06
2-11-1	3,0E-06	not tested	3,0E-06	3,0E-06	3,0E-06	2,9E-06
2-12-1	1,3E-06	not tested	1,5E-06	1,6E-06	1,4E-06	1,4E-06
2-16-1	1,2E-06	2,0E-06	2,9E-06	2,0E-06	2,6E-06	9,9E-07
2-24-1	1,3E-06	not tested	2,0E-06	1,3E-06	1,5E-06	1,4E-06
2-25-1	1,0E-05	not tested	1,0E-05	1,0E-05	1,0E-05	1,0E-05
2-26-1	3,9E-07	not tested	1,0E-06	5,3E-07	3,8E-07	4,2E-07
2-32-1	2,3E-06	not tested	8,5E-06	5,3E-06	2,4E-06	1,3E-06
2-34-1	1,2E-06	not tested	6,6E-06	2,6E-06	3,4E-06	1,2E-06
2-46-1	3,8E-07	not tested	8,8E-07	8,5E-07	9,0E-07	7,1E-07
2-11-2	1,0E-05	not tested	2,3E-06	3,6E-06	8,0E-06	2,1E-06
2-4-3	1,0E-07	not tested	9,0E-06	2,5E-06	1,9E-06	1,5E-06
4-2-1	5,8E-06	not tested	6,5E-06	1,0E-05	9,9E-06	3,7E-06
4-4	1,2E-06	not tested	3,5E-06	4,5E-06	9,0E-07	5,0E-07

Example Nr.	Biological Assay 2: Proliferation assay (HeLa-MaTu-ADR cell line) median IC50 [mol/l]	Biological Assay 2: Proliferation assay (MCF7 cell line) median IC50 [mol/l]	Biological Assay 2: Proliferation assay (H460 cell line) median IC50 [mol/l]	Biological Assay 2: Proliferation assay (DU145 cell line) median IC50 [mol/l]	Biological Assay 2: Proliferation assay (Caco2 cell line) median IC50 [mol/l]	Biological Assay 2: Proliferation assay (B16F10 cell line) median IC50 [mol/l]
4-8	3,6E-07	not tested	1,1E-06	1,2E-06	7,6E-07	5,7E-07
4-9	8,6E-07	not tested	1,3E-06	1,3E-06	7,8E-07	5,3E-07
4-19	1,0E-05	not tested	2,2E-06	2,3E-06	1,0E-05	5,3E-07
4-22	1,0E-05	not tested	2,1E-06	3,6E-06	9,5E-06	1,2E-06
5-2	3,0E-06	not tested	3,0E-06	3,0E-06	3,0E-06	3,0E-06
6-2	1,6E-06	not tested	1,7E-06	1,4E-06	1,2E-06	1,1E-06
10-2	5,9E-07	not tested	1,5E-06	1,4E-06	1,1E-06	9,0E-07
12-1	1,0E-05	not tested	1,0E-05	1,0E-05	1,0E-05	1,0E-05
13-1	1,3E-06	not tested	1,3E-06	1,6E-06	1,2E-06	7,9E-07
15-1	1,2E-06	not tested	2,2E-06	1,2E-06	1,2E-06	7,6E-07
20-1	3,0E-06	not tested	3,0E-06	3,0E-06	3,0E-06	2,4E-06
38-2	1,1E-06	not tested	1,1E-06	1,3E-06	6,0E-07	6,0E-07
41-1	1,0E-05	not tested	1,0E-05	1,0E-05	3,3E-06	1,8E-06

Claims

1. A compound of formula (I)



(I)

in which

R^1 is hydrogen, halogen, 1-3C-alkyl,

R^2/R^3 are independently from each other hydrogen, halogen, cyano, hydroxy 1-6C-haloalkyl, 1-6C-haloalkoxy, 1-6C-alkoxy,

R^4 is independently hydrogen, hydroxy, halogen, cyano, NO_2, 1-6C-alkyl, 2-6C-alkenyl, 2-6C-alkynyl, 1-6C-haloalkyl, 1-6C-hydroxyalkyl, 1-6C-alkoxy, -O-(2-6C-alkylen)-O-C(O)-(1-6C-alkyl), 1-6C-haloalkoxy, $-C(O)OR^9$, -(1-6C-alkylen)-$C(O)OR^9$, -C(O)-(1-6C-alkyl), $-C(O)NR^{10}R^{11}$, 3-7C-cycloalkyl, -S-(1-6C-haloalkyl), SF_5, $-SO_2NH$-(3-7C-cycloalkyl), $-SO_2NR^{10}R^{11}$, $NR^{10}R^{11}$, heteroaryl which optionally is substituted independently one or more times with cyano, 1-4C-alkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,

whereby two of R^2, R^3 $(R^4)_n$, when positioned ortho to each other, may form together with the two carbon atoms to which they are attached, a heterocyclic 5-, 6- or 7-membered ring containing 1 or 2 heteroatoms selected from O or N, and optionally containing an additional double bond and/or optionally substituted by an oxo (=O) group and/or an 1-4C-alkyl group,

n 0 - 3

R^6 is (a) hydrogen;

(b) hydroxy;

(c) cyano;

(d) 1-6C-alkoxy optionally substituted independently one or more times with

(d1) OH,

(d2) –O-(1-6C-alkyl)

(d3) $C(O)OR^9$,

(d4) $C(O)NR^{10}R^{11}$,

(d5) $NR^{10}R^{11}$,

(d6) –S-(1-6C-alkyl),

(d7) –S(O)-(1-6C-alkyl),

(d8) $–SO_2$-(1-6C-alkyl)

(d9) $SO_2NR^{10}R^{11}$,

(d10) heterocyclyl, which is optionally substituted with $C(O)OR^9$, or oxo (=O),

(d11) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-4C-alkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, (1-6C-alkylen)-O-(1-6C-alkyl),

(e) $SO_2NR^{10}R^{11}$,

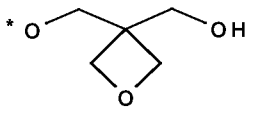
(f) 3-7C-cycloalkoxy,

(g) 1-6C-haloalkoxy,

(h) $COOR^9$,

(i) $-C(O)NR^{10}R^{11}$,

(j) -O-heteroaryl opt. subst. with CN

(k) 

, whereby the * is the point of attachment,

(l) –O-(2-6C-alkylen)-O-(1-6C-alkyl) which is optionally substituted with hydroxy, $NH(CO)OR^9$,

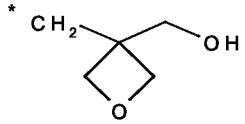
R^7 is

(a) hydrogen,

(b)1-6C-alkyl, which is optionally substituted with heteroaryl

(c) 1-6C-haloalkyl,

(d) 1-6C-hydroxyalkyl,

(e) 

, whereby the * is the point of attachment,

(f) -C(O)-(1-6C-alkyl),

(g) –C(O)-(1-6C-alkylen)-O-(1-6C-alkyl),

(h) –C(O)-(1-6C-alkylen)-O-(2-6C-alkylen)-O-(1-6C-alkyl),

(i) –C(O)-heterocyclyl,

(j) benzyl whereby the phenyl ring is opt. subst with 1-5 substituents independently selected from the group consisting of hydrogen, halogen, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-alkoxy, 1-4C-haloalkoxy, cyano, $C(O)OR^9$,

(k) heteroaryl

or

optionally, R^6 and R^7 together with the nitrogen atom to which R^7 is attached form a 6-membered ring which may contain one further heteroatom selected from the group consisting of O, S, N,

and which is optionally substituted by (1-6C-alkyl)-OH,

(1-6C-alkyl)-$NR^{10}R^{11}$,

R^8 is hydrogen, halogen, hydroxy, cyano, 1-6C-alkyl, 1-6C-hydroxyalkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,

m is 0-4

R^9 is (a) hydrogen,

(b) 1-6C-alkyl which optionally is substituted with hydroxy,

R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl, 1-4C-hydroxyalkyl, 1-4C-alkoxy, -(CO)-(1-6C-alkyl), CHO, $COOR^9$, or together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, and which is optionally substituted with 1-2 fluorine atoms or $COOR^9$,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

2. The compound of formula (I) according to claim 1,

wherein

R^1 is hydrogen, halogen, 1-3C-alkyl,

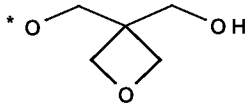
R^2/R^3 are independently from each other hydrogen, halogen, cyano, 1-6C-haloalkyl,
1-6C-haloalkoxy,

R^4 is independently hydrogen, halogen, cyano, 1-6C-alkyl, 2-6C-alkenyl, 1-6C-haloalkyl, 1-6C-hydroxyalkyl, 1-6C-alkoxy, 1-6C-haloalkoxy, $-C(O)OR^9$, -(1-6C-alkylen)-$C(O)OR^9$, $-C(O)$-(1-6C-alkyl), $-C(O)NR^{10}R^{11}$, 3-7C-cycloalkyl, -S-(1-6C-haloalkyl), SF_5, $-SO_2NH$-(3-7-cycloalkyl), $-SO_2NR^{10}R^{11}$,
heteroaryl which optionally is substituted independently one or more times with cyano, 1-4C-alkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,
whereby two of R^2, R^3 $(R^4)_n$, when positioned ortho to each other, may form together with the two carbon atoms to which they are attached, a heterocyclic 5-, 6- or 7-membered ring containing 1 or 2 heteroatoms selected from O or N, and optionally an additional double bond and/or a carbonyl group and/or an 1-4C-alkyl group,

n 0 - 3

R^6 is (a) hydrogen;
(b) hydroxy;
(c) cyano;
(d) 1-6C-alkoxy opt. subst. with
(d1) 1-2 OH,
(d2) $NR^{10}R^{11}$,
(d3) $SO_2NR^{10}R^{11}$,
(d4) heterocyclyl,
(d5) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-4Calkyl, 1-6C-haloalkyl, 1-6C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,
(e) $SO_2NR^{10}R^{11}$, ;
(f) 3-7C-cycloalkoxy,
(g) 1-6C-haloalkoxy,
(h) $-C(O)NR^{10}R^{11}$,

(i) -O-heteroaryl opt. subst. with CN



(j) , whereby the * is the point of attachment,

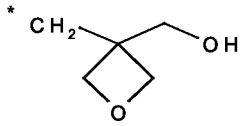
R^7 is

(a) hydrogen,

(b)1-6C-alkyl, which is optionally substituted with heteroaryl

(c) 1-6C-haloalkyl,

(d) 1-6C-hydroxyalkyl,



(e) , whereby the * is the point of attachment,

(f) -C(O)-(1-6C-alkyl)

(g) –C(O)-(1-6C-alkylen)-O-(1-6C-alkyl)

(h) –C(O)-(1-6C-alkylen)-O-(1-6C-alkylen)-O-(1-6C-alkyl)

(i) –C(O)-heterocyclyl,

(j) benzyl whereby the phenyl ring is opt. subst with 1-5 substituents independently selected from the group consisting of

hydrogen, halogen, 1-4Calkyl, 1-4C-haloalkyl, 1-4C-alkoxy, 1-4C-haloalkoxy, cyano,

$C(O)OR^9$,

(k) heteroaryl

or

optionally R^6 and R^7 together with the nitrogen atom to which they are attached form a 6-membered ring which may contain one further heteroatom selected from the group consisting of O, S, N,

and which is optionally substituted by hydroxy-(1-6alkyl),

R^8 is hydrogen, halogen, cyano, 1-6C-haloalkyl, 1-6C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,

m is 0-4

R^9 is (a) hydrogen,

(b) 1-6C-alkyl which optionally may be substituted with hydroxy,

R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl, 1-4C-hydroxyalkyl, 1-4C-alkoxy, or
together with the nitrogen atom to which they are attached form a 5-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

3. The compound of formula (I) according to claim 1,

wherein

R^1 is hydrogen, halogen, 1-3C-alkyl,

R^2/R^3 are independently from each other hydrogen, halogen, cyano, hydroxy, 1-3C-haloalkyl, 1-3C-haloalkoxy, 1-3C-alkoxy,

R^4 is independently hydrogen, hydroxy, halogen, cyano, NO_2, 1-3C-alkyl, 2-3C-alkenyl, 2-3C-alkynyl, 1-3C-haloalkyl, 1-3C-hydroxyalkyl, 1-3C-alkoxy, -O-(2-3C-alkylen)-O-C(O)-(1-3C-alkyl), 1-3C-haloalkoxy, -C(O)OR^9, -(1-3C-alkylen)-C(O)OR^9, -C(O)-(1-3C-alkyl), -C(O)$NR^{10}R^{11}$, 3-7C-cycloalkyl, -S-(1-3C-haloalkyl), SF_5, -SO_2NH-(3-7C-cycloalkyl), -$SO_2NR^{10}R^{11}$, $NR^{10}R^{11}$, heteroaryl which optionally is substituted independently one or more times with cyano, 1-3C-alkyl, 1-3C-haloalkyl, 1-3C-haloalkoxy, C(O)OR^9, C(O)$NR^{10}R^{11}$,
whereby two of R^2, R^3 $(R^4)_n$, when positioned ortho to each other, may form together with the two carbon atoms to which they are attached, a heterocyclic 5-, 6- or 7-membered ring containing 1 or 2 heteroatoms selected from O or N, and optionally containing an additional double bond and/or optionally substituted by an oxo (=O) group and/or an 1-3C-alkyl group,

n 0 - 3

R^6 is (a) hydrogen;
(b) hydroxy;
(c) cyano;
(d) 1-6C-alkoxy optionally substituted independently one or more times with
(d1) OH,
(d2) –O-(1-3C-alkyl)

(d3) $C(O)OR^9$,

(d4) $C(O)NR^{10}R^{11}$,

(d5) $NR^{10}R^{11}$,

(d6) –S-(1-3C-alkyl),

(d7) –S(O)-(1-3C-alkyl),

(d8) $–SO_2$-(1-3C-alkyl),

(d9) $SO_2NR^{10}R^{11}$,

(d10) heterocyclyl, which is optionally substituted with $C(O)OR^9$, or oxo (=O),

(d11) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-3C-alkyl, 1-3C-haloalkyl, 1-3C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, (1-3C-alkylen)-O-(1-3C-alkyl),

(e) $SO_2NR^{10}R^{11}$,

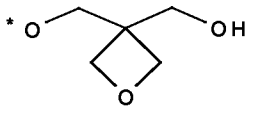
(f) 3-7C-cycloalkoxy,

(g) 1-6C-haloalkoxy,

(h) $COOR^9$,

(i) $-C(O)NR^{10}R^{11}$,

(j) -O-heteroaryl opt. subst. with CN



(k) , whereby the * is the point of attachment,

(l) –O-(2-3C-alkylen)-O-(1-3C-alkyl) which is optionally substituted with hydroxy, $NH(CO)OR^9$,

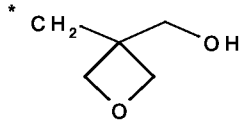
R^7 is

(a) hydrogen,

(b)1-3C-alkyl, which is optionally substituted with heteroaryl

(c) 1-3C-haloalkyl,

(d) 1-3C-hydroxyalkyl,



(e) , whereby the * is the point of attachment,

(f) -C(O)-(1-3C-alkyl)

(g) –C(O)-(1-3C-alkylen)-O-(1-3C-alkyl)

(h) –C(O)-(1-3C-alkylen)-O-(2-3C-alkylen)-O-(1-3C-alkyl)

(i) –C(O)-heterocyclyl,

(j) benzyl whereby the phenyl ring is opt. subst with 1-5 substituents independently selected from the group consisting of hydrogen, halogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-haloalkoxy, cyano, $C(O)OR^9$,

(k) heteroaryl

or

optionally, R^6 and R^7 together with the nitrogen atom to which R^7 is attached form a 6-membered ring which may contain one further heteroatom selected from the group consisting of O, S, N,

and which is optionally substituted by (1-3C-alkyl)-OH, (1-3C-alkyl)-$NR^{10}R^{11}$,

R^8 is hydrogen, halogen, hydroxy, cyano, 1-3C-alkyl, 1-3C-hydroxyalkyl, 1-3C-haloalkyl, 1-3C-haloalkoxy, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,

m is 0-4

R^9 is (a) hydrogen,

(b) 1-3C-alkyl which optionally is substituted with hydroxy,

R^{10}, R^{11} are independently from each other hydrogen, 1-3C-alkyl, 1-3C-hydroxyalkyl, 1-3C-alkoxy, -(CO)-(1-3C-alkyl), CHO, $COOR^9$ or together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, which is optionally substituted with 1-2 fluorine atoms or $COOR^9$,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

4. The compound of formula (I) according to claim 1,

in which

R^1 is hydrogen, 1-3C-alkyl,

R^2/R^3 are independently from each other hydrogen, halogen, cyano, hydroxy, 1-4C-haloalkyl, 1-4C-alkoxy,

R^4 is independently hydrogen, hydroxy, halogen, cyano, 1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl, 1-4C-haloalkyl, 1-4C-hydroxyalkyl, 1-4C-alkoxy, -O-(2-4C-alkylen)-O-C(O)-(1-4C-alkyl), 1-4C-haloalkoxy, -C(O)OR^9, -(1-4C-alkylen)-C(O)OR^9, -C(O)-(1-4C-alkyl), -C(O)$NR^{10}R^{11}$, 3-7C-cycloalkyl, -S-(1-4C-haloalkyl), SF_5, -SO_2NH-(3-7C-cycloalkyl), -$SO_2NR^{10}R^{11}$, $NR^{10}R^{11}$, heteroaryl which optionally is substituted independently one or more times with cyano, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy, C(O)OR^9, C(O)$NR^{10}R^{11}$,

whereby two of R^2, R^3 $(R^4)_n$, when positioned ortho to each other, may form together with the two carbon atoms to which they are attached, a heterocyclic 5-, 6- or 7-membered ring containing 1 or 2 heteroatoms selected from O or N, and optionally containing an additional double bond and/or optionally substituted by an oxo (=O) group and/or an 1-4C-alkyl group,

n 0 - 3

R^6 is (a) hydrogen;

(b) hydroxy;

(d) 1-4C-alkoxy optionally substituted independently one or more times with

(d1) OH,

(d2) –O-(1-4C-alkyl)

(d3) C(O)OR^9,

(d4) C(O)$NR^{10}R^{11}$,

(d5) $NR^{10}R^{11}$,

(d6) –S-(1-4C-alkyl),

(d7) –S(O)-(1-4C-alkyl),

(d8) –SO_2-(1-4C-alkyl)

(d9) $SO_2NR^{10}R^{11}$,

(d10) heterocyclyl, which is optionally substituted with C(O)OR^9, or oxo (=O),

(d11) heteroaryl, which is optionally substituted independently one or more times with cyano, 1-4C-alkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy, C(O)OR^9, C(O)$NR^{10}R^{11}$, (1-4C-alkylen)-O-(1-4C-alkyl),

(e) $SO_2NR^{10}R^{11}$,

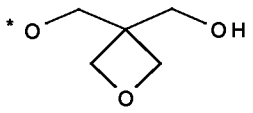
(f) 3-7C-cycloalkoxy,

(g) 1-6C-haloalkoxy,

(h) $COOR^9$,

(i) $-C(O)NR^{10}R^{11}$,

(j) -O-heteroaryl opt. subst. with CN



(k) , whereby the * is the point of attachment,

(l) –O-(2-4C-alkylen)-O-(1-4C-alkyl) which is optionally substituted with hydroxy, $NH(CO)OR^9$,

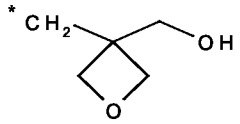
R^7 is

(a) hydrogen,

(b) (1-4C-alkyl)-heteroaryl

(c) 1-4C-haloalkyl,

(d) 1-4C-hydroxyalkyl,



(e) , whereby * is the point of attachment,

(f) -C(O)-(1-4C-alkyl)

(g) –C(O)-(1-4C-alkylen)-O-(1-4C-alkyl)

(h) –C(O)-(1-4C-alkylen)-O-(2-4C-alkylen)-O-(1-4C-alkyl)

(i) –C(O)-heterocyclyl,

(j) benzyl whereby the phenyl ring is opt. subst with 1-5 substituents independently selected from the group consisting of

hydrogen, halogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-haloalkoxy, cyano, $C(O)OR^9$,

(k) heteroaryl

or

optionally, R^6 and R^7 together with the nitrogen atom to which R^7 is attached form a 6-membered ring which may contain one further heteroatom selected from the group consisting of O, S, N,

and which is optionally substituted by (1-4C-alkyl)-OH, $(1\text{-}4C\text{-alkyl})\text{-}NR^{10}R^{11}$,

R^8 is hydrogen, halogen, hydroxy, cyano, $C(O)NR^{10}R^{11}$, 1-4C-alkyl, 1-4C-hydroxyalkyl, 1-4C-haloalkyl, 1-4C-haloalkoxy,

m is 0-2,

R^9 is hydrogen, 1-4C-alkyl which optionally is substituted with hydroxy,

R^{10}, R^{11} are independently from each other hydrogen, 1-4C-alkyl, 1-4C-hydroxyalkyl, 1-4C-alkoxy, -C(O)-(1-4C-alkyl), or $COOR^9$ or together with the nitrogen atom to which they are attached form a 4-6-membered heterocyclic ring optionally containing one further heteroatom selected from the group consisting of O, S or N, which is optionally substituted with 1-2 fluorine atoms or $COOR^9$,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

5. The compound of formula (I) according to claim 1,

wherein,

R^1 is hydrogen,

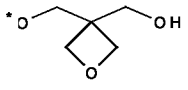
R^2/R^3 is independently hydrogen, fluorine, chlorine, bromine, cyano, hydroxy, CF_3, $-O-CH_3$ or $-O-CH_2-CF_3$,

R^4 is independently of each other hydrogen, fluorine, chlorine, bromine or iodine, cyano, NO_2, hydroxy, $-CH_3$, $-C_3H_7$, cyclopropyl, 1-propenyl, $-C\equiv CH$, $-CF_3$, $-CH_2-OH$, $-CH_2-CH_2-OH$, $-C(CH_3)_2-OH$, $-CH_2-C(CH_3)_2-OH$, $-C(CH_3)_2-CH_2-OH$, $-OCH_3$, $-O-CH_2-CH_3$, $-OCF_3$, $-OCF_2H$, $-OCH_2CF_3$, $-O-(CH_2)-O-C(O)-CH3$, $-C(O)CH_3$, $-COOH$, $-C(O)OCH_3$, $-C(O)OC_2H_5$, $-C(O)OC(CH_3)_3$, $-CH_2-COOH$, $-CH_2-COOC_2H_5$, $-C(CH_3)_2-COOC_2H_5$, $-C(O)NH_2$, $-C(O)NH(CH_3)$, $-C(O)N(CH_3)_2$, $-C(O)NH-(CH_2)_2-OH$, -C(O)-(N-morpholinyl), $-SO_2-NH$-cyclopropyl, $-SO_2-$(N-morpholino), NH_2, $NH-C(O)(CH_3)$, 5-methyl-oxa-diazol-3-yl, N-pyrrolyl, N-pyrazolyl, $-S-CF_3$, SF_5,

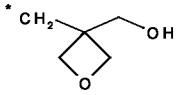
whereby two of R^2, R^3 $(R^4)_n$, when positioned ortho to each other, form together

$-O-CH_2-CH_2-CH_2-O-$, $-O-CH_2-CH_2-$, $-(CH_3)C=CH-(C=O)-O-$, $-CH_2-(C=O)-O-$, $-(CH_2)_2-(C=O)-NH-$, which together with the two carbon atoms to which they are attached form a 5-, 6- or 7-membered ring,

n is 0, 1, 2, 3,

R^6 is hydrogen, hydroxy, cyano, -O-cyclopropyl, $-OCH_3$, $-OCF_3$, $-OCF_2H$, $-OCH_2CF_3$, $-O-(CH_2)_2-OH$, $-O-(CH_2)_2-NH_2$, $-O(CH_2)_2-N(CH_3)_2$, $-O-(CH_2)_2-O-CH_3$, $-O-(CH_2)_2-O-(CH_2)_2-OH$, $-O-CH_2-CH(OH)-CH_2OH$, $-O-CH_2-CH(OH)-CH_2-NH-C(O)OC(CH_3)_3$, $-O-CH_2-COOH$, $-O-CH_2-COOC_2H_5$, $C(O)NH_2$, $-O-CH_2-C(O)-$(3-fluoro-N-azetidine), $-O-CH_2-C(O)-$(3,3-difluoro-N-azetidine), $-O-CH_2-CH(OH)-CH_2-$N-piperidinyl, $-O-(CH_2)_2$(morpholine-4-yl), $-O-CH_2-$(morpholine-2-yl), $-O-CH_2-$(morpholine-2-yl-4-tert.-butoxycarboxylate), $-O-CH_2-$(pyrrolidin-2-one-5-yl), $-O-(CH_2)_2-S-CH_3$, $-O-(CH_2)_2-SO-CH_3$, $-O-(CH_2)_2-SO_2-CH_2$, $-O-CH_2-SO_2NH_2$, $-SO_2-CH(CH_3)_2$,  , whereby * is the point of attachment,

$-O-(CH_2)_2-$tetrazolyl, $-O-CH_2-$tetrazolyl, -O-pyridine-4-yl, -O-(3-cyano-pyridine-4-yl), or $-O-CH_2-$(oxadiazole)$-CH_2-O-CH_3$,

R^7 is hydrogen, methyl, difluoromethyl, hydroxyethyl,  , whereby * is the point of attachment,

$-(CH_2)_2-$tetrazolyl, pyridine-4-yl, $-C(O)-$tetrahydropyran-4-yl, $-C(O)-CH_2-O-CH_3$, $-C(O)-CH_3$, $-C(O)CH_2-O-(CH_2)_2-O-CH_3$, $C(O)OCH_2-CH=CH_2$, or benzyl which is optionally substituted one or more times with fluorine, chlorine, bromine, cyano, methyl, difluoromethyl, methoxy, ethoxy, difluormethoxy, trifluoromethoxy, $-O-CH_2-CF_3$, $-C(O)OCH_3$, or

optionally, R^6 and R^7 together with the nitrogen atom to which R^7 is attached form a 6-membered ring which may contain one further heteroatom selected from the group consisting of O, S, N and which in addition is optionally substituted by $-CH_2-OH$ or $-CH_2-NH-CHO$

R^8 is hydrogen, fluorine, hydroxy, cyano, CH_3, CF_3, CH_2-OH, OCH_3, C(O)OH, $C(O)OCH_3$, $C(O)OC_2H_5$, $C(O)O(CH_2)_2-OH$, $C(O)NH_2$, $C(O)NHCH_3$,

m is 0, 1 or 2

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

6. Compounds of formula (I) according to claim 1, which is selected from the group consisting of:

2-[1-(6-chloro-2-fluoro-3-methylbenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(6-chloro-2-fluoro-3-methoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

5-methoxy-2-{1-[3-(5-methyl-1,2,4-oxadiazol-3-yl)benzyl]-1H-indazol-3-yl}-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-chloro-4,5-dimethylbenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

5-methoxy-2-{1-[4-(pentafluoro-λ^6-sulfanyl)benzyl]-1H-indazol-3-yl}-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2,6-difluoro-3-methoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-(2,6-difluoro-3-methoxybenzyl)-2-[1-(2,6-difluoro-3-methoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-{1-[(6-bromo-1,3-benzodioxol-5-yl)methyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-(4-ethoxy-2,6-difluorobenzyl)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzonitrile,

2-[1-(2-chloro-4-methoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(3,4-dihydro-2H-1,5-benzodioxepin-6-ylmethyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-(2,6-difluorobenzyl)-2-[1-(2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

5-methoxy-N-(pyridin-4-yl)-2-(1-{3-[(trifluoromethyl)sulfanyl]benzyl}-1H-indazol-3-yl)pyrimidin-4-amine,

2-[1-(2,3-difluoro-4-methylbenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-(2,3-difluoro-4-methylbenzyl)-2-[1-(2,3-difluoro-4-methylbenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

5-methoxy-2-{1-[4-(1H-pyrazol-1-yl)benzyl]-1H-indazol-3-yl}-N-(pyridin-4-yl)pyrimidin-4-amine

2-[1-(2,6-dichlorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-

amine,

N-(2,6-dichlorobenzyl)-2-[1-(2,6-dichlorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

5-methoxy-N-(pyridin-4-yl)-2-(1-{4-[(trifluoromethyl)sulfanyl]benzyl}-1H-indazol-3-yl)pyrimidin-4-amine,

2-[1-(2-chlorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-(2-chlorobenzyl)-2-[1-(2-chlorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

methyl 3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzoate,

methyl 3-chloro-4-{[(2-{1-[2-chloro-4-(methoxycarbonyl)benzyl]-1H-indazol-3-yl}-5-methoxypyrimidin-4-yl)(pyridin-4-yl)amino]methyl}benzoate,

2-[1-(4-bromo-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-chloro-4-fluoro-3-methoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-ethoxy-2,3-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-(4-ethoxy-2,3-difluorobenzyl)-2-[1-(4-ethoxy-2,3-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

5-methoxy-N-(pyridin-4-yl)-2-{1-[2,3,5,6-tetrafluoro-4-(2,2,2-trifluoroethoxy)benzyl]-1H-indazol-3-yl}pyrimidin-4-amine,

5-methoxy-N-(pyridin-4-yl)-N-[2,3,5,6-tetrafluoro-4-(2,2,2-trifluoroethoxy)benzyl]-2-{1-[2,3,5,6-tetrafluoro-4-(2,2,2-trifluoroethoxy)benzyl]-1H-indazol-3-yl}pyrimidin-4-amine,

methyl 2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzoate,

5-methoxy-N-(pyridin-4-yl)-2-[1-(2,4,6-trifluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-amine,

5-methoxy-N-(pyridin-4-yl)-N-(2,4,6-trifluorobenzyl)-2-[1-(2,4,6-trifluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-amine,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine

2-[1-(2,4-dichlorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-fluoro-4-iodobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-bromobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-(2-bromobenzyl)-2-[1-(2-bromobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

[3-fluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]acetic acid,

5-methoxy-N-(pyridin-4-yl)-2-[1-(2,3,5,6-tetrafluoro-4-methoxybenzyl)-1H-indazol-3-yl]pyrimidin-4-amine,

5-methoxy-2-[1-(4-propylbenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-{1-[2,6-dichloro-4-(trifluoromethoxy)benzyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-[2,6-dichloro-4-(trifluoromethoxy)benzyl]-2-{1-[2,6-dichloro-4-(trifluoromethoxy)benzyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

7-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)-3,4-dihydroquinolin-2(1H)-one,

2-[1-(2-chloro-4-iodobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(3,5-dimethoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-{1-[2-chloro-6-(trifluoromethyl)benzyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-chloro-5-fluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

7-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)-4-methyl-2H-chromen-2-one,

3-fluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzonitrile,

4-{[{2-[1-(4-cyano-2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}(pyridin-4-yl)amino]methyl}-3-fluorobenzonitrile,

2-{1-[2,6-dichloro-3-(trifluoromethyl)benzyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

ethyl [3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]acetate,

2-[1-(4-fluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-cyclopropyl-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzenesulfonamide,

6-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)-1-benzofuran-2(3H)-one,

2-{1-[4-(difluoromethoxy)-2,6-difluorobenzyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

tert-butyl 3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzoate,

ethyl 2-[3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]-2-methylpropanoate,

4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzonitrile,

5-methoxy-2-{1-[4-(morpholin-4-ylsulfonyl)benzyl]-1H-indazol-3-yl}-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2,6-dichloro-3-nitrobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzonitrile,

N-[4-(difluoromethoxy)-2,6-difluorobenzyl]-2-{1-[4-(difluoromethoxy)-2,6-difluorobenzyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

5-methoxy-N-(pyridin-4-yl)-2-{1-[3-(1H-pyrrol-1-yl)benzyl]-1H-indazol-3-yl}pyrimidin-4-amine,

3,5-difluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzonitrile

5-methoxy-2-{1-[2-methoxy-4-(trifluoromethyl)benzyl]-1H-indazol-3-yl}-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2,6-difluoro-3-methylbenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-fluoro-6-methoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

3,5-difluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzamide,

2-[3,5-difluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenoxy]ethyl acetate,

2-[1-(2,6-difluoro-4-propoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-ethoxy-2-fluoro-6-methoxybenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol

2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol,

2-[1-(4-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-ol,

{3-[({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methyl]oxetan-3-yl}methanol,

{3-[({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methyl]oxetan-3-yl}methanol,

(3-{[(2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-{[3-(hydroxymethyl)oxetan-3-

yl]methoxy}pyrimidin-4-yl)(pyridin-4-yl)amino]methyl}oxetan-3-yl)methanol,

1-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methanesulfonamide,

5-[2-(dimethylamino)ethoxy]-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)-5-[2-(1H-tetrazol-5-yl)ethoxy]pyrimidin-4-amine,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)-5-[2-(1H-tetrazol-5-yl)ethoxy]-N-[2-(1H-tetrazol-5-yl)ethyl]pyrimidin-4-amine,

5-[2-(dimethylamino)ethoxy]-2-[1-(4-fluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)-5-(1H-tetrazol-5-ylmethoxy)pyrimidin-4-amine,

5-[2-(dimethylamino)ethoxy]-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

1-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)-3-(piperidin-1-yl)propan-2-ol,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-(2-methoxyethoxy)-N-(pyridin-4-yl)pyrimidin-4-amine,

tert-butyl 2-[({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methyl]morpholine-4-carboxylate,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(morpholin-4-yl)ethoxy]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-{[3-(methoxymethyl)-1,2,4-oxadiazol-5-yl]methoxy}-N-(pyridin-4-yl)pyrimidin-4-amine,

ethyl ({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)acetate,

1-(3,3-difluoroazetidin-1-yl)-2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanone,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(methylsulfanyl)ethoxy]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethoxy]ethanol,

formic acid - (5S)-5-[({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methyl]pyrrolidin-2-one (1:1),

(5R)-5-[({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methyl]pyrrolidin-2-one,

tert-butyl {2-[2-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethoxy]ethyl}carbamate,

2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)-1-(3-fluoroazetidin-1-yl)ethanone,

(5S)-5-[({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)methyl]pyrrolidin-2-one,

tert-butyl [2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethyl]carbamate,

N-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-8-(pyridin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-7-yl}methyl)formamide,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-cyclopropyl-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-(1-{2,6-difluoro-4-[(1E)-prop-1-en-1-yl]benzyl}-1H-indazol-3-yl)-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

1-[3,5-difluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]ethanone,

[2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]methanol,

2-[3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]ethanol,

2-[3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]-2-methylpropan-1-ol,

[4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridin-3-yl]methanol,

2-[3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]propan-2-ol,

1-[3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]-2-methylpropan-2-ol,

2-[2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]propan-2-ol,

5-(difluoromethoxy)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

5-(difluoromethoxy)-N-(difluoromethyl)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

4-[(difluoromethyl)(pyridin-4-yl)amino]-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]pyrimidin-5-ol,

2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)-5-(2,2,2-trifluoroethoxy)pyrimidin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)-5-(2,2,2-trifluoroethoxy)pyrimidin-4-amine,

3-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)propane-1,2-diol,

(2S)-3-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)propane-1,2-diol,

(2R)-3-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)propane-1,2-diol,

2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanol,

2-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanol,

ethyl 4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)pyridine-3-carboxylate,

4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)-N-methylpyridine-3-carboxamide,

4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)pyridine-3-carboxamide,

2-hydroxyethyl 4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)pyridine-3-carboxylate,

5-(cyclopropyloxy)-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine hydrochloride (1:1),

(2S)-3-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)propane-1,2-diol hydrochloride (1:1),

2-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)ethanol hydrochloride (1:1),

2-[1-(2,6-dichlorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine hydrochloride (1:1),

[2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]methanol hydrochloride (1:1),

(2R)-3-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)propane-1,2-diol hydrochloride (1:1),

N-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}-N-(pyridin-4-yl)acetamide,

N-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}-2-methoxy-N-(pyridin-4-yl)acetamide,

N-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}-N-(pyridin-4-yl)tetrahydro-2H-pyran-4-carboxamide,

N-{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}-2-(2-methoxyethoxy)-N-(pyridin-4-yl)acetamide,

2-[{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}(pyridin-4-yl)amino]ethanol,

(3-{[{2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}(pyridin-4-yl)amino]methyl}oxetan-3-yl)methanol,

2-{1-[4-bromo-2-fluoro-6-(2,2,2-trifluoroethoxy)benzyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2-{1-[4-bromo-2,6-bis(2,2,2-trifluoroethoxy)benzyl]-1H-indazol-3-yl}-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzoic acid,

({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidin-5-yl}oxy)acetic acid,

2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)-N-methylbenzamide,

2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzamide,

2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)-N,N-dimethylbenzamide,

2,4-dichloro-N-(2-hydroxyethyl)-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzamide,

[2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl](morpholin-4-yl)methanone,

3,5-difluoro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)-N-methylbenzamide,

2-[1-(4-ethynyl-2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

{2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-8-(pyridin-4-yl)-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazin-7-yl}methanol,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-methyl-N-(pyridin-4-yl)pyrimidin-4-amine,

4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carbonitrile,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N,N-di(pyridin-4-yl)pyrimidin-4-amine,

methyl 4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carboxylate,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carbonitrile,

2-[(3-{4-[(2,6-dimethylpyridin-4-yl)amino]-5-methoxypyrimidin-2-yl}-1H-indazol-1-

yl)methyl]-5-ethoxy-3-fluorophenol,

4-({5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}amino)pyridin-2(1H)-one,

4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridin-2(1H)-one,

4-({5-methoxy-2-[1-(4-propylbenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}amino)nicotinonitrile,

4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carboxamide,

4-({5-methoxy-2-[1-(4-propylbenzyl)-1H-indazol-3-yl]pyrimidin-4-yl}amino)pyridine-3-carboxamide,

4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carboxamide,

4-({2-[1-(2,6-difluoro-4-hydroxybenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carboxamide,

4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)pyridine-3-carbonitrile,

4-({4-[(3-cyanopyridin-4-yl)amino]-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]pyrimidin-5-yl}oxy)pyridine-3-carbonitrile,

5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]-N-[3-(trifluoromethyl)pyridin-4-yl]pyrimidin-4-amine,

3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)benzoic acid,

formic acid - 3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)-N-methylbenzamide (1:1),

3-chloro-4-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)-N-methylbenzamide,

4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)pyridine-3-carboxamide,

4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)pyridine-3-carboxylic acid,

ethyl 4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-hydroxypyrimidin-4-yl}amino)pyridine-3-carboxylate,

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidine-5-carbonitrile

2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-4-(pyridin-4-ylamino)pyrimidine-5-carboxamide,

4-({2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-(2-hydroxyethoxy)pyrimidin-4-yl}amino)pyridine-3-carboxylic acid hydrochloride (1:1),

N-(2-fluoropyridin-4-yl)-5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]pyrimidin-4-amine,

N-(2,6-difluoropyridin-4-yl)-5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]pyrimidin-4-amine,

N-(3-fluoropyridin-4-yl)-5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]pyrimidin-4-amine,

5-methoxy-2-[1-(4-methoxybenzyl)-1H-indazol-3-yl]-N-(2-methylpyridin-4-yl)pyrimidin-4-amine,

N-(difluoromethyl)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(methylsulfinyl)ethoxy]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(methylsulfinyl)ethoxy]-N-(pyridin-4-yl)pyrimidin-4-amine (Enantiomer 1),

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(methylsulfinyl)ethoxy]-N-(pyridin-4-yl)pyrimidin-4-amine (Enantiomer 2),

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-[2-(methylsulfonyl)ethoxy]-N-(pyridin-4-yl)pyrimidin-4-amine,

5-(2-aminoethoxy)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-N-(pyridin-4-yl)pyrimidin-4-amine,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-(morpholin-2-ylmethoxy)-N-(pyridin-4-yl)pyrimidin-4-amine,

Preparation of ethyl 4-({2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-yl}amino)pyridine-3-carboxylate,

N-(3,5-difluoropyridin-4-yl)-2-[1-(4-ethoxy-2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methoxypyrimidin-4-amine,

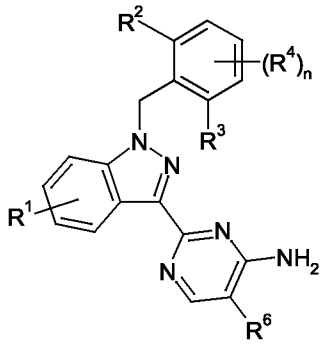
2-[1-(3-amino-2,6-dichlorobenzyl)-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

N-[2,4-dichloro-3-({3-[5-methoxy-4-(pyridin-4-ylamino)pyrimidin-2-yl]-1H-indazol-1-yl}methyl)phenyl]acetamide,

2-[1-(4-ethoxy-2,6-difluorobenzyl)-4-methyl-1H-indazol-3-yl]-5-methoxy-N-(pyridin-4-yl)pyrimidin-4-amine,

or an N-oxide, a salt, a tautomer or a stereoisomer of said compound, or a salt of said N-oxide, tautomer or stereoisomer.

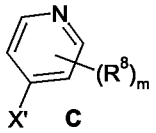
7. Process for the manufacture of compounds of general formula (I) according to claim 1, wherein R^7 is hydrogen as reflected in formula (Ia), characterized in that a compound of formula (1-4)



1-4

whereby R^1, R^2, R^3, R^4, R^6 and n have the meaning according to claim 1,

is reacted with a compound of formula (C)

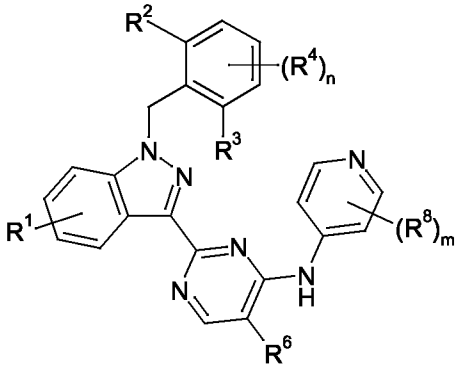


C

whereby R^8 and m have the meaning according to claim 1, and X' represents F, Cl, Br, I, boronic acid or a boronic acid ester

in the presence of a suitable base, and a suitable palladium catalyst, optionally in the presence of a suitable ligand,

forming a compound of formula (Ia)

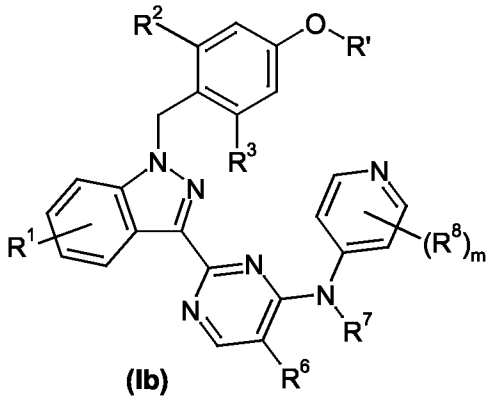


(Ia)

which is optionally subsequently deprotected to form a compound of general formula (I) wherein R^7 is hydrogen and R^1, R^2, R^3, R^4, R^6, R^8 and n and m have the meaning as defined in claim 1.

8. Process for the manufacture of compounds of general formula (I) according to claim 1, wherein

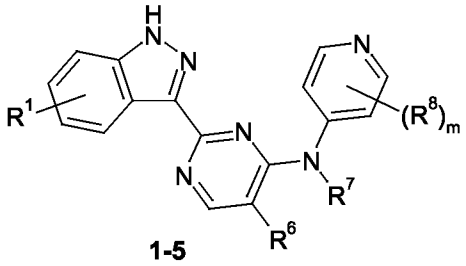
a compound of formula (Ib)



(Ib)

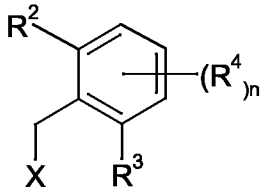
whereby R^1, R^2, R^3, R^6, R^7, R^8 and m have the meaning according to claim 1 and R' is 1-6C-alkyl or benzyl,

is treated with a suitable acid system to cleave the benzylic group in order to obtain a compound of formula 1-5



1-5

followed by reacting the compound of formula 1-5 with a compound of general formula (B),



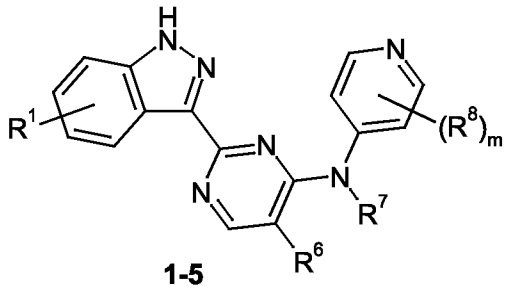
B

wherein R^2, R^3, R^4 and n have the meaning according to claim 1 and

X represents a leaving group,

in a suitable solvent system, in the presence of a suitable base, in a temperature range from room temperature to the boiling point of the respective solvent, to furnish compounds of general formula (I).

9. An intermediate compound of general formula (1-5) according to claim 7,



1-5

whereby R^1, R^6, R^7 R^8 and m have the meaning according to claim 1.

10. Use of a compound of formula 1-6 for the manufacture of a compound of formula (I) according to claim 1.

11. Use of a compound of general formula (I) according to any of claims 1 to 6 for the treatment or prophylaxis of diseases.

12. Use of a compound of general formula (I) according to claim 11, whereby the diseases are hyperproliferative diseases and/or disorders responsive to induction of apoptosis.

13. Use of a compound of general formula (I) according to according to claim 12, whereby the hyperproliferative diseases and/or disorders responsive to induction of apoptosis are haemotological tumours, solid tumours and/or metastases thereof.

14. Use of a compound of formula (I) according to claim 13, whereby the tumors are cervical -, breast -, non-small cell lung -, prostate -, colon – or melanoma tumors and/or metastases thereof.

15. A pharmaceutical composition comprising at least one compound of general formula (I) according to any of claims 1 to 6, together with at least one pharmaceutically acceptable auxiliary.

16. A composition according to claim 15 for the treatment of haemotological tumours, solid tumours and/or metastases thereof.

17. A combination comprising one or more first active ingredients selected from a compound of general formula (I) according to any of claims 1 to 6, and one or more second active ingredients selected from chemotherapeutic anti-cancer agents and target-specific anti-cancer agents.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2012/069562

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 10
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/069562

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D405/14 C07D413/14 C07D498/04 A61K31/506 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 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 2010 111624 A (SHIONOGI & CO) 20 May 2010 (2010-05-20) General formula (I); page 117; example 191	1-17

A	JUNGSEOG KANG ET AL: "Structure and Substrate Recruitment of the Human Spindle Checkpoint Kinase Bub1", MOLECULAR CELL, vol. 32, no. 3, 1 November 2008 (2008-11-01), pages 394-405, XP55041762, ISSN: 1097-2765, DOI: 10.1016/j.molcel.2008.09.017 paragraph on p. 395 entitled "Identification of a Chemical Inhibitor of Bub1"; figure 1D	1-17

☐ 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 application or patent 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
22 October 2012	30/10/2012

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	Johnson, Claire

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2012/069562

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 2010111624 A	20-05-2010	NONE	

Continuation of Box II.2

Claims Nos.: 10

Claim 10 is directed to the use of a compound of formula 1-6. A compound of formula 1-6 is not defined in the claims. This claim is therefore not clear and has not been searched or examined.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2) declaration be overcome.

BENZILINDAZOLES SUSTITUIDOS PARA USO COMO INHIBIDORES DE LA QUINASA BUB1 EN EL TRATAMIENTO DE ENFERMEDADES HIPERPROLIFERATIVAS

Campo de aplicación de la invención

La invención se relaciona con compuestos de benzilindazol sustituidos, un proceso para su producción y el uso de los mismos.

ANTECEDENTES DE LA INVENCIÓN

Una de las características más fundamentales de las células cancerosas es su capacidad para mantener una proliferación crónica, en tanto en los tejidos normales las células ingresan y avanzan por el ciclo de división celular estrictamente controladas para asegurar la homeostasis de la cantidad de células y el mantenimiento de la función del tejido normal. La pérdida del control de la proliferación se destacó como uno de las seis características del cáncer [Hanahan D y Weinberg RA, *Cell* 100, 57, 2000; Hanahan D y Weinberg RA, *Cell* 144, 646, 2011].

El ciclo de división celular (o ciclo celular) eucariota asegura la duplicación del genoma y su distribución en las células hijas mediante el paso por una secuencia de eventos coordinada y regulada. El ciclo celular se divide en cuatro fases sucesivas:

1. La fase G1 representa el tiempo antes de la replicación del ADN, durante el cual la célula crece y es sensible a los estímulos externos.

2. En la fase S la célula replica su ADN y

3. En la fase G2 se preparan para ingresar en la mitosis.

4. En la mitosis (fase M), los cromosomas duplicados se separan sostenidos por un dispositivo de husos conformado por microtúbulos, y se completa la división celular en dos células hijas.

Para asegurar la extraordinaria fidelidad elevada necesaria para una distribución precisa de los cromosomas a las células hijas, el pasaje por el ciclo celular está estrictamente regulado y controlado. Las enzimas necesarias para el avance por el ciclo deben ser activadas en el momento preciso y también deben desactivarse tan pronto como haya pasado la fase correspondiente. Los correspondientes puntos de control ("puntos de comprobación") detienen o demoran el avance por el ciclo celular si se detectan daños del ADN o si no se ha completado aún la replicación del ADN o la creación del dispositivo de husos. El punto de comprobación mitótico (también conocido como punto de comprobación de husos o punto de comprobación del ensamblaje de husos) controla la unión precisa de los mircrotúbulos del dispositivo de husos a los cinetocoros (el sitio de unión de los microtúbulos) de los cromosomas duplicados. El punto de comprobación mitótico es activo mientras haya cinetocoros y genera una señal de espera para darle tiempo a la célula en división para que asegure si cada cinetocoro está unido a un polo del huso y para corregir los errores de unión. Por consiguiente, el punto de comprobación mitótico impide que una célula mitótica complete la división celular con cromosomas no unidos o erróneamente unidos [Suijkerbuijk SJ y Kops GJ, *Biochem. Biophys. Acta* 1786, 24, 2008; Musacchio

A y Salmon ED, *Nat. Rev. Mol. Cell. Biol*. 8, 379, 2007]. Una vez que todos los cinetocoros están conectados con los polos del huso mitótico de una manera bipolar (anfitélica) correcta, el punto de comprobación se completó apropiadamente y la célula ingresa en anafase y avanza por la mitosis.

El punto de comprobación mitótico está determinado por una red compleja de numerosas proteínas esenciales, incluyendo miembros de las familias MAD (deficiente en arresto mitótico, MAD 1-3) y Bub (brotación desinhibida por benzimidazol, Bub 1-3), Mps1 quinasa, cdc20, así como otros componentes [revisado en Bolanos-Garcia VM y Blundell TL, *Trends Biochem. Sci*. 36, 141, 2010], muchos de los cuales están sobreexpresados en las células en proliferación (por ejemplo, células cancerosas) y en los tejidos [Yuan B *et al*., *Clin. Cancer Res*., 12, 405, 2006]. La principal función de un punto de comprobación mitótico no cumplido es la de mantener el complejo/ciclosoma que promueve a la anafase (APC/C) en un estado inactivo. Tan pronto como el punto de comprobación es considerado cumplido, la APC/C ubiquitina-ligasa es dirigida la ciclina B y a la securina para una degradación proteolítica que conduce a la separación de los cromosomas apareados y la salida de la mitosis.

Las mutaciones inactivas de la Ser/Thr quinasa Bub1 impidieron la demora en el avance por la mitosis con el tratamiento de células de la levadura *S. cerevisiae* con drogas desestabilizantes de los microtúbulos, lo cual condujo a la identificación de Bub1 como la proteína del

punto de comprobación mitótico [Roberts BT *et al.*, *Mol. Cell Biol.*, 14, 8282, 1994]. Algunas publicaciones recientes ofrecen evidencia que Bub1 cumple múltiples roles durante la mitosis que fueron revisados por Elowe [Elowe S, *Mol. Cell. Biol.* 31, 3085, 2011. En particular, Bub1 es una de las primeras proteínas del punto de comprobación mitótico que se une a los cinetocoros de los cromosomas duplicados y probablemente actúa como una proteína del andamiaje para constituir el complejo del punto de comprobación mitótico. Aún más, por medio de la fosforilación de la histona H2A, Bub1 localiza a la proteína shugoshina en la región centromérica de los cromosomas para impedir una segregación prematura de los cromosomas apareados [Kawashima *et al.*, *Science* 327, 172, 2010]. Además, junto con la Histona H3 fosforilada con Thr-3, la proteína shugoshina funciona como un sitio de unión para el complejo pasajero de cromosomas que incluye a las proteínas survivina, borealina, INCENP y Aurora B. El complejo pasajero de cromosomas es considerado como un sensor de tensión dentro del mecanismo del punto de comprobación mitótico, que disuelve las uniones de microtúbulos-cinetocoros formados erróneamente tales como las uniones sintélicas (ambos cinetocoros hermanas están unidos a un polo de huso) o merotélico (un cinetocoro está unido a dos polos de husos) [Watanabe Y, *Cold Spring Harb. Symp. Quant. Biol.* 75, 419, 2010].

La función de un punto de comprobación mitótico incompleto se ha relacionado con la aneuploidía y la tumourigénesis [Weaver BA y Cleveland DW, *Cancer Res.*, 67,

10103, 2007; King RW, *Biochim Biophys Acta* 1786, 4, 2008]. Por el contrario, se ha observado que una inhibición completa del punto de comprobación mitótico resulta en una severa segregación errónea de cromosomas y en la inducción de apoptosis en células tumorales [Kops GJ *et al.*, *Nature Rev. Cancer* 5, 773, 2005; Schmidt M y Medema RH, *Cell Cycle* 5, 159, 2006; Schmidt M y Bastians H, *Drug Res. Updates* 10, 162, 2007]. Por consiguiente, la anulación del punto de comprobación mitótico por inhibición farmacológica de los componentes del punto de comprobación mitótico, tal como la Bub1 quinasa, representa un nuevo enfoque para el tratamiento de trastornos proliferativos, incluyendo tumores sólidos tales como carcinomas, sarcomas, leucemias y formas malignas linfoides o otros trastornos, asociados con una proliferación celular descontrolada.

La presente invención se relaciona con compuestos químicos que inhiben la Bub1 quinasa.

Las drogas anti-mitóticas establecidas, tales como los vinca alcaloides, los taxanos o las epotilonas, activan el punto de comprobación mitótico, induciendo un arresto mitótico ya sea por estabilización o desestabilización de la dinámica de los microtúbulos. Este arresto impide la separación de los cromosomas duplicados para formar las dos células hijas. Un arresto prolongado en la mitosis fuerza a la célula hacia una salida de la mitosis sin una citoquinesis (retraso o adaptación mitótica) o hacia una catástrofe mitótica que conduce a la muerte celular [Rieder CL y Maiato H, *Dev. Cell* 7, 637, 2004]. Por el contrario, los inhibidores de Bub1 impiden el establecimiento y/o la

funcionalidad del punto de comprobación mitótico, lo cual finalmente da como resultado una segregación errónea severa de los cromosomas, inducción de apoptosis y muerte celular.

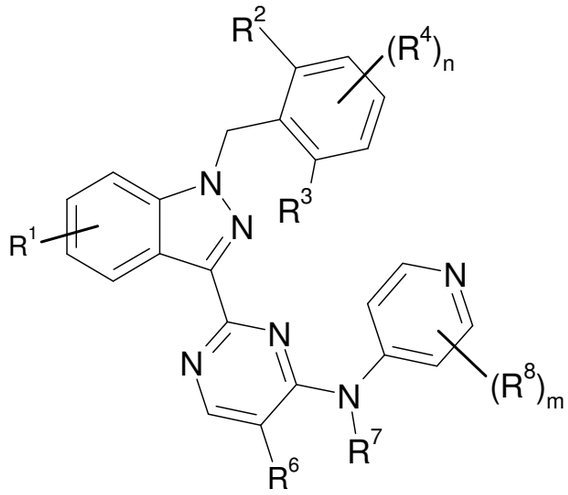
Estos hallazgos sugieren que los inhibidores de Bub1 deberían tener valor terapéutico para el tratamiento de los trastornos proliferativos asociados con un aumento de los procesos celulares proliferativos descontrolados tales como, por ejemplo, cáncer, inflamación, artritis, enfermedades virales, enfermedades cardiovasculares o enfermedades fúngicas en un animal de sangre caliente tal como el hombre.

Debido al hecho que se considera que especialmente la enfermedad del cáncer, expresada por procesos celulares proliferativos en tejidos de diferentes órganos del cuerpo humano o animal, aún no se considera como una enfermedad controlada a pesar del hecho que ya existen suficientes terapias con drogas, aún persiste una fuerte necesidad de proveer otras drogas terapéuticamente útiles nuevas, que preferiblemente inhiban nuevos blancos y proporcionen nuevas opciones terapéuticas.

Descripción de la invención

Por ello, los inhibidores de Bub1 representan compuestos valiosos que deberían complementar las opciones terapéuticas, ya sea como agentes individuales o en combinación con otras drogas.

De acuerdo con un primer aspecto, la invención se relaciona con compuestos de fórmula (I)



(I)

en donde

R^1 es hidrógeno, halógeno, 1-3C-alquilo,

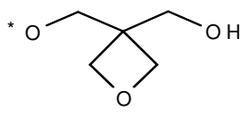
R^2/R^3 son en forma independiente entre sí hidrógeno, halógeno, ciano, hidroxi, 1-6C-haloalquilo, 1-6C-haloalcoxi, 1-6C-alcoxi,

R^4 es en forma independiente hidrógeno, hidroxi, halógeno, ciano, NO_2, 1-6C-alquilo, 2-6C-alquenilo, 2-6C-alquinilo, 1-6C-haloalquilo, 1-6C-hidroxialquilo, 1-6C-alcoxi, -O-(2-6Calquilen)-O-C(O)-(1-6C-alquilo), 1-6C-haloalcoxi, $-C(O)OR^9$, -(1-6C-alquilen)-$C(O)OR^9$, -C(O)-(1-6C-alquilo), $-C(O)NR^{10}R^{11}$, 3-7C-cicloalquilo, -S-(1-6C-haloalquilo), SF_5, $-SO_2NH$-(3-7C-cicloalquilo), $-SO_2NR^{10}R^{11}$, $NR^{10}R^{11}$, heteroarilo que está opcionalmente sustituido en forma independiente una o más veces con ciano, 1-4C-alquilo, 1-6C-haloalquilo, 1-6C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, donde dos de R^2, R^3 $(R^4)_n$, cuando se encuentran en posición *orto* entre sí, pueden formar junto con los dos átomos de carbono a los cuales están unidos un anillo heterocíclico de 5, 6 o 7 miembros que contiene 1 o 2 heteroátomos seleccionados entre O

o N, y que opcionalmente contiene un enlace doble adicional y/o está opcionalmente sustituido con un grupo oxo (=O) y/o un grupo 1-4C-alquilo,

n 0 - 3

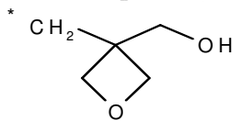
R^6 es (a) hidrógeno; (b) hidroxi; (c) ciano; (d) 1-6C-alcoxi opcionalmente sustituido en forma independiente una o más veces con (d1) OH, (d2) -O-(1-6C-alquilo) (d3) $C(O)OR^9$, (d4) $C(O)NR^{10}R^{11}$, (d5) $NR^{10}R^{11}$, (d6) -S-(1-6C-alquilo), (d7) -S(O)-(1-6C-alquilo), (d8) $-SO_2$-(1-6C-alquilo) (d9) $SO_2NR^{10}R^{11}$, (d10) heterociclilo, que está opcionalmente sustituido con $C(O)OR^9$, o oxo (=O), (d11) heteroarilo, que está opcionalmente sustituido en forma independiente una o más veces con ciano, 1-4C-alquilo, 1-6C-haloalquilo, 1-6C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, (1-6C-alquilen)-O-(1-6C-alquilo), (e) $SO_2NR^{10}R^{11}$, (f) 3-7C-cicloalcoxi, (g) 1-6C-haloalcoxi, (h) $COOR^9$, (i) $-C(O)NR^{10}R^{11}$, (j) -O-heteroarilo opcionalmente sustituido con CN(k)



, donde * es el punto de unión,

(l) -O-(2-6C-alquilen)-O-(1-6C-alquilo) que está opcionalmente sustituido con hidroxi, $NH(CO)OR^9$,

R^7 es (a) hidrógeno, (b)1-6C-alquilo, que está opcionalmente sustituido con heteroarilo(c) 1-6C-haloalquilo, (d) 1-6C-hidroxialquilo, (e)



, donde * es el punto de unión, (f) -C(O)-(1-6C-alquilo) (g) -C(O)-(1-6C-alquilen)-O-(1-6C-alquilo) (h) -C(O)-(1-6C-alquilen)-O-(2-6C-alquilen)-

O-(1-6C-alquilo) (i) -C(O)-heterociclilo, (j) bencilo donde el anillo fenilo está opcionalmente sustituido con 1-5 sustituyentes seleccionados en forma independiente entre el grupo que consiste en hidrógeno, halógeno, 1-4C-alquilo, 1-4C-haloalquilo, 1-4C-alcoxi, 1-4C-haloalcoxi, ciano, $C(O)OR^9$, (k) heteroarilo, u opcionalmente R^6 y R^7 junto con el átomo de nitrógeno al cual R^7 está unido forman un anillo de 6 miembros que puede contener otro heteroátomo seleccionado entre el grupo que consiste en O, S, N, y que está opcionalmente sustituido con (1-6C-alquil)-OH, (1-6C-alquil)-$NR^{10}R^{11}$,

R^8 es hidrógeno, halógeno, hidroxi, ciano, 1-6C-alquilo, 1-6C-hidroxialquilo, 1-6C-haloalquilo, 1-6C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,

m es 0-4

R^9 es (a) hidrógeno, (b) 1-6C-alquilo que está opcionalmente sustituido con hidroxi,

R^{10}, R^{11} son en forma independiente entre sí hidrógeno, 1-4C-alquilo, 1-4C-hidroxialquilo, 1-4C-alcoxi, -(CO)-(1-6C-alquilo), CHO, $COOR^9$, o junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de entre 4 y 6 miembros que opcionalmente contiene otro heteroátomo seleccionado entre el grupo que consiste en O, S o N, y que está opcionalmente sustituido con 1-2 átomos de flúor o $COOR^9$,

o un N-óxido, una sal, un tautómero o un estereoisómero de dichos compuestos, o una sal de dicho N-

óxido, tautómero o estereoisómero.

De acuerdo con un aspecto adicional de la invención, la invención se relaciona con compuestos de fórmula (I)

donde

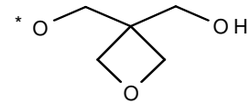
R^1 es hidrógeno, halógeno, 1-3C-alquilo,

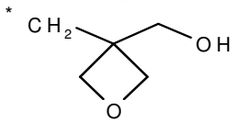
R^2/R^3 son en forma independiente entre sí hidrógeno, halógeno, ciano, 1-6C-haloalquilo, 1-6C-haloalcoxi,

R^4 es en forma independiente hidrógeno, halógeno, ciano, 1-6C-alquilo, 2-6C-alquenilo, 1-6C-haloalquilo, 1-6C-hidroxialquilo, 1-6C-alcoxi, 1-6C-haloalcoxi, $-C(O)OR^9$, -(1-6C-alquilen)-$C(O)OR^9$, -C(O)-(1-6C-alquilo), $-C(O)NR^{10}R^{11}$, 3-7C-cicloalquilo, -S-(1-6C-haloalquilo), SF_5, $-SO_2NH$-(3-7-cicloalquilo), $-SO_2NR^{10}R^{11}$, heteroarilo que está opcionalmente sustituido en forma independiente una o más veces con ciano, 1-4C-alquilo, 1-6C-haloalquilo, 1-6C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, donde dos de R^2, R^3 $(R^4)_n$, cuando se encuentran en posición *orto* entre sí, pueden formar junto con los dos átomos de carbono a los cuales están unidos un anillo heterocíclico de 5, 6 o 7 miembros que contiene 1 o 2 heteroátomos seleccionados entre O o N, y opcionalmente un enlace doble adicional y/o un grupo carbonilo y/o un grupo 1-4C-alquilo,

n 0 - 3

R^6 es (a) hidrógeno; (b) hidroxi; (c) ciano; (d) 1-6C-alcoxi opcionalmente sustituido con (d1) 1-2 OH, (d2) $NR^{10}R^{11}$, (d3) $SO2NR^{10}R^{11}$, (d4) heterociclilo,

(d5) heteroarilo, que está opcionalmente sustituido en forma independiente una o más veces con ciano, 1-4Calquilo, 1-6C-haloalquilo, 1-6C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, (e) $SO_2NR^{10}R^{11}$, (f) 3-7C-cicloalcoxi, (g) 1-6C-haloalcoxi, (h) $-C(O)NR^{10}R^{11}$, (i) -O-heteroarilo opcionalmente sustituido con CN(j)  , donde * es el punto de unión,

R^7 es (a) hidrógeno, (b)1-6C-alquilo, que está opcionalmente sustituido con heteroarilo(c) 1-6C-haloalquilo, (d) 1-6C-hidroxialquilo, (e)  , donde * es el punto de unión, (f) -C(O)-(1-6C-alquilo) (g) -C(O)-(1-6C-alquilen)-O-(1-6C-alquilo) (h) -C(O)-(1-6C-alquilen)-O-(1-6C-alquilen)-O-(1-6C-alquilo) (i) -C(O)-heterociclilo, (j) bencilo donde el anillo fenilo está opcionalmente sustituido con 1-5 sustituyentes seleccionados en forma independiente entre el grupo que consiste en hidrógeno, halógeno, 1-4Calquilo, 1-4C-haloalquilo, 1-4C-alcoxi, 1-4C-haloalcoxi, ciano, $C(O)OR^9$, (k) heteroarilo, u opcionalmente R^6 y R^7 junto con el átomo de nitrógeno al cual están unidos forman un anillo de 6 miembros que puede contener otro heteroátomo seleccionado entre el grupo que consiste en O, S, N, y que está opcionalmente sustituido con hidroxi-(1-6alquilo),

R^8 es hidrógeno, halógeno, ciano, 1-6C-haloalquilo, 1-6C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,

m es 0–4

R^9 es (a) hidrógeno, (b) 1–6C–alquilo que puede estar opcionalmente sustituido con hidroxi,

R^{10}, R^{11} son en forma independiente entre sí hidrógeno, 1–4C–alquilo, 1–4C–hidroxialquilo, 1–4C–alcoxi, o junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 5 o 6 miembros que opcionalmente contiene otro heteroátomo seleccionado entre el grupo que consiste en O, S o N,

o un N–óxido, una sal, un tautómero o un estereoisómero de dichos compuestos, o una sal de dicho N–óxido, tautómero o estereoisómero.

Otro aspecto de la invención consiste en compuestos de fórmula (I) de acuerdo con la reivindicación 1, donde

R^1 es hidrógeno, halógeno, 1–3C–alquilo,

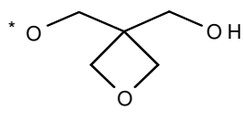
R^2/R^3 son en forma independiente entre sí hidrógeno, halógeno, ciano, hidroxi, 1–3C–haloalquilo, 1–3C–haloalcoxi, 1–3C–alcoxi,

R^4 es en forma independiente hidrógeno, hidroxi, halógeno, ciano, NO_2, 1–3C–alquilo, 2–3C–alquenilo, 2–3C–alquinilo, 1–3C–haloalquilo, 1–3C–hidroxialquilo, 1–3C–alcoxi, –O–(2–3C–alquilen)–O–C(O)–(1–3C–alquilo), 1–3C–haloalcoxi, $-C(O)OR^9$, –(1–3C–alquilen)–$C(O)OR^9$, –C(O)–(1–3C–alquilo), $-C(O)NR^{10}R^{11}$, 3–7C–cicloalquilo, –S–(1–3C–haloalquilo), SF_5, $-SO_2NH$–(3–7C–cicloalquilo), $-SO_2NR^{10}R^{11}$, $NR^{10}R^{11}$, heteroarilo que está opcionalmente sustituido en forma independiente una o más veces con ciano, 1–3C–alquilo, 1–3C–haloalquilo, 1–3C–haloalcoxi, $C(O)OR^9$,

$C(O)NR^{10}R^{11}$, donde dos de R^2, R^3 $(R^4)_n$, cuando se encuentran en posición *orto* entre sí, pueden formar junto con los dos átomos de carbono a los cuales están unidos un anillo heterocíclico de 5, 6 o 7 miembros que contiene 1 o 2 heteroátomos seleccionados entre O o N, y que opcionalmente contiene un enlace doble adicional y/o está opcionalmente sustituido con un grupo oxo (=O) y/o un grupo 1-3C-alquilo,

n 0 - 3

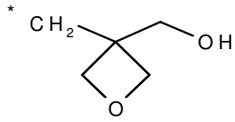
R^6 es (a) hidrógeno; (b) hidroxi; (c) ciano; (d) 1-6C-alcoxi opcionalmente sustituido en forma independiente una o más veces con (d1) OH, (d2) -O-(1-3C-alquilo) (d3) $C(O)OR^9$, (d4) $C(O)NR^{10}R^{11}$, (d5) $NR^{10}R^{11}$, (d6) -S-(1-3C-alquilo), (d7) -S(O)-(1-3C-alquilo), (d8) $-SO_2$-(1-3C-alquilo) (d9) $SO_2NR^{10}R^{11}$, (d10) heterociclilo, que está opcionalmente sustituido con $C(O)OR^9$, o oxo (=O), (d11) heteroarilo, que está opcionalmente sustituido en forma independiente una o más veces con ciano, 1-3C-alquilo, 1-3C-haloalquilo, 1-3C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, (1-3C-alquilen)-O-(1-3C-alquilo), (e) $SO_2NR^{10}R^{11}$, (f) 3-7C-cicloalcoxi, (g) 1-6C-haloalcoxi, (h) $COOR^9$, (i) $-C(O)NR^{10}R^{11}$, (j) -O-heteroarilo opcionalmente sustituido con CN(k)



, donde * es el punto de unión,

(l) -O-(2-3C-alquilen)-O-(1-3C-alquilo) que está opcionalmente sustituido con hidroxi, $NH(CO)OR^9$,

R^7 es (a) hidrógeno, (b)1-3C-alquilo, que está opcionalmente sustituido con heteroarilo(c) 1-3C-

haloalquilo, (d) 1-3C-hidroxialquilo, (e) 

, donde * es el punto de unión, (f) -C(O)-(1-3C-alquilo) (g) -C(O)-(1-3C-alquilen)-O-(1-3C-alquilo) (h) -C(O)-(1-3C-alquilen)-O-(2-3C-alquilen)-O-(1-3C-alquilo) (i) -C(O)-heterociclilo, (j) bencilo donde el anillo fenilo está opcionalmente sustituido con 1-5 sustituyentes seleccionados en forma independiente entre el grupo que consiste en hidrógeno, halógeno, 1-4C-alquilo, 1-4C-alcoxi, 1-4C-haloalcoxi, ciano, $C(O)OR^9$, (k) heteroarilo, u opcionalmente R^6 y R^7 junto con el átomo de nitrógeno al cual R^7 está unido forman un anillo de 6 miembros que puede contener otro heteroátomo seleccionado entre el grupo que consiste en O, S, N, y que está opcionalmente sustituido con (1-3C-alquil)-OH, (1-3C-alquil)-$NR^{10}R^{11}$,

R^8 es hidrógeno, halógeno, hidroxi, ciano, 1-3C-alquilo, 1-3C-hidroxialquilo, 1-3C-haloalquilo, 1-3C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,

m es 0-4

R^9 es (a) hidrógeno, (b) 1-3C-alquilo que está opcionalmente sustituido con hidroxi,

R^{10}, R^{11} son en forma independiente entre sí hidrógeno, 1-3C-alquilo, 1-3C-hidroxialquilo, 1-3C-alcoxi, -(CO)-(1-3C-alquilo), CHO, $COOR^9$ o junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de entre 4 y 6 miembros que opcionalmente contiene otro heteroátomo seleccionado

entre el grupo que consiste en O, S o N, que está opcionalmente sustituido con 1–2 átomos de flúor o $COOR^9$,

o un N–óxido, una sal, un tautómero o un estereoisómero de dichos compuestos, o una sal de dicho N–óxido, tautómero o estereoisómero.

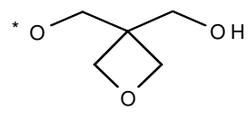
Un aspecto adicional de la invención son compuestos de fórmula (I) de acuerdo con la reivindicación 1, donde

R^1 es hidrógeno, halógeno, 1–4C–alquilo,

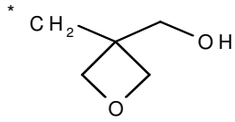
R^2/R^3 son en forma independiente entre sí hidrógeno, halógeno, ciano, 1–4C–haloalquilo, 1–4C–haloalcoxi,

R^4 es en forma independiente hidrógeno, halógeno, ciano, 1–4C–alquilo, 2–4C–alquenilo, 1–4C–haloalquilo, 1–4C–hidroxialquilo, 1–4C–alcoxi, 1–4C–haloalcoxi, $-C(O)OR^9$, –(1–4C–alquilen)–$C(O)OR^9$, –C(O)–(1–4C–alquilo), $-C(O)NR^{10}R^{11}$, 3–6C–cicloalquilo, –S–(1–6C–haloalquilo), SF_5, $-SO_2NH$–(3–6–cicloalquilo), $-SO_2NR^{10}R^{11}$, heteroarilo que está opcionalmente sustituido en forma independiente una o más veces con ciano, 1–4C–alquilo, 1–6C–haloalquilo, 1–6C–haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, donde dos de R^2, R^3 $(R^4)_n$, cuando se encuentran en posición *orto* entre sí, pueden formar junto con los dos átomos de carbono a los cuales están unidos un anillo heterocíclico de 5, 6 o 7 miembros que contiene 1 o 2 heteroátomos seleccionados entre O o N, y opcionalmente un enlace doble adicional y/o un grupo carbonilo y/o un grupo 1–4C–alquilo,

n 0 – 3

R^6 es (a) hidrógeno; (b) hidroxi; (c) ciano; (d) 1–4C–alcoxi opcionalmente sustituido con (d1) 1–2 OH, (d2) $NR^{10}R^{11}$, (d3) $SO2NR^{10}R^{11}$, (d4) heterociclilo, (d5) heteroarilo, que está opcionalmente sustituido en forma independiente una o más veces con ciano, 1–4C–alquilo, 1–6C–haloalquilo, 1–6C–haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, (e) $SO2NR^{10}R^{11}$, ; (f) 3–6C–cicloalcoxi, (g) 1–4C–haloalcoxi, (h) $–C(O)NR^{10}R^{11}$, (i) O–heteroarilo opcionalmente sustituido con CN(j) 

, donde * es el punto de unión,

R^7 es (a) hidrógeno, (b)1–4C–alquilo, que está opcionalmente sustituido con heteroarilo(c) 1–4C–haloalquilo, (d) 1–4C–hidroxialquilo, (e) 

, donde * es el punto de unión, (f) –C(O)–(1–4C–alquilo) (g) –C(O)–(1–4C–alquilen)–O–(1–4C–alquilo) (h) –C(O)–(1–4C–alquilen)–O–(1–4C–alquilen)–O–(1–4C–alquilo) (i) –C(O)–heterociclilo, (j) bencilo donde el anillo fenilo está opcionalmente sustituido con 1–5 sustituyentes seleccionados en forma independiente entre el grupo que consiste en hidrógeno, halógeno, 1–4C–alquilo, 1–4C–haloalquilo, 1–4C–alcoxi, 1–4C–haloalcoxi, ciano, C(O)OR9, (k) heteroarilo, u opcionalmente R^6 y R^7 junto con el átomo de nitrógeno al cual están unidos forman un anillo de 6 miembros que puede contener otro heteroátomo seleccionado entre el grupo que consiste

en O, S, N, y que está opcionalmente sustituido con hidroxi-(1-4-alquilo),

R^8 es hidrógeno, halógeno, $C(O)NR^{10}R^{11}$, $C(O)OR^9$, 1-4C-haloalquilo, 1-4C-haloalcoxi, ciano,

m es 0-4

R^9 es (a) hidrógeno, (b) 1-4C-alquilo que puede estar opcionalmente sustituido con hidroxi,

R^{10}, R^{11} son en forma independiente entre sí hidrógeno, 1-4C-alquilo, 1-4C-hidroxialquilo, 1-4C-alcoxi, o junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 5 o 6 miembros que opcionalmente contiene otro heteroátomo seleccionado entre el grupo que consiste en O, S o N,

o un N-óxido, una sal, un tautómero o un estereoisómero de dichos compuestos, o una sal de dicho N-óxido, tautómero o estereoisómero.

Otro aspecto de la invención consiste en compuestos de fórmula (I) de acuerdo con la reivindicación 1, donde

R^1 es hidrógeno, 1-3C-alquilo,

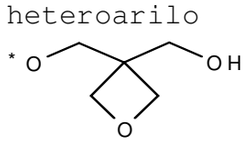
R^2/R^3 son en forma independiente entre sí hidrógeno, halógeno, ciano, hidroxi, 1-4C-haloalquilo, 1-4C-alcoxi,

R^4 es en forma independiente hidrógeno, hidroxi, halógeno, ciano, 1-4C-alquilo, 2-4C-alquenilo, 2-4C-alquinilo, 1-4C-haloalquilo, 1-4C-hidroxialquilo, 1-4C-alcoxi, -O-(2-4C-alquilen)-O-C(O)-(1-4C-alquilo), 1-4C-haloalcoxi, $-C(O)OR^9$, -(1-4C-alquilen)-$C(O)OR^9$, -C(O)-(1-4C-alquilo), -$C(O)NR^{10}R^{11}$, 3-7C-cicloalquilo, -S-(1-4C-haloalquilo),

SF_5, $-SO_2NH-$(3-7C-cicloalquilo), $-SO_2NR^{10}R^{11}$, $NR^{10}R^{11}$, heteroarilo que está opcionalmente sustituido en forma independiente una o más veces con ciano, 1-4C-alquilo, 1-4C-haloalquilo, 1-4C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, donde dos de R^2, R^3 $(R^4)_n$, cuando se encuentran en posición *orto* entre sí, pueden formar junto con los dos átomos de carbono a los cuales están unidos un anillo heterocíclico de 5, 6 o 7 miembros que contiene 1 o 2 heteroátomos seleccionados entre O o N, y que opcionalmente contiene un enlace doble adicional y/o está opcionalmente sustituido con un grupo oxo (=O) y/o un grupo 1-4C-alquilo,

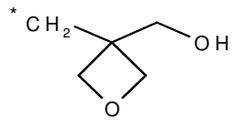
n 0 - 3

R^6 es (a) hidrógeno; (b) hidroxi; (d) 1-4C-alcoxi opcionalmente sustituido en forma independiente una o más veces con (d1) OH, (d2) -O-(1-4C-alquilo) (d3) $C(O)OR^9$, (d4) $C(O)NR^{10}R^{11}$, (d5) $NR^{10}R^{11}$, (d6) -S-(1-4C-alquilo), (d7) -S(O)-(1-4C-alquilo), (d8) $-SO_2-$(1-4C-alquilo) (d9) $SO_2NR^{10}R^{11}$, (d10) heterociclilo, que está opcionalmente sustituido con $C(O)OR^9$, o oxo (=O), (d11) heteroarilo, que está opcionalmente sustituido en forma independiente una o más veces con ciano, 1-4C-alquilo, 1-4C-haloalquilo, 1-4C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, (1-4C-alquilen)-O-(1-4C-alquilo), (e) $SO_2NR^{10}R^{11}$, (f) 3-7C-cicloalcoxi, (g) 1-6C-haloalcoxi, (h) $COOR^9$, (i) $-C(O)NR^{10}R^{11}$, (j) -O-heteroarilo opcionalmente sustituido con CN(k)



, donde * es el punto de unión,

(l) –O–(2–4C–alquilen)–O–(1–4C–alquilo) que está opcionalmente sustituido con hidroxi, NH(CO)OR^{9},

R^{7} es (a) hidrógeno, (b) (1–4C–alquil)–heteroarilo(c) 1–4C–haloalquilo, (d) 1–4C–hidroxialquilo, (e) 

, donde * es el punto de unión, (f) –C(O)–(1–4C–alquilo) (g) –C(O)–(1–4C–alquilen)–O–(1–4C–alquilo) (h) –C(O)–(1–4C–alquilen)–O–(2–4C–alquilen)–O–(1–4C–alquilo) (i) –C(O)–heterociclilo, (j) bencilo donde el anillo fenilo está opcionalmente sustituido con 1–5 sustituyentes seleccionados en forma independiente entre el grupo que consiste en hidrógeno, halógeno, 1–4C–alquilo, 1–4C–alcoxi, 1–4C–haloalcoxi, ciano, C(O)OR^{9}, (k) heteroarilo, u opcionalmente R^{6} y R^{7} junto con el átomo de nitrógeno al cual R^{7} está unido forman un anillo de 6 miembros que puede contener otro heteroátomo seleccionado entre el grupo que consiste en O, S, N, y que está opcionalmente sustituido con (1–4C–alquil)–OH, (1–4C–alquil)–NR^{10}R^{11},

R^{8} es hidrógeno, halógeno, hidroxi, ciano, C(O)NR^{10}R^{11}, 1–4C–alquilo, 1–4C–hidroxialquilo, 1–4C–haloalquilo, 1–4C–haloalcoxi,

m es 0–2,

R^{9} es hidrógeno, 1–4C–alquilo que está opcionalmente sustituido con hidroxi,

R^{10}, R^{11} son en forma independiente entre sí hidrógeno, 1–4C–alquilo, 1–4C–hidroxialquilo, 1–4C–alcoxi, –C(O)–(1–4C–alquilo), o COOR^{9} o junto con el

átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de entre 4 y 6 miembros que opcionalmente contiene otro heteroátomo seleccionado entre el grupo que consiste en O, S o N, que está opcionalmente sustituido con 1–2 átomos de flúor o $COOR^9$,

o un N–óxido, una sal, un tautómero o un estereoisómero de dichos compuestos, o una sal de dicho N–óxido, tautómero o estereoisómero.

Un aspecto adicional de la invención son compuestos de fórmula (I) de acuerdo con la reivindicación 1, donde

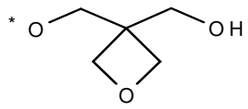
R^1 es hidrógeno, halógeno,

R^2/R^3 son en forma independiente entre sí hidrógeno, halógeno, ciano, 1–4C–haloalquilo,

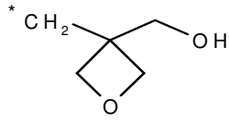
R^4 es en forma independiente hidrógeno, halógeno, ciano, 1–4C–alquilo, 2–4C–alquenilo, 1–4C–haloalquilo, 1–4C–hidroxialquilo, 1–4C–alcoxi, 1–4C–haloalcoxi, $-C(O)OR^9$, –(1–4C–alquilen)–$C(O)OR^9$, –C(O)–(1–4C–alquilo), –C(O)NR10R11, 3–7C–cicloalquilo, –S–(1–4C–haloalquilo), SF_5, $-SO_2NH$–(3–7–cicloalquilo), $-SO_2NR^{10}R^{11}$, heteroarilo que está opcionalmente sustituido en forma independiente una o más veces con ciano, 1–4C–alquilo, 1–6C–haloalquilo, 1–6C–haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, donde dos de R^2, R^3 $(R^4)_n$, cuando se encuentran en posición *orto* entre sí, pueden formar junto con los dos átomos de carbono a los cuales están unidos un anillo heterocíclico de 5, 6 o 7 miembros que contiene 1 o 2 heteroátomos seleccionados entre O o N, y opcionalmente un enlace

doble adicional y/o un grupo carbonilo y/o un grupo 1-4C-alquilo,

n 0 - 3

R^6 es (a) hidrógeno; (b) hidroxi; (d) 1-6C-alcoxi opcionalmente sustituido con (d1) 1-2 OH, (d2) $NR^{10}R^{11}$, (d3) $SO_2NR^{10}R^{11}$, (g) 1-6C-haloalcoxi, (k) 

, donde * es el punto de unión,

R^7 es (a) hidrógeno, (c) 1-6C-haloalquilo, (d) 1-4C-hidroxialquilo, (e) 

, donde * es el punto de unión, (f) -C(O)-(1-4C-alquilo) (g) -C(O)-(1-4C-alquilen)-O-(1-4C-alquilo) (h) -C(O)-(1-4C-alquilen)-O-(1-4C-alquilen)-O-(1-4C-alquilo) (i) -C(O)-heterociclilo, (j) bencilo donde el anillo fenilo está opcionalmente sustituido con 1-5 sustituyentes seleccionados en forma independiente entre el grupo que consiste en hidrógeno, halógeno, 1-4C-alquilo, 1-4C-haloalquilo, 1-4C-alcoxi, 1-4C-haloalcoxi, ciano, $C(O)OR^9$, u opcionalmente R^6 y R^7 junto con el átomo de nitrógeno al cual están unidos forman un anillo de 6 miembros que puede contener otro heteroátomo seleccionado entre el grupo que consiste en O, S, N, y que está opcionalmente sustituido con hidroxi-(1-4alquilo),

R^8 es hidrógeno, halógeno, $C(O)NR^{10}R^{11}$, 1-4C-haloalquilo, 1-4C-haloalcoxi, ciano,

m es 0-2,

R^9 es 1-4C-alquilo que puede estar

opcionalmente sustituido con hidroxi,

R^{10}, R^{11} son en forma independiente entre sí hidrógeno, 1-4C-alquilo, 1-4C-hidroxialquilo, 1-4C-alcoxi, o junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 5 o 6 miembros que opcionalmente contiene otro heteroátomo seleccionado entre el grupo que consiste en O, S o N,

o un N-óxido, una sal, un tautómero o un estereoisómero de dichos compuestos, o una sal de dicho N-óxido, tautómero o estereoisómero.

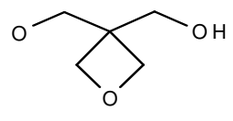
Un aspecto adicional de la invención son compuestos de fórmula (I) de acuerdo con la reivindicación 1, donde

R^1 es hidrógeno,

R^2/R^3 son en forma independiente entre sí hidrógeno, halógeno,

R^4 es en forma independiente hidrógeno, 1-3C-alquilo, 2-3C-alquenilo, 1-3C-haloalquilo, 1-3C-hidroxialquilo, 1-3C-alcoxi, 1-3C-haloalcoxi, $-C(O)OR^9$, $-C(O)-$(1-3C-alquilo), $-C(O)NR^{10}R^{11}$, 3-4C-cicloalquilo, $-SO_2NR^{10}R^{11}$,

n 0 - 3

R^6 es (a) hidrógeno; (b) hidroxi; (d) 1-3C-alcoxi opcionalmente sustituido con (d1) 1-2 OH, (d2) $NR^{10}R^{11}$, (g) 1-3C-haloalcoxi, (k) 

,

R^7 es hidrógeno,

R^8 es hidrógeno, $C(O)NR^{10}R^{11}$, 1-3C-haloalquilo,

m es 0 - 2,

R^9 es 1-3C-alquilo que puede estar

opcionalmente sustituido con hidroxi,

R^{10}, R^{11} son en forma independiente entre sí hidrógeno, 1-3C-alquilo, 1-3C-hidroxialquilo, 1-3C-alcoxi, o junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 5 o 6 miembros que opcionalmente contiene otro heteroátomo seleccionado entre el grupo que consiste en O, S o N,

o un N-óxido, una sal, un tautómero o un estereoisómero de dichos compuestos, o una sal de dicho N-óxido, tautómero o estereoisómero.

Un aspecto adicional de la invención son compuestos de fórmula (I) de acuerdo con la reivindicación 1, compuestos de fórmula (I) de acuerdo con la reivindicación 1, donde,

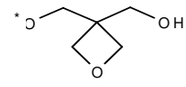
R^1 es hidrógeno, ,

R^2/R^3 es en forma independiente halógeno, ciano, hidroxi, 1-3C-haloalquilo, 1-4C-alcoxi o 1-3C-haloalcoxi,

R^4 es en forma independiente en cada caso hidrógeno, halógeno, ciano, NO_2, hidroxi, -1-4C-alquilo, 2-3C-alquenilo, 2-3C-alquinilo, 1-3C-haloalquilo, (1-4C-alquil)-OH, 1-3C-alcoxi, 1-3C-haloalcoxi, -O-(2-3C-alquilen)-O-C(O)-(1-3C-alquilo), -C(O)(1-3C-alquilo), -COOH, -C(O)O(1-4C-alquilo), (1-3C-alquil)-COOH, -(1-4C-alquil)-C(O)O(1-3C-alquilo), -C(O)$NR^{10}R^{11}$, $-SO_2$-NH-(3-6C-cicloalquilo), $-SO_2-NR^{10}R^{11}$, $NR^{10}R^{11}$, heteroarilo, $-S-CF_3$, SF_5, donde dos de R^2, R^3 $(R^4)_n$, cuando se encuentran en posición *orto* entre sí pueden formar juntos $-O-CH_2-CH_2-CH_2-O-$, $-O-CH_2-CH_2-$, $-(CH_3)C=CH-(C=O)-O-$, $-CH_2-(C=O)-O-$, $-(CH_2)_2-(C=O)-NH-$,

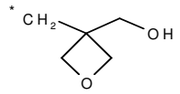
que además junto con los dos átomos de carbono a los cuales están unidos forman un anillo de entre 5 y 7 miembros,

n es 0, 1, 2, 3,

R^6 es hidrógeno, hidroxi, ciano, –O–ciclopropilo, 1–3C–alkyoxi, 1–3C–haloalcoxi, –O–(2–3C–alquil)–OH, –O–(2–3C–alquil)–NH_2, –O–(2–3C–alquil)–O(1–3C–alquilo), –O–(2–3C–alquil)–O–(2–3C–alquil)–OH, –O–CH_2–CH(OH)–CH_2OH, –O–(1–3C–alquil)–COOH, –O–(1–3C–alquil)C(O)–O–(1–3C–alquilo), –O–(2–3C–alquil)–O–(2–3C–alquil)–NH–C(O)–O–(1–4C–alquilo), C(O)–NH_2, –O–CH_2–C(O)–(3–fluoro–N–azetidina), –O–CH_2–C(O)–(3,3–difluoro–N–azetidina), –O(1–3C–alquilo) –$NR^{10}R^{11}$, –O–CH_2–CH(OH)–CH_2–N–piperidinilo, –O–(2–3C–alquil)–S–(2–3C–alquilo), –O–(2–3C–alquil)–SO_2NH_2, –O–(2–3C–alquil)–SO_2–(1–3C–alquilo), –O–(2–3C–alquil)–SO–(1–3C–alquilo), 

, donde * es el punto de unión, –O–(1–3C–alquil)heteroarilo, –O–heteroarilo el cual está opcionalmente sustituido una o más veces con ciano, –O–(1–3C–alquil)–(heterociclilo, con 1–2 heteroátomos seleccionados entre el grupo que consiste en N, O y que está opcionalmente sustituido con oxo (=O)), –O–(1–3C–alquil)–(heteroaril)–(1–3C–alquil)–O–(1–3C–alquilo), –O–(1–3C–alquil)– heterociclilo el cual está opcionalmente sustituido con –C(O)–O–(1–4C–alquilo), C(O)NH_2, o R^6 junto con R^7 es un anillo de 6 miembros incluyendo el átomo de nitrógeno del grupo amino unido a R^7 que puede contener otro heteroátomo

seleccionado entre O, S o N y que además puede estar sustituido con oxo (=O), $-CH_2-NH-CHO$ o (1-3C-alquil)-OH,

R^7 es hidrógeno, 1-3C-alquilo, 1-3C-haloalquilo, 1-3C-hidroxialquilo,  , donde * es el punto de unión, -(1-3C-alquil)heteroarilo, heteroarilo, -C(O)-heterociclilo, -C(O)-(1-3C-alquil)-O-(1-3C-alquilo), -C(O)-(1-3C-alquilo), -C(O)(1-3C-alquil)-O-(2-3C-alquil)-O-(1-3C-alquilo), o bencilo el cual está opcionalmente sustituido una o más veces con halógeno, ciano, metilo, difluorometilo, 1-3C-alcoxi, 1-3C-haloalcoxi, -C(O)O(1-3C-alquilo),

R^8 es hidrógeno, flúor, ciano, CF_3, $C(O)NH_2$, $C(O)NHCH_3$, C(O)OH, C(O)O(1-3Calquilo), C(O)(1-3C-alquil)-OH,

m es 0, 1 o 2

R^{10}/R^{11} hidrógeno, 1-3C-alquilo, (1-3C-alquil)-OH, C(O)(1-3Calquilo),

o un N-óxido, una sal, un tautómero o un estereoisómero de dichos compuestos, o una sal de dicho N-óxido, tautómero o estereoisómero.

Un aspecto adicional de la invención son compuestos de fórmula (I) de acuerdo con la reivindicación 1, donde

R^1 es hidrógeno, ,

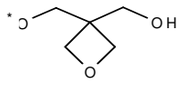
R^2/R^3 es en forma independiente flúor, cloro, bromo, ciano, CF_3, o $-O-CH_2-CF3$,

R^4 es en forma independiente en cada caso hidrógeno, flúor, cloro, bromo o iodo, ciano, -CH3, -

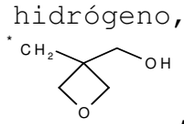
C3H9, ciclopropilo, 1-propenilo, -CF3, $-CH_2-OH$, $-CH_2-CH_2-OH$, -C(CH3)2-OH, $-CH_2-C(CH3)2-OH$, $-C(CH3)2-CH_2-OH$, -OCH3, -OCF3, -OCF2H, $-OCH_2CF3$, -C(O)CH3, -COOH, -C(O)OCH3, -C(O)OC2H5, -C(O)OC(CH3)3, $-CH_2-COOC2H5$, $-CH_2-COOH$, -C(CH3)2-COOC2H5, -C(O)NH2, -C(O)NH(CH3), -C(O)N(CH3)2, $-C(O)NH-(CH_2)2-OH$, -C(O)-(N-morfolino), -SO2-NH-ciclopropilo, -SO2-(N-morfolino), 5-metil-oxadiazol-3-ilo, $-S-CF_3$, SF_5, donde dos de R^2, R^3 $(R^4)_n$, cuando se encuentran en posición *orto* entre sí, forman junto con los dos átomos de carbono a los cuales están unidos, $-O-CH_2-CH_2-CH_2-O-$, $-O-CH_2-CH_2-$, -(CH3)C=CH-(C=O)-O-, $-CH_2-(C=O)-O-$, $-(CH_2)2-(C=O)-NH-$,

n es 0, 1, 2, 3,

R^6 es hidrógeno, hidroxi, ciano, -O-ciclopropilo, -OCH3, -OCF3, -OCF2H, $-OCH_2CF3$, $-O-(CH_2)2-OH$, $-O(CH_2)2-N(CH3)2$, $-O-CH_2-SO2NH2$,



, donde * es el punto de unión, $-O-(CH_2)2$-tetrazolilo, $-O-CH_2$-tetrazolilo, -O-piridin-4-ilo, -O-(3-ciano-piridin-4-ilo), -C(O)NH2, o R^6 junto con R^7 es un anillo de 6 miembros incluyendo el átomo de nitrógeno del grupo amino unido a R^7 que puede contener otro heteroátomo seleccionado entre O, S o N y que además puede estar sustituido con un grupo carbonilo o $-CH_2-OH$,

R^7 es hidrógeno, metilo, difluorometilo, hidroxietilo,  , donde * es el punto de unión, $-(CH_2)2$-tetrazolilo, piridin-4-ilo, -C(O)-tetrahidropiran-4-ilo, $-C(O)-CH_2-O-CH3$, -C(O)-CH3, -

C(O)CH_2–O–(CH_2)2–O–CH3 o bencilo el cual está opcionalmente sustituido una o más veces con flúor, cloro, ciano, metilo, difluorometilo, metoxi, etoxi, difluormetoxi, trifluorometoxi, –O–CH_2–CF3, –C(O)OCH3,

R^8 es hidrógeno, flúor, ciano, CF3, C(O)NH2, C(O)OH, C(O)OC2H5, C(O)(CH_2)2–OH,

m es 0, 1 o 2

R^9 es hidrógeno, metilo, etilo, tert.-butilo, hidroxietilo,

R^{10}/R^{11} es en forma independiente en cada caso hidrógeno, metilo, hidroxietilo,

o un N-óxido, una sal, un tautómero o un estereoisómero de dichos compuestos, o una sal de dicho N-óxido, tautómero o estereoisómero.

Un aspecto adicional de la invención son compuestos de fórmula (I) de acuerdo con la reivindicación 1, donde

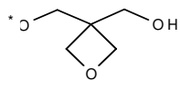
R^1 es hidrógeno,

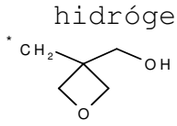
R^2/R^3 es en forma independiente flúor, cloro, bromo, ciano, CF_3, o –O–CH_2–CF_3,

R^4 es en forma independiente en cada caso hidrógeno, flúor, cloro, bromo o iodo, ciano, –CH_3, –C_3H_9, ciclopropilo, 1-propenilo, –CF_3, –CH_2–OH, –CH_2–CH_2–OH, –C(CH_3)$_2$–OH, –CH_2–C(CH_3)$_2$–OH, –C(CH_3)$_2$–CH_2–OH, –OCH_3, –OCF_3, –OCF_2H, –OCH_2CF_3, –C(O)CH_3, –COOH, –C(O)OCH_3, –C(O)OC_2H_5, –C(O)OC(CH_3)$_3$, –CH_2–$COOC_2H_5$, –CH_2–COOH, –C(CH_3)$_2$–$COOC_2H_5$, –C(O)NH_2, –C(O)NH(CH_3), –C(O)N(CH_3)$_2$, –C(O)NH–(CH_2)$_2$–OH, –C(O)–(N-morfolino), –SO_2–NH–ciclopropilo, –SO_2–(N-morfolino), 5-metil-oxa-diazol-3-ilo, donde dos de R^2, R^3 (R^4)$_n$, cuando se encuentran en posición *orto* entre sí,

forman junto con los dos átomos de carbono a los cuales están unidos, $-O-CH_2-CH_2-CH_2-O-$, $-O-CH_2-CH_2-$, $-(CH_3)C=CH-(C=O)-O-$, $-CH_2-(C=O)-O-$, $-(CH_2)_2-(C=O)-NH-$,

n 0, 1, 2, o 3,

R^6 es hidrógeno, hidroxi, $-OCH_3$, $-OCF_3$, $-OCF_2H$, $-OCH_2CF_3$, $-O-(CH_2)_2-OH$, $-O(CH_2)_2-N(CH_3)_2$, $-O-CH_2-SO_2NH_2$,  , donde * es el punto de unión,

R^7 es hidrógeno, metilo, difluorometilo, hidroxietilo,  , donde * es el punto de unión, $-C(O)$-tetrahidropiran-4-ilo, $-C(O)-CH_2-O-CH_3$, $-C(O)-CH_3$, $-C(O)CH_2-O-(CH_2)_2-O-CH_3$ o bencilo el cual está opcionalmente sustituido una o más veces con flúor, cloro, ciano, metilo, difluorometilo, metoxi, etoxi, difluormetoxi, trifluorometoxi, $-O-CH_2-CF_3$, $-C(O)OCH_3$,

R^8 es hidrógeno, flúor, ciano, $C(O)NH_2$,

m es 0, 1 o 2

R^9 es hidrógeno, metilo, etilo, tert.-butilo, hidroxietilo,

R^{10}/R^{11} es en forma independiente en cada caso hidrógeno, metilo, hidroxietilo,

o un N-óxido, una sal, un tautómero o un estereoisómero de dichos compuestos, o una sal de dicho N-óxido, tautómero o estereoisómero.

Un aspecto adicional de la invención son compuestos de fórmula (I) de acuerdo con la reivindicación 1, donde,

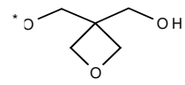
R^1 es hidrógeno, ,

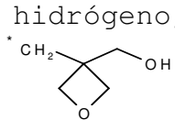
R^2/R^3 es en forma independiente hidrógeno, flúor, cloro, bromo, ciano, hidroxi, CF_3, $-O-CH_3$ o $-O-CH_2-CF_3$,

R^4 es en forma independiente en cada caso hidrógeno, flúor, cloro, bromo o iodo, ciano, NO_2, hidroxi, $-CH_3$, $-C_3H_7$, ciclopropilo, 1-propenilo, $-C\equiv CH$, $-CF_3$, $-CH_2-OH$, $-CH_2-CH_2-OH$, $-C(CH_3)_2-OH$, $-CH_2-C(CH_3)_2-OH$, $-C(CH_3)_2-CH_2-OH$, $-OCH_3$, $-O-CH_2-CH_3$, $-OCF_3$, $-OCF_2H$, $-OCH_2CF_3$, $-O-(CH_2)-O-C(O)-CH3$, $-C(O)CH_3$, $-COOH$, $-C(O)OCH_3$, $-C(O)OC_2H_5$, $-C(O)OC(CH_3)_3$, $-CH_2-COOH$, $-CH_2-COOC_2H_5$, $-C(CH_3)_2-COOC_2H_5$, $-C(O)NH_2$, $-C(O)NH(CH_3)$, $-C(O)N(CH_3)_2$, $-C(O)NH-(CH_2)_2-OH$, $-C(O)-$(N-morfolinilo), $-SO_2-NH-$ciclopropilo, $-SO_2-$(N-morfolinilo), NH_2, $NH-C(O)(CH_3)$, 5-metil-oxa-diazol-3-ilo, N-pirrolilo, N-pirazolilo, $-S-CF_3$, SF_5, donde dos de R^2, R^3 $(R^4)_n$, cuando se encuentran en posición *orto* entre sí, forman juntos $-O-CH_2-CH_2-CH_2-O-$, $-O-CH_2-CH_2-$, $-(CH_3)C=CH-(C=O)-O-$, $-CH_2-(C=O)-O-$, $-(CH_2)_2-(C=O)-NH-$, que junto con los dos átomos de carbono a los cuales están unidos forman un anillo de 5, 6 o 7 miembros,

n es 0, 1, 2, 3,

R^6 es hidrógeno, hidroxi, ciano, $-O-$ciclopropilo, $-OCH_3$, $-OCF_3$, $-OCF_2H$, $-OCH_2CF_3$, $-O-(CH_2)_2-OH$, $-O-(CH_2)_2-NH_2$, $-O(CH_2)_2-N(CH_3)_2$, $-O-(CH_2)_2-O-CH_3$, $-O-(CH_2)_2-O-(CH_2)_2-OH$, $-O-CH_2-CH(OH)-CH_2OH$, $-O-CH_2-CH(OH)-CH_2-NH-C(O)OC(CH_3)_3$, $-O-CH_2-COOH$, $-O-CH_2-COOC_2H_5$, $C(O)NH_2$, $-O-CH_2-C(O)-$(3-fluoro-N-azetidina), $-O-CH_2-C(O)-$(3,3-difluoro-N-azetidina), $-O-CH_2-CH(OH)-CH_2-$N-piperidinilo, $-O-(CH_2)_2$(morfolina-4-ilo), $-O-CH_2-$(morfolina-2-ilo), $-O-CH_2-$(morfolina-2-il-4-tert.-butoxicarboxilato), $-O-CH_2-$(pirrolidin-2-ona-5-ilo), $-O-(CH_2)_2-S-CH_3$, $-O-(CH_2)_2-SO-CH_3$, $-O-(CH_2)_2-SO_2-CH_2$, $-O-$

$CH_2-SO_2NH_2$, $-SO_2-CH(CH_3)_2$,  , donde * es el punto de unión, $-O-(CH_2)_2$-tetrazolilo, $-O-CH_2$-tetrazolilo, -O-piridin-4-ilo, -O-(3-ciano-piridin-4-ilo), o $-O-CH_2-$(oxadiazol)$-CH_2-O-CH_3$,

R^7 es hidrógeno, metilo, difluorometilo, hidroxietilo,  , donde * es el punto de unión, $-(CH_2)_2$-tetrazolilo, piridin-4-ilo, -C(O)-tetrahidropiran-4-ilo, $-C(O)-CH_2-O-CH_3$, $-C(O)-CH_3$, $-C(O)CH_2-O-(CH_2)_2-O-CH_3$, o bencilo el cual está opcionalmente sustituido una o más veces con flúor, cloro, bromo, ciano, metilo, difluorometilo, metoxi, etoxi, difluormetoxi, trifluorometoxi, $-O-CH_2-CF_3$, $-C(O)OCH_3$, u opcionalmente cuando R^6 se encuentra en la posición 5 del sistema cíclico pirimidina, R^6 y R^7 junto con el átomo de nitrógeno al cual R^7 está unido forman un anillo de 6 miembros que puede contener otro heteroátomo seleccionado entre O, S o N y que además está opcionalmente sustituido con $-CH_2-OH$ o $-CH_2-NH-CHO$

R^8 es hidrógeno, flúor, hidroxi, ciano, CH_3, CF_3, CH_2-OH, OCH_3, C(O)OH, $C(O)OCH_3$, $C(O)OC_2H_5$, $C(O)O(CH_2)_2-OH$, $C(O)NH_2$, $C(O)NHCH_3$,

m es 0, 1 o 2

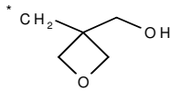
o un N-óxido, una sal, un tautómero o un estereoisómero de dichos compuestos, o una sal de dicho N-óxido, tautómero o estereoisómero.

Un aspecto adicional de la invención son compuestos de fórmula (I) de acuerdo con la reivindicación 1, donde

R^1 es hidrógeno o metilo,

R^2/R^3 es en forma independiente hidrógeno, flúor, cloro, metilo,

R^4 es hidrógeno, ciclopropilo, CH_2–OH, –$C(CH_3)_2$–OH, –O–CHF_2, –O–CH_2–CH_3, –CH=CH–CH_3,

R^6 es hidrógeno, OCH_3, $OCHF_2$, O–CH_2–CF_3, –O–$(CH_2)_2$–OH, –O–$(CH_2)_2$–NH_2, –O–CH_2–CH(OH)CH_2–OH,  , –O–$(CH_2)_2$–SO–CH_3, –O–$(CH_2)_2$–SO_2–CH_3, –O–CH_2–SO_2NH_2, –O–CH_2–(pirrolidin–2–on–5–ilo), –O–CH_2–CH(OH)–CH_2–(piperidin–4–ilo), –O–CH_2–(morfolin–2–ilo),

R^7 es hidrógeno

R^8 es hidrógeno, CH_2–OH, C(O)NH_2, C(O)$NHCH_3$,

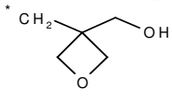
Un aspecto adicional de la invención son compuestos de fórmula (I) de acuerdo con la reivindicación 1, donde

R^1 es hidrógeno o metiloR^2 /R^3 es hidrógeno, flúor, cloro, hidroxi, metilo, metoxi, R^4 es ciano, hidroxi, nitro, metilo, tert.–butoxi, CF_3, metoxi, etoxi, propoxi, NH_2, NH–C(O)–CH_3, –O–$(CH_2)_2$–OC(O)CH_3, C(O)NH_2,

n es 1

R^6 es OCH_3, –O–CH_2–C(O)OH, –O–$(CH_2)_2$–S–CH_3, O–$(CH_2)_2$–SO–CH_3, –O–$(CH_2)_2$–SO_2–CH_2, –O–$(CH_2)_2$–NH_2, –O–$(CH_2)_2$–O–CH_3, –O–$(CH_2)_2$–O–$(CH_2)_2$–OH, ,–O–$(CH_2)_2$–O–$(CH_2)_2$–NH–C(O)$OC(CH_3)_3$, –O–CH_2–[morfolin–2–il–(4–C(O)$OC(CH_3)_3$)], –O–$(CHy)_2$–morfolin–4–ilo, –O–CH_2–(3–metoximetil–oxadiazol–5–ilo), –O–CH_2–C(O)OC_2H_2, –O–CH_2–C(O)–(3,3–difluoroazetidin), –O–CH_2–C(O)–(3–fluoroazetidin), –O–CH_2–(pirrolidin–2–on–5–ilo), –O–CH_2–CH(OH)–CH_2–(1–piperidin), SO_2–$CH(CH_2)_2$, C(O)OC_2H_5, R^7 es NH–C(O)$OC(CH_3)_3$, R^8 es flúor, ciano, hidroxi, metilo, ,C(O)NH_2,

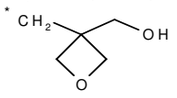
$C(O)OC_2H_5$, CH_2–OH, y m es 1, 2 o un N–óxido, una sal, un tautómero o un estereoisómero de dichos compuestos, o una sal de dicho N–óxido, tautómero o estereoisómero.

Aun otro aspecto de la invención consiste en compuestos de fórmula (I) de acuerdo con la reivindicación 1, donde R^1 es hidrógeno, R^2/R^3 es en forma independiente en cada caso hidrógeno, flúor, cloro, R^4 es –O–(1–4C–alquilo), (2–4C–alquil)–OH, 3–5C–cicloalquilo, 2–3C–alquenilo, R^6 es  , donde * es el punto de unión, –O–(2–3C–alquil)–NH_2, –O–(CH_2)heterociclilo (que está opcionalmente sustituido con oxo (=O) o $C(O)OR^9$), –O–(1–3C–alquilo), –O–(2–3C–alquil)–OH, –O–(2–3C–alquil)–SO–(2–3C–alquilo), –O–(2–3C–alquil)–SO_2–(2–3C–alquilo), –O–(2–3Calquil)–SO_2NH_2, –O–(CH_2)–CH(OH)–(CH_2)–heterociclilo, –O–(CH_2)–CH(OH)–(CH_2)–OH, –O–(CH_2)–$C(O)NR^{10}R^{11}$, R^7 es hidrógeno, R^8 es hidrógeno, $C(O)NR^{10}R^{11}$, R^9 es hidrógeno, 1–4C–alquilo que está opcionalmente sustituido con hidroxi,

R^{10}, R^{11} son en forma independiente entre sí hidrógeno, 1–4C–alquilo, 1–4C–hidroxialquilo, 1–4C–alcoxi, –C(O)–(1–4C–alquilo), o $COOR^9$ o junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de entre 4 y 6 miembros que opcionalmente contiene otro heteroátomo seleccionado entre el grupo que consiste en O, S o N, que está opcionalmente sustituido con 1–2 átomos de flúor o $COOR^9$,

o una sal de los mismos.

Un aspecto adicional de la invención son compuestos de fórmula (I) de acuerdo con la reivindicación 1, donde R^1 es

hidrógeno, R^2/R^3 es en forma independiente en cada caso hidrógeno, flúor, cloro, R^4 es $-O-CH_2-CH_3$, CH_2-OH, $C(CH_3)_3-OH$, ciclopropilo, propenilo, $-O-C(CH_3)_3$, R^6 es  , donde * es el punto de unión, $-O(CH_2)_2-NH_2$, $-O-(CH_2)$heterociclilo (que está opcionalmente sustituido con oxo (=O)), $-O-CH_3$, $-O-(CH_2)_2-OH$, $-O-(CH_2)_2-SO-CH_3$, $-O-(CH_2)_2-SO_2-CH_3$, $-O-(CH_2)_2-SO_2NH_2$, $-O-(CH_2)-CH(OH)-(CH_2)-$heterociclilo, $-O-(CH_2)-CH(OH)-(CH_2)-OH$, $-O-(CH_2)-C(O)NR^{10}R^{11}$, R^7 es hidrógeno, R^8 es hidrógeno, $C(O)NR^{10}R^{11}$,

R^9 es hidrógeno, 1-4C-alquilo que está opcionalmente sustituido con hidroxi,

R^{10}, R^{11} son en forma independiente entre sí hidrógeno, 1-4C-alquilo, 1-4C-hidroxialquilo, 1-4C-alcoxi, -C(O)-(1-4C-alquilo), o $COOR^9$ o junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de entre 4 y 6 miembros que opcionalmente contiene otro heteroátomo seleccionado entre el grupo que consiste en O, S o N, que está opcionalmente sustituido con 1-2 átomos de flúor o $COOR^9$, o una sal de los mismos.

En un aspecto de la invención, los compuestos de fórmula (I) como se describen precedentemente se seleccionan entre el grupo que consiste en:

2-[1-(6-cloro-2-fluoro-3-metilbencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(6-cloro-2-fluoro-3-metoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

5-metoxi-2-{1-[3-(5-metil-1,2,4-oxadiazol-3-il)bencil]-1H-indazol-3-il}-N-(piridin-4-

il)pirimidin-4-amina,

2-[1-(2-cloro-4,5-dimetilbencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

5-metoxi-2-{1-[4-(pentafluoro-λ^6-sulfanil)bencil]-1H-indazol-3-il}-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2,6-difluoro-3-metoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

N-(2,6-difluoro-3-metoxibencil)-2-[1-(2,6-difluoro-3-metoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-{1-[(6-bromo-1,3-benzodioxol-5-il)metil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

N-(4-etoxi-2,6-difluorobencil)-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzonitrilo,

2-[1-(2-cloro-4-metoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(3,4-dihidro-2H-1,5-benzodioxepin-6-ilmetil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2,6-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

N-(2,6-difluorobencil)-2-[1-(2,6-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-

amina,
5-metoxi-N-(piridin-4-il)-2-(1-{3-[(trifluorometil)sulfanil]bencil}-1H-indazol-3-il)pirimidin-4-amina,
2-[1-(2,3-difluoro-4-metilbencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
N-(2,3-difluoro-4-metilbencil)-2-[1-(2,3-difluoro-4-metilbencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
5-metoxi-2-{1-[4-(1H-pirazol-1-il)bencil]-1H-indazol-3-il}-N-(piridin-4-il)pirimidin-4-amina,
2-[1-(2,6-diclorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
N-(2,6-diclorobencil)-2-[1-(2,6-diclorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
5-metoxi-N-(piridin-4-il)-2-(1-{4-[(trifluorometil)sulfanil]bencil}-1H-indazol-3-il)pirimidin-4-amina,
2-[1-(2-clorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
N-(2-clorobencil)-2-[1-(2-clorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzoato de metilo,
3-cloro-4-{[(2-{1-[2-cloro-4-(metoxicarbonil)bencil]-1H-indazol-3-il}-5-metoxipirimidin-4-il)(piridin-4-

il)amino]metil}benzoato de metilo,
2-[1-(4-bromo-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
2-[1-(2-cloro-4-fluoro-3-metoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
2-[1-(4-etoxi-2,3-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
N-(4-etoxi-2,3-difluorobencil)-2-[1-(4-etoxi-2,3-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
5-metoxi-N-(piridin-4-il)-2-{1-[2,3,5,6-tetrafluoro-4-(2,2,2-trifluoroetoxi)bencil]-1H-indazol-3-il}pirimidin-4-amina,
5-metoxi-N-(piridin-4-il)-N-[2,3,5,6-tetrafluoro-4-(2,2,2-trifluoroetoxi)bencil]-2-{1-[2,3,5,6-tetrafluoro-4-(2,2,2-trifluoroetoxi)bencil]-1H-indazol-3-il}pirimidin-4-amina,
2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzoato de metilo,
5-metoxi-N-(piridin-4-il)-2-[1-(2,4,6-trifluorobencil)-1H-indazol-3-il]pirimidin-4-amina,
5-metoxi-N-(piridin-4-il)-N-(2,4,6-trifluorobencil)-2-[1-(2,4,6-trifluorobencil)-1H-indazol-3-il]pirimidin-4-amina,
2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
2-[1-(2,4-diclorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2-fluoro-4-iodobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2-bromobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

N-(2-bromobencil)-2-[1-(2-bromobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

ácido [3-fluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]acético,

5-metoxi-N-(piridin-4-il)-2-[1-(2,3,5,6-tetrafluoro-4-metoxibencil)-1H-indazol-3-il]pirimidin-4-amina

5-metoxi-2-[1-(4-propilbencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

2-{1-[2,6-dicloro-4-(trifluorometoxi)bencil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

N-[2,6-dicloro-4-(trifluorometoxi)bencil]-2-{1-[2,6-dicloro-4-(trifluorometoxi)bencil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

7-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)-3,4-dihidroquinolin-2(1H)-ona,

2-[1-(2-cloro-4-iodobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(3,5-dimetoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-{1-[2-cloro-6-(trifluorometil)bencil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2-cloro-5-fluorobencil)-1H-indazol-3-il]-5-

metoxi-N-(piridin-4-il)pirimidin-4-amina,
7-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)-4-metil-2H-cromen-2-ona,
3-fluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzonitrilo,
4-{[{2-[1-(4-ciano-2-fluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}(piridin-4-il)amino]metil}-3-fluorobenzonitrilo,
2-{1-[2,6-dicloro-3-(trifluorometil)bencil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
acetato de [3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]etilo,
2-[1-(4-fluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
N-ciclopropil-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)bencensulfonamida,
6-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)-1-benzofuran-2(3H)-ona,
2-{1-[4-(difluorometoxi)-2,6-difluorobencil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzoato de tert-butilo,
2-[3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-

il]-1H-indazol-1-il}metil)fenil]-2-metilpropanoato de etilo,

4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzonitrilo,

5-metoxi-2-{1-[4-(morfolin-4-ilsulfonil)bencil]-1H-indazol-3-il}-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2,6-dicloro-3-nitrobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzonitrilo,

N-[4-(difluorometoxi)-2,6-difluorobencil]-2-{1-[4-(difluorometoxi)-2,6-difluorobencil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

5-metoxi-N-(piridin-4-il)-2-{1-[3-(1H-pirrol-1-il)bencil]-1H-indazol-3-il}pirimidin-4-amina,

3,5-difluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzonitrilo,

5-metoxi-2-{1-[2-metoxi-4-(trifluorometil)bencil]-1H-indazol-3-il}-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2,6-difluoro-3-metilbencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2-fluoro-6-metoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

3,5-difluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzamida,

acetato de 2-[3,5-difluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-

il}metil)fenoxi]etilo,

2-[1-(2,6-difluoro-4-propoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(4-etoxi-2-fluoro-6-metoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ol,

2-[1-(4-metoxibencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ol,

2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ol,

2-[1-(4-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ol,

{3-[({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metil]oxetan-3-il}metanol,

{3-[({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metil]oxetan-3-il}metanol,

(3-{[(2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-{[3-(hidroximetil)oxetan-3-il]metoxi}pirimidin-4-il)(piridin-4-il)amino]metil}oxetan-3-il)metanol,

1-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metansulfonamida,

5-[2-(dimetilamino)etoxi]-2-[1-(2-fluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2-fluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)-5-[2-(1H-tetrazol-5-il)etoxi]pirimidin-4-amina,

2-[1-(2-fluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)-5-[2-(1H-tetrazol-5-il)etoxi]-N-[2-(1H-tetrazol-5-il)etil]pirimidin-4-amina,

5-[2-(dimetilamino)etoxi]-2-[1-(4-fluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2-fluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)-5-(1H-tetrazol-5-ilmetoxi)pirimidin-4-amina,

5-[2-(dimetilamino)etoxi]-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina

1-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)-3-(piperidin-1-il)propan-2-ol,

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-(2-metoxietoxi)-N-(piridin-4-il)pirimidin-4-amina,

2-[({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metil]morfolina-4-carboxilato de tert-butilo,

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-[2-(morfolin-4-il)etoxi]-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-{[3-(metoximetil)-1,2,4-oxadiazol-5-il]metoxi}-N-(piridin-4-il)pirimidin-4-amina,

({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)acetato de etilo,

1-(3,3-difluoroazetidin-1-il)-2-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-

ilamino)pirimidin-5-il}oxi)etanona,
2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-[2-(metilsulfanil)etoxi]-N-(piridin-4-il)pirimidin-4-amina,
2-[2-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)etoxi]etanol,
ácido fórmico - (5S)-5-[({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metil]pirrolidin-2-ona (1:1),
(5R)-5-[({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metil]pirrolidin-2-ona,
{2-[2-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)etoxi]etil}carbamato de tert-butilo,
2-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)-1-(3-fluoroazetidin-1-il)etanona,
(5S)-5-[({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metil]pirrolidin-2-ona,
[2-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)etil]carbamato de tert-butilo,
N-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-8-(piridin-4-il)-7,8-dihidro-6H-pirimido[5,4-b][1,4]oxazin-7-il}metil)formamida,

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(4-metoxibencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2-fluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(4-ciclopropil-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-(1-{2,6-difluoro-4-[(1E)-prop-1-en-1-il]bencil}-1H-indazol-3-il)-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

1-[3,5-difluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]etanona,

[2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]metanol,

2-[3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]etanol,

2-[3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]-2-metilpropan-1-ol,

[4-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-il]metanol,

2-[3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]propan-2-ol,

1-[3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]-2-metilpropan-2-ol,

2-[2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]propan-2-ol

5-(difluorometoxi)-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

5-(difluorometoxi)-N-(difluorometil)-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

4-[(difluorometil)(piridin-4-il)amino]-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]pirimidin-5-ol,

2-[1-(4-metoxibencil)-1H-indazol-3-il]-N-(piridin-4-il)-5-(2,2,2-trifluoroetoxi)pirimidin-4-amina,

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)-5-(2,2,2-trifluoroetoxi)pirimidin-4-amina,

3-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)propan-1,2-diol,

(2S)-3-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)propan-1,2-diol,

(2R)-3-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)propan-1,2-diol,

2-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)etanol,

2-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-

(piridin-4-ilamino)pirimidin-5-il}oxi)etanol,
4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-(2-hidroxietoxi)pirimidin-4-il}amino)piridin-3-carboxilato de etilo,
4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-(2-hidroxietoxi)pirimidin-4-il}amino)-N-metilpiridin-3-carboxamida,
4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-(2-hidroxietoxi)pirimidin-4-il}amino)piridin-3-carboxamida,
4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-(2-hidroxietoxi)pirimidin-4-il}amino)piridin-3-carboxilato de 2-hidroxietilo,
5-(ciclopropiloxi)-2-[1-(4-metoxibencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,
clorhidrato de 2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina (1:1),
clorhidrato de (2S)-3-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)propan-1,2-diol (1:1),
clorhidrato de 2-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)etanol (1:1),
clorhidrato de 2-[1-(2,6-diclorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina (1:1),
clorhidrato de [2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-

il}metil)fenil]metanol (1:1),

clorhidrato de (2R)-3-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)propan-1,2-diol (1:1),

N-{2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]pirimidin-4-il}-N-(piridin-4-il)acetamida,

N-{2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]pirimidin-4-il}-2-metoxi-N-(piridin-4-il)acetamida,

N-{2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]pirimidin-4-il}-N-(piridin-4-il)tetrahidro-2H-piran-4-carboxamida,

N-{2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]pirimidin-4-il}-2-(2-metoxietoxi)-N-(piridin-4-il)acetamida,

2-[{2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]pirimidin-4-il}(piridin-4-il)amino]etanol,

(3-{[{2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]pirimidin-4-il}(piridin-4-il)amino]metil}oxetan-3-il)metanol,

2-{1-[4-bromo-2-fluoro-6-(2,2,2-trifluoroetoxi)bencil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-{1-[4-bromo-2,6-bis(2,2,2-trifluoroetoxi)bencil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

ácido 2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzoico,

ácido ({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)acético,

2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)-N-metilbenzamida,

2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzamida,

2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)-N,N-dimetilbenzamida,

2,4-dicloro-N-(2-hidroxietil)-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzamida,

[2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil](morfolin-4-il)metanona,

3,5-difluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)-N-metilbenzamida,

2-[1-(4-etinil-2-fluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

{2-[1-(2-fluorobencil)-1H-indazol-3-il]-8-(piridin-4-il)-7,8-dihidro-6H-pirimido[5,4-b][1,4]oxazin-7-il}metanol,

2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-metoxi-N-metil-N-(piridin-4-il)pirimidin-4-amina,

4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-

metoxipirimidin-4-il}amino)piridin-3-carbonitrilo,
2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-metoxi-N,N-di(piridin-4-il)pirimidin-4-amina,
4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-carboxilato de metilo,
2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
4-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-carbonitrilo,
2-[(3-{4-[(2,6-dimetilpiridin-4-il)amino]-5-metoxipirimidin-2-il}-1H-indazol-1-il)metil]-5-etoxi-3-fluorofenol,
4-({5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]pirimidin-4-il}amino)piridin-2(1H)-ona,
4-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-2(1H)-ona,
4-({5-metoxi-2-[1-(4-propilbencil)-1H-indazol-3-il]pirimidin-4-il}amino)nicotinonitrilo,
4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-carboxamida,
4-({5-metoxi-2-[1-(4-propilbencil)-1H-indazol-3-il]pirimidin-4-il}amino)piridin-3-carboxamida,
4-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-carboxamida,
4-({2-[1-(2,6-difluoro-4-hidroxibencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-

carboxamida,
4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-hidroxipirimidin-4-il}amino)piridin-3-carbonitrilo,
4-({4-[(3-cianopiridin-4-il)amino]-2-[1-(2-fluorobencil)-1H-indazol-3-il]pirimidin-5-il}oxi)piridin-3-carbonitrilo,
5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]-N-[3-(trifluorometil)piridin-4-il]pirimidin-4-amina,
ácido 3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzoico,
ácido fórmico – 3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)-N-metilbenzamida (1:1),
3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)-N-metilbenzamida,
4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-hidroxipirimidin-4-il}amino)piridin-3-carboxamida,
ácido 4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-hidroxipirimidin-4-il}amino)piridin-3-carboxílico,
4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-hidroxipirimidin-4-il}amino)piridin-3-carboxilato de etilo,
2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-carbonitrilo,
2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-carboxamida,
clorhidrato de ácido 4-({2-[1-(2-fluorobencil)-1H-

indazol-3-il]-5-(2-hidroxietoxi)pirimidin-4-il}amino)piridin-3-carboxílico (1:1),
N-(2-fluoropiridin-4-il)-5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]pirimidin-4-amina,
N-(2,6-difluoropiridin-4-il)-5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]pirimidin-4-amina,
N-(3-fluoropiridin-4-il)-5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]pirimidin-4-amina,
5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]-N-(2-metilpiridin-4-il)pirimidin-4-amina,
N-(difluorometil)-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,
2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-[2-(metilsulfinil)etoxi]-N-(piridin-4-il)pirimidin-4-amina,
2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-[2-(metilsulfinil)etoxi]-N-(piridin-4-il)pirimidin-4-amina (Enantiómero 1),
2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-[2-(metilsulfinil)etoxi]-N-(piridin-4-il)pirimidin-4-amina (Enantiómero 2),
2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-[2-(metilsulfonil)etoxi]-N-(piridin-4-il)pirimidin-4-amina,
5-(2-aminoetoxi)-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,
2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-(morfolin-2-ilmetoxi)-N-(piridin-4-il)pirimidin-4-amina,

4-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-carboxilato de etilo,
N-(3,5-difluoropiridin-4-il)-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-amina,
2-[1-(3-amino-2,6-diclorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
N-[2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]acetamida,
2-[1-(4-etoxi-2,6-difluorobencil)-4-metil-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

o un N-óxido, una sal, un tautómero o un estereoisómero de dichos compuestos, o una sal de dicho N-óxido, tautómero o estereoisómero.

Un aspecto de la invención son todos los compuestos mencionados en la siguiente lista.
2-[1-(2,6-dicloro-3-nitrobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzonitrilo,
3,5-difluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzonitrilo,
5-metoxi-2-{1-[2-metoxi-4-(trifluorometil)bencil]-1H-indazol-3-il}-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2,6-difluoro-3-metilbencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2-fluoro-6-metoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

3,5-difluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzamida,

acetato de 2-[3,5-difluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenoxi]etilo,

2-[1-(2,6-difluoro-4-propoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(4-etoxi-2-fluoro-6-metoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

1-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)-3-(piperidin-1-il)propan-2-ol,

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-(2-metoxietoxi)-N-(piridin-4-il)pirimidin-4-amina,

2-[({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metil]morfolina-4-carboxilato de tert-butilo,

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-[2-(morfolin-4-il)etoxi]-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-{[3-(metoximetil)-1,2,4-oxadiazol-5-il]metoxi}-N-(piridin-4-il)pirimidin-4-amina,

({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-

il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)acetato de etilo,

1-(3,3-difluoroazetidin-1-il)-2-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)etanona,

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-[2-(metilsulfanil)etoxi]-N-(piridin-4-il)pirimidin-4-amina,

2-[2-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)etoxi]etanol,

ácido fórmico - (5S)-5-[({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metil]pirrolidin-2-ona (1:1),

(5R)-5-[({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metil]pirrolidin-2-ona,

{2-[2-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)etoxi]etil}carbamato de tert-butilo,

2-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)-1-(3-fluoroazetidin-1-il)etanona,

(5S)-5-[({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metil]pirrolidin-2-ona,

N-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-8-(piridin-4-il)-7,8-dihidro-6H-pirimido[5,4-

b][1,4]oxazin-7-il}metil)formamida,
[4-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-il]metanol,
ácido ({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)acético,
2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
4-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-carbonitrilo,
2-[(3-{4-[(2,6-dimetilpiridin-4-il)amino]-5-metoxipirimidin-2-il}-1H-indazol-1-il)metil]-5-etoxi-3-fluorofenol,
4-({5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]pirimidin-4-il}amino)piridin-2(1H)-ona,
4-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-2(1H)-ona,
4-({5-metoxi-2-[1-(4-propilbencil)-1H-indazol-3-il]pirimidin-4-il}amino)nicotinonitrilo,
4-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-carboxamida,
4-({2-[1-(2,6-difluoro-4-hidroxibencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-carboxamida,
5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]-N-(2-metilpiridin-4-il)pirimidin-4-amina,

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-[2-(metilsulfinil)etoxi]-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-[2-(metilsulfinil)etoxi]-N-(piridin-4-il)pirimidin-4-amina (Enantiómero 1),

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-[2-(metilsulfinil)etoxi]-N-(piridin-4-il)pirimidin-4-amina (Enantiómero 2),

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-[2-(metilsulfonil)etoxi]-N-(piridin-4-il)pirimidin-4-amina,

5-(2-aminoetoxi)-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-(morfolin-2-ilmetoxi)-N-(piridin-4-il)pirimidin-4-amina,

4-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-carboxilato de etilo,

N-(3,5-difluoropiridin-4-il)-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-amina,

2-[1-(3-amino-2,6-diclorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

N-[2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]acetamida,

2-[1-(4-etoxi-2,6-difluorobencil)-4-metil-1H-

indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina

o un N-óxido, una sal, un tautómero o un estereoisómero de dichos compuestos, o una sal de dicho N-óxido, tautómero o estereoisómero.

En un aspecto de la invención, los compuestos de fórmula (I) como se describen precedentemente se seleccionan entre el grupo que consiste en:
2-[1-(6-cloro-2-fluoro-3-metilbencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
2-[1-(6-cloro-2-fluoro-3-metoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
5-metoxi-2-{1-[3-(5-metil-1,2,4-oxadiazol-3-il)bencil]-1H-indazol-3-il}-N-(piridin-4-il)pirimidin-4-amina,
2-[1-(2-cloro-4,5-dimetilbencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
5-metoxi-2-{1-[4-(pentafluoro-lambda⁶-sulfanil)bencil]-1H-indazol-3-il}-N-(piridin-4-il)pirimidin-4-amina,
2-[1-(2,6-difluoro-3-metoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
N-(2,6-difluoro-3-metoxibencil)-2-[1-(2,6-difluoro-3-metoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
2-{1-[(6-bromo-1,3-benzodioxol-5-il)metil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-

5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
N-(4-etoxi-2,6-difluorobencil)-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
2-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzonitrilo,
2-[1-(2-cloro-4-metoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
2-[1-(3,4-dihidro-2H-1,5-benzodioxepin-6-ilmetil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
2-[1-(2,6-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
N-(2,6-difluorobencil)-2-[1-(2,6-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
5-metoxi-N-(piridin-4-il)-2-(1-{3-[(trifluorometil)sulfanil]bencil}-1H-indazol-3-il)pirimidin-4-amina,
2-[1-(2,3-difluoro-4-metilbencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
N-(2,3-difluoro-4-metilbencil)-2-[1-(2,3-difluoro-4-metilbencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
5-metoxi-2-{1-[4-(1H-pirazol-1-il)bencil]-1H-indazol-3-il}-N-(piridin-4-il)pirimidin-4-amina,
2-[1-(2,6-diclorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
N-(2,6-diclorobencil)-2-[1-(2,6-diclorobencil)-1H-

indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
5-metoxi-N-(piridin-4-il)-2-(1-{4-[(trifluorometil)sulfanil]bencil}-1H-indazol-3-il)pirimidin-4-amina,
2-[1-(2-clorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
N-(2-clorobencil)-2-[1-(2-clorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzoato de metilo,
3-cloro-4-{[(2-{1-[2-cloro-4-(metoxicarbonil)bencil]-1H-indazol-3-il}-5-metoxipirimidin-4-il)(piridin-4-il)amino]metil}benzoato de metilo,
2-[1-(4-bromo-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
2-[1-(2-cloro-4-fluoro-3-metoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
2-[1-(4-etoxi-2,3-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
N-(4-etoxi-2,3-difluorobencil)-2-[1-(4-etoxi-2,3-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
5-metoxi-N-(piridin-4-il)-2-{1-[2,3,5,6-tetrafluoro-4-(2,2,2-trifluoroetoxi)bencil]-1H-indazol-3-il}pirimidin-4-amina,
5-metoxi-N-(piridin-4-il)-N-[2,3,5,6-tetrafluoro-4-

(2,2,2-trifluoroetoxi)bencil]-2-{1-[2,3,5,6-tetrafluoro-4-(2,2,2-trifluoroetoxi)bencil]-1H-indazol-3-il}pirimidin-4-amina,

2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzoato de metilo,

5-metoxi-N-(piridin-4-il)-2-[1-(2,4,6-trifluorobencil)-1H-indazol-3-il]pirimidin-4-amina,

5-metoxi-N-(piridin-4-il)-N-(2,4,6-trifluorobencil)-2-[1-(2,4,6-trifluorobencil)-1H-indazol-3-il]pirimidin-4-amina,

2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2,4-diclorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2-fluoro-4-iodobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2-bromobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

N-(2-bromobencil)-2-[1-(2-bromobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

ácido [3-fluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]acético,

5-metoxi-N-(piridin-4-il)-2-[1-(2,3,5,6-tetrafluoro-4-metoxibencil)-1H-indazol-3-il]pirimidin-4-amina,

5-metoxi-2-[1-(4-propilbencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

2-{1-[2,6-dicloro-4-(trifluorometoxi)bencil]-1H-

indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

N-[2,6-dicloro-4-(trifluorometoxi)bencil]-2-{1-[2,6-dicloro-4-(trifluorometoxi)bencil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina

7-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)-3,4-dihidroquinolin-2(1H)-ona,

2-[1-(2-cloro-4-iodobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(3,5-dimetoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-{1-[2-cloro-6-(trifluorometil)bencil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2-cloro-5-fluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

7-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)-4-metil-2H-cromen-2-ona,

3-fluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzonitrilo,

4-{[{2-[1-(4-ciano-2-fluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}(piridin-4-il)amino]metil}-3-fluorobenzonitrilo,

2-{1-[2,6-dicloro-3-(trifluorometil)bencil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

[3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]acetato de etilo,

2-[1-(4-fluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

N-ciclopropil-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)bencensulfonamida,

6-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)-1-benzofuran-2(3H)-ona,

2-{1-[4-(difluorometoxi)-2,6-difluorobencil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzoato de tert-butilo,

2-[3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]-2-metilpropanoato de etilo,

4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzonitrilo

5-metoxi-2-{1-[4-(morfolin-4-ilsulfonil)bencil]-1H-indazol-3-il}-N-(piridin-4-il)pirimidin-4-amina

N-[4-(difluorometoxi)-2,6-difluorobencil]-2-{1-[4-(difluorometoxi)-2,6-difluorobencil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

5-metoxi-N-(piridin-4-il)-2-{1-[3-(1H-pirrol-1-il)bencil]-1H-indazol-3-il}pirimidin-4-amina,

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ol,

2-[1-(4-metoxibencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ol,

2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ol,

2-[1-(4-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ol,

{3-[({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metil]oxetan-3-il}metanol,

{3-[({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metil]oxetan-3-il}metanol,

(3-{[(2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-{[3-(hidroximetil)oxetan-3-il]metoxi}pirimidin-4-il)(piridin-4-il)amino]metil}oxetan-3-il)metanol,

1-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metansulfonamida,

5-[2-(dimetilamino)etoxi]-2-[1-(2-fluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2-fluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)-5-[2-(1H-tetrazol-5-il)etoxi]pirimidin-4-amina,

2-[1-(2-fluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)-5-[2-(1H-tetrazol-5-il)etoxi]-N-[2-(1H-tetrazol-5-il)etil]pirimidin-4-amina,

5-[2-(dimetilamino)etoxi]-2-[1-(4-fluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2-fluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)-5-(1H-tetrazol-5-ilmetoxi)pirimidin-4-amina,

5-[2-(dimetilamino)etoxi]-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-N-(piridin-4-

il)pirimidin-4-amina,

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(4-metoxibencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2-fluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(4-ciclopropil-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-(1-{2,6-difluoro-4-[(1E)-prop-1-en-1-il]bencil}-1H-indazol-3-il)-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

1-[3,5-difluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]etanona,

[2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]metanol,

2-[3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]etanol,

2-[3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]-2-metilpropan-1-ol,

2-[3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]propan-2-ol,

1-[3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]-2-metilpropan-2-ol,

2-[2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-

il}metil)fenil]propan-2-ol,
5-(difluorometoxi)-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,
5-(difluorometoxi)-N-(difluorometil)-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,
4-[(difluorometil)(piridin-4-il)amino]-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]pirimidin-5-ol,
2-[1-(4-metoxibencil)-1H-indazol-3-il]-N-(piridin-4-il)-5-(2,2,2-trifluoroetoxi)pirimidin-4-amina,
2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)-5-(2,2,2-trifluoroetoxi)pirimidin-4-amina,
3-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)propan-1,2-diol,
(2S)-3-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)propan-1,2-diol,
(2R)-3-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)propan-1,2-diol,
2-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)etanol,
2-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)etanol,
4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-(2-

hidroxietoxi)pirimidin-4-il}amino)piridin-3-carboxilato de etilo,

4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-(2-hidroxietoxi)pirimidin-4-il}amino)-N-metilpiridin-3-carboxamida,

4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-(2-hidroxietoxi)pirimidin-4-il}amino)piridin-3-carboxamida,

4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-(2-hidroxietoxi)pirimidin-4-il}amino)piridin-3-carboxilato de 2-hidroxietilo,

5-(ciclopropiloxi)-2-[1-(4-metoxibencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

clorhidrato de 2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina (1:1),

clorhidrato de (2S)-3-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)propan-1,2-diol (1:1),

clorhidrato de 2-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)etanol (1:1),

clorhidrato de 2-[1-(2,6-diclorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina (1:1),

clorhidrato de [2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]metanol (1:1),

clorhidrato de (2R)-3-({2-[1-(2-fluorobencil)-1H-

indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)propan-1,2-diol (1:1),

N-{2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]pirimidin-4-il}-N-(piridin-4-il)acetamida,

N-{2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]pirimidin-4-il}-2-metoxi-N-(piridin-4-il)acetamida,

N-{2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]pirimidin-4-il}-N-(piridin-4-il)tetrahidro-2H-piran-4-carboxamida,

N-{2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]pirimidin-4-il}-2-(2-metoxietoxi)-N-(piridin-4-il)acetamida,

2-[{2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]pirimidin-4-il}(piridin-4-il)amino]etanol,

(3-{[{2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]pirimidin-4-il}(piridin-4-il)amino]metil}oxetan-3-il)metanol,

2-{1-[4-bromo-2-fluoro-6-(2,2,2-trifluoroetoxi)bencil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-{1-[4-bromo-2,6-bis(2,2,2-trifluoroetoxi)bencil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

ácido 2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzoico,

2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)-N-

metilbenzamida,
2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzamida,
2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)-N,N-dimetilbenzamida,
2,4-dicloro-N-(2-hidroxietil)-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzamida,
[2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil](morfolin-4-il)metanona,
3,5-difluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)-N-metilbenzamida,
2-[1-(4-etinil-2-fluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
{2-[1-(2-fluorobencil)-1H-indazol-3-il]-8-(piridin-4-il)-7,8-dihidro-6H-pirimido[5,4-b][1,4]oxazin-7-il}metanol,
2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-metoxi-N-metil-N-(piridin-4-il)pirimidin-4-amina,
4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-carbonitrilo,
2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-metoxi-N,N-di(piridin-4-il)pirimidin-4-amina,
4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-carboxilato de

metilo,
4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-carboxamida,
4-({5-metoxi-2-[1-(4-propilbencil)-1H-indazol-3-il]pirimidin-4-il}amino)piridin-3-carboxamida,
4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-hidroxipirimidin-4-il}amino)piridin-3-carbonitrilo,
4-({4-[(3-cianopiridin-4-il)amino]-2-[1-(2-fluorobencil)-1H-indazol-3-il]pirimidin-5-il}oxi)piridin-3-carbonitrilo,
5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]-N-[3-(trifluorometil)piridin-4-il]pirimidin-4-amina,
ácido 3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzoico,
ácido fórmico - 3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)-N-metilbenzamida (1:1),
3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)-N-metilbenzamida,
4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-hidroxipirimidin-4-il}amino)piridin-3-carboxamida,
ácido 4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-hidroxipirimidin-4-il}amino)piridin-3-carboxílico,
4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-hidroxipirimidin-4-il}amino)piridin-3-carboxilato de etilo,
2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-

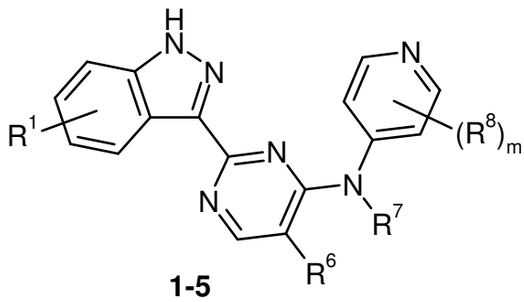
ilamino)pirimidin-5-carbonitrilo,
2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-carboxamida,
clorhidrato de ácido 4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-(2-hidroxietoxi)pirimidin-4-il}amino)piridin-3-carboxílico (1:1),
N-(2-fluoropiridin-4-il)-5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]pirimidin-4-amina,
N-(2,6-difluoropiridin-4-il)-5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]pirimidin-4-amina,
N-(3-fluoropiridin-4-il)-5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]pirimidin-4-amina,
N-(difluorometil)-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina

o un N-óxido, una sal, un tautómero o un estereoisómero de dichos compuestos, o una sal de dicho N-óxido, tautómero o estereoisómero.

Un aspecto de la invención consiste en compuestos de fórmula (I) como se describen en los ejemplos caracterizados por sus nombres en el título de acuerdo con la reivindicación 5 y sus estructuras así como también las subcombinaciones de todos los residuos específicamente descritas en los compuestos de los ejemplos.

Otro aspecto de la presente invención son los intermediarios que se utilizan para su síntesis.

Un aspecto especial de la invención es el intermediario (1-5),



1-5

donde R^1, R^6, R^7 R^8 y m tienen los significados de acuerdo con la reivindicación 1.

Si las formas de realización de la invención como se revelan en la presente hacen referencia a compuestos de fórmula (I), debe comprenderse que aquellas formas de realización hacen referencia a los compuestos de fórmula (I) como se revelan en las reivindicaciones y los ejemplos.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^1 es hidrógeno, halógeno, 1-3C-alquilo,

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^1 es halógeno.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^1 es 1-3C-alquilo.

Un aspecto adicional de la invención son compuestos de fórmula (I), donde R^1 es hidrógeno, 1-3C-alquilo.

Aun otro aspecto de la invención consiste en compuestos de fórmula (I) de acuerdo con las reivindicaciones 1, 2, 3, 4, 5 o 6, donde R^1 es hidrógeno.

Un aspecto adicional de la invención son compuestos de fórmula (I), donde R^2/R^3 son en forma independiente entre sí hidrógeno, halógeno, ciano, hidroxi, 1-6C-haloalquilo, 1-6C-haloalcoxi, 1-6C-alcoxi,

Un aspecto adicional de la invención son compuestos de fórmula (I) de acuerdo con la reivindicación 1, donde R^2

y/o R^3 son en forma independiente entre sí hidrógeno, halógeno, ciano, 1-6C-haloalquilo, 1-6C-haloalcoxi.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^2 y/o R^3 es halógeno, especialmente flúor, cloro o bromo, preferentemente flúor o cloro.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^2 y/o R^3 es 1-3C-haloalquilo, especialmente CF_3.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^2 y/o R^3 es 1-3C-haloalcoxi, especialmente $-O-CH_2-CF_3$.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^2 y/o R^3 es flúor, cloro, bromo, CF_3, o $-O-CH_2-CF_3$.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^2 y/o R^3 es flúor, cloro, bromo, hidroxi, metoxi, CF_3, o $-O-CH_2-CF_3$.

Aun otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^2 y R^3 son halógeno o 1-3C-haloalcoxi, especialmente flúor, cloro, o $-O-CH_2-CF_3$.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^2 y/o R^3 son hidroxi, (1-6C-alcoxi).

Un aspecto adicional de la invención son compuestos de fórmula (I), donde R^2 y R^3 son diferentes.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde una posición de R^2 y R^3 es hidrógeno y la otra es halógeno, 1-3C-haloalquilo, 1-3C-haloalcoxi o especialmente flúor, cloro, bromo, CF_3, o $-O-CH_2-CF3$.

Otro aspecto de la invención consiste en compuestos de

fórmula (I), donde

R^4 es en forma independiente hidrógeno, hidroxi, halógeno, ciano, NO_2, 1-6C-alquilo, 2-6C-alquenilo, 2-6C-alquinilo, 1-6C-haloalquilo, 1-6C-hidroxialquilo, 1-6C-alcoxi, -O-(2-6Calquilen)-O-C(O)-(1-6C-alquilo), 1-6C-haloalcoxi, $-C(O)OR^9$, -(1-6C-alquilen)-$C(O)OR^9$, -C(O)-(1-6C-alquilo), $-C(O)NR^{10}R^{11}$, 3-7C-cicloalquilo, -S-(1-6C-haloalquilo), SF_5, $-SO_2NH$-(3-7C-cicloalquilo), $-SO_2NR^{10}R^{11}$, $NR^{10}R^{11}$, heteroarilo que está opcionalmente sustituido en forma independiente una o más veces con ciano, 1-4C-alquilo, 1-6C-haloalquilo, 1-6C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, donde dos de R^2, R^3 $(R^4)_n$, cuando se encuentran en posición *orto* entre sí, pueden formar junto con los dos átomos de carbono a los cuales están unidos un anillo heterocíclico de 5, 6 o 7 miembros que contiene 1 o 2 heteroátomos seleccionados entre O o N, y que opcionalmente contiene un enlace doble adicional y/o está opcionalmente sustituido con un grupo oxo (=O) y/o un grupo 1-4C-alquilo,

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^4 es hidrógeno.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^4 es hidrógeno o halógeno, especialmente hidrógeno o flúor.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^4 se selecciona entre el grupo que consiste en hidroxi, NO_2 o $NR^{10}R^{11}$.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^4 se selecciona entre el grupo que consiste en es en forma independiente hidrógeno, halógeno,

ciano, 1-6C-alquilo, 2-6C-alquenilo, 1-6C-haloalquilo, 1-6C-hidroxialquilo, 1-6C-alcoxi, 1-6C-haloalcoxi, $-C(O)OR^9$, $-(1-6C-alquilen)-C(O)OR^9$, $-C(O)-(1-6C-alquilo)$, $-C(O)NR^{10}R^{11}$, 3-7C-cicloalquilo, $-S-(1-6C-haloalquilo)$, SF_5, $-SO_2NH-(3-7C-cicloalquilo)$, $-SO_2NR^{10}R^{11}$, heteroarilo que está opcionalmente sustituido en forma independiente una o más veces con ciano, 1-4C-alquilo, 1-6C-haloalquilo, 1-6C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, donde dos de R^2, R^3 $(R^4)_n$, cuando se encuentran en posición *orto* entre sí, pueden formar junto con los dos átomos de carbono a los cuales están unidos un anillo heterocíclico de 5, 6 o 7 miembros que contiene 1 o 2 heteroátomos seleccionados entre O o N, y opcionalmente un enlace doble adicional y/o un grupo carbonilo y/o un grupo 1-4C-alquilo.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^4 se selecciona entre el grupo que consiste en hidrógeno, halógeno, ciano, 1-3C-alquilo, 3-6C-cicloalquilo, 2-3C-alquenilo, 1-3C-haloalquilo, 1-3C-hidroxialquilo, 1-3C-alcoxi, 1-3C-haloalcoxi, $-C(O)-(1-3C-alquilo)$, COOH, $(1-3C-alquilen)-COOH$, $-(1-3C-alquilen)-COO-(1-3C-alquilo)$, $-COO-(1-4C-alquilo)$, $-C(O)NH_2$, $-C(O)NH(1-3C-alquilo)$, $-C(O)N(1-3C-alquil)_2$, $-C(O)NH-(1-3C-alquil)-OH$, $-C(O)-(N-heterociclilo)$, $-SO_2-NH-(3-6C-cicloalquilo)$, $-SO_2-(N-heterociclilo)$,

Aun otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^4 se selecciona entre el grupo que consiste en hidrógeno, hidroxi, flúor, cloro, bromo o iodo, ciano, nitro, $-CH_3$, $-C_3H_9$, ciclopropilo, 1-propenilo, $-CF_3$, $-CH_2-OH$, $-CH_2-CH_2-OH$, $-C(CH_3)_2-OH$,

$-CH_2-C(CH_3)_2-OH$, $-C(CH_3)_2-CH_2-OH$, $-OCH3$, $-OCF_3$, $-OCF_2H$, $-OCH_2CF_3$, $-C(O)CH_3$, $-COOH$, $-C(O)OCH_3$, $-C(O)OC_2H_5$, $-C(O)OC(CH_3)_3$, $-CH_2-COOC_2H_5$, $-CH_2-COOH$, $-C(CH_3)_2-COOC_2H_5$, $-C(O)NH2$, $-C(O)NH(CH_3)$, $-C(O)N(CH_3)_2$, $-C(O)NH-(CH_2)_2-OH$, $-C(O)-$(N-morfolino), $-SO_2-NH-$ciclopropilo, $-SO_2-$(N-morfolino), NH_2.

Aun otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^4 se selecciona entre el grupo que consiste en hidrógeno, flúor, cloro, bromo o iodo, ciano, $-CH_3$, $-C_3H_9$, ciclopropilo, 1-propenilo, $-CF_3$, $-CH_2-OH$, $-CH_2-CH_2-OH$, $-C(CH_3)_2-OH$, $-CH_2-C(CH_3)_2-OH$, $-C(CH_3)_2-CH_2-OH$, $-OCH_3$, $-OCF_3$, $-OCF_2H$, $-OCH_2CF_3$, $-C(O)CH_3$, $-COOH$, $-C(O)OCH_3$, $-C(O)OC_2H_5$, $-C(O)OC(CH_3)3$, $-CH_2-COOC_2H_5$, $-CH_2-COOH$, $-C(CH_3)_2-COOC_2H_5$, $-C(O)NH_2$, $-C(O)NH(CH_3)$, $-C(O)N(CH_3)_2$, $-C(O)NH-(CH_2)_2-OH$, $-C(O)-$(N-morfolino), $-SO_2-NH-$ciclopropilo, $-SO_2-$(N-morfolino).

Un aspecto adicional de la invención son compuestos de fórmula (I), donde donde dos de R^2, R^3 $(R^4)_n$, cuando se encuentran en posición *orto* entre sí, pueden formar junto con los dos átomos de carbono a los cuales están unidos un anillo heterocíclico de 5, 6 o 7 miembros que contiene 1 o 2 heteroátomos seleccionados entre O o N, y opcionalmente un enlace doble adicional y/o un grupo carbonilo y/o un grupo 1-4C-alquilo, especialmente donde dos de R^2, R^3 $(R^4)_n$, cuando se encuentran en posición *orto* entre sí, forman junto con los dos átomos de carbono a los cuales están unidos, $-O-CH_2-CH_2-CH_2-O-$, $-O-CH_2-CH_2-$, $-(CH3)C=CH-(C=O)-O-$, $-CH_2-(C=O)-O-$, $-(CH_2)2-(C=O)-NH-$.

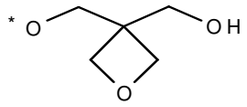
En otra realización de los aspectos previamente

mencionados, la invención se relaciona con compuestos de fórmula (I), donde n es 0, 1 o 2.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde n es al menos 1.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde n es 1.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^6 es (a) hidrógeno; (b) hidroxi; (c) ciano; (d) 1-6C-alcoxi opcionalmente sustituido en forma independiente una o más veces con (d1) OH, (d2) -O-(1-6C-alquilo) (d3) $C(O)OR^9$, (d4) $C(O)NR^{10}R^{11}$, (d5) $NR^{10}R^{11}$, (d6) -S-(1-6C-alquilo), (d7) -S(O)-(1-6C-alquilo), (d8) $-SO_2$-(1-6C-alquilo) (d9) $SO_2NR^{10}R^{11}$, (d10) heterociclilo, que está opcionalmente sustituido con $C(O)OR^9$, o oxo (=O), (d11) heteroarilo, que está opcionalmente sustituido en forma independiente una o más veces con ciano, 1-4C-alquilo, 1-6C-haloalquilo, 1-6C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, (1-6C-alquilen)-O-(1-6C-alquilo), (e) $SO_2NR^{10}R^{11}$, (f) 3-7C-cicloalcoxi, (g) 1-6C-haloalcoxi, (h) $COOR^9$, (i) -$C(O)NR^{10}R^{11}$, (j) -O-heteroarilo opcionalmente sustituido con



CN(k) , donde * es el punto de unión,

(l) -O-(2-6C-alquilen)-O-(1-6C-alquilo) que está opcionalmente sustituido con hidroxi, $NH(CO)OR^9$,

Un aspecto adicional de la invención son compuestos de fórmula (I), donde R^6 es 1-6C-alcoxi que está opcionalmente sustituido en forma independiente una o más veces.

Un aspecto adicional de la invención son compuestos de fórmula (I), donde R^6 es heteroarilo, que está

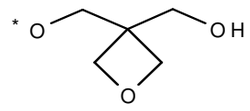
opcionalmente sustituido en forma independiente una o más veces con ciano, 1-4C-alquilo, 1-6C-haloalquilo, 1-6C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, (1-6C-alquil)-O-(1-6C-alquilo). Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^6 es -O-(2-6Calquil)-O-(1-6C-alquilo) que está opcionalmente sustituido con hidroxi o NH-C(O)OR^9.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^6 es 1-6C-alcoxi que está opcionalmente sustituido en forma independiente una o más veces con (d1) OH, (d2) -O-(1-6C-alquilo) (d3) $C(O)OR^9$, (d4) $C(O)NR^{10}R^{11}$, (d5) $NR^{10}R^{11}$, (d6) -S-(1-6C-alquilo), (d7) -S(O)-(1-6C-alquilo), (d8) $-SO_2$-(1-6C-alquilo) (d9) $SO_2NR^{10}R^{11}$, (d10) heterociclilo, que está opcionalmente sustituido con $C(O)OR^9$, o oxo (=O), (d11) heteroarilo, que está opcionalmente sustituido en forma independiente una o más veces con ciano, 1-4C-alquilo, 1-6C-haloalquilo, 1-6C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, (2-6C-alquilen)-O-(1-6C-alquilo),

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^6 es 1-6C-alcoxi que está opcionalmente sustituido en forma independiente una o más veces con (d2) $C(O)OR^9$, (d3) $C(O)NR^{10}R^{11}$, (d4) -S-(1-6C-alquilo), (d6) -S(O)-(1-6C-alquilo), (d7) $-SO_2$-(1-6C-alquilo), (d9) heterociclilo, que está opcionalmente sustituido con $C(O)OR^9$, oxo (=O).

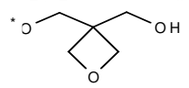
Otro aspecto de la invención consiste en compuestos de fórmula (I), donde

R^6 es (a) hidrógeno; (b) hidroxi; (c) ciano; (d)

1-6C-alcoxi opcionalmente sustituido con (d1) 1-2 OH, (d2) $NR^{10}R^{11}$, (d3) $SO_2NR^{10}R^{11}$, (d4) heterociclilo, (d5) heteroarilo, que está opcionalmente sustituido en forma independiente una o más veces con ciano, 1-4Calquilo, 1-6C-haloalquilo, 1-6C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, (e) $SO_2NR^{10}R^{11}$, ; (f) 3-7C-cicloalcoxi, (g) 1-6C-haloalcoxi, (h) $-C(O)NR^{10}R^{11}$, (i) -O-heteroarilo opcionalmente sustituido con CN(j)  , donde * es el punto de unión,

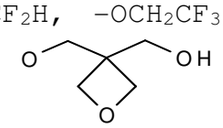
Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^6 es hidrógeno, hidroxi, ciano, -O-(3-6C-cicloalquilo), 1-3C-alcoxi, 1-3C-haloalcoxi, -O-(1-3C-alquilen)-OH, -O-(1-3C-alquilen)-NH2, -O-(1-3C-alquilen)-NH(1-3C-alquilo), -O-(1-3C-alquilen)-$N(1\text{-}3C\text{-}alquil)_2$, -O-(1-3C-alquilen)-SO2NH2, -O-(1-3C-alquilen)-SO2N(1-3C-$alquil)_2$, -O-(1-3C-alquilen)-(heteroarilo opcionalmente sustituido), -C(O)NH2, $-C(O)N(1\text{-}3C\text{-}alquil)_2$.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde .R^6 es hidrógeno, hidroxi, ciano, -O-ciclopropilo, $-OCH_3$, $-OCF_3$, $-OCF_2H$, $-OCH_2CF_3$, $-O-(CH_2)_2-OH$, $-O-(CH_2)_2-NH_2$, $-O(CH_2)_2-N(CH_3)_2$, $-O-(CH_2)_2-O-CH_3$, $-O-(CH_2)_2-O-(CH_2)_2-OH$, $-O-CH_2-CH(OH)-CH_2OH$, $-O-CH_2-CH(OH)-CH_2-NH-C(O)OC(CH_3)_3$, $-O-CH_2-COOH$, $-O-CH_2-COOC_2H_5$, $C(O)NH_2$, $-O-CH_2-C(O)-$(3-fluoro-N-azetidina), $-O-CH_2-C(O)-$(3,3-difluoro-N-azetidina), $-O-CH_2-CH(OH)-CH_2-$N-piperidinilo, $-O-(CH_2)_2$(morfolina-4-ilo), $-O-CH_2-$(morfolina-2-ilo), $-O-CH_2-$(morfolina-2-il-4-tert.-butoxicarboxilato), $-O-CH_2-$

(pirrolidin-2-ona-5-ilo), -O-$(CH_2)_2$-S-CH_3, -O-$(CH_2)_2$-SO-CH_3, 

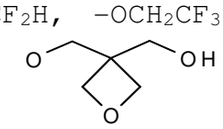
-O-$(CH_2)_2$-SO_2-CH_2, -O-CH_2-SO_2NH_2, -SO_2-CH$(CH_3)_2$, , donde * es el punto de unión, -O-$(CH_2)_2$-tetrazolilo, -O-CH_2-tetrazolilo, -O-piridin-4-ilo, -O-(3-ciano-piridin-4-ilo), o - O-CH_2-(oxadiazol)-CH_2-O-CH_3,

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^6 es hidrógeno, hidroxi, ciano, -O-ciclopropilo, -OCH_3, -OCF_3, -OCF_2H, -OCH_2CF_3, -O-$(CH_2)_2$-



OH, -O$(CH_2)_2$-N$(CH_3)_2$, -O-CH_2-SO_2NH_2, , -O-(CH_2)2-tetrazolilo, -O-CH_2-tetrazolilo, -O-piridin-4-ilo, -O-(3-ciano-piridin-4-ilo), -C(O)NH_2.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^6 es hidrógeno, hidroxi, ciano, -O-ciclopropilo, -OCH_3, -OCF_3, -OCF_2H, -OCH_2CF_3, -O-$(CH_2)_2$-

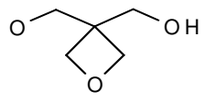


OH, -O$(CH_2)_2$-N$(CH_3)_2$, -O-CH_2-SO_2NH_2, , -O-$(CH_2)_2$-tetrazolilo, -O-CH_2-tetrazolilo, -O-piridin-4-ilo, -O-(3-ciano-piridin-4-ilo), -C(O)NH_2.

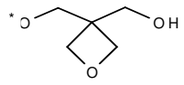
Otro aspecto de la invención consiste en compuestos de fórmula (I), donde si R^6 se encuentra en la posición 5 del anillo pirimidina directamente adyacente al sustituyente amino unido a R^7, R^6 junto con R^7 es un anillo de 5 o 6 miembros incluyendo el átomo de nitrógeno del sustituyente amino que puede contener otro heteroátomo seleccionado entre O, S o N y que además puede estar sustituido con un grupo carbonilo o -CH_2-OH.

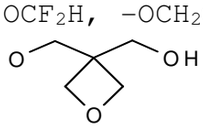
Otro aspecto de la invención consiste en compuestos de fórmula (I), donde si R^6 se encuentra en la posición 5 del

anillo pirimidina directamente adyacente al sustituyente amino unido a R^7, R^6 junto con R^7 es un anillo de 5 o 6 miembros incluyendo el átomo de nitrógeno del sustituyente amino que puede contener otro heteroátomo seleccionado entre O, S o N y que además puede estar sustituido con un grupo carbonilo o $-CH_2-OH$ o $-NH-CHO$.

Otro aspecto preferido de la invención son compuestos de fórmula (I), donde R^6 es –O–(3–6C–cicloalquilo), 1–3C–alcoxi, 1–3C–haloalcoxi, –O–(1–3C–alquilen)–OH, –O–(1–3C–alquilen)–NH2, –O–(1–3C–alquilen)–NH(1–3C–alquilo), –O–(1–3C–alquilen)–N(1–3C–alquil)$_2$, –O–(1–3C–alquilen)–SO2NH2, –O–(1–3C–alquilen)–SO2N(1–3C–alquil)$_2$, –O–(1–3C–alquilen)–(heteroarilo opcionalmente sustituido), especialmente –O–ciclopropilo, –OCH3, –OCF3, –OCF2H, $-OCH_2CF3$, –O–(CH$_2$)2–OH, –O(CH$_2$)2–N(CH3)2, $-O-CH_2-SO2NH2$,  , –O–(CH$_2$)2–tetrazolilo, $-O-CH_2-$tetrazolilo, –O–piridin–4–ilo, –O–(3–ciano–piridin–4–ilo).

Otro aspecto preferido de la invención son compuestos de fórmula (I), donde R^6 es hidrógeno, hidroxi, ciano, –O–ciclopropilo, –O(1–3C–alquilo), –O–(1–3C–haloalquilo), –O–(1–3C–alquilen opcionalmente sustituido con un grupo hidroxi)–OH, –O(1–3C–alquilen opcionalmente sustituido con un grupo hidroxi)–$NR^{10}R^{11}$, –O–(1–3–alquilen)–O–(1–3C–alquilo), –O–(1–3C–alquilen)–O–(1–3C–alquil)–OH, –O–(1–3C–alquilen)–$COOR^9$, C(O)$NR^{10}R^{11}$, –O–(1–3C–alquilen)–C(O)–(heterociclilo opcionalmente sustituido 1 o dos veces con flúor), –O–(1–3–alquilen)–(heterociclilo opcionalmente sustituido con un grupo oxo (=O) y/o $COOR^9$ o un grupo

hidroxi), –O–(1–3C–alquilen)–S–CH_3, –O–(1–3C–alquilen)–SO–CH_3, –O–(1–3C–alquilen)$_2$–SO_2–CH_3, –O–(1–3C–alquilen)–SO_2NH_2, –SO_2–(1–3C–alquilo),  , donde * es el punto de unión, –O–(1–3–alquilen)–[heteroarilo opcionalmente sustituido con CN o (1–3C–alquilen)–O–(1–3C–alquilo)],

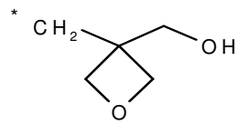
Otro aspecto preferido de la invención son compuestos de fórmula (I), donde R^6 es –O–(3–6C–cicloalquilo), 1–3C–alcoxi, 1–3C–haloalcoxi, –O–(1–3C–alquilen)–OH, –O–(1–3C–alquilen)–NH_2, –O–(1–3C–alquilen)–NH(1–3C–alquilo), –O–(1–3C–alquilen)–N(1–3C–alquil)$_2$, –O–(1–3C–alquilen)–SO_2NH_2, –O–(1–3C–alquilen)–SO_2N(1–3C–alquil)$_2$, –O–(1–3C–alquilen)–(heteroarilo opcionalmente sustituido), especialmente –O–ciclopropilo, –OCH_3, –OCF_3, –OCF_2H, –OCH_2CF_3, –O–$(CH_2)_2$–OH, –O$(CH_2)_2$–$N(CH_3)_2$, –O–CH_2–SO_2NH_2,  , –O–$(CH_2)_2$–tetrazolilo, –O–CH_2–tetrazolilo, –O–piridin–4–ilo, –O–(3–ciano–piridin–4–ilo).

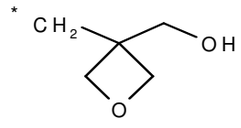
Un aspecto adicional de la invención son compuestos de fórmula (I), donde R^6 es 1–6C–alcoxi que está sustituido con –S–(1–6C–alquilo), –SO–(1–6C–alquilo) o –SO_2–(1–6C–alquilo).

Un aspecto adicional de la invención son compuestos de fórmula (I), donde R^6 es $SO_2NR^{10}R^{11}$.

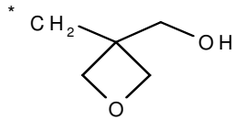
Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^6 es –C(O)NH_2, –C(O)N(1–3C–alquil)$_2$ o ciano, especialmente –C(O)NH_2.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^7 es (a) hidrógeno, (b)1–6C–alquilo, que está opcionalmente sustituido con heteroarilo(c) 1–6C–

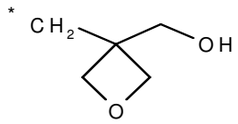
haloalquilo, (d) 1-6C-hidroxialquilo, (e)  , donde * es el punto de unión, (f) -C(O)-(1-6C-alquilo) (g) -C(O)-(1-6C-alquilen)-O-(1-6C-alquilo) (h) -C(O)-(1-6C-alquilen)-O-(2-6C-alquilen)-O-(1-6C-alquilo) (i) -C(O)-heterociclilo, (j) bencilo donde el anillo fenilo está opcionalmente sustituido con 1-5 sustituyentes seleccionados en forma independiente entre el grupo que consiste en hidrógeno, halógeno, 1-4C-alquilo, 1-4C-haloalquilo, 1-4C-alcoxi, 1-4C-haloalcoxi, ciano, $C(O)OR^9$, (k) heteroarilo, u opcionalmente R^6 y R^7 junto con el átomo de nitrógeno al cual R^7 está unido forman un anillo de 6 miembros que puede contener otro heteroátomo seleccionado entre el grupo que consiste en O, S, N, y que está opcionalmente sustituido con (1-6C-alquil)-OH, (1-6C-alquil)-$NR^{10}R^{11}$,

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^7 es (a) hidrógeno, (b)1-6C-alquilo, que está opcionalmente sustituido con heteroarilo(c) 1-6C-haloalquilo, (d) 1-6C-hidroxialquilo, (e)  , donde * es el punto de unión, (f) -C(O)-(1-6C-alquilo) (g) -C(O)-(1-6C-alquilen)-O-(1-6C-alquilo) (h) -C(O)-(1-6C-alquilen)-O-(2-6C-alquilen)-O-(1-6C-alquilo) (i) -C(O)-heterociclilo, (j) bencilo donde el anillo fenilo está opcionalmente sustituido con 1-5 sustituyentes seleccionados en forma independiente entre el grupo que consiste en hidrógeno, halógeno, 1-4C-alquilo, 1-4C-alcoxi, 1-4C-haloalcoxi, ciano, $C(O)OR^9$, (k) heteroarilo, u

opcionalmente R^6 y R^7 junto con el átomo de nitrógeno al cual R^7 está unido forman un anillo de 6 miembros que puede contener otro heteroátomo seleccionado entre el grupo que consiste en O, S, N, y que está opcionalmente sustituido con (1-6C-alquil)-OH, (1-6C-alquil)-$NR^{10}R^{11}$,

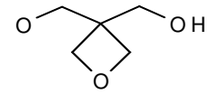
Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^7 es (a) hidrógeno, (b)1-3C-alquilo, que está opcionalmente sustituido con heteroarilo(c) 1-3C-haloalquilo, (d) 1-3C-hidroxialquilo, (e) 

, donde * es el punto de unión, (f) -C(O)-(1-3C-alquilo) (g) -C(O)-(1-3C-alquilen)-O-(1-3C-alquilo) (h) -C(O)-(1-3C-alquilen)-O-(2-3C-alquilen)-O-(1-3C-alquilo) (i) -C(O)-heterociclilo, (j) bencilo donde el anillo fenilo está opcionalmente sustituido con 1-5 sustituyentes seleccionados en forma independiente entre el grupo que consiste en hidrógeno, halógeno, 1-3C-alquilo, 1-3C-alcoxi, 1-3C-haloalcoxi, ciano, $C(O)OR^9$, (k) heteroarilo, u opcionalmente R^6 y R^7 junto con el átomo de nitrógeno al cual R^7 está unido forman un anillo de 6 miembros que puede contener otro heteroátomo seleccionado entre el grupo que consiste en O, S, N, y que está opcionalmente sustituido con (1-3C-alquil)-OH, (1-3C-alquil)-$NR^{10}R^{11}$.

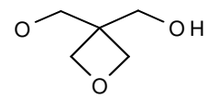
Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^7 es (a) hidrógeno, (b)1-6C-alquilo, que está opcionalmente sustituido con heteroarilo(c) 1-6C-haloalquilo, (d) 1-6C-hidroxialquilo, (e) 

, donde * es el punto de unión, (f) -C(O)-(1-6C-alquilo) (g)

-C(O)-(1-6C-alquilen)-O-(1-6C-alquilo) (h) -C(O)-(1-6C-alquilen)-O-(1-6C-alquilen)-O-(1-6C-alquilo) (i) -C(O)-heterociclilo, (j) bencilo donde el anillo fenilo está opcionalmente sustituido con 1-5 sustituyentes seleccionados en forma independiente entre el grupo que consiste en hidrógeno, halógeno, 1-4Calquilo, 1-4C-haloalquilo, 1-4C-alcoxi, 1-4C-haloalcoxi, ciano, $C(O)OR^9$, (k) heteroarilo, u opcionalmente R^6 y R^7 junto con el átomo de nitrógeno al cual están unidos forman un anillo de 6 miembros que puede contener otro heteroátomo seleccionado entre el grupo que consiste en O, S, N, y que está opcionalmente sustituido con hidroxi-(1-6alquilo),

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^7 es hidrógeno, 1-3C-alquilo, 1-3C-haloalquilo, -(1-3C-alquilen)-OH, 

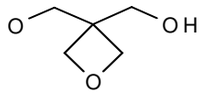
, (1-3C-alquilen)-arilo, -(1-3C-alquilen)-heteroarilo, heteroarilo, -C(O)-(1-3C-alquilo), -C(O)-(1-3C-alquilen)-O-(1-3C-alquilo), -C(O)-(1-3C-alquilen)-O-(1-3C-alquilen)-O-(1-3C-alquilo), -C(O)-heterociclilo.

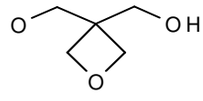
Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^7 es hidrógeno, 1-3C-alquilo, 1-3C-haloalquilo, 1-3C-hidroxialquilo, 

, donde * es el punto de unión,

Heteroarilo, -(1-3C-alquilen)-heteroarilo, , -C(O)-heterociclilo, -C(O)-(1-3C-alquilen)-O-(1-3C-alquilo), -C(O)-(1-3C-alquilo), $-C(O)CH_2$-O-(1-3C-alquilen)-O-(1-3C-alquilo), o bencilo el cual está opcionalmente sustituido

una o más veces con halógeno, ciano, 1-3C-alquilo, 1-3C-haloalquilo, 1-3C-alcoxi, 1-3C-haloalcoxi, -C(O)O(1-3-alquilo), u opcionalmente cuando R^6 se encuentra en la posición 5 del sistema cíclico pirimidina, R^6 y R^7 junto con el átomo de nitrógeno al cual R^7 está unido forman un anillo de 6 miembros que puede contener otro heteroátomo seleccionado entre O, S o N y que además está opcionalmente sustituido con CH_2-OH o $-CH_2$-NH-CHO

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^7 es hidrógeno, metilo, difluorometilo, hidroxietilo,  , $-(CH_2)_2$-tetrazolilo, piridin-4-ilo, -C(O)-tetrahidropiran-4-ilo, $-C(O)-CH_2-O-CH_3$, $-C(O)-CH_3$, $-C(O)CH_2-O-(CH_2)_2-O-CH_3$ o bencilo el cual está opcionalmente sustituido una o más veces con flúor, cloro, bromo, ciano, metilo, metoxi, etoxi, difluormetoxi, trifluorometoxi, $-O-CH_2-CF_3$, $-C(O)OCH_3$.

Aun otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^7 es hidrógeno, metilo, difluorometilo, hidroxietilo,  , $-(CH_2)_2$-tetrazolilo, piridin-4-ilo, -C(O)-tetrahidropiran-4-ilo, $-C(O)-CH_2-O-CH_3$, $-C(O)-CH_3$, $-C(O)CH_2-O-(CH_2)_2-O-CH_3$ o bencilo el cual está opcionalmente sustituido una o más veces con flúor, cloro, ciano, metilo, metoxi, etoxi, difluormetoxi, trifluorometoxi, $-O-CH_2-CF_3$, $-C(O)OCH_3$.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^7 es bencilo opcionalmente sustituido una o más veces, donde los sustituyentes se seleccionan

entre el grupo que consiste en halógeno (especialmente flúor, cloro), ciano, 1-3C-alcoxi (especialmente metoxi, etoxi), 1-3C-haloalcoxi (especialmente $-OCF_3$, $-O-CF_2H$, $-O-CH_2-CF_3$). En otro aspecto el grupo bencilo está sustituido 1-, 2-, 3- o 4 veces.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^8 es hidrógeno, halógeno, hidroxi, ciano, 1-6C-alquilo, 1-6C-hidroxialquilo, 1-6C-haloalquilo, 1-6C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^8 es hidrógeno, halógeno, ciano, 1-6C-haloalquilo, 1-6C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^8 es hidrógeno, ciano, 1-3C-haloalquilo, $-C(O)NH_2$, -C(O)N(1-3C-alquilo), C(O)OH, -C(O)-O(1-4C-alquilo), -C(O)-(1-3C-alquilen)-OH, especialmente hidrógeno, ciano, CF_3, $C(O)NH_2$, C(O)OH, $C(O)OC_2H_5$, $C(O)O(CH_2)_2-OH$.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^8 es hidroxi-(1-6C-alquilo).

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^8 es hidrógeno, flúor, hidroxi, ciano, 1-3C-alquilo, 1-3C-haloalquilo, 1-3C-hydoxialquilo, 1-3C-alcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, especialmente hidrógeno, flúor, hidroxi, ciano, metilo, CF_3, metoxi, hidroximetilo, COOH, $COOCH_3$, $COOC_2H_5$, $C(O)NH_2$, $C(O)NHCH_3$.

Aun otro aspecto de la invención consiste en compuestos de fórmula (I), donde m es 0.

Otro aspecto de la invención consiste en

compuestos de fórmula (I), donde m es 0 o 1.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde m se selecciona entre 0, 1 o 2.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^9 es (a) hidrógeno,

(b) 1-6C-alquilo que está opcionalmente sustituido con hidroxi,

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^9 es hidrógeno, 1-4C-alquilo, 1-3C-hidroxialquilo, especialmente hidrógeno, metilo, etilo, tert.-butilo, hidroxietilo.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde

R^{10}, R^{11} son en forma independiente entre sí hidrógeno, 1-4C-alquilo, 1-4C-hidroxialquilo, 1-4C-alcoxi, -(CO)-(1-6C-alquilo), CHO, $COOR^9$, o junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de entre 4 y 6 miembros que opcionalmente contiene otro heteroátomo seleccionado entre el grupo que consiste en O, S o N, y que está opcionalmente sustituido con 1-2 átomos de flúor o $COOR^9$,

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^{10}/R^{11} es en forma independiente en cada caso hidrógeno, 1-3C-alquilo, 1-3C-hidroxialquilo, especialmente hidrógeno, metilo, hidroxietilo,

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^{10}, R^{11} son en forma independiente entre sí hidrógeno, 1-4C-alquilo, 1-4C-hidroxialquilo, 1-4C-alcoxi, -(CO)-(1-6C-alquilo) o junto con el átomo de

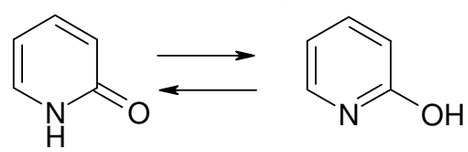
nitrógeno al cual están unidos forman un anillo heterocíclico de entre 4 y 6 miembros que opcionalmente contiene otro heteroátomo seleccionado entre el grupo que consiste en O, S o N, que está opcionalmente sustituido con 1–2 átomos de halógeno, especialmente átomos de flúor.

En otro aspecto de la invención se proven compuestos de fórmula (I), donde R^{10}, R^{11} son en forma independiente entre sí hidrógeno, 1–4C–alquilo, 1–4C–hidroxialquilo, 1–4C–alcoxi, o junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 5 o 6 miembros que opcionalmente contiene otro heteroátomo seleccionado entre el grupo que consiste en O, S o N.

Otro aspecto de la invención consiste en compuestos de fórmula (I), donde R^{10}, R^{11} forman junto con el átomo de nitrógeno al cual están unidos un anillo heterocíclico de 4 miembros, que está opcionalmente sustituido con 1–2 átomos de halógeno, especialmente átomos de flúor.

Un aspecto adicional de la invención comprende compuestos de la fórmula (I), que están presente como sus sales, en especial como sus clorhidratos.

Otra forma de realización de la invención comprende las formas tautoméricas de una hidroxipiridina que se consideran incluidas en la reivindicación, si el compuesto de la fórmula I incluye dicha hidroxipiridina:



Otra forma de realización de la invención comprende los compuestos de acuerdo con las reivindicaciones

divulgadas en la sección de Reivindicaciones, en donde las definiciones están limitadas de acuerdo con las definiciones preferidas o más preferidas divulgadas a continuación o los residuos divulgados específicamente de los compuestos ejemplificados y subcombinaciones de los mismos.

Definiciones

Los constituyentes que están opcionalmente sustituidos como se define en la presente, pueden estar sustituidos, a menos que se indique de otra manera, una o más veces, de forma independiente entre sí en cualquier posición posible. Cuando una variable cualquiera aparece más de una vez en cualquier constituyente, cada definición es independiente.

A menos que se defina de otra manera en las reivindicaciones y en la descripción, los constituyentes definidos a continuación pueden estar opcionalmente sustituidos, una o más veces, de manera idéntica o diferente, con un sustituyente seleccionado entre:

hidroxi, halógeno, ciano, 1-6C-alquilo, 1-4C-haloalquilo, 1-6C-alcoxi, $-NR^{10}R^{11}$, ciano, (=O), $-C(O)NR^{10}R^{11}$, $-C(O)OR^{9}$, $-NHC(O)R^{11}$, $-NHS(O)_2R^{11}$. Un constituyente alquilo con múltiples sustituciones de halógeno incluye también un grupo alquilo completamente halogenado tal como, por ejemplo, CF_3.

Si un constituyente está compuesto por más de una parte, por ejemplo, -O-(1-6Calquil)-3-7C-cicloalquilo, el sustituyente posible puede estar localizado en cualquier posición apropiada en cualquiera de las partes. Un guión en la parte inicial del constituyente representa el punto de

unión con el resto de la molécula. Si un anillo está sustituido, el sustituyente puede hallarse en cualquier posición, lo que también incluye un átomo de nitrógeno.

El uso del término “que comprende” en la memoria descriptiva abarca la denotación “que consiste en”.

En la descripción, el término “como se indicó con anterioridad” y sus variaciones se emplean para hacer referencia a cualquier descripción en una porción precedente de la memoria descriptiva.

En el contexto de la invención, el término “apropiado” hace referencia a una situación que es posible desde el punto de vista químico, sobre la base de la aplicación de métodos conocidos por aquellos versados en la técnica.

“1-6C-alquilo” es un grupo alquilo de cadena lineal o ramificada que tiene entre 1 y 6 átomos de carbono. Los ejemplos abarcan los grupos metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, sec-butilo, ter-butilo, pentilo o hexilo. Preferiblemente, tienen 1-4 átomos de carbono (se trata de 1-4C-alquilo), y más preferiblemente tienen 1-3 átomos de carbono (se trata de 1-3C-alquilo). En la presente se mencionan otros constituyentes que son alquilos y que tienen una cantidad diferente de átomos de carbono. Las partes de los constituyentes que contienen cadenas de alquilo como unidades que hacen las veces de puentes entre otras dos partes usualmente se conocen como “alquilenos”, de acuerdo con la definición que se proporcionó con anterioridad para los grupos alquilo, incluyendo la longitud preferida de la cadena. Abarcan, por ejemplo, los grupos metileno, etileno, n-propileno,

isopropileno, n-butileno, isobutileno y ter-butileno.

Un “2-6C-alquenilo” hace referencia a un radical alquenilo de cadena lineal o ramificada que tiene entre 2 y 4 átomos de carbono. Los ejemplos abarcan los radicales but-2-enilo, but-3-enilo (homoalilo), prop-1-enilo, prop-2-enilo (alilo) y etenilo (vinilo).

Además, del átomo de nitrógeno, los radicales de “mono o di-1-4C-alquilamino” pueden contener uno o dos de los radicales 1-4C-alquilo que se mencionaron con anterioridad. En este caso, los ejemplos incluyen los radicales metilamino, etilamino, isopropilamino, dimetilamino, dietilamino y diisopropilamino.

En el contexto de la presente invención, un “halógeno” hace referencia al iodo, al bromo, al cloro o al flúor. Preferiblemente, en el contexto de la presente invención, un “halógeno” hace referencia al cloro o al flúor.

Un “1-6C-haloalquilo” es un grupo alquilo de cadena lineal o ramificada que tiene entre 1 y 6 átomos de carbono en el cual al menos un hidrógeno está sustituido por un átomo de halógeno. Los ejemplos incluyen clorometilo o 2-bromoetilo. Para grupos C_1-C_3-alquilo parcial o totalmente fluorados, se pueden considerar los siguientes grupos parcial o totalmente fluorados, por ejemplo: fluorometilo, difluorometilo, trifluorometilo, fluoroetilo, 1,1-difluoroetilo, 1,2-difluoroetilo, 1,1,1-trifluoroetilo, tetrafluoroetilo y penta-fluoroetilo, donde se prefiere difluorometilo, trifluorometilo o 1,1,1-trifluoroetilo. Se considera que todos los grupos 1-6C-alquilo parcialmente o completamente fluorados posibles están abarcados por el

término 1-6C-haloalquilo.

Un “1-6C-hidroxialquilo” es un grupo alquilo de cadena lineal o ramificada que tiene 1 a 6 átomos de carbono en el cual al menos un átomo de hidrógeno está sustituido por un grupo hidroxi. Los ejemplos incluyen hidroximetilo, 1-hidroxietilo, 2-hidroxietilo, 1,2-dihidroxietilo, 3-hidroxipropilo, 2-hidroxipropilo, 2,3-dihidroxipropilo, 3-hidroxi-2-metil-propilo, 2-hidroxi-2-metil-propilo, 1-hidroxi-2-metil-propilo.

Un “1-6C-alcoxi” representa un radical que, además del átomo de oxígeno, contiene un grupo alquilo de cadena lineal o ramificada que tiene entre 1 y 6 átomos de carbono. A modo de ejemplo, pueden mencionarse los radicales hexoxilo, pentoxilo, butoxilo, isobutoxilo, sec-butoxilo, ter-butoxilo, propoxilo, isopropoxilo, etoxilo y metoxilo, de los cuales se prefiere el metoxilo, el etoxilo, el propoxilo el isopropoxilo.

Un “1-6C-haloalcoxi” representa radicales, que además del átomo de oxígeno, contienen un radical alquilo de cadena lineal o ramificada de 1 a 6 átomos de carbono en el cual al menos un hidrógeno está sustituido por un átomo de halógeno. Los ejemplos incluyen –O-CFH2, –O-CF2H, –O-CF3, –O-CH2-CFH2, –O-CH2-CF2H, –O-CH2-CF3. Se prefieren –O-CF2H, –O-CF3, –O-CH2-CF3.

Un “3-7C-cicloalquilo” hace referencia a un radical ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo o cicloheptilo, preferiblemente ciclopropilo.

Un “3-7C-cicloalquiloxilo” o un “-O-(3-7C-cicloalquilo)” hacen referencia, por ejemplo, a un radical

ciclopropiloxilo, ciclobutiloxilo, ciclopentiloxilo, ciclohexiloxilo o cicloheptiloxilo, preferiblemente ciclopropiloxilo.

Un “3-7C-heterociclilo”, o “heterociclilo” representa un radical heterocíclico no aromático mono o policíclico, preferiblemente mono o bicíclico, más preferiblemente monocíclico, que contiene 4 a 10, preferiblemente 4 a 7, más preferiblemente 5 a 6 átomos del anillo, y 1, 2 ó 3, preferiblemente 1 ó 2, heteroátomos y/o heterogrupos seleccionados de manera independiente de la serie que consiste de N, O, S, SO, SO_2. Los radicales heterociclilo pueden ser saturados o parcialmente insaturados y, a menos que se defina de otra manera, pueden estar opcionalmente sustituidos, una o más veces, de manera idéntica o diferente, con un sustituyente seleccionado entre: 1-4C-alquilo, 1-4C-haloalquilo, 1-4C-alcoxi, hidroxi, flúor o (=O) donde el 1-4C-alquilo además puede estar opcionalmente sustituido con hidroxi y el átomo de oxígeno unido mediante doble enlace, lo cual conduce a un grupo carbonilo junto con el átomo de carbono del anillo heterociclilo en cualquier posición adecuada. Los radicales heterocíclicos particularmente preferidos son radicales heterociclilo saturados monocíclicos de 4 a 7 miembros que contienen hasta dos heteroátomos de la serie que consiste de O, N y S, más preferidos son los radicales heterocíclicos de 5-6 miembros. Se pueden mencionar los siguientes grupos a modo de ejemplo y de preferencia: oxetanilo, tetrahidrofuranilo, tetrahidropiranilo, azetidinilo, 3-hidroxiazetidinilo, 3-fluoroazetidinilo, 3,3-difluoroazetidinilo, pirrolidinilo,

3-hidroxipirrolidinilo, pirrolinilo, pirazolidinilo, imidazolidinilo, piperidinilo, 3-hidroxipiperidinilo, 4-hidroxipiperidinilo, 3-fluoropiperidinilo, 3,3-difluoropiperidinilo, 4-fluoropiperidinilo, 4,4-difluoropiperidinilo, piperazinilo, N-metil-piperazinilo, N-(2-hidroxietil)-piperazinilo, morfolinilo, tiomorfolinilo, azepanilo, homopiperazinilo, N-metil-homopiperazinilo.

Un “N-heterociclilo” representa un radical heterocíclico que está unido a la molécula remanente a través del átomo de nitrógeno contenido en el anillo heterocíclico.

El término “heteroarilo” hace referencia a una unidad que es un heterociclo aromático de 5 ó 6 miembros o un biciclo aromático fusionado que comprende, en un sentido no limitativo, los siguientes radicales heteroarílicos de 5 miembros: furilo, tienilo, pirrolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, imidazolilo, pirazolilo, triazolilo (1,2,4-triazolilo, 1,3,4-triazolilo o 1,2,3-triazolilo), tiadiazolilo (1,3,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,2,3-tiadiazolilo o 1,2,4-tiadiazolilo) y oxadiazolilo (1,3,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,2,3-oxadiazolilo o 1,2,4-oxadiazolilo), los siguientes radicales heteroarílicos de 6 miembros: piridinilo, pirimidinilo, pirazinilo o piridazinilo, y los siguientes ejemplos de sistemas de anillos fusionados: ftalidilo, tioftalidilo, indolilo, isoindolilo, dihidroindolilo, dihidroisoindolilo, indazolilo, benzotiazolilo, benzofuranilo, benzimidazolilo,

benzoxazinonilo, quinolinilo, isoquinolinilo, chinazolinilo, chinoxalinilo, cinolinilo, ftalazinilo, 1,7 ó 1,8-naftiridinilo. cumarinilo, isocumarinilo, indolizinilo, isobenzofuranilo, azaindolilo, azaisoindolilo, furanopiridilo, furanopirimidinilo, furanopirazinilo o furanopiridazinilo, de los cuales se prefiere en particular el indazolilo. Los radicales de 5 ó 6 miembros preferidos abarcan el furanilo, el tienilo, el pirrolilo, el tiazolilo, el oxazolilo, el tiadiazolilo, el oxadiazolilo, el piridinilo, el pirimidinilo, el pirazinilo o el piridazinilo. Los radicales de 5 ó 6 miembros más preferidos abarcan el furan-2-ilo, el tien-2-ilo, el pirrol-2-ilo, el tiazolilo, el oxazolilo, el 1,3,4-tiadiazolilo, el 1,3,4-oxadiazolilo, el piridin-2-ilo, el piridin-4-ilo, el pirimidin-2-ilo, el pirimidin-4-ilo, el pirazin-2-ilo o el piridazin-3-ilo.

En general, y a menos que se mencione de otra manera, los radicales heteroarílico o heteroarilénico incluyen todas las formas isoméricas posibles de los mismos, por ejemplo los isómeros de posición de los mismos. Así, a modo de ejemplo ilustrativo no limitativo, 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.

Los grupos heteroarílicos, heteroarilénicos o heterocíclicos mencionados en la presente pueden estar sustituidos por sus sustituyentes dados o grupos moleculares de origen, a menos que se indique lo contrario,

en cualquier posición posible, tal como por ejemplo, en cualquier átomo de carbono del anillo o átomo de nitrógeno del anillo que sea sustituible. De manera análoga, se comprenderá que es posible unir cualquier grupo heteroarilo o heterociclilo al resto de la molécula a través de cualquier átomo adecuado si fuera químicamente apropiado. A menos que se indique lo contrario, se asume que cualquier heteroátomo de un anillo heteroarílico o heteroarilénico con valencias libres que se mencione en la presente tiene el/los átomo/s de hidrógeno para corresponderse con las valencias. A menos que se indique lo contrario, los anillos que contienen átomos de nitrógeno en el anillo amino o tipo imino cuaternizables (-N=) preferentemente no se cuaternizan en estos átomos de nitrógeno del anillo amino o tipo imino por los sustituyentes mencionados o grupos moleculares de origen.

El grupo $NR^{10}R^{11}$ incluye, por ejemplo, NH_2, $N(H)CH_3$, $N(CH_3)_2$, $N(H)CH_2CH_3$ y $N(CH_3)CH_2CH_3$. En el caso de $-NR^{10}R^{11}$, cuando R^{10} y R^{11} junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 4-6 miembros que opcionalmente contiene un heteroátomo adicional seleccionado del grupo que consiste de O, S o N, el término “anillo heterocíclico” definido previamente. Se prefiere especialmente el morfolinilo.

El grupo $C(O)NR^{10}R^{11}$ incluye, por ejemplo, $C(O)NH_2$, $C(O)N(H)CH_3$, $C(O)N(CH_3)_2$, $C(O)N(H)CH_2CH_3$, $C(O)N(CH_3)CH_2CH_3$ o $C(O)N(CH_2CH_3)_2$. Si R^{10} o R^{11} no son hidrógeno, pueden sustituirse con hidroxi. En el caso de $-NR^{10}R^{11}$, cuando R^{10} y R^{11} junto con el átomo de nitrógeno al cual están unidos

forman un grupo heterocíclico de 4-6 miembros, el término “anillo heterocíclico” es como se definió previamente y se puede usar de manera análoga con $C(O)NR^{10}R^{11}$.

El grupo $C(O)OR^{9}$ incluye, por ejemplo, $C(O)OH$, $C(O)OCH_3$, $C(O)OC_2H_5$, $C(O)C_3H_7$, $C(O)CH(CH_3)_2$, $C(O)OC_4H_9$, $C(O)OC_5H_{11}$, $C(O)OC_6H_{13}$; en el caso de C(O)O(1-6Calquilo), la parte alquilo puede ser de cadena lineal o ramificada y puede estar sustituida.

En el contexto de las propiedades de los compuestos de la presente invención, el término “perfil farmacocinético” hace referencia a un único parámetro o una combinación de parámetros, por ejemplo, la permeabilidad, la biodisponibilidad y la exposición, así como a parámetros farmacocinéticos como la duración o la magnitud del efecto farmacológico, los cuales pueden medirse a través de cualquier experimento apropiado. Los compuestos con perfiles farmacocinéticos mejorados pueden usarse, por ejemplo, en dosis más bajas para obtener un efecto idéntico, para obtener una acción con una duración más prolongada o para obtener una combinación de ambos efectos.

Las sales de los compuestos de acuerdo con la invención incluyen todas las sales de adición ácida inorgánicas y orgánicas, y las sales con bases, especialmente todas las sales de adición ácida inorgánicas y orgánicas, y las sales con bases farmacéuticamente aceptables, en particular todas las sales de adición ácida inorgánicas y orgánicas, y las sales con bases farmacéuticamente aceptables que son de uso común en farmacia.

Un aspecto de la invención son sales de los compuestos de la invención que incluyen todas las sales de adición inorgánicas u orgánicas, en especial todas las sales de adición inorgánicas u orgánicas farmacéuticamente aceptables, en particular todas las sales de adición inorgánicas u orgánicas farmacéuticamente aceptables usadas habitualmente en farmacia. Otro aspecto de la invención son las sales con ácidos di y tricarboxílicos.

Los ejemplos de sales de adición ácida incluyen, en un sentido no limitativo, clorhidratos, bromhidratos, fosfatos, nitratos, sulfatos, sales de ácido sulfámico, formatos, acetatos, propionatos, citratos, D-gluconatos, benzoatos, 2-(4-hidroxibenzoil)benzoatos, butiratos, salicilatos, sulfosalicilatos, lactatos, maleatos, lauratos, malatos, fumaratos, succinatos, oxalatos, malonatos, piruvatos, acetoacetatos, tartaratos, estearatos, toluensulfonatos, metansulfonatos, trifluorometansulfonatos, 3-hidroxi-2-naftoatos, bencensulfonatos, naftalindisulfonatos y trifluoroacetatos.

Los ejemplos de sales con bases incluyen, en un sentido no taxativo, sales de litio, sodio, potasio, calcio, aluminio, magnesio, titanio, meglumina, amonio, sales opcionalmente derivadas NH3 o aminas orgánicas que tienen entre 1 y 16 átomos de carbono tales como por ejemplo sales de etilamina, dietilamina, trietilamina, etildiisopropilamina, monoetanolamina, dietanolamina, trietanolamina, diciclohexilamina, dimetilaminoetanol, procaína, dibencilamina, N-metilmorfolina, arginina, lasina, etilendiamina, N-metilpiperindina y guanidinio.

Las sales incluyen sales insolubles en agua, y en particular, sales solubles en agua.

De acuerdo con los especialistas en el arte, los compuestos de la fórmula (I) de acuerdo con esta invención, así como sales de los mismos, pueden contener, por ejemplo, cuando se los aísla en forma cristalina, cantidades variables de solventes. Por consiguiente, el alcance de la invención incluye todos los solvatos, y en particular, todos los hidratos de los compuestos de la fórmula (I) de acuerdo con esta invención, y también todos los solvatos, y en particular, todos los hidratos de las sales de los compuestos de la fórmula (I) de acuerdo con esta invención.

En la presente invención, el término “combinación” se usa de una manera conocida por los especialistas en el arte, y puede estar presente como una combinación fija, una combinación no fija o un conjunto de partes.

En la presente invención, una “combinación fija” se usa de una manera conocida por los especialistas en el arte, y se define como una combinación donde dicho primer ingrediente activo y dicho segundo ingrediente activo están presentes juntos en una dosificación individual o una sola entidad. Un ejemplo de una “combinación fija” es una composición farmacéutica donde están presentes dicho primer ingrediente activo y dicho segundo ingrediente activo combinados para una administración simultánea, tal como en una formulación. Otro ejemplo de una “combinación fija” es una combinación farmacéutica donde dicho primer ingrediente activo y dicho segundo ingrediente activo están presentes en una unidad, pero no combinados.

En la presente invención, una combinación no fija o un “conjunto de partes” se usa de una manera conocida por los especialistas en el arte, y se define como una combinación donde dicho primer ingrediente activo y dicho segundo ingrediente activo están presentes en más de una unidad. Un ejemplo de una combinación no fija o un conjunto de partes es una combinación donde dicho primer ingrediente activo y dicho segundo ingrediente activo están presentes separados. Los componentes de la combinación no fija o el conjunto de partes pueden administrarse de manera separada, consecutiva, simultánea, concurrente o escalonada cronológicamente.

El término “agentes anti-cancerosos (quimioterapéutico)”, incluye pero en un sentido no limitativo:

^{131}I-chTNT, abarelix, abiraterona, aclarubicina, aldesleuquina alemtuzumab, alitretinoína, altretamina, aminoglutetimida, amrubicina, amsacrina, anastrozol, arglabina, trióxido de arsénico, asparaginasa, azacitidina, basiliximab, BAY 80-6946, BAY 1000394, belotecano, bendamustina, bevacizumab, bexaroteno, bicalutamida, bisantreno, bleomicina, bortezomib, buserelina, busulfán, cabazitaxel, folinato de calcio, levofolinato de calcio, capecitabina, carboplatino, carmofur, carmustina, catumaxomab, celecoxib, celmoleuquina cetuximab, clorambucilo, clormadinona, clormetina, cisplatino, cladribina, ácido clodrónico, clofarabina, crisantaspasa, ciclofosfamida, ciproterona, citarabina, dacarbazina, dactinomicina, darbepoyetina alfa, dasatinib,

daunorubicina, decitabina, degarelix, denileuquina diftitox, denosumab, deslorelina, cloruro de dibrospidio, docetaxel, doxifluridina, doxorubicina, doxorubicina + estrona, eculizumab, edrecolomab, acetato de eliptinio, eltrombopag, endostatina, enocitabina, epirubicina, epitioestanol, epoyetina alfa, epoyetina beta, eptaplatino, eribulina, erlotinib, estradiol, estramustina, etopósido, everolimus, exemestano, fadrozol, filgrastim, fludarabina, fluorouracilo, flutamida, formestano, fotemustina, fulvestrant, nitrato de galio, ganirelix, gefitinib, gemcitabina, gemtuzumab, glutoxim, goserelina, diclorhidrato de histamina, histrelina, hidroxicarbamida, semillas de $I-^{125}$, ácido ibandrónico, ibritumomab tiuxetano, idarubicina, ifosfamida, imatinib, imiquimod, improsulfán, interferón alfa, interferón beta, interferón gamma, ipilimumab, irinotecano, ixabepilona, lanreotide, lapatinib, lenalidomide, lenograstim, lentinan, letrozol, leuprorelina, levamisole, lisuride, lobaplatino, lomustina, lonidamina, masoprocol, medroxiprogesterona, megestrol, melfalán, mepitioestano, mercaptopurina, metotrexato, metoxsalén, aminolevulinato de metilo, metiltestosterona, mifamurtide, miltefosina, miriplatino, mitobronitol, mitoguazona, mitolactol, mitomicina, mitotane, mitoxantrona, nedaplatino, nelarabina, nilotinib, nilutamida, nimotuzumab, nimustina, nitracrina, ofatumumab, omeprazol, oprelvekin, oxaliplatino, terapia con el gen p53, paclitaxel, palifermina, semilla de paladio-^{103}, ácido pamidrónico, panitumumab, pazopanib, pegaspargasa, PEG-epoyetina beta (metoxi PEG-epoyetina beta), pegfilgrastim,

peginterferón alfa-2b, pemetrexed, pentazocina, pentostatina, peplomicina, perfosfamida, picibanilo, pirarubicina, plerixafor, plicamicina, poliglusam, fosfato de poliestradiol, polisacárido-K, porfímero sódico, pralatrexato, prednimustina, procarbazina, quinagolida, cloruro de radio-223, raloxifeno, raltitrexed, ranimustina, razoxano, refametinib, regorafenib, ácido risedrónico, rituximab, romidepsina, romiplostim, sargramostim, sipuleucel-T, sizofirano, sobuzoxano, glicididazol sodio, sorafenib, estreptozocina, sunitinib, talaporfina, tamibaroteno, tamoxifeno, tasonermino, teceleuquina tegafur, tegafur + gimeracilo + oteracilo, temoporfina, temozolomida, temsirolimus, tenipósido, testosterona, tetrofosmina, talidomida, tiotepa, timalfasina, tioguanina, tocilizumab, topotecano, toremifeno, tositumomab, trabectedina, trastuzumab, treosulfano, tretinoína, trilostano, triptorelina, trofosfamida, triptofano, ubenimex, valrubicina, vandetanib, vapreotida, vemurafenib, vinblastina, vincristina, vindesina, vinflunina, vinorelbina, vorinostat, vorozol, itrio-^{90} microesferas de vidrio, zinostatina, zinostatina estimalámero, ácido zoledrónico, zorubicina.

Los compuestos de acuerdo con la invención y las sales de los mismos pueden existir en la forma de tautómeros que están incluidos en las formas de realización de la invención.

Dependiendo de su estructura, los compuestos de la invención pueden existir en diversas formas estereoisoméricas. Estas formas incluyen los isómeros de

configuración, u opcionalmente los isómeros de conformación (los enantiómeros y/o los diastereoisómeros, lo que abarca los atropisómeros). Por lo tanto, la presente invención abarca los enantiómeros, los diastereoisómeros y las mezclas de éstos. A partir de estas mezclas de enantiómeros y/o diastereoisómeros, pueden aislarse formas estereoisoméricas puras de acuerdo con métodos conocidos en la técnica, preferiblemente con métodos de cromatografía, especialmente de cromatografía líquida de alto desempeño (HPLC), usando una fase aquiral o quiral. Además, la invención incluye todas las mezclas de los estereoisómeros mencionados previamente, independientemente de la relación, incluyendo los racematos.

Algunos de los compuestos y las sales de acuerdo con la invención pueden existir en distintas formas cristalinas (formas polimórficas) que se hallan dentro del alcance de la invención.

Además, la invención abarca los derivados de los compuestos de la fórmula (I) que son convertidos en un compuesto de la fórmula (I) o una sal del mismo en un sistema biológico (bioprecursores o pro-drogas), o las sales de los mismos. Dicho sistema biológico es, por ejemplo, un organismo mamífero, en particular un sujeto humano. El bioprecursor, por ejemplo, es convertido en el compuesto de la fórmula (I) o una sal del mismo en procesos metabólicos.

Ahora se ha encontrado, y esto constituye la base de la presente invención, que dichos compuestos de la presente invención presentan propiedades sorprendentes y ventajosas.

En particular, se ha encontrado sorprendentemente que dichos compuestos de la presente invención inhiben efectivamente la Bub1 quinasa y por ello se pueden usar para el tratamiento o la profilaxis de enfermedades de crecimiento, proliferación y/o supervivencia celular descontrolado, respuestas celulares inmunes inapropiadas o respuestas celulares inflamatorias inapropiadas o enfermedades acompañadas de un crecimiento, proliferación y/o supervivencia celular descontrolado, respuestas celulares inmunes inapropiadas o respuestas celulares inflamatorias inapropiadas, en particular en donde el crecimiento, la proliferación y/o la supervivencia celular descontrolada, las respuestas celulares inmunes inapropiadas o las respuestas celulares inflamatorias inapropiadas están mediadas por la Bub1 quinasa, tal como, por ejemplo, tumores hematológicos, tumores sólidos, y/o metástasis de los mismos, por ejemplo leucemias y síndrome mielodisplásico, linfomas malignos, tumores de cabeza y cuello incluyendo tumores de cerebro y metástasis de cerebro, tumores de tórax incluyendo tumores de pulmón de células no pequeñas y de células pequeñas, tumores gastrointestinales, tumores endócrinos, 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.

Los intermediarios usados para la síntesis de los compuestos de las reivindicaciones 1-6 que se describen a continuación así como su uso para la síntesis de los compuestos de las reivindicaciones 1-6 son un aspecto

adicional de la presente invención. Los intermediarios preferidos son los ejemplos de intermediarios, divulgados más adelante.

Procedimientos generales

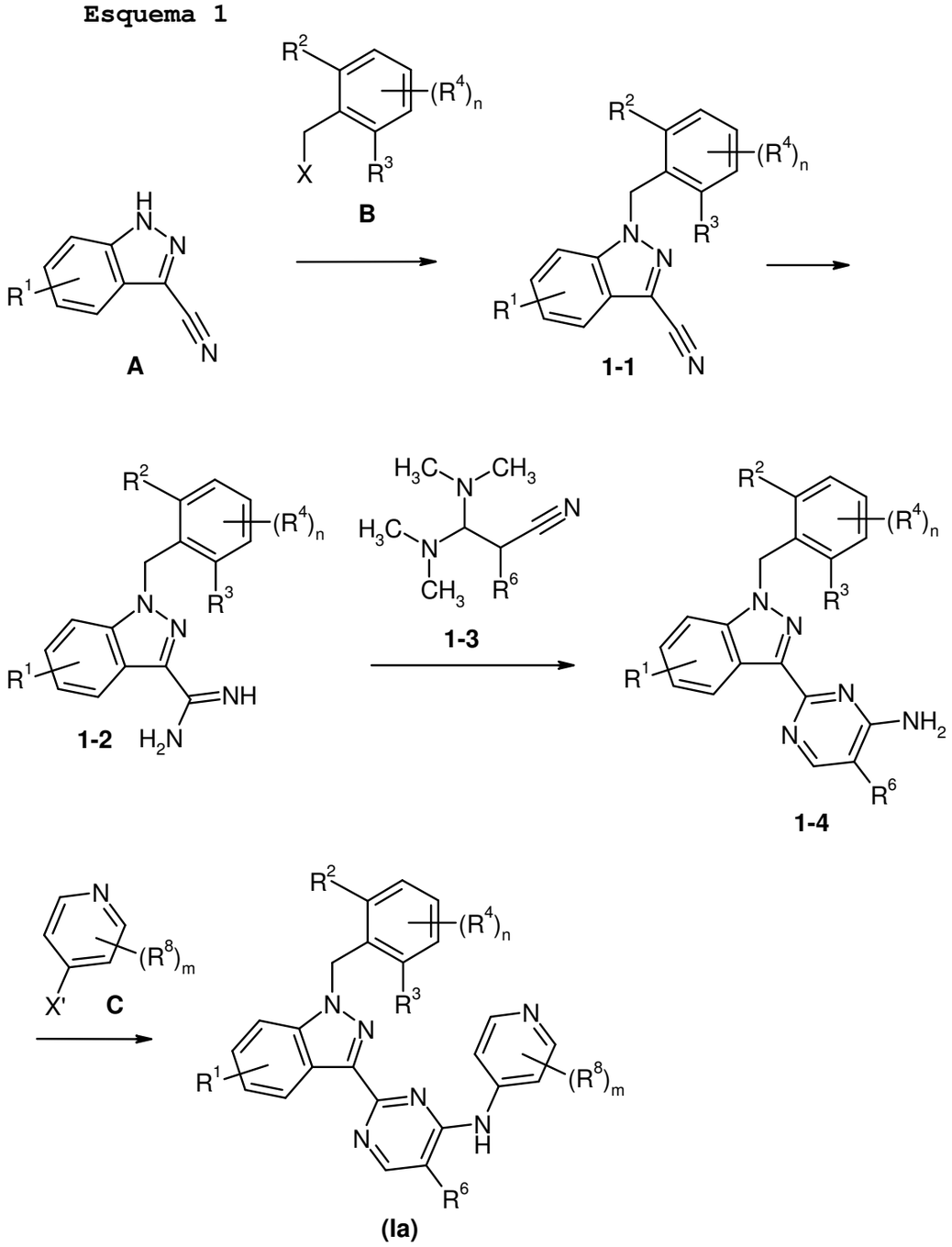
Los compuestos de acuerdo con la invención se pueden preparar de acuerdo con los siguientes esquemas 1 a 6,

En los esquemas y procedimientos que se describen a continuación se ilustran rutas de síntesis para preparar los compuestos de la fórmula general (I) de la invención, y no deben interpretarse en un sentido limitativo. Para el especialista en la técnica resultará evidente que se puede modificar el orden de las transformaciones ejemplificadas en los Esquemas de diversas maneras. Por ello es que el orden de las transformaciones ejemplificadas en los Esquemas no pretende ser limitativo. Además, se puede lograr una interconversión de cualquiera de los sustituyentes, R^1, R^2, R^3, R^4, R^6, R^7 o R^8 antes y/o después de las transformaciones ejemplificadas. Estas modificaciones pueden comprender la introducción de grupos protectores, la escisión de grupos protectores, la reducción o la oxidación de grupos funcionales, la halogenación, la metalación, la sustitución u otras reacciones conocidas por aquellos versados en la técnica. Estas transformaciones incluyen las que dan como resultado la introducción de una funcionalidad que permite una interconversión adicional de los sustituyentes. Los grupos protectores apropiados, su introducción y su escisión son bien conocidos por aquellos versados en la técnica (véase, por ejemplo, T.W. Greene y P.G.M. Wuts en *Protective Groups*

in Organic Synthesis, 3ª edición, Wiley 1999). En los párrafos subsiguientes se describen ejemplos específicos.

En el Esquema 1 se describe una ruta para la preparación de los compuestos de la fórmula general (Ia). En los casos donde esta ruta no sea factible, se puede aplicar el esquema 2.

Esquema 1



Esquema 1: Ruta para la preparación de los compuestos de la fórmula general (Ia), en donde R^1, R^2, R^3, R^4, R^6, R^8, m y n tienen el significado indicado para la fórmula general (I), *supra*. Además, se puede lograr una interconversión de cualquiera de los sustituyentes, R^1, R^2, R^3, R^4, R6 o R^8 antes y/o después de las transformaciones ejemplificadas. Estas modificaciones pueden comprender la introducción de grupos protectores, la escisión de grupos protectores, la reducción o la oxidación de grupos funcionales, la halogenación, la metalación, la sustitución u otras reacciones conocidas por aquellos versados en la técnica. Estas transformaciones incluyen las que dan como resultado la introducción de una funcionalidad que permite una interconversión adicional de los sustituyentes. Los grupos protectores apropiados, su introducción y su escisión son bien conocidos por aquellos versados en la técnica (véase, por ejemplo, T.W. Greene y P.G.M. Wuts en *Protective Groups in Organic Synthesis*, 3ª edición, Wiley 1999). En los párrafos subsiguientes se describen ejemplos específicos.

Los compuestos A, B y C se encuentran disponibles comercialmente o se pueden preparar de acuerdo con procedimientos disponibles de dominio público, conocidos por un especialista en el arte. Los ejemplos específicos de los mismos se describen en los párrafos siguientes. X representa un grupo saliente tal como por ejemplo un Cl, Br o I, o X representa un sulfonato de arilo tal como por ejemplo sulfonato de p-tolueno o un sulfonato de alquilo tal como por ejemplo sulfonato de metano o sulfonato de

trifluorometano. X' representa F, Cl, Br, I, ácido borónico o un éster de ácido borónico, tal como por ejemplo 4,4,5,5-tetrametil-2-fenil-1,3,2-dioxaborolano (pinacoléster de ácido borónico).

Se puede hacer reaccionar un 1*H*-indazol-3-carbonitrilo convenientemente sustituido (A) con un haluro de bencilo o un sulfonato de bencilo de la fórmula general (B) convenientemente sustituido, tal como, por ejemplo, un bromuro de bencilo, en un sistema de solventes adecuado, tal como, por ejemplo, *N,N*-dimetilformamida, en la presencia de una base adecuada, tal como, por ejemplo, carbonato de cesio a temperaturas en el rango de entre −78°C y temperatura ambiente, preferiblemente la reacción tiene lugar a temperatura ambiente, para proveer los intermediarios 1-bencil-1H-indazol-3-carbonitrilo de la fórmula general (1-1).

Los intermediarios de la fórmula general (1-1) se pueden convertir en los intermediarios de la fórmula general (1-2) mediante reacción con un alcoholato adecuado, tal como, por ejemplo metanolato de sodio, en un sistema de solventes adecuado, tal como, por ejemplo, el alcohol correspondiente, por ejemplo metanol, a una temperatura de entre temperatura ambiente y el punto de ebullición del solvente respectivo, preferiblemente la reacción tiene lugar a temperatura ambiente, y el tratamiento subsiguiente con una fuente adecuada de amonio, tal como por ejemplo, cloruro de amonio, en la presencia de un ácido adecuado, tal como por ejemplo ácido acético en un rango de temperaturas de entre temperatura ambiente y el punto de

ebullición del solvente respectivo, preferiblemente la reacción se lleva a cabo a 50°C.

Los intermediarios de la fórmula general (1-2) se hacen reaccionar con un 3,3-bis(dimetilamino)propan-nitrilo convenientemente sustituido de la fórmula general (1-3), tal como, por ejemplo 3,3-bis(dimetilamino)-2-metoxipropan-nitrilo, en la presencia de una base adecuada, tal como, por ejemplo piperidina, en un sistema de solventes adecuado, tal como, por ejemplo, 3-metilbutan-1-ol, en un rango de temperaturas de entre temperatura ambiente y el punto de ebullición del solvente respectivo, preferiblemente la reacción se lleva a cabo a 100°C, para proveer intermediarios de la fórmula general (1-4).

Los intermediarios de la fórmula general (1-4) se pueden hacer reaccionar con una 4-halopiridina adecuada de la fórmula general (C), tal como, por ejemplo 4-bromopiridina, en la presencia de una base adecuada, tal como, por ejemplo 2-metilpropan-2-olato de sodio o carbonato de potasio. Opcionalmente, se puede agregar un catalizador de paladio adecuado, tal como por ejemplo (1*E*,4*E*)-1,5-difenilpenta-1,4-dien-3-on-paladio, y un ligando adecuado, tal como por ejemplo 1'-binaftalen-2,2'-diilbis(difenilfosfano). La reacción se lleva a cabo en un sistema de solventes adecuado, tal como, por ejemplo, *N,N*-dimetilformamida, en un rango de temperaturas de entre temperatura ambiente y el punto de ebullición del solvente respectivo, preferiblemente la reacción se lleva a cabo a 100°C, para proveer compuestos de la fórmula general (Ia). Como alternativa, se pueden usar los siguientes

catalizadores de paladio:

dímero de cloruro de alilpaladio, diclorobis(benzonitrilo)paladio (II), acetato de paladio (II), cloruro de paladio (II), tetrakis(trifenilfosfina)paladio (0), tris(dibencilidenacetona)dipaladio (0), opcionalmente con la adición de los siguientes ligandos:

2,2'-bis(difenilfosfino)-1,1'-binaftilo racémico, BINAP-rac, 1,1'-bis(difenilfosfino)ferroceno, bis(2-difenilfosfinofenil)éter, tetrafluoroborato de di-t-butilmetilfosfonio, 2-(di-t-butilfosfino)bifenilo, tetrafluoroborato de tri-t-butilfosfonio, tri-2-furilfosfina, tris(2,4-di-t-butilfenil)fosfito, tri-o-tolilfosfina o, favorablemente, (9,9-dimetil-9*H*-xanten-4,5-diil)bis(difenilfosfina).

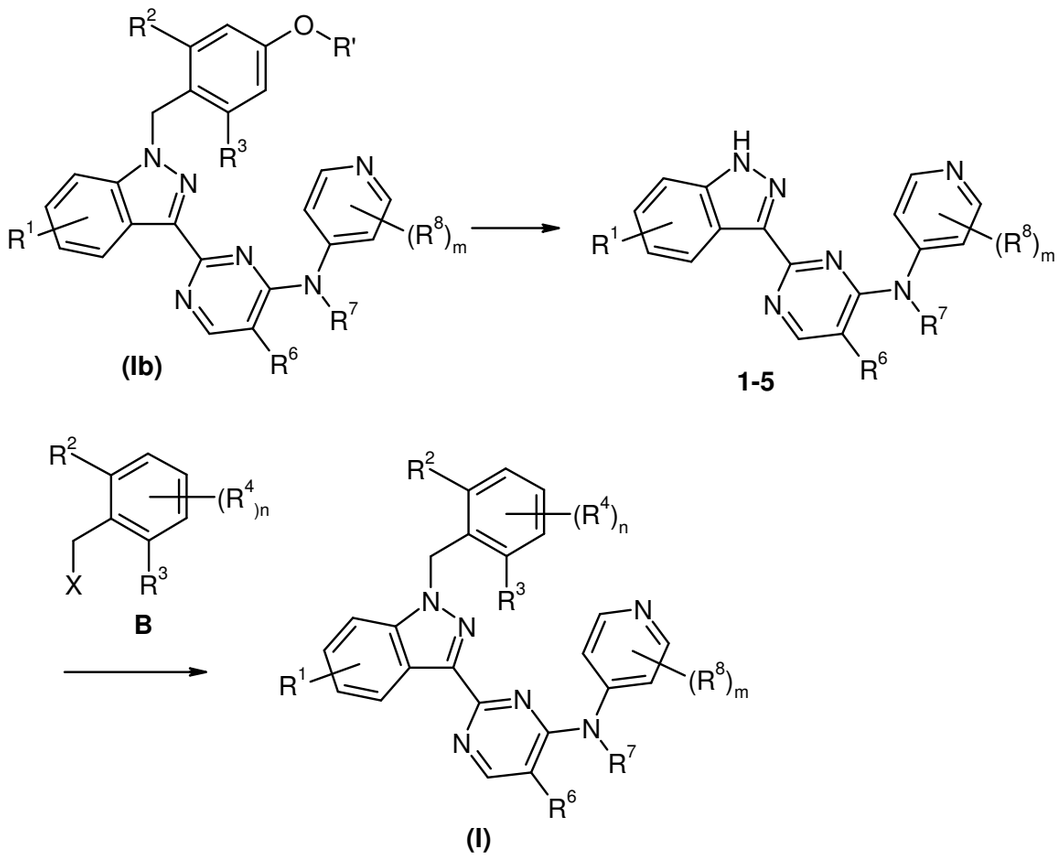
Como alternativa, los intermediarios de la fórmula general (1-4) se pueden hacer reaccionar con un ácido borónico o un pinacoléster de ácido borónico adecuado de la fórmula general (C), tal como, por ejemplo ácido (2-fluoropiridin-4-il)borónico, en la presencia de una base adecuada, tal como, por ejemplo trietilamina, un agente de activación adecuado, tal como por ejemplo N,N-dimetilpiridin-4-amina y una sal de cobre adecuada, tal como por ejemplo acetato de cobre (II), en un sistema de solventes adecuado, tal como, por ejemplo, triclorometano, en un rango de temperaturas de entre temperatura ambiente y el punto de ebullición del solvente respectivo, preferiblemente la reacción tiene lugar a temperatura ambiente para proveer compuestos de la fórmula general

(Ia).

Como alternativa, los intermediarios de la fórmula general (1-4) se pueden hacer reaccionar con un fluoruro de piridilo adecuado de la fórmula general (C, donde X' es F), tal como, por ejemplo clorhidrato de 4-fluoropiridina, en la presencia de una base adecuada, tal como, por ejemplo hidruro de sodio, en un sistema de solventes adecuado, tal como, por ejemplo, dimetilformamida, en un rango de temperaturas de entre temperatura ambiente y el punto de ebullición del solvente respectivo, preferiblemente la reacción se lleva a cabo a 90°C para proveer compuestos de la fórmula general (Ia).

Los compuestos de la fórmula general (I) también se pueden sintetizar de acuerdo con el procedimiento representado en el Esquema 2.

Esquema 2



Esquema 2: Ruta alternativa para la preparación de los compuestos de la fórmula general (I), en donde R^1, R^2, R^3, R^4, R^6, R^7, R^8, m y n tienen el significado indicado para la fórmula general (I), *supra*. R' es, por ejemplo, alquilo o bencilo, preferiblemente metilo o etilo. Además, se puede lograr una interconversión de cualquiera de los sustituyentes, R^1, R^2, R^3, R^4, R^6, R^7 o R^8 antes y/o después de las transformaciones ejemplificadas. Estas modificaciones pueden comprender la introducción de grupos protectores, la escisión de grupos protectores, la reducción o la oxidación de grupos funcionales, la halogenación, la metalación, la sustitución u otras reacciones conocidas por aquellos versados en la técnica. Estas transformaciones incluyen las que dan como resultado la introducción de una funcionalidad que permite una

interconversión adicional de los sustituyentes. Los grupos protectores apropiados, su introducción y su escisión son bien conocidos por aquellos versados en la técnica (véase, por ejemplo, T.W. Greene y P.G.M. Wuts en *Protective Groups in Organic Synthesis*, 3ª edición, Wiley 1999). Además, en los párrafos subsiguientes se describen ejemplos específicos.

Los compuestos de la fórmula (Ib) se pueden preparar usando los métodos de síntesis descritos en el contexto del Esquema 1; la introducción de un R^7 diferente de hidrógeno se puede llevar a cabo, entre otros, mediante los métodos descritos en el Esquema 5. Los compuestos B se encuentran disponibles comercialmente o se pueden preparar de acuerdo con procedimientos disponibles de dominio público, conocidos por un especialista en el arte como se indicó previamente debajo del esquema 1.

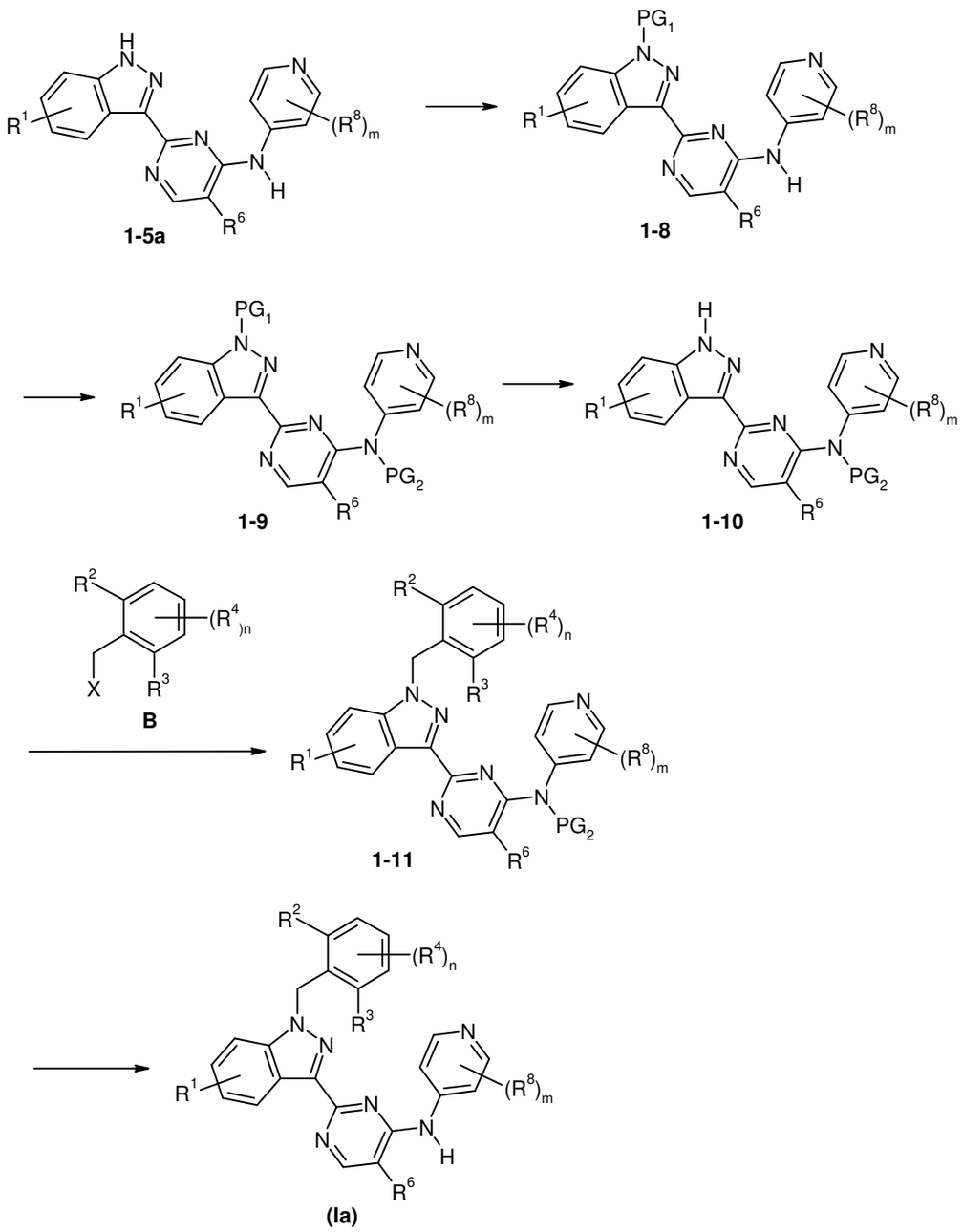
Los compuestos de la fórmula general (Ib) son convertidos en intermediarios de la fórmula general (1-5) mediante tratamiento con un sistema ácido adecuado, tal como, por ejemplo una mezcla de ácido trifluoroacético y ácido trifluorometansulfónico, en un solvente adecuado, tal como, por ejemplo, dicloroetano, en un rango de temperaturas de entre temperatura ambiente y el punto de ebullición del solvente respectivo, preferiblemente la reacción tiene lugar a temperatura ambiente.

Los intermediarios de la fórmula general (1-5) se puede hacer reaccionar con un haluro de bencilo o un sulfonato de bencilo de la fórmula general (B) convenientemente sustituido, tal como, por ejemplo, un

bromuro de bencilo, en un sistema de solventes adecuado, tal como, por ejemplo, tetrahidrofurano, en la presencia de una base adecuada, tal como, por ejemplo, hidruro de sodio en un rango de temperaturas de entre temperatura ambiente y el punto de ebullición del solvente respectivo, preferiblemente la reacción tiene lugar a temperatura ambiente, para proveer compuestos de la fórmula general (I). Dicha reacción también puede dar como resultado una conversión doble del intermediario (1-5) si R^7 es hidrógeno, dando lugar a compuestos formados junto con los compuestos de interés, en donde R^7 es un grupo bencílico idéntico a la porción bencílica unida al nitrógeno del indazol.

En algunos casos, los compuestos de la fórmula general (Ia) se pueden preparar ventajosamente mediante una ruta que emplea grupos protectores adicionales, de acuerdo con el procedimiento representado en el Esquema 2a, con el fin de evitar la bisbencilación mencionada previamente. Preferiblemente, los ejemplos 2-1-3, 2-2-3, 2-3-3, 2-4-3, 2-5-3, 2-6-3, 2-7-3, 2-8-3, 2-9-3 se prepararon utilizando esta ruta.

Esquema 2a



Esquema 2a: Una ruta modificada para la preparación de los compuestos de la fórmula general (Ia), en donde R^1, R^2, R^3, R^4, R^6, R^8, m y n tienen el significado indicado para la fórmula general (I), *supra*. PG_1 y PG_2 son, de manera independiente entre sí, un grupo protector, por ejemplo t-butoxicarbonilo (boc), aliloxicarbonilo (aloc) o benzoílo. Además, se puede lograr una interconversión de cualquiera de los sustituyentes, R^1, R^2, R^3, R^4, R^6 o R^8 antes y/o

después de las transformaciones ejemplificadas. Estas modificaciones pueden comprender la introducción de grupos protectores, la escisión de grupos protectores, la reducción o la oxidación de grupos funcionales, la halogenación, la metalación, la sustitución u otras reacciones conocidas por aquellos versados en la técnica. Estas transformaciones incluyen las que dan como resultado la introducción de una funcionalidad que permite una interconversión adicional de los sustituyentes. Los grupos protectores apropiados, su introducción y su escisión son bien conocidos por aquellos versados en la técnica (véase, por ejemplo, T.W. Greene y P.G.M. Wuts en *Protective Groups in Organic Synthesis*, 3ª edición, Wiley 1999). Además, en los párrafos subsiguientes se describen ejemplos específicos.

Los compuestos B se encuentran disponibles comercialmente o se pueden preparar de acuerdo con procedimientos disponibles de dominio público, conocidos por un especialista en el arte como se indicó previamente debajo del esquema 1.

Los intermediarios de la fórmula general (1-5a), que se pueden obtener por analogía con el Esquema 2, se pueden preparar mediante un grupo protector adecuado tal como, por ejemplo, ter-butoxicarbonilo con un reactivo adecuado, tal como, por ejemplo, di-ter-butildicarbonato, en la presencia de una base adecuada, tal como, por ejemplo, hidróxido de sodio en agua, en un sistema de solventes adecuado, tal como, por ejemplo, metanol, en un rango de temperatura de entre 0 °C y temperatura ambiente, preferiblemente la

reacción tiene lugar a temperatura ambiente, para proveer compuestos de la fórmula general (1-8).

Los intermediarios de la fórmula general (1-8) se pueden preparar con un grupo protector adecuado tal como, por ejemplo, aliloxicarbonilo o benzoílo con un reactivo adecuado, tal como, por ejemplo, cloroformiato de alilo o cloruro de benzoílo, en un sistema de solventes adecuado, tal como, por ejemplo, piridina, en un rango de temperaturas de entre temperatura ambiente y el punto de ebullición del solvente respectivo, preferiblemente la reacción tiene lugar a temperatura ambiente, para proveer compuestos de la fórmula general (1-9).

Los intermediarios de la fórmula general (1-9) se pueden desproteger bajo condiciones adecuadas tal como, por ejemplo, ácido clorhídrico o ácido trifluoroacético, en un sistema de solventes adecuado, tal como, por ejemplo, dioxano o diclorometano, en un rango de temperatura de entre 0 °C y temperatura ambiente, para proveer compuestos de la fórmula general (1-10)

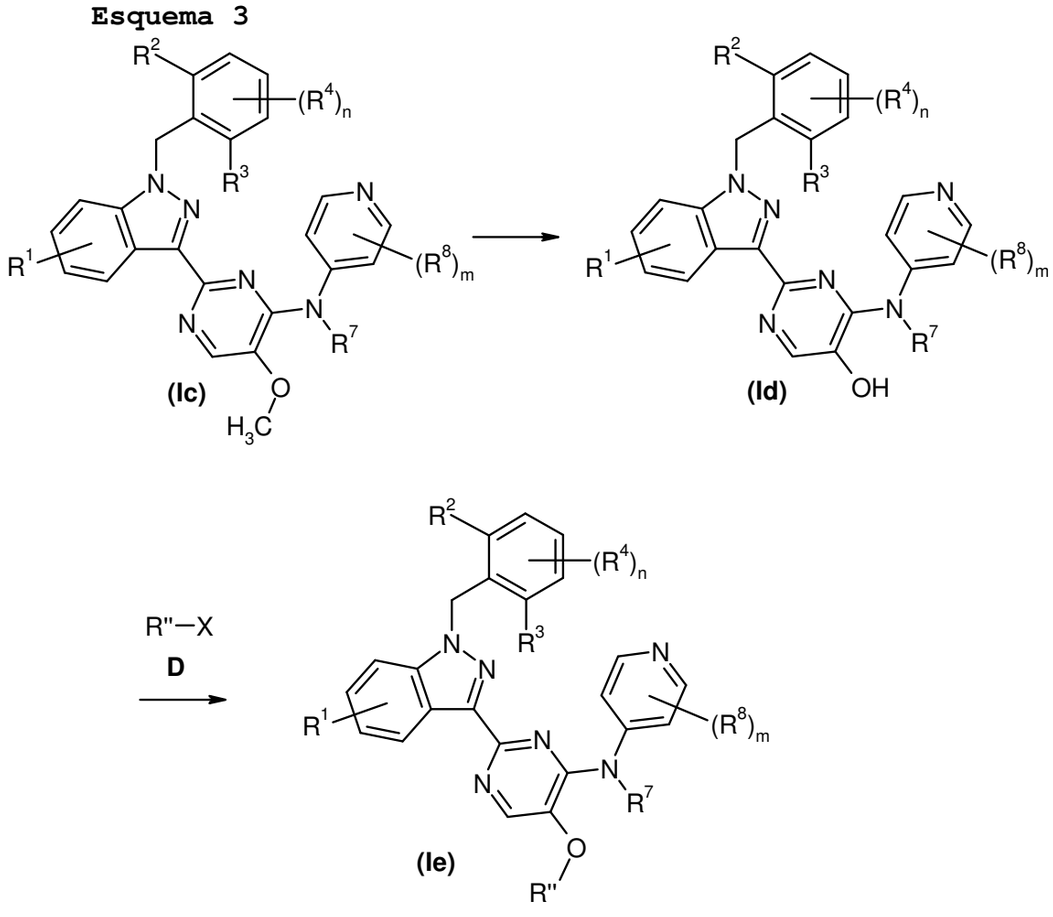
Los intermediarios de la fórmula general (1-10) se puede hacer reaccionar con un haluro de bencilo o un sulfonato de bencilo de la fórmula general (B) convenientemente sustituido, tal como, por ejemplo, un bromuro de bencilo, en un sistema de solventes adecuado, tal como, por ejemplo, tetrahidrofurano, en la presencia de una base adecuada, tal como, por ejemplo, hidruro de sodio en un rango de temperaturas de entre temperatura ambiente y el punto de ebullición del solvente respectivo, preferiblemente la reacción tiene lugar a temperatura

ambiente, para proveer compuestos de la fórmula general (1-11).

Los intermediarios de la fórmula general (1-11) se pueden desproteger bajo condiciones adecuadas tal como, por ejemplo, pirrolidina, tetrakis(trifenilfosfin)paladio o hidruro de sodio, o hidróxido de potasio, en un sistema de solventes adecuado, tal como, por ejemplo, dioxano, agua, tetrahidrofurano o etanol, en un rango de temperatura de entre 0 °C y temperatura ambiente para proveer compuestos de la fórmula general (Ia).

Los compuestos de la fórmula general (Ie) y (Id) se pueden sintetizar a partir de compuestos de la fórmula general (Ic), de acuerdo con el procedimiento representado en el Esquema 3.

Esquema 3

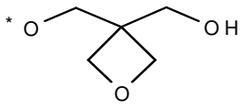


Esquema 3: Proceso para la preparación de compuestos de la fórmula general (Id) por des-metilación de compuestos de la fórmula general (Ic) y subsiguiente eterificación para proveer compuestos de la fórmula general (Ie), en donde R^1, R^2, R^3, R^4, R^7, R^8, m y n tienen el significado indicado para la fórmula general (I), *supra*. Además, se puede lograr una interconversión de cualquiera de los sustituyentes, R^1, R^2, R^3, R^4, R7 o R^8 antes y/o después de las transformaciones ejemplificadas. Estas modificaciones pueden comprender la introducción de grupos protectores, la escisión de grupos protectores, la reducción o la oxidación de grupos funcionales, la halogenación, la metalación, la sustitución u otras reacciones conocidas por aquellos versados en la técnica. Estas transformaciones incluyen las que dan como resultado la introducción de una funcionalidad que permite una interconversión adicional de los sustituyentes. Los grupos protectores apropiados, su introducción y su escisión son bien conocidos por aquellos versados en la técnica (véase, por ejemplo, T.W. Greene y P.G.M. Wuts en *Protective Groups in Organic Synthesis*, 3ª edición, Wiley 1999).

Los compuestos de la fórmula (Ic) se pueden preparar usando los métodos de síntesis descritos en el contexto del Esquema 1; la introducción de un R^7 diferente de hidrógeno se puede llevar a cabo, entre otros, mediante los métodos descritos en el Esquema 5.

Los compuestos de la fórmula general D se encuentran disponibles comercialmente, en donde X representa un grupo saliente tal como por ejemplo un Cl, Br o I, o X representa

un sulfonato de arilo tal como, por ejemplo, sulfonato de p-tolueno, o un sulfonato de alquilo tal como por ejemplo sulfonato de metano o trifluorosulfonato de metano (grupo triflato). R'' = 1-6C-alquilo (de manera independiente sustituido opcionalmente uno o más veces con hidroxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{10}R^{11}$, -S-(1-6C-alquilo), -S(O)-(1-6C-alquilo), $-S(O)_2$-(1-6C-alquilo), $SO_2NR^{10}R^{11}$, heterociclilo (que a su vez está sustituido opcionalmente con $C(O)OR^9$ u oxo (=O)), heteroarilo (que a su vez está sustituido opcionalmente una o más veces con ciano, 1-4C-alquilo, 1-6C-haloalquilo, 1-6C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, -(2-6C-alquil)-O-1-6C-alquilo), 3-7C-cicloalquilo, halógeno o



, donde * es el punto de unión.

Los compuestos de la fórmula general (Ic) son convertidos en compuestos de la fórmula general (Id) mediante tratamiento con un agente de desmetilación adecuado, tal como por ejemplo benzentiol, en un solvente adecuado, tal como, por ejemplo, 1-metilpirrolidin-2-ona, en la presencia de una base adecuada, tal como, por ejemplo carbonato de potasio, en un rango de temperaturas de entre temperatura ambiente y el punto de ebullición del solvente respectivo, preferiblemente la reacción se lleva a cabo a 190°C.

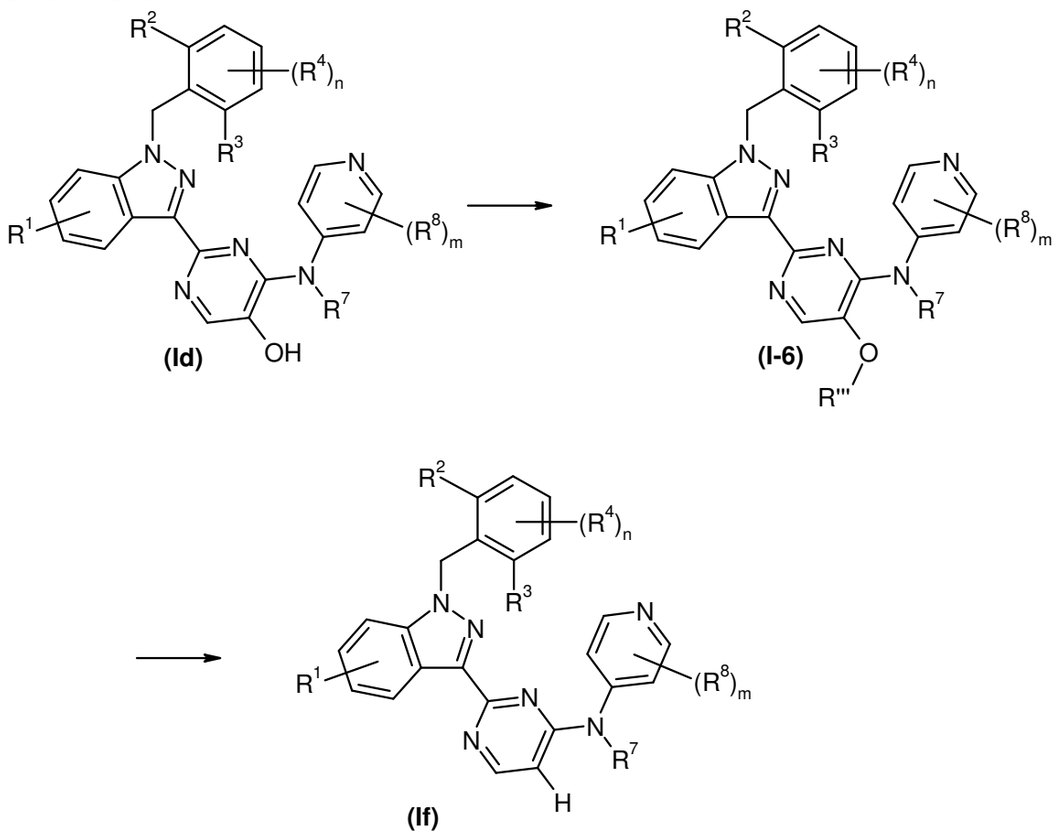
Los compuestos de la fórmula general (Id) se hacen reaccionar luego con un compuesto de la fórmula general (D) mencionado precedentemente, en un solvente adecuado, tal como, por ejemplo, *N,N*-dimetilformamida, en la presencia de una base adecuada, tal como, por ejemplo, carbonato de

potasio en un rango de temperaturas de entre temperatura ambiente y el punto de ebullición del solvente respectivo, preferiblemente la reacción tiene lugar a temperatura ambiente, para proveer compuestos de la fórmula general (Ie).

Los compuestos de la fórmula general (Id) se pueden convertir en compuestos de la fórmula general (If) de acuerdo con el procedimiento representado en el Esquema 4.

Esquema 4

Durante el paso 2 de esta secuencia los residuos potencialmente podrían sufrir una modificación, por ejemplo reducción.



Esquema 4: Proceso para la transformación de compuestos de la fórmula general (Id) en compuestos de la fórmula general (If), por medio de un intermediario de la

fórmula general (I-6), en donde R^1, R^2, R^3, R^4, R^7, R^8, m y n tienen el significado indicado para la fórmula general (I), *supra*. Además, se puede lograr una interconversión de cualquiera de los sustituyentes, R^1, R^2, R^3, R^4, R7 o R^8 antes y/o después de las transformaciones ejemplificadas. Estas modificaciones pueden comprender la introducción de grupos protectores, la escisión de grupos protectores, la reducción o la oxidación de grupos funcionales, la halogenación, la metalación, la sustitución u otras reacciones conocidas por aquellos versados en la técnica. Estas transformaciones incluyen las que dan como resultado la introducción de una funcionalidad que permite una interconversión adicional de los sustituyentes. Los grupos protectores apropiados, su introducción y su escisión son bien conocidos por aquellos versados en la técnica (véase, por ejemplo, T.W. Greene y P.G.M. Wuts en *Protective Groups in Organic Synthesis*, 3ª edición, Wiley 1999).

O-R''' representa un grupo saliente adecuado, por ejemplo un grupo triflato, un grupo nonaflato.

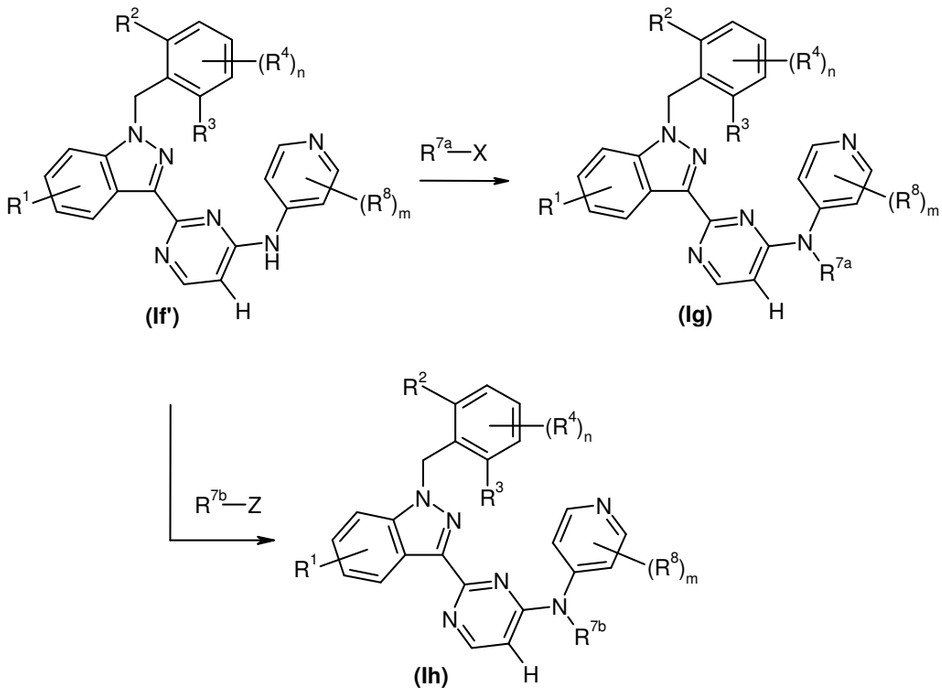
Los compuestos de la fórmula general (Id) se pueden convertir en intermediarios de la fórmula general (I-6) por reacción con un derivado de ácido sulfónico adecuado, tal como, por ejemplo anhídrido trifluorometansulfónico o fluoruro de 1,1,2,2,3,3,4,4,4-nonafluorobutan-1-sulfonilo, en un solvente adecuado, tal como, por ejemplo, diclorometano, en la presencia de una base adecuada, tal como, por ejemplo piridina, en un rango de temperaturas de entre temperatura ambiente y el punto de ebullición del solvente respectivo, preferiblemente la reacción tiene

lugar a temperatura ambiente.

Los intermediarios de la fórmula general (I-6) se hacen reaccionar luego con una fuente de hidruro adecuada, tal como, por ejemplo, trietilsilano, en un solvente adecuado tal como, por ejemplo, *N,N*-dimetilformamida (DMF), en la presencia de un catalizador de Pd adecuado, tal como, por ejemplo, acetato de paladio (II) junto con un ligando adecuado, tal como, por ejemplo, propan-1,3-diilbis(difenilfosfano) en un rango de temperaturas de entre temperatura ambiente y el punto de ebullición del solvente respectivo, preferiblemente la reacción se lleva a cabo a 60°C, para proveer compuestos de la fórmula general (If).

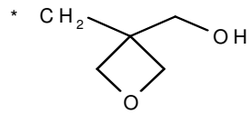
Los compuestos de la fórmula general (If ') que es un compuesto de la fórmula (If) en donde R^7 = hidrógeno, se pueden convertir en compuestos de la fórmula general (Ig y Ih) de acuerdo con el procedimiento representado en el Esquema 5.

Esquema 5



Esquema 5: Proceso para la transformación de compuestos de la fórmula general (If') en compuestos de la fórmula general (Ig) y (Ih), en donde R^1, R^2, R^3, R^4, R^8, m y n tienen el significado indicado para la fórmula general (I), *supra*. Además, se puede lograr una interconversión de cualquiera de los sustituyentes, R^1, R^2, R^3, R^4, R^{7a}, R^{7b} o R^8 antes y/o después de las transformaciones ejemplificadas. Estas modificaciones pueden comprender la introducción de grupos protectores, la escisión de grupos protectores, la reducción o la oxidación de grupos funcionales, la halogenación, la metalación, la sustitución u otras reacciones conocidas por aquellos versados en la técnica. Estas transformaciones incluyen las que dan como resultado la introducción de una funcionalidad que permite una interconversión adicional de los sustituyentes. Los grupos protectores apropiados, su introducción y su escisión son bien conocidos por aquellos versados en la técnica (véase, por ejemplo, T.W. Greene y P.G.M. Wuts en *Protective Groups*

in Organic Synthesis, 3ª edición, Wiley 1999).

R^{7a} representa 1-6C-alquilo, de manera independiente opcionalmente sustituido una o más veces con heteroarilo, halógeno, hidroxi, o R^{7a} representa 

, donde * es el punto de unión, o R^{7a} representa bencilo, donde el anillo fenilo está sustituido opcionalmente con 1-5 sustituyentes seleccionados de manera independiente del grupo que consiste en hidrógeno, halógeno, 1-4Calquilo, 1-4C-haloalquilo, 1-4C-alcoxi, 1-4C-haloalcoxi, ciano, $C(O)OR^9$. X es como se define debajo del esquema 1, *supra*, o por ejemplo 2-óxido de 1,3,2-dioxatiolano.

R^{7b} representa una porción acilo, tal como -C(O)-(1-6C-alquilo), -C(O)-(1-6C-alquilen)-O-(1-6C-alquilo), -C(O)-(1-6C-alquilen)-O-(2-6C-alquilen)-O-(1-6C-alquilo), -C(O)-heterociclilo y Z representa un halógeno, hidroxi o $-O-R^{7b}$.

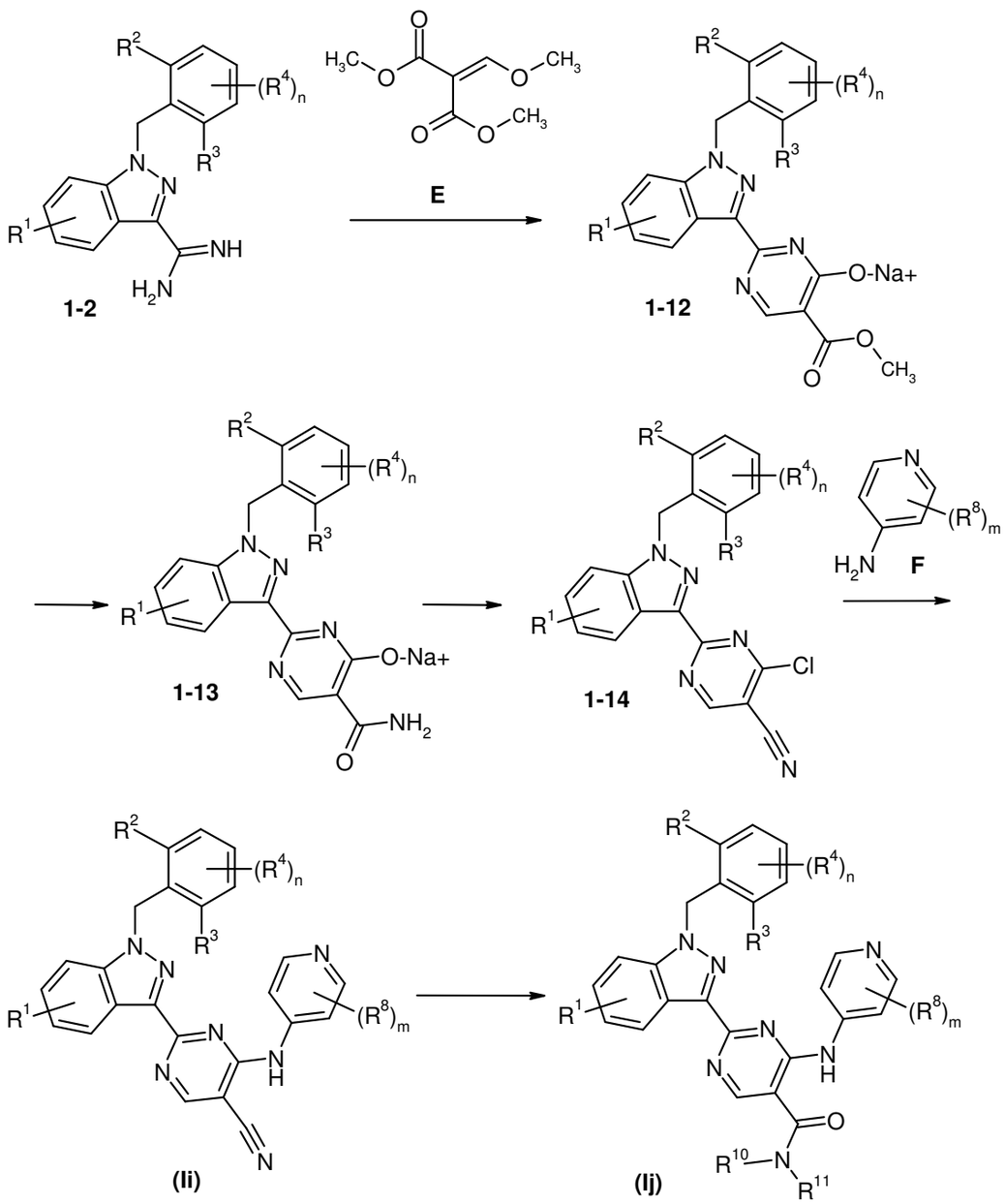
Los compuestos de la fórmula general (If') son convertidos en compuestos de la fórmula general (Ig) por reacción con un haloalquilo o dioxatiolano 2-óxido adecuado, tal como, por ejemplo 1,3,2-dioxatiolano 2-óxido, en un sistema de solventes adecuado, tal como, por ejemplo, N,N-dimetilformamida, en la presencia de una base adecuada, tal como, por ejemplo carbonato de cesio, en un rango de temperaturas de entre temperatura ambiente y el punto de ebullición del solvente respectivo, preferiblemente la reacción se lleva a cabo a 60°C.

Los compuestos de la fórmula general (If') son convertidos en compuestos de la fórmula general (Ih) por reacción con un derivado de ácido carboxílico adecuado, tal

como por ejemplo un halogenuro de ácido carboxílico por ejemplo cloruro de ácido carboxílico, o un anhídrido de ácido carboxílico, en un solvente adecuado, tal como, por ejemplo, diclorometano, en la presencia de una base adecuada, tal como, por ejemplo *N,N*-dietiletanamina, en un rango de temperaturas de entre temperatura ambiente y el punto de ebullición del solvente respectivo, preferiblemente la reacción tiene lugar a temperatura ambiente.

Los compuestos de las fórmulas generales (Ii) y (Ij) se pueden sintetizar de acuerdo con el procedimiento representado en el Esquema 6.

Esquema 6



Esquema 6: Ruta para la preparación de compuestos de la fórmula general (Ii) y (Ij), en donde R^1, R^2, R^3, R^4, R^8, m y n tienen el significado indicado para la fórmula general (I), *supra*. Además, se puede lograr una interconversión de cualquiera de los sustituyentes, R^1, R^2, R^3, R^4 o R^8 antes y/o después de las transformaciones ejemplificadas. Estas modificaciones pueden comprender la introducción de grupos protectores, la escisión de grupos protectores, la reducción o la oxidación de grupos

funcionales, la halogenación, la metalación, la sustitución u otras reacciones conocidas por aquellos versados en la técnica. Estas transformaciones incluyen las que dan como resultado la introducción de una funcionalidad que permite una interconversión adicional de los sustituyentes. Los grupos protectores apropiados, su introducción y su escisión son bien conocidos por aquellos versados en la técnica (véase, por ejemplo, T.W. Greene y P.G.M. Wuts en *Protective Groups in Organic Synthesis*, 3ª edición, Wiley 1999).

Los compuestos E y F se encuentran disponibles comercialmente. R^{10} y R^{11} tienen el significado indicado para la fórmula general (I), *supra*.

Una carboximidamida convenientemente sustituida o su respectivo clorhidrato de la fórmula general (1-2), tal como por ejemplo, clorhidrato de 1-(2-fluorobencil)-1H-indazol-3-carboximidamida (1:1), se puede hacer reaccionar con (metoximetiliden)propandioato de dimetilo (E), en un sistema de solventes adecuado, tal como, por ejemplo, metanol, en la presencia de una base adecuada, tal como, por ejemplo, metanolato de sodio a temperaturas en el rango de entre temperatura ambiente y el punto de ebullición del solvente, preferiblemente la reacción se lleva a cabo a 60°C, para proveer intermediarios de la fórmula general (1-12).

Los intermediarios de la fórmula general (1-12) se pueden convertir en intermediarios de la fórmula general (1-13) por reacción con una fuente adecuada de amoníaco, tal como, por ejemplo amoníaco 7 N, en un sistema de

solventes adecuado, tal como, por ejemplo metanol, a temperaturas en el rango de entre temperatura ambiente y el punto de ebullición del solvente, preferiblemente la reacción se lleva a cabo a 60°C, para proveer intermediarios de la fórmula general (1-13).

Los intermediarios de la fórmula general (1-13) se pueden convertir en intermediarios de la fórmula general (1-14) por reacción con una fuente adecuada de cloruro, tal como, por ejemplo tricloruro fosfórico, puro, en la presencia de una base adecuada, tal como, por ejemplo, N,N-dietilanilina, a temperaturas en el rango de entre temperatura ambiente y el punto de ebullición del solvente, preferiblemente la reacción se lleva a cabo a 90°C, para proveer intermediarios de la fórmula general (1-14).

Los intermediarios de la fórmula general (1-14) se pueden convertir en intermediarios de la fórmula general (Ii) por reacción con una piridin-4-amina convenientemente sustituida, tal como, por ejemplo piridin-4-amina, en un sistema de solventes adecuado, tal como, por ejemplo N,N-dimetilformamida, a temperaturas en el rango de entre temperatura ambiente y el punto de ebullición del solvente, preferiblemente la reacción tiene lugar a temperatura ambiente, para proveer compuestos de la fórmula general (Ii).

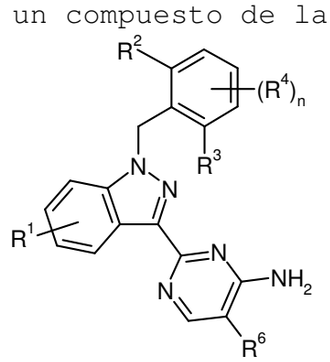
Los compuestos de la fórmula general (Ii) se pueden convertir en compuestos de la fórmula general (Ij) mediante tratamiento con un ácido adecuado, tal como, por ejemplo ácido sulfúrico concentrado, a temperaturas en el rango de entre 0°C y temperatura ambiente, preferiblemente la

reacción tiene lugar a temperatura ambiente, para proveer compuestos de la fórmula general (Ij).

Un aspecto preferido de la invención es el proceso para la preparación de los compuestos de las reivindicaciones 1–6 de acuerdo con los ejemplos.

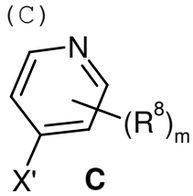
Un aspecto especial de la presente invención son los siguientes dos pasos de proceso:

1. Proceso para la elaboración de compuestos de la fórmula general (I) de acuerdo con la reivindicación 1, en donde R^7 es hidrógeno como se muestra en la fórmula (Ia), caracterizado porque un compuesto de la fórmula (1–4)



1-4

donde R^1, R^2, R^3, R^4, R^6 y n tienen el significado de acuerdo con la reivindicación 1, se hace reaccionar con un compuesto de la fórmula (C)

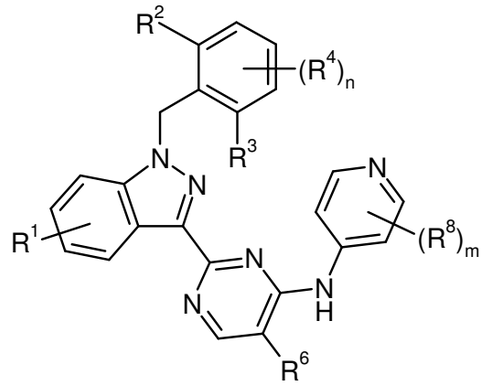


C

donde R^8 y m tienen el significado de acuerdo con la reivindicación 1, y X' representa F, Cl, Br, I, ácido borónico o un éster de ácido borónico,

en la presencia de una base adecuada, y un catalizador de paladio adecuado, opcionalmente en la presencia de un ligando adecuado, formando así un compuesto de la fórmula

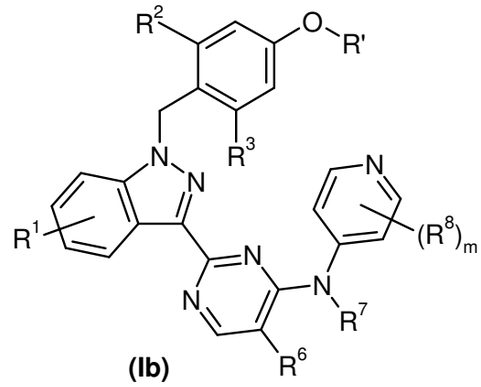
(Ia)



(Ia)

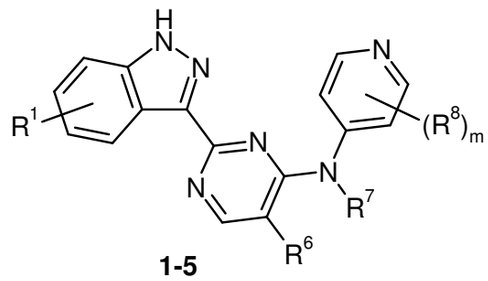
que luego se desprotege opcionalmente para formar un compuesto de la fórmula general (I) en donde R^7 es hidrógeno y R^1, R^2, R^3, R^4, R^6, R^8 y n y m tienen el significado definido en la reivindicación 1.

2. Proceso para la elaboración de compuestos de la fórmula general (I) de acuerdo con la reivindicación 1, en donde un compuesto de la fórmula (Ib)



(Ib)

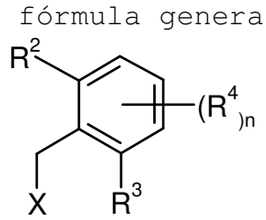
donde R^1, R^2, R^3, R^6, R^7 R^8 y m tienen el significado de acuerdo con la reivindicación 1 y R' es 1-6C-alquilo o bencilo, se trata con un sistema ácido adecuado para clivar el grupo bencílico con el fin de obtener un compuesto de la fórmula 1-5



1-5

.

seguido por reacción del compuesto de la fórmula 1-5 con un compuesto de la fórmula general (B),



B

en donde R^2, R^3, R^4 y n tienen el significado de acuerdo con la reivindicación 1, y en donde X representa un grupo saliente, en un sistema de solventes adecuado, en la presencia de una base adecuada, en un rango de temperaturas de entre temperatura ambiente y el punto de ebullición del solvente respectivo, para proveer compuestos de la fórmula general (I).

Otro aspecto de la invención es el intermediario de la fórmula general (1-5).

Los especialistas en el arte han de saber que, si hay una cantidad de centros reactivos en un compuesto de partida o intermediario, puede ser necesario bloquear uno o más centros reactivos de manera temporal para permitir que la reacción tenga lugar específicamente en el centro de reacción deseado. Por una descripción detallada del uso de una gran cantidad de grupos protectores efectivos véase, por ejemplo, T. W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1999, 3ª edición, o en P.

Kocienski, Protecting Groups, Thieme Medical Publishers, 2000.

Los compuestos de acuerdo con la invención se aíslan y se purifican de una manera conocida *per se*, por ejemplo, eliminando el solvente por destilación al vacío y cristalizando el residuo obtenido a partir de un solvente apropiado, o sometiéndolo a un método de purificación convencional conocido, tal como una cromatografía en un material de soporte apropiado. Además, la HPLC preparativa de fase reversa de los métodos de purificación que se describieron previamente pueden proporcionar aquellos compuestos de la presente invención que poseen una funcionalidad suficientemente básica o ácida puede dar como resultado la formación de una sal, tal como, en el caso de un compuesto de la presente invención que sea suficientemente básico, por ejemplo una sal trifluoroacetato o formiato o, en el caso de un compuesto de la presente invención que sea suficientemente ácido, por ejemplo una sal de amonio. Las sales de este tipo se pueden transformar en la forma de su base libre o de su ácido libre, respectivamente, utilizando diversos métodos conocidos por el especialista en el arte o se pueden usar como sales en los subsiguientes ensayos biológicos. Además, el proceso de secado durante el aislamiento de los compuestos de la presente invención probablemente no elimine por completo las trazas de cosolventes, en especial ácido fórmico o ácido trifluoroacético, para dar solvatos o complejos de inclusión. El especialista en el arte podrá reconocer los solvatos o complejos de inclusión que son

aceptables para su uso en los subsiguientes ensayos biológicos. Se podrá comprender que la forma específica (por ejemplo, la sal, la base libre, solvato, complejo de inclusión) de un compuesto de la presente invención aislado como se describe en la presente no es necesariamente la única forma en la cual se puede emplear dicho compuesto en un ensayo biológico con el fin de cuantificar la actividad biológica específica.

Las sales de los compuestos de la fórmula (I) de acuerdo con la invención se pueden obtener disolviendo el compuesto libre en un solvente apropiado (por ejemplo, una cetona, tal como acetona, metiletilcetona o metilisobutilcetona, un éter, tal como éter dietílico, tetrahidrofurano o dioxano, un hidrocarburo clorado, tal como cloruro de metileno o cloroformo, o un alcohol alifático de bajo peso molecular, tal como metanol, etanol o isopropanol) que contiene el ácido o la base deseada, o al cual se le agrega posteriormente el ácido o la base deseada. El ácido o la base se pueden emplear en la preparación de la sal, dependiendo de si se usa un ácido o una base mono o polibásica, y dependiendo de qué sal se desea, en una relación cuantitativa equimolar o una que difiere de ésta. Las sales se obtienen realizando una filtración, una nueva precipitación o una precipitación con una sustancia que no sirve como solvente para la sal, o evaporando el solvente. Las sales obtenidas se pueden convertir en los compuestos libres, que a su vez, se pueden convertir en las sales. De este modo, las sales no farmacéuticamente aceptables que se pueden obtener, por

ejemplo, como productos de un proceso de elaboración a escala industrial, se pueden convertir en sales farmacéuticamente aceptables en procesos conocidos por los especialistas en el arte.

Se prefieren especialmente los clorhidratos y el proceso usado en la sección de ejemplos.

Los diastereómeros puros y los enantiómeros puros de los compuestos y las sales de acuerdo con la invención se pueden obtener, por ejemplo, por síntesis asimétrica, usando compuestos de partida quirales en la síntesis, y separando las mezclas enantioméricas y diasterioméricas obtenidas en la síntesis.

Las mezclas enantioméricas y diasterioméricas se pueden separar en los enantiómeros puros y los diastereómeros puros de acuerdo con métodos conocidos por los especialistas en el arte. Preferentemente, las mezclas diastereoméricas se separan por cristalización, en particular, cristalización fraccionada, o cromatografía. Las mezclas enantioméricas se pueden separar, por ejemplo, formando diastereómeros con un agente auxiliar quiral, resolviendo los diastereómeros obtenidos y eliminando el agente auxiliar quiral. Por ejemplo, como agentes auxiliares quirales se pueden usar ácidos quirales tal como por ejemplo ácido mandélico, para separar las bases enantioméricas, y se pueden usar bases quirales para separar los ácidos enantioméricos, por medio de la formación de sales diastereoméricas. Además, se pueden formar derivados diastereoméricos, tales como ésteres diastereoméricos, a partir de mezclas enantioméricas de

alcoholes o mezclas enantioméricas de ácidos, usando ácidos quirales o alcoholes quirales, respectivamente, como agentes auxiliares quirales. Además, se pueden usar complejos diastereoméricos o clatratos diastereoméricos para separar las mezclas enantioméricas. Como alternativa, las mezclas enantioméricas se pueden separar usando columnas de separación quiral en cromatografía. Otro método apropiado para aislar enantiómeros es la separación enzimática.

Un aspecto preferido de la invención es el proceso para la preparación de los compuestos de las reivindicaciones 1–5 de acuerdo con los ejemplos.

Opcionalmente, los compuestos de la fórmula (I) se pueden convertir en sus sales, u opcionalmente, las sales de los compuestos de la fórmula (I) se pueden convertir en los compuestos libres. Los procesos correspondientes son conocidos por los especialistas en el arte.

Opcionalmente, los compuestos de la fórmula (I) se pueden convertir en sus N-óxidos. El N-óxido también se puede introducir por medio de un intermediario. Los N-óxidos se pueden preparar por tratamiento de un precursor apropiado con un agente oxidante, tal como ácido meta-cloroperbenzoico, en un solvente apropiado, tal como diclorometano, a temperaturas adecuadas, tal como entre 0 °C y 40 °C, en general se prefiere temperatura ambiente. Otros procesos correspondientes para formar N-óxidos son conocidos por el especialista.

Utilidad comercial

Como se mencionó precedentemente, se ha encontrado

sorprendentemente que los compuestos de la presente invención inhiben efectivamente Bub1, dando como resultado finalmente la apoptosis y la muerte celular y por ello se puede usar para el tratamiento o la profilaxis de enfermedades de crecimiento, proliferación y/o supervivencia celular descontrolado, respuestas celulares inmunes inapropiadas o respuestas celulares inflamatorias inapropiadas, o enfermedades acompañadas de un crecimiento, proliferación y/o supervivencia celular descontrolado, respuestas celulares inmunes inapropiadas o respuestas celulares inflamatorias inapropiadas, en particular donde dicho crecimiento, proliferación y/o supervivencia celular descontrolado, dichas respuestas celulares inmunes inapropiadas o dichas respuestas celulares inflamatorias inapropiadas están mediados por Bub1, tal como, por ejemplo, neoplasias benignas y malignas, más específicamente tumores hematológicos, tumores sólidos y/o metástasis de los mismos, por ejemplo leucemias y síndrome mielodisplásico, linfomas malignos, tumores de cabeza y cuello incluyendo tumores de cerebro y metástasis de cerebro, tumores de tórax incluyendo tumores de pulmón de células no pequeñas y de células pequeñas, tumores gastrointestinales, tumores endócrinos, 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, en especial tumores hematológicos, tumores sólidos y/o metástasis de mama, vejiga, hueso, cerebro, sistema nervioso central y periférico, cérvicouterino, colon, glándulas endócrinas

(por ejemplo, tiroides y corteza adrenal), tumores endócrinos, de endometrio, esófago, tumores gastrointestinales, de células germinales, de riñón, de hígado, de pulmón, de laringe e hipofaringe, mesotelioma, de ovario, de páncreas, de próstata, rectal, renal, de intestino delgado, de tejidos blandos, de estómago, de piel, de testículo, de uréter, de vagina y vulva, así como neoplasias malignas incluyendo tumores primarios en dichos órganos y los correspondientes tumores secundarios en órganos distantes ("metástasis de tumores"). Los tumores hematológicos pueden ser, por ejemplo, formas agresivas e indolentes de leucemia y linfoma, a saber enfermedad no Hodgkin, leucemia mieloide crónica y aguda (CML / AML), leucemia linfoblástica aguda (ALL), enfermedad de Hodgkin, mieloma múltiple y linfoma de células T. También está incluido el síndrome mielodisplásico, la neoplasia de células plasmáticas, síndromes paraneoplásicos y distintos tipos de cáncer de sitio primario desconocido, así como formas malignas relacionadas con SIDA.

Un aspecto adicional de la invención es el uso de los compuestos de acuerdo con la fórmula (I) para el tratamiento de tumores cérvicouterinos, de mama, de pulmón de células no pequeñas, de próstata, de colon y melanoma y/o metástasis de los mismos, especialmente preferidos para el tratamiento de los mismos, así como un método de tratamiento de tumores cérvicouterinos, de mama, de pulmón de células no pequeñas, de próstata, de colon y melanoma y/o metástasis de los mismos, que comprende administrar una cantidad efectiva de un compuesto de la fórmula (I).

Un aspecto de la invención es el uso de los compuestos de acuerdo con la fórmula (I) para el tratamiento de tumores cérvicouterinos, así como un método de tratamiento de tumores cérvicouterinos que comprende administrar una cantidad efectiva de un compuesto de la fórmula (I).

De acuerdo con un aspecto de la presente invención, la invención se relaciona entonces con un compuesto de la fórmula general **I**, o un N-óxido, una sal, un tautómero o un estereoisómero de dicho compuesto, o una sal de dichos N-óxido, tautómero o estereoisómero, en particular una sal farmacéuticamente aceptable del mismo, o una mezcla del mismo, según se describe y define en la presente, para su uso en el tratamiento o la profilaxis de una enfermedad, en especial para su uso en el tratamiento de una enfermedad.

Otro aspecto particular de la presente invención es entonces el uso de un compuesto de la fórmula general **I**, descrito *supra*, o un estereoisómero, un tautómero, un N-óxido, un hidrato, un solvato o una sal del mismo, en particular una sal farmacéuticamente aceptable del mismo o una mezcla de los mismos, para la profilaxis o el tratamiento de trastornos hiperproliferativos o trastornos que responden a la inducción de la apoptosis, en especial para el tratamiento de trastornos hiperproliferativos o trastornos que responden a la inducción de la apoptosis .

El término “inapropiado” en el contexto de la presente invención, en particular en el contexto de “respuestas celulares inmunes inapropiadas o respuestas celulares inflamatorias inapropiadas”, según se usa en la presente, se considerará como significar preferiblemente una

respuesta que es menor o mayor que la normal, y que está asociado con la patología de dichas enfermedades, es responsable de la misma o da como resultado la patología.

Preferentemente, el uso es en el tratamiento o la profilaxis de enfermedades, en especial el tratamiento, donde las enfermedades son tumores hematológicos, tumores sólidos y/o metástasis de los mismos. Un aspecto preferido es el uso de un compuesto de la fórmula (I) para la profilaxis y/o el tratamiento de tumores cérvicouterinos, de mama, de pulmón de células no pequeñas, de próstata, de colon y/o melanoma, con especial preferencia para el tratamiento de los mismos.

Otro aspecto es el uso de un compuesto de la fórmula (I) para el tratamiento de tumores cérvicouterinos, de mama, de pulmón de células no pequeñas, de próstata, de colon y melanoma y/o metástasis de los mismos, con especial preferencia para el tratamiento de los mismos.

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 en un sentido no limitativo, 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, en un sentido no limitativo, carcinoma ductal invasivo, carcinoma lobular invasivo, carcinoma ductal en situ y carcinoma lobular en situ.

Los ejemplos de cáncer del tracto respiratorio incluyen, en un sentido no limitativo, carcinomas de las células pulmonares pequeñas y no pequeñas, así como adenomas bronquiales y blastomas pleuropulmonares.

Los ejemplos de cáncer de cerebro incluyen, en un sentido no limitativo gliomas del tallo cerebral y el hipotálamo, astrocitoma cerebelar y cerebral, meduloblastoma, ependimoma, así como tumores neuroectodermales y pineales.

Los tumores de los órganos reproductores masculinos incluyen, en un sentido no limitativo, cáncer de próstata y testicular. Los tumores de los órganos reproductores femeninos incluyen, en un sentido no limitativo, cáncer del endometrio, cérvicouterinos, ovárico, vaginal y vulvar, así como sarcoma de útero.

Los tumores del tracto digestivo incluyen, en un sentido no limitativo, cáncer anal, 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.

El cáncer ocular incluye, en un sentido no limitativo, melanoma intraocular y retinoblastoma.

Los ejemplos de cáncer hepático incluyen, en un sentido no limitativo, carcinoma hepatocelular (carcinomas de células hepáticas con o sin variantes fibrolamelares), colangiocarcinoma (carcinoma del conducto biliar intrahepático) y colangiocarcinoma hepatocelular mixto.

El cáncer de piel incluye, en un sentido no limitativo, 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, en un sentido no limitativo, sarcoma de los tejidos blandos, osteosarcoma, histiocitoma

fibroso maligno, linfosarcoma y rabdomiosarcoma.

Las leucemias incluyen, en un sentido no limitativo, leucemia mieloide aguda, leucemia linfoblástica aguda, leucemia linfocítica crónica, leucemia mielogénica 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 en un sentido no limitativo, 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, independientemente 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 retiniana 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. Opththalmol. Vis. Sci.* **1996**, *37*, 855), glaucoma neovascular, psoriasis, fibroplasias retrolentales, angiofibroma, inflamación, artritis reumatoide (RA), restenosis, restenosis *en-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.

Preferiblemente, las enfermedades de dicho método

comprenden tumores hematológicos, tumores sólidos y/o metástasis de los mismos.

Los compuestos de la presente invención se pueden usar en particular en terapias y en la prevención, es decir en la profilaxis, en especial en terapias de crecimiento y metástasis tumorales, especialmente en tumores sólidos de todas las indicaciones y etapas con o sin pretratamiento del crecimiento tumoral.

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 o auxiliar farmacéuticamente aceptable y una cantidad eficaz para uso farmacéutico de un compuesto, o una sal de éste, de la presente invención.

Otro aspecto de la invención es una composición farmacéutica que comprende una cantidad farmacéuticamente eficaz de un compuesto de la fórmula (I) y un auxiliar farmacéuticamente aceptable para el tratamiento de una de las enfermedades mencionadas *supra*, en especial para el tratamiento de tumores hematológicos, tumores sólidos y/o

metástasis de los mismos.

Un vehículo farmacéuticamente aceptable es preferiblemente un vehículo o auxiliar que es 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. Los vehículos y auxiliares comprenden todos los tipos de aditivos que ayudan a que una composición sea adecuada para su administración.

Una cantidad efectiva para el uso farmacéutico del compuesto es preferiblemente una cantidad que produce un resultado o ejerce la influencia buscada sobre la condición particular a tratar.

Los compuestos de la presente invención pueden administrarse con vehículos o auxiliares 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, los compuestos se pueden formular en preparaciones sólidas o líquidas, tales como cápsulas, píldoras, tabletas, pastillas, grageas, líquidos fundidos, polvos, soluciones, suspensiones o emulsiones, y se pueden preparar de acuerdo con métodos conocidos en la técnica para la elaboración 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 auxiliares, 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 tabletas con bases para tabletas 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 la tableta una vez administrada, tal como almidón de papa, ácido algínico, almidón de maíz y goma guar, goma tragacanto, acacia, lubricantes dirigidos a mejorar el flujo de granulación de la tableta y a evitar la adhesión del material de la tableta a las superficies de los colorantes de la tableta 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 las tabletas y volverlas 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 emulsionante 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 tabletas, 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 conservantes. 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 conservantes, 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.

Se pueden formular jarabes y elíxires con agentes edulcorantes, por ejemplo, glicerol, propilenglicol, sorbitol o sacarosa. Dichas formulaciones pueden contener un demulcente y un conservante, tal como metil y propil parabeno, 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, metilcelulosa, 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 conservantes 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, hidroxipropilmetilcelulosa, 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.

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)-Parte-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, en un sentido no limitativo, ácido acético, ácido cítrico, ácido fumárico, ácido clorhídrico, ácido nítrico);

agentes alcalinizantes (los ejemplos incluyen, en un sentido no limitativo, 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, en un sentido no limitativo, celulosa en polvo y carbón activado);

propelentes de aerosol (los ejemplos incluyen, en un

sentido no limitativo, dióxido de carbono, CCl_2F_2, $F_2ClC-CClF_2$ y $CClF_3$);

agentes de desplazamiento aéreo (los ejemplos incluyen, en un sentido no limitativo, nitrógeno y argón);

conservantes antifúngicos (los ejemplos incluyen, en un sentido no limitativo, ácido benzoico, butilparabeno, etilparabeno, metilparabeno, propilparabeno, benzoato de sodio);

conservantes antimicrobianos (los ejemplos incluyen, en un sentido no limitativo, cloruro de benzalconio, cloruro de benzetonio, alcohol bencílico, cloruro de cetilpiridinio, clorobutanol, fenol, alcohol feniletílico, nitrato fenilmercúrico y timerosal);

antioxidantes (los ejemplos incluyen, en un sentido no limitativo, ácido ascórbico, palmitato de ascorbilo, 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, en un sentido no limitativo, polímeros de bloque, goma natural y sintética, poliacrilatos, poliuretanos, siliconas, polisiloxanos y copolímeros de estireno-butadieno);

agentes amortiguadores (los ejemplos incluyen, en un sentido no limitativo, 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, en un sentido no limitativo, 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, en un sentido no limitativo, edetato disódico y ácido edético);

colorantes (los ejemplos incluyen, en un sentido no limitativo, FD&C Rojo N° 3, FD&C Rojo N° 20, FD&C Amarillo N° 6, FD&C Azul N° 2, D&C Verde N° 5, D&C Naranja N° 5, D&C Rojo N° 8, caramelo y óxido férrico rojo);

agentes de transparentado (los ejemplos incluyen, en un sentido no limitativo, bentonita);

agentes emulsionantes (los ejemplos incluyen, en un sentido no limitativo, acacia, cetomacrogol, alcohol cetílico, monoestearato de glicerilo, lecitina, monooleato de sorbitano, monoestearato de polioxietileno 50);

agentes de encapsulamiento (los ejemplos incluyen, en un sentido no limitativo, gelatina y acetato de ftalato de celulosa);

saborizantes (los ejemplos incluyen, en un sentido no limitativo, aceite de anís, aceite de canela, cacao, mentol, aceite de naranja, aceite de menta salvaje y vainillina);

humectantes (los ejemplos incluyen, en un sentido no limitativo, glicerol, propilenglicol y sorbitol);

agentes levigantes (los ejemplos incluyen, en un sentido no limitativo, aceite mineral y glicerina);

aceites (los ejemplos incluyen, en un sentido no limitativo, aceite de araquís, aceite mineral, aceite de

oliva, aceite de maní, aceite de sésamo y aceite vegetal);

bases de ungüentos (los ejemplos incluyen, en un sentido no limitativo, 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, en un sentido no limitativo, 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, en un sentido no limitativo, ftalato de dietilo y glicerol);

solventes (los ejemplos incluyen, en un sentido no limitativo, 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, en un sentido no limitativo, alcohol cetílico, ceras de ésteres cetílicos, cera microcristalina, parafina, alcohol estearílico, cera blanca y cera amarilla);

bases para supositorios (los ejemplos incluyen, en un sentido no limitativo, manteca de cacao y polietilenglicoles (mezclas));

agentes tensioactivos (los ejemplos incluyen, en un sentido no limitativo, cloruro de benzalconio, nonoxinol 10, oxtoxinol 9, polisorbato 80, laurilsulfato de sodio y mono-palmitato de sorbitano);

agentes de suspensión (los ejemplos incluyen, en un sentido no limitativo, agar, bentonita, carbómeros, carboximetilcelulosa de sodio, hidroxietilcelulosa, hidroxipropilcelulosa, hidroxipropilmetilcelulosa, caolín, metilcelulosa, tragacanto y goma Vee);

agentes edulcorantes (los ejemplos incluyen, en un sentido no limitativo, aspartame, dextrosa, glicerol, manitol, propilenglicol, sacarina de sodio, sorbitol y sacarosa);

anti-adherentes para tabletas (los ejemplos incluyen, en un sentido no limitativo, estearato de magnesio y talco);

aglutinantes para tabletas (los ejemplos incluyen, en un sentido no limitativo, acacia, ácido algínico, carboximetilcelulosa de sodio, azúcar compresible, etilcelulosa, gelatina, glucosa líquida, metilcelulosa, polivinilpirrolidona no reticulada y almidón pregelificado);

diluyentes para tabletas y cápsulas (los ejemplos incluyen, en un sentido no limitativo, fosfato de calcio dibásico, caolín, lactosa, manitol, celulosa microcristalina, celulosa en polvo, carbonato de calcio precipitado, carbonato de sodio, fosfato de sodio, sorbitol y almidón);

agentes de recubrimiento para tabletas (los ejemplos

incluyen, en un sentido no limitativo, glucosa líquida, hidroxietilcelulosa, hidroxipropilcelulosa, hidroxipropilmetilcelulosa, metilcelulosa, etilcelulosa, acetato de ftalato de celulosa y Shellac);

excipientes para la compresión directa de tabletas (los ejemplos incluyen, en un sentido no limitativo, fosfato de calcio dibásico);

desintegradores para tabletas (los ejemplos incluyen, en un sentido no limitativo, ácido algínico, carboximetilcelulosa de calcio, celulosa microcristalina, poloacrilina de potasio, polivinilpirrolidona reticulada, alginato de sodio, glicolato de almidón de sodio y almidón);

deslizantes para tabletas (los ejemplos incluyen, en un sentido no limitativo, sílice coloidal, almidón de maíz y talco);

lubricantes para tabletas (los ejemplos incluyen, en un sentido no limitativo, estearato de calcio, estearato de magnesio, aceite mineral, ácido esteárico y estearato de cinc);

opacantes para tabletas/cápsulas (los ejemplos incluyen, en un sentido no limitativo, dióxido de titanio);

agentes de acabado de tabletas (los ejemplos incluyen, en un sentido no limitativo, cera de carnuba y cera blanca);

agentes espesantes (los ejemplos incluyen, en un sentido no limitativo, cera de abeja, alcohol cetílico y parafina);

agentes para proporcionar tonicidad (los ejemplos

incluyen, en un sentido no limitativo, dextrosa y cloruro de sodio);

agentes para incrementar la viscosidad (los ejemplos incluyen, en un sentido no limitativo, ácido algínico, bentonita, carbómeros, carboximetilcelulosa de sodio, metilcelulosa, polivinilpirrolidona, alginato de sodio y tragacanto); y

agentes humectantes (los ejemplos incluyen, en un sentido no limitativo, 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 i.v. estéril: Se puede preparar 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 i.v.: 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 Dextrano 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: Se puede preparar 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

809 mg/ml de cloruro de sodio

9 mg/ml de alcohol bencílico

Cápsulas de gelatina dura: 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. El ingrediente activo se puede disolver en una mezcla de polietilenglicol, glicerina y sorbitol para preparar una mezcla medicinal miscible con agua.

Tabletas: Se prepara una gran cantidad de tabletas 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.

Tabletas/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 tabletas 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.

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.

Terapias combinadas

Los compuestos de esta invención se pueden administrar como el único agente farmacéutico o en combinación con uno o más agentes farmacéuticos adicionales, donde la

combinación no posee efectos adversos inaceptables. Dichos agentes farmacéuticos combinados pueden ser otros agentes con efectos antiproliferativos tal como por ejemplo para el tratamiento de tumores hematológicos, tumores sólidos y/o metástasis de los mismos y/o agentes para el tratamiento de efectos secundarios indeseados. La presente invención también se relaciona con dichas combinaciones.

Otros agentes antihiperproliferativos adecuados de utilidad con la composición de la invención incluyen pero en un sentido no limitativo aquellos compuestos cuyo uso es reconocido en el tratamiento de enfermedades neoplásicas en Goodman y Gilman's *The Pharmacological Basis of Therapeutics* (novena edición), editor Molinoff *et al.*, publicado por McGraw-Hill, páginas 1225-1287, (1996), que se incorpora a modo de referencia, en especial los agentes anti-cancerosos (quimioterapéuticos) definidos *supra*. La combinación puede ser una combinación no fija o una combinación de dosis fija, según sea el caso.

Los métodos para evaluar una propiedad farmacológica o farmacéutica particular son bien conocidos por los especialistas en el arte.

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.

Como podrán apreciar los especialistas en el arte, la invención no se limita a las realizaciones particulares descriptas en la presente, sino que abarca todas las modificaciones de dichas realizaciones que están dentro del espíritu y el alcance de la invención, tal como se lo

define en las reivindicaciones adjuntas.

En los siguientes ejemplos se ilustra la invención con mayor detalle sin restringirla. De manera análoga, es posible preparar otros compuestos de acuerdo con la invención, cuya preparación no se describe de manera explícita.

Los compuestos que se mencionan en los ejemplos y sus sales representan realizaciones preferidas de la invención así como la reivindicación que abarca todas las subcombinaciones de los residuos del compuesto de la fórmula (I) según se divulga en los ejemplos específicos.

El término “de acuerdo con” dentro de la sección experimental se utiliza en el sentido de que el procedimiento en cuestión se utilizará en “forma análoga”..

PARTE EXPERIMENTAL

En la siguiente tabla se indican las abreviaturas usadas en este párrafo y la sección de ejemplos de intermediarios y de ejemplos, siempre que no estén explicadas en el cuerpo del texto.

Abreviatura	**Significado**
aq.	acuoso
alloc	aliloxicarbonilo
boc	t-butoxicarbonilo
br	amplio
IC	ionización química
d	doblete
dd	doblete de dobletes
DAD	detector por arreglo de diodos
DCM	diclorometano

DMF	N,N-dimetilformamida
ELSD	detector de dispersión de luz evaporativa
EtOAc	acetato de etilo
Eq	equivalente
ESI	ionización por electroatomización (ES)
HATU	hexafluorofosfato de 2-(7-aza-1*H*-benzotriazol-1-il)-1,1,3,3-tetrametiluronio (N° CAS 148893-10-1)
HPLC	cromatografía líquida de alta presión
LC-MS	Cromatografía líquida - espectrometría de masa
m	multiplete
MS	espectrometría de masas
n-BuLi	n-butillitio
RMN	espectroscopia de resonancia magnética nuclear: los desplazamientos químicos (δ) se expresan en ppm . Los desplazamientos químicos se corrigieron estableciendo la señal de DMSO en 2,50 ppm a menos que se defina de otra manera.
PDA	Arreglo de fotodiodos
PoraPak™;	una HPLC columna disponible de Waters
q	cuarteto
r.t. o rt	temperatura ambiente
RT	tiempo de retención (medido con HPLC o UPLC) en minutos
s	singulete

SM	Material de partida
SQD	Detector-cuadrupolo-individual
t	triplete
THF	tetrahidrofurano
UPLC	cromatografía líquida de ultra presión

Otras abreviaturas tienen los significados conocidos *per se* por el especialista.

Los diversos aspectos de la invención que se describen en esta solicitud se ilustran con los siguientes ejemplos que no pretenden limitar la invención en modo alguno.

Descripciones experimentales específicas

Las formas de los picos de NMR en las siguientes descripciones experimentales específicas se indican tal como aparecen en los espectros, no habiéndose considerado los posibles efectos de orden superior. Las reacciones que emplean irradiación con microondas se pueden conducir con un horno de microondas Biotage Initator®, opcionalmente equipado con una unidad robótica. Los tiempos de reacción informados que emplean calentamiento con microondas deben interpretarse como tiempos de reacción fijos después de alcanzar la temperatura de reacción indicada. Puede ser necesario purificar los compuestos y los intermediarios que se producen de acuerdo con los métodos de la invención. La purificación de los compuestos orgánicos ha de ser conocida para aquellos versados en la técnica, y puede haber diversas maneras para purificar un mismo compuesto. En algunos casos, puede no ser necesaria una purificación. 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 cromatografía en columna instantánea, usando, por ejemplo, cartuchos de gel de sílice preenvasado, por ejemplo, de Separtis, tales como el gel de sílice Isolute® Flash o el gel de sílice Isolute® Flash NH_2, en combinación con un autopurificador Isolera® (Biotage), y eluyentes tales como gradientes de hexano/acetato de etilo o DCM/metanol. En algunos casos, los compuestos pueden purificarse por HPLC preparativa usando, por ejemplo, un autopurificador Waters equipado con un detector con una serie de diodos y/o un espectrómetro de ionización de masa en línea por chorro de electrones, en combinación con una columna de fase inversa preenvasada apropiada, y eluyentes tales como gradientes de agua y acetonitrilo, que pueden contener aditivos, tales como ácido trifluoroacético, ácido fórmico o amoníaco acuoso. En algunos casos, los métodos de purificación que se describieron previamente pueden proporcionar aquellos compuestos de la presente invención que poseen una funcionalidad suficientemente básica o ácida en la forma de una sal, tal como, en el caso de un compuesto de la presente invención que sea suficientemente básico, por ejemplo una sal trifluoroacetato o formiato o, en el caso de un compuesto de la presente invención que sea suficientemente ácido, por ejemplo una sal de amonio. Una sal de este tipo se puede transformar en la forma de su base libre o de su ácido libre, respectivamente, utilizando diversos métodos conocidos por el especialista en el arte o

se pueden usar como sales en los subsiguientes ensayos biológicos. Se podrá comprender que la forma específica (por ejemplo, la sal, la base libre, etc.) de un compuesto de la presente invención aislado como se describe en la presente no es necesariamente la única forma en la cual se puede emplear dicho compuesto en un ensayo biológico con el fin de cuantificar la actividad biológica específica.

El porcentaje de los rendimientos informado en los siguientes ejemplos se basan en el componente de partida que se usó a la cantidad molar más baja. Los líquidos y las soluciones sensibles al aire y a la humedad fueron transferidos mediante una jeringa o cánula y se introdujeron en los recipientes de reacción a través de diafragmas de goma. Se usaron reactivos y solventes de grado comercial, sin purificaciones adicionales. El término “se concentró bajo vacío” se refiere al uso de un evaporador rotatorio Buchi a una presión mínima de aproximadamente 15 mm de Hg. Todas las temperaturas se informan sin corregir en grados Celsius (°C).

Con el fin de comprender mejor esta invención, se ofrecen los siguientes ejemplos. Estos ejemplos solamente sirven fines ilustrativos y no deben considerarse como limitativos del alcance de la invención en modo alguno. Todas las publicaciones mencionadas se incorporan por completo en la presente a modo de referencia.

Condiciones de LC-MS analíticas

Los datos de LC-MS indicados en las siguientes descripciones experimentales específicas se refieren (a menos que se indique lo contrario) a las siguientes

condiciones:

Sistema:	Waters Acquity UPLC-MS: Inyector de solvente binario, inyector/organizador de muestras, controlador de columna, PDA, ELSD, SQD 3001 o ZQ4000
Columna:	Acquity UPLC BEH C18 1,7 50x2,1 mm
Solvente:	A1 = agua + 0,1% vol. de ácido fórmico (99%) A2 = agua + 0,2% vol. de amoníaco (32%)
	B1 = acetonitrilo
Gradiente:	0-1,6 min, 1-99% de B; 1,6-2,0 min, 99% de B
Flujo:	0,8 ml/min
Temperatura:	60°C
Inyección:	2,0 µl
Detección:	DAD, rango de barrido 210-400 nm -> Tabla Picos
	ELSD
Métodos:	MS ESI+, ESI-Switch -> son posibles diversos rangos de barrido (Encabezado de Informe) **Método 1:** A1 + B1 = C:\MassLynx**Mass_100_1000**.flp **Método 2:** A1 + B1 = C:\MassLynx**Mass_160_1000**.flp **Método 3:** A1 + B1 = C:\MassLynx**Mass_160_2000**.flp **Método 4:** A1 + B1 = C:\MassLynx**Mass_160_1000_BasicReport**.flp **Método 5:** A2 + B1 = C:\MassLynx**NH_3_Mass_100_1000**.flp **Método 6:** A2 + B1 =

	C:\MassLynx**NH_3_Mass_160_1000_BasicReport**.flp

Condiciones de HPLC preparativa

La "purificación por HPLC preparativa" en las subsiguientes descripciones experimentales específicas se refiere a las siguientes condiciones (a menos que se indique lo contrario):

Datos analíticos (pre- y post analíticos: Método B):

Sistema:	Waters Acquity UPLC-MS: Inyector de solvente binario, inyector/organizador de muestras, controlador de columna, PDA, ELSD, SQD 3001
Columna:	Acquity BEH C18 1,7 50x2,1 mm
Solvente:	A = agua + 0,1% vol. de ácido fórmico (99%)
	B = Acetonitrilo
Gradiente:	0-1,6 min, 1-99% de B; 1,6-2,0 min, 99% de B
Flujo:	0,8 ml/min
Temperatura:	60°C
Inyección:	2,0 µl
Detección:	DAD, rango de barrido 210-400 nm
	MS ESI+, ESI-, rango de barrido 160-1000 m/z
	ELSD
Métodos:	Purify_pre.flp Purify_post.flp

Preparación:

Sistema:	Sistema de purificación automática Waters: Bomba 2545, Inyector de Muestras 2767, CFO, DAD 2996, ELSD 2424, SQD 3001
Columna:	XBrigde C18 5 µm 100x30 mm
Solvente:	A = agua + 0,1% vol. de ácido fórmico (99%)

	B = Acetonitrilo
Gradiente:	0–1 min, 1% de B; 1–8 min, 1–99% de B; 8–10 min, 99% de B
Flujo:	50 ml/min
Temperatura:	RT
Solución:	máx. 250 mg / 2,5 ml de dimetilsufóxido o DMF
Inyección:	1 x 2,5 ml
Detección:	DAD, rango de barrido 210–400 nm
	MS ESI+, ESI–, rango de barrido 160–1000 m/z

Condiciones de HPLC quiral

Si no se especifica lo contrario, los datos de HPLC quiral indicados en las siguientes descripciones experimentales específicas se refieren a las siguientes condiciones:

Valores analíticos:

Sistema:	Dionex: Bomba 680, ASI 100, Waters: Detector UV 2487
Columna:	Chiralpak IC 5 µm 150x4,6 mm
Solvente:	hexano / etanol 80:20 + 0,1% de dietilamina
Flujo:	1,0 ml/min
Temperatura:	25°C
Solución:	1,0 mg/ml de etanol/metanol 1:1
Inyección:	5,0 µl
Detección:	UV 280 nm

Preparación:

Sistema:	Agilent: Prep 1200, bomba 2xPrep, DLA, MWD, Prep FC, ESA: Corona

Columna:	Chiralpak IC 5 µm 250x30 mm
Solvente:	hexano / etanol 80:20 + 0,1% de dietilamina
Flujo:	40 ml/min
Temperatura:	RT
Solución:	660 mg / 5,6 ml de etanol
Inyección:	8 x 0,7 ml
Detección:	UV 280 nm

Condiciones de cromatografía en columna flash

La “Purificación por cromatografía en columna (flash)” indicada en las siguientes descripciones experimentales específicas se refiere al uso de los sistemas de purificación Biotage Isolera. Por consultas sobre las especificaciones técnicas véase el “catálogo de producto Biotage” en www.biotage.com.

Determinación de las condiciones de rotación óptica

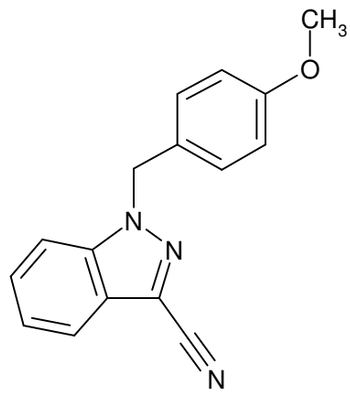
Las rotaciones ópticas se midieron en dimetilsulfóxido, a 589 nm de longitud de onda, 20 °C, a una concentración de 1,0000 g/100 ml, tiempo de integración de 10 s, espesor de película 100,00 mm.

EJEMPLOS

Intermediarios de Síntesis

Intermediario 1-1-1

Preparación de 1-(4-metoxibencil)-1*H*-indazol-3-carbonitrilo



Se disolvieron 6,47 g de 1*H*-indazol-3-carbonitrilo (45,2 mmol, 1 eq.) en 65 ml de DMF seco. Se agregaron 10 g de 1-(bromometil)-4-metoxibenceno (49,7 mmol, 1,1 eq.) y 17,7 g de carbonato de cesio (54,2 mmol, 1,2 eq.). La mezcla se agitó a temperatura ambiente durante 18 horas bajo una atmósfera de nitrógeno. Luego la mezcla de reacción se particionó entre agua y éter tert-butílico metílico. La fase acuosa separada se extrajo dos veces con éter tert-butílico metílico. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre sulfato de magnesio y se concentró al vacío. La cristalización desde metanol dio 9,25 g (35,1 mmol, 77,7%) del compuesto buscado analíticamente puro.

^{1}H RMN (300 MHz, DMSO-d6) δ [ppm]= 3,64 - 3,71 (s, 3 H), 5,70 (s, 2 H) 6,81 - 6,89 (m, 2 H), 7,22 - 7,29 (m, 2 H), 7,38 (ddd, 1 H), 7,55 (ddd, 1 H), 7,85 (dt, 1 H) 7,97 (dt, 1 H)

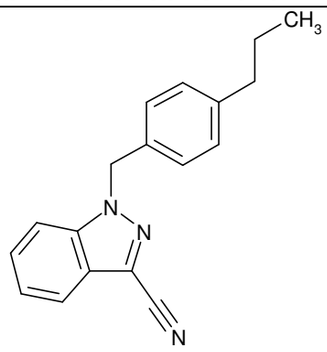
LC-MS:

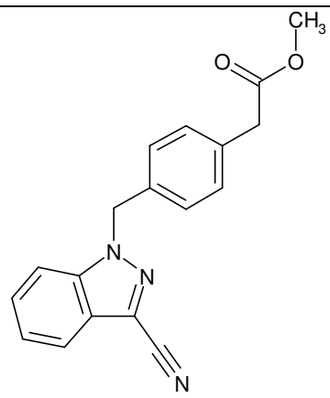
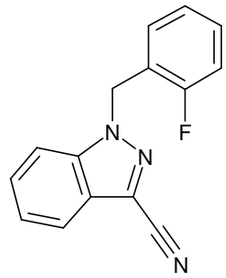
tiempo de retención: 1,27 min

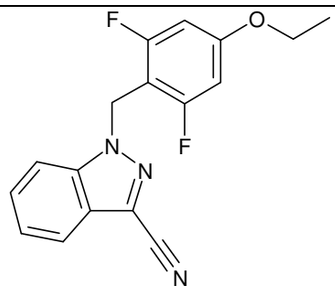
MS ES^{+}: 264,31 $[M+H]^{+}$

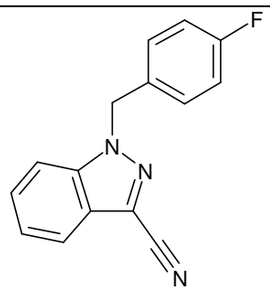
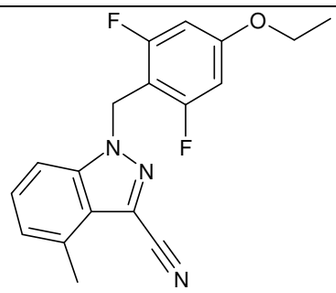
Los siguientes intermediarios se prepararon de acuerdo con el mismo procedimiento usando los materiales de partida

disponibles comercialmente repectivos:

1-1-2		1-(4-propilbencil)-1*H*-indazol-3-carbonitrilo	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 0,75 - 0,86 (m, 3H), 1,41 - 1,56 (m, 2H), 2,41 - 2,51 (t, 2H), 5,74 (s, 2H), 7,08 - 7,13 (d, 2H), 7,16 - 7,22 (d, 2H), 7,38 (ddd, 1H), 7,55 (ddd, 1H), 7,85 (dt, 1H), 7,92 - 7,98 (dt, 1H). LC-MS: tiempo de retención: 1,50 min MS ES$^+$: 276,0 $[M+H]^+$ Método B

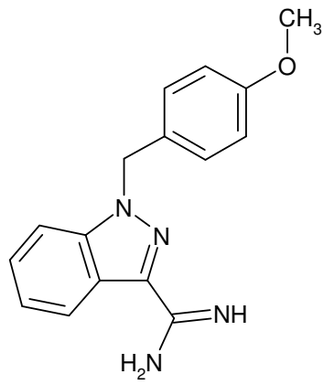
1-1-3		{4-[(3-ciano-1*H*-indazol-1-il)metil]fenil}acetato de metilo	^{1}H-RMN (500MHz, DMSO-d_6): δ [ppm]= 3,58 (s, 3H), 3,64 (s, 2H), 5,81 (s, 2H), 7,21 – 7,25 (m, 2H), 7,25 – 7,29 (m, 2H), 7,43 (td, 1H), 7,59 (ddd, 1H), 7,89 – 7,92 (m, 1H), 8,00 (d, 1H). LC-MS: tiempo de retención: 1,24 min MS ES$^+$: 306,0 $[M+H]^+$ Método B
1-1-4		1-(2-fluorobencil)-1H-indazol-3-carbonitrilo	^{1}H-RMN (300MHz, DMSO-d6): δ [ppm]= 5,84 (s, 2H), 7,11 – 7,45 (m, 5H), 7,58 (ddd, 1H), 7,87 (d, 1H), 7,96 (d, 1H). LC-MS:

			tiempo de retención: 1,29 min MS ES+: 251,9 [M+H]+ Método B
1-15		1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-carbonitrilo	1H-RMN (300MHz, DMSO-d6): δ [ppm]= 1,26 (t, 3H), 4,01 (q, 2H), 5,72 (s, 2H), 6,70 - 6,76 (m, 2H), 7,34 - 7,47 (m, 1H), 7,56 - 7,67 (m, 1H), 7,80 - 7,88 (m, 1H), 7,91 - 8,01 (m, 1H). LC-MS: tiempo de retención: 1,44 min MS ES+: 314,2 [M+H]+

1-16		1-(4-fluorobencil)-1H-indazol-3-carbonitrilo	^{1}H-RMN (500MHz, DMSO-d_6): δ [ppm]= 5,79 (s, 2H), 7,14 (m, 2H), 7,31 - 7,43 (m, 3H), 7,56 (ddd, 1H), 7,87 (d, 1H), 7,98 (d, 1H).
1-17		1-(4-etoxi-2,6-difluorobencil)-4-metil-1H-indazol-3-carbonitrilo	H-RMN (400MHz, DMSO-d6): δ [ppm]= 1,26 (t, 3H), 2,64 (s, 3H), 4,01 (q, 2H), 5,68 (s, 2H), 6,70 - 6,76 (m, 2H), 7,13 (d, 1H), 7,46 (dd, 1H), 7,74 (d, 1H).

Intermediario 1-2-1

Preparación de 1-(4-metoxibencil)-1*H*-indazol-3-carboximidamida



Se suspendieron 9,25 g de 1-(4-metoxibencil)-1*H*-indazol-3-carbonitrilo (1-1-1, 35,1 mmol, 1 eq.) en 128 ml de metanol seco bajo una atmósfera de nitrógeno. Se agregaron 0,949 g (17,6 mmol, 0,5 eq.) de metanolato de sodio. La mezcla de reacción se agitó durante 18 horas a temperatura ambiente. A la mezcla resultante se agregaron 2,82 g (52,7 mmol, 1,5 eq.) de cloruro de amonio y 1,0 ml (17,6 mmol, 0,5 eq.) de ácido acético 100% y se agitó durante 5 horas a 50°C. Luego de enfriar a temperatura ambiente la mezcla se concentró al vacío. El residuo se particionó entre solución acuosa parcialmente saturada de carbonato ácido de sodio y diclorometano/isopropanol 4:1. La capa acuosa se extrajo tres veces con diclorometano/isopropanol 4:1. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre sulfato de magnesio y se concentró al vacío. El residuo se purificó mediante cromatografía flash para dar 6,45 g (23 mmol, 65,5%) del compuesto buscado analíticamente puro.

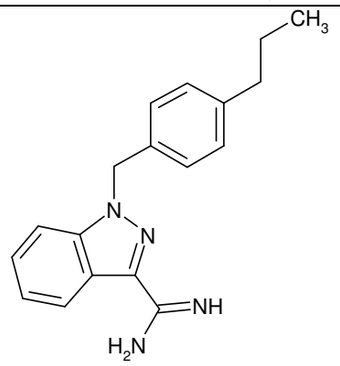
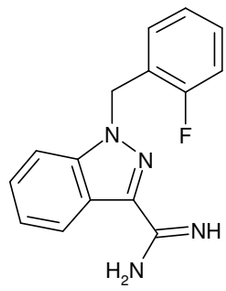
^{1}H RMN (300 MHz, DMSO-d6) δ [ppm]= 3,62 - 3,70 (s, 3 H), 5,57 (s, 2 H), 6,37 (s ancho, 3 H), 6,78 - 6,88 (m, 2 H), 7,10 - 7,23 (m, 3 H), 7,35 (ddd, 1 H), 7,68 (d, 1 H), 8,27 (d, 1 H)

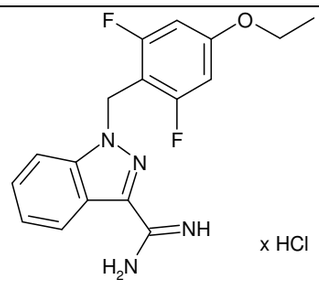
LC-MS:

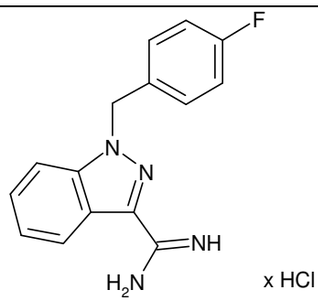
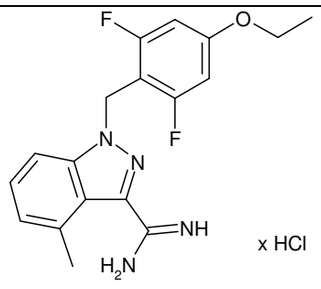
tiempo de retención: 0,75 min

MS ES+: 281,34 [M+H]+

Los siguientes intermediarios se prepararon de acuerdo con el mismo procedimiento a partir de los materiales de partida indicados (SM = material de partida):

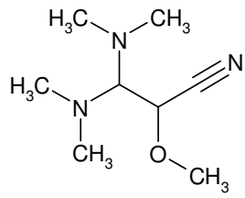
1-2-2 SM = 1-12		1-(4-propilbencil)-1*H*-indazol-3-carboximidamida	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 0,80 (t, 3H), 1,38 - 1,56 (m, 2H), 2,41 - 2,49 (t, 2H), 5,61 (s, 2H), 6,41 (s ancho, 3H), 7,04 - 7,19 (m, 5H), 7,36 (ddd, 1H), 7,67 (d, 1H), 8,28 (d, 1H). LC-MS: tiempo de retención: 0,94 min MS ES+: 293,0 [M+H]+ Método B
1-2-3 SM = 1		1-(2-fluorobencil)-1H-indazol-3-carboximidamida	^{1}H-RMN (300MHz, DMSO-d6): δ [ppm]= 5,72 (s, 2H), 6,73 (s ancho, 3H), 7,01 - 7,13 (m, 2H), 7,15 - 7,23 (m, 2H), 7,27 - 7,36 (m, 1H), 7,40

- 1 - 4			(ddd, 1H), 7,69 (d, 1H), 8,27 (d, 1H). LC-MS: tiempo de retención: 0,75 min MS ES+: 268,9 [M+H]+ Método B
1 - 2 - 4 S M = 1 - 1 - 5		clorhidrato de 1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-carboximidamida (1:1)	^{1}H-RMN (400MHz, DMSO-d6): δ [ppm]= 1,26 (t, 3H), 4,01 (q, 2H), 5,73 (s, 2H), 6,70 -6,76 (m, 2H), 7,33 - 7,41 (m, 1H), 7,52 - 7,63 (m, 1H), 7,88 (d, 1H), 7,97 (d, 1H), 9,26 (s ancho, 3H). LC-MS: tiempo de retención: 0,87 min MS ES+: 332,2 [M+H]+

1-25SM=1-16		clorhidrato de 1-(4-fluorobencil)-1H-indazol-3-carboximidamida (1:1)	^{1}H-RMN (400MHz, DMSO-d6): δ [ppm]= 5,81 (s, 2H), 7,10 - 7,17 (m, 2H), 7,35 - 7,42 (m, 3H), 7,51 - 7,57 (m, 1H), 7,93 (d, 1H), 8,00 (d, 1H), 9,34 (s ancho, 3H). LC-MS: tiempo de retención: 0,71 min MS ES$^+$: 269,0 $[M+H]^+$ Método B
1-26SM=1-11-		clorhidrato de 1-(4-etoxi-2,6-difluorobencil)-4-metil-1H-indazol-3-carboximidamida (1:1)	^{1}H-RMN (400MHz, DMSO-d6): δ [ppm]= 1,26 (t, 3H), 2,49 (s, 3H), 3,99 (q, 2H), 5,66 (s, 2H), 6,69 - 6,79 (m, 2H), 7,10 (d, 1H), 7,46 (t, 1H), 7,74 (d, 1H), 7,77 (s ancho, 3H). LC-MS (Método 1): tiempo de retención: 0,93 min

7			MS ES+: 345,0 [M+H]+

Intermediario 1-3-1 Preparación de 3,3-bis(dimetilamino)-2-metoxipropanonitrilo



Se agitaron 360,4 g de 1-*tert*-butoxi-*N,N,N',N'*-tetrametilmetanediamina (reactivo de Bredereck) (2068 mmol, 1 eq.) y 150,0 g de metoxiacetonitrilo (2068 mmol, 1 eq.) durante 18 horas a 80°C. La mezcla de reacción se concentró al vacío. El residuo se purificó por destilación al vacío para dar 117 g (687 mmol, 33,0%) del compuesto buscado analíticamente puro como un líquido amarillento.

1H-RMN (400 MHz, DMSO-d6): δ [ppm]= 2,23 (s, 6H), 2,29 (s, 6H), 3,23 (d, 1H), 3,36 - 3,41 (s, 3H), 4,73 (d, 1H).

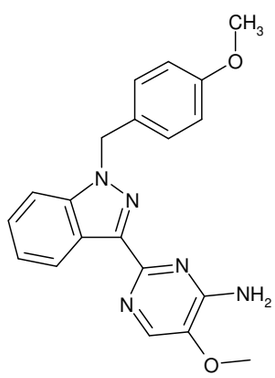
LC-MS:

tiempo de retención: 0,79 min

MS ES+: 172,09 [M+H]+

Intermediario 1-4-1

Preparación de 5-metoxi-2-[1-(4-metoxibencil)-1*H*-indazol-3-il]pirimidin-4-amina



Se disolvieron 6,45 g de 1-(4-metoxibencil)-1*H*-indazol-3-carboximidamida (23,0 mmol, 1 eq.), 5,40 g de 3,3-bis(dimetilamino)-2-metoxipropanonitrilo (1-2-1, 31,5 mmol, 1,37 eq.) y 0,455 ml de piperidina (4,60 mmol, 0,2 eq.) en 82,7 ml de 3-metilbutan-1-ol seco, se colocó bajo una atmósfera de nitrógeno y se agitó a 100°C durante 3 días. La mezcla se enfrió a temperatura ambiente y se agitó durante 18 horas hasta ocurrir la cristalización. La suspensión resultante se retiró por filtración. Los cristales se lavaron con metanol frío y se secó al vacío a 50°C. La cristalización se repitió dos veces con metanol frío para obtener otras dos almohadillas de filtrado y un rendimiento combinado de 6,87 g (19 mmol, 82,5%) del compuesto buscado analíticamente puro.

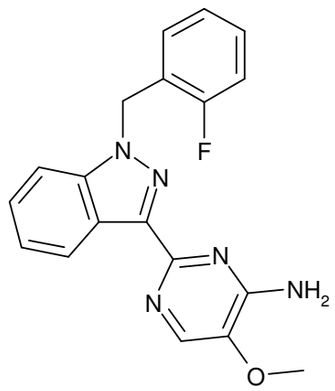
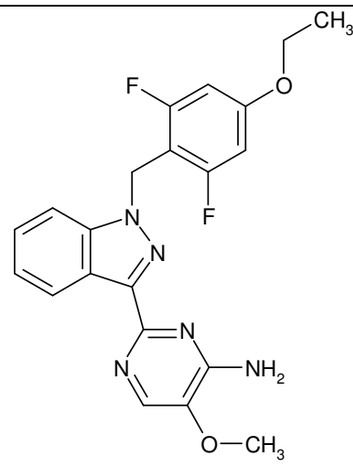
^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 3,62 - 3,69 (s, 3H), 3,85 (s, 3H), 5,59 (s, 2H), 6,78 - 6,90 (m, 4H), 7,11 - 7,23 (m, 3H), 7,35 (ddd, 1H), 7,68 (d, 1H), 7,95 (s, 1H), 8,53 (d, 1H).

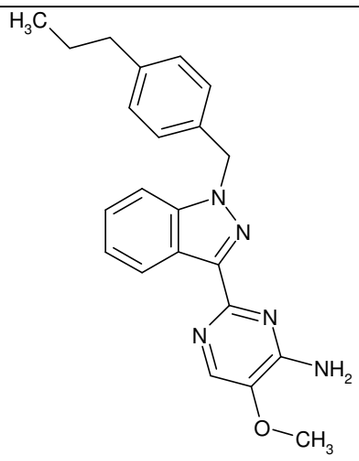
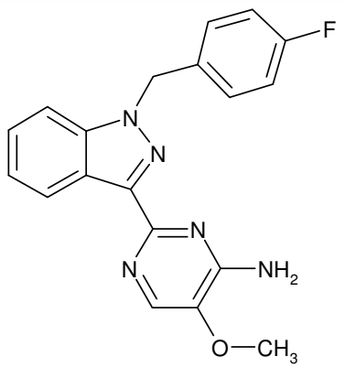
LC-MS: Método B

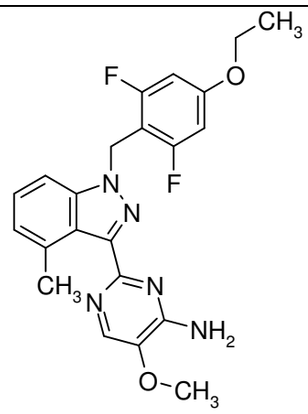
tiempo de retención: 0,87 min

MS ES$^+$: 362,0 $[M+H]^+$

Los siguientes intermediarios se prepararon de acuerdo con el mismo procedimiento a partir de los materiales de partida indicados (SM = material de partida):

1-4-2SM=1-2-3		2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-5-metoxipirimidin-4-amina	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 3,85 (s, 3H), 5,73 (s, 2H), 6,85 (s ancho, 2H), 7,01 - 7,13 (m, 2H), 7,15 - 7,24 (m, 2H), 7,27 - 7,42 (m, 2H), 7,69 (d, 1H), 7,95 (s, 1H), 8,55 (d, 1H). LC-MS: tiempo de retención: 0,88 min MS ES$^+$: 350,0 $[M+H]^+$ Método B
1-4-3SM=1-2-4		2-[1-(4-etoxi-2,6-difluorobencil)-1*H*-indazol-3-il]-5-metoxipirimidin-4-amina	^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 1,26 (t, 3H), 3,84 (s, 3H), 3,96 - 4,05 (m, 2H), 5,59 (s, 2H), 6,72 (d, 2H), 6,77 - 6,86 (s ancho, 2H), 7,15 - 7,21 (m, 1H), 7,40 (ddd, 1H), 7,69 (d, 1H), 7,93 (s, 1H), 8,52 (d, 1H). LC-MS: tiempo de retención:

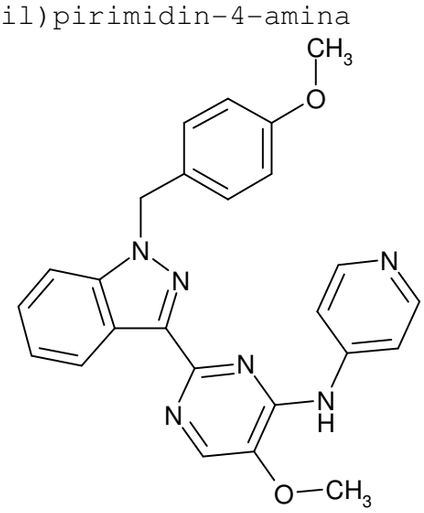
			1,03 min MS ES+: 412,2 [M+H]+
1-4-4SM=1-2-2		5-metoxi-2-[1-(4-propilbencil)-1*H*-indazol-3-il]pirimidin-4-amina	^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 0,80 (t, 3H), 1,40 - 1,54 (m, 2H), 2,42 - 2,46 (t, 2H), 3,85 (s, 3H), 5,62 (s, 2H), 6,83 (s ancho, 2H), 7,06 - 7,20 (m, 5H), 7,35 (ddd, 1H), 7,68 (d, 1H), 7,95 (s, 1H), 8,54 (d, 1H). LC-MS: tiempo de retención: 1,06 min MS ES+: 374,0 [M+H]+ Método B
1-4-5SM=		2-[1-(4-fluorobencil)-1*H*-indazol-3-il]-5-metoxipirimidin-4-amina	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 3,85 (s, 3H), 5,67 (s, 2H), 6,84 (s ancho, 2H), 7,06 - 7,21 (m, 3H), 7,23 - 7,31 (m,

1-2-5			2H), 7,36 (td, 1H), 7,70 (d, 1H), 7,95 (s, 1H), 8,54 (d, 1H). LC-MS: tiempo de retención: 0,87 min MS ES+: 350,0 [M+H]+ Método B
1-4-6SM=1-2-6		2-[1-(4-etoxi-2,6-difluorobencil)-4-metil-1H-indazol-3-il]-5-metoxipirimidin-4-amina	1H-RMN (400MHz, DMSO-d6): δ [ppm]= 1,26 (t, 3H), 2,34 (s, 3H), 3,85 (s, 3H), 4,00 (q, 2H), 5,52 (s, 2H), 6,63 - 6,74 (m, 2H),6,78 (br s, 2H), 6,87 (d, 1H), 7,27 (dd, 1H), 7,54 (d, 1H), 7,90 (s, 1H). LC-MS: tiempo de retención: 1,32 min

			MS ES+: 427,08 [M+H]+

Intermediario 1-5-1

Preparación de 5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina



Se suspendieron 205 mg de 5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]pirimidin-4-amina (1-4-1, 0,568 mmol, 1 eq.), 121,6 mg de clorhidrato de 4-bromopiridina (1:1) (0,625 mmol. 1,1 eq.), 136,5 mg de 2-metilpropan-2-olato de sodio (1,42 mmol, 2,5 eq.), 106,2 mg de 1'-binaftalen-2,2'-diilbis(difenilfosfano) (0,171 mmol, 0,3 eq.) y 52,0 mg de (1E,4E)-1,5-difenilpenta-1,4-dien-3-ona - paladio (3:2) (0,057 mmol, 0,1 eq.) en 3 ml de DMF seco bajo una atmósfera de nitrógeno. La mezcla de reacción se agitó durante dos días a 100°C. Se agregaron 122 mg de clorhidrato de 4-bromopiridina (1:1) (0,625 mmol. 1,1 eq.), 137 mg de 2-metilpropan-2-olato de sodio (1,42 mmol, 2,5 eq.), 106 mg de 1'-binaftalen-2,2'-diilbis(difenilfosfano) (0,171 mmol, 0,3 eq.) y 52,0 mg de (1E,4E)-1,5-difenilpenta-1,4-dien-3-ona - paladio (3:2) (0,057 mmol,

0,1 eq.) y se agitó durante otras 24 horas. La mezcla se enfrió hasta temperatura ambiente, se diluyó con 10 ml de diclorometano y se retiró por filtración. El material filtrado se concentró al vacío. El residuo se purificó mediante cromatografía flash para dar 126 mg (0,23 mmol, 81%) del compuesto buscado analíticamente puro.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 3,66 (s, 3H), 4,02 (s, 3H), 5,65 (s, 2H), 6,86 (d, 2H), 7,15 – 7,25 (m, 1H), 7,27 – 7,44 (m, 3H), 7,78 (d, 1H), 8,08 – 8,17 (m, 2H), 8,31 – 8,46 (m, 4H), 9,42 (s, 1H).

LC-MS:

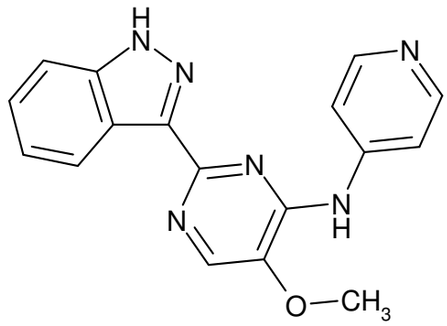
tiempo de retención: 0,95 min

MS ES$^+$: 439,31 $[M+H]^+$

Método B

Intermediario 1-6-1

Preparación de 2-(1*H*-indazol-3-il)-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina



Se suspendieron 13,4 g de 5-metoxi-2-[1-(4-metoxibencil)-1*H*-indazol-3-il]-*N*-(piridin-4-il)pirimidin-4-amina (1-5-1, 30,6 mmol, 1 eq.) en 121 ml de 1,2-dicloroetano. Se agregaron 71 ml de ácido trifluoroacético (918 mmol, 30 eq.) por goteo, seguidos por 27 ml de ácido trifluorometansulfónico (306 mmol, 10 eq.). La mezcla de reacción se agitó durante tres días bajo una atmósfera de

nitrógeno. La mezcla se enfrió con un baño de hielo hasta + 3°C, y luego se agregó solución acuosa de hidróxido de sodio 2M hasta pH = 12. La suspensión marrón resultante se agitó durante 18 horas a temperatura ambiente y luego el precipitado se retiró por filtración y se secó bajo vacío a 70°C para dar 9,74g (27,7 mmol, 90,3%) del compuesto buscado analíticamente puro como un sólido marrón claro.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 4,02 (s, 3H), 7,11 - 7,26 (m, 1H), 7,37 (t, 1H), 7,56 (d, 1H), 8,17 (d, 2H), 8,32 - 8,53 (m, 4H), 9,39 (s, 1H), 13,39 (s, 1H).

LC-MS:

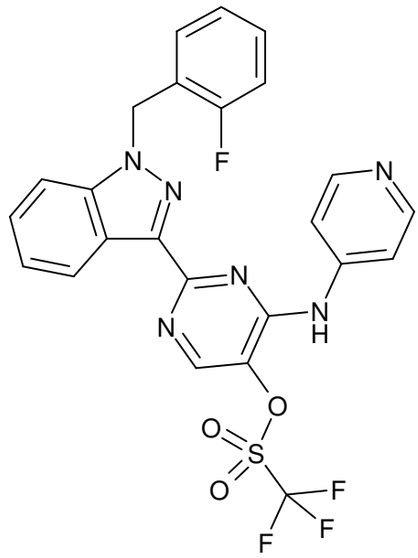
tiempo de retención: 0,68 min

MS ES$^+$: 319,0 $[M+H]^+$

Método B

Intermediario 1-7-1

Preparación de trifluorometansulfonato de 2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ilo



Se suspendieron 120 mg de 2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ol (3-3, 0,291 mmol,

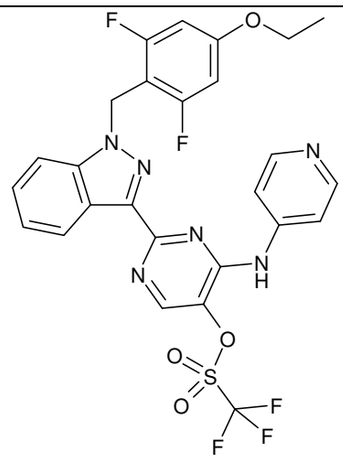
1 eq.) en 1,9 ml de diclorometano seco y se agregaron 0,059 ml de piridina (0,73 mmol, 2,5 eq.) bajo una atmósfera de nitrógeno. La mezcla se enfrió con un baño de hielo hasta +3°C y se agregaron 0,061ml de anhídrido trifluorometansulfónico (0,364 mmol, 1,25 eq.) por goteo. Al completarse la adición, el baño de hielo se retiró y la mezcla de reacción se agitó durante 18 horas. La mezcla de reacción se enfrió nuevamente con un baño de hielo y se agregaron 0,059 ml de piridina (0,727 mmol, 2,5 eq.) y 0,061 ml de anhídrido trifluorometansulfónico (0,364 mmol, 1,25 eq.) y se agitó durante 3 horas. Este procedimiento se repitió y se agitó durante otras 24 horas. La mezcla de reacción se retiró por filtración a través de una columna de sílice corta y se diluyó con diclorometano. El material filtrado se concentró al vacío. EL residuo líquido se disolvió con tolueno y nuevamente se concentró al vacío. Rendimiento = 106,1 mg con 37% de pureza (0,07 mmol, 24,78%)

LC-MS:

tiempo de retención: 1,18 min

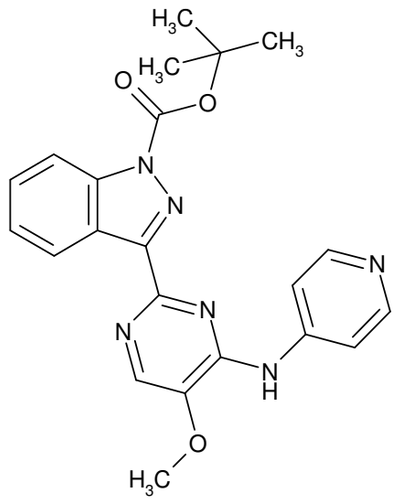
MS ES^+: 545,08 $[M+H]^+$

El siguiente intermediario se preparó de acuerdo con el mismo procedimiento usando los materiales de partida indicados (SM = material de partida):

1-7-2 SM = 3-1		trifluorometansulfonato de 2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ilo	(1H-RMN (300MHz, DMSO-d6): δ [ppm]= 1,20 - 1,30 (m, 3H), 4,00 (q, 2H), 5,68 - 5,78 (m, 2H), 6,78 (d,2H), 7,26 - 7,36 (m, 1H), 7,52 (t, 1H), 7,89 (d, 1H), 8,30 - 8,45 (m, 3H), 8,66 (d, 2H), 9,05 (s, 1H), 11,15 - 11,43 (m, 1H).) LC-MS: tiempo de retención: 1,03 min MS ES$^+$: 475,1 $[M+H]^+$ Método B

Intermediario 1-8-1

Preparación de 3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-carboxilato de tert-butilo



Se disolvió 100 mg de [2-(1H-Indazol-3-il)-5-metoxi-pirimidin-4-il]-piridin-4-il-amina (1-6-1, 0,314 mmol, 1 eq.) en 2 ml de acetonitrilo y 0,131 ml de trietilamina (0,942 mmol, 3 eq.). Se agregaron 3,83 mg de 4-dimetilaminopiridina (0,031 mmol, 0,1 eq.) y 89,1 mg de dicarbonato de di-tert-butilo (0,408 mmol, 1,3 eq.) disuelto en 0,5 ml de acetonitrilo. La solución se agitó durante 24 horas a temperatura ambiente bajo una atmósfera de nitrógeno. La suspensión resultante se retiró por filtración y la torta de filtrado se lavó con acetonitrilo para dar 100 mg (0,24 mmol, 76,1%) del compuesto buscado analíticamente puro.

^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 1,68 (s ancho, 9H), 4,05 (s ancho, 3H), 7,43 (s ancho, 1H), 7,62 (s ancho, 1H), 8,18 (s ancho, 3H), 8,33 – 8,45 (m, 3H), 8,57 (d, 1H), 9,53 (s ancho, 1H).

LC-MS:

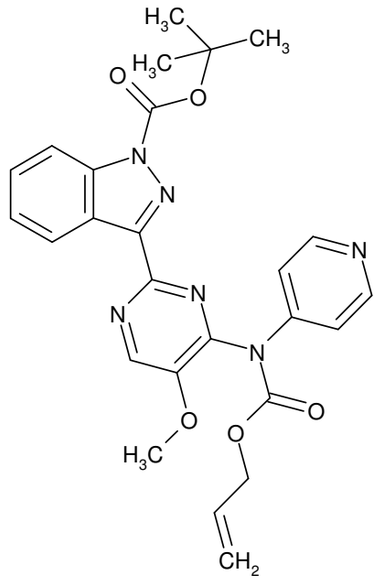
tiempo de retención: 0,97 min

MS ES$^+$: 419,1 $[M+H]^+$

Intermediario 1-9-1

Preparación de 3-(5-metoxi-4-{[(prop-2-en-1-

iloxi)carbonil](piridin-4-il)amino}pirimidin-2-il)-1H-indazol-1-carboxilato de tert-butilo



Se suspendieron 96,3 mg de 3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-carboxilato de tert-butilo (1-8-1, 0,23 mmol, 1 eq.) en 7 ml de piridina. Se agregaron 27,7 mg de carbonocloridato de prop-2-en-1-ilo (0,23 mmol, 1 eq.) y se agitó durante dos horas a temperatura ambiente. Se agregaron 27,7 mg de carbonocloridato de prop-2-en-1-ilo (0,23 mmol, 1 eq.) nuevamente dos veces y se agitó la primera vez durante 24 horas y la segunda vez durante tres días a temperatura ambiente. La mezcla de reacción se concentró al vacío. Al residuo se agregó agua y se acidificó con solución acuosa de cloruro de hidrógeno 1M. Esta fase acuosa se extrajo tres veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre un filtro de silicona y se concentró bajo vacío. La purificación mediante cromatografía flash (acetato de etilo/ metanol 0-50%) dio 50,8 mg (0,09 mmol, 39,97%) del compuesto buscado

analíticamente puro.

^{1}H-RMN (300MHz, CLOROFORMO-d): δ [ppm]= 1,74 (s, 9H), 4,01 (s, 3H), 4,71 (d, 2H), 5,14 - 5,29 (m, 2H), 5,76 - 5,95 (m, 1H), 7,20 - 7,25 (m, 2H), 7,28 - 7,36 (m, 1H), 7,50 - 7,59 (m, 1H), 8,25 (t, 2H), 8,50 - 8,61 (m, 2H), 8,71 (s, 1H)

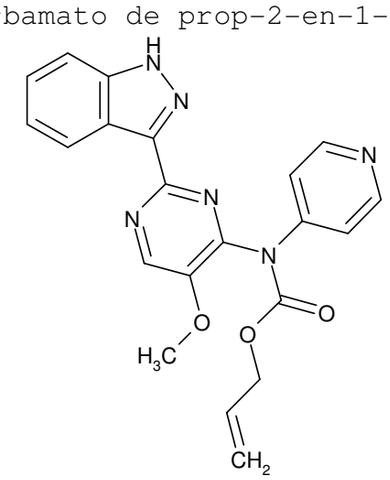
LC-MS:

tiempo de retención: 1,21 min

MS ES$^+$: 503,3 $[M+H]^+$

Intermediario 1-10-1

Preparación de [2-(1H-indazol-3-il)-5-metoxipirimidin-4-il]piridin-4-ilcarbamato de prop-2-en-1-ilo



Se suspendieron 1,22 g de 3-(5-metoxi-4-{[(prop-2-en-1-iloxi)carbonil](piridin-4-il)amino}pirimidin-2-il)-1H-indazol-1-carboxilato de tert-butilo (1-9-1, 2,43 mmol, 1 eq.) en 1,4-dioxano. Se agregaron 2,43 ml de ácido clorhídrico 4M en 1,4-dioxano (9,711 mmol, 4 eq.) por goteo. La mezcla de reacción se agitó durante 24 horas a temperatura ambiente. Se agregaron 2,43 ml de ácido clorhídrico 4M en 1,4-dioxano (9,711 mmol, 4 eq.) por goteo nuevamente y se agitó durante otras dos horas. La mezcla de reacción se concentró bajo vacío. El residuo se extrajo con solución acuosa saturada de carbonato ácido de sodio y

acetato de etilo. La capa acuosa se extrajo nuevamente dos veces con acetato de etilo. Las capas orgánicas combinadas se secaron sobre un filtro de silicona y se concentró bajo vacío. La purificación mediante cromatografía flash (acetato de etilo/ metanol 0-25%) dio 877 mg (1,96 mmol, 80,8%) del compuesto buscado analíticamente puro.

^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 4,00 (s, 3H), 4,71 - 4,81 (m, 2H), 5,12 - 5,23 (m, 2H), 5,79 - 5,93 (m, 1H), 7,13 - 7,23 (m, 1H), 7,33 - 7,41 (m, 1H), 7,54 - 7,62 (m, 1H), 7,82 - 7,91 (m, 2H), 8,25 - 8,31 (m, 1H), 8,71 - 8,79 (m, 2H), 9,09 (s, 1H)

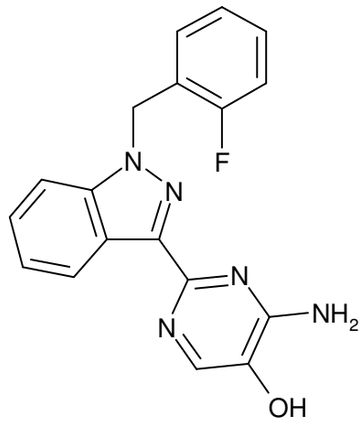
LC-MS:

tiempo de retención: 0,84 min

MS ES$^+$: 403,3 $[M+H]^+$

Intermediario 1-11-1

Preparación de 4-amino-2-[1-(2-fluorobencil)-1H-indazol-3-il]pirimidin-5-ol



Se suspendieron 558 mg de 2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-amina (1-4-2, 1,60mmol, 1 eq.) en 10 ml de 1-metil-2-pirrolidona. Se agregaron 623 mg de sulfuro de sodio (7,99 mmol, 5 eq.) y se agitó durante una hora a 140°C. La mezcla de reacción se extrajo con solución

acuosa parcialmente saturada de cloruro de amonio y acetato de etilo. La capa acuosa se extrajo nuevamente dos veces con acetato de etilo. La capa acuosa dio un precipitado, que se retiró por filtración y se purificó primero mediante cromatografía flash (hexano/ diclorometano/ metanol), seguida por purificación por HPLC. Esto dio 23,4 mg (0,07 mmol, 4,37%) del compuesto buscado analíticamente puro.

^{1}H-RMN (400MHz, DMSO-d6): δ [ppm]= 5,68 - 5,74 (s, 2H), 6,61 - 6,67 (d, 1H), 7,01 - 7,13 (m, 2H), 7,14 - 7,23 (m, 2H), 7,25 - 7,33 (m, 2H), 7,34 - 7,42 (t, 1H), 7,64 - 7,71 (d, 1H), 7,74 - 7,80 (s, 1H), 8,51 - 8,56 (d, 1H), 9,74 - 9,87 (s, 1H).

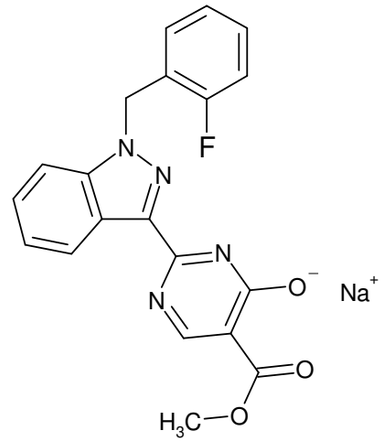
LC-MS:

tiempo de retención: 0,92 min

MS ES$^+$: 336,1 $[M+H]^+$

Intermediario 1-12-1

Preparación de 2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-(metoxicarbonil)pirimidin-4-olato de sodio



Se agitaron 2,5 g de clorhidrato de 1-(2-fluorobencil)-1H-indazol-3-carboximidamida (1:1) (1-2-3 x HCl, 8,20 mmol, 1 eq.), 1,43 g de (metoximetiliden)propanodioato de dimetilo (8,20 mmol, 1 eq.) y 50 ml de metanol y 443 mg de

metanolato de sodio bajo una atmósfera de nitrógeno a 60°C de temperatura de baño durante 24 horas. La solución amarillenta transparente se tornó una suspensión que se retiró por filtración. Los cristales se lavaron con metanol frío para dar 1,64 g (4,1 mmol, 50%) del compuesto buscado analíticamente puro.

^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 3,67 (s, 3H), 5,76 (s, 2H), 7,05 - 7,36 (m, 5H), 7,42 (ddd, 1H), 7,71 (d, 1H), 8,44 - 8,55 (m, 2H).

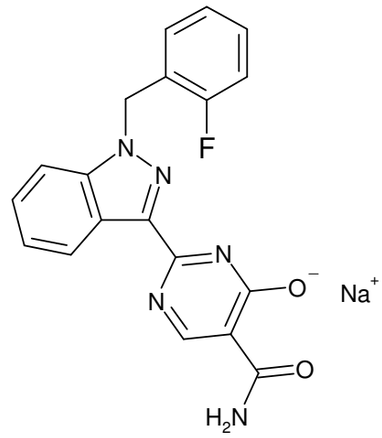
LC-MS:

tiempo de retención: 1,16 min

MS ES$^+$: 379,1 $[M+H]^+$

Intermediario 1-13-1

Preparación de 5-carbamoil-2-[1-(2-fluorobencil)-1H-indazol-3-il]pirimidin-4-olato de sodio



Se disolvieron 100 mg de 2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-(metoxicarbonil)pirimidin-4-olato de sodio (1-12-1, 0,25 mmol, 1 eq.) en 26,8 ml de amoníaco en metanol 7N (187 mmol, 750 eq.) y se agitó bajo una atmósfera de nitrógeno a 60°C de temperatura de baño durante 24 horas, luego a 65°C de temperatura de baño durante seis horas y otras 24 horas a 70°C de temperatura de baño. La mezcla de reacción se

concentró al vacío para dar 96 mg (0,22 mmol, 89,8%) del compuesto buscado analíticamente puro.

^{1}H-RMN (400MHz, DMSO-d6): δ [ppm]= 5,82 (s, 2H), 7,07 – 7,26 (m, 3H), 7,27 – 7,42 (m, 3H), 7,47 (t, 1H), 7,77 (d, 1H), 8,47 (d, 1H), 8,58 (s ancho, 1H), 9,07 – 9,32 (m, 1H).

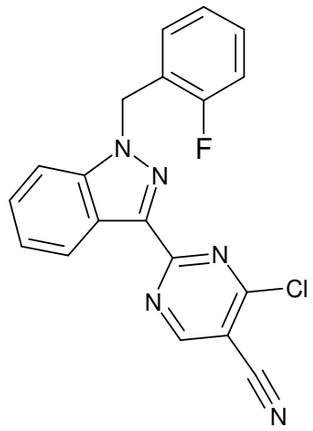
LC-MS:

tiempo de retención: 1,10 min

MS ES$^+$: 364,12 $[M+H]^+$

Intermediario 1-14-1

Preparación de 4-cloro-2-[1-(2-fluorobencil)-1H-indazol-3-il]pirimidin-5-carbonitrilo



Se suspendieron 88 mg de 5-carbamoil-2-[1-(2-fluorobencil)-1H-indazol-3-il]pirimidin-4-olato de sodio (1-13-1, 0,228 mmol, 1 eq.) en 0,915 ml de tricloruro fosfórico (9,82 mmol, 43 eq.) y 69 µl de N,N-dietilanilina (0,457 mmol, 2 eq.). La suspensión se agitó a 90°C de temperatura de baño durante 24 horas y luego se agregó sobre una solución acuosa saturada de carbonato ácido de sodio enfriada con hielo. La suspensión resultante se retiró por filtración y se secó al vacío para dar 82 mg (0,21 mmol, 93,77%) del compuesto buscado analíticamente puro.

^{1}H-RMN (400MHz, DMSO-d6): δ [ppm]= 5,87 – 5,91 (m, 2H),

7,08 – 7,26 (m, 3H), 7,30 – 7,44 (m, 2H), 7,53 (td, 1H), 7,88 (d, 1H), 8,45 (d, 1H), 9,39 (s, 1H).

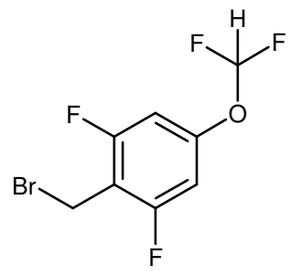
LC–MS: Método B

tiempo de retención: 1,38 min

MS ES^+: 364,0 $[M+H]^+$

Intermediario 1–15–1

Preparación de 2–(bromometil)–5–(difluorometoxi)–1,3–difluorobenceno



Paso 1: [4–(difluorometoxi)–2,6–difluorofenil]metanol

Se disolvieron 1 g de 3,5–difluoro–4–(hidroximetil)fenol (6,245 mmol, 1 eq.) en 16 ml de DMF. Se agregaron 1,047 g de cloro(difluoro)acetato de sodio (6,87 mmol, 1,1 eq.), 2,442 g de carbonato de cesio (7,494 mmol, 1,2 eq.) y 400 µl de agua. La mezcla se agitó a 100 °C de temperatura de baño durante 2 horas bajo una atmósfera de nitrógeno. Luego la mezcla de reacción se particionó entre agua y acetato de etilo. La fase acuosa separada se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre un filtro de silicona y se concentró al vacío. El residuo se purificó mediante cromatografía flash para dar 763,3 mg (3,63 mmol, 58,2%) del compuesto buscado analíticamente puro.

^{1}H–RMN (400MHz, DMSO–d_6): δ [ppm]= 4,42 (d, 2H), 5,21 (t, 1H), 6,99 (d, 2H), 7,09 – 7,50 (t, 1H).

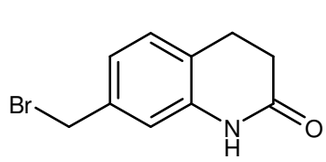
Paso 2: 2-(bromometil)-5-(difluorometoxi)-1,3-difluorobenceno

Se disolvieron 0,76 g de [4-(difluorometoxi)-2,6-difluorofenil]metanol (3,62 mmol, 1 eq.) en 1,72 ml de bromuro de hidrógeno en ácido acético glacial 33% (9,97 mmol, 2,75 eq.) y se agitó a temperatura ambiente durante 2 horas. Se agregaron 25 ml de éter dietílico y la mezcla se agitó a temperatura ambiente durante 15 min. La mezcla de reacción se agregó por goteo a 80 ml de solución acuosa saturada de carbonato ácido de sodio y se agitó nuevamente a temperatura ambiente durante 15 min. La fase acuosa separada se extrajo dos veces con éter dietílico. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre un filtro de silicona y se concentró al vacío para dar 991 mg (3,56 mmol, 98,4%) del compuesto buscado analíticamente puro.

^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 4,60 (s, 2H), 7,08 – 7,14 (d, 2H), 7,08 – 7,59 (t, 1H).

Intermediario 1-16-1

Preparación de 7-bromometil-3,4-dihidro-1H-quinolin-2-ona



Se disolvieron 500 mg de 7-(hidroximetil)-3,4-dihidroquinolin-2(1*H*)-ona (2,82 mmol, 1 eq.) en 1,77 ml de bromuro de hidrógeno en ácido acético glacial 33% (31,0 mmol, 11 eq.) bajo una atmósfera de nitrógeno y se agitó a temperatura ambiente durante 30 minutos. La mezcla de

reacción se particionó entre solución acuosa saturada de carbonato ácido de sodio y diclorometano/ isopropanol 4+1. La capa acuosa se extrajo tres veces con diclorometano/ isopropanol 4+1. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre un filtro de silicona y se concentró al vacío. El producto crudo se purificó mediante cromatografía flash para dar 175 mg (0,66 mmol, 23,3%) del compuesto buscado analíticamente puro.

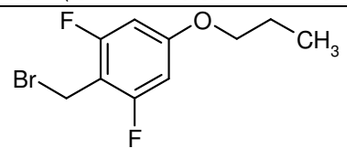
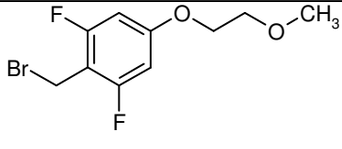
^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 2,40 (dd, 2H), 2,82 (t, 2H), 4,60 (s, 2H), 6,87 (d, 1H), 6,94 (dd, 1H), 7,10 (d, 1H).

LC-MS:

tiempo de retención: 0,91 min

MS ES$^+$: 240,2 $[M+H]^+$

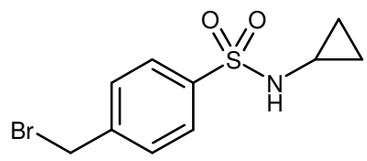
Los siguientes compuestos se prepararon de acuerdo con el mismo procedimiento a partir de los materiales de partida indicados (SM = material de partida):

1-16-2 SM = 1-18-1		2-(bromometil)-1,3-difluoro-5-propoxibenceno	
1-16-3 SM = 1-18-2		2-(bromometil)-1,3-difluoro-5-(2-metoxietoxi)	

		benceno	

Intermediario 1-17-1

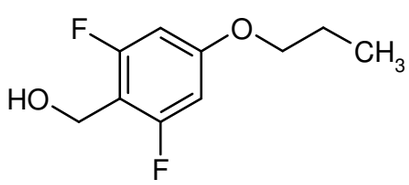
Preparación de 4-(bromometil)-N-ciclopropilbencensulfonamida



Se disolvieron 5 g de cloruro de 4-(bromometil)bencensulfonilo (18,6 mmol, 1 eq.) bajo atmósfera de argón en 82,5 ml de diclorometano y se enfrió a -10°C de temperatura interna. Se agregó una solución de 1,29 ml de ciclopropanamina (18,6 mmol, 1 eq.) y 2,59 ml de trietilamina (18,6 mmol, 1 eq.) en 82,5 ml de diclorometano por goteo a - 10°C de temperatura interna y se agitó a esta temperatura durante una hora. La mezcla de reacción se lavó una vez con solución acuosa de ácido 1 M y dos veces con agua destilada. La capa orgánica se secó sobre sulfato de sodio y se concentró al vacío. El producto crudo contenía una mezcla de sustituyentes bromometilo y clorometilo.

Intermediario 1-18-1

Preparación de (2,6-difluoro-4-propoxifenil)metanol

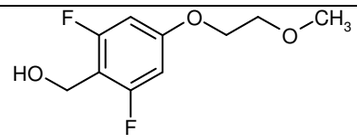


Se disolvieron 200 mg de 3,5-difluoro-4-(hidroximetil)fenol (1,25 mmol, 1,0 eq.) y 184 mg 1-bromopropano (1,50 mmol,

1,2 eq.) en 17 ml de N,N-dimetilformamida. Se agregaron 863 mg de potasio (6,25 mmol, 5,0 eq.) y la mezcla de reacción se agitó a 0 °C durante la noche. La mezcla de reacción se separó entre agua y acetato de etilo. La capa acuosa se extrajo con acetato de etilo dos veces. Las capas orgánicas combinadas se secaron sobre un filtro de silicona y se concentró al vacío para dar 283 mg (1,19 mmol, 95 %) del producto crudo el cual se usó sin purificación adicional.

^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 0,92 (t, 3H), 1,54 - 1,78 (m, 2H), 3,90 (t, 2H), 4,36 (s, 2H), 5,06 (s ancho, 1H), 6,53 - 6,79 (m, 2H).

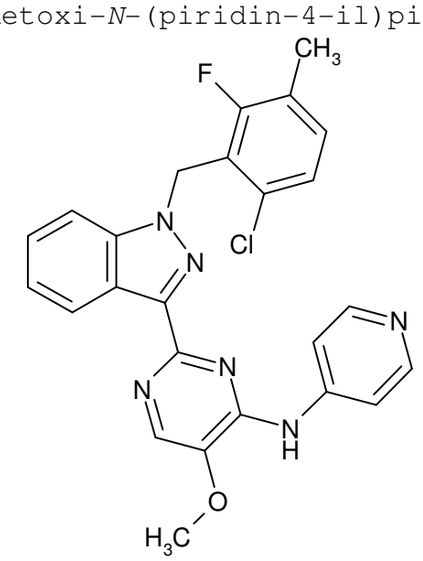
El siguiente intermediario se preparó de acuerdo con el mismo procedimiento a partir de (2-brometil)-metiléter y 3,5-difluoro-4-(hidroximetil)fenol comercialmente disponibles:

1-18-2		[2,6-difluoro-4-(2-metoxietoxi)fenil]metanol	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 3,25 (s, 3H), 3,50 - 3,65 (m, 2H), 3,99 - 4,14 (m, 2H), 4,37 (s ancho, 2H), 5,07 (s ancho, 1H), 6,52 - 6,75 (m, 2H)

EJEMPLOS

Ejemplo 2-1-1

Preparación de 2-[1-(6-cloro-2-fluoro-3-metilbencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina



Se suspendieron 80 mg de 2-(1H-indazol-3-il)-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina (1-6-1, 0,251 mmol, 1. eq.) en tetrahidrofurano seco bajo una atmósfera de nitrógeno. Se agregaron 30,2 mg de hidruro de sodio (60% de pureza) y se agitó a temperatura ambiente durante 10 minutos. Luego se agregaron 59,7 mg de 2-(bromometil)-1-cloro-3-fluoro-4-metilbenceno. La mezcla de reacción se agitó durante 18 horas a temperatura ambiente. Luego la mezcla se particionó entre solución acuosa parcialmente saturada de cloruro de amonio y diclorometano/ isopropanol 4:1. Las fases se separaron y la capa acuosa se extrajo dos veces con diclorometano/isopropanol 4:1. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre un filtro de silicona y se concentró al vacío. La purificación por HPLC preparativa dio 29 mg (0,06 mmol, 24,1%) del compuesto buscado analíticamente puro.

1H-RMN (300 MHz, DMSO-d6): δ [ppm]= 2,19 (d, 3H), 4,00 (s, 3H), 5,80 (d, 2H), 7,17 - 7,37 (m, 3H), 7,42 - 7,53 (m,

1H), 7,89 (d, 1H), 8,13 – 8,22 (m, 2H), 8,29 – 8,40 (m, 3H), 8,46 (d, 1H), 9,39 (s, 1H).

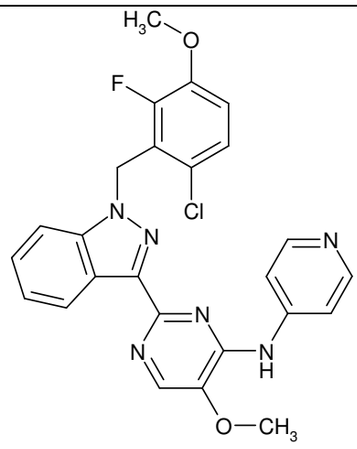
LC–MS:

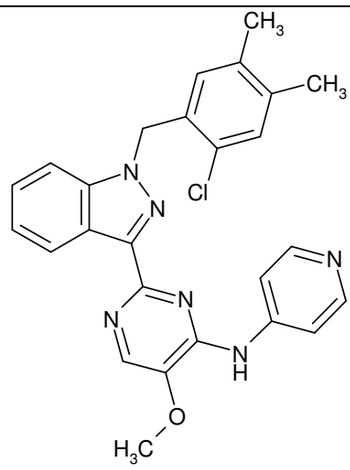
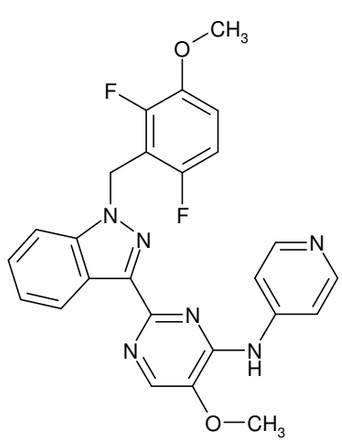
tiempo de retención: 1,01 min

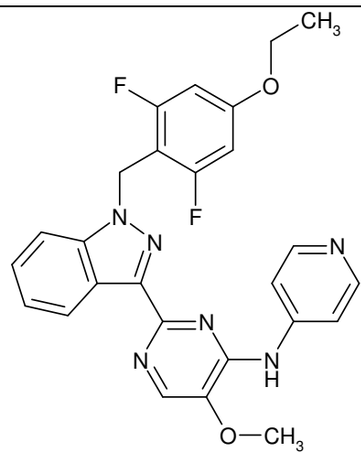
MS ES+: 475,4 $[M+H]^+$

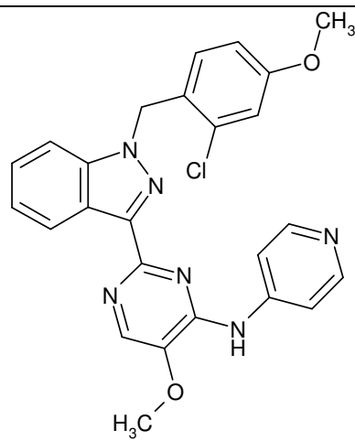
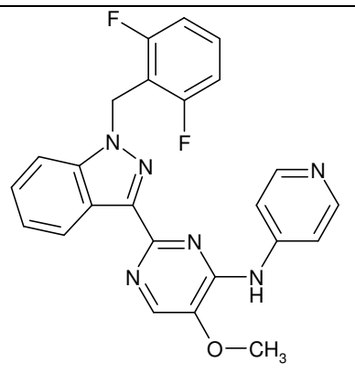
Método B

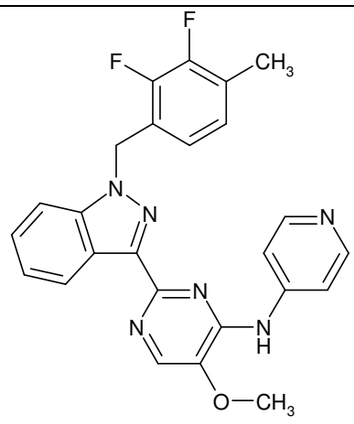
Los siguientes compuestos se prepararon de acuerdo con el mismo procedimiento a partir de los materiales de partida indicados (SM = material de partida):

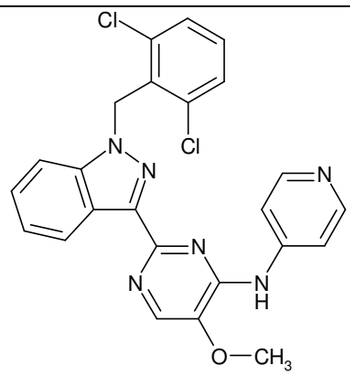
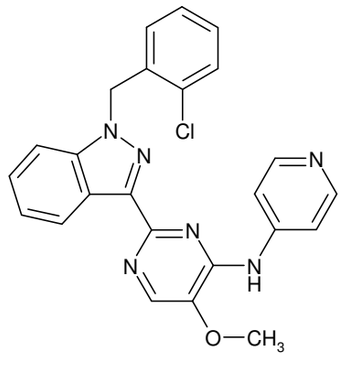
2-2-1 SM = 1-6-1		2-[1-(6-cloro-2-fluoro-3-metoxibencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 3,82 (s, 3H), 4,00 (s, 3H), 5,77 (d, 2H), 7,17 – 7,36 (m, 3H), 7,47 (ddd, 1H), 7,89 (d, 1H), 8,13 – 8,20 (m, 2H), 8,29 – 8,40 (m, 3H), 8,46 (d, 1H), 9,39 (s, 1H). LC–MS: tiempo de retención: 0,99 min MS ES$^+$: 491,3 $[M+H]^+$ Método B

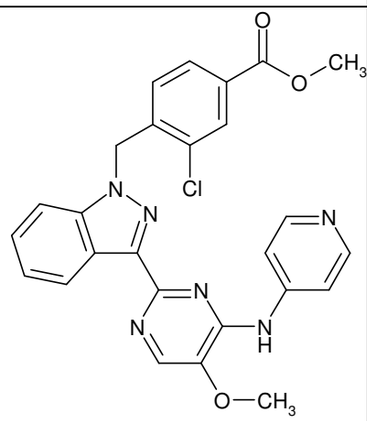
2-3-1 SM = 1-6-1		2-[1-(2-cloro-4,5-dimetilbencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 2,09 (s, 3H), 2,15 (s, 3H), 3,96 - 4,05 (m, 3H), 5,71 (s, 2H), 7,09 (s, 1H), 7,19 - 7,31 (m, 2H), 7,43 (s, 1H), 7,78 (d, 1H), 8,11 - 8,17 (m, 2H), 8,30 - 8,40 (m, 3H), 8,46 (d, 1H), 9,44 (s, 1H). LC-MS: tiempo de retención: 1,04 min MS ES$^+$: 471,4 $[M+H]^+$ Método B
2-4-1 SM = 1-6-1		2-[1-(2,6-difluoro-3-metoxibencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 3,78 (s, 3H), 4,00 (s, 3H), 5,74 (s, 2H), 7,02 - 7,30 (m, 3H), 7,42 - 7,52 (m, 1H), 7,84 (d, 1H), 8,10 - 8,19 (m, 2H), 8,28

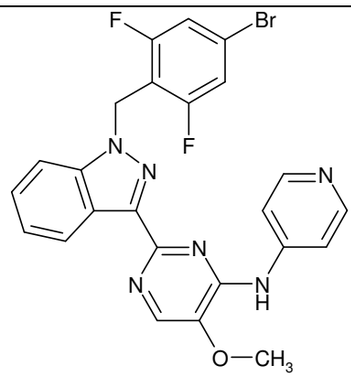
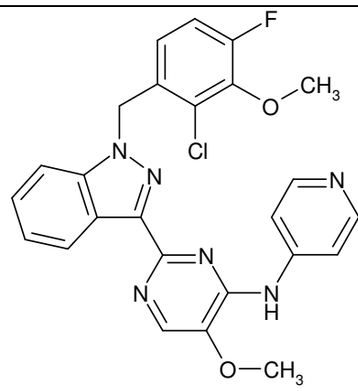
		-4-amina	- 8,48 (m, 4H), 9,38 (s, 1H). LC-MS: tiempo de retención: 0,95 min MS ES+: 475,0 [M+H]+ Método B
2-5-1 SM = 1-6-1		2-[1-(4-etoxi-2,6-difluorobencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 1,25 (t, 3H), 3,93 - 4,09 (m, 5H), 5,64 (s, 2H), 6,68 - 6,82 (m, 2H), 7,23 (t, 1H), 7,40 - 7,51 (m, 1H), 7,81 (d, 1H), 8,11 - 8,20 (m, 2H), 8,29 - 8,48 (m, 4H), 9,37 (s, 1H). LC-MS: tiempo de retención: 1,05 min MS ES+: 489,0 [M+H]+ Método B

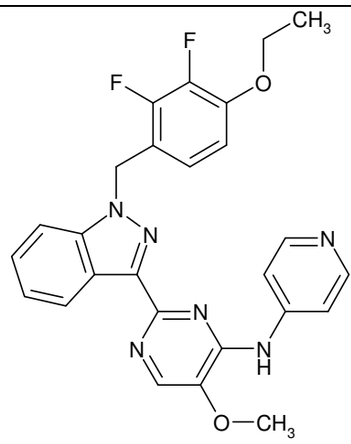
2-6-1 SM = 1-6-1		2-[1-(2-cloro-4-metoxibencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 3,72 (s, 3H), 4,01 (s, 3H), 5,72 (s, 2H), 6,90 (dd, 1H), 7,07 (d, 1H), 7,19 - 7,28 (m, 2H), 7,43 (t, 1H), 7,79 (d, 1H), 8,08 - 8,16 (m, 2H), 8,30 - 8,41 (m, 3H), 8,45 (d, 1H), 9,40 (s, 1H). LC-MS: tiempo de retención: 0,99 min MS ES$^+$: 473,4 $[M+H]^+$ Método B
2-7-1 SM = 1-6-1		2-[1-(2,6-difluorobencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 4,00 (s, 3H), 5,75 (s, 2H), 7,15 (t, 1H), 7,24 (t, 1H), 7,38 - 7,52 (m, 2H), 7,81 - 7,89 (m, 1H), 7,85 (d, 1H), 8,09 - 8,18

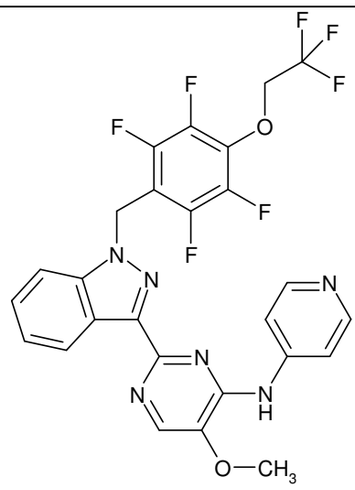
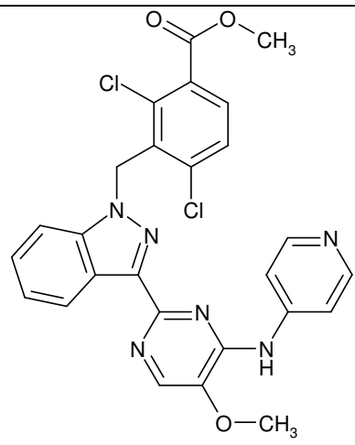
			(m, 2H), 8,29 – 8,39 (m, 3H), 8,41 – 8,47 (m, 1H), 9,38 (s, 1H). LC-MS: tiempo de retención: 0,97 min MS ES+: 445,0 [M+H]+ Método B
2-8-1 SM = 1-6-1		2-[1-(2,3-difluoro-4-metilbencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 2,21 (d, 3H), 4,01 (s, 3H), 5,77 (s, 2H), 7,00 – 7,09 (m, 2H), 7,24 (t, 1H), 7,44 (t, 1H), 7,81 (d, 1H), 8,08 – 8,17 (m, 2H), 8,30 – 8,50 (m, 4H), 9,39 (s, 1H). LC-MS: tiempo de retención: 1,01 min MS ES+: 459,0 [M+H]+ Método B

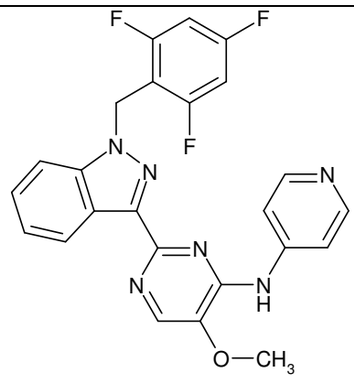
2-9-1 SM = 1-6-1		2-[1-(2,6-diclorobencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 3,99 (s, 3H), 5,87 (s, 2H), 7,25 (t, 1H), 7,39 - 7,53 (m, 2H), 7,55 - 7,62 (m, 2H), 7,90 (d, 1H), 8,13 (d, 2H), 8,28 - 8,40 (m, 3H), 8,48 (d, 1H), 9,32 (s, 1H). LC-MS: tiempo de retención: 1,13min MS ES$^+$: 477,22 $[M+H]^+$
2-10-1 SM = 1-6-1		2-[1-(2-clorobencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 4,01 (s, 3H), 5,81 (s, 2H), 7,15 (dd, 1H), 7,20 - 7,38 (m, 3H), 7,39 - 7,54 (m, 2H), 7,78 (d, 1H), 8,05 - 8,15 (m, 2H), 8,29 - 8,40 (m, 3H), 8,47 (d, 1H), 9,38 (s, 1H).

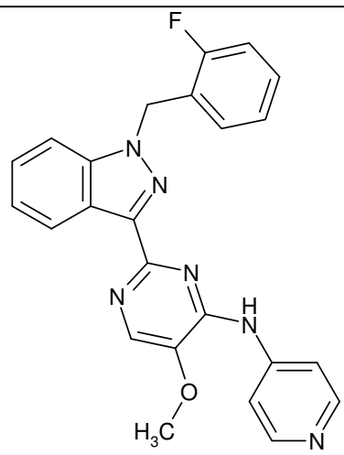
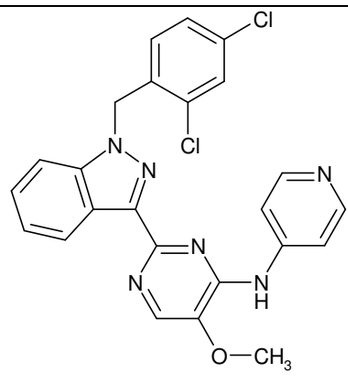
			LC-MS: tiempo de retención: 1,00 min MS ES+: 443,0 [M+H]+ Método B
2-11-1 SM = 1-6-1		3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)benzoato de metilo	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 3,81 (s, 3H), 4,01 (s, 3H), 5,89 (s, 2H), 7,18 - 7,31 (m, 2H), 7,45 (t, 1H), 7,79 (d, 1H), 7,85 (dd, 1H), 7,98 (d, 1H), 8,06 - 8,13 (m, 2H), 8,30 - 8,39 (m, 3H), 8,48 (d, 1H), 9,40 (s, 1H). LC-MS: tiempo de retención: 0,96 min MS ES+: 501,1 [M+H]+ Método B

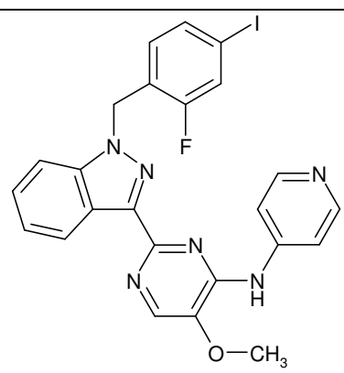
2-12-1 SM = 1-6-1		2-[1-(4-bromo-2,6-difluorobencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 4,00 (s, 3H), 5,72 (s, 2H), 7,25 (t, 1H), 7,44 - 7,52 (m, 1H), 7,54 - 7,61 (m, 2H), 7,85 (d, 1H), 8,12 - 8,18 (m, 2H), 8,32 (s, 1H), 8,35 - 8,40 (m, 2H), 8,44 (d, 1H), 9,40 (s, 1H). LC-MS: tiempo de retención: 0,99 min MS ES$^+$: 525,3 $[M+H]^+$ Método B
2-13-1 SM = 1-6-1		2-[1-(2-cloro-4-fluoro-3-metoxibencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 3,85 (d, 3H), 4,01 (s, 3H), 5,79 (s, 2H), 6,91 (dd, 1H), 7,21 - 7,32 (m, 2H), 7,44 (td, 1H), 7,80 (d, 1H), 8,08 - 8,13 (m,

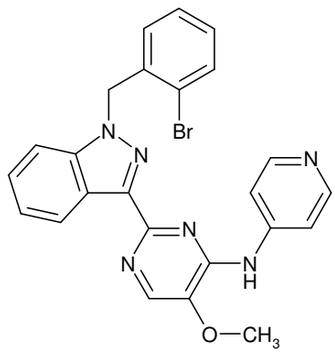
		il)pirimidin-4-amina	2H), 8,33 (s, 1H), 8,35 – 8,39 (m, 2H), 8,47 (d, 1H), 9,42 (s, 1H). LC-MS: tiempo de retención: 0,98 min MS ES+: 491,3 [M+H]+ Método B
2-14-1 SM = 1-6-1		2-[1-(4-etoxi-2,3-difluorobencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 1,28 (t, 3H), 3,94 – 4,13 (m, 5H), 5,73 (s, 2H), 6,92 – 7,03 (m, 1H), 7,08 – 7,18 (m, 1H), 7,23 (t, 1H), 7,44 (t, 1H), 7,83 (d, 1H), 8,10 – 8,16 (m, 2H), 8,33 (s, 1H), 8,36 – 8,40 (m, 2H), 8,43 (d, 1H), 9,41 (s, 1H). LC-MS: tiempo de retención: 1,03

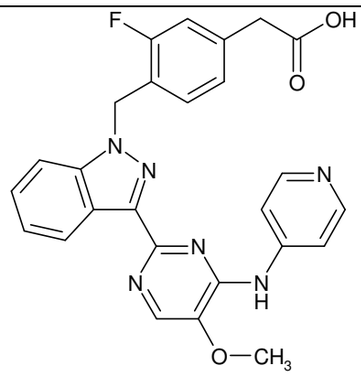
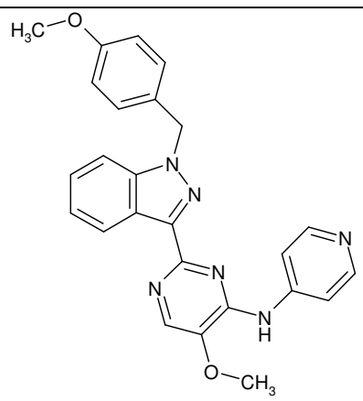
			min MS ES+: 489,0 [M+H]+ Método B
2-15-1 SM = 1-6-1		5-metoxi-*N*-(piridin-4-il)-2-{1-[2,3,5,6-tetrafluoro-4-(2,2,2-trifluoroetoxi)bencil]-1*H*-indazol-3-il}pirimidin-4-amina	^{1}H-RMN (500MHz, DMSO-d_6): δ [ppm]= 4,04 - 4,07 (s, 3H), 4,99 (q, 2H), 5,90 (s, 2H), 7,31 (t, 1H), 7,55 (t, 1H), 7,93 (d, 1H), 8,23 (d, 2H), 8,38 (s, 1H), 8,42 (d, 2H), 8,49 (d, 1H), 9,46 (s, 1H). LC-MS: tiempo de retención: 1,21 min MS ES+: 579,1 [M+H]+ Método B
2-16-1 SM = 1-6-1		2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 3,85 (s, 3H), 4,02 (s, 3H), 5,96 (s, 2H), 7,29 (t, 1H), 7,48 - 7,55 (m, 1H), 7,73 - 7,78

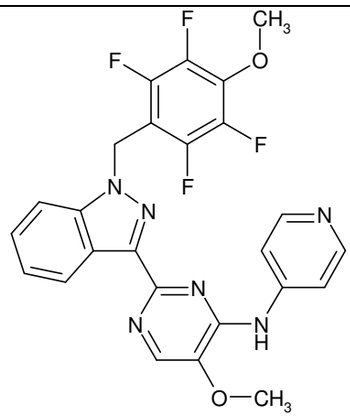
		1-il}metil)benzoato de metilo	(m, 1H), 7,80 - 7,84 (m, 1H), 7,94 (d, 1H), 8,11 - 8,16 (m, 2H), 8,34 (s, 1H), 8,38 (d, 2H), 8,52 (d, 1H), 9,34 (s, 1H). LC-MS: tiempo de retención: 1,08 min MS ES+: 535,22 [M+H]+
2-17-1 SM = 1-6-1		5-metoxi-*N*-(piridin-4-il)-2-[1-(2,4,6-trifluorobencil)-1*H*-indazol-3-il]pirimidin-4-amina	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 4,00 (s, 3H), 5,68 - 5,76 (m, 2H), 7,20 - 7,34 (m, 3H), 7,43 - 7,51 (m, 1H), 7,84 (d, 1H), 8,12 - 8,18 (m, 2H), 8,32 (s, 1H), 8,37 (d, 2H), 8,44 (d, 1H), 9,35 - 9,40 (m, 1H). LC-MS: tiempo de retención: 1,03

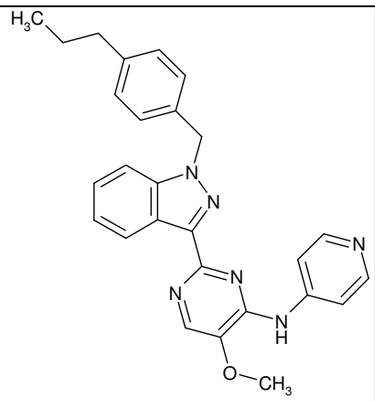
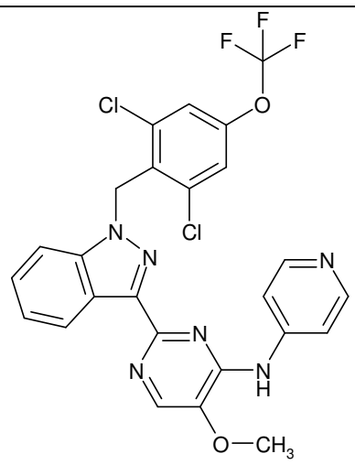
			min MS ES+: 463,31 [M+H]+
2-18-1 SM = 1-6-1		2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina	1H-RMN (300MHz, DMSO-d6): δ [ppm]= 4,01 (s, 3H), 5,77 (s, 2H), 7,10 - 7,49 (m, 6H), 7,75 - 7,84 (m, 1H), 8,07 - 8,17 (m, 2H), 8,33 (s, 1H), 8,35 - 8,40 (m, 2H), 8,40 - 8,48 (m, 1H), 9,35 - 9,45 (m, 1H). LC-MS: tiempo de retención: 1,01 min MS ES+: 427,19 [M+H]+
2-19-1 SM = 1-6-1		2-[1-(2,4-diclorobencil)-1*H*-indazol-3-il]-5-metoxi-*N*-	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 4,01 (s, 3H), 5,80 (s, 2H), 7,15 - 7,29 (m, 2H), 7,38 - 7,49 (m, 2H),

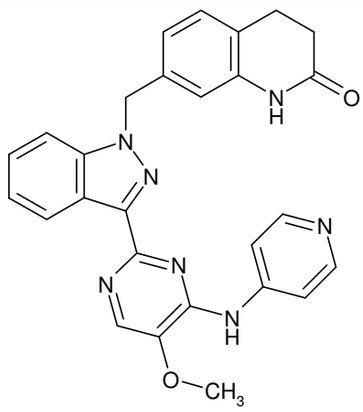
		(piridin-4-il)pirimidin-4-amina	7,68 (d, 1H), 7,79 (d, 1H), 8,05 - 8,13 (m, 2H), 8,31 - 8,40 (m, 3H), 8,47 (d, 1H), 9,40 (s, 1H). LC-MS: tiempo de retención: 1,07 min MS ES+: 477,35 [M+H]+
2-20-1 SM = 1-6-1		2-[1-(2-fluoro-4-iodobencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 4,01 (s, 3H), 5,73 (s, 2H), 7,07 (t, 1H), 7,24 (t, 1H), 7,44 (ddd, 1H), 7,55 (dd, 1H), 7,67 (dd, 1H), 7,79 (d, 1H), 8,08 - 8,13 (m, 2H), 8,33 (s, 1H), 8,36 - 8,40 (m, 2H), 8,44 (d, 1H), 9,42 (s, 1H). LC-MS: tiempo de

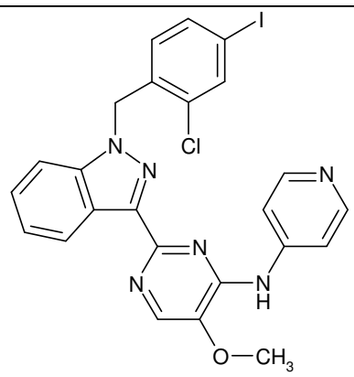
			retención: 1,00 min MS ES+: 553,3 [M+H]+ Método B
2-21-1 SM = 1-6-1		2-[1-(2-bromobencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 4,01 (s, 3H), 5,79 (s, 2H), 7,08 (dd, 1H), 7,22 - 7,28 (m, 2H), 7,30 - 7,36 (m, 1H), 7,44 (ddd, 1H), 7,67 (dd, 1H), 7,78 (d, 1H), 8,08 - 8,13 (m, 2H), 8,32 - 8,39 (m, 3H), 8,48 (d, 1H), 9,38 (s, 1H). LC-MS: tiempo de retención: 1,02 min MS ES+: 486,9 [M+H]+ Método B

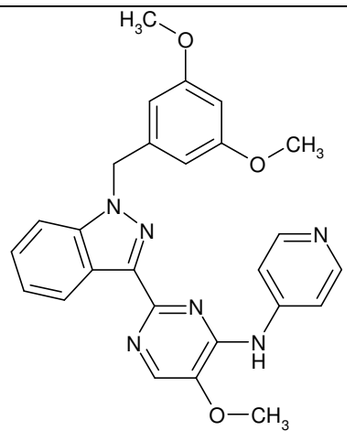
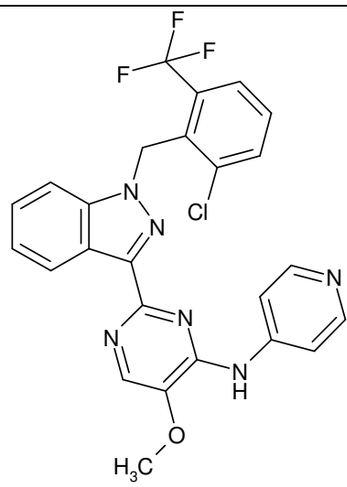
2-22-1 SM = 1-6-1		ácido [3-fluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)fenil]acético	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 3,54 (s, 2H), 4,01 (s, 3H), 5,74 (s, 2H), 7,01 - 7,07 (m, 1H), 7,12 (d, 1H), 7,19 - 7,29 (m, 2H), 7,38 - 7,47 (m, 1H), 7,79 (d, 1H), 8,08 - 8,16 (m, 2H), 8,33 (s, 1H), 8,36 - 8,48 (m, 3H), 9,39 (s, 1H). LC-MS: tiempo de retención: 0,86 min MS ES$^+$: 485,1 $[M+H]^+$ Método B
2-23-1 SM = 1-6-1		5-metoxi-2-[1-(4-metoxibencil)-1*H*-indazol-3-il]-*N*-(piridin-4-il)pirimidin	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 3,66 (s, 3H), 4,02 (s, 3H), 5,65 (s, 2H), 6,86 (d, 2H), 7,15 - 7,25 (m, 1H), 7,27 - 7,44 (m, 3H), 7,78 (d,

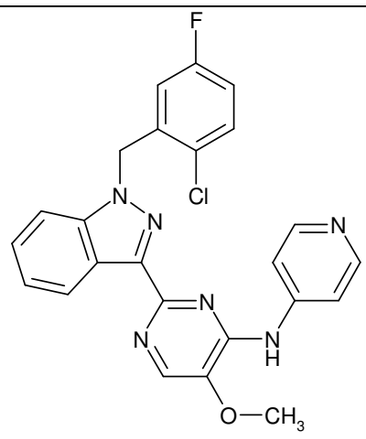
		-4-amina	1H), 8,08 - 8,17 (m, 2H), 8,31 - 8,46 (m, 4H), 9,42 (s, 1H). LC-MS: tiempo de retención: 0,95 min MS ES+: 439,31 $[M+H]^+$ Método B
2-24-1 SM = 1-6-1		5-metoxi-*N*-(piridin-4-il)-2-[1-(2,3,5,6-tetrafluoro-4-metoxibencil)-1*H*-indazol-3-il]pirimidin-4-amina	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 4,00 (s, 3H), 4,01 (s, 3H), 5,81 (s, 2H), 7,26 (t, 1H), 7,49 (t, 1H), 7,87 (d, 1H), 8,14 - 8,22 (m, 2H), 8,31 - 8,40 (m, 3H), 8,45 (d, 1H), 9,40 - 9,45 (m, 1H). LC-MS: tiempo de retención: 1,09 min MS ES+: 511,17 $[M+H]^+$

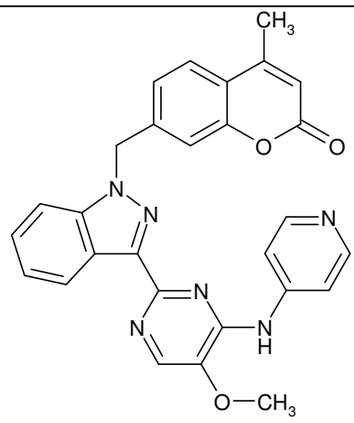
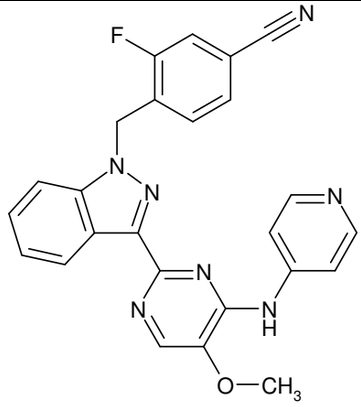
2-25-1 SM = 1-6-1		5-metoxi-2-[1-(4-propilbencil)-1*H*-indazol-3-il]-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 0,80 (t, 3H), 1,20 (s ancho, 2H), 1,40 - 1,57 (m, 2H), 4,02 (s, 3H), 5,68 (s, 2H), 7,12 (d, 2H), 7,17 - 7,30 (m, 2H), 7,40 (t, 1H), 7,78 (d, 1H), 8,12 (d, 2H), 8,21 (s, 1H), 8,32 - 8,46 (m, 4H), 9,42 (s, 1H). LC-MS: tiempo de retención: 1,15 min MS ES$^+$: 451,3 $[M+H]^+$
2-26-1 SM = 1-6-1		2-{1-[2,6-dicloro-4-(trifluorometoxi)bencil]-1*H*-indazol-3-il}-5-metoxi-*N*-(piridin-4-	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 4,02 (s, 3H), 5,90 (s, 2H), 7,29 (t, 1H), 7,52 (ddd, 1H), 7,83 (d, 2H), 7,94 (d, 1H), 8,12 - 8,18 (m, 2H),

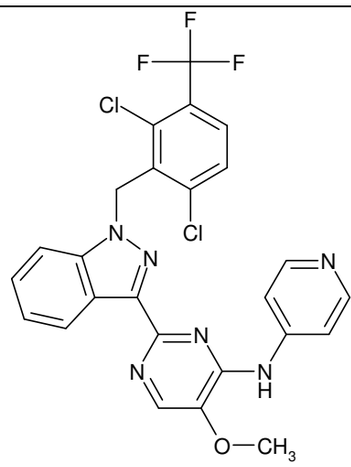
		il)pirimidin-4-amina	8,35 (s, 1H), 8,37 - 8,40 (m, 2H), 8,51 (d, 1H), 9,35 (s, 1H). LC-MS: tiempo de retención: 1,15 min MS ES+: 561,0 $[M+H]^+$ Método B
2-27-1 SM = 1-6-1		7-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)-3,4-dihidroquinolin-2(1*H*)-ona	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 2,35 (t, 2H), 2,77 (t, 2H), 4,02 (s, 3H), 5,65 (s, 2H), 6,77 (s, 1H), 6,88 (d, 1H), 7,09 (d, 1H), 7,22 (t, 1H), 7,40 (t, 1H), 7,71 (d, 1H), 8,11 (d, 2H), 8,28 - 8,51 (m, 4H), 9,42 (s, 1H), 10,01 (s, 1H). LC-MS: tiempo de retención: 1,04 min

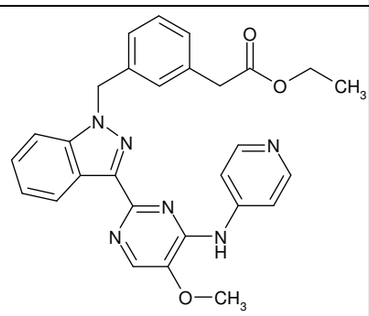
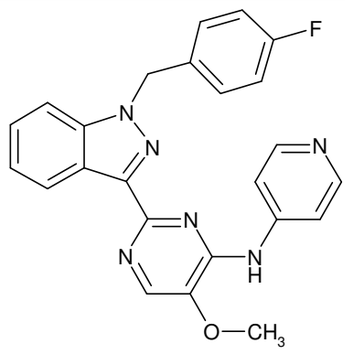
			MS ES+: 478,1 [M+H]+ Método B
2-28-1 SM = 1-6-1		2-[1-(2-cloro-4-iodobencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 4,01 (s, 3H), 5,76 (s, 2H), 6,93 (d, 1H), 7,25 (t, 1H), 7,44 (ddd, 1H), 7,68 (dd, 1H), 7,78 (d, 1H), 7,89 (d, 1H), 8,07 - 8,12 (m, 2H), 8,31 - 8,40 (m, 3H), 8,47 (d, 1H), 9,39 (s, 1H). LC-MS: tiempo de retención: 1,08 min MS ES+: 568,9 [M+H]+ Método B

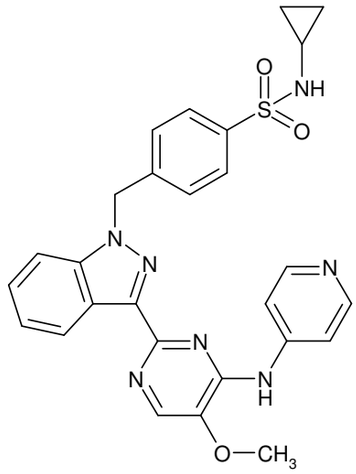
2-29-1 SM = 1-6-1		2-[1-(3,5-dimetoxibencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 3,64 (s, 6H), 4,02 (s, 3H), 5,65 (s, 2H), 6,38 (s, 1H), 6,48 (d, 2H), 7,22 (t, 1H), 7,36 - 7,45 (m, 1H), 7,77 (d, 1H), 8,09 - 8,17 (m, 2H), 8,31 - 8,47 (m, 4H), 9,42 (s, 1H). LC-MS: tiempo de retención: 0,89 min MS ES$^+$: 469,4 $[M+H]^+$ Método B
2-30-1 SM = 1-6-1		2-{1-[2-cloro-6-(trifluorometil)bencil]-1*H*-indazol-3-il}-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 3,98 (s, 3H), 5,83 (s, 2H), 7,26 (t, 1H), 7,44 - 7,53 (m, 1H), 7,63 - 7,71 (m, 1H), 7,83 - 7,97 (m, 3H), 8,02 - 8,10 (m, 2H), 8,22 - 8,33

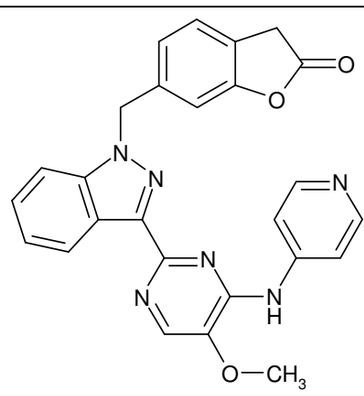
			(m, 3H), 8,48 (d, 1H), 9,32 (s, 1H). LC-MS: tiempo de retención: 1,12 min MS ES+: 511,36 [M+H]+
2-31-1 SM = 1-6-1		2-[1-(2-cloro-5-fluorobencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 4,01 (s, 3H), 5,80 (s, 2H), 7,11 (dd, 1H), 7,20 - 7,29 (m, 2H), 7,42 - 7,50 (m, 1H), 7,56 (dd, 1H), 7,83 (d, 1H), 8,07 - 8,15 (m, 2H), 8,31 - 8,40 (m, 3H), 8,47 (d, 1H), 9,42 (s, 1H). LC-MS: tiempo de retención: 1,02 min MS ES+: 461,0 [M+H]+ Método B

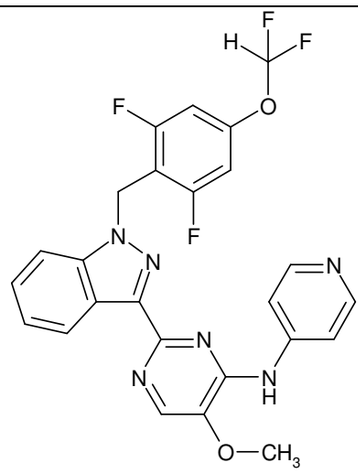
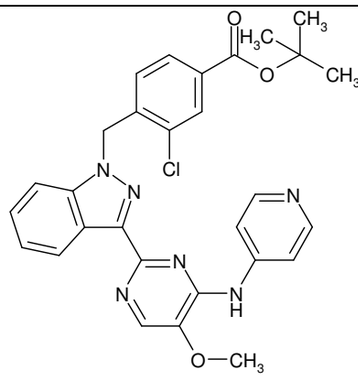
2-32-1 SM = 1-6-1		7-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)-4-metil-2*H*-cromen-2-ona	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 2,34 (d, 3H), 4,02 (s, 3H), 5,86 (s, 2H), 6,32 (d, 1H), 7,19 - 7,31 (m, 2H), 7,34 (s, 1H), 7,42 (t, 1H), 7,71 (d, 1H), 7,81 (d, 1H), 8,07 - 8,15 (m, 2H), 8,31 - 8,48 (m, 4H), 9,41 (s, 1H). LC-MS: tiempo de retención: 0,89 min MS ES$^+$: 491,0 $[M+H]^+$ Método B
2-33-1 SM = 1-6-1		3-fluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)ben	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 4,01 (s, 3H), 5,87 (s, 2H), 7,21 - 7,30 (m, 1H), 7,38 (t, 1H), 7,42 - 7,50 (m, 1H), 7,67 (dd, 1H), 7,81 (d, 1H), 7,90 (dd,

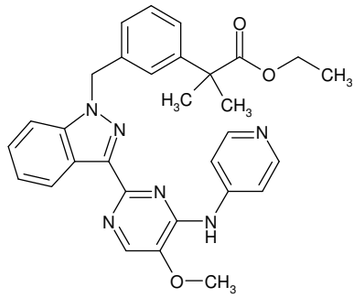
		zonitrilo	1H), 8,04 – 8,12 (m, 2H), 8,33 (s, 1H), 8,37 (d, 2H), 8,45 (d, 1H), 9,37 – 9,43 (m, 1H). LC-MS: tiempo de retención: 0,92 min MS ES+: 452,0 $[M+H]^+$ Método B
2-34-1 SM = 1-6-1		2-{1-[2,6-dicloro-3-(trifluorometil)bencil]-1*H*-indazol-3-il}-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 3,99 (s, 3H), 5,97 (s, 2H), 7,27 (t, 1H), 7,48 – 7,54 (m, 1H), 7,83 – 7,89 (m, 1H), 7,93 (d, 2H), 8,08 – 8,13 (m, 2H), 8,31 – 8,36 (m, 3H), 8,49 (d, 1H), 9,35 (s, 1H). LC-MS: tiempo de retención: 1,17 min MS ES+: 545,0

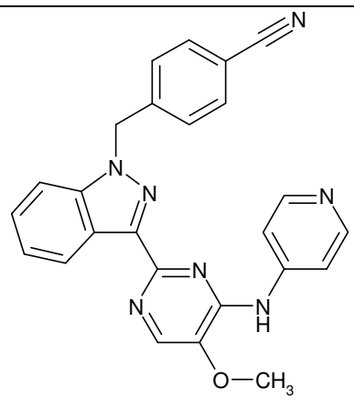
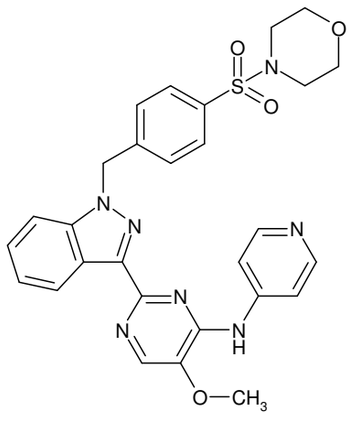
			[M+H]+ Método B
2-35-1 SM = 1-6-1		[3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)fenil]acetato de etilo	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 0,28 (t, 3H), 2,72 - 2,77 (m, 2H), 3,20 (q, 2H), 4,05 (s, 3H), 4,92 (s, 2H), 6,30 - 6,49 (m, 5H), 6,54 - 6,63 (m, 1H), 6,69 - 6,77 (m, 1H), 7,21 - 7,27 (m, 2H), 7,45 (s, 1H), 7,53 - 7,61 (m, 2H), 7,65 (d, 1H). LC-MS: tiempo de retención: 0,97 min MS ES+: 495,39 [M+H]+
2-36-1 SM = 1-6-1		2-[1-(4-fluorobencil)-1*H*-indazol-3-il]-5-metoxi-N-	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 4,02 (s, 3H), 5,73 (s, 2H), 7,10 - 7,18 (m, 2H), 7,19 - 7,27 (m, 1H),

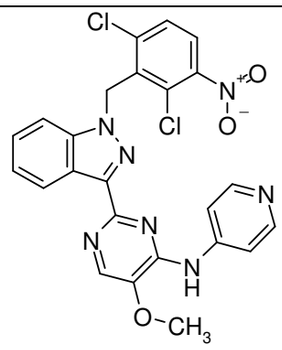
		(piridin-4-il)pirimidin-4-amina	7,35 – 7,46 (m, 3H), 7,80 (d, 1H), 8,08 – 8,14 (m, 2H), 8,34 (s, 1H), 8,37 – 8,44 (m, 3H), 9,43 (s, 1H). LC-MS: tiempo de retención: 0,92 min MS ES$^+$: 427,0 $[M+H]^+$ Método B
2-37-1 SM = 1-6-1		*N*-ciclopropil-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)bencensulfonamida	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 0,31 (d, 2H), 0,38 (d, 2H), 1,91 – 2,06 (m, 1H), 4,02 (s, 3H), 5,86 (s, 2H), 7,24 (t, 1H), 7,37 – 7,46 (m, 1H), 7,51 (d, 2H), 7,68 – 7,81 (m, 3H), 7,84 (s ancho, 1H), 8,10 (d, 2H), 8,32 – 8,41 (m, 3H), 8,45 (d, 1H), 9,37 – 9,44 (m, 1H).

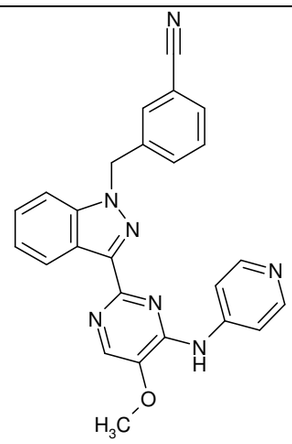
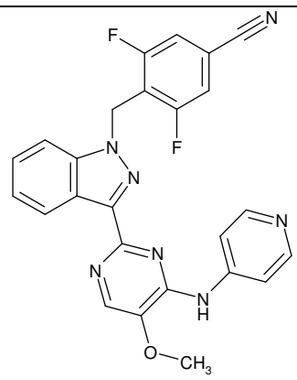
			LC-MS: tiempo de retención: 0,90 min MS ES+: 528,24 [M+H]+
2-38-1 SM = 1-6-1		6-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)-1-benzofuran-2(3H)-ona	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 4,05 (s, 3H), 5,34 (s, 2H), 5,95 (s, 2H), 7,26 (t, 1H), 7,45 (t, 1H), 7,52 - 7,58 (m, 2H), 7,83 (t, 2H), 8,10 - 8,15 (m, 2H), 8,37 (s, 1H), 8,39 - 8,43 (m, 2H), 8,48 (d, 1H), 9,43 (s, 1H). LC-MS: tiempo de retención: 0,81 min MS ES+: 465,0 [M+H]+ Método B

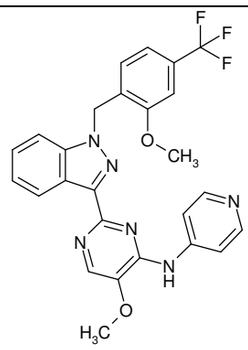
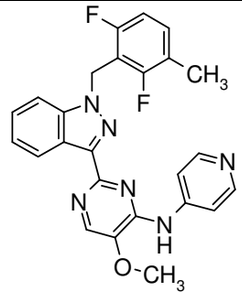
2-39-1 SM = 1-6-1		2-{1-[4-(difluorometoxi)-2,6-difluorobencil]-1*H*-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300MHz, DMSO-d6): δ [ppm]= 3,93 - 4,05 (s, 3H), 5,73 (s, 2H), 7,13 (d, 2H), 7,20 - 7,28 (m, 1H), 7,30 (t, 1H), 7,47 (t, 1H), 7,84 (d, 1H), 8,15 (d, 2H), 8,32 (s, 1H), 8,38 (d, 2H), 8,44 (d, 1H), 9,38 (s, 1H). LC-MS: tiempo de retención: 1,01 min MS ES$^+$: 511,0 $[M+H]^+$ Método B
2-40-1 SM = 1-6-1		3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)benzoato de	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 1,52 (s, 9H), 4,04 (s, 3H), 5,90 (s, 2H), 7,25 - 7,33 (m, 2H), 7,44 - 7,51 (m, 1H), 7,78 - 7,86 (m, 2H), 7,93 (d, 1H), 8,07 - 8,12 (m, 2H),

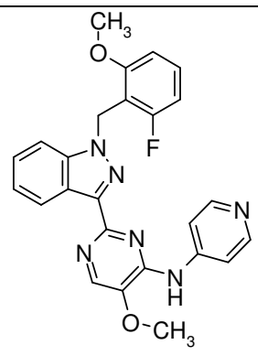
		tert-butilo	8,33 – 8,40 (m, 3H), 8,47 – 8,52 (m, 1H), 9,40 (s, 1H). LC-MS: tiempo de retención: 1,18 min MS ES+: 543,1 $[M+H]^+$ Método B
2-41-1 SM = 1-6-1		2-[3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)fenil]-2-metilpropanoato de etilo	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 0,89 (t, 3H), 1,39 (s, 6H), 3,87 (d, 2H), 4,02 (s, 3H), 5,74 (s, 2H), 7,14 – 7,31 (m, 5H), 7,40 (t, 1H), 7,77 (d, 1H), 8,08 – 8,16 (m, 2H), 8,31 – 8,47 (m, 4H), 9,41 (s, 1H). LC-MS: tiempo de retención: 1,04 min MS ES+: 523,88 $[M+H]^+$

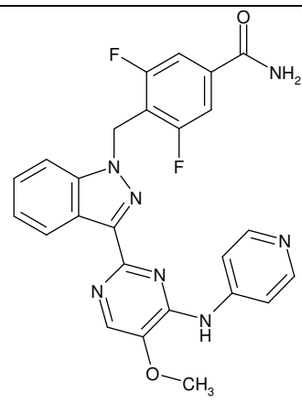
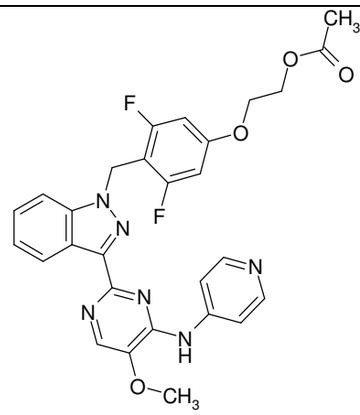
2-42-1 SM = 1-6-1		4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)benzonitrilo	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 4,02 (s, 3H), 5,86 (s, 2H), 7,20 - 7,28 (m, 1H), 7,41 - 7,48 (m, 3H), 7,73 - 7,83 (m, 3H), 8,06 - 8,12 (m, 2H), 8,31 - 8,49 (m, 4H), 9,42 (s, 1H). LC-MS: tiempo de retención: 0,82 min MS ES$^+$: 434,4 $[M+H]^+$ Método B
2-43-1 SM = 1-6-1		5-metoxi-2-{1-[4-(morfolin-4-ilsulfonil)bencil]-1*H*-indazol-3-il}-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 2,73 - 2,83 (m, 4H), 3,50 - 3,59 (m, 4H), 4,02 (s, 3H), 5,89 (s, 2H), 7,20 - 7,28 (m, 1H), 7,43 (t, 1H), 7,54 (d, 2H), 7,70 (d, 2H), 7,79 (d, 1H), 8,06 - 8,14

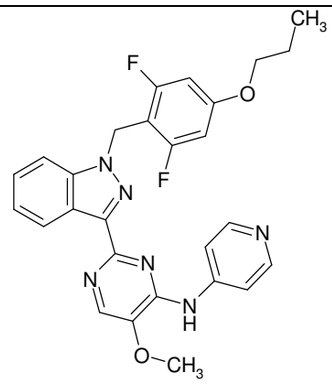
			(m, 2H), 8,32 - 8,49 (m, 4H), 9,39 - 9,43 (m, 1H). LC-MS: tiempo de retención: 0,90 min MS ES+: 558,23 [M+H]+
2-44-1 SM = 1-6-1		2-[1-(2,6-dicloro-3-nitrobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 3,99 (s, 3H), 5,96 (s, 2H), 7,20 - 7,34 (m, 1H), 7,46 - 7,56 (m, 1H), 7,86 - 7,99 (m, 2H), 8,06 - 8,16 (m, 3H), 8,29 - 8,39 (m, 3H), 8,50 (d, 1H), 9,36 (s, 1H). LC-MS: tiempo de retención: 1,03 min MS ES+: 522,1 [M+H]+

2-45-1 SM = 1-6-1		3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzonitrilo	^{1}H-RMN (400MHz, METANOL-d_4): δ [ppm]= 4,08 (s, 3H), 5,79 (s, 2H), 7,20 - 7,28 (m, 1H), 7,41 - 7,50 (m, 2H), 7,55 - 7,63 (m, 3H), 7,70 (s, 1H), 8,06 (d, 2H), 8,27 (s, 1H), 8,36 - 8,42 (m, 2H), 8,47 (s, 1H). LC-MS: tiempo de retención: 0,94 min MS ES$^+$: 434,44 $[M+H]^+$
2-46-1 SM = 1-6-1		3,5-difluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzonitrilo	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 4,00 (s, 3H), 5,82 (s, 2H), 7,25 (t, 1H), 7,49 (t, 1H), 7,85 - 7,94 (m, 3H), 8,08 - 8,20 (m, 2H), 8,32 (s, 1H), 8,37 - 8,46 (m, 3H), 9,41 (s, 1H).

			LC-MS: tiempo de retención: 0,99 min MS ES+: 470,35 [M+H]+
2-47-1 SM = 1-6-1		5-metoxi-2-{1-[2-metoxi-4-(trifluorometil)bencil]-1H-indazol-3-il}-N-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 3,93 (s, 3H), 4,12 (s, 3H), 5,61 (s, 2H), 7,17 - 7,26 (m, 1H), 7,34-7,45 (m, 3H), 7,58 (d, 1H), 7,63 - 7,70 (m, 1H), 8,42 - 8,50 (m, 1H), 8,51 - 8,68 (m, 6H). LC-MS: tiempo de retención: 1,03 min MS ES+: 507,42 [M+H]+
2-48-1 SM = 1-6-1		2-[1-(2,6-difluoro-3-metilbencil)-1H-indazol-3-il]-5-metoxi-N-	^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 2,16 (s, 3H), 4,00 (s, 3H), 5,74 (s, 2H), 7,06 (t, 1H), 7,21 - 7,34 (m,

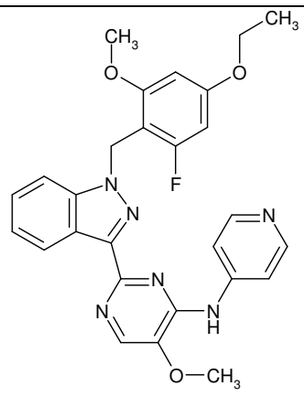
		(piridin-4-il)pirimidin-4-amina	2H), 7,47 (t, 1H), 7,85 (d, 1H), 8,07 - 8,20 (m, 2H), 8,28 - 8,50 (m, 4H), 9,40 (s ancho, 1H). LC-MS: tiempo de retención: 1,03 min MS ES+: 459,2 [M+H]+
2-49-1 SM = 1-6-1		2-[1-(2-fluoro-6-metoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina	1H-RMN (400MHz, DMSO-d6): δ [ppm]= 3,80 (s, 3H), 3,85 (s, 3H), 5,09 (s, 2H), 6,85 - 6,99 (m, 4H), 7,06 (t, 1H), 7,31 (t, 1H), 7,36 - 7,48 (m, 1H), 7,51 (d, 1H), 7,62 (d, 2H), 8,16 (s, 1H), 8,39 (d, 1H), 13,15 (br.s., 1H). LC-MS: tiempo de retención: 0,90 min

			MS ES+: 457,2 [M+H]+
2-50-1 SM = 1-6-1		3,5-difluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzamida	1H-RMN (400MHz, Metanol-d4): δ [ppm]= 4,07 (s, 3H), 5,81 (s, 2H), 7,25 (t, 1H), 7,47 (t, 1H), 7,50 - 7,58 (m, 2H), 7,72 (d, 1H), 8,18 (s, 1H), 8,27 - 8,38 (m, 3H), 8,39 - 8,49 (m, 3H) LC-MS: tiempo de retención: 0,87 min MS ES+:488,39 [M+H]+
2-51-1 SM = 1-6-1		acetato de 2-[3,5-difluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-	1H-RMN (600MHz, DMSO-d6): δ [ppm]= 2,00 (s, 3H), 4,04 (s, 3H), 4,21 (t, 2H), 4,29 (t, 2H), 5,69 (s, 2H), 6,80 - 6,94 (m, 2H), 7,19 - 7,34 (m, 1H), 7,42 - 7,55

		1-il}metil)fenoxi]etilo	(m, 1H), 7,79 - 7,90 (m, 1H), 8,10 - 8,25 (m, 2H), 8,35 (s, 1H), 8,39 - 8,44 (m, 2H), 8,44 - 8,51 (m, 1H), 9,41 (s, 1H). LC-MS (Método 5): tiempo de retención: 1,22 min MS ES+: 547,3 [M+H]+
2-52-1 SM = 1-6-1		2-[1-(2,6-difluoro-4-propoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 0,93 (t, 3H), 1,59 - 1,79 (m, 2H), 3,94 (t, 2H), 4,04 (s, 3H), 5,68 (s, 2H), 6,74 - 6,94 (m, 2H), 7,21 - 7,35 (m, 1H), 7,42 - 7,62 (m, 1H), 7,80 - 7,90 (m, 1H), 8,15 - 8,26 (m, 2H), 8,36 (s, 1H), 8,37 - 8,43 (m, 2H), 8,43 -

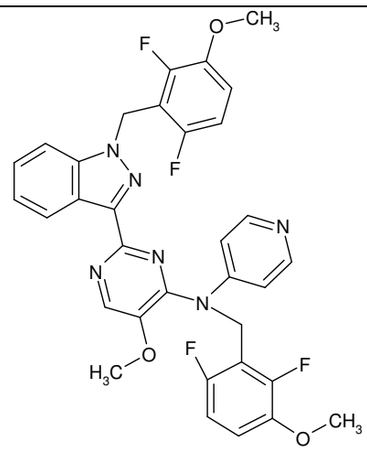
			8,51 (m, 1H), 9,44 (s, 1H). LC-MS: tiempo de retención: 1,14 min MS ES+: 503,37 [M+H]+

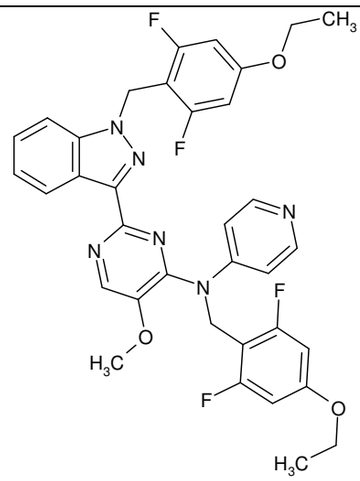
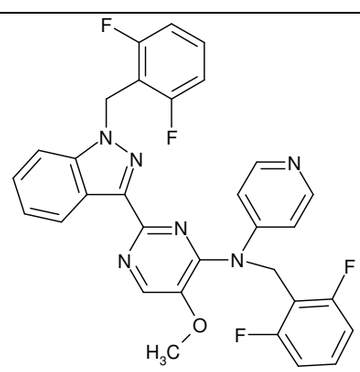
El siguiente compuesto también se aisló en la reacción que provee 2-5-1:

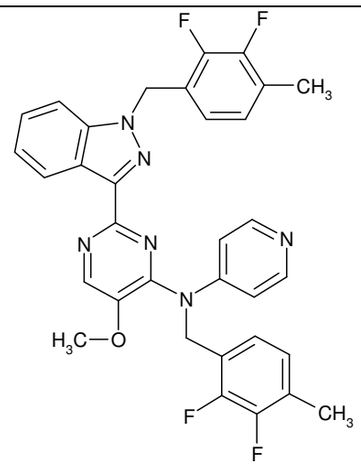
2-53-1 SM = 1-6-1		2-[1-(4-etoxi-2-fluoro-6-metoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 1,26 (t, 3H), 3,72 (s, 3H), 3,92 - 4,10 (m, 5H), 5,54 (s, 2H), 6,40 (s, 1H), 6,50 (dd, 1H), 7,13 - 7,27 (m, 1H), 7,37 - 7,49 (m, 1H), 7,79 (d, 1H), 8,16 (d, 2H), 8,31 (s, 1H), 8,35 - 8,47 (m, 3H), 9,38 (s, 1H).

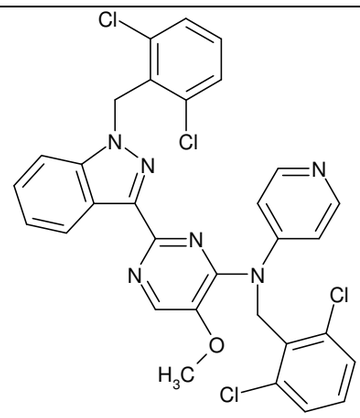
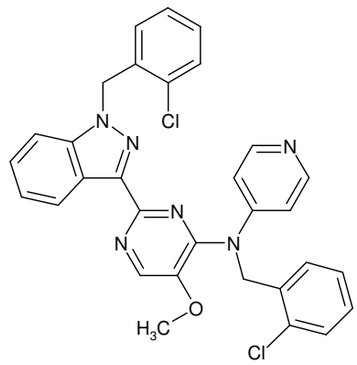
Los siguientes compuestos bis-bencilo también se formaron

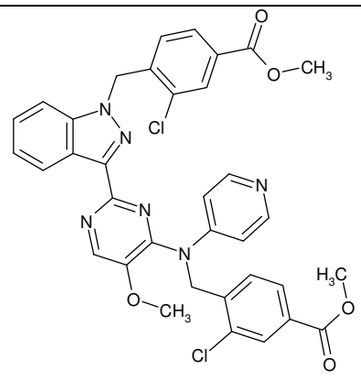
durante el procedimiento que se ha descrito usando los materiales de partida indicados (SM = material de partida):

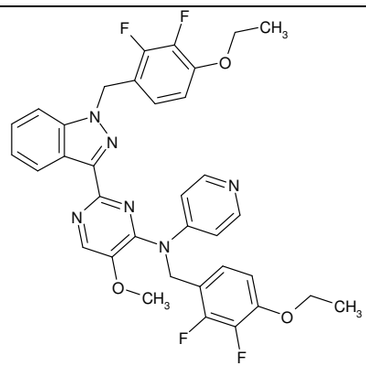
2-4-2 SM = 1-6-1		*N*-(2,6-difluoro-3-metoxibencil)-2-[1-(2,6-difluoro-3-metoxibencil)-1*H*-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 3,77 (d, 6H), 3,82 (s, 3H), 5,22 (s, 2H), 5,69 (s, 2H), 6,86 (d, 2H), 6,97 - 7,06 (m, 1H), 7,06 - 7,19 (m, 3H), 7,21 - 7,30 (m, 1H), 7,41 (t, 1H), 7,57 (d, 2H), 7,74 (d, 1H), 8,12 (s, 1H), 8,37 (d, 1H). LC-MS: tiempo de retención: 1,16 min MS ES$^+$: 631,24 [M+H]$^+$

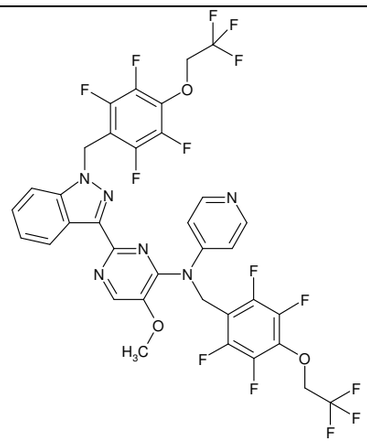
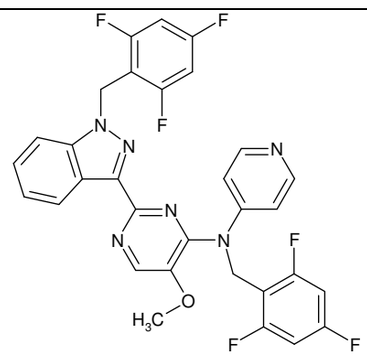
2-5-2 SM = 1-6-1		*N*-(4-etoxi-2,6-difluorobencil)-2-[1-(4-etoxi-2,6-difluorobencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 1,21 - 1,32 (m, 6H), 3,78 (s, 3H), 4,02 (dq, 4H), 5,13 (s, 2H), 5,59 (s, 2H), 6,69 (d, 2H), 6,78 - 6,93 (m, 4H), 7,09 (t, 1H), 7,39 (t, 1H), 7,56 (d, 2H), 7,71 (d, 1H), 8,12 (s, 1H), 8,37 (d, 1H). LC-MS: tiempo de retención: 1,26 min MS ES$^+$: 659,0 $[M+H]^+$ Método B
2-7-2 SM = 1-6-1		*N*-(2,6-difluorobencil)-2-[1-(2,6-difluorobencil)-1*H*-indazol-3-	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 3,77 (s, 3H), 5,24 (s, 2H), 5,69 (s, 2H), 6,89 (d, 2H), 7,03 - 7,15 (m,

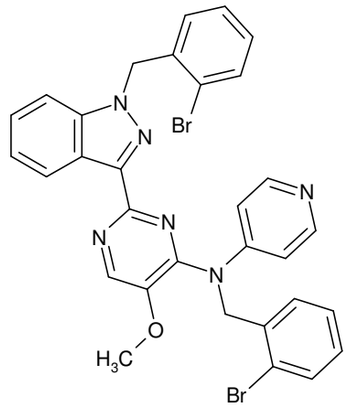
		il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	3H), 7,22 (t, 3H), 7,36 - 7,46 (m, 2H), 7,58 (d, 2H), 7,75 (d, 1H), 8,12 (s, 1H), 8,38 (d, 1H). LC-MS: tiempo de retención: 1,13 min MS ES$^+$: 571,18 $[M+H]^+$
2-8-2 SM = 1-6-1		*N*-(2,3-difluoro-4-metilbencil)-2-[1-(2,3-difluoro-4-metilbencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 2,19 (d, 3H), 2,25 (d, 3H), 3,79 (s, 3H), 5,19 (s, 2H), 5,68 - 5,77 (s, 2H), 6,77 - 6,87 (m, 3H), 6,98 (t, 1H), 7,03 - 7,19 (m, 3H), 7,38 (t, 1H), 7,61 - 7,74 (m, 3H), 8,11 - 8,17 (m, 1H), 8,37 - 8,45 (m, 1H). LC-MS: tiempo de retención: 1,20 min MS ES$^+$: 599,25

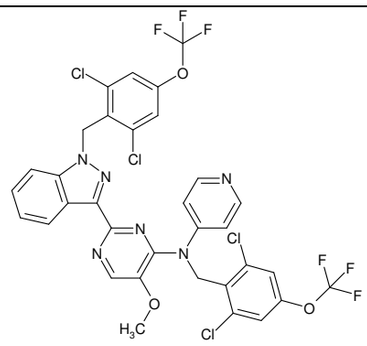
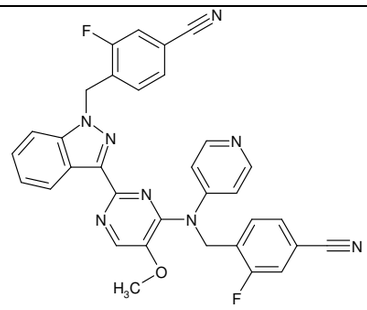
			[M+H]+
2-9-2 SM = 1-6-1		*N*-(2,6-diclorobencil)-2-[1-(2,6-diclorobencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 3,78 (s, 3H), 5,43 (s, 2H), 5,79 (s, 2H), 7,09 - 7,18 (m, 3H), 7,30 - 7,45 (m, 4H), 7,50 - 7,60 (m, 3H), 7,63 - 7,68 (d, 2H), 7,77 (d, 1H), 8,12 (s, 1H), 8,42 (d, 1H). LC-MS: tiempo de retención: 1,26 min MS ES+: 637,09 [M+H]+
2-10-2 SM = 1-6-1		*N*-(2-clorobencil)-2-[1-(2-clorobencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin	^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 3,81 (s, 3H), 5,23 (s, 2H), 5,76 (s, 2H), 6,81 - 6,89 (m, 3H), 7,12 (t, 1H), 7,19 (td, 1H), 7,23 - 7,30

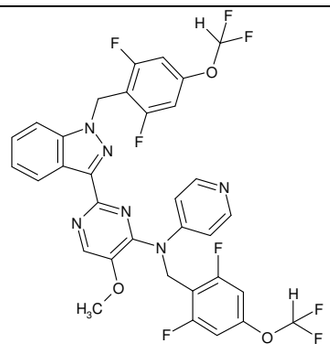
		-4-amina	(m, 2H), 7,34 - 7,42 (m, 3H), 7,47 (dd, 1H), 7,54 (dd, 1H), 7,63 - 7,69 (m, 3H), 8,15 (s, 1H), 8,47 (d, 1H). LC-MS: tiempo de retención: 1,12 min MS ES+: 567,2 [M+H]+
2-11-2 SM = 1-6-1		3-cloro-4-{[(2-{1-[2-cloro-4-(metoxicarbonil)bencil]-1*H*-indazol-3-il}-5-metoxipirimidin-4-il)(piridin-4-il)amino]metil}benzoato de metilo	^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 3,79 (s, 3H), 3,85 (s, 3H), 3,97 (s, 3H), 5,60 (s, 2H), 5,87 (s, 2H), 7,00 (d, 1H), 7,23 (t, 1H), 7,33 (d, 1H), 7,40 - 7,46 (m, 1H), 7,71 - 7,80 (m, 2H), 7,90 - 7,97 (m, 3H), 8,01 (d, 1H), 8,25 (s, 1H),

			8,29 (d, 2H), 8,42 – 8,50 (m, 2H). LC-MS: tiempo de retención: 1,17 min MS ES+: 683,1 $[M+H]^+$ Método B
2-14-2 SM = 1-6-1		*N*-(4-etoxi-2,3-difluorobencil)-2-[1-(4-etoxi-2,3-difluorobencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 1,22 – 1,36 (m, 6H), 3,79 (s, 3H), 3,99 – 4,18 (m, 4H), 5,14 (s, 2H), 5,68 (s, 2H), 6,81 (d, 2H), 6,92 (d, 2H), 7,00 – 7,22 (m, 3H), 7,38 (t, 1H), 7,61 – 7,74 (m, 3H), 8,14 (s, 1H), 8,40 (d, 1H). LC-MS: tiempo de retención: 1,22 min MS ES+: 659,0 $[M+H]^+$ Método B

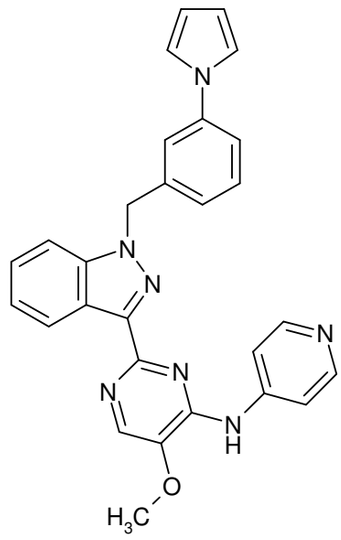
2-15-2 SM = 1-6-1		5-metoxi-*N*-(piridin-4-il)-*N*-[2,3,5,6-tetrafluoro-4-(2,2,2-trifluoroetoxi)bencil]-2-{1-[2,3,5,6-tetrafluoro-4-(2,2,2-trifluoroetoxi)bencil]-1*H*-indazol-3-il}pirimidin-4-amina	^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 4,00 (s, 3H), 4,93 (qd, 4H), 5,31 (s, 2H), 5,63 (s, 2H), 7,21 (t, 1H), 7,36 (ddd, 1H), 7,64 (d, 1H), 8,04 - 8,11 (m, 2H), 8,27 - 8,33 (m, 2H), 8,43 (d, 1H), 9,35 (s, 1H). LC-MS: tiempo de retención: 1,42 min MS ES$^+$: 837,1 $[M+H]^+$ Método B
2-17-2 SM = 1-6-1		5-metoxi-*N*-(piridin-4-il)-*N*-(2,4,6-trifluorobencil)-2-[1-(2,4,6-trifluorobencil)-1*H*-	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 3,78 (s, 3H), 5,20 (s, 2H), 5,66 (s, 2H), 6,86 (d, 2H), 7,07 - 7,26 (m, 3H), 7,29 - 7,46 (m, 3H), 7,58 (d,

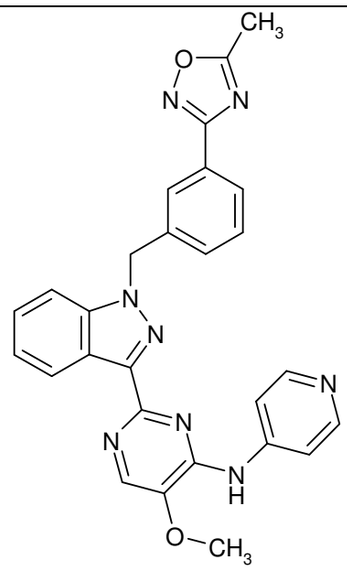
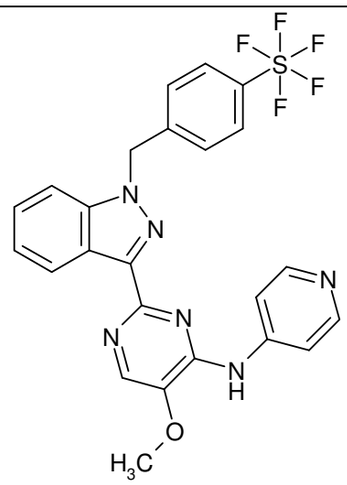
		indazol-3-il]pirimidin-4-amina	2H), 7,75 (d, 1H), 8,13 (s, 1H), 8,38 (d, 1H). LC-MS: tiempo de retención: 1,12 min MS ES+: 608,17 [M+H]+
2-21-2 SM = 1-6-1		*N*-(2-bromobencil)-2-[1-(2-bromobencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 3,81 (s, 3H), 5,20 (s, 2H), 5,73 (s, 2H), 6,69 - 6,76 (m, 1H), 6,87 (d, 2H), 7,08 - 7,26 (m, 4H), 7,28 - 7,48 (m, 3H), 7,60 - 7,73 (m, 5H), 8,15 (s, 1H), 8,48 (d, 1H). LC-MS: tiempo de retención: 1,30 min MS ES+: 657,04 [M+H]+

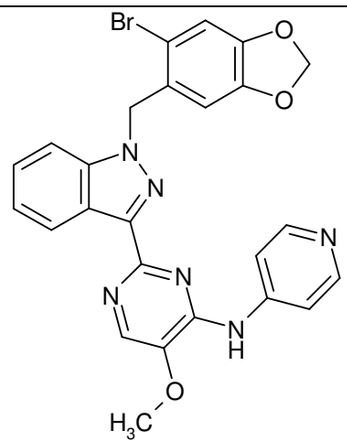
2-26-2 SM = 1-6-1		*N*-[2,6-dicloro-4-(trifluorometoxi)bencil]-2-{1-[2,6-dicloro-4-(trifluorometoxi)bencil]-1*H*-indazol-3-il}-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 3,78 (s, 3H), 5,40 (s, 2H), 5,81 (s, 2H), 6,99 (d, 2H), 7,12 (t, 1H), 7,42 (t, 1H), 7,55 (d, 2H), 7,64 (s, 2H), 7,76 - 7,85 (m, 3H), 8,12 (s, 1H), 8,42 (d, 1H). LC-MS: tiempo de retención: 1,39 min MS ES$^+$: 804,9 $[M+H]^+$ Método B
2-33-2 SM = 1-6-1		4-{[{2-[1-(4-ciano-2-fluorobencil)-1*H*-indazol-3-il]-5-metoxipirimidin-4-il}(piridin-4-il)amino]metil}-3-	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 3,80 (s, 3H), 5,28 (s, 2H), 5,84 (s, 2H), 6,83 (d, 2H), 7,09 - 7,19 (m, 2H), 7,43 (dt, 2H), 7,56 - 7,79 (m, 5H), 7,84 - 7,98 (m, 2H), 8,17 (s, 1H), 8,44 (d, 1H). LC-MS: tiempo de retención:

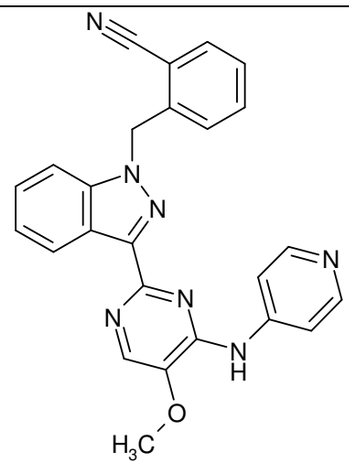
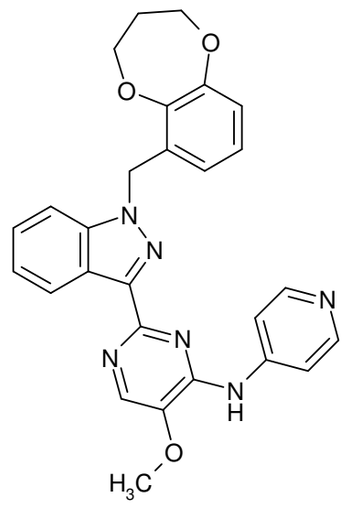
		fluorobenzonitrilo	1,01 min MS ES+: 586,2 [M+H]+
2-39-2 SM = 1-6-1		*N*-[4-(difluorometoxi)-2,6-difluorobencil]-2-{1-[4-(difluorometoxi)-2,6-difluorobencil]-1*H*-indazol-3-il}-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 3,78 (s, 3H), 5,20 (s, 2H), 5,67 (s, 2H), 6,84 (d, 2H), 7,01 - 7,21 (m, 5H), 7,31 (d, 1H), 7,41 (t, 1H), 7,51 - 7,60 (m, 3H), 7,75 (d, 1H), 8,13 (s, 1H), 8,38 (d, 1H). LC-MS: tiempo de retención: 1,17 min MS ES+: 703,1 [M+H]+ Método B

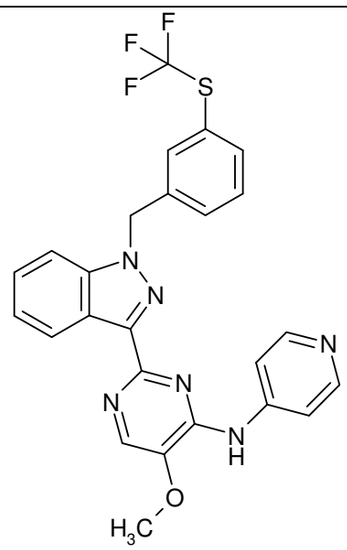
Los siguientes compuestos se prepararon siguiendo el procedimiento descrito en el esquema 2a usando los materiales de partida indicados (SM = material de partida):

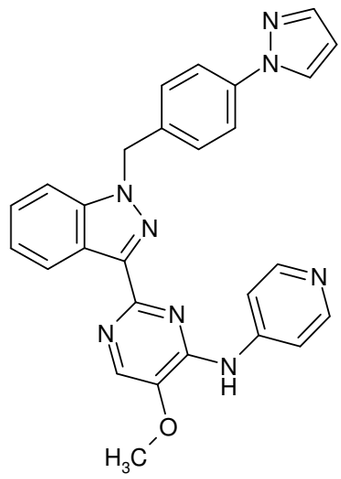
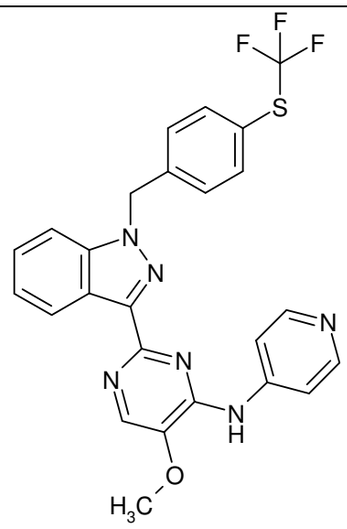
2-1-3 SM = 1-10-1		5-metoxi-N-(piridin-4-il)-2-{1-[3-(1H-pirrol-1-il)bencil]-1H-indazol-3-il}pirimidin-4-amina	H-RMN (300MHz, METANOL-d4): δ [ppm]= 4,06 (s, 3H), 5,77 (s, 2H), 6,16 - 6,25 (m, 2H), 7,09 (s, 3H), 7,18 - 7,27 (m, 1H), 7,30 - 7,37 (m, 2H), 7,37 - 7,49 (m, 2H), 7,57 - 7,64 (m, 1H), 8,05 - 8,14 (m, 2H), 8,24 - 8,41 (m, 3H), 8,42 - 8,51 (m, 1H) LC-MS: tiempo de retención: 1,07 min MS ES+: 474,4 [M+H]+ Método B

2-2-3 SM = 1-10-1		5-metoxi-2-{1-[3-(5-metil-1,2,4-oxadiazol-3-il)bencil]-1H-indazol-3-il}-N-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (400MHz, CLOROFORMO-d): δ [ppm]= 2,64 (s, 3H), 4,08 (s, 3H), 5,82 (s, 2H), 7,35 - 7,45 (m, 5H), 7,82 - 7,90 (m, 2H), 7,94 - 8,01 (m, 1H), 8,12 (s, 1H), 8,25 (s, 1H), 8,52 - 8,63 (m, 3H) LC-MS: tiempo de retención: 0,95 min MS ES$^+$: 491,3 $[M+H]^+$
2-3-3 SM = 1-10-1		5-metoxi-2-{1-[4-(pentafluoro-λ^6-sulfanil)bencil]-1H-indazol-3-il}-N-	^{1}H-RMN (300MHz, CLOROFORMO-d): δ [ppm]= 4,08 (s, 3H), 5,79 (s, 2H), 7,28 - 7,50 (m, 5H), 7,68 (d, 2H), 7,80 - 7,89 (m, 2H), 8,24 (s, 1H),

		(piridin-4-il)pirimidin-4-amina	8,53 - 8,66 (m, 3H) LC-MS: tiempo de retención: 1,07 min MS ES+: 535,2 [M+H]+
2-4-31-10-1		2-{1-[(6-bromo-1,3-benzodioxol-5-il)metil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina	1H-RMN (300MHz, CLOROFORMO-d): δ [ppm]= 4,08 (s, 3H), 5,76 (s, 2H), 5,89 (s, 2H), 6,45 (s, 1H), 7,04 (s, 1H), 7,41 - 7,43 (m, 3H), 7,79 - 7,90 (m, 2H), 8,24 (s, 1H), 8,47 - 8,65 (m, 3H) LC-MS: tiempo de retención: 1,09 min MS ES+: 509,1 [M+H]+ Método B

2-5-3 SM = 1-10-1		2-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzonitrilo	^{1}H-RMN (300MHz, CLOROFORMO-d): δ [ppm]= 4,08 (s, 3H), 5,98 (s, 2H), 7,13 - 7,22 (m, 1H), 7,30 - 7,53 (m, 5H), 7,67 - 7,77 (m, 1H), 7,79 - 7,94 (m, 2H), 8,25 (s, 1H), 8,51 - 8,70 (m, 3H) LC-MS: tiempo de retención: 0,90 min MS ES$^+$: 434,2 $[M+H]^+$
2-6-3 SM = 1-10-1		2-[1-(3,4-dihidro-2H-1,5-benzodioxepin-6-ilmetil)-1H-indazol-3-il]-5-metoxi-N-(piridin-	^{1}H-RMN (300MHz, CLOROFORMO-d): δ [ppm]= 2,20 (quint, 2H), 4,06 (s, 3H), 4,14 (t, 2H), 4,19 (t, 2H), 5,76 (s, 2H), 6,73 - 6,83 (m, 2H), 6,87 - 6,96 (m, 1H), 7,33 - 7,54 (m, 3H), 7,80 -

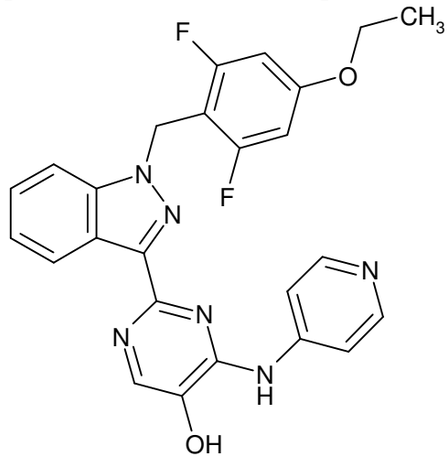
		4-il)pirimidin-4-amina	7,91 (m, 2H), 8,23 (s, 1H), 8,54 - 8,58 (m, 3H) LC-MS: tiempo de retención: 0,95 min MS ES+: 481,3 [M+H]+
2-7-3 SM = 1-10-1		5-metoxi-N-(piridin-4-il)-2-(1-{3-[(trifluorometil)sulfanil]bencil}-1H-indazol-3-il)pirimidin-4-amina	1H-RMN (300MHz, CLOROFORMO-d): δ [ppm]= 4,08 (s, 3H), 5,77 (s, 2H), 7,30 -7,42 (m, 5H), 7,51 - 7,66 (m, 2H), 7,83 (d, 2H), 8,24 (s, 1H), 8,55 - 8,61 (m, 3H) LC-MS: tiempo de retención: 1,08 min MS ES+: 509,2 [M+H]+

2-8-3 SM = 1-10-1		5-metoxi-2-{1-[4-(1H-pirazol-1-il)bencil]-1H-indazol-3-il}-N-(piridin-4-il)pirimidin-4-amina	LC-MS: tiempo de retención: 0,98 min MS ES+: 475,42 [M+H]+
2-9-3 SM = 1-10-1		5-metoxi-N-(piridin-4-il)-2-(1-{4-[(trifluorometil)sulfanil]bencil}-1H-indazol-3-il)pirimidin-4-amina	H-RMN (300MHz, METANOL-d4): δ [ppm]= 4,09 (s, 3H), 5,82 (s, 2H), 7,21 - 7,30 (m, 1H), 7,34 - 7,49 (m, 2H), 7,49 - 7,73 (m, 4H), 8,01 - 8,09 (m, 2H), 8,28 (s, 1H), 8,35 - 8,43 (m, 2H), 8,50 (d, 1H) LC-MS: tiempo de retención: 1,16 min MS ES+: 509,39

			$[M+H]^+$

Ejemplo 3-1

Preparación de 2-[1-(4-etoxi-2,6-difluorobencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ol



Se disolvieron 1,32 g de 2-[1-(4-etoxi-2,6-difluorobencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina (2-5-1, 2,70 mmol, 1. eq.) en 117 ml de 1-metilpirrolidin-2-ona seca. Se agregaron 142 mg de carbonato de potasio bajo una atmósfera de nitrógeno. Luego se agregaron 0,42 ml de bencenotiol por goteo. La mezcla de reacción se agitó durante una hora a 190°C y se enfrió a lo largo del fin de semana a temperatura ambiente. Luego la mezcla se particionó entre solución acuosa parcialmente saturada de cloruro de amonio y diclorometano/ isopropanol 4:1. Las fases se separaron y la capa acuosa se extrajo dos veces con diclorometano/ isopropanol 4:1. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre un filtro de silicona y se concentró al vacío. El residuo se purificó mediante cromatografía flash para dar 781 mg (1,65 mmol,

60,9%) del compuesto buscado analíticamente puro.

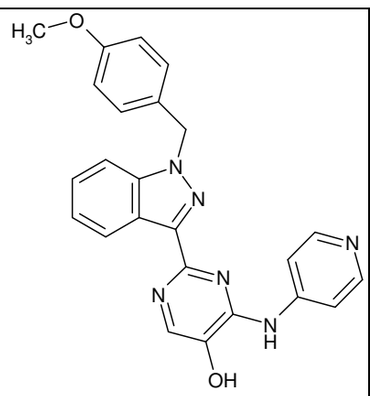
^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 1,25 (t, 3H), 4,00 (q, 2H), 5,63 (s, 2H), 6,71 - 6,81 (m, 2H), 7,21 (t, 1H), 7,44 (td, 1H), 7,80 (d, 1H), 8,09 - 8,18 (m, 3H), 8,33 - 8,38 (m, 2H), 8,42 (d, 1H), 9,28 (s, 1H), 10,78 (s ancho, 1H).

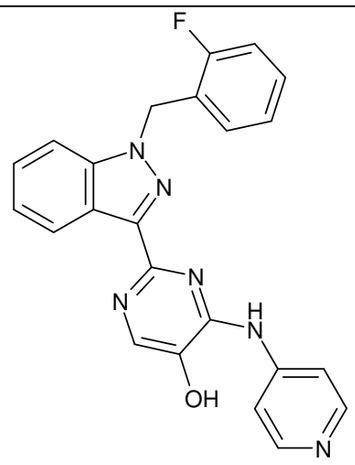
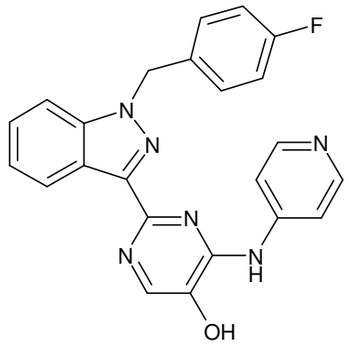
LC-MS:

tiempo de retención: 0,97 min

MS ES$^+$: 475,59 $[M+H]^+$

Los siguientes compuestos se prepararon de acuerdo con el mismo procedimiento usando los materiales de partida indicados (SM = material de partida):

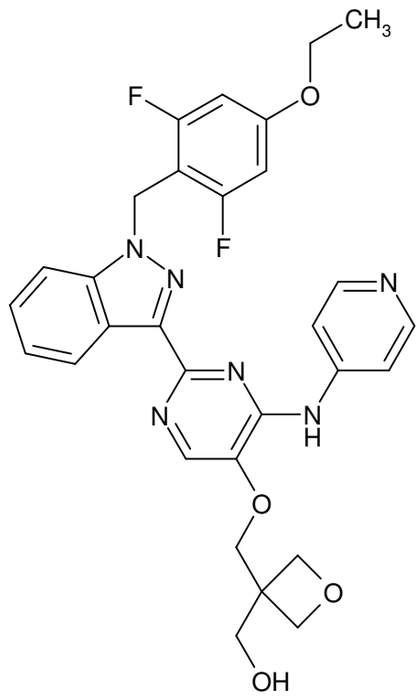
3-2 SM = 1-5-1		2-[1-(4-metoxibencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ol	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 3,66 (s, 3H), 5,64 (s, 2H), 6,83 - 6,88 (m, 2H), 7,19 (t, 1H), 7,27 - 7,33 (m, 2H), 7,38 (ddd, 1H), 7,76 (d, 1H), 8,10 - 8,15 (m, 3H), 8,34 - 8,43 (m, 2H), 9,31 (s, 1H). LC-MS: tiempo de retención: 0,83 min MS ES$^+$: 425,1 $[M+H]^+$ Método B

3-3 SM = 2-18-1		2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ol	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 5,76 (s, 2H), 7,12 - 7,18 (m, 1H), 7,19 - 7,38 (m, 4H), 7,43 (ddd, 1H), 7,78 (d, 1H), 8,09 - 8,14 (m, 3H), 8,33 - 8,37 (m, 2H), 8,43 (d, 1H), 9,30 (s, 1H), 10,71 - 10,92 (s, 1H). LC-MS: tiempo de retención: 0,86 min MS ES$^+$: 413,2 $[M+H]^+$
3-4 SM = 2-36-1		2-[1-(4-fluorobencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ol	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 5,70 - 5,73 (m, 2H), 7,10 - 7,23 (m, 3H), 7,34 - 7,44 (m, 3H), 7,78 (d, 1H), 8,07 - 8,14 (m, 3H), 8,34 - 8,39 (m, 2H), 8,42 (d, 1H), 9,31 (s, 1H), 10,83 - 11,18 (m, 1H). LC-MS: tiempo de retención: 0,85 min

			MS ES$^+$: 413,0 [M+H]$^+$ Método B

Ejemplo 4-1

Preparación de {3-[({2-[1-(4-etoxi-2,6-difluorobencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metil]oxetan-3-il}metanol



Se disolvieron 100 mg de 2-[1-(4-etoxi-2,6-difluorobencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ol (3-1, 0,21 mmol, 1. eq.) en 1,6 ml de DMF bajo una atmósfera de nitrógeno, luego se agregaron 87 mg de carbonato de potasio (0,63 mmol, 3 eq.) y 40 mg de [3-(bromometil)oxetan-3-il]metanol (0,21 mmol, 1 eq.). La mezcla resultante se agitó a temperatura ambiente durante 18 horas. Se agregaron

6,0mg de [3-(bromometil)oxetan-3-il]metanol (0,032 mmol, 0,15 eq.) y se agitó nuevamente durante 24 horas. Luego la mezcla se particionó entre solución acuosa parcialmente saturada de cloruro de amonio y diclorometano/ isopropanol 4:1. Las fases se separaron y la capa acuosa se extrajo dos veces con diclorometano/isopropanol 4:1. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre un filtro de silicona y se concentró al vacío. El residuo se purificó mediante cromatografía flash para dar 75 mg (0,13 mmol, 61,9%) del compuesto buscado analíticamente puro.

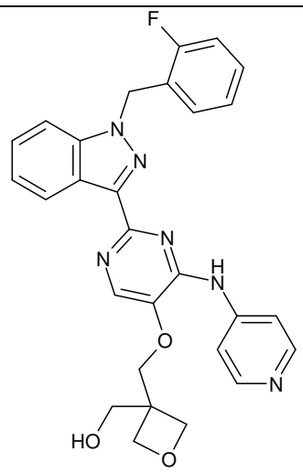
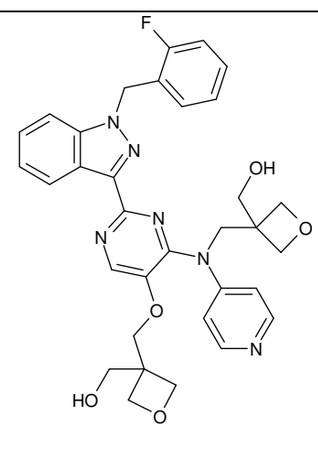
^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 1,26 (t, 3H), 3,83 (d, 2H), 4,01 (q, 2H), 4,39 – 4,50 (m, 6H), 5,06 (t, 1H), 5,65 (s, 2H), 6,72 – 6,81 (m, 2H), 7,23 (t, 1H), 7,46 (ddd, 1H), 7,82 (d, 1H), 8,01 – 8,09 (m, 2H), 8,38 – 8,46 (m, 4H), 8,90 (s, 1H).

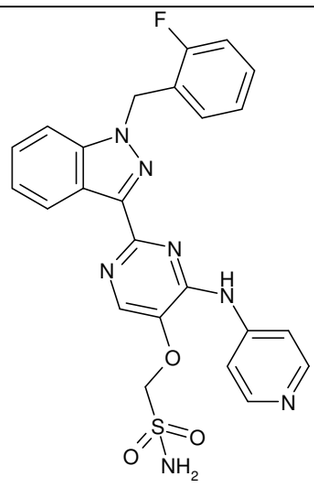
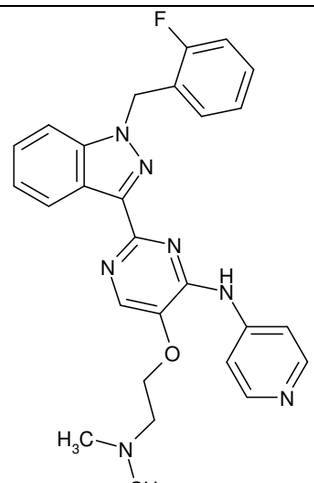
LC-MS:

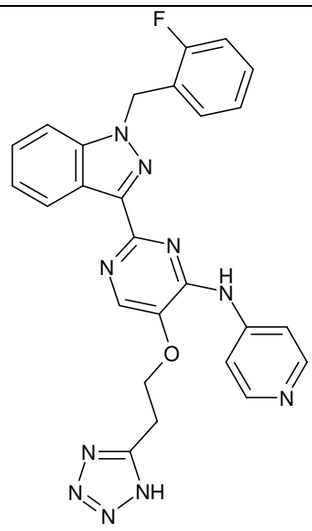
tiempo de retención: 1,00 min

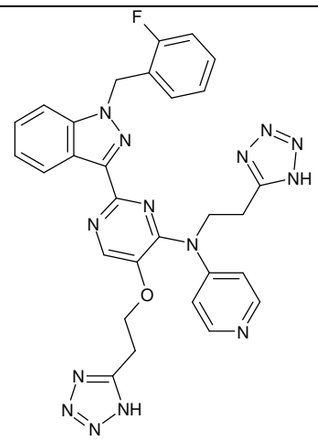
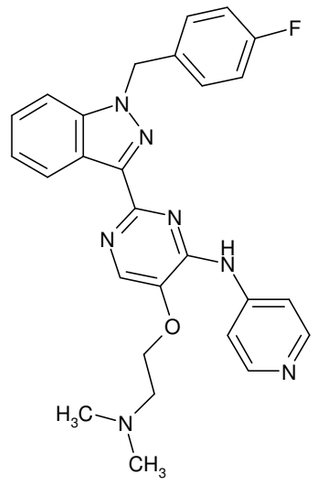
MS ES$^+$: 574,82 $[M+H]^+$

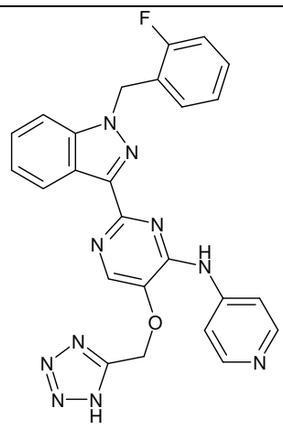
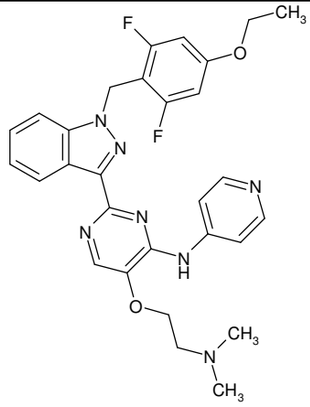
Los siguientes compuestos se prepararon de acuerdo con el mismo procedimiento usando los materiales de partida indicados (SM = material de partida):

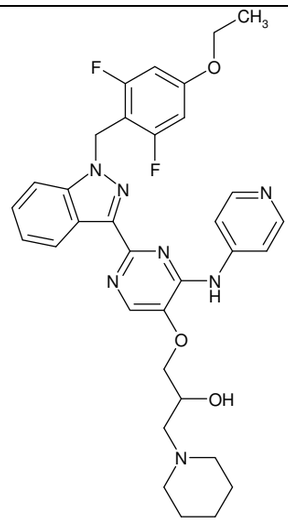
4-2-1 SM = 3-3		{3-[({2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metil]oxetan-3-il}metanol	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 3,83 (s ancho, 2H), 4,39 - 4,48 (m, 6H), 5,06 (s ancho, 1H), 5,78 (s, 2H), 7,11 - 7,38 (m, 5H), 7,40 - 7,49 (m, 1H), 7,80 (d, 1H), 8,00 (d, 2H), 8,37 - 8,46 (m, 4H), 8,92 (s ancho, 1H). LC-MS: tiempo de retención: 0,92 min MS ES$^+$: 513,25 $[M+H]^+$
4-2-2 SM = 3-3		(3-{[(2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-{[3-(hidroximetil)oxetan-3-il]metoxi}pirimidin-4-il)(piridin-	LC-MS: tiempo de retención: 0,93 min MS ES$^+$: 613,26 $[M+H]^+$

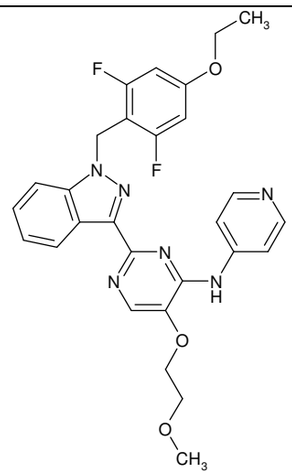
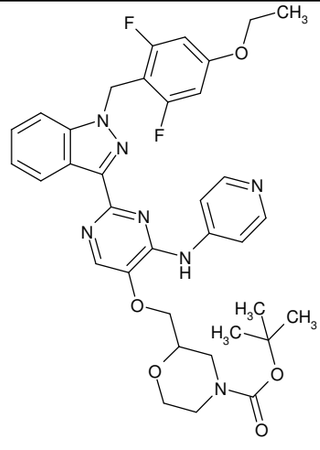
		4-il)amino]metil}oxetan-3-il)metanol	
4-3 SM = 3-3		1-({2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metansulfonamida	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 5,30 (s, 2H), 5,79 (s, 2H), 7,12 - 7,38 (m, 5H), 7,41 - 7,48 (m, 3H), 7,82 (d, 1H), 8,03 - 8,09 (m, 2H), 8,39 - 8,45 (m, 3H), 8,56 (s, 1H), 9,18 - 9,22 (m, 1H). LC-MS (Método 2): tiempo de retención: 1,32 min MS ES$^+$: 506,00 $[M+H]^+$
4-4 SM = 3-3		5-[2-(dimetilamino)etoxi]-2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-N-(piridin-4-	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 2,25 (s, 6H), 2,68 - 2,75 (m, 2H), 4,29 (t, 2H), 5,78 (s, 2H), 7,12 - 7,38 (m, 5H), 7,44 (ddd, 1H), 7,80 (d, 1H), 8,01 - 8,06 (m, 2H), 8,37 -

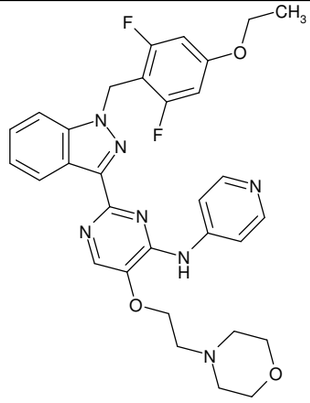
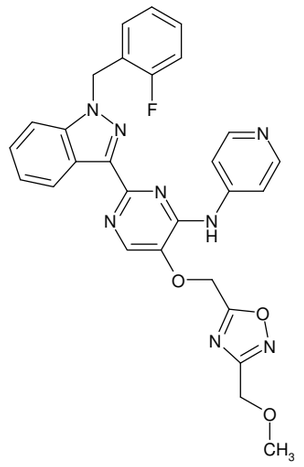
		il)pirimidin-4-amina	8,46 (m, 4H), 9,42 (s, 1H). LC-MS: tiempo de retención: 0,77 min MS ES+: 484,3 [M+H]+
4-5-1 SM = 3-3		2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-*N*-(piridin-4-il)-5-[2-(1*H*-tetrazol-5-il)etoxi]pirimidin-4-amina	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 3,17 - 3,24 (m, 4H), 4,41 (t, 2H), 5,79 (s, 2H), 7,12 - 7,39 (m, 5H), 7,40 - 7,49 (m, 1H), 7,80 (d, 1H), 8,39 - 8,49 (m, 6H). LC-MS: tiempo de retención: 0,91 min MS ES+: 509,36 [M+H]+

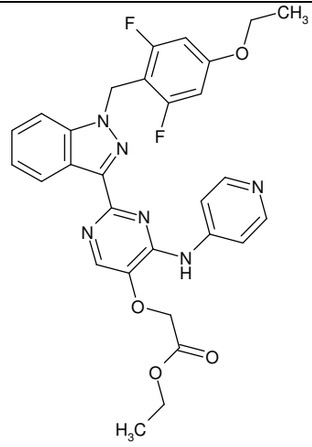
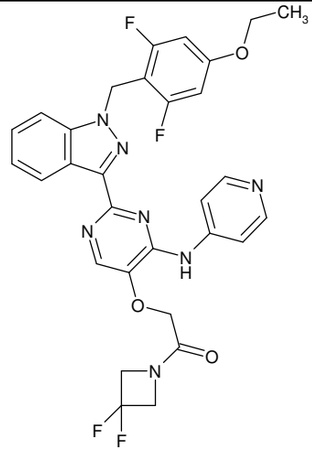
4-5-2 SM = 3-3		2-[1-(2-fluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)-5-[2-(1H-tetrazol-5-il)etoxi]-N-[2-(1H-tetrazol-5-il)etil]pirimidin-4-amina	LC-MS: tiempo de retención: 0,95 min MS ES$^+$: 605,32 [M+H]$^+$
4-6 SM = 3-4		5-[2-(dimetilamino)etoxi]-2-[1-(4-fluorobencil)-1*H*-indazol-3-il]-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 2,24 (s, 6H), 2,65 - 2,75 (m, 2H), 4,29 (s, 2H), 5,73 (s, 2H), 7,09 - 7,30 (m, 4H), 7,35 - 7,45 (m, 2H), 7,74 - 7,83 (m, 1H), 8,03 (d, 2H), 8,36 - 8,46 (m, 4H), 9,41 - 9,47 (m, 1H). LC-MS: tiempo de retención: 0,88 min

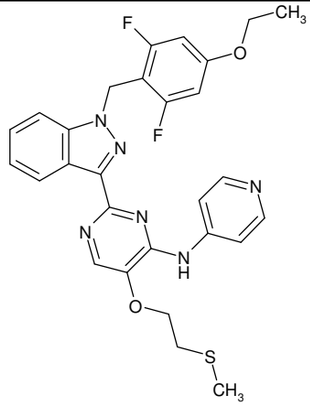
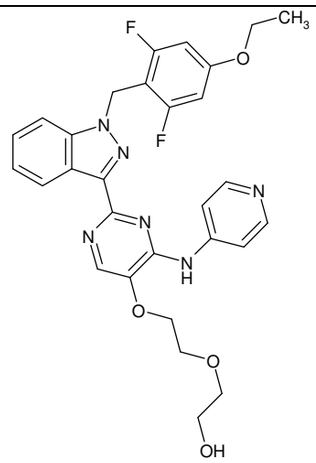
			MS ES+: 484,0 [M+H]+ Método B
4-7 SM = 3-3		2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-*N*-(piridin-4-il)-5-(1*H*-tetrazol-5-ilmetoxi)pirimidin-4-amina	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 5,70 (s, 2H), 5,79 (s, 2H), 7,11 - 7,39 (m, 5H), 7,45 (t, 1H), 7,81 (d, 1H), 8,19 (d, 2H), 8,39 - 8,50 (m, 3H), 8,59 (s, 1H), 9,61 (br.s., 1H). LC-MS: tiempo de retención: 0,92 min MS ES+: 495,2 [M+H]+
4-8 SM = 3-1		5-[2-(dimetilamino)etoxi]-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-N-(piridin-4-	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 1,25 (t, 3H), 2,24 (s, 6H), 2,69 (t, 2H), 4,01 (q, 2H), 4,20 (t, 2H), 5,56 (s, 2H), 6,76 (d, 2H), 7,23 (t, 1H), 7,46 (td, 1H), 7,82 (d, 1H), 8,07 (dd,

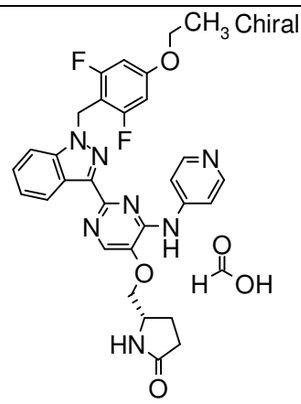
		il)pirimidin-4-amina	2H), 8,36 - 8,45 (m, 4H), 9,38 (s, 1H). LC-MS: tiempo de retención: 0,80 min MS ES+: 546,2 [M+H]+
4-9 SM = 3-1		1-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)-3-(piperidin-1-il)propan-2-ol	1H-RMN (500 MHz, DMSO-d6): δ [ppm]= 1,30 (t, 3H), 1,38 (m, 2H), 1,50 (m, 4H), 2,37 (m, 1H), 2,38-2,54 (m, 4H), 2,65 (m, 1H), 4,06 (q, 2H), 4,09 (br. d, 1H), 4,11 (s ancho, 1H), 4,29 (br. d, 1H), 5,19 (br. d, 1H), 5,70 (s, 2H), 6,81 (d, 2H), 7,28 (t, 1H), 7,50 (br. t, 1H), 7,86 (d, 1H), 8,12 (br. d, 2H), 8,38 (s, 1H), 8,45 - 8,48 (m, 3H), 9,14 (s, 1H). LC-MS (Método 5): tiempo de retención:

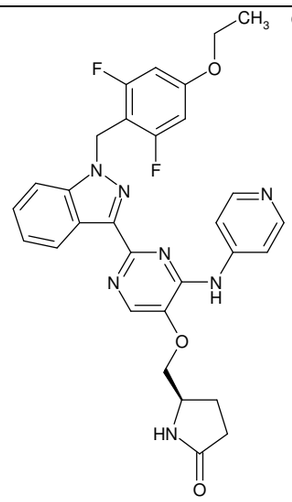
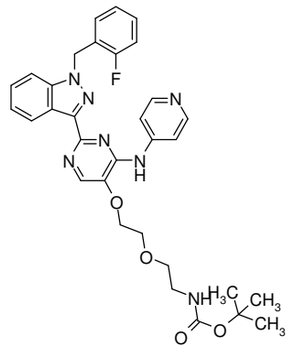
			1,45 min MS ES+: 616,3 [M+H]+
4-10 SM = 3-1		2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-(2-metoxietoxi)-N-(piridin-4-il)pirimidin-4-amina	1H-RMN (300 MHz, DMSO-d6): δ [ppm]= 1,25 (t, 3H), 3,32 (s, 3H), 3,76 (m, 2H), 4,01 (q, 2H), 4,36 (m, 2H), 5,65 (s, 2H), 6,76 (m, 2H), 7,23 (t, 1H), 7,46 (br. t, 1H), 7,82 (d, 1H), 8,12 (br. d, 2H), 8,35 - 8,45 (m, 4H), 9,13 (s, 1H).
4-11 SM = 3-1		2-[({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metil]morfolina-4-	1H-RMN (300 MHz, DMSO-d6): δ [ppm]= 1,25 (t, 3H), 1,37 (s, 9H), 2,91 (m, 2H), 3,45 (br. t, 1H), 3,70 (br. d, 1H), 3,80 - 4,06 (m, 5H), 4,27 (d, 2H), 5,65 (s, 2H), 6,76 (m, 2H), 7,23 (t, 1H), 7,46 (t, 1H), 7,82 (d, 1H), 8,11 (br. d, 2H), 8,35 -

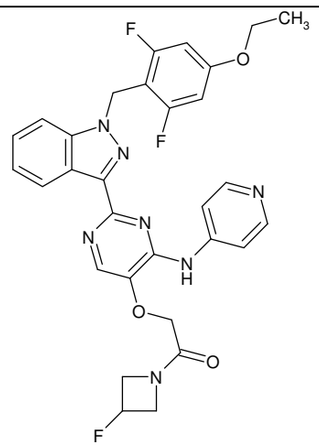
		carboxilato de tert-butilo	8,45 (m, 4H), 9,10 (s, 1H).
4-12 SM = 3-1		2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-[2-(morfolin-4-il)etoxi]-N-(piridin-4-il)pirimidin-4-amina	1H-RMN (300MHz, DMSO-d6): δ [ppm]= 1,25 (t, 3H), 2,79 (t, 2H), 3,51(m, 4H), 3,70 (br. d, 1H), 4,01 (q, 2H), 4,34 (t, 2H), 5,65 (s, 2H), 6,76 (m, 2H), 7,23 (t, 1H), 7,46 (t, 1H), 7,82 (d, 1H), 8,12 (br. d, 2H), 8,35 - 8,45 (m, 4H), 9,08 (s, 1H). LC-MS (Método 5): tiempo de retención: 1,14 min MS ES+: 588,2 [M+H]+
4-13 SM = 3-3		2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-{[3-(metoximetil)-1,2,4-oxadiazol-5-il]metoxi}-	1H-RMN (300MHz, DMSO-d6): δ [ppm]= 3,30 (s, 3H), 4,55 (s, 2H), 5,78 (s, 4H), 7,12-7,39 (m, 5H), 7,44 (br. t, 1H), 7,81 (d, 1H), 8,12 (br. d, 2H), 8,37 - 8,47 (m, 4H), 9,50

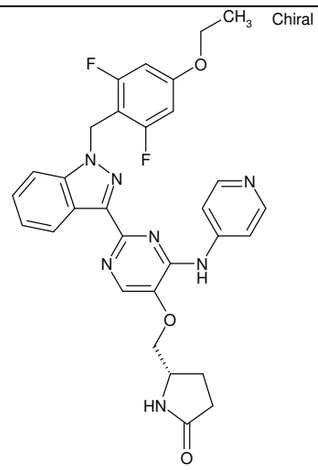
		N-(piridin-4-il)pirimidin-4-amina	(s, 1H). LC-MS (Método 5): tiempo de retención: 1,20 min MS ES+: 539,3 [M+H]+
4-14 SM = 3-1		({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)acetato de etilo	LC-MS (Método 5): tiempo de retención: 1,38 min MS ES+: 561,2 [M+H]+
4-15 SM = 3-1		1-(3,3-difluoroazetidin-1-il)-2-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)etano	1H-RMN (300MHz, DMSO-d6): δ [ppm]= 1,25 (t, 3H), 4,01 (q, 2H), 4,39 (br. t, 2H), 4,73 (br. t, 2H), 4,98 (s, 2H), 5,66 (s, 2H), 6,76 (m, 2H), 7,23 (t, 1H), 7,46 (t, 1H), 7,82 (d, 1H), 8,17 (d, 2H), 8,30 (s, 1H), 8,38 - 8,45 (m, 3H), 9,56 (s, 1H).

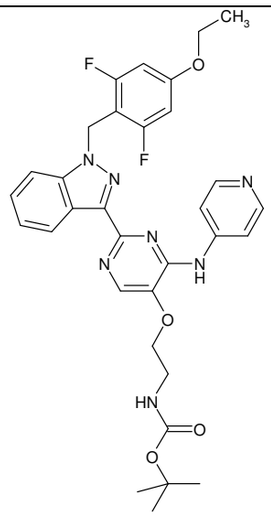
		na	LC-MS (Método 5): tiempo de retención: 1,31 min MS ES+: 608,2 [M+H]+
4-16 SM = 3-1		2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-[2-(metilsulfanil)etoxi]-N-(piridin-4-il)pirimidin-4-amina	1H-RMN (300MHz, DMSO-d6): δ [ppm]= 1,25 (t, 3H), 2,15 (s, 3H), 2,96 (t, 2H), 4,01 (q, 2H), 4,39 (t, 2H), 5,56 (s, 2H), 6,76 (m, 2H), 7,23 (t, 1H), 7,46 (t, 1H), 7,82 (d, 1H), 8,12 (d, 2H), 8,37 - 8,45 (m, 4H), 9,11 (s, 1H). LC-MS (Método 5): tiempo de retención: 1,42 min MS ES+: 550,5 [M+H]+
4-17 SM = 3-1		2-[2-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)piri	1H-RMN (300MHz, DMSO-d6): δ [ppm]= 1,26 (t, 3H), 3,52 (s, 4H), 3,85 (m, 2H), 4,01 (q, 2H), 4,36 (m, 2H), 4,63 (m, 1H), 5,56 (s, 2H), 6,76 (m, 2H), 7,23 (t, 1H), 7,46 (t,

		midin-5-il}oxi)etoxi]etanol	1H), 7,82 (d, 1H), 8,12 (d, 2H), 8,35 - 8,45 (m, 4H), 9,10 (s, 1H). LC-MS (Método 5): tiempo de retención: 1,24 min MS ES+: 561,4 [M+H]+
4-18 SM = 3-1		ácido fórmico - (5S)-5-[({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metil]pirrolidin-2-ona (1:1)	1H-RMN (400MHz, DMSO-d6): δ [ppm]= 1,25 (t, 3H), 1,64 - 1,85 (m, 1H), 2,13 - 2,29 (m, 3H), 3,86 - 4,09 (m, 4H), 4,28 - 4,38 (m, 1H), 5,65 (s, 2H), 6,71 - 6,88 (m, 2H), 7,23 (t, 1H), 7,43 - 7,48 (m, 1H), 7,81 (d, 1H), 8,00 - 8,15 (m, 3H), 8,23 - 8,35 (m, 2H), 8,37 - 8,50 (m, 3H), 8,90 (s, 1H). LC-MS: tiempo de retención: 0,96 min MS ES+: 572,3 [M+H]+

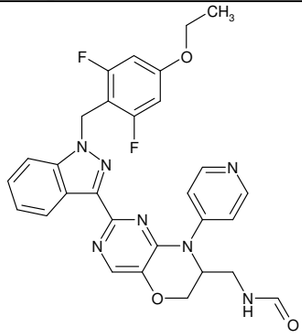
4-19 SM = 3-1		(5R)-5-[({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metil]pirrolidin-2-ona	1H-RMN (300MHz, DMSO-d6): δ [ppm]= 1,26 (t, 3H), 2,14-2,28 (m, 4H), 3,88-4,06 (m, 2H), 4,01 (q, 2H), 4,32 (br. d, 1H), 5. 65 (s, 2H), 6,76 (m, 2H), 7,23 (t, 1H), 7,46 (t, 1H), 7,82 (d, 1H), 8,07 (d, 2H), 8,26-8,33 (m, 2H), 8,39-8,46 (m, 3H), 8,90 (s, 1H). LC-MS (Método 5): tiempo de retención: 1,22 min MS ES+: 572,3 [M+H]+
4-20 SM = 3-3		{2-[2-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)etoxi]etil}carbam	1H-RMN (400MHz, DMSO-d6): δ [ppm]= 1,31 (s, 9H), 3,03 - 3,13 (m, 2H), 3,46 (t, 2H), 3,77 - 3,87 (m, 2H), 4,31 - 4,42 (m, 2H), 5,78 (s, 2H), 6,76 - 6,85 (m, 1H), 7,12 - 7,38 (m, 5H), 7,40 - 7,48 (m, 1H), 7,80 (d, 1H), 8,08 -

		ato de tert-butilo	8,12 (m, 2H), 8,35 - 8,47 (m, 4H), 9,18 (s, 1H) LC-MS: tiempo de retención: 1,07 min MS ES+: 600,3 [M+H]+
4-21 SM = 3-1		2-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)-1-(3-fluoroazetidin-1-il)etanona	1H-RMN (300MHz, DMSO-d6): δ [ppm]= 1,25 (t, 3H), 3,90 - 3,97 (m, 1 H), 4,01 (q, 2H), 4,29 (m, 2H), 4,56 (m, 1H), 4,91 (s, 2H), 5,29 - 5,54 (m, 1H), 5,66 (s, 2H), 6,76 (m, 2H), 7,24 (t, 1H), 7,46 (t, 1H), 7,82 (d, 1H), 8,16 (d, 2H), 8,26 (s, 1H), 8,38 - 8,45 (m, 3H), 9,61 (s, 1H). LC-MS (Método 5): tiempo de retención: 1,29 min MS ES+: 590,4 [M+H]+

4-22 SM = 3-1		(5S)-5-[({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metil]pirrolidin-2-ona	1H-RMN (300MHz, DMSO-d6): δ [ppm]= 1,25 (t, 3H), 1,64 - 1,88 (m, 1H), 2,15 - 2,28 (m, 3H), 3,84 - 4,09 (m, 4H), 4,32 (dd, 1H), 5,65 (s, 2H), 6,73 - 6,81 (m, 2H), 7,24 (t, 1H), 7,46 (t, 1H), 7,82 (d, 1H), 8,07 (d, 2H), 8,24 - 8,50 (m, 5H), 8,94 (s, 1H). LC-MS: tiempo de retención: 1,21 min MS ES+: 572,3 [M+H]+

4-23 SM = 3-1		[2-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)etil] carbamato de tert-butilo	LC-MS (Método 5): tiempo de retención: 1,43 min MS ES+: 618,3 [M+H]+

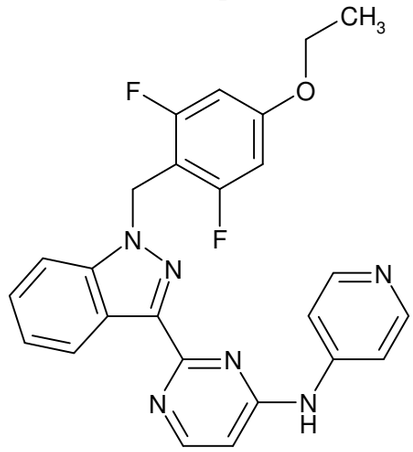
El siguiente compuesto se formó de acuerdo con el mismo procedimiento usando 5-clorometil-2-oxazolidinona y el material de partida indicado (SM = material de partida):

4-24 SM = 3-1		N-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-8-(piridin-4-il)-7,8-dihidro-6H-pirimido[5,4-b][1,4]oxazin-7-	

		il}metil)formamida	

Ejemplo 5-1

Preparación de 2-[1-(4-etoxi-2,6-difluorobencil)-1*H*-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina



Se disolvieron 100 mg de trifluorometansulfonato de 2-[1-(4-etoxi-2,6-difluorobencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ilo (1-7-2, 0,165 mmol, 1. eq.), 0,74 mg de acetato de paladio (II) (0,003 mmol, 0,02 eq.) y 1,36 mg de propan-1,3-diilbis(difenilfosfano) en 1 ml de DMF bajo una atmósfera de nitrógeno. La mezcla se calentó a 60°C de temperatura de baño. Luego se agregaron 0,66 ml de trietilsilano (0,41 mmol, 2,5 eq.). La mezcla resultante se agitó a 60 °C de temperatura de baño durante 18 horas.

Luego la mezcla se particionó entre solución acuosa saturada de carbonato ácido de sodio y diclorometano. Las fases se separaron y la capa acuosa se extrajo dos veces con diclorometano. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre un filtro de silicona y se concentró al vacío. La purificación por HPLC preparativa dio 16 mg (0,03 mmol, 20,1%) del compuesto buscado analíticamente puro.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 1,25 (t, 3H), 4,00 (q, 2H), 5,68 (s, 2H), 6,70 - 6,86 (m, 3H), 7,26 (t, 1H), 7,42 - 7,53 (m, 1H), 7,78 - 7,97 (m, 2H), 8,11 (s, 1H), 8,38 (s ancho, 2H), 8,44 - 8,57 (m, 2H), 10,07 (s, 1H).

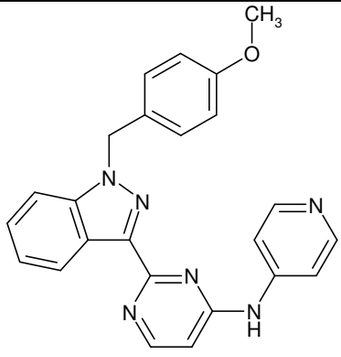
LC-MS:

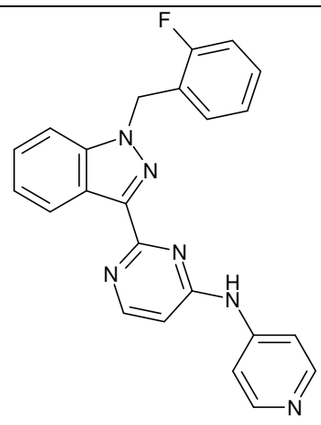
tiempo de retención: 0,97 min

MS ES$^+$: 459,1 $[M+H]^+$

Método B

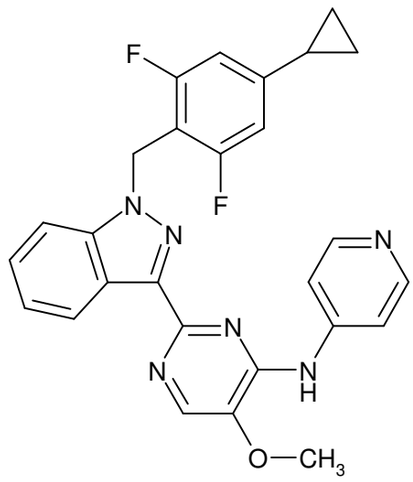
Los siguientes compuestos se prepararon de acuerdo con el mismo procedimiento usando los materiales de partida indicados (SM = material de partida):

5-2		2-[1-(4-metoxibencil)-1*H*-indazol-3-il]-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 3,70 (s, 3H), 5,72 (s, 2H), 6,90 (d, 3H), 7,28 (t, 1H), 7,35 (d, 2H), 7,45 (t, 1H), 7,83 (d, 1H), 7,92 (s ancho, 2H), 8,37 - 8,55 (m, 3H), 8,58 (d, 1H), 10,13

			(s, 1H). LC-MS: tiempo de retención: 0,86 min MS ES+: 409,1 $[M+H]^+$ Método B
5-3 SM = 1-7-1		2-[1-(2-fluorobencil)-1H-indazol-3-il]-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 5,81 (s, 2H), 6,84 (d, 1H), 7,13 - 7,39 (m, 5H), 7,43 - 7,49 (m, 1H), 7,79 - 7,89 (m, 3H), 8,38 (d, 2H), 8,49 (d, 1H), 8,53 (d, 1H), 10,07 (s, 1H). LC-MS: tiempo de retención: 0,93 min MS ES+: 397,25 $[M+H]^+$

Ejemplo 6-1

Preparación de 2-[1-(4-ciclopropil-2,6-difluorobencil)-1*H*-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina



Se suspendieron 100 mg de 2-[1-(4-bromo-2,6-difluorobencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina (2-12-1, 0,191 mmol, 1. eq.) en 3 ml de tolueno seco. Se agregaron 21,3 mg de ácido ciclopropilborónico (0,248 mmol, 1,3 eq.) 5,36 mg de triciclohexilfosfano (0,019 mmol, 0,1 eq.), 142 mg de fosfato de potasio (0,669 mmol, 3,5 eq.) y 50 µl de agua. Luego se agregaron 2,15 mg de acetato de paladio (II) (0,01 mmol, 0,05 eq.) bajo una atmósfera de nitrógeno. La mezcla se agitó a 100 °C de temperatura de baño durante 5 horas. Después de enfriar la mezcla a temperatura ambiente se particionó entre agua y diclorometano/ isopropanol 4:1. Las fases se separaron y la capa acuosa se extrajo dos veces con diclorometano/ isopropanol 4:1. Las capas orgánicas combinadas se secaron sobre sulfato de magnesio y se concentró al vacío. La purificación por HPLC preparativa dio 28,7 mg (0,06 mmol, 31%) del compuesto buscado analíticamente puro.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 0,66-0,74 (m, 2H), 0,89-0,98 (m, 2H), 1,93 (m, 1H), 4,00 (s, 3H), 5,67 (s, 2H), 6,85 - 6,92 (m, 2H), 7,23 (t, 1H), 7,46 (t, 1H), 7,83

(d, 1H), 8,13 – 8,20 (m, 2H), 8,32 (s, 1H), 8,34 – 8,40 (m, 2H), 8,43 (d, 1H), 9,41 (s, 1H).

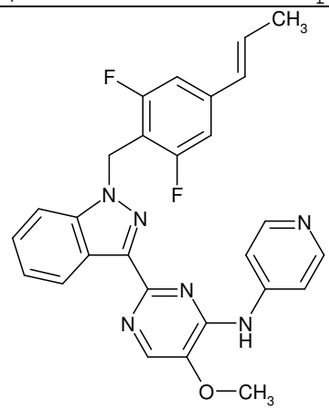
LC–MS:

tiempo de retención: 1,06 min

MS ES$^+$: 485,1 $[M+H]^+$

Método B

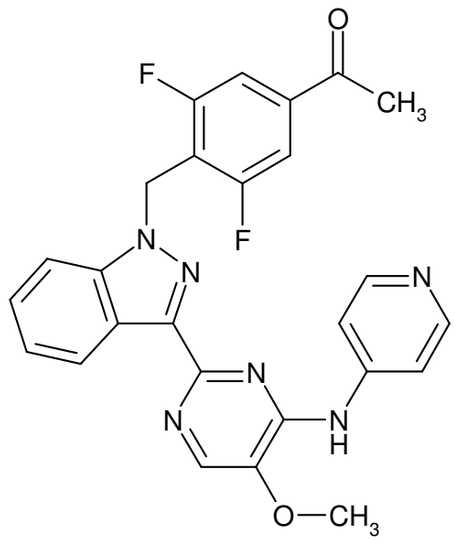
Los siguientes compuestos se prepararon de acuerdo con el mismo procedimiento usando los materiales de partida indicados (SM = material de partida):

6–2 SM = 2–12–1		2-(1-{2,6-difluoro-4-[(1*E*)-prop-1-en-1-il]bencil}-1*H*-indazol-3-il)-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 1,82 (d, 3H), 4,03 (s, 3H), 5,73 (s, 2H), 6,33 – 6,55 (m, 2H), 7,17 – 7,30 (m, 3H), 7,45 – 7,53 (m, 1H), 7,86 (d, 1H), 8,14 – 8,22 (m, 2H), 8,34 (s, 1H), 8,37 – 8,42 (m, 2H), 8,46 (d, 1H), 9,40 (s, 1H). LC–MS: tiempo de

			retención: 8,67 min MS ES+: 485,1 [M+H]+

Ejemplo 7-1

Preparación de 1-[3,5-difluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)fenil]etanona



Paso 1: 2-{1-[4-(1-etoxietenil)-2,6-difluorobencil]-1*H*-indazol-3-il}-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina

Se suspendieron 100mg de 2-[1-(4-bromo-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina (2-12-1, 0,191 mmol, 1 eq.) en toluol seco. Se agregaron 1,34 mg de dicloropaladio - trifenilfosfano (1:2) (0,002 mmol, 0,01 eq.) y 71 µl de tributil(1-etoxietenil)estannano (0,21 mmol, 1,2 eq.). La mezcla se agitó durante 5 horas a 100°C de temperatura de baño y durante 18 horas a 120°C de temperatura de baño. Se agregaron 5 mg de dicloropaladio - trifenilfosfano (1:2) (0,007 mmol, 0,035 eq.) y 140 µl de

tributil(1-etoxietenil)estannano (0,42 mmol, 2,4 eq.) y 1 ml de 1-metilpirrolidin-2-ona. La solución se agitó durante 3 días a 100°C de temperatura de baño. Se agregaron 5 mg de dicloropaladio - trifenilfosfano (1:2) (0,007 mmol, 0,035 eq.) y 140 µl de tributil(1-etoxietenil)estannano (0,42 mmol, 2,4 eq.) y se agitó a 100 °C nuevamente durante 22 horas. La mezcla de reacción se concentró al vacío y se purificó mediante cromatografía flash para dar 119 mg (0,2 mmol, 107%) del compuesto buscado analíticamente puro.

^{1}H-RMN (300MHz, DMSO-d6): δ [ppm]= 1,25 - 1,33 (t, 3H), 3,78 - 3,89 (m, 2H), 4,00 (s, 3H), 4,34 - 4,41 (d, 1H), 4,91 - 4,97 (d, 1H), 5,74 (s, 2H), 7,24 (t, 1H), 7,37 (d, 1H), 7,43 - 7,64 (m, 2H), 7,84 (d, 1H), 8,09 - 8,18 (dd, 2H), 8,32 (s, 1H), 8,34 - 8,39 (dd, 2H), 8,44 (d, 1H), 9,32 - 9,41 (s, 1H).

LC-MS:

tiempo de retención: 1,09 min

MS ES$^+$: 515,1 $[M+H]^+$

Método B

Paso 2: 1-[3,5-difluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)fenil]etanona

Se disolvieron 119 mg de 2-{1-[4-(1-etoxietenil)-2,6-difluorobencil]-1*H*-indazol-3-il}-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina (0,231 mmol, 1 eq.) y 66 mg de ácido 4-metilbencensulfónico hidratado (1:1) (0,347 mmol, 1,5 eq.) en 2,4 ml de etanol y 0,6 ml de agua. La mezcla se agitó durante una hora a 80°C de temperatura de baño. La mezcla de reacción se concentró al vacío. El residuo se particionó entre acetato de etilo y solución saturada de

carbonato ácido de sodio. Las fases se separaron y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se secaron sobre sulfato de magnesio y se concentró al vacío. El residuo se purificó mediante cromatografía flash y purificación por HPLC preparativa para dar 26 mg (0,05 mmol, 22,7%) del compuesto buscado analíticamente puro.

^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 2,54 (s, 3H), 4,00 (s, 3H), 5,82 (s, 2H), 7,25 (t, 1H), 7,49 (t, 1H), 7,69 (d, 2H), 7,87 (d, 1H), 8,14 (d, 2H), 8,31 (s, 1H), 8,37 (d, 2H), 8,44 (d, 1H), 9,38 (s, 1H).

LC-MS:

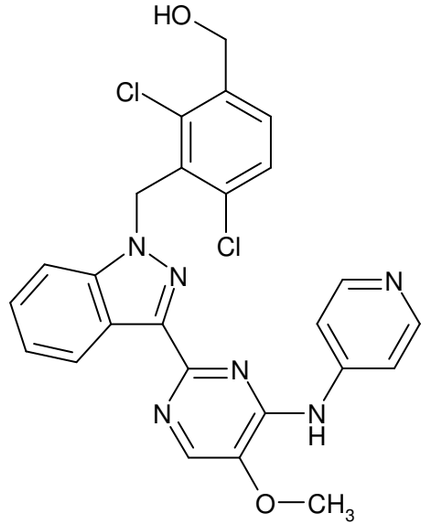
tiempo de retención: 0,95 min

MS ES$^+$: 487,1 $[M+H]^+$

Método B

Ejemplo 8-1

Preparación de [2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)fenil]metanol



Se suspendieron 80 mg de 2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-

il}metil)benzoato de metilo (2-16-1, 0,149 mmol, 1. eq.) en 2,4 ml de tetrahidrofurano seco bajo una atmósfera de nitrógeno. La suspensión se enfrió con un baño de hielo hasta +3 °C, y luego se agregaron 254 µl de una solución de hidruro de litio y aluminio 1 M en tetrahidrofurano (0,254 mmol, 1,7 eq.) por goteo. El baño de hielo se eliminó y la mezcla se agitó a temperatura ambiente durante 30 minutos. Luego la mezcla se acidificó con ácido sulfúrico 2 M. La mezcla formó una suspensión que se retiró por filtración y se lavó con agua. El precipitado se secó al vacío a 60 °C durante 18 horas para dar 60 mg (0,11 mmol, 74,4%) del compuesto buscado analíticamente puro.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 4,02 (s, 3H), 4,51 (s, 2H), 5,47 – 5,57 (m, 1H), 5,90 (s, 2H), 7,26 (t, 1H), 7,49 (t, 1H), 7,54 – 7,67 (m, 2H), 7,91 (d, 1H), 8,34 – 8,41 (m, 2H), 8,42 – 8,49 (m, 4H), 9,98 (s, 1H).

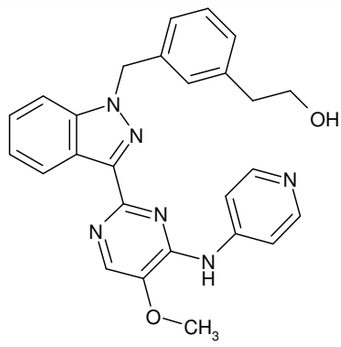
LC-MS:

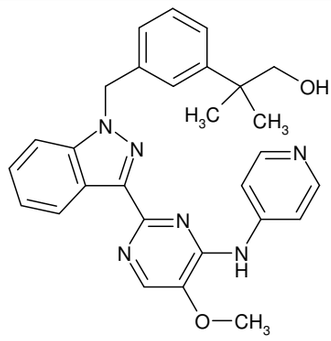
tiempo de retención: 0,91 min

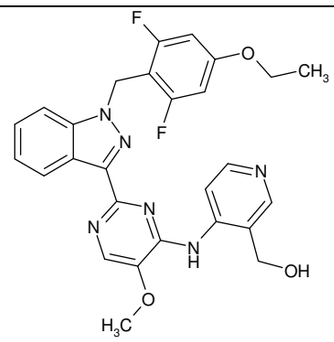
MS ES$^+$: 507,3 $[M+H]^+$

Método B

Los siguientes compuestos se prepararon de acuerdo con el mismo procedimiento usando los materiales de partida indicados (SM = material de partida):

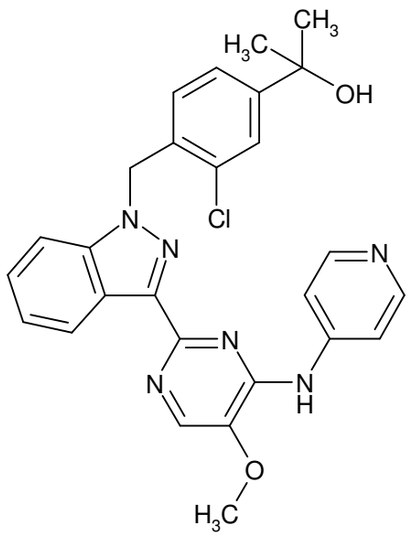
8-2 SM = 2-35-1		2-[3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)fenil]etanol	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 2,59 - 2,67 (m, 2H), 3,51 (d, 2H), 4,02 (s, 3H), 4,58 (s, 1H), 5,69 (s, 2H), 7,06 - 7,14 (m, 2H), 7,16 - 7,26 (m, 3H), 7,40 (t, 1H), 7,77 (d, 1H), 8,12 (dd, 2H), 8,31 - 8,46 (m, 4H), 9,42 (s, 1H). LC-MS: tiempo de retención: 0,87 min MS ES$^+$: 453,22 $[M+H]^+$

8-3 SM = 2-41-1		2-[3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)fenil]-2-metilpropan-1-ol	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 1,13 (s, 6H), 4,05 (s, 3H), 4,57 - 4,66 (m, 1H), 5,69 - 5,76 (m, 4H), 7,03 (d, 1H), 7,15 - 7,27 (m, 3H), 7,37 - 7,48 (m, 2H), 7,79 (d, 1H), 8,32 - 8,54 (m, 6H), 9,97 - 10,04 (m, 1H). LC-MS: tiempo de retención: 0,87 min MS ES$^+$: 481,4 $[M+H]^+$ Método B

8-4 SM = 39-1		[4-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-il]metanol	1H-RMN (300MHz, DMSO-d6): δ [ppm]= 1,25 (t, 3H),3,99 (s, 3H), 4,01 (q, 2H), 4,67 (d, 2H), 5. 64 (s, 2H), 5. 96 (t, 1H), 6,76 (m, 2H), 7,23 (t, 1H), 7,45 (t, 1H), 7,81 (d, 1H), 8,32-8,44 (m, 4H), 8,82 (d, 1H), 9,52 (s, 1H). LC-MS (Método 1): tiempo de retención: 1,03 min MS ES+: 481,4 $[M+H]^+$

Ejemplo 9-1

Preparación de 2-[3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)fenil]propan-2-ol



Se suspendieron 36 mg de 3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)benzoato de metilo (2-11-1, 0,072 mmol, 1. eq.) en 583 µl de tetrahidrofurano seco bajo una atmósfera de nitrógeno. La suspensión se enfrió con una mezcla de congelamiento a -75 °C. Luego se agregaron 90 µl de solución de metillitio en éter dietílico 1,6 M (0,144 mmol, 2 eq.) por goteo. La mezcla de congelamiento se retiró y la mezcla de reacción se agitó a temperatura ambiente durante 24 horas. La mezcla de reacción se enfrió con una mezcla de congelamiento a -75 °C. Se agregaron 90 µl de solución de metillitio en éter dietílico 1,6 M (0,144 mmol, 2 eq.) por goteo nuevamente. La mezcla de congelamiento se retiró y la mezcla de reacción se agitó a temperatura ambiente durante otras 24 horas. Luego la mezcla se particionó entre agua y diclorometano/ isopropanol 4:1. Las fases se separaron y la capa acuosa se extrajo dos veces con diclorometano/ isopropanol 4:1. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre un filtro de silicona y se concentró al vacío. El residuo se purificó mediante TLC

preparativa para dar 3,5 mg (0,01 mmol, 9,3%) del compuesto buscado analíticamente puro.

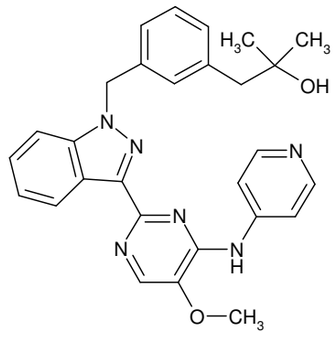
^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 1,34 (s, 6H), 4,01 (s, 3H), 5,11 (s, 1H), 5,77 (s, 2H), 7,13 (d, 1H), 7,21 – 7,27 (m, 1H), 7,34 (dd, 1H), 7,44 (ddd, 1H), 7,54 (d, 1H), 7,79 (d, 1H), 8,10 – 8,15 (m, 2H), 8,34 (s, 1H), 8,35 – 8,40 (m, 2H), 8,46 (d, 1H), 9,41 (s, 1H).

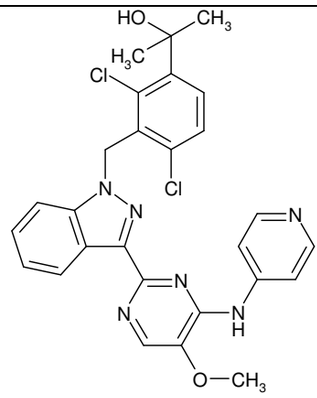
LC-MS:

tiempo de retención: 0,99 min

MS ES$^+$: 501,2 $[M+H]^+$

Los siguientes compuestos se prepararon de acuerdo con el mismo procedimiento usando los materiales de partida indicados (SM = material de partida):

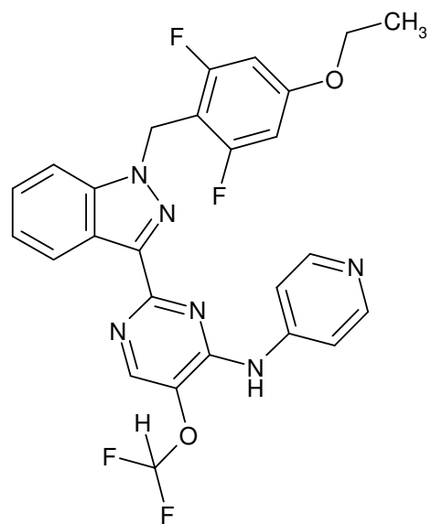
9-2 SM = 2-35-1		1-[3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)fenil]-2-metilpropan-2-ol	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 0,94 (s, 6H), 1,18 – 1,22 (m, 2H), 4,02 (s, 3H), 4,24 (s, 1H), 5,70 (s, 2H), 7,03 – 7,25 (m, 5H), 7,38 (t, 1H), 7,74 (d, 1H), 8,12 (dd, 2H), 8,32 – 8,46 (m, 4H), 9,40

			- 9,45 (m, 1H). LC-MS: tiempo de retención: 0,95 min MS ES+: 481,26 $[M+H]^+$
9-3 SM = 2-16-1		2-[2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)fenil]propan-2-ol	^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 1,51 (s, 6H), 4,00 (s, 3H), 5,37 (s, 1H), 5,91 (s, 2H), 7,22 - 7,28 (t, 1H), 7,45 - 7,50 (m, 1H), 7,62 (d, 1H), 7,86 - 7,91 (m, 2H), 8,14 (d, 2H), 8,32 (s, 1H), 8,37 (d, 2H), 8,48 (d, 1H), 9,35 (s, 1H). LC-MS: tiempo de retención:

			1,09 min MS ES$^+$: 535,2 $[M+H]^+$

Ejemplo 10-1

Preparación de 5-(difluorometoxi)-2-[1-(4-etoxi-2,6-difluorobencil)-1*H*-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina



Se suspendieron 100 mg de 2-[1-(4-etoxi-2,6-difluorobencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ol (3-1, 0,211 mmol, 1. eq.) en 843 µl de solución acuosa de hidróxido de potasio 30% (5,72 mmol, 27 eq.) y 843µl de acetonitrilo. La suspensión se enfrió con una mezcla de congelamiento a -75 °C. Se agregaron 93 µl de 2-cloro-2,2-difluoro-1-feniletanona (0,632 mmol, 3 eq.) por goteo. La mezcla de congelamiento se retiró. La mezcla de reacción se agitó a 80 °C de temperatura de baño durante 4 horas. Luego la mezcla se particionó entre agua y diclorometano/ isopropanol 4:1. Las fases se separaron y la capa acuosa se extrajo dos veces con diclorometano/

isopropanol 4:1. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre un filtro de silicona y se concentró al vacío. La purificación por HPLC preparativa dio 4 mg (0,01 mmol, 3,2%) del compuesto buscado analíticamente puro.

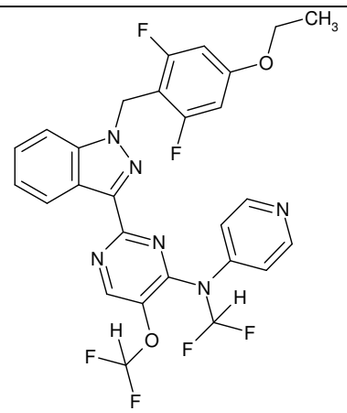
^{1}H-RMN (500 MHz, DMSO-d_6): δ [ppm]= 1,30 (t, 3H), 4,05 (q, 2H), 5,73 (s, 2H), 6,81 (d, 2H), 7,16 – 7,48 (m, 2H), 7,50 – 7,57 (m, 1H), 7,90 (d, 1H), 8,12 – 8,17 (m, 2H), 8,44 – 8,49 (m, 3H), 8,54 (s, 1H), 9,71 (s, 1H).

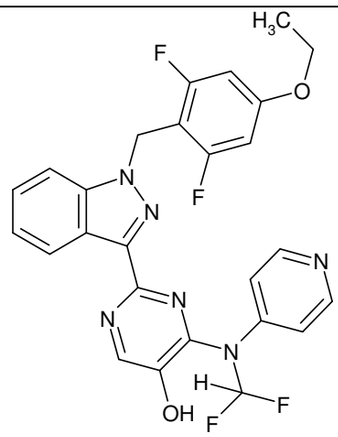
LC-MS:

tiempo de retención: 1,65 min

MS ES$^+$: 525,02 $[M+H]^+$

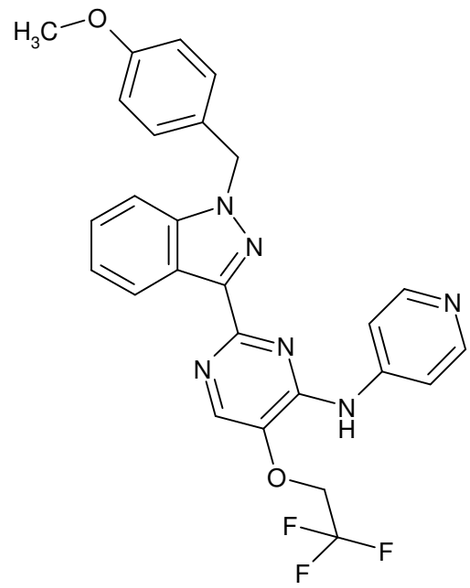
Los siguientes compuestos también se formaron durante el mismo procedimiento:

10-2 SM = 3-1		5-(difluorometoxi)-*N*-(difluorometil)-2-[1-(4-etoxi-2,6-difluorobencil)-1*H*-indazol-3-il]-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 1,25 (t, 3H), 4,00 (q, 2H), 5,65 (s, 2H), 6,72 (d, 2H), 6,91 (d, 1H), 7,16 – 7,25 (m, 1H), 6,97 – 7,47 (t, 2H), 7,34 – 7,60 (m, 2H), 7,76 (d, 1H), 7,91 (d, 2H), 8,36 (d, 1H), 8,46 (s, 1H). LC-MS:

			tiempo de retención: 1,15 min MS ES+: 575,1 [M+H]+
10-3 SM = 3-1		4-[(difluorometil)(piridin-4-il)amino]-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]pirimidin-5-ol	1H-RMN (600MHz, DMSO-d6): δ [ppm]= 1,29 (t, 4H), 4,04 (q, 3H), 5,63 (s, 2H), 6,71 - 6,79 (m, 2H), 7,04 (s ancho, 1H), 7,20 (t, 1H), 7,44 (td, 1H), 7,49 - 7,71 (m, 1H), 7,74 (d, 1H), 7,91 (d, 2H), 8,15 (s, 1H), 8,41 (d, 1H). LC-MS: tiempo de retención: 1,10 min MS ES+: 525,0 [M+H]+

Ejemplo 11-1

Preparación de 2-[1-(4-metoxibencil)-1*H*-indazol-3-il]-N-(piridin-4-il)-5-(2,2,2-trifluoroetoxi)pirimidin-4-amina



Se disolvieron 143 mg de 2-[1-(4-metoxibencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ol (3-2, 0,337 mmol, 1. eq.) en 500 µl de DMF seco. Luego se agregaron 117 mg de 2,2,2-trifluoroetilo trifluorometansulfonato de (0,505 mmol, 1,5 eq.), 93,1 mg de carbonato de potasio (0,674 mmol, 2 eq.) y 24 µl de acetonitrilo. La mezcla resultante se agitó a 150 °C durante 30 minutos en un microondas. Luego la mezcla se particionó entre agua y diclorometano/ isopropanol 4:1. Las fases se separaron y la capa acuosa se extrajo dos veces con diclorometano/ isopropanol 4:1. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre un filtro de silicona y se concentró al vacío. El residuo se purificó mediante cromatografía flash y TLC preparativa para dar 7,7 mg (0,01 mmol, 3,9%) del compuesto buscado analíticamente puro.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 3,66 (s, 3H), 4,95 - 5,08 (m, 2H), 5,65 (s, 2H), 6,83 - 6,90 (m, 2H), 7,16 - 7,24 (m, 1H), 7,30 (d, 2H), 7,36 - 7,45 (m, 1H), 7,78 (d, 1H), 8,00 - 8,11 (m, 2H), 8,35 - 8,52 (m, 4H), 9,32 (s,

1H).

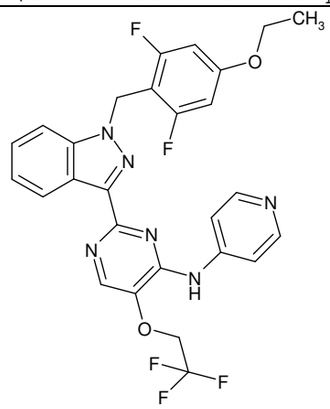
LC-MS:

tiempo de retención: 1,03 min

MS ES+: 507,1 [M+H]+

Método B

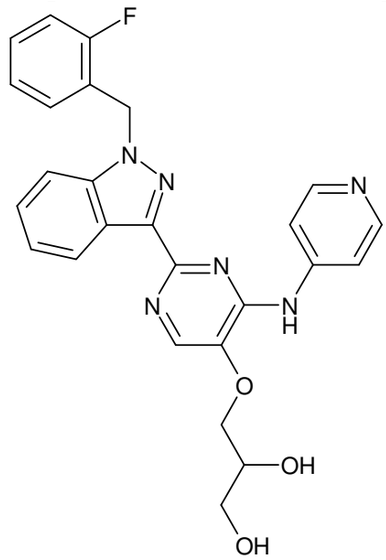
Los siguientes compuestos se prepararon de acuerdo con el mismo procedimiento usando los materiales de partida indicados (SM = material de partida):

11-2 SM = 3-1		2-[1-(4-etoxi-2,6-difluorobencil)-1*H*-indazol-3-il]-*N*-(piridin-4-il)-5-(2,2,2-trifluoroetoxi)pirimidin-4-amina	^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 1,28 (t, 3H), 4,04 (q, 2H), 5,03 (q, 2H), 5,69 (s, 2H), 6,79 (d, 2H), 7,22 - 7,30 (m, 1H), 7,49 (ddd, 1H), 7,85 (d, 1H), 8,10 - 8,16 (m, 2H), 8,40 - 8,46 (m, 3H), 8,50 (s,

			1H), 9,32 (s, 1H). LC-MS: tiempo de retención: 1,11 min MS ES+: 557,1 [M+H]+ Método B

Ejemplo 12-1

Preparación de 3-({2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)propan-1,2-diol



Se suspendieron 25,0 mg de 2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ol (3-3, 0,06 mmol, 1 eq.), 28,2 mg de 3-bromo-propan-1,2-diol (0,18 mmol, 3 eq.) y 41,9 mg de carbonato de potasio (0,30 mmol, 5 eq.) en 466 µl de DMF seco. La mezcla de reacción se agitó a 100 °C de temperatura de baño de aceite durante 18 horas. Luego la mezcla se particionó entre solución acuosa

parcialmente saturada de cloruro de sodio y acetato de etilo. Las fases se separaron y la fase acuosa se extrajo otra vez con acetato de etilo y una vez con diclorometano/isopropanol 4:1. Las capas orgánicas combinadas se secaron sobre sulfato de magnesio y se concentró al vacío. El residuo se purificó mediante cromatografía preparativa en capa delgada para dar 2,60 mg (5,34 µmol, 9%) del compuesto buscado analíticamente puro.

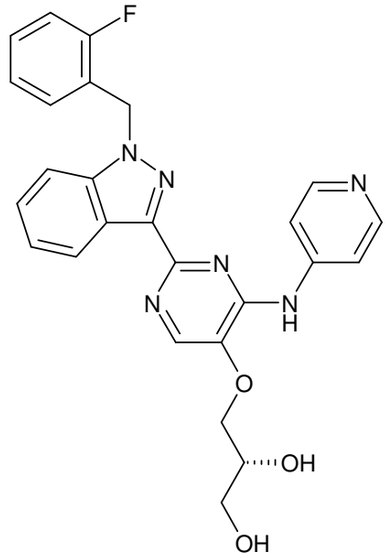
LC–MS:

tiempo de retención: 1,00 min

MS ES$^+$: 487,41 $[M+H]^+$

Ejemplo 12–2

Preparación de (2*R*)–3–({2–[1–(2–fluorobencil)–1*H*–indazol–3–il]–4–(piridin–4–ilamino)pirimidin–5–il}oxi)propan–1,2–diol



Paso 1: 5–{[(4*S*)–2,2–dimetil–1,3–dioxolan–4–il]metoxi}–2–[1–(2–fluorobencil)–1*H*–indazol–3–il]–*N*–(piridin–4–il)pirimidin–4–amina

Se suspendieron 200 mg de 2–[1–(2–fluorobencil)–1H–indazol–3–il]–4–(piridin–4–ilamino)pirimidin–5–ol (3–3, 0,49 mmol, 1 eq.), 94,6 mg de 2,2–dimetil–4(R)–4–bromometil–1,3–

dioxalano (0,49 mmol, 1 eq.) y 134 mg de carbonato de potasio (0,97 mmol, 2 eq.) en 3,7 ml de DMF seco. La mezcla de reacción se agitó a 50 °C de temperatura de baño de aceite durante 18 horas. Se agregaron 201 mg de carbonato de potasio (1,46 mmol, 3 eq.) y la mezcla se agitó a 90 °C de temperatura de baño de aceite durante otras 24 horas. Luego la mezcla se particionó entre solución acuosa parcialmente saturada de cloruro de amonio y diclorometano/isopropanol 4:1. Las fases se separaron y la capa acuosa se extrajo dos veces con diclorometano/isopropanol 4:1. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre un filtro de silicona y se concentró al vacío. El residuo se purificó mediante cromatografía flash para dar 126 mg (0,27 mmol, 44%) del compuesto buscado analíticamente puro.

^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 1,29 (s, 3H), 1,34 (s, 3H), 3,86 (dd, 1H), 4,15 (dd, 1H), 4,27 (dd, 2H), 4,54 (m, 1H), 5,78 (s, 2H), 7,12 – 7,38 (m, 5H), 7,40 – 7,47 (m, 1H), 7,80 (d, 1H), 8,04 – 8,09 (m, 2H), 8,38 – 8,46 (m, 4H), 9,11 (s, 1H).

LC-MS:

tiempo de retención: 1,00 min

MS ES$^+$: 527,39 $[M+H]^+$

Paso 2: clorhidrato de (2*R*)-3-({2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)propan-1,2-diol (1:1)

Se disolvieron 124 mg de 5-{[(4*S*)-2,2-dimetil-1,3-dioxolan-4-il]metoxi}-2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-*N*-(piridin-4-il)pirimidin-4-amina (0,24 mmol, 1. eq.) en 12

ml de acetonitrilo. Se agregaron 515 µl de cloruro de hidrógeno conc. (6,00 mmol, 20,8 eq.) por goteo. La mezcla de reacción se agitó a temperatura ambiente durante 18 horas. La suspensión se retiró por filtración y se lavó con acetonitrilo. El precipitado se secó a 45 °C bajo vacío para dar 119 mg (0,23 mmol, 97%) del compuesto buscado analíticamente puro.

^{1}H-RMN (600MHz, DMSO d_6): δ [ppm]= 3,49 (m, 2H), 3,94 (m, 1H), 4,14 (dd, 1H), 4,34 (dd, 1H), 4,73 (s ancho, 2H), 5,82 (s, 2H), 7,15 (td, 1H), 7,19 – 7,30 (m, 2H), 7,34 (m, 1H), 7,46 (td, 1H), 7,49 (ddd, 1H), 7,80 (d, 1H), 8,41 (d, 1H), 8,58 (s, 1H), 8,65 (d, 2H), 8,75 (d, 2H), 10,72 (s, 1H), 14,82 (s ancho, 1H).

LC-MS:

tiempo de retención: 0,86 min

MS ES$^+$: 487,34 $[M+H]^+$

Paso 3: (2*R*)-3-({2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)propan-1,2-diol

Se disolvieron 84,5 mg de clorhidrato de (2*R*)-3-({2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)propan-1,2-diol (1:1) en agua. Se agregó solución acuosa de hidróxido de sodio 2M. La mezcla se agitó a temperatura ambiente durante 3 horas. La suspensión resultante se retiró por filtración y se lavó con agua para dar 52,9 mg (0,11 mmol, 67%) del compuesto buscado analíticamente puro.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 3,50 (d, 2H), 3,85 – 3,97 (m, 1H), 4,01 – 4,13 (m, 1H), 4,23 – 4,30 (m, 1H), 4,79 (s, 1H), 5,20 – 5,27 (m, 1H), 5,78 (s, 2H), 7,11 –

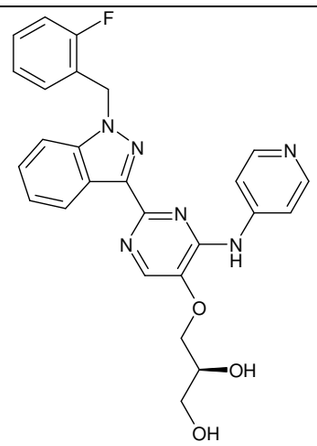
7,39 (m, 5H), 7,44 (t, 1H), 7,80 (d, 1H), 7,99 – 8,07 (m, 2H), 8,33 (s, 1H), 8,39 – 8,46 (m, 3H), 9,14 (s, 1H).

LC–MS (quiral):

tiempo de retención: 0,85 min

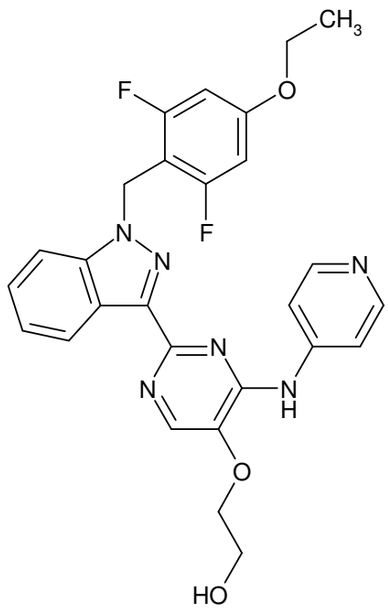
MS ES$^+$: 487,35 $[M+H]^+$

El siguiente enantiómero se preparó de acuerdo con el mismo procedimiento usando el material de partida indicado (SM = material de partida) y 2,2-dimetil-4(S)-4-bromometil-1,3-dioxalano:

12-3 SM = 3-3		(2*S*)-3-({2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)propan-1,2-diol	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 3,50 (d, 2H), 3,86 – 3,98 (m, 1H), 4,08 (s, 1H), 4,19 – 4,30 (m, 1H), 4,79 (s, 1H), 5,25 (d, 1H), 5,78 (s, 2H), 7,11 – 7,39 (m, 5H), 7,44 (t, 1H), 7,80 (d, 1H), 8,01 – 8,07 (m, 2H), 8,33 (s, 1H), 8,39 – 8,47 (m, 3H), 9,14 (s, 1H). LC–MS (quiral): tiempo de retención: 0,90 min MS ES$^+$: 487,21 $[M+H]^+$

Ejemplo 13-1

Preparación de 2-({2-[1-(4-etoxi-2,6-difluorobencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)etanol



Paso 1:

Se suspendieron 182 mg de 2-[1-(4-etoxi-2,6-difluorobencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ol (3-1, 0,383 mmol, 1 eq.), 110 mg de (2-bromoetoxi)(*tert*-butil)dimetilsilano (0,459 mmol, 1,2 eq.) y 159 mg de carbonato de potasio en 3 ml de DMF seco bajo una atmósfera de nitrógeno y se agitó durante 3 días a temperatura ambiente. Luego la mezcla se particionó entre agua y diclorometano. Las fases se separaron y la capa acuosa se extrajo dos veces con diclorometano. Las capas orgánicas combinadas se lavaron con solución acuosa parcialmente saturada de cloruro de sodio, se secó sobre un filtro de silicona y se concentró al vacío para dar 224 mg (0,32 mmol, 82,3%) del compuesto buscado analíticamente puro.

^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 0,00 (s, 6H), 0,79 (s,

9H), 1,25 (t, 3H), 4,01 (d, 4H), 4,30 – 4,39 (m, 2H), 5,65 (s, 2H), 6,77 (d, 2H), 7,23 (t, 1H), 7,46 (t, 1H), 7,82 (d, 1H), 8,07 – 8,14 (m, 2H), 8,34 – 8,45 (m, 4H), 9,07 – 9,14 (m, 1H).

LC–MS:

tiempo de retención: 1,70 min

MS ES^+: 633,4 $[M+H]^+$

Paso 2:

Se disolvieron 224 mg de 5-(2-{[*tert*-butil(dimetil)silil]oxi}etoxi)-2-[1-(4-etoxi-2,6-difluorobencil)-1*H*-indazol-3-il]-*N*-(piridin-4-il)pirimidin-4-amina (0,337 mmol, 1. eq.) en 3 ml de dioxano seco bajo una atmósfera de nitrógeno. Se agregaron 442 µl de solución de cloruro de hidrógeno en dioxano 4 M y se obtuvo inmediatamente una suspensión. Esta suspensión se agitó durante 30 minutos. Luego se agregaron 10 ml de una solución acuosa saturada de carbonato ácido de sodio. La suspensión se retiró por filtración y se lavó con agua para dar 210 mg (0,34 mmol, 97,0%) del compuesto buscado analíticamente puro.

^{1}H–RMN (400 MHz, DMSO-d_6): δ [ppm]= 1,28 (t, 3H), 3,83 (d, 2H), 4,04 (q, 2H), 4,24 (t, 2H), 5,11 (s ancho, 1H), 5,68 (s, 2H), 6,75 – 6,84 (m, 2H), 7,26 (t, 1H), 7,45 – 7,52 (m, 1H), 7,85 (d, 1H), 8,09 – 8,14 (m, 2H), 8,36 (s, 1H), 8,41 – 8,48 (m, 3H), 9,12 (s, 1H).

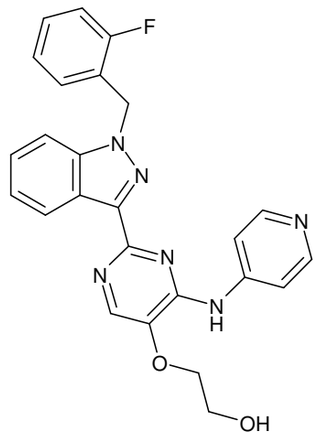
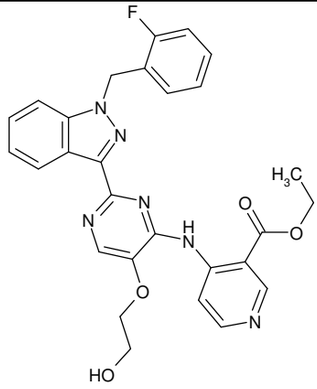
LC–MS:

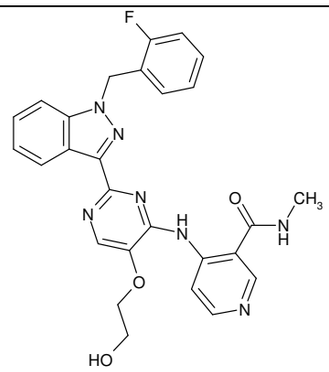
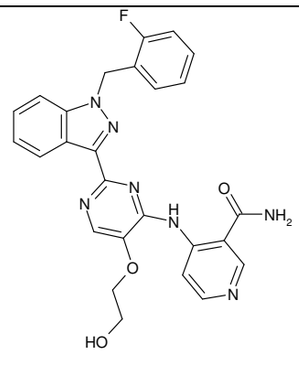
tiempo de retención: 0,95 min

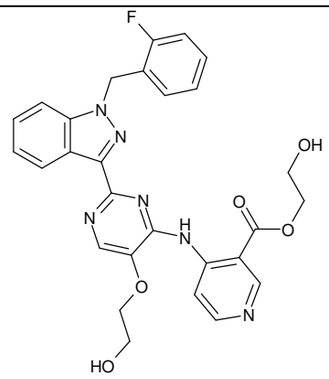
MS ES^+: 519,4 $[M+H]^+$

Método B

Los siguientes compuestos se prepararon de acuerdo con el mismo procedimiento en dos pasos usando los materiales de partida indicados (SM = material de partida):

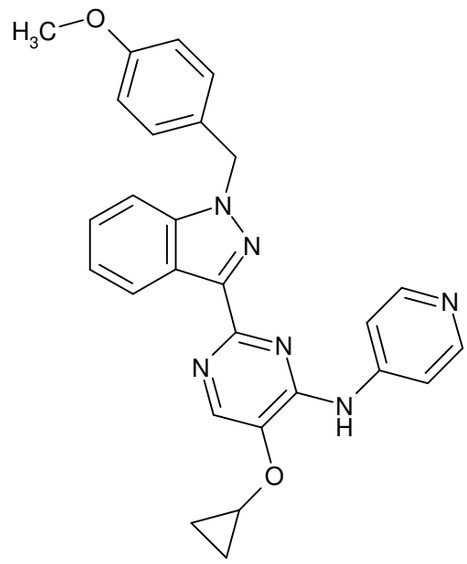
13-2 SM = 3-3		2-({2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)etanol	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 3,77 - 3,85 (m, 2H), 4,22 (t, 2H), 5,10 (t, 1H), 5,78 (s, 2H), 7,12 - 7,39 (m, 5H), 7,44 (td, 1H), 7,80 (d, 1H), 8,04 - 8,09 (m, 2H), 8,35 (s, 1H), 8,40 - 8,46 (m, 3H), 9,17 (s, 1H). LC-MS: tiempo de retención: 0,95 min MS ES$^+$: 457,32 [M+H]$^+$
13-3 SM = 30-3		4-({2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-5-(2-hidroxietoxi)pirimidin-4-il}amino)piridin-3-carboxilato de etilo	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 1,35 (t, 3H), 3,83 (q, 2H), 4,33 (t, 2H), 4,40 (q, 2H), 4,90 (t, 1H), 5,79 (s, 2H), 7,12 - 7,39 (m, 5H), 7,46 (t, 1H), 7,82 (d, 1H), 8,45 (d, 1H), 8,50 (s, 1H), 8,58 (d, 1H), 9,02 - 9,09 (m, 1H), 9,29 (d, 1H), 11,23 (s, 1H). LC-MS: tiempo de retención: 1,12

			min MS ES+: 529,0 [M+H]+ Método B
13-4 SM = 13-3	 (derivado de 13-3 por amidación y desililación subsecuente)	4-({2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-5-(2-hidroxietoxi)pirimidin-4-il}amino)-*N*-metilpiridin-3-carboxamida	^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 2,81 (d, 3H), 3,83 (q, 2H), 4,29 (t, 2H), 4,83 (t, 1H), 5,79 (s, 2H), 7,12 - 7,38 (m, 5H), 7,41 - 7,49 (m, 1H), 7,81 (d, 1H), 8,42 - 8,47 (m, 2H), 8,50 (d, 1H), 8,84 (s, 1H), 8,91 (d, 1H), 9,15 (d, 1H), 11,91 (s, 1H). LC-MS: tiempo de retención: 0,93 min MS ES+: 514,4 [M+H]+ Método B
13-5 SM = 30-1		4-({2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-5-(2-hidroxietoxi)pirimidin-4-	LC-MS: tiempo de retención: 0,96 min MS ES+: 500,1 [M+H]+ Método B

		il}amino)piridin-3-carboxamida	
13-6 SM = 30-2		4-({2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-5-(2-hidroxietoxi)pirimidin-4-il}amino)piridin-3-carboxilato de 2-hidroxietilo	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 3,69 - 3,77 (m, 2H), 3,79 - 3,88 (m, 2H), 4,28 - 4,40 (m, 4H), 4,86 - 4,94 (m, 1H), 4,96 - 5,04 (m, 1H), 5,76 - 5,83 (m, 2H), 7,13 - 7,40 (m, 5H), 7,46 (t, 1H), 7,82 (d, 1H), 8,45 (d, 1H), 8,51 (s, 1H), 8,59 (d, 1H), 9,15 (s, 1H), 9,30 (d, 1H), 11,22 - 11,27 (m, 1H). LC-MS: tiempo de retención: 1,15 min MS ES$^+$: 545,0 $[M+H]^+$ Método B

Ejemplo 14-1

Preparación de 5-(ciclopropiloxi)-2-[1-(4-metoxibencil)-1*H*-indazol-3-il]-*N*-(piridin-4-il)pirimidin-4-amina



Se suspendieron 100 mg de 2-[1-(4-metoxibencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ol (3-2, 0,236 mmol, 1. eq.), 34,2 mg de bromociclopropano (0,283 mmol, 1,2 eq.), 44,9 mg de cloruro de cobre (I) (0,236 mmol, 1 eq.) y 154 mg de carbonato de cesio (0,471 mmol, 2 eq.) en 3 ml de DMF seco. La mezcla de reacción se agitó a 60 °C de temperatura de baño durante 18 horas. Luego la mezcla se particionó entre solución acuosa parcialmente saturada de cloruro de amonio y diclorometano/ isopropanol 4:1. Las fases se separaron y la capa acuosa se extrajo dos veces con diclorometano/ isopropanol 4:1. Las capas orgánicas combinadas se lavaron con salmuera incluyendo un precipitado que se separó por filtración. El precipitado se purificó mediante HPLC preparativa para dar 2,58 mg (0,047 mmol, 2%) del compuesto buscado analíticamente puro.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 3,65 (s, 3H), 4,90 (d, 2H), 5,19 - 5,40 (m, 2H), 5,60 (s, 2H), 6,01 - 6,18 (m, 1H), 6,85 (d, 2H), 7,09 - 7,18 (m, 1H), 7,26 (d, 2H), 7,34 (t, 1H), 7,65 (d, 1H), 7,94 (s, 1H), 8,28 (s ancho, 1H), 8,43 (dd, 3H), 8,57 (s ancho, 2H).

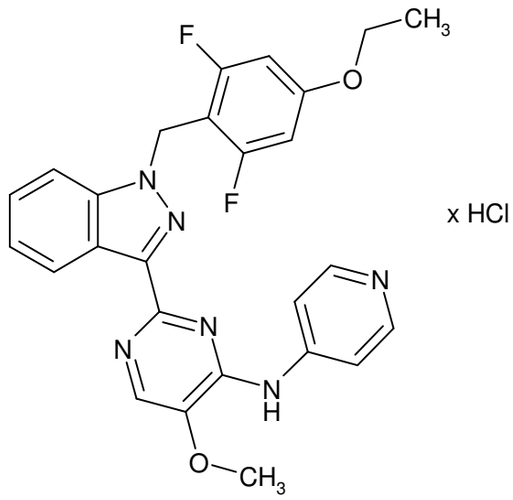
LC–MS:

tiempo de retención: 0,95 min

MS ES$^+$: 465,1 $[M+H]^+$Método B

Ejemplo 15–1

Preparación de clorhidrato de 2–[1–(4–etoxi–2,6–difluorobencil)–1*H*–indazol–3–il]–5–metoxi–*N*–(piridin–4–il)pirimidin–4–amina (1:1)



Se disolvieron 150 mg de 2–[1–(4–etoxi–2,6–difluorobencil)–1*H*–indazol–3–il]–5–metoxi–*N*–(piridin–4–il)pirimidin–4–amina (2–5–1, 0,307 mmol, 1. eq.) en una mezcla de 5,9 ml de diclorometano seco y 2,5 ml de metanol seco. Se agregaron 0,25 ml de solución de cloruro de hidrógeno en metanol 1,25 M. La mezcla se agitó a temperatura ambiente durante 1 hora. Luego la mezcla se concentró al vacío para dar 161 mg (0,29 mmol, 95,9%) del compuesto buscado analíticamente puro.

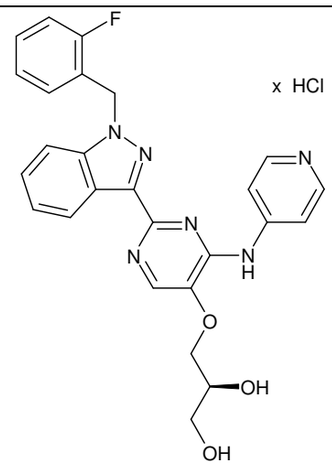
^{1}H–RMN (300 MHz, DMSO–d_6): δ [ppm]= 1,25 (t, 3H), 3,93 – 4,08 (m, 5H), 5,66 (s, 2H), 6,72 – 6,82 (m, 2H), 7,24 (t, 1H), 7,42 – 7,51 (m, 1H), 7,82 (d, 1H), 8,34 (d, 2H), 8,39 – 8,48 (m, 4H), 9,85 (s, 1H).

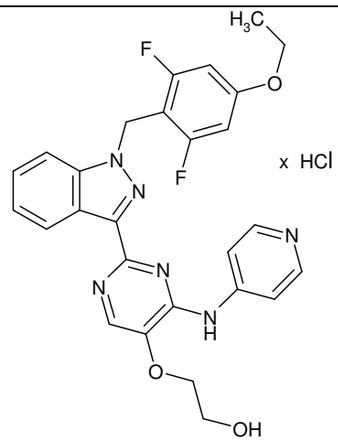
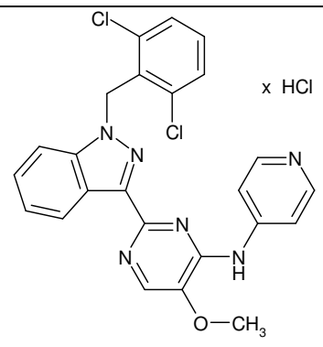
LC–MS:

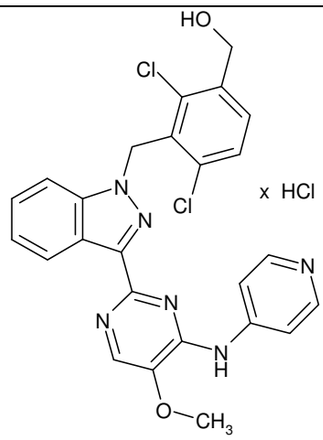
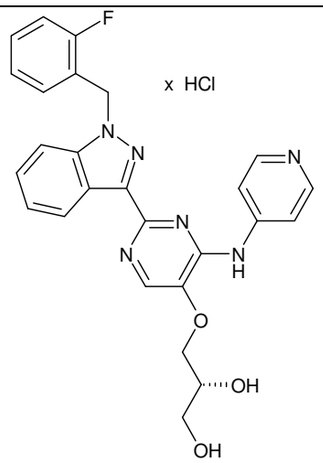
tiempo de retención: 1,08 min

MS ES+: 489,1 [M+H]+

Método B

15-2 SM = 12-2		clorhidrato de (2*S*)-3-({2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)propan-1,2-diol (1:1)	^{1}H-RMN (600MHz, DMSO d_6): δ [ppm]= 3,50 - 3,58 (m, 2H), 3,95 - 4,01 (m, 1H), 4,18 (dd, 1H), 4,38 (dd, 1H), 5,85 (s, 2H), 7,18 (td, 1H), 7,24 - 7,28 (m, 1H), 7,28 - 7,33 (m, 2H), 7,35 - 7,40 (m, 1H), 7,49 (ddd, 1H), 7,83 (d, 1H), 8,45 (d, 1H), 8,62 (s, 1H), 8,68 (d, 2H), 8,76 (d, 2H), 10,69 (s, 1H), 14,79 (s ancho, 1H). LC-MS: tiempo de retención: 0,87 min MS ES+: 487,45 [M+H]+

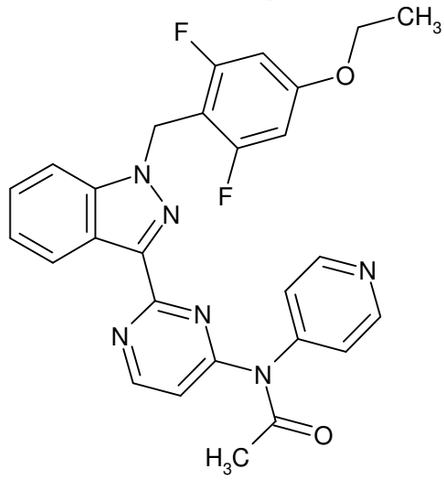
15-3 SM = 13-1		clorhidrato de 2-({2-[1-(4-etoxi-2,6-difluorobencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)etanol (1:1)	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 1,25 (t, 3H), 3,81 (d, 2H), 4,01 (q, 2H), 4,26 (t, 2H), 5,09 (s ancho, 1H), 5,66 (s, 2H), 6,73 - 6,81 (m, 2H), 7,25 (t, 1H), 7,47 (t, 1H), 7,82 (d, 1H), 8,33 - 8,44 (m, 3H), 8,45 - 8,54 (m, 3H), 9,74 (s ancho, 1H). LC-MS: tiempo de retención: 1,04 min MS ES$^+$: 519,1 $[M+H]^+$ Método B
15-4 SM = 2-9-1		clorhidrato de 2-[1-(2,6-diclorobencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina (1:1)	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 4,01 (s, 3H), 5,88 (s, 2H), 7,26 (t, 1H), 7,39 - 7,53 (m, 2H), 7,56 - 7,62 (m, 2H), 7,91 (d, 1H), 8,27 (d, 2H), 8,37 - 8,43 (m, 3H), 8,47 (d, 1H), 9,69 (s, 1H). LC-MS: tiempo de retención:

			1,05 min MS ES+: 476,9 [M+H]+
15-5 SM = 8-1		clorhidrato de [2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)fenil]metanol (1:1)	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]= 3,96 - 4,02 (m, 3H), 4,52 (s, 2H), 5,47 - 5,55 (m, 1H), 5,89 (s, 2H), 7,25 (t, 1H), 7,48 (t, 1H), 7,55 - 7,66 (m, 2H), 7,90 (d, 1H), 8,09 - 8,15 (m, 2H), 8,31 (s, 1H), 8,34 - 8,39 (m, 2H), 8,48 (d, 1H), 9,32 (s, 1H). LC-MS: tiempo de retención: 0,99 min MS ES+: 507,0 [M+H]+ Método B
15-6 SM = 12-3		clorhidrato de (2*R*)-3-({2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimid	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm]= 3,43 - 3,54 (m, 2H), 3,90 - 3,98 (m, 1H), 4,14 (dd, 1H), 4,34 (dd, 1H), 5,82 (s, 2H), 7,11 - 7,18 (m, 1H), 7,19 - 7,38 (m, 4H), 7,46

		in-5-il}oxi)propan-1,2-diol (1:1)	(ddd, 1H), 7,80 (d, 1H), 8,41 (d, 1H), 8,58 (s, 1H), 8,65 (d, 2H), 8,74 (d, 2H), 10,72 (s, 1H). LC-MS: tiempo de retención: 0,86 min MS ES+: 487,34 [M+H]+

Ejemplo 16-1

Preparación de *N*-{2-[1-(4-etoxi-2,6-difluorobencil)-1*H*-indazol-3-il]pirimidin-4-il}-*N*-(piridin-4-il)acetamida



Se disolvió 100 mg de 2-[1-(4-etoxi-2,6-difluorobencil)-1*H*-indazol-3-il]-*N*-(piridin-4-il)pirimidin-4-amina (5-1-1, 0,218 mmol, 1. eq.) en 2 ml de diclorometano seco. Se agregaron 94 µl de *N,N*-dietiletanamina seca (0,676 mmol, 3,1 eq.) y luego 23 µl de cloruro de acetilo (0,327 mmol, 1,5 eq,) bajo una atmósfera de nitrógeno. La mezcla de

reacción se agitó a temperatura ambiente durante 18 horas. Luego la mezcla se particionó entre agua y diclorometano. Las fases se separaron y la capa acuosa se extrajo dos veces con diclorometano. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre un filtro de silicona y se concentró al vacío. El residuo se purificó mediante cromatografía flash y TLC preparativa para dar 29,8 mg (0,06 mmol, 26,8%) del compuesto buscado analíticamente puro.

^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 1,25 (t, 3H), 2,08 (s, 3H), 4,00 (q, 2H), 5,61 (s, 2H), 6,63 - 6,75 (m, 2H), 6,85 - 6,93 (m, 1H), 7,09 (d, 1H), 7,36 (ddd, 1H), 7,52 - 7,57 (m, 2H), 7,70 (d, 1H), 7,93 (d, 1H), 8,73 - 8,83 (m, 3H).

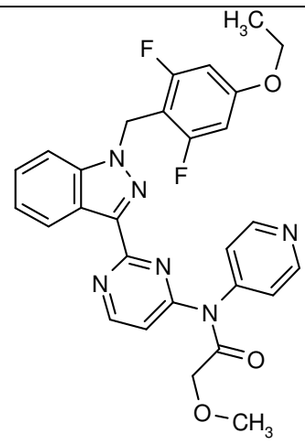
LC-MS:

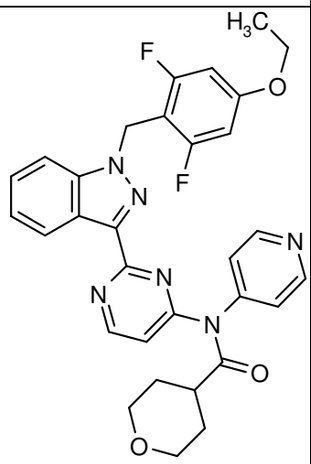
tiempo de retención: 1,21 min

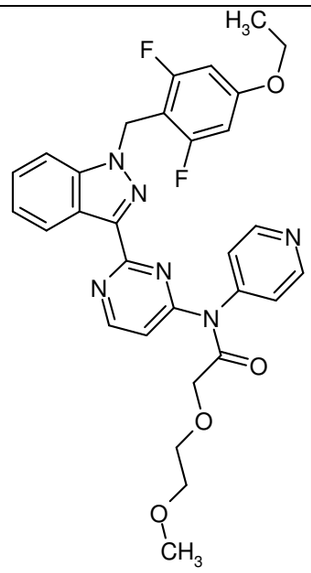
MS ES$^+$: 501,1 $[M+H]^+$

Método B

Los siguientes compuestos se prepararon de acuerdo con el mismo procedimiento usando los materiales de partida indicados (SM = material de partida):

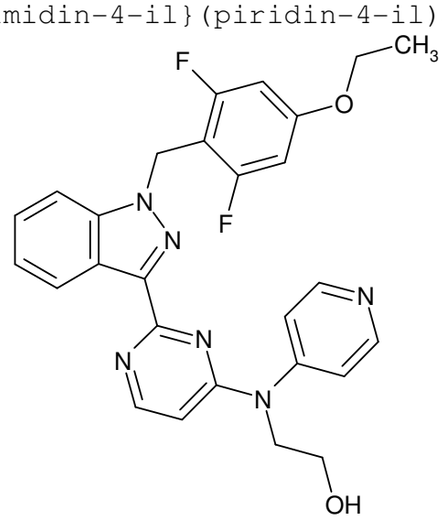
16-2 SM = 5-1-1		*N*-{2-[1-(4-etoxi-2,6-difluorobencil)-1*H*-indazol-3-il]pirimidin-4-il}-2-metoxi-*N*-	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 1,25 (s, 3H), 3,94 - 4,05 (m, 2H), 4,11 (s, 3H), 5,62 (s, 2H), 5,72 (s, 2H), 6,71 (d, 2H), 6,90 - 7,00 (m, 1H), 7,28 (d, 1H), 7,38 (t,

		(piridin-4-il)acetamida	1H), 7,52 - 7,58 (m, 2H), 7,70 - 7,77 (m, 2H), 8,72 - 8,84 (m, 3H). LC-MS: tiempo de retención: 1,22 min MS ES+: 531,1 $[M+H]^+$ Método B
16-3 SM = 5-1-1		*N*-{2-[1-(4-etoxi-2,6-difluorobencil)-1*H*-indazol-3-il]pirimidin-4-il}-*N*-(piridin-4-il)tetrahidro-2*H*-piran-4-carboxamida	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 1,25 (t, 3H), 1,59 - 1,83 (m, 4H), 2,71 - 2,84 (m, 1H), 3,00 - 3,13 (m, 2H), 3,76 (d, 2H), 3,95 - 4,04 (m, 2H), 5,62 (s, 2H), 6,67 - 6,75 (m, 2H), 6,99 (t, 1H), 7,36 - 7,44 (m, 2H), 7,49 - 7,53 (m, 2H), 7,62 (d, 1H), 7,74 (d, 1H), 8,71 - 8,76 (m, 2H), 8,80 (d, 1H). LC-MS:

			tiempo de retención: 1,25 min MS ES+: 571,2 [M+H]+ Método B
16-4 SM = 5-1-1		*N*-{2-[1-(4-etoxi-2,6-difluorobencil)-1*H*-indazol-3-il]pirimidin-4-il}-2-(2-metoxietoxi)-*N*-(piridin-4-il)acetamida	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 1,18 - 1,31 (m, 3H), 3,12 - 3,16 (m, 3H), 3,34 (dd, 2H), 3,51 (dd, 2H), 4,00 (d, 2H), 4,19 (s, 2H), 5,62 (s, 2H), 6,71 (d, 2H), 6,95 (t, 1H), 7,28 (d, 1H), 7,34 - 7,42 (m, 1H), 7,51 - 7,56 (m, 2H), 7,69 - 7,77 (m, 2H), 8,74 - 8,77 (m, 2H), 8,80 (d, 1H). LC-MS: tiempo de retención: 1,22 min MS ES+: 575,2 [M+H]+ Método B

Ejemplo 17-1

Preparación de 2-[{2-[1-(4-etoxi-2,6-difluorobencil)-1*H*-indazol-3-il]pirimidin-4-il}(piridin-4-il)amino]etanol



Se suspendieron 120 mg de 2-[1-(4-etoxi-2,6-difluorobencil)-1*H*-indazol-3-il]-*N*-(piridin-4-il)pirimidin-4-amina (5-1-1, 0,262 mmol, 1. eq.) en 12 ml de DMF seco. Se agregaron 426 mg de carbonato de cesio (1,31 mmol, 5 eq.) y 142 mg de 2-óxido de 1,3,2-dioxatiolano (1,31 mmol, 5 eq.) bajo una atmósfera de nitrógeno. La mezcla de reacción se agitó a 60 °C de temperatura de baño durante 18 horas. Se agregaron 142 mg de 2-óxido de 1,3,2-dioxatiolano (1,31 mmol, 5 eq.) y la mezcla se agitó a 60 °C de temperatura de baño durante otras 22 horas. Luego la mezcla se particionó entre agua y diclorometano/ isopropanol 4:1. Las fases se separaron y la capa acuosa se extrajo dos veces con diclorometano/ isopropanol 4:1. Las capas orgánicas combinadas se secaron sobre sulfato de magnesio y se concentró al vacío. El residuo se purificó mediante cromatografía flash y TLC preparativa para dar 14,2 mg (0,03 mmol, 10,5%) del compuesto buscado analíticamente puro.

^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 1,26 (t, 3H), 3,64 - 3,76 (m, 2H), 4,01 (q, 2H), 4,11 (t, 2H), 4,91 (t, 1H), 5,64 (s, 2H), 6,66 - 6,80 (m, 3H), 7,13 (t, 1H), 7,42 (t, 1H), 7,47 - 7,53 (m, 2H), 7,75 (d, 1H), 8,16 (d, 1H), 8,37 (d, 1H), 8,54 - 8,62 (m, 2H).

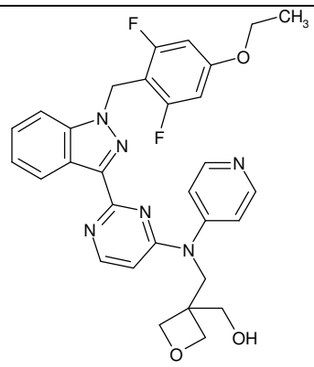
LC-MS:

tiempo de retención: 0,96 min

MS ES$^+$: 503,1 $[M+H]^+$

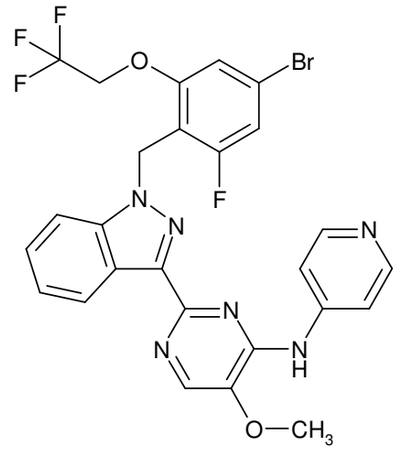
Método B

Los siguientes compuestos se prepararon de acuerdo con el mismo procedimiento usando los materiales de partida indicados (SM = material de partida):

17-2 SM = 5-1-1		(3-{[{2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]pirimidin-4-il}(piridin-4-il)amino]metil}oxetan-3-il)metanol	^{1}H-RMN (500MHz, DMSO-d6): δ [ppm]= 1,29 (t, 3H), 3,65 (d, 2H), 4,03 (q, 2H), 4,35 (d, 2H), 4,57 (d, 2H), 4,83 (s, 2H), 5,39 (t, 1H), 5,75 (s, 2H), 6,79 - 6,86 (m, 2H), 7,08 (d, 1H), 7,33 (t, 1H), 7,54 (ddd, 1H), 7,90 (d, 1H), 8,38 - 8,55 (m, 3H), 8,63 (d, 2H), 8,81 (d, 1H), 11,45 (s ancho, 1H).

Ejemplo 18-1

Preparación de 2-{1-[4-bromo-2-fluoro-6-(2,2,2-trifluoroetoxi)bencil]-1*H*-indazol-3-il}-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina



Se disolvieron 38,2 mg de 2,2,2-trifluoroetanol (0,382 mmol, 2 eq.) en 1,5 ml de DMF seco bajo una atmósfera de nitrógeno. Se agregaron 16,8 mg de hidruro de sodio 60% en aceite de parafina (0,42 mmol, 2,2 eq.). La suspensión se agitó a temperatura ambiente durante 15 minutos. Se agregaron 100 mg de 2-[1-(4-bromo-2,6-difluorobencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina (2-12-1, 0,191 mmol, 1 eq.). La mezcla de reacción se agitó a temperatura ambiente durante 18 horas. Se agregó agua por goteo. La suspensión se retiró por filtración. El precipitado se secó a 50 °C bajo vacío. El precipitado se purificó mediante HPLC preparativa para dar 34 mg (0,05 mmol, 28%) del compuesto buscado analíticamente puro.

^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 4,00 (s, 3H), 4,82 (q, 2H), 5,60 (s, 2H), 7,22 (t, 1H), 7,30 (s, 1H), 7,39 – 7,46 (m, 1H), 7,74 (d, 1H), 8,10 – 8,16 (m, 3H), 8,32 (s, 1H),

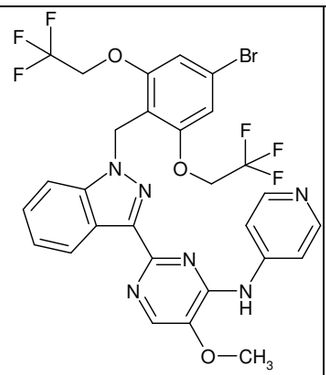
8,35 – 8,39 (m, 2H), 8,42 (d, 1H), 9,38 (s, 1H).

LC-MS:

tiempo de retención: 1,05 min

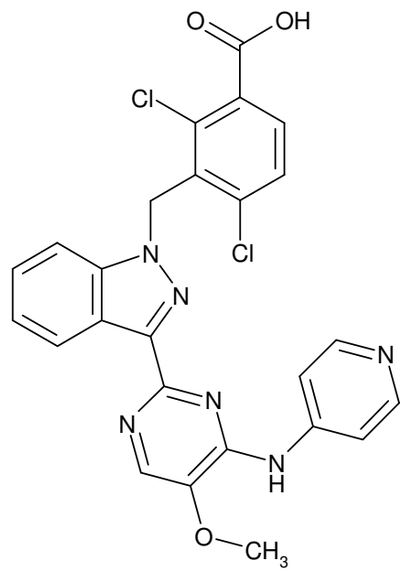
MS ES$^+$: 605,0 [M+H]$^+$

Se obtuvo el siguiente compuesto como segundo producto:

18-2 SM = 2-12-1		2-{1-[4-bromo-2,6-bis(2,2,2-trifluoroetoxi)bencil]-1*H*-indazol-3-il}-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 4,00 (s, 3H), 4,82 (q, 4H), 5,55 (s, 2H), 7,16 - 7,22 (t, 1H), 7,26 (s, 2H), 7,38 (ddd, 1H), 7,68 (d, 1H), 8,02 – 8,06 (m, 2H), 8,29 – 8,34 (m, 3H), 8,41 (d, 1H), 9,33 (s, 1H). LC-MS: tiempo de retención: 1,12 min MS ES$^+$: 685,0 [M+H]$^+$ Método B

Ejemplo 19-1

Preparación de ácido 2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzoico



Se disolvió 1 g de 2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzoato de metilo (2-16-1, 1,868 mmol, 1. eq.) en 19 ml de THF seco y 2,2 ml de metanol. Se agregaron 4,67 ml de solución acuosa de hidróxido de sodio 2 M (9,34 mmol, 5 eq.). La mezcla se agitó durante tres horas a temperatura ambiente. La mezcla de reacción se particionó entre ácido cítrico (pH 3) y acetato de etilo. Este proceso dio un precipitado blanco que se retiró por filtración y se secó durante tres días para dar 992 mg (1,86 mmol, 99,8%) del compuesto buscado analíticamente puro.

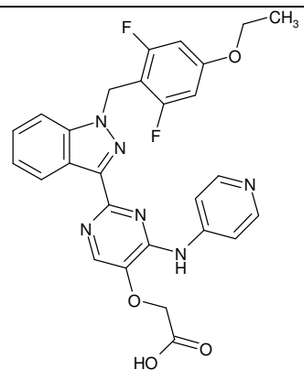
^{1}H-RMN (400MHz, DMSO-d6): δ [ppm]= 3,99 (s, 3H), 5,91 (s, 2H), 7,26 (t, 1H), 7,44 - 7,54 (m, 1H), 7,62 - 7,66 (m, 2H), 7,84 - 7,94 (m, 1H), 8,07 - 8,16 (m, 2H), 8,32 (s, 1H), 8,35 - 8,42 (m, 2H), 8,49 (d, 1H), 9,33 (s, 1H)

LC-MS:

tiempo de retención: 0,96 min

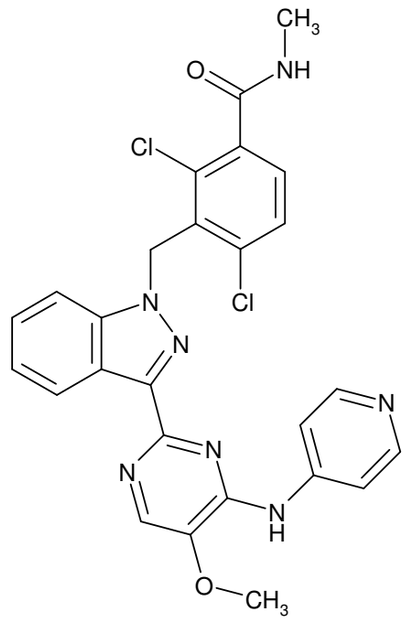
MS ES$^+$: 521,1 $[M+H]^+$

El siguiente compuesto se obtuvo de acuerdo con el mismo procedimiento usando el material de partida indicado (SM):

19-2 SM = 4-14		ácido ({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)acético	1H-RMN (300MHz, DMSO-d6): δ [ppm]= 1,24 (t, 3H), 4,00 (q, 2H), 5,04 (d, 2H), 5. 68 (s, 2H), 6. 78 (m, 2H), 7,26 (t, 1H), 7,48 (t, 1H), 7,83 (d, 1H), 8,39 (d, 1H), 8,51 (s, 1H), 8,53-8,63 (m, 4H), 10,58 (s, 1H), 14,33 (s ancho, 1H). LC-MS (Método 1): tiempo de retención: 1,03 min MS ES+: 481,4 [

Ejemplo 20-1

Preparación de 2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)-*N*-metilbenzamida



Se disolvieron 100 mg de ácido 2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)benzoico (19-1, 0,192 mmol, 1. eq.) en 0,953 ml de dimetilsulfóxido seco. Se agregaron 80,2 mg de hexafluorofosfato de *N*-[(dimetilamino)(3*H*-[1,2,3]triazolo[4,5-b]piridin-3-iloxi)metiliden]-*N*-metilmetanaminio (0,211 mmol, 1,1 eq.), 67 µl de *N*-etil-*N*-(propan-2-il)propan-2-amina (0,384 mmol, 2 eq.) y 96 µl de 2 N metilamina en tetrahidrofurano en ese orden. La mezcla de reacción se agitó a temperatura ambiente durante 18 horas. Se agregaron 80,2 mg de hexafluorofosfato de *N*-[(dimetilamino)(3*H*-[1,2,3]triazolo[4,5-b]piridin-3-iloxi)metiliden]-*N*-metilmetanaminio (0,211 mmol, 1,1 eq.), 67 µl de *N*-etil-*N*-(propan-2-il)propan-2-amina (0,384 mmol, 2 eq.) y 96 µl de metilamina 2 N en tetrahidrofurano en ese orden nuevamente dos veces y se agitó cada vez a temperatura ambiente durante 24 horas. La mezcla de reacción se agitó a 50 °C de temperatura de baño durante otras 2 horas. Luego la mezcla se retiró por filtración

purificando mediante HPLC preparativa para dar 15 mg (0,03 mmol, 14,3%) del compuesto buscado analíticamente puro.

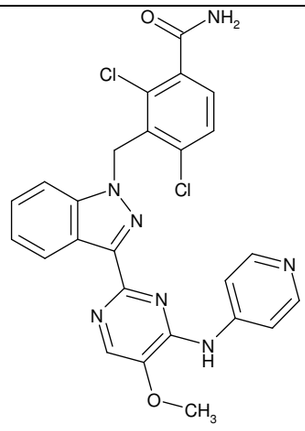
^{1}H-RMN (300MHz, DMSO-d6): δ [ppm]= 2,68 (d, 3H), 3,99 (s, 3H), 5,91 (s, 2H), 7,19 - 7,32 (m, 1H), 7,42 - 7,51 (m, 2H), 7,63 - 7,72 (m, 1H), 7,87 - 7,98 (m, 1H), 8,07 - 8,23 (m, 2H), 8,32 - 8,50 (m, 5H), 9,33 (s, 1H)

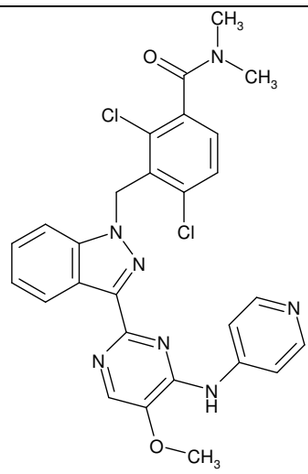
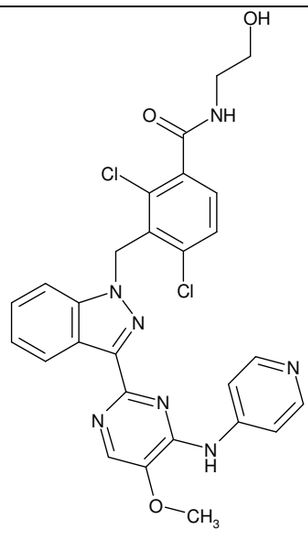
LC-MS:

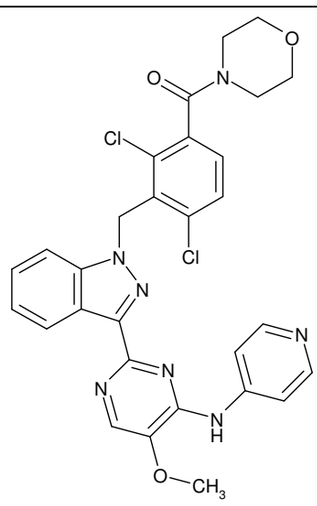
tiempo de retención: 0,92 min

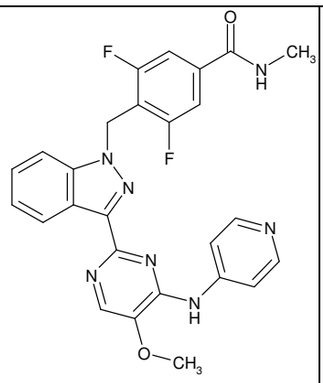
MS ES$^+$: 534,2 $[M+H]^+$

Los siguientes compuestos se obtuvieron de acuerdo con el mismo procedimiento usando los materiales de partida indicados (SM):

20-2 SM = 19-1		2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)benzamida	^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 4,00 (s, 3H), 5,91 (s, 2H), 7,19 - 7,33 (m, 1H), 7,39 - 7,54 (m, 2H), 7,56 - 7,63 (m, 1H), 7,63 - 7,71 (m, 1H), 7,85 - 7,97 (m, 2H), 8,06 - 8,22 (m, 2H), 8,32 (s, 4H), 9,23 - 9,42 (m, 1H) LC-MS: tiempo de retención: 0,91 min MS ES$^+$: 520,1 $[M+H]^+$

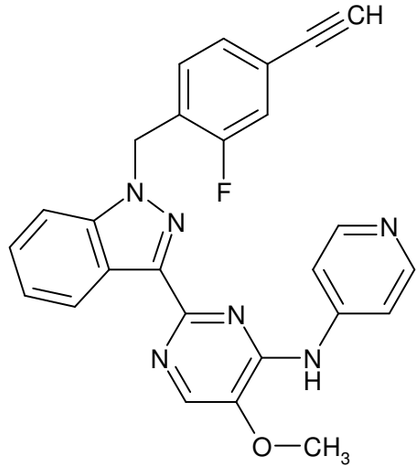
20-3 SM = 19-1		2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)-*N*,*N*-dimetilbenzamida	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 2,64 (s, 3H), 2,92 (s, 3H), 3,99 (s, 3H), 5,77 - 6,01 (m, 2H), 7,25 (t, 1H), 7,40 (d, 1H), 7,44 - 7,53 (m, 1H), 7,68 (d, 1H), 7,84 - 7,96 (m, 1H), 8,06 - 8,18 (m, 2H), 8,26 - 8,41 (m, 3H), 8,49 (d, 1H), 9,31 (s, 1H) LC-MS: tiempo de retención: 0,98min MS ES$^+$: 548,2 $[M+H]^+$
20-4 SM = 19-1		2,4-dicloro-*N*-(2-hidroxietil)-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)benzamida	^{1}H-RMN (400MHz, Cloroformo-d): δ [ppm]= 3,62 - 3,73 (m, 2H), 3,81 - 3,91 (m, 2H), 4,03 (s, 3H), 5,90 (s, 2H), 6,69 - 6,81 (m, 1H), 7,31 (t, 1H), 7,37 - 7,45 (m, 2H), 7,45 - 7,56 (m, 2H), 7,66 (d, 1H), 7,97 (d,

			2H), 8,18 (s, 1H), 8,48 (d, 2H), 8,64 (d, 1H) LC-MS: tiempo de retención: 0,89 min MS ES+: 564,2 [M+H]+
20-5 SM = 19-1		[2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)fenil](morfolin-4-il)metanona	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 2,99 - 3,11 (m, 2H), 3,37 - 3,45 (m, 2H), 3,56 - 3,64 (m, 4H), 4,03 (s, 3H), 5,91 (s, 2H), 7,28 (t, 1H), 7,45 (d, 1H), 7,47 - 7,55 (m, 1H), 7,69 (d, 1H), 7,92 (d, 1H), 8,36 - 8,44 (m, 2H), 8,46 - 8,50 (m, 4H), 10,08 (s ancho, 1H) LC-MS: tiempo de retención: 0,95 min MS ES+: 590,1 [M+H]+

20-6 SM = 19-1		3,5-difluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)-*N*-metilbenzamida	^{1}H-RMN (300MHz, METANOL-d_4): δ [ppm]= 2,91 (s, 3H), 4,13 (s, 3H), 5,77 - 5,82 (m, 2H), 7,20 - 7,28 (m, 1H), 7,44 (td, 1H), 7,60 (d, 3H), 8,47 (d, 1H), 8,56 (s, 1H), 8,59 - 8,67 (m, 4H). LC-MS: tiempo de retención: 0,80 min MS ES$^+$: 502,1 $[M+H]^+$

Ejemplo 21-1

Preparación de 2-[1-(4-etinil-2-fluorobencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina



Paso 1: 2-(1-{2-fluoro-4-[(trimetilsilil)etinil]bencil}-1*H*-indazol-3-il)-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina

Se suspendieron 144,7 mg de 2-[1-(2-fluoro-4-iodobencil)-

1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina (2-201, 0,262 mmol, 1 eq.), 6,02 mg de (1*E*,4*E*)-1,5-difenilpenta-1,4-dien-3-ona – paladio (2:1) (0,01 mmol, 0,04 eq.), 2,0 mg de ioduro de cobre (I) (0,01 mmol, 0,04 eq.), y 13,7 mg de trifenilfosfano (0,052 mmol, 0,2 mmol) en 2,6 ml de *N,N*-dietiletanamina seca y se purgó con nitrógeno. Luego se agregaron 3,86 ml de etinil(trimetil)silano (1,57 mmol, 6 eq.) y la mezcla de reacción se agitó a 60 °C durante 18 horas. La mezcla se concentró bajo vacío. El producto crudo se usó sin purificación adicional en paso 2.

LC-MS:

tiempo de retención: 1,14 min

MS ES$^+$: 523,4 $[M+H]^+$

Método B

Paso 2: 2-[1-(4-etinil-2-fluorobencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina

Se disolvieron 37,3 mg de 2-(1-{2-fluoro-4-[(trimetilsilil)etinil]bencil}-1*H*-indazol-3-il)-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina (0,071 mmol, 1. eq.) en 1,0 ml de tetrahidrofurano seco. Se agregaron 71 µl de una solución de fluoruro de *N,N,N*-tributilbutan-1-amonio en tetrahidrofurano 1 M (0,071 mmol, 1 eq.) bajo una atmósfera de nitrógeno y se agitó a temperatura ambiente durante 18 horas. Luego la mezcla se particionó entre una solución acuosa parcialmente saturada de carbonato ácido de sodio y diclorometano/ isopropanol 4:1. Las fases se separaron y la capa acuosa se extrajo dos veces con diclorometano/ isopropanol 4:1. Las capas orgánicas combinadas se secaron

sobre sulfato de magnesio y se concentró al vacío. El residuo se purificó mediante TLC preparativa en acetato de etilo/ metanol 7:3 para dar 23,2 mg (0,05 mmol, 68,4%) del compuesto buscado analíticamente puro.

^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 4,01 (s, 3H), 4,28 (s, 1H), 5,79 (s, 2H), 7,20 – 7,31 (m, 3H), 7,34 – 7,48 (m, 2H), 7,80 (d, 1H), 8,07 – 8,13 (m, 2H), 8,33 (s, 1H), 8,35 – 8,40 (m, 2H), 8,44 (d, 1H), 9,41 (s, 1H).

LC-MS:

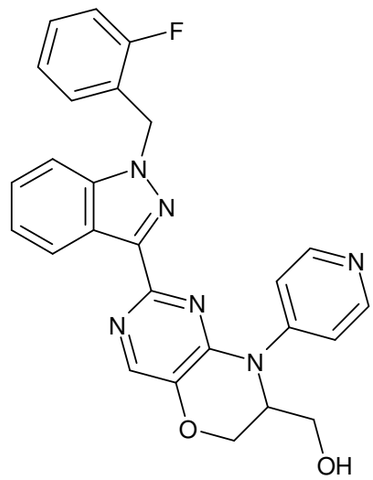
tiempo de retención: 0,91 min

MS ES$^+$: 451,4 $[M+H]^+$

Método B

Ejemplo 22-1

Preparación de {2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-8-(piridin-4-il)-7,8-dihidro-6*H*-pirimido[5,4-b][1,4]oxazin-7-il}metanol



Se suspendieron 25 mg de 2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ol (3-3, 0,061 mmol, 1. eq.), 28,2 mg de 3-bromopropan-1,2-diol (0,182 mmol, 3 eq.) y 41,9 mg de carbonato de potasio (0,303 mmol, 5 eq.) en 470 µl de DMF seco bajo una atmósfera de nitrógeno. La

mezcla de reacción se agitó a 100 °C de temperatura de baño durante 18 horas. Luego la mezcla se particionó entre solución acuosa parcialmente saturada de cloruro de sodio y acetato de etilo. Las fases se separaron y la capa acuosa se extrajo una vez con acetato de etilo y una vez con diclorometano/ isopropanol 4:1. Las capas orgánicas combinadas se secaron sobre sulfato de magnesio y se concentró al vacío. El residuo se purificó mediante TLC preparativa en diclorometano/ metanol 9:1 para dar 6,26 mg (0,01 mmol, 19,8%) del compuesto buscado analíticamente puro.

^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 3,53 – 3,67 (m, 2H), 4,14 – 4,23 (m, 1H), 4,25 – 4,32 (m, 1H), 4,53 – 4,61 (m, 1H), 5,26 – 5,33 (m, 1H), 5,73 (s, 2H), 7,01 – 7,24 (m, 4H), 7,27 – 7,42 (m, 2H), 7,68 – 7,78 (m, 3H), 8,13 (d, 1H), 8,26 (s, 1H), 8,50 – 8,57 (m, 2H).

LC-MS:

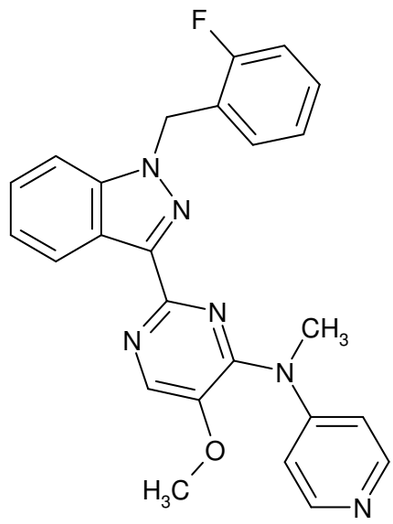
tiempo de retención: 0,89 min

MS ES$^+$: 469,0 $[M+H]^+$

Método B

Ejemplo 23-1

Preparación de 2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-5-metoxi-*N*-metil-*N*-(piridin-4-il)pirimidin-4-amina



Se disolvieron 135 mg de 2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-5-metoxi-*N*-(piridin-4-il)pirimidin-4-amina (2-18-1, 0,316 mmol, 1. eq.) en 3 ml de 1-metilpirrolidin-2-ona y se agregaron 514 mg de carbonato de cesio (1,58 mmol, 5 eq.). La mezcla de reacción se agitó a 190 °C de temperatura de baño durante 18 horas. Luego de enfriar a temperatura ambiente la mezcla se particionó entre agua y butan-2-ona. Las fases se separaron y la capa acuosa se extrajo dos veces con butan-2-ona. Las capas orgánicas combinadas se lavaron con salmuera y se secó sobre sulfato de magnesio y se concentró al vacío. El residuo se purificó mediante cromatografía flash y TLC preparativa para dar 10,9 mg (0,02 mmol, 7,2%) del compuesto buscado analíticamente puro.

^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 3,77 (s, 3H), 3,89 (s, 3H), 5,80 (s, 2H), 7,15 - 7,19 (m, 3H), 7,21 - 7,29 (m, 3H), 7,34 - 7,41 (m, 2H), 7,44 (ddd, 1H), 7,75 (d, 1H), 7,79 (s ancho, 1H), 8,23 (s, 1H), 8,50 (d, 1H).

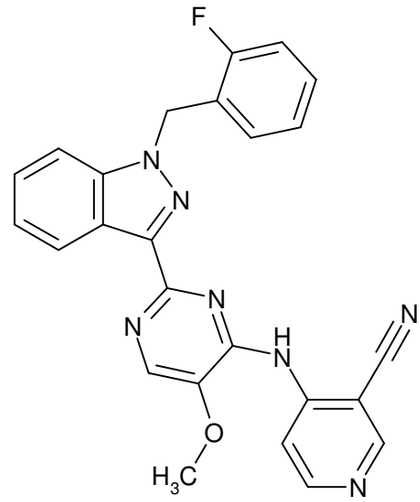
LC-MS:

tiempo de retención: 1,02 min

MS ES$^+$: 441,53 $[M+H]^+$

Ejemplo 24-1

Preparación de 4-({2-[1-(2-fluorobencil)-*1H*-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-carbonitrilo



Se agitaron 175 mg de 2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-amina (1-11-1, 0,501 mmol, 1. eq.), 101 mg de 4-bromopiridin-3-carbonitrilo (0,551 mmol, 1,1 eq.), 115 mg de Tris(dibencilidenacetona)dipaladio (0) (0,125 mmol, 0,25 eq.), 156 mg de 1,1'-binaftalen-2,2'-diilbis(difenilfosfano) (0,25 mmol, 0,5 eq), 144 mg de sodio de 2-metilpropan-2-olato (97%) (1,503 mmol, 3 eq.) y 52 ml de N,N-dimetilformamida bajo una atmósfera de nitrógeno durante 30 minutos a 100 °C y 300 W en un microondas CEM. La mezcla de reacción se lavó con solución acuosa parcialmente saturada de cloruro de sodio. La capa orgánica se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera y se secó sobre sulfato de sodio y se concentró al vacío. El residuo se purificó mediante cromatografía flash (hexano/ diclorometano/ metanol) y HPLC preparativa. La cristalización desde diclorometano/metanol dio 5,8 mg (0,01

mmol, 2,6%) del compuesto buscado analíticamente puro.

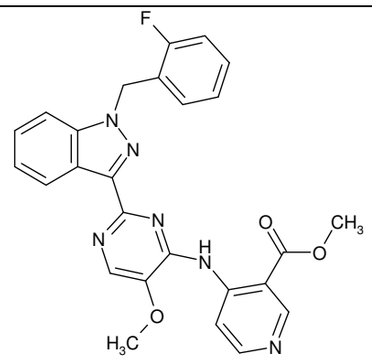
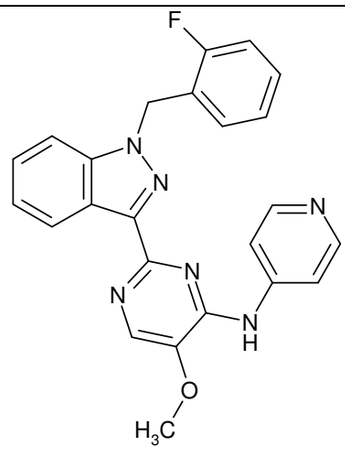
^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 4,04 (s, 3H), 5,76 (s, 2H), 7,08 – 7,26 (m, 4H), 7,28 – 7,46 (m, 2H), 7,75 (d, 1H), 8,20 – 8,31 (m, 2H), 8,45 (s, 1H), 8,68 (d, 1H), 8,88 (s, 1H), 9,23 (s, 1H).

LC-MS:

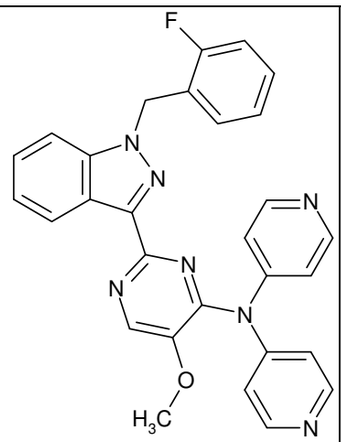
tiempo de retención: 1,28 min

MS ES$^+$: 452,33 $[M+H]^+$

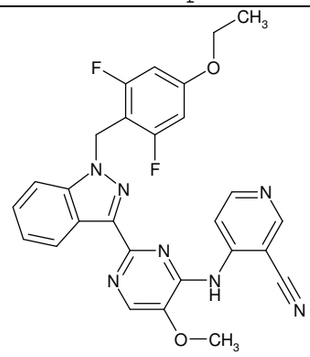
Los siguientes compuestos se prepararon de acuerdo con el mismo procedimiento usando los materiales de partida indicados (SM = material de partida), y las halopiridinas respectivas:

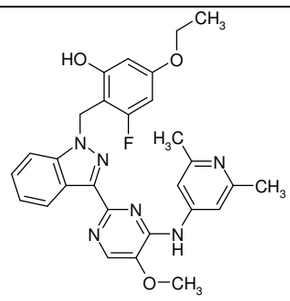
24-2 SM = 1-4-2		4-({2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-carboxilato de metilo	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 4,05 (s, 3H), 4,11 (s, 3H), 5,80 - 5,85 (m, 2H), 7,10 - 7,40 (m, 6H), 7,49 - 7,59 (m, 2H), 7,86 (d, 1H), 8,06 (d, 1H), 8,39 (dd, 1H), 8,95 - 9,06 (m, 2H). LC-MS: tiempo de retención: 0,91 min MS ES$^+$: 485,11 $[M+H]^+$
24-3 SM = 1-4-2		2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina	1H-RMN (300MHz, DMSO-d6): δ [ppm]= 4,01 (s, 3H), 5,77 (s, 2H), 7,10 - 7,49 (m, 6H), 7,75 - 7,84 (m, 1H), 8,07 - 8,17 (m, 2H), 8,33 (s, 1H), 8,35 - 8,40 (m, 2H), 8,40 - 8,48 (m, 1H), 9,35 - 9,45 (m, 1H). LC-MS: tiempo de retención: 1,01 min MS ES$^+$: 427,19 $[M+H]^+$ Método B

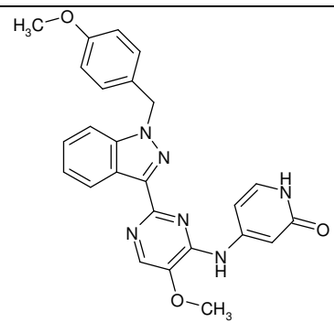
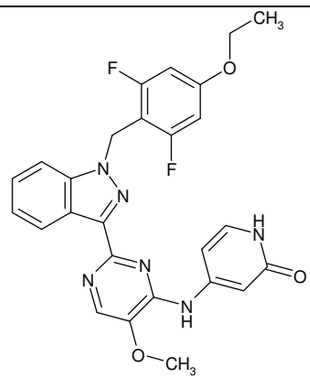
El siguiente compuesto también se formó durante la reacción que provee 24-3:

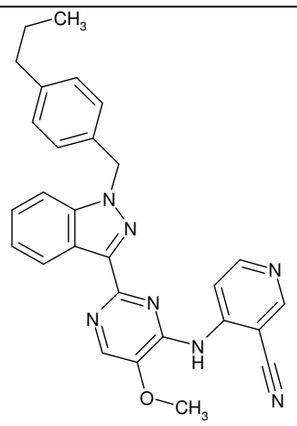
24-4 SM = 1-4-2		2-[1-(2-fluorobencil)-*1H*-indazol-3-il]-5-metoxi-*N*,*N*-di(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 3,74 (s, 3H), 5,75 (s, 2H), 6,92 (t, 1H), 6,99 - 7,12 (m, 6H), 7,13 - 7,23 (m, 1H), 7,26 - 7,38 (m, 2H), 7,65 (dd, 2H), 8,41 - 8,50 (m, 4H), 8,71 (s, 1H). LC-MS: tiempo de retención: 0,90 min MS ES$^+$: 504,57 $[M+H]^+$

Los siguientes compuestos se prepararon de acuerdo con el mismo procedimiento usando los materiales de partida indicados (SM = material de partida), y las halopiridinas / halopiridonas respectivas:

24-5 SM = 1-4-3		4-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridi	1H-RMN (500MHz, DMSO-d6): δ [ppm]= 1,30 (t, 3H), 4,05 (q, 2H), 4,07 (s, 3H), 5. 67 (s, 2H), 6. 80 (m, 2H), 7,22 (t, 1H), 7,48 (t, 1H), 7,83 (d, 1H),

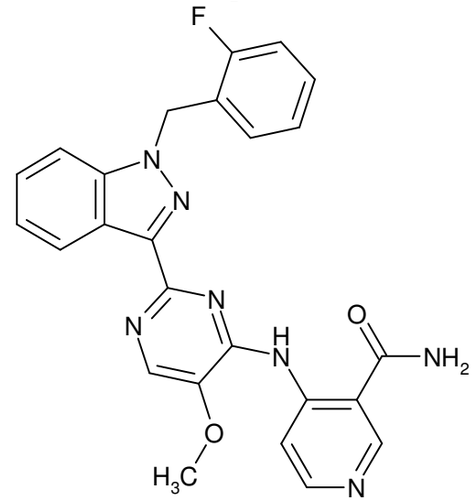
		n-3-carbonitrilo	8,32 (d, 1H), 8,45 (s ancho, 1H), 8,68 (s ancho, 1H), 8,90 (s ancho, 1H), 9,15 (s ancho, 1H). Falta un H LC-MS (Método 5): tiempo de retención: 1,43 min MS ES+: 514,2 [5
24-6 SM = 1-4-3		2-[(3-{4-[(2,6-dimetilpiridin-4-il)amino]-5-metoxipirimidin-2-il}-1H-indazol-1-il)metil]-5-etoxi-3-fluorofenol	1H-RMN (400MHz, DMSO-d6): δ [ppm]= 1,24 (t, 3H), 2,36 (s, 6H), 3,90 (q, 2H), 3,99 (s, 3H), 5. 54 (s, 2H), 6. 20 (s ancho, 1H), 6. 24 (br. d, 1H), 7,18 (t, 1H), 7,39 (t, 1H), 7,78 (s, 1H), 7,78 (d, 1H), 8,28 (s, 1H), 8,44 (d, 1H), , 9,09 (s, 1H), 10,26 (s ancho, 1H). LC-MS (Método 5): tiempo de retención: 0,68 min MS ES+: 515,2

24-7 SM = 1-4-1		4-({5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]pirimidin-4-il}amino)piridin-2(1H)-ona	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 3,65 (s, 3H), 4,00 (s, 3H), 5,62 (s, 2H), 6,79 - 6,87 (m, 3H), 7,13 - 7,27 (m, 2H), 7,27 - 7,45 (m, 4H), 7,76 (d, 1H), 8,33 (s, 1H), 8,42 (d, 1H), 9,06 (s, 1H), 11,03 (s ancho, 1H). LC-MS: tiempo de retención: 0,97 min MS ES$^+$: 455,2 $[M+H]^+$
24-8 SM = 1-4-3		4-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-2(1H)-ona	1H-RMN (300MHz, DMSO-d6): δ [ppm]= 1,25 (t, 3H), 3,98 (s, 3H), 4,00 (q, 2H), 5. 63 (s, 2H), 6. 72 (m, 2H), 6. 97 (s ancho, 1H), 7. 05 (br. d, 1H), 7,20 (m, 1H), 7,44 (t, 1H), 7,75 (m, 2H), 8,31 (s, 1H),

			8,41 (d, 1H), 9,06 (s, 1H), 11,02 (s ancho, 1H). LC–MS (Método 2): tiempo de retención: 0,94 min MS ES+: 505,0
24–9 SM = 1–4–4		4–({5–metoxi–2–[1–(4–propilbencil)–1H–indazol–3–il]pirimidin–4–il}amino)nicotinonitrilo	LC–MS: tiempo de retención: 1,51min MS ES+: 476,27 $[M+H]^+$

Ejemplo 25–1

Preparación de 4–({2–[1–(2–fluorobencil)–*1H*–indazol–3–il]–5–metoxipirimidin–4–il}amino)piridin–3–carboxamida



Se disolvieron 54 mg de 4–({2–[1–(2–fluorobencil)–1H–indazol–3–il]–5–metoxipirimidin–4–il}amino)piridin–3–carbonitrilo (24–1, 0,12 mmol, 1. eq.) en 1,6 ml de

dimetilsulfóxido bajo atmósfera de nitrógeno. Se agregaron 42 µl de solución acuosa de hidróxido de sodio 3 M (0,126 mmol, 1,05 eq.). La mezcla se calentó en baño de aceite a 63 °C de temperatura de baño. A esta temperatura se agregaron 302µl de peróxido de hidrógeno (30% en agua) (9,87 mmol, 82,2 eq.) por goteo. La mezcla de reacción se agitó a 65 °C de temperatura de baño durante 3 horas y a temperatura ambiente durante 24 horas. Luego de agitar la mezcla una hora con hielo-agua, se extrajo tres veces con diclorometano/ isopropanol 4:1. Las capas orgánicas combinadas se secaron sobre sulfato de magnesio y se concentró al vacío. El residuo se purificó mediante TLC preparativa (diclorometano/ metanol 9:1) para dar 12,0 mg (0,02 mmol, 20,5%) del compuesto buscado analíticamente puro.

^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 4,01 (s, 3H), 5,79 (s, 2H), 7,10 - 7,39 (m, 5H), 7,45 (t, 1H), 7,81 (d, 2H), 8,34 - 8,55 (m, 4H), 8,91 (s, 1H), 9,22 (d, 1H), 12,10 - 12,19 (m, 1H).

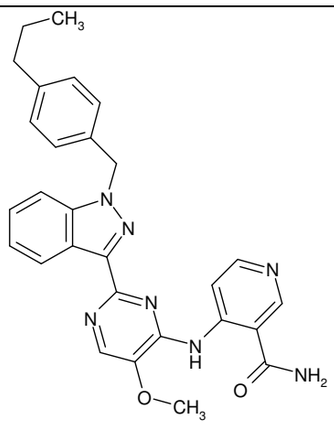
LC-MS:

tiempo de retención: 1,01 min

MS ES$^+$: 470,1 $[M+H]^+$

Método B

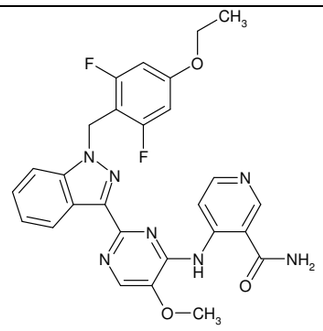
Los siguientes compuestos se obtuvieron de acuerdo con el mismo procedimiento usando los materiales de partida indicados (SM = material de partida):

25-2 SM = 24-9		4-({5-metoxi-2-[1-(4-propilbencil)-*1H*-indazol-3-il]pirimidin-4-il}amino)piridin-3-carboxamida	^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 0,81 (t, 3H), 1,43 - 1,55 (m, 2H), 2,44 - 2,56 (m, 2H), 4,02 (s, 3H), 5,70 (s, 2H), 7,12 (d, 2H), 7,21 - 7,29 (m, 3H), 7,41 (ddd, 1H), 7,78 (d, 1H), 7,86 (s ancho, 1H), 8,38 - 8,46 (m, 3H), 8,54 (d, 1H), 8,92 (s, 1H), 9,25 (d, 1H), 12,19 (s, 1H). LC-MS: tiempo de retención: 1,24 min MS ES$^+$: 494,3 $[M+H]^+$

El siguiente compuesto se preparó de acuerdo con el siguiente método alternativo:

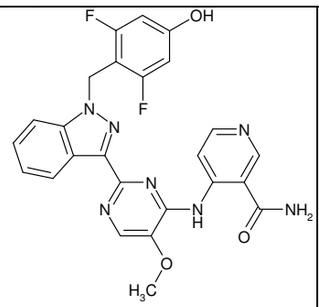
Se disolvieron 105 mg de 4-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-carbonitrilo (24-5, 0,204 mmol) en 311 µl de ácido sulfúrico concentrado (5,83 mmol) y se agitó a temperatura ambiente durante 18 horas. La mezcla se volcó

sobre agua helada y luego se agregó hidróxido de sodio 2M hasta alcanzar pH básico. La fase acuosa se extrajo 3 veces con CH_2Cl2/isopropanol 4:1, se secó sobre sulfato de magnesio, se retiró por filtración y se concentró al vacío. El residuo se purificó mediante TLC preparativa (diclorometano/ metanol 9:1) para dar 6,9 mg (0,01 mmol, 6,3%) del compuesto buscado analíticamente puro.

25-3 SM = 24-5		4-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-carboxamida	^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 1,26 (t, 3H), 3,94 - 4,08 (m, 5H), 5,65 (s, 2H), 6,77 (d, 2H), 7,19 - 7,32 (m, 1H), 7,40 - 7,53 (m, 1H), 7,74 - 7,87 (m, 2H), 8,29 - 8,55 (m, 4H), 8,92 (s, 1H), 9,20 - 9,30 (m, 1H), 12,17 (s, 1H). LC-MS: tiempo de retención: 1,13 min MS ES$^+$: 532,3 $[M+H]^+$

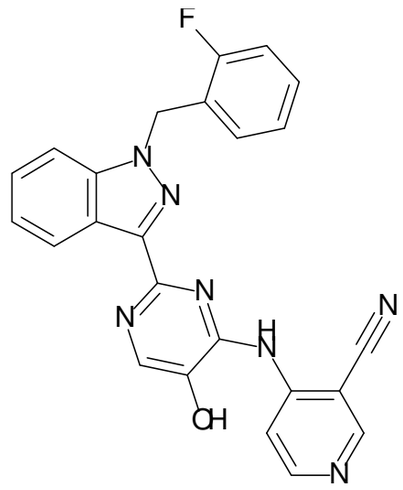
El siguiente compuesto también se formó durante la misma

reacción:

25-4 SM = 24-5		4-({2-[1-(2,6-difluoro-4-hidroxibencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-carboxamida	^{1}H-RMN (500MHz, DMSO-d_6): δ [ppm]= 4,05 (s, 3H), 5,66 (s, 2H), 6,54 (m, 2H), 7,30 (t, 1H), 7,51 (t, 1H), 7,85-7,88 (m, 2H), 8,42 (s, 1H), 8,46 (s ancho, 1H), 8,48 (s, 1H), 8,49 (s, 1H), 8,53 (d, 1H), 8,96 (s, 1H), 9,33 (d, 1H), 10,56 (s ancho, 1H). LC-MS (Método 5): tiempo de retención: 0,75 min MS ES$^+$: 504,2 $[M+H]^+$

Ejemplo 26-1

Preparación de 4-({2-[1-(2-fluorobencil)-*1H*-indazol-3-il]-5-hidroxipirimidin-4-il}amino)piridin-3-carbonitrilo



Se disolvieron 50 mg de 4-amino-2-[1-(2-fluorobencil)-1H-indazol-3-il]pirimidin-5-ol (1-11-1, 0,149 mmol, 1. eq.) en 3 ml de N,N-dimetilformamida. Se agregaron 103 mg de carbonato de potasio (0,746 mmol, 5 eq.) y 32,8 mg de 4-bromopiridin-3-carbonitrilo (0,179 mmol, 1,2 eq.). La mezcla de reacción se agitó a 100 °C de temperatura de baño durante 18 horas. Luego de enfriar a temperatura ambiente la mezcla se retiró por filtración y se lavó con diclorometano. El material filtrado se concentró al vacío. El residuo se purificó mediante HPLC preparativa y TLC preparativa para dar 4,21 mg (0,01 mmol, 6,1%) del compuesto buscado analíticamente puro.

^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 5,75 (s, 2H), 7,10 - 7,25 (m, 4H), 7,29 - 7,37 (m, 1H), 7,41 (ddd, 1H), 7,76 (d, 1H), 8,21 (s, 1H), 8,30 (d, 1H), 8,48 (d, 1H), 8,65 (d, 1H), 8,86 (s, 1H), 8,90 - 9,03 (m, 1H), 11,09 - 11,44 (m, 1H).

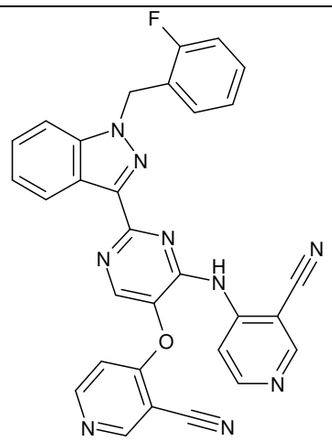
LC-MS:

tiempo de retención: 1,13 min

MS ES$^+$: 438,32 $[M+H]^+$

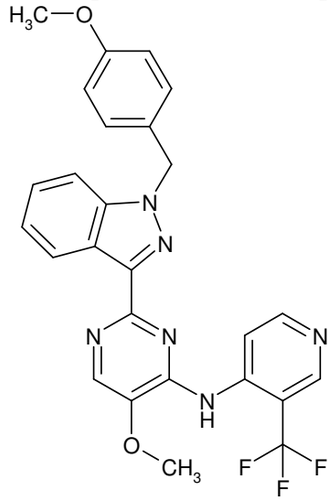
El siguiente compuesto se formó durante el mismo

procedimiento usando el material de partida indicado (SM = material de partida):

26-2 SM = 1-11-1		4-({4-[(3-cianopiridin-4-il)amino]-2-[1-(2-fluorobencil)-*1H*-indazol-3-il]pirimidin-5-il}oxi)piridin-3-carbonitrilo	LC-MS: tiempo de retención: 1,10 min MS ES$^+$: 540,30 $[M+H]^+$

Ejemplo 27-1

Preparación de 5-metoxi-2-[1-(4-metoxibencil)-*1H*-indazol-3-il]-N-[3-(trifluorometil)piridin-4-il]pirimidin-4-amina



Se agitaron 1 g de 5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]pirimidin-4-amina (1-4-1, 2,77 mmol, 1. eq.), 938 mg de 4-bromo-3-(trifluorometil)piridina (4,15 mmol, 1,5 eq.), 127 mg de Tris(dibencilidenacetona)dipaladio (0) (0,138 mmol, 0,05 eq.), 345 mg de 1,1'-binaftalen-2,2'-diilbis(difenilfosfano) (0,553 mmol, 0,2 eq), 1,06 g de 2-

metilpropan-2-olato de sodio (97%) (11,1 mmol, 4 eq.) y 15 ml de N,N-dimetilformamida bajo una atmósfera de nitrógeno durante 24 horas a 100 °C de temperatura de baño en un recipiente para presión. La mezcla de reacción se lavó con solución acuosa parcialmente saturada de cloruro de amonio. La capa orgánica se extrajo tres veces con diclorometano. Las capas orgánicas combinadas se lavaron con salmuera y se secó sobre sulfato de magnesio y se concentró al vacío. El residuo se purificó dos veces mediante cromatografía flash (hexano/ acetato de etilo/ metanol) y TLC preparativa. La cristalización dio 56,9 mg (0,1 mmol, 3,73%) del compuesto buscado analíticamente puro.

^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 3,66 (s, 3H), 4,05 (s, 3H), 5,65 (s, 2H), 6,81 - 6,89 (m, 2H), 7,17 (t, 1H), 7,28 (d, 2H), 7,34 - 7,42 (m, 1H), 7,76 (d, 1H), 8,18 - 8,28 (m, 2H), 8,45 (s, 1H), 8,76 - 8,89 (m, 3H).

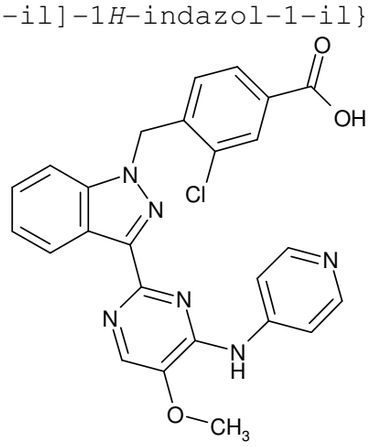
LC-MS:

tiempo de retención: 1,39 min

MS ES$^+$: 507,0 $[M+H]^+$

Ejemplo 28-1

Preparación de ácido 3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)benzoico



Se disolvieron 150 mg de 3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzoato de metilo (2-11-1, 0,299 mmol, 1. eq.) en 0,364 ml de metanol. Se agregaron 60 mg de hidróxido de sodio (1,50 mmol, 5 eq.). La mezcla de reacción se agitó a temperatura ambiente durante 3 horas. La suspensión resultante se neutralizó con ácido acético. La solución se diluyó con acetato de etilo. El precipitado obtenido se retiró por filtración y se lavó con acetato de etilo y se secó al vacío a 50 °C para dar 138 mg (0,28 mmol, 92,8%) del compuesto buscado analíticamente puro.

^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 4,01 (s, 3H), 5,88 (s, 2H), 7,20 (d, 1H), 7,26 (t, 1H), 7,45 (td, 1H), 7,76 – 7,85 (m, 2H), 7,95 (d, 1H), 8,07 – 8,11 (m, 2H), 8,32 – 8,37 (m, 3H), 8,48 (d, 1H), 9,39 (s, 1H).

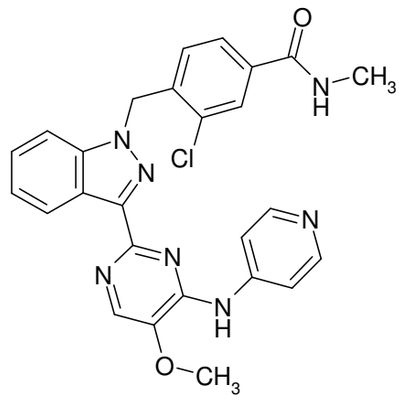
LC-MS:

tiempo de retención: 0,93 min

MS ES$^+$: 487,2 $[M+H]^+$

Ejemplo 29-1

Preparación de ácido fórmico – 3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1*H*-indazol-1-il}metil)-*N*-metilbenzamida (1:1)



x HCOOH

Se agitaron 130,9 mg de ácido 3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzoico (28-1, 0,269 mmol, 1. eq.), 1,1 ml de sulfóxido de dimetilo, 269 µl de metanamina en tetrahidrofurano 2 M (0,538 mmol, 2 eq.), 225 mg de hexafluorofosfato de N-[(dimetilamino)(3H-[1,2,3]triazolo[4,5-b]piridin-3-iloxi)metiliden]-N-metilmetanaminio (HATU; 0,591 mmol, 2,2 eq.) y 140 µl de N-etil-N-(propan-2-il)propan-2-amina (0,806 mmol, 3eq.) a 50 °C de temperatura de baño durante 5 horas. La mezcla de reacción se retiró por filtración y se purificó mediante HPLC preparativa para dar 91 mg (0,17 mmol, 62%) del compuesto buscado analíticamente puro.

^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 2,72 (d, 3H), 4,01 (s, 3H), 5,85 (s, 2H), 7,19 - 7,29 (m, 2H), 7,40 - 7,48 (m, 1H), 7,73 (dd, 1H), 7,79 (d, 1H), 7,92 (d, 1H), 8,06 - 8,13 (m, 3H), 8,31 - 8,39 (m, 3H), 8,44 - 8,54 (m, 2H), 9,39 (s, 1H).

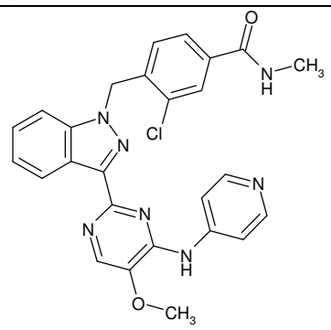
LC-MS:

tiempo de retención: 0,82 min

MS ES$^+$: 500,1 $[M+H]^+$

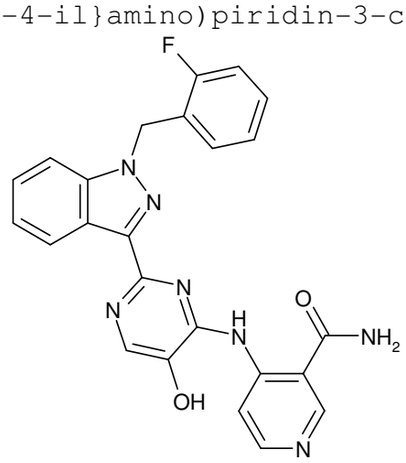
Método B

El compuesto se trató con base para formar el análogo base libre:

29-2 SM = 28-1		3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)-N-metilbenzamida	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 2,72 (d, 3H), 4,01 (s, 3H), 5,85 (s, 2H), 7,20 - 7,28 (m, 2H), 7,44 (td, 1H), 7,73 (dd, 1H), 7,79 (d, 1H), 7,92 (d, 1H), 8,10 (dd, 2H), 8,32 - 8,39 (m, 3H), 8,45 - 8,54 (m, 2H), 9,38 (s, 1H).

Ejemplo 30-1

Preparación de 4-({2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-5-hidroxipirimidin-4-il}amino)piridin-3-carboxamida



Se disolvieron 25 mg de 4-amino-2-[1-(2-fluorobencil)-1H-indazol-3-il]pirimidin-5-ol (1-11-1, 0,075 mmol, 1. eq.) en 1,5 ml de N,N-dimetilformamida. 51,52 mg de carbonato de potasio (0,373 mmol, 5 eq.) y se agregaron 23,35 mg de 4-cloropiridin-3-carboxamida (0,149 mmol, 2 eq.). La mezcla de reacción se agitó a 100 °C de temperatura de baño en un recipiente para presión durante 48 horas. La mezcla de reacción se retiró por filtración. El residuo se purificó mediante HPLC preparativa para dar 2,07 mg (0,004 mmol, 5,6%) del compuesto buscado analíticamente puro.

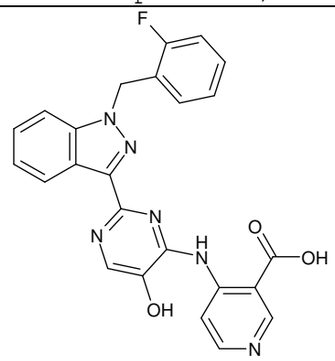
^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 5,77 (s, 2H), 7,11 - 7,37 (m, 5H), 7,40 - 7,48 (m, 1H), 7,74 - 7,83 (m, 2H), 8,18 (s, 1H), 8,38 (s ancho, 1H), 8,41 - 8,50 (m, 2H), 8,89 (s, 1H), 9,20 (d, 1H), 10,90 (s ancho, 1H), 11,94 (s, 1H).

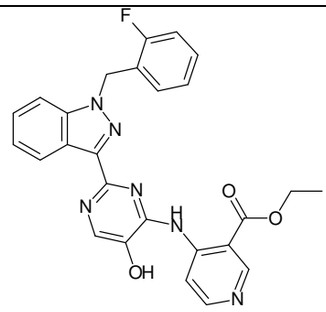
LC-MS:

tiempo de retención: 0,94 min

MS ES$^+$: 456,2 $[M+H]^+$

El siguiente compuesto se formó durante el mismo procedimiento usando el material de partida indicado (SM = material de partida):

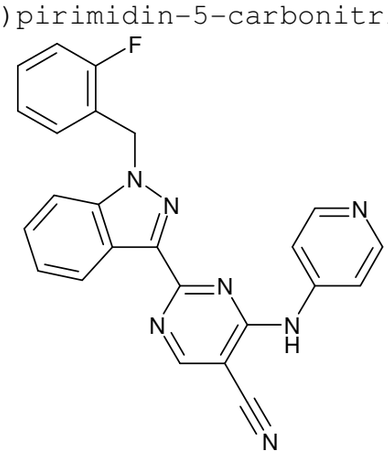
30-2 SM = 1-11-1		ácido 4-({2-[1-(2-fluorobencil)-*1H*-indazol-3-il]-5-hidroxipirimidin-4-il}amino)piridin-3-carboxílico	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 5,78 (s, 2H), 7,12 - 7,39 (m, 6H), 7,44 (t, 1H), 7,79 (d, 1H), 8,23 (s, 1H), 8,44 (d,

			1H), 8,50 (d, 1H), 8,98 (s, 1H), 9,33 (d, 1H), 11,02 (s ancho, 1H), 13,66 - 14,11 (s ancho, 1H). LC-MS: tiempo de retención: 0,95 min MS ES+: 456,9 [M+H]+ Método B
30-3 SM = 1-11-1		4-({2-[1-(2-fluorobencil)-*1H*-indazol-3-il]-5-hidroxipirimidin-4-il}amino)piridin-3-carboxilato de etilo	^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 1,36 (t, 3H), 4,35 (q, 2H), 5,68 (s, 2H), 7,07 - 7,38 (m, 7H), 7,47 (s, 1H), 7,63 (d, 1H), 8,32 - 8,42 (m, 1H), 8,43 - 8,53 (m, 1H), 8,90 (s, 1H), 9,43 (d, 1H), 11,26

			(s, 1H). LC-MS: tiempo de retención: 1,09 min MS ES+: 485,21 [M+H]+

Ejemplo 31-1

Preparación de 2-[1-(2-fluorobencil)-*1H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-carbonitrilo



Se agitaron 73 mg de 4-cloro-2-[1-(2-fluorobencil)-1H-indazol-3-il]pirimidin-5-carbonitrilo (1-14-1, 0,201 mmol, 1. eq.), 22,66 mg de piridin-4-amina (0,241 mmol, 1,2 eq.), 42 µl de N-etil-N-(propan-2-il)propan-2-amina (0,241 mmol, 1,2 eq.) y 1 ml de N,N-dimetilformamida a temperatura ambiente durante 24 horas. La mezcla de reacción se particionó entre solución acuosa parcialmente saturada de carbonato ácido de sodio y diclorometano/ isopropanol 4:1. La capa acuosa se extrajo dos veces con diclorometano/ isopropanol 4:1. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre un filtro de silicona y se

concentró al vacío. El residuo se purificó mediante cromatografía flash y HPLC preparativa para dar 24,4 mg (0,06 mmol, 28,9%) del compuesto buscado analíticamente puro.

^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 5,83 (s, 2H), 7,08 – 7,40 (m, 5H), 7,47 (td, 1H), 7,82 – 7,92 (m, 3H), 8,34 (d, 1H), 8,46 (d, 2H), 8,99 (s, 1H), 10,16 – 10,37 (m, 1H).

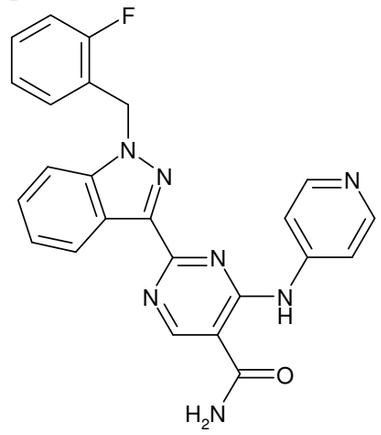
LC-MS:

tiempo de retención: 1,00 min

MS ES$^+$: 422,2 $[M+H]^+$

Ejemplo 32-1

Preparación de 2-[1-(2-fluorobencil)-*1H*-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-carboxamida



Se agregaron 20,7 mg de 2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-carbonitrilo (31-1, 0,049 mmol, 1 eq.) a ácido sulfúrico conc. enfriado con baño de hielo (1,84 mmol, 37,5 eq.) y se agitó durante cinco minutos a 5 °C y otras 24 horas a temperatura ambiente. Se agregó hielo a la suspensión. La suspensión se retiró por filtración, se lavó con agua y la torta de filtrado se secó bajo vacío a 50 °C para dar 23,0 mg (0,05 mmol, 106%) del compuesto buscado analíticamente puro.

^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 5,86 (s, 2H), 7,13 – 7,27 (m, 2H), 7,29 – 7,41 (m, 3H), 7,46 – 7,55 (m, 1H), 7,88 (d, 1H), 8,07 (s ancho, 1H), 8,28 (d, 2H), 8,46 (d, 1H), 8,57 (d, 3H), 9,19 (s, 1H), 12,07 (s, 1H).

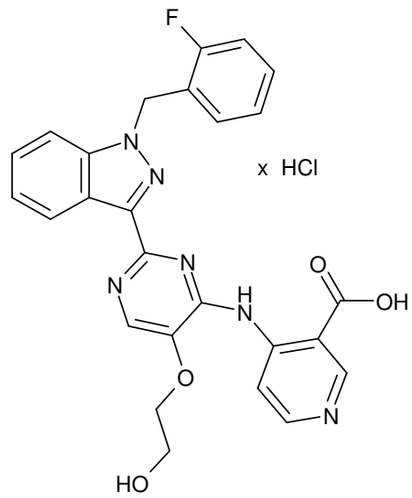
LC-MS:

tiempo de retención: 1,02 min

MS ES$^+$: 440,37 $[M+H]^+$

Ejemplo 33-1

Preparación de clorhidrato de ácido 4-({2-[1-(2-fluorobencil)-1*H*-indazol-3-il]-5-(2-hidroxietoxi)pirimidin-4-il}amino)piridin-3-carboxílico (1:1)



Se disolvieron 183 mg de ácido 4-({5-(2-{[tert-butil(dimetil)silil]oxi}etoxi)-2-[1-(2-fluorobencil)-1H-indazol-3-il]pirimidin-4-il}amino)piridin-3-carboxílico (derivado de 30-3 como SM por medio del paso 1 del procedimiento descrito en 13-1 y subsecuente hidrólisis de éster) (0,297 mmol, 1. eq.) en 10 ml de solución de cloruro de hidrógeno en dioxano 4 M y se agitó a temperatura ambiente durante 24 horas. El precipitado se retiró por filtración, se lavó con diclorometano y la torta de filtrado se secó bajo vacío para dar 157 mg (0,26 mmol,

88,4%) del compuesto buscado analíticamente puro.

^{1}H-RMN (300MHz, DMSO-d_6): δ [ppm]= 3,52 (s, 2H), 3,79 – 3,88 (m, 2H), 4,35 (t, 2H), 5,82 (s, 2H), 7,08 – 7,38 (m, 5H), 7,46 (t, 1H), 7,81 (d, 1H), 8,43 (d, 1H), 8,65 – 8,70 (m, 1H), 8,76 (d, 1H), 9,11 (s, 1H), 9,66 (d, 1H), 12,53 (s, 1H).

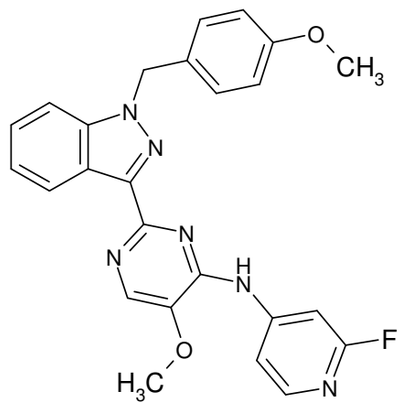
LC-MS:

tiempo de retención: 0,98 min

MS ES$^+$: 501,33 $[M+H]^+$

Ejemplo 34-1

Preparación de N-(2-fluoropiridin-4-il)-5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]pirimidin-4-amina



Se suspendieron 100 mg de ácido 5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]pirimidin-4-amina (1-4-1, 0,277 mmol, 1. eq.), 78,0 mg de (2-fluoropiridin-4-il)borónico (0,553 mmol, 2 eq.) y 205 mg de acetato de cobre (II) en 4 ml de triclorometano. Se agregaron 154 µl de trietilamina (1,11 mmol, 4 eq.) y 16,9 mg de N,N-dimetilpiridin-4-amina (138 mmol, 0,5 eq.). La mezcla de reacción se agitó a temperatura ambiente durante 24 horas. La mezcla de reacción se retiró por filtración sobre Celite 545 y se lavó con diclorometano. El material filtrado se

concentró al vacío. El residuo se purificó mediante cromatografía flash y HPLC preparativa para dar 13 mg (0,03 mmol, 10,9%) del compuesto buscado analíticamente puro.

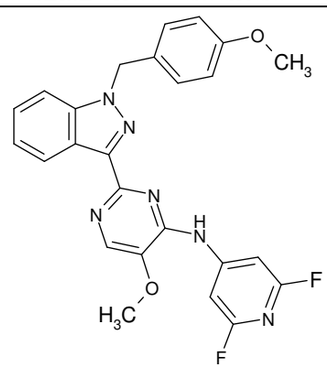
^{1}H-RMN (300MHz, DMSO-d6): δ [ppm]= 3,66 (s, 3H), 4,03 (s, 3H), 5,63 (s ancho, 2H), 6,85 (d, 2H), 7,23 (d, 1H), 7,29 - 7,48 (m, 3H), 7,75 - 7,92 (m, 2H), 8,05 (d, 1H), 8,26 (s, 1H), 8,42 (d, 2H), 9,75 (s, 1H).

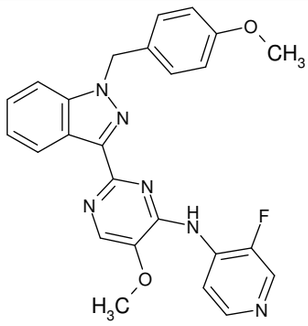
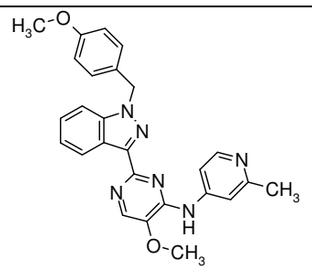
LC-MS:

tiempo de retención: 1,25 min

MS ES$^+$: 457,2 $[M+H]^+$

El siguiente compuesto se formó de acuerdo con el mismo procedimiento usando el material de partida indicado (SM):

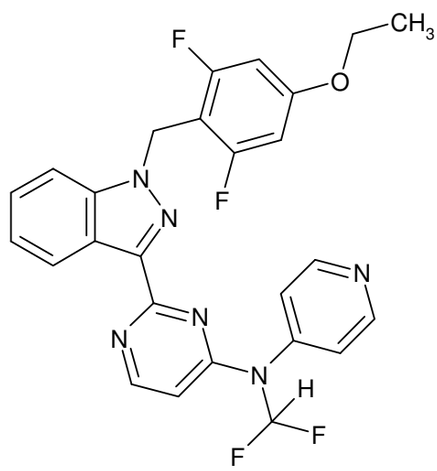
34-2 SM = 1-4-1		N-(2,6-difluoropiridin-4-il)-5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]pirimidin-4-amina	^{1}H-RMN (400MHz, DMSO-d6): δ [ppm]= 3,66 (s, 3H), 4,04 (s, 3H), 5,63 (s, 2H), 6,84 (d, 2H), 7,22 (t, 1H), 7,36 (d, 2H), 7,40 (d, 1H), 7,83 (d, 1H), 7,98 (s, 2H), 8,38 - 8,49 (m, 2H), 10,04 (s, 1H). LC-MS: tiempo de retención: 1,40 min MS ES$^+$: 475,3 $[M+H]^+$ Método B

34-3 SM = 1-4-1		N-(3-fluoropiridin-4-il)-5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]pirimidin-4-amina	^{1}H-RMN (300MHz, DMSO-d6): δ [ppm]= 3,65 (s, 3H), 4,02 (s, 3H), 5,62 (s ancho, 2H), 6,83 (d, 2H), 7,07 - 7,18 (m, 1H), 7,24 (s ancho, 2H), 7,38 (t, 1H), 7,74 (d, 1H), 8,22 (d, 1H), 8,29 - 8,79 (m, 5H). LC-MS: tiempo de retención: 1,17 min MS ES$^+$: 457,43 $[M+H]^+$ Método B
34-4 SM = 1-4-1		5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]-N-(2-metilpiridin-4-il)pirimidin-4-amina	^{1}H-RMN (300MHz, DMSO-d6): δ [ppm]= 2,41 (s, 3H), 3,66 (s, 3H), 4,01 (s, 3H), 5,65 (s ancho, 2H), 6,85 (d, 2H), 7,20 (t, 1H), 7,31 (d, 2H), 7,40 (t, 1H), 7,72 (br. d, 1H), 7,79 (d, 1H), 8,23-8,27

			(m, 2H), 8,32 (s, 1H) 8,44 (d, 1H), 9,30 (m, 1H). LC-MS (Método 2): tiempo de retención: 0,96min MS ES+: 453,1 [M+H]+

Ejemplo 35-1

Preparación de N-(difluorometil)-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina



Se disolvieron 119,176 mg de 2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina (5-1, 0,260 mmol, 1. eq.) en 2 ml de N,N-dimetilformamida seca. Se agregaron 254,09 mg de carbonato de cesio y 39,63 mg de cloro(difluoro)acetato de sodio y se agitó durante dos horas a 100 °C de temperatura de baño bajo una atmósfera de nitrógeno. Luego la mezcla se particionó entre agua y diclorometano/ isopropanol 4:1. Las fases se separaron y la capa acuosa (levemente marrón) se

extrajo dos veces con diclorometano/ isopropanol 4:1. Las capas orgánicas combinadas se lavaron con salmuera, se secó sobre un filtro de silicona y se concentró al vacío. El residuo se purificó mediante cromatografía flash para dar 9 mg (0,02 mmol, 6,13%) del compuesto buscado analíticamente puro.

^{1}H-RMN (500MHz, DMSO-d 6): δ [ppm]= 1,27 - 1,31 (t, 3H), 4,04 (q, 2H), 5,69 (s, 2H), 6,70 - 6,82 (m, 5H), 7,24 (t, 1H), 7,42 - 7,68 (m, 1H), 7,47 (ddd, 1H), 7,79 (dd, 3H), 8,47 (d, 1H), 8,60 (d, 1H).

LC-MS:

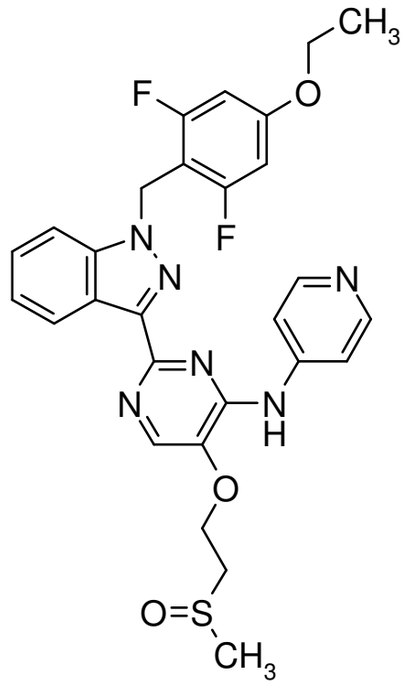
tiempo de retención: 1,09 min

MS ES$^+$: 509,1 $[M+H]^+$

Método B

Ejemplo 36-1

Preparación de 2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-[2-(metilsulfinil)etoxi]-N-(piridin-4-il)pirimidin-4-amina



A una solución de 1,24 g 2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-[2-(metilsulfanil)etoxi]-N-(piridin-4-il)pirimidin-4-amina (4-16, 2,26 mmol, 1. eq.) en 2,15 ml de cloroformo seco, se agregó lentamente a 0 °C una solución de 557 mg ácido 2-clorobencenocarboperoxoico (77%, 2,49 mmol, 1,1 eq.) en 2,15 ml de cloroformo. Luego de 30 min se agregaron diclorometano y solución tiosulfato de sodio (10 %). La suspensión se agitó durante 5 min. Después de separar el sólido (producto) la capa acuosa se lavó con diclorometano dos veces. Las capas orgánicas se secaron con sulfato de sodio y se concentró al vacío. El residuo se purificó mediante cromatografía flash y se combinó el sólido aislado para dar 1,22 g (2,05 mmol, 91%) del compuesto buscado analíticamente puro.

^{1}H-RMN (400MHz, DMSO-d 6): δ [ppm]= 1,29 (t, 3H), 2,72 (s, 3H), 3,18 - 3,28 (m, 1H), 3,34 - 3,47 (m, 1H), 4,04 (q, 2H), 4,58 - 4,78 (m, 2H), 5,69 (s, 2H), 6,73 - 6,87 (m, 2H), 7,21 - 7,34 (m, 1H), 7,43 - 7,56 (m, 1H), 7,80 - 7,92 (m, 1H), 8,08 - 8,17 (m, 2H), 8,39 - 8,52 (m, 4H), 9,40 (s, 1H)

LC-MS:

tiempo de retención: 0,98 min

MS ES$^+$: 564,0 $[M+H]^+$

El Ejemplo 36-1 se separó en sus enantiómeros por separación por HPLC quiral

(Método:

Columna: Quiralpak AD-H 5µ 150x4,6 Canal: UV_VIS_3

Solvenet: A:Hexano C:EtOH Longitud de onda (nm): 280

Solución reguladora: 0,1% DEA Flujo (ml/min): 1,000

Gradiente: Iso_70%A+30%C Tiempo de corrida (min): 15,00

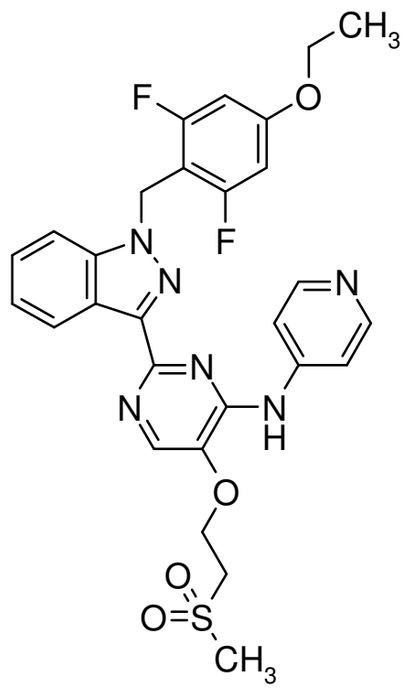
Solución: 1 mg/mL EtOH/MeOH 2:1 Number de Vial: 6

Comentario: 25°C Volumen Inyección: 10,0)

36-2 SM = 36-1		2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-[2-(metilsulfinil)etoxi]-N-(piridin-4-il)pirimidin-4-amina (Enantiómero 1)	^{1}H-RMN (400MHz, DMSO-d 6): δ [ppm]= 1,29 (t, 3H), 2,72 (s, 3H), 3,18 - 3,28 (m, 1H), 3,34 - 3,47 (m, 1H), 4,04 (q, 2H), 4,58 - 4,78 (m, 2H), 5,69 (s, 2H), 6,73 - 6,87 (m, 2H), 7,21 - 7,34 (m, 1H), 7,43 - 7,56 (m, 1H), 7,80 - 7,92 (m, 1H), 8,08 - 8,17 (m, 2H), 8,39 - 8,52 (m, 4H), 9,40 (s, 1H). tiempo de retención: 10,08 min rotación específica: 18,5° +/- 0,08°
36-3 SM = 36-1		2-[1-(4-etoxi-2,6-difluorobencil)	^{1}H-RMN (400MHz, DMSO-d 6): δ [ppm]= 1,29 (t, 3H), 2,72

		-1H-indazol-3-il]-5-[2-(metilsulfinil)etoxi]-N-(piridin-4-il)pirimidin-4-amina (Enantiómero 2)	(s, 3H), 3,18 - 3,28 (m, 1H), 3,34 - 3,47 (m, 1H), 4,04 (q, 2H), 4,58 - 4,78 (m, 2H), 5,69 (s, 2H), 6,73 - 6,87 (m, 2H), 7,21 - 7,34 (m, 1H), 7,43 - 7,56 (m, 1H), 7,80 - 7,92 (m, 1H), 8,08 - 8,17 (m, 2H), 8,39 - 8,52 (m, 4H), 9,40 (s, 1H) tiempo de retención: 12,87 min rotación específica: -14,7° +/- 0,15°

Ejemplo 37-1 Preparación de 2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-[2-(metilsulfonil)etoxi]-N-(piridin-4-il)pirimidin-4-amina



Se disolvieron 100 mg de 2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-[2-(metilsulfinil)etoxi]-N-(piridin-4-il)pirimidin-4-amina (36-1, 0,177 mmol, 1,0 eq.) en 0,9 ml de tetrahidrofurano anhidro. Se agregaron 0,09 ml de peróxido de hidrógeno acuoso (30 %, 0,886 mmol, 5,0 eq.) y 37,0 mg de dietilazodicarboxilato. La mezcla de reacción se agitó a 50 °C durante 2 h. Un precipitado blanco se retiró por filtración y se purificó mediante cromatografía flash para dar 18,1 mg (0,03 mmol, 17,6%) del compuesto buscado analíticamente puro.

^{1}H-RMN (300MHz, DMSO-d 6): δ [ppm]= 1,28 (t, 3H), 3,14 (s, 3H), 3,78 (t, 2H), 4,03 (q, 2H), 4,66 (t, 2H), 5,69 (s, 2H), 6,72 - 6,95 (m, 2H), 7,27 (t, 1H), 7,49 (t, 1H), 7,86 (d, 1H), 8,05 - 8,13 (m, 2H), 8,36 - 8,55 (m, 4H), 9,06 (s, 1H).

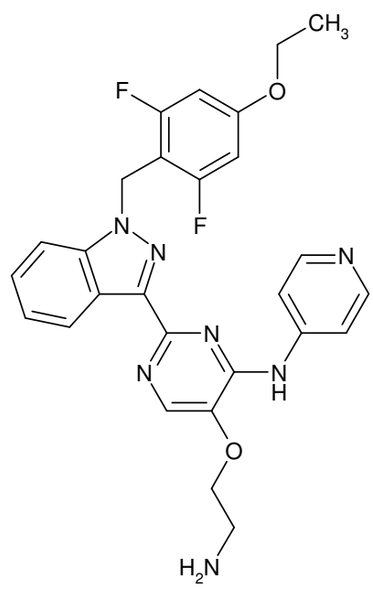
LC-MS (Método 1):

tiempo de retención: 1,03 min

MS ES$^+$: 581,2 $[M+H]^+$

Ejemplo 38-1

Preparación de 5-(2-aminoetoxi)-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina



Se disolvieron 28,6 mg de [2-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)etil]carbamato de tert-butilo (4-23, 0,046 mmol, 1,0 eq.) en 2 ml de diclorometano seco. Se agregaron 0,071 ml de ácido trifluoroacético (0,926 mmol, 20,0 eq.) a 0 °C. La mezcla de reacción se agitó durante la noche a temperatura ambiente. Luego se agregó una mezcla carbonato de sodio 2 N y diclorometano/ isopropanol 4:1 y la mezcla se agitó durante 30 min. Las fases se separaron y la capa acuosa (levemente marrón) se extrajo dos veces con diclorometano/ isopropanol 4:1. Las capas orgánicas combinadas se secaron sobre sulfato de magnesio y se concentró al vacío. El residuo se purificó mediante cristalización desde acetato de etilo para dar 6,8 mg (0,01 mmol, 27,0 %) del compuesto buscado analíticamente

puro.

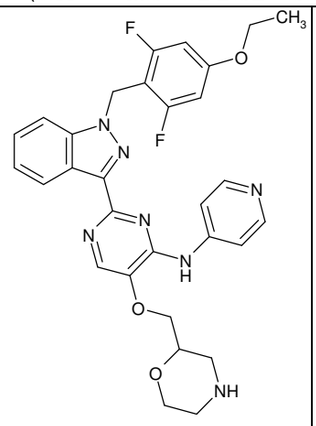
^{1}H-RMN (600MHz, DMSO-d 6): δ [ppm]= 1,29 (t, 3H), 2,98 (t, 2H), 4,05 (q, 2H), 4,15 (t, 2H), 5,68 (s, 2H), 6,75 - 6,82 (m, 2H), 7,23 - 7,29 (m, 1H), 7,47 - 7,50 (m, 1H), 7,85 (d, 1H), 8,13 - 8,17 (m, 2H), 8,31 (s, 1H), 8,35 (s, 1H), 8,42 - 8,45 (m, 2H), 8,46 (d, 1H).

LC-MS (Método 5):

tiempo de retención: 1,24 min

MS ES$^+$: 518,2 $[M+H]^+$

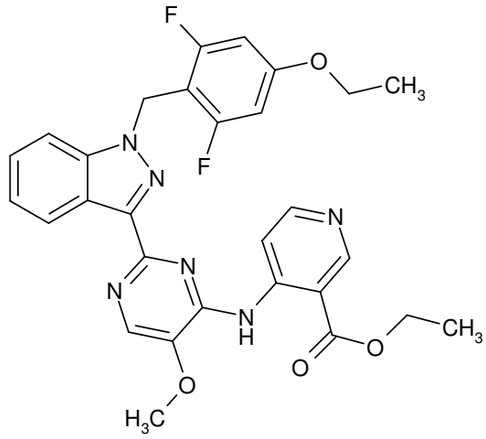
Los siguientes compuestos se prepararon de acuerdo con el mismo procedimiento usando los materiales de partida indicados (SM = material de partida):

38-2 SM = 4-11		2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-(morfolin-2-ilmetoxi)-N-(piridin-4-il)pirimidin-4-amina	^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 1,28 (t, 3H), 2,51 - 2,57 (m, 1H), 2,64 - 2,71 (m, 2H), 2,94 - 3,02 (m, 1H), 3,45 - 3,56 (m, 1H), 3,74 - 3,81 (m, 1H), 3,83 - 3,92 (m, 1H), 4,02 (q, 2H), 4,12 - 4,27 (m, 2H), 5,67 (s, 2H), 6,73 - 6,84 (m, 2H), 7,20 - 7,30 (m, 1H), 7,43 - 7,53 (m, 1H), 7,80

			– 7,87 (m, 1H), 8,10 – 8,17 (m, 2H), 8,38 (s, 1H), 8,39 – 8,47 (m, 3H), 9,14 (s, 1H). LC–MS (Método 5): tiempo de retención: 1,24 min MS ES$^+$: 574,5 $[M+H]^+$

Ejemplo 39–1

Preparación de 4–({2–[1–(4–etoxi–2,6–difluorobencil)–1H–indazol–3–il]–5–metoxipirimidin–4–il}amino)piridin–3–carboxilato de etilo



Se suspendieron 150 mg de 2–[1–(4–etoxi–2,6–difluorobencil)–1H–indazol–3–il]–5–metoxipirimidin–4–amina (1–4–3, 0,365 mmol, 1,0 eq.), 89 mg de 4–cloronicotinato de etilo comercialmente disponible (0,401 mmol, 1,1 eq.), 31,6 mg de (9,9–dimetil–9H–xanten–4,5–diil)bis(difenilfosfina) (0,055 mmol, 0,15 eq.), 356 mg de carbonato de cesio (1,09

mmol, 3,0 eq.) y 8,2 mg de diacetato de paladio (0,036 mmol, 0,1 eq.) en 4,7 mL de dioxano seco y se agitó bajo una atmósfera de nitrógeno a 105°C de temperatura de baño durante 3 h. Los sólidos se retiraron por filtración, se lavó con dioxano y el material filtrado se concentró al vacío. El residuo se purificó mediante cromatografía flash dando 77 mg de los cuales solamente 15,7 mg se purificaron adicionalmente mediante cristalización a partir de THF para dar 3,1 mg (0,01 mmol, 1,44 %) del compuesto buscado analíticamente puro.

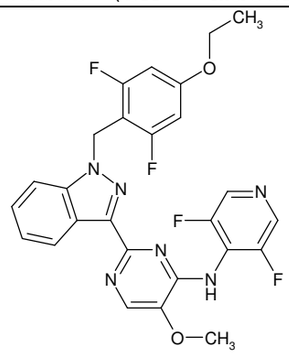
^{1}H-RMN (300MHz, DMSO-d 6): δ [ppm]= 1,26 (t, 3H), 1,36 (t, 3H), 3,95 – 4,10 (m, 5H), 4,37 (q, 2H), 5,68 (s, 2H), 6,71 – 6,87 (m, 2H), 7,19 – 7,33 (m, 1H), 7,41 – 7,54 (m, 1H), 7,83 (d, 1H), 8,37 – 8,48 (m, 2H), 8,59 (d, 1H), 9,07 (s, 1H), 9,39 (d, 1H), 11,29 (s, 1H).

LC-MS:

tiempo de retención: 1,55min

MS ES$^+$: 560,0 $[M+H]^+$

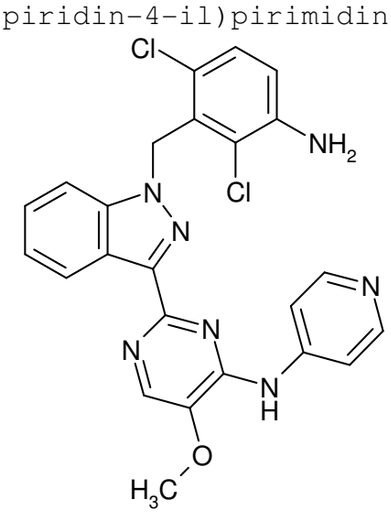
Los siguientes compuestos se prepararon de acuerdo con el mismo procedimiento usando los materiales de partida indicados (SM = material de partida):

39-2 SM = 1-4-3		N-(3,5-difluoropiridin-4-il)-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-	^{1}H-RMN (400MHz, DMSO-d_6): δ [ppm]= 1,26 (t, 3H), 3,90 – 4,12 (m, 5H), 5,58 (s, 2H), 6,62 – 6,79 (m, 2H), 6,94 – 7,04 (m, 1H), 7,25 – 7,40

		4-amina	(m, 1H), 7,65 - 7,74 (m, 1H), 7,76 - 7,85 (m, 1H), 8,24 (s, 1H), 8,59 (s, 2H), 9,36 (s, 1H). LC-MS (Método 5): tiempo de retención: 1,34 min MS ES+: 525,2 $[M+H]^+$

Ejemplo 40-1

Preparación de 2-[1-(3-amino-2,6-diclorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina



Se disolvieron 52 mg de 2-[1-(2,6-dicloro-3-nitrobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina (2-44-1, 0,10 mmol, 1,0 eq.) en 5,2 ml de metanol seco. Se agregaron 23,4 mg de níquel raney (50 %, 0,199 mmol, 2,0 eq.) y 0,045 ml de hidrazina (35 %, 0,498 mmol, 5,0 eq). La mezcla de reacción se agitó a temperatura ambiente

enérgicamente durante la noche. La suspensión se filtró sobre celite y se lavó con metanol dos veces. El material filtrado se concentró al vacío y el residuo se purificó mediante cromatografía flash para dar 19,2 mg (0,04 mmol, 38%) del compuesto buscado analíticamente puro.

^{1}H-RMN (300MHz, DMSO-d 6): δ [ppm]= 4,00 (s, 3H), 5,62 (s, 2H), 5,78 (s, 2H), 6,82 (d, 1H), 7,22 (t, 2H), 7,46 (t, 1H), 7,86 (d, 1H), 8,14 (d, 2H), 8,32 (s, 1H), 8,38 (d, 2H), 8,47 (d, 1H), 9,34 (s, 1H).

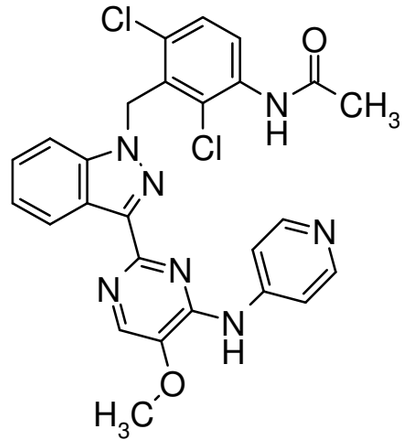
LC-MS:

tiempo de retención: 0,97 min

MS ES$^+$: 492,1 $[M+H]^+$

Ejemplo 41-1

Preparación de N-[2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]acetamida



Se disolvieron 50 mg de 2-[1-(3-amino-2,6-diclorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina (40-1, 0,102 mmol, 1,0 eq.) en 0,6 ml de N,N-dimetilformamida seca. Se agregaron 0,014 ml de N,N-dietiletanamina (0,102 mmol, 1,0 eq.) y 0,010 ml de anhídrido acético (0,102 mmol, 1,0 eq.) a 0 °C y se agitó

durante 3,5 h Luego se agregaron nuevamente 0,014 ml de N,N-dietiletanamina (0,102 mmol, 1,0 eq.) y 0,010 ml de anhídrido acético (0,102 mmol, 1,0 eq.) a 0 °C y se agitó durante la noche a temperatura ambiente. Se agregaron solución saturada de carbonato ácido de sodio y acetato de etilo y la mezcla de reacción se agitó durante 30 min. La capa orgánica se lavó con acetato de etilo dos veces. Las capas orgánicas combinadas se secaron sobre un filtro de silicona y se concentró al vacío. El residuo se purificó mediante cromatografía flash para dar 17,3 mg (0,03 mmol, 30%) del compuesto buscado analíticamente puro.

^{1}H-RMN (400MHz, DMSO-d 6): δ [ppm]= 2,07 (s, 3H), 3,99 (s, 3H), 5,89 (s, 2H), 7,22 - 7,29 (m, 1H), 7,44 - 7,52 (m, 1H), 7,58 (d, 1H), 7,79 (d, 1H), 7,90 (d, 1H), 8,09 - 8,16 (m, 2H), 8,31 (s, 1H), 8,34 - 8,39 (m, 2H), 8,48 (d, 1H), 9,32 (s, 1H), 9,60 (s, 1H).

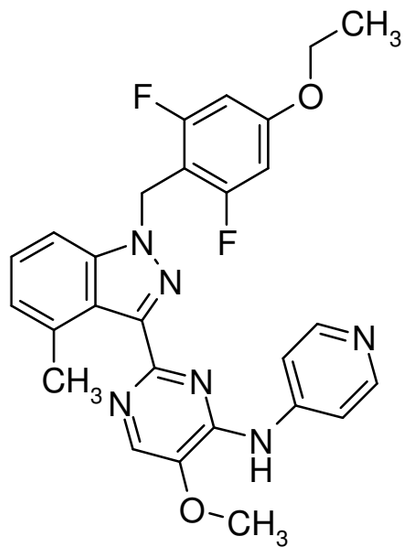
LC-MS (Método 1):

tiempo de retención: 0,97 min

MS ES$^+$: 534,1 $[M+H]^+$

Ejemplo 42-1

Preparación de 2-[1-(4-etoxi-2,6-difluorobencil)-4-metil-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina



Se disolvieron 100 mg de clorhidrato de 2-[1-(4-etoxi-2,6-difluorobencil)-4-metil-1H-indazol-3-il]-5-metoxipirimidin-4-amina (1-4-6, 0,236 mmol, 1,0 eq.) y 94,2 mg de 4-fluoropiridina (0,705 mmol, 3,0 eq.) en 1,1 ml de N,N-dimetilformamida seca. Se agregaron 113 mg hidruro de sodio (60 %, 2,82 mmol, 12 eq.). La mezcla de reacción se agitó a 90 °C durante 2 h. Se agregaron agua y acetato de etilo y la capa acuosa se lavó con acetato de etilo dos veces. Las capas orgánicas combinadas se secaron sobre un filtro de silicona y se concentró al vacío. El residuo se purificó mediante HPLC para dar 46 mg (0,09 mmol, 38%) del compuesto buscado analíticamente puro.

^{1}H-RMN (300MHz, DMSO-d 6): δ [ppm]= 1,26 (t, 3H), 2,42 (s, 3H), 3,93 - 4,07 (m, 5H), 5,59 (s, 2H), 6,68 - 6,78 (m, 2H), 6,94 (d, 1H), 7,32 (t, 1H), 7,59 (d, 1H), 7,91 - 8,02 (m, 2H), 8,22 - 8,36 (m, 3H), 9,36 (s, 1H).

LC-MS (Método B):

tiempo de retención: 1,32 min

MS ES$^+$: 503,03 $[M+H]^+$

Investigaciones biológicas

Los siguientes ensayos se pueden usar para ilustrar la utilidad comercial de los compuestos de acuerdo con la presente invención.

Los ejemplos fueron evaluados en ensayos biológicos seleccionados una o más veces. Cuando se evaluaban más de una vez, los datos se informan ya sea como valores promedio o como valores de mediana, en donde

- al valor promedio, también conocido como el valor de la media aritmética, representa la suma de los valores obtenidos dividida por la cantidad de veces evaluada, y
- el valor de la mediana representa el número del medio del grupo de valores cuando se clasifican en orden ascendente o descendente. Si el número de valores del conjunto de datos es impar, la mediana es el valor del medio. Si el número de valores del conjunto de datos es par, la mediana es la media aritmética de los dos valores del medio.

Los ejemplos se sintetizaron una o más veces. Cuando se sintetizaban más de una vez, los datos de los ensayos biológicos representan los valores promedio calculados utilizando conjuntos de datos obtenidos de la evaluación de uno o más lotes de síntesis.

Ensayo biológico 1.0:

Ensayo con Bub1 quinasa

Las actividades inhibidoras de Bub1 de los compuestos que se describen en la presente invención se cuantificaron usando un ensayo quinasa por transferencia de energía fluorescente con resolución temporal (TR-FRET) que mide la fosforilación del péptido sintético Biotina-Ahx-

VLLPKKSFAEPG (C-terminal con forma de amida), obtenido, por ejemplo, de Biosyntan (Berlín, Alemania) por el dominio catalítico (recombinante) de la Bub1 humana (aminoácidos 704-1085), expresado en células de insecto Hi5 con una marca His6 N-terminal y purificado por cromatografía de afinidad (Ni-NTA) y por exclusión de tamaño.

En un ensayo típico, se evaluaron 11 concentraciones diferentes de cada compuesto (0,1 nM, 0,33 nM, 1,1 nM, 3,8 nM, 13 nM, 44 nM, 0,15 µM, 0,51 µM, 1,7 µM, 5,9 µM y 20 µM) por duplicado dentro de la misma placa para microtitulación. Para tal fin, se prepararon previamente soluciones de compuesto concentradas 100X (en DMSO) por dilución en serie (1:3,4) de soluciones madre 2 mM en una placa para microtitulación de fuente, claro de bajo volumen, 384 pocillos (Greiner Bio-One, Frickenhausen, Alemania), de la cual se transfirieron 50 nl de los compuestos en una placa para microtitulación de prueba, de bajo volumen, negra, del mismo proveedor. A continuación, se agregaron 2 µl de Bub1 (la concentración final de Bub1 se ajustó dependiendo de la actividad del lote de enzima con el fin de que estuviera dentro del rango dinámico lineal del ensayo: típicamente se usaron ~ 200 µg/ml) en solución amortiguadora de ensayo acuosa [50 mM Tris/HCl pH 7,5, cloruro de magnesio 10 mM (MgCl2), cloruro de potasio 200 mM (KCl), ditiotreitol 1,0 mM (DTT), orto-vanadato de sodio 0,1 mM, glicerol 1% (v/v), albúmina de suero bovino 0,01 % (p/v) (BSA), Tritón X-100 0,005% (v/v) (Sigma), 1x mezcla de inhibidores de proteasas completo sin EDTA 1x (Roche)] a los compuestos en la placa de prueba y la mezcla

se incubó por 15 min a 22°C para permitir el pre-equilibrio de los complejos putativos de enzima-inhibidor antes de comenzar la reacción quinasa, que se inició por la adición de 3 µl de solución concentrada 1,67X (en solución amortiguadora de ensayo) de adenosina-trifosfato (ATP, 10 µM de concentración final) y sustrato de final (1 µM de concentración final). La mezcla resultante(5 µl de volumen final) se incubó a 22°C durante 60 min., y la reacción se detuvo por la adición de 5 µl de una solución acuosa de EDTA (EDTA 50 mM, en HEPES 100 mM pH 7,5 y albúmina de suero bovino 0,2% (p/v)) que también contenía a los reactivos de detección TR-FRET (estreptavidina-XL665 0,2 µM [Cisbio Bioassays, Codolet, Francia] y anticuerpo anti-fosfoserina 1 nM [Merck Millipore, N° cat. 35-001] y anticuerpo anti-IgG de ratón marcado con LANCE EU-W1024 0,4 nM [Perkin-Elmer, N° producto AD0077; como alternativa, se puede usar un anticuerpo anti-IgG de ratón marcado con criptato de terbio de Cisbio Bioassays]). La mezcla de reacción detenida se incubó además 1 h a 22°C con el fin de permitir la formación de complejos entre los péptidos y los reactivos de detección. Subsiguientemente, se evaluó la cantidad de producto por medición de la transferencia de energía de resonancia del complejo de anticuerpo-quelato-Eu que reconoce al residuo fosfoserina de la estreptavidina-XL665 unida a la porción biotina del péptido. Para tal fin, se midieron las emisiones de fluorescencia a 620 nm y 665 nm después de una excitación a 330-350 nm en un lector de placas TR-FRET, por ejemplo un lector Rubystar o Pherastar (ambos de BMG Labtechnologies, Offenburg, Alemania) o un

lector Viewlux (Perkin-Elmer) y la relación de las emisiones (665 nm/622 nm) se tomó como un indicador de la cantidad de sustrato fosforilado. Los datos se normalizaron dos juegos de (típicamente 32) pocillos control para una actividad de Bub1 alta (= reacción de la enzima sin inhibidor = 0 % = inhibición mínima) y baja (= todos los componentes del ensayo sin enzima = 100 % = inhibición máxima). Los valores de IC50 se calcularon ajustando los datos de inhibición normalizados a una ecuación logística de 4 parámetros (mínima, máxima, IC50, Hill; Y = Máx + (Mín - Máx) / (1 + (X/IC50)Hill)) usando un software de análisis propiedad de Bayer.

Ensayo biológico 2.0:

Ensayo de proliferación:

Se plaquearon células tumorales cultivadas (las células se obtuvieron de ATCC, excepto las células HeLa-MaTu y HeLa-MaTu-ADR, que se obtuvieron de EPO-GmbH, Berlín) a una densidad de entre 1000 y 5000 células/pocillo, dependiendo del índice de crecimiento de la respectiva línea celular, en una placa para multititulación de 96 pocillos en 200 µl de su respectivo medio de crecimiento suplementado con suero fetal bovino 10%. Después de 24 horas, se tiñeron las células de una placa (placa del punto cero) con violeta cristal (véase más adelante), en tanto el medio de las otras placas era reemplazado por medio de cultivo fresco (200 µl), al cual se agregaron las sustancias de prueba a diversas concentraciones (0 µM, así como en el rango de 0,001-10 µM; la concentración final del solvente dimetilsulfóxido era de

0,5%). Las células se incubaron durante 4 días en presencia de las sustancias de prueba. La proliferación de las células se determinó por coloración de las células con violeta cristal: las células se fijaron por adición de 20 µl/punto de medición de una solución de aldehído glutárico 11% durante 15 minutos a temperatura ambiente. Después de tres ciclos de lavado con agua de las células fijadas, las placas se secaron a temperatura ambiente. Las células se tiñeron por adición de 100 µl/punto de medición de una solución de violeta cristal 0,1% (pH 3,0). Después de tres ciclos de lavado con agua de las células teñidas, las placas se secaron a temperatura ambiente. El colorante se disolvió por adición de 100 µl/punto de medición de una solución de ácido acético 10%. La absorción se determinó por fotometría a una longitud de onda de 595 nm. El cambio en la cantidad de células, como un porcentaje, se calculó normalizando los valores medidos con respecto a los valores de absorción de la placa del punto cero (=0%) y la extinción de las células no tratadas (0 µm) (=100%). Los valores de IC50 se determinaron por medio de un ajuste de 4 parámetros usando el software de la empresa.

Tabla 1. Los compuestos fueron evaluados en las siguientes líneas celulares, que ejemplifican las subindicaciones enumeradas

Indicación tumoral	**Línea celular**
Cáncer cérvicouterino	HeLa HeLa-MaTu-ADR

Cáncer de mama	MDA-MB 453 HCC-70 MCF7 MDA MB231 MDA-MB-468
Cáncer de ovario	SKBR-3 A2780 COLO-704 Caov-3 ES-2 SK-OV-3 IGROV-1 OVCAR8
Cáncer de pulmón de células no pequeñas (NSCLC)	A549 NCI-H460 NCI-H1299
Cáncer de próstata	DU145
Cáncer de colon	Caco2 HCT15 HT29
Cáncer de páncreas	MIAPaCa2
Osteosarcoma	U2OS
Leucemia mielogénica aguda	KG1 MOLM-13 MV-4-11
Linfoma de	RAMOS

Burkitt	
Mieloma múltiple	OPM-2
Melanomas	B16F10

En la siguiente tabla se muestran los datos relativos a la inhibición de la Bub1 quinasa y la inhibición de la proliferación de células HeLa, para los ejemplos de la presente invención de los ensayos biológicos 1 y 2:

Nº ejemplo	**Ensayo biológico 1: Mediana de IC50 de ensayo para Bub1 quinasa [mol/l]**	**Ensayo biológico 2: Mediana de IC50 para el ensayo de proliferación (línea de células HeLa) [mol/l]**
2-1-1	2,6e-009	3,8e-006
2-1-3	1.2e-007	no evaluado
2-10-1	6,7e-009	≥1,0e-005
2-10-2	1.2e-006	no evaluado
2-11-1	7,1e-009	2,9e-007
2-11-2	5,4e-007	3,4e-006
2-12-1	7,3e-009	1,6e-006
2-13-1	8,0e-009	3,8e-006
2-14-1	8,3e-009	4,7e-006
2-14-2	7,3e-007	no evaluado
2-15-1	3,8e-008	4,7e-006
2-15-2	3.2e-006	no evaluado
2-16-1	8,4e-009	1,6e-006
2-17-1	8,8e-009	≥1,0e-005
2-17-2	8,9e-007	no evaluado

2-18-1	1,3e-008	9,3e-006
2-19-1	1,0e-008	3,4e-006
2-2-1	2,6e-009	3,4e-006
2-2-3	2,5e-008	no evaluado
2-20-1	1,1e-008	7,3e-006
2-21-1	1.2e-008	≥1,0e-005
2-21-2	2,0e-005	no evaluado
2-22-1	3.2e-006	no evaluado
2-23-1	1,3e-008	9,3e-006
2-24-1	1,4e-008	3,1e-006
2-25-1	1,5e-008	9,8e-006
2-26-1	1,6e-008	5,6e-007
2-26-2	8,4e-007	2,9e-006
2-27-1	2,0e-008	≥1,0e-005
2-28-1	2.2e-008	8,1e-006
2-29-1	2,3e-008	9,0e-006
2-3-1	4,4e-009	3,0e-006
2-3-3	3,6e-007	8,5e-006
2-30-1	2,3e-008	2.2e-006
2-31-1	2,8e-008	≥1,0e-005
2-32-1	2,9e-008	4.2e-006
2-33-1	3,8e-008	≥1,0e-005
2-33-2	1,1e-006	no evaluado
2-34-1	3,8e-008	1,6e-006
2-35-1	5.2e-008	≥1,0e-005
2-36-1	5,8e-008	≥1,0e-005

2-37-1	7,1e-008	≥1,0e-005
2-38-1	7,6e-008	≥1,0e-005
2-39-1	5,6e-009	3,6e-006
2-39-2	6,9e-006	no evaluado
2-4-1	4,5e-009	3,5e-006
2-4-2	3,5e-006	no evaluado
2-4-3	1,4e-008	3,9e-006
2-40-1	1.2e-007	5,6e-006
2-41-1	1,5e-007	7,9e-006
2-42-1	1,9e-007	≥1,0e-005
2-43-1	1.2e-006	≥1,0e-005
2-44-1	4,1E-8	no evaluado
2-45-1	1,1E-7	no evaluado
2-46-1	1,6e-008	1,4e-006
2-47-1	2,4E-6	no evaluado
2-48-1	5,5E-9	≥1,0e-005
2-49-1	1,5E-6	no evaluado
2-5-1	4,6e-009	2,1e-006
2-5-2	9,3e-006	no evaluado
2-5-3	2,1e-008	≥1,0e-005
2-50-1	1,1e-008	≥1,0e-005
2-51-1	1,0E-8	2,7E-6
2-52-1	1,1E-8	2,1E-6
2-53-1	8,3e-008	3,4e-006
2-6-1	4,7e-009	3,8e-006

2-6-3	5,9e-008	≥1,0e-005
2-7-1	4,8e-009	≥1,0e-005
2-7-2	2,1e-007	no evaluado
2-7-3	4,3e-007	≥1,0e-005
2-8-1	6,7e-009	≥1,0e-005
2-8-2	2,9e-007	no evaluado
2-8-3	5,7e-008	1,0e-005
2-9-1	6,7e-009	≥1,0e-005
2-9-2	2,4e-007	no evaluado
2-9-3	2,0e-005	no evaluado
3-1	4,7e-009	≥1,0e-005
3-2	9,8e-009	≥1,0e-005
3-3	1,5e-008	≥1,0e-005
3-4	4,8e-008	≥1,0e-005
4-1	2,4e-009	3,5e-006
4-10	9,0e-009	4,4e-006
4-11	2,4e-008	no evaluado
4-12	7,8e-009	9,0e-006
4-13	7,6e-009	8,0e-006
4-14	1.2e-008	≥1,0e-005
4-15	8,0e-009	3,9e-006
4-16	1,4e-008	4,4e-006
4-17	7,4E-9	4,8E-6
4-18	1.2E-8	no evaluado
4-19	1,0E-8	1.2E-6

4-2-1	3,3e-009	8,7e-006
4-2-2	4,3e-007	no evaluado
4-2-3	9,3E-9	4,9E-6
4-20	2,1E-7	no evaluado
4-21	7,8E-9	3,8E-6
4-22	5,8E-9	1,9E-6
4-23	no evaluado	no evaluado
4-3	7,5e-009	1,4e-005
4-4	1,4e-008	3,4e-006
4-5	1,8e-008	≥1,0e-005
4-5-2	3,3e-007	no evaluado
4-6	2,9e-008	3,6e-006
4-7	3,5e-008	≥1,0e-005
4-8	8,0e-009	1,3E-6
4-9	5,4E-9	1,7E-6
4-10	9,0E-9	4,4E-6
4-11	2,4E-8	no evaluado
4-12	7,8E-9	9,0E-6
4-13	7,6E-8	8,0E-6
4-14	1.2E-8	≥1,0e-005
4-15	8,0E-9	3,9E-6
4-16	1,4E-8	4,4E-6
4-17	7,4E-9	4,8E-6
4-18	1.2E-8	no evaluado
4-19	1,0E-8	1.2E-6
4-20	2,1E-7	no evaluado

4-21	7,8E-9	3,8E-6
4-22	5,8E-9	1,9E-6
4-23	9,3E-9	4,9E-6
5-1	5.2e-009	1,4e-006
5-2	2,7e-008	7,1e-007
5-3	2,8e-008	7,4e-006
6-1	3,9e-009	3,1e-006
6-2	7,4e-009	1,4e-006
7-1	3,0e-009	4,4e-006
8-1	7,4e-009	3.2e-006
8-2	2,1e-008	5,5e-006
8-3	2,4e-007	≥1,0e-005
8-4	1,3E-8	5,0E-6
9-1	9,8e-009	no evaluado
9-2	2,1e-008	≥1,0e-005
9-3	2,3e-008	7,0e-006
10-1	1.2e-008	2,0e-006
10-2	4.2e-007	1,7e-006
10-3	3,6e-007	9,6e-006
11-1	1,8e-008	8,1e-006
11-2	1,0e-008	≥1,0e-005
12-1	1,1e-008	≥1,0e-005
12-2	4,6e-009	≥1,0e-005
12-3	4,8e-009	≥1,0e-005
13-1	3,3e-009	1,5e-006
13-2	7.2e-009	9,6e-006

13-3	1,7e-008	≥1,0e-005
13-4	4,7e-009	8,0e-006
13-5	6,5e-009	≥1,0e-005
13-6	8,6e-009	≥1,0e-005
14-1	3,3e-006	≥1,0e-005
15-1	5.2e-009	1,4e-006
15-2	5,5e-009	≥1,0e-005
15-3	5,7e-009	1,7e-006
15-4	7,3e-009	≥1,0e-005
15-5	1.2e-008	9,9e-006
15-6	4,6e-009	≥1,0e-005
16-1	1,7e-007	2,8e-006
16-2	2,3e-008	3,5e-006
16-3	2,1e-007	4,1e-006
16-4	2,0e-008	2,7e-006
17-1	1,7e-007	≥1,0e-005
17-2	2,4e-006	≥1,0e-005
18-1	1,6e-008	1,4e-006
18-2	2,8e-006	3,5e-006
19-1	2,0e-005	no evaluado
19-2	6,3E-9	≥1,0E-5
20-1	2,0e-007	1,9e-007
20-2	4,0e-008	3,3e-006
20-3	1.2e-006	4,1e-006
20-4	7,5e-007	≥1,0e-005
20-5	8,8e-006	5,9e-006

20-6	6,7e-006	no evaluado
21-1	2,8e-008	3,8e-006
22-1	7,7e-007	no evaluado
23-1	1,4e-006	≥1,0e-005
24-1	6.2e-008	≥1,0e-005
24-2	2,0e-005	no evaluado
24-3	1,3e-008	9,3e-006
24-4	4.28e-006	no evaluado
24-5	1,1E-8	no evaluado
24-6	9,4E-7	no evaluado
24-7	1.2E-6	1,0e-005
24-8	2,6E-8	1,0e-005
24-9	no evaluado	no evaluado
25-1	1,3e-008	≥1,0e-005
25-2	5,4e-009	≥1,0e-005
25-3	8,8E-9	4,4E-6
25-4	5,03E-9	1,0e-005
26-1	1,7e-008	9.2e-006
26-2	2,4e-006	no evaluado
27-1	5,5e-008	3,9e-006
28-1	3,7e-006	no evaluado
29-1	1,1e-008	≥1,0e-005
29-2	8,9e-009	≥1,0e-005
30-1	1,7e-008	≥1,0e-005
30-2	2,0e-008	≥1,0e-005
30-3	8,4e-009	≥1,0e-005

31-1	4,7e-006	no evaluado
32-1	1.2e-007	≥1,0e-005
33-1	1,1e-008	≥1,0e-005
34-1	2,3e-007	≥1,0e-005
34-2	6.2E-6	≥1,0e-005
34-3	2,8e-008	8,7e-006
34-4	1.2E-7	no evaluado
35-1	1,3e-006	no evaluado
36-1	4,91E-9	3,3E-6
36-2	6.2E-9	4,4E-7
36-3	6,3E-9	4,3E-7
37-1	5,7E-9	4.2E-6
38-1	3,4E-9	1,4E-6
38-2	3,8E-9	1.2E-6
39-1	bajo evaluación	bajo evaluación
39-2	6,7E-7	≥1,0e-005
40-1	3,9E-8	no evaluado
41-1	1,9E-8	6,0E-6
42-1	6,7E-9	3,6E-6

Inhibición de la proliferación de células HeLa-MaTu-ADR, NCI-H460, DU145, Caco-2 y B16F10 por los compuestos de acuerdo con la presente invención, determinada como se describe en los Ensayos biológicos 2.0. Todos los valores de IC_{50} (concentración inhibidora a un 50% de efecto máximo) están indicados en [mol/l].

N°	**Ensayo**	**Ensayo**	**Ensayo**	**Ensayo**	**Ensayo**	**Ensayo**

ejemplo	**biológico 2: Ensayo de proliferación (línea celular HeLa-MaTu-ADR) Mediana de IC50 [mol/l]**	**biológico 2: Ensayo de proliferación (línea celular MCF7) Mediana de IC50 [mol/l]**	**biológico 2: Ensayo de proliferación (línea celular H460) Mediana de IC50 [mol/l]**	**biológico 2: Ensayo de proliferación (línea celular DU145) Mediana de IC50 [mol/l]**	**biológico 2: Ensayo de proliferación (línea celular Caco2) Mediana de IC50 [mol/l]**	**biológico 2: Ensayo de proliferación (línea celular B16F10) Mediana de IC50 [mol/l]**
2-4-1	1,3E-06	no evaluado	4,2E-06	3,3E-06	1,4E-06	1,2E-06
2-5-1	1,2E-06	3,1E-06	1,4E-06	1,7E-06	1,2E-06	1,1E-06
2-9-1	8,1E-06	no evaluado	1,0E-05	1,0E-05	1,0E-05	9,5E-06
2-11-1	3,0E-06	no evaluado	3,0E-06	3,0E-06	3,0E-06	2,9E-06

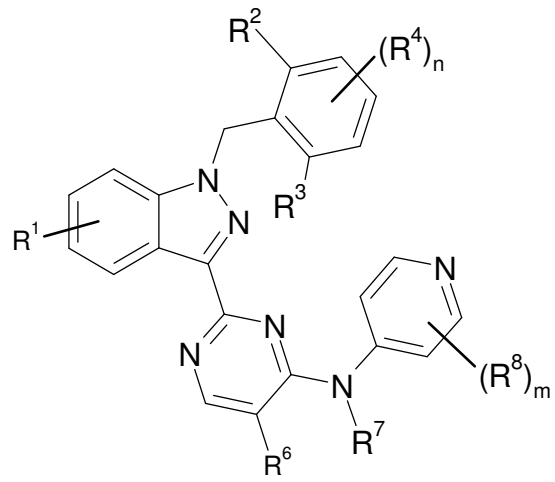
2-12-1	1,3E-06	no evaluado	1,5E-06	1,6E-06	1,4E-06	1,4E-06
2-16-1	1,2E-06	2,0E-06	2,9E-06	2,0E-06	2,6E-06	9,9E-07
2-24-1	1,3E-06	no evaluado	2,0E-06	1,3E-06	1,5E-06	1,4E-06
2-25-1	1,0E-05	no evaluado	1,0E-05	1,0E-05	1,0E-05	1,0E-05
2-26-1	3,9E-07	no evaluado	1,0E-06	5,3E-07	3,8E-07	4,2E-07
2-32-1	2,3E-06	no evaluado	8,5E-06	5,3E-06	2,4E-06	1,3E-06
2-34-1	1,2E-06	no evaluado	6,6E-06	2,6E-06	3,4E-06	1,2E-06
2-46-1	3,8E-07	no evaluado	8,8E-07	8,5E-07	9,0E-07	7,1E-07
2-11-2	1,0E-05	no evaluado	2,3E-06	3,6E-06	8,0E-06	2,1E-06
2-4-3	1,0E-07	no evaluado	9,0E-06	2,5E-06	1,9E-06	1,5E-06

4-2-1	5,8E-06	no evaluado	6,5E-06	1,0E-05	9,9E-06	3,7E-06
4-4	1,2E-06	no evaluado	3,5E-06	4,5E-06	9,0E-07	5,0E-07
4-8	3,6E-07	no evaluado	1,1E-06	1,2E-06	7,6E-07	5,7E-07
4-9	8,6E-07	no evaluado	1,3E-06	1,3E-06	7,8E-07	5,3E-07
4-19	1,0E-05	no evaluado	2,2E-06	2,3E-06	1,0E-05	5,3E-07
4-22	1,0E-05	no evaluado	2,1E-06	3,6E-06	9,5E-06	1,2E-06
5-2	3,0E-06	no evaluado	3,0E-06	3,0E-06	3,0E-06	3,0E-06
6-2	1,6E-06	no evaluado	1,7E-06	1,4E-06	1,2E-06	1,1E-06
10-2	5,9E-07	no evaluado	1,5E-06	1,4E-06	1,1E-06	9,0E-07
12-1	1,0E-05	no evalua	1,0E-05	1,0E-05	1,0E-05	1,0E-05

		do				
13-1	1,3E-06	no evaluado	1,3E-06	1,6E-06	1,2E-06	7,9E-07
15-1	1,2E-06	no evaluado	2,2E-06	1,2E-06	1,2E-06	7,6E-07
20-1	3,0E-06	no evaluado	3,0E-06	3,0E-06	3,0E-06	2,4E-06
38-2	1,1E-06	no evaluado	1,1E-06	1,3E-06	6,0E-07	6,0E-07
41-1	1,0E-05	no evaluado	1,0E-05	1,0E-05	3,3E-06	1,8E-06

Reivindicaciones

1. Un compuesto de fórmula (I)



(I)

en donde

R^1 es hidrógeno, halógeno, 1-3C-alquilo,

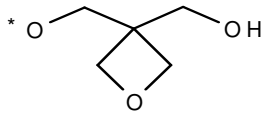
R^2/R^3 son en forma independiente entre sí hidrógeno, halógeno, ciano, hidroxi, 1-6C-haloalquilo, 1-6C-haloalcoxi, 1-6C-alcoxi,

R^4 es en forma independiente hidrógeno, hidroxi, halógeno, ciano, NO_2, 1-6C-alquilo, 2-6C-alquenilo, 2-6C-alquinilo, 1-6C-haloalquilo, 1-6C-hidroxialquilo, 1-6C-alcoxi, -O-(2-6C-alquilen)-O-C(O)-(1-6C-alquilo), 1-6C-haloalcoxi, $-C(O)OR^9$, -(1-6C-alquilen)-$C(O)OR^9$, -C(O)-(1-6C-alquilo), -$C(O)NR^{10}R^{11}$, 3-7C-cicloalquilo, -S-(1-6C-haloalquilo), SF_5, -SO_2NH-(3-7C-cicloalquilo), -$SO_2NR^{10}R^{11}$, $NR^{10}R^{11}$, heteroarilo que está opcionalmente sustituido en forma independiente una o más veces con ciano, 1-4C-alquilo, 1-6C-haloalquilo, 1-6C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, donde dos de R^2, R^3 $(R^4)_n$, cuando se encuentran en posición *orto* entre sí, pueden formar junto con los

dos átomos de carbono a los cuales están unidos un anillo heterocíclico de 5, 6 o 7 miembros que contiene 1 o 2 heteroátomos seleccionados entre O o N, y que opcionalmente contiene un enlace doble adicional y/o está opcionalmente sustituido con un grupo oxo (=O) y/o un grupo 1-4C-alquilo,

n 0 - 3

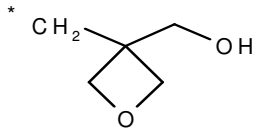
R^6 es (a) hidrógeno; (b) hidroxi; (c) ciano; (d) 1-6C-alcoxi opcionalmente sustituido en forma independiente una o más veces con (d1) OH, (d2) -O-(1-6C-alquilo) (d3) $C(O)OR^9$, (d4) $C(O)NR^{10}R^{11}$, (d5) $NR^{10}R^{11}$, (d6) -S-(1-6C-alquilo), (d7) -S(O)-(1-6C-alquilo), (d8) $-SO_2$-(1-6C-alquilo) (d9) $SO_2NR^{10}R^{11}$, (d10) heterociclilo, que está opcionalmente sustituido con $C(O)OR^9$, o oxo (=O), (d11) heteroarilo, que está opcionalmente sustituido en forma independiente una o más veces con ciano, 1-4C-alquilo, 1-6C-haloalquilo, 1-6C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, (1-6C-alquilen)-O-(1-6C-alquilo), (e) $SO_2NR^{10}R^{11}$, (f) 3-7C-cicloalcoxi, (g) 1-6C-haloalcoxi, (h) $COOR^9$, (i) $-C(O)NR^{10}R^{11}$, (j) -O-heteroarilo opcionalmente sustituido con CN(k)



, donde * es el punto de unión,

(l) -O-(2-6C-alquilen)-O-(1-6C-alquilo) que está opcionalmente sustituido con hidroxi, $NH(CO)OR^9$,

R^7 es (a) hidrógeno, (b)1-6C-alquilo, que está opcionalmente sustituido con heteroarilo(c) 1-6C-

haloalquilo, (d) 1-6C-hidroxialquilo, (e)  , donde * es el punto de unión, (f) -C(O)-(1-6C-alquilo), (g) -C(O)-(1-6C-alquilen)-O-(1-6C-alquilo), (h) -C(O)-(1-6C-alquilen)-O-(2-6C-alquilen)-O-(1-6C-alquilo), (i) -C(O)-heterociclilo, (j) bencilo donde el anillo fenilo está opcionalmente sustituido con 1-5 sustituyentes seleccionados en forma independiente entre el grupo que consiste en hidrógeno, halógeno, 1-4C-alquilo, 1-4C-haloalquilo, 1-4C-alcoxi, 1-4C-haloalcoxi, ciano, $C(O)OR^9$, (k) heteroarilo, u opcionalmente R^6 y R^7 junto con el átomo de nitrógeno al cual R^7 está unido forman un anillo de 6 miembros que puede contener otro heteroátomo seleccionado entre el grupo que consiste en O, S, N, y que está opcionalmente sustituido con (1-6C-alquil)-OH, (1-6C-alquil)-$NR^{10}R^{11}$,

R^8 es hidrógeno, halógeno, hidroxi, ciano, 1-6C-alquilo, 1-6C-hidroxialquilo, 1-6C-haloalquilo, 1-6C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,

m es 0-4

R^9 es (a) hidrógeno, (b) 1-6C-alquilo que está opcionalmente sustituido con hidroxi,

R^{10}, R^{11} son en forma independiente entre sí hidrógeno, 1-4C-alquilo, 1-4C-hidroxialquilo, 1-4C-alcoxi, -(CO)-(1-6C-alquilo), CHO, $COOR^9$, o junto con el átomo de nitrógeno al cual están unidos forman un

anillo heterocíclico de entre 4 y 6 miembros que opcionalmente contiene otro heteroátomo seleccionado entre el grupo que consiste en O, S o N, y que está opcionalmente sustituido con 1–2 átomos de flúor o $COOR^9$,

o un N–óxido, una sal, un tautómero o un estereoisómero de dicho compuesto, o una sal de dicho N–óxido, tautómero o estereoisómero.

2. El compuesto de fórmula (I) de acuerdo con la reivindicación 1,

donde

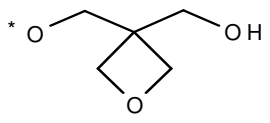
R^1 es hidrógeno, halógeno, 1–3C–alquilo,

R^2/R^3 son en forma independiente entre sí hidrógeno, halógeno, ciano, 1–6C–haloalquilo, 1–6C–haloalcoxi,

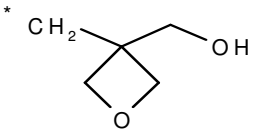
R^4 es en forma independiente hidrógeno, halógeno, ciano, 1–6C–alquilo, 2–6C–alquenilo, 1–6C–haloalquilo, 1–6C–hidroxialquilo, 1–6C–alcoxi, 1–6C–haloalcoxi, $-C(O)OR^9$, -(1–6C–alquilen)$-C(O)OR^9$, $-C(O)-$(1–6C–alquilo), $-C(O)NR^{10}R^{11}$, 3–7C–cicloalquilo, –S–(1–6C–haloalquilo), SF_5, $-SO_2NH-$(3–7–cicloalquilo), $-SO_2NR^{10}R^{11}$, heteroarilo que está opcionalmente sustituido en forma independiente una o más veces con ciano, 1–4C–alquilo, 1–6C–haloalquilo, 1–6C–haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, donde dos de R^2, R^3 $(R^4)_n$, cuando se encuentran en posición *orto* entre sí, pueden formar junto con los dos átomos de carbono a

los cuales están unidos un anillo heterocíclico de 5, 6 o 7 miembros que contiene 1 o 2 heteroátomos seleccionados entre O o N, y opcionalmente un enlace doble adicional y/o un grupo carbonilo y/o un grupo 1-4C-alquilo,

n 0 - 3

R^6 es (a) hidrógeno; (b) hidroxi; (c) ciano; (d) 1-6C-alcoxi opcionalmente sustituido con (d1) 1-2 OH, (d2) $NR^{10}R^{11}$, (d3) $SO_2NR^{10}R^{11}$, (d4) heterociclilo, (d5) heteroarilo, que está opcionalmente sustituido en forma independiente una o más veces con ciano, 1-4Calquilo, 1-6C-haloalquilo, 1-6C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, (e) $SO_2NR^{10}R^{11}$, ; (f) 3-7C-cicloalcoxi, (g) 1-6C-haloalcoxi, (h) $-C(O)NR^{10}R^{11}$, (i) -O-heteroarilo opcionalmente sustituido con CN(j) 

, donde * es el punto de unión,

R^7 es (a) hidrógeno, (b)1-6C-alquilo, que está opcionalmente sustituido con heteroarilo(c) 1-6C-haloalquilo, (d) 1-6C-hidroxialquilo, (e) 

, donde * es el punto de unión, (f) -C(O)-(1-6C-alquilo) (g) -C(O)-(1-6C-alquilen)-O-(1-6C-alquilo) (h) -C(O)-(1-6C-alquilen)-O-(1-6C-alquilen)-O-(1-6C-alquilo) (i) -C(O)-heterociclilo, (j) bencilo donde el anillo fenilo está opcionalmente sustituido con 1-5 sustituyentes seleccionados en forma

independiente entre el grupo que consiste en hidrógeno, halógeno, 1-4Calquilo, 1-4C-haloalquilo, 1-4C-alcoxi, 1-4C-haloalcoxi, ciano, $C(O)OR^9$, (k) heteroarilo, u opcionalmente R^6 y R^7 junto con el átomo de nitrógeno al cual están unidos forman un anillo de 6 miembros que puede contener otro heteroátomo seleccionado entre el grupo que consiste en O, S, N, y que está opcionalmente sustituido con hidroxi-(1-6alquilo),

R^8 es hidrógeno, halógeno, ciano, 1-6C-haloalquilo, 1-6C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,

m es 0-4

R^9 es (a) hidrógeno, (b) 1-6C-alquilo que puede estar opcionalmente sustituido con hidroxi,

R^{10}, R^{11} son en forma independiente entre sí hidrógeno, 1-4C-alquilo, 1-4C-hidroxialquilo, 1-4C-alcoxi, o junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 5 o 6 miembros que opcionalmente contiene otro heteroátomo seleccionado entre el grupo que consiste en O, S o N,

o un N-óxido, una sal, un tautómero o un estereoisómero de dicho compuesto, o una sal de dicho N-óxido, tautómero o estereoisómero.

3. El compuesto de fórmula (I) de acuerdo con la reivindicación 1, donde

R^1 es hidrógeno, halógeno, 1-3C-alquilo,

R^2/R^3 son en forma independiente entre sí

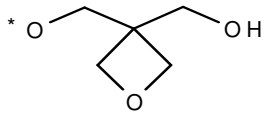
hidrógeno, halógeno, ciano, hidroxi, 1-3C-haloalquilo, 1-3C-haloalcoxi, 1-3C-alcoxi,

R^4 es en forma independiente hidrógeno, hidroxi, halógeno, ciano, NO_2, 1-3C-alquilo, 2-3C-alquenilo, 2-3C-alquinilo, 1-3C-haloalquilo, 1-3C-hidroxialquilo, 1-3C-alcoxi, -O-(2-3C-alquilen)-O-C(O)-(1-3C-alquilo), 1-3C-haloalcoxi, $-C(O)OR^9$, -(1-3C-alquilen)-$C(O)OR^9$, -C(O)-(1-3C-alquilo), -$C(O)NR^{10}R^{11}$, 3-7C-cicloalquilo, -S-(1-3C-haloalquilo), SF_5, -SO_2NH-(3-7C-cicloalquilo), -$SO_2NR^{10}R^{11}$, $NR^{10}R^{11}$, heteroarilo que está opcionalmente sustituido en forma independiente una o más veces con ciano, 1-3C-alquilo, 1-3C-haloalquilo, 1-3C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, donde dos de R^2, R^3 $(R^4)_n$, cuando se encuentran en posición *orto* entre sí, pueden formar junto con los dos átomos de carbono a los cuales están unidos un anillo heterocíclico de 5, 6 o 7 miembros que contiene 1 o 2 heteroátomos seleccionados entre O o N, y que opcionalmente contiene un enlace doble adicional y/o está opcionalmente sustituido con un grupo oxo (=O) y/o un grupo 1-3C-alquilo,

n 0 - 3

R^6 es (a) hidrógeno; (b) hidroxi; (c) ciano; (d) 1-6C-alcoxi opcionalmente sustituido en forma independiente una o más veces con (d1) OH, (d2) -O-(1-3C-alquilo) (d3) $C(O)OR^9$, (d4) $C(O)NR^{10}R^{11}$, (d5) $NR^{10}R^{11}$, (d6) -S-(1-3C-alquilo), (d7) -S(O)-(1-3C-alquilo),

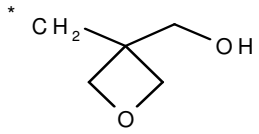
(d8) $-SO_2-$(1-3C-alquilo), (d9) $SO_2NR^{10}R^{11}$, (d10) heterociclilo, que está opcionalmente sustituido con $C(O)OR^9$, o oxo (=O), (d11) heteroarilo, que está opcionalmente sustituido en forma independiente una o más veces con ciano, 1-3C-alquilo, 1-3C-haloalquilo, 1-3C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, (1-3C-alquilen)-O-(1-3C-alquilo), (e) $SO_2NR^{10}R^{11}$, (f) 3-7C-cicloalcoxi, (g) 1-6C-haloalcoxi, (h) $COOR^9$, (i) $-C(O)NR^{10}R^{11}$, (j) -O-heteroarilo opcionalmente sustituido con CN(k)



, donde * es el punto de unión,

(l) -O-(2-3C-alquilen)-O-(1-3C-alquilo) que está opcionalmente sustituido con hidroxi, $NH(CO)OR^9$,

R^7 es (a) hidrógeno, (b)1-3C-alquilo, que está opcionalmente sustituido con heteroarilo(c) 1-3C-haloalquilo, (d) 1-3C-hidroxialquilo, (e)



, donde * es el punto de unión, (f) -C(O)-(1-3C-alquilo) (g) -C(O)-(1-3C-alquilen)-O-(1-3C-alquilo) (h) -C(O)-(1-3C-alquilen)-O-(2-3C-alquilen)-O-(1-3C-alquilo) (i) -C(O)-heterociclilo, (j) bencilo donde el anillo fenilo está opcionalmente sustituido con 1-5 sustituyentes seleccionados en forma independiente entre el grupo que consiste en hidrógeno, halógeno, 1-4C-alquilo, 1-4C-alcoxi, 1-4C-haloalcoxi, ciano, $C(O)OR^9$, (k) heteroarilo, u opcionalmente R^6 y R^7 junto con el átomo de nitrógeno

al cual R^7 está unido forman un anillo de 6 miembros que puede contener otro heteroátomo seleccionado entre el grupo que consiste en O, S, N, y que está opcionalmente sustituido con (1-3C-alquil)-OH, (1-3C-alquil)-$NR^{10}R^{11}$,

R^8 es hidrógeno, halógeno, hidroxi, ciano, 1-3C-alquilo, 1-3C-hidroxialquilo, 1-3C-haloalquilo, 1-3C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$,

m es 0-4

R^9 es (a) hidrógeno, (b) 1-3C-alquilo que está opcionalmente sustituido con hidroxi,

R^{10}, R^{11} son en forma independiente entre sí hidrógeno, 1-3C-alquilo, 1-3C-hidroxialquilo, 1-3C-alcoxi, -(CO)-(1-3C-alquilo), CHO, $COOR^9$ o junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de entre 4 y 6 miembros que opcionalmente contiene otro heteroátomo seleccionado entre el grupo que consiste en O, S o N, que está opcionalmente sustituido con 1-2 átomos de flúor o $COOR^9$,

o un N-óxido, una sal, un tautómero o un estereoisómero de dicho compuesto, o una sal de dicho N-óxido, tautómero o estereoisómero.

4. El compuesto de fórmula (I) de acuerdo con la reivindicación 1, en donde

R^1 es hidrógeno, 1-3C-alquilo,

R^2/R^3 son en forma independiente entre sí

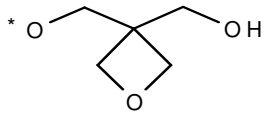
hidrógeno, halógeno, ciano, hidroxi, 1-4C-haloalquilo, 1-4C-alcoxi,

R^4 es en forma independiente hidrógeno, hidroxi, halógeno, ciano, 1-4C-alquilo, 2-4C-alquenilo, 2-4C-alquinilo, 1-4C-haloalquilo, 1-4C-hidroxialquilo, 1-4C-alcoxi, -O-(2-4C-alquilen)-O-C(O)-(1-4C-alquilo), 1-4C-haloalcoxi, $-C(O)OR^9$, -(1-4C-alquilen)-$C(O)OR^9$, -C(O)-(1-4C-alquilo), -$C(O)NR^{10}R^{11}$, 3-7C-cicloalquilo, -S-(1-4C-haloalquilo), SF_5, -SO_2NH-(3-7C-cicloalquilo), -$SO_2NR^{10}R^{11}$, $NR^{10}R^{11}$, heteroarilo que está opcionalmente sustituido en forma independiente una o más veces con ciano, 1-4C-alquilo, 1-4C-haloalquilo, 1-4C-haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, donde dos de R^2, R^3 $(R^4)_n$, cuando se encuentran en posición *orto* entre sí, pueden formar junto con los dos átomos de carbono a los cuales están unidos un anillo heterocíclico de 5, 6 o 7 miembros que contiene 1 o 2 heteroátomos seleccionados entre O o N, y que opcionalmente contiene un enlace doble adicional y/o está opcionalmente sustituido con un grupo oxo (=O) y/o un grupo 1-4C-alquilo,

n 0 - 3

R^6 es (a) hidrógeno; (b) hidroxi; (d) 1-4C-alcoxi opcionalmente sustituido en forma independiente una o más veces con (d1) OH, (d2) -O-(1-4C-alquilo) (d3) $C(O)OR^9$, (d4) $C(O)NR^{10}R^{11}$, (d5) $NR^{10}R^{11}$, (d6) -S-(1-4C-alquilo), (d7) -S(O)-(1-4C-alquilo), (d8) -SO_2-(1-

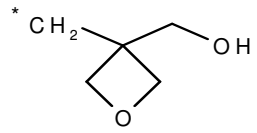
4C–alquilo) (d9) $SO_2NR^{10}R^{11}$, (d10) heterociclilo, que está opcionalmente sustituido con $C(O)OR^9$, o oxo (=O), (d11) heteroarilo, que está opcionalmente sustituido en forma independiente una o más veces con ciano, 1–4C–alquilo, 1–4C–haloalquilo, 1–4C–haloalcoxi, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, (1–4C–alquilen)–O–(1–4C–alquilo), (e) $SO_2NR^{10}R^{11}$, (f) 3–7C–cicloalcoxi, (g) 1–6C–haloalcoxi, (h) $COOR^9$, (i) $-C(O)NR^{10}R^{11}$, (j) –O–heteroarilo opcionalmente sustituido con CN(k)



, donde * es el punto de unión,

(l) –O–(2–4C–alquilen)–O–(1–4C–alquilo) que está opcionalmente sustituido con hidroxi, $NH(CO)OR^9$,

R^7 es (a) hidrógeno, (b) (1–4C–alquil)–heteroarilo(c) 1–4C–haloalquilo, (d) 1–4C–hidroxialquilo, (e)



, donde * es el punto de unión, (f) –C(O)–(1–4C–alquilo) (g) –C(O)–(1–4C–alquilen)–O–(1–4C–alquilo) (h) –C(O)–(1–4C–alquilen)–O–(2–4C–alquilen)–O–(1–4C–alquilo) (i) –C(O)–heterociclilo, (j) bencilo donde el anillo fenilo está opcionalmente sustituido con 1–5 sustituyentes seleccionados en forma independiente entre el grupo que consiste en hidrógeno, halógeno, 1–4C–alquilo, 1–4C–alcoxi, 1–4C–haloalcoxi, ciano, $C(O)OR^9$, (k) heteroarilo, u opcionalmente R^6 y R^7 junto con el átomo de nitrógeno al cual R^7 está unido forman un anillo de

6 miembros que puede contener otro heteroátomo seleccionado entre el grupo que consiste en O, S, N, y que está opcionalmente sustituido con (1-4C-alquil)-OH, (1-4C-alquil)-$NR^{10}R^{11}$,

R^8 es hidrógeno, halógeno, hidroxi, ciano, $C(O)NR^{10}R^{11}$, 1-4C-alquilo, 1-4C-hidroxialquilo, 1-4C-haloalquilo, 1-4C-haloalcoxi,

m es 0-2,

R^9 es hidrógeno, 1-4C-alquilo que está opcionalmente sustituido con hidroxi,

R^{10}, R^{11} son en forma independiente entre sí hidrógeno, 1-4C-alquilo, 1-4C-hidroxialquilo, 1-4C-alcoxi, -C(O)-(1-4C-alquilo), o $COOR^9$ o junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de entre 4 y 6 miembros que opcionalmente contiene otro heteroátomo seleccionado entre el grupo que consiste en O, S o N, que está opcionalmente sustituido con 1-2 átomos de flúor o $COOR^9$,

o un N-óxido, una sal, un tautómero o un estereoisómero de dicho compuesto, o una sal de dicho N-óxido, tautómero o estereoisómero.

5. El compuesto de fórmula (I) de acuerdo con la reivindicación 1, donde,

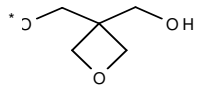
R^1 es hidrógeno,

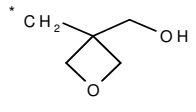
R^2/R^3 es en forma independiente hidrógeno, flúor, cloro, bromo, ciano, hidroxi, CF_3, $-O-CH_3$ o $-O-CH_2-CF_3$,

R^4 es en forma independiente en cada caso hidrógeno, flúor, cloro, bromo o iodo, ciano, NO_2, hidroxi, $-CH_3$, $-C_3H_7$, ciclopropilo, 1-propenilo, $-C\equiv CH$, $-CF_3$, $-CH_2-OH$, $-CH_2-CH_2-OH$, $-C(CH_3)_2-OH$, $-CH_2-C(CH_3)_2-OH$, $-C(CH_3)_2-CH_2-OH$, $-OCH_3$, $-O-CH_2-CH_3$, $-OCF_3$, $-OCF_2H$, $-OCH_2CF_3$, $-O-(CH_2)-O-C(O)-CH3$, $-C(O)CH_3$, $-COOH$, $-C(O)OCH_3$, $-C(O)OC_2H_5$, $-C(O)OC(CH_3)_3$, $-CH_2-COOH$, $-CH_2-COOC_2H_5$, $-C(CH_3)_2-COOC_2H_5$, $-C(O)NH_2$, $-C(O)NH(CH_3)$, $-C(O)N(CH_3)_2$, $-C(O)NH-(CH_2)_2-OH$, $-C(O)-$(N-morfolinilo), $-SO_2-NH-$ciclopropilo, $-SO_2-$(N-morfolino), NH_2, $NH-C(O)(CH_3)$, 5-metil-oxa-diazol-3-ilo, N-pirrolilo, N-pirazolilo, $-S-CF_3$, SF_5, donde dos de R^2, R^3 $(R^4)_n$, cuando se encuentran en posición *orto* entre sí, forman juntos $-O-CH_2-CH_2-CH_2-O-$, $-O-CH_2-CH_2-$, $-(CH_3)C=CH-(C=O)-O-$, $-CH_2-(C=O)-O-$, $-(CH_2)_2-(C=O)-NH-$, que junto con los dos átomos de carbono a los cuales están unidos forman un anillo de 5, 6 o 7 miembros,

n es 0, 1, 2, 3,

R^6 es hidrógeno, hidroxi, ciano, $-O-$ciclopropilo, $-OCH_3$, $-OCF_3$, $-OCF_2H$, $-OCH_2CF_3$, $-O-(CH_2)_2-OH$, $-O-(CH_2)_2-NH_2$, $-O(CH_2)_2-N(CH_3)_2$, $-O-(CH_2)_2-O-CH_3$, $-O-(CH_2)_2-O-(CH_2)_2-OH$, $-O-CH_2-CH(OH)-CH_2OH$, $-O-CH_2-CH(OH)-CH_2-NH-C(O)OC(CH_3)_3$, $-O-CH_2-COOH$, $-O-CH_2-COOC_2H_5$, $C(O)NH_2$, $-O-CH_2-C(O)-$(3-fluoro-N-azetidina), $-O-CH_2-C(O)-$(3,3-difluoro-N-azetidina), $-O-CH_2-CH(OH)-CH_2-N-$piperidinilo, $-O-(CH_2)_2$(morfolina-4-ilo), $-O-CH_2-$(morfolina-2-ilo), $-O-CH_2-$(morfolina-2-il-4-tert.-

butoxicarboxilato), $-O-CH_2-$(pirrolidin-2-ona-5-ilo), $-O-(CH_2)_2-S-CH_3$, $-O-(CH_2)_2-SO-CH_3$, $-O-(CH_2)_2-SO_2-CH_2$, $-O-CH_2-SO_2NH_2$, $-SO_2-CH(CH_3)_2$,  , donde * es el punto de unión, $-O-(CH_2)_2$-tetrazolilo, $-O-CH_2$-tetrazolilo, -O-piridin-4-ilo, -O-(3-ciano-piridin-4-ilo), o - $O-CH_2-$(oxadiazol)$-CH_2-O-CH_3$,

R^7 es hidrógeno, metilo, difluorometilo, hidroxietilo,  , donde * es el punto de unión, $-(CH_2)_2$-tetrazolilo, piridin-4-ilo, -C(O)-tetrahidropiran-4-ilo, $-C(O)-CH_2-O-CH_3$, $-C(O)-CH_3$, $-C(O)CH_2-O-(CH_2)_2-O-CH_3$, $C(O)OCH_2-CH=CH_2$, o bencilo el cual está opcionalmente sustituido una o más veces con flúor, cloro, bromo, ciano, metilo, difluorometilo, metoxi, etoxi, difluormetoxi, trifluorometoxi, $-O-CH_2-CF_3$, $-C(O)OCH_3$, u opcionalmente R^6 y R^7 junto con el átomo de nitrógeno al cual R^7 está unido forman un anillo de 6 miembros que puede contener otro heteroátomo seleccionado entre el grupo que consiste en O, S, N y que además está opcionalmente sustituido con $-CH_2-OH$ o $-CH_2-NH-CHO$

R^8 es hidrógeno, flúor, hidroxi, ciano, CH_3, CF_3, CH_2-OH, OCH_3, C(O)OH, $C(O)OCH_3$, $C(O)OC_2H_5$, $C(O)O(CH_2)_2-OH$, $C(O)NH_2$, $C(O)NHCH_3$,

m es 0, 1 o 2

o un N-óxido, una sal, un tautómero o un estereoisómero de dicho compuesto, o una sal de dicho N-

óxido, tautómero o estereoisómero.

6. Los compuestos de fórmula (I) de acuerdo con la reivindicación 1, que se seleccionan entre el grupo que consiste en:

2-[1-(6-cloro-2-fluoro-3-metilbencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(6-cloro-2-fluoro-3-metoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

5-metoxi-2-{1-[3-(5-metil-1,2,4-oxadiazol-3-il)bencil]-1H-indazol-3-il}-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2-cloro-4,5-dimetilbencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

5-metoxi-2-{1-[4-(pentafluoro-λ^6-sulfanil)bencil]-1H-indazol-3-il}-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2,6-difluoro-3-metoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

N-(2,6-difluoro-3-metoxibencil)-2-[1-(2,6-difluoro-3-metoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-{1-[(6-bromo-1,3-benzodioxol-5-il)metil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

N-(4-etoxi-2,6-difluorobencil)-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-

indazol-1-il}metil)benzonitrilo,

2-[1-(2-cloro-4-metoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(3,4-dihidro-2H-1,5-benzodioxepin-6-ilmetil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2,6-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

N-(2,6-difluorobencil)-2-[1-(2,6-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

5-metoxi-N-(piridin-4-il)-2-(1-{3-[(trifluorometil)sulfanil]bencil}-1H-indazol-3-il)pirimidin-4-amina,

2-[1-(2,3-difluoro-4-metilbencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

N-(2,3-difluoro-4-metilbencil)-2-[1-(2,3-difluoro-4-metilbencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

5-metoxi-2-{1-[4-(1H-pirazol-1-il)bencil]-1H-indazol-3-il}-N-(piridin-4-il)pirimidin-4-amina

2-[1-(2,6-diclorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

N-(2,6-diclorobencil)-2-[1-(2,6-diclorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

5-metoxi-N-(piridin-4-il)-2-(1-{4-[(trifluorometil)sulfanil]bencil}-1H-indazol-3-il)pirimidin-4-amina,

2-[1-(2-clorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-

il)pirimidin-4-amina,

N-(2-clorobencil)-2-[1-(2-clorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzoato de metilo,

3-cloro-4-{[(2-{1-[2-cloro-4-(metoxicarbonil)bencil]-1H-indazol-3-il}-5-metoxipirimidin-4-il)(piridin-4-il)amino]metil}benzoato de metilo,

2-[1-(4-bromo-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2-cloro-4-fluoro-3-metoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(4-etoxi-2,3-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

N-(4-etoxi-2,3-difluorobencil)-2-[1-(4-etoxi-2,3-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

5-metoxi-N-(piridin-4-il)-2-{1-[2,3,5,6-tetrafluoro-4-(2,2,2-trifluoroetoxi)bencil]-1H-indazol-3-il}pirimidin-4-amina,

5-metoxi-N-(piridin-4-il)-N-[2,3,5,6-tetrafluoro-4-(2,2,2-trifluoroetoxi)bencil]-2-{1-[2,3,5,6-tetrafluoro-4-(2,2,2-trifluoroetoxi)bencil]-1H-indazol-3-il}pirimidin-4-amina,

2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzoato de metilo,

5-metoxi-N-(piridin-4-il)-2-[1-(2,4,6-trifluorobencil)-1H-indazol-3-il]pirimidin-4-amina,

5-metoxi-N-(piridin-4-il)-N-(2,4,6-trifluorobencil)-2-[1-(2,4,6-trifluorobencil)-1H-indazol-3-il]pirimidin-4-amina,

2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina

2-[1-(2,4-diclorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2-fluoro-4-iodobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2-bromobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

N-(2-bromobencil)-2-[1-(2-bromobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

ácido [3-fluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]acético,

5-metoxi-N-(piridin-4-il)-2-[1-(2,3,5,6-tetrafluoro-4-metoxibencil)-1H-indazol-3-il]pirimidin-4-amina,

5-metoxi-2-[1-(4-propilbencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

2-{1-[2,6-dicloro-4-(trifluorometoxi)bencil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

N-[2,6-dicloro-4-(trifluorometoxi)bencil]-2-{1-[2,6-dicloro-4-(trifluorometoxi)bencil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

7-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)-3,4-dihidroquinolin-2(1H)-ona,

2-[1-(2-cloro-4-iodobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(3,5-dimetoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-{1-[2-cloro-6-(trifluorometil)bencil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2-cloro-5-fluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

7-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)-4-metil-2H-cromen-2-ona,

3-fluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzonitrilo,

4-{[{2-[1-(4-ciano-2-fluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}(piridin-4-il)amino]metil}-3-fluorobenzonitrilo,

2-{1-[2,6-dicloro-3-(trifluorometil)bencil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

[3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]acetato de etilo,

2-[1-(4-fluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

N-ciclopropil-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)bencensulfonamida,

6-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)-1-benzofuran-2(3H)-ona,

2-{1-[4-(difluorometoxi)-2,6-difluorobencil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

tert-butilo 3-cloro-4-({3-[5-metoxi-4-(piridin-4-

ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzoato de,
2-[3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]-2-metilpropanoato de etilo,
4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzonitrilo,
5-metoxi-2-{1-[4-(morfolin-4-ilsulfonil)bencil]-1H-indazol-3-il}-N-(piridin-4-il)pirimidin-4-amina,
2-[1-(2,6-dicloro-3-nitrobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzonitrilo,
N-[4-(difluorometoxi)-2,6-difluorobencil]-2-{1-[4-(difluorometoxi)-2,6-difluorobencil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
5-metoxi-N-(piridin-4-il)-2-{1-[3-(1H-pirrol-1-il)bencil]-1H-indazol-3-il}pirimidin-4-amina,
3,5-difluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzonitrilo
5-metoxi-2-{1-[2-metoxi-4-(trifluorometil)bencil]-1H-indazol-3-il}-N-(piridin-4-il)pirimidin-4-amina,
2-[1-(2,6-difluoro-3-metilbencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
2-[1-(2-fluoro-6-metoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
3,5-difluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzamida,
acetato de 2-[3,5-difluoro-4-({3-[5-metoxi-4-(piridin-4-

ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenoxi]etilo,

2-[1-(2,6-difluoro-4-propoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(4-etoxi-2-fluoro-6-metoxibencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ol

2-[1-(4-metoxibencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ol,

2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ol,

2-[1-(4-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-ol,

{3-[({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metil]oxetan-3-il}metanol,

{3-[({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metil]oxetan-3-il}metanol,

(3-{[(2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-{[3-(hidroximetil)oxetan-3-il]metoxi}pirimidin-4-il)(piridin-4-il)amino]metil}oxetan-3-il)metanol,

1-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metansulfonamida,

5-[2-(dimetilamino)etoxi]-2-[1-(2-fluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2-fluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)-5-[2-(1H-tetrazol-5-il)etoxi]pirimidin-4-amina,

2-[1-(2-fluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)-5-[2-(1H-tetrazol-5-il)etoxi]-N-[2-(1H-tetrazol-5-il)etil]pirimidin-4-amina,

5-[2-(dimetilamino)etoxi]-2-[1-(4-fluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2-fluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)-5-(1H-tetrazol-5-ilmetoxi)pirimidin-4-amina,

5-[2-(dimetilamino)etoxi]-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

1-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)-3-(piperidin-1-il)propan-2-ol,

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-(2-metoxietoxi)-N-(piridin-4-il)pirimidin-4-amina,

2-[({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metil]morfolina-4-carboxilato de tert-butilo,

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-[2-(morfolin-4-il)etoxi]-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-{[3-(metoximetil)-1,2,4-oxadiazol-5-il]metoxi}-N-(piridin-4-il)pirimidin-4-amina,

({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)acetato de etilo,

1-(3,3-difluoroazetidin-1-il)-2-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)etanona,

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-[2-(metilsulfanil)etoxi]-N-(piridin-4-il)pirimidin-4-amina,

2-[2-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)etoxi]etanol,

ácido fórmico - (5S)-5-[({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metil]pirrolidin-2-ona (1:1),

(5R)-5-[({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metil]pirrolidin-2-ona,

{2-[2-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)etoxi]etil}carbamato de tert-butilo,

2-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)-1-(3-fluoroazetidin-1-il)etanona,

(5S)-5-[({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)metil]pirrolidin-2-ona,

[2-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)etil]carbamato de tert-butilo,

N-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-8-(piridin-4-il)-7,8-dihidro-6H-pirimido[5,4-b][1,4]oxazin-7-il}metil)formamida,

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(4-metoxibencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(2-fluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(4-ciclopropil-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-(1-{2,6-difluoro-4-[(1E)-prop-1-en-1-il]bencil}-1H-indazol-3-il)-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

1-[3,5-difluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]etanona,

[2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]metanol,

2-[3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]etanol,

2-[3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]-2-metilpropan-1-ol,

[4-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-il]metanol,

2-[3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]propan-2-ol,

1-[3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]-2-metilpropan-2-ol,

2-[2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]propan-2-ol,

5-(difluorometoxi)-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

5-(difluorometoxi)-N-(difluorometil)-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

4-[(difluorometil)(piridin-4-il)amino]-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]pirimidin-5-ol,

2-[1-(4-metoxibencil)-1H-indazol-3-il]-N-(piridin-4-il)-5-(2,2,2-trifluoroetoxi)pirimidin-4-amina,

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)-5-(2,2,2-trifluoroetoxi)pirimidin-4-amina,

3-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)propan-1,2-diol,

(2S)-3-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)propan-1,2-diol,

(2R)-3-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)propan-1,2-diol,

2-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)etanol,

2-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)etanol,

4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-(2-hidroxietoxi)pirimidin-4-il}amino)piridin-3-carboxilato de etilo,

4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-(2-hidroxietoxi)pirimidin-4-il}amino)-N-metilpiridin-3-carboxamida,

4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-(2-hidroxietoxi)pirimidin-4-il}amino)piridin-3-carboxamida,

4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-(2-hidroxietoxi)pirimidin-4-il}amino)piridin-3-carboxilato de 2-hidroxietilo,

5-(ciclopropiloxi)-2-[1-(4-metoxibencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

clorhidrato de 2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina (1:1),

clorhidrato de (2S)-3-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)propan-1,2-diol (1:1),

clorhidrato de 2-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)etanol (1:1),

2-[1-(2,6-diclorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina clorhidrato de (1:1),

clorhidrato de [2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]metanol (1:1),

clorhidrato de (2R)-3-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)propan-1,2-diol (1:1),

N-{2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]pirimidin-4-il}-N-(piridin-4-il)acetamida,

N-{2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]pirimidin-4-il}-2-metoxi-N-(piridin-4-il)acetamida,

N-{2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]pirimidin-4-il}-N-(piridin-4-il)tetrahidro-2H-piran-4-

carboxamida,

N-{2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]pirimidin-4-il}-2-(2-metoxietoxi)-N-(piridin-4-il)acetamida,

2-[{2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]pirimidin-4-il}(piridin-4-il)amino]etanol,

(3-{[{2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]pirimidin-4-il}(piridin-4-il)amino]metil}oxetan-3-il)metanol,

2-{1-[4-bromo-2-fluoro-6-(2,2,2-trifluoroetoxi)bencil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

2-{1-[4-bromo-2,6-bis(2,2,2-trifluoroetoxi)bencil]-1H-indazol-3-il}-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

ácido 2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzoico,

ácido ({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-il}oxi)acético,

2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)-N-metilbenzamida,

2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzamida,

2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)-N,N-dimetilbenzamida,

2,4-dicloro-N-(2-hidroxietil)-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzamida,

[2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil](morfolin-4-il)metanona,

3,5-difluoro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)-N-metilbenzamida,

2-[1-(4-etinil-2-fluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

{2-[1-(2-fluorobencil)-1H-indazol-3-il]-8-(piridin-4-il)-7,8-dihidro-6H-pirimido[5,4-b][1,4]oxazin-7-il}metanol,

2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-metoxi-N-metil-N-(piridin-4-il)pirimidin-4-amina,

4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-carbonitrilo,

2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-metoxi-N,N-di(piridin-4-il)pirimidin-4-amina,

4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-carboxilato de metilo,

2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

4-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-carbonitrilo,

2-[(3-{4-[(2,6-dimetilpiridin-4-il)amino]-5-metoxipirimidin-2-il}-1H-indazol-1-il)metil]-5-etoxi-3-fluorofenol,

4-({5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]pirimidin-4-il}amino)piridin-2(1H)-ona,

4-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-2(1H)-ona,

4-({5-metoxi-2-[1-(4-propilbencil)-1H-indazol-3-il]pirimidin-4-il}amino)nicotinonitrilo,

4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-

metoxipirimidin-4-il}amino)piridin-3-carboxamida,

4-({5-metoxi-2-[1-(4-propilbencil)-1H-indazol-3-il]pirimidin-4-il}amino)piridin-3-carboxamida,

4-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-carboxamida,

4-({2-[1-(2,6-difluoro-4-hidroxibencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-carboxamida,

4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-hidroxipirimidin-4-il}amino)piridin-3-carbonitrilo,

4-({4-[(3-cianopiridin-4-il)amino]-2-[1-(2-fluorobencil)-1H-indazol-3-il]pirimidin-5-il}oxi)piridin-3-carbonitrilo,

5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]-N-[3-(trifluorometil)piridin-4-il]pirimidin-4-amina,

ácido 3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)benzoico,

ácido fórmico - 3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)-N-metilbenzamida (1:1),

3-cloro-4-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)-N-metilbenzamida,

4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-hidroxipirimidin-4-il}amino)piridin-3-carboxamida,

ácido 4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-hidroxipirimidin-4-il}amino)piridin-3-carboxílico,

4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-hidroxipirimidin-4-il}amino)piridin-3-carboxilato de etilo,

2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-

ilamino)pirimidin-5-carbonitrilo

2-[1-(2-fluorobencil)-1H-indazol-3-il]-4-(piridin-4-ilamino)pirimidin-5-carboxamida,

clorhidrato de ácido 4-({2-[1-(2-fluorobencil)-1H-indazol-3-il]-5-(2-hidroxietoxi)pirimidin-4-il}amino)piridin-3-carboxílico (1:1),

N-(2-fluoropiridin-4-il)-5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]pirimidin-4-amina,

N-(2,6-difluoropiridin-4-il)-5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]pirimidin-4-amina,

N-(3-fluoropiridin-4-il)-5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]pirimidin-4-amina,

5-metoxi-2-[1-(4-metoxibencil)-1H-indazol-3-il]-N-(2-metilpiridin-4-il)pirimidin-4-amina,

N-(difluorometil)-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-[2-(metilsulfinil)etoxi]-N-(piridin-4-il)pirimidin-4-amina,

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-[2-(metilsulfinil)etoxi]-N-(piridin-4-il)pirimidin-4-amina (Enantiómero 1),

2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-[2-(metilsulfinil)etoxi]-N-(piridin-4-il)pirimidin-4-amina (Enantiómero 2),

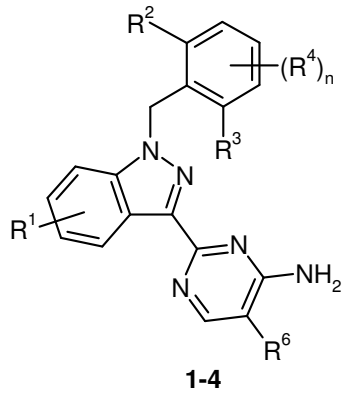
2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-[2-(metilsulfonil)etoxi]-N-(piridin-4-il)pirimidin-4-amina,

5-(2-aminoetoxi)-2-[1-(4-etoxi-2,6-difluorobencil)-1H-

indazol-3-il]-N-(piridin-4-il)pirimidin-4-amina,
2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-(morfolin-2-ilmetoxi)-N-(piridin-4-il)pirimidin-4-amina,
4-({2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-il}amino)piridin-3-carboxilato de etilo,
N-(3,5-difluoropiridin-4-il)-2-[1-(4-etoxi-2,6-difluorobencil)-1H-indazol-3-il]-5-metoxipirimidin-4-amina,
2-[1-(3-amino-2,6-diclorobencil)-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,
N-[2,4-dicloro-3-({3-[5-metoxi-4-(piridin-4-ilamino)pirimidin-2-il]-1H-indazol-1-il}metil)fenil]acetamida,
2-[1-(4-etoxi-2,6-difluorobencil)-4-metil-1H-indazol-3-il]-5-metoxi-N-(piridin-4-il)pirimidin-4-amina,

o un N-óxido, una sal, un tautómero o un estereoisómero de dicho compuesto, o una sal de dicho N-óxido, tautómero o estereoisómero.

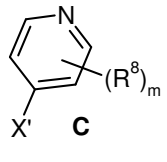
7. Un proceso para la fabricación de compuestos de fórmula general (I) de acuerdo con la reivindicación 1, donde R^7 es hidrógeno se indica en la fórmula (Ia), caracterizado porque un compuesto de fórmula (1-4)



1-4

donde R^1, R^2, R^3, R^4, R^6 y n tienen los significados de acuerdo con la reivindicación 1,

se hace reaccionar con un compuesto de fórmula (C)

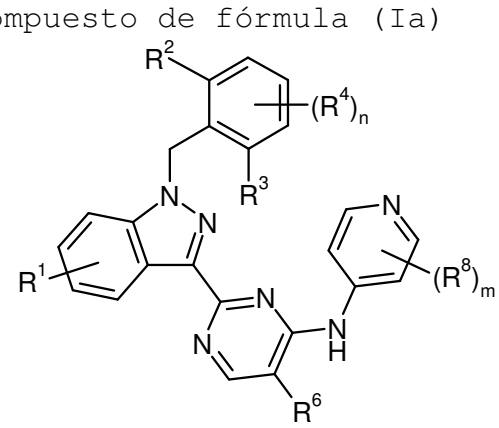


C

donde R^8 y m tienen los significados de acuerdo con la reivindicación 1, y X' representa F, Cl, Br, I, ácido borónico o un ester de ácido borónico

en presencia de una base adecuada, y un catalizador de paladio adecuado, opcionalmente en presencia de un ligando adecuado,

formando un compuesto de fórmula (Ia)



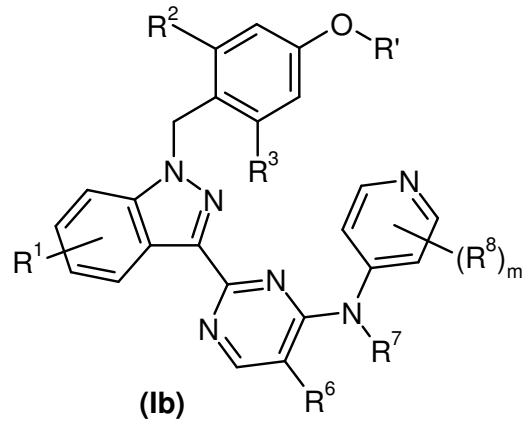
(Ia)

que opcionalmente luego se desprotege para formar un compuesto de fórmula general (I) donde R^7 es hidrógeno y R^1, R^2, R^3, R^4, R^6, R^8 y n y m tienen los significados que se

definen en la reivindicación 1.

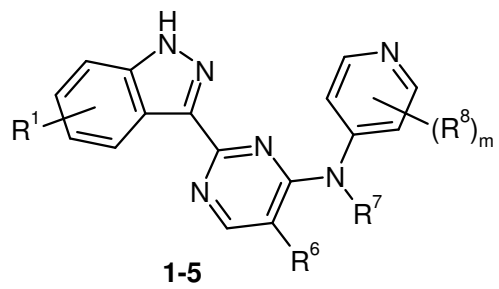
8. Un proceso para la fabricación de compuestos de fórmula general (I) de acuerdo con la reivindicación 1, donde

un compuesto de fórmula (Ib)



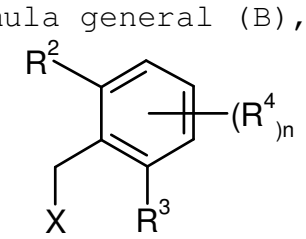
(Ib)

donde R^1, R^2, R^3, R^6, R^7, R^8 y m tienen los significados de acuerdo con la reivindicación 1 y R’ es 1-6C-alquilo o bencilo, se trata con un sistema ácido adecuado para separar el grupo bencílico con el fin de obtener un compuesto de fórmula 1-5



1-5

y luego se hace reaccionar el compuesto de fórmula 1-5 con un compuesto de fórmula general (B),



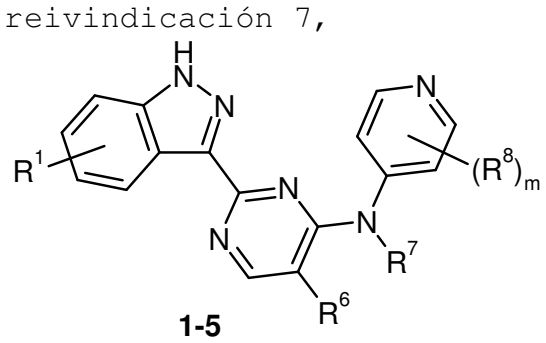
B

donde R^2, R^3, R^4 y n tienen los significados de acuerdo

con la reivindicación 1 y X representa un grupo saliente,

en un sistema de solventes adecuado, en presencia de una base adecuada, en un rango de temperatura entre temperatura ambiente y el punto de ebullición del solvente respectivo, para obtener compuestos de fórmula general (I).

9. Un compuesto intermediario de fórmula general (1-5) de acuerdo con la reivindicación 7,



1-5

donde R^1, R^6, R^7 R^8 y m tienen los significados de acuerdo con la reivindicación 1.

10. El uso de un compuesto de fórmula 1-6 para la fabricación de un compuesto de fórmula (I) de acuerdo con la reivindicación 1.

11. Uso de un compuesto de la fórmula general (I) de acuerdo con cualquiera de las reivindicaciones 1 a 6 para el tratamiento o la profilaxis de enfermedades.

12. Uso de un compuesto de la fórmula general (I) de acuerdo con la reivindicación 11, en donde las enfermedades son enfermedades hiperproliferativas y/o trastornos que responden a la inducción de apoptosis.

13. Uso de un compuesto de la fórmula general (I) de acuerdo con la reivindicación 12, en donde las enfermedades hiperproliferativas y/o los trastornos que responden a una inducción de apoptosis son tumores hematológicos, tumores

sólidos y/o metástasis de los mismos.

14. Uso de un compuesto de la fórmula (I) de acuerdo con la reivindicación 13, donde los tumores son tumores cérvicouterinos, de mama, de pulmón de células no pequeñas, de próstata, de colon o melanoma y/o metástasis de los mismos.

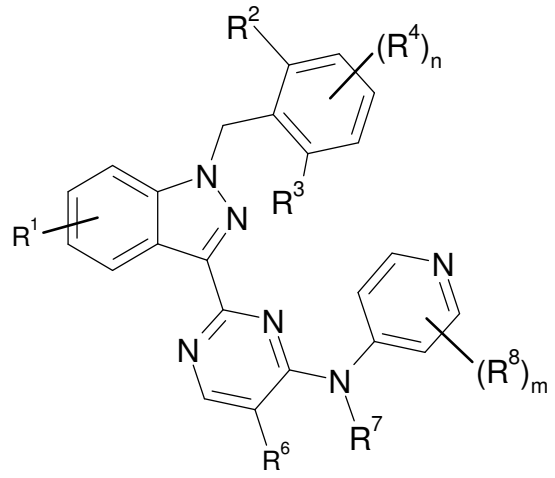
15. Una composición farmacéutica que comprende al menos un compuesto de la fórmula general (I) de acuerdo con cualquiera de las reivindicaciones 1 a 6, junto con al menos un auxiliar farmacéuticamente aceptable.

16. La composición de acuerdo con la reivindicación 15 para el tratamiento de tumores hematológicos, tumores sólidos y/o metástasis de los mismos.

17. Una combinación que comprende uno o más primeros ingredientes activos seleccionados entre un compuesto de la fórmula general (I) de acuerdo con cualquiera de las reivindicaciones 1 a 6, y uno o más segundos ingredientes activos seleccionados entre agentes anticancerosos quimioterapéuticos y agentes anticancerosos específicos del blanco.

RESUMEN

Compuestos de la fórmula (I).



,

que son inhibidores de la quinasa Bub1; procesos para su producción y su uso como fármacos.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

BAYER INTELLECTUAL PROPERTY GMBH
Alfred-Nobel-Str. 10
40789 Monheim
ALLEMAGNE

Date of mailing *(day/month/year)*
18 March 2014 (18.03.2014)

Applicant's or agent's file reference
BHC113049-WO

IMPORTANT NOTIFICATION

International application No.
PCT/EP2012/069562

International filing date *(day/month/year)*
04 October 2012 (04.10.2012)

1. The following indications appeared on record concerning:

☐ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
FANGHÄNEL, Jörg
Fortune Plaza No. 7, 16th Floor
Beijing 100020
China

State of Nationality | State of Residence

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
FANGHÄNEL, Jörg
Saarbrücker Str. 28
10405 Berlin
Germany

State of Nationality | State of Residence

Telephone No.

Facsimile No.

E-mail address
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

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 89 70

Authorized officer
Buloz Isabel
e-mail pt06.pct@wipo.int
Telephone No. +41 22 338 74 06

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.
BHC113049-WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2012/069562	04/10/2012	06/10/2011
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 5 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. [X] **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,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established by this Authority to read as follows:

   SUBSTITUTED BENZYLINDAZOLES FOR USE AS BUB1 KINASE INHIBITORS IN THE TREATMENT OF HYPERPROLIFERATIVE DISEASES.

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2012/069562

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 10
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/069562

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D405/14 C07D413/14 C07D498/04 A61K31/506 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 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 2010 111624 A (SHIONOGI & CO) 20 May 2010 (2010-05-20) General formula (I); page 117; example 191	1-17
A	JUNGSEOG KANG ET AL: "Structure and Substrate Recruitment of the Human Spindle Checkpoint Kinase Bub1", MOLECULAR CELL, vol. 32, no. 3, 1 November 2008 (2008-11-01), pages 394-405, XP55041762, ISSN: 1097-2765, DOI: 10.1016/j.molcel.2008.09.017 paragraph on p. 395 entitled "Identification of a Chemical Inhibitor of Bub1"; figure 1D	1-17

☐ 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 application or patent 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
22 October 2012	30/10/2012

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	Johnson, Claire

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2012/069562

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 2010111624 A	20-05-2010	NONE	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 10

Claim 10 is directed to the use of a compound of formula 1-6. A compound of formula 1-6 is not defined in the claims. This claim is therefore not clear and has not been searched or examined.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2) declaration be overcome.