Industria y Comercio

SUPERINTENDE

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 14-115091- -00000-0000
Fecha: 2014-05-28 14:12:11 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 6

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: NUEVOS 2H–INDAZOLES COMO ANTAGONISTAS DEL RECEPTOR EP2

SOLICITANTE: Bayer Intellectual Property GmbH

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

APODERADO: CARLOS R. OLARTE

BOGOTÁ mayo 28 de 2014

P2014/000080

OLARTEMOURE

OLARTE MOURE & AS(

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 14-115091- -00000-0000
Fecha: 2014-05-28 14:12:11 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 56

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

P2014/000080

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
Dirección: Alfred-Nobel-Str. 10, 40789 Monheim, Alemania
Nacionalidad o Domicilio Alemana
Lugar de Constitución: Alemania

Teléfono: _____ **Fax:** _____
E-mail: _____

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

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
Dirección: Carrera 5 No. 34-03 Bogotá
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olartemoure.com

IDENTIFICACIÓN
C.C. [x] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número 79.782.747Bta
TP 74.295

INVENTOR (ES) (72)

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

(5)

PCT (86)
Solicitud Internacional No. PCT/EP2012/073556 Fecha Noviembre 26, 2012
Publicación Internacional No. WO 2013/079425 Fecha Junio 06, 2013

(6)

Título (54)NUEVOS 2H–INDAZOLES COMO ANTAGONISTAS DEL RECEPTOR EP2

Clasificación Internacional (51) C07D 401/06, C07D 401/14, C07D 403/06, C07D 403/14, C07D 407/14, C07D 413/14, C07D 417/14, A61K 31/416, A61K 31/4439, A61K 31/4545, A61K 31/506, A61K 31/5377, A61P 15/00

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
DE	Noviembre 28, 2011	102011087170.5
DE	abril 24,2012	102012206715.9

(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. 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.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional. PCT/IB306.
- [x] Otros. Búsqueda Internacional.

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79. 782.747Bta T.P. 74.295

LISTA DE INVENTORES

PCT/EP2012/073556

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14612 Falkensee,
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13503 Berlin,
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Alemania
Nacionalidad: Alemana

Antonius TER LAAK
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12159 Berlin,
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Nacionalidad: Neerlandesa

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 14 - 0051218

Bogotá D.C., Mayo 14 de 2014 - 16:17:43

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	601309041	14/05/2014	10.609.000.00

*** 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. 14-115091- -00000-0000
Fecha: 2014-05-28 14:12:11 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 5 / 6

Industria y Comercio SUPERINTENDENCIA	**TESTIGO DOCUMENTAL**	Folio: 5

Dependencia Jerárquica: **Del. Propiedad Industrial**	Código: **2000**
Dependencia Productora: Dir. Nuevas Creaciones	Código: **2020**
Tipo de Radicación: Entrada: ✗ Salida: □ Traslado: □ Convenio: □	
Radicador:	

DESCRIPCIÓN DE LA PRUEBA

Nombre de la Serie / Subserie:	Código:
Expediente: 14-115091-0	Solicitante / ***Quejoso / Demandante / otros.***
Prueba excluida: CD	
N°. de Pruebas excluidas: 1	
Fecha de emisión de la Prueba:	

UBICACIÓN DE LA PRUEBA EN LA SECCIÓN DE MATERIAL GRÁFICO

N°. de bloque:		Otras especificaciones:
Nº. de rodante:		
Nº. de estante:		
N°. de archivador:		
Nº. de entrepaño:		
Nº. de gaveta:		
N°. de caja:		

IMPORTANTE:

- El material gráfico ***o especial*** que se encuentra ***dentro o anexo a*** las unidades documentales o expedientes, debe extraerse y llevarse a aquella sección del archivo que se haya dispuesto para conservar documentos en distintos formatos.
- Entiéndase por material gráfico todos aquellos dibujos, croquis, mapas, planos, fotografías, ilustraciones, pictografías, códices, prensa, objetos tridimensionales, entre otros.

Observaciones:

El cd contiene:
7 archivos en formato pdf, procesados y cargados al sistema

ulvl

Unidad de Conservación

- ○ Bolsa
- ○ Caja
- ○ Libro
- ○ Sobre
- ○ Tomo
- ○ Otro

Soporte Documental

- ✗ CD
- ○ Disquete
- ○ DVD
- ○ Folleto
- ○ Periódico
- ○ Plano
- ○ Publicación Periódica
- ○ USB
- ○ Otro

6

Industria y Comercio
SUPERINTENDENCIA

LISTA DE CHEQUEO
ADMISIÓN A TRÁMITE – NUEVAS CREACIONES

PATENTE DE INVENCIÓN [/] **MODELO DE UTILIDAD** [ ] **Art 33 Decisión 486/00**

- [X] Indicación que se solicita una patente.
- [X] Datos de identificación del solicitante o de la persona que presenta la solicitud
- [X] 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. 14-115091- -00000-0000

Fecha: 2014-05-28 14:12:11 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 86

PI02-F08 (2009-11-18)

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 **P2014/000080**

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**
Dirección: Alfred-Nobel-Str. 10, 40789 Monheim, Alemania
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Lugar de Constitución: Alemania

Teléfono: _____ **Fax:** _____
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IDENTIFICACIÓN
C.C. [ ] **NIT** [ ]
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Número _____

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
Dirección: Carrera 5 No. 34-03 Bogotá
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olartemoure.com

IDENTIFICACIÓN
C.C. [x] **NIT** [ ]
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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/EP2012/073556 Fecha Noviembre 26, 2012
Publicación Internacional No. WO 2013/079425 Fecha Junio 06, 2013

6

Título (54) **NUEVOS 2H–INDAZOLES COMO ANTAGONISTAS DEL RECEPTOR EP2**

Clasificación Internacional (51) C07D 401/06, C07D 401/14, C07D 403/06, C07D 403/14, C07D 407/14, C07D 413/14, C07D 417/14, A61K 31/416, A61K 31/4439, A61K 31/4545, A61K 31/506, A61K 31/5377, A61P 15/00

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
DE	Noviembre 28, 2011	102011087170.5
DE	abril 24,2012	102012206715.9

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. Bajo la Regla 4.17 (ii) del PCT.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
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- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional. PCT/IB306.
- [x] Otros. Búsqueda Internacional.

11 FIGURA CARACTERÍSTICA:

12

Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA: _____

C.C. 79. 782.747Bta T.P. 74.295

LISTA DE INVENTORES

PCT/EP2012/073556

Nico BRÄUER
Ruppiner Str. 103,
14612 Falkensee,
Alemania
Nacionalidad: Alemana

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13187 Berlin,
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Nacionalidad: Alemana

Ulrike RÖHN
Boyenstr. 42,
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Nacionalidad: Alemana

Bernhard LINDENTHAL
Wilkestr. 19
13507 Berlin,
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Nacionalidad: Alemana

Antonius TER LAAK
Hedwigstr. 11
12159 Berlin,
Alemania
Nacionalidad: Neerlandesa

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

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LEGALIZACION
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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

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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

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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

PCT

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, BRÄUER, Nico
VIII-2-1(ii)		Bayer Pharma Aktiengesellschaft is entitled as employer of the inventor, MENGEL, Anne
VIII-2-1(ii)		Bayer Pharma Aktiengesellschaft is entitled as employer of the inventor, RÖHN, Ulrike
VIII-2-1(ii)		Bayer Pharma Aktiengesellschaft is entitled as employer of the inventor, ROTGERI, Andrea
VIII-2-1(ii)		Bayer Pharma Aktiengesellschaft is entitled as employer of the inventor, BUCHMANN, Bernd
VIII-2-1(ii)		Bayer Pharma Aktiengesellschaft is entitled as employer of the inventor, LINDENTHAL, Bernhard
VIII-2-1(ii)		Bayer Pharma Aktiengesellschaft is entitled as employer of the inventor, TER LAAK, Antonius
VIII-2-1(iii)		an agreement between Bayer Pharma Aktiengesellschaft and Bayer Intellectual Property GmbH, dated 01 April 2012 (01.04.2012)

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(74) Agent: **BAYER INTELLECTUAL PROPERTY GMBH**; Alfred-Nobel-Str. 10, 40789 Monheim (DE).

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Declarations under Rule 4.17:

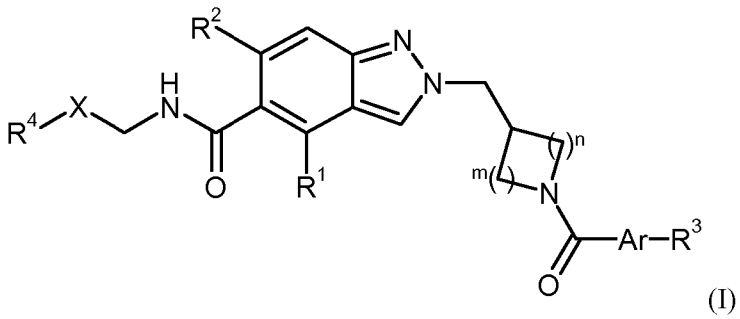
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Published:

— *with international search report (Art. 21(3))*

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(54) **Title**: NOVEL 2H-INDAZOLES AS EP_2 RECEPTOR ANTAGONISTS



(I)

(57) **Abstract**: The present invention relates to novel 2H-indazoles of the general formula (I), methods for the preparation thereof and the use thereof for the production of pharmaceutical agents for the treatment of diseases and indications which are linked with the EP_2- receptor.

Novel *2H*-indazoles as EP_2 Receptor Antagonists

The present invention relates to novel EP_2 receptor antagonists, the production thereof and the use thereof as drugs, and pharmaceutical preparations which contain the new *2H*-indazoles.

It has already long been known that prostaglandins are key molecules in the processes of female reproductive biology, such as for example the regulation of ovulation and fertilization. Effects on uterine contractions, implantation, deciduation (e.g. placenta formation) and menstruation have also been described, or are the subject of scientific studies. Prostaglandins also play an important part in pathological changes in the reproductive tract, including menorrhagia, dysmenorrhoea, endometriosis, fibroids (myomas) and cancer, and in general in inflammatory (e.g. Crohn disease), infections (e.g. bacterial infections) and neurodegenerative processes (e.g. Alzheimer, ALS), and functions in the immune defence, angiogenesis, pain, wound healing and interactions with the endocrine system (e.g. aromatase induction) are known. Hitherto, the mechanism through which prostaglandins effect the changes has not been completely elucidated. Recent findings indicate that prostaglandins, their receptors and their signal transduction paths are involved in processes such as angiogenesis, apoptosis, proliferation and in inflammatory/anti-inflammatory processes.

The effects of the prostaglandins are mediated through their G protein coupled receptors, which are located in the cell membrane. Of particular interest is prostaglandin E_2 (PGE_2), which effects a great variety of cellular actions by binding to functionally different receptor subtypes, namely the EP_1, EP_2, EP_3 and EP_4 receptors. The receptor subtypes to which prostaglandin E_2 binds appear to be of particular importance for the receptor-mediated actions which are involved in the regulation of fertility. Thus it could be shown that the reproductive functions are impaired in EP_2 knockout mice ($EP_2^{-/-}$), e.g. in mice which no longer have a functional PGE_2 receptor subtype EP_2, and that these animals have a smaller "litter" (Matsumoto *et al.*, 2001, Biology of Reproduction 64, 1557-1565). Likewise it could be shown that these EP_2 knockout mice (Hizaki *et al.*, 1999, Proc Natl Acad Sci U. S. A,. Aug 31; 96(18):10501-10506) display markedly decreased cumulus expansion and severe subfertility, which is to be regarded as being causally linked with decreased reproductive processes such as ovulation and fertilization.

Accordingly, the EP_2 receptor is an important target for the development of drugs for the regulation of female fertility. The existence of the 4 subclasses of the PGE_2 receptor opens up the possibility of targeted development of selectively active compounds. Previously, however, hardly any selective EP_2 receptor antagonists were known, since most known compounds also

bind to the other PGE_2 receptor subtypes, such as for example to the EP_4 receptor or other prostaglandin receptors such as the DP receptor.

EP_2 receptor antagonists are for example described in the application US2005059742 and EP1467738 (Jabbour, Medical Research Council). A method is claimed wherein an EP_2 and/or an EP_4 antagonist can be used for the treatment of menorrhagia and dysmenorrhoea. AH6809 is disclosed as an antagonist of the EP_2 or EP_4 receptor, and no other specific antagonists and no new compounds are disclosed.

In the application WO03/016254, Ono Pharmaceutical claims the production of arylcarboxylic acids or saturated carboxylic acid derivatives which are aryl group or heterocycle-substituted inter alia as PGE_2 receptor antagonists. The disclosed compounds are claimed for the treatment of a large number of diseases, also including allergic diseases, Alzheimer's disease, pain, abortion, menstrual problems, menorrhagia and dysmenorrhoea, endometriosis, diseases of the bones, ischaemia etc. However, the compounds described are characterized by a particularly high affinity for the EP_3 receptor. In a further application (WO04/032964), newer compounds are described which are also characterized by a particularly high affinity for the EP_3 receptor, but also find use as EP_2 antagonists, for the treatment and prophylaxis of allergic diseases.

In the applications from the company Applied Research Systems WO03/053923 (substituted pyrrolidines) or WO03/035064 (substituted pyrazolidiones), compounds for the treatment of diseases which are associated with prostaglandins, such as for example infertility, hypertension and osteoporosis, are claimed. The compounds bind to the EP_4 and the EP_2 receptor subtypes.

In the application WO03/064391 (Pfizer Products), metabolites of [3-[[N-(4-tert-butylbenzyl)-(pyridin-3-ylsulphonyl)amino]methyl] acetic acid are described, which inhibit the binding of [^{3}H] prostaglandin E_2 to the EP_2 receptor. The use of these metabolites for the treatment of osteoporosis is disclosed.

In the application US2005124577, Tani *et al.* claim 8-azaprostaglandin derivatives for the treatment of immunological diseases, allergic diseases, premature labour, abortion, etc. The compounds bind to the EP_2 and the EP_4 receptor.

In the patent applications from Bayer Schering Pharma AG (WO2007/057232, WO2007/071456, WO2008/028689, WO2008/028690 WO2008/028691, WO2008/0152099,

WO2008/0152097, WO2008/0152094, WO2009/007421, WO2009/007422) and DE 10 2009 049 662 A1, selective antagonists of the EP_2 receptors are for the first time claimed.

In the applications from Summit Corporation PLC (WO2007/091107) and CM Sun *et al.* (WO2008/070599) *2H*-indazoles are disclosed, but not for the treatment of fertility disorders.

In the applications from Pfizer WO2009/063365 and WO2008/139287, azetidines and in WO2010/052625 pyrrolidones as antagonists of the EP_2 receptor, and the use thereof for the treatment of EP_2-mediated conditions such as endometriosis and leiomyomata are claimed.

In a publication (British Journal of Pharmacology (2011), 164, 1847-1856), Forselles *et al.* (Pfizer) describe selective antagonists of the EP_2 receptors. The compounds are azetidines which display an *in-vivo* influence on the blood flow. The compounds display high protein binding.

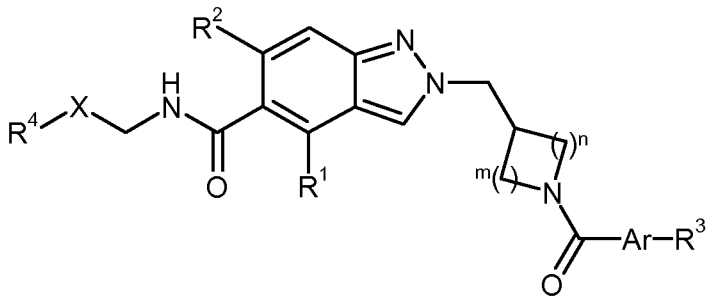
In a publication by P.M. Roveto *et al.* (239. ACS National Meeting of the Division of Medicinal Chemistry, 21.-25. March 2010, San Francisco, USA; MEDI 173), novel thiazoles are described as EP_2 antagonists.

EP_2 receptor antagonists are also described in the application by Ligand Pharmaceuticals Inc. (WO2010/008777). These compounds are bicyclic pyridine derivatives. The compounds are claimed for the treatment of pain, but also for the treatment of Alzheimer's disease, multiple sclerosis and fertility disorders.

For the regulation of the processes which are ultimately responsible for ovulation and fertilization and which thus contribute to the inhibition of fertility, other *in vivo* active antagonists of the EP_2 receptor with improved properties are needed.

Hence the purpose of the present invention was to provide other antagonists of the EP_2 receptor with improved properties which are available *in vivo*, and thus effective, and stable.

This problem was solved through the compounds of the general formula I,



(I),

wherein

R^1: means H, C_1-C_2 alkyl or C_1-C_2 alkyloxy;

R^2: H or methyl;

subject to the proviso that one of the two residues R^1 or R^2 equals H;

X: $-(CH_2)_l-$, $-(CH_2)_k-O-$, $-CH_2-S-$, $CH_2-S(O)_2-$, $-CH(CH_3)-$, $-CH(CH_3)-O-$ or $-C(CH_3)_2-O-$;

k: 1 or 2;

l: 0, 1 or 2;

R^4: H, C_1-C_4 alkyl, C_3-C_4 cycloalkyl, or CH_2-C_3-C_4 cycloalkyl;

and in the case of X: $-CH_2-$ or $-CH(CH_3)-$

R^4: additionally a 4-6-membered heterocyclyl residue;

and in the case of X: $-(CH_2)_l-$ or $-CH(CH_3)-$

R^4: additionally CN;

or

X together with R^4 form a 4-6-membered heterocyclyl residue via a ring carbon linkage;

m: 1 or 2;

n: 1 or 2;

Ar: a 6-10-membered aryl or 5-10-membered hetaryl residue,

R^3: halogen, CN, SF_5, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_4-C_6 heterocyclyl, O-C_1-C_4 alkyl, O-C_3-C_6 cycloalkyl, O-C_4-C_6 heterocyclyl, S-C_1-C_4 alkyl, S(O)$_2$-C_1-C_4 alkyl, Ar′, O-Ar′, $C(CH_3)_2$-CN or $C(CH_3)_2$-OH;

Ar′: an optionally singly or doubly substituted 6-membered aryl or 5-6-membered heteroaryl residue;
wherein the substituents are selected from F, Cl, CN, C_1-C_4 alkyl, O-C_1-C_4 alkyl, $C(CH_3)_2$-CN, $C(CH_3)_2$-OH and $C(O)NH_2$;

and isomers, diastereomers, enantiomers and salts or cyclodextrin clathrates thereof, **for the production of drugs** which overcome the known disadvantages and have improved properties such as good *in-vivo* activity, good solubility and stability.

The compounds according to the invention have an antagonistic action on the EP_2 receptor and thus inter alia serve for female fertility control.

C_1-C_2 alkyl or C_1-C_4 alkyl should each be understood to mean a linear or branched alkyl residue, such as for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl.
The alkyl residues can optionally be singly or multiply substituted with fluorine.

The hydrogen atoms can optionally be replaced by deuterium.

C_1-C_2 alkoxy or C_1-C_4 alkoxy should be understood to mean a linear or branched residue of the formula alkyl-O-, such as for example methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy, isobutoxy or tert-butyloxy.
The alkoxy residues can optionally be singly or multiply substituted with fluorine.

C_3-C_6 cycloalkyl should be understood to mean monocyclic alkyl rings such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.
The cycloalkyl residues can optionally be singly or multiply substituted with fluorine.

4-6-membered heterocyclyl should be understood to mean monocyclic rings which instead of the carbon atoms contain one or more hetero atoms, such as oxygen, sulphur and/or nitrogen or a hetero group such as -S(O)- or -SO_2-. The linking bond can be at any carbon atom or at a nitrogen atom.

For example, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, 1,4-diazepanyl, morpholinyl, thiomorpholinyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl and 2-oxo-oxazolidinyl may be mentioned.

The heterocyclyl residues can optionally be singly or multiply substituted with fluorine, hydroxy, methoxy or with oxo.

Halogen should in each case be understood to mean fluorine, chlorine, bromine or iodine.

The C_6-C_{10}-membered aryl residue in each case comprises 6 - 10 carbon atoms and can be benzo-condensed. Phenyl and naphthyl may be mentioned

The C_6-C_{10}-membered aryl residue can optionally be singly substituted with fluorine, chlorine or a methyl group.

The C_5-C_{10} heteroaryl residue should be understood to mean mono- or bicyclic ring systems which each contain 5 - 10 ring atoms and which instead of the carbon can contain one or more identical or different hetero atoms, such as oxygen, sulphur or nitrogen. The linking bond can be at any carbon atom or at a nitrogen atom.

For example, thienyl, thiazolyl, furyl, pyrrolyl, oxazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, phthalidyl, thiophthalidyl, indolyl, isoindolyl, indazolyl, benzothiazolyl, benzofuryl, benzothienyl, benzimidazolyl, benzoxazolyl, azocinyl, indolizinyl, purinyl, isoquinolinyl, quinolinyl, quinolizinyl, quinazolinyl, quinoxalinyl, cinnolinyl, phthalazinyl, 1,7- or 1,8-naphthyridinyl and pteridinyl may be mentioned.

The C_5-C_{10}-membered heteroaryl residue can optionally be singly substituted by fluorine, chlorine or a methyl group.

If a basic functional group is contained, the physiologically compatible salts of organic and inorganic acids, such as inter alia hydrochloric acid, sulphuric acid, phosphoric acid, citric acid and tartaric acid, are suitable

Preferred are compounds of the formula I, wherein

R^1, R^2: mean H or methyl;

subject to the proviso that one of the two residues R^1 or R^2 equals H;

X: $-(CH_2)_l-$ or $-(CH_2)_k-O-$;

k: 1 or 2;

l: 0, 1 or 2;

R^4: C_1-C_4 alkyl, C_3-C_4 cycloalkyl or CH_2-C_3-C_4 cycloalkyl;

m, n: 2;

and isomers, diastereomers, enantiomers and salts or cyclodextrin clathrates thereof and R^3, Ar and Ar´ have the aforesaid meanings.

Also preferred are compounds of the formula I, wherein

R^1, R^2: mean H or methyl;

subject to the proviso that one of the two residues R^1 or R^2 equals H;

X: $-(CH_2)_l-$ or $-(CH_2)_k-O-$;

k: 1 or 2;

l: 0, 1 or 2;

R^4: C_1-C_4 alkyl, -C_3-C_4 cycloalkyl or CH_2-C_3-C_4 cycloalkyl;

m, n: 1;

and isomers, diastereomers, enantiomers and salts or cyclodextrin clathrates thereof and R^3, Ar and Ar´ have the aforesaid meanings.

Also preferred are compounds of the formula I, wherein

R^1: means a methyl group;

R^2: H;

X: $-(CH_2)_l-$ or $-(CH_2)_k-O-$;

k: 1;

l: 0 or 1;

R^4: C_1-C_4 alkyl, C_3-C_4 cycloalkyl or CH_2-C_3-C_4 cycloalkyl;

m, n: 2;

Ar: a phenyl residue;

and isomers, diastereomers, enantiomers and salts or cyclodextrin clathrates thereof and R^3 and Ar′ have the aforesaid meanings.

Additionally preferred are compounds of the formula I, wherein

R^1: means a methyl group;

R^2: H;

X: $-(CH_2)_l-$ or $-(CH_2)_k-O-$;

k: 1;

l: 0 or 1;

R^4: C_1-C_4 alkyl, C_3-C_4 cycloalkyl or CH_2-C_3-C_4 cycloalkyl;

m, n: 1;

Ar: a phenyl residue;

and isomers, diastereomers, enantiomers and salts or cyclodextrin clathrates thereof and R^3 and Ar′ have the aforesaid meanings.

The following compounds according to the present invention are quite particularly preferred:

1. 2-{[1-(4-cyano-2-fluorobenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
2. 2-{[1-(4-tert-butoxybenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
3. 2-({1-[4-(4-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
4. N-(2-methoxyethyl)-4-methyl-2-{[1-(4-morpholinobenzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide
5. 2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
6. 2-{[1-(2-fluoro-4-mesylbenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
7. 2-{[1-(2-fluoro-4-methoxybenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
8. 2-{[1-(4-bromo-2-fluorobenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
9. 2-{[1-(2-fluoro-4-methylbenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
10. 2-({1-[2-fluoro-4-(trifluoromethyl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
11. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(pentafluoro-λ^6-sulphanyl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide
12. N-(2-methoxyethyl)-4-methyl-2-{[1-(4-methylbenzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide
13. 2-({1-[4-(4-chlorophenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

14. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(4-methylphenoxy)benzoyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide
15. 2-({1-[4-(4-tert-butylphenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
16. N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
17. N-(2-methoxyethyl)-2-({1-[4-(4-methoxyphenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-2H-indazol-5-carboxamide
18. N-(2-methoxyethyl)-4-methyl-2-{[1-(4-phenoxybenzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide
19. 2-{[1-(4-cyclopropylbenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
20. 2-{[1-(4-methoxybenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
21. 2-{[1-(4-fluorobenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
22. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(trifluoromethyl)benzoyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide
23. 2-{[1-(2-methoxybenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
24. N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[(trifluoromethyl)sulphonyl]benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
25. N-(2-methoxyethyl)-4-methyl-2-({1-[3-(trifluoromethyl)benzoyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide
26. N-(2-methoxyethyl)-4-methyl-2-{[1-(3-methylbenzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide
27. 2-{[1-(3-chlorobenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
28. 2-({1-[4-(4-carbamoylphenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
29. 2-({1-[4-(cyclopentyloxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
30. 2-({1-[4-(difluoromethyl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
31. 2-{[1-(4-cyanobenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

32. 2-({1-[4-(1H-imidazol-1-yl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
33. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(oxazol-2-yl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide
34. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(oxazol-5-yl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide
35. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(isoxazol-5-yl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide
36. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(1H-pyrazol-1-yl)benzoyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide
37. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(1H-1,2,4-triazol-1-yl)benzoyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide
38. 2-({1-[4-(difluoromethoxy)-2-fluorobenzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
39. 2-({1-[2-fluoro-4-(pyrrolidin-1-yl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
40. 2-({1-[(3,4'-difluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
41. 2-({1-[(3-fluoro-4'-methoxybiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
42. 2-({1-[(3-fluoro-4'-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
43. 2-[(1-{[3-fluoro-3'-(trifluoromethyl)biphenyl-4-yl]carbonyl}piperidin-4-yl)methyl]-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
44. 2-[(1-{[3-fluoro-2'-(trifluoromethoxy)biphenyl-4-yl]carbonyl}piperidin-4-yl)methyl]-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
45. 2-({1-[(2'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
46. 2-({1-[(2',4'-difluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
47. 2-({1-[(2-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
48. N-(2-methoxyethyl)-4-methyl-2-({1-[(2'-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide
49. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(4-pyridyloxy)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide

50. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(4H-1,2,4-triazol-4-yl)benzoyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide
51. 2-{[1-(2-fluoro-4-morpholinobenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
52. 2-{[1-(4-bromobenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
53. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(trifluoromethoxy)benzoyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide
54. 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
55. N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[(trifluoromethyl)sulphanyl]benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
56. 4-methyl-2-({1-[4-(pentafluoro-λ^6-sulphanyl)benzoyl]piperidin-4-yl}methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
57. 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
58. 4-methyl-N-(2,2,2-trifluoroethyl)-2-({1-[4-(trifluoromethoxy)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide
59. 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-[2-(cyclopropylmethoxy)ethyl]-4-methyl-2H-indazole-5-carboxamide
60. N-[2-(cyclopropylmethoxy)ethyl]-4-methyl-2-{[1-(4-methylbenzoyl)piperidin-4-yl]-methyl}-2H-indazol-5-carboxamide
61. N-[2-(cyclopropylmethoxy)ethyl]-2-({1-[4-(4-fluorophenoxy)benzoyl]piperidin-4-yl}-methyl)-4-methyl-2H-indazol-5-carboxamide
62. N-[2-(cyclopropylmethoxy)ethyl]-4-methyl-2-({1-[4-(trifluoromethyl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide
63. N-[2-(cyclopropylmethoxy)ethyl]-2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-4-methyl-2H-indazol-5-carboxamide
64. 2-{[1-(4-cyclopropylbenzoyl)piperidin-4-yl]methyl}-N-[2-(cyclopropylmethoxy)ethyl]-4-methyl-2H-indazol-5-carboxamide
65. 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methyl-N-[2-(2,2,2-trifluoroethoxy)-ethyl]-2H-indazol-5-carboxamide
66. 4-methyl-2-{[1-(4-methylbenzoyl)piperidin-4-yl]methyl}-N-[2-(2,2,2-trifluoroethoxy)-ethyl]-2H-indazol-5-carboxamide
67. 2-({1-[4-(4-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-[2-(2,2,2-trifluoroethoxy)ethyl]-2H-indazol-5-carboxamide

68. 4-methyl-N-[2-(2,2,2-trifluoroethoxy)ethyl]-2-({1-[4-(trifluoromethyl)benzoyl]-piperidin-4-yl}methyl)-2H-indazol-5-carboxamide
69. 2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-4-methyl-N-[2-(2,2,2-trifluoroethoxy)ethyl]-2H-indazol-5-carboxamide
70. 2-{[1-(4-cyclopropylbenzoyl)piperidin-4-yl]methyl}-4-methyl-N-[2-(2,2,2-trifluoro-ethoxy)ethyl]-2H-indazol-5-carboxamide
71. 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-(2-isopropoxyethyl)-4-methyl-2H-indazol-5-carboxamide
72. N-(2-isopropoxyethyl)-4-methyl-2-{[1-(4-methylbenzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide
73. 2-({1-[4-(4-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-isopropoxyethyl)-4-methyl-2H-indazol-5-carboxamide
74. N-(2-isopropoxyethyl)-4-methyl-2-({1-[4-(trifluoromethyl)benzoyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide
75. 2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-isopropoxyethyl)-4-methyl-2H-indazol-5-carboxamide
76. 2-{[1-(4-cyclopropylbenzoyl)piperidin-4-yl]methyl}-N-(2-isopropoxyethyl)-4-methyl-2H-indazol-5-carboxamide
77. 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methyl-N-[2-(trifluoromethoxy)ethyl]-2H-indazol-5-carboxamide
78. 2-({1-[4-(4-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-[2-(trifluoro-methoxy)ethyl]-2H-indazol-5-carboxamide
79. 2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-4-methyl-N-[2-(trifluoromethoxy)ethyl]-2H-indazol-5-carboxamide
80. 4-methyl-N-[2-(trifluoromethoxy)ethyl]-2-[(1-{4-[4-(trifluoromethyl)phenoxy]-benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
81. N-(2-tert-butoxyethyl)-2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methyl-2H-indazol-5-carboxamide
82. N-(2-tert-butoxyethyl)-2-({1-[4-(4-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-2H-indazol-5-carboxamide
83. N-(2-tert-butoxyethyl)-2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-4-methyl-2H-indazol-5-carboxamide
84. N-(2-tert-butoxyethyl)-4-methyl-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
85. 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methyl-N-{2-[(^{2}H3)methyloxy]-(^{2}H4)ethyl}-2H-indazol-5-carboxamide

86. 2-({1-[4-(4-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-{2-[(^{2}H3)methyloxy](^{2}H4)ethyl}-2H-indazol-5-carboxamide
87. 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
88. N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[(trifluoromethyl)sulphanyl]benzoyl}azetidin-3-yl)methyl]-2H-indazol-5-carboxamide
89. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(trifluoromethoxy)benzoyl]azetidin-3-yl}-methyl)-2H-indazol-5-carboxamide
90. 2-({1-[2-fluoro-4-(trifluoromethyl)benzoyl]azetidin-3-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
91. 2-{[1-(4-chloro-2-fluorobenzoyl)azetidin-3-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
92. 2-({1-[3-fluoro-4-(trifluoromethyl)benzoyl]azetidin-3-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
93. 2-({1-[4-chloro-3-(trifluoromethyl)benzoyl]azetidin-3-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
94. 2-{[1-(4-cyclopropylbenzoyl)azetidin-3-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
95. N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}azetidin-3-yl)methyl]-2H-indazol-5-carboxamide
96. 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
97. 4-methyl-N-(2,2,2-trifluoroethyl)-2-({1-[4-(trifluoromethoxy)benzoyl]azetidin-3-yl}-methyl)-2H-indazol-5-carboxamide
98. 2-({1-[2-fluoro-4-(trifluoromethyl)benzoyl]azetidin-3-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
99. 4-methyl-2-({1-[4-(pentafluoro-λ^6-sulphanyl)benzoyl]azetidin-3-yl}methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
100. N-[2-(cyclopropyloxy)ethyl]-4-methyl-2-({1-[4-(trifluoromethoxy)benzoyl]azetidin-3-yl}methyl)-2H-indazol-5-carboxamide
101. N-[2-(cyclobutyloxy)ethyl]-4-methyl-2-({1-[4-(trifluoromethoxy)benzoyl]azetidin-3-yl}methyl)-2H-indazol-5-carboxamide
102. 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-N-[2-(cyclopropylmethoxy)ethyl]-4-methyl-2H-indazol-5-carboxamide
103. N-[2-(cyclopropylmethoxy)ethyl]-2-({1-[4-(4-fluorophenoxy)benzoyl]azetidin-3-yl}-methyl)-4-methyl-2H-indazol-5-carboxamide

104. N-[2-(cyclopropylmethoxy)ethyl]-4-methyl-2-{[1-(4-methylbenzoyl)azetidin-3-yl]-methyl}-2H-indazol-5-carboxamide

105. 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-4-methyl-N-[2-(trifluoromethoxy)ethyl]-2H-indazol-5-carboxamide

106. N-(2-tert-butoxyethyl)-2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-4-methyl-2H-indazol-5-carboxamide

107. N-[2-(cyclopropylmethoxy)ethyl]-2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]azetidin-3-yl}methyl)-4-methyl-2H-indazol-5-carboxamide

108. 2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]azetidin-3-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

109. 2-({1-[4-(4-fluorophenoxy)benzoyl]azetidin-3-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

110. 2-({1-[4-(4-fluorophenoxy)benzoyl]azetidin-3-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide

111. 2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]azetidin-3-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide

112. 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-4-methyl-N-[2-(2,2,2-trifluoroethoxy)-ethyl]-2H-indazol-5-carboxamide

113. 4-methyl-N-[2-(2,2,2-trifluoroethoxy)ethyl]-2-[(1-{4-[4-(trifluoromethyl)phenoxy]-benzoyl}azetidin-3-yl)methyl]-2H-indazol-5-carboxamide

114. 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}-azetidin-3-yl)methyl]-2H-indazol-5-carboxamide

115. 2-({1-[4-(4-chlorophenoxy)benzoyl]azetidin-3-yl}methyl)-4-methyl-N-(2,2,2-trifluoro-ethyl)-2H-indazol-5-carboxamide

116. 2-({1-[4-(4-chlorophenoxy)benzoyl]azetidin-3-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

117. N-(2-methoxyethyl)-4-methyl-2-{[1-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}benzoyl)-azetidin-3-yl]methyl}-2H-indazol-5-carboxamide

118. 4-methyl-N-(2,2,2-trifluoroethyl)-2-{[1-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}benzoyl)azetidin-3-yl]methyl}-2H-indazol-5-carboxamide

119. 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-ethyl-4-methyl-2H-indazol-5-carboxamide

120. 2-({1-[4-(4-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoro-ethyl)-2H-indazol-5-carboxamide

121. 2-({1-[4-(4-chlorophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoro-ethyl)-2H-indazol-5-carboxamide

122. 4-methyl-2-({1-[4-(4-methylphenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
123. 2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
124. 4-methyl-2-{[1-(4-morpholinobenzoyl)piperidin-4-yl]methyl}-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
125. 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{4-[(trifluoromethyl)sulphanyl]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
126. 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
127. 4-methyl-N-(2,2,2-trifluoroethyl)-2-{[1-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}-benzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide
128. 4-methyl-N-(2,2,2-trifluoroethyl)-2-{[1-(4-{[6-(trifluoromethyl)pyridin-3-yl]oxy}-benzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide
129. 4-methyl-N-(2,2,2-trifluoroethyl)-2-{[1-(4-{[6-(trifluoromethyl)pyridin-2-yl]oxy}-benzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide
130. 2-({1-[4-(4-cyanophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
131. 2-({1-[4-(3-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
132. 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{4-[3-(trifluoromethyl)phenoxy]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
133. 2-[(1-{4-[(5-cyanopyridin-2-yl)oxy]benzoyl}piperidin-4-yl)methyl]-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
134. 2-[(1-{4-[(5-chloropyridin-2-yl)oxy]benzoyl}piperidin-4-yl)methyl]-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
135. 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{4-[5-(trifluoromethyl)pyridin-2-yl]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
136. 2-({1-[4-(2,4-difluorophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
137. 2-({1-[4-(3,4-difluorophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
138. 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{[4'-(trifluoromethyl)biphenyl-4-yl]carbonyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
139. 2-{[1-(4-bromobenzoyl)piperidin-4-yl]methyl}-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide

140. 2-({1-[4-(5-chloropyridin-2-yl)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide

141. 2-({1-[(4'-methoxy-2'-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide

142. 4-methyl-2-({1-[4-(6-methylpyridin-3-yl)benzoyl]piperidin-4-yl}methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide

143. 2-({1-[(4'-fluoro-2'-methoxybiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide

144. 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{4-[6-(trifluoromethyl)pyridin-3-yl]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide

145. 2-({1-[4-(6-methoxypyridin-3-yl)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide

146. 2-({1-[4-(6-methoxypyridin-2-yl)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide

147. 4-methyl-2-({1-[4-(5-methylpyridin-2-yl)benzoyl]piperidin-4-yl}methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide

148. 2-({1-[4-(5-fluoropyridin-2-yl)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide

149. 2-({1-[4-(5-methoxypyridin-2-yl)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide

150. 4-methyl-2-({1-[4-(2-methylpyrimidin-5-yl)benzoyl]piperidin-4-yl}methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide

151. 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{4-[2-(trifluoromethyl)pyrimidin-5-yl]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide

152. 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{4-[6-(trifluoromethyl)pyridin-2-yl]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide

153. 2-({1-[4-(4-cyanophenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

154. 2-{[1-(4-bromo-3-methylbenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

155. 2-{[1-(4-tert-butylbenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

156. 2-({1-[4-(1-hydroxy-1-methylethyl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxy-ethyl)-4-methyl-2H-indazol-5-carboxamide

157. 2-{[1-(4-cyclohexylbenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

158. 2-({1-[4-(1-cyano-1-methylethyl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

159. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(pyrimidin-2-yloxy)benzoyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide

160. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(3-pyridyloxy)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide

161. N-(2-methoxyethyl)-4-methyl-2-{[1-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}benzoyl)-piperidin-4-yl]methyl}-2H-indazol-5-carboxamide

162. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(2-pyridyloxy)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide

163. N-(2-methoxyethyl)-4-methyl-2-{[1-(4-{[4-(trifluoromethyl)pyrimidin-2-yl]oxy}-benzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide

164. N-(2-methoxyethyl)-4-methyl-2-{[1-(4-{[6-(trifluoromethyl)pyridin-3-yl]oxy}benzoyl)-piperidin-4-yl]methyl}-2H-indazol-5-carboxamide

165. N-(2-methoxyethyl)-4-methyl-2-{[1-(4-{[6-(trifluoromethyl)pyridin-2-yl]oxy}benzoyl)-piperidin-4-yl]methyl}-2H-indazol-5-carboxamide

166. 2-({1-[(4'-methoxybiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

167. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(3,4,5,6-tetrahydro-2H-pyran-4-yloxy)benzoyl]-piperidin-4-yl}methyl)-2H-indazol-5-carboxamide

168. N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[3-(trifluoromethyl)phenoxy]benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide

169. 2-[(1-{4-[(5-cyanopyridin-2-yl)oxy]benzoyl}piperidin-4-yl)methyl]-N-(2-methoxy-ethyl)-4-methyl-2H-indazol-5-carboxamide

170. 2-[(1-{4-[(5-chloropyridin-2-yl)oxy]benzoyl}piperidin-4-yl)methyl]-N-(2-methoxy-ethyl)-4-methyl-2H-indazol-5-carboxamide

171. 2-({1-[4-(2,4-difluorophenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

172. 2-({1-[4-(3,4-difluorophenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

173. N-(2-methoxyethyl)-4-methyl-2-[(1-{[4'-(trifluoromethyl)biphenyl-4-yl]carbonyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide

174. 2-({1-[4-(3-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

175. 2-{[1-(2-fluoro-4-isopropoxybenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

176. 2-({1-[(3-fluoro-3',4'-dimethylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

177. 2-({1-[(2',3-difluoro-4'-methoxybiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

178. 2-({1-[4-(difluoromethoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

179. 2-({1-[4-(2-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

180. 2-({1-[(4'-cyano-2'-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

181. 2-({1-[4-(5-chloropyridin-2-yl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

182. N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[6-(trifluoromethyl)pyridin-2-yl]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide

183. N-(2-methoxyethyl)-2-({1-[(4'-methoxy-2'-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-4-methyl-2H-indazol-5-carboxamide

184. 2-({1-[(4'-chloro-2'-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

185. 2-[(1-{[4'-(1-cyano-1-methylethyl)biphenyl-4-yl]carbonyl}piperidin-4-yl)methyl]-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

186. N-(2-methoxyethyl)-2-({1-[4-(5-methoxypyridin-2-yl)benzoyl]piperidin-4-yl}methyl)-4-methyl-2H-indazol-5-carboxamide

187. N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[6-(trifluoromethyl)pyridin-3-yl]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide

188. N-(2-methoxyethyl)-2-({1-[4-(6-methoxypyridin-3-yl)benzoyl]piperidin-4-yl}methyl)-4-methyl-2H-indazol-5-carboxamide

189. 2-({1-[(4'-fluoro-2'-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

190. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(6-methylpyridin-3-yl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide

191. N-(2-methoxyethyl)-2-({1-[4-(6-methoxypyridin-2-yl)benzoyl]piperidin-4-yl}methyl)-4-methyl-2H-indazol-5-carboxamide

192. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(2-methylpyrimidin-5-yl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide

193. 2-({1-[(4'-fluoro-2'-methoxybiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

194. 2-({1-[(4'-chloro-2'-methoxybiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

195. N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[2-(trifluoromethyl)pyrimidin-5-yl]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide

196. 2-({1-[(4'-chloro-2'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

197. 2-({1-[(2'-chloro-4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

198. 2-({1-[4-(5-chloropyridin-3-yl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

199. 2-({1-[4-(5-fluoropyridin-3-yl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

200. N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[5-(trifluoromethyl)pyridin-3-yl]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide

201. 2-[(1-{[4'-(1-hydroxy-1-methylethyl)biphenyl-4-yl]carbonyl}piperidin-4-yl)methyl]-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

202. 2-({1-[(3',5'-difluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

203. 2-({1-[(4'-fluoro-2-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

204. 2-({1-[(3',5'-difluoro-2-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

205. N-(2-methoxyethyl)-4-methyl-2-({1-[3-methyl-4-(3-pyridyl)benzoyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide

206. N-(2-methoxyethyl)-4-methyl-2-({1-[3-methyl-4-(4-pyridyl)benzoyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide

207. N-(2-methoxyethyl)-4-methyl-2-({1-[(2-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide

A subject of the present invention is the use of the compounds according to the invention for the production of drugs which contain at least one of the compounds according to formula I.

Also a subject of the present invention are drugs which contain the compounds according to the invention, with suitable formulation and carrier substances.

Compared to known prostaglandin EP_2 antagonists, the new EP_2 antagonists are characterized by improved properties such as better availability and stability.

A subject of the present invention are drugs for fertility control/contraception and for the treatment and prophylaxis of diseases, which include infectious diseases, cancer, cardiovascular diseases, angiogenic diseases, uterine contraction disorders, pain, inflammatory diseases, neuroinflammatory diseases, neurodegenerative diseases, autoimmune diseases, immuno-dependent diseases/therapies, nephrological diseases and ophthalmological diseases.

Infectious diseases should be understood to mean diseases caused by unicellular parasites (e.g. Klebsiella or Streptococcus). With infectious diseases, the drugs can have an immunomodulatory action such that the diseases can be treated prophylactically (diminution of the infection risk, such as for example in bone marrow transplants) or therapeutically. Cancer should be understood to mean solid tumours and leukaemias; viral infections e.g. cytomegalus infections, hepatitis, hepatitis B and C and HIV diseases; cardiovascular diseases ischaemic reperfusion disease, stenoses, arterioscleroses, restenoses, arthritis, Kawasaki syndrome and aneurysms; angiogenic diseases e.g. endometriosis and fibrosis and fibroids in the uterus; uterine contraction disorders e.g. menstrual problems; pain, for example inflammatory hyperalgesia and arthritis, inflammatory diseases, for example inflammatory intestinal diseases; neuroinflammatory and neuro-degenerative diseases e.g. multiple sclerosis, Alzheimer, Parkinson, ALS and stroke; immuno-dependent diseases/therapies e.g. transplants in which immunomodulation increases the therapeutic success; autoimmune diseases for example the ophthalmological disease Graves' disease, and nephrological diseases polycystic kidney diseases and glomerulonephritis.

Also a subject of the present invention are drugs for treatment and prophylaxis of the diseases listed above which contain at least one compound according to the general formula I, and drugs with suitable formulation and carrier substances.

For the use of the compounds according to the invention as drugs, these are converted into the form of a pharmaceutical preparation which as well as the active substance contains pharmaceutical, organic or inorganic inert carrier materials suitable for enteral or parenteral administration, such as for example water, gelatine, gum Arabic, lactose, starch, magnesium stearate, talc, plant oils, polyalkylene glycols etc. The pharmaceutical preparations can be in solid form, for example as tablets, coated tablets or capsules, in semisolid form, for example as ointments, creams, gels or suppositories or in liquid form, for example as solutions, suspensions or emulsions.

They optionally contain additives, which are for example intended to function as fillers, binders, disintegrants, lubricants, solvents, solution mediators, masking flavours, colorant, or emulsifiers. Types of additive in the sense of the invention are for example saccharides (mono-, di-, tri-, oligo-, and/or polysaccharides), fats, waxes, oils, hydrocarbons, anionic, nonionic, cationic, natural, synthetic or semisynthetic surfactants. In addition, they optionally contain additives such as preservatives, stabilizers, wetting agents or emulsifiers; salts for alteration of the osmotic pressure or buffers.

These pharmaceutical preparations are also a subject of the present invention.

For inhalation, aerosol solutions, or else suitable solid substance preparations for inhalation, are advantageously prepared.

For oral use, tablets, coated tablets or capsules with talc and/or hydrocarbon carriers or binders, such as for example lactose, maize or potato starch are particularly suitable. Use is also possible in liquid form, such as for example as syrup, to which a sweetener is optionally added. Likewise, for the oral use of such compounds, clathrates are also suitable, for example the clathrates with alpha, beta or gamma cyclodextrin or else beta-hydroxypropyl cyclodextrin may be mentioned.

For parenteral administration, sterile, injectable, aqueous or oily solutions are used. Injection solutions or suspensions are particularly suitable, in particular aqueous solutions of the active compounds in polyethoxylated castor oil.

For vaginal application, for example suppositories, tampons, gels, foams or intrauterine pessaries are suitable and usual.

For intraarticular injection, suitably prepared crystal suspensions can be used.

For intramuscular injection, aqueous and oily injection solutions or suspensions and corresponding depot preparations can be used.

For rectal application, the new compounds can be used in the form of suppositories, capsules, solutions (e.g. in the form of enemas) and ointments both for systemic and also for local therapy.

For pulmonary application of the new compounds, these can be used in the form of aerosols and inhalation formulations.

For local use on eyes, external auditory canal, middle ear, nostrils and paranasal sinuses, the new compounds can be used as drops, ointments and tinctures in appropriate pharmaceutical preparations.

For topical application, formulations in gels, ointments, fatty ointments, creams, pastes, powders, milk and tinctures are possible. The dosage of the compounds of the general formula I in these preparations should be 0.01% - 20% in order to achieve an adequate pharmacological action.

The dosage of the active substances can vary depending on the administration route, age and weight of the patient, nature and severity of the disease to be treated and similar factors. The treatment can be effected by single doses or by a large number of doses over a longer period. The daily dose is 0.5 - 1000 mg, preferably 50 - 200 mg, and the dose can be given as a single dose for administration once or subdivided into 2 or more daily doses.

As carrier systems, surface-active additives such as salts of the bile acids or animal or plant phospholipids, but also mixtures thereof and liposomes or components thereof can also be used.

The formulations and presentations described above are also a subject of the present invention.

The administration of the compounds according to the invention can be effected by any conventional method, including oral and parenteral, e.g. by subcutaneous or intramuscular injections, and various inhalation techniques. The enteral, parenteral, vaginal, intrauterine and oral applications are also a subject of the present invention.

The compounds according to the invention of the general formula I bind to the EP_2 receptor and have an antagonistic action. The antagonistic action can be determined by an antagonism test (see Example 1.2.1 of the biological examples).

Antagonists should be understood to mean molecules which bind to their appropriate receptors and which inhibit the initiation of the signal transduction pathway(s) coupled with the receptor through the naturally occurring ligand(s). Normally, the antagonists compete with the naturally occurring ligand of the receptors for the binding to the receptor. However, other modifications of

the receptor by molecules which prevent the signal transduction pathways coupled with the receptor from being activated by the naturally occurring ligand(s) are also possible (e.g. non-competitive, steric modifications of the receptor).

More preferably, the antagonists bind reversibly to their corresponding receptors.

The EP_2 receptor antagonist has a preferential affinity for the EP_2 receptor compared to any other EP receptor. The antagonism is measured in the presence of the natural agonist (PGE_2).
For the determination of the selectivity, the action of the EP_2 antagonist on a human EP_4 receptor (Example 2.2.1) or PGD receptor (Example 3.2.1) can be determined (Table 1).
Furthermore, the substances according to the invention are more stable *in vivo* than the EP_2 receptor antagonists which are described in the closest state of the art (DE 10 2009 049 662 A1), and this results in higher half-lives (see Table 3).

Also a subject of the present invention is the use of the substances according to the invention as EP_2 receptor antagonists for the treatment of diseases which are caused by disorders in the signal transduction chain in which the EP_2 receptor is involved, such as for example pain and fertility disorders. The EP_2 receptor antagonists are also suitable for fertility control.

In the pre-ovulatory antral follicle, the oocyte is surrounded by cumulus cells which form a dense cell crown around the oocyte. After the peak of the luteinizing hormone (LH peak), a series of processes is activated, which results in a marked morphological change in this cell crown of cumulus cells. During this, the cumulus cells form an extracellular matrix, which leads to the so-called cumulus expansion (Vanderhyden *et al.* 1990, Dev Biol., Aug;140(2):307-317). This cumulus expansion is an important component of the ovulatory process and the subsequent possibility of fertilization.
During the cumulus expansion, prostaglandins and here prostaglandin E_2, synthesis whereof is induced by the LH peak, are of decisive importance. Prostanoid EP_2 knockout mice (Hizaki *et al.*, 1999, Proc Natl Acad Sci U S A., Aug 31;96(18):10501-6.) show a markedly decreased cumulus expansion and severe subfertility, which demonstrates the importance of the prostanoid EP_2 receptors for this process.
The action of an EP_2 antagonist on cumulus expansion can be measured in a cumulus expansion test (see Example 4.2).

The substances according to the invention have inhibitory effects in cumulus expansion tests and an influence on the fertilizability of ovulated cumulus-oocyte complexes (see Example 4.3 and

Table 4). The substances according to the invention have a contraceptive effect in non-human primates (Cynomolgus), where they cause a markedly decreased pregnancy rate without having an influence on the cycle (length of the cycle and hormones) (see Example 4.4 and Table 5). This for the first time shows a contraceptive effect of EP_2 receptor antagonists in non-human primates. This effect is based on non-hormonal mechanisms, which demonstrates the possibility of hormone-free contraception with the substances according to the invention.

A subject of the present invention is the use of the substances according to the invention for fertility control.

While the EP_2 receptor antagonist AH6809 first suppresses the expansion of the cumulus, by only ca. 30%, at a concentration of 100 - 200 µM, in the presence of the substance according to the invention according to Example 17 a ca. 70% suppression of the cumulus expansion can already be attained at a 100-200 times lower concentration (0.5 µM; IC_{50}: 3.4 nM, see Table 1). In these experiments, the test substances compete with the natural EP_2 receptor agonist PGE_2 (0.3 µM).

By administration of the substance of example 62 from the application DE 10 2009 049 662 A1, a ca. 70% suppression of the cumulus expansion can likewise be achieved, however for this a concentration of 10 µM is necessary, which represents a 10-20 times lower concentration in comparison to AH6809. However, this is markedly higher than the concentration of 0.5 µM for Example 17 from the present invention (see Table 2).

Example 17 according to the invention from the present invention is also characterized by a better terminal half-life. While example 62 from the application DE 10 2009 049 662 A1 has a $t_{1/2}$ of 0.4 hours, for Example 17 this is 2.5 hours (see Table 3).

Accordingly substance 17 of the present invention is markedly superior to this compound known from the state of the art.

A subject of the present invention is the use of the substances according to the invention for the inhibition of cumulus expansion and thereby of ovulation and fertilization for contraception.

A particular form of contraception is emergency protection (also known as “morning-after pill”). This should be understood to mean the taking of one or more substances which is intended to prevent a possible pregnancy after unprotected sexual intercourse and in the event of a presumable failure of the protective method.

A subject of the present invention is the use of the substances according to the invention for emergency protection.

Also a subject of the present invention is the use of the substances according to the invention as EP_2 receptor antagonists for the prophylaxis and direct treatment of diseases which are causally linked with the EP_2 receptor or of diseases which can be treated by influencing the EP_2 receptor.

Prostaglandins play an important part in angiogenesis (Sales, Jabbour, 2003, Reproduction 126, 559 – 567; Kuwano *et al.*, 2004, FASEB J. 18, 300–310; Kamiyama *et al.*, 2006, Oncogene 25, 7019–7028; Chang *et al.*, 2005, prostaglandins & other Lipid Mediators 76, 48–58).
Endometriosis is a chronic disease wherein inflammatory, immunmodulatory and angiogenic processes are involved. Together with other factors, prostaglandins and here in particular the PGE_2 and the EP_2 receptor are of particular importance (Banu *et al.*, 2009, Molecular Endocrinology 23: 1291–1305; Bulun 2009, N Engl J Med; 360, 268-279).
Circa 10% of women suffer regularly from severe bleeding during menstruation, caused by changes in the blood vessels of the endometrium. Additionally, structural differences in the blood vessels have been observed, such as for example the incomplete formation of the smooth muscle layer (Abberton *et al.*, 1999, Hum. Reprod. 14, 1072-1079, Rogers *et al.* 2003, Microsc Res Tech. 60(4), 412-419). Since the blood loss during menstruation is partly regulated by the constriction of the blood vessels, it is obvious that the defects in the smooth musculature contribute substantially to the bleeding.

A subject of the present invention is the use of the substances of the general formula I for the prophylaxis and treatment of endometriosis.

Prostaglandins play an important part in uterine contraction, and excessively strong contractions are responsible for menstrual problems (Sales, Jabbour, 2003, Reproduction 126, 559 – 567). Prostaglandins and here especially the EP_2 and the EP_4 receptor have been linked with severe menstrual bleeding (Smith *et al.*, 2007 (Human Reproduction, Vol.22, No.5 pp. 1450–1456).

A subject of the present invention is the use of the substances of the general formula I for the prophylaxis and treatment of menstrual problems and severe menstrual bleeding and pains during menstruation.

Fibroids (myomas) are benign tumours in the uterus with a high dissemination rate. Via the stimulation of aromatase by a PGE_2/cAMP-mediated signal pathway, and by other possible

mechanisms, there is a link to the prostaglandin metabolism (Imir *et al.*, 2007, J Clin Endocrinol Metab 92, 1979–1982).

A subject of the present invention is the use of the substances of the general formula I for the prophylaxis and treatment of fibroids (myomas).

An increasing number of research results also confirm the importance of the EP receptors, and in particular also of the EP_2 receptor in a large number of cancer types (e.g. breast cancer, colon carcinoma, lung cancer, prostate cancer, leukaemia and skin cancer), which points to future possibilities for the use of modulators (antagonists or agonists) of the EP_2 receptor for the therapy and prevention (prophylactic and/or adjuvant) of cancer (Fulton *et al.*, 2006, Cancer Res; 66(20): 9794-7; Castellone *et al.*, 2005, Science Vol 310, 1504-1510; Chang *et al.*, 2005, Cancer Res; 65(11): 4496-9); Hull *et al.*, 2004, Mol Cancer Ther;3(8):1031–9; Richards *et al.*, 2003, J Clin Endocrinol Metab 88: 2810–2816,; Sinha *et al.*, 2007, Cancer Res; 67(9): 4507–13; Wang *et al.*, 2004, Seminars in Oncology, Vol 31, No 1, Suppl 3: pp 64-73), Yu *et al.*, 2008; JPET Published on June 26, as DOI:10.1124/jpet.108.141275, Denizot *et al.*, 2005, Int. J. Cancer: 115, 499–501; Fiancette *et al.*, 2011, J Oncol. pii: 389021, Chun *et al.*, 2011, Mol Carcinog. 50(6):439-48).

A subject of the present invention is the use of the substances of the general formula I for the treatment and prevention of cancer diseases.

The activation of endothelial cells plays an important part in the pathogenic process of arteriosclerosis. Here oxidation products of low density lipoprotein (LDL) are significant in the onset and development of arteriosclerotic diseases. More recent researches indicate involvement of the EP_2 receptor (Li *et al.*, 2006; Circ Res. 98:642-650).

A subject of the present invention is the use of the substances of the general formula I for the treatment and prevention of arteriosclerosis.

More recent scientific publications show that in neurodegenerative, neuroinflammatory and ischaemic diseases (Alzheimer, Parkinson, ALS and stroke), prostaglandins and the EP_2 receptor are important components of the pathological process (Hoshino *et al.*, 2007, J Biol Chem.; 282(45): 32676-88; Liang *et al.*, 2005, The Journal of Neuroscience; 25(44): 10180 –10187; Jin *et al.*, 2007, J Neuroinflammation. Jan 4;4:2.; Liang *et al.*, 2008, Ann Neurol;64: 304–314; Cimino *et al.*, 2008, Current Medicinal Chemistry, 1863-1869).

Multiple sclerosis is a chronic inflammation of the nervous system. Prostaglandins, especially PGE_2, and effects mediated via the EP_2 receptor are causally linked with the pathological processes in multiple sclerosis (Palumbo *et al.*, 2011, Prostaglandins, Leukotrienes and Essential Fatty Acids 85: 29–35; Palumbo *et al.*, 2011, J. Neurochem. 10.1111/j.1471-4159, Kihara *et al.*, 2009, Proc Natl Acad Sci U. S. A, 106, No. 51: 21807–21812).

A subject of the present invention is the use of the substances of the general formula I for the treatment and prevention of neurodegenerative, neuroinflammatory and ischaemic diseases such as for example Alzheimer's, Parkinson's, ALS and stroke and for the treatment of multiple sclerosis.

Polycystic kidney diseases are also linked with the EP_2 receptor (Song *et al.*, 2009, Human Molecular Genetics, 18, No. 13: 2328–2343; Elberg *et al.*, 2007, Am J Physiol Renal Physiol 293: F1622–F1632.)
A subject of the present invention is the use of the substances of the general formula I for the treatment and prevention of polycystic kidney diseases.

Reinold *et al.* (J. Clin. Invest. 115, 673-679 (2005)) describe PGE_2 receptors of the EP_2 subtype as the key signal elements in inflammatory hyperalgesia. Mice which no longer carry this receptor ($EP_2^{-/-}$) feel no spinal inflammatory pain. There are indications that an inflammatory, increased sensitivity to pain can be treated by specifically modulating EP_2 receptors. Furthermore, the EP_2 receptor is linked with other types of pain (Zeilhofer, 2007, Biochemical Pharmacology 73; 165– 174), inter alia in facial nerves (Patwardhan *et al.* (J Dent Res 87(3):262-266, 2008)).

A subject of the present invention is the use of the substances according to the invention for the treatment and prevention of pain of various origins such as for example inflammatory hyperalgesia.

Recent scientific publications refer to a use of EP_2 inhibitors for the prevention and/or treatment of infections of the respiratory tract. Serezani *et al.* (Am Respir Cell Mol Biol Vol 37. pp 562-570, 2007) states that the ability of macrophages of the respiratory tract to destroy bacteria is impaired via the activation of the EP_2 receptor by PGE_2. Bacterial infections lead to increased production of prostaglandins, inter alia PGE_2, which via this mechanism weakens the endogenous defence against bacteria. As shown in this publication, this ability to combat bacteria can be restored by inactivation of the EP_2 receptor (and of the EP_4 receptor). Further

relevant publications which explain these connections are: Sadikot *et al.*, 2007, Eur. J. Immunol.. 37: 1001–1009; Aronoff *et al.*, 2004, The Journal of Immunology, 173: 559–565 and Medeiros *et al.*, 2009, J Exp Med. 206(1):61-68.

A subject of the present invention is the use of the substances according to the invention for the prevention and treatment of infectious diseases of the lung.

Fibroblasts and here in particular their functions in the restoration of damaged tissue play a decisive part in chronic obstructive pulmonary disease. During this, an excess of PGE_2 suppresses important repair functions of the fibroblasts (Togo *et al.*, 2008, Am J Respir Crit Care Med, 178: 248–260).

A subject of the present invention is the use of the substances according to the invention for prophylaxis and treatment in chronic obstructive pulmonary diseases.

Intestinal inflammatory diseases (e.g. Crohn's disease) are also linked with the prostaglandin EP_2 receptor (Sheibanie *et al.*, 2007, The Journal of Immunology, 178: 8138–8147).

A subject of the present invention is the use of the substances according to the invention for the prevention and treatment of intestinal inflammatory diseases.

During bone marrow transplantation, complications often occur through infections, wherein an overproduction of PGE_2 is linked with decreased immune defence (Ballinger *et al.*, 2006, The Journal of Immunology, 177: 5499–5508).

A subject of the present invention is the use of the substances according to the invention for prophylaxis and treatment in bone marrow transplantation.

Graves' disease is an autoimmune disease of the thyroid, in which the clinical picture can also include pathological changes in the eye (endocrine orbitopathy; protrusion of the eyeballs (exophthalmus)). During this, invading lymphocytes activate fibroblasts that are present, which leads inter alia to an accumulation of mucopolysaccharides. Possible consequences are impairment of the vision even extending to blindness. Studies show that interleukin-6 is of decisive importance for the pathological mechanisms and that interleukin-6 is induced via PGE_2 and the EP_2 receptor (Raychaudhuri *et al.*, 2010, PloS ONE, 5: e15296; Wang *et al.*, 1995, J Clin Endocrinol Metab 80: 3553-3560).

A subject of the present invention is the use of the substances according to the invention for prophylaxis and treatment in orbitopathy in connection with Graves' disease or other pathological diseases of the eye.

Aneurysms are vascular dilations with the risk of leading with vascular ruptures to haemorrhages with grave and life-threatening effects, e.g. paralysis, loss or impairment of speech, cognitive limitations and other neurological consequences in case of cerebral haemorrhages. Even without ruptures, cerebral aneurysms can cause severe neurological symptoms through the pressure on nerve fibres. Cerebral aneurysms are found in about 1 – 5% of the population, there being a higher incidence in women. Ruptures of aneurysms in the peripheral blood vessels involve a high risk of thromboses, cardiac infarctions, pain and a number of other clinical pictures. Pharmacological therapies mainly comprise the limitation of risk factors such as hypertension.
Recent scientific studies were able to show that the EP_2 receptor plays a substantial part in the pathogenesis of cerebral aneurysms. In this, via the cascade COX-2 – PGE_2 – EP_2- NF-κ-β an inflammatory state is created which is causally involved in aneurysm formation (Aoki *et al.*, 2011, British Journal of Pharmacology 163: 1237–1249; Aoki *et al.* 2007, 116:2830-2840).

A subject of the present invention is the use of the substances according to the invention for the prophylaxis and treatment of aneurysms.

Kawasaki syndrome is an acute, systemic feverish disease, by which children under 5 years are predominantly affected. Long-term damage can include changes in the blood vessels, in particular the coronary blood vessels (e.g. formation of aneurysms) and diseases connected therewith such as cardiac rhythm disorders and cardiac infarction. The incidence differs regionally, thus for example 185 out of 100000 children under 5 years in Japan and about 9 out of 100000 children in Germany. Prostaglandin E_2 is elevated in the acute phase of the disease (Lee *et al.*, 1988, Prostaglandins Leukot Essent Fatty Acids, 31(2):53-57). Through recent research studies it could be shown that β1 integrin is activated by PGE_2 and mediated via the EP_2 receptor, which is causally linked with the vascular damage (Kajimoto *et al.*, 2009, Inflamm. Res. 58: 224–228).

A subject of the present invention is the use of the substances according to the invention for the prophylaxis and treatment of Kawasaki syndrome, in particular also for the prevention and avoidance of vascular damage.

Recent researches show that the EP_2 receptor has an important role in arthritis and here exerts an influence on the pathogenesis of this disease via immunmodulatory mechanisms (Harizi *et al.*, 2010, Immunology and Cell Biology, 1–8).

A subject of the present invention is the use of the substances according to the invention for the prophylaxis and treatment of arthritis.

The natural ligand (agonist) of the EP_2 receptor is PGE_2, the synthesis whereof is mediated via cyclooxygenases (COX) enzymes (COX-1, COX-2). These enzymes are mostly involved in the said clinical pictures and indications and the onset thereof via increased expression and activity. Hence in all the use possibilities mentioned, a combination of a COX inhibitor (COX-2 and/or COX-1) is possible, with the aim of

a) achieving a higher and more effective pharmacological activity than with one substance class and
b) enabling a lower dosage of one of the two or of both substance classes, which leads to a reduction of possible side effects and better tolerance.

Hence drugs containing a compound of the general formula (I) in combination with a COX inhibitor for the treatment of diseases (combination preparations) are also a subject of the present invention. As COX inhibitors, for example the non-selective COX inhibitors such as aspirin, naproxen, indomethacin, ibuprofen and the selective COX inhibitors meloxicam, ketoprofen, piroxicam, tenoxicam, nimesulide, mefanemic acid, ketoralac, celecoxib (4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulphonamide) parecoxib (N-[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulphonylpropionamide), rofecoxib (4-(4-mesylphenyl)-3-phenyl-furan-2(5H)-one), valdecoxib (4-[5-methyl-3-phenyl-4-isoxazoyl)benzenesulphonamide), NS-398 (N-methyl-2-cyclohexanoxy-4-nitrobenzenesulphonamide), lumiracoxib [2-(2'-chloro-6'-fluoro-phenyl)-amino-5-methylbenzeneacetic acid], ceracoxib and etoricoxib may be mentioned.

These combination preparations can be used for the treatment of the following diseases: infectious diseases, cancer, cardiovascular diseases, angiogenic diseases, uterine contraction disorders, pain, inflammatory diseases, neuroinflammatory diseases, neurodegenerative diseases, autoimmune diseases, immunodependent diseases/therapies, nephrological diseases and ophthalmological diseases.

They can also be used for fertility control.

In addition, the invention relates to a process for the production of the compounds according to the invention of the general formula I.

For this, for example a carboxylic acid of the formula VIII is reacted with an amine of the general formula XI by methods known to those skilled in the art to give the compounds according to the invention of the general formula I (Scheme 1).

The reaction takes place in that for example a carboxylic acid of the formula VIII is converted with isobutyl chloroformate in the presence of a tertiary amine, for example triethylamine, into a mixed anhydride, which reacts with an alkali metal salt of the appropriate amine XI in an inert solvent or solvent mixture, for example tetrahydrofuran, N,N-dimethylformamide or dimethoxyethane at temperatures between -30°C and +60°C to give the target compounds of the formula I.

It is also possible to activate a carboxylic acid VIII with reagents such as for example dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), N-hydroxybenzotriazole (HOBT) or N-[(dimethylamino)-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy)methyliden]-N-methylmethanaminium hexafluorophosphate (HATU). For example the reaction with HATU takes place in an inert solvent, for example N,N-dimethylformamide or dimethyl sulphoxide in the presence of the appropriate amine XI and a tertiary amine, for example triethylamine or diisopropylamine, at temperatures between -30°C and +60°C.

It is also possible, to convert a carboxylic acid of the formula VIII into the corresponding carboxylic acid chloride with an inorganic acid chloride, for example phosphorus pentachloride, phosphorus trichloride or thionyl chloride and then into the target compounds of the general formula I in pyridine or an inert solvent, such as for example N,N-dimethylformamide, in the presence of the appropriate amine XI and a tertiary amine, for example triethylamine, at temperatures between -30°C and +60°C.

The compounds according to the invention of the general formula I can also be obtained from bromoindazoles of the general formula VI under palladium(0) catalysis by reaction with an appropriate amine XI and carbon monoxide (CO) or a carbon monoxide source, such as for example molybdenum hexacarbonyl in a suitable solvent or solvent mixture, for example 1,4-dioxan/water or tetrahydrofuran, addition of a base such as for example sodium carbonate or 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) and a catalyst-ligand mixture, for example palladium(II) acetate or trans bis(acetato)bis[o-(di-o-tolylphosphino)benzyl]-dipalladium(II) / tri-tert-butylphosphinotetrafluoroborate at temperatures between 80°C and 160°C (optionally with microwave irradiation between 80-200 watts), and in case of the use of carbon monoxide at a CO pressure of 5-15 bar (Scheme 1).

The compounds according to the invention of the general formula I can also be obtained from amines of the general formula XV by reaction with carboxylic acids (Y = OH), chlorides (Y = Cl) or anhydrides (e.g. Y = O-C(O)-O-$CH_2(CH)_3CH_3$) of the formula IX in the manner described for the production of the compounds I from the compounds VIII and XI (Scheme 2).

Likewise, the compounds of the general formula I can be obtained from compounds of the general formula XVI, wherein LG′ for example means Br or I, by reaction with compounds of the formula XVIII (Scheme 2).

Compounds of the formula XVIII are for example (Het)Arylboronic acids (R^3-Met = (Het)Ar-$B(OH)_2$) or boronic acid pinacol esters (R^3-Met= (Het)Ar-BPin), which are converted to biaryl compounds of the formula I by methods known to those skilled in the art in a suitable solvent, for example N,N-dimethylformamide, tetrahydrofuran, dimethoxyethane and optionally water and addition of a base, for example triethylamine, potassium carbonate, caesium carbonate and a catalyst-ligand mixture, for example of palladium(II) acetate / triphenylphosphine, bis(diphenylphosphino)ferrocenedichloropalladium (II) (/ 1,1'-bis(diphenylphosphino)ferrocene/ Cu(I)Cl) at temperatures between 20°C and 120°C.

Compounds of the formula XVIII can also be (Het)Arylalcohols (R^3-Met = (Het)ArO-H), which are converted into biaryl ethers of the formula I by methods known to those skilled in the art in a suitable solvent, for example N,N-dimethylformamide or dimethyl sulphoxide with addition of a base, for example potassium carbonate, caesium carbonate under copper-(I) catalysis e.g. with copper(I) bromide at temperatures between 60°C and 120°C.

The carboxylic acids of the general formula VIII can for example be obtained from esters of the formula VII by ester saponification in a suitable solvent or solvent mixture, for example methanol, ethanol or tetrahydrofuran, water with addition of an aqueous solution of an alkali metal hydroxide, for example sodium hydroxide or lithium hydroxide at temperatures between 20°C and 60°C (Scheme 1).

In the same manner, the carboxylic acids XIII can be obtained from the esters XII (Scheme 2, PG: e.g. Boc (tert-butyloxycarbonyl) and the carboxylic acids XXI from the esters XX (Scheme 3, LG′: e.g. Br or I).

The esters of the general formula VII can be obtained from bromoindazoles of the general formula VI under palladium(0) catalysis by reaction with carbon monoxide or a carbon monoxide source, such as for example molybdenum hexacarbonyl, and methanol in a suitable solvent, for example dimethyl sulphoxide, N,N-dimethylformamide or tetrahydrofuran and addition of a base, for example triethylamine or 1,8-diazabicyclo(5.4.0)undec-7-ene and a

catalyst-ligand mixture, for example of palladium(II) acetate / bis-1,3-diphenylphosphino-propane or trans bis(acetato)bis[o-(di-o-tolylphosphino)benzyl]dipalladium(II) / tri-tert-butylphosphinotetrafluoroborate at temperatures between 20°C and 140°C (optionally with microwave irradiation between 80 - 200 watts), and in case of the use of carbon monoxide at a CO pressure of 5 – 15 bar (Scheme 1).

This method is not restricted to methyl esters, i.e. to the use of methanol, but can also be extended to other esters. Thus for example by use of ethanol instead of methanol in this manner, the corresponding ethyl esters can be synthesized.

In the same manner, the esters XII can be obtained from the bromides IV (Scheme 2, -PG: e.g. -Boc).

The amides of the general formula VII can also be obtained from the amines of the general formula XIX by reaction with compounds of the general formula IX (Scheme 3), analogously to the synthesis of the compounds I from the compounds XV (Scheme 2).

The compounds of the general formula VII can also be obtained from compounds of the formula XX and reaction with compounds of the formula XVIII (Scheme 3), analogously to the described conversion of the compounds XVI to the compounds of the formula I (Scheme 2).

The amides of the general formula VI can be obtained from amines of the general formula V by reaction with carboxylic acids (Y = OH), chlorides (Y = Cl) or anhydrides (e.g. Y = O-C(O)-O-$CH_2(CH)_3CH_3$) of the formula IX (Scheme 1), as described for the conversion of amines XV to amides I (Scheme 2).

The amides of the general formula XVI can be obtained in analogous manner from amines XV and carboxylic acids or carboxylic acid derivatives XVII (Y: e.g. OH, Cl or O-C(O)-O-$CH_2(CH)_3CH_3$; LG′: e.g. Br or I) (Scheme 2).

Analogously, amines XX (LG′: e.g. Br or I) can be obtained from amines XIX and carboxylic acids or carboxylic acid derivatives XVII (Y: e.g. OH, Cl or O-C(O)-O-$CH_2(CH)_3CH_3$; LG′: e.g. Br or I) (Scheme 3).

Likewise, carboxylic acids XIII (PG: e.g. Boc) can be converted with amines XI to amides XIV (Scheme 2) and carboxylic acids XXI (LG′: e.g. Br, I) with amines XI to amides XVI (Scheme 3) in this manner.

The secondary amines V can be obtained from the corresponding carbamates IV (PG: e.g. Boc) by methods known to those skilled in the art (Scheme 1).

Thus for example tert-butyl carbamates can be converted into the amines V in an acidic medium with the use of e.g. trifluoroacetic acid or hydrochloric acid in a suitable solvent or solvent mixture such as for example dichloromethane, dioxan or acetone/water. In an anhydrous medium the amines V are formed as the corresponding salts.

Analogously, the amines XV can be obtained from the carbamates XIV (Scheme 2) and the amines XIX from the carbamates XII (Scheme 3).

The *2H*-indazoles of the general formulae IV and VI can be produced in various ways.

For example, *2H*-indazoles IV can be obtained from *1H*-indazoles of the general formula II by alkylation with compounds of the general formula III (PG: e.g. Boc, LG: e.g. Br, I, O-Ts (tosyloxy) or O-Ms (mesyloxy)) in a suitable solvent, for example N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulphoxide or else THF, 1,4-dioxan and addition of a base such as for example potassium carbonate or caesium carbonate (optionally with addition of tetrabutylammonium iodide) or else sodium bis(trimethylsilyl)amide, at temperatures between 25°C and 100°C or else in case of the use of sodium bis(trimethylsilyl)amide 0°C and 25°C (Scheme 1).

Analogously the *2H*-indazoles of the general formula VI can be obtained from *1H*-indazoles of the general formula II and compounds of the general formula X (LG: e.g. Br, I, O-Ts or O-Ms) (Scheme 1).

The *2H*-indazoles of the general formula IV can also be obtained from ortho-nitrobenzaldehydes of the general formula XXVII by reaction with an appropriate amine XXVIII (PG: e.g. Boc) in a suitable solvent, for example 1,4-dioxan and addition of a reducing agent such as for example triethyl phosphite, possibly with addition of potassium carbonate or caesium carbonate or powdered molecular sieve, at temperatures between 100°C and 160°C (Scheme 4).

Analogously, the *2H*-indazoles of the general formula VI can be obtained from ortho-nitrobenzaldehydes XXVII by reaction with amines XXIX (Scheme 4).

The compounds of the general formula XIV (PG: e.g. Boc) can also be obtained from bromo-indazoles of the general formula IV (PG: e.g. Boc) under palladium(0) catalysis by reaction with an appropriate amine XI and carbon monoxide or a carbon monoxide source, such as for example molybdenum hexacarbonyl (Scheme 2), analogously to the described process for the conversion of the bromoindazoles VI to the compounds of the general formula I, (Scheme 1).

The ortho-nitrobenzaldehydes of the general formula XXVII can be produced from the ortho-nitrotoluenes of the general formula XXVI by methods known to those skilled in the art in two reaction steps (Scheme 4).

For this, an ortho-nitrotoluene XXVI is dissolved in a suitable solvent such as N,N-dimethylformamide and converted with N,N-dimethylformamide dimethyl acetal at temperatures of 100 – 140°C to the corresponding enamine, which is immediately oxidized at temperatures of 0°C – 20°C to the corresponding ortho-nitrobenzaldehyde with a suitable oxidizing agent such as for example $NaIO_4$ in a suitable aqueous solvent mixture such as water/N,N-dimethylformamide and optionally with addition of a base such as for example triethylamine, N,N-diisopropylethylamine, sodium hydrogen carbonate or sodium carbonate.

The ortho-nitrotoluenes of the general formula XXVI can be produced from the ortho-methylanilines of the general formula XXV by methods known to those skilled in the art (Scheme 4).

For this, an ortho-methylaniline XXV is dissolved in a suitable solvent such as dichloromethane or chloroform, treated with zirconium(IV) tert-butoxide, ground molecular sieve 3Å and tert-butyl hydroperoxide and reacted at temperatures of 20-40°C.

The *1H*-indazoles of the general formula II can be liberated from the acetamides of the general formula XXIV by methods known to those skilled in the art (Scheme 4).

For this, for example an acetamide XXIV is reacted in a suitable solvent such as methanol or ethanol and addition of 37% hydrochloric acid at temperatures of 40 – 80°C.

Analogously thereto, the anilines of the formula XXV can be liberated from the acetanilides of the formula XXIII (Scheme 4).

The acetamides of the general formula XXIV can be produced from the ortho-methyl-acetanilides of the general formula XXIII by methods known to those skilled in the art (Scheme 4).

For this, the ortho-methyl-acetanilides XXIII are dissolved in a suitable solvent such as chloroform or toluene, treated with acetic anhydride, isopentyl or tert-butyl nitrite, and optionally potassium acetate and 18-crown-6, and reacted at temperatures of 60 – 100°C.

The ortho-methyl-acetanilides XXIII can be produced from the acetanilides of the general formula XXII by bromination by methods known to those skilled in the art (Scheme 4).

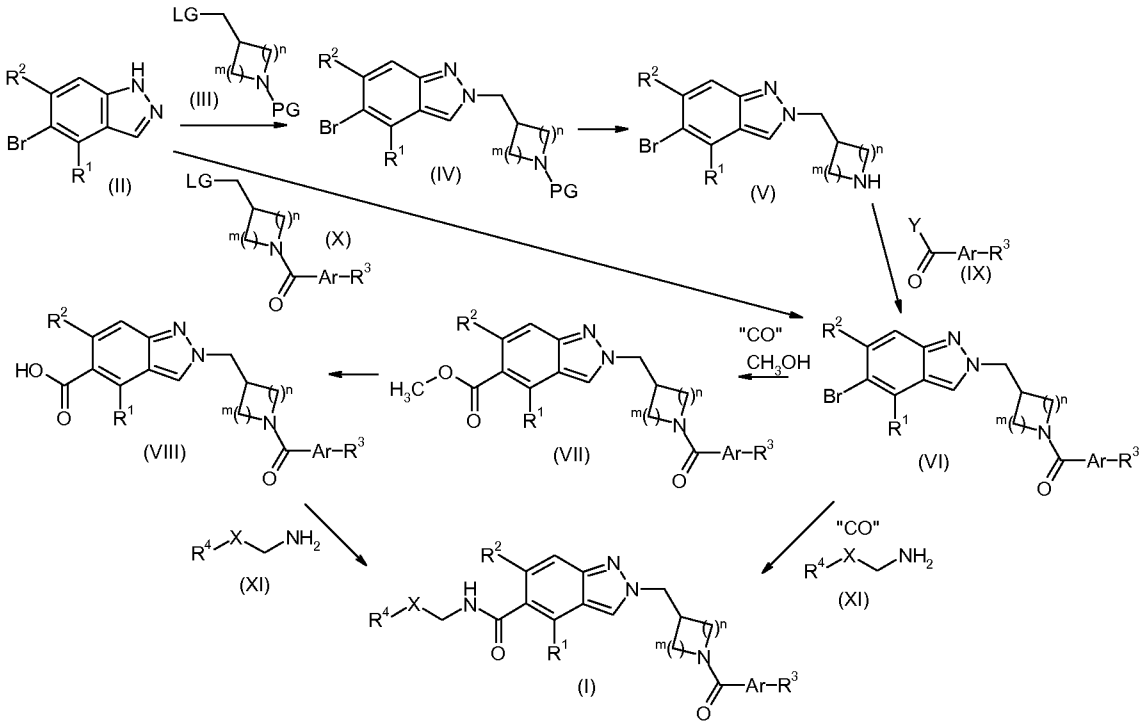
For this, the acetanilides XXII, which can for example be obtained from the corresponding anilines by reaction with acetic anhydride in a suitable solvent (e.g. toluene) at temperatures of 80-110°C, is reacted with bromine in glacial acetic acid at temperatures of 10-25°C.

The compounds of the general formula III wherein LG means -OTs or -OMs can be produced by methods known to those skilled in the art from the corresponding alcohols.
For this, the alcohols are reacted with p-toluenesulphonyl chloride or methanesulphonyl chloride at temperatures between 0°C and 40°C in a suitable solvent, e.g. dichloromethane or tetrahydrofuran or toluene and addition of a suitable base, e.g. pyridine or triethylamine.

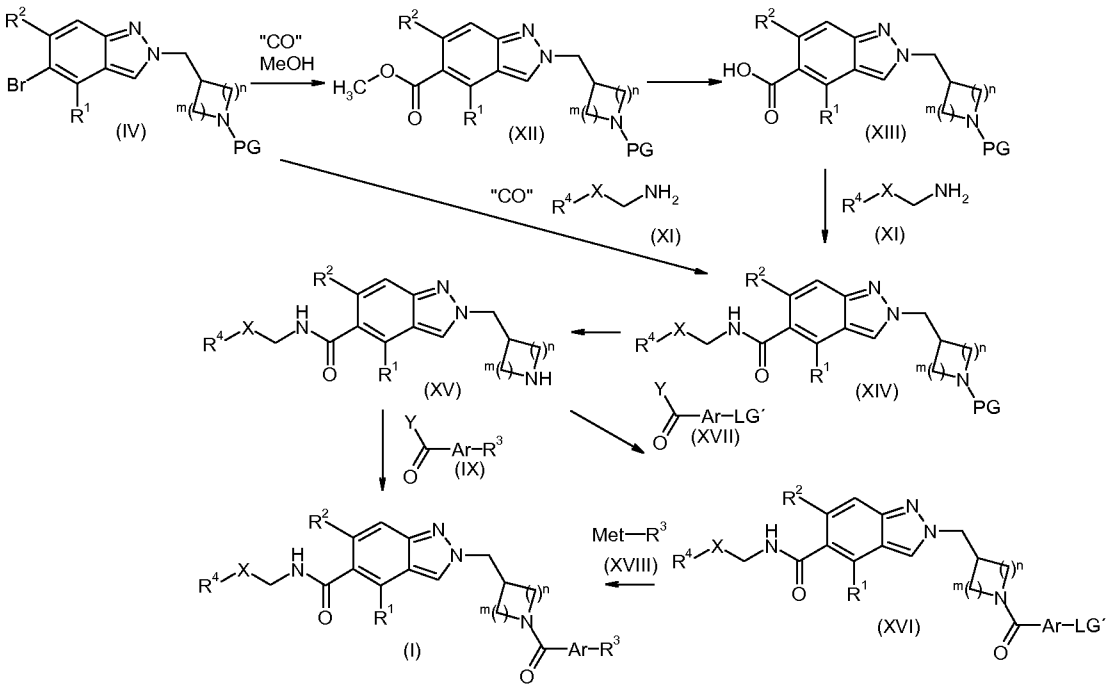
The compounds of the general formula X, wherein LG means -OTs or -OMs, can be produced from the corresponding amino alcohols XXX by methods known to those skilled in the art (Scheme 4).
For this, in a first step the amino alcohols XXX are converted to the corresponding amides XXXI in a suitable solvent, e.g. dichloromethane, with arylcarboxylic acid chlorides of the formula Cl-C(O)-Ar-R^3 and addition of a suitable base, e.g. triethylamine, at temperatures between 0°C and 25°C. Optionally, corresponding esters formed as by-products can be separated or else saponified to the corresponding alcohols XXXI under standard conditions, e.g. with use of a base, e.g. potassium hydroxide, in a suitable solvent mixture, e.g. ethanol/water, at temperatures between 20°C and 40°C
The N-protected alcohols XXXI thus obtained can be converted into the compounds of the formula X with LG: -OTs or -OMs analogously to the process described for the synthesis of the compounds III. Compounds of the formula X with LG: -Br can be obtained from the corresponding alcohols XXXI by methods known to those skilled in the art by reaction with a brominating agent such as for example CBr_4 with addition of PPh_3 as an oxophile in a suitable solvent, e.g. chloroform, at temperatures between 20°C and 40°C.

The compounds of the general formula XXIX, can be produced by methods known to those skilled in the art for example from the amines of the formula XXXII (Scheme 4).
For this, in a first step, the amines XXXII are converted to the corresponding amides XXXIII analogously to the synthesis of the compounds I from the compounds XV.
The tert-butyloxycarbonyl group in compounds of the formula XXXIII is cleaved analogously to the conversion of the compounds IV to the compounds V, hence the compounds of the formula XXIX can be obtained.

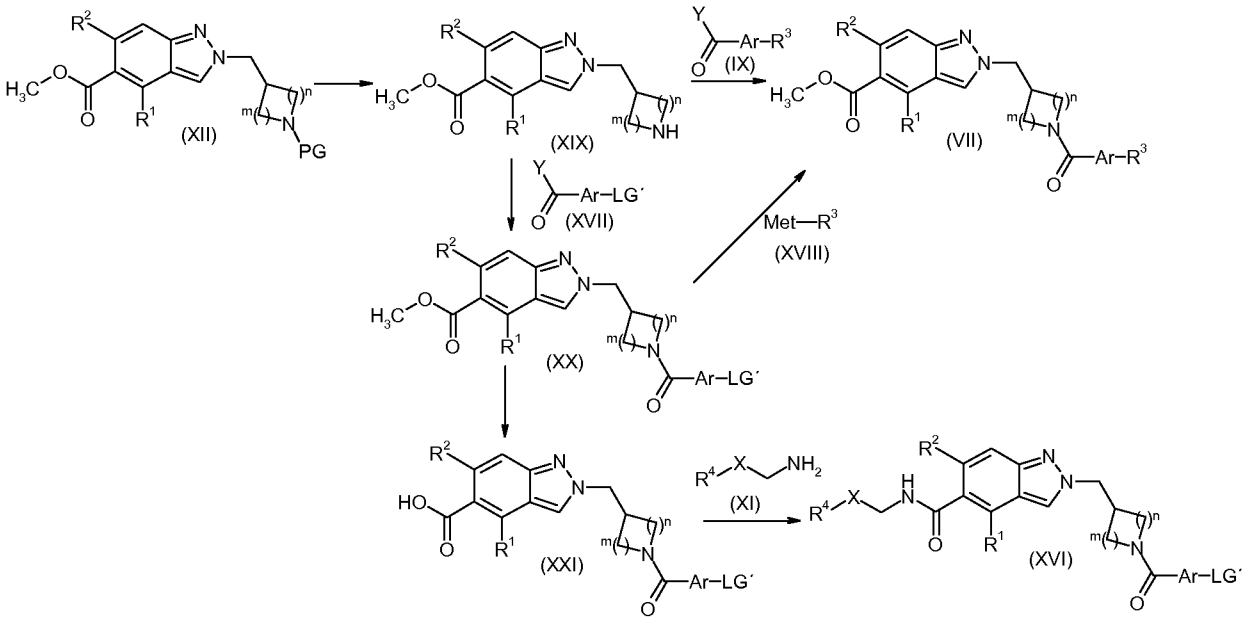
Scheme 1



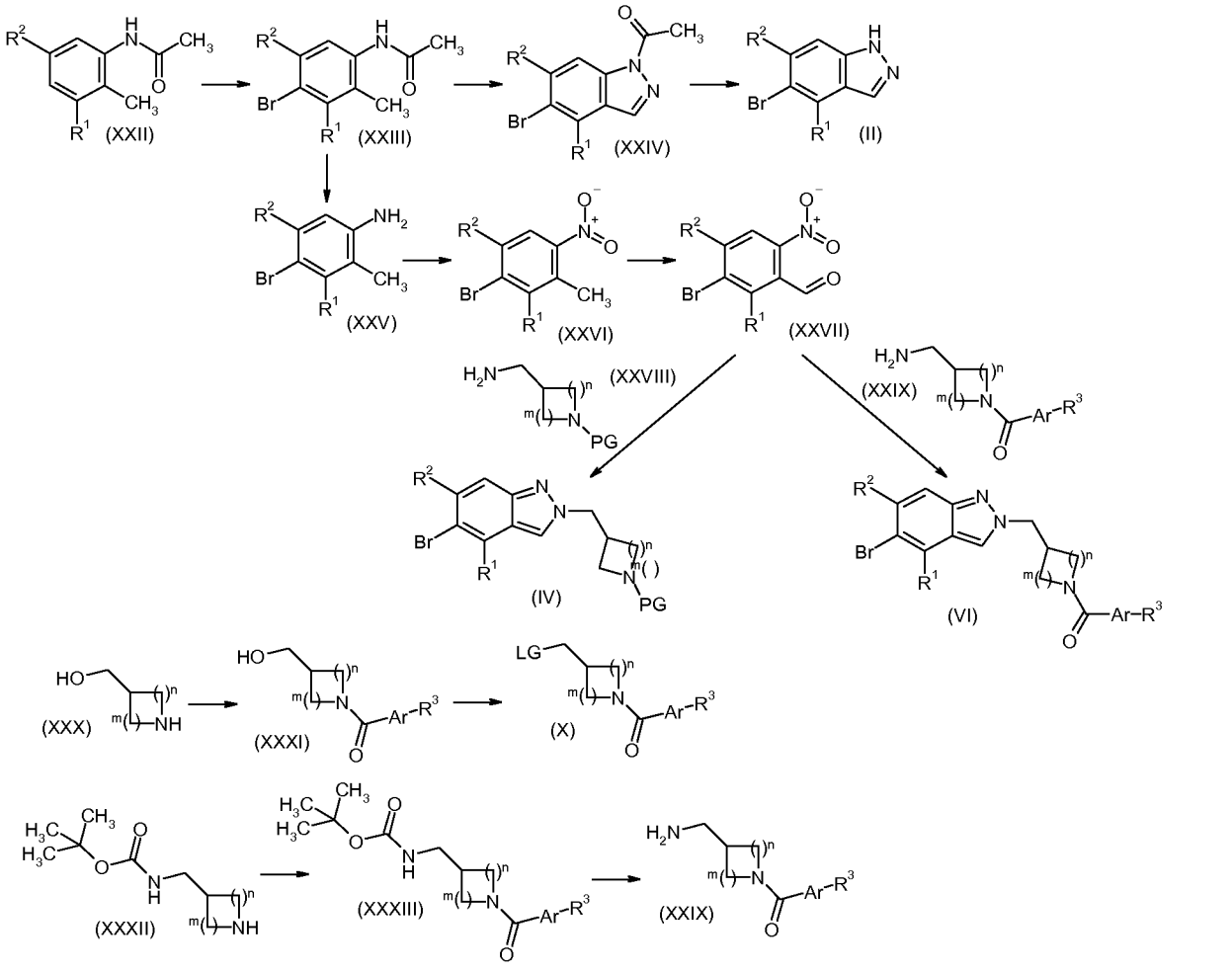
Scheme 2



Scheme 3



Scheme 4



Production of the compounds according to the invention

The following examples illustrate the production of the compounds according to the invention of the general formula (I), without limiting the range of the claimed compounds to these examples. The compounds according to the invention of the general formula (I) can be produced and characterized as described below.

LC-MS: Waters Acquity HPLC / MS 100-800 Daltons; 20 V (Micromass / Waters ZQ 4000); Column: BEHC 18 (Waters), 2.1 x 50 mm, BEH 1.7 µm; Mobile phase: A: H_2O/0.05% HCOOH, B: CH_3CN/0.05% HCOOH. Gradient: 10-90% B in 1.7 min, 90% B for 0.2 min, 98-2% B in 0.6 min; Flow rate: 1.3 ml / min, Detection: UV = 200 - 400 nm.

Chiral HPLC separation method A:
Preparative chiral HPLC: System: Dionex: Pump P 580, Gilson: Liquid Handler 215, Knauer: UV detector K-2501 Column: Chiralpak AD-H 5 µm 250x20 mm; Solvent: hexane / ethanol 50:50; Flow rate: 15 ml/min; injection volume: 0.5 ml; Detection: UV 254 nm.
Analytical chiral HPLC: System: Waters: Alliance 2695, DAD 996, ESA: Corona; Column: Chiralpak AD-H 5 µm 150x4.6 mm Solvent: hexane / ethanol 50:50; Flow rate: 1.0 ml/min; Temperature: 25°C; injection: 5 µl; Detection: DAD 254 nm.

Chiral HPLC separation method B:
Preparative chiral HPLC: System: Dionex: Pump P 580, Gilson: Liquid Handler 215, Knauer: UV detector K-2501 Column: Chiralpak IC 5 µm 250x30 mm; Solvent: ethanol / methanol 50:50; Flow rate: 30 ml/min; injection volume: 0.5 ml; Detection: UV 254 nm.
Analytical chiral HPLC: System: Waters: Alliance 2695, DAD 996, ESA: Corona; Column: Chiralpak IC 5 µm 150x4.6 mm Solvent: ethanol / methanol 50:50; Flow rate: 1.0 ml/min; Temperature: 25°C; injection: 5 µl; Detection: DAD 254 nm.

Chiral HPLC separation method C:
Preparative chiral HPLC: System: Dionex: Pump P 580, Gilson: Liquid Handler 215, Knauer: UV detector K-2501 Column: Chiralpak AD-H 5 µm 250x20 mm; Solvent: hexane / 2-propanol 50:50; Flow rate: 15 ml/min; injection volume: 0.25 ml; Detection: UV 254 nm.
Analytical chiral HPLC: System: Waters: Alliance 2695, DAD 996, ESA: Corona; Column: Chiralpak AD-H 5 µm 150x4.6 mm Solvent: hexane / 2-propanol 50:50; Flow rate: 1.0 ml/min; Temperature: 25°C; injection: 5 µl; Detection: DAD 254 nm.

Chiral HPLC separation method D:

Preparative chiral HPLC: System: Dionex: Pump P 580, Gilson: Liquid Handler 215, Knauer: UV detector K-2501 Column: Chiralpak IB 5 µm 250x20 mm; Solvent: hexane / ethanol 70:30; Flow rate: 20 ml/min; injection volume: 0.1 ml; Detection: UV 210 nm.

Analytical chiral HPLC: System: Waters: Alliance 2695, DAD 996, ESA: Corona; Column: Chiralpak IB 5 µm 150x4.6 mm Solvent: hexane / ethanol 70:30; Flow rate: 1.0 ml/min; Temperature: 25°C; injection: 5 µl; Detection: DAD 230 nm.

Chiral HPLC separation method E:

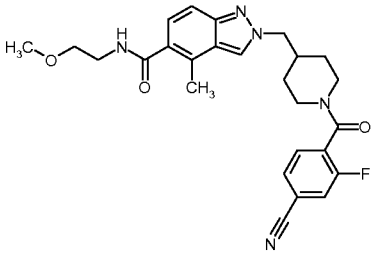
Preparative chiral HPLC: System: Dionex: Pump P 580, Gilson: Liquid Handler 215, Knauer: UV detector K-2501 Column: Chiralpak IC 5 µm 250x20 mm; Solvent: ethanol / methanol 50:50; Flow rate: 15 ml/min; injection volume: 0.3 ml; Detection: UV 230 nm.

Analytical chiral HPLC: System: Waters: Alliance 2695, DAD 996, ESA: Corona; Column: Chiralpak IC 5 µm 150x4.6 mm Solvent: ethanol / methanol 50:50; Flow rate: 1.0 ml/min; Temperature: 25°C; injection: 5 µl; Detection: DAD 230 nm.

Abbreviations

Boc	tert-butoxycarbonyl
CO	carbon monoxide
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DMF	N,N-dimethylformamide
DMSO	dimethyl sulphoxide
ESI; ES+	electrospray ionization (in MS); positive charged ion trace
hr(s)	hour(s)
HATU	N-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylen]-N-methylmethanaminium hexafluorophosphate N-oxide
HPLC	high pressure, high performance liquid chromatography
conc.	concentrated
LC-MS	liquid chromatography-coupled mass spectroscopy
M	molar
min(s)	minute(s)
MS	mass spectroscopy
N	normal
NMR	nuclear resonance spectroscopy
R_t	retention time (in HPLC and LC)
RT	room temperature
tert	tertiary
THF	tetrahydrofuran

Example 1: 2-{[1-(4-cyano-2-fluorobenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

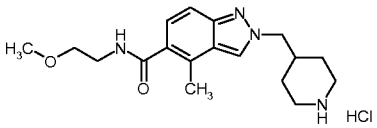


To a solution of 33.7 mg of 4-cyano-2-fluorobenzoic acid in 1.0 ml dimethyl sulphoxide were added 85.5 mg of HATU, 75 mg of the amine prepared in Example 1a and 0.071 ml of N,N-diisopropylethylamine and this was stirred for 1 hour at 25°C. The mixture was concentrated in vacuo and the residue thus obtained purified by HPLC. Yield: 43.3 mg of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.07 - 1.28 (2H), 1.30 - 1.44 (1H), 1.47 - 1.61 (1H), 2.18 - 2.34 (1H), 2.49 (3H), 2.71 - 2.83 (1H), 2.92 - 3.08 (1H), 3.32 (4H), 3.36 (2H), 3.42 (2H), 4.31 (2H), 4.39 - 4.51 (1H), 7.14 (1H), 7.38 (1H), 7.50 - 7.63 (1H), 7.71 - 7.79 (1H), 7.95 (1H), 8.09 - 8.15 (1H), 8.47 (1H).

The starting material for the above title compound was prepared as follows:

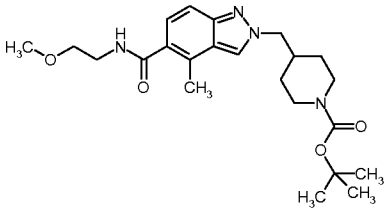
Example 1a: N-(2-methoxyethyl)-4-methyl-2-(4-piperidylmethyl)-2H-indazol-5-carboxamide hydrochloride



To 855.1 mg of 1b were added 4.5 ml of 4M hydrochloric acid in dioxan and 1 ml dioxan. An oily mass was formed, which dissolved on vigorous stirring and gentle warming. The mixture was stirred for 1 hr at ca. 30°C. The reaction mixture was concentrated. Yield: 764.7 mg of the title compound, which was further reacted without further purification.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.33 - 1.50 (2H), 1.52 – 1.62 (2H), 2.17 - 2.31 (1H), 2.32 – 2.38 (1H), 2.49 (3H), 2.67 - 2.86 (2H), 3.13 - 3.28 (5H), 3.31 - 3.46 (4H), 4.33 (2H), 7.16 (1H), 7.38 (1H), 8.13 (1H), 8.53 (1H), 8.71 - 8.88 (1H), 8.99 - 9.11 (1H).

Example 1b: Tert-butyl 4-({5-[N-(2-methoxyethyl)carbamoyl]-4-methyl-2H-indazol-2-yl}-methyl)piperidin-1-carboxylate

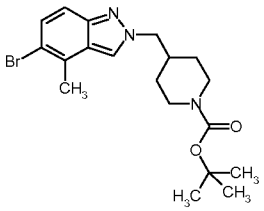


Version A: 2820 mg of 1c, 1556 mg of 2-methoxyethylamine, 1823 mg of molybdenum hexacarbonyl, 200.4 mg of tri-tert-butylphosphine tetrafluoroborate and 647.5 mg of trans-bis(acetato)-bis[o-(di-o-tolylphosphino)benzyl]dipalladium(II) were placed in portions in three microwave tubes and suspended with 56 ml THF. Then 3.1 ml of DBU were added and the mixtures stirred for 20 mins at 125°C and 200 watts in the microwave. The reaction mixtures were combined, filtered and diluted with some ethyl acetate and the organic phase washed twice with water and once with saturated sodium chloride solution. This was dried over sodium sulphate, filtered and concentrated. The residue was chromatographed on the Biotage SP4. Gradient: ethyl acetate/methanol 0-10%. Yield: 885.1 mg of the title compound.

Version B: 780 mg of 1d and 1747 mg of HATU were first dissolved in 10 ml DMSO. Next, 314 mg of 2-methoxyethylamine and 1080 mg of N,N-diisopropylethylamine were added. The mixture was stirred for 1 hr at RT. The reaction mixture was poured into water and extracted three times with ethyl acetate. The combined organic phases were washed with saturated sodium chloride solution, dried over sodium sulphate, filtered and concentrated. The residue was purified chromatographically on the Biotage SP4. Gradient: ethyl acetate/methanol 0-10%. Yield: 740 mg of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.01 - 1.13 (2H), 1.34 (9H), 1.36 - 1.43 (2H), 2.06 - 2.19 (1H), 2.49 (3H), 2.59 – 2.70 (2H), 3.29 (3H), 3.33 - 3.39 (2H), 3.40 - 3.45 (2H), 3.82 - 3.93 (2H), 4.28 (2H), 7.14 (1H), 7.38 (1H), 8.09 - 8.14 (1H), 8.46 (1H).

Example 1c: Tert-butyl 4-[(5-bromo-4-methyl-2H-indazol-2-yl)methyl]piperidin-1-carboxylate

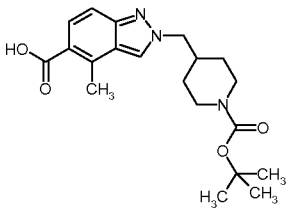


5 g of 5-bromo-4-methyl-1H-indazole was dissolved in 110 ml DMF and treated with 11.5 g of caesium carbonate and 7.9 g of N-Boc-4-(bromomethyl)piperidine. The mixture was stirred for 3 hrs at 60°C and overnight at RT. The reaction mixture was next diluted with ethyl acetate, and the organic phase was washed twice with water, dried over sodium sulphate, filtered and concentrated. The residue was purified chromatographically on the Biotage SP4 via a 65i-Si

column. Gradient: hexane/ethyl acetate 0-100%. Yield: 3.53 g of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 0.99 - 1.12 (2H), 1.34 (9H), 1.36 - 1.44 (2H), 2.04 - 2.19 (1H), 2.47 (3H), 2.54 - 2.72 (2H), 3.82 - 3.93 (2H), 4.27 (2H), 7.29 (1H), 7.34 (1H), 8.46 (1H).

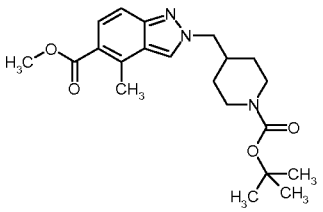
Example 1d: 2-{[1-(tert-butoxycarbonyl)piperidin-4-yl]methyl}-4-methyl-2H-indazol-5-carboxylic acid



1080 mg of 1e were dissolved in 8 ml methanol and treated with 1235 mg of lithium hydroxide in 10 ml water. A further 2 ml THF were added as solubilizer. The mixture was stirred for 24 hrs at RT. Next the methanol and THF were distilled off. The aqueous residue was diluted with water and washed once with ethyl acetate. The aqueous phase was acidified with 10% sulphuric acid and extracted twice with ethyl acetate. The combined organic phases were dried over sodium sulphate, filtered and concentrated. Yield: 880 mg of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 0.99 - 1.18 (2H), 1.37 - 1.48 (2H), 1.34 (9H), 2.05 - 2.21 (1H), 2.53 - 2.70 (2H), 2.73 (3H), 3.81 - 3.94 (2H), 4.29 (2H), 7.39 (1H), 7.62 (1H), 8.62 (1H), 11.92 - 12.31 (1H).

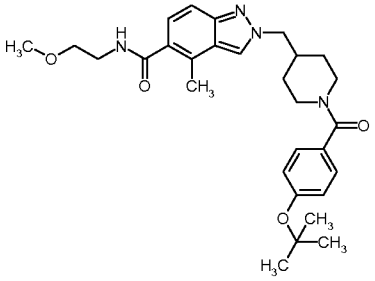
Example 1e: Methyl 2-{[1-(tert-butoxycarbonyl)piperidin-4-yl]methyl)}-4-methyl-2H-indazol-5-carboxylate



666 mg of 1c, 156.8 mg of methanol, 645.8 mg of molybdenum hexacarbonyl, 47.3 mg of tri-tert-butylphosphine tetrafluoroborate and 123.5 mg of trans-bis(acetato)-bis[o-(di-o-tolyl-phosphino)benzyl]dipalladium(II) were placed in a microwave tube and suspended in 15 ml THF. Then 0.7 ml of DBU were added and the mixture was stirred for 20 mins at 125°C and 150 watts in the microwave. Next, it was concentrated, taken up in ethyl acetate and the organic phase washed twice with water and once with saturated sodium chloride solution. It was dried over sodium sulphate, filtered and concentrated. The residue was chromatographed on the Biotage SP4. Gradient: hexane/ethyl acetate 0-100%. Yield: 363 mg of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.01 - 1.12 (2H), 1.34 (9H), 1.37 - 1.45 (2H), 2.08 - 2.19 (1H), 2.53 - 2.69 (2H), 2.73 (3H), 3.79 (3H), 3.83 - 3.93 (2H), 4.30 (2H), 7.42 (1H), 7.62 (1H), 8.67 (1H).

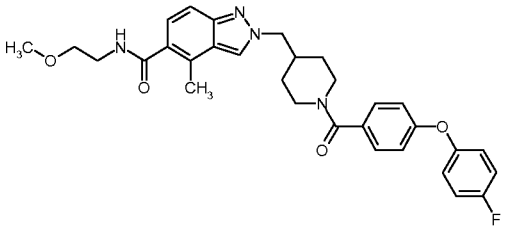
Example 2: 2-({1-[4-tert-(butoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 35.9 mg of the title compound was obtained from 75 mg of the amine prepared in Example 1a and 39.7 mg of 4-(tert-butoxy)benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.09 - 1.26 (2H), 1.29 (9H), 1.35 - 1.58 (2H), 2.15 - 2.35 (1H), 2.49 (3H), 2.69 - 2.97 (2H), 3.24 (3H), 3.32 - 3.47 (4H), 4.23 - 4.40 (2H), 6.98 (2H), 7.14 (1H), 7.23 (2H), 7.38 (1H), 8.10 (1H), 8.47 (1H).

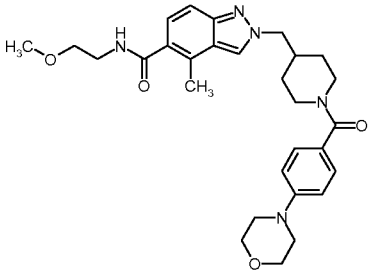
Example 3: 2-({1-[4-(4-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 51.6 mg of the title compound was obtained from 75 mg of the amine prepared in Example 1a and 47.5 mg of 4-(4-fluorophenoxy)benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.10 - 1.30 (2H), 1.32 - 1.58 (2H), 2.19 - 2.35 (1H), 2.49 (3H), 2.71 - 3.02 (2H), 3.25 (3H), 3.32 - 3.39 (2H), 3.40 - 3.47 (2H), 4.32 (2H), 6.95 (2H), 7.06 - 7.14 (3H), 7.15 - 7.27 (3H), 7.31 - 7.42 (3H), 8.07 - 8.15 (1H), 8.47 (1H).

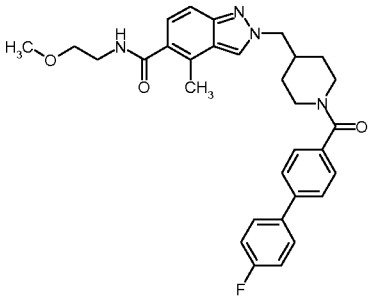
Example 4: N-(2-methoxyethyl)-4-methyl-2-{[1-(4-morpholinobenzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide



Analogously to Example 1, 48.1 mg of the title compound was obtained from 75 mg of the amine prepared in Example 1a and 42.3 mg of 4-morpholinobenzoic acid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.09 - 1.29 (2H), 1.36 - 1.53 (2H), 2.16 - 2.34 (1H), 2.49 (3H), 2.72 - 2.94 (2H), 3.13 (4H), 3.24 (3H), 3.42 (4H), 3.64 - 3.75 (4H), 3.92 - 4.15 (1H), 4.32 (2H), 6.92 (2H), 7.14 (1H), 7.20 (2H), 7.38 (1H), 8.07 - 8.15 (1H), 8.47 (1H).

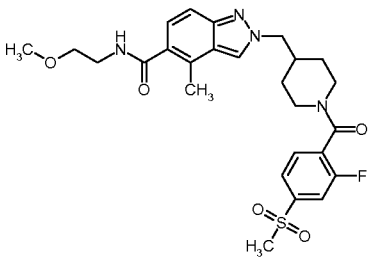
Example 5: 2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 50.1 mg of the title compound was obtained from 75 mg of the amine prepared in Example 1a and 44.2 mg of 4-(4-fluorophenyl)benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.11 - 1.32 (2H), 1.32 - 1.64 (2H), 2.20 - 2.36 (1H), 2.49 (3H), 2.63 - 3.08 (2H), 3.24 (3H), 3.42 (4H), 3.50 - 3.73 (1H), 4.24 - 4.55 (3H), 7.10 - 7.20 (1H), 7.27 2H), 7.41 (3H), 7.67 (4H), 8.03 - 8.16 (1H), 8.48 (1H).

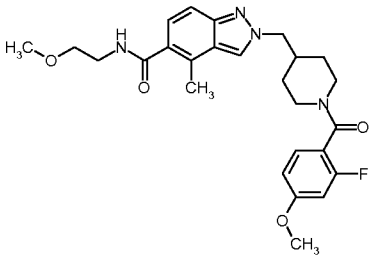
Example 6: 2-{[1-(2-fluoro-4-mesylbenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 40.1 mg of the title compound was obtained from 75 mg of the amine prepared in Example 1a and 44.6 mg of 2-fluoro-4-mesylbenzoic acid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.06 - 1.30 (2H), 1.31 - 1.45 (1H), 1.51 - 1.64 (1H), 2.20 - 2.37 (1H), 2.49 (3H), 2.71 - 2.85 (1H), 2.91 - 3.10 (1H), 3.24 (3H), 3.26 (3H), 3.33 - 3.39 (2H), 3.42 (2H), 4.24 - 4.39 (2H), 4.40 - 4.51 (1H), 7.14 (1H), 7.38 (1H), 7.59 - 7.69 (1H), 7.76 - 7.89 (2H), 8.07 - 8.14 (1H), 8.47 (1H).

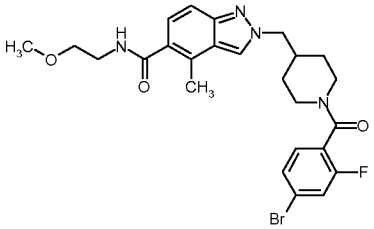
Example 7: 2-{[1-(2-fluoro-4-methoxybenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 43.1 mg of the title compound was obtained from 75 mg of the amine prepared in Example 1a and 34.8 mg of 2-fluoro-4-methoxybenzoic acid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.05 - 1.25 (2H), 1.32 - 1.44 (1H), 1.48 - 1.61 (1H), 2.18 - 2.33 (1H), 2.49 (3H), 2.63 - 2.79 (1H), 2.88 - 3.05 (1H), 3.24 (3H), 3.42 (d, 5H), 3.75 (3H), 4.27 - 4.35 (2H), 4.37 - 4.49 (1H), 6.77 - 6.89 (2H), 7.14 (1H), 7.24 (1H), 7.38 (1H), 8.07 - 8.15 (1H), 8.47 (1H).

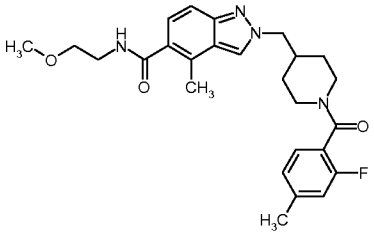
Example 8: 2-{[1-(4-bromo-2-fluorobenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 51.8 mg of the title compound was obtained from 75 mg of the amine prepared in Example 1a and 44.7 mg of 4-bromo-2-fluorobenzoic acid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.04 - 1.27 (2H), 1.32 - 1.43 (1H), 1.49 - 1.61 (1H), 2.20 - 2.33 (1H), 2.48 (3H), 2.67 - 2.80 (1H), 2.91 - 3.05 (1H), 3.24 (3H), 3.33 - 3.46 (5H), 4.24 - 4.36 (2H), 4.38 - 4.49 (1H), 7.15 (1H), 7.27 - 7.34 (1H), 7.35 - 7.41 (1H), 7.44 - 7.50 (1H), 7.60 - 7.66 (1H), 8.07 - 8.15 (1H), 8.47 (1H).

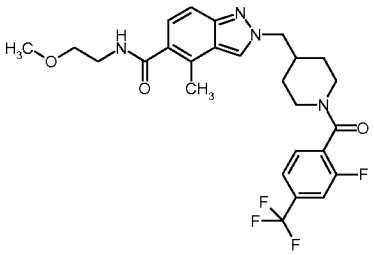
Example 9: 2-{[1-(2-fluoro-4-methylbenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 38.3 mg of the title compound was obtained from 75 mg of the amine prepared in Example 1a and 31.5 mg of 2-fluoro-4-methylbenzoic acid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.04 - 1.26 (2H), 1.31 - 1.43 (1H), 1.48 - 1.60 (1H), 2.18 - 2.35 (4H), 2.48 (3H), 2.64 - 2.79 (1H), 2.89 - 3.04 (1H), 3.24 (3H), 3.33 - 3.39 (3H), 3.39 – 3.45 (2H), 4.23 - 4.36 (2H), 4.39 - 4.49 (1H), 7.01 - 7.10 (2H), 7.13 (1H), 7.16 - 7.24 (1H), 7.38 (1H), 8.07 - 8.14 (1H), 8.47 (1H).

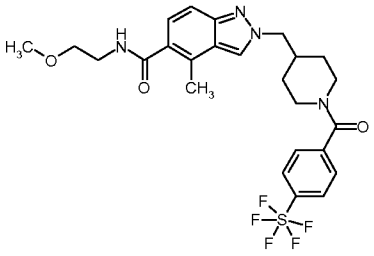
Example 10: 2-({1-[2-fluoro-4-(trifluoromethyl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 57.8 mg of the title compound was obtained from 75 mg of the amine prepared in Example 1a and 42.5 mg of 2-fluoro-4-(trifluoromethyl)benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.07 - 1.29 (2H), 1.32 - 1.44 (1H), 1.52 - 1.62 (1H), 2.20 - 2.36 (1H), 2,49 (3H), 2.67 - 2.84 (1H), 2.93 - 3.07 (1H), 3.24 (3H), 3.32 - 3.39 (3H), 3.39 - 3.46 (2H), 4.24 - 4.39 (2H), 4.40 - 4.51 (1H), 7.14 (1H), 7.38 (1H), 7.56 - 7.68 (2H), 7.76 (1H), 8.07 - 8.14 (1H), 8.47 (1H).

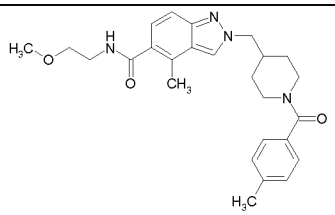
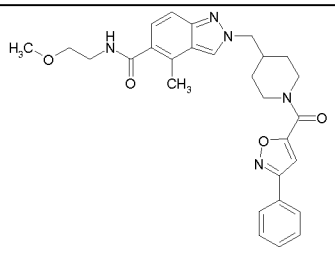
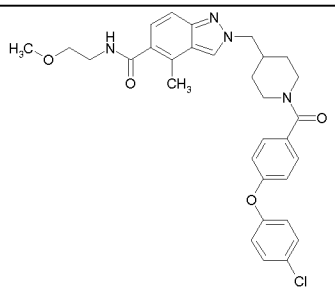
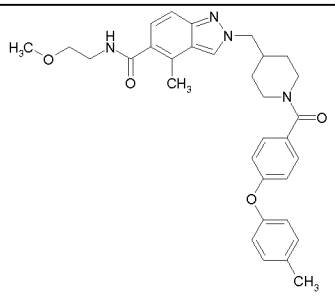
Example 11: N-(2-methoxyethyl)-4-methyl-2-({1-[4-(pentafluoro-λ^6-sulphanyl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide

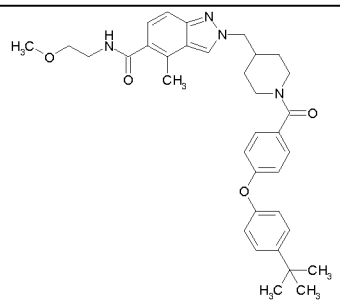
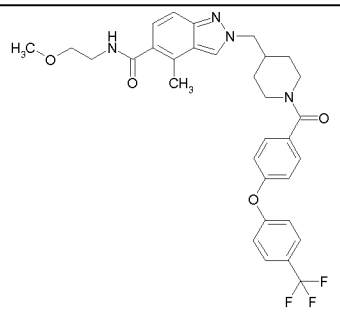
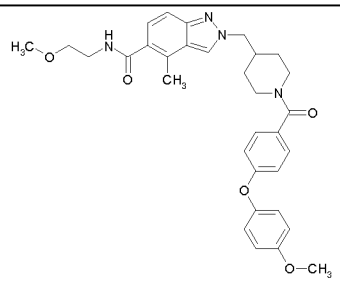
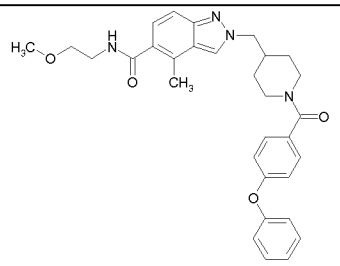
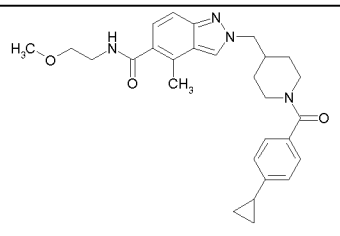


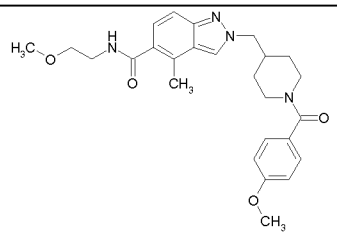
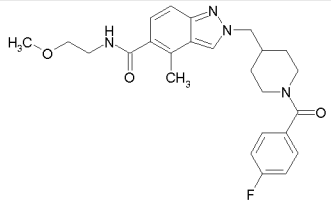
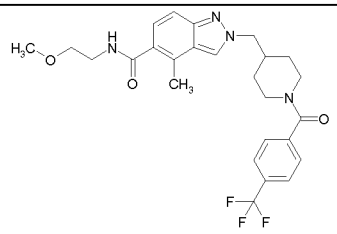
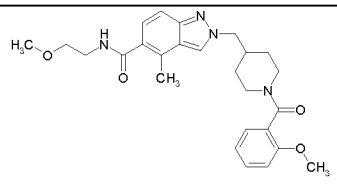
Analogously to Example 1, 135.1 mg of the title compound was obtained from 150 mg of the amine prepared in Example 1a and 101.5 mg of 4-(pentafluoro-λ^6-sulphanyl)benzoic acid.

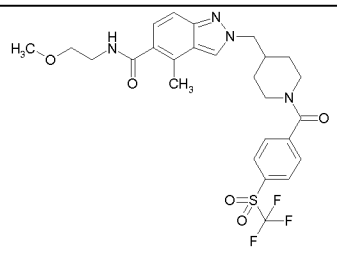
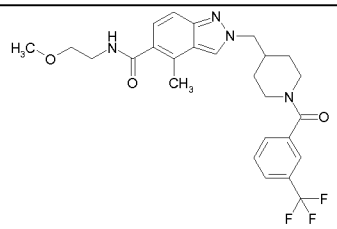
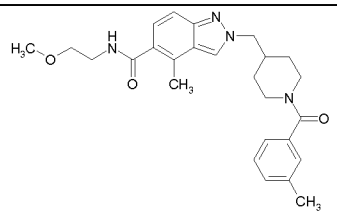
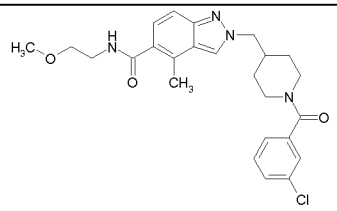
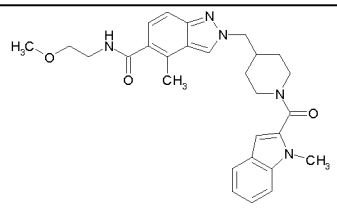
^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.10 - 1.30 (2H), 1.31 - 1.42 (1H), 1.50 - 1.62 (1H), 2.20 - 2.33 (1H), 2.49 (3H), 2.67 - 2.83 (1H), 2.91 - 3.06 (1H), 3.24 (3H), 3.32 - 3.39 (2H), 3.41 (3H), 4.32 (2H), 4.37 - 4.48 (1H), 7.14 (1H), 7.38 (1H), 7.55 (2H), 7.94 (2H), 8.12 (1H), 8.47 (1H).

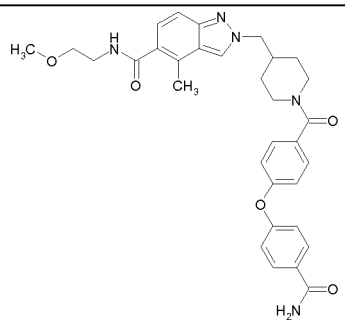
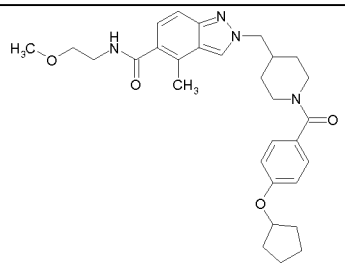
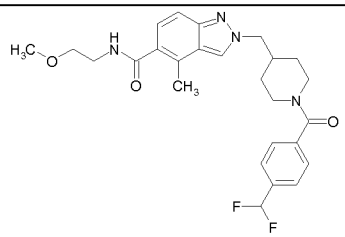
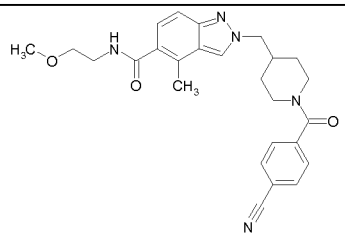
The following compounds were prepared analogously:

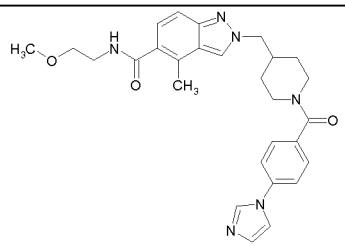
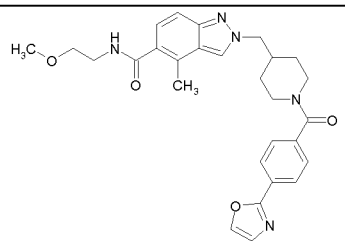
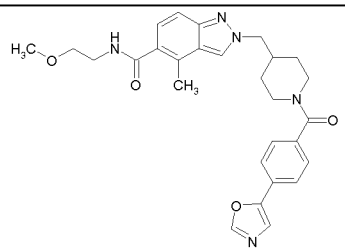
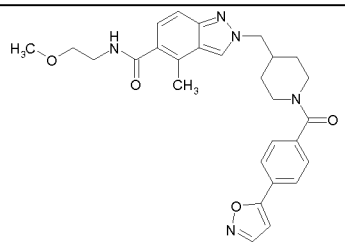
Ex.	Structure	IUPAC name	Analysis
12		N-(2-methoxyethyl)-4-methyl-2-{[1-(4-methylbenzoyl)-piperidin-4-yl]-methyl}-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.20 (2H), 1.42 (2H), 2.29 (4H), 2.49 (3H), 2.73 (1H), 2.93 (1H), 3.25 (3H), 3.37 (2H), 3.43 (2H), 3.57 (1H), 4.31 (2H), 4.40 (1H), 7.14 (1H), 7.21 (4H), 7.38 (1H), 8.09 (1H), 8.46 (1H).
13		N-(2-methoxyethyl)-4-methyl-2-({1-[(3-phenylisoxazol-5-yl)carbonyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.25 (2H), 1.55 (2H), 2.34 (1H), 2.49 (3H), 2.83 (1H), 3.15 (1H), 3.24 (3H), 3.40 (4H), 3.87 (1H), 4.35 (3H), 7.15 (1H), 7.40 (1H), 7.46 (1H), 7.50 (3H), 7.90 (2H), 8.13 (1H), 8.49 (1H).
14		2-({1-[4-(4-chloro-phenoxy)benzoyl]-piperidin-4-yl}-methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.21 (2H), 1.45 (2H), 2.26 (1H), 2.49 (3H), 2.76 (1H), 2.94 (1H), 3.24 (3H), 3.40 (4H), 3.62 (1H), 4.33 (3H), 7.04 (4H), 7.15 (1H), 7.40 (5H), 8.12 (1H), 8.47 (1H).
15		N-(2-methoxyethyl)-4-methyl-2-({1-[4-(4-methylphenoxy)-benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.20 (2H), 1.43 (2H), 2.26 (4H), 2.48 (3H), 2.76 (1H), 2.90 (1H), 3.24 (3H), 3.38 (4H), 3.62 (1H), 4.32 (3H), 6.92 (4H), 7.71 (3H), 7.34 (3H), 8.12 (1H), 8.47 (1H).

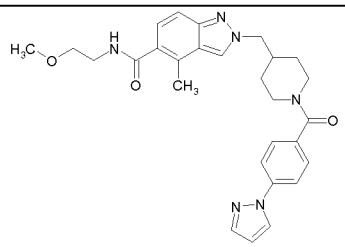
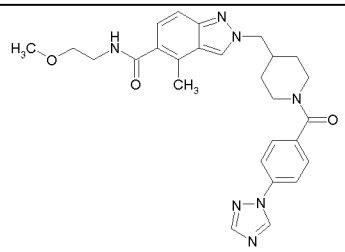
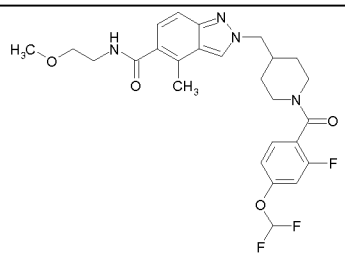
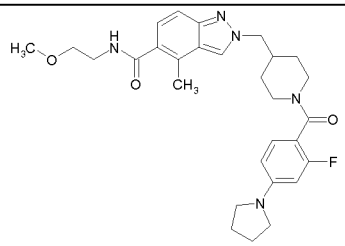
Ex.	Structure	IUPAC name	Analysis
16		2-({1-[4-(4-tert-butylphenoxy)-benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.21 (2H), 1.25 (9H), 1.44 (2H), 2.26 (1H), 2.48 (3H), 2.77 (1H), 2.291 (1H), 3.24 (3H), 3.39 (4H), 3.64 (1H), 4.32 (3H), 6.95 (4H), 7.14 (1H), 7.36 (5H), 8.12 (1H), 8.47 (1H).
17		N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[4-(trifluoromethyl)-phenoxy]benzoyl}-piperidin-4-yl)-methyl]-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.22 (2H), 1.45 (2H), 2.27 (1H), 2.49 (3H), 2.77 (1H), 2.97 (1H), 3.24 (3H), 3.39 (4H), 3.61 (1H), 4.33 (3H), 7.15 (5H), 7.39 (3H), 7.73 (2H), 8.12 (1H), 8.48 (1H).
18		N-(2-methoxyethyl)-2-({1-[4-(4-methoxy-phenoxy)benzoyl]-piperidin-4-yl}-methyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.19 (2H), 1.44 (2H), 2.25 (1H), 2.48 (3H), 2.86 (2H), 3.24 (3H), 3.40 (4H), 3.64 (1H), 3.72 (3H), 4.32 (3H), 6.88 (2H), 6.95 (2H), 7.02 (2H), 7.14 (1H), 7.31 (2H), 7.38 (1H), 8.12 (1H), 8.47 (1H).
19		N-(2-methoxyethyl)-4-methyl-2-{[1-(4-phenoxybenzoyl)-piperidin-4-yl]-methyl}-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.21 (2H), 1.44 (2H), 2.26 (1H), 2.49 (3H), 2.77 (1H), 2.92 (1H), 3.24 (3H), 3.38 (4H), 3.64 (1H), 4.32 (3H), 6.97 (2H), 7.04 (2H), 7.16 (2H), 7.26 (5H), 8.12 (1H), 8.47 (1H).
20		2-{[1-(4-cyclopropyl-benzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 0.65 (2H), 0.93 (2H), 1.19 (2H), 1.43 (2H), 1.90 (1H), 2.25 (1H), 2.48 (3H), 2.73 (1H), 2.92 (1H), 3.24 (3H), 3.39 (4H), 3.59 (1H), 4.32 (3H), 7.14 (5H),

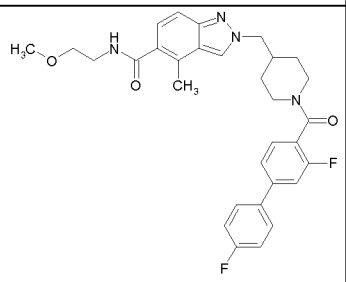
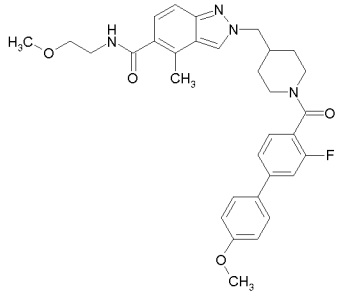
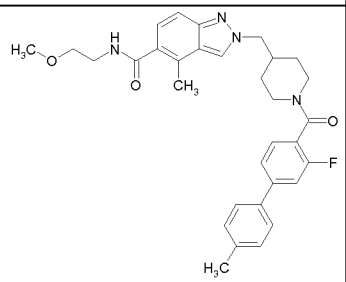
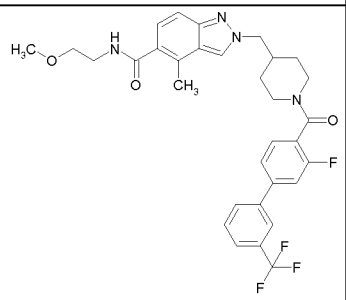
Ex.	Structure	IUPAC name	Analysis
			7.38 (1H), 8.12 (1H), 8.47 (1H).
21		2-{[1-(4-methoxy-benzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.19 (2H), 1.44 (2H), 2.26 (1H), 2.49 (3H), 2.82 (2H), 3.24 (3H), 3.36 (2H), 3.42 (2H), 3.50 (1H), 3.74 (3H), 4.31 (3H), 6.93 (2H), 7.14 (1H), 7.29 (2H), 7.38 (1H), 8.12 (1H), 8.47 (1H).
22		2-{[1-(4-fluoro-benzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.20 (2H), 1.37 (1H), 1.51 (1H), 2.27 (1H), 2.49 (3H), 2.72 (1H), 2.97 (1H), 3.24 (3H), 3.36 (2H), 3.42 (2H), 3.52 (1H), 4.31 (2H), 4.40 (1H), 7.14 (1H), 7.23 (2H), 7.39 (3H), 8.12 (1H), 8.47 (1H).
23		N-(2-methoxyethyl)-4-methyl-2-({1-[4-(trifluoromethyl)-benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.22 (2H), 1.34 (1H), 1.56 (1H), 2.28 (1H), 2.49 (3H), 2.75 (1H), 2.99 (1H), 3.24 (3H), 3.35 (2H), 3.42 (3H), 4.32 (2H), 4.44 (1H), 7.14 (1H), 7.38 (1H), 7.55 (2H), 7.77 (2H), 8.12 (1H), 8.47 (1H).
24		2-{[1-(2-methoxy-benzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.11 (2H), 1.35 (1H), 1.52 (1H), 2.23 (1H), 2.49 (3H), 2.66 (1H), 2.87 (1H), 3.22 (1H), 3.24 (3H), 3.35 (2H), 3. 42 (2H), 3.71 (3H), 4.29 (1H), 4.33 (1H), 4.45 (1H), 6. 94 (1H), 7.07 (3H), 7.33 (1H), 7.39 (1H), 8.12 (1H), 8.48 (1H).

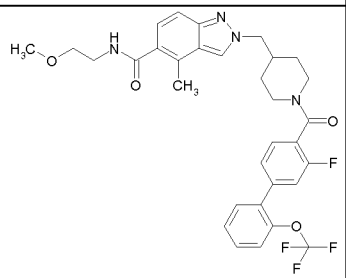
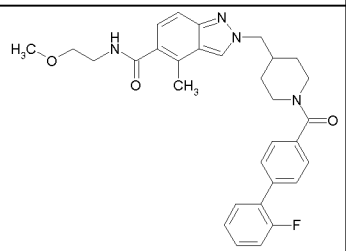
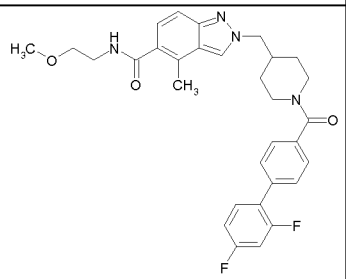
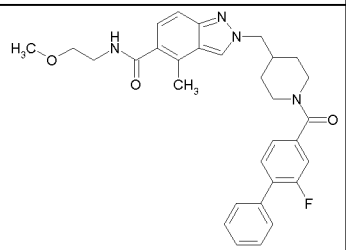
Ex.	Structure	IUPAC name	Analysis
25		N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[(trifluoromethyl)-sulphonyl]benzoyl}-piperidin-4-yl)-methyl]-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.23 (2H), 1.36 (1H), 1.57 (1H), 2.29 (1H), 2.49 (3H), 2.77 (1H), 3.01 (1H), 3.24 (3H), 3.35 (3H), 3.42 (2H), 4.32 (2H), 4.44 (1H), 7.14 (1H), 7.38 (1H), 7.77 (2H), 8.15 (3H), 8.47 (1H).
26		N-(2-methoxyethyl)-4-methyl-2-({1-[3-(trifluoromethyl)-benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.24 (2H), 1.37 (1H), 1.55 (1H), 2.28 (1H), 2.49 (3H), 2.75 (1H), 3.01 (1H), 3.24 (3H), 3.36 (2H), 3.42 (3H), 4. 32 (2H), 4. 43 (1H), 7.14 (1H), 7.38 (1H), 7.65 (3H), 7.78 (1H), 8.12 (1H), 8.47 (1H).
27		N-(2-methoxyethyl)-4-methyl-2-{[1-(3-methylbenzoyl)-piperidin-4-yl]-methyl}-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.20 (2H), 1.36 (1H), 1.52 (1H), 2.29 (4H), 2.49 (3H), 2.69 (1H), 2.95 (1H), 3.24 (3H), 3.36 (2H), 3.42 (2H), 3.53 (1H), 4.31 (2H), 4.41 (1H), 7.12 (3H), 7.21 (1H), 7.27 (1H), 7.38 (1H), 8.12 (1H), 8.47 (1H).
28		2-{[1-(3-chloro-benzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.21 (2H), 1.36 (1H), 1.53 (1H), 2.27 (1H), 2.49 (3H), 2.72 (1H), 2.98 (1H), 3.24 (3H), 3.35 (2H), 3.42 (3H), 4.31 (2H), 4.40 (1H), 7.14 (1H), 7.28 (1H), 7.43 (4H), 8.12 (1H), 8.47 (1H).
29		N-(2-methoxyethyl)-4-methyl-2-({1-[(1-methyl-1H-indol-2-yl)carbonyl]-piperidin-4-	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.25 (2H), 1.50 (2H), 2.31 (1H), 2.49 (3H), 2.82 (1H), 3.05 (1H), 3.24 (3H), 3.36 (2H), 3.42 (2H), 3.69 (3H), 3.98 (1H),

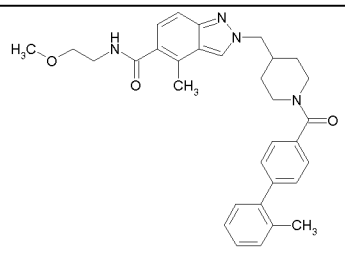
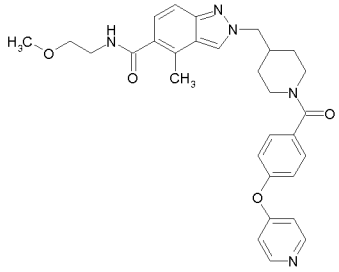
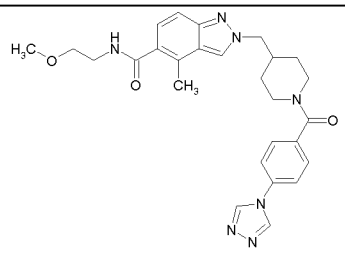
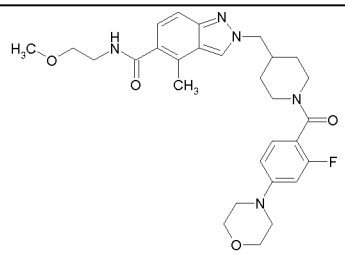
Ex.	Structure	IUPAC name	Analysis
		yl}methyl)-2H-indazol-5-carboxamide	4.34 (2H), 4.44 (1H), 6.57 (1H), 7.05 (1H), 7.15 (1H), 7.20 (1H), 7.39 (1H), 7.46 (1H), 7.56 (1H), 8.12 (1H), 8.49 (1H).
30		2-({1-[4-(4-carbamoylphenoxy)-benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.22 (2H), 1.49 (2H), 2.31 (1H), 2.52 (3H), 2.82 (1H), 2.98 (1H), 3.27 (3H), 3.39 (2H), 3.45 (2H), 3.65 (1H), 4.35 (2H), 4.43 (1H), 7.08 (4H), 7.17 (1H), 7.29 (1H), 7.41 (3H), 7.91 (3H), 8.12 (1H), 8.50 (1H).
31		2-({1-[4-(cyclo-pentyloxy)benzoyl]-piperidin-4-yl}-methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.23 (2H), 1.47 (2H), 1.57 (2H), 1.68 (4H), 1.90 (2H), 2.28 (1H), 2.52 (3H), 2.86 (2H), 3.27 (3H), 3.39 (2H), 3.45 (2H), 3.85 (2H), 4.34 (2H), 4.83 (1H), 6.91 (2H), 7.17 (1H), 7.28 (2H), 7.41 (1H), 8.12 (1H), 8.49 (1H).
32		2-({1-[4-(difluoro-methyl)benzoyl]-piperidin-4-yl}-methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.24 (2H), 1.39 (1H), 1.57 (1H), 2.30 (1H), 2.52 (3H), 2.76 (1H), 3.01 (1H), 3.27 (3H), 3.39 (2H), 3.45 (3H), 4.35 (2H), 4.45 (1H), 7.18 (2H), 7.41 (1H), 7.49 (2H), 7.62 (2H), 8.12 (1H), 8.49 (1H).
33		2-{[1-(4-cyano-benzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.24 (2H), 1.39 (1H), 1.58 (1H), 2.30 (1H), 2.52 (3H), 2.77 (1H), 3.01 (1H), 3.27 (3H), 3.39 (3H), 3.45 (2H), 4.34 (2H), 4.44 (1H), 7.17 (1H), 7.41 (1H), 7.54 (2H), 7.90 (2H), 8.12 (1H),

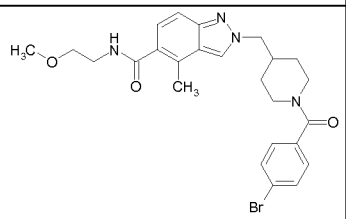
Ex.	Structure	IUPAC name	Analysis
			8.49 (1H).
34		2-({1-[4-(1H-imidazol-1-yl)-benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.24 (2H), 1.39 (1H), 156 (1H), 2.29 (1H), 2.49 (3H), 2.76 (1H), 3.04 (1H), 3.24 (3H), 3.37 (3H), 3.42 (3H), 4.33 (2H), 4.44 (1H), 7.15 (1H), 7.39 (1H), 7.61 (2H), 7.84 (3H), 8.11 (1H), 8.26 (1H), 8.48 (1H).
35		N-(2-methoxyethyl)-4-methyl-2-({1-[4-(oxazol-2-yl)-benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.24 (2H), 1.37 (1H), 1.54 (1H), 2.27 (1H), 2.49 (3H), 2.75 (1H), 3.00 (1H), 3.24 (3H), 3.36 (2H), 3.42 (2H), 3.53 (1H), 4.32 (2H), 4.43 (1H), 7.14 (1H), 7.38 (2H), 7.48 (2H), 8.00 (2H), 8.12 (1H), 8.23 (1H), 8.48 (1H).
36		N-(2-methoxyethyl)-4-methyl-2-({1-[4-(oxazol-5-yl)-benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.22 (2H), 1.38 (1H), 1.53 (1H), 2.28 (1H), 2.49 (3H), 2.74 (1H), 2.98 (1H), 3.24 (3H), 3.36 (2H), 3.41 (2H), 3.55 (1H), 4.32 (2H), 4.41 (1H), 7.15 (1H), 7.42 (3H), 7.74 (3H), 8.12 (1H), 8.47 (2H).
37		N-(2-methoxyethyl)-4-methyl-2-({1-[4-(isoxazol-5-yl)-benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.22 (2H), 1.36 (1H), 1.55 (1H), 2.28 (1H), 2.49 (3H), 2.74 (1H), 2.99 (1H), 3.24 (3H), 3.39 (5H), 4.31 (2H), 4.43 (1H), 4.74 (2H), 7.14 (1H), 7.38 (1H), 7.50 (2H), 7.95 (2H), 8.12 (1H), 8.47 (1H).

Ex.	Structure	IUPAC name	Analysis
38		N-(2-methoxyethyl)-4-methyl-2-({1-[4-(1H-pyrazol-1-yl)-benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.22 (2H), 1.46 (2H), 2.28 (1H), 2.49 (3H), 2.76 (1H), 2.99 (1H), 3.24 (3H), 3.39 (4H), 3.61 (1H), 4.32 (2H), 4.41 (1H), 6.54 (1H), 7.15 (1H), 7.39 (1H), 7.46 (2H), 7.74 (1H), 7.87 (2H), 8.12 (1H), 8.50 (2H).
39		N-(2-methoxyethyl)-4-methyl-2-({1-[4-(1H-1,2,4-triazol-1-yl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.22 (2H), 1.39 (1H), 1.53 (1H), 2.27 (1H), 2.49 (3H), 2.76 (1H), 3.00 (1H), 3.24 (3H), 3.39 (4H), 3.54 (1H), 4.32 (2H), 4.43 (1H), 7.15 (1H), 7.39 (1H), 7.53 (2H), 7.90 (2H), 8.12 (1H), 8.24 (1H), 8.48 (1H), 9.32 (1H).
40		2-({1-[4-(difluoro-methoxy)-2-fluoro-benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.16 (2H), 1.38 (1H), 1.55 (1H), 2.26 (1H), 2.48 (3H), 2.73 (1H), 2.98 (1H), 3.24 (3H), 3.38 (5H), 4.31 (2H), 4.44 (1H), 7.12 (3H), 7.31 (1H), 7.40 (2H), 8.12 (1H), 8.47 (1H).
41		2-({1-[2-fluoro-4-(pyrrolidin-1-yl)-benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.14 (2H), 1.43 (2H), 1.90 (4H), 2.23 (1H), 2.48 (3H), 2.68 (1H), 2.94 (1H), 3.19 (4H), 3.24 (3H), 3.36 (2H), 3.42 (3H), 4.31 (2H), 4.39 (1H), 6.29 (2H), 7.10 (2H), 7.38 (1H), 8.12 (1H), 8.47 (1H).

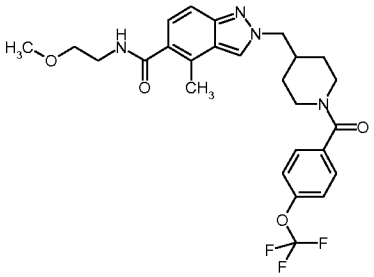
Ex.	Structure	IUPAC name	Analysis
42		2-({1-[(3,4'-difluoro-biphenyl-4-yl)-carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.19 (2H), 1.39 (1H), 1.57 (1H), 2.28 (1H), 2.49 (3H), 2.76 (1H), 3.01 (1H), 3.24 (3H), 3.38 (5H), 4.32 (2H), 4.47 (1H), 7.15 (1H), 7.28 (2H), 7.40 (2H), 7.56 (2H), 7.76 (2H), 8.12 (1H), 8.48 (1H).
43		2-({1-[(3-fluoro-4'-methoxybiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.19 (2H), 1.39 (1H), 1.57 (1H), 2.28 (1H), 2.49 (3H), 2.76 (1H), 3.01 (1H), 3.24 (3H), 3.38 (5H), 4.32 (2H), 4.47 (1H), 7.15 (1H), 7.28 (2H), 7.40 (2H), 7.56 (2H), 7.76 (2H), 8.12 (1H), 8.48 (1H).
44		2-({1-[(3-fluoro-4'-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.19 (2H), 1.39 (1H), 1.57 (1H), 2.31 (4H), 2.49 (3H), 2.75 (1H), 3.01 (1H), 3.24 (3H), 3.36 (2H), 3.42 (3H), 4.32 (2H), 4.48 (1H), 7.14 (1H), 7.26 (2H), 7.39 (2H), 7.56 (4H), 8.12 (1H), 8.48 (1H).
45		2-[(1-{[3-fluoro-3'-(trifluoromethyl)-biphenyl-4-yl]-carbonyl}-piperidin-4-yl)-methyl]-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.20 (2H), 1.40 (1H), 1.57 (1H), 2.29 (1H), 2.49 (3H), 2.76 (1H), 3.03 (1H), 3.24 (3H), 3.36 (2H), 3.41 (3H), 4.33 (2H), 4.48 (1H), 7.15 (1H), 7.39 (1H), 7.45 (1H), 7.69 (4H), 8.03 (2H), 8.12 (1H), 8.49 (1H).

Ex.	Structure	IUPAC name	Analysis
46		2-[(1-{[3-fluoro-2'-(trifluoromethoxy)-biphenyl-4-yl]-carbonyl}piperidin-4-yl)methyl]-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 1.20 (2H), 1.42 (1H), 1.57 (1H), 2.29 (1H), 2.49 (3H), 2.76 (1H), 3.04 (1H), 3.24 (3H), 3.36 (5H), 4.32 (2H), 4.48 (1H), 7.15 (1H), 7.44 (8H), 8.12 (1H), 8.49 (1H).
47		2-({1-[(2'-fluoro-biphenyl-4-yl)-carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 1.23 (2H), 1.41 (1H), 1.53 (1H), 2.29 (1H), 2.49 (3H), 2.74 (1H), 3.01 (1H), 3.24 (3H), 3.36 (4H), 3.60 (1H), 4.33 (2H), 4.44 (1H), 7.15 (1H), 7.29 (2H), 7.40 (4H), 7.55 (3H), 8.12 (1H), 8.48 (1H).
48		2-({1-[(2',4'-difluoro-biphenyl-4-yl)-carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 1.23 (2H), 1.39 (1H), 1.53 (1H), 2.28 (1H), 2.49 (3H), 2.75 (1H), 3.01 (1H), 3.24 (3H), 3.39 (4H), 3.60 (1H), 4.33 (2H), 4.43 (1H), 7.16 (2H), 7.40 (4H), 7.56 (3H), 8.12 (1H), 8.48 (1H).
49		2-({1-[(2-fluoro-biphenyl-4-yl)-carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.24 (2H), 1.39 (1H), 1.56 (1H), 2.29 (1H), 2.49 (3H), 2.74 (1H), 3.02 (1H), 3.25 (3H), 3.37 (2H), 3.42 (2H), 3.59 (1H), 4.33 (2H), 4.43 (1H), 7.15 (1H), 7.28 (2H), 7.40 (2H), 7.46 (2H), 7.54 (3H), 8.12 (1H), 8.48 (1H).

Ex.	Structure	IUPAC name	Analysis
50		N-(2-methoxyethyl)-4-methyl-2-({1-[(2'-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.24 (2H), 1.42 (1H), 1.55 (1H), 2.20 (3H), 2.29 (1H), .249 (3H), 2.75 (1H), 3.02 (1H), 3.25 (3H), 3.37 (2H), 3.42 (2H), 3.64 (1H), 4.33 (2H), 4.42 (1H), 7.21 (5H), 7.38 (5H), 8.12 (1H), 8.49 (1H).
51		N-(2-methoxyethyl)-4-methyl-2-({1-[4-(pyridyloxy)benzoyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.24 (2H), 1.42 (1H), 1.55 (1H), 2.29 (1H), 2.49 (3H), 2.76 (1H), 3.02 (1H), 3.25 (3H), 3.37 (2H), 3.43 (2H), 3.60 (1H), 4.33 (2H), 4.44 (1H), 7.15 (1H), 7.37 (3H), 7.48 (2H), 7.53 (2H), 8.12 (1H), 8.48 (1H), 8.75 (2H).
52		N-(2-methoxyethyl)-4-methyl-2-({1-[4-(4H-1,2,4-triazol-4-yl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.23 (2H), 1.38 (1H), 1.54 (1H), 2.28 (1H), 2.49 (3H), 2.74 (1H), 3.02 (1H), 3.24 (3H), 3.36 (2H), 3.42 (2H), 3.53 (1H), 4.32 (2H), 4.42 (1H), 7.14 (1H), 7.38 (1H), 7.55 (2H), 7.75 (2H), 8.14 (1H), 8.48 (1H), 9.15 (2H).
53		2-{[1-(2-fluoro-4-morpholinobenzoyl)-piperidin-4-yl]-methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (600 MHz, DMSO-d_6): δ [ppm]= 1.01 (1H), 1.21 (1H), 1.36 (1H), 1.48 (1H), 1.57 (1H), 2.08 (1H), 2.53 (3H), 2.96 (7H), 3.29 (3H), 3.41 (2H), 3.47 (2H), 3.67 (4H), 4.34 (2H), 4.50 (1H), 6.86 (2H), 7.14 (2H), 7.41 (1H), 8.11 (1H), 8.47 (1H), 8.56 (1H).

Ex.	Structure	IUPAC name	Analysis
54		2-{[1-(4-bromo-benzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]=1.22 (2H), 1.36 (1H), 1.52 (1H), 2.26 (1H), 2.49 (3H), 2.72 (1H), 2.97 (1H), 3.24 (3H), 3.36 (2H), 3.42 (2H), 3.49 (1H), 4.31 (2H), 4.40 (1H), 7.14 (1H), 7.29 (2H), 7.38 (1H), 7.60 (2H), 8.12 (1H), 8.47 (1H).

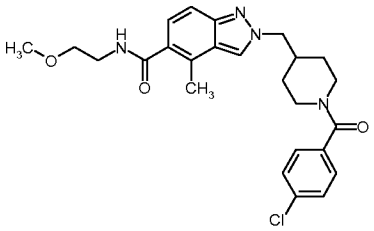
Example 55: N-(2-methoxyethyl)-4-methyl-2-({1-[4-(trifluoromethoxy)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



150 mg of the amine prepared in Example 1a were first dissolved in 1.5 ml pyridine. 101 mg of 4-(trifluoromethoxy)benzoyl chloride were then added and the mixture stirred for 30 min at RT. The reaction mixture was then treated with some toluene and concentrated. The residue was taken up in ethyl acetate and washed twice with water, twice with saturated sodium hydrogen carbonate solution (pH 9) and once with saturated sodium chloride solution. The organic phase was dried over sodium sulphate, filtered and concentrated. The residue was purified chromatographically on the Biotage SP4. Gradient: ethyl acetate/methanol 0-10%. Yield: 118.2 mg of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.17 - 1.30 (2H), 1.30 - 1.45 (1H), 1.45 - 1.62 (1H), 2.19 - 2.35 (1H), 2.49 (3H), 2.64 - 2.86 (1H), 2.86 - 3.07 (1H), 3.24 (3H), 3.31 - 3.56 (5H), 4.31 (2H), 4.36 - 4.49 (1H), 7.14 (1H), 7.35 - 7.42 (3H), 7.43 - 7.50 (2H), 8.11 (1H), 8.47 (1H).

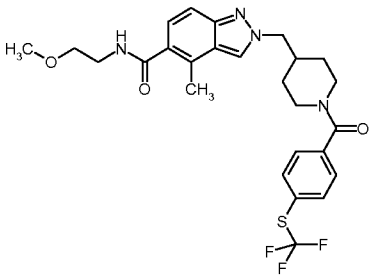
Example 56: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 55, 183 mg of the title compound was obtained from 300 mg of the amine prepared in Example 1a and 157.4 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.10 - 1.29 (2H), 1.29 - 1.43 (1H), 1.44 - 1.61 (1H), 2.20 - 2.34 (1H), 2.49 (3H), 2.66 - 2.83 (1H), 2.84 - 3.06 (1H), 3.25 (3H), 3.32 - 3.39 (2H), 3.40 – 3.45 (2H), 3.45 - 3.55 (1H), 4.26 - 4.35 (2H), 4.35 - 4.46 (1H), 7.14 (1H), 7.32 - 7.41 (3H), 7.47 (2H), 8.09 - 8.15 (1H), 8.47 (1H).

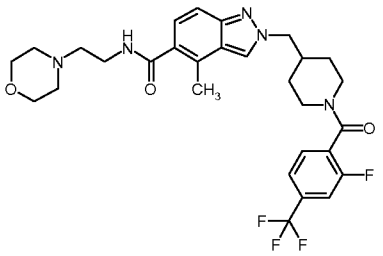
Example 57: N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[(trifluoromethyl)sulphanyl]benzoyl} piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



60 mg of the amine prepared in Example 1a were first dissolved in 2 ml DCM at 0°C. 0.034 ml of triethylamine and 43.2 mg of 4-[(trifluoromethyl)sulphanyl]benzoyl chloride were then added and the mixture stirred for 2 hrs at 0°C. The reaction mixture was then diluted with DCM and washed with 1-molar hydrochloric acid, saturated sodium hydrogen carbonate solution (pH 9) and saturated sodium chloride solution. The organic phase was dried over sodium sulphate, filtered and concentrated. The residue was purified chromatographically on the Biotage SP4. Gradient: DCM/Methanol 0-10%. The product fraction was taken up in ethyl acetate and extracted twice with saturated sodium hydrogen carbonate solution. The organic phase was concentrated and the residue again purified by HPLC. Yield: 26.5 mg of the title compound.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.14 - 1.30 (2H), 1.31 - 1.42 (1H), 1.49 - 1.61 (1H), 2.21 - 2.32 (1H), 2.49 (3H), 2.67 - 2.80 (1H), 2.93 - 3.05 (1H), 3.25 (3H), 3.36 (2H), 3.42 (3H), 4.27 - 4.36 (2H), 4.38 - 4.48 (1H), 7.14 (1H), 7.38 (1H), 7.48 (2H), 7.75 (2H), 8.09 - 8.14 (1H), 8.47 (1H).

Example 58: 2-({1-[2-fluoro-4-(trifluoromethyl)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2-morpholinoethyl)-2H-indazol-5-carboxamide

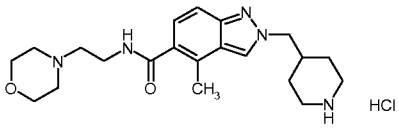


Analogously to Example 1, 34.6 mg of the title compound was obtained from 75 mg of the amine prepared in Example 58a and 37.0 mg of 2-fluoro-4-(trifluoromethyl)benzoic acid.

^{1}H-NMR (400 MHz, methanol-d_4): δ [ppm]= 1.24 - 1.43 (2H), 1.50 - 1.59 (1H), 1.65 - 1.73 (1H), 2.33 - 2.45 (1H), 2.65 (3H), 2.80 - 2.91 (1H), 3.05 - 3.18 (1H), 3.19 - 3.26 (2H), 3.39 - 3.44 (2H), 3.45 - 3.52 (1H), 3.63 - 3.70 (2H), 3.71 - 3.82 (4H), 4.06 - 4.14 (2H), 4.39 (2H), 4.62 - 4.70 (1H), 7.39 (1H), 7.47 (1H), 7.54 - 7.62 (3H), 8.45 (1H).

The starting material was prepared as follows:

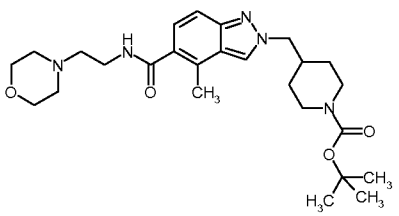
Example 58a: 4-methyl-N-(2-morpholinoethyl)-2-(4-piperidylmethyl)-2H-indazol-5-carboxamide hydrochloride



To 624.4 mg of 58b were added 2.9 ml of 4M hydrochloric acid in dioxan and 0.5 ml dioxan. An oily mass was formed, which dissolved on vigorous stirring and gentle warming. The mixture was stirred for 1 hr at ca. 30°C. The reaction mixture was concentrated. Yield: 980 mg of the title compound, which was further reacted without further purification.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.33 - 1.51 (2H), 1.58 - 1.64 (1H), 2.17 - 2.31 (1H), 2.55 (3H), 2.70 - 2.86 (2H), 3.02 - 3.31 (7H), 3.43 - 3.51 (2H), 3.61 - 3.71 (2H), 3.72 - 3.88 (3H), 3.89 - 3.99 (2H), 4.30 - 4.36 (2H), 7.29 (1H), 7.40 (1H), 8.46 - 8.52 (1H), 8.54 - 8.58 (1H), 8.69 - 8.85 (1H), 8.96 - 9.10 (1H).

Example 58b: Tert-butyl 4-({4-methyl-5-[N-(2-morpholinoethyl)carbamoyl]-1H-indazol-2-yl}-methyl)piperidin-1-carboxylate

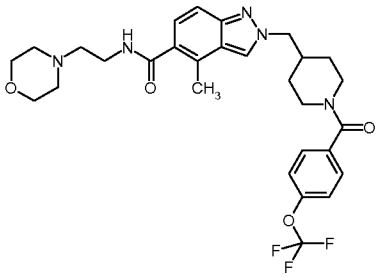


896 mg of 1c, 857 mg of 2-morpholinoethylamine, 579.3 mg of molybdenum hexacarbonyl, 63.6 mg of tri-tert-butylphosphine tetrafluoroborate and 205.8 mg of trans-bis(acetato)-bis[o-(di-

o-tolylphosphino)benzyl]dipalladium(II) were placed in a microwave tube and suspended in 18 ml THF. 1.0 ml of DBU was then added and the mixture was stirred for 20 mins at 125°C and 200 watts in the microwave. The reaction mixture was diluted with some ethyl acetate and firstly filtered through Celite. The filtrate was diluted with ethyl acetate and the organic phase washed twice with water and once with saturated sodium chloride solution. It was then dried over sodium sulphate, filtered and concentrated. The residue was chromatographed on the Biotage SP4. Gradient: ethyl acetate/methanol 0-10%. Yield: 624.4 mg of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 0.98 - 1.13 (2H), 1.34 (11H), 2.05 - 2.27 (2H), 2.33 - 2.41 (5H), 2.51 (3H), 2.56 - 2.73 (2H), 3.25 - 3.37 (2H), 3.51 - 3.57 (4H), 3.81 - 3.93 (2H), 4.28 (2H), 7.14 (1H), 7.36 - 7.41 (1H), 7.95 - 8.02 (1H), 8.46 (1H).

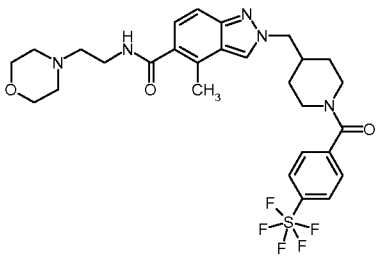
Example 59: 4-methyl-N-(2-morpholinoethyl)-2-({1-[4-(trifluoromethoxy)benzoyl] piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 55, 10.1 mg of the title compound was obtained from 75 mg of the amine prepared in Example 58a and 43.9 mg of 4-(trifluoromethoxy)benzoyl chloride.

^{1}H-NMR (400 MHz, methanol-d_4): δ [ppm]= 1.24 - 1.44 (2H), 1.44 - 1.58 (1H), 1.59 - 1.74 (1H), 2.32 - 2.44 (1H), 2.51 - 2.58 (4H), 2.59 - 2.65 (5H), 2.77 - 2.90 (1H), 3.02 - 3.17 (1H), 3.53 (2H), 3.62 - 3.72 (5H), 4.35 - 4.41 (2H), 4.55 - 4.67 (1H), 7.29 (1H), 7.34 (2H), 7.43 (1H), 7.49 (2H), 8.39 (1H).

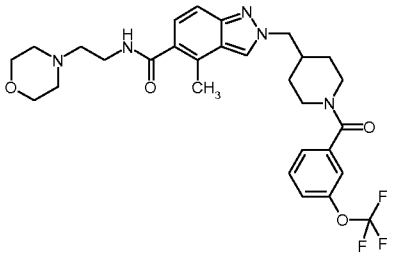
Example 60: 4-methyl-N-(2-morpholinoethyl)-2-({1-[4-(pentafluoro-λ^6-sulphanyl)benzoyl]-piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 14.0 mg of the title compound was obtained from 75 mg of the amine prepared in Example 58a and 44.1 mg of 4-(pentafluoro-λ^6-sulphanyl)benzoic acid.

^{1}H-NMR (400 MHz, chloroform-d): δ [ppm]= 1.16 - 1.32 (1H), 1.33 - 1.48 (1H), 1.50 - 1.63 (1H), 1.71 - 1.83 (1H), 1.84 - 2.08 (2H), 2.44 (1H), 2.55 (4H), 2.60 - 2.71 (5H), 2.72 - 2.85 (1H), 2.96 - 3.10 (1H), 3.60 (2H), 3.67 - 3.78 (4H), 4.33 (2H), 4.71 - 4.81 (1H), 6.45 (1H), 7.34 (1H), 7.47 (2H), 7.54 (1H), 7.79 (2H), 7.96 (1H).

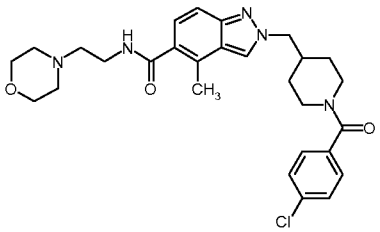
Example 61: 4-methyl-N-(2-morpholinoethyl)-2-({1-[3-(trifluoromethoxy)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 55, 18.1 mg of the title compound was obtained from 75 mg of the amine prepared in Example 58a and 43.9 mg of 3-(trifluoromethoxy)benzoyl chloride.

^{1}H-NMR (400 MHz, chloroform-d): δ [ppm]= 1.18 - 1.46 (2H), 1.49 - 1.63 (1H), 1.66 - 1.82 (1H), 2.37 - 2.49 (1H), 2.62 (3H), 2.67 (3H), 2.70 - 2.78 (4H), 2.79 - 2.86 (2H), 2.93 - 3.09 (1H), 3.66 - 3.74 (2H), 3.83 (4H), 4.32 (2H), 4.66 - 4.82 (1H), 6.83 - 6.96 (1H), 7.23 - 7.29 (2H), 7.29 - 7.34 (1H), 7.39 (1H), 7.43 (1H), 7.54 (1H), 7.96 (1H).

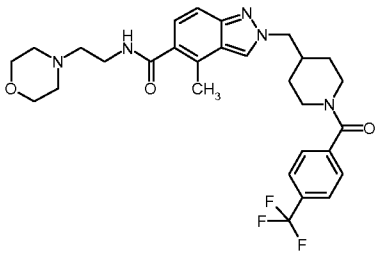
Example 62: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methyl-N-(2-morpholinoethyl)-2H-indazol-5-carboxamide



Analogously to Example 55, 14.9 mg of the title compound was obtained from 75 mg of the amine prepared in Example 58a and 34.2 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (400 MHz, methanol-d$_4$): δ [ppm]= 1.24 - 1.42 (2H), 1.46 - 1.58 (1H), 1.58 - 1.71 (1H), 2.31 - 2.43 (1H), 2.63 (5H), 2.65 (3H), 2.73 - 2.91 (1H), 3.00 - 3.15 (1H), 3.25 – 3.33 (2H), 3.63 - 3.77 (3H), 3.79 - 4.03 (3H), 4.38 (2H), 4.54 - 4.67 (1H), 7.38 (3H), 7.42 - 7.49 (3H), 8.44 (1H).

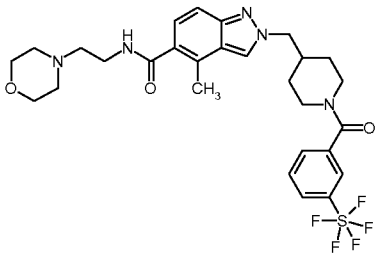
Example 63: 4-methyl-N-(2-morpholinoethyl)-2-({1-[4-(trifluoromethyl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 31.7 mg of the title compound was obtained from 75 mg of the amine prepared in Example 58a and 33.8 mg of 4-(trifluoromethyl)benzoic acid.

^{1}H-NMR (400 MHz, methanol-d$_4$): δ [ppm]= 1.24 - 1.43 (2H), 1.45 - 1.57 (1H), 1.63 - 1.73 (1H), 2.33 - 2.45 (1H), 2.66 (3H), 2.79 - 2.90 (1H), 3.04 - 3.17 (1H), 3.18 - 3.27 (2H), 3.39 - 3.45 (2H), 3.56 - 3.70 (3H), 3.76 (4H), 4.06 - 4.14 (2H), 4.36 - 4.42 (2H), 4.59 - 4.68 (1H), 7.39 (1H), 7.47 (1H), 7.57 (2H), 7.73 (2H), 8.45 (1H).

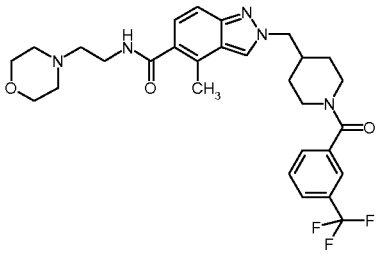
Example 64: 4-methyl-N-(2-morpholinoethyl)-2-({1-[4-(pentafluoro-λ^6-sulphanyl)benzoyl]-piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 24.7 mg of the title compound was obtained from 75 mg of the amine prepared in Example 58a and 44.1 mg of 3-(pentafluoro-λ^6-sulphanyl)benzoic acid.

^{1}H-NMR (400 MHz, methanol-d$_4$): δ [ppm]= 1.27 - 1.47 (2H), 1.48 - 1.60 (1H), 1.60 - 1.74 (1H), 2.31 - 2.46 (1H), 2.66 (3H), 2.78 - 2.93 (1H), 3.04 - 3.18 (1H), 3.18 - 3.26 (2H), 3.39 – 3.43 (2H), 3.57 - 3.70 (3H), 3.72 – 3.82 (4H), 4.06 - 4.14 (2H), 4.39 (2H), 4.55 - 4.67 (1H), 7.38 (1H), 7.47 (1H), 7.60 - 7.67 (2H), 7.82 - 7.86 (1H), 7.89 - 7.94 (1H), 8.45 (1H).

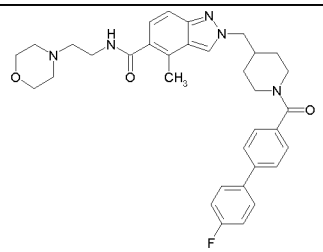
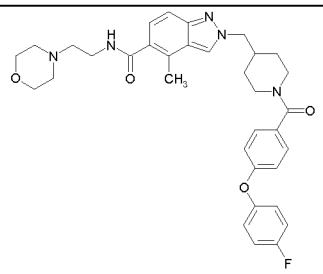
Example 65: 4-methyl-N-(2-morpholinoethyl)-2-({1-[3-(trifluoromethyl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



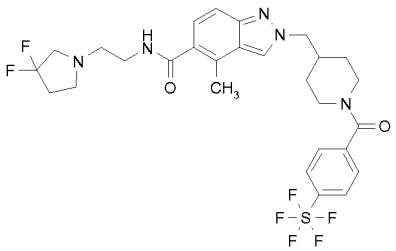
Analogously to Example 1, 14.0 mg of the title compound was obtained from 75 mg of the amine prepared in Example 58a and 33.8 mg of 3-(trifluoromethyl)benzoic acid.

^{1}H-NMR (400 MHz, methanol-d_4): δ [ppm]= 1.28 - 1.45 (2H), 1.47 - 1.59 (1H), 1.59 - 1.73 (1H), 2.32 - 2.45 (1H), 2.66 (3H), 2.79 - 2.93 (1H), 3.05 - 3.18 (1H), 3.19 - 3.27 (2H), 3.39 - 3.45 (2H), 3.58 - 3.70 (3H), 3.72 - 3.82 (4H), 4.06 - 4.14 (2H), 4.39 (2H), 4.57 - 4.68 (1H), 7.39 (1H), 7.47 (1H), 7.64 (2H), 7.67 - 7.70 (1H), 7.73 - 7.78 (1H), 8.45 (1H).

The following compounds were prepared analogously:

Ex.	Structure	IUPAC name	Analysis
66		2-({1-[(4'-fluoro-biphenyl-4-yl)-carbonyl]piperidin-4-yl}methyl)-4-methyl-N-(2-morpholino-ethyl)-2H-indazol-5-carboxamide	1H-NMR (400 MHz, methanol-d_4): δ [ppm]= 1.35 (2H), 1.53 (1H), 1.66 (1H), 2.40 (1H), 2.66 (3H), 2.85 (1H), 3.11 (1H), 3.24 (2H), 3.42 (2H), 3.65 (2H), 3.76 (5H), 4.08 (2H), 4.40 (2H), 4.63 (1H), 7.17 (2H), 7.38 (1H), 7.47 (3H), 7.65 (4H), 8.45 (1H).
67		2-({1-[4-(4-fluoro-phenoxy)benzoyl]-piperidin-4-yl}-methyl)-4-methyl-N-(2-morpholinoethyl)-2H-indazol-5-carboxamide	1H-NMR (400 MHz, methanol-d_4): δ [ppm]= 1.33 (2H), 1.68 (2H), 2.38 (1H), 2.66 (3H), 2.84 (1H), 3.11 (1H), 3.25 (2H), 3.42 (2H), 3.65 (2H), 3.76 (5H), 4.11 (2H), 4.38 (2H), 4.59 (1H), 6.98 (2H), 7.04 (2H), 7.11 (2H), 7.38 (3H), 7.47 (1H), 8.44 (1H).

Example 68: N-[2-(3,3-difluoropyrrolidin-1-yl)ethyl]-4-methyl-2-({1-[4-(pentafluoro-λ^6-sulphanyl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide

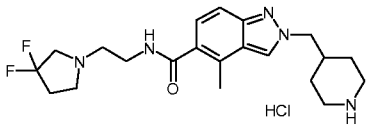


Analogously to Example 57, 61.7 mg of the title compound was obtained from 266.5 mg of the amine prepared in Example 68a and 150.3 mg of 4-(pentafluoro-λ^6-sulphanyl)benzoyl chloride.

^{1}H-NMR (300 MHz, chloroform-d): δ [ppm]= 1.13 - 1.46 (2H), 1.48 - 1.65 (1H), 1.66 - 1.87 (1H), 2.26 - 2.50 (3H), 2.66 (3H), 2.71 - 3.23 (8H), 3.57 – 3.72 (3H), 4.25 - 4.42 (2H), 4.67 - 4.84 (1H), 6.40 - 6.61 (1H), 7.38 (1H), 7.47 (2H), 7.53 (1H), 7.79 (2H), 7.96 (1H).

The starting material was prepared as follows:

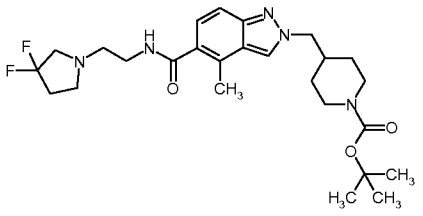
Example 68a: *N*-[2-(3,3-difluoropyrrolidin-1-yl)ethyl]-4-methyl-2-(4-piperidylmethyl)-2H-indazol-5-carboxamide hydrochloride



To 416.6 mg of 68b were added 1.85 ml of 4M hydrochloric acid in dioxan and 0.5 ml dioxan. An oily mass was formed, which dissolved on vigorous stirring and gentle warming. The mixture was stirred for 1 hr at ca. 30°C. The reaction mixture was concentrated. Yield: 439.2 mg of the title compound, which was further reacted without further purification.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.36 - 1.48 (2H), 1.54 - 1.63 (2H), 2.18 - 2.28 (1H), 2.40 – 2.45 (2H), 2.55 (3H), 2.72 - 2.83 (2H), 3.14 - 3.22 (2H), 3.38 - 3.44 (2H), 3.56 - 3.63 (2H), 3.65 - 3.95 (2H), 4.11 - 4.21 (2H), 7.32 (1H), 7.40 (1H), 8.43 - 8.48 (1H), 8.57 (1H), 8.68 - 8.82 (1H), 8.96 - 9.07 (1H).

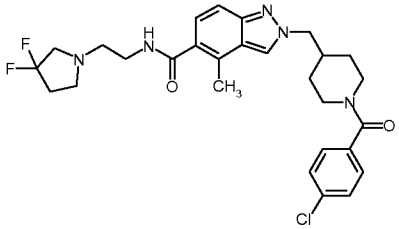
Example 68b: Tert-butyl 4-[(5-{N-[2-(3,3-difluoropyrrolidin-1-yl)ethyl]carbamoyl}-4-methyl-2H-indazol-2-yl)methyl]-piperidin-1-carboxylate



220 mg of 1c, 242.7 mg of 2-(3,3-difluoro-pyrrolidin-1-yl)ethylamine, 142.2 mg of molybdenum hexacarbonyl, 15.6 mg of tri-tert-butylphosphine tetrafluoroborate and 50.5 mg of trans-bis(acetato)-bis-[o-(di-o-tolylphosphino)benzyl]dipalladium(II) were placed in a microwave tube and suspended in 4.4 ml THF. 0.24 ml of DBU were then added and the mixture stirred for 20 mins at 125°C and 200 watts in the microwave. The reaction mixture was diluted with some ethyl acetate and firstly filtered through Celite. The filtrate was diluted with ethyl acetate and the organic phase washed twice with water and once with saturated sodium chloride solution. It was dried over sodium sulphate, filtered and concentrated. The residue (209.3 mg) was chromatographed on the Biotage SP4. Gradient: DCM/methanol 0-10%. Yield: 53.4 mg of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.00 - 1.12 (2H), 1.32 - 1.42 (2H), 1.34 (9H), 2.07 - 2.25 (3H), 2.50 (3H), 2.57 (2H), 2.60 - 2.68 (2H), 2.72 (2H), 2.91 (2H), 3.30 - 3.35 (2H), 3.83 - 3.92 (2H), 4.28 (2H), 7.15 (1H), 7.39 (1H), 8.04 - 8.09 (1H), 8.47 (1H).

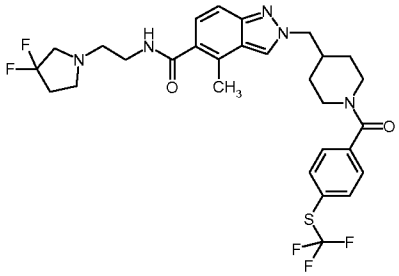
Example 69: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-[2-(3,3-difluoropyrrolidin-1-yl)ethyl]-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 57, 79.9 mg of the title compound was obtained from 125.0 mg of the amine prepared in Example 68a and 54.5 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, chloroform-d): δ [ppm]= 1.13 - 1.35 (2H), 1.46 - 1.84 (2H), 2.27 - 2.50 (3H), 2.66 (3H), 2.80 - 3.26 (8H), 3.59 - 3.83 (3H), 4.25 - 4.39 (2H), 4.62 - 4.85 (1H), 6.41 - 6.69 (1H), 7.30 - 7.40 (6H), 7.55 (1H), 7.96 (1H).

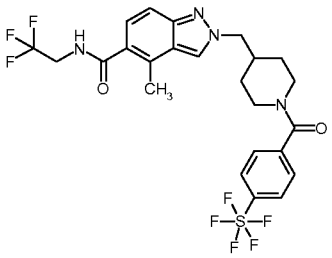
Example 70: N-[2-(3,3-difluoropyrrolidin-1-yl)ethyl]-4-methyl-2-[(1-{4-[(trifluoromethyl) sulphanyl]benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 55, 15.2 mg of the title compound was obtained from 23.4 mg of the amine prepared in Example 68a and 14.0 mg of 4-[(trifluoromethyl)sulphanyl]benzoyl chloride.

^{1}H-NMR (400 MHz, chloroform-d): δ [ppm]= 1.23 – 1.26 (1H), 1.33 - 1.46 (1H), 1.48 - 1.61 (1H), 1.77 (1H), 2.20 – 2.35 (2H), 2.36 - 2.49 (1H), 2.64 (3H), 2.73 – 2.85 (5H), 2.90 – 3.10 (3H), 3.56 (2H), 3.63 - 3.76 (1H), 4.26 - 4.39 (2H), 4.70 - 4.82 (1H), 6.28 (1H), 7.33 (1H), 7.42 (2H), 7.53 (1H), 7.68 (2H), 7.96 (1H).

Example 71: 4-methyl-2-({1-[4-(pentafluoro-λ^6-sulphanyl)benzoyl]piperidin-4-yl}methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide

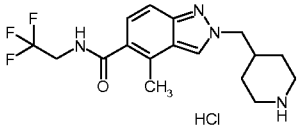


Analogously to Example 1, 124.8 mg of the title compound was obtained from 146.9 mg of the amine prepared in Example 71a and 93.3 mg of 4-(pentafluoro-λ^6-sulphanyl)benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.12 - 1.31 (2H), 1.31 - 1.45 (1H), 1.47 - 1.63 (1H), 2.20 - 2.36 (1H), 2.50 (3H), 2.67 - 2.83 (1H), 2.91 - 3.07 (1H), 3.36 - 3.47 (1H), 3.96 - 4.10 (2H), 4.29 - 4.37 (2H), 4.37 - 4.48 (1H), 7.17 (1H), 7.43 (1H), 7.56 (2H), 7.94 (2H), 8.50 - 8.54 (1H), 8.75 - 8.83 (1H).

The starting material was prepared as follows:

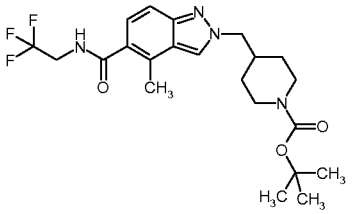
Example 71a: 4-methyl-2-(4-piperidylmethyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide hydrochloride



To 425.2 mg of 71b were added 2.35 ml of 4M hydrochloric acid in dioxan and 0.5 ml dioxan. An oily mass was formed, which dissolved on vigorous stirring and gentle warming. The mixture was stirred for 1 hr at ca. 30°C. The reaction mixture was concentrated. Yield: 440.6 mg of the title compound, which was further reacted without further purification.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.35 - 1.49 (2H), 1.53 - 1.62 (2H), 2.20 - 2.32 (1H), 2.51 (3H), 2.72 - 2.85 (2H), 3.14 - 3.23 (2H), 3.97 - 4.09 (2H), 4.34 (2H), 7.18 (1H), 7.43 (1H), 8.58 (1H), 8.64 - 8.77 (1H), 8.78 - 8.85 (1H), 8.93 - 9.08 (1H).

Example 71b: Tert-butyl 4-({4-methyl-5-[N-(2,2,2-trifluoroethyl)carbamoyl]-2H-indazol-2-yl}-methyl)piperidin-1-carboxylate

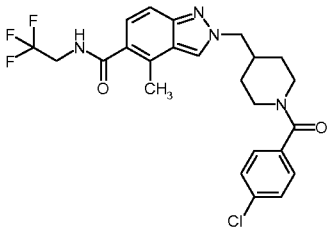


2820 mg of 1c, 2052 mg of 2,2,2-trifluoroethylamine, 1823.2 mg of molybdenum hexacarbonyl, 200.4 mg of tri-tert-butylphosphine tetrafluoroborate and 647.5 mg of trans-bis(acetato)-bis[o-(di-o-tolylphosphino)-benzyl]dipalladium(II) were placed in a microwave tube and suspended in

56 ml THF. 3.1 ml of DBU were then added and the mixture was stirred for 20 mins at 125°C and 200 watts in the microwave. The reaction mixture was diluted with some ethyl acetate, washed twice with water and once with saturated sodium chloride solution. It was dried over sodium sulphate, filtered and concentrated. The residue was chromatographed on the Biotage SP4. Gradient: hexane/ethyl acetate 0-100%. Yield: 475.2 mg of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 0.99 - 1.17 (2H), 1.30 – 1.44 (11H), 2.05 - 2.21 (1H), 2.50 (3H), 2.54 - 2.73 (2H), 3.81 - 3.94 (2H), 3.95 - 4.10 (2H), 4.29 (2H), 7.18 (1H), 7.43 (1H), 8.51 (1H), 8.74 - 8.83 (1H).

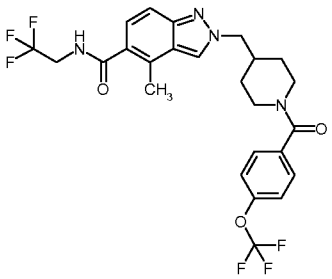
Example 72: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 97.8 mg of the title compound was obtained from 146.9 mg of the amine prepared in Example 71a and 58.8 mg of 4-chlorobenzoic acid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.11 - 1.29 (2H), 1.31 - 1.45 (1H), 1.45 - 1.61 (1H), 2.20 - 2.35 (1H), 2.50 (3H), 2.63 - 2.84 (1H), 2.85 - 3.08 (1H), 3.42 - 3.59 (1H), 3.96 - 4.10 (2H), 4.29 - 4.47 (3H), 7.17 (1H), 7.36 (2H), 7.40 - 7.50 (3H), 8.52 (1H), 8.75 - 8.82 (1H).

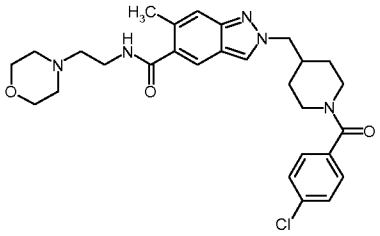
Example 73: 4-methyl-N-(2,2,2-trifluoroethyl)-2-({1-[4-(trifluoromethoxy)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 105.4 mg of the title compound was obtained from 146.9 mg of the amine prepared in Example 71a and 77.5 mg of 4-(trifluoromethoxy)benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.12 - 1.30 (2H), 1.31 - 1.46 (1H), 1.47 - 1.64 (1H), 2.20 - 2.36 (1H), 2.50 (3H), 2.66 - 2.85 (1H), 2.86 - 3.09 (1H), 3.40 - 3.55 (1H), 3.96 - 4.10 (2H), 4.29 - 4.48 (3H), 7.17 (1H), 7.36 - 7.50 (5H), 8.52 (1H), 8.75 - 8.82 (1H).

Example 74: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-6-methyl-N-(2-morpholinoethyl)-2H-indazol-5-carboxamide

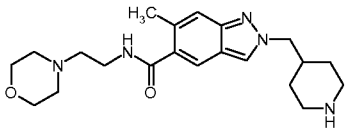


Analogously to Example 55, 30 mg of the title compound was obtained from 79 mg of the amine prepared in Example 74a and 26 mg of 4-chlorobenzoyl chloride.

^{1}NMR (400 MHz, methanol-d_4): δ [ppm]= 1.31 (2H), 1.50 (1H), 1.65 (1H), 2.35 (1H), 2.47 (3H), 2.63 (6H), 2.81 (1H), 3.07 (1H), 3.53 (2H), 3.71 (5H), 4.34 (2H), 4.59 (1H), 7.36 (2H), 7.43 (3H), 7.75 (1H), 8.24 (1H).

The starting material was prepared as follows:

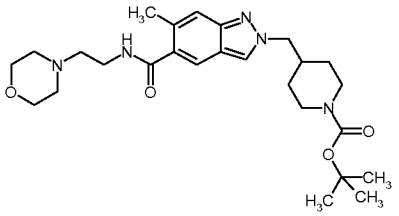
Example 74a: 6-methyl-N-(2-morpholinoethyl)-2-(4-piperidylmethyl)-2H-indazol-5-carboxamide



768 mg of (1.58 mmol) of tert-butyl carbamate 74b were dissolved in 4.0 ml 4M hydrochloric acid in dioxan and stirred under nitrogen at room temperature. A further 0.8 ml 4M hydrochloric acid in dioxan were added and the mixture stirred at room temperature. The reaction solution was concentrated and yielded 760 mg of the title compound, which was used in the next reaction without further purification.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.34 - 1.50 (2H), 1.53 - 1.67 (2H), 2.21 - 2.30 (1H), 2.41 (3H), 2.74 - 2.89 (2H), 3.07 - 3.33 (8H), 3.62 - 3.71 (2H), 3.77 - 3.90 (2H), 3.90 - 4.03 (2H), 4.35 (2H), 7.39 (1H), 7.88 (1H), 8.44 (1H), 8.57 (1H), 8.62 - 8.79 (1H), 8.87 - 9.02 (1H), 11.17 (1H).

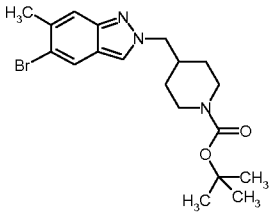
Example 74b: Tert-butyl 4-({6-methyl-5-[N-(2-morpholinoethyl)carbamoyl]-2H-indazol-2-yl}-methyl)piperidin-1-carboxylate



3.00 g (7.35 mmol) of 5-bromoindazole 74c and 2.87 g (22.04 mmol) of 2-morpholino-ethylamine were dissolved in 134 ml dioxan and 1.94 g (7.35 mmol) of molybdenum hexacarbonyl, 167 mg (1.47 mmol) of palladium acetate, 213 mg (0.74 mmol) of tributylphosphonium tetrafluoroborate, 2.34 g (22.0 mmol) of sodium carbonate and 2 drops of water were added. The reaction mixture was heated to 125°C under nitrogen and stirred at this temperature for 2.5 hrs. For the work-up, the suspension was filtered over Celite, rewashed with dioxan, concentrated in vacuo and dried. The crude product was separated by column chromatography. Yield: 518 mg of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 0.93 - 1.16 (2H), 1.26-1.37 (2H), 1.34 (9H), 1.99 - 2.17 (1H), 2.32 - 2.43 (10H), 2.54 - 2.72 (2H), 3.34 (1H), 3.48 - 3.59 (4H), 3.86 (2H), 4.26 (2H), 7.35 (1H), 7.63 (1H), 8.09 (1H), 8.32 (1H).

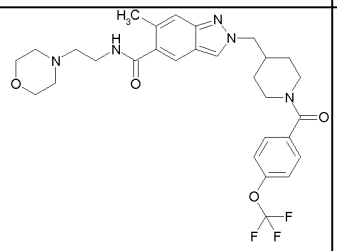
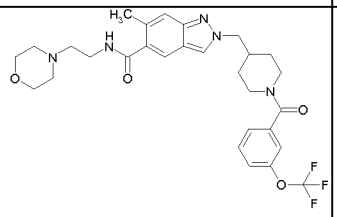
Example 74c: Tert-butyl 4-[(5-bromo-6-methyl-2H-indazol-2-yl)methyl]piperidin-1-carboxylate



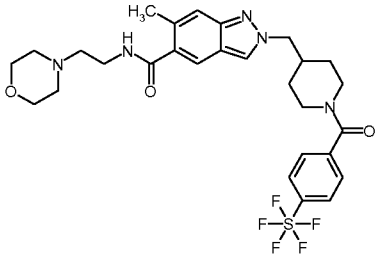
10.0 g (47.4 mmol) of 5-bromo-4-methyl-1H-indazole and 21.0 g (56.9 mmol) of tert-butyl 4-[(tosyloxy)methyl]piperidin-1-carboxylate were dissolved in 726 ml DMF. To this were added 21.0 g (56.9 mmol) of tetrabutylammonium iodide and 18.5 g (56.9 mmol) of caesium carbonate and the reaction mixture was heated under nitrogen at 80°C for 1.5 hrs. For the work-up, it was treated with water and ethyl acetate, the organic phase separated and the aqueous phase extracted several times with ethyl acetate. The organic phases were washed with saturated sodium chloride solution, dried over sodium sulphate and concentrated in vacuo. After purification by column chromatography, this yielded the title compound in 5 g yield.

^{1}H-NMR (600 MHz, chloroform-d): δ [ppm]= 1.16 - 1.30 (2H), 1.45 (9H), 1.54 (2H), 2.22 - 2.33 (1H), 2.51 (3H), 2.67 (2H), 4.03 - 4.17 (2H), 4.27 - 4.32 (2H), 7.60 (1H), 7.81 (1H), 7.90 (1H).

The following compounds were prepared analogously:

Ex.	Structure	IUPAC name	Analysis
75		6-methyl-N-(2-morpholinoethyl)-2-({1-[4-(trifluoromethoxy)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, methanol-d_4): δ [ppm]= 1.32 (2H), 1.51 (1H), 1.65 (1H), 2.36 (1H), 2.47 (3H), 2.60 (6H), 2.83 (1H), 3.10 (1H), 3.52 (2H), 3.70 (5H), 4.35 (2H), 4.61 (1H), 7.37 (3H), 7.49 (2H), 7.74 (1H), 8.24 (1H).
76		6-methyl-N-(2-morpholinoethyl)-2-({1-[3-(trifluoromethoxy)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, methanol-d_4): δ [ppm]= 1.32 (2H), 1.49 (1H), 1.65 (1H), 2.36 (1H), 2.46 (3H), 2.59 (6H), 2.83 (1H), 3.10 (1H), 3.51 (2H), 3.69 (5H), 4.35 (2H), 4.60 (1H), 7.33 (2H), 7.40 (2H), 7.54 (1H), 7.74 (1H), 8.24 (1H).

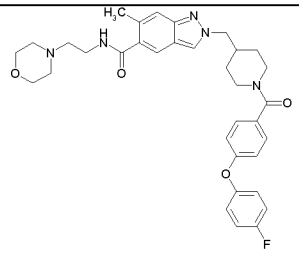
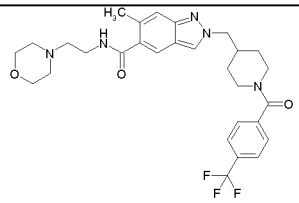
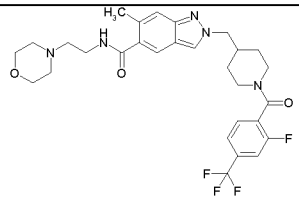
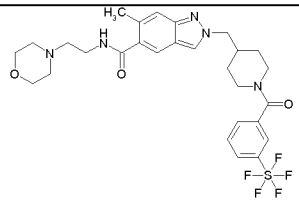
Example 77: 6-methyl-N-(2-morpholinoethyl)-2-({1-[4-(pentafluoro-λ^6-sulphanyl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide

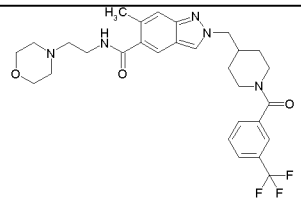
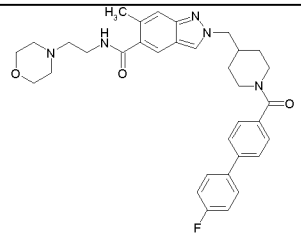


Analogously to Example 1, 23 mg of the title compound was obtained from 79 mg of the amine prepared in Example 74a and 47 mg of the acid.

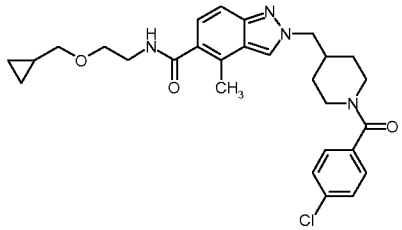
^{1}H-NMR (400 MHz, methanol-d_4): δ [ppm]= 1.34 (2H), 1.52 (1H), 1.66 (1H), 2.37 (1H), 2.49 (3H), 2.84 (1H), 3.10 (1H), 3.25 (2H), 3.42 (2H), 3.63 (3H), 3.75 (4H), 4.10 (2H), 4.36 (2H), 4.62 (1H), 7.43 (1H), 7.56 (2H), 7.89 (3H), 8.28 (1H).

The following compounds were prepared analogously:

Ex.	Structure	IUPAC name	Analysis
78		2-({1-[4-(4-fluoro-phenoxy)benzoyl]-piperidin-4-yl}-methyl)-6-methyl-N-(2-morpholinoethyl)-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, methanol-d_4): δ [ppm]= 1.31 (2H), 1.58 (2H), 2.35 (1H), 2.49 (3H), 2.40-4.20 (15H), 4.35 (2H), 4.58 (1H), 6.97 (2H), 7.04 (2H), 7.11 (2H), 7.37 (2H), 7.43 (1H), 7.87 (1H), 8.27 (1H).
79		6-methyl-N-(2-morpholinoethyl)-2-({1-[4-(trifluoro-methyl)benzoyl]-piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, methanol-d_4): δ [ppm]= 1.34 (2H), 1.51 (1H), 1.67 (1H), 2.38 (1H), 2.50 (3H), 2.85 (1H), 3.10 (1H), 3.25 (2H), 3.43 (2H), 3.64 (3H), 3.76 (4H), 4.10 (2H), 4.38 (2H), 4.64 (1H), 7.44 (1H), 7.57 (2H), 7.76 (2H), 7.89 (1H), 8.31 (1H).
80		2-({1-[2-fluoro-4-(trifluoromethyl)benzoyl]piperidin-4-yl}-methyl)-6-methyl-N-(2-morpholinoethyl)-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, methanol-d_4): δ [ppm]= 1.34 (2H), 1.54 (1H), 1.68 (1H), 2.38 (1H), 2.50 (3H), 2.86 (1H), 3.12 (1H), 3.26 (2H), 3.43 (3H), 3.66 (2H), 3.76 (4H), 4.11 (2H), 4.37 (2H), 4.67 (1H), 7.44 (1H), 7.59 (3H), 7.89 (1H), 8.31 (1H).
81		6-methyl-N-(2-morpholinoethyl)-2-({1-[3-(pentafluoro-λ^6-sulphanyl)benzoyl]-piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, methanol-d_4): δ [ppm]= 1.35 (2H), 1.53 (1H), 1.65 (1H), 2.38 (1H), 2.50 (3H), 2.86 (1H), 3.14 (1H), 3.26 (2H), 3.43 (2H), 3.66 (3H), 3.76 (4H), 4.11 (2H), 4.37 (2H), 4.62 (1H), 7.44 (1H), 7.63 (2H), 7.89 (3H), 8.30 (1H).

Ex.	Structure	IUPAC name	Analysis
82		6-methyl-N-(2-morpholinoethyl)-2-({1-[3-(trifluoromethyl)-benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, methanol-d_4): δ [ppm]= 1.35 (2H), 1.53 (1H), 1.65 (1H), 2.38 (1H), 2.50 (3H), 2.85 (1H), 3.12 (1H), 3.26 (2H), 3.43 (2H), 3.66 (3H), 3.76 (4H), 4.11 (2H), 4.38 (2H), 4.63 (1H), 7.45 (1H), 7.66 (3H), 7.77 (1H), 7.90 (1H), 8.33 (1H).
83		2-({1-[(4'-fluoro-biphenyl-4-yl)-carbonyl]piperidin-4-yl}methyl)-6-methyl-N-(2-morpholino-ethyl)-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, methanol-d_4): δ [ppm]= 1.35 (2H), 1.53 (1H), 1.65 (1H), 2.39 (1H), 2.50 (3H), 2.85 (1H), 3.12 (1H), 3.26 (2H), 3.42 (2H), 3.63 (3H), 3.74 (4H), 4.08 (2H), 4.37 (2H), 4.64 (1H), 7.18 (2H), 7.46 (3H), 7.66 (4H), 7.88 (1H), 8.30 (1H).

Example 84: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-[2-(cyclopropylmethoxy)ethyl]-4-methyl-2H-indazol-5-carboxamide

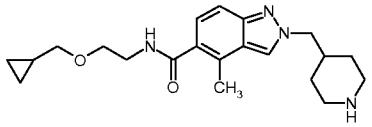


Analogously to Example 1, 38 mg of the title compound was obtained from 75 mg of the amine prepared in Example 84a and 29 mg of 4-chlorobenzoic acid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 0.14 (2H), 0.42 (2H), 0.97 (1H), 1.21 (2H), 1.36 (1H), 1.52 (1H), 2.27 (1H), 2.50 (3H), 2.72 (1H), 2.97 (1H), 3.23 (2H), 3.36 (2H), 3.48 (3H), 4.31 (2H), 4.40 (1H), 7.14 (1H), 7.36 (3H), 7.46 (2H), 8.12 (1H), 8.47 (1H).

The starting material was prepared as follows:

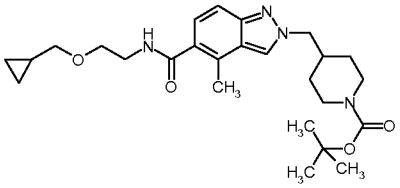
Example 84a: N-[2-(cyclopropylmethoxy)ethyl]-4-methyl-2-(4-piperidylmethyl)-2H-indazol-5-carboxamide



To 781 mg of 84b were added 3.7 ml of 4M hydrochloric acid in dioxan and 0.5 ml dioxan. The mixture was stirred for 30 mins at ca. 30°C. The reaction mixture was concentrated, taken up in some toluene and again concentrated. Yield: 751 mg of the title compound, which was further reacted without further purification.

^{1}H-NMR (400 MHz, DMSO-d6): δ [ppm]= 0.14 (2H), 0.42 (2H), 0.97 (1H), 1.43 (2H), 1.58 (2H), 2.26 (1H), 2.50 (3H), 2.65 (1H), 2.78(2H), 3.18 (2H), 3.22 (2H), 3.36 (2H), 3.49 (2H), 4.33 (2H), 7.16 (2H), 7.38 (1H), 8.11 (1H), 8.53 (1H), 8.80 (1H), 9.06 (1H).

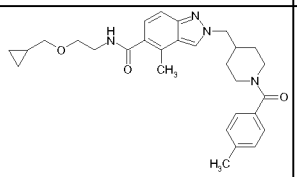
Example 84b: Tert-butyl 4-[(5-{N-[2-(cyclopropylmethoxy)ethyl]carbamoyl}-4-methyl-2H-indazol-2-yl)methyl]piperidin-1-carboxylate

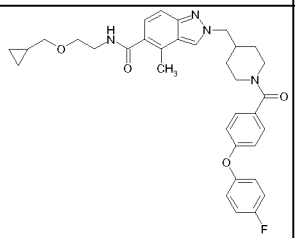
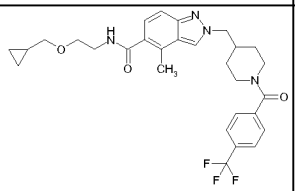
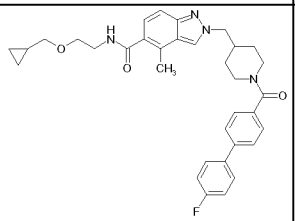
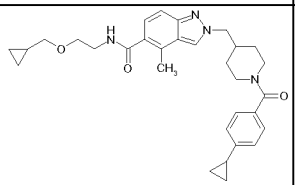


500 mg of 1d was reacted with 203 mg of amine analogously to 1b version B. Yield: 781 mg of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 0.98 - 1.13 (2H), 1.34 (11H), 2.05 - 2.27 (2H), 2.33 - 2.41 (5H), 2.51 (3H), 2.56 - 2.73 (2H), 3.25 - 3.37 (2H), 3.51 - 3.57 (4H), 3.81 - 3.93 (2H), 4.28 (2H), 7.14 (1H), 7.36 - 7.41 (1H), 7.95 - 8.02 (1H), 8.46 (1H).

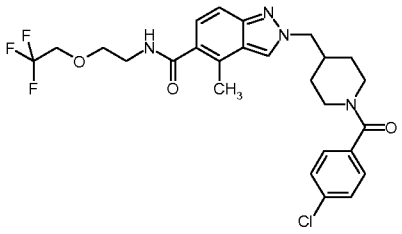
The following compounds were prepared analogously:

Ex.	Structure	IUPAC name	Analysis
85		N-[2-(cyclopropyl-methoxy)ethyl]-4-methyl-2-{[1-(4-methylbenzoyl)-piperidin-4-yl]-methyl}-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 0.14 (2H), 0.42 (2H), 0.97 (1H), 1.19 (2H), 1.37 (1H), 1.50 (1H), 2.26 (1H), 2.29 (3H), 2.50 (3H), 2.72 (1H), 2.94 (1H), 3.23 (2H), 3.36 (2H), 3.48 (2H), 3.57 (1H), 4.30 (2H), 4.39 (1H), 7.14 (1H), 7.21 (4H), 7.38 (1H), 8.12 (1H), 8.47 (1H).

Ex.	Structure	IUPAC name	Analysis
86		N-[2-(cyclopropyl-methoxy)ethyl]-2-({1-[4-(4-fluorophenoxy)-benzoyl]piperidin-4-yl}methyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d6): δ [ppm]= 0.14 (2H), 0.42 (2H), 0.97 (1H), 1.19 (2H), 1.45 (2H), 2.26 (1H), 2.50 (3H), 2.75 (1H), 2.96 (1H), 3.23 (2H), 3.36 (2H), 3.48 (2H), 3.62 (1H), 4.31 (2H), 4.39 (1H), 6.95 (2H), 7.12 (3H), 7.23 (2H), 7.36 (3H), 8.12 (1H), 8.47 (1H).
87		N-[2-(cyclopropyl-methoxy)ethyl]-4-methyl-2-({1-[4-(tri-fluoromethyl)benzoyl] piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 0.14 (2H), 0.42 (2H), 0.96 (1H), 1.22 (2H), 1.36 (1H), 1.56 (1H), 2.28 (1H), 2.50 (3H), 2.74 (1H), 2.99 (1H), 3.23 (2H), 3.36 (2H), 2.43 (1H), 3.48 (2H), 4.31 (2H), 4.43 (1H), 7.15 (1H), 7.38 (1H), 7.55 (2H), 7.77 (2H), 8.12 (1H), 8.47 (1H).
88		N-[2-(cyclopropyl-methoxy)ethyl]-2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d6): δ [ppm]= 0.14 (2H), 0.42 (2H), 0.96 (1H), 1.23 (2H), 1.39 (1H), 1.55 (1H), 2.28 (1H), 2.50 (3H), 2.74 (1H), 3.01 (1H), 3.23 (2H), 3.36 (2H), 3.48 (2H), 3.61 (1H), 4.33 (2H), 4.44 (1H), 7.15 (1H), 7.28 (2H), 7.40 (3H), 7.69 (4H), 8.12 (1H), 8.48 (1H).
89		2-{[1-(4-cyclopropyl-benzoyl)piperidin-4-yl]methyl}-N-[2-(cyclopropylmethoxy) ethyl]-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 0.17 (2H), 0.45 (2H), 0.69 (2H), 0.97 (3H), 1.21 (2H), 1.47 (2H), 1.93 (1H), 2.27 (1H), 2.52 (3H), 2.78 (1H), 2.93 (1H), 3.26 (2H), 3.37 (2H), 3.51 (2H), 3.62 (1H), 4.34 (2H), 4.41 (1H), 7.10 (2H), 7.17 (1H), 7.22 (2H), 7.41

Ex.	Structure	IUPAC name	Analysis
			(1H), 8.11 (1H), 8.49 (1H).

Example 90: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methyl-N-[2-(2,2,2-trifluoroethoxy)ethyl]-2H-indazol-5-carboxamide

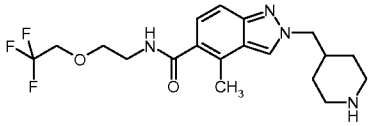


Analogously to Example 1, 40 mg of the title compound was obtained from 75 mg of the amine prepared in Example 90a and 27 mg of 4-chlorobenzoic acid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.20 (2H), 1.36 (1H), 1.53 (1H), 2.27 (1H), 2.49 (3H), 2.72 (1H), 2.97 (1H), 3.40 (2H), 3.49 (1H), 3.69 (2H), 4.07 (2H), 4.31 (2H), 4.40 (1H), 7.15 (1H), 7.37 (3H), 7.46 (2H), 8.19 (1H), 8.48 (1H).

The starting material was prepared as follows:

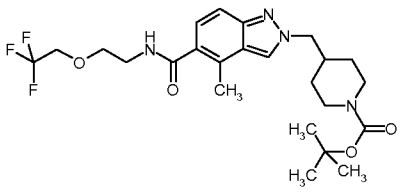
Example 90a: 4-methyl-2-(4-piperidylmethyl)-N-[2-(2,2,2-trifluoroethoxy)ethyl]-2H-indazol-5-carboxamide



To 610 mg of 90b were added 3.0 ml of 4M hydrochloric acid in dioxan and 0.5 ml dioxan. The mixture was stirred for 30 mins at ca. 30°C. The reaction mixture was concentrated, taken up in some toluene and again concentrated. Yield: 619 mg of the title compound, which was further reacted without further purification.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.42 (2H), 1.59 (2H), 2.26 (1H), 2.50 (3H), 2.64 (1H), 2.79 (2H), 3.20 (2H), 3.40 (2H), 3.70 (2H), 4.07 (2H), 4.33 (2H), 5.67(1H), 7.16 (1H), 7.39 (1H), 8.18 (1H), 8.53 (1H), 8.69 (1H), 8.94 (1H).

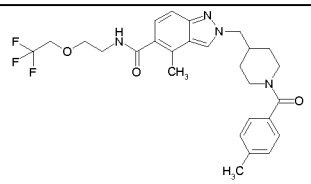
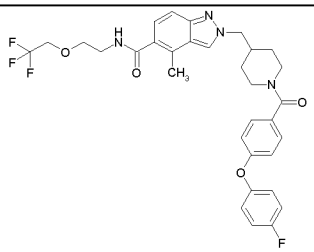
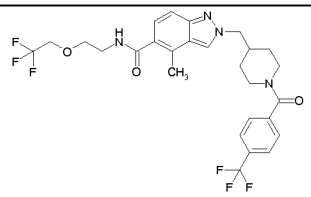
Example 90b: Tert-butyl 4-[(4-methyl-5-{N-[2-(2,2,2-trifluoroethoxy)ethyl]carbamoyl}-2H-indazol-2-yl)methyl]piperidin-1-carboxylate

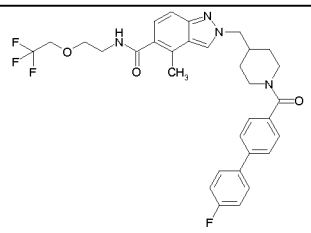
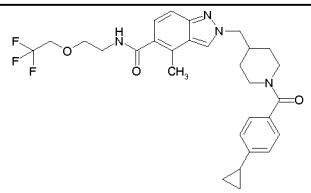


500 mg of 1d was reacted with 240 mg of amine analogously to 1b version B. Yield: 670 mg of the title compound.

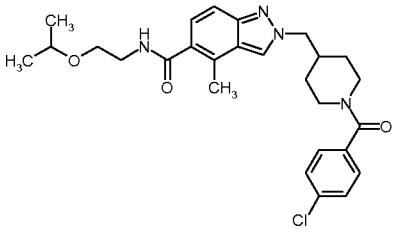
^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.07 (2H), 1.34 (9H), 1.37 (2H), 2.14 (1H), 2.49 (3H), 2.63 (2H), 3.40 (2H), 3.70 (2H), 3.88 (2H), 4.06 (2H), 4.29 (2H), 7.15 (1H), 7.39 (1H), 8.16 (1H), 8.47 (1H).

The following compounds were prepared analogously:

Ex.	Structure	IUPAC name	Analysis
91		4-methyl-2-{[1-(4-methylbenzoyl)-piperidin-4-yl]-methyl}-N-[2-(2,2,2-trifluoro-ethoxy)ethyl]-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.19 (2H), 1.36 (1H), 1.49 (1H), 2.25 (1H), 2.29 (3H), 2.49 (3H), 2.71 (1H), 2.93 (1H), 3.40 (2H), 3.56 (1H), 3.69 (2H), 4.07 (2H), 4.31 (2H), 4.40 (1H), 7.15 (1H), 7.21 (4H), 7.39 (1H), 8.19 (1H), 8.48 (1H).
92		2-({1-[4-(4-fluoro-phenoxy)benzoyl]-piperidin-4-yl}-methyl)-4-methyl-N-[2-(2,2,2-tri-fluoroethoxy)ethyl]-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.19 (2H), 1.44 (2H), 2.26 (1H), 2.49 (3H), 2.73 (1H), 2.95 (1H), 3.40 (2H), 3.60 (1H), 3.69 (2H), 4.07 (2H), 4.31 (2H), 4.38 (1H), 6.95 (2H), 7.12 (3H), 7.22 (2H), 7.37 (3H), 8.19 (1H), 8.48 (1H).
93		4-methyl-N-[2-(2,2,2-trifluoro-ethoxy)ethyl]-2-({1-[4-(trifluoro-methyl)benzoyl]-piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.22 (2H), 1.36 (1H), 1.56 (1H), 2.28 (1H), 2.49 (3H), 2.74 (1H), 2.99 (1H), 3.40 (3H), 3.69 (2H), 4.07 (2H), 4.32 (2H), 4.43 (1H), 7.15 (1H), 7.39 (1H), 7.55 (2H), 7.77 (2H), 8.19 (1H), 8.48 (1H).

Ex.	Structure	IUPAC name	Analysis
94		2-({1-[(4'-fluoro-biphenyl-4-yl)-carbonyl]piperidin-4-yl}methyl)-4-methyl-N-[2-(2,2,2-trifluoroethoxy)-ethyl]-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.23 (2H), 1.39 (1H), 1.52 (1H), 2.28 (1H), 2.49 (3H), 2.75 (1H), 3.00 (1H), 3.39 (2H), 3.60 (1H), 3.69 (2H), 4.07 (2H), 4.33 (2H), 4.43 (1H), 7.15 (1H), 7.27 (2H), 7.40 (3H), 7.68 (4H), 8.19 (1H), 8.49 (1H).
95		2-{[1-(4-cyclo-propylbenzoyl)-piperidin-4-yl]-methyl}-4-methyl-N-[2-(2,2,2-tri-fluoroethoxy)ethyl]-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 0.69 (2H), 0.96 (2H), 1.21 (2H), 1.47 (2H), 1.93 (1H), 2.28 (1H), 2.52 (3H), 2.77 (1H), 2.94 (1H), 3.43 (2H), 3.61 (1H), 3.72 (2H), 4.09 (2H), 4.34 (2H), 4.42 (1H), 7.10 (2H), 7.17 (1H), 7.22 (2H), 7.41 (1H), 8.18 (1H).

Example 96: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-(2-isopropoxyethyl)-4-methyl-2H-indazol-5-carboxamide

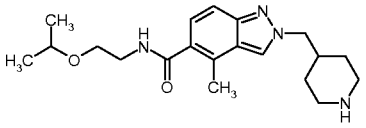


Analogously to Example 1, 36 mg of the title compound was obtained from 75 mg of the amine prepared in Example 96a and 30 mg of 4-chlorobenzoic acid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.07 (6H), 1.22 (2H), 1.39 (1H), 1.51 (1H), 2.26 (1H), 2.50 (3H), 2.75 (1H), 2.97 (1H), 3.33 (2H), 3.45 (3H), 3.55 (1H), 4.31 (2H), 4.39 (1H), 7.14 (1H), 7.36 (3H), 7.47 (2H), 8.05 (1H), 8.46 (1H).

The starting material was prepared as follows:

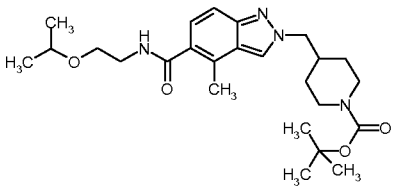
Example 96a: N-(2-isopropoxyethyl)-4-methyl-2-(4-piperidylmethyl)-2H-indazol-5-carboxamide



To 650 mg of 96b were added 3.2 ml of 4M hydrochloric acid in dioxan and 0.5 ml dioxan. The mixture was stirred for 30 mins at ca. 30°C. The reaction mixture was concentrated, taken up in some toluene and again concentrated. Yield: 529 mg of the title compound, which was further reacted without further purification.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.06 (3H), 1.07 (3H), 1.42 (2H), 1.57 (2H), 2.25 (1H), 2.50 (3H), 2.65 (1H), 2.78 (2H), 3.19 (2H), 3.32 (2H), 3.45 (2H), 3.55 (1H), 4.32 (1H), 6.61 (1H), 7.15 (1H), 7.38 (1H), 8.11 (1H), 8.53 (1H), 8.78 (1H), 9.04 (1H).

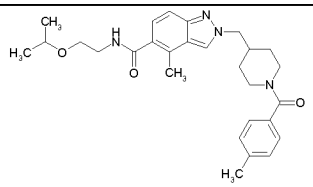
Example 96b: Tert-butyl 4-({5-[N-(2-isopropoxyethyl)carbamoyl]-4-methyl-2H-indazol-2-yl}-methyl)piperidin-1-carboxylate

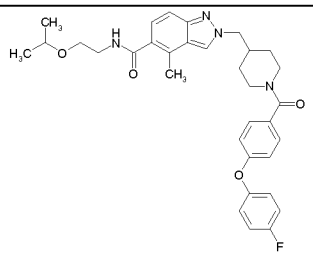
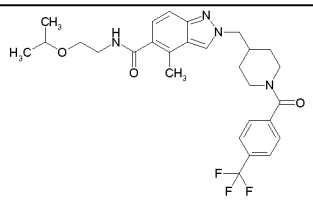
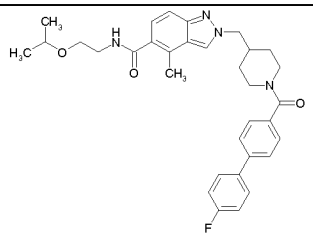
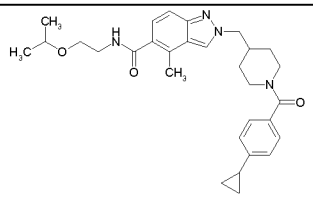


500 mg of 1d was reacted with 138 mg of amine analogously to 1b version B. Yield: 650 mg of the title compound.

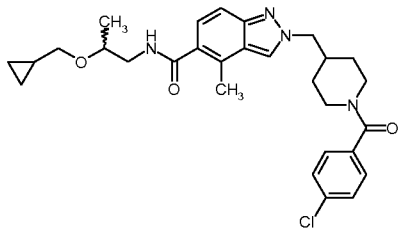
^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.07 (8H), 1.34 (9H), 1.38 (2H), 2.13 (1H), 2.50 (3H), 2.63 (2H), 3.33 (2H), 3.46 (2H), 3.55 (1H), 3.87 (2H), 4.28 (2H), 7.14 (1H), 7.38 (1H), 8.05 (1H), 8.46 (1H).

The following compounds were prepared analogously:

Ex.	Structure	IUPAC name	Analysis
97		N-(2-isopropoxy-ethyl)-4-methyl-2-{[1-(4-methyl-benzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.07 (6H), 1.19 (2H), 1.45 (2H), 2.29 (4H), 2.50 (3H), 2.75 (1H), 2.92 (1H), 3.33 (2H), 3.45 (2H), 3.55 (2H), 4.31 (2H), 4.40 (1H), 7.14 (1H), 7.20 (4H), 7.38 (1H), 8.05 (1H), 8.46 (1H).

Ex.	Structure	IUPAC name	Analysis
98		2-({1-[4-(4-fluoro-phenoxy)benzoyl]-piperidin-4-yl}-methyl)-N-(2-isopropoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 1.07 (6H), 1.21 (2H), 1.45 (2H), 2.25 (1H), 2.49 (3H), 2.85 (2H), 3.31 (2H), 3.45 (2H), 3.55 (2H), 4.31 (2H), 4.40 (1H), 6.95 (2H), 7.10 (3H), 7.22 (2H), 7.36 (3H), 8.05 (1H), 8.46 (1H).
99		N-(2-isopropoxy-ethyl)-4-methyl-2-({1-[4-(trifluoro-methyl)benzoyl]-piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 1.06 (6H), 1.22 (2H), 1.37 (1H), 1.56 (1H), 2.28 (1H), 2.50 (3H), 2.75 (1H), 2.99 (1H), 3.33 (2H), 3.45 (3H), 3.55 (1H), 4.32 (2H), 4.43 (1H), 7.15 (1H), 7.38 (1H), 7.55 (2H), 7.77 (2H), 8.05 (1H), 8.46 (1H).
100		2-({1-[(4'-fluoro-biphenyl-4-yl)-carbonyl]piperidin-4-yl}methyl)-N-(2-isopropoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 1.06 (6H), 1.23 (2H), 1.47 (2H), 2.28 (1H), 2.50 (3H), 2.76 (1H), 2.98 (1H), 3.33 (2H), 3.45 (2H), 3.55 (2H), 4.33 (2H), 4.43 (1H), 7.15 (1H), 7.27 (2H), 7.39 (3H), 7.68 (4H), 8.05 (1H), 8.47 (1H).
101		2-{[1-(4-cyclopropyl-benzoyl)piperidin-4-yl]methyl}-N-(2-isopropoxyethyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 0.66 (2H), 0.94 (2H), 1.06 (6H), 1.20 (2H), 1.44 (2H), 1.90 (1H), 2.24 (1H), 2.49 (3H), 2.82 (2H), 3.32 (2H), 3.45 (2H), 3.55 (2H), 4.31 (2H), 4.39 (1H), 7.12 (5H), 7.38 (1H), 8.05 (1H), 8.46 (1H).

Example 102: (+/-)-2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-[2-(cyclopropylmethoxy) propyl]-4-methyl-2H-indazol-5-carboxamide

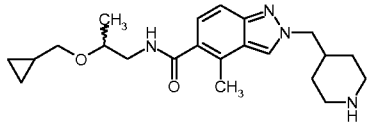


Analogously to Example 1, 41 mg of the title compound was obtained from 100 mg of the amine prepared in Example 102a and 37 mg of 4-chlorobenzoic acid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 0.16 (2H), 0.43 (2H), 0.97 (1H), 1.10 (3H), 1.23 (2H), 1.40 (1H), 1.55 (1H), 2.29 (1H), 2.53 (3H), 2.75 (1H), 2.99 (1H), 3.23 (2H), 3.20 (2H), 3.51 (1H), 3.59 (1H), 4.34 (2H), 4.43 (1H), 7.17 (1H), 7.39 (3H), 7.49 (2H), 8.09 (1H), 8.49 (1H).

The starting material was prepared as follows:

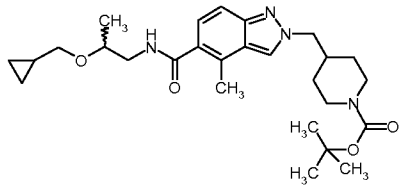
Example 102a: (+/-)-N-[2-(cyclopropylmethoxy)propyl]-4-methyl-2-(4-piperidylmethyl)-2H-indazol-5-carboxamide



To 632 mg of 102b were added 2.9 ml of 4M hydrochloric acid in dioxan and 0.5 ml dioxan. The mixture was stirred for 30 mins at ca. 30°C. The reaction mixture was concentrated, taken up in some toluene and again concentrated. Yield: 561 mg of the title compound, which was further reacted without further purification.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 0.13 (2H), 0.40 (2H), 0.94 (1H), 1.07 (3H), 1.44 (2H), 1.57 (2H), 2.26 (1H), 2.50 (3H), 2.77 (2H), 3.20 (6H), 3.57 (1H), 4.33 (2H), 6.33 (1H), 7.16 (1H), 7.39 (1H), 8.11 (1H), 8.53 (1H), 8.79 (1H), 9.06 (1H).

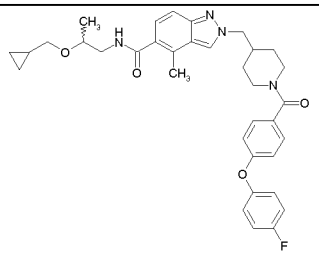
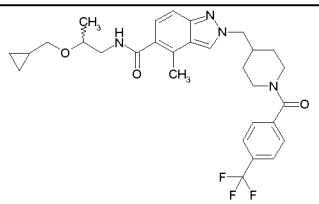
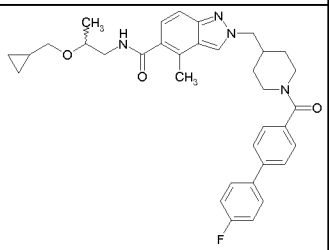
Example 102b: (+/-)-tert-butyl 4-[(5-{N-[2-(cyclopropylmethoxy)propyl]carbamoyl}-4-methyl-2H-indazol-2-yl)methyl]piperidin-1-carboxylate

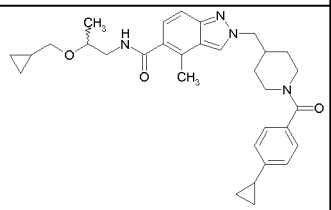


500 mg of 1d was reacted with 222 mg of amine analogously to 1b version B. Yield: 631 mg of the title compound.

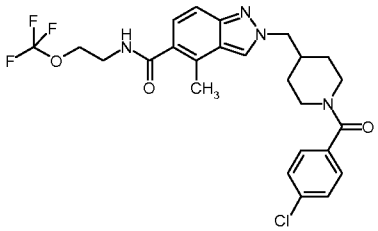
^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 0.13 (2H), 0.40 (2H), 0-94 (1H), 1.07 (3H), 1.14 (2H), 1.34 (9H), 1.38 (2H), 2.13 (1H), 2.50 (3H), 3.24 (6H), 3.57 (1H), 3.87 (2H), 4.28 (2H), 7.15 (1H), 7.39 (1H), 8.09 (1H), 8.46 (1H).

The following compounds were prepared analogously:

Ex.	Structure	IUPAC name	Analysis
103		(+/-)-N-[2-(cyclo-propylmethoxy)-propyl]-2-({1-[4-(4-fluorophenoxy)-benzoyl]piperidin-4-yl}-methyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 0.16 (2H), 0.43 (2H), 0.97 (1H), 1.10 (3H), 1.22 (2H), 1.48 (2H), 2.29 (1H), 2.53 (3H), 2.81 (1H), 2.92 (1H), 3.23 (2H), 3.28 (2H), 3.60 (1H), 3.70 (1H), 4.34 (2H), 4.42 (1H), 6.98 (2H), 7.14 (3H), 7.25 (2H), 7.39 (3H), 8.09 (1H), 8.49 (1H).
104		(+/-)-N-[2-(cyclo-propylmethoxy)-propyl]-4-methyl-2-({1-[4-(trifluoro-methyl)benzoyl]-piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 0.16 (2H), 0.43 (2H), 0.97 (1H), 1.10 (3H), 1.24 (2H), 1.38 (1H), 1.59 (1H), 2.30 (1H), 2.53 (3H), 2.78 (1H), 3.02 (1H), 3.23 (2H), 3.28 (2H), 3.45 (1H), 3.60 (1H), 4.34 (2H), 4.46 (1H), 7.17 (1H), 7.41 (1H), 7.57 (2H), 7.80 (2H), 8.09 (1H), 8.49 (1H).
105		(+/-)-N-[2-(cyclo-propylmethoxy)-propyl]-2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]-piperidin-4-yl}-methyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 0.16 (2H), 0.42 (2H), 0.97 (1H), 1.10 (3H), 1.26 (2H), 1.45 (1H), 1.55 (1H), 2.32 (1H), 2.53 (3H), 2.7 9(1H), 3.03 (1H), 3.23 (2H), 3.27 (2H), 3.60 (2H), 4.36 (2H), 4.46 (1H), 7.17 (1H), 7.30 (2H), 7.42 (3H), 7.71 (4H), 8.09 (1H), 8.50 (1H).

Ex.	Structure	IUPAC name	Analysis
106		(+/-)-2-{[1-(4-cyclopropylbenzoyl) piperidin-4-yl]-methyl}-N-[2-(cyclopropyl-methoxy)propyl]-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 0.16 (2H), 0.43 (2H), 0.69 (2H), 0.96 (3H), 1.10 (3H), 1.20 (2H), 1.47 (2H), 1.93 (1H), 2.28 (1H), 2.53 (3H), 2.77 (1H), 2.93 (1H), 3.23 (2H), 3.28 (2H), 3.59 (2H), 4.34 (2H), 4.40 (1H), 7.10 (2H), 7.17 (1H), 7.22 (2H), 7.41 (1H), 8.09 (1H), 8.49 (1H).

Example 107: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methyl-N-[2-(trifluoromethoxy) ethyl]-2H-indazol-5-carboxamide

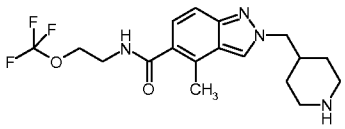


Analogously to Example 1, 26 mg of the title compound was obtained from 75 mg of the amine prepared in Example 107a and 28 mg of 4-chlorobenzoic acid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.20 (2H), 1.36 (1H), 1.52 (1H), 2.27 (1H), 2.49 (3H), 2.72 (1H), 2.97 (1H), 3.51 (3H), 4.17 (2H), 4.33 (3H), 7.15 (1H), 7.41 (5H), 8.37 (1H), 8.49 (1H).

The starting material was prepared as follows:

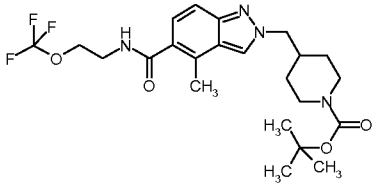
Example 107a: 4-methyl-2-(4-piperidylmethyl)-N-[2-(trifluoromethoxy)ethyl]-2H-indazol-5-carboxamide



To 648 mg of 107b were added 3.0 ml of 4M hydrochloric acid in dioxan and 0.5 ml dioxan. The mixture was stirred for 30 mins at ca. 30°C. The reaction mixture was concentrated, taken up in some toluene and again concentrated. Yield: 766 mg of the title compound, which was further reacted without further purification.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.43 (2H), 1.57 (2H), 2.24 (1H), 2.50 (3H), 2.78 (2H), 3.19 (2H), 3.50 (1H), 4.17 (2H), 4.33 (2H), 6.49 (1H), 7.17 (2H), 7.40 (1H), 8.39 (1H), 8.55 (1H), 8.70 (1H), 8.98 (1H).

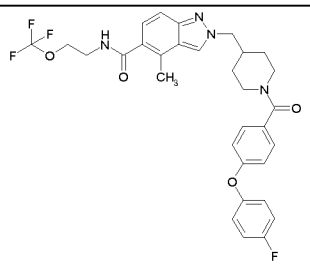
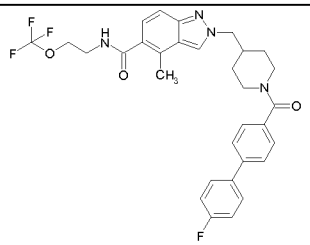
Example 107b: Tert-butyl 4-[(4-methyl-5-{N-[2-(trifluoromethoxy)ethyl]carbamoyl}-2H-indazol-2-yl)methyl]piperidin-1-carboxylate

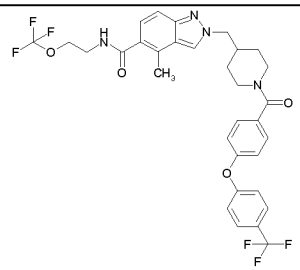


500 mg of 1d was reacted with 293 mg of amine analogously to 1b version B. Yield: 748 mg of the title compound.

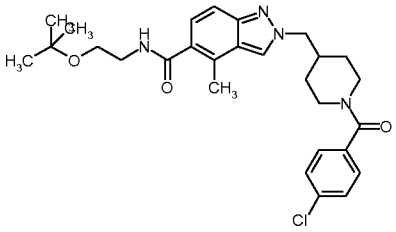
^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.07 (2H), 1.34 (9H), 1.37 (2H), 2.12 (1H), 2.50 (3H), 2.63 (1H), 3.52 (2H), 3.87 (2H), 4.17 (2H), 4.29 (2H), 7.16 (2H), 7.41 (1H), 8.37 (1H), 8.48 (1H).

The following compounds were prepared analogously:

Ex.	Structure	IUPAC name	Analysis
108		2-({1-[4-(4-fluoro-phenoxy)benzoyl]-piperidin-4-yl}methyl)-4-methyl-N-[2-(tri-fluoromethoxy)ethyl]-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.19 (2H), 1.46 (2H), 2.26 (1H), 2.49 (3H), 2.87 (2H), 3.51 (3H), 4.17 (2H), 4.33 (3H), 6.95 (2H), 7.16 (5H), 7.38 (3H), 8.36 (1H), 8.49 (1H).
109		2-({1-[(4'-fluoro-biphenyl-4-yl)-carbonyl]piperidin-4-yl}-methyl)-4-methyl-N-[2-(trifluoro-methoxy)ethyl]-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.23 (2H), 1.47 (2H), 2.28 (1H), 2.50 (3H), 2.74 (1H), 2.99 (1H), 3.51 (2H), 3.61 (1H), 4.17 (2H), 4.34 (3H), 7.16 (1H), 7.27 (2H), 7.40 (3H), 7.68 (4H), 8.37 (1H), 8.50 (1H).

110		4-methyl-N-[2-(trifluoromethoxy)ethyl]-2-[(1-{4-[4-(trifluoromethyl)phenoxy]-benzoyl}piperidin-4-yl)-methyl]-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.21 (2H), 1.46 (2H), 2.27 (1H), 2.50 (3H), 2.76 (1H), 2.98 (1H), 3.51 (2H), 3.61 (1H), 4.17 (2H), 4.33 (2H), 4.43 (1H), 7.14 (5H), 7.41 (3H), 7.73 (2H), 8.37 (1H), 8.49 (1H).

Example 111: N-(2-tert-butoxyethyl)-2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methyl-2H-indazol-5-carboxamide

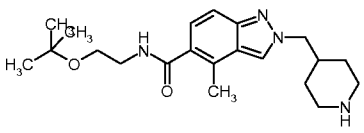


Analogously to Example 1, 8 mg of the title compound was obtained from 75 mg of the amine prepared in Example 111a and 28 mg of 4-chlorobenzoic acid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.12 (9H), 1.21 (2H), 1.36 (1H), 1.53 (1H), 2.27 (1H), 2.50 (3H), 2.72 (1H), 2.97 (1H), 3.29 (2H), 3.43 (3H), 4.31 (2H), 4.40 (1H), 7.14 (1H), 7.36 (3H), 7.46 (2H), 8.04 (1H), 8.46 (1H).

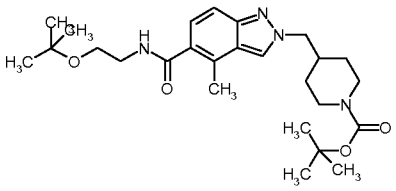
The starting material was prepared as follows:

Example 111a: N-(2-tert-butoxyethyl)-4-methyl-2-(4-piperidylmethyl)-2H-indazol-5-carboxamide



To 743 mg of 111b were added 3.5 ml of 4M hydrochloric acid in dioxan and 0.5 ml dioxan. The mixture was stirred for 30 mins at ca. 30°C. The reaction mixture was concentrated, taken up in some toluene and again concentrated. Yield: 677 mg of the title compound in a mixture with N-(2-hydroxyethyl)-4-methyl-2-(4-piperidylmethyl)-2H-indazol-5-carboxamide, which was further reacted without further purification.

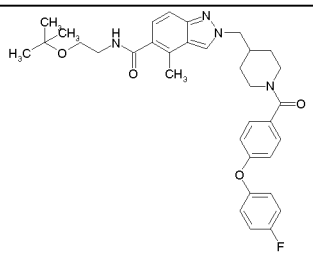
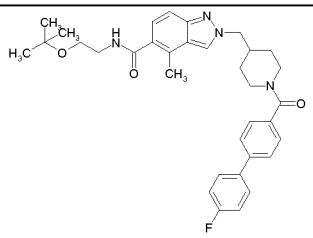
Example 111b: Tert-butyl 4-({5-[N-(2-tert-butoxyethyl)carbamoyl]-4-methyl-2H-indazol-2-yl}methyl)piperidin-1-carboxylate

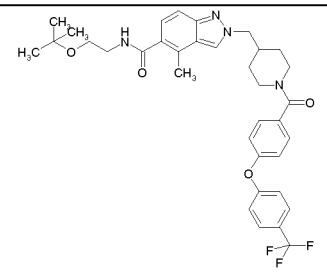


500 mg of 1d was reacted with 206 mg of amine analogously to 1b version B. Yield: 743 mg of the title compound.

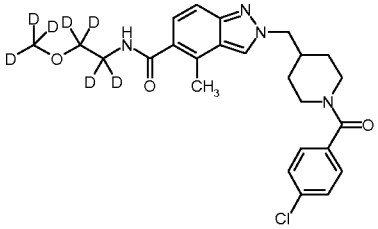
^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 1.06 (2H), 1.11 (9H), 1.34 (9H), 1.39 (2H), 2.13 (1H), 2.50 (3H), 2.65 (2H), 3.27 (2H), 3.40 (2H), 3.87 (2H), 4.28 (2H), 7.14 (1H), 7.38 (1H), 8.05 (1H), 8.46 (1H).

The following compounds were prepared analogously:

Ex.	Structure	IUPAC name	Analysis
112		N-(2-tert-butoxyethyl)-2-({1-[4-(4-fluoro-phenoxy)benzoyl]-piperidin-4-yl}methyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.12 (9H), 1.20 (2H), 1.44 (2H), 2.26 (1H), 2.50 (3H), 2.76 (1H), 2.93 (1H), 3.30 (2H), 3.40 (2H), 3.57 (1H), 4.31 (2H), 4.39 (1H), 6.95 (2H), 7.12 (3H), 7.23 (2H), 7.36 (3H), 8.04 (1H), 8.46 (1H).
113		N-(2-tert-butoxyethyl)-2-({1-[(4'-fluoro-biphenyl-4-yl)-carbonyl]piperidin-4-yl}methyl)-4-methyl-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.11 (9H), 1.23 (2H), 1.40 (1H), 1.54 (1H), 2.29 (1H), 2.50 (3H), 2.75 (1H), 3.00 (1H), 3.29 (2H), 3.40 (2H), 3.65 (1H), 4.32 (2H), 4.43 (1H), 7.15 (1H), 7.28 (2H), 7.40 (3H), 7.69 (4H), 8.05 (1H), 8.47 (1H).

114		N-(2-tert-butoxyethyl)-4-methyl-2-[(1-{4-[4-(trifluoromethyl)-phenoxy]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.12 (9H), 1.21 (2H), 1.40 (1H), 1.52 (1H), 2.27 (1H), 2.50 (3H), 2.75 (1H), 2.99 (1H), 3.28 (2H), 3.40 (2H), 3.60 (1H), 4.32 (2H), 4.40 (1H), 7.15 (5H), 7.40 (3H), 7.73 (2H), 8.04 (1H), 8.47 (1H).

Example 115: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-(2-[^{2}H$_3$]methoxy[^{2}H$_4$]ethyl)-4-methyl-2H-indazol-5-carboxamide

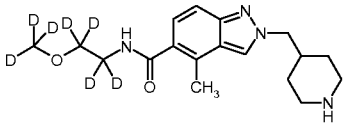


Analogously to Example 1, 1 mg of the title compound was obtained from 54 mg of the amine prepared in Example 115a and 22 mg of 4-chlorobenzoic acid.

^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 1.20 (2H), 1.40 (1H), 1.51 (1H), 2.27 (1H), 2.49 (3H), 2.75 (1H), 2.96 (1H), 3.50 (1H), 4.31 (2H), 4.40 (1H), 7.15 (1H), 7.36 (3H), 7.47 (2H), 8.07 (1H), 8.46 (1H).

The starting material was prepared as follows:

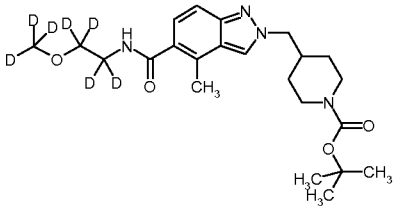
Example 115a: 4-methyl-N-(2-[^{2}H$_3$]methyloxy[^{2}H$_4$]ethyl)-2-(4-piperidylmethyl)-2H-indazol-5-carboxamide



To 131 mg of 115b were added 0.7 ml of 4M hydrochloric acid in dioxan and 0.5 ml dioxan. The mixture was stirred for 30 mins at ca. 30°C. The reaction mixture was concentrated, taken up in some toluene and again concentrated. Yield: 108 mg of the title compound, which was further reacted without further purification.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.42 (2H), 1.58 (2H), 2.26 (1H), 2.49 (3H), 2.78 (2H), 3.19 (2H), 4.33 (2H), 5.55 (1H), 7.16 (1H), 7.38 (1H), 8.12 (1H), 8.53 (1H), 8.70 (1H), 8.97 (1H).

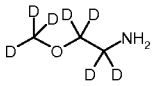
Example 115b: Tert-butyl 4-({4-methyl-5-[N-(2-[$^2H_3$]methyloxy[$^2H_4$]ethyl)carbamoyl]-2H-indazol-2-yl}methyl)piperidin-1-carboxylate



500 mg of 1d was reacted analogously to 1b version B with 110 mg of amine prepared in 115c. Yield: 131 mg of the title compound.

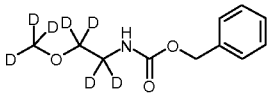
^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.07 (2H), 1.34 (9H), 1.37 (2H), 2.13 (1H), 2.49 (3H), 2.62 (2H), 3.88 (2H), 4.28 (2H), 7.15 (1H), 7.38 (1H), 8.07 (1H), 8.46 (1H).

Example 115c: 2-[$^2H_3$]methyloxy[$^2H_4$]ethan-1-amine



110 mg of (0.51 mmol) of 115d was first placed in 2.2 ml toluene. After addition of 11 mg of palladium/charcoal (10%) and hydrogen under normal pressure, the mixture was stirred for 50 mins at room temperature. The reaction mixture was filtered through Celite and rewashed with toluene. The colourless filtrate was used as solution in the subsequent reaction.

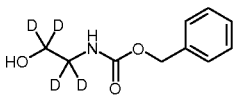
Example 115d: Benzyl *N*-(2-[$^2H_3$]methyloxy[$^2H_4$]ethyl)carbamate



1.32 g (6.6 mmol) of 115e) was dissolved in 23 ml acetonitrile. 2.3 g (9.9 mmol) of silver oxide and 1.64 ml (3.8 g, 26 mmol) of deuterated iodomethane were then added. The reaction mixture was stirred for 1.5 hrs at 40°C, 7.5 hrs at 72°C and then overnight at room temperature. A further 2.3 g (9.9 mmol) of silver oxide was added and the mixture stirred for 1.5 hrs at 72°C. For the work-up, the black solid was filtered off at the pump and the clear filtrate concentrated. The residue was purified by column chromatography (hexane/ethyl acetate 0-10%). Yield: 1.13 g of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 4.97 (2H), 7.31 (5H).

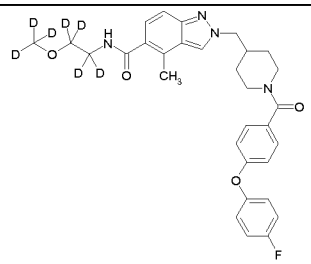
Example 115e: Benzyl *N*-(2-hydroxy[$^2H_4$]ethyl)carbamate



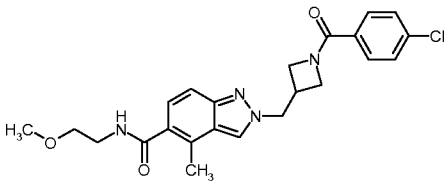
1.0 g (15 mmol) of deuterated aminoethanol was first dissolved in 29 ml dichloromethane. Then 2.5 ml (1.8 g, 18mmol) of triethylamine was added and the reaction mixture cooled to 0°C. At this temperature 2.75 ml (3.34 g, 19.6 mmol) of benzyl chloroformate was now cautiously added dropwise. After completion of the addition, the mixture was stirred for 1 hr more with no ice-bath and in the process warmed up to RT. The reaction mixture was diluted once with some dichloromethane and washed once with saturated sodium chloride solution. The organic phase was dried over sodium sulphate, filtered and concentrated. The crude product was purified twice by column chromatography (dichloromethane/methanol 0-10% and ethyl acetate). Yield: 1.32 g of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 4.54 (1H), 4.97 (2H), 7.12 (1H), 7.81 (5H).

The following compound was prepared analogously:

Ex.	Structure	IUPAC name	Analysis
116		2-({1-[4-(4-fluoro-phenoxy)benzoyl]-piperidin-4-yl}methyl)-4-methyl-N-(2-[$^2H_3$]-methyloxy[$^2H_4$]ethyl)-2H-indazol-5-carboxamide	^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.19 (2H), 1.46 (2H), 2.25 (1H), 2.49 (3H), 2.85 (2H), 3.66 (1H), 4.31 (2H), 4.38 (1H), 6.95 (2H), 7.16 (5H), 7.36 (3H), 8.07 (1H), 8.46 (1H).

Example 117: 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

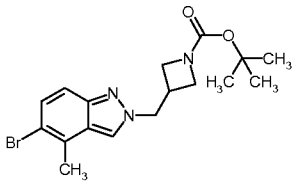


Analogously to Example 55, 471 mg of the title compound was obtained from 500 mg of the compound prepared in Example 117e) and 287 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.49 (3H), 3.22 (1H), 3.25 (3H), 3.32-3.46 (4H), 3.89 (1H), 4.09 (1H), 4.19 (1H), 4.37 (1H), 4.67 (2H), 7.15 (1H), 7.38 (1H), 7.48 (2H), 7.59 (2H), 8.12 (1H), 8.54 (1H).

The starting material was prepared as follows:

Example 117a: Tert-butyl 3-[(5-bromo-4-methyl-2H-indazol-2-yl)methyl]-azetidin-1-carboxylate

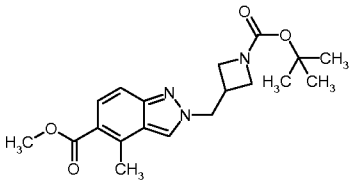


To a solution of 21.1 g of 5-bromo-4-methyl-1H-indazole and 37.6 g of tert-butyl-3-[(tosyloxy)-methyl]azetidin-1-carboxylate in 100 ml dioxan were added 150 ml of a 1M solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran at 25°C and this was stirred for 6 hrs at 90°C. After cooling, the reaction mixture was treated with ethyl acetate and water, the organic phases separated and the aqueous phase extracted twice with 100 ml portions of ethyl acetate. The combined organic phases were washed with saturated sodium chloride solution, dried over sodium sulphate, and concentrated in vacuo after filtration.

The residue thus obtained was purified by chromatography on the Flashmaster (hexane/ethyl acetate 1:0-0:1). 15.0 g of the title compound was obtained.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.32 (9H), 2.48 (3H), 3.07 (1H), 3.69 (2H), 3.87 (2H), 4.59 (2H), 7.28 (1H), 7.35 (1H), 8.53 (1H).

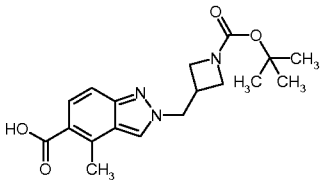
Example 117b: Methyl 2-{[1-(tert-butoxycarbonyl)azetidin-3-yl]methyl}-4-methyl-2H-indazol-5-carboxylate



To a solution of 8.16 g of the bromide prepared in Example 117a in 65.4 ml methanol, 6.5 g of 1,1 bis(diphenylphosphino)ferrocen-palladium(II) dichloride and 15 g of potassium acetate were added at 25°C and the mixture was stirred under CO at 10.15 bar and 120°C for 24 hours in an autoclave. The reaction mixture was then cooled, filtered through Celite at the pump and the filtrate concentrated in vacuo. The residue thus obtained was purified by chromatography on the Flashmaster (hexane/ethyl acetate 1:0-0:1). 6.97g of the title compound was obtained.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.32 (9H), 2.73 (3H), 3.09 (1H), 3.71 (2H), 3.79 (3H), 3.87 (2H), 4.62 (2H), 7.42 (1H), 7.63 (1H), 8.74 (1H).

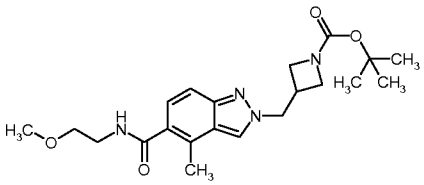
Example 117c: 2-{[1-(tert-butoxycarbonyl)azetidin-3-yl]methyl}-4-methyl-2H-indazol-5-carboxylic acid



Analogously to Example 1d, 5.2 g of the title compound was obtained from 15.1 g of the ester prepared in Example 117b.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.32 (9H), 2.73 (3H), 3.09 (1H), 3.71 (2H), 3.87 (2H), 4.61 (2H), 7.39 (1H), 7.64 (1H), 8.70 (1H), 12.57 (1H).

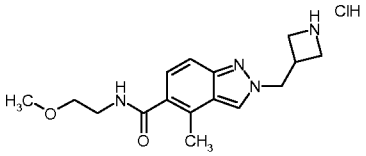
Example 117d: Tert-butyl 3-({5-[N-(2-methoxyethyl)carbamoyl]-4-methyl-2H-indazol-2-yl}-methyl)azetidin-1-carboxylate



Analogously to Example 1, from 2.5 g of the acid prepared in Example 117c and 0.54 g of 2-methoxyethylamine, a crude product was obtained which through purification with a Biotage unit (ethyl acetate : 0 to 30% methanol) yielded 2.69 g of the title compound.

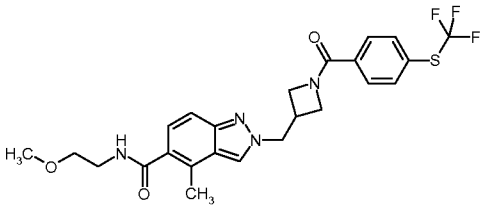
^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.32 (9H), 2.49 (3H), 3.08 (1H), 3.25 (3H), 3.32-3.46 (4H), 3.70 (2H), 3.86 (2H), 4.60 (2H), 7.15 (1H), 7.38 (1H), 8.11 (1H), 8.54 (1H).

Example 117e: 2-(azetidin-3-ylmethyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 2.69 g of the amide prepared in Example 117d, 2.59 g of the title compound was obtained, which was reacted without further purification.

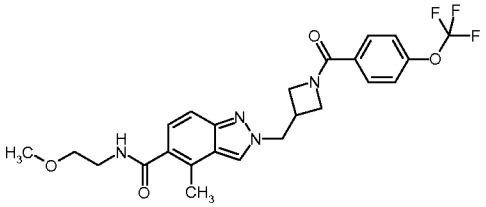
Example 118: N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[(trifluoromethyl)sulphanyl]benzoyl}azetidin-3-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 55, 29 mg of the title compound was obtained from 55 mg of the compound prepared in Example 117e and 43 mg of 4-[(trifluoromethyl)sulphanyl]benzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.49 (3H), 3.22 (1H), 3.25 (3H), 3.36 (2H), 3.42 (2H), 3.92 (1H), 4.11 (1H), 4.20 (1H), 4.39 (1H), 4.67 (2H), 7.15 (1H), 7.38 (1H), 7.69 (2H), 7.76 (2H), 8.12 (1H), 8.54 (1H).

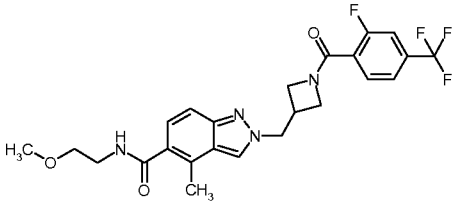
Example 119: N-(2-methoxyethyl)-4-methyl-2-({1-[4-(trifluoromethoxy)benzoyl]azetidin-3-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 55, 27 mg of the title compound was obtained from 55 mg of the compound prepared in Example 117e and 40 mg of 4-(trifluoromethoxy)benzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.49 (3H), 3.20 (1H), 3.24 (3H), 3.32-3.46 (4H), 3.91 (1H), 4.10 (1H), 4.20 (1H), 4.39 (1H), 4.67 (2H), 7.15 (1H), 7.35-7.44 (3H), 7.70 (2H), 8.12 (1H), 8.54 (1H).

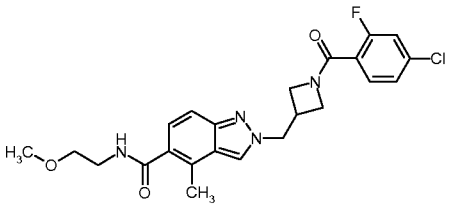
Example 120: 2-({1-[2-fluoro-4-(trifluoromethyl)benzoyl]azetidin-3-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 55, 17 mg of the title compound was obtained from 55 mg of the compound prepared in Example 117e and 41 mg of 2-fluoro-4-(trifluoromethyl)benzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.48 (3H), 3.23 (1H), 3.25 (3H), 3.36 (2H), 3.42 (2H), 3.94 (2H), 4.11 (2H), 4.66 (2H), 7.15 (1H), 7.38 (1H), 7.64 (2H), 7.79 (1H), 8.12 (1H), 8.54 (1H).

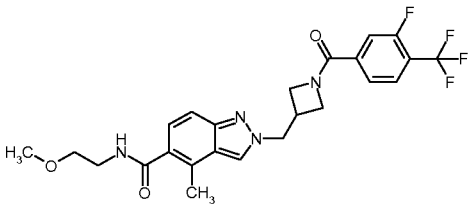
Example 121: 2-{[1-(4-chloro-2-fluorobenzoyl)azetidin-3-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 55, 19 mg of the title compound was obtained from 42 mg of the compound prepared in Example 117e and 26 mg of 4-chloro-2-fluorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.48 (3H), 3.21 (1H), 3.24 (3H), 3.33-3.46 (4H), 3.86-3.97 (2H), 4.08 (2H), 4.65 (2H), 7.15 (1H), 7.34 (1H), 7.37 (1H), 7.44 (1H), 7.52 (1H), 8.12 (1H), 8.53 (1H).

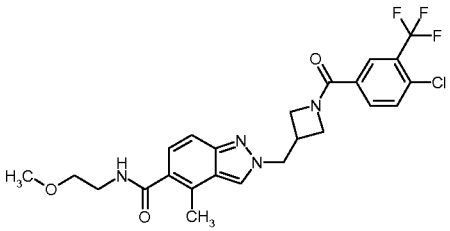
Example 122: 2-({1-[3-fluoro-4-(trifluoromethyl)benzoyl]azetidin-3-yl}methyl)-N-(2-methoxy-ethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 55, 15 mg of the title compound was obtained from 42 mg of the compound prepared in Example 117e and 31 mg of 3-fluoro-4-(trifluoromethyl)benzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.49 (3H), 3.21 (1H), 3.25 (3H), 3.36 (2H), 3.42 (2H), 3.93 (1H), 4.12 (1H), 4.22 (1H), 4.40 (1H), 4.67 (2H), 7.15 (1H), 7.37 (1H), 7.57 (1H), 7.64 (1H), 7.85 (1H), 8.12 (1H), 8.54 (1H).

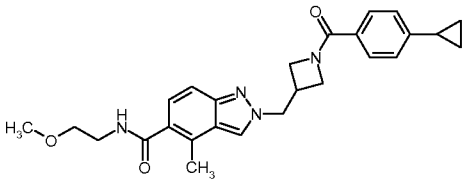
Example 123: 2-({1-[4-chloro-3-(trifluoromethyl)benzoyl]azetidin-3-yl}methyl)-N-(2-methoxy-ethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 55, 6 mg of the title compound was obtained from 42 mg of the compound prepared in Example 117e and 33 mg of 4-chloro-3-(trifluoromethyl)benzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.49 (3H), 3.21 (1H), 3.25 (3H), 3.31-3.46 (4H), 3.92 (1H), 4.11 (1H), 4.22 (1H), 4.41 (1H), 4.67 (2H), 7.15 (1H), 7.37 (1H), 7.79 (1H), 7.86 (1H), 7.94 (1H), 8.12 (1H), 8.53 (1H).

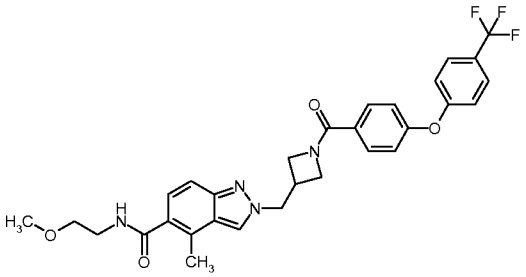
Example 124: 2-{[1-(4-cyclopropylbenzoyl)azetidin-3-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 76 mg of the title compound was obtained from 163 mg of the compound prepared in Example 117e and 78 mg of 4-cyclopropylbenzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.71 (2H), 0.99 (2H), 1.95 (1H), 2.52 (3H), 3.24 (1H), 3.34-3.41 (5H), 3.45 (2H), 3.90 (1H), 4.09 (1H), 4.20 (1H), 4.38 (1H), 4.68 (2H), 7.12 (2H), 7.18 (1H), 7.41 (1H), 7.48 (2H), 8.12 (1H), 8.57 (1H).

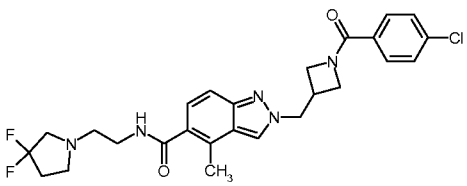
Example 125: N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}azetidin-3-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 1, 478 mg of the title compound was obtained from 1.20 g of the compound prepared in Example 117e and 850 mg of 4-[4-(trifluoromethyl)phenoxy]benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.52 (3H), 3.25 (1H), 3.27 (3H), 3.39 (2H), 3.45 (2H), 3.94 (1H), 4.12 (1H), 4.24 (1H), 4.42 (1H), 4.70 (2H), 7.14 (2H), 7.18 (1H), 7.22 (2H), 7.41 (1H), 7.69 (2H), 7.77 (2H), 8.12 (1H), 8.57 (1H).

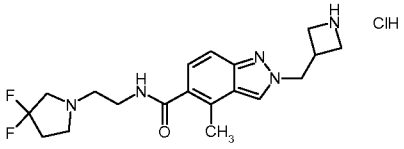
Example 126: 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-N-[2-(3,3-difluoropyrrolidin-1-yl)ethyl]-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 55, 38 mg of the title compound was obtained from 43 mg of the compound prepared in Example 126a and 20 mg of 4-chlorobenzoyl chloride.

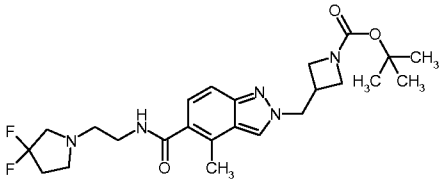
^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.10-2.27 (3H), 2.49 (3H), 2.57 (2H), 2.72 (2H), 2.91 (2H), 3.17-3.36 (2H), 3.89 (1H), 4.08 (1H), 4.19 (1H), 4.36 (1H), 4.67 (2H), 7.14 (1H), 7.38 (1H), 7.48 (2H), 7.59 (2H), 8.05 (1H), 8.54 (1H).

Example 126a: 2-(azetidin-3-ylmethyl)-N-[2-(3,3-difluoropyrrolidin-1-yl)ethyl]-4-methyl-2H-indazol-5-carboxamide hydrochloride



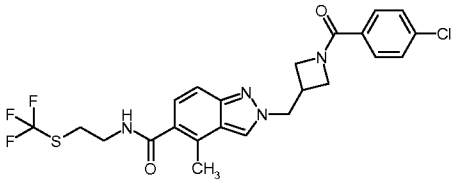
Analogously to Example 1a, from 50 mg of the compound prepared in Example 126b, 43 mg of the title compound was obtained, which was reacted without further purification.

Example 126b: Tert-butyl 3-[(5-{N-[2-(3,3-difluoropyrrolidin-1-yl)ethyl]carbamoyl}-4-methyl-2H-indazol-2-yl)methyl]azetidin-1-carboxylate



Analogously to Example 1b, 71 mg of the title compound was obtained from 70 mg of the compound prepared in Example 117a and 83 mg of 2-(3,3-difluoropyrrolidin-1-yl)ethylamine.
^{1}H-NMR (300 MHz, DMSO-d6): 1.32 (9H), 2.10-2.28 (2H), 2.50 (3H), 2.57 (2H), 2.66-2.77 (2H), 2.84-2.98 (2H), 3.08 (1H), 3.23-3.36 (2H), 3.69 (2H), 3.86 (2H), 4.60 (2H), 7.14 (1H), 7.39 (1H), 8.05 (1H), 8.55 (1H).

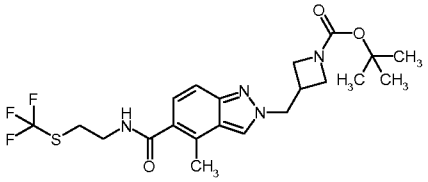
Example 127: 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-4-methyl-N-{2-[(trifluoromethyl) sulphanyl]ethyl}-2H-indazol-5-carboxamide



Analogously to Example 55, 143 mg of the title compound was obtained from 130 mg of the compound prepared in Example 127b and 61 mg of 4-chlorobenzoyl chloride.
^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.51 (3H), 3.13-3.29 (3H), 3.50 (2H), 3.90 (1H), 4.09 (1H), 4.19 (1H), 4.37 (1H), 4.67 (2H), 7.19 (1H), 7.40 (1H), 7.48 (2H), 7.59 (2H), 8.38 (1H), 8.57 (1H).

The starting material was prepared as follows:

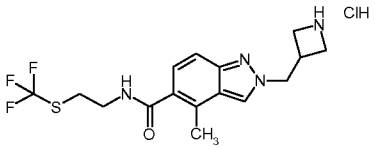
Example 127a: Tert-butyl 3-{[4-methyl-5-(N-{2-[(trifluoromethyl)sulphanyl]ethyl}carbamoyl)-indazol-2-yl]methyl}azetidin-1-carboxylate



Analogously to Example 1, 674 mg of the title compound was obtained from 500 mg of the compound prepared in Example 117c.

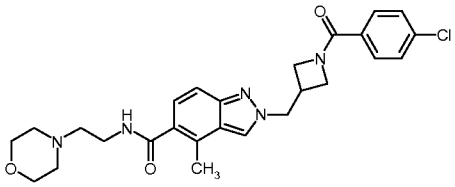
^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.32 (9H), 2.52 (3H), 3.08 (1H), 3.17 (2H), 3.50 (2H), 3.69 (2H), 3.86 (2H), 4.61 (2H), 7.19 (1H), 7.41 (1H), 8.38 (1H), 8.57 (1H).

Example 127b: 2-(azetidin-3-ylmethyl)-4-methyl-N-{2-[(trifluoromethyl)sulphanyl]ethyl}-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 150 mg of the compound prepared in Example 127a, 130 mg of the title compound was obtained, which was further reacted without purification.

Example 128: 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-4-methyl-N-(2-morpholinoethyl)-2H-indazol-5-carboxamide

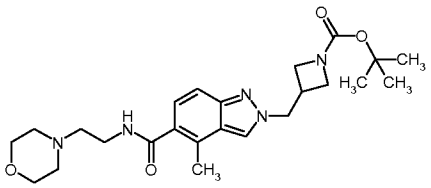


Analogously to Example 55, 30 mg of the title compound was obtained from 50 mg of the compound prepared in Example 128b and 24 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.34-2.45 (6H), 2.51 (3H), 3.22 (1H), 3.33 (2H), 3.54 (4H), 3.89 (1H), 4.08 (1H), 4.19 (1H), 4.36 (1H), 4.67 (2H), 7.15 (1H), 7.38 (1H), 7.48 (2H), 7.59 (2H), 7.99 (1H), 8.54 (1H).

The starting material was prepared as follows:

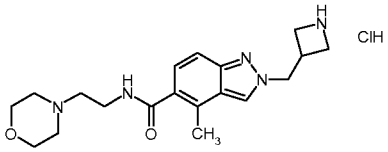
Example 128a: Tert-butyl 3-({4-methyl-5-[N-(2-morpholinoethyl)carbamoyl]-2H-indazol-2-yl}methyl)azetidin-1-carboxylate



Analogously to Example 1b, 59 mg of the title compound was obtained from 200 mg of the compound prepared in Example 117a and 205 mg of 2-morpholinoethylamine.

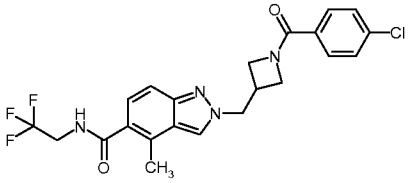
^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.32 (9H), 2.34-2.44 (6H), 2.52 (3H), 3.08 (1H), 3.33 (2H), 3.54 (4H), 3.69 (2H), 3.86 (2H), 4.61 (2H), 7.15 (1H), 7.39 (1H), 7.98 (1H), 8.55 (1H).

Example 128b: 2-(azetidin-3-ylmethyl)-4-methyl-N-(2-morpholinoethyl)-2H-indazole-5-carboxamide hydrochloride



Analogously to Example 1a, from 59 mg of the compound prepared in Example 128a, 63 mg of the title compound was obtained, which was further reacted without purification.

Example 129: 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide

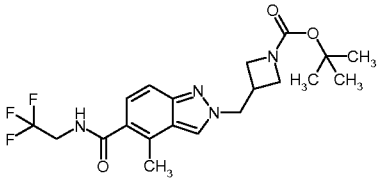


Analogously to Example 55, 127 mg of the title compound was obtained from 128 mg of the compound prepared in Example 129b and 68 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.50 (3H), 3.22 (1H), 3.90 (1H), 3.96-4.13 (3H), 4.19 (1H), 4.37 (1H), 4.68 (2H), 7.18 (1H), 7.42 (1H), 7.48 (2H), 7.59 (2H), 8.59 (1H), 8.79 (1H).

The starting material was prepared as follows:

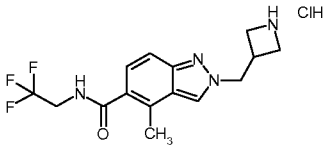
Example 129a: Tert-butyl 3-({4-methyl-5-[N-(2,2,2-trifluoroethyl)carbamoyl]-2H-indazol-2-yl}methyl)azetidin-1-carboxylate



Analogously to Example 1, 1.02 g of the title compound was obtained from 1.0 g of the compound prepared in Example 117c and 287 mg of 2,2,2-trifluoroethylamine.

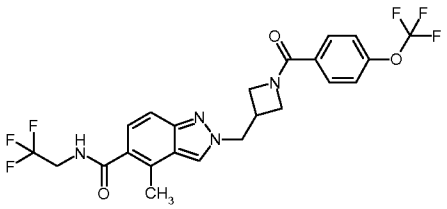
^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.32 (9H), 2.51 (3H), 3.09 (1H), 3.70 (2H), 3.86 (2H), 4.03 (2H), 4.62 (2H), 7.17 (1H), 7.43 (1H), 8.60 (1H), 8.79 (1H).

Example 129b: 2-(azetidin-3-ylmethyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 1.0 g of the compound prepared in Example 129a, 852 mg of the title compound was obtained, which was further reacted without purification.

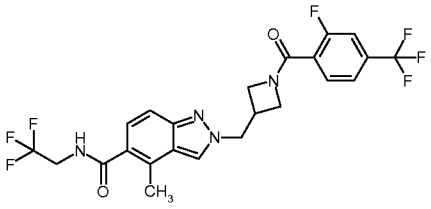
Example 130: 4-methyl-N-(2,2,2-trifluoroethyl)-2-({1-[4-(trifluoromethoxy)benzoyl]azetidin-3-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 55, 113 mg of the title compound was obtained from 128 mg of the compound prepared in Example 129b and 87 mg of 4-(trifluoromethoxy)benzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.50 (3H), 3.23 (1H), 3.92 (1H), 3.96-4.14 (3H), 4.20 (1H), 4.39 (1H), 4.68 (2H), 7.18 (1H), 7.36-7.46 (3H), 7.70 (2H), 8.59 (1H), 8.79 (1H).

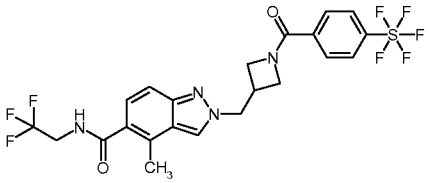
Example 131: 2-({1-[2-fluoro-4-(trifluoromethyl)benzoyl]azetidin-3-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 55, 128 mg of the title compound was obtained from 128 mg of the compound prepared in Example 129b and 88 mg of 2-fluoro-4-(trifluoromethyl)benzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.49 (3H), 3.23 (1H), 3.89-4.16 (6H), 4.67 (2H), 7.17 (1H), 7.42 (1H), 7.60-7.67 (2H), 7.79 (1H), 8.58 (1H), 8.80 (1H).

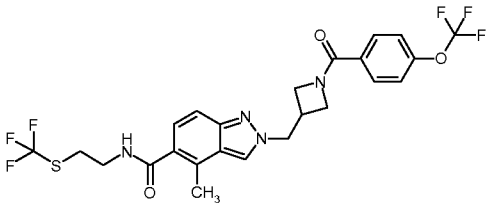
Example 132: 4-methyl-2-({1-[4-(pentafluoro-λ^6-sulphanyl)benzoyl]azetidin-3-yl}methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 121 mg of the title compound was obtained from 128 mg of the compound prepared in Example 129b and 96 mg of 4-(pentafluoro-λ^6-sufanyl)benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.50 (3H), 3.24 (1H), 3.94 (1H), 3.98-4.08 (2H), 4.12 (1H), 4.20 (1H), 4.39 (1H), 4.69 (2H), 7.18 (1H), 7.42 (1H), 7.76 (2H), 7.95 (2H), 8.59 (1H), 8.80 (1H).

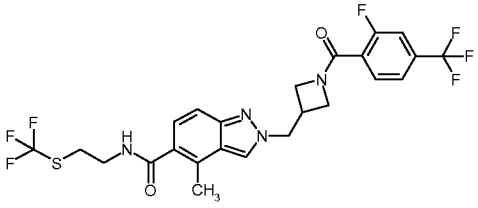
Example 133: 4-methyl-2-({1-[4-(trifluoromethoxy)benzoyl]azetidin-3-yl}methyl)-N-{2-[(trifluoromethyl)sulphanyl]ethyl}-2H-indazol-5-carboxamide



Analogously to Example 55, 178 mg of the title compound was obtained from 130 mg of the compound prepared in Example 127b and 78 mg of 4-(trifluoromethoxy)benzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.51 (3H), 3.13-3.28 (3H), 3.51 (2H), 3.91 (1H), 4.10 (1H), 4.20 (1H), 4.39 (1H), 4.67 (2H), 7.19 (1H), 7.40 (3H), 7.70 (2H), 8.38 (1H), 8.57 (1H).

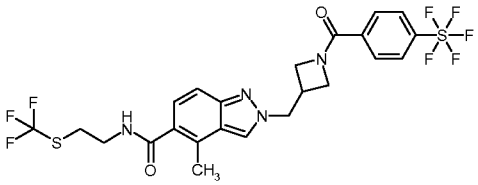
Example 134: 2-({1-[2-fluoro-4-(trifluoromethyl)benzoyl]azetidin-3-yl}methyl)-4-methyl-N-{2-[(trifluoromethyl)sulphanyl]ethyl}-2H-indazol-5-carboxamide



Analogously to Example 55, 128 mg of the title compound was obtained from 130 mg of the compound prepared in Example 127b and 79 mg of 2-fluoro-4-(trifluoromethyl)benzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.51 (3H), 3.12-3.25 (3H), 3.50 (2H), 3.89-3.98 (2H), 4.06-4.16 (2H), 4.67 (2H), 7.19 (1H), 7.40 (1H), 7.64 (2H), 7.79 (1H), 8.39 (1H), 8.56 (1H).

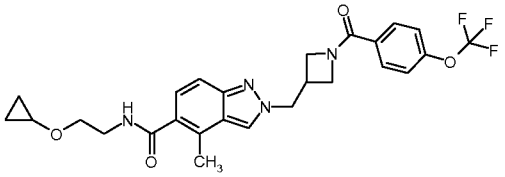
Example 135: 4-methyl-2-({1-[4-(pentafluoro-λ^6-sulphanyl)benzoyl]azetidin-3-yl}methyl)-N-{2-[(trifluoromethyl)sulphanyl]ethyl}-2H-indazol-5-carboxamide



Analogously to Example 1, 84 mg of the title compound was obtained from 130 mg of the compound prepared in Example 127b and 87 mg of 4-(pentafluoro-λ^6-sulphanyl)benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.51 (3H), 3.18 (2H), 3.23 (1H), 3.51 (2H), 3.94 (1H), 4.12 (1H), 4.20 (1H), 4.39 (1H), 4.68 (2H), 7.19 (1H), 7.41 (1H), 7.76 (2H), 7.95 (2H), 8.39 (1H), 8.56 (1H).

Example 136: N-[2-(cyclopropyloxy)ethyl]-4-methyl-2-({1-[4-(trifluoromethoxy)benzoyl]azetidin-3-yl}methyl)-2H-indazol-5-carboxamide

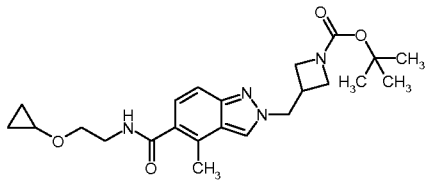


Analogously to Example 55, 172 mg of the title compound was obtained from 161 mg of the compound prepared in Example 136b and 109 mg of 4-(trifluoromethoxy)benzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.36-0.48 (4H), 2.48 (3H), 3.22 (1H), 3.27 (1H), 3.35 (2H), 3.53 (2H), 3.91 (1H), 4.10 (1H), 4.20 (1H), 4.39 (1H), 4.67 (2H), 7.14 (1H), 7.35-7.44 (3H), 7.71 (2H), 8.11 (1H), 8.54 (1H).

The starting material was prepared as follows:

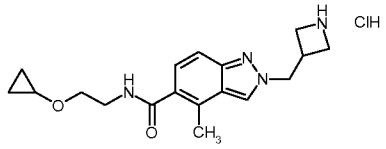
Example 136a: Tert-butyl 3-[(5-{N-[2-(cyclopropyloxy)ethyl]carbamoyl}-4-methyl-2H-indazol-2-yl)methyl]azetidin-1-carboxylate



Analogously to Example 1, 189 mg of the title compound was obtained from 150 mg of the compound prepared in Example 118c and 140 mg of 2-cyclopropoxy-ethylammonium trifluoroacetate (preparable according to Example 154a) and 154b) starting from cyclopropanol and bromoacetamide followed by Boc cleavage with trifluoroacetic acid analogously to Example 1a)).

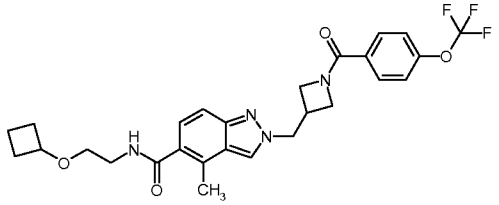
^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.36-0.48 (4H), 1.33 (9H), 2.49 (3H), 3.08 (1H), 3.25-3.39 (3H), 3.53 (2H), 3.70 (2H), 3.87 (2H), 4.61 (2H), 7.14 (1H), 7.38 (1H), 8.10 (1H), 8.54 (1H).

Example 136b: 2-(azetidin-3-ylmethyl)-N-[(2-cyclopropyloxy)ethyl]-4-methyl-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 189 mg of the compound prepared in Example 136a, 161 mg of the title compound was obtained, which was further reacted without purification.

Example 137: N-[2-(cyclobutyloxy)ethyl]-4-methyl-2-({1-[4-(trifluoromethoxy)benzoyl] azetidin-3-yl}methyl)-2H-indazol-5-carboxamide

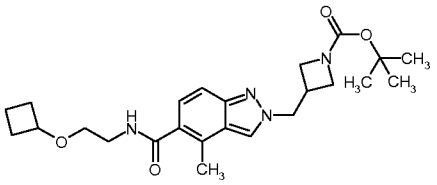


Analogously to Example 55, 207 mg of the title compound was obtained from 254 mg of the compound prepared in Example 137b and 166 mg of 4-(trifluoromethoxy)benzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.42 (1H), 1.59 (1H), 1.80 (2H), 2.11 (2H), 2.50 (3H), 3.17-3.28 (1H), 3.31-3.41 (4H), 3.85-3.95 (2H), 4.10 (1H), 4.20 (1H), 4.39 (1H), 4.67 (2H), 7.15 (1H), 7.35-7.44 (3H), 7.71 (2H), 8.11 (1H), 8.54 (1H).

The starting material was prepared as follows:

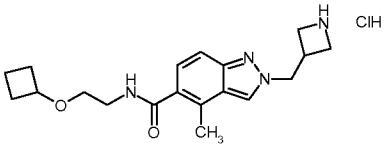
Example 137a: Tert-butyl 3-[(5-{N-[2-(cyclobutyloxy)ethyl]carbamoyl}-4-methyl-2H-indazol-2-yl)methyl]azetidin-1-carboxylate



Analogously to Example 1, 297 mg of the title compound was obtained from 220 mg of the compound prepared in Example 117c and 143 mg of 2-(cyclobutyloxy)ethylammonium trifluoroacetate (preparable according to Example 154a) and 154b) starting from cyclobutanol and bromoacetamide followed by Boc cleavage with trifluoroacetic acid analogously to Example 1a)).

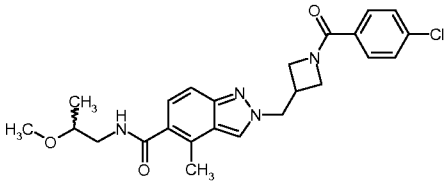
^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.33 (9H), 1.35-1.49 (1H), 1.59 (1H), 1.80 (2H), 2.11 (2H), 2.50 (3H), 3.08 (1H), 3.30-3.41 (4H), 3.69 (2H), 3.82-3.95 (3H), 4.61 (2H), 7.15 (1H), 7.38 (1H), 8.10 (1H), 8.54 (1H).

Example 137b: 2-(azetidin-3-ylmethyl)-N-[(2-(cyclobutyloxy)ethyl]-4-methyl-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 297 mg of the compound prepared in Example 137a, 254 mg of the title compound was obtained, which was further reacted without purification.

Example 138: (+/-)-2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-N-(2-methoxypropyl)-4-methyl-2H-indazol-5-carboxamide

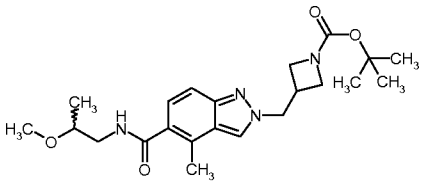


Analogously to Example 55, 166 mg of the title compound was obtained from 237 mg of the compound prepared in Example 138b and 129 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.07 (3H), 2.49 (3H), 3.14-3.28 (3H), 3.43 (1H), 3.89 (1H), 4.08 (1H), 4.19 (1H), 4.36 (1H), 4.67 (2H), 7.15 (1H), 7.38 (1H), 7.48 (2H), 7.59 (2H), 8.11 (1H), 8.54 (1H).

The starting material was prepared as follows:

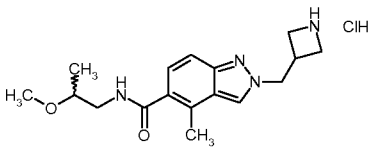
Example 138a: (+/-)-tert-butyl 3-({5-[N-(2-methoxypropyl)carbamoyl]-4-methyl-2H-indazol-2-yl}methyl)azetidin-1-carboxylate



Analogously to Example 1, 331 mg of the title compound was obtained from 323 mg of the compound prepared in Example 117c and 117 mg of 2-methoxypropylamine.

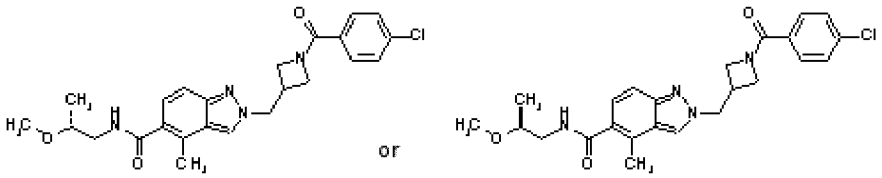
^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.08 (3H), 1.33 (9H), 2.50 (3H), 3.09 (1H), 3.16-3.31 (2H), 3.44 (1H), 3.69 (2H), 3.85 (2H), 4.61 (2H), 7.15 (1H), 7.39 (1H), 8.08 (1H), 8.54 (1H).

Example 138b: (+/-)-2-(azetidin-3-ylmethyl)-N-(2-methoxypropyl)-4-methyl-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 280 mg of the compound prepared in Example 138a, 247 mg of the title compound was obtained, which was further reacted without purification.

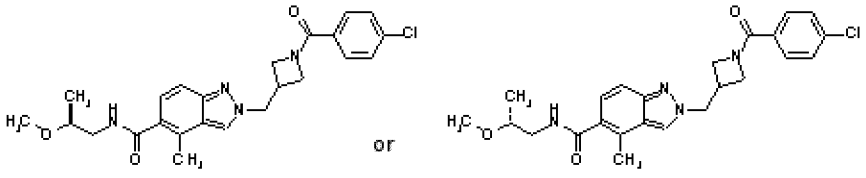
Example 139: (R or S)-2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-N-(2-methoxypropyl)-4-methyl-2H-indazol-5-carboxamide



From 158 mg of the racemate prepared in Example 138, 52 mg of the title compound together with 48 mg of the slower-eluting enantiomer (Example 140) were obtained by racemate separation by means of preparative chiral HPLC (Method A).

Analytical chiral HPLC: 14.5 min.

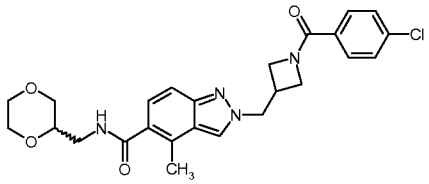
Example 140: (S or R)-2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-N-(2-methoxypropyl)-4-methyl-2H-indazol-5-carboxamide



From 158 mg of the racemate prepared in Example 138, 48 mg of the title compound together with 52 mg of the faster-eluting enantiomer (Example 139) were obtained by racemate separation by means of preparative chiral HPLC (Method A).

Analytical chiral HPLC: 17.1 min.

Example 141: (+/-)-2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-N-(1,4-dioxan-2-ylmethyl)-4-methyl-2H-indazol-5-carboxamide

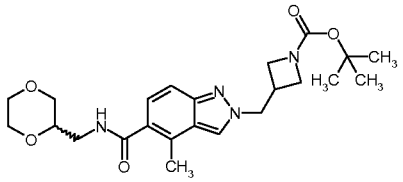


Analogously to Example 55, 177 mg of the title compound was obtained from 269 mg of the compound prepared in Example 141b and 136 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.49 (3H), 3.13-3.28 (4H), 3.38-3.66 (4H), 3.67-3.77 (2H), 3.89 (1H), 4.08 (1H), 4.19 (1H), 4.37 (1H), 4.67 (2H), 7.15 (1H), 7.38 (1H), 7.48 (2H), 7.59 (2H), 8.17 (1H), 8.55 (1H).

The starting material was prepared as follows:

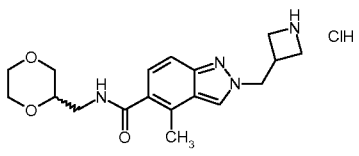
Example 141a: (+/-)-tert-butyl 3-({5-[N-(1,4-dioxan-2-ylmethyl)carbamoyl]-4-methyl-2H-indazol-2-yl}methyl)azetidin-1-carboxylate



Analogously to Example 1, 364 mg of the title compound was obtained from 323 mg of the compound prepared in Example 117c and 110 mg of 1,4-dioxan-2-ylmethylamine.

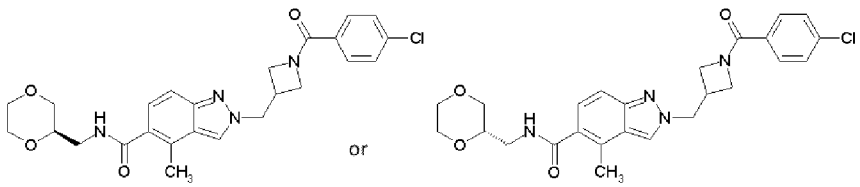
^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.33 (9H), 2.50 (3H), 3.09 (1H), 3.16-3.29 (3H), 3.40-3.77 (8H), 3.86 (2H), 4.61 (2H), 7.16 (1H), 7.39 (1H), 8.14 (1H), 8.55 (1H).

Example 141b: (+/-)-2-(azetidin-3-ylmethyl)-N-(1,4-dioxan-2-ylmethyl)-4-methyl-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 314 mg of the compound prepared in Example 141a, 274 mg of the title compound was obtained, which was further reacted without purification.

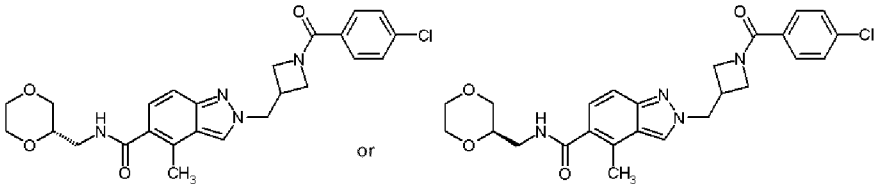
Example 142: (R or S)-2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-N-(1,4-dioxan-2-ylmethyl)-4-methyl-2H-indazol-5-carboxamide



From 172 mg of the racemate prepared in Example 141, 60 mg of the title compound together with 60 mg of the slower-eluting enantiomer (Example 143) were obtained by racemate separation by means of preparative chiral HPLC (Method B).

Analytical chiral HPLC: 5.84 min.

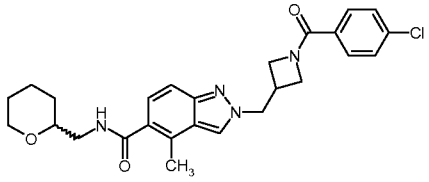
Example 143: (S or R)-2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-N-(1,4-dioxan-2-ylmethyl)-4-methyl-2H-indazol-5-carboxamide



From 172 mg of the racemate prepared in Example 141, 60 mg of the title compound together with 60 mg of the faster-eluting enantiomer (Example 142) were obtained by racemate separation by means of preparative chiral HPLC (Method B).

Analytical chiral HPLC: 6.28 min.

Example 144: (+/-)-2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-4-methyl-N-(3,4,5,6-tetrahydro-2H-pyran-2-ylmethyl)-2H-indazol-5-carboxamide

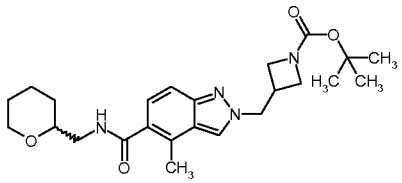


Analogously to Example 55, 144 mg of the title compound was obtained from 255 mg of the compound prepared in Example 144b and 130 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.10-1.23 (1H), 1.35-1.47 (3H), 1.61 (1H), 1.71-1.81 (1H), 2.48 (3H), 3.15-3.27 (4H), 3.37 (1H), 3.80-3.93 (2H), 4.08 (1H), 4.19 (1H), 4.36 (1H), 4.66 (2H), 7.14 (1H), 7.37 (1H), 7.48 (2H), 7.59 (2H), 8.09 (1H), 8.54 (1H).

The starting material was prepared as follows:

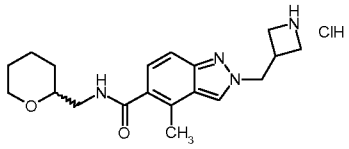
Example 144a: (+/-)-tert-butyl 3-({4-methyl-5-[N-(3,4,5,6-tetrahydro-2H-pyran-2-ylmethyl)-carbamoyl]-2H-indazol-2-yl}methyl)azetidin-1-carboxylate



Analogously to Example 1, 342 mg of the title compound was obtained from 323 mg of the compound prepared in Example 117c and 141 mg of 3,4,5,6-tetrahydro-2H-pyran-2-ylmethyl-amine hydrochloride.

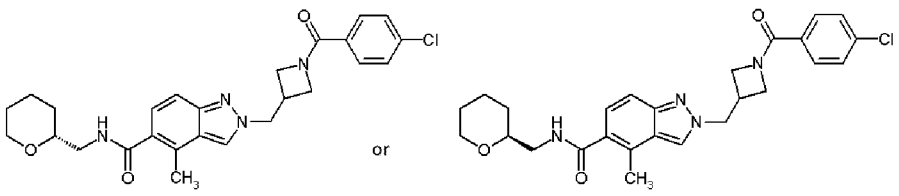
^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.14-1.21 (1H), 1.33 (9H), 1.37-1.49 (3H), 1.61 (1H), 1.71-1.80 (1H), 2.49 (3H), 3.09 (1H), 3.21 (2H), 3.27-3.43 (2H), 3.69 (2H), 3.81-3.91 (3H), 4.61 (2H), 7.15 (1H), 7.38 (1H), 8.06 (1H), 8.53 (1H).

Example 144b: (+/-)-2-(azetidin-3-ylmethyl)-4-methyl-N-(3,4,5,6-tetrahydro-2H-pyran-2-yl-methyl)-2H-indazole-5-carboxamide hydrochloride



Analogously to Example 1a, from 298 mg of the compound prepared in Example 144a, 261 mg of the title compound was obtained, which was further reacted without purification.

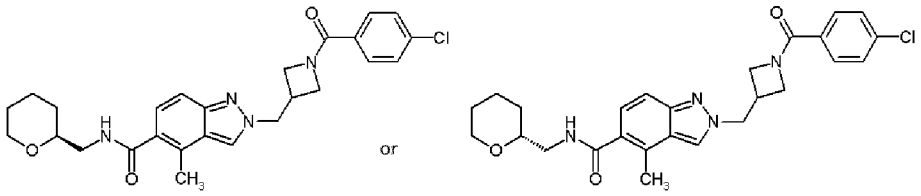
Example 145: (R or S)-2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-4-methyl-N-(3,4,5,6-tetrahydro-2H-pyran-2-ylmethyl)-2H-indazol-5-carboxamide



From 140 mg of the racemate prepared in Example 144, 43 mg of the title compound together with 35 mg of the slower-eluting enantiomer (Example 146) were obtained by racemate separation by means of preparative chiral HPLC (Method C).

Analytical chiral HPLC: 4.38 min.

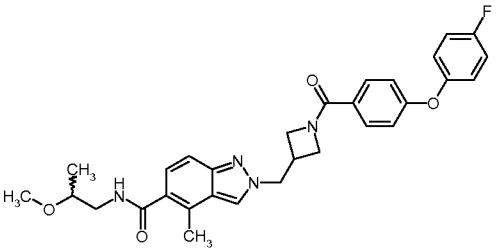
Example 146: (S or R)-2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-4-methyl-N-(3,4,5,6-tetrahydro-2H-pyran-2-ylmethyl)-2H-indazol-5-carboxamide



From 140 mg of the racemate prepared in Example 144, 35 mg of the title compound together with 43 mg of the faster-eluting enantiomer (Example 145) were obtained by racemate separation by means of preparative chiral HPLC (Method C).

Analytical chiral HPLC: 4.88 min.

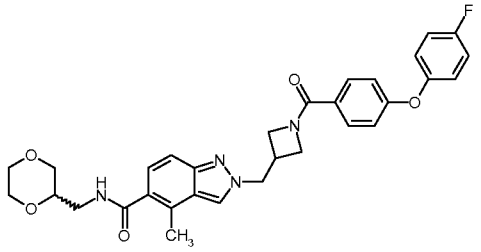
Example 147: (+/-)-2-({1-[4-(4-fluorophenoxy)benzoyl]azetidin-3-yl}methyl)-N-(2-methoxy-propyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, from 42 mg of the compound prepared in Example 138b and 28 mg of 4-(4-fluorophenoxy)benzoic acid, a material still contaminated after HPLC purification was obtained, which was further purified by an additional preparative thick layer chromatography with ethyl acetate / methanol in the ratio 9:1 as mobile phase. Yield in this manner: 15 mg of the title compound.

^{1}H-NMR (300 MHz, CDCl3): δ = 1.22 (3H), 2.64 (3H), 3.28 (1H), 3.36 (3H), 3.40 (1H), 3.57 (1H), 3.76 (1H), 3.97-4.46 (4H), 4.66 (2H), 6.14 (1H), 6.93 (2H), 6.97-7.11 (4H), 7.32 (1H), 7.51 (1H), 7.60 (2H), 8.00 (1H).

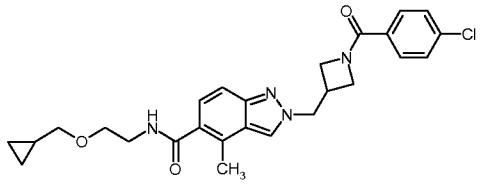
Example 148: (+/-)-N-(1,4-dioxan-2-ylmethyl)-2-({1-[4-(4-fluorophenoxy)benzoyl]azetidin-3-yl}methyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 18 mg of the title compound was obtained from 43 mg of the compound prepared in Example 141b and 26 mg of 4-(4-fluorophenoxy)benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.49 (3H), 3.13-3.28 (4H), 3.38-3.66 (4H), 3.67-3.77 (2H), 3.89 (1H), 4.07 (1H), 4.19 (1H), 4.37 (1H), 4.66 (2H), 6.94 (2H), 7.08-7.18 (3H), 7.24 (2H), 7.38 (1H), 7.60 (2H), 8.17 (1H), 8.55 (1H).

Example 149: 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-N-[2-(cyclopropylmethoxy)ethyl]-4-methyl-2H-indazol-5-carboxamide

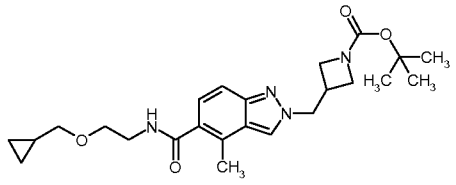


Analogously to Example 55, 72 mg of the title compound was obtained from 127 mg of the compound prepared in Example 149b and 65 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.17 (2H), 0.45 (2H), 0.99 (1H), 2.51-2.54 (3H), 3.20-3.28 (3H), 3.38 (2H), 3.51 (2H), 3.92 (1H), 4.11 (1H), 4.21 (1H), 4.39 (1H), 4.69 (2H), 7.18 (1H), 7.40 (1H), 7.50 (2H), 7.62 (2H), 8.12 (1H), 8.56 (1H).

The starting material was prepared as follows:

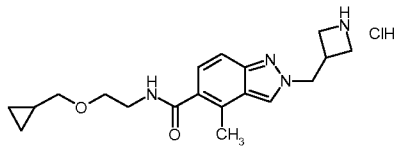
Example 149a: Tert-butyl 3-[(5-{N-[2-(cyclopropylmethoxy)ethyl]carbamoyl}-4-methyl-2H-indazol-2-yl)methyl]azetidin-1-carboxylate



Analogously to Example 1, 448 mg of the title compound was obtained from 400 mg of the compound prepared in Example 117c and 133 mg of 2-(cyclopropylmethoxy)ethylamine hydrochloride.

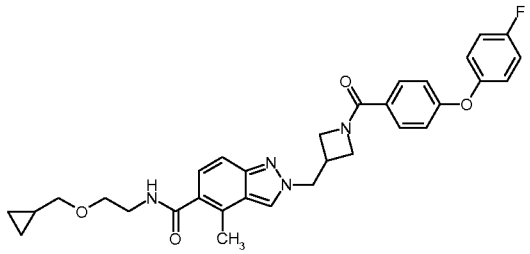
^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.14 (2H), 0.42 (2H), 0.97 (1H), 1.33 (9H), 2.50 (3H), 3.09 (1H), 3.24 (2H), 3.36 (2H), 3.49 (2H), 3.69 (2H), 3.86 (2H), 4.61 (2H), 7.15 (1H), 7.38 (1H), 8.08 (1H), 8.54 (1H).

Example 149b: 2-(azetidin-3-ylmethyl)-N-[2-(cyclopropylmethoxy)ethyl]-4-methyl-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 448 mg of the compound prepared in Example 149a, 390 mg of the title compound was obtained, which was further reacted without purification.

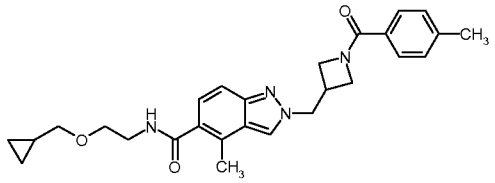
Example 150: N-[2-(cyclopropylmethoxy)ethyl]-2-({1-[4-(4-fluorophenoxy)benzoyl]azetidin-3-yl}methyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 48 mg of the title compound was obtained from 102 mg of the compound prepared in Example 149b and 63 mg of 4-(4-fluorophenoxy)benzoic acid.

^{1}H-NMR (300 MHz, CDCl3): δ = 0.20 (2H), 0.54 (2H), 1.05 (1H), 2.65 (3H), 3.32 (2H), 3.35-3.45 (1H), 3.63-3.75 (4H), 3.99-4.50 (4H), 4.66 (2H), 6.22 (1H), 6.93 (2H), 6.97-7.11 (4H), 7.34 (1H), 7.51 (1H), 7.61 (2H), 8.00 (1H).

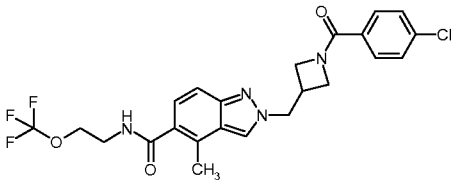
Example 151: N-[2-(cyclopropylmethoxy)ethyl]-4-methyl-2-{[1-(4-methylbenzoyl)azetidin-3-yl]methyl}-2H-indazol-5-carboxamide



Analogously to Example 1, 55 mg of the title compound was obtained from 127 mg of the compound prepared in Example 149b and 46 mg of 4-methylbenzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.17 (2H), 0.45 (2H), 0.99 (1H), 2.33 (3H), 2.53 (3H), 3.19-3.28 (3H), 3.38 (2H), 3.51 (2H), 3.90 (1H), 4.09 (1H), 4.20 (1H), 4.38 (1H), 4.69 (2H), 7.18 (1H), 7.24 (2H), 7.41 (1H), 7.50 (2H), 8.11 (1H), 8.57 (1H).

Example 152: 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-4-methyl-N-[2-(trifluoromethoxy)ethyl]-2H-indazol-5-carboxamide

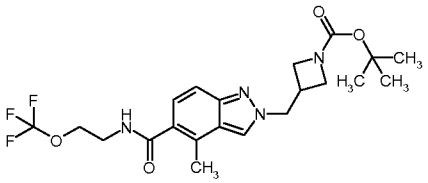


Analogously to Example 55, 122 mg of the title compound was obtained from 234 mg of the compound prepared in Example 152b and 115 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.52 (3H), 3.25 (1H), 3.54 (2H), 3.93 (1H), 4.11 (1H), 4.17-4.25 (3H), 4.40 (1H), 4.70 (2H), 7.19 (1H), 7.43 (1H), 7.50 (2H), 7.61 (2H), 8.38 (1H), 8.58 (1H).

The starting material was prepared as follows:

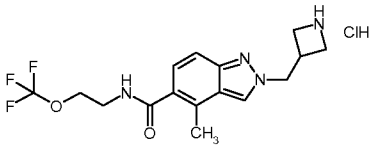
Example 152a: Tert-butyl 3-[(4-methyl-5-{N-[2-(trifluoromethoxy)ethyl]carbamoyl}-2H-indazol-2-yl)methyl]azetidin-1-carboxylate



Analogously to Example 1, 272 mg of the title compound was obtained from 250 mg of the compound prepared in Example 117c and 120 mg of 2-(trifluoromethoxy)ethylamine hydrochloride.

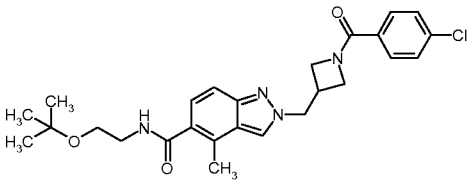
^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.32 (9H), 2.50 (3H), 3.08 (1H), 3.51 (2H), 3.70 (2H), 3.86 (2H), 4.17 (2H), 4.61 (2H), 7.16 (1H), 7.41 (1H), 8.36 (1H), 8.56 (1H).

Example 152b: 2-(azetidin-3-ylmethyl)-4-methyl-N-[2-(trifluoromethoxy)ethyl]-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 272 mg of the compound prepared in Example 152a, 240 mg of the title compound was obtained, which was further reacted without purification.

Example 153: N-(2-tert-butoxyethyl)-2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-4-methyl-2H-indazol-5-carboxamide

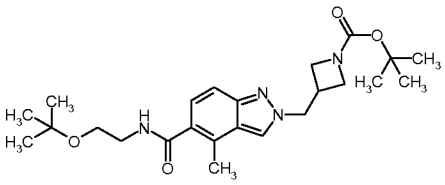


Analogously to Example 55) 12 mg of the title compound was obtained from 160 mg of the compound prepared in Example 153b) and 81 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.14 (9H), 2.53 (3H), 3.19-3.34 (3H), 3.43 (2H), 3.92 (1H), 4.11 (1H), 4.21 (1H), 4.39 (1H), 4.69 (2H), 7.18 (1H), 7.40 (1H), 7.50 (2H), 7.62 (2H), 8.05 (1H), 8.56 (1H).

The starting material was prepared as follows:

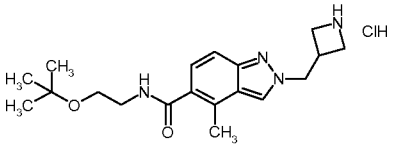
Example 153a: Tert-butyl 3-({5-[N-(2-tert-butoxyethyl)carbamoyl]-4-methyl-2H-indazol-2-yl}-methyl)azetidin-1-carboxylate



Analogously to Example 1, 284 mg of the title compound was obtained from 250 mg of the compound prepared in Example 117c and 111 mg of 2-tert-butoxyethylamine hydrochloride.

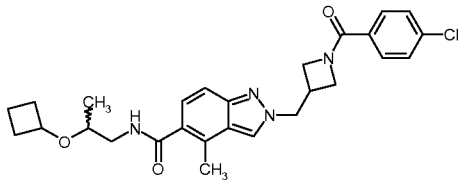
^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.11 (9H), 1.32 (9H), 2.50 (3H), 3.08 (1H), 3.27 (2H), 3.40 (2H), 3.69 (2H), 3.86 (2H), 4.60 (2H), 7.15 (1H), 7.38 (1H), 8.04 (1H), 8.54 (1H).

Example 153b: 2-(azetidin-3-ylmethyl)-N-(2-tert-butoxyethyl)-4-methyl-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 284 mg of the compound prepared in Example 153a, 240 mg of the title compound was obtained, which was further reacted without purification.

Example 154: (+/-)-2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-N-[2-(cyclobutyloxy)propyl]-4-methyl-2H-indazol-5-carboxamide

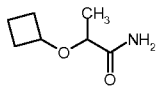


Analogously to Example 55, 135 mg of the title compound was obtained from 222 mg of the compound prepared in Example 154d and 109 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.05 (3H), 1.39 (1H), 1.55 (1H), 1.80 (2H), 2.11 (2H), 2.50 (3H), 3.08-3.23 (3H), 3.55 (1H), 3.89 (1H), 4.03-4.13 (1H), 4.19 (1H), 4.37 (1H), 4.67 (2H), 7.15 (1H), 7.38 (1H), 7.48 (2H), 7.59 (2H), 8.07 (1H), 8.53 (1H).

The starting material was prepared as follows:

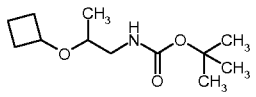
Example 154a: (+/-)-2-(cyclobutyloxy)-propanamide



To a suspension of 732 mg of sodium hydride in 15 ml THF, 2.0 g of cyclobutanol in 0.5 ml THF were added dropwise and stirred for 30 minutes at 25°C. The reaction mixture was then cooled to 0°C and 2.11 g of (+/-) 2-bromopropanamide in 0.5 ml tetrahydrofuran were added dropwise and then stirred for 18 hours at 25°C. The reaction mixture was poured onto ice-water and extracted once with 75 ml dichloromethane. The organic phase was washed with saturated sodium chloride solution, dried over sodium sulphate and concentrated in vacuo after filtration. The crude product thus obtained was purified by column chromatography on silica gel with hexane / 0-50% ethyl acetate. Yield: 0.79 g of the title compound.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.14 (3H), 1.38 (1H), 1.56 (1H), 1.83 (2H), 2.08 (2H), 3.62 (1H), 3.90 (1H), 7.07 (2H).

Example 154b: (+/-)-tert-butyl N-[2-(cyclobutyloxy)propyl]carbamate



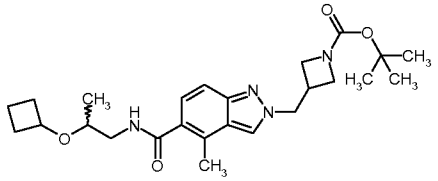
To a suspension of 6.9 g of lithium aluminium hydride in 250 ml THF, 6.5 g of the amide prepared in Example 154a in 81 ml THF were cautiously added dropwise at 0°C. The mixture was then first stirred for 30 minutes at 0°C and then heated for 5 hours under reflux. After cooling, the mixture was cautiously treated with 20 g of sodium sulphate decahydrate and 20 g of potassium fluoride and solid matter removed by filtration shortly afterwards. The filtrate was concentrated in vacuo. The residue thus obtained (5.8 g) was dissolved without further purification in 174 ml dichloromethane and treated with 11.9 g of di-tert-butyl dicarbonate. After

16 hours' stirring at 25°C, this was concentrated in vacuo and the residue thus obtained purified by two-fold column chromatography on silica gel with hexane / 0-40% ethyl acetate.

Yield: 8.54 g of the title compound.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.94 (3H), 1.28-1.42 (10H), 1.53 (1H), 1.76 (2H), 2.07 (2H), 2.76 (1H), 2.90 (1H), 3.34 (1H), 3.92 (1H), 6.72 (1H).

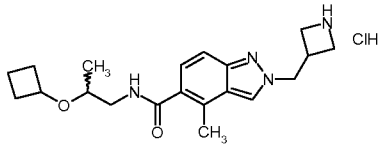
Example 154c: (+/-)-tert-butyl 3-[(5-{N-[2-(cyclobutyloxy)propyl]carbamoyl}-4-methyl-2H-indazol-2-yl)methyl]azetidin-1-carboxylate



Analogously to Example 1a, from 200 mg of the compound prepared in Example 154b), 2-(cyclobutyloxy)propylamine was obtained as the hydrochloride, which without further purification together with 250 mg of the compound prepared in Example 117c analogously to Example 1, yielded 259 mg of the title compound.

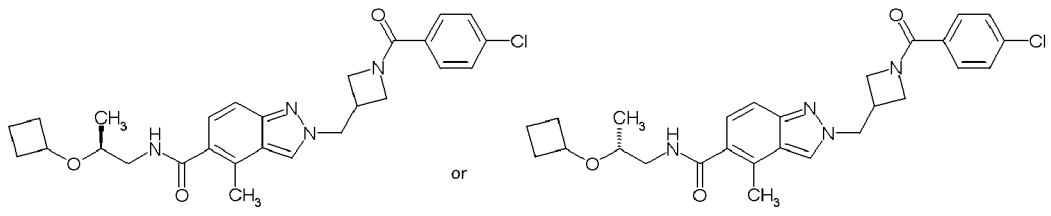
^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.05 (3H), 1.32 (9H), 1.39 (1H), 1.55 (1H), 1.80 (2H), 2.11 (2H), 2.50 (3H), 3.02-3.17 (2H), 3.22 (1H), 3.54 (1H), 3.69 (2H), 3.86 (2H), 3.99 (1H), 4.61 (2H), 7.15 (1H), 7.39 (1H), 8.09 (1H), 8.55 (1H).

Example 154d: (+/-)-2-(azetidin-3-ylmethyl)-N-[2-(cyclobutyloxy)propyl]-4-methyl-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 259 mg of the compound prepared in Example 154c, 225 mg of the title compound was obtained, which was further reacted without purification.

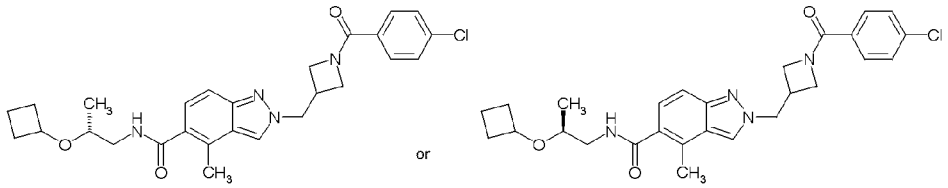
Example 155: (S or R)-2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-N-[2-(cyclobutyloxy)-propyl]-4-methyl-2H-indazol-5-carboxamide



From 135 mg of the racemate prepared in Example 154, 41 mg of the title compound together with 21 mg of the slower-eluting enantiomer (Example 156) were obtained by racemate separation by means of preparative chiral HPLC (Method A).

Analytical chiral HPLC: 10.05 min.

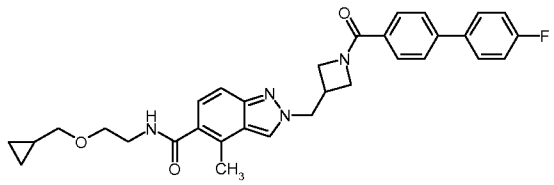
Example 156: (R or S)-2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-N-[2-(cyclobutyloxy)-propyl]-4-methyl-2H-indazol-5-carboxamide



From 135 mg of the racemate prepared in Example 154, 21 mg of the title compound together with 41 mg of the faster-eluting enantiomer (Example 155) were obtained by racemate separation by means of preparative chiral HPLC (Method A).

Analytical chiral HPLC: 13.14 min.

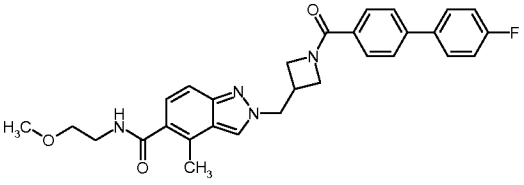
Example 157: N-[2-(cyclopropylmethoxy)ethyl]-2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl] azetidin-3-yl}methyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 54 mg of the title compound was obtained from 102 mg of the compound prepared in Example 149b and 58 mg of 4'-fluorobiphenyl-4-carboxylic acid.

^{1}H-NMR (300 MHz, CDCl3): δ = 0.20 (2H), 0.54 (2H), 1.05 (1H), 2.66 (3H), 3.32 (2H), 3.42 (1H), 3.61-3.73 (4H), 4.09 (1H), 4.28 (1H), 4.38 (1H), 4.49 (1H), 4.69 (2H), 6.22 (1H), 7.10-7.18 (2H), 7.26 (2H), 7.35 (1H), 7.50-7.59 (3H), 7.70 (2H), 8.01 (1H).

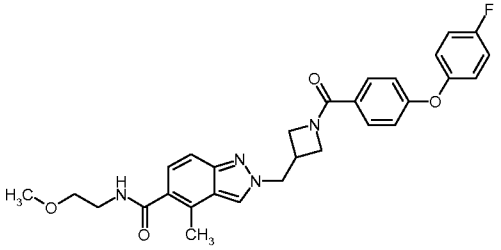
Example 158: 2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]azetidin-3-yl}methyl)-N-(2-methoxy-ethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 54 mg of the title compound was obtained from 108 mg of the compound prepared in Example 117e and 69 mg of 4'-fluorobiphenyl-4-carboxylic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.49 (3H), 3.17-3.29 (4H), 3.36 (2H), 3.43 (2H), 3.92 (1H), 4.11 (1H), 4.24 (1H), 4.42 (1H), 4.68 (2H), 7.15 (1H), 7.29 (2H), 7.39 (1H), 7.63-7.78 (6H), 8.12 (1H), 8.56 (1H).

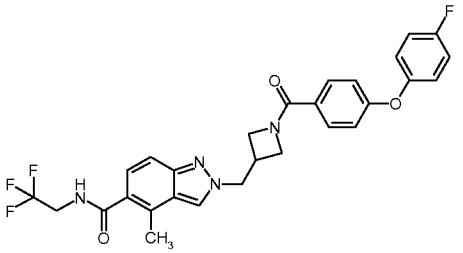
Example 159: 2-({1-[4-(4-fluorophenoxy)benzoyl]azetidin-3-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 28 mg of the title compound was obtained from 108 mg of the compound prepared in Example 117e and 74 mg of 4-(4-fluorophenoxy)benzoic acid.

^{1}H-NMR (300 MHz, CDCl3): δ = 2.65 (3H), 3.31-3.46 (4H), 3.58 (2H), 3.67 (2H), 4.06 (1H), 4.24 (1H), 4.40 (2H), 4.66 (2H), 6.15 (1H), 6.89-7.13 (6H), 7.33 (1H), 7.51 (1H), 7.61 (2H), 8.00 (1H).

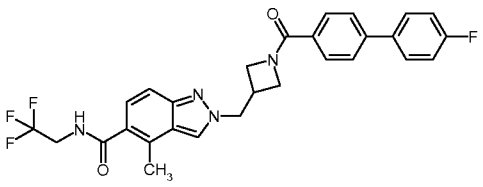
Example 160: 2-({1-[4-(4-fluorophenoxy)benzoyl]azetidin-3-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 47 mg of the title compound was obtained from 115 mg of the compound prepared in Example 129b and 74 mg of 4-(4-fluorophenoxy)benzoic acid.

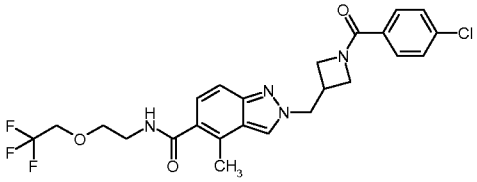
^{1}H-NMR (300 MHz, CDCl3): δ = 2.65 (3H), 3.39 (1H), 3.97-4.52 (6H), 4.67 (2H), 6.04 (1H), 6.89-7.12 (6H), 7.31 (1H), 7.53 (1H), 7.60 (2H), 8.03 (1H).

Example 161: 2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]azetidin-3-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 28 mg of the title compound was obtained from 115 mg of the compound prepared in Example 129b and 69 mg of 4'-fluorobiphenyl-4-carboxylic acid.
^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.65 (3H), 3.42 (1H), 4.01-4.54 (6H), 4.69 (2H), 6.02 (1H), 7.15 (2H), 7.32 (1H), 7.51-7.62 (5H), 7.69 (2H), 8.04 (1H).

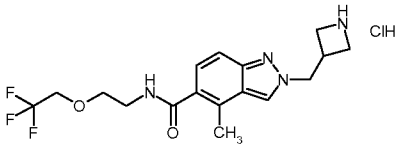
Example 162: 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-4-methyl-N-[2-(2,2,2-trifluoroethoxy)ethyl]-2H-indazol-5-carboxamide



Analogously to Example 55, 197 mg of the title compound was obtained from 252 mg of the compound prepared in Example 162a and 108 mg of 4-chlorobenzoyl chloride.
^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.49 (3H), 3.22 (1H), 3.40 (2H), 3.69 (2H), 3.90 (1H), 4.03-4.13 (3H), 4.19 (1H), 4.37 (1H), 4.67 (2H), 7.15 (1H), 7.38 (1H), 7.48 (2H), 7.59 (2H), 8.19 (1H), 8.55 (1H).

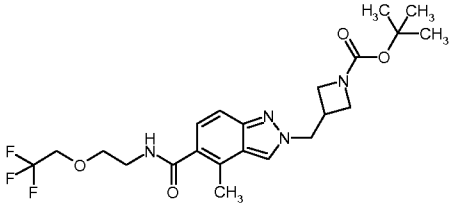
The starting material was prepared as follows:

Example 162a: 2-(azetidin-3-ylmethyl)-4-methyl-N-[2-(2,2,2-trifluoroethoxy)ethyl]-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 583 mg of the compound prepared in Example 162b, 505 mg of the title compound was obtained, which was further reacted without purification.

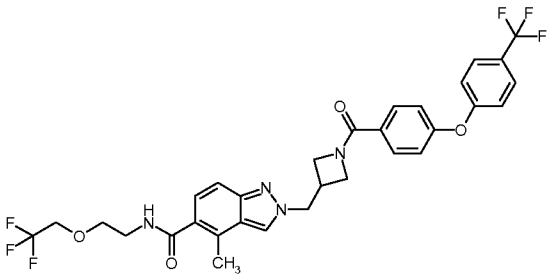
Example 162b: Tert-butyl 3-[(4-methyl-5-{N-[2-(2,2,2-trifluoroethoxy)ethyl]carbamoyl}-2H-indazol-2-yl)methyl]azetidin-1-carboxylate



Analogously to Example 1, 580 mg of the title compound was obtained from 500 mg of the compound prepared in Example 117c and 260 mg of 2-(2,2,2-trifluoroethoxy)ethylamine hydrochloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.32 (9H), 2.50 (3H), 3.08 (1H), 3.40 (2H), 3.61-3.76 (4H), 3.86 (2H), 4.07 (2H), 4.61 (2H), 7.15 (1H), 7.39 (1H), 8.18 (1H), 8.55 (1H).

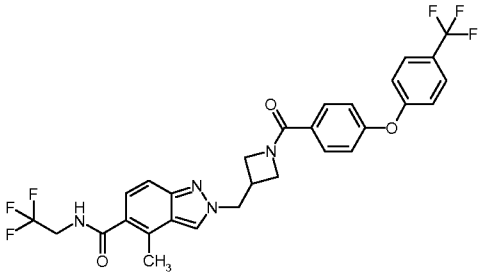
Example 163: 4-methyl-N-[2-(2,2,2-trifluoroethoxy)ethyl]-2-[(1-{4-[4-(trifluoromethyl) phenoxy]benzoyl}azetidin-3-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 1, 89 mg of the title compound was obtained from 252 mg of the compound prepared in Example 162a and 175 mg of 4-[4-(trifluoromethyl)phenoxy]benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.49 (3H), 3.23 (1H), 3.40 (2H), 3.69 (2H), 3.90 (1H), 4.01-4.14 (3H), 4.21 (1H), 4.40 (1H), 4.68 (2H), 7.11 (2H), 7.15 (1H), 7.20 (2H), 7.39 (1H), 7.66 (2H), 7.75 (2H), 8.19 (1H), 8.56 (1H).

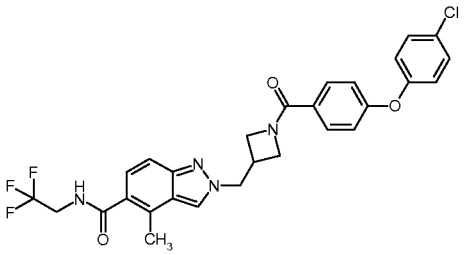
Example 164: 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{4-[4-(trifluoromethyl)phenoxy] benzoyl}azetidin-3-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 1, 64 mg of the title compound was obtained from 225 mg of the compound prepared in Example 129b and 149 mg of 4-[4-(trifluoromethyl)phenoxy]benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.50 (3H), 3.24 (1H), 3.91 (1H), 3.95-4.15 (3H), 4.22 (1H), 4.40 (1H), 4.69 (2H), 7.11 (2H), 7.15-7.23 (3H), 7.43 (1H), 7.66 (2H), 7.75 (2H), 8.60 (1H), 8.79 (1H).

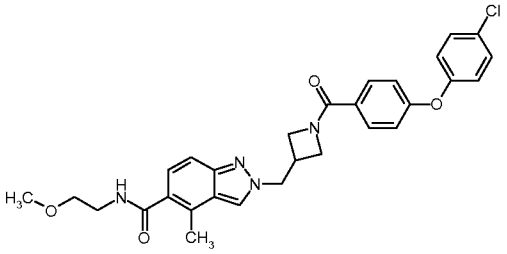
Example 165: 2-({1-[4-(4-chlorophenoxy)benzoyl]azetidin-3-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 97 mg of the title compound was obtained from 225 mg of the compound prepared in Example 129b and 131 mg of 4-(4-chlorophenoxy)benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.50 (3H), 3.23 (1H), 3.90 (1H), 3.96-4.12 (3H), 4.20 (1H), 4.38 (1H), 4.68 (2H), 7.00 (2H), 7.09 (2H), 7.18 (1H), 7.40-7.48 (3H), 7.62 (2H), 8.60 (1H), 8.79 (1H)

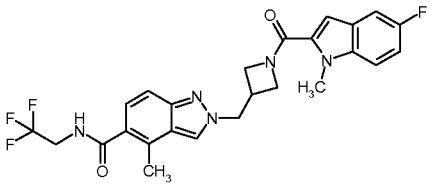
Example 166: 2-({1-[4-(4-chlorophenoxy)benzoyl]azetidin-3-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 99 mg of the title compound was obtained from 225 mg of the compound prepared in Example 117e and 140 mg of 4-(4-chlorophenoxy)benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.49 (3H), 3.16-3.27 (4H), 3.36 (2H), 3.42 (2H), 3.89 (1H), 4.08 (1H), 4.19 (1H), 4.38 (1H), 4.67 (2H), 7.00 (2H), 7.09 (2H), 7.15 (1H), 7.38 (1H), 7.45 (2H), 7.62 (2H), 8.12 (1H), 8.55 (1H).

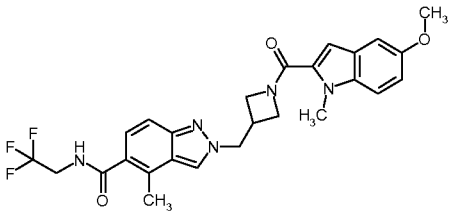
Example 167: 2-({1-[(5-fluoro-1-methyl-1H-indol-2-yl)carbonyl]azetidin-3-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 48 mg of the title compound was obtained from 180 mg of the compound prepared in Example 129b and 82 mg of 5-fluoro-1-methyl-1H-indol-2-carboxylic acid.

^{1}H-NMR (300 MHz, CDCl3): δ = 2.66 (3H), 2.80 (3H), 3.36-3.51 (1H), 4.01 (3H), 4.04-4.63 (6H), 4.70 (2H), 6.03 (1H), 6.68 (1H), 7.08 (1H), 7.22-7.36 (3H), 7.55 (1H), 8.05 (1H).

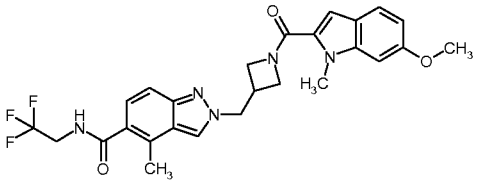
Example 168: 2-({1-[(5-methoxy-1-methyl-1H-indol-2-yl)carbonyl]azetidin-3-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 15 mg of the title compound was obtained from 180 mg of the compound prepared in Example 129b and 87 mg of 5-methoxy-1-methyl-1H-indol-2-carboxylic acid.

^{1}H-NMR (300 MHz, CDCl3): δ = 2.66 (3H), 3.43 (1H), 3.84 (3H), 4.00 (3H), 4.03-4.59 (6H), 4.70 (2H), 6.02 (1H), 6.66 (1H), 7.02 (1H), 7.27-7.35 (3H), 7.56 (1H), 8.06 (1H).

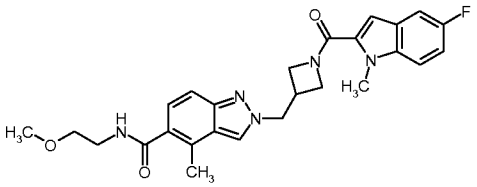
Example 169: 2-({1-[(6-methoxy-1-methyl-1H-indol-2-yl)carbonyl]azetidin-3-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 57 mg of the title compound was obtained from 180 mg of the compound prepared in Example 129b and 87 mg of 6-methoxy-1-methyl-1H-indol-2-carboxylic acid.

^{1}H-NMR (300 MHz, CDCl3): δ = 2.66 (3H), 3.43 (1H), 3.89 (3H), 3.99 (3H), 4.05-4.60 (6H), 4.70 (2H), 6.01 (1H), 6.69 (1H), 6.77 (1H), 6.81 (1H), 7.32 (1H), 7.48 (1H), 7.56 (1H), 8.05 (1H).

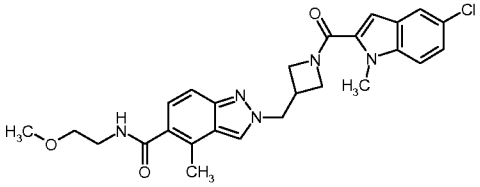
Example 170: 2-({1-[(5-fluoro-1-methyl-1H-indol-2-yl)carbonyl]azetidin-3-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 95 mg of the title compound was obtained from 180 mg of the compound prepared in Example 117e and 87 mg of 5-fluoro-1-methyl-1H-indol-2-carboxylic acid.

vNMR (300 MHz, CDCl3): δ = 2.65 (3H), 3.35-3.51 (4H), 3.58 (2H), 3.67 (2H), 4.01 (3H), 4.02-4.62 (4H), 4.69 (2H), 6.15 (1H), 6.68 (1H), 7.08 (1H), 7.21-7.38 (3H), 7.53 (1H), 8.02 (1H).

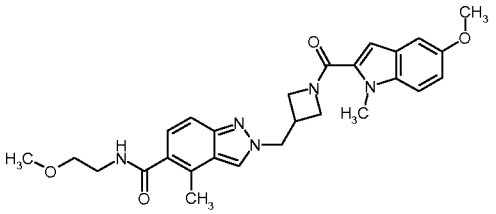
Example 171: 2-({1-[(5-chloro-1-methyl-1H-indol-2-yl)carbonyl]azetidin-3-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 90 mg of the title compound was obtained from 180 mg of the compound prepared in Example 117e and 95 mg of 5-chloro-1-methyl-1H-indol-2-carboxylic acid.

^{1}H-NMR (300 MHz, CDCl3): δ = 2.66 (3H), 3.37-3.49 (4H), 3.58 (2H), 3.67 (2H), 4.00 (3H), 4.08 (1H), 4.37 (2H), 4.56 (1H), 4.70 (2H), 6.15 (1H), 6.66 (1H), 7.27-7.38 (3H), 7.53 (1H), 7.58 (1H), 8.02 (1H).

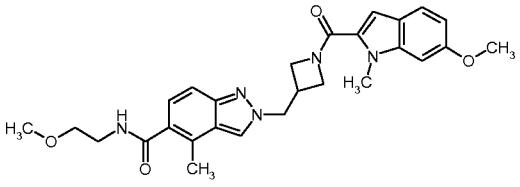
Example 172: N-(2-methoxyethyl)-2-({1-[(5-methoxy-1-methyl-1H-indol-2-yl)carbonyl]azetidin-3-yl}methyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 86 mg of the title compound was obtained from 180 mg of the compound prepared in Example 117e and 93 mg of 5-methoxy-1-methyl-1H-indol-2-carboxylic acid.

^{1}H-NMR (300 MHz, CDCl3): δ = 2.65 (3H), 3.36-3.50 (4H), 3.58 (2H), 3.67 (2H), 3.84 (3H), 4.00 (3H), 4.07 (1H), 4.35 (2H), 4.55 (1H), 4.69 (2H), 6.15 (1H), 6.66 (1H), 6.97-7.06 (2H), 7.28 (1H), 7.34 (1H), 7.53 (1H), 8.02 (1H).

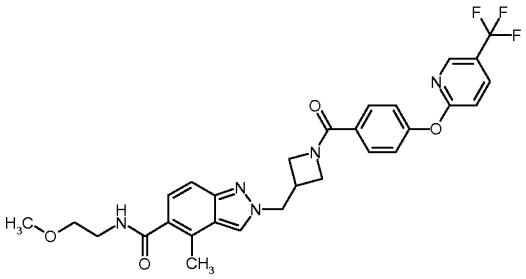
Example 173: N-(2-methoxyethyl)-2-({1-[(6-methoxy-1-methyl-1H-indol-2-yl)carbonyl]azetidin-3-yl}methyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 97 mg of the title compound was obtained from 180 mg of the compound prepared in Example 117e and 93 mg of 6-methoxy-1-methyl-1H-indol-2-carboxylic acid.

^{1}H-NMR (300 MHz, CDCl3): δ = 2.66 (3H), 3.37-3.47 (4H), 3.58 (2H), 3.67 (2H), 3.89 (3H), 3.99 (3H), 4.02-4.60 (4H), 4.69 (2H), 6.15 (1H), 6.69 (1H), 6.77 (1H), 6.81 (1H), 7.34 (1H), 7.48 (1H), 7.53 (1H), 8.02 (1H).

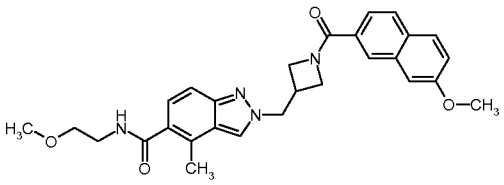
Example 174: N-(2-methoxyethyl)-4-methyl-2-{[1-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}benzoyl)azetidin-3-yl]methyl}-2H-indazol-5-carboxamide



Analogously to Example 1, 66 mg of the title compound was obtained from 135 mg of the compound prepared in Example 117e and 96 mg of 4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}-benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.50 (3H), 3.18-3.27 (4H), 3.36 (2H), 3.42 (2H), 3.91 (1H), 4.10 (1H), 4.24 (1H), 4.42 (1H), 4.68 (2H), 7.15 (1H), 7.24 (2H), 7.28 (1H), 7.39 (1H), 7.67 (2H), 8.12 (1H), 8.24 (1H), 8.56 (2H).

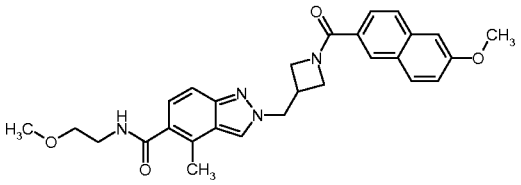
Example 175: N-(2-methoxyethyl)-2-{[1-(7-methoxy-2-naphthoyl)azetidin-3-yl]methyl}-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 72 mg of the title compound was obtained from 135 mg of the compound prepared in Example 117e and 69 mg of 7-methoxy-naphthalen-2-carboxylic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.50 (3H), 3.21-3.28 (4H), 3.36 (2H), 3.42 (2H), 3.85 (3H), 3.93-3.99 (1H), 4.14 (1H), 4.26 (1H), 4.47 (1H), 4.69 (2H), 7.15 (1H), 7.22 (1H), 7.38 (1H), 7.43 (1H), 7.50 (1H), 7.81-7.88 (2H), 8.05 (1H), 8.12 (1H), 8.56 (1H).

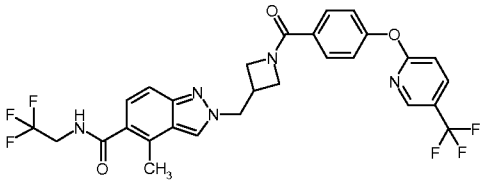
Example 176: N-(2-methoxyethyl)-2-{[1-(6-methoxy-2-naphthoyl)azetidin-3-yl]methyl}-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 72 mg of the title compound was obtained from 135 mg of the compound prepared in Example 117e and 69 mg of 6-methoxynaphthalen-2-carboxylic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.49 (3H), 3.21-3.28 (4H), 3.33-3.39 (2H), 3.42 (2H), 3.86 (3H), 3.91-3.98 (1H), 4.13 (1H), 4.27 (1H), 4.48 (1H), 4.69 (2H), 7.15 (1H), 7.19 (1H), 7.34 (1H), 7.38 (1H), 7.63 (1H), 7.82 (1H), 7.92 (1H), 8.08-8.14 (2H), 8.56 (1H).

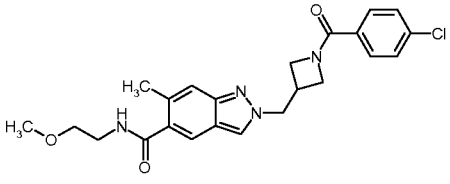
Example 177: 4-methyl-N-(2,2,2-trifluoroethyl)-2-{[1-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}benzoyl)azetidin-3-yl]methyl}-2H-indazol-5-carboxamide



Analogously to Example 1, 68 mg of the title compound was obtained from 170 mg of the compound prepared in Example 129b and 113 mg of 4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.35 (3H), 3.21 (1H), 3.89 (1H), 3.96-4.13 (3H), 4.21 (1H), 4.40 (1H), 4.68 (2H), 7.24 (2H), 7.28 (1H), 7.40 (1H), 7.66 (2H), 7.72 (1H), 8.24 (1H), 8.48 (1H), 8.56 (1H), 8.89 (1H).

Example 178: 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-N-(2-methoxyethyl)-6-methyl-2H-indazol-5-carboxamide

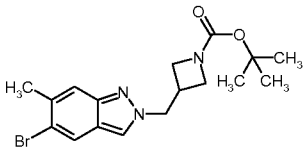


Analogously to Example 55, 154 mg of the title compound was obtained from 210 mg of the compound prepared in Example 178e and 119 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.34 (3H), 3.19 (1H), 3.24 (3H), 3.34 (2H), 3.42 (2H), 3.87 (1H), 4.07 (1H), 4.16 (1H), 4.34 (1H), 4.65 (2H), 7.35 (1H), 7.48 (2H), 7.59 (2H), 7.63 (1H), 8.21 (1H), 8.41 (1H).

The starting material was prepared as follows:

Example 178a: Tert-butyl 3-[(5-bromo-6-methyl-2H-indazol-2-yl)methyl]azetidin-1-carboxylate

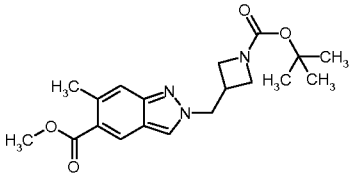


To a solution of 6.18 g of 5-bromo-6-methyl-1H-indazole and 15 g of tert-butyl-3-[(tosyl-oxy)methyl]azetidin-1-carboxylate in 200 ml DMF were added 9.54 g of caesium carbonate and 10.8 g of tetrabutylammonium iodide at 25°C, and this was then heated under reflux for 1.5 hrs. After cooling, the reaction mixture was treated with 1:1 hexane / ether and water, the phases separated and the aqueous phase extracted twice with 250 ml portions of 1:1 hexane / ether. The combined organic phases were washed with saturated sodium chloride solution, dried over sodium sulphate, and concentrated in vacuo after filtration.

The residue thus obtained was purified by twofold column chromatography on silica gel with hexane / 0-20% ethyl acetate. 2.88 g of the title compound was obtained.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.32 (9H), 2.37 (3H), 3.05 (1H), 3.67 (2H), 3.85 (2H), 4.59 (2H), 7.56 (1H), 7.97 (1H), 8.33 (1H).

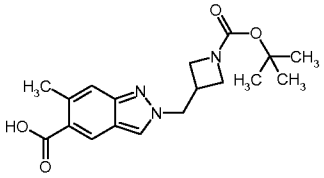
Example 178b: Methyl 2-{[1-(tert-butoxycarbonyl)azetidin-3-yl]methyl}-6-methyl-2H-indazol-5-carboxylate



To a solution of 730 mg of the bromide prepared in Example 178a in 17.5 ml tetrahydrofuran were added 0.23 ml of methanol, 145 mg of trans-bis(acetato)-bis[o-(di-o-tolylphosphino)-benzyl]dipalladium(II), 877 mg of DBU and 760 mg of molybdenum hexacarbonyl This reaction mixture was then heated in the microwave (120 watts) for 20 minutes at 125°C. Seven further preparations were performed in the same manner and all worked up together. For this, they were concentrated in vacuo and the residue taken up in water and ethyl acetate. After phase separation, the aqueous phase was extracted three times with 75 ml portions of ethyl acetate and the combined organic phases washed with saturated sodium chloride solution, dried over sodium sulphate and concentrated in vacuo after filtration. The residue thus obtained was purified by twofold column chromatography on silica gel with hexane / 0-30% ethyl acetate. Yield: 4.0 g of the title compound.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.32 (9H), 2.52 (3H), 3.07 (1H), 3.69 (2H), 3.86 (2H), 3.78 (3H), 4.62 (2H), 7.43 (1H), 8.33 (1H), 8.53 (1H).

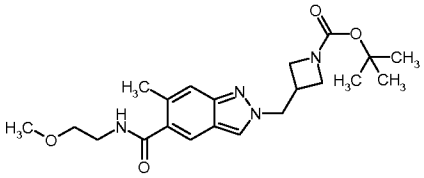
Example 178c: 2-{[1-(tert-butoxycarbonyl)azetidin-3-yl]methyl}-6-methyl-2H-indazol-5-carboxylic acid



Analogously to Example 1d, 3.2 g of the title compound was obtained from 4.0 g of the ester prepared in Example 178b.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.32 (9H), 2.53 (3H), 3.07 (1H), 3.69 (2H), 3.86 (2H), 4.61 (2H), 7.39 (1H), 8.31 (1H), 8.50 (1H), 12.48 (1H).

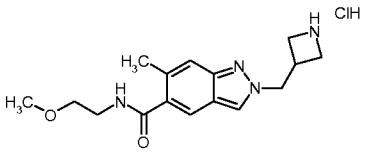
Example 178d: Tert-butyl 3-({5-[N-(2-methoxyethyl)carbamoyl]-6-methyl-2H-indazol-2-yl}-methyl)azetidin-1-carboxylate



Analogously to Example 1, 603 mg of the title compound was obtained from 500 mg of the acid prepared in Example 178c and 109 mg of 2-methoxyethylamine.

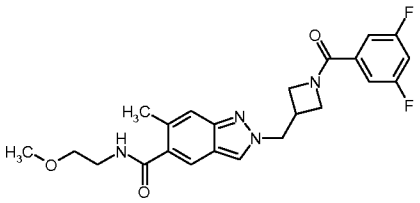
^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.32 (9H), 2.34 (3H), 3.06 (1H), 3.25 (3H), 3.32-3.45 (4H), 3.67 (2H), 3.84 (2H), 4.59 (2H), 7.35 (1H), 7.64 (1H), 8.21 (1H), 8.41 (1H).

Example 178e: 2-(azetidin-3-ylmethyl)-N-(2-methoxyethyl)-6-methyl-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 250 mg of the amide prepared in Example 178d, 275 mg of the title compound was obtained, which was reacted without further purification.

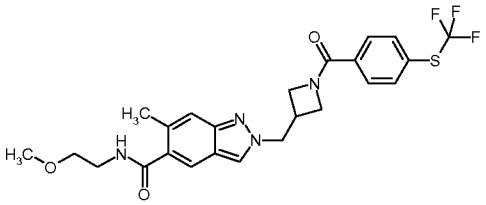
Example 179: 2-{[1-(3,5-Difluorobenzoyl)azetidin-3-yl]methyl}-N-(2-methoxyethyl)-6-methyl-2H-indazol-5-carboxamide



Analogously to Example 55, 51 mg of the title compound was obtained from 77 mg of the compound prepared in Example 178e and 44 mg of 3,5-difluorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.33 (3H), 3.18 (1H), 3.24 (3H), 3.34 (2H), 3.42 (2H), 3.87 (1H), 4.03-4.11 (1H), 4.20 (1H), 4.38 (1H), 4.65 (2H), 7.20-7.28 (2H), 7.34 (1H), 7.36-7.45 (2H), 7.64 (1H), 8.22 (1H), 8.42 (1H).

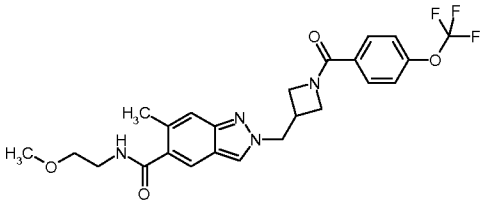
Example 180: N-(2-methoxyethyl)-6-methyl-2-[(1-{4-[(trifluoromethyl)sulphanyl]benzoyl}azetidin-3-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 55, 30 mg of the title compound was obtained from 43 mg of the compound prepared in Example 178e and 34 mg of 4-[(trifluoromethyl)sulphanyl]benzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.34 (3H), 3.20 (1H), 3.24 (3H), 3.34 (2H), 3.42 (2H), 3.89 (1H), 4.09 (1H), 4.17 (1H), 4.36 (1H), 4.65 (2H), 7.34 (1H), 7.63 (1H), 7.69 (2H), 7.76 (2H), 8.21 (1H), 8.41 (1H).

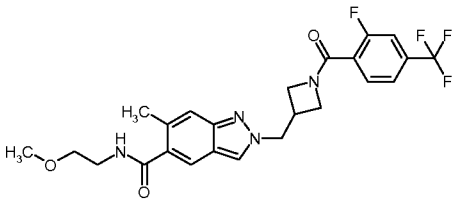
Example 181: N-(2-methoxyethyl)-6-methyl-2-({1-[4-(trifluoromethoxy)benzoyl]azetidin-3-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 55, 221 mg of the title compound was obtained from 294 mg of the compound prepared in Example 178e and 214 mg of 4-(trifluoromethoxy)benzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.34 (3H), 3.20 (1H), 3.25 (3H), 3.34 (2H), 3.42 (2H), 3.89 (1H), 4.08 (1H), 4.18 (1H), 4.36 (1H), 4.65 (2H), 7.35 (1H), 7.40 (2H), 7.64 (1H), 7.70 (2H), 8.21 (1H), 8.42 (1H).

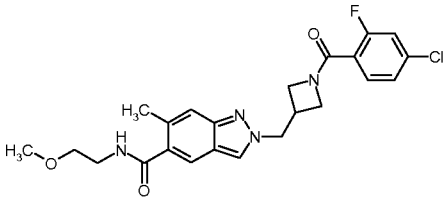
Example 182: 2-({1-[2-fluoro-4-(trifluoromethyl)benzoyl]azetidin-3-yl}methyl)-N-(2-methoxyethyl)-6-methyl-2H-indazol-5-carboxamide



Analogously to Example 55, 11 mg of the title compound was obtained from 43 mg of the compound prepared in Example 178e and 32 mg of 2-fluoro-4-(trifluoromethyl)benzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.33 (3H), 3.20 (1H), 3.24 (3H), 3.35 (2H), 3.42 (2H), 3.86- 3.95 (2H), 4.02-4.16 (2H), 4.65 (2H), 7.34 (1H), 7.61-7.69 (3H), 7.79 (1H), 8.21 (1H), 8.41 (1H).

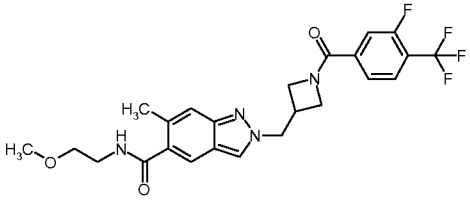
Example 183: 2-{[1-(4-chloro-2-fluorobenzoyl)azetidin-3-yl]methyl}-N-(2-methoxyethyl)-6-methyl-2H-indazol-5-carboxamide



Analogously to Example 55, from 70 mg of the compound prepared in Example 178e and 44 mg of 4-chloro-2-fluorobenzoyl chloride, a material still contaminated after HPLC purification was obtained, which was further purified by additional preparative thick layer chromatography with ethyl acetate / methanol in the ratio 9:1 as mobile phase. This yielded 12 mg of the title compound.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.34 (3H), 3.19 (1H), 3.25 (3H), 3.34 (2H), 3.42 (2H), 3.84-3.93 (2H), 4.02-4.10 (2H), 4.64 (2H), 7.32-7.36 (2H), 7.46 (1H), 7.53 (1H), 7.63 (1H), 8.22 (1H), 8.41 (1H).

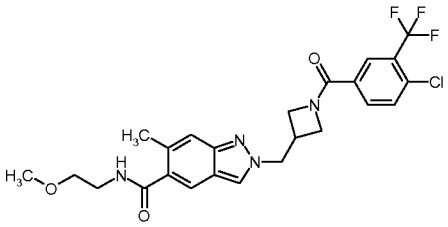
Example 184: 2-({1-[3-fluoro-4-(trifluoromethyl)benzoyl]azetidin-3-yl}methyl)-N-(2-methoxyethyl)-6-methyl-2H-indazol-5-carboxamide



Analogously to Example 55, 32 mg of the title compound was obtained from 70 mg of the compound prepared in Example 178e and 52 mg of 3-fluoro-4-(trifluoromethyl)benzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.34 (3H), 3.20 (1H), 3.24 (3H), 3.30-3.38 (2H), 3.42 (2H), 3.90 (1H), 4.10 (1H), 4.19 (1H), 4.38 (1H), 4.66 (2H), 7.34 (1H), 7.57 (1H), 7.60-7.67 (2H), 7.85 (1H), 8.21 (1H), 8.41 (1H).

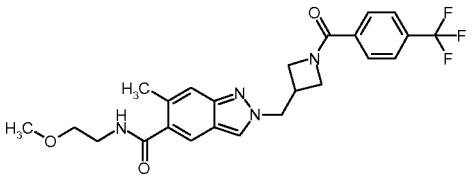
Example 185: 2-({1-[4-chloro-3-(trifluoromethyl)benzoyl]azetidin-3-yl}methyl)-N-(2-methoxyethyl)-6-methyl-2H-indazol-5-carboxamide



Analogously to Example 55, 30 mg of the title compound was obtained from 70 mg of the compound prepared in Example 178e and 55 mg of 4-chloro-3-(trifluoromethyl)benzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.34 (3H), 3.19 (1H), 3.24 (3H), 3.34 (2H), 3.42 (2H), 3.89 (1H), 4.10 (1H), 4.20 (1H), 4.35-4.43 (1H), 4.65 (2H), 7.33 (1H), 7.64 (1H), 7.78 (1H), 7.85 (1H), 7.93 (1H), 8.21 (1H), 8.40 (1H).

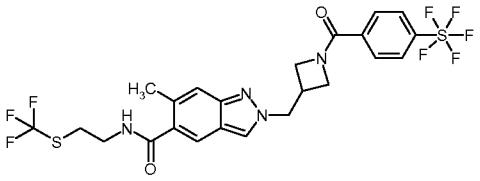
Example 186: N-(2-methoxyethyl)-6-methyl-2-({1-[4-(trifluoromethyl)benzoyl]azetidin-3-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 55, 31 mg of the title compound was obtained from 70 mg of the compound prepared in Example 178e and 47 mg of 4-(trifluoromethyl)benzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.34 (3H), 3.20 (1H), 3.24 (3H), 3.35 (2H), 3.42 (2H), 3.90 (1H), 4.06-4.21 (2H), 4.35 (1H), 4.66 (2H), 7.34 (1H), 7.63 (1H), 7.73-7.82 (4H), 8.21 (1H), 8.41 (1H).

Example 187: 6-methyl-2-({1-[4-(pentafluoro-λ^6-sulphanyl)benzoyl]azetidin-3-yl}methyl)-N-{2-[(trifluoromethyl)sulphanyl]ethyl}-2H-indazol-5-carboxamide

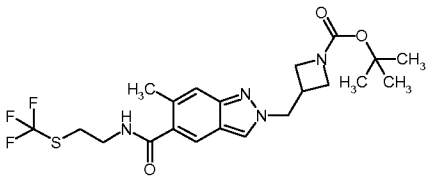


Analogously to Example 1, 35 mg of the title compound was obtained from 170 mg of the compound prepared in Example 187b and 103 mg of 4-(pentafluoro-λ^6-sulphanyl)benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.36 (3H), 3.12-3.23 (3H), 3.49 (2H), 3.91 (1H), 4.06-4.21 (2H), 4.36 (1H), 4.66 (2H), 7.36 (1H), 7.69 (1H), 7.76 (2H), 7.95 (2H), 8.44 (1H), 8.46 (1H).

The starting material was prepared as follows:

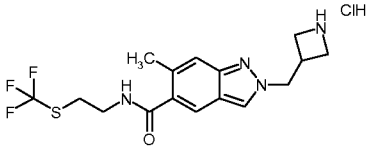
Example 187a: Tert-butyl 3-{[6-methyl-5-(N-{2-[(trifluoromethyl)sulphanyl]ethyl}carbamoyl)-2H-indazol-2-yl]methyl}azetidin-1-carboxylate



Analogously to Example 1, 998 mg of the title compound was obtained from 800 mg of the acid prepared in Example 178c and 336 mg of 2-[(trifluoromethyl)sulphanyl]ethylamine.

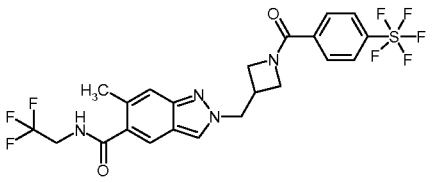
^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.32 (9H), 2.36 (3H), 3.06 (1H), 3.13-3.21 (2H), 3.49 (2H), 3.67 (2H), 3.84 (2H), 4.59 (2H), 7.37 (1H), 7.70 (1H), 8.44 (1H), 8.47 (1H).

Example 187b: 2-(azetidin-3-ylmethyl)-6-methyl-N-{2-[(trifluoromethyl)sulphanyl]ethyl}-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a), from 395 mg of the amide prepared in Example 187a), 402 mg of the title compound was obtained, which was reacted without further purification.

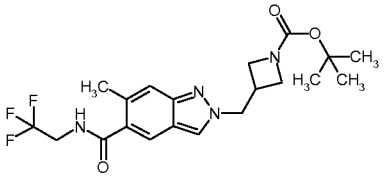
Example 188: 6-methyl-2-({1-[4-(pentafluoro-λ^6-sulphanyl)benzoyl]azetidin-3-yl}methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 25 mg of the title compound was obtained from 136 mg of the compound prepared in Example 188b and 93 mg of 4-(pentafluoro-λ^6-sulphanyl)benzoic acid.
^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.34 (3H), 3.20 (1H), 3.91 (1H), 3.95-4.21 (4H), 4.36 (1H), 4.67 (2H), 7.38 (1H), 7.71 (1H), 7.76 (2H), 7.95 (2H), 8.45 (1H), 8.86 (1H).

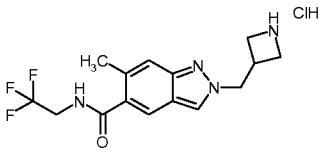
The starting material was prepared as follows:

Example 188a: Tert-butyl 3-({6-methyl-5-[N-(2,2,2-trifluoroethyl)carbamoyl]-2H-indazol-2-yl}methyl)azetidin-1-carboxylate



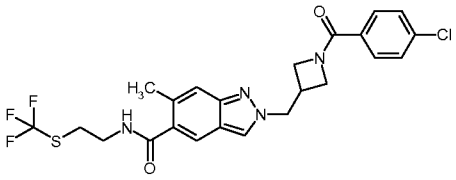
Analogously to Example 1, 550 mg of the title compound was obtained from 560 mg of the acid prepared in Example 178c and 160 mg of 2,2,2-trifluoroethylamine.
^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.32 (9H), 2.34 (3H), 3.06 (1H), 3.67 (2H), 3.84 (2H), 3.93-4.10 (2H), 4.60 (2H), 7.40 (1H), 7.71 (1H), 8.46 (1H), 8.88 (1H).

Example 188b: 2-(azetidin-3-ylmethyl)-6-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 550 mg of the amide prepared in Example 188a, 530 mg of the title compound was obtained, which was reacted without further purification.

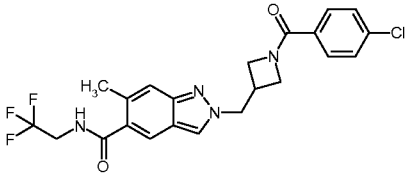
Example 189: 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-6-methyl-N-{2-[(trifluoromethyl) sulphanyl]ethyl}-2H-indazol-5-carboxamide



Analogously to Example 55, 45 mg of the title compound was obtained from 170 mg of the compound prepared in Example 187b and 80 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.39 (3H), 3.17-3.27 (3H), 3.52 (2H), 3.90 (1H), 4.10 (1H), 4.19 (1H), 4.37 (1H), 4.68 (2H), 7.39 (1H), 7.50 (2H), 7.61 (2H), 7.72 (1H), 8.47 (1H), 8.49 (1H).

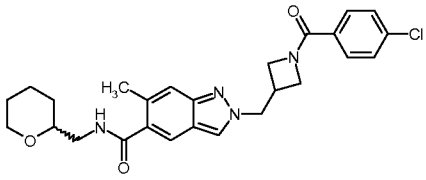
Example 190: 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-6-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 55, 60 mg of the title compound was obtained from 136 mg of the compound prepared in Example 188b and 72 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.34 (3H), 3.20 (1H), 3.87 (1H), 3.94-4.11 (3H), 4.16 (1H), 4.35 (1H), 4.66 (2H), 7.39 (1H), 7.48 (2H), 7.59 (2H), 7.71 (1H), 8.46 (1H), 8.89 (1H).

Example 191: (+/-)-2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-6-methyl-N-(3,4,5,6-tetrahydro-2H-pyran-2-ylmethyl)-2H-indazol-5-carboxamide

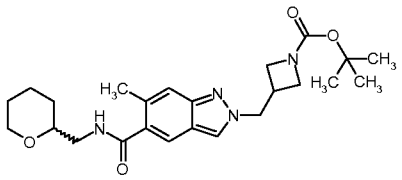


Analogously to Example 55, 49 mg of the title compound was obtained from 120 mg of the compound prepared in Example 191b and 61 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.08-1.23 (1H), 1.36-1.49 (3H), 1.62 (1H), 1.72-1.80 (1H), 2.34 (3H), 3.10-3.43 (5H), 3.80-3.92 (2H), 4.07 (1H), 4.16 (1H), 4.34 (1H), 4.65 (2H), 7.34 (1H), 7.47 (2H), 7.59 (2H), 7.63 (1H), 8.16 (1H), 8.40 (1H).

The starting material was prepared as follows:

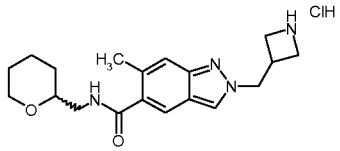
Example 191a: (+/-)-tert-butyl 3-({6-methyl-5-[N-(3,4,5,6-tetrahydro-2H-pyran-2-ylmethyl)-carbamoyl]-2H-indazol-2-yl}methyl)azetidin-1-carboxylate



Analogously to Example 1, 140 mg of the title compound was obtained from 300 mg of the acid prepared in Example 178c and 105 mg of 3,4,5,6-tetrahydro-2H-pyran-2-ylmethylamine.

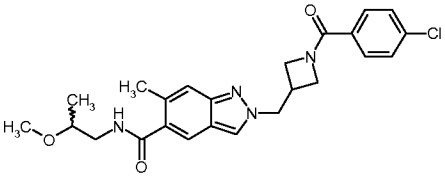
^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.07-1.24 (1H), 1.27-1.49 (12H), 1.62 (1H), 1.76 (1H), 2.33 (3H), 3.06 (1H), 3.20 (2H), 3.29-3.45 (2H), 3.67 (2H), 3.78-3.90 (3H), 4.59 (2H), 7.35 (1H), 7.63 (1H), 8.16 (1H), 8.40 (1H).

Example 191b: (+/-)-2-(azetidin-3-ylmethyl)-6-methyl-N-(3,4,5,6-tetrahydro-2H-pyran-2-ylmethyl)-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 140 mg of the amide prepared in Example 191a, 132 mg of the title compound was obtained, which was reacted without further purification.

Example 192: (+/-)-2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-N-(2-methoxypropyl)-6-methyl-2H-indazol-5-carboxamide

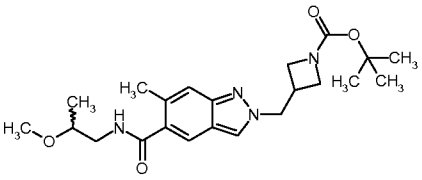


Analogously to Example 55, 89 mg of the title compound was obtained from 151 mg of the compound prepared in Example 192b and 82 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.08 (3H), 2.34 (3H), 3.13-3.32 (6H), 3.43 (1H), 3.87 (1H), 4.07 (1H), 4.16 (1H), 4.34 (1H), 4.65 (2H), 7.35 (1H), 7.48 (2H), 7.59 (2H), 7.63 (1H), 8.18 (1H), 8.41 (1H).

The starting material was prepared as follows:

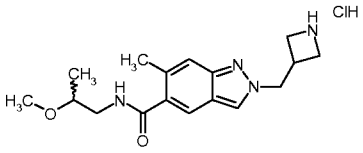
Example 192a: (+/-)-tert-butyl 3-({5-[N-(2-methoxypropyl)carbamoyl]-6-methyl-2H-indazol-2-yl}methyl)azetidin-1-carboxylate



Analogously to Example 1, 358 mg of the title compound was obtained from 300 mg of the acid prepared in Example 178c and 77 mg of 2-methoxypropan-1-amine.

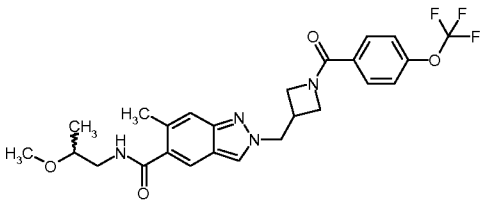
^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.08 (3H), 1.32 (9H), 2.34 (3H), 3.06 (1H), 3.13-3.31 (5H), 3.43 (1H), 3.67 (2H), 3.84 (2H), 4.59 (2H), 7.35 (1H), 7.64 (1H), 8.18 (1H), 8.40 (1H).

Example 192b: (+/-)-2-(azetidin-3-ylmethyl)-N-(2-methoxypropyl)-6-methyl-2H-indazol-5-carboxamide hydrochloride



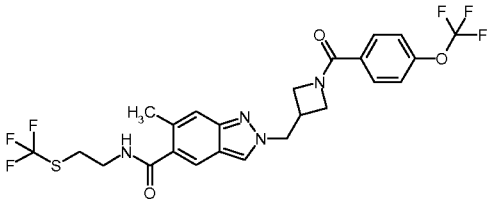
Analogously to Example 1a), from 358 mg of the amide prepared in Example 192a), 319 mg of the title compound was obtained, which was reacted without further purification.

Example 193: (+/-)-N-(2-methoxypropyl)-6-methyl-2-({1-[4-(trifluoromethoxy)benzoyl]-azetidin-3-yl}methyl)-2H-indazol-5-carboxamide



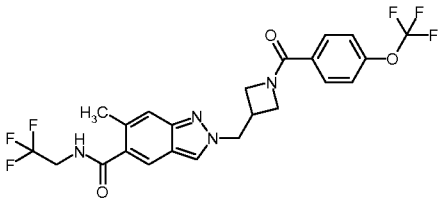
Analogously to Example 55, 87 mg of the title compound was obtained from 151 mg of the compound prepared in Example 192b and 106 mg of 4-(trifluoromethoxy)benzoyl chloride.
^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.08 (3H), 2.34 (3H), 3.13-3.31 (6H), 3.43 (1H), 3.88 (1H), 4.08 (1H), 4.17 (1H), 4.36 (1H), 4.65 (2H), 7.35 (1H), 7.40 (2H), 7.64 (1H), 7.70 (2H), 8.18 (1H), 8.41 (1H).

Example 194: 6-methyl-2-({1-[4-(trifluoromethoxy)benzoyl]azetidin-3-yl}methyl)-N-{2-[(trifluoromethyl)sulphanyl]ethyl}-2H-indazol-5-carboxamide



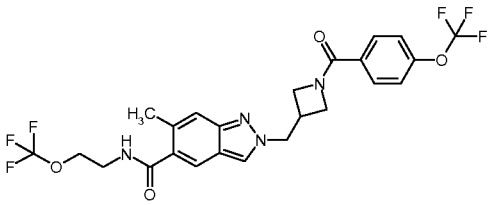
Analogously to Example 55, 87 mg of the title compound was obtained from 173 mg of the compound prepared in Example 187b and 105 mg of 4-(trifluoromethoxy)benzoyl chloride.
^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.36 (3H), 3.11-3.24 (3H), 3.49 (2H), 3.89 (1H), 4.09 (1H), 4.17 (1H), 4.36 (1H), 4.66 (2H), 7.36 (1H), 7.40 (2H), 7.66-7.74 (3H), 8.44 (1H), 8.46 (1H).

Example 195: 6-methyl-N-(2,2,2-trifluoroethyl)-2-({1-[4-(trifluoromethoxy)benzoyl]azetidin-3-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 55, 70 mg of the title compound was obtained from 170 mg of the compound prepared in Example 188b and 116 mg of 4-(trifluoromethoxy)benzoyl chloride.
^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.35 (3H), 3.21 (1H), 3.89 (1H), 3.95-4.13 (3H), 4.18 (1H), 4.36 (1H), 4.67 (2H), 7.40 (3H), 7.66-7.75 (3H), 8.45 (1H), 8.86 (1H).

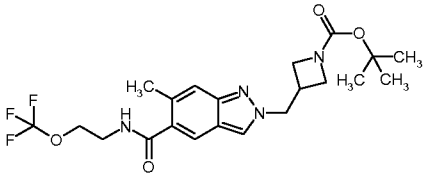
Example 196: 6-methyl-2-({1-[4-(trifluoromethoxy)benzoyl]azetidin-3-yl}methyl)-N-[2-(trifluoromethoxy)ethyl]-2H-indazol-5-carboxamide



Analogously to Example 55, 22 mg of the title compound was obtained from 179 mg of the compound prepared in Example 196b and 113 mg of 4-(trifluoromethoxy)benzoyl chloride.
^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.34 (3H), 3.20 (1H), 3.50 (2H), 3.89 (1H), 4.08 (1H), 4.14-4.21 (3H), 4.36 (1H), 4.66 (2H), 7.36 (1H), 7.40 (2H), 7.66 (1H), 7.70 (2H), 8.44 (1H), 8.46 (1H).

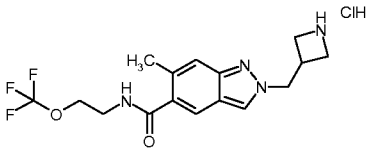
The starting material was prepared as follows:

Example 196a: Tert-butyl 3-[(6-methyl-5-{N-[2-(trifluoromethoxy)ethyl]carbamoyl}-2H-indazol-2-yl)methyl]azetidin-1-carboxylate



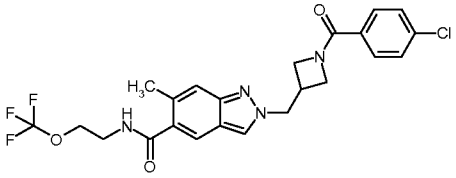
Analogously to Example 1, 417 mg of the title compound was obtained from 300 mg of the acid prepared in Example 178c and 144 mg of 2-(trifluoromethoxy)ethylamine hydrochloride.
^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.32 (9H), 2.34 (3H), 3.06 (1H), 3.50 (2H), 3.68 (2H), 3.84 (2H), 4.16 (2H), 4.59 (2H), 7.37 (1H), 7.66 (1H), 8.44 (1H), 8.46 (1H).

Example 196b: 2-(azetidin-3-ylmethyl)-6-methyl-N-[2-(trifluoromethoxy)ethyl]-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 417 mg of the amide prepared in Example 196a, 369 mg of the title compound was obtained, which was reacted without further purification.

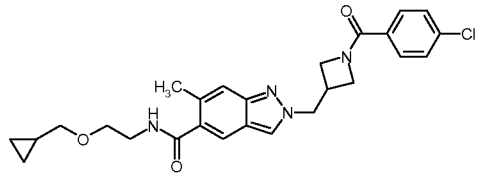
Example 197: 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-6-methyl-N-[2-(trifluoromethoxy) ethyl]-2H-indazol-5-carboxamide



Analogously to Example 55, 41 mg of the title compound was obtained from 179 mg of the compound prepared in Example 196b and 88 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.34 (3H), 3.19 (1H), 3.50 (2H), 3.87 (1H), 4.07 (1H), 4.13-4.21 (3H), 4.34 (1H), 4.65 (2H), 7.36 (1H), 7.48 (2H), 7.59 (2H), 7.66 (1H), 8.44 (1H), 8.46 (1H).

Example 198: 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-N-[2-(cyclopropylmethoxy)ethyl]-6-methyl-2H-indazol-5-carboxamide

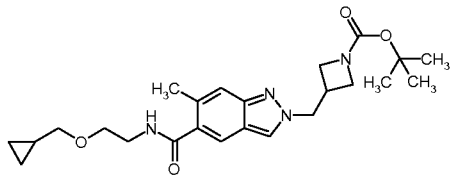


Analogously to Example 55, 107 mg of the title compound was obtained from 214 mg of the compound prepared in Example 198b and 109 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.14 (2H), 0.42 (2H), 0.97 (1H), 2.34 (3H), 3.12-3.26 (3H), 3.34 (2H), 3.47 (2H), 3.87 (1H), 4.07 (1H), 4.16 (1H), 4.34 (1H), 4.65 (2H), 7.35 (1H), 7.48 (2H), 7.59 (2H), 7.63 (1H), 8.21 (1H), 8.42 (1H).

The starting material was prepared as follows:

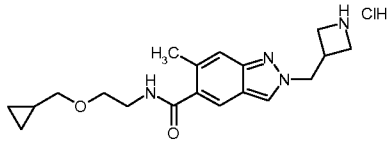
Example 198a: Tert-butyl 3-[(5-{N-[2-(cyclopropylmethoxy)ethyl]carbamoyl}-6-methyl-2H-indazol-2-yl)methyl]azetidin-1-carboxylate



Analogously to Example 1, 247 mg of the title compound was obtained from 245 mg of the acid prepared in Example 178c and 82 mg of 2-(cyclopropylmethoxy)ethylamine hydrochloride.

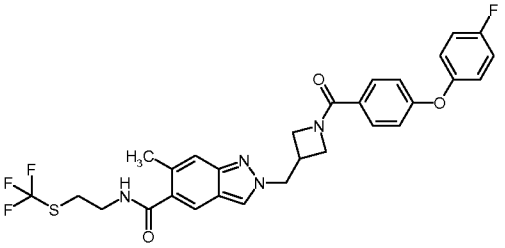
^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.14 (2H), 0.43 (2H), 0.97 (1H), 1.32 (9H), 2.35 (3H), 3.06 (1H), 3.23 (2H), 3.34 (2H), 3.48 (2H), 3.67 (2H), 3.85 (2H), 4.59 (2H), 7.35 (1H), 7.64 (1H), 8.18 (1H), 8.41 (1H).

Example 198b: 2-(azetidin-3-ylmethyl)-N-[2-(cyclopropylmethoxy)ethyl]-6-methyl-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 247 mg of the amide prepared in Example 198a, 214 mg of the title compound was obtained, which was reacted without further purification.

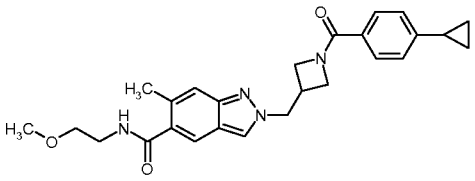
Example 199: 2-({1-[4-(4-fluorophenoxy)benzoyl]azetidin-3-yl}methyl)-6-methyl-N-{2-[(trifluoromethyl)sulphanyl]ethyl}-2H-indazol-5-carboxamide



Analogously to Example 1, 56 mg of the title compound was obtained from 173 mg of the compound prepared in Example 187b and 98 mg of 4-(4-fluorophenoxy)benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.38 (3H), 3.16-3.27 (3H), 3.52 (2H), 3.90 (1H), 4.08 (1H), 4.19 (1H), 4.38 (1H), 4.68 (2H), 6.97 (2H), 7.14 (2H), 7.27 (2H), 7.39 (1H), 7.62 (2H), 7.72 (1H), 8.47 (1H), 8.49 (1H).

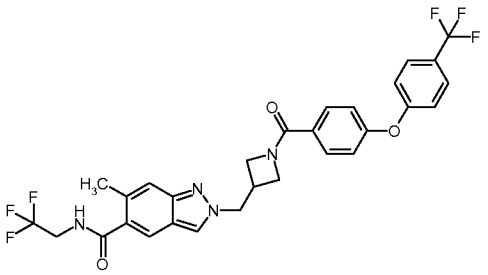
Example 200: 2-{[1-(4-cyclopropylbenzoyl)azetidin-3-yl]methyl}-N-(2-methoxyethyl)-6-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 86 mg of the title compound was obtained from 168 mg of the compound prepared in Example 178e and 80 mg of 4-cyclopropylbenzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.71 (2H), 0.99 (2H), 1.95 (1H), 2.37 (3H), 3.21 (1H), 3.27 (3H), 3.37 (2H), 3.45 (2H), 3.88 (1H), 4.07 (1H), 4.17 (1H), 4.35 (1H), 4.67 (2H), 7.12 (2H), 7.38 (1H), 7.47 (2H), 7.66 (1H), 8.22 (1H), 8.44 (1H).

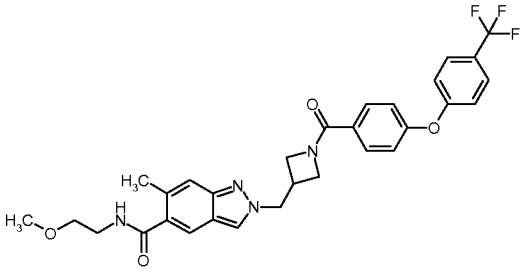
Example 201: 6-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}azetidin-3-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 1, 71 mg of the title compound was obtained from 180 mg of the compound prepared in Example 188b and 95 mg of 4-[4-(trifluoromethyl)phenoxy]benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.34 (3H), 3.21 (1H), 3.88 (1H), 3.95-4.13 (3H), 4.19 (1H), 4.37 (1H), 4.67 (2H), 7.11 (2H), 7.19 (2H), 7.39 (1H), 7.65 (2H), 7.69-7.79 (3H), 8.47 (1H), 8.88 (1H).

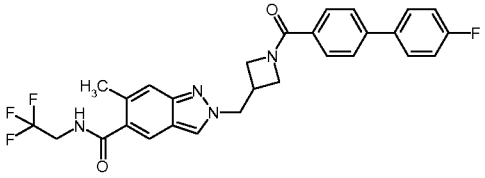
Example 202: N-(2-methoxyethyl)-6-methyl-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}-azetidin-3-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 1, 108 mg of the title compound was obtained from 180 mg of the compound prepared in Example 178e and 102 mg of 4-[4-(trifluoromethyl)phenoxy]benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.34 (3H), 3.14-3.26 (4H), 3.34 (2H), 3.42 (2H), 3.88 (1H), 4.07 (1H), 4.19 (1H), 4.37 (1H), 4.66 (2H), 7.11 (2H), 7.19 (2H), 7.35 (1H), 7.61-7.68 (3H), 7.75 (2H), 8.21 (1H), 8.42 (1H).

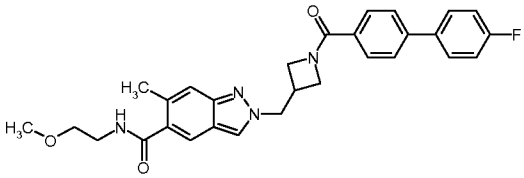
Example 203: 2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]azetidin-3-yl}methyl)-6-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 104 mg of the title compound was obtained from 180 mg of the compound prepared in Example 188b and 73 mg of 4'-fluorobiphenyl-4-carboxylic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.34 (3H), 3.22 (1H), 3.90 (1H), 3.95-4.14 (3H), 4.21 (1H), 4.40 (1H), 4.68 (2H), 7.28 (2H), 7.40 (1H), 7.60-7.77 (7H), 8.48 (1H), 8.89 (1H).

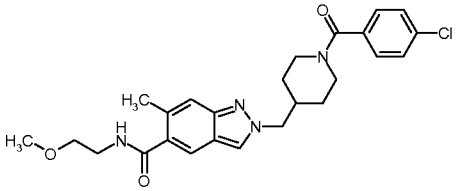
Example 204: 2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]azetidin-3-yl}methyl)-N-(2-methoxyethyl)-6-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 73 mg of the title compound was obtained from 180 mg of the compound prepared in Example 178e and 78 mg of 4'-fluorobiphenyl-4-carboxylic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.34 (3H), 3.14-3.26 (4H), 3.34 (2H), 3.41 (2H), 3.89 (1H), 4.09 (1H), 4.21 (1H), 4.39 (1H), 4.66 (2H), 7.28 (2H), 7.35 (1H), 7.61-7.77 (7H), 8.21 (1H), 8.43 (1H).

Example 205: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-6-methyl-2H-indazol-5-carboxamide



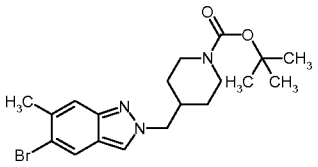
Analogously to Example 55, from 85 mg of the compound prepared in Example 205c and 45 mg of 4-chlorobenzoyl chloride, a material still contaminated after column chromatography was obtained which was further purified by additional preparative thick layer chromatography with

dichloromethane / methanol in the ratio 95:5 as mobile phase. Yield: 48 mg of the title compound.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.09-1.53 (4H), 2.24 (1H), 2.34 (3H), 2.71 (1H), 2.97 (1H), 3.24 (3H), 3.34 (2H), 3.38-3.54 (3H), 7.31-7.37 (3H), 7.46 (2H), 7.63 (1H), 8.21 (1H), 8.33 (H).

The starting material was prepared as follows:

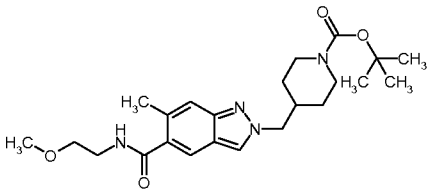
Example 205a: Tert-butyl 4-[(5-bromo-6-methyl-2H-indazol-2-yl)methyl]piperidin-1-carboxylate



Analogously to Example 1c, 2.99 g of the title compound was obtained from 5.7 g of 5-bromo-6-methyl-1H-indazole and 15.0 g of tert-butyl-4-[(tosyloxy)methyl]piperidin-1-carboxylate.

^{1}H-NMR (300 MHz, CDCl3): δ = 1.14-1.30 (2H), 1.44 (9H), 1.53 (2H), 2.24 (1H), 2.50 (3H), 2.66 (2H), 4.11 (2H), 4.23 (2H), 7.55 (1H), 7.77 (1H), 7.87 (1H).

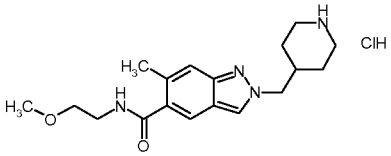
Example 205b: Tert-butyl 4-({5-[N-(2-methoxyethyl)carbamoyl]-6-methyl-2H-indazol-2-yl}-methyl)piperidin-1-carboxylate



Analogously to Example 1b, 3.56 g of the title compound was obtained from 600 mg of the bromide prepared in Example 205a and 331 mg of 2-methoxyethylamine after four runs and twofold purification by chromatography.

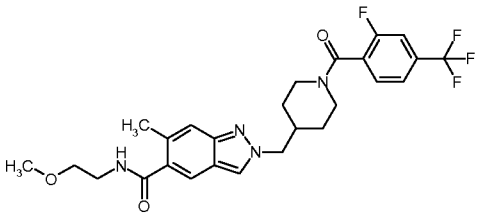
^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.96-1.15 (2H), 1.29-1.42 (10H), 2.03-2.18 (1H), 2.34 (3H), 2.51-2.73 (3H), 3.25 (3H), 3.31-3.45 (4H), 3.86 (2H), 4.26 (2H), 7.35 (1H), 7.63 (1H), 8.21 (1H), 8.32 (1H).

Example 205c: N-(2-methoxyethyl)-6-methyl-2-(4-piperidylmethyl)-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 100 mg of the amide prepared in Example 205b, 85 mg of the title compound was obtained, which was reacted without further purification.

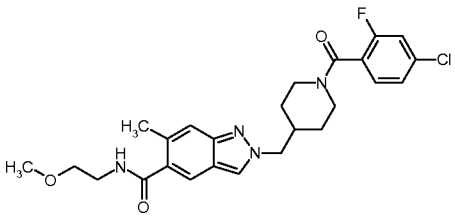
Example 206: 2-({1-[2-fluoro-4-(trifluoromethyl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxy-ethyl)-6-methyl-2H-indazol-5-carboxamide



Analogously to Example 55, from 85 mg of the compound prepared in Example 205c and 58 mg of 2-fluoro-4-(trifluoromethyl)benzoyl chloride, a material still contaminated after column chromatography was obtained which was further purified by additional preparative thick layer chromatography with dichloromethane / methanol in the ratio 95:5 as mobile phase. Yield: 40 mg of the title compound.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.03-1.28 (2H), 1.37 (1H), 1.53 (1H), 2.23 (1H), 2.34 (3H), 2.77 (1H), 3.00 (1H), 3.26-3.49 (11H), 4.30 (2H), 4.44 (1H), 7.35 (1H), 7.54-7.67 (3H), 7.78 (1H), 8.21 (1H), 8.34 (1H).

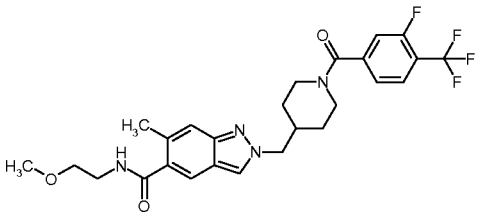
Example 207: 2-{[1-(4-chloro-2-fluorobenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-6-methyl-2H-indazol-5-carboxamide



Analogously to Example 55, 68 mg of the title compound was obtained from 85 mg of the compound prepared in Example 205c and 49 mg of 4-chloro-2-fluorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.04-1.25 (2H), 1.37 (1H), 1.51 (1H), 2.23 (1H), 2.34 (3H), 2.73 (1H), 2.98 (1H), 3.21-3.48 (3H), 3.30-3.38 (3H), 3.42 (2H), 4.29 (2H), 4.42 (1H), 7.29-7.42 (3H), 7.51 (1H), 7.63 (1H), 8.21 (1H), 8.33 (1H).

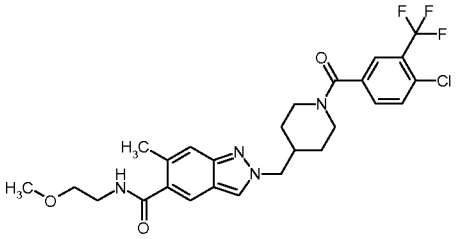
Example 208: 2-({1-[3-fluoro-4-(trifluoromethyl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-6-methyl-2H-indazol-5-carboxamide



Analogously to Example 55, 70 mg of the title compound was obtained from 85 mg of the compound prepared in Example 205c and 58 mg of 3-fluoro-4-(trifluoromethyl)benzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.13-1.27 (2H), 1.35 (1H), 1.51 (1H), 2.23 (1H), 2.34 (3H), 2.74 (1H), 2.98 (1H), 3.22-3.45 (8H), 4.29 (2H), 4.40 (1H), 7.32-7.38 (2H), 7.52 (1H), 7.63 (1H), 7.82 (1H), 8.21 (1H), 8.33 (1H).

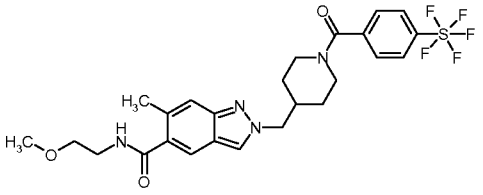
Example 209: 2-({1-[4-chloro-3-(trifluoromethyl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-6-methyl-2H-indazol-5-carboxamide



Analogously to Example 55, 92 mg of the title compound was obtained from 85 mg of the compound prepared in Example 205c and 62 mg of 4-chloro-3-(trifluoromethyl)benzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.14-1.28 (2H), 1.35 (1H), 1.44-1.53 (1H), 2.25 (1H), 2.34 (3H), 2.74 (1H), 3.01 (1H), 3.24 (3H), 3.34 (2H), 3.39-3.50 (3H), 4.29 (2H), 4.39 (1H), 7.35 (1H), 7.61-7.68 (2H), 7.74-7.80 (2H), 8.21 (1H), 8.33 (1H).

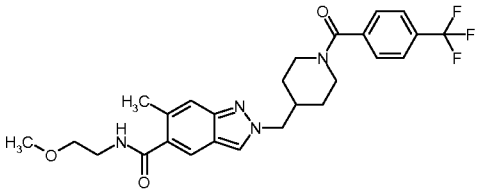
Example 210: N-(2-methoxyethyl)-6-methyl-2-({1-[4-(pentafluoro-λ^6-sulphanyl)benzoyl]-piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 126 mg of the title compound was obtained from 85 mg of the compound prepared in Example 205c and 58 mg of 4-(pentafluoro-λ^6-sulphanyl)benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.12-1.27 (2H), 1.35 (1H), 1.51 (1H), 2.24 (1H), 2.34 (3H), 2.74 (1H), 2.99 (1H), 3.24 (3H), 3.34-3.46 (5H), 4.30 (2H), 4.41 (1H), 7.35 (1H), 7.55 (2H), 7.63 (1H), 7.94 (2H), 8.21 (1H), 8.33 (1H).

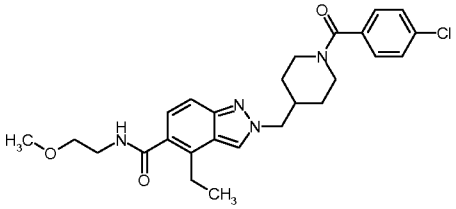
Example 211: N-(2-methoxyethyl)-6-methyl-2-({1-[4-(trifluoromethyl)benzoyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide



Analogously to Example 55, 69 mg of the title compound was obtained from 85 mg of the compound prepared in Example 205c and 53 mg of 4-(trifluoromethyl)benzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.10-1.26 (2H), 1.35 (1H), 1.51 (1H), 2.19-2.30 (1H), 2.34 (3H), 2.74 (1H), 2.98 (1H), 3.21-3.47 (8H), 4.30 (2H), 4.42 (1H), 7.35 (1H), 7.54 (2H), 7.63 (1H), 7.77 (2H), 8.21 (1H), 8.33 (1H).

Example 212: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-ethyl-N-(2-methoxyethyl)-2H-indazol-5-carboxamide

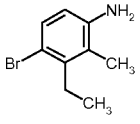


Analogously to Example 55, 61 mg of the title compound was obtained from 91 mg of the compound prepared in Example 212i and 46 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.14-1.28 (5H), 1.31-1.60 (2H), 2.27 (1H), 2.63-3.04 (4H), 3.24 (3H), 3.31-3.56 (5H), 4.31 (2H), 4.39 (1H), 7.10 (1H), 7.32-7.41 (3H), 7.46 (2H), 8.11 (1H), 8.50 (1H).

The starting material was prepared as follows:

Example 212a: 4-bromo-3-ethyl-2-methylaniline

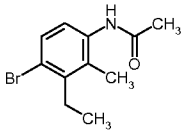


A suspension of 3 g of 3-ethyl-2-methylaniline hydrochloride in 200 ml ethyl acetate was washed twice with 30 ml portions of saturated sodium carbonate solution and twice with 20 ml

portions of saturated sodium chloride solution, dried over sodium sulphate and concentrated in vacuo after filtration. This yielded 2.69 g of ethyl-2-methylaniline, which was further reacted without purification.

To a solution of 2.36 g of the amine prepared above in 29 ml DMF, a solution of 3.1 g of N-bromosuccinimide in 14.5 ml DMF was added dropwise at 0°C and stirred for 30 minutes at 0°C. Then the reaction mixture was diluted with 400 ml ethyl acetate and washed once with 30 ml of a 10% aqueous sodium carbonate solution and once with 30 ml water. After drying over sodium sulphate and filtration, this was concentrated in vacuo. The crude product thus obtained (3.86 g) was used in the next step without purification.

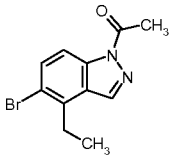
Example 212b: N-(4-bromo-3-ethyl-2-methylphenyl)acetamide



To a solution of 3.86 g of the bromide prepared in Example 212a in 48 ml pyridine, 2.04 ml of acetic anhydride was added dropwise at 0°C and stirred for 20 hours at 25°C. The reaction mixture was concentrated in vacuo and the crude product thus obtained was purified by column chromatography on silica gel with hexane / 0-100% ethyl acetate. In this manner, 3.73 g of the title compound was obtained.

^{1}H-NMR (300 MHz, CDCl3): δ = 1.13 (3H), 2.20 (3H), 2.25 (3H), 2.86 (2H), 6.91 (1H), 7.33 (1H), 7.40 (1H).

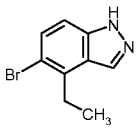
Example 212c: 1-(5-bromo-4-ethyl-1H-indazol-1-yl)ethan-1-one



To a solution of 3.72 g of the acetamide prepared in Example 212b in 31.5 ml chloroform were added 4.1 ml of acetic anhydride and 2.85 g of potassium acetate, and 192 mg of 18-crown-6 and 3.4 g of isopentyl nitrite were then added dropwise. The reaction mixture was heated for 20 hours under reflux and after cooling diluted with 200 ml ethyl acetate. The organic phase was washed with 20 ml sodium carbonate solution and once with saturated sodium chloride solution. After drying over sodium sulphate and filtration, this was concentrated in vacuo and the crude product thus obtained purified by column chromatography on silica gel with hexane / 0-50% ethyl acetate. Yield: 3.78 g of the title compound.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.18 (3H), 2.68 (3H), 3.04 (2H), 7.73 (1H), 8.03 (1H), 8.64 (1H).

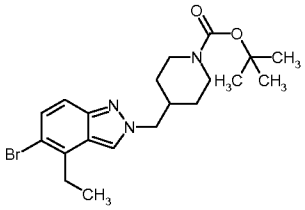
Example 212d: 5-bromo-4-ethyl-1H-indazole



A mixture of 3.78 g of the compound prepared in Example 212c in 7.3 ml methanol and 26.3 ml of 37% hydrochloric acid was heated under reflux for 2 hours. This was then diluted with 400 ml ethyl acetate. The organic phase was washed three times with 50 ml portions of sodium hydrogen carbonate solution and once with 50 ml saturated sodium chloride solution, dried over sodium sulphate and concentrated in vacuo. The crude product thus obtained was purified by column chromatography on silica gel with hexane / 0-50% ethyl acetate. Yield: 2.97 g of the title compound.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.17 (3H), 2.98 (2H), 7.30 (1H), 7.41 (1H), 8.16 (1H), 13.17 (1H).

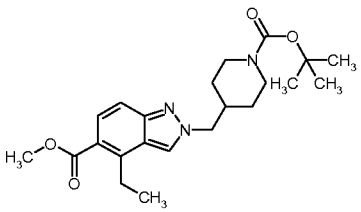
Example 212e: Tert-butyl 4-[(5-bromo-4-ethyl-2H-indazol-2-yl)methyl]piperidin-1-carboxylate



Analogously to Example 1c, 961 mg of the title compound was obtained from 2.97 g of the indazole prepared in Example 212d and 7.3 g of tert-butyl-4-[(tosyloxy)methyl]piperidin-1-carboxylate.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.01-1.13 (2H), 1.16 (3H), 1.34 (9H), 1.41 (2H), 2.12 (1H), 2.63 (2H), 2.90 (2H), 3.87 (2H), 4.27 (2H), 7.27 (1H), 7.35 (1H), 8.49 (1H).

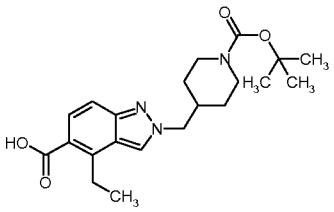
Example 212f: Methyl 2-{[1-(tert-butoxycarbonyl)piperidin-4-yl]methyl}-4-ethyl-2H-indazol-5-carboxylate



Analogously to Example 1e, after two runs 571 mg of the title compound was obtained from 347 mg of the bromide prepared in Example 212e and 0.1 ml of methanol.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.02-1.15 (2H), 1.17-1.24 (3H), 1.34 (9H), 1.42 (2H), 2.14 (1H), 2.63 (2H), 3.17 (2H), 3.79 (3H), 3.88 (2H), 4.30 (2H), 7.43 (1H), 7.60 (1H), 8.68 (1H).

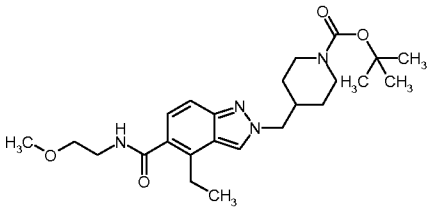
Example 212g: 2-{[1-(tert-butoxycarbonyl)piperidin-4-yl]methyl}-4-ethyl-2H-indazol-5-carboxylic acid



Analogously to Example 1d, 427 mg of the title compound was obtained from 371 mg of the ester in Example 212f.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.00-1.15 (2H), 1.20 (3H), 1.34 (9H), 1.42 (2H), 2.14 (1H), 2.64 (2H), 3.19 (2H), 3.88 (2H), 4.29 (2H), 7.39 (1H), 7.61 (1H), 8.63 (1H), 12.33 (1H).

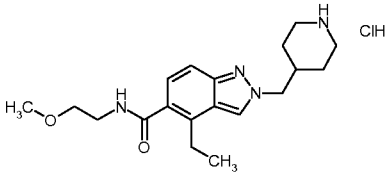
Example 212h: Tert-butyl 4-({4-ethyl-5-[N-(2-methoxyethyl)carbamoyl]-2H-indazol-2-yl}-methyl)piperidin-1-carboxylate



Analogously to Example 1, 215 mg of the title compound was obtained from 427 mg of the acid prepared in Example 212g and 83 mg of 2-methoxy-ethylamine.

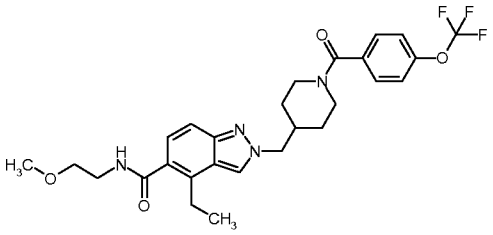
^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.98-1.14 (2H), 1.19 (3H), 1.30-1.47 (11H), 2.13 (1H), 2.65 (2H), 2.90 (2H), 3.24 (3H), 3.32-3.45 (4H), 3.87 (2H), 4.28 (2H), 7.10 (1H), 7.38 (1H), 8.12 (1H), 8.50 (1H).

Example 212i: 4-ethyl-N-(2-methoxyethyl)-2-(4-piperidylmethyl)-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 215 mg of the amide prepared in Example 212h, 258 mg of the title compound was obtained, which was reacted without further purification.

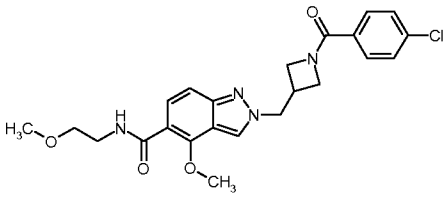
Example 213: 4-Ethyl-N-(2-methoxyethyl)-2-({1-[4-(trifluoromethoxy)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 55, 32 mg of the title compound was obtained from 91 mg of the compound prepared in Example 212i and 59 mg of 4-(trifluoromethoxy)benzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.14-1.29 (5H), 1.31-1.61 (2H), 2.20-2.35 (1H), 2.66-3.06 (4H), 3.24 (3H), 3.30-3.56 (5H), 4.31 (2H), 4.41 (1H), 7.10 (1H), 7.34-7.43 (3H), 7.47 (2H), 8.11 (1H), 8.50 (1H).

Example 214: 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-4-methoxy-N-(2-methoxyethyl)-2H-indazol-5-carboxamide

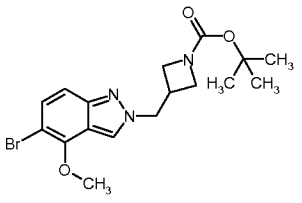


Analogously to Example 55, 691 mg of the title compound was obtained from 68 mg of the compound prepared in Example 214c and 37 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 3.22 (1H), 3.27 (3H), 3.40-3.47 (4H), 3.92 (1H), 4.10 (1H), 4.16 (3H), 4.19 (1H), 4.38 (1H), 4.66 (2H), 7.21 (1H), 7.48 (2H), 7.55-7.67 (3H), 8.18 (1H), 8.87 (1H).

The starting material was prepared as follows:

Example 214a: Tert-butyl 3-[(5-bromo-4-methoxy-2H-indazol-2-yl)methyl]azetidin-1-carboxylate



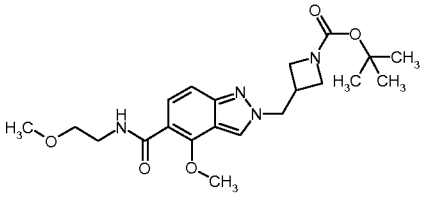
To a solution of 1.94 g of tert-butyl 3-[(tosyloxy)methyl]azetidin-1-carboxylate in 15.5 ml acetone were added 837 mg of lithium iodide and the reaction mixture was stirred for 16 hours at 35°C. After cooling, it was diluted with 200 ml ethyl acetate and the organic phase washed twice

with 30 ml portions of water and once with 20 ml saturated sodium chloride solution. After drying over sodium sulphate and filtration, this was concentrated in vacuo. In this manner, 1.6 g of tert-butyl-3-(iodomethyl)azetidin-1-carboxylate were obtained, which was further reacted without purification.

To a solution of 620 mg of 5-bromo-7-methoxy-1H-indazole in 24 ml DMF were added 1.11 g of potassium carbonate and the mixture stirred at 25°C for 30 minutes. Then 1.25 g of the iodide prepared above was added and the reaction mixture stirred for 3 hours at 60°C. After cooling, it was diluted with 200 ml 1:1 tert-butyl methyl ether/hexane, washed once each with 20 ml portions of water and saturated sodium chloride solution, dried over sodium sulphate and concentrated in vacuo and the crude product thus obtained purified by column chromatography on silica gel with a hexane / ethyl acetate gradient. Yield: 263 mg of the title compound.

^{1}H-NMR (300 MHz, CDCl3): δ = 1.43 (9H), 3.23 (1H), 3.78 (2H), 4.07 (2H), 4.10 (3H), 4.59 (2H), 7.28 (1H), 7.36 (1H), 8.03 (1H).

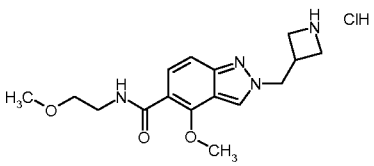
Example 214b: Tert-butyl 3-({4-methoxy-5-[N-(2-methoxyethyl)carbamoyl]-2H-indazol-2-yl}methyl)azetidin-1-carboxylate



Analogously to Example 1b, a total of 193 mg of the title compound was obtained from 110 and 252 mg respectively of the compound prepared in Example 214a and 63 and 143 mg respectively of 2-methoxyethylamine.

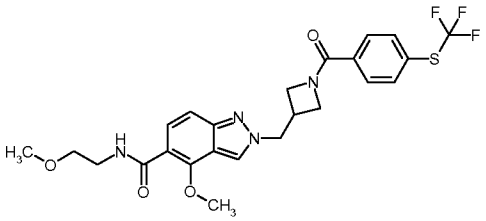
^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.32 (9H), 3.10 (1H), 3.27 (3H), 3.38-3.48 (4H), 3.72 (2H), 3.82-3.94 (2H), 4.17 (3H), 4.60 (2H), 7.21 (1H), 7.63 (1H), 8.18 (1H), 8.87 (1H).

Example 214c: 2-(azetidin-3-ylmethyl)-4-methoxy-N-(2-methoxyethyl)-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 50 mg of the compound prepared in Example 214b, 42 mg of the title compound was obtained, which was further reacted without purification.

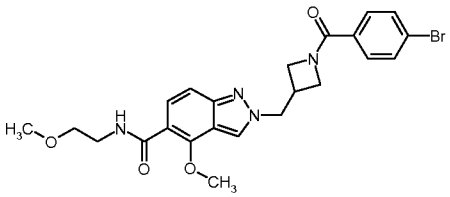
Example 215: 4-methoxy-N-(2-methoxyethyl)-2-[(1-{4-[(trifluoromethyl)sulphanyl]benzoyl}azetidin-3-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 55, 56 mg of the title compound was obtained from 42 mg of the compound prepared in Example 214c and 32 mg of 4-[(trifluoromethyl)sulphany]benzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 3.21 (1H), 3.27 (3H), 3.38-3.49 (4H), 3.95 (1H), 4.12 (1H), 4.16 (3H), 4.21 (1H), 4.40 (1H), 4.67 (2H), 7.20 (1H), 7.63 (1H), 7.69 (2H), 7.76 (2H), 8.18 (1H), 8.87 (1H).

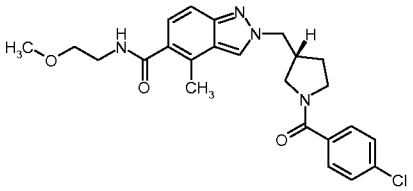
Example 216: 2-{[1-(4-bromobenzoyl)azetidin-3-yl]methyl}-4-methoxy-N-(2-methoxyethyl)-2H-indazol-5-carboxamide



Analogously to Example 55, 48 mg of the title compound was obtained from 42 mg of the compound prepared in Example 214c and 29 mg of 4-bromobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 3.23 (1H), 3.26 (3H), 3.38-3.48 (4H), 3.92 (1H), 4.09 (1H), 4.16 (3H), 4.19 (1H), 4.38 (1H), 4.66 (2H), 7.20 (1H), 7.51 (2H), 7.58-7.68 (3H), 8.18 (1H), 8.86 (1H).

Example 217: 2-{[(R)-1-(4-chlorobenzoyl)pyrrolidin-3-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

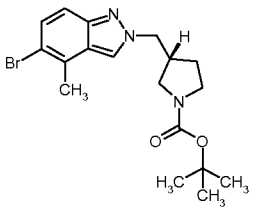


Analogously to Example 55, 50 mg of the title compound was obtained from 106 mg of the compound prepared in Example 217e and 58 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.57-1.73 (1H), 1.81-1.97 (1H), 2.47 / 2.51 (3H), 2.78-2.93 (1H), 3.25 (3H), 3.19-3.61 (8H), 4.39 / 4.51 (2H), 7.11-7.18 (1H), 7.33-7.43 (1H), 7.45 (2H), 7.50 (2H), 8.09-8.16 (1H), 8.47 / 8.55 (1H).

The starting material was prepared as follows:

Example 217a: (R)-tert-butyl-3-[(5-bromo-4-methyl-2H-indazol-2-yl)methyl]pyrrolidine-1-carboxylate

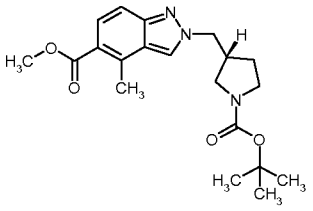


To a solution of 9.0 g of (R)-tert-butyl 3-(hydroxymethyl)pyrrolidin-1-carboxylate in 100 ml pyridine was added 12.8 g of p-toluenesulphonyl chloride at 0°C under nitrogen and stirred for 3 hours at 25°C. The reaction mixture was diluted with ethyl acetate and stirred for 30 minutes with sodium hydrogen carbonate. The phases were then separated and the organic phase washed with saturated sodium chloride solution, dried over sodium sulphate and concentrated in vacuo after filtration. The residue thus obtained was purified by column chromatography on silica gel with hexane / 0-100% ethyl acetate. Yield: 11.4 g of (R)-tert-butyl-3-[(tosyloxy)methyl]pyrrolidin-1-carboxylate.

Analogously to Example 1c, 1.97 g of the title compound was obtained from 4.53 g of 5-bromo-4-methyl-1H-indazole and 11.4 g of the (R)-tert-butyl-3-[(tosyloxy)methyl]pyrrolidin-1-carboxylate prepared above with addition of 7.9 g of tetrabutylammonium iodide.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.34 (9H), 1.50-1.66 (1H), 1.81 (1H), 2.48 (3H), 2.78 (1H), 3.01 (1H), 3.16 (1H), 3.25-3.37 (2H), 4.41 (2H), 7.29 (1H), 7.36 (1H), 8.51 (1H).

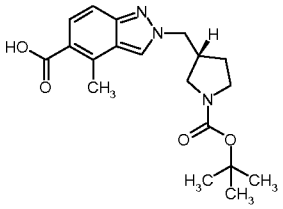
Example 217b: Methyl 2-{[(R)-1-(tert-butoxycarbonyl)pyrrolidin-3-yl]methyl}-4-methyl-2H-indazol-5-carboxylate



Analogously to Example 1e, after two runs 820 mg of the title compound was obtained from 563 mg of the bromide prepared in Example 217a and 0.17 ml of methanol.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.34 (9H), 1.58 (1H), 1.83 (1H), 2.73 (3H), 2.80 (1H), 3.03 (1H), 3.17 (1H), 3.25-3.37 (2H), 3.79 (3H), 4.37-4.49 (2H), 7.44 (1H), 7.64 (1H), 8.72 (1H).

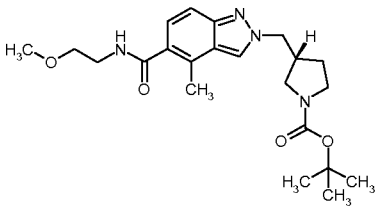
Example 217c: 2-{[(R)-1-(tert-butoxycarbonyl)pyrrolidin-3-yl]methyl}-4-methyl-2H-indazol-5-carboxylic acid



Analogously to Example 1d, 701 mg of the title compound was obtained from 620 mg of the ester prepared in Example 217b.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.34 (9H), 1.50-1.69 (1H), 1.82 (1H), 1.75-1.86 (1H), 2.69-2.88 (4H), 3.03 (1H), 3.17 (1H), 3.24-3.38 (1H), 4.42 (2H), 7.40 (1H), 7.65 (1H), 8.68 (1H), 12.28 (1H).

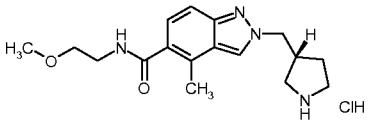
Example 217d: (R)-tert-butyl 3-({5-[N-(2-methoxyethyl)carbamoyl]-4-methyl-2H-indazol-2-yl}methyl)pyrrolidin-1-carboxylate



Analogously to Example 1, 376 mg of the title compound was obtained from 350 mg of the acid prepared in Example 217c and 73 mg of 2-methoxyethylamine.

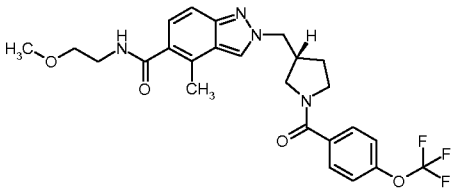
^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.35 (9H), 1.57 (1H), 1.80 (1H), 2.50 (3H), 2.73-2.86 (1H), 3.01 (1H), 3.11-3.22 (1H), 3.25 (3H), 3.26-3.39 (3H), 3.39-3.46 (2H), 4.42 (2H), 7.15 (1H), 7.39 (1H), 8.13 (1H), 8.52 (1H).

Example 217e: N-(2-methoxyethyl)-4-methyl-2-[(R)-pyrrolidin-3-ylmethyl]-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 376 mg of the amide prepared in Example 217d, 465 mg of the title compound was obtained, which was reacted without further purification.

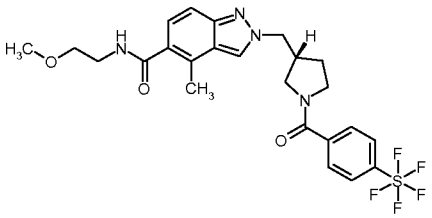
Example 218: N-(2-methoxyethyl)-4-methyl-2-({(R)-1-[4-(trifluoromethoxy)benzoyl]-pyrrolidin-3-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 55, 61 mg of the title compound was obtained from 106 mg of the compound prepared in Example 217e and 74 mg of 4-(trifluoromethoxy)benzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.57-1.74 (1H), 1.81-1.97 (1H), 2.47 / 2.51 (3H), 2.77-2.94 (1H), 3.25-3.62 (11H), 4.40 / 4.51 (2H), 7.09-7.19 (1H), 7.31-7.44 (3H), 7.61 (2H), 8.08-8.16 (1H), 8.47 / 8.55 (1H).

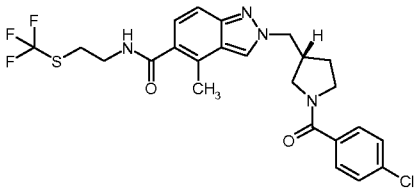
Example 219: N-(2-methoxyethyl)-4-methyl-2-({(3R)-1-[4-(pentafluoro-λ^6-sulphanyl)benzoyl]-pyrrolidin-3-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 29 mg of the title compound was obtained from 106 mg of the compound prepared in Example 217e and 75 mg of 4-(pentafluoro-λ^6-sulphanyl)benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.57-1.76 (1H), 1.81-1.99 (1H), 2.50 (3H), 2.77-2.94 (1H), 3.16-3.62 (11H), 4.39 / 4.52 (2H), 7.09-7.19 (1H), 7.32-7.44 (1H), 7.68 (2H), 7.90-7.97 (2H), 8.10-8.17 (1H), 8.46 / 8.55 (1H).

Example 220: 2-{[(R)-1-(4-chlorobenzoyl)pyrrolidin-3-yl]methyl}-4-methyl-N-{2-[(trifluoro-methyl)sulphanyl]ethyl}-2H-indazol-5-carboxamide

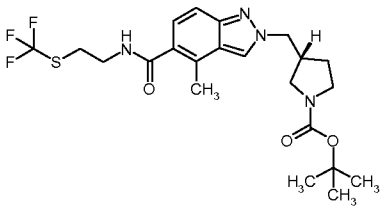


Analogously to Example 55, 29 mg of the title compound was obtained from 106 mg of the compound prepared in Example 220b and 48 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.57-1.73 (1H), 1.81-1.96 (1H), 2.48 / 2.53 (3H), 2.79-2.93 (1H), 3.13-3.60 (8H), 4.40 / 4.51 (2H), 7.14-7.23 (1H), 7.33-7.53 (5H), 8.35-8.42 (1H), 8.49 / 8.58 (1H).

The starting material was prepared as follows:

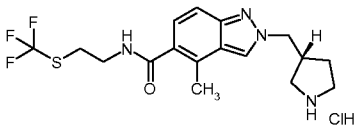
Example 220a: (R)-tert-butyl 3-{[4-methyl-5-(N-{2-[(trifluoromethyl)sulphanyl]ethyl}-carbamoyl)-2H-indazol-2-yl]methyl}pyrrolidin-1-carboxylate



Analogously to Example 1, 245 mg of the title compound was obtained from 350 mg of the acid prepared in Example 217c and 141 mg of 2-[(trifluoromethyl)sulphanyl]ethylamine.

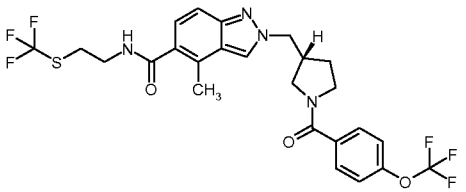
^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.35 (9H), 1.52-1.64 (1H), 1.81 (1H), 2.52 (3H), 2.71-2.96 (2H), 2.97-3.05 (12H), 3.18 (2H), 3.23-3.28 (1H), 3.51 (2H), 4.42 (2H), 7.19 (1H), 7.42 (1H), 8.39 (1H), 8.54 (1H).

Example 220b: 4-methyl-2-[(R)-pyrrolidin-3-ylmethyl]-N-{2-[(trifluoromethyl)sulphanyl]-ethyl}-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 245 mg of the amide prepared in Example 220a, 410 mg of the title compound was obtained, which was reacted without further purification.

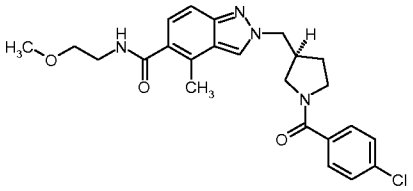
Example 221: 4-methyl-2-({(R)-1-[4-(trifluoromethoxy)benzoyl]pyrrolidin-3-yl}methyl)-N-{2-[(trifluoromethyl)sulphanyl]ethyl}-2H-indazol-5-carboxamide



Analogously to Example 55, 49 mg of the title compound was obtained from 106 mg of the compound prepared in Example 220b and 62 mg of 4-(trifluoromethoxy)benzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.58-1.74 (1H), 1.81-1.98 (1H), 2.48 / 2.53 (3H), 2.78-2.94 (1H), 3.12-3.62 (8H), 4.40 / 4.52 (2H), 7.14-7.23 (1H), 7.32-7.49 (3H), 7.61 (2H), 8.35-8.43 (1H), 8.49 / 8.58 (1H).

Example 222: 2-{[(S)-1-(4-chlorobenzoyl)pyrrolidin-3-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

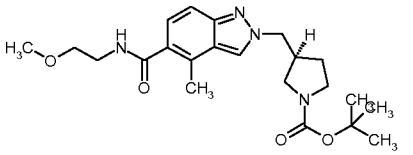


Analogously to Example 55, 67 mg of the title compound was obtained from 134 mg of the compound prepared in Example 222a and 73 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, CDCl3): δ = 1.72-1.86 (1H), 1.99-2.20 (1H), 2.64 (3H), 2.93-3.13 (1H), 3.29-3.36 (1H), 3.39 (3H), 3.45-3.71 (6H), 3.76-3.86 (1H), 4.31-4.57 (2H), 6.12-6.20 (1H), 7.30-7.42 (3H), 7.43-7.56 (3H), 7.90 / 8.02 (1H).

The starting material was prepared as follows:

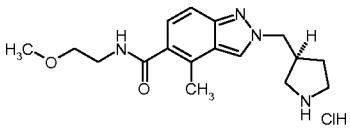
Example 222a: (S)-tert-butyl 3-({5-[N-(2-methoxyethyl)carbamoyl]-4-methyl-2H-indazol-2-yl}methyl)pyrrolidin-1-carboxylate



Analogously to Example 217a to 217d, this title compound was prepared in a quantity of 760 mg starting from (S)-tert-butyl-3-(hydroxymethyl)pyrrolidin-1-carboxylate.

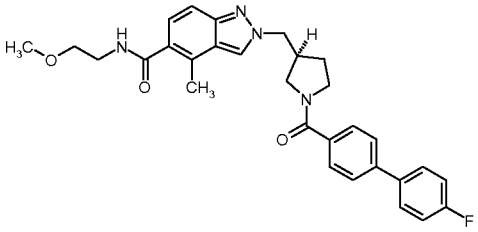
^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.35 (9H), 1.52-1.64 (1H), 1.77-1.87 (1H), 1.76-1.82 (1H), 2.50 (3H), 2.74-2.86 (1H), 3.02 (1H), 3.12-3.20 (1H), 3.25 (3H), 3.31 (1H), 3.36 (2H), 3.43 (2H), 4.42 (2H), 7.16 (1H), 7.39 (1H), 8.10 (1H), 8.51 (1H).

Example 222b: N-(2-methoxyethyl)-4-methyl-2-[(S)-pyrrolidin-3-ylmethyl]-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 159 mg of the amide prepared in Example 222a, 134 mg of the title compound was obtained, which was reacted without further purification.

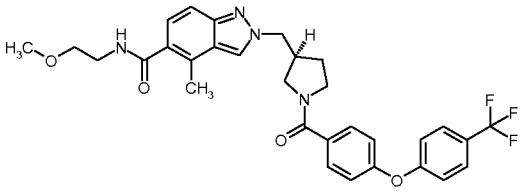
Example 223: 2-({(S)-1-[(4'-fluorobiphenyl-4-yl)carbonyl]pyrrolidin-3-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 128 mg of the title compound was obtained from 230 mg of the compound prepared in Example 222b and 141 mg of 4'-fluorobiphenyl-4-carboxylic acid.

^{1}H-NMR (300 MHz, CDCl3): δ = 1.73-1.89 (1H), 1.98-2.24 (1H), 2.60 / 2.67 (3H), 2.94-3.18 (1H), 3.37 / 3.39 (3H), 3.49-3.76 (6H), 3.79-3.91 (2H), 4.32-4.61 (2H), 6.08-6.21 (1H), 7.09-7.20 (2H), 7.28-7.38 (1H), 7.46-7.62 (7H), 7.91 / 8.04 (1H).

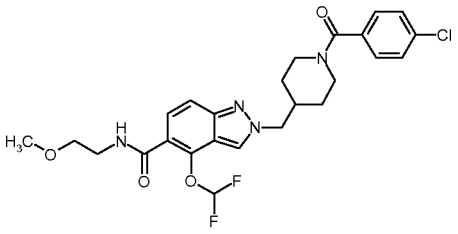
Example 224: N-(2-methoxyethyl)-4-methyl-2-{[(S)-1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}pyrrolidin-3-yl]methyl}-2H-indazol-5-carboxamide



Analogously to Example 1, 102 mg of the title compound was obtained from 230 mg of the compound prepared in Example 222b and 184 mg of 4-[4-(trifluoromethyl)phenoxy]benzoic acid.

^{1}H-NMR (300 MHz, CDCl3): δ = 1.70-2.25 (2H), 2.63 / 2.66 (3H), 2.94-3.17 (1H), 3.39 (3H), 3.47-3.92 (8H), 4.33-4.59 (2H), 6.15 (1H), 7.00-7.11 (4H), 7.30-7.40 (1H), 7.47-7.65 (5H), 7.91 / 8.03 (1H).

Example 225: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-(difluoromethoxy)-N-(2-methoxyethyl)-2H-indazol-5-carboxamide

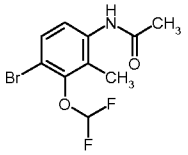


Analogously to Example 55, 90 mg of the title compound was obtained from 106 mg of the compound prepared in Example 225h and 49 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.14-1.58 (4H), 2.19-2.34 (1H), 2.67-2.81 (1H), 2.97 (1H), 3.22-3.53 (9H), 4.37 (2H), 7.13 (1H), 7.31-7.39 (3H), 7.47 (2H), 7.54 (1H), 8.21 (1H), 8.50 (1H).

The starting material was prepared as follows:

Example 225a: N-[4-bromo-3-(difluoromethoxy)-2-methylphenyl]acetamide

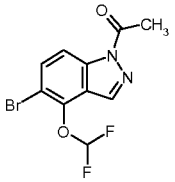


To a solution of 5.0 g of 3-difluoromethoxy-2-methylaniline in 48 ml DMF, a solution of 5.1 g of N-bromosuccinimide in 24 ml DMF was added dropwise at 0°C and stirred for 1 hour at 0°C. Then the reaction mixture was diluted with 400 ml hexane / ethyl acetate, and washed once with 50 ml of a 10% aqueous sodium carbonate solution and three times with 50 ml portions of water. After drying over sodium sulphate and filtration, this was concentrated in vacuo. The crude product thus obtained (6.68 g) was used in the next step without purification.

To a solution of 6.39 g of the bromide prepared above in 70 ml pyridine, 3.0 ml of acetic anhydride were added dropwise at 0°C and stirred for 20 hours at 25°C. The reaction mixture was concentrated in vacuo and the crude product thus obtained purified by column chromatography on silica gel with hexane / 0-100% ethyl acetate. The substance was then recrystallized from hexane. In this manner, 6.39 g of the title compound was obtained.

^{1}H-NMR (300 MHz, CDCl3): δ = 2.22 (3H), 2.27 (3H), 6.51 (1H), 6.95 (1H), 7.46 (1H), 7.71 (1H).

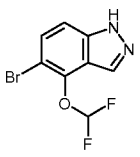
Example 225b: 1-[5-bromo-4-(difluoromethoxy)-1H-indazol-1-yl]ethan-1-one



Analogously to Example 212c, 5.32 g of the title compound was obtained from 6.38 g of the amide prepared in Example 225a.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.70 (3H), 7.34 (1H), 7.90 (1H), 8.16 (1H), 8.46 (1H).

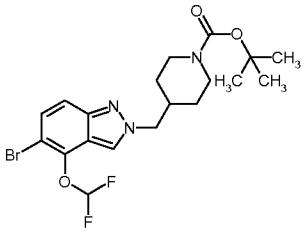
Example 225c: 5-bromo-4-(difluoromethoxy)-1H-indazole



Analogously to Example 212d, 4.12 g of the title compound was obtained from 5.32 g of the indazole prepared in Example 225b.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 7.30 (1H), 7.44 (1H), 7.56 (1H), 8.06 (1H), 13.54 (1H).

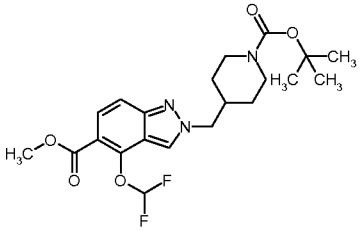
Example 225d: Tert-butyl 4-{[5-bromo-4-(difluoromethoxy)-2H-indazol-2-yl]methyl}-piperidin-1-carboxylate



Analogously to Example 212e, 2.06 g of the title compound was obtained from 4.1 g of the indazole prepared in Example 225c and 8.7 g of tert-butyl 4-[(tosyloxy)methyl]piperidin-1-carboxylate.

^{1}H-NMR (300 MHz, CDCl3): δ = 1.19-1.28 (2H), 1.45 (9H), 1.51-1.59 (2H), 2.25 (1H), 2.68 (2H), 4.12 (2H), 4.27 (2H), 6.61 (1H), 7.41 (1H), 7.50 (1H), 7.95 (1H).

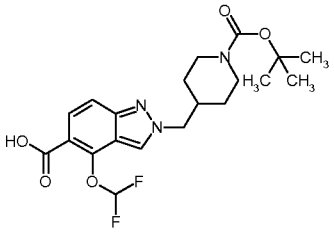
Example 225e: Methyl 2-{[1-(tert-butoxycarbonyl)piperidin-4-yl]methyl}-4-(difluoromethoxy)-2H-indazol-5-carboxylate



Analogously to Example 1e, after three runs 1.28 g of the title compound was obtained from 683 mg of the bromide prepared in Example 225d and 0.18 ml of methanol.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.96-1.22 (2H), 1.28-1.47 (11H), 2.14 (1H), 2.54-2.74 (2H), 3.81 (3H), 3.87 (2H), 4.36 (2H), 7.17 (1H), 7.58 (1H), 7.65 (1H), 8.62 (1H).

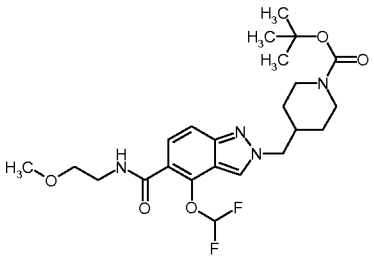
Example 225f: 2-{[1-(tert-butoxycarbonyl)piperidin-4-yl]methyl}-4-(difluoromethoxy)-2H-indazol-5-carboxylic acid



Analogously to Example 1d, 1.05 g of the title compound was obtained from 1.28 g of the ester prepared in Example 225e.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.97-1.16 (2H), 1.28-1.47 (11H), 2.13 (1H), 2.63 (2H), 3.87 (2H), 4.35 (2H), 7.14 (1H), 7.54 (1H), 7.65 (1H), 8.58 (1H), 13.05 (1H).

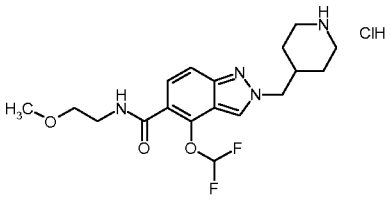
Example 225g: Tert-butyl 4-({4-(difluoromethoxy)-5-[N-(2-methoxyethyl)carbamoyl]-2H-indazol-2-yl}methyl)piperidin-1-carboxylate



Analogously to Example 1, 503 mg of the title compound was obtained from 520 mg of the compound prepared in Example 225f and 92 mg of 2-methoxyethylamine.

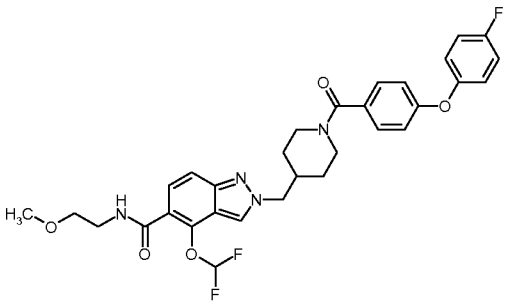
^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.01-1.13 (2H), 1.34 (9H), 1.38 (2H), 2.13 (1H), 2.59-2.71 (6H), 3.24 (3H), 3.34-3.44 (2H), 3.87 (2H), 4.34 (2H), 7.14 (1H), 7.33 (1H), 7.54 (1H), 8.21 (1H), 8.50 (1H).

Example 225h: 4-(difluoromethoxy)-N-(2-methoxyethyl)-2-(4-piperidylmethyl)-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 122 mg of the amide prepared in Example 225g, 106 mg of the title compound was obtained, which was reacted without further purification.

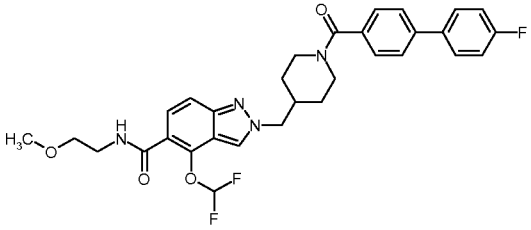
Example 226: 4-(difluoromethoxy)-2-({1-[4-(4-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 11 mg of the title compound was obtained from 106 mg of the compound prepared in Example 225h and 59 mg of 4-(4-fluorophenoxy)benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.10-1.59 (4H), 2.23-2.33 (1H), 2.75-3.01 (2H), 3.24 (3H), 3.33-3.51 (5H), 3.51-3.72 (1H), 4.37 (2H), 6.95 (2H), 7.07-7.12 (2H), 7.13 (1H), 7.17-7.26 (2H), 7.28-7.39 (3H), 7.54 (1H), 8.21 (1H), 8.50 (1H).

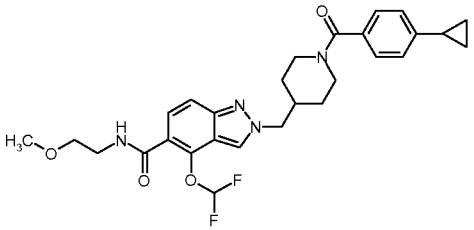
Example 227: 4-(difluoromethoxy)-2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 38 mg of the title compound was obtained from 106 mg of the compound prepared in Example 225h and 55 mg of 4'-fluorobiphenyl-4-carboxylic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.14-1.62 (4H), 2.23-2.35 (1H), 2.68-2.85 (1H), 2.91-3.09 (1H), 3.24 (3H), 3.32-3.48 (5H), 3.50-3.70 (1H), 4.38 (2H), 7.14 (1H), 7.28 (2H), 7.33 (1H), 7.40 (2H), 7.55 (1H), 7.64-7.75 (4H), 8.21 (1H), 8.51 (1H).

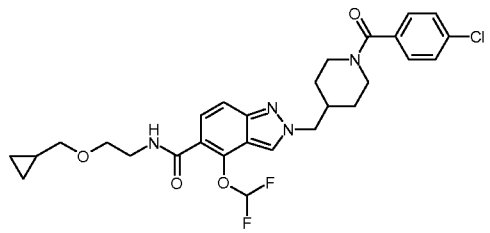
Example 228: 2-{[1-(4-cyclopropylbenzoyl)piperidin-4-yl]methyl}-4-(difluoromethoxy)-N-(2-methoxyethyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 75 mg of the title compound was obtained from 106 mg of the compound prepared in Example 225h and 41 mg of 4-cyclopropylbenzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.66 (2H), 0.94 (2H), 1.10-1.54 (4H), 1.90 (1H), 2.14-2.31 (1H), 2.72-3.02 (2H), 3.03-3.18 (1H), 3.24 (3H), 3.33-3.47 (4H), 3.49-3.68 (1H), 4.37 (2H), 7.07 (2H), 7.13 (1H), 7.19 (2H), 7.33 (1H), 7.54 (1H), 8.21 (1H), 8.50 (1H).

Example 229: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-[2-(cyclopropylmethoxy)-ethyl]-4-(difluoromethoxy)-2H-indazol-5-carboxamide

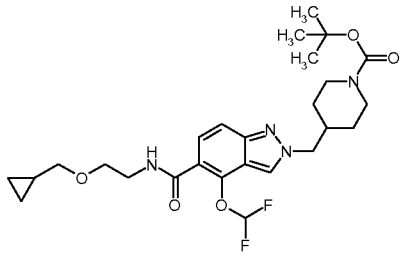


Analogously to Example 55, 170 mg of the title compound was obtained from 127 mg of the compound prepared in Example 229b and 53 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.14 (2H), 0.42 (2H), 0.96 (1H), 1.10-1.27 (2H), 1.37 (1H), 1.51 (1H), 2.26 (1H), 2.71 (1H), 2.97 (1H), 3.20-3.55 (8H), 4.37 (2H), 7.14 (1H), 7.31-7.38 (3H), 7.47 (2H), 7.55 (1H), 8.21 (1H), 8.51 (1H).

The starting material was prepared as follows:

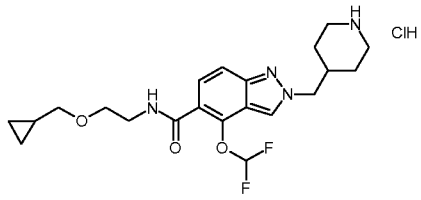
Example 229a: Tert-butyl 4-{[5-{N-[2-(cyclopropylmethoxy)ethyl]carbamoyl}-4-(difluoromethoxy)-2H-indazol-2-yl]methyl}piperidin-1-carboxylate



Analogously to Example 1, 453 mg of the title compound was obtained from 520 mg of the compound prepared in Example 225f and 185 mg of 2-(cyclopropylmethoxy)ethylamine.

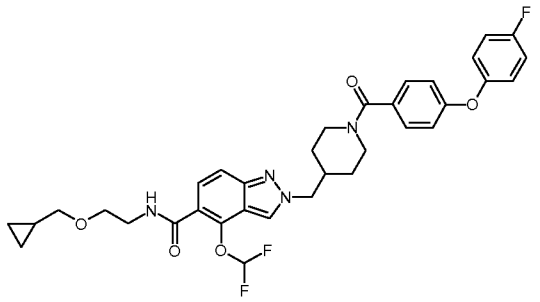
^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.14 (2H), 0.42 (2H), 0.97 (1H), 1.07 (2H), 1.34 (9H), 1.39 (2H), 2.13 (1H), 2.56-2.72 (2H), 3.23 (2H), 3.37 (2H), 3.48 (2H), 3.87 (2H), 4.34 (2H), 7.15 (1H), 7.34 (1H), 7.55 (1H), 8.21 (1H), 8.50 (1H).

Example 229b: N-[(2-cyclopropylmethoxy)ethyl]-4-(difluoromethoxy)-2-(4-piperidylmethyl)-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 145 mg of the amide prepared in Example 229a, 127 mg of the title compound was obtained, which was reacted without further purification.

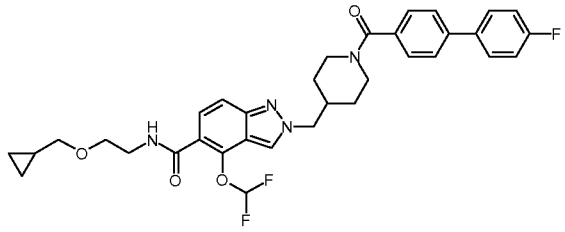
Example 230: N-[2-(cyclopropylmethoxy)ethyl]-4-(difluoromethoxy)-2-({1-[4-(4-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 156 mg of the title compound was obtained from 127 mg of the compound prepared in Example 229b and 64 mg of 4-(4-fluorophenoxy)benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.14 (2H), 0.42 (2H), 0.96 (1H), 1.10-1.54 (4H), 2.18-2.33 (1H), 2.71-3.02 (2H), 3.03-3.16 (1H), 3.22 (2H), 3.37 (2H), 3.47 (2H), 3.55-3.68 (1H), 4.37 (2H), 6.95 (2H), 7.10 (2H), 7.14 (1H), 7.22 (2H), 7.34 (3H), 7.55 (1H), 8.21 (1H), 8.51 (1H).

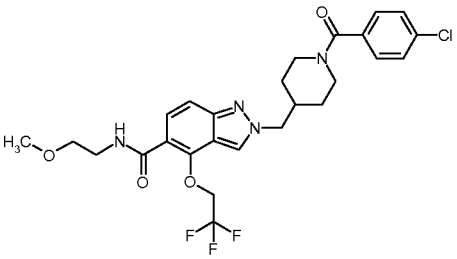
Example 231: N-[2-(cyclopropylmethoxy)ethyl]-4-(difluoromethoxy)-2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 164 mg of the title compound was obtained from 127 mg of the compound prepared in Example 229b and 60 mg of 4'-fluorobiphenyl-4-carboxylic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.14 (2H), 0.42 (2H), 0.96 (1H), 1.14-1.60 (4H), 2.27 (1H), 2.70-3.04 (1H), 2.87 (1H), 3.03-3.15 (1H), 3.22 (2H), 3.37 (2H), 3.47 (2H), 3.60 (1H), 4.38 (2H), 7.14 (1H), 7.28 (2H), 7.34 (1H), 7.41 (2H), 7.55 (1H), 7.64-7.75 (4H), 8.21 (1H), 8.52 (1H).

Example 232: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-(2,2,2-trifluoroethoxy)-2H-indazol-5-carboxamide

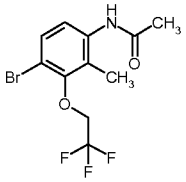


Analogously to Example 55, 113 mg of the title compound was obtained from 109 mg of the compound prepared in Example 232h and 46 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.12-1.61 (3H), 2.19-2.34 (1H), 2.67-3.07 (2H), 3.23 (3H), 3.33-3.56 (4H), 4.28-4.47 (3H), 4.95 (2H), 7.31-7.39 (3H), 7.40-7.50 (3H), 7.99 (1H), 8.65 (1H).

The starting material was prepared as follows:

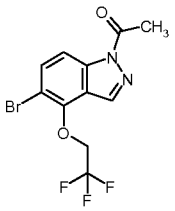
Example 232a: N-[4-bromo-2-methyl-3-(2,2,2-trifluoroethoxy)phenyl]acetamide



Analogously to Example 225a, 6.13 g of the title compound was obtained from 5.0 g of 2-methyl-3-(2,2,2-trifluoroethoxy)aniline.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.07 (3H), 2.18 (3H), 4.55 (2H), 7.29 (1H), 7.45 (1H), 9.42 (1H).

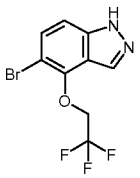
Example 232b: 1-[5-bromo-4-(2,2,2-trifluoroethoxy)-1H-indazol-1-yl]ethan-1-one



Analogously to Example 212c, 5.08 g of the title compound was obtained from 6.13 g of the amide prepared in Example 232a.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 2.69 (3H), 5.14 (2H), 7.80 (1H), 7.99 (1H), 8.64 (1H).

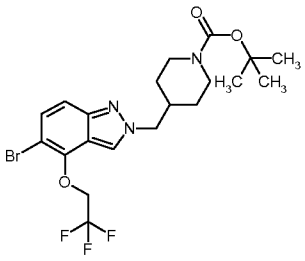
Example 232c: 5-bromo-4-(2,2,2-trifluoroethoxy)-1H-indazole



Analogously to Example 212d, 3.57 g of the title compound was obtained from 5.08 g of the indazole prepared in Example 232b.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 5.05 (2H), 7.24 (1H), 7.45 (1H), 8.26 (1H), 13.38 (1H).

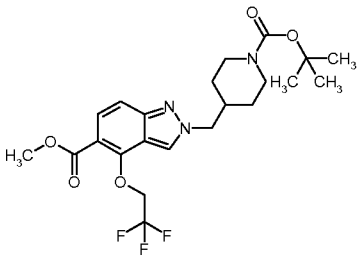
Example 232d: Tert-butyl 4-{[5-bromo-4-(2,2,2-trifluoroethoxy)-2H-indazol-2-yl]methyl}-piperidin-1-carboxylate



Analogously to Example 212e, 1.77 g of the title compound was obtained from 3.57 g of the indazole prepared in Example 232c and 6.7 g of tert-butyl 4-[(tosyloxy)methyl]piperidin-1-carboxylate.

^{1}H-NMR (300 MHz, CDCl3): δ = 1.16-1.31 (2H), 1.45 (9H), 1.54 (2H), 2.25 (1H), 2.68 (2H), 4.05-4.21 (2H), 4.27 (2H), 4.54 (2H), 7.35 (1H), 7.41 (1H), 7.91 (1H).

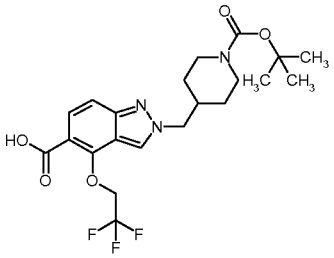
Example 232e: Methyl 2-{[1-(tert-butoxycarbonyl)piperidin-4-yl]methyl}-4-(2,2,2-trifluoro-ethoxy)-2H-indazole-5-carboxylate



Analogously to Example 1e, after three runs 857 mg of the title compound was obtained from 590 mg of the bromide prepared in Example 232d and 0.15 ml of methanol.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.00-1.17 (2H), 1.34 (9H), 1.37-1.47 (2H), 2.13 (1H), 2.55-2.74 (2H), 3.79 (3H), 3.87 (2H), 4.32 (2H), 4.89 (2H), 7.39 (1H), 7.56 (1H), 8.67 (1H).

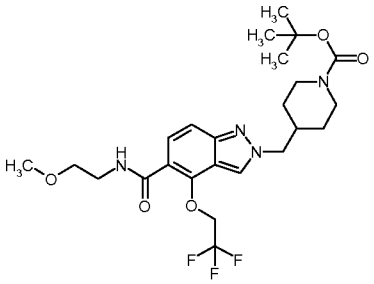
Example 232f: 2-{[1-(tert-butoxycarbonyl)piperidin-4-yl]methyl}-4-(2,2,2-trifluoroethoxy)-2H-indazole-5-carboxylic acid



Analogously to Example 1d, 724 mg of the title compound was obtained from 854 mg of the ester prepared in Example 232e.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.01-1.17 (2H), 1.34 (9H), 1.40 (2H), 2.13 (1H), 2.53-2.75 (2H), 3.87 (2H), 4.32 (2H), 4.84 (2H), 7.37 (1H), 7.58 (1H), 8.60 (1H), 12.74 (1H).

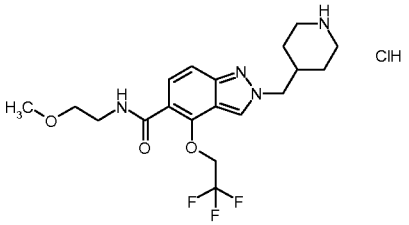
Example 232g: Tert-butyl 4-({5-[N-(2-methoxyethyl)carbamoyl]-4-(2,2,2-trifluoroethoxy)-2H-indazol-2-yl}methyl)piperidin-1-carboxylate



Analogously to Example 1, 386 mg of the title compound was obtained from 360 mg of the compound prepared in Example 232f and 59 mg of 2-methoxyethylamine.

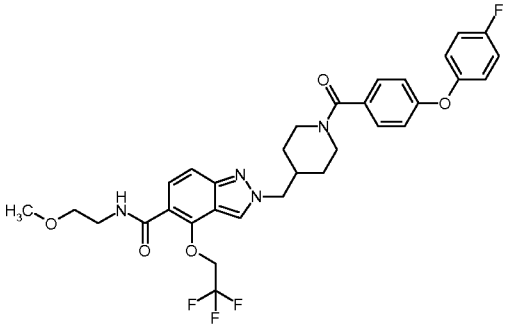
^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.98-1.18 (2H), 1.34 (9H), 1.43 (2H), 2.14 (1H), 2.65 (2H), 3.23 (3H), 3.35-3.47 (4H), 3.88 (2H), 4.30 (2H), 4.96 (2H), 7.35 (1H), 7.43 (1H), 7.99 (1H), 8.65 (1H).

Example 232h: N-(2-methoxyethyl)-2-(4-piperidylmethyl)-4-(2,2,2-trifluoroethoxy)-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 109 mg of the amide prepared in Example 232g, 113 mg of the title compound was obtained, which was reacted without further purification.

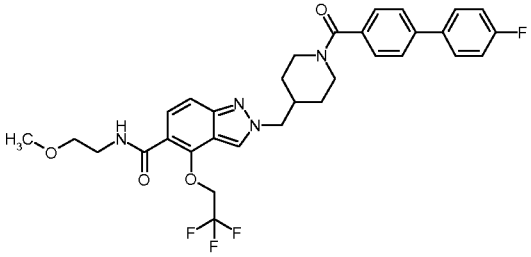
Example 233: 2-({1-[4-(4-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-(2,2,2-trifluoroethoxy)-2H-indazol-5-carboxamide



Analogously to Example 1, 51 mg of the title compound was obtained from 109 mg of the compound prepared in Example 232h and 56 mg of 4-(4-fluorophenoxy)benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.10-1.31 (1H), 1.48 (2H), 2.18-2.37 (1H), 2.69-3.04 (2H), 3.23 (3H), 3.37-3.48 (4H), 3.56-3.71 (1H), 4.33 (2H), 4.95 (2H), 6.95 (2H), 7.06-7.15 (2H), 7.18-7.27 (2H), 7.31-7.38 (3H), 7.40-7.47 (1H), 7.99 (1H), 8.66 (1H).

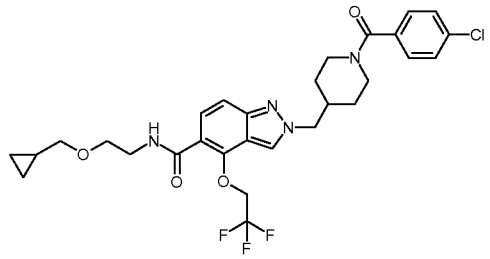
Example 234: 2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-(2,2,2-trifluoroethoxy)-2H-indazol-5-carboxamide



Analogously to Example 1, 61 mg of the title compound was obtained from 109 mg of the compound prepared in Example 232h and 52 mg of 4-(4-fluorophenyl)benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.14-1.63 (3H), 2.19-2.37 (1H), 2.68-3.09 (2H), 3.23 (3H), 3.34-3.48 (4H), 3.62 (1H), 4.28-4.42 (2H), 4.96 (2H), 7.22-7.47 (6H), 7.64-7.76 (4H), 7.99 (1H), 8.66 (1H).

Example 235: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-[2-(cyclopropylmethoxy)ethyl]-4-(2,2,2-trifluoroethoxy)-2H-indazol-5-carboxamide

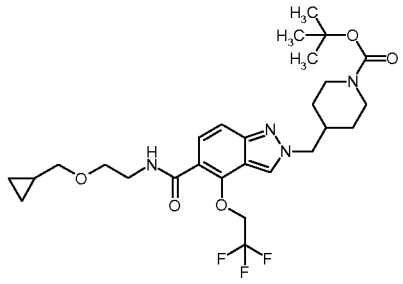


Analogously to Example 55, 122 mg of the title compound was obtained from 122 mg of the compound prepared in Example 235b and 48 mg of 4-chlorobenzoyl chloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.13 (2H), 0.41 (2H), 0.95 (1H), 1.11-1.62 (3H), 2.19-2.34 (1H), 2.73 (1H), 2.98 (1H), 3.21 (2H), 3.33-3.57 (5H), 4.33 (2H), 4.95 (2H), 7.31-7.51 (6H), 8.00 (1H), 8.65 (1H).

The starting material was prepared as follows:

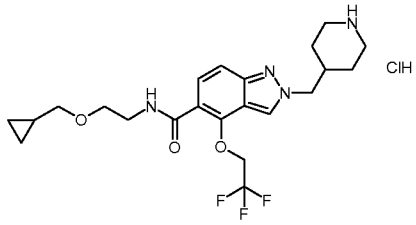
Example 235a: Tert-butyl 4-{[5-{N-[2-(cyclopropylmethoxy)ethyl]carbamoyl}-4-(2,2,2-trifluoroethoxy)-2H-indazol-2-yl]methyl}piperidin-1-carboxylate



Analogously to Example 1, 429 mg of the title compound was obtained from 360 mg of the compound prepared in Example 232f and 119 mg of 2-(cyclopropylmethoxy)ethylamine.

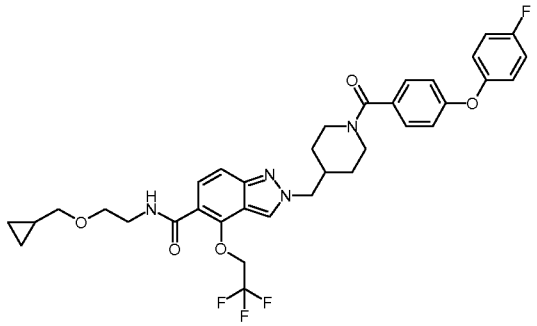
^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.13 (2H), 0.42 (2H), 0.95 (1H), 1.08 (2H), 1.34 (9H), 1.41 (2H), 2.14 (1H), 3.22 (2H), 3.41 (2H), 3.48 (2H), 3.88 (2H), 4.30 (2H), 4.95 (2H), 7.35 (1H), 7.42 (1H), 8.00 (1H), 8.65 (1H).

Example 235b: N-[2-(cyclopropylmethoxy)ethyl]-2-(4-piperidylmethyl)-4-(2,2,2-trifluoroethoxy)-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 138 mg of the amide prepared in Example 235a, 122 mg of the title compound was obtained, which was reacted without further purification.

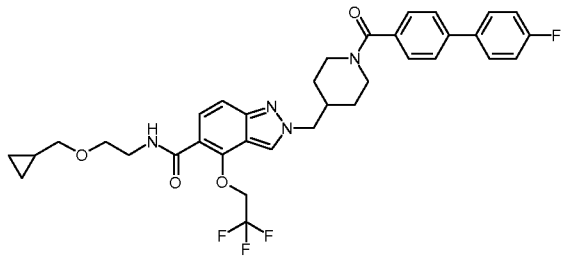
Example 236: N-[2-(cyclopropylmethoxy)ethyl]-2-({1-[4-(4-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-4-(2,2,2-trifluoroethoxy)-2H-indazol-5-carboxamide



Analogously to Example 1, 95 mg of the title compound was obtained from 122 mg of the compound prepared in Example 235b and 58 mg of 4-(4-fluorophenoxy)benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.13 (2H), 0.41 (2H), 0.95 (1H), 1.09-1.60 (3H), 2.17-2.36 (1H), 2.68-3.06 (2H), 3.22 (2H), 3.34-3.76 (5H), 4.33 (2H), 4.95 (2H), 6.95 (2H), 7.06-7.14 (2H), 7.17-7.27 (2H), 7.30-7.38 (3H), 7.42 (1H), 7.99 (1H), 8.65 (1H).

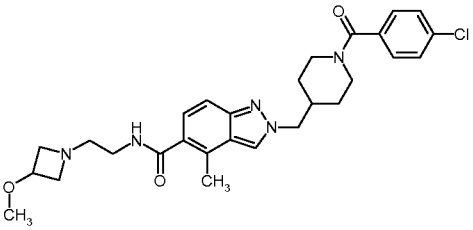
Example 237: N-[2-(cyclopropylmethoxy)ethyl]-2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl] piperidin-4-yl}methyl)-4-(2,2,2-trifluoroethoxy)-2H-indazol-5-carboxamide



Analogously to Example 1, 98 mg of the title compound was obtained from 122 mg of the compound prepared in Example 235b and 54 mg of 4-(4-fluorophenoxy)benzoic acid.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.12 (2H), 0.41 (2H), 0.95 (1H), 1.15-1.64 (3H), 2.21-2.36 (1H), 2.70-3.10 (2H), 3.21 (2H), 3.35-3.69 (5H), 4.35 (2H), 4.95 (2H), 7.22-7.46 (6H), 7.63-7.77 (4H), 7.99 (1H), 8.66 (1H).

Example 238: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-[2-(3-methoxyazetidin-1-yl) ethyl]-4-methyl-2H-indazol-5-carboxamide

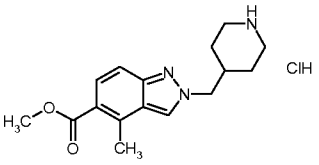


Analogously to Example 1, 33 mg of the title compound was obtained from 120 mg of the compound prepared in Example 238c and 40 mg of 2-(3-methoxyazetidin-1-yl)ethylamine (prepared analogously to WO2006/104406).

^{1}H-NMR (300 MHz, CDCl3): δ = 0.83 (1H), 1.20-2.01 (4H), 2.38 (1H), 2.66 (3H), 2.69-3.09 (2H), 3.31 (3H), 3.43 (2H), 3.56-3.90 (5H), 4.18-4.32 (3H), 4.43 (2H), 6.91 (1H), 7.30-7.41 (5H), 7.52 (1H), 7.95 (1H).

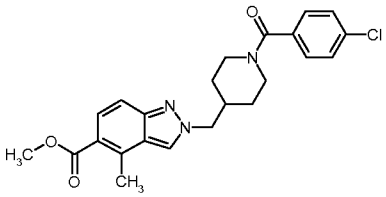
The starting material was prepared as follows:

Example 238a: methyl 4-methyl-2-(4-piperidylmethyl)-2H-indazol-5-carboxylate hydrochloride



Analogously to Example 1a, from 3.0 g of the ester prepared in Example 1e, 2.51 g of the title compound was obtained, which was reacted without further purification.

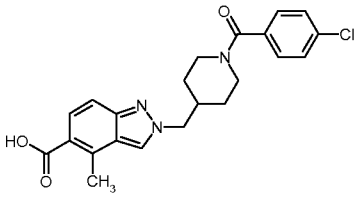
Example 238b: Methyl 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methyl-2H-indazol-5-carboxylate



Analogously to Example 55, 3.27 g of the title compound was obtained from 2.5 g of the compound prepared in Example 238a and 1.5 g of 4-chlorobenzoyl chloride.

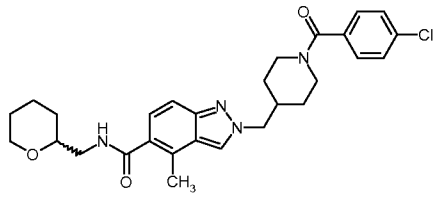
^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.16-1.63 (4H), 2.21-2.33 (1H), 2.73 (4H), 2.90-3.05 (1H), 3.44-3.55 (1H), 3.79 (3H), 4.32 (2H), 4.36-4.47 (1H), 7.36 (2H), 7.42 (1H), 7.46 (2H), 7.63 (1H), 8.67 (1H).

Example 238c: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methyl-2H-indazol-5-carboxylic acid



Analogously to Example 1d, 470 mg of the title compound was obtained from 485 mg of the ester prepared in Example 238b.

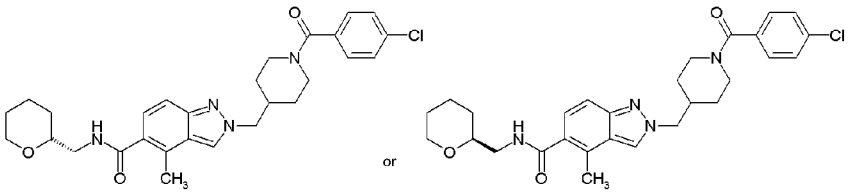
Example 239: (+/-)-2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methyl-N-(3,4,5,6-tetrahydro-2H-pyran-2-ylmethyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 188 mg of the title compound was obtained from 300 mg of the compound prepared in Example 238c and 92 mg of 3,4,5,6-tetrahydro-2H-pyran-2-ylmethylamine hydrochloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.01-1.27 (3H), 1.29-1.64 (7H), 2.19-2.32 (1H), 2.48 (3H), 2.66-2.80 (1H), 2.89-3.00 (1H), 3.00-3.08 (1H), 3.16-3.25 (2H), 3.34-3.42 (1H), 3.43-3.55 (1H), 3.77-3.88 (1H), 4.31 (2H), 4.39 (1H), 7.14 (1H), 7.32-7.40 (2H), 7.46 (2H), 7.83 (1H), 8.09 (1H), 8.46 (1H).

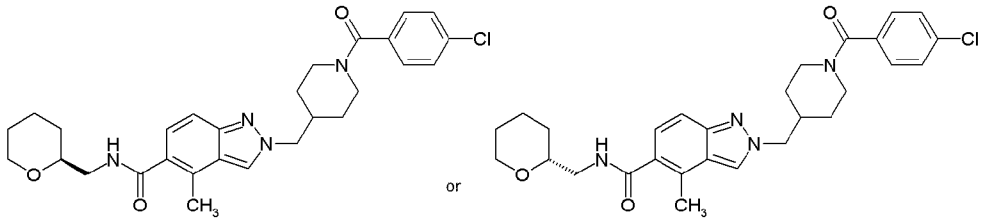
Example 240: (R or S)-2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methyl-N-(3,4,5,6-tetrahydro-2H-pyran-2-ylmethyl)-2H-indazol-5-carboxamide



From 185 mg of the racemate prepared in Example 239, 51 mg of the title compound together with 53 mg of the slower-eluting enantiomer (Example 241) were obtained by racemate separation by means of preparative chiral HPLC (Method B).

Analytical chiral HPLC: 7.02 min.

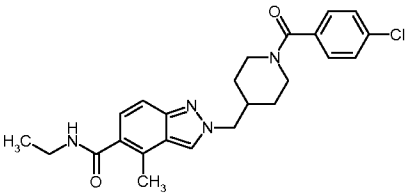
Example 241: (S or R)-2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methyl-N-(3,4,5,6-tetrahydro-2H-pyran-2-ylmethyl)-2H-indazol-5-carboxamide



From 185 mg of the racemate prepared in Example 239, 53 mg of the title compound together with 51 mg of the faster-eluting enantiomer (Example 240) were obtained by racemate separation by means of preparative chiral HPLC (Method B).

Analytical chiral HPLC: 8.24 min.

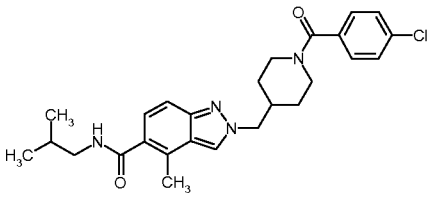
Example 242: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-ethyl-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 85 mg of the title compound was obtained from 300 mg of the compound prepared in Example 238c and 43 mg of ethylamine 2M in THF.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.08 (3H), 1.16-1.60 (4H), 2.20-2.33 (1H), 2.48 (3H), 2.63-3.07 (2H), 3.22 (2H), 3.48 (1H), 4.24-4.46 (3H), 7.14 (1H), 7.31-7.42 (3H), 7.46 (2H), 8.08 (1H), 8.46 (1H).

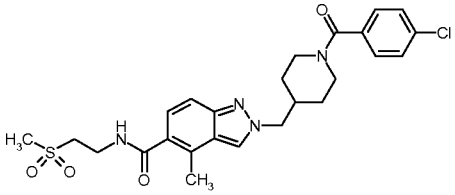
Example 243: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-isobutyl-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 92 mg of the title compound was obtained from 300 mg of the compound prepared in Example 238c and 69 mg of isobutylamine.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.85-0.90 (6H), 1.13-1.57 (4H), 1.75-1.83 (1H), 2.21-2.34 (1H), 2.49 (3H), 3.03 (4H), 3.48 (1H), 4.27-4.45 (3H), 7.14 (1H), 7.31-7.41 (3H), 7.46 (2H), 8.11 (1H), 8.47 (1H).

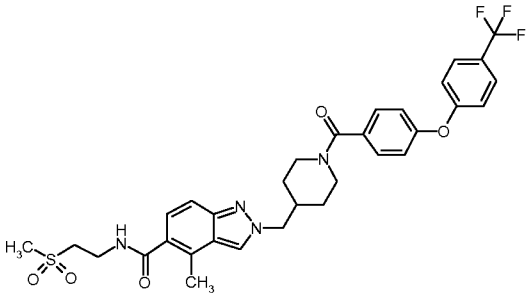
Example 244: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-(2-mesylethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 132 mg of the title compound was obtained from 300 mg of the compound prepared in Example 238c and 151 mg of 2-mesylethylamine hydrochloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.19-1.62 (4H), 2.24-2.36 (1H), 2.54 (3H), 2.70-3.05 (2H), 3.05 (3H), 3.38 (2H), 3.52 (1H), 3.65 (2H), 4.30-4.49 (3H), 7.22 (1H), 7.38 (2H), 7.42 (1H), 7.49 (2H), 8.33 (1H), 8.52 (1H).

Example 245: N-(2-mesylethyl)-4-methyl-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide

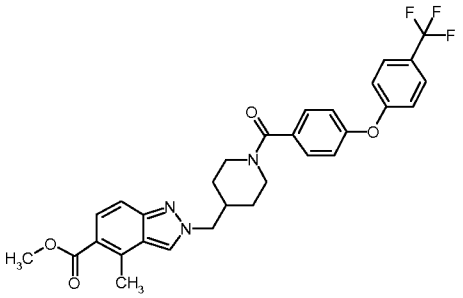


Analogously to Example 1, 67 mg of the title compound was obtained from 137 mg of the compound prepared in Example 245b and 41 mg of 2-mesylethylamine hydrochloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.15-1.62 (4H), 2.22-2.33 (1H), 2.50 (3H), 2.68-3.01 (2H), 3.02 (2H), 3.35 (1H), 3.52-3.69 (3H), 4.28-4.47 (2H), 7.12 (1H), 7.15-7.22 (2H), 7.37-7.44 (2H), 7.73 (1H), 8.32 (1H), 8.50 (1H).

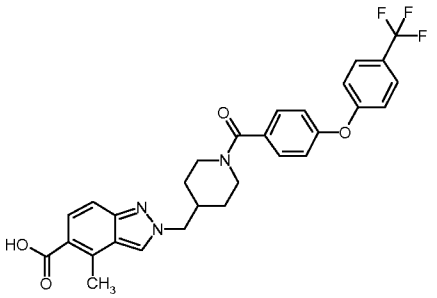
The starting material was prepared as follows:

Example 245a: Methyl 4-methyl-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxylate



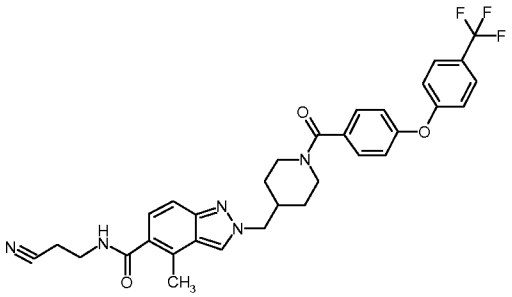
Analogously to Example 1, 2.73 g of the title compound was obtained from 3.76 g of the compound prepared in Example 238a and 3.28 g of 4-[4-(trifluoromethyl)phenoxy]benzoic acid.
^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.25 (2H), 1.35-1.70 (2H), 2.20-2.37 (1H), 2.65-2.70 (3H), 2.75-3.10 (2H), 3.52-3.72 (1H), 3.82 (4H), 4.36 (2H), 7.14 (2H), 7.20 (2H), 7.39-7.48 (3H), 7.66 (1H), 7.75 (2H), 8.70 (1H).

Example 245b: 4-methyl-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}piperidin-4-yl)-methyl]-2H-indazol-5-carboxylic acid



Analogously to Example 1d, 1.1 g of the title compound was obtained from 2.73 g of the ester prepared in Example 245a.

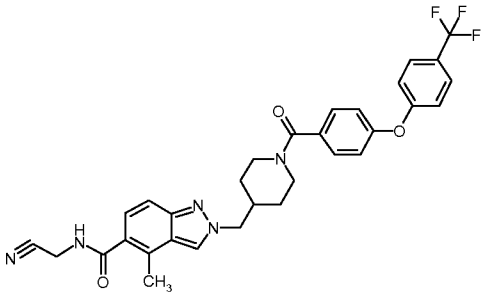
Example 246: N-(2-cyanoethyl)-4-methyl-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 1, 144 mg of the title compound was obtained from 137 mg of the compound prepared in Example 245b and 18 mg of 3-aminopropanenitrile.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.13-1.58 (4H), 2.21-2.33 (1H), 2.52 (3H), 2.75 (2H), 2.80-3.16 (2H), 3.44 (2H), 3.59 (1H), 4.27-4.50 (3H), 7.12 (2H), 7.15-7.21 (3H), 7.37-7.44 (3H), 7.73 (2H), 8.46 (1H), 8.51 (1H)

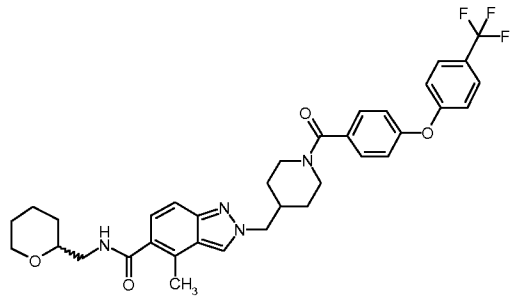
Example 247: N-(cyanomethyl)-4-methyl-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 1, 125 mg of the title compound was obtained from 137 mg of the compound prepared in Example 245b and 24 mg of 2-aminoacetonitrile hydrochloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.16-1.60 (4H), 2.23-2.34 (1H), 2.53 (3H), 2.69-3.06 (2H), 3.59 (1H), 4.26 (2H), 4.29-4.50 (3H), 7.08-7.23 (5H), 7.38-7.46 (3H), 7.73 (2H), 8.54 (1H), 8.83 (1H).

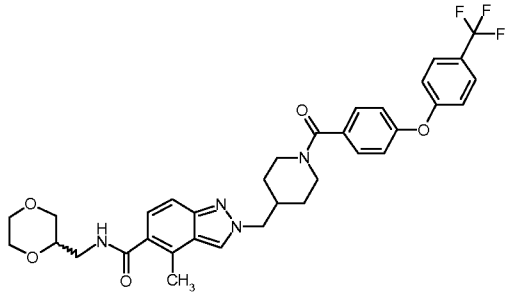
Example 248: (+/-)-4-methyl-N-(3,4,5,6-tetrahydro-2H-pyran-2-ylmethyl)-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 1, 231 mg of the title compound was obtained from 254 mg of the compound prepared in Example 245b and 72 mg of 3,4,5,6-tetrahydro-2H-pyran-2-ylmethylamine.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.01-1.66 (10H), 2.24-2.32 (1H), 2.70-3.15 (4H), 3.21 (3H), 3.34-3.43 (1H), 3.54-3.64 (1H), 3.76-3.89 (2H), 4.32 (3H), 7.09-7.21 (5H), 7.35-7.44 (3H), 7.73 (2H), 8.09 (1H), 8.47 (1H).

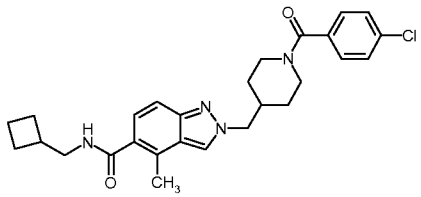
Example 249: (+/-)-N-(1,4-dioxan-2-ylmethyl)-4-methyl-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 1, 280 mg of the title compound was obtained from 254 mg of the compound prepared in Example 245b and 73 mg of 1,4-dioxan-2-ylmethylamine.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.13-1.61 (4H), 2.23-2.32 (1H), 2.49 (3H), 2.75 (1H), 2.94-3.27 (4H), 3.38-3.77 (8H), 4.32 (2H), 7.09-7.21 (5H), 7.36-7.44 (3H), 7.73 (2H), 8.16 (1H), 8.48 (1H).

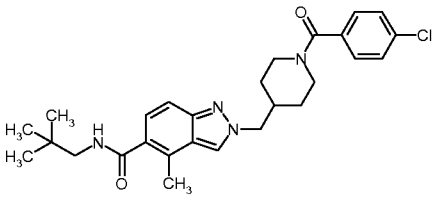
Example 250: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-(cyclobutylmethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 79 mg of the title compound was obtained from 300 mg of the compound prepared in Example 238c and 115 mg of cyclobutylmethylamine hydrochloride.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.16-1.58 (4H), 1.64-1.86 (4H), 1.90-2.01 (2H), 2.19-2.32 (1H), 2.48 (3H), 2.50 (1H), 2.66-3.05 (2H), 3.19-3.25 (2H), 3.48 (1H), 4.27-4.47 (3H), 7.12 (1H), 7.31-7.40 (3H), 7.46 (2H), 8.09 (1H), 8.46 (1H).

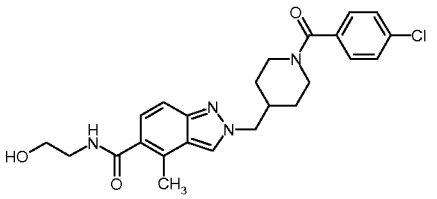
Example 251: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-(2,2-dimethylpropyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 108 mg of the title compound was obtained from 300 mg of the compound prepared in Example 238c and 83 mg of 2,2-dimethylpropan-1-amine.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 0.91 (9H), 1.17-1.63 (4H), 2.24-2.36 (1H), 2.52 (3H), 2.70-3.04 (2H), 3.07 (2H), 3.52 (1H), 4.30-4.50 (3H), 7.17 (1H), 7.38 (2H), 7.42 (1H), 7.49 (2H), 8.07 (1H), 8.49 (1H).

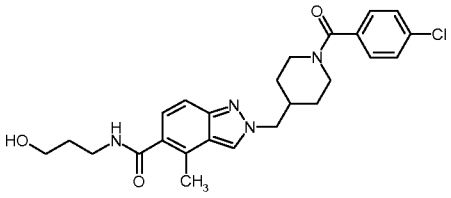
Example 252: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-(2-hydroxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 84 mg of the title compound was obtained from 370 mg of the compound prepared in Example 238c and 54 mg of 2-aminoethanol.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.14-1.64 (4H), 2.24-2.35 (1H), 2.53 (3H), 2.69-3.09 (2H), 3.30 (2H), 3.43-3.58 (3H), 4.27-4.50 (3H), 4.67 (1H), 7.20 (1H), 7.35-7.43 (3H), 7.49 (2H), 8.02 (1H), 8.49 (1H).

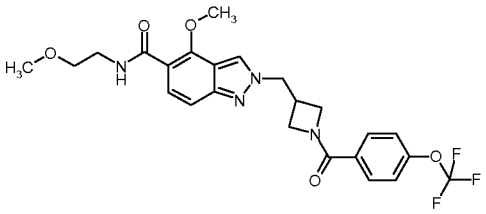
Example 253: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-(3-hydroxypropyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1, 95 mg of the title compound was obtained from 370 mg of the compound prepared in Example 238c and 66 mg of 3-aminopropan-1-ol.

^{1}H-NMR (300 MHz, DMSO-d6): δ = 1.17-1.60 (4H), 1.66 (2H), 2.22-2.35 (1H), 2.53 (3H), 2.70-3.09 (2H), 3.27 (2H), 3.47 (2H), 3.47-3.67 (1H), 4.34 (2H), 4.41 (1H), 4.45 (1H), 7.17 (1H), 7.35-7.43 (3H), 7.49 (2H), 8.07 (1H), 8.49 (1H).

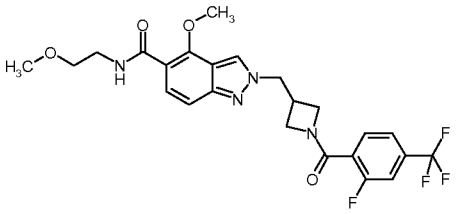
Example 254: 4-methoxy-N-(2-methoxyethyl)-2-({1-[4-(trifluoromethoxy)benzoyl]azetidin-3-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 90 mg of the title compound was obtained from 100 mg of the compound prepared in Example 214c and 97 mg of 4-(trifluoromethoxy)benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 3.24 - 3.29 (1H), 3.29 - 3.32 (3H), 3.43 - 3.51 (4H), 3.91 - 4.04 (1H), 4.10 - 4.18 (1H), 4.20 (3H), 4.22 - 4.29 (1H), 4.44 (1H), 4.70 (2H), 7.24 (1H), 7.37 - 7.51 (2H), 7.66 (1H), 7.70 - 7.80 (2H), 8.22 (1H), 8.91 (1H).

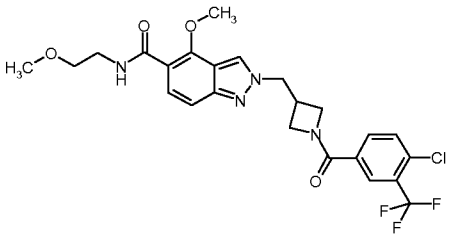
Example 255: 2-({1-[2-fluoro-4-(trifluoromethyl)benzoyl]azetidin-3-yl}methyl)-4-methoxy-N-(2-methoxyethyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 40 mg of the title compound was obtained from 100 mg of the compound prepared in Example 214c and 98 mg of 2-fluoro-4-(trifluoromethyl)benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 3.30 (4H), 3.44 - 3.50 (4H), 3.94 - 4.04 (2H), 4.15 (2H), 4.20 (3H), 4.70 (2H), 7.24 (1H), 7.60 - 7.75 (3H), 7.78 - 7.89 (1H), 8.16 - 8.27 (1H), 8.90 (1H).

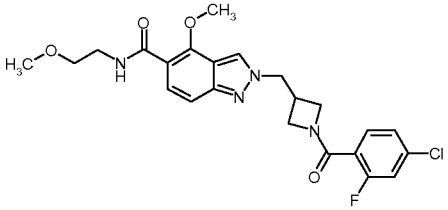
Example 256: 2-({1-[4-chloro-3-(trifluoromethyl)benzoyl]azetidin-3-yl}methyl)-4-methoxy-N-(2-methoxyethyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 40 mg of the title compound was obtained from 100 mg of the compound prepared in Example 214c and 106 mg of 4-chloro-3-(trifluoromethyl)benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 3.30 (4H), 3.43 - 3.53 (4H), 3.95 - 4.05 (1H), 4.20 (4H), 4.23 - 4.31 (1H), 4.47 (1H), 4.71 (2H), 7.23 (1H), 7.67 (1H), 7.78 - 7.85 (1H), 7.86 - 7.93 (1H), 7.96 (1H), 8.22 (1H), 8.90 (1H).

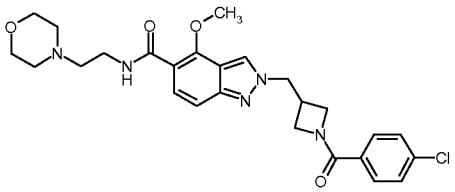
Example 257: 2-{[1-(4-chloro-2-fluorobenzoyl)azetidin-3-yl]methyl}-4-methoxy-N-(2-methoxyethyl)-2H-indazol-5-carboxamide



Analogously to Example 1, 20 mg of the title compound was obtained from 100 mg of the compound prepared in Example 214c and 82 mg of 4-chloro-2-fluorobenzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 3.30 (4H), 3.42 - 3.51 (4H), 3.98 (2H), 4.14 (2H), 4.20 (3H), 4.69 (2H), 7.24 (1H), 7.38 (1H), 7.48 (1H), 7.56 (1H), 7.66 (1H), 8.15 - 8.30 (1H), 8.90 (1H).

Example 258: 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-4-methoxy-N-(2-morpholino-ethyl)-2H-indazol-5-carboxamide

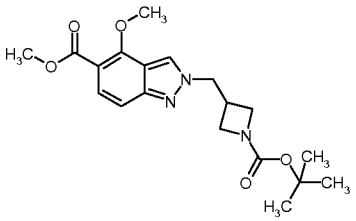


Analogously to Example 1b Version B, 67 mg of the title compound was obtained from 66 mg of the compound prepared in Example 258d and 32 mg of 2-morpholinoethylamine in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 2.44 (4H), 3.21 - 3.36 (3H), 3.42 (2H), 3.61 (4H), 3.88 - 4.04 (1H), 4.07 - 4.18 (1H), 4.23 (4H), 4.35 - 4.50 (1H), 4.70 (2H), 7.25 (1H), 7.41 - 7.56 (2H), 7.59 - 7.66 (2H), 7.70 (1H), 8.32 (1H), 8.91 (1H).

The starting material was prepared as follows:

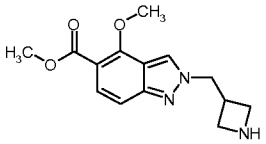
Example 258a: Methyl 2-{[1-(tert-butoxycarbonyl)azetidin-3-yl]methyl}-4-methoxy-2H-indazol-5-carboxylate



Analogously to Example 1e, 448 mg of the title compound was obtained from 750 mg of the compound prepared in Example 214a and 546 mg of methanol.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.27 - 1.44 (9H), 3.01 - 3.22 (1H), 3.78 (5H), 3.85 - 3.99 (2H), 4.14 (3H), 4.64 (2H), 7.24 (1H), 7.51 (1H), 8.94 (1H).

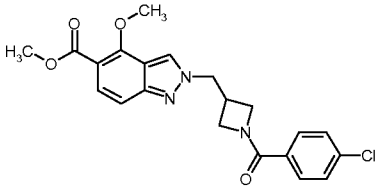
Example 258b: Methyl 2-(azetidin-3-ylmethyl)-4-methoxy-2H-indazol-5-carboxylate



800 mg of 258a were first placed in 40 ml acetone, treated with 40 ml of semiconcentrated hydrochloric acid, stirred until complete conversion and concentrated to dryness. Yield: 414 mg of the title compound.

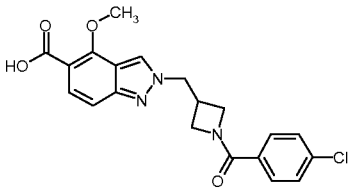
^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 3.39 (1H), 3.79 (3H), 3.84 - 3.95 (2H), 3.96 - 4.07 (2H), 4.15 (3H), 4.72 (2H), 7.25 (1H), 7.52 (1H), 8.92 (1H).

Example 258c: Methyl 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-4-methoxy-2H-indazol-5-carboxylate



404 mg of 258b were first placed in 30 ml DCM at 0°C, treated with 0.21 ml of 4-chlorobenzoyl chloride and 0.75 ml of N-ethyldiisopropylamine and stirred at room temperature until complete conversion. For the work-up, the reaction solution was treated with saturated sodium hydrogen carbonate solution, extracted with DCM and the combined organic phases dried with sodium sulphate and concentrated to dryness. This yielded 608 mg of the title compound, which was used in the next step without further purification.

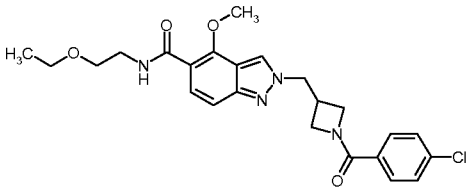
Example 258d: 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-4-methoxy-2H-indazol-5-carboxylic acid



550 mg of 258c were first placed in 20 ml ethanol, treated with 20 ml of 2N sodium hydroxide and stirred until complete conversion. For the work-up, the reaction solution was adjusted to a pH of 3 with 1N hydrochloric acid, extracted with ethyl acetate, and the combined organic phases dried with sodium sulphate and concentrated to dryness. Yield after purification by column chromatography on silica gel with a hexane/ ethyl acetate gradient: 213 mg of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 3.27 (1H), 3.97 (1H), 4.07 - 4.17 (4H), 4.24 (1H), 4.42 (1H), 4.70 (2H), 7.22 (1H), 7.46 - 7.57 (3H), 7.59 - 7.68 (2H), 8.88 (1H), 12.61 (m, 1H).

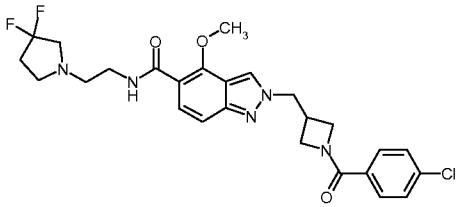
Example 259: 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-N-(2-ethoxyethyl)-4-methoxy-2H-indazol-5-carboxamide



Analogously to Example 1b Version B, 30 mg of the title compound was obtained from 66 mg of the compound prepared in Example 258d and 22 mg of 2-ethoxyethylamine in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.07 - 1.21 (3H), 3.30 (1H), 3.40 - 3.57 (6H), 3.90 - 4.02 (1H), 4.08 - 4.17 (1H), 4.21 (4H), 4.34 - 4.48 (1H), 4.70 (2H), 7.24 (1H), 7.45 - 7.57 (2H), 7.60 - 7.74 (3H), 8.24 (1H), 8.91 (1H).

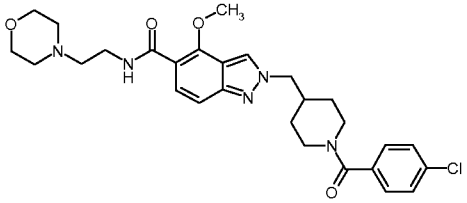
Example 260: 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-N-[2-(3,3-difluoropyrrolidin-1-yl)ethyl]-4-methoxy-2H-indazol-5-carboxamide



Analogously to Example 1b Version B, 58 mg of the title compound was obtained from 66 mg of the compound prepared in Example 258d and 37 mg of 2-(3,3-difluoropyrrolidin-1-yl)ethyl-amine in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 2.27 (2H), 2.64 (2H), 2.77 (2H), 2.96 (2H), 3.22 - 3.30 (1H), 3.41 (2H), 3.92 - 4.01 (1H), 4.11 (1H), 4.19 (4H), 4.35 - 4.48 (1H), 4.70 (2H), 7.24 (1H), 7.51 (2H), 7.57 - 7.75 (3H), 8.32 (1H), 8.90 (1H).

Example 261: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methoxy-N-(2-morpholino-ethyl)-2H-indazol-5-carboxamide

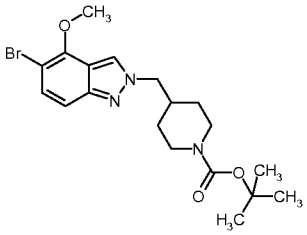


Analogously to Example 1b, Version B, 77 mg of the title compound was obtained from 100 mg of the compound prepared in Example 261e and 46 mg of 2-morpholinoethylamine in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.11 - 1.33 (2H), 1.35 - 1.75 (2H), 2.18 - 2.39 (1H), 2.65 - 2.88 (2H), 2.90 - 3.23 (3H), 3.41 - 3.82 (8H), 3.84 - 4.12 (2H), 4.24 (3H), 4.35 (3H), 7.26 (1H), 7.33 - 7.44 (2H), 7.46 - 7.58 (2H), 7.69 (1H), 8.27 - 8.52 (1H), 8.87 (1H).

The starting material was prepared as follows:

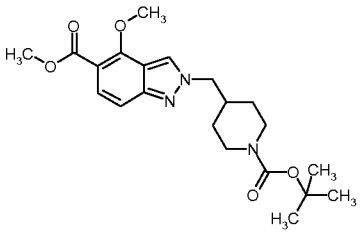
Example 261a: Tert-butyl 4-[(5-bromo-4-methoxy-2H-indazol-2-yl)methyl]piperidin-1-carboxylate



Analogously to Example 1c, 5.57 g of the title compound was obtained from 9.65 g of 5-bromo-4-methoxy-1H-indazole and 23.55 g of tert-butyl-4-[(tosyloxy)methyl]piperidin-1-carboxylate.

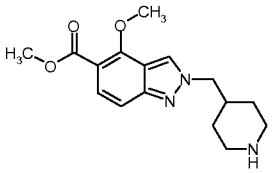
^{1}H-NMR (400 MHz, chloroform-d): δ [ppm]= 1.16 - 1.31 (2H), 1.39 - 1.49 (9H), 1.52 - 1.64 (2H), 2.16 - 2.36 (1H), 2.56 - 2.80 (2H), 4.11 (5H), 4.26 (2H), 7.28 - 7.33 (1H), 7.34 - 7.39 (1H), 7.99 (1H).

Example 261b: Methyl 2-{[1-(tert-butoxycarbonyl)piperidin-4-yl]methyl}-4-methoxy-2H-indazol-5-carboxylate



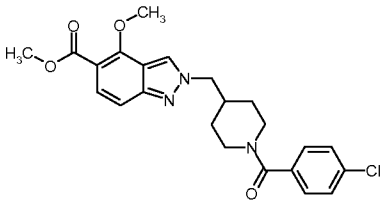
Analogously to Example 1e, 1.1 g of the title compound was obtained from 2.4 g of the compound prepared in Example 261a and 1.63 g of methanol.

Example 261c: Methyl 4-methoxy-2-(4-piperidylmethyl)-2H-indazol-5-carboxylate



Analogously to Example 258b, from 1.1 g of the compound prepared in Example 261b 1.1 g of the title compound was obtained, which was reacted in the next step without further purification.

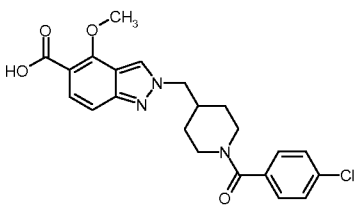
Example 261d: Methyl 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methoxy-2H-indazol-5-carboxylate



Analogously to Example 258c, from 1.1 g of the compound prepared in Example 261c and 762 mg of 4-chlorobenzoyl chloride, 980 mg of the title compound was obtained after purification by column chromatography on silica gel with a hexane/ethyl acetate gradient.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.24 (2H), 1.36 - 1.76 (2H), 2.18 - 2.40 (1H), 2.65 - 2.88 (1H), 2.91 - 3.12 (1H), 3.42 - 3.67 (1H), 3.78 (3H), 4.05 - 4.21 (3H), 4.35 (3H), 7.24 (1H), 7.34 - 7.43 (2H), 7.45 - 7.56 (3H), 8.86 (1H).

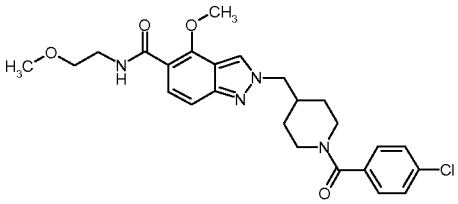
Example 261e: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methoxy-2H-indazol-5-carboxylic acid



Analogously to Example 258d, 547 mg of the title compound was obtained from 980 mg of the compound prepared in Example 261d.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.12 - 1.35 (2H), 1.35 - 1.73 (2H), 2.21 - 2.40 (1H), 2.63 - 3.12 (2H), 3.14 - 3.70 (3H), 4.34 (3H), 5.76 (s, 1H), 7.21 (1H), 7.32 - 7.45 (2H), 7.46 - 7.58 (3H), 8.76 (1H).

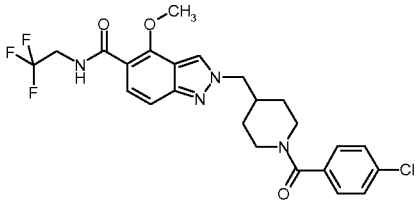
Example 262: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methoxy-N-(2-methoxyethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 50 mg of the title compound was obtained from 100 mg of the compound prepared in Example 261e and 26 mg of 2-methoxyethylamine in DMF.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.11 - 1.35 (2H), 1.35 - 1.72 (2H), 2.21 - 2.39 (1H), 2.69 - 2.88 (1H), 2.92 - 3.11 (1H), 3.30 (s, 3H), 3.38 - 3.64 (5H), 4.20 (3H), 4.34 (3H), 7.25 (1H), 7.34 - 7.43 (2H), 7.45 - 7.57 (2H), 7.66 (1H), 8.22 (1H), 8.83 (1H).

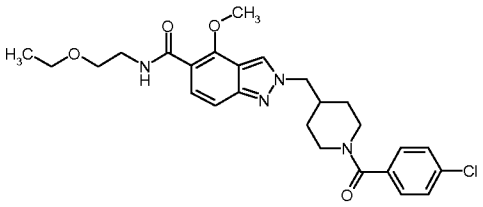
Example 263: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methoxy-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 68 mg of the title compound was obtained from 100 mg of the compound prepared in Example 261e and 35 mg of 2,2,2-trifluoroethylamine in DMF.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.09 - 1.35 (2H), 1.37 - 1.75 (2H), 2.21 - 2.41 (1H), 2.69 - 2.88 (1H), 2.92 - 3.19 (1H), 3.42 - 3.69 (1H), 4.13 (2H), 4.23 (3H), 4.35 (3H), 7.26 (1H), 7.34 - 7.45 (2H), 7.46 - 7.55 (2H), 7.61 (1H), 8.59 (1H), 8.88 (1H).

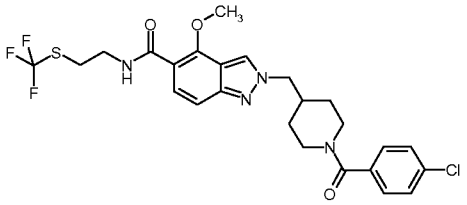
Example 264: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-(2-ethoxyethyl)-4-methoxy-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 60 mg of the title compound was obtained from 100 mg of the compound prepared in Example 261e and 31 mg of 2-ethoxyethylamine in DMF.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.14 (3H), 1.19 - 1.35 (2H), 1.37 - 1.72 (2H), 2.23 - 2.43 (1H), 2.68 - 2.88 (1H), 2.91 - 3.15 (1H), 3.41 - 3.56 (m, 7H), 4.20 (3H), 4.34 (3H), 7.25 (1H), 7.33 - 7.45 (2H), 7.46 - 7.55 (2H), 7.67 (1H), 8.23 (1H), 8.83 (1H).

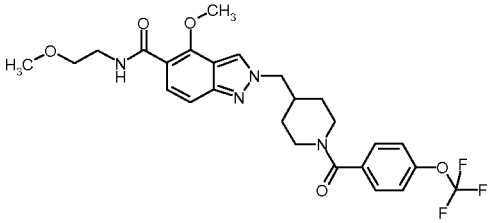
Example 265: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methoxy-N-{2-[(trifluoromethyl)sulphanyl]ethyl}-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 68 mg of the title compound was obtained from 100 mg of the compound prepared in Example 261e and 51 mg of 2-[(trifluoromethyl)sulphanyl]-ethylamine in DMF.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.14 - 1.35 (2H), 1.36 - 1.72 (2H), 2.18 - 2.40 (1H), 2.66 - 2.87 (1H), 2.91 - 3.11 (1H), 3.21 (2H), 3.42 - 3.70 (3H), 4.22 (3H), 4.34 (3H), 7.24 (1H), 7.32 - 7.45 (2H), 7.46 - 7.55 (2H), 7.64 (1H), 8.45 (1H), 8.85 (1H).

Example 266: 4-methoxy-N-(2-methoxyethyl)-2-({1-[4-(trifluoromethoxy)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide

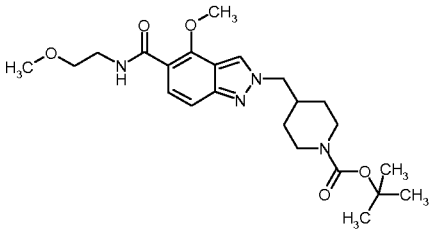


Analogously to Example 1b, Version B, 84 mg of the title compound was obtained from 100 mg of the compound prepared in Example 266b and 89 mg of 4-(trifluoromethoxy)benzoic acid in DMF.

LC-MS: R_t = 1.16 min, MS (ES+): m/z = 435 $(M+H)^+$.

The starting material was prepared as follows:

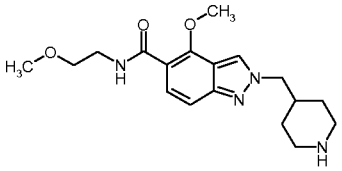
Example 266a: Tert-butyl 4-({4-methoxy-5-[N-(2-methoxyethyl)carbamoyl]-2H-indazol-2-yl}methyl)piperidin-1-carboxylate



3 g of compound 261a, 1.59 g of 2-methoxyethylamine, 1.87 g of molybdenum hexacarbonyl, 204 mg of tri-tert-butylphosphine tetrafluoroborate and 316 mg of palladium(II) acetate were first suspended in 100 ml 1,4-dioxan. Then 2.25 g of sodium carbonate and a few drops of water were added, and the mixture stirred for 25 mins at 140°C and 150 watts in the microwave. The reaction mixture was concentrated and the residue was purified by column chromatography on silica gel using a hexane/ ethyl acetate/ methanol gradient. Yield: 1.3 g of the title compound.

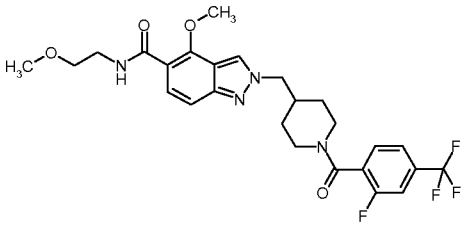
^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 0.99 - 1.22 (2H), 1.29 - 1.55 (11H), 2.03 - 2.33 (1H), 2.60 - 2.83 (2H), 3.28 - 3.31 (3H), 3.43 - 3.52 (4H), 3.82 - 4.03 (2H), 4.20 (3H), 4.31 (2H), 7.25 (1H), 7.66 (1H), 8.21 (1H), 8.82 (1H).

Example 266b: 4-methoxy-N-(2-methoxyethyl)-2-(4-piperidylmethyl)-2H-indazol-5-carboxamide



Analogously to Example 258b, from 1.3 g of the compound prepared in Example 266a, 1.48 g of the title compound was obtained, which was used in the subsequent reactions without further purification.

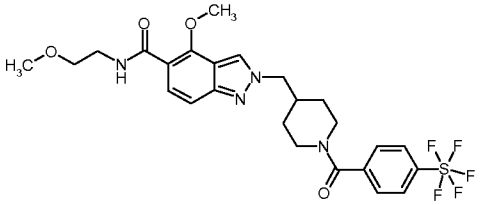
Example 267: 2-({1-[2-fluoro-4-(trifluoromethyl)benzoyl]piperidin-4-yl}methyl)-4-methoxy-N-(2-methoxyethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 20 mg of the title compound was obtained from 100 mg of the compound prepared in Example 266b and 90 mg of 2-fluoro-4-(trifluoromethyl)benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.05 - 1.36 (2H), 1.39 - 1.53 (1H), 1.56 - 1.72 (1H), 2.21 - 2.40 (1H), 2.75 - 2.90 (1H), 2.92 - 3.15 (1H), 3.27 - 3.35 (4H), 3.44 - 3.53 (4H), 4.20 (3H), 4.27 - 4.43 (2H), 4.44 - 4.58 (1H), 7.25 (1H), 7.54 - 7.74 (3H), 7.81 (1H), 8.20 (1H), 8.83 (1H).

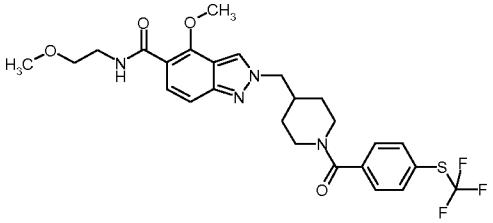
Example 268: 4-methoxy-N-(2-methoxyethyl)-2-({1-[4-(pentafluoro-λ^6-sulphanyl)benzoyl]-piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 39 mg of the title compound was obtained from 100 mg of the compound prepared in Example 266b and 107 mg of 4-(pentafluoro-λ^6-sulphanyl)benzoic acid in DMF.

LC-MS: R_t = 1.18 min, MS (ES+): m/z = 577 $(M+H)^+$.

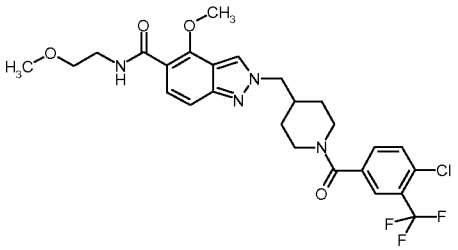
Example 269: 4-methoxy-N-(2-methoxyethyl)-2-[(1-{4-[(trifluoromethyl)sulphanyl]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 25 mg of the title compound was obtained from 100 mg of the compound prepared in Example 266b and 96 mg of 4-[(trifluoromethyl)sulphanyl]benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.09 - 1.37 (2H), 1.38 - 1.72 (2H), 2.23 - 2.39 (1H), 2.70 - 2.93 (1H), 2.95 - 3.16 (1H), 3.30 (3H), 3.40 - 3.55 (5H), 4.20 (3H), 4.35 (d, 3H), 7.25 (1H), 7.46 - 7.58 (2H), 7.66 (1H), 7.78 (2H), 8.20 (1H), 8.82 (1H).

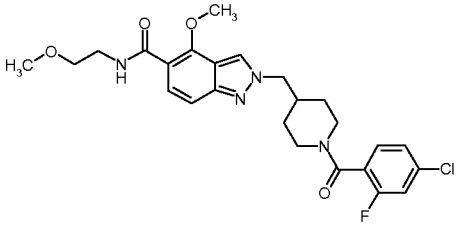
Example 270: 2-({1-[4-chloro-3-(trifluoromethyl)benzoyl]piperidin-4-yl}methyl)-4-methoxy-N-(2-methoxyethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 27 mg of the title compound was obtained from 100 mg of the compound prepared in Example 266b and 97 mg of 4-chloro-3-(trifluoromethyl)benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.15 - 1.37 (2H), 1.38 - 1.73 (2H), 2.14 - 2.41 (1H), 2.70 - 2.88 (1H), 2.95 - 3.18 (1H), 3.30 (3H), 3.39 - 3.62 (5H), 4.20 (3H), 4.35 (3H), 7.25 (1H), 7.59 - 7.73 (2H), 7.75 - 7.86 (2H), 8.20 (1H), 8.82 (1H).

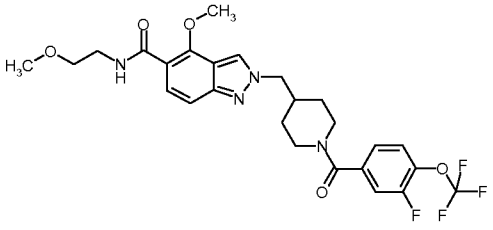
Example 271: 2-{[1-(4-chloro-2-fluorobenzoyl)piperidin-4-yl]methyl}-4-methoxy-N-(2-methoxyethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 17 mg of the title compound was obtained from 100 mg of the compound prepared in Example 266b and 75 mg of 4-chloro-2-fluorobenzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.08 - 1.33 (2H), 1.37 - 1.52 (1H), 1.53 - 1.70 (1H), 2.20 - 2.42 (1H), 2.72 - 2.88 (1H), 2.94 - 3.12 (1H), 3.30 (3H), 3.37 (1H), 3.43 - 3.51 (4H), 4.20 (3H), 4.34 (2H), 4.42 - 4.55 (1H), 7.25 (1H), 7.31 - 7.48 (2H), 7.55 (1H), 7.66 (1H), 8.20 (1H), 8.83 (1H).

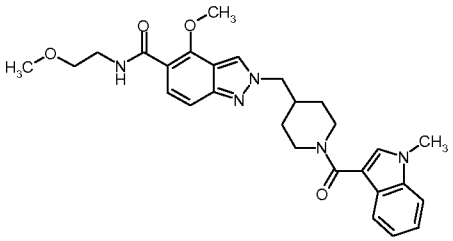
Example 272: 2-({1-[3-fluoro-4-(trifluoromethoxy)benzoyl]piperidin-4-yl}methyl)-4-methoxy-N-(2-methoxyethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 12 mg of the title compound was obtained from 100 mg of the compound prepared in Example 266b and 97 mg of 3-fluoro-4-(trifluoromethoxy)benzoic acid in DMF.

LC-MS: R_t = 1.18 min, MS (ES+): m/z = 553 $(M+H)^+$.

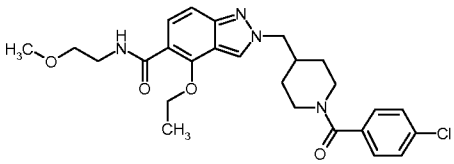
Example 273: 4-methoxy-N-(2-methoxyethyl)-2-({1-[(1-methyl-1H-indol-3-yl)carbonyl]-piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 19 mg of the title compound was obtained from 100 mg of the compound prepared in Example 266b and 76 mg of 1-methyl-1H-indol-3-carboxylic acid in DMF.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.11 - 1.40 (2H), 1.54 (2H), 2.18 - 2.42 (1H), 2.93 (2H), 3.30 (3H), 3.40 - 3.45 (4H), 3.70 - 3.91 (3H), 4.12 - 4.48 (7H), 7.00 - 7.34 (3H), 7.48 (1H), 7.66 (3H), 8.22 (1H), 8.84 (1H).

Example 274: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-ethoxy-N-(2-methoxyethyl)-2H-indazol-5-carboxamide

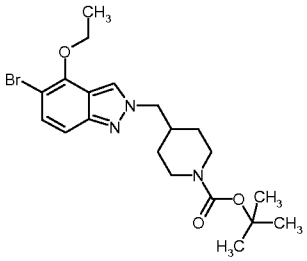


Analogously to Example 1b, Version B, 47 mg of the title compound was obtained from 110 mg of the compound prepared in Example 274c and 72 mg of 4-chlorobenzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.10 - 1.33 (2H), 1.44 (5H), 2.20 - 2.39 (1H), 2.68 - 2.85 (1H), 2.92 - 3.12 (1H), 3.32 (7H), 3.51 - 3.62 (1H), 4.20 - 4.59 (5H), 7.26 (1H), 7.33 - 7.44 (2H), 7.47 - 7.55 (2H), 7.70 (1H), 8.30 (1H), 8.79 (1H).

The starting material was prepared as follows:

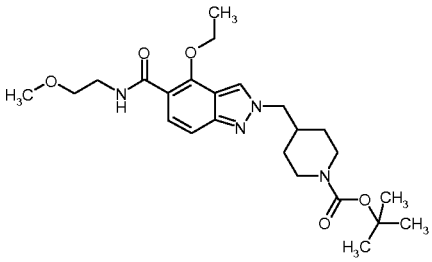
Example 274a: Tert-butyl 4-[(5-bromo-4-ethoxy-2H-indazol-2-yl)methyl]piperidin-1-carboxylate



Analogously to Example 74c, 285 mg of the title compound was obtained from 484 mg of 5-bromo-4-ethoxy-1H-indazole and 1.11 g of tert-butyl-4-[(5-bromo-4-ethoxy-2H-indazol-2-yl)-methyl]piperidin-1-carboxylate.

^{1}H-NMR (400 MHz, chloroform-d): δ [ppm]= 1.13 - 1.34 (2H), 1.46 (9H), 1.49 (3H), 1.56 - 1.63 (2H), 2.16 - 2.37 (1H), 2.54 - 2.80 (2H), 4.02 - 4.21 (2H), 4.26 (2H), 4.33 (2H), 7.28 - 7.43 (2H), 7.93 (1H).

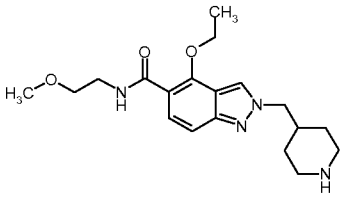
Example 274b: Tert-butyl 4-({4-ethoxy-5-[N-(2-methoxyethyl)carbamoyl]-2H-indazol-2-yl}-methyl)piperidin-1-carboxylate



Analogously to Example 266a, 235 mg of the title compound was obtained from 285 mg of the compound prepared in Example 274a and 146 mg of 2-methoxyethylamine.

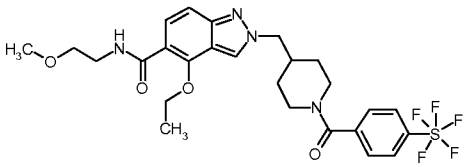
^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 0.97 - 1.22 (2H), 1.29 - 1.56 (14H), 2.06 - 2.31 (1H), 2.59 - 2.86 (2H), 3.33 (3H), 3.49 (4H), 3.80 - 4.02 (2H), 4.30 (2H), 4.51 (2H), 7.26 (1H), 7.71 (1H), 8.31 (1H), 8.79 (1H).

Example 274c: 4-ethoxy-N-(2-methoxyethyl)-2-(4-piperidylmethyl)-2H-indazol-5-carboxamide



Analogously to Example 258b, from 235 mg of the compound prepared in Example 274b, 237 mg of the title compound was obtained, which was reacted in the next step without further purification.

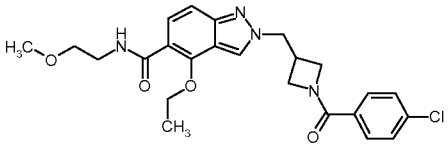
Example 275: 4-ethoxy-N-(2-methoxyethyl)-2-({1-[4-(pentafluoro-λ^6-sulphanyl)benzoyl]-piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 30 mg of the title compound was obtained from 110 mg of the compound prepared in Example 274c and 113 mg of 4-(pentafluoro-λ^6-sulphanyl)benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.10 - 1.36 (2H), 1.44 (4H), 1.54 - 1.69 (1H), 2.22 - 2.40 (1H), 2.70 - 2.87 (1H), 2.93 - 3.13 (1H), 3.30 (3H), 3.48 (5H), 4.34 (2H), 4.41 - 4.63 (3H), 7.26 (1H), 7.59 (2H), 7.70 (1H), 7.98 (2H), 8.30 (1H), 8.79 (1H).

Example 276: 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-4-ethoxy-N-(2-methoxyethyl)-2H-indazol-5-carboxamide

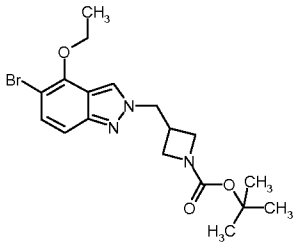


Analogously to Example 1b, Version B, 25 mg of the title compound was obtained from 50 mg of the compound prepared in Example 276c and 35 mg of 4-chlorobenzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.44 (3H), 3.21 - 3.29 (1H), 3.31 (3H), 3.49 (4H), 3.96 (1H), 4.06 - 4.30 (2H), 4.34 - 4.59 (3H), 4.69 (2H), 7.25 (1H), 7.51 (2H), 7.62 (2H), 7.71 (1H), 8.30 (1H), 8.86 (1H).

The starting material was prepared as follows:

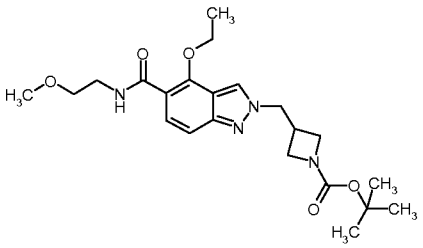
Example 276a: Tert-butyl 3-[(5-bromo-4-ethoxy-2H-indazol-2-yl)methyl]azetidin-1-carboxylate



Analogously to Example 74c, 204 mg of the title compound was obtained from 500 mg of 5-bromo-4-ethoxy-1H-indazole and 1.06 g of tert-butyl-3-[(tosyloxy)methyl]azetidin-1-carboxylate.

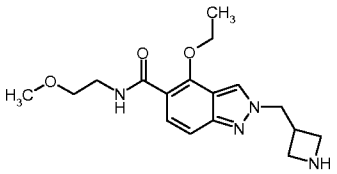
^{1}H-NMR (600 MHz, chloroform-d): δ [ppm]= 1.44 (9H), 1.49 (3H), 3.14 - 3.30 (1H), 3.72 - 3.83 (2H), 4.07 (2H), 4.33 (2H), 4.59 (2H), 7.29 (1H), 7.37 (1H), 7.98 (1H).

Example 276b: Tert-butyl 3-({4-ethoxy-5-[N-(2-methoxyethyl)carbamoyl]-2H-indazol-2-yl}-methyl)azetidin-1-carboxylate



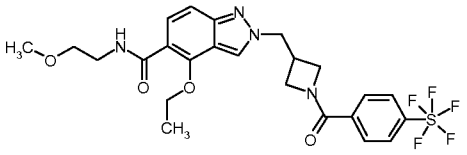
Analogously to Example 266a, from 191 mg of the compound prepared in Example 276a and 105 mg of 2-methoxyethylamine, 121 mg of the title compound was obtained, which was reacted in the next step without further purification.

Example 276c: 2-(azetidin-3-ylmethyl)-4-ethoxy-N-(2-methoxyethyl)-2H-indazol-5-carboxamide



Analogously to Example 258b, from 121 mg of the compound prepared in Example 276b, 93 mg of the title compound was obtained, which was reacted in the next step without further purification.

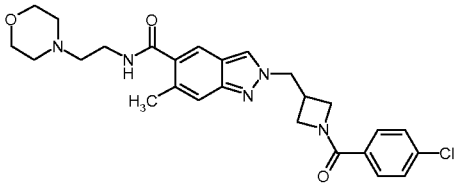
Example 277: 4-ethoxy-N-(2-methoxyethyl)-2-({1-[4-(pentafluoro-λ^6-sulphanyl)benzoyl]-azetidin-3-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 35 mg of the title compound was obtained from 50 mg of 276c and 56 mg of 4-(pentafluoro-λ^6-sulphanyl)benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.37 - 1.50 (3H), 3.26 (1H), 3.31 (3H), 3.43 - 3.57 (4H), 3.92 - 4.05 (1H), 4.10 - 4.31 (2H), 4.38 - 4.57 (3H), 4.70 (2H), 7.25 (1H), 7.66 - 7.87 (3H), 7.98 (2H), 8.30 (1H), 8.86 (1H).

Example 278: 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-6-methyl-N-(2-morpholinoethyl)-2H-indazol-5-carboxamide

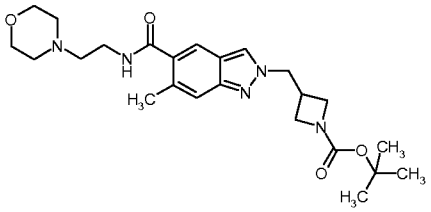


Analogously to Example 1b, Version B, 23 mg of the title compound was obtained from 100 mg of 278b and 66 mg of 4-chlorobenzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 2.42 (s, 3H), 3.09 - 3.27 (m, 3H), 3.29 - 3.33 (2H), 3.49 - 3.73 (m, 6H), 3.84 - 3.96 (m, 1H), 3.97 - 4.15 (m, 3H), 4.16 - 4.27 (m, 1H), 4.31 - 4.45 (m, 1H), 4.62 - 4.80 (m, 2H), 7.36 - 7.47 (1H), 7.48 - 7.57 (2H), 7.58 - 7.70 (2H), 7.77 - 7.89 (1H), 8.41 - 8.58 (2H).

The starting material was prepared as follows:

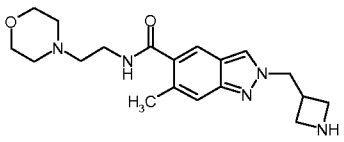
Example 278a: Tert-butyl 3-({6-methyl-5-[N-(2-morpholinoethyl)carbamoyl]-2H-indazol-2-yl}methyl)azetidin-1-carboxylate



Analogously to Example 1b, Version B, 418 mg of the title compound was obtained from 410 mg of 178c and 232 mg of 2-morpholinoethylamine in DMF.

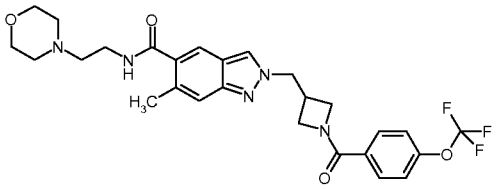
^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.36 (9H), 2.39 (3H), 2.44 (4H), 2.95 - 3.17 (1H), 3.24 - 3.43 (4H), 3.58 (4H), 3.64 - 3.79 (2H), 3.88 (2H), 4.62 (2H), 7.39 (1H), 7.68 (1H), 8.04 - 8.22 (1H), 8.45 (1H).

Example 278b: 2-(azetidin-3-ylmethyl)-6-methyl-N-(2-morpholinoethyl)-2H-indazol-5-carboxamide



Analogously to Example 258b, from 400 mg of the compound prepared in Example 278a, 372 mg of the title compound was obtained, which was reacted in the next step without further purification.

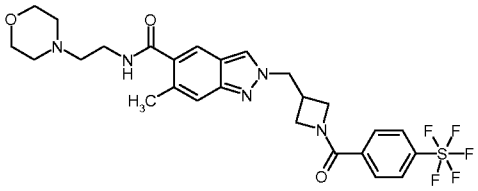
Example 279: 6-methyl-N-(2-morpholinoethyl)-2-({1-[4-(trifluoromethoxy)benzoyl]azetidin-3-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 44 mg of the title compound was obtained from 100 mg of 278b and 86 mg of 4-(trifluoromethoxy)benzoic acid in DMF.

^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 2.42 (3H), 3.07 - 3.27 (5H), 3.48 - 3.74 (6H), 3.85 - 4.17 (4H), 4.18 - 4.29 (1H), 4.33 - 4.48 (1H), 4.61 - 4.82 (2H), 7.30 - 7.54 (3H), 7.68 - 7.78 (2H), 7.79 - 7.88 (1H), 8.43 - 8.60 (2H).

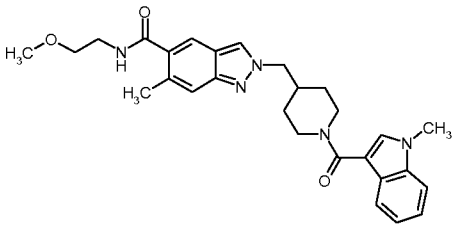
Example 280: 6-methyl-N-(2-morpholinoethyl)-2-({1-[4-(pentafluoro-λ^6-sulphanyl)benzoyl]-azetidin-3-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 37 mg of the title compound was obtained from 100 mg of 278b and 104 mg of 4-(pentafluoro-λ^6-sulphanyl)benzoic acid in DMF.

^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 2.42 (3H), 3.06 - 3.27 (5H), 3.47 - 3.75 (6H), 3.87 - 4.08 (3H), 4.09 - 4.29 (2H), 4.33 - 4.49 (1H), 4.61 - 4.80 (2H), 7.34 - 7.52 (1H), 7.71 - 7.88 (3H), 7.92 - 8.07 (2H), 8.39 - 8.59 (2H).

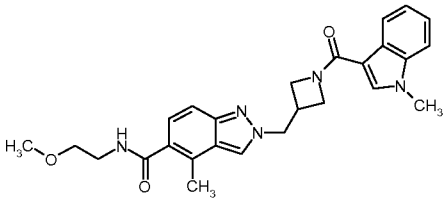
Example 281: N-(2-methoxyethyl)-6-methyl-2-({1-[(1-methyl-1H-indol-3-yl)carbonyl]-piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 4.2 mg of the title compound was obtained from 150 mg of 205c and 119 mg of 1-methyl-1H-indol-3-carboxylic acid in DMF.

LC-MS: R_t = 1.01 min, MS (ES+): m/z = 489 $(M+H)^+$.

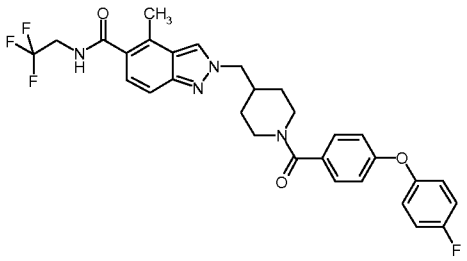
Example 282: N-(2-methoxyethyl)-4-methyl-2-({1-[(1-methyl-1H-indol-3-yl)carbonyl]azetidin-3-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 35 mg of the title compound was obtained from 175 mg of 117e and 122 mg of 1-methyl-1H-indol-3-carboxylic acid in DMF.

LC-MS: R_t = 0.95 min, MS (ES+): m/z = 460 $(M+H)^+$.

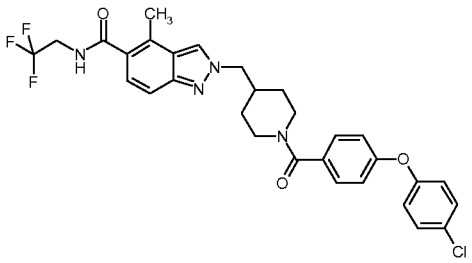
Example 283: 2-({1-[4-(4-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 267 mg of the title compound was obtained from 250 mg of 71a and 246 mg of 4-(4-fluorophenoxy)benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.16 - 1.32 (2H), 1.35 - 1.69 (2H), 2.20 - 2.39 (1H), 2.54 (3H), 2.70 - 3.15 (2H), 3.50 - 3.83 (1H), 4.07 (2H), 4.36 (3H), 6.91 - 7.05 (2H), 7.08 - 7.31 (5H), 7.34 - 7.42 (2H), 7.46 (1H), 8.56 (1H), 8.83 (1H).

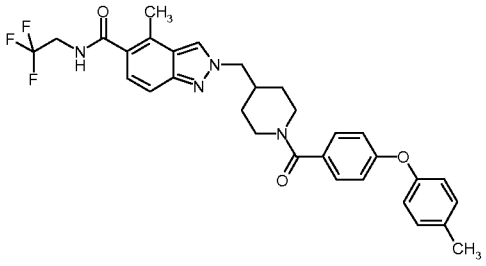
Example 284: 2-({1-[4-(4-chlorophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 55 mg of the title compound was obtained from 100 mg of 71a and 105 mg of 4-(4-chlorophenoxy)benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.23 (2H), 1.34 - 1.72 (2H), 2.21 - 2.41 (1H), 2.54 (3H), 2.67 - 3.20 (2H), 3.51 - 3.83 (1H), 4.07 (2H), 4.36 (3H), 6.92 - 7.15 (4H), 7.20 (1H), 7.35 - 7.53 (5H), 8.56 (1H), 8.84 (1H).

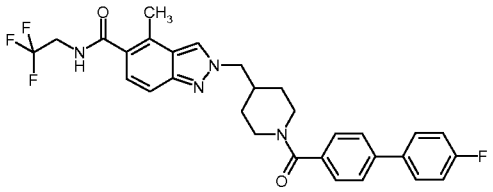
Example 285: 4-methyl-2-({1-[4-(4-methylphenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 60 mg of the title compound was obtained from 100 mg of 71a and 97 mg of 4-(4-methylphenoxy)benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.23 (2H), 1.36 - 1.71 (2H), 2.30 (4H), 2.54 (3H), 2.64 - 3.17 (2H), 3.49 - 3.82 (1H), 4.07 (2H), 4.36 (3H), 6.85 - 7.04 (4H), 7.21 (3H), 7.29 - 7.41 (2H), 7.46 (1H), 8.56 (1H), 8.84 (s1H).

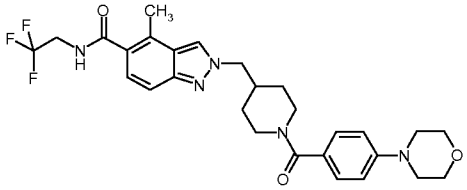
Example 286: 2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 39 mg of the title compound was obtained from 100 mg of 71a and 92 mg of 4-(4-fluorophenyl)benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.14 - 1.36 (2H), 1.36 - 1.73 (2H), 2.18 - 2.41 (1H), 2.54 (3H), 2.70 - 3.16 (2H), 3.51 - 3.82 (1H), 4.07 (2H), 4.38 (3H), 7.21 (1H), 7.31 (2H), 7.40 - 7.53 (3H), 7.64 - 7.85 (4H), 8.56 (1H), 8.81 (1H).

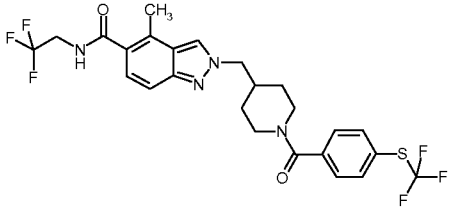
Example 287: 4-methyl-2-{[1-(4-morpholinobenzoyl)piperidin-4-yl]methyl}-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 45 mg of the title compound was obtained from 100 mg of 71a and 88 mg of 4-morpholinobenzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.24 (2H), 1.40 - 1.60 (2H), 2.20 - 2.40 (1H), 2.54 (3H), 2.73 - 3.01 (2H), 3.38 (4H), 3.64 - 3.81 (5H), 4.07 (3H), 4.36 (2H), 6.94 (2H), 7.16 - 7.30 (3H), 7.46 (1H), 8.55 (1H), 8.81 (1H).

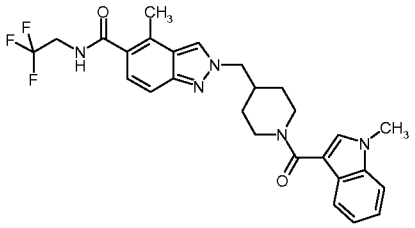
Example 288: 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{4-[(trifluoromethyl)sulphanyl]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 67 mg of the title compound was obtained from 100 mg of 71a and 94 mg of 4-[(trifluoromethyl)sulphanyl]benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.12 - 1.35 (2H), 1.35 - 1.70 (2H), 2.21 - 2.40 (1H), 2.54 (3H), 2.70 - 2.88 (1H), 2.94 - 3.12 (1H), 3.38 - 3.61 (1H), 4.07 (2H), 4.36 (3H), 7.21 (1H), 7.37 - 7.60 (3H), 7.78 (2H), 8.55 (1H), 8.81 (1H).

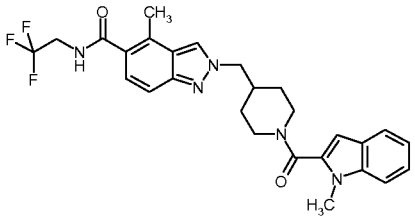
Example 289: 4-methyl-2-({1-[(1-methyl-1H-indol-3-yl)carbonyl]piperidin-4-yl}methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 43 mg of the title compound was obtained from 100 mg of 71a and 74 mg of 1-methyl-1H-indol-3-carboxylic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.27 (2H), 1.52 (2H), 2.20 - 2.40 (1H), 2.54 (3H), 2.92 (2H), 3.82 (3H), 4.07 (2H), 4.27 (2H), 4.38 (2H), 6.92 - 7.33 (3H), 7.47 (2H), 7.61 - 7.76 (2H), 8.56 (1H), 8.81 (1H).

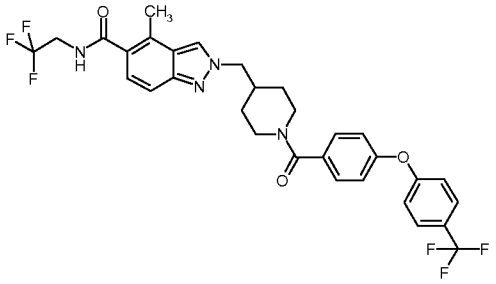
Example 290: 4-methyl-2-({1-[(1-methyl-1H-indol-2-yl)carbonyl]piperidin-4-yl}methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 51 mg of the title compound was obtained from 100 mg of 71a and 74 mg of 1-methyl-1H-indol-2-carboxylic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.17 - 1.41 (2H), 1.43 - 1.73 (2H), 2.19 - 2.43 (1H), 2.54 (3H), 2.74 - 3.23 (2H), 3.73 (3H), 4.07 (3H), 4.39 (3H), 6.60 (s, 1H), 7.03 - 7.14 (1H), 7.16 - 7.30 (2H), 7.48 (2H), 7.59 (1H), 8.57 (1H), 8.81 (1H).

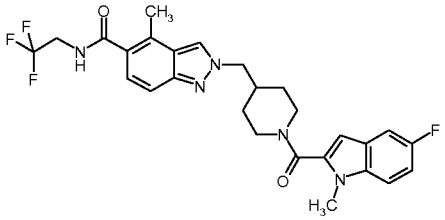
Example 291: 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{4-[4-(trifluoromethyl)phenoxy]-benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 156 mg of the title compound was obtained from 150 mg of 71a and 179 mg of 4-[4-(trifluoromethyl)phenoxy]benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.23 (2H), 1.36 - 1.68 (2H), 2.20 - 2.43 (1H), 2.54 (3H), 2.68 - 3.17 (2H), 3.50 - 3.79 (1H), 4.07 (2H), 4.37 (3H), 7.09 - 7.28 (5H), 7.35 - 7.51 (3H), 7.76 (2H), 8.56 (1H), 8.83 (1H).

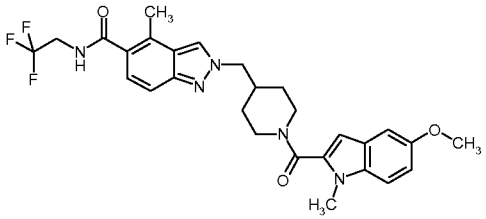
Example 292: 2-({1-[(5-fluoro-1-methyl-1H-indol-2-yl)carbonyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 28 mg of the title compound was obtained from 100 mg of 71a and 82 mg of 5-fluoro-1-methyl-1H-indol-2-carboxylic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.18 - 1.38 (2H), 1.39 - 1.72 (2H), 2.25 - 2.42 (1H), 2.54 (3H), 2.74 - 3.25 (2H), 3.73 (3H), 4.07 (3H), 4.38 (3H), 6.58 (1H), 7.09 (1H), 7.21 (1H), 7.36 (1H), 7.47 (2H), 8.57 (1H), 8.83 (1H).

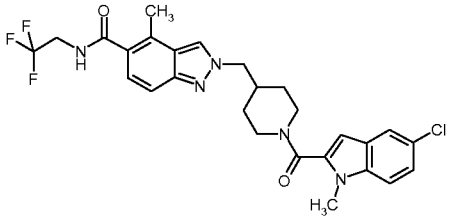
Example 293: 2-({1-[(5-methoxy-1-methyl-1H-indol-2-yl)carbonyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 37 mg of the title compound was obtained from 100 mg of 71a and 87 mg of 5-methoxy-1-methyl-1H-indol-2-carboxylic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.30 (2H), 1.41 - 1.71 (2H), 2.26 - 2.43 (1H), 2.54 (3H), 2.71 - 3.22 (2H), 3.69 (3H), 3.75 (3H), 4.07 (3H), 4.39 (3H), 6.51 (1H), 6.88 (1H), 7.07 (1H), 7.21 (1H), 7.34 - 7.54 (2H), 8.57 (1H), 8.83 (1H).

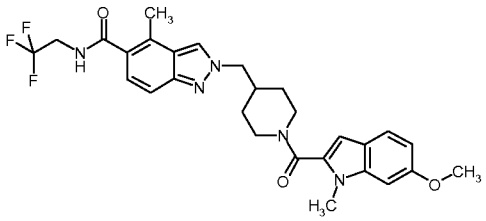
Example 294: 2-({1-[(5-chloro-1-methyl-1H-indol-2-yl)carbonyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 43 mg of the title compound was obtained from 100 mg of 71a and 89 mg of 5-chloro-1-methyl-1H-indol-2-carboxylic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.29 (2H), 1.38 - 1.72 (2H), 2.26 - 2.43 (1H), 2.54 (3H), 2.71 - 3.21 (2H), 3.73 (3H), 3.84 - 4.18 (3H), 4.38 (3H), 6.59 (1H), 7.15 - 7.28 (2H), 7.47 (1H), 7.55 (1H), 7.65 (1H), 8.57 (1H), 8.83 (1H).

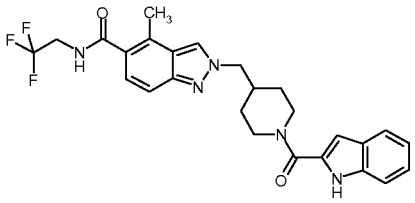
Example 295: 2-({1-[(6-methoxy-1-methyl-1H-indol-2-yl)carbonyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 36 mg of the title compound was obtained from 100 mg of 71a and 87 mg of 6-methoxy-1-methyl-1H-indol-2-carboxylic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.28 (2H), 1.52 (2H), 2.25 - 2.43 (1H), 2.54 (3H), 2.78 - 3.16 (2H), 3.70 (3H), 3.82 (3H), 3.97 - 4.63 (6H), 6.54 (1H), 6.73 (1H), 7.01 (1H), 7.21 (1H), 7.39 - 7.53 (2H), 8.57 (1H), 8.83 (t1H).

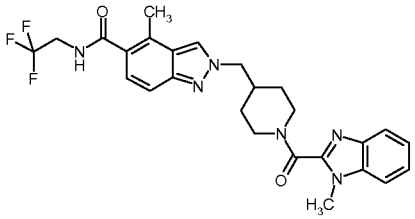
Example 296: 2-{[1-(1H-Indol-2-ylcarbonyl)piperidin-4-yl]methyl}-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 43 mg of the title compound was obtained from 100 mg of 71a and 68 mg of indol-2-carboxylic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.16 - 1.40 (2H), 1.58 (2H), 2.27 - 2.44 (1H), 2.55 (3H), 2.77 - 3.24 (2H), 4.07 (2H), 4.30 - 4.59 (4H), 6.74 (1H), 6.95 - 7.08 (1H), 7.10 - 7.26 (2H), 7.40 (1H), 7.48 (1H), 7.59 (1H), 8.58 (1H), 8.84 (1H), 11.54 (1H).

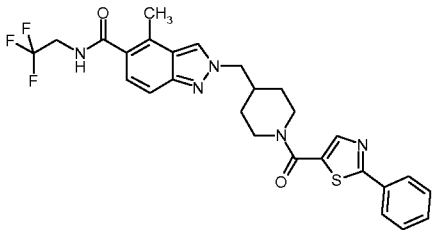
Example 297: 4-methyl-2-({1-[(1-methyl-1H-benzimidazol-2-yl)carbonyl]piperidin-4-yl}-methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 26 mg of the title compound was obtained from 100 mg of 71a and 75 mg of 1-methyl-1H-benzimidazol-2-carboxylic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.17 - 1.42 (2H), 1.46 (1H), 1.57 - 1.75 (1H), 2.27 - 2.44 (1H), 2.54 (3H), 2.87 (1H), 3.11 (1H), 3.83 (3H), 4.07 (3H), 4.40 (2H), 4.48 - 4.62 (1H), 7.13 - 7.41 (3H), 7.47 (1H), 7.58 - 7.76 (2H), 8.58 (1H), 8.83 (1H).

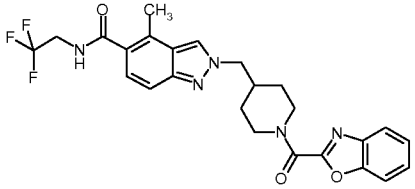
Example 298: 4-methyl-2-({1-[(2-phenylthiazol-5-yl)carbonyl]piperidin-4-yl}methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 53 mg of the title compound was obtained from 100 mg of 71a and 87 mg of 2-phenylthiazol-5-carboxylic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.18 - 1.41 (2H), 1.56 (2H), 2.27 - 2.44 (1H), 2.54 (3H), 2.73 - 3.29 (2H), 3.93 - 4.53 (6H), 7.21 (1H), 7.42 - 7.61 (4H), 7.93 - 8.03 (2H), 8.14 (1H), 8.57 (1H), 8.83 (1H).

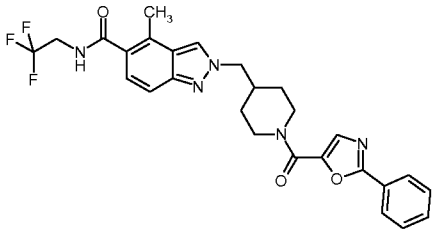
Example 299: 2-{[1-(benzoxazol-2-ylcarbonyl)piperidin-4-yl]methyl}-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 20 mg of the title compound was obtained from 100 mg of 71a and 69 mg of benzoxazol-2-carboxylic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.19 - 1.44 (2H), 1.48 - 1.72 (2H), 2.29 - 2.46 (1H), 2.54 (3H), 2.82 - 3.01 (1H), 3.12 - 3.31 (1H), 4.07 (2H), 4.40 (4H), 7.21 (1H), 7.42 - 7.61 (3H), 7.78 - 7.95 (2H), 8.58 (1H), 8.83 (1H).

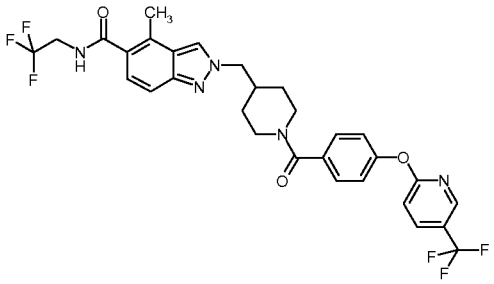
Example 300: 4-methyl-2-({1-[(2-phenyloxazol-5-yl)carbonyl]piperidin-4-yl}methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 20 mg of the title compound was obtained from 100 mg of 71a and 80 mg of 2-phenyloxazol-5-carboxylic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.15 - 1.43 (2H), 1.59 (2H), 2.31 - 2.45 (1H), 2.55 (3H), 2.70 - 3.35 (2H), 4.07 (2H), 4.39 (4H), 7.21 (1H), 7.48 (1H), 7.53 - 7.67 (3H), 7.80 (1H), 7.94 - 8.07 (2H), 8.58 (1H), 8.83 (1H).

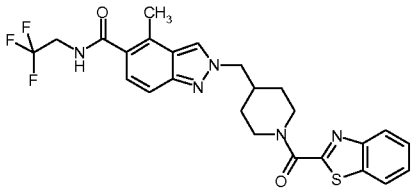
Example 301: 4-methyl-N-(2,2,2-trifluoroethyl)-2-{[1-(4-{[5-(trifluoromethyl)pyridin-2-yl]-oxy}benzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 23 mg of the title compound was obtained from 75 mg of 71a and 90 mg of 4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}benzoic acid in DMF.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.13 - 1.35 (2H), 1.37 - 1.72 (2H), 2.19 - 2.42 (1H), 2.54 (3H), 2.69 - 3.17 (2H), 3.55 - 3.82 (1H), 3.91 - 4.18 (2H), 4.26 - 4.60 (3H), 7.28 (4H), 7.38 - 7.56 (3H), 8.16 - 8.33 (1H), 8.49 - 8.63 (2H), 8.75 - 8.91 (1H).

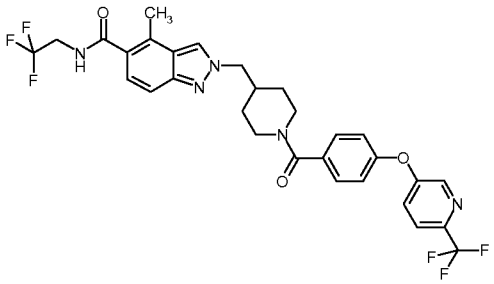
Example 302: 2-{[1-(benzothiazol-2-ylcarbonyl)piperidin-4-yl]methyl}-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 35 mg of the title compound was obtained from 75 mg of 71a and 57 mg of benzothiazol-2-carboxylic acid in DMF.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.36 (2H), 1.59 (2H), 2.31 - 2.46 (1H), 2.55 (3H), 2.91 (1H), 3.26 (1H), 4.07 (2H), 4.31 - 4.61 (3H), 4.95 - 5.23 (1H), 7.21 (1H), 7.41 - 7.69 (3H), 8.05 - 8.28 (2H), 8.58 (1H), 8.83 (1H).

Example 303: 4-methyl-N-(2,2,2-trifluoroethyl)-2-{[1-(4-{[6-(trifluoromethyl)pyridin-3-yl]-oxy}benzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide

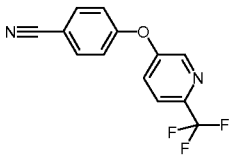


Analogously to Example 1b, Version B, 42 mg of the title compound was obtained from 75 mg of 71a and 90 mg of the carboxylic acid prepared in Example 303b) in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.16 - 1.33 (2H), 1.34 - 1.67 (2H), 2.21 - 2.39 (1H), 2.54 (3H), 2.68 - 3.16 (2H), 3.52 - 3.76 (1H), 3.95 - 4.16 (2H), 4.28 - 4.61 (3H), 7.13 - 7.31 (3H), 7.46 (3H), 7.59 - 7.71 (1H), 7.92 (1H), 8.52 - 8.65 (2H), 8.84 (1H).

The starting material was prepared as follows:

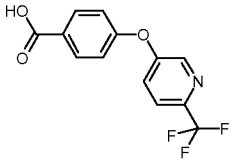
Example 303a: 4-{[6-(trifluoromethyl)pyridin-3-yl]oxy}benzonitrile



2.5 g of 5-bromo-2-(trifluoromethyl)pyridine, 5.8 g of 4-hydroxybenzonitrile, 10.8 g of caesium carbonate and 1.87 g of molybdenum hexacarbonyl in 100 ml 1,4-dioxan were heated under reflux until complete conversion. The reaction mixture was diluted with water, extracted several times with ethyl acetate, and the combined organic phases washed with saturated sodium chloride solution, dried over sodium sulphate and concentrated. The residue was purified by column chromatography on silica gel using a hexane/ ethyl acetate gradient. Yield: 1.35 g of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 7.35 (2H), 7.75 - 7.84 (1H), 7.89 - 8.03 (3H), 8.66 (1H).

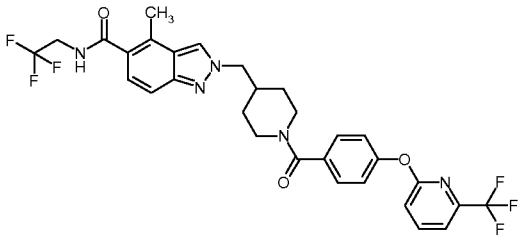
Example 303b: 4-{[6-(trifluoromethyl)pyridin-2-yl]oxy}benzoic acid



1.33 g of the compound prepared in Example 303a in 64 ml ethanol was treated with 32 ml of 40% potassium hydroxide solution and heated under reflux until complete conversion. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried over sodium sulphate and concentrated. Yield: 1.32 g of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 7.19 - 7.33 (2H), 7.68 - 7.81 (1H), 7.90 - 8.08 (3H), 8.64 (1H), 12.71 - 13.28 (1H).

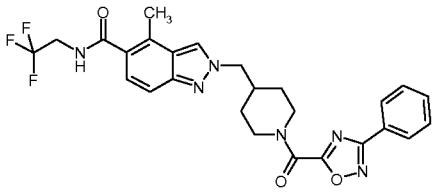
Example 304: 4-methyl-N-(2,2,2-trifluoroethyl)-2-{[1-(4-{[6-(trifluoromethyl)pyridin-2-yl]-oxy}benzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 48 mg of the title compound was obtained from 75 mg of 71a and 90 mg of 4-{[6-(trifluoromethyl)pyridin-2-yl]oxy}benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.15 - 1.34 (2H), 1.35 - 1.71 (2H), 2.23 - 2.41 (1H), 2.54 (3H), 2.67 - 3.17 (2H), 3.51 - 3.77 (1H), 3.97 - 4.18 (2H), 4.22 - 4.65 (3H), 7.13 - 7.31 (3H), 7.37 (1H), 7.41 - 7.53 (3H), 7.67 (1H), 8.07 - 8.20 (1H), 8.57 (1H), 8.75 - 8.92 (1H).

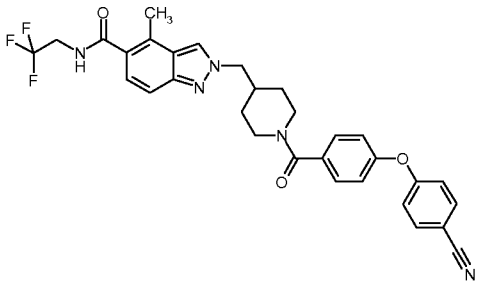
Example 305: 4-methyl-2-({1-[(3-phenyl-1,2,4-oxadiazol-5-yl)carbonyl]piperidin-4-yl}methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 40 mg of the title compound was obtained from 90 mg of 71a and 73 mg of 3-phenyl-1,2,4-oxadiazol-5-carboxylic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.18 - 1.43 (2H), 1.48 - 1.72 (2H), 2.33 - 2.47 (1H), 2.54 (3H), 2.95 (1H), 3.24 (1H), 3.94 - 4.17 (3H), 4.33 - 4.53 (3H), 7.21 (1H), 7.47 (1H), 7.55 - 7.70 (3H), 7.96 - 8.12 (2H), 8.57 (1H), 8.83 (1H).

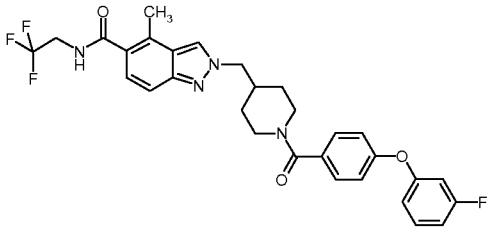
Example 306: 2-({1-[4-(4-cyanophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 59 mg of the title compound was obtained from 110 mg of 71a and 101 mg of 4-(4-cyanophenoxy)benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.17 - 1.34 (2H), 1.35 - 1.70 (2H), 2.18 - 2.41 (1H), 2.54 (3H), 2.70 - 3.18 (2H), 3.54 - 3.79 (1H), 4.07 (2H), 4.37 (3H), 7.10 - 7.28 (5H), 7.41 - 7.52 (3H), 7.79 - 7.94 (2H), 8.56 (s1H), 8.81 (s1H).

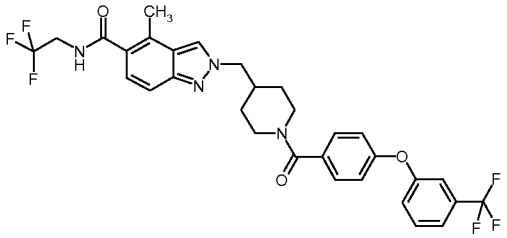
Example 307: 2-({1-[4-(3-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 40 mg of the title compound was obtained from 100 mg of 71a and 89 mg of 4-(3-fluorophenoxy)benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.14 - 1.34 (2H), 1.36 - 1.70 (2H), 2.22 - 2.44 (1H), 2.54 (3H), 2.70 - 3.13 (2H), 3.52 - 3.86 (1H), 4.07 (2H), 4.37 (3H), 6.79 - 7.12 (5H), 7.21 (1H), 7.35 - 7.52 (4H), 8.55 (1H), 8.81 (1H).

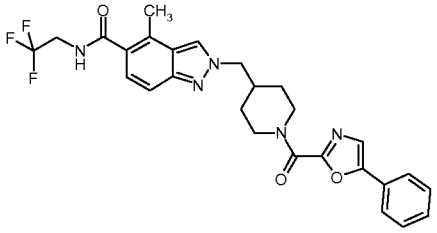
Example 308: 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{4-[3-(trifluoromethyl)phenoxy]-benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 47 mg of the title compound was obtained from 100 mg of 71a and 119 mg of 4-[3-(trifluoromethyl)phenoxy]benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.16 - 1.34 (2H), 1.37 - 1.66 (2H), 2.22 - 2.38 (1H), 2.54 (3H), 2.69 - 3.14 (2H), 3.50 - 3.83 (1H), 4.07 (2H), 4.37 (3H), 7.10 (2H), 7.21 (1H), 7.36 (1H), 7.39 - 7.50 (4H), 7.54 (1H), 7.61 - 7.75 (1H), 8.55 (1H), 8.81 (1H).

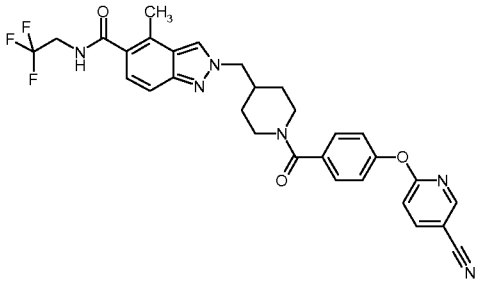
Example 309: 4-methyl-2-({1-[(5-phenyloxazol-2-yl)carbonyl]piperidin-4-yl}methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 10 mg of the title compound was obtained from 100 mg of 71a and 73 mg of 5-phenyloxazol-2-carboxylic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.24 (2H), 1.58 (2H), 2.29 - 2.45 (1H), 2.55 (3H), 2.86 (1H), 3.21 (1H), 4.07 (2H), 4.31 - 4.52 (3H), 4.62 (1H), 7.21 (1H), 7.39 - 7.57 (4H), 7.74 - 7.83 (2H), 7.88 (1H), 8.57 (1H), 8.81 (1H).

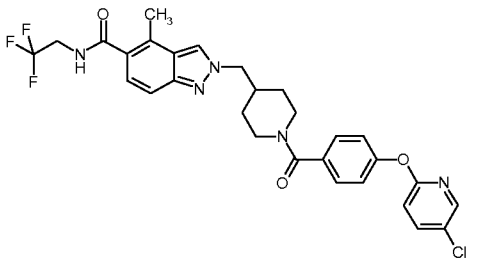
Example 310: 2-[(1-{4-[(5-cyanopyridin-2-yl)oxy]benzoyl}piperidin-4-yl)methyl]-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 47 mg of the title compound was obtained from 100 mg of 71a and 119 mg of 4-[3-(trifluoromethyl)phenoxy]benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.16 - 1.34 (2H), 1.37 - 1.66 (2H), 2.22 - 2.38 (1H), 2.54 (3H), 2.69 - 3.14 (2H), 3.50 - 3.83 (1H), 4.07 (2H), 4.37 (3H), 7.10 (2H), 7.21 (1H), 7.36 (1H), 7.39 - 7.50 (4H), 7.54 (1H), 7.61 - 7.75 (1H), 8.55 (1H), 8.81 (1H).

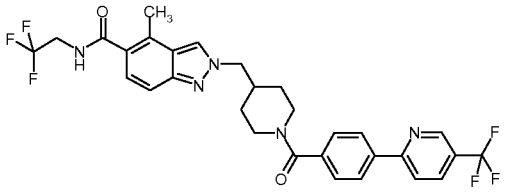
Example 311: 2-[(1-{4-[(5-chloropyridin-2-yl)oxy]benzoyl}piperidin-4-yl)methyl]-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 72 mg of the title compound was obtained from 100 mg of 71a and 96 mg of 4-[(5-chloropyridin-2-yl)oxy]benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.17 - 1.34 (2H), 1.36 - 1.73 (2H), 2.22 - 2.41 (1H), 2.54 (3H), 2.69 - 3.18 (2H), 3.47 - 3.88 (1H), 4.07 (2H), 4.37 (3H), 7.06 - 7.28 (4H), 7.34 - 7.52 (3H), 7.99 (1H), 8.22 (1H), 8.56 (1H), 8.81 (1H).

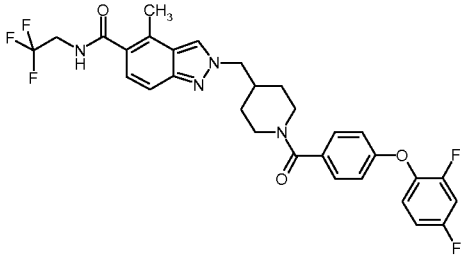
Example 312: 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{4-[5-(trifluoromethyl)pyridin-2-yl]-benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 83 mg of the title compound was obtained from 100 mg of 71a and 103 mg of 4-[5-(trifluoromethyl)pyridin-2-yl]benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.28 (2H), 1.36 - 1.73 (2H), 2.33 (1H), 2.54 (3H), 2.70 - 3.18 (2H), 3.47 - 3.76 (1H), 3.96 - 4.16 (2H), 4.38 (3H), 7.21 (1H), 7.41 - 7.60 (3H), 8.17 - 8.40 (4H), 8.56 (1H), 8.81 (1H), 9.07 (1H).

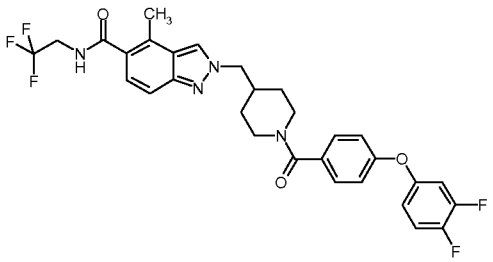
Example 313: 2-({1-[4-(2,4-difluorophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 87 mg of the title compound was obtained from 100 mg of 71a and 96 mg of 4-(2,4-difluorophenoxy)benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.23 (2H), 1.34 - 1.72 (2H), 2.18 - 2.42 (1H), 2.52 - 2.58 (3H), 2.69 - 3.20 (2H), 3.43 - 3.84 (1H), 4.07 (2H), 4.36 (3H), 6.92 - 7.06 (2H), 7.09 - 7.25 (2H), 7.28 - 7.42 (3H), 7.43 - 7.61 (2H), 8.55 (1H), 8.81 (1H).

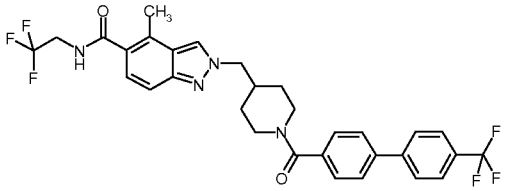
Example 314: 2-({1-[4-(3,4-difluorophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 48 mg of the title compound was obtained from 100 mg of 71a and 96 mg of 4-(3,4-difluorophenoxy)benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.24 (2H), 1.36 - 1.72 (2H), 2.19 - 2.42 (1H), 2.54 (3H), 2.70 - 3.17 (2H), 3.44 - 3.86 (1H), 3.99 - 4.17 (2H), 4.36 (3H), 6.86 - 6.97 (1H), 7.01 - 7.11 (2H), 7.21 (1H), 7.29 (1H), 7.35 - 7.55 (4H), 8.55 (1H), 8.81 (1H).

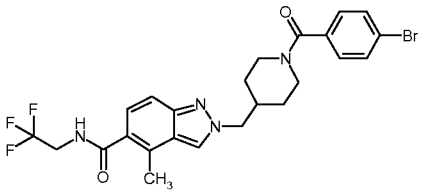
Example 315: 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{[4'-(trifluoromethyl)biphenyl-4-yl]-carbonyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 32 mg of the title compound was obtained from 100 mg of 71a and 102 mg of 4'-(trifluoromethyl)biphenyl-4-carboxylic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.27 (2H), 1.37 - 1.71 (2H), 2.24 - 2.39 (1H), 2.53 (3H), 2.70 - 3.18 (2H), 3.43 - 3.51 (2H), 3.54 - 3.86 (1H), 4.37 (3H), 7.18 (1H), 7.38 - 7.57 (3H), 7.72 - 7.88 (4H), 7.89 - 7.98 (2H), 8.13 (1H), 8.51 (1H).

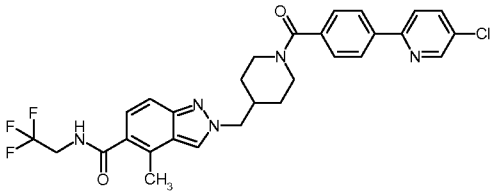
Example 316: 2-{[1-(4-bromobenzoyl)piperidin-4-yl]methyl}-4-methyl-N-(2,2,2-trifluoro-ethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 6.96 g of the title compound was obtained from 5.61 g 71a and 2.89 g of 4-bromobenzoic acid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.17 - 1.32 (2H), 1.34 - 1.74 (2H), 2.19 - 2.41 (1H), 2.54 (3H), 2.88 - 3.22 (2H), 3.42 - 3.74 (1H), 3.94 - 4.18 (2H), 4.36 (3H), 7.20 (1H), 7.32 (2H), 7.46 (1H), 7.64 (2H), 8.55 (1H), 8.83 (1H).

Example 317: 2-({1-[4-(5-chloropyridin-2-yl)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide

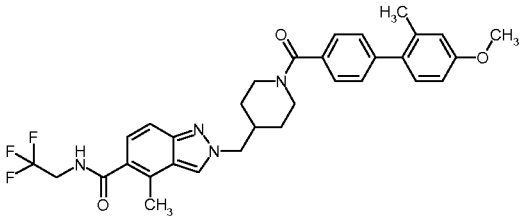


80 mg of the aryl bromide prepared in Example 316 together with 32 mg of (5-chloropyridin-2-yl)boronic acid was first placed in 1 ml tetrahydrofuran, treated with 17.3 mg of 1,1'-bis(diphenylphosphino)ferrocenodichloropalladium(II) and 0.17 ml of 1M potassium carbonate solution and heated in the microwave for 10 minutes at 120°C (100 watts). After fresh addition of 11 mg of (5-chloropyridin-2-yl)boronic acid and 17.3 mg of the palladium(II)

catalyst, the reaction mixture was again heated in the microwave for 10 minutes at 120°C (100 watts) until complete conversion. The reaction mixture was concentrated. After HPLC purification, this yielded 15 mg of the title compound.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.18 - 1.36 (2H), 1.37 - 1.75 (2H), 2.28 - 2.38 (1H), 2.54 (3H), 2.73 - 3.18 (2H), 3.49 - 3.74 (1H), 3.95 - 4.16 (2H), 4.28 - 4.62 (3H), 7.22 (1H), 7.33 - 7.65 (5H), 7.98 - 8.22 (3H), 8.56 (1H), 8.77 - 8.91 (1H).

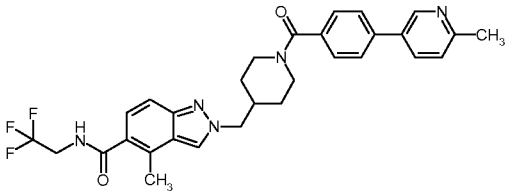
Example 318: 2-({1-[(4'-methoxy-2'-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 317, 50 mg of the title compound was obtained from 125 mg of 316 and 53 mg of (4-methoxy-2-methyl-phenyl)boronic acid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.16 - 1.36 (2H), 1.37 - 1.74 (2H), 2.23 (3H), 2.29 - 2.38 (1H), 2.54 (3H), 2.72 - 3.12 (2H), 3.77 (4H), 3.97 - 4.17 (2H), 4.38 (3H), 6.75 - 6.94 (2H), 7.07 - 7.26 (2H), 7.29 - 7.56 (5H), 8.56 (1H), 8.81 (1H).

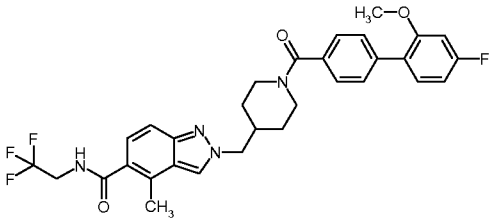
Example 319: 4-methyl-2-({1-[4-(6-methylpyridin-3-yl)benzoyl]piperidin-4-yl}methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 317, 37 mg of the title compound was obtained from 125 mg of 316 and 44 mg of (6-methylpyridin-3-yl)boronic acid under reflux.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.15 - 1.35 (2H), 1.37 - 1.71 (2H), 2.20 - 2.40 (1H), 2.52 (3H), 2.54 (3H), 2.74 - 3.15 (2H), 3.52 - 3.82 (1H), 4.07 (2H), 4.38 (3H), 7.20 (1H), 7.37 (1H), 7.47 (3H), 7.77 (2H), 8.01 (1H), 8.57 (1H), 8.72 - 8.92 (2H).

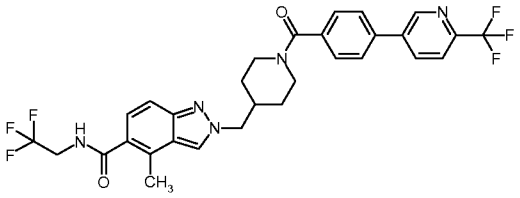
Example 320: 2-({1-[(4'-fluoro-2'-methoxybiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 317, 60 mg of the title compound was obtained from 125 mg of 316 and 75 g of (4-fluoro-2-methoxyphenyl)boronic acid under reflux.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.16 - 1.37 (2H), 1.38 - 1.75 (2H), 2.25 - 2.37 (1H), 2.54 (3H), 2.72 - 3.17 (2H), 3.79 (4H), 4.07 (2H), 4.38 (3H), 6.87 (1H), 7.04 (1H), 7.21 (1H), 7.27 - 7.58 (6H), 8.56 (1H), 8.81 (1H).

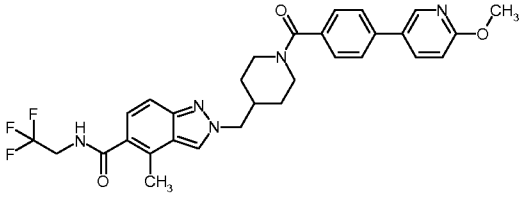
Example 321: 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{4-[6-(trifluoromethyl)pyridin-3-yl]-benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 317, 45 mg of the title compound was obtained from 125 mg of 316 and 84 mg of [6-(trifluoromethyl)pyridin-3-yl]boronic acid under reflux.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.15 - 1.37 (2H), 1.37 - 1.71 (2H), 2.22 - 2.41 (1H), 2.54 (3H), 2.73 - 3.20 (2H), 3.45 - 3.74 (1H), 3.93 - 4.17 (2H), 4.29 - 4.62 (3H), 7.21 (1H), 7.39 - 7.62 (4H), 7.89 (2H), 8.01 (1H), 8.57 (1H), 8.73 - 8.92 (1H), 9.13 (1H).

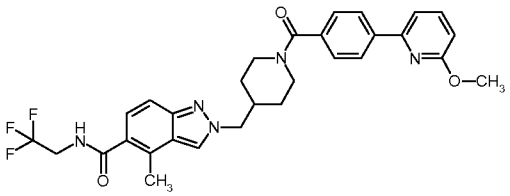
Example 322: 2-({1-[4-(6-methoxypyridin-3-yl)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 317, 54 mg of the title compound was obtained from 125 mg of 316 and 68 mg of (6-methoxypyridin-3-yl)boronic acid under reflux.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.13 - 1.35 (2H), 1.36 - 1.71 (2H), 2.20 - 2.40 (1H), 2.54 (3H), 2.73 - 3.16 (2H), 3.51 - 3.77 (1H), 3.90 (3H), 3.96 - 4.19 (2H), 4.37 (3H), 6.93 (1H), 7.20 (1H), 7.39 - 7.52 (3H), 7.73 (2H), 8.05 (1H), 8.47 - 8.63 (2H), 8.83 (1H).

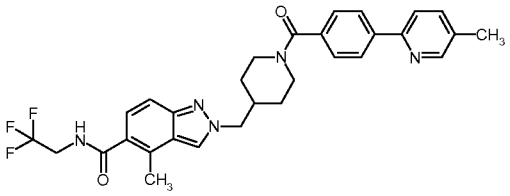
Example 323: 2-({1-[4-(6-methoxypyridin-2-yl)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 317, 55 mg of the title compound was obtained from 125 mg of 316 and 49 mg of (6-methoxypyridin-2-yl)boronic acid under reflux.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.16 - 1.36 (2H), 1.37 - 1.69 (2H), 2.20 - 2.41 (1H), 2.54 (3H), 2.74 - 3.16 (2H), 3.47 - 3.81 (1H), 3.96 (3H), 4.06 (2H), 4.38 (3H), 6.81 (1H), 7.21 (1H), 7.47 (3H), 7.60 (1H), 7.74 - 7.90 (1H), 8.15 (2H), 8.56 (1H), 8.81 (1H).

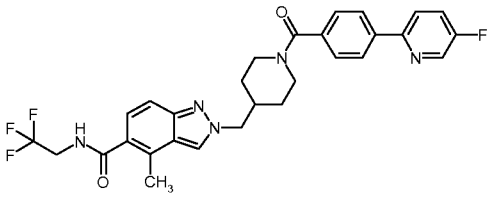
Example 324: 4-methyl-2-({1-[4-(5-methylpyridin-2-yl)benzoyl]piperidin-4-yl}methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 317, 9 mg of the title compound was obtained from 125 mg of 316 and 44 mg of (5-methylpyridin-2-yl)boronic acid under reflux.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.16 - 1.36 (2H), 1.37 - 1.71 (2H), 2.24 - 2.30 (1H), 2.34 (3H), 2.54 (3H), 2.74 - 3.16 (2H), 3.52 - 3.79 (1H), 3.93 - 4.17 (2H), 4.38 (3H), 7.20 (1H), 7.37 - 7.54 (3H), 7.66 - 7.78 (1H), 7.89 (1H), 8.11 (2H), 8.45 - 8.61 (2H), 8.74 - 8.88 (1H).

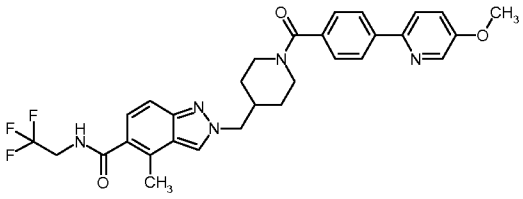
Example 325: 2-({1-[4-(5-fluoropyridin-2-yl)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 317, 35 mg of the title compound was obtained from 125 mg of 316 and 45 mg of (5-fluoropyridin-2-yl)boronic acid under reflux.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.17 - 1.34 (2H), 1.35 - 1.69 (2H), 2.22 - 2.41 (1H), 2.54 (3H), 2.69 - 3.19 (2H), 3.51 - 3.78 (1H), 4.07 (2H), 4.38 (3H), 7.20 (1H), 7.40 - 7.53 (3H), 7.85 (1H), 8.04 - 8.17 (3H), 8.57 (1H), 8.68 (1H), 8.83 (1H).

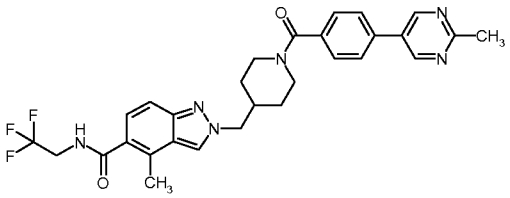
Example 326: 2-({1-[4-(5-methoxypyridin-2-yl)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 317, 94 mg of the title compound was obtained from 125 mg of 316 and 49 mg of (5-methoxypyridin-2-yl)boronic acid under reflux.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.19 - 1.36 (2H), 1.37 - 1.69 (2H), 2.28 - 2.40 (1H), 2.54 (3H), 2.73 - 3.19 (2H), 3.48 - 3.79 (1H), 3.88 (3H), 4.07 (2H), 4.38 (3H), 7.20 (1H), 7.38 - 7.55 (4H), 7.96 (1H), 8.07 (2H), 8.39 (1H), 8.57 (1H), 8.82 (1H).

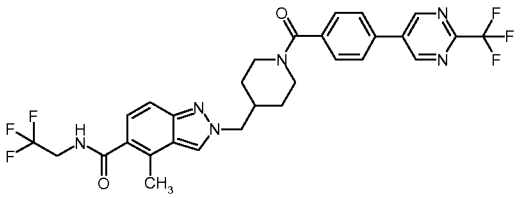
Example 327: 4-methyl-2-({1-[4-(2-methylpyrimidin-5-yl)benzoyl]piperidin-4-yl}methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide



Analogously to Example 317, 46 mg of the title compound was obtained from 125 mg of 316 and 102 mg of (2-methylpyrimidin-5-yl)boronic acid pinacol ester under reflux.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.16 - 1.35 (2H), 1.35 - 1.67 (2H), 2.21 - 2.42 (1H), 2.54 (3H), 2.67 (3H), 2.71 - 2.89 (1H), 2.93 - 3.20 (1H), 3.50 - 3.73 (1H), 4.07 (2H), 4.37 (3H), 7.20 (1H), 7.40 - 7.57 (3H), 7.85 (2H), 8.57 (1H), 8.84 (1H), 9.05 (2H).

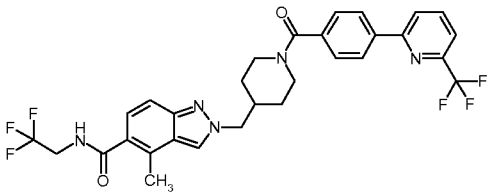
Example 328: 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{4-[2-(trifluoromethyl)pyrimidin-5-yl]-benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 317, 34 mg of the title compound was obtained from 125 mg of 316 and 89 mg of [2-(trifluoromethyl)pyrimidin-5-yl]boronic acid under reflux.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.21 - 1.35 (2H), 1.36 - 1.71 (2H), 2.23 - 2.41 (1H), 2.54 (3H), 2.71 - 2.89 (1H), 2.94 - 3.17 (1H), 3.48 - 3.72 (1H), 4.05 (2H), 4.28 - 4.61 (3H), 7.21 (1H), 7.47 (1H), 7.57 (2H), 7.98 (2H), 8.57 (1H), 8.84 (1H), 9.44 (2H).

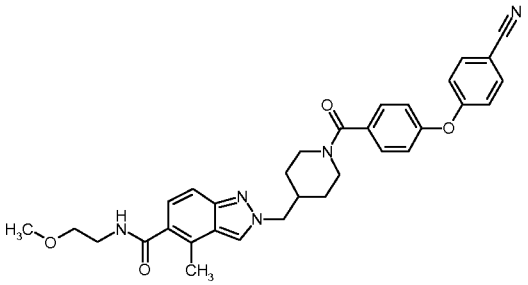
Example 329: 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{4-[6-(trifluoromethyl)pyridin-2-yl]-benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 317, 70 mg of the title compound was obtained from 125 mg of 316 and 121 mg of [6-(trifluoromethyl)pyridin-2-yl]boronic acid pinacol ester under reflux.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.19 - 1.36 (2H), 1.37 - 1.72 (2H), 2.23 - 2.39 (1H), 2.54 (3H), 2.68 - 2.90 (1H), 2.92 - 3.16 (1H), 3.50 - 3.73 (1H), 4.06 (2H), 4.38 (3H), 7.20 (1H), 7.41 - 7.60 (3H), 7.89 (1H), 8.11 - 8.27 (3H), 8.33 (1H), 8.56 (1H), 8.81 (1H).

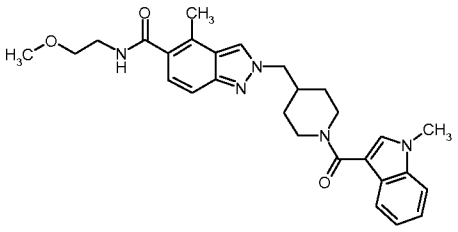
Example 330: 2-({1-[4-(4-cyanophenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 151 mg of the title compound was obtained from 213 mg of 71a and 153 mg of 4-(4-cyanophenoxy)benzoic acid in DMF.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.22 (2H), 1.31 - 1.66 (2H), 2.15 - 2.36 (1H), 2.49 (3H), 2.70 - 3.12 (2H), 3.24 (3H), 3.36 (2H), 3.39 - 3.46 (2H), 3.50 - 3.79 (1H), 4.32 (3H), 7.00 - 7.23 (5H), 7.30 - 7.49 (3H), 7.75 - 7.91 (2H), 8.12 (1H), 8.48 (1H).

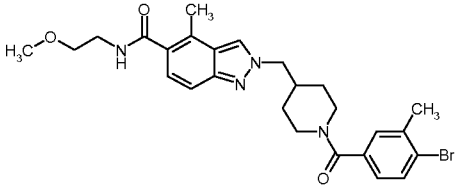
Example 331: N-(2-methoxyethyl)-4-methyl-2-({1-[(1-methyl-1H-indol-3-yl)carbonyl]-piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 26 mg of the title compound was obtained from 38 mg of 71a and 36 mg of 1-methyl-1H-indol-3-carboxylic acid in DMF.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.23 (2H), 1.43 - 1.64 (2H), 2.20 - 2.39 (1H), 2.53 (3H), 2.80 - 3.03 (2H), 3.28 (3H), 3.37 - 3.50 (4H), 3.81 (3H), 4.37 (4H), 7.18 (3H), 7.36 - 7.53 (2H), 7.67 (2H), 8.04 - 8.25 (1H), 8.52 (1H).

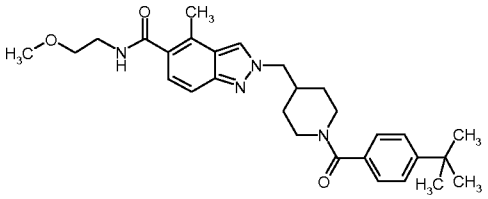
Example 332: 2-{[1-(4-bromo-3-methylbenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 498 mg of the title compound was obtained from 807 mg of 71a and 788 mg of 4-bromo-3-methylbenzoic acid in DMF.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.20 - 1.32 (2H), 1.33 - 1.67 (2H), 2.24 - 2.33 (1H), 2.36 (3H), 2.52 (3H), 2.73 (1H), 2.91 - 3.13 (1H), 3.28 (3H), 3.35 - 3.63 (5H), 4.34 (3H), 7.03 - 7.23 (2H), 7.30 - 7.49 (2H), 7.63 (1H), 8.15 (1H), 8.51 (1H).

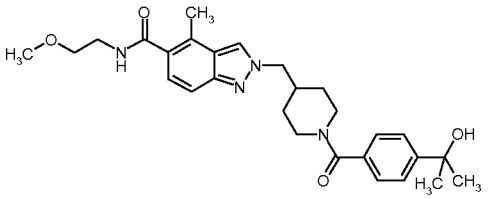
Example 333: 2-{[1-(4-tert-butylbenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 50 mg of the title compound was obtained from 100 mg of 71a and 81 mg of 4-tert-butylbenzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.20 - 1.33 (11H), 1.33 - 1.67 (2H), 2.21 - 2.37 (1H), 2.52 (3H), 2.68 - 3.10 (2H), 3.28 (3H), 3.36 - 3.43 (2H), 3.45 (2H), 3.52 - 3.74 (1H), 4.35 (3H), 7.18 (1H), 7.25 - 7.35 (2H), 7.36 - 7.52 (3H), 8.15 (1H), 8.50 (1H).

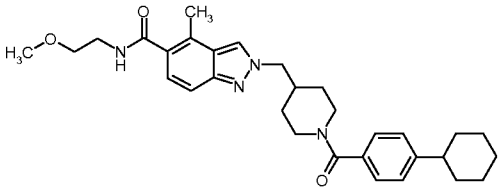
Example 334: 2-({1-[4-(1-hydroxy-1-methylethyl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 28 mg of the title compound was obtained from 100 mg of 71a and 82 mg of 4-(1-hydroxy-1-methylethyl)benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.24 (2H), 1.42 (8H), 2.20 - 2.40 (1H), 2.52 (3H), 2.64 - 3.11 (2H), 3.28 (3H), 3.34 - 3.43 (2H), 3.43 - 3.51 (2H), 3.53 - 3.71 (1H), 4.35 (3H), 4.76 - 5.43 (1H), 7.18 (1H), 7.28 (2H), 7.42 (1H), 7.46 - 7.56 (2H), 8.15 (1H), 8.51 (1H).

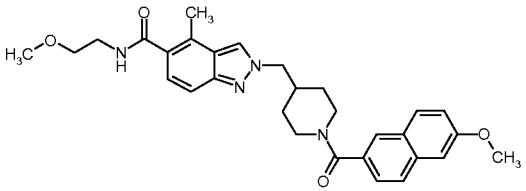
Example 335: 2-{[1-(4-cyclohexylbenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 75 mg of the title compound was obtained from 100 mg of 71a and 93 mg of 4-cyclohexylbenzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.10 - 1.63 (9H), 1.64 - 1.89 (5H), 2.17 - 2.40 (1H), 2.52 (3H), 2.69 - 3.08 (2H), 3.28 (3H), 3.38 - 3.43 (2H), 3.43 - 3.49 (2H), 3.53 - 3.73 (1H), 4.35 (3H), 7.18 (1H), 7.27 (4H), 7.42 (1H), 8.15 (1H), 8.50 (1H).

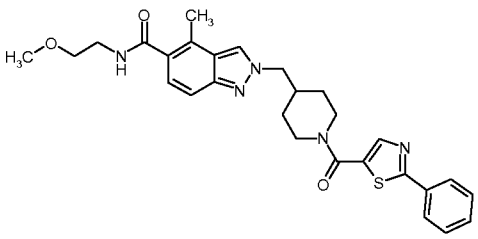
Example 336: N-(2-methoxyethyl)-2-{[1-(6-methoxy-2-naphthoyl)piperidin-4-yl]methyl}-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 23 mg of the title compound was obtained from 100 mg of 71a) and 92 mg of 6-methoxy-naphthalen-2-carboxylic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.23 (2H), 1.37 - 1.72 (2H), 2.23 - 2.39 (1H), 2.52 (3H), 2.72 - 3.12 (2H), 3.28 (3H), 3.36 - 3.42 (2H), 3.43 - 3.49 (2H), 3.59 - 3.81 (1H), 3.89 (3H), 4.36 (3H), 7.09 - 7.27 (2H), 7.33 - 7.49 (3H), 7.79 - 7.95 (3H), 8.15 (1H), 8.51 (1H).

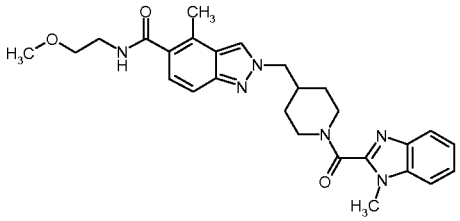
Example 337: N-(2-methoxyethyl)-4-methyl-2-({1-[(2-phenylthiazol-5-yl)carbonyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 36 mg of the title compound was obtained from 100 mg of 71a and 93 mg of 2-phenylthiazol-5-carboxylic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.23 (2H), 1.55 (2H), 2.19 - 2.45 (1H), 2.52 - 2.56 (3H), 2.70 - 3.24 (2H), 3.28 (3H), 3.36 - 3.43 (2H), 3.44 - 3.49 (2H), 4.37 (4H), 7.19 (1H), 7.43 (1H), 7.49 - 7.62 (3H), 7.90 - 8.03 (2H), 8.08 - 8.25 (2H), 8.52 (1H).

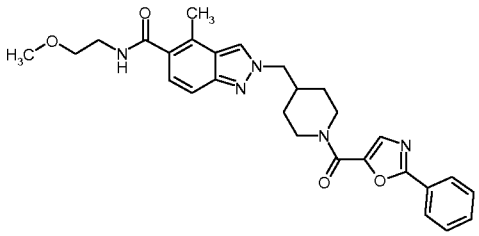
Example 338: N-(2-methoxyethyl)-4-methyl-2-({1-[(1-methyl-1H-benzimidazol-2-yl)carbonyl]-piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 39 mg of the title compound was obtained from 100 mg of 71a and 80 mg of 1-methyl-1H-benzimidazol-2-carboxylic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.22 - 1.43 (2H), 1.43 - 1.53 (1H), 1.59 - 1.70 (1H), 2.27 - 2.44 (1H), 2.53 (3H), 2.87 (1H), 3.11 (1H), 3.28 (3H), 3.36 - 3.42 (2H), 3.43 - 3.48 (2H), 3.83 (3H), 4.00 - 4.14 (1H), 4.39 (2H), 4.48 - 4.61 (1H), 7.18 (1H), 7.23 - 7.46 (3H), 7.58 - 7.74 (2H), 8.10 - 8.20 (1H), 8.53 (1H).

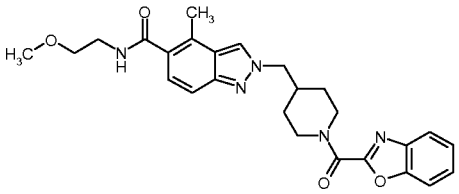
Example 339: N-(2-methoxyethyl)-4-methyl-2-({1-[(2-phenyloxazol-5-yl)carbonyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 30 mg of the title compound was obtained from 100 mg of 71a and 86 mg of 2-phenyloxazol-5-carboxylic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.14 - 1.48 (2H), 1.59 (2H), 2.24 - 2.46 (1H), 2.52 - 2.56 (3H), 2.71 - 3.01 (1H), 3.11 - 3.26 (1H), 3.28 (3H), 3.36 - 3.43 (2H), 3.43 - 3.50 (2H), 4.38 (4H), 7.19 (1H), 7.43 (1H), 7.52 - 7.67 (3H), 7.80 (1H), 7.97 - 8.05 (2H), 8.16 (1H), 8.53 (1H).

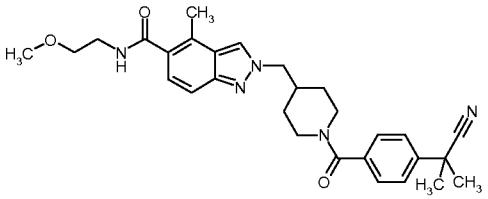
Example 340: 2-{[1-(benzoxazol-2-ylcarbonyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 37 mg of the title compound was obtained from 100 mg of 71a and 84 mg of benzoxazol-2-carboxylic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.19 - 1.43 (2H), 1.48 - 1.73 (2H), 2.28 - 2.45 (1H), 2.53 (3H), 2.91 (1H), 3.22 (1H), 3.33 - 3.57 (m, 7H), 4.25 - 4.60 (4H), 7.18 (1H), 7.36 - 7.62 (3H), 7.78 - 7.95 (2H), 8.16 (1H), 8.53 (1H).

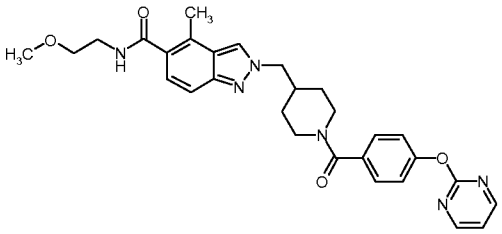
Example 341: 2-({1-[4-(1-cyano-1-methylethyl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 20 mg of the title compound was obtained from 100 mg of 71a and 86 mg of 4-(1-cyano-1-methylethyl)benzoic acid in DMF.

^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 1.17 - 1.34 (2H), 1.35 - 1.64 (2H), 1.70 (6H), 2.16 - 2.40 (1H), 2.52 (3H), 2.64 - 3.13 (2H), 3.28 (3H), 3.40 (2H), 3.43 - 3.49 (2H), 3.49 - 3.67 (1H), 4.35 (3H), 7.18 (1H), 7.42 (3H), 7.58 (2H), 8.15 (1H), 8.50 (1H).

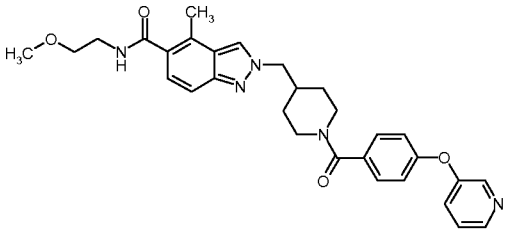
Example 342: N-(2-methoxyethyl)-4-methyl-2-({1-[4-(pyrimidin-2-yloxy)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 37 mg of the title compound was obtained from 100 mg of 71a and 98 mg of 4-(2-pyrimidinyloxy)benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.26 (2H), 1.38 - 1.66 (2H), 2.20 - 2.40 (1H), 2.52 - 2.56 (3H), 2.70 - 3.16 (2H), 3.28 (3H), 3.36 - 3.43 (2H), 3.43 - 3.49 (2H), 3.64 - 3.77 (m, 1H), 4.36 (3H), 7.18 (1H), 7.22 - 7.33 (3H), 7.39 - 7.49 (3H), 8.15 (1H), 8.43 - 8.57 (1H), 8.66 (2H).

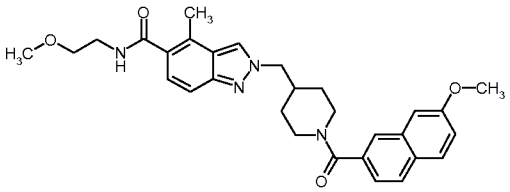
Example 343: N-(2-methoxyethyl)-4-methyl-2-({1-[4-(3-pyridyloxy)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 7 mg of the title compound was obtained from 75 mg of 71a and 73 mg of 4-(3-pyridyloxy)benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.17 - 1.32 (2H), 1.35 - 1.69 (2H), 2.19 - 2.38 (1H), 2.52 (3H), 2.70 - 3.14 (2H), 3.28 (3H), 3.34 - 3.43 (2H), 3.43 - 3.51 (2H), 3.55 - 3.70 (1H), 4.35 (3H), 7.04 - 7.13 (2H), 7.18 (1H), 7.37 - 7.46 (3H), 7.47 - 7.54 (1H), 7.58 (1H), 8.15 (1H), 8.38 - 8.55 (3H).

Example 344: N-(2-methoxyethyl)-2-{[1-(7-methoxy-2-naphthoyl)piperidin-4-yl]methyl}-4-methyl-2H-indazol-5-carboxamide

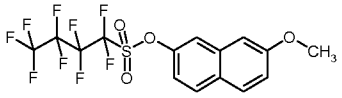


Analogously to Example 1b, Version B, 28 mg of the title compound was obtained from 75 mg of 71a and 69 mg of the carboxylic acid prepared in Example 344c) in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.21 - 1.35 (2H), 1.37 - 1.75 (2H), 2.23 - 2.39 (1H), 2.52 (3H), 2.73 - 3.13 (2H), 3.28 (3H), 3.35 - 3.42 (2H), 3.45 (2H), 3.53 - 3.74 (1H), 3.88 (3H), 4.37 (3H), 7.13 - 7.25 (2H), 7.29 (1H), 7.36 - 7.48 (2H), 7.77 - 7.93 (3H), 8.15 (1H), 8.52 (1H).

The starting material was prepared as follows:

Example 344a: : 7-methoxynaphthalen-2-yl-1,1,2,2,3,3,4,4,4-nonafluorobutan-1-sulphonate

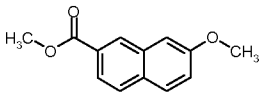


5.12 g of 7-methoxy-2-naphthol were dissolved in 50 ml toluene and cooled to 0°C. 30.7 ml of N,N-diisopropylethylamine and 17.6 ml of nonafluorobutanesulphonyl fluoride were successively added dropwise to this and the reaction mixture was then stirred at room temperature until complete conversion. The reaction mixture was poured into 600 ml of saturated ammonium chloride solution, the deposited brown oil separated and the aqueous phase

extracted several times with ethyl acetate. The combined organic phases were washed with water and saturated sodium chloride solution, dried and concentrated. The residue was purified by column chromatography on silica gel using a hexane/ ethyl acetate gradient. Yield: 11.45 g of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 3.89 (3H), 7.28 (1H), 7.41 (1H), 7.52 (1H), 7.90 - 8.00 (2H), 8.05 (1H).

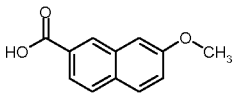
Example 344b: Methyl 7-methoxynaphthalen-2-carboxylate



Analogously to Example 1e, 2.34 g of the title compound was obtained from 11.0 g of 344a and 8.8 ml of methanol.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 3.89 (3H), 3.91 (3H), 7.31 (1H), 7.57 (1H), 7.82 (1H), 7.94 (2H), 8.54 (1H).

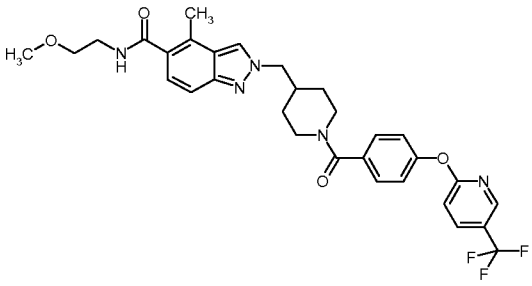
Example 344c: 7-methoxynaphthalen-2-carboxylic acid



Analogously to Example 258d, 1.27 g of the title compound was obtained from 2.0 g of 344b.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 3.89 (3H), 7.30 (1H), 7.53 (1H), 7.78 - 7.86 (1H), 7.87 - 8.01 (2H), 8.50 (1H), 12.99 (1H).

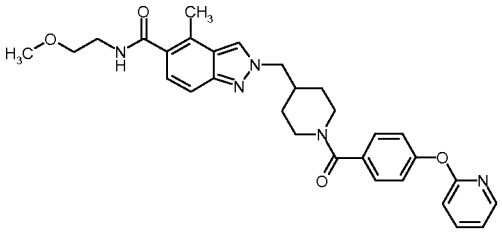
Example 345: N-(2-methoxyethyl)-4-methyl-2-{[1-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}-benzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 221 mg of the title compound was obtained from 200 mg of 71a and 232 mg of 4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.21 - 1.34 (2H), 1.36 - 1.72 (2H), 2.23 - 2.39 (1H), 2.53 (3H), 2.89 (2H), 3.31 (3H), 3.36 - 3.43 (2H), 3.43 - 3.50 (2H), 3.53 - 3.86 (1H), 4.36 (3H), 7.18 (1H), 7.23 - 7.33 (3H), 7.37 - 7.50 (3H), 8.13 (1H), 8.25 (1H), 8.51 (1H), 8.55 - 8.63 (1H).

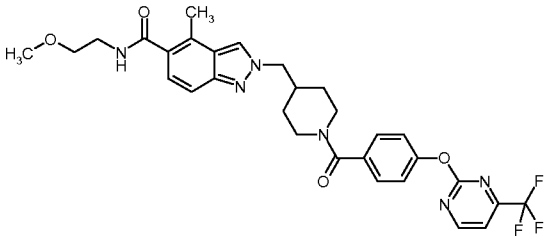
Example 346: N-(2-methoxyethyl)-4-methyl-2-({1-[4-(2-pyridyloxy)benzoyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 29 mg of the title compound was obtained from 100 mg of 71a and 98 mg of 4-(2-pyridyloxy)benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.23 (2H), 1.39 - 1.68 (2H), 2.24 - 2.39 (1H), 2.52 - 2.56 (3H), 2.71 - 3.13 (2H), 3.28 (3H), 3.36 - 3.43 (2H), 3.45 (2H), 3.53 - 3.87 (1H), 4.36 (3H), 7.08 (1H), 7.13 - 7.26 (4H), 7.34 - 7.52 (3H), 7.88 (1H), 8.07 - 8.23 (2H), 8.51 (1H).

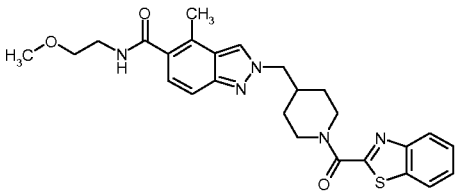
Example 347: N-(2-methoxyethyl)-4-methyl-2-{[1-(4-{[4-(trifluoromethyl)pyrimidin-2-yl]-oxy}benzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 11 mg of the title compound was obtained from 75 mg of 71a and 97 mg of 4-{[4-(trifluoromethyl)pyrimidin-2-yl]oxy}benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.23 (2H), 1.37 - 1.69 (2H), 2.19 - 2.39 (1H), 2.53 (3H), 2.68 - 3.18 (2H), 3.28 (3H), 3.36 - 3.43 (2H), 3.45 (2H), 3.51 - 3.79 (1H), 4.36 (3H), 7.18 (1H), 7.31 - 7.39 (2H), 7.39 - 7.53 (3H), 7.81 (1H), 8.15 (1H), 8.51 (1H), 9.00 (1H).

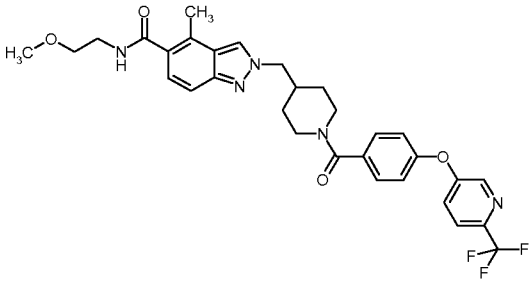
Example 348: 2-{[1-(benzothiazol-2-ylcarbonyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 28 mg of the title compound was obtained from 75 mg of 71a and 61 mg of benzothiazol-2-carboxylic acid in DMF.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.34 (2H), 1.62 (2H), 2.32 - 2.45 (1H), 2.53 (3H), 2.82 - 3.00 (1H), 3.26 (1H), 3.28 (3H), 3.40 (2H), 3.43 - 3.50 (2H), 4.38 (3H), 4.98 - 5.23 (1H), 7.19 (1H), 7.43 (1H), 7.59 (2H), 8.01 - 8.30 (3H), 8.53 (1H).

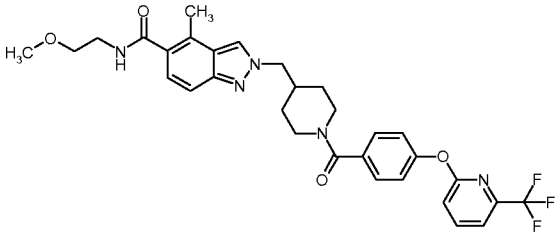
Example 349: N-(2-methoxyethyl)-4-methyl-2-{[1-(4-{[6-(trifluoromethyl)pyridin-3-yl]oxy}-benzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 34 mg of the title compound was obtained from 75 mg of 71a and 96 mg of 303b in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.24 (2H), 1.37 - 1.68 (2H), 2.22 - 2.38 (1H), 2.53 (3H), 2.71 - 3.14 (2H), 3.28 (3H), 3.36 - 3.43 (2H), 3.44 - 3.49 (2H), 3.52 - 3.84 (1H), 4.36 (3H), 7.09 - 7.29 (3H), 7.35 - 7.53 (3H), 7.65 (1H), 7.92 (1H), 8.13 (1H), 8.51 (1H), 8.60 (1H).

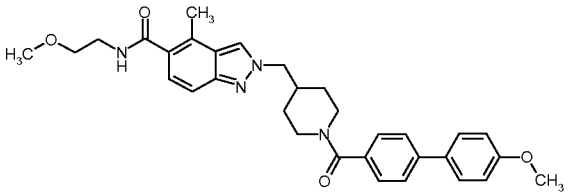
Example 350: N-(2-methoxyethyl)-4-methyl-2-{[1-(4-{[6-(trifluoromethyl)pyridin-2-yl]oxy}-benzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 36 mg of the title compound was obtained from 100 mg of 71a and 129 mg of 4-{[6-(trifluoromethyl)pyridin-2-yl]oxy}benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.20 - 1.34 (2H), 1.36 - 1.66 (2H), 2.24 - 2.39 (1H), 2.53 (3H), 2.70 - 3.16 (2H), 3.28 (3H), 3.36 - 3.43 (2H), 3.44 - 3.49 (2H), 3.53 - 3.82 (1H), 4.36 (3H), 7.18 (1H), 7.22 - 7.30 (2H), 7.32 - 7.50 (4H), 7.67 (1H), 8.06 - 8.21 (2H), 8.51 (1H).

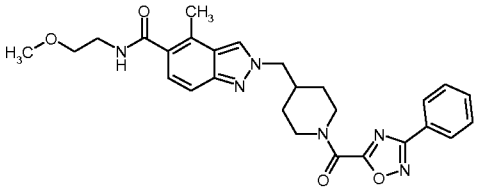
Example 351: 2-({1-[(4'-methoxybiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxy-ethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 15 mg of the title compound was obtained from 100 mg of 71a and 104 mg of 4'-methoxy-biphenyl-4-carboxylic acid in DMF.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.24 (2H), 1.37 - 1.64 (2H), 2.19 - 2.32 (1H), 2.53 (3H), 2.74 - 3.10 (2H), 3.28 (3H), 3.40 (2H), 3.45 (2H), 3.67 - 3.91 (4H), 4.21 - 4.64 (3H), 7.04 (2H), 7.19 (1H), 7.41 (2H), 7.66 (5H), 8.04 - 8.22 (1H), 8.51 (1H).

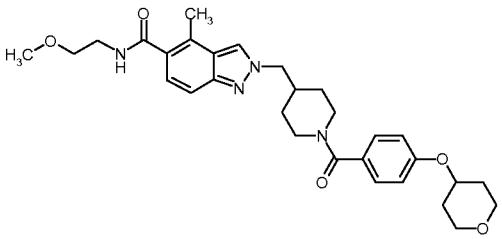
Example 352: N-(2-methoxyethyl)-4-methyl-2-({1-[(3-phenyl-1,2,4-oxadiazol-5-yl)carbonyl]-piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 12 mg of the title compound was obtained from 100 mg of 71a and 78 mg of 3-phenyl-1,2,4-oxadiazol-5-carboxylic acid in DMF.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.33 (2H), 1.50 - 1.72 (2H), 2.31 - 2.45 (1H), 2.53 (3H), 2.86 - 3.04 (1H), 3.16 - 3.26 (1H), 3.28 (3H), 3.41 (2H), 3.43 - 3.51 (2H), 3.94 - 4.13 (1H), 4.28 - 4.55 (3H), 7.19 (1H), 7.43 (1H), 7.52 - 7.72 (3H), 7.96 - 8.09 (2H), 8.13 (1H), 8.52 (1H).

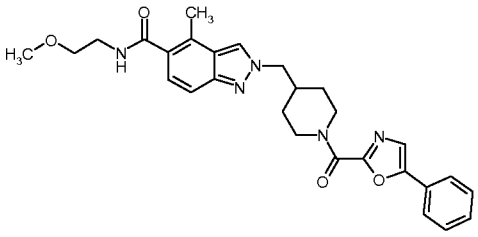
Example 353: N-(2-methoxyethyl)-4-methyl-2-({1-[4-(3,4,5,6-tetrahydro-2H-pyran-4-yloxy)-benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 21 mg of the title compound was obtained from 100 mg of 71a and 91 mg of 4-(3,4,5,6-tetrahydro-2H-pyran-4-yloxy)benzoic acid in DMF.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.23 (2H), 1.38 - 1.70 (4H), 1.97 (2H), 2.18 - 2.41 (1H), 2.53 (3H), 2.75 - 3.02 (2H), 3.28 (3H), 3.35 - 3.54 (8H), 3.84 (2H), 4.35 (2H), 4.52 - 4.77 (1H), 7.00 (2H), 7.18 (1H), 7.30 (2H), 7.42 (1H), 8.13 (1H), 8.50 (1H).

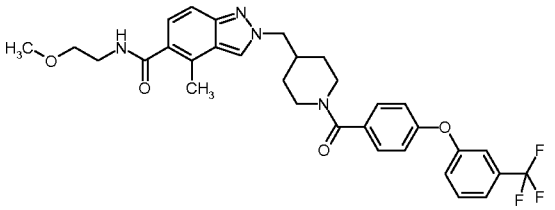
Example 354: N-(2-methoxyethyl)-4-methyl-2-({1-[(5-phenyloxazol-2-yl)carbonyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 10 mg of the title compound was obtained from 100 mg of 71a and 77 mg of 5-phenyl-oxazol-2-carboxylic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.17 - 1.41 (2H), 1.59 (2H), 2.28 - 2.45 (1H), 2.52 - 2.56 (3H), 2.85 (1H), 3.20 (1H), 3.28 (3H), 3.36 - 3.43 (2H), 3.44 - 3.50 (2H), 4.38 (3H), 4.57 - 4.74 (1H), 7.19 (1H), 7.39 - 7.57 (4H), 7.74 - 7.82 (2H), 7.88 (1H), 8.13 (1H), 8.52 (1H).

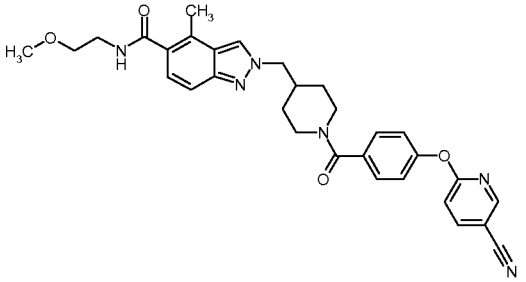
Example 355: N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[3-(trifluoromethyl)phenoxy]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 40 mg of the title compound was obtained from 100 mg of 71a and 115 mg of 4-[(3-(trifluoromethyl)phenoxy]benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.23 (2H), 1.35 - 1.65 (2H), 2.19 - 2.38 (1H), 2.52 - 2.56 (3H), 2.71 - 3.12 (2H), 3.28 (3H), 3.36 - 3.43 (2H), 3.43 - 3.50 (2H), 3.53 - 3.87 (1H), 4.35 (3H), 7.07 - 7.15 (2H), 7.18 (1H), 7.30 - 7.48 (5H), 7.54 (1H), 7.64 (1H), 8.13 (1H), 8.50 (1H).

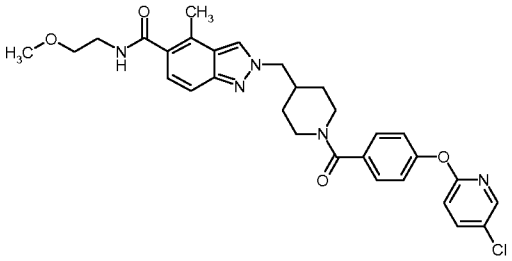
Example 356: 2-[(1-{4-[(5-cyanopyridin-2-yl)oxy]benzoyl}piperidin-4-yl)methyl]-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 15 mg of the title compound was obtained from 100 mg of 71a and 98 mg of 4-[(5-cyanopyridin-2-yl)oxy]benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.21 - 1.35 (2H), 1.36 - 1.75 (2H), 2.23 - 2.39 (1H), 2.53 (3H), 2.69 - 3.19 (2H), 3.28 (3H), 3.36 - 3.43 (2H), 3.46 (2H), 3.53 - 3.85 (1H), 4.36 (3H), 7.18 (1H), 7.23 - 7.33 (3H), 7.36 - 7.53 (3H), 8.13 (1H), 8.34 (1H), 8.51 (1H), 8.66 (1H).

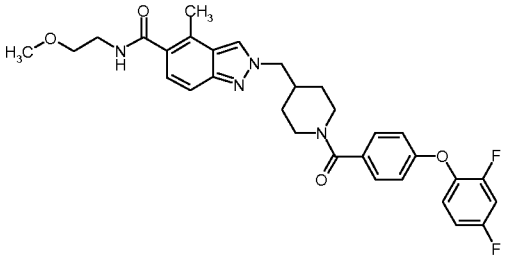
Example 357: 2-[(1-{4-[(5-chloropyridin-2-yl)oxy]benzoyl}piperidin-4-yl)methyl]-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 40 mg of the title compound was obtained from 100 mg of 71a and 102 mg of 4-[(5-chloropyridin-2-yl)oxy]benzoic acid in DMF.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.25 (2H), 1.36 - 1.70 (2H), 2.20 - 2.39 (1H), 2.53 (3H), 2.66 - 3.15 (2H), 3.28 (3H), 3.40 (2H), 3.43 - 3.50 (2H), 3.55 - 3.90 (1H), 4.36 (3H), 7.08 - 7.28 (4H), 7.42 (3H), 7.99 (1H), 8.10 - 8.30 (2H), 8.51 (1H).

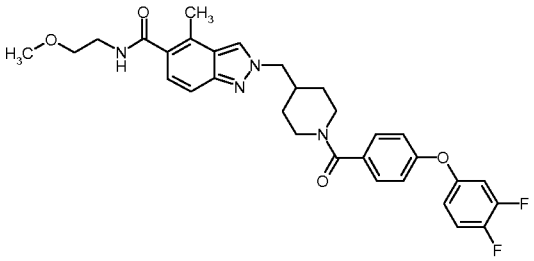
Example 358: 2-({1-[4-(2,4-difluorophenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 22 mg of the title compound was obtained from 100 mg of 71a and 102 mg of 4-(2,4-difluorophenoxy)benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.21 (2H), 1.33 - 1.76 (2H), 2.20 - 2.39 (1H), 2.52 (3H), 2.69 - 3.13 (2H), 3.28 (3H), 3.36 - 3.43 (2H), 3.43 - 3.50 (2H), 3.53 - 3.90 (1H), 4.35 (3H), 6.91 - 7.04 (2H), 7.11 - 7.22 (2H), 7.30 - 7.46 (4H), 7.51 (1H), 8.13 (1H), 8.50 (1H).

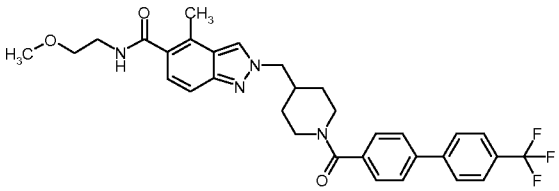
Example 359: 2-({1-[4-(3,4-difluorophenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 23 mg of the title compound was obtained from 100 mg of 71a and 102 mg of 4-(3,4-difluorophenoxy)benzoic acid in DMF.

^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 1.17 - 1.30 (2H), 1.35 - 1.70 (2H), 2.20 - 2.40 (1H), 2.52 (3H), 2.74 - 3.14 (2H), 3.28 (3H), 3.40 (2H), 3.43 - 3.51 (2H), 3.52 - 3.89 (1H), 4.35 (3H), 6.94 (1H), 7.05 (2H), 7.18 (1H), 7.30 (1H), 7.36 - 7.59 (4H), 8.15 (1H), 8.51 (1H).

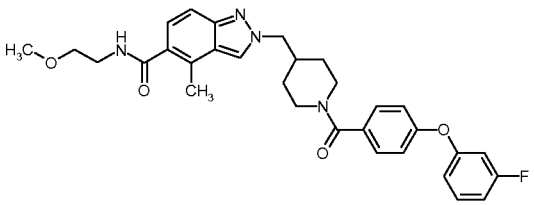
Example 360: N-(2-methoxyethyl)-4-methyl-2-[(1-{[4'-(trifluoromethyl)biphenyl-4-yl]-carbonyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 44 mg of the title compound was obtained from 100 mg of 71a and 109 mg of 4'-(trifluoromethyl)biphenyl-4-carboxylic acid in DMF

LC-MS: R_t = 1.28 min, MS (ES+): m/z = 579 $(M+H)^+$.

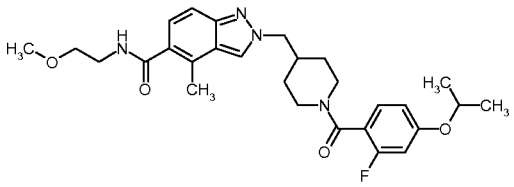
Example 361: 2-({1-[4-(3-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 43 mg of the title compound was obtained from 100 mg of 71a and 95 mg of 4-(3-fluorophenoxy)benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.17 - 1.31 (2H), 1.33 - 1.69 (2H), 2.19 - 2.38 (1H), 2.52 (3H), 2.70 - 3.11 (2H), 3.28 (3H), 3.36 - 3.43 (2H), 3.43 - 3.49 (2H), 3.54 - 3.85 (1H), 4.35 (3H), 6.85 - 7.13 (5H), 7.18 (1H), 7.35 - 7.55 (4H), 8.15 (1H), 8.51 (1H).

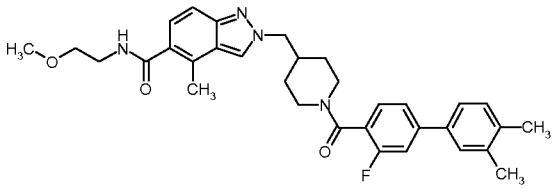
Example 362: 2-{[1-(2-fluoro-4-isopropoxybenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 31 mg of the title compound was obtained from 75 mg of 71a and 41 mg of 2-fluoro-4-isopropoxybenzoic acid.

^{1}H-NMR (300 MHz, chloroform-d): δ [ppm]= 1.21 - 1.42 (8H), 1.51 (1H), 1.69 (1H), 2.38 (1H), 2.56 - 2.80 (4H), 2.87 - 3.08 (1H), 3.36 (3H), 3.48 - 3.73 (4H), 4.28 (2H), 4.51 (1H), 4.74 (1H), 5.28 (1H), 6.19 (1H), 6.54 (1H), 6.67 (1H), 7.13 - 7.38 (2H), 7.50 (1H), 7.94 (1H).

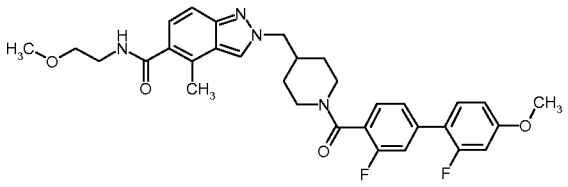
Example 363: 2-({1-[(3-fluoro-3',4'-dimethylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 35 mg of the title compound was obtained from 75 mg of 71a and 50 mg of 3-fluoro-3',4'-dimethylbiphenyl-4-carboxylic acid.

^{1}H-NMR (300 MHz, chloroform-d): δ [ppm]= 1.25 - 1.51 (2H), 1.57 (1H), 1.76 (1H), 2.25 - 2.37 (6H), 2.45 (1H), 2.61 - 2.71 (3H), 2.79 (1H), 3.06 (1H), 3.40 (3H), 3.53 - 3.77 (5H), 4.34 (2H), 4.83 (1H), 6.04 - 6.30 (1H), 7.15 - 7.47 (7H), 7.55 (1H), 7.98 (1H).

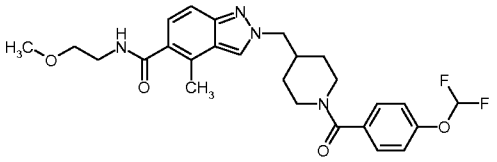
Example 364: 2-({1-[(2',3-difluoro-4'-methoxybiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 28 mg of the title compound was obtained from 90 mg of 71a and 65 mg of 3,2'-difluoro-4'-methoxybiphenyl-4-carboxylic acid.

^{1}H-NMR (300 MHz, chloroform-d): δ [ppm]= 1.25 - 1.50 (2H), 1.50 - 1.84 (2H), 2.44 (1H), 2.66 (3H), 2.78 (1H), 3.03 (1H), 3.39 (3H), 3.53 - 3.76 (5H), 3.85 (3H), 4.23 - 4.45 (2H), 4.83 (1H), 6.17 (1H), 6.64 - 6.92 (2H), 7.18 - 7.48 (5H), 7.54 (1H), 7.97 (1H).

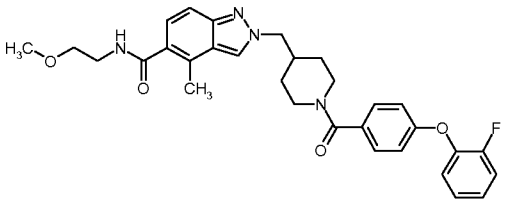
Example 365: 2-({1-[4-(difluoromethoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 23 mg of the title compound was obtained from 75 mg of 71a and 38 mg of 4-(difluoromethoxy)benzoic acid.

^{1}H-NMR (300 MHz, chloroform-d): δ [ppm]= 1.26 (2H), 1.59 (2H), 2.26 - 2.49 (1H), 2.62 (3H), 2.84 (2H), 3.36 (3H), 3.43 (1H), 3.50 - 3.96 (4H), 4.29 (2H), 4.46 - 5.02 (1H), 6.13 - 6.25 (1H), 6.26 - 6.82 (1H), 7.11 (2H), 7.22 - 7.43 (3H), 7.50 (1H), 7.93 (1H).

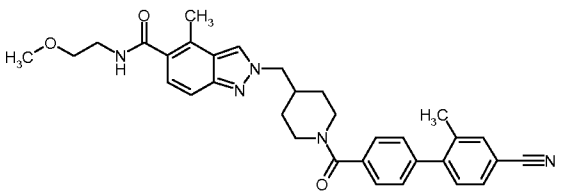
Example 366: 2-({1-[4-(2-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



120 mg of compound 54, 26 mg of o-fluorophenol, 152 mg of caesium carbonate, 6.7 mg of copper(I) bromide and 3.2 mg of (2-pyridyl)acetone were suspended in 6 ml dimethyl sulphoxide and stirred for 3 days at 80°C. The reaction mixture was filtered, the filter cake washed with water and ethyl acetate, and the aqueous phase extracted several times with ethyl acetate. The combined organic phases were dried with sodium sulphate and concentrated. The residue was purified by HPLC and 12 mg of the title compound was obtained.

^{1}H-NMR (300 MHz, chloroform-d): δ [ppm]= 1.16 - 1.47 (2H), 1.62 (2H), 2.43 (1H), 2.66 (3H), 2.85 (2H), 3.39 (3H), 3.53 - 3.74 (4H), 3.79 - 4.19 (1H), 4.33 (2H), 4.47 - 5.02 (1H), 6.15 (1H), 6.96 (2H), 7.07 - 7.23 (3H), 7.30 - 7.45 (3H), 7.54 (1H), 7.96 (1H).

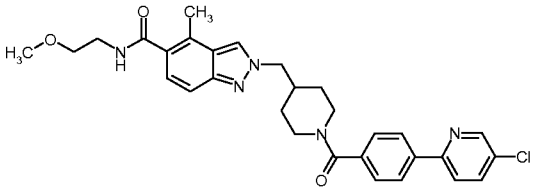
Example 367: 2-({1-[(4'-cyano-2'-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 317, 40 mg of the title compound was obtained from 80 mg of 54 and 38 mg of (2-methyl-4-cyanophenyl)boronic acid under reflux.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.20 - 1.34 (2H), 1.36 - 1.69 (2H), 2.28 (4H), 2.53 (3H), 2.69 - 3.19 (2H), 3.28 (3H), 3.36 - 3.43 (2H), 3.43 - 3.50 (2H), 3.54 - 3.77 (1H), 4.37 (3H), 7.18 (1H), 7.37 - 7.50 (6H), 7.74 (1H), 7.83 (1H), 8.15 (1H), 8.52 (1H).

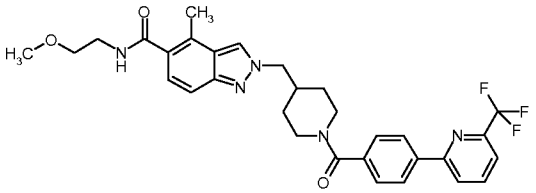
Example 368: 2-({1-[4-(5-chloropyridin-2-yl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



200 mg of the aryl bromide prepared in Example 54 together with 187 mg of (5-chloropyridin-2-yl)-2-boronic acid pinacol ester were first placed in 3 ml DMF, treated with 48 mg of 1,1'-bis(diphenylphosphino)ferrocenodichloropalladium(II), 39 mg of copper(I)chloride 254 mg of caesium carbonate and 22 mg of 1,1'-bis(diphenylphosphino)ferrocene and heated for ca. 1 day at 70°C, until further progress of the reaction could no longer be observed. The reaction mixture was treated with water and saturated sodium hydrogen carbonate solution, treated several times with ethyl acetate, and the combined organic phases dried with sodium sulphate and concentrated. After HPLC purification, this yielded 92 mg of the title compound.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.19 - 1.36 (2H), 1.37 - 1.72 (2H), 2.23 - 2.41 (1H), 2.52 - 2.57 (3H), 2.70 - 3.13 (2H), 3.28 (3H), 3.39 (2H), 3.45 (2H), 3.51 - 3.80 (1H), 4.36 (3H), 7.18 (1H), 7.36 - 7.52 (3H), 8.05 (2H), 8.09 - 8.22 (3H), 8.51 (1H), 8.73 (1H).

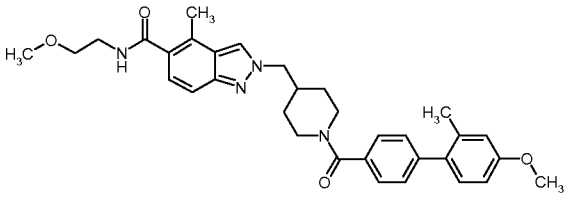
Example 369: N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[6-(trifluoromethyl)pyridin-2-yl]-benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 317, 33 mg of the title compound was obtained from 100 mg of 54 and 80 mg of [6-(trifluoromethyl)pyridin-2-yl]boronic acid pinacol ester under reflux.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.18 - 1.35 (2H), 1.36 - 1.67 (2H), 2.25 - 2.41 (1H), 2.53 (3H), 2.70 - 3.15 (2H), 3.28 (3H), 3.35 - 3.43 (2H), 3.43 - 3.51 (2H), 3.53 - 3.73 (1H), 4.37 (3H), 7.18 (1H), 7.42 (1H), 7.53 (2H), 7.89 (1H), 8.06 - 8.26 (4H), 8.33 (1H), 8.51 (1H).

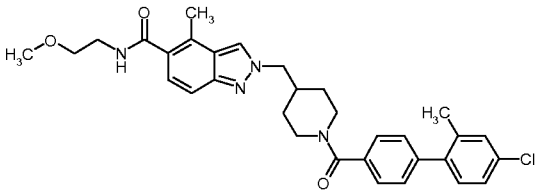
Example 370: N-(2-methoxyethyl)-2-({1-[(4'-methoxy-2'-methylbiphenyl-4-yl)carbonyl]-piperidin-4-yl}methyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 317, 52 mg of the title compound was obtained from 100 mg of 54 and 48 mg of (4-methoxy-2-methylphenyl)boronic acid under reflux.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.16 - 1.35 (2H), 1.37 - 1.67 (2H), 2.23 (3H), 2.26 - 2.42 (1H), 2.53 (3H), 2.70 - 3.12 (2H), 3.28 (3H), 3.36 - 3.43 (2H), 3.43 - 3.50 (2H), 3.77 (4H), 4.36 (3H), 6.77 - 6.92 (2H), 7.10 - 7.22 (2H), 7.39 (5H), 8.15 (1H), 8.52 (1H).

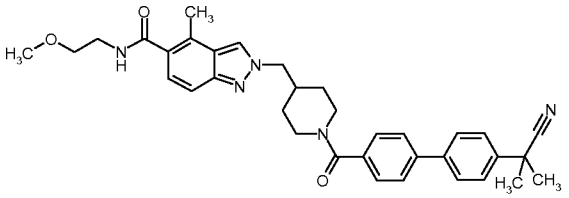
Example 371: 2-({1-[(4'-chloro-2'-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 317, 43 mg of the title compound was obtained from 100 mg of 54 and 50 mg of (4-chloro-2-methylphenyl)boronic acid under reflux.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.27 (2H), 1.38 - 1.70 (2H), 2.23 (4H), 2.53 (3H), 2.70 - 3.15 (2H), 3.28 (3H), 3.36 - 3.43 (2H), 3.43 - 3.49 (2H), 3.55 - 3.84 (1H), 4.36 (3H), 7.12 - 7.27 (2H), 7.28 - 7.35 (1H), 7.36 - 7.47 (6H), 8.15 (1H), 8.52 (1H).

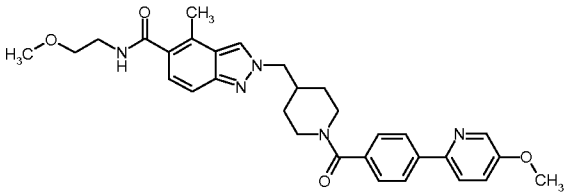
Example 372: 2-[(1-{[4'-(1-cyano-1-methylethyl)biphenyl-4-yl]carbonyl}piperidin-4-yl)-methyl]-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 317, 67 mg of the title compound was obtained from 100 mg of 54 and 55 mg of [4-(1-cyano-1-methylethyl)phenyl]boronic acid under reflux.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.28 (2H), 1.36 - 1.65 (2H), 1.72 (6H), 2.24 - 2.40 (1H), 2.53 (3H), 2.70 - 3.14 (2H), 3.28 (3H), 3.36 - 3.43 (2H), 3.43 - 3.49 (2H), 3.54 - 3.77 (1H), 4.36 (3H), 7.18 (1H), 7.38 - 7.50 (3H), 7.62 (2H), 7.75 (4H), 8.15 (1H), 8.52 (1H).

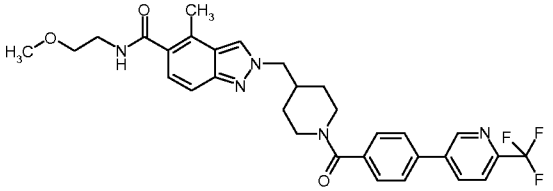
Example 373: N-(2-methoxyethyl)-2-({1-[4-(5-methoxypyridin-2-yl)benzoyl]piperidin-4-yl}-methyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 368, 12 mg of the title compound was obtained from 200 mg of 54 and 183 mg of (5-methoxypyridin-2-yl)boronic acid pinacol ester under reflux.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.22 - 1.33 (2H), 1.36 - 1.66 (2H), 2.23 - 2.38 (1H), 2.53 (3H), 2.68 - 3.12 (2H), 3.28 (3H), 3.35 - 3.42 (2H), 3.43 - 3.50 (2H), 3.54 - 3.78 (1H), 3.88 (3H), 4.36 (3H), 7.18 (1H), 7.36 - 7.55 (4H), 7.96 (1H), 8.07 (2H), 8.13 (1H), 8.39 (1H), 8.51 (1H).

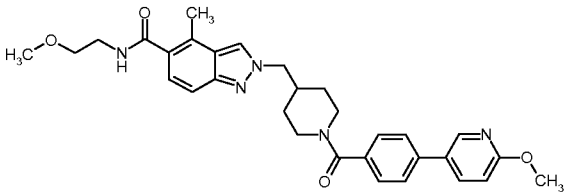
Example 374: N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[6-(trifluoromethyl)pyridin-3-yl]-benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 317, 37 mg of the title compound was obtained from 100 mg of 54 and 56 mg of [2-(trifluoromethyl)pyridin-5-yl]boronic acid under reflux.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.19 - 1.36 (2H), 1.36 - 1.69 (2H), 2.21 - 2.42 (1H), 2.53 (3H), 2.70 - 3.14 (2H), 3.28 (3H), 3.36 - 3.43 (2H), 3.43 - 3.50 (2H), 3.53 - 3.72 (1H), 4.36 (3H), 7.18 (1H), 7.42 (1H), 7.53 (2H), 7.89 (2H), 8.01 (1H), 8.15 (1H), 8.41 (1H), 8.52 (1H), 9.13 (1H).

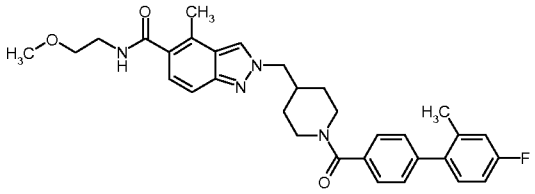
Example 375: N-(2-methoxyethyl)-2-({1-[4-(6-methoxypyridin-3-yl)benzoyl]piperidin-4-yl}-methyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 317, 50 mg of the title compound was obtained from 100 mg of 54 and 47 mg of (2-methoxypyridin-5-yl)boronic acid under reflux.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.26 (2H), 1.34 - 1.70 (2H), 2.21 - 2.40 (1H), 2.53 (3H), 2.69 - 3.15 (2H), 3.28 (3H), 3.36 - 3.43 (2H), 3.43 - 3.49 (2H), 3.51 - 3.79 (1H), 3.90 (3H), 4.36 (3H), 6.93 (1H), 7.18 (1H), 7.36 - 7.52 (3H), 7.72 (2H), 8.05 (1H), 8.15 (1H), 8.46 - 8.57 (2H).

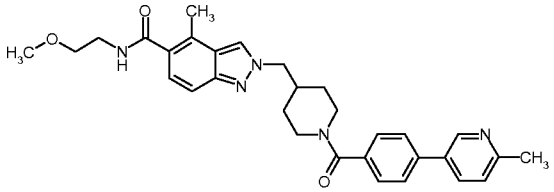
Example 376: 2-({1-[(4'-fluoro-2'-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 317, 261 mg of the title compound was obtained from 300 mg of 54 and 135 mg of (4-fluoro-2-methylphenyl)boronic acid under reflux.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.27 (2H), 1.37 - 1.70 (2H), 2.24 (4H), 2.53 (3H), 2.71 - 3.14 (2H), 3.28 (3H), 3.36 - 3.43 (2H), 3.43 - 3.50 (2H), 3.55 - 3.83 (1H), 4.37 (3H), 7.05 - 7.12 (1H), 7.18 (2H), 7.22 - 7.30 (1H), 7.40 (5H), 8.14 (1H), 8.52 (1H).

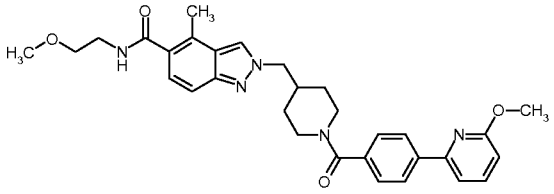
Example 377: N-(2-methoxyethyl)-4-methyl-2-({1-[4-(6-methylpyridin-3-yl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 317, 45 mg of the title compound was obtained from 80 mg of 54 and 32 mg of (2-methylpyridin-5-yl)boronic acid under reflux.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.26 (2H), 1.37 - 1.71 (2H), 2.18 - 2.39 (1H), 2.52 - 2.58 (3H), 2.73 - 3.16 (2H), 3.28 (3H), 3.36 - 3.43 (2H), 3.45 (2H), 3.54 - 3.79 (1H), 4.36 (3H), 7.18 (1H), 7.30 - 7.54 (4H), 7.76 (2H), 8.00 (1H), 8.15 (1H), 8.51 (1H), 8.78 (1H).

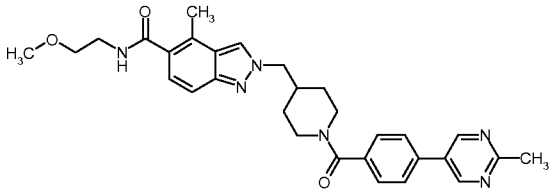
Example 378: N-(2-methoxyethyl)-2-({1-[4-(6-methoxypyridin-2-yl)benzoyl]piperidin-4-yl}methyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 317, 30 mg of the title compound was obtained from 100 mg of 54 and 45 mg of (6-methoxypyridin-2-yl)boronic acid under reflux.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.26 (2H), 1.35 - 1.68 (2H), 2.32 (1H), 2.52 (3H), 2.70 - 3.13 (2H), 3.28 (3H), 3.36 - 3.43 (2H), 3.43 - 3.50 (2H), 3.53 - 3.74 (1H), 3.96 (3H), 4.36 (3H), 6.81 (1H), 7.18 (1H), 7.37 - 7.67 (4H), 7.81 (1H), 8.15 (3H), 8.51 (1H).

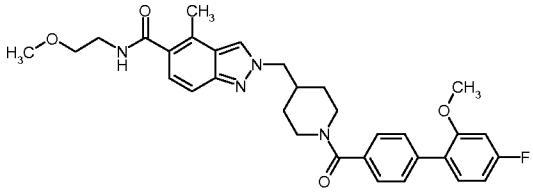
Example 379: N-(2-methoxyethyl)-4-methyl-2-({1-[4-(2-methylpyrimidin-5-yl)benzoyl]-piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 317, 36 mg of the title compound was obtained from 100 mg of 54 and 64 mg of (2-methylpyrimidin-5-yl)boronic acid pinacol ester under reflux.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.27 (2H), 1.38 - 1.70 (2H), 2.21 - 2.40 (1H), 2.53 (3H), 2.67 (3H), 2.73 - 3.16 (2H), 3.28 (3H), 3.40 (2H), 3.43 - 3.50 (2H), 3.53 - 3.76 (1H), 4.36 (3H), 7.18 (1H), 7.42 (1H), 7.51 (2H), 7.84 (2H), 8.13 (1H), 8.51 (1H), 9.05 (2H).

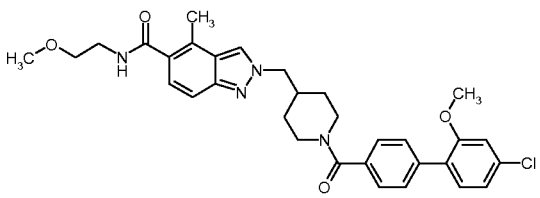
Example 380: 2-({1-[(4'-fluoro-2'-methoxybiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 317, 47 mg of the title compound was obtained from 100 mg of 54 and 50 mg of (4-fluoro-2-methoxyphenyl)boronic acid under reflux.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.19 - 1.34 (2H), 1.37 - 1.71 (2H), 2.22 - 2.40 (1H), 2.53 (3H), 2.70 - 3.15 (2H), 3.28 (3H), 3.36 - 3.43 (2H), 3.43 - 3.50 (2H), 3.56 - 3.75 (1H), 3.79 (3H), 4.36 (3H), 6.87 (1H), 6.99 - 7.10 (1H), 7.18 (1H), 7.30 - 7.46 (4H), 7.50 (2H), 8.13 (1H), 8.51 (1H).

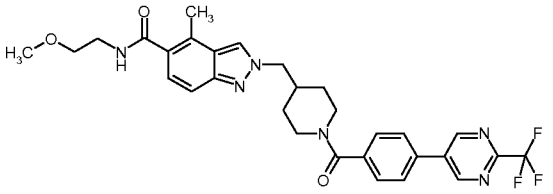
Example 381: 2-({1-[(4'-chloro-2'-methoxybiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 317, 87 mg of the title compound was obtained from 100 mg of 54 and 54 mg of (4-fluoro-2-methoxyphenyl)boronic acid under reflux.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.26 (2H), 1.39 - 1.69 (2H), 2.19 - 2.39 (1H), 2.53 (3H), 2.75 - 3.14 (2H), 3.28 (3H), 3.40 (2H), 3.45 (2H), 3.57 - 3.74 (1H), 3.81 (3H), 4.36 (3H), 7.04 - 7.25 (3H), 7.28 - 7.62 (6H), 8.13 (1H), 8.51 (1H).

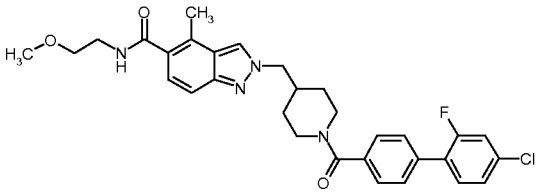
Example 382: N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[2-(trifluoromethyl)pyrimidin-5-yl]-benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 317, 14 mg of the title compound was obtained from 100 mg of 54 and 56 mg of [2-(trifluoromethyl)pyrimidin-5-yl]boronic acid under reflux.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.24 (2H), 1.38 - 1.73 (2H), 2.22 - 2.41 (1H), 2.53 (3H), 2.70 - 2.89 (1H), 2.94 - 3.18 (1H), 3.28 (3H), 3.36 - 3.43 (2H), 3.44 - 3.49 (2H), 3.51 - 3.70 (1H), 4.37 (3H), 7.18 (1H), 7.42 (1H), 7.57 (2H), 7.97 (2H), 8.13 (1H), 8.51 (1H), 9.43 (2H).

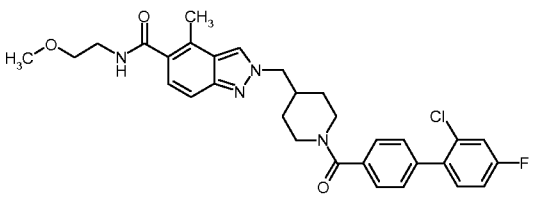
Example 383: 2-({1-[(4'-chloro-2'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 317, 51 mg of the title compound was obtained from 100 mg of 54 and 51 mg of (4-chloro-2-fluorophenyl)boronic acid under reflux.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.27 (2H), 1.38 - 1.68 (2H), 2.32 (1H), 2.53 (3H), 2.71 - 2.91 (1H), 2.93 - 3.16 (1H), 3.28 (3H), 3.40 (2H), 3.45 (2H), 3.53 - 3.78 (m, 1H), 4.37 (3H), 7.18 (1H), 7.33 - 7.52 (4H), 7.53 - 7.74 (4H), 8.13 (1H), 8.51 (1H).

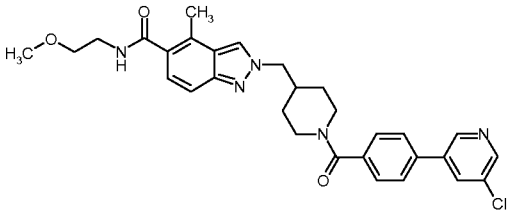
Example 384: 2-({1-[(2'-chloro-4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 317, 26 mg of the title compound was obtained from 100 mg of 54 and 51 mg of (2-chloro-4-fluorophenyl)boronic acid under reflux.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.28 (2H), 1.38 - 1.67 (2H), 2.23 - 2.39 (1H), 2.53 (3H), 2.71 - 2.91 (1H), 2.94 - 3.15 (1H), 3.28 (3H), 3.36 - 3.43 (2H), 3.43 - 3.50 (2H), 3.54 - 3.74 (1H), 4.37 (3H), 7.18 (1H), 7.33 (1H), 7.39 - 7.63 (7H), 8.13 (1H), 8.51 (1H).

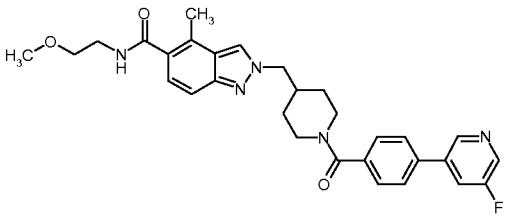
Example 385: 2-({1-[4-(5-chloropyridin-3-yl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 317, 22 mg of the title compound was obtained from 100 mg of 54 and 46 mg of (5-chloropyridin-3-yl)boronic acid under reflux.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.21 - 1.35 (2H), 1.36 - 1.69 (2H), 2.23 - 2.40 (1H), 2.53 (3H), 2.69 - 2.90 (1H), 2.92 - 3.16 (1H), 3.28 (3H), 3.40 (2H), 3.45 (2H), 3.53 - 3.73 (1H), 4.36 (3H), 7.18 (1H), 7.35 - 7.57 (3H), 7.86 (2H), 8.15 (1H), 8.30 (1H), 8.52 (1H), 8.65 (1H), 8.90 (1H).

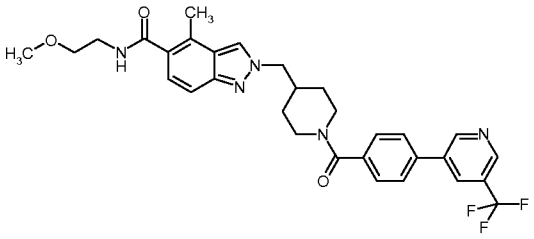
Example 386: 2-({1-[4-(5-fluoropyridin-3-yl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 317, 57 mg of the title compound was obtained from 100 mg of 54 and 41 mg of (5-fluoropyridin-3-yl)boronic acid under reflux.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.27 (2H), 1.37 - 1.70 (2H), 2.24 - 2.40 (1H), 2.52 - 2.55 (3H), 2.70 - 2.89 (1H), 2.93 - 3.15 (1H), 3.28 (3H), 3.36 - 3.43 (2H), 3.43 - 3.50 (2H), 3.53 - 3.73 (1H), 4.36 (3H), 7.18 (1H), 7.42 (1H), 7.50 (2H), 7.86 (2H), 8.07 - 8.18 (2H), 8.51 (1H), 8.61 (1H), 8.84 (1H).

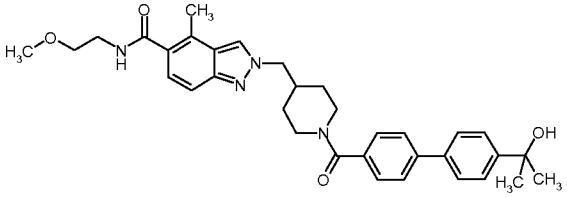
Example 387: N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[5-(trifluoromethyl)pyridin-3-yl]-benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 317, 73 mg of the title compound was obtained from 100 mg of 54 and 56 mg of [5-(trifluoromethyl)pyridin-3-yl]boronic acid under reflux.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.20 - 1.35 (2H), 1.36 - 1.67 (2H), 2.23 - 2.40 (1H), 2.53 (3H), 2.69 - 2.92 (1H), 2.93 - 3.17 (1H), 3.28 (3H), 3.35 - 3.43 (2H), 3.43 - 3.49 (2H), 3.53 - 3.75 (1H), 4.37 (3H), 7.18 (1H), 7.42 (1H), 7.52 (2H), 7.93 (2H), 8.07 - 8.20 (1H), 8.45 - 8.58 (2H), 9.00 (1H), 9.24 (1H).

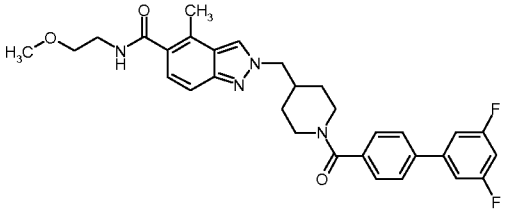
Example 388: 2-[(1-{[4'-(1-hydroxy-1-methylethyl)biphenyl-4-yl]carbonyl}piperidin-4-yl)-methyl]-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 317, 46 mg of the title compound was obtained from 100 mg of 54 and 77 mg of (4-hydroxy-tert-butylphenyl)boronic acid pinacol ester under reflux.

^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 1.26 (2H), 1.45 (8H), 2.22 - 2.42 (1H), 2.53 (3H), 2.71 - 2.90 (1H), 2.91 - 3.14 (1H), 3.28 (3H), 3.40 (2H), 3.43 - 3.50 (2H), 3.56 - 3.80 (1H), 4.36 (3H), 5.06 (1H), 7.18 (d, 1H), 7.37 - 7.50 (3H), 7.50 - 7.67 (4H), 7.71 (2H), 8.15 (1H), 8.52 (1H).

Example 389: 2-({1-[(3',5'-difluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

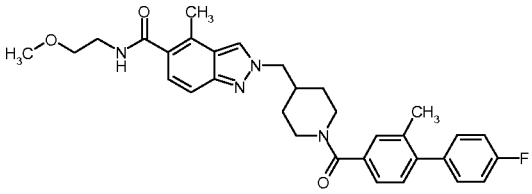


Analogously to Example 317, 22 mg of the title compound was obtained from 100 mg of 54 and 46 mg of (3,5-difluorophenyl)boronic acid under reflux.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 1.18 - 1.35 (2H), 1.36 - 1.70 (2H), 2.19 - 2.39 (1H), 2.52 - 2.56 (3H), 2.71 - 2.92 (1H), 2.93 - 3.17 (1H), 3.28 (3H), 3.36 - 3.43 (2H), 3.43 - 3.49

(2H), 3.52 - 3.71 (1H), 4.36 (3H), 7.11 - 7.33 (2H), 7.37 - 7.54 (5H), 7.81 (2H), 8.13 (1H), 8.51 (1H).

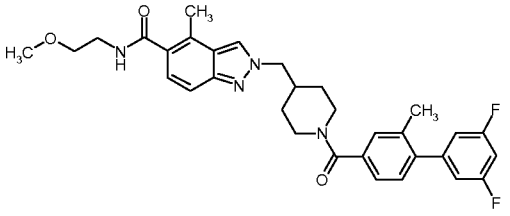
Example 390: 2-({1-[(4'-fluoro-2-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 317, 25 mg of the title compound was obtained from 60 mg of 332 and 19 mg of (4-fluorophenyl)boronic acid under reflux.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.25 (2H), 1.37 - 1.67 (2H), 2.24 (4H), 2.53 (3H), 2.69 - 2.87 (1H), 2.92 - 3.14 (1H), 3.28 (3H), 3.36 - 3.43 (2H), 3.43 - 3.50 (2H), 3.56 - 3.81 (1H), 4.36 (3H), 7.11 - 7.34 (6H), 7.36 - 7.46 (3H), 8.15 (1H), 8.52 (1H).

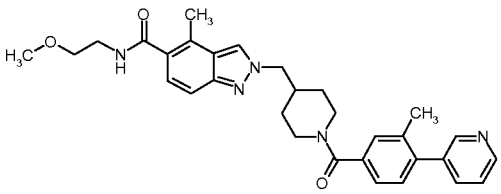
Example 391: 2-({1-[(3',5'-difluoro-2-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 317, 30 mg of the title compound was obtained from 60 mg of 332 and 27 mg of (3,5-difluorophenyl)boronic acid under reflux.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.23 (2H), 1.36 - 1.69 (2H), 2.27 (4H), 2.53 (3H), 2.69 - 2.90 (1H), 2.92 - 3.15 (1H), 3.28 (3H), 3.36 - 3.43 (2H), 3.45 (2H), 3.53 - 3.76 (1H), 4.36 (3H), 7.08 - 7.21 (3H), 7.22 - 7.34 (4H), 7.42 (1H), 8.15 (1H), 8.52 (1H).

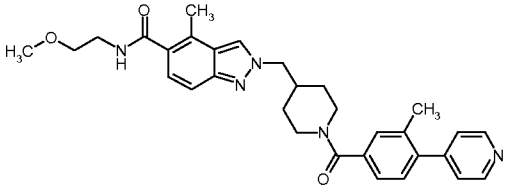
Example 392: N-(2-methoxyethyl)-4-methyl-2-({1-[3-methyl-4-(3-pyridyl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 317, 19 mg of the title compound was obtained from 60 mg of 332 and 21 mg of pyridine-3-ylboronic acid under reflux.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.20 - 1.33 (2H), 1.37 - 1.71 (2H), 2.26 (4H), 2.53 (3H), 2.70 - 2.88 (1H), 2.94 - 3.17 (1H), 3.28 (3H), 3.36 - 3.43 (2H), 3.43 - 3.49 (2H), 3.56 - 3.82 (1H), 4.36 (3H), 7.18 (1H), 7.23 - 7.37 (3H), 7.39 - 7.56 (2H), 7.83 (1H), 8.15 (1H), 8.52 (1H), 8.56 - 8.65 (2H).

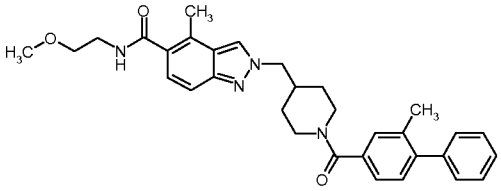
Example 393: N-(2-methoxyethyl)-4-methyl-2-({1-[3-methyl-4-(4-pyridyl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 317, 19 mg of the title compound was obtained from 60 mg of 332 and 21 mg of pyridine-4-ylboronic acid under reflux.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.18 - 1.33 (2H), 1.37 - 1.67 (2H), 2.27 (4H), 2.52 - 2.56 (3H), 2.70 - 2.86 (1H), 2.93 - 3.13 (1H), 3.28 (3H), 3.36 - 3.43 (2H), 3.43 - 3.49 (2H), 3.55 - 3.75 (1H), 4.36 (3H), 7.18 (1H), 7.23 - 7.36 (3H), 7.38 - 7.48 (3H), 8.15 (1H), 8.52 (1H), 8.60 - 8.69 (2H).

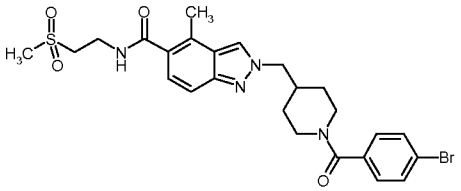
Example 394: N-(2-methoxyethyl)-4-methyl-2-({1-[(2-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide



Analogously to Example 317, 57 mg of the title compound was obtained from 60 mg of 332 and 21 mg of phenylboronic acid under reflux.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.19 - 1.34 (2H), 1.37 - 1.67 (2H), 2.25 (4H), 2.53 (3H), 2.68 - 2.88 (1H), 2.92 - 3.17 (1H), 3.28 (3H), 3.36 - 3.43 (2H), 3.45 (2H), 3.59 - 3.81 (1H), 4.36 (3H), 7.13 - 7.32 (4H), 7.33 - 7.50 (6H), 8.15 (1H), 8.52 (1H).

Example 395: 2-{[1-(4-bromobenzoyl)piperidin-4-yl]methyl}-N-(2-mesylethyl)-4-methyl-2H-indazol-5-carboxamide

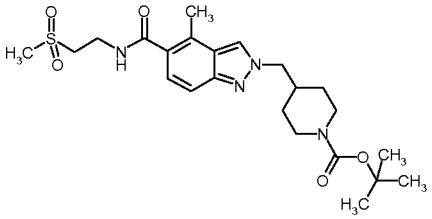


Analogously to Example 1b, Version B, 383 mg of the title compound was obtained from 1 g of 395b and 797 mg of 4-bromobenzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.21 - 1.32 (2H), 1.34 - 1.67 (2H), 2.21 - 2.38 (1H), 2.55 (3H), 2.68 - 2.87 (1H), 3.05 (4H), 3.39 (2H), 3.45 - 3.59 (1H), 3.66 (2H), 4.35 (3H), 7.23 (1H), 7.28 - 7.37 (2H), 7.43 (1H), 7.59 - 7.70 (2H), 8.34 (1H), 8.52 (1H).

The starting material was prepared as follows:

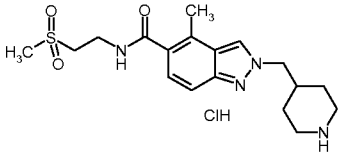
Example 395a: Tert-butyl 4-({5-[N-(2-mesylethyl)carbamoyl]-4-methyl-2H-indazol-2-yl}-methyl)piperidin-1-carboxylate



Analogously to Example 266a, 1.26 g of the title compound was obtained from 2.506 g of 1c and 3.022 g of 2-mesylethylamine hydrochloride.

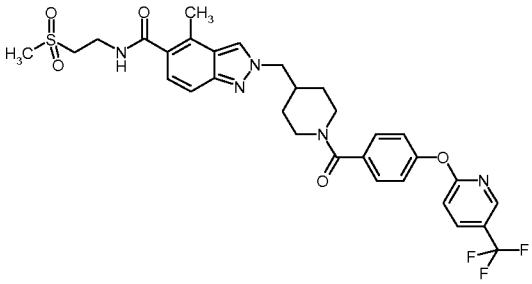
^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.02 - 1.17 (2H), 1.34 - 1.54 (11H), 2.08 - 2.24 (1H), 2.55 (3H), 2.73 (2H), 3.06 (3H), 3.34 - 3.47 (2H), 3.57 - 3.76 (2H), 3.91 (2H), 4.32 (2H), 7.23 (1H), 7.43 (1H), 8.33 (1H), 8.52 (1H).

Example 395b: N-(2-mesylethyl)-4-methyl-2-(4-piperidylmethyl)-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 258b from 1.26 g of compound 395a, 1.29 g of the title compound was obtained, which was reacted without further purification.

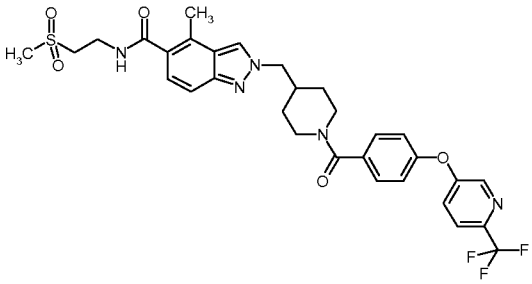
Example 396: N-(2-mesylethyl)-4-methyl-2-{[1-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}-benzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 30 mg of the title compound was obtained from 80 mg of 395b and 90 mg of 4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}benzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.19 - 1.35 (2H), 1.36 - 1.72 (2H), 2.22 - 2.41 (1H), 2.55 (3H), 3.06 (5H), 3.39 (2H), 3.49 - 3.89 (3H), 4.37 (3H), 7.20 - 7.32 (4H), 7.40 - 7.49 (3H), 8.25 (1H), 8.34 (1H), 8.53 (1H), 8.58 (1H).

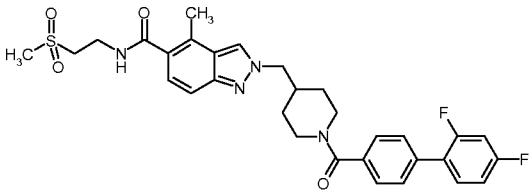
Example 397: N-(2-mesylethyl)-4-methyl-2-{[1-(4-{[6-(trifluoromethyl)pyridin-3-yl]oxy}-benzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 30 mg of the title compound was obtained from 80 mg of 395b and 90 mg of 303b in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.24 (2H), 1.35 - 1.70 (2H), 2.22 - 2.40 (1H), 2.55 (3H), 3.06 (5H), 3.39 (2H), 3.55 - 3.75 (3H), 4.36 (3H), 7.20 - 7.28 (3H), 7.40 - 7.49 (3H), 7.65 (1H), 7.92 (1H), 8.34 (1H), 8.53 (1H), 8.60 (1H).

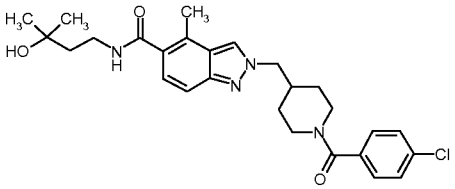
Example 398: 2-({1-[(2',4'-difluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-mesyl-ethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 25 mg of the title compound was obtained from 80 mg of 395b and 74 mg of 2',4'-difluoro-biphenyl-4-carboxylic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.21 - 1.35 (2H), 1.37 - 1.70 (2H), 2.22 - 2.41 (1H), 2.55 (3H), 3.05 (5H), 3.38 (2H), 3.50 - 3.83 (3H), 4.37 (3H), 7.15 - 7.29 (2H), 7.31 - 7.52 (4H), 7.55 - 7.73 (3H), 8.34 (1H), 8.53 (1H).

Example 399: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-(3-hydroxy-3-methylbutyl)-4-methyl-2H-indazol-5-carboxamide

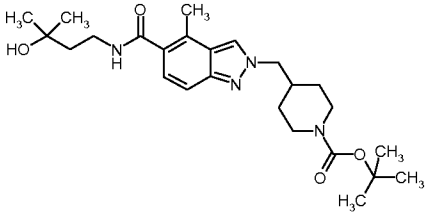


Analogously to Example 1b, Version B, 37 mg of the title compound was obtained from 160 mg of 399b and 105 mg of 4-chlorobenzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.14 (6H), 1.17 - 1.32 (2H), 1.33 - 1.71 (4H), 2.23 - 2.37 (1H), 2.51 (3H), 2.68 - 2.87 (1H), 2.87 - 3.13 (1H), 3.31 (2H), 3.47 - 3.55 (1H), 4.34 (s, 4H), 7.17 (1H), 7.33 - 7.45 (3H), 7.50 (2H), 7.97 - 8.09 (1H), 8.50 (1H).

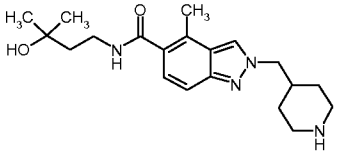
The starting material was prepared as follows:

Example 399a: Tert-butyl 4-({5-[N-(3-hydroxy-3-methylbutyl)carbamoyl]-4-methyl-2H-indazol-2-yl}methyl)piperidin-1-carboxylate



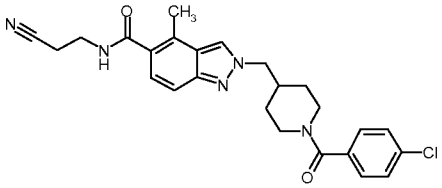
Analogously to Example 1b, Version B, 150 mg of 1d and 69 mg of 4-amino-2-methylbutan-2-ol in DMF were reacted at 60°C. After phase separation and extraction, the combined organic phases were additionally washed with 0.1 N hydrochloric acid and saturated sodium hydrogen carbonate solution. This yielded 132 mg of the title compound, which was used in the next step without further purification.

Example 399b: N-(3-hydroxy-3-methylbutyl)-4-methyl-2-(4-piperidylmethyl)-2H-indazol-5-carboxamide



Analogously to Example 258b, from 132 mg of 399a, 162 mg of the title compound was obtained, which was used in the next step without further purification.

Example 400: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-(2-cyanoethyl)-4-methyl-2H-indazol-5-carboxamide

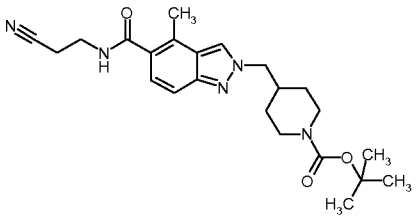


Analogously to Example 1b, Version B, 55 mg of the title compound was obtained from 177 mg of 400b and 128 mg of 4-chlorobenzoic acid in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.23 (2H), 1.33 - 1.70 (2H), 2.20 - 2.38 (1H), 2.56 (3H), 2.78 (3H), 2.90 - 3.11 (1H), 3.47 (3H), 4.35 (3H), 7.22 (1H), 7.34 - 7.56 (5H), 8.44 - 8.57 (2H).

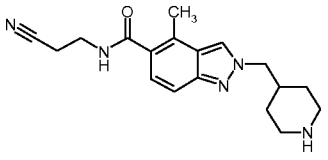
The starting material was prepared as follows:

Example 400a: Tert-butyl 4-({5-[N-(2-cyanoethyl)carbamoyl]-4-methyl-2H-indazol-2-yl}-methyl)-piperidin-1-carboxylate



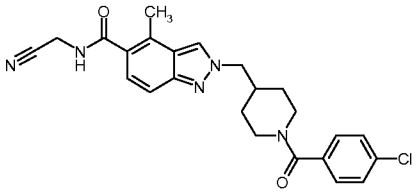
Analogously to Example 1b, Version B, 150 mg of 1d and 42 mg of 3-aminopropannitrile in DMF were reacted at 60°C. After phase separation and extraction, the combined organic phases were additionally washed with 0.1 N hydrochloric acid and saturated sodium hydrogen carbonate solution. This yielded 137 mg of the title compound, which was used in the next step without further purification.

Example 400b: N-(2-cyanoethyl)-4-methyl-2-(4-piperidylmethyl)-2H-indazol-5-carboxamide



Analogously to Example 258b, from 137 mg of 400a 177 mg of the title compound was obtained, which was used in the next step without further purification.

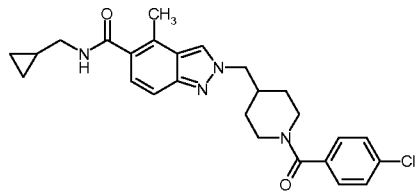
Example 401: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-(cyanomethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 75 mg of the title compound was obtained from 90 mg of 238c and 29 mg of aminoacetonitrile in DMF.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.21 - 1.33 (23H), 1.34 - 1.69 (2H), 2.15 - 2.41 (1H), 2.57 (3H), 2.75 - 2.86 (1H), 2.93 - 3.14 (1H), 3.39 - 3.69 (1H), 4.29 (2H), 4.33 - 4.55 (3H), 7.18 - 7.28 (1H), 7.39 (2H), 7.43 - 7.55 (3H), 8.57 (1H), 8.77 - 8.90 (1H).

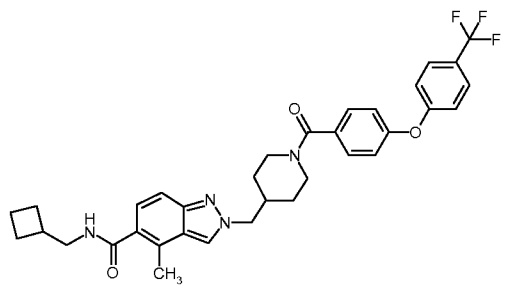
Example 402: 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-(cyclopropylmethyl)-4-methyl-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 44 mg of the title compound was obtained from 90 mg of 238c) and 19 mg of cyclopropylmethylamine in DMF.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 0.23 (2H), 0.33 - 0.53 (2H), 0.94 - 1.11 (1H), 1.20 - 1.33 (2H), 1.34 - 1.68 (2H), 2.21 - 2.41 (1H), 2.54 (3H), 2.69 - 2.85 (1H), 2.93 - 3.08 (1H), 3.13 (2H), 3.44 - 3.68 (1H), 4.35 (3H), 7.18 (1H), 7.33 - 7.46 (3H), 7.47 - 7.60 (2H), 8.07 - 8.30 (1H), 8.51 (1H).

Example 403: N-(cyclobutylmethyl)-4-methyl-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide

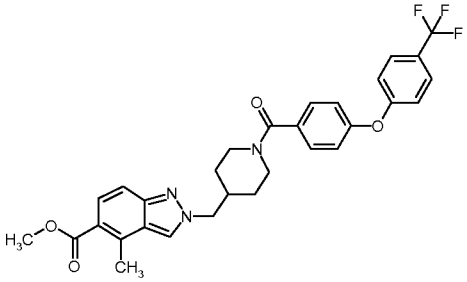


Analogously to Example 1b, Version B, 48 mg of the title compound was obtained from 137 mg of 403b and 31 mg of (cyclobutylamino)methylamine hydrochloride.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.17 - 1.32 (2H), 1.35 - 1.64 (2H), 1.67 - 1.90 (4H), 1.93 - 2.08 (2H), 2.22 - 2.38 (1H), 2.51 - 2.52 (3H), 2.69 - 2.88 (1H), 2.90 - 3.13 (1H), 3.20 - 3.30 (2H), 3.51 - 3.83 (1H), 4.36 (3H), 7.09 - 7.27 (5H), 7.35 - 7.52 (3H), 7.76 (2H), 8.13 (1H), 8.51 (1H).

The starting material was prepared as follows:

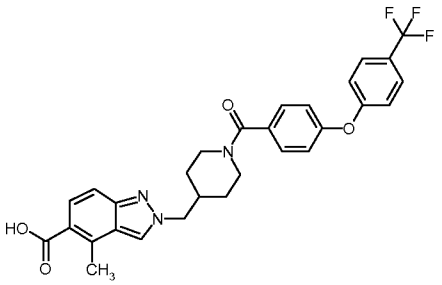
Example 403a: Methyl 4-methyl-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxylate



Analogously to Example 1b, Version B, 2.73 g of the title compound was obtained from 3.76 g of 238a and 3.28 g of 4-[4-(trifluoromethyl)phenoxy]benzoic acid.

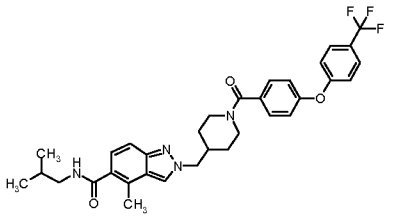
^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.19 - 1.35 (2H), 1.38 - 1.74 (2H), 2.17 - 2.41 (1H), 2.76 (3H), 2.78 - 3.14 (2H), 3.44 - 3.76 (1H), 3.82 (3H), 4.37 (3H), 7.06 - 7.28 (4H), 7.38 - 7.50 (3H), 7.67 (1H), 7.76 (2H), 8.71 (1H).

Example 403b: 4-methyl-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}piperidin-4-yl)-methyl]-2H-indazol-5-carboxylic acid



Analogously to Example 1d, from 1.05 g of 403a, 970 mg of the title compound was obtained, which was used in the next step without further purification.

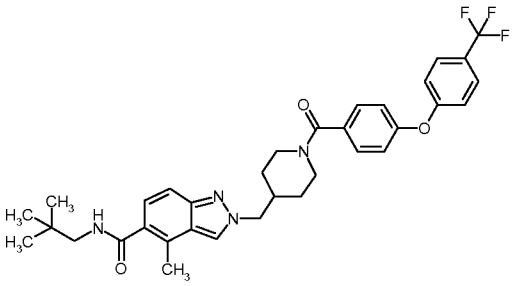
Example 404: N-isobutyl-4-methyl-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 35 mg of the title compound was obtained from 100 mg of 403b and 14 mg of isobutylamine.

^{1}H-NMR (300 MHz, DMSO-d$_6$): δ [ppm]= 0.91 (6H), 1.24 (2H), 1.34 - 1.69 (2H), 1.82 (1H), 2.19 - 2.42 (1H), 2.52 (3H), 2.71 - 2.90 (1H), 3.06 (3H), 3.51 - 3.85 (1H), 4.36 (3H), 7.05 - 7.27 (5H), 7.37 - 7.52 (3H), 7.76 (2H), 8.16 (1H), 8.51 (1H).

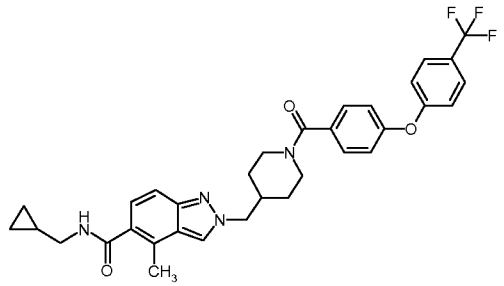
Example 405: 4-methyl-N-neopentyl-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 36 mg of the title compound was obtained from 100 mg of 403b and 16 mg of neopentylamine.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm]= 0.92 (9H), 1.17 - 1.32 (2H), 1.34 - 1.69 (2H), 2.21 - 2.38 (1H), 2.52 - 2.57 (3H), 2.70 - 2.88 (1H), 3.08 (3H), 3.53 - 3.85 (1H), 4.36 (3H), 7.04 - 7.28 (5H), 7.35 - 7.52 (3H), 7.76 (2H), 8.12 (1H), 8.51 (1H).

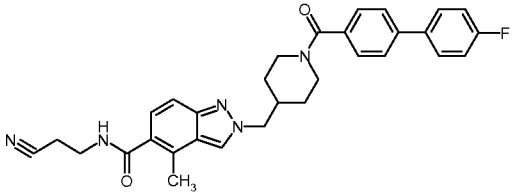
Example 406: N-(cyclopropylmethyl)-4-methyl-2-[(1-{4-[4-(trifluoromethyl)phenoxy]-benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 33 mg of the title compound was obtained from 100 mg of 403b and 26 mg of cyclopropylmethylamine.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 0.23 (2H), 0.35 - 0.54 (2H), 0.93 - 1.11 (1H), 1.23 (2H), 1.36 - 1.67 (2H), 2.18 - 2.41 (1H), 2.54 (3H), 2.66 - 3.22 (4H), 3.47 - 3.85 (1H), 4.36 (3H), 7.03 - 7.29 (5H), 7.35 - 7.53 (3H), 7.76 (2H), 8.22 (1H), 8.52 (1H).

Example 407: N-(2-cyanoethyl)-2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}-methyl)-4-methyl-2H-indazol-5-carboxamide

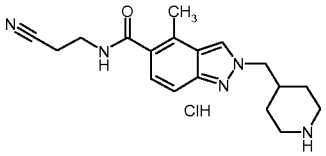


Analogously to Example 1b, Version B, 37 mg of the title compound was obtained from 140 mg of 407a and 84 mg of 4'-fluorobiphenyl-4-carboxylic acid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.18 - 1.37 (2H), 1.37 - 1.68 (2H), 2.22 - 2.41 (1H), 2.56 (3H), 2.78 (4H), 3.39 - 3.53 (2H), 3.56 - 3.82 (1H), 4.37 (3H), 7.14 - 7.37 (3H), 7.39 - 7.53 (3H), 7.63 - 7.83 (4H), 8.36 - 8.60 (2H).

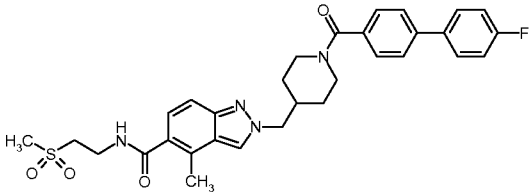
The starting material was prepared as follows:

Example 407a: N-(2-cyanoethyl)-4-methyl-2-(4-piperidylmethyl)-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 165 mg of 400a, 140 mg of the title compound was obtained, which was used in the next step without further purification.

Example 408: 2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-mesyl-ethyl)- 4-methyl-2H-indazol-5-carboxamide

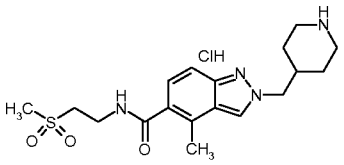


Analogously to Example 1b), Version B, 126 mg of the title compound was obtained from 300 mg of 408a) and 156 mg of 4'-fluorobiphenyl-4-carboxylic acid.

LC-MS: R_t = 1.20 min, MS (ES+): m/z = 577 $(M+H)^+$.

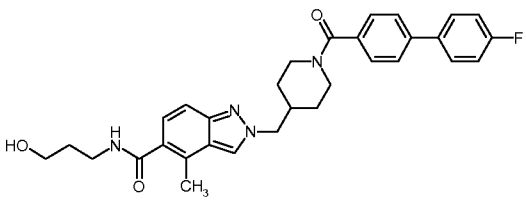
The starting material was prepared as follows:

Example 408a: N-(2-mesylethyl)-4-methyl-2-(4-piperidylmethyl)-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 346 mg of 395a, 300 mg of the title compound was obtained, which was used in the next step without further purification.

Example 409: 2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(3-hydroxypropyl)-4-methyl-2H-indazol-5-carboxamide

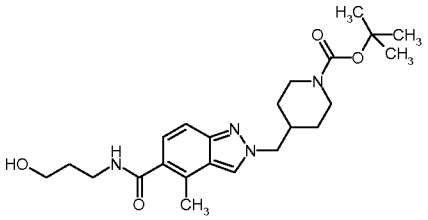


Analogously to Example 1b, Version B, 20 mg of the title compound was obtained from 124 mg of 409b) and 73 mg of 4'-fluorobiphenyl-4-carboxylic acid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.26 (2H), 1.38 - 1.59 (2H), 1.67 (2H), 2.23 - 2.42 (1H), 2.52 - 2.57 (3H), 2.69 - 3.17 (2H), 3.19 - 3.94 (6H), 4.36 (3H), 7.18 (1H), 7.31 (2H), 7.38 - 7.51 (3H), 7.63 - 7.86 (4H), 8.08 (1H), 8.51 (1H).

The starting material was prepared as follows:

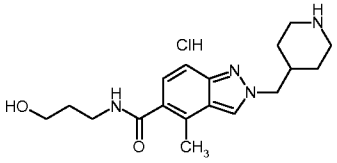
Example 409a: Tert-butyl 4-({5-[N-(3-hydroxypropyl)carbamoyl]-4-methyl-2H-indazol-2-yl}-methyl)piperidin-1-carboxylate



Analogously to Example 1b, Version B, 151 mg of the title compound was obtained from 150 mg of 1d and 30 mg of 3-amino-propan-1-ol.

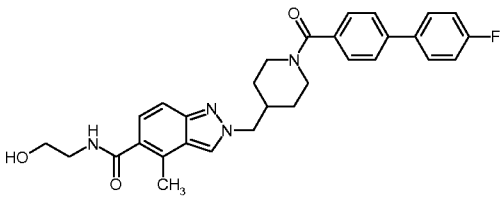
^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.01 - 1.30 (3H), 1.32 - 1.49 (10H), 1.67 (2H), 2.08 - 2.27 (1H), 2.52 (3H), 2.57 - 2.80 (2H), 3.29 (2H), 3.41 - 3.54 (2H), 3.81 - 4.00 (2H), 4.32 (2H), 4.48 (1H), 7.18 (1H), 7.42 (1H), 8.10 (1H), 8.50 (1H).

Example 409b: N-(3-hydroxypropyl)-4-methyl-2-(4-piperidylmethyl)-2H-indazol-5-carboxamide



Analogously to Example 1a, from 246 mg of 409a, 124 mg of the title compound was obtained, which was used in the next step without further purification.

Example 410: 2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-hydroxyethyl)-4-methyl-2H-indazol-5-carboxamide

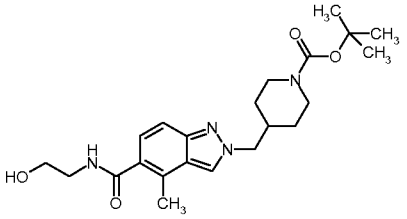


Analogously to Example 1b, Version B, 36 mg of the title compound was obtained from 117 mg of 410b and 72 mg of 4'-fluorobiphenyl-4-carboxylic acid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.26 (2H), 1.39 - 1.74 (2H), 2.21 - 2.40 (1H), 2.53 (3H), 2.75 - 3.16 (2H), 3.20 - 3.37 (2H), 3.43 - 3.74 (4H), 4.36 (3H), 7.21 (1H), 7.31 (2H), 7.38 - 7.52 (3H), 7.65 - 7.81 (4H), 8.03 (1H), 8.51 (1H).

The starting material was prepared as follows:

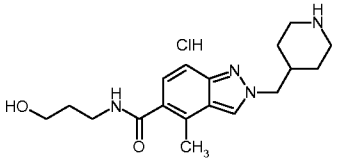
Example 410a: Tert-butyl 4-({5-[N-(2-hydroxyethyl)carbamoyl]-4-methyl-2H-indazol-2-yl}-methyl)piperidin-1-carboxylate



Analogously to Example 1b, Version B, 143 mg of the title compound was obtained from 150 mg of 1d) and 25 mg of 2-aminoethan-1-ol.

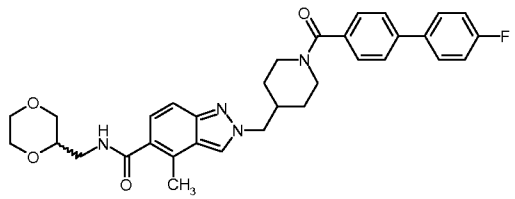
^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.01 - 1.30 (3H), 1.32 - 1.51 (10H), 2.07 - 2.26 (1H), 2.52 - 2.55 (3H), 2.58 - 2.82 (2H), 3.30 (2H), 3.45 - 3.58 (2H), 3.83 - 3.98 (2H), 4.32 (2H), 4.69 (1H), 7.21 (1H), 7.41 (1H), 8.05 (1H), 8.50 (1H).

Example 410b: N-(3-hydroxypropyl)-4-methyl-2-(4-piperidylmethyl)-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a) from 138 mg of 410a, 117 mg of the title compound was obtained, which was used in the next step without further purification.

Example 411: (+/-)-N-(1,4-dioxan-2-ylmethyl)-2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]-piperidin-4-yl}methyl)-4-methyl-2H-indazol-5-carboxamide

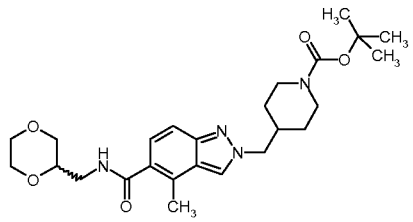


Analogously to Example 1b, Version B, 62 mg of the title compound was obtained from 226 mg of 411b) and 119 mg of 4'-fluorobiphenyl-4-carboxylic acid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.19 - 1.34 (2H), 1.37 - 1.73 (2H), 2.23 - 2.42 (1H), 2.53 (3H), 2.69 - 2.90 (1H), 2.90 - 3.14 (1H), 3.17 - 3.30 (3H), 3.47 (1H), 3.58 (1H), 3.59 - 3.70 (3H), 3.71 - 3.82 (2H), 4.37 (3H), 7.19 (1H), 7.31 (2H), 7.38 - 7.53 (3H), 7.66 - 7.81 (4H), 8.18 (1H), 8.52 (1H).

The starting material was prepared as follows:

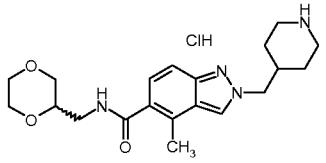
Example 411a: (+/-)-tert-butyl 4-({5-[N-(1,4-dioxan-2-ylmethyl)carbamoyl]-4-methyl-2H-indazol-2-yl}methyl)piperidin-1-carboxylate



Analogously to Example 1b, Version B, 267 mg of the title compound was obtained from 250 mg of 1d and 78 mg of (+/-)-1,4-dioxan-2-ylmethylamine.

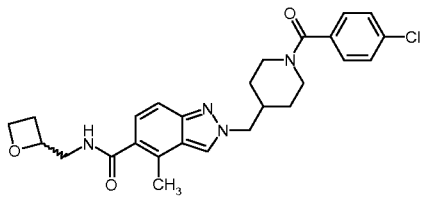
^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm]= 0.99 - 1.18 (2H), 1.38 (11H), 2.09 - 2.24 (1H), 2.53 (3H), 3.10 - 3.29 (4H), 3.41 - 3.52 (1H), 3.53 - 3.70 (4H), 3.70 - 3.81 (2H), 3.84 - 3.98 (2H), 4.32 (2H), 7.18 (1H), 7.41 (1H), 8.12 - 8.24 (1H), 8.51 (1H).

Example 411b: (+/-)-N-(1,4-dioxan-2-ylmethyl)-4-methyl-2-(4-piperidylmethyl)-2H-indazol-5-carboxamide hydrochloride



Analogously to Example 1a, from 261 mg of 411a, 226 mg of the title compound was obtained, which was used in the next step without further purification.

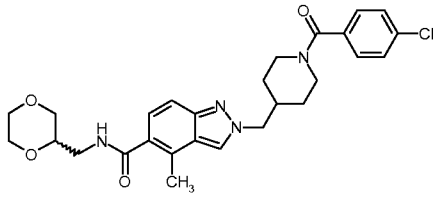
Example 412: (+/-)-2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methyl-N-(oxetan-2-ylmethyl)-2H-indazol-5-carboxamide



Analogously to Example 1b, Version B, 55 mg of the title compound was obtained from 350 mg of 238c) and 83 mg of (+/-)-oxetan-2-ylmethylamine.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.16 - 1.31 (2H), 1.33 - 1.69 (2H), 2.19 - 2.38 (2H), 2.53 (3H), 2.58 - 2.66 (1H), 2.66 - 2.86 (1H), 2.90 - 3.14 (1H), 3.38 - 3.64 (3H), 4.35 (5H), 4.71 - 4.96 (1H), 7.19 (1H), 7.33 - 7.45 (3H), 7.47 - 7.55 (2H), 8.21 - 8.37 (1H), 8.51 (1H).

Example 413: (+/-)-2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-(1,4-dioxan-2-ylmethyl)-4-methyl-2H-indazol-5-carboxamide

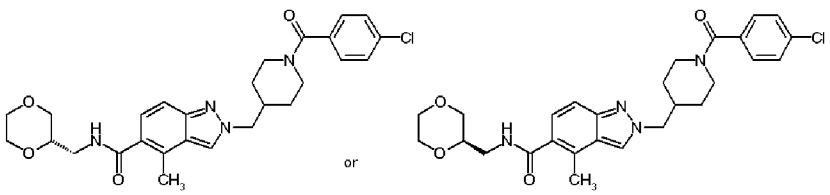


Analogously to Example 1b, Version B, 185 mg of the title compound was obtained from 376 mg of 238c and 111 mg of (+/-)-1,4-dioxan-2-ylmethylamine hydrochloride.

^{1}H-NMR (300 MHz, DMSO-d_6): δ [ppm]= 1.19 - 1.32 (2H), 1.33 - 1.66 (2H), 2.20 - 2.40 (1H), 2.53 (3H), 2.71 - 2.86 (1H), 2.90 - 3.11 (1H), 3.16 - 3.32 (3H), 3.40 - 3.59 (3H), 3.60 - 3.70

(2H), 3.71 - 3.83 (2H), 4.35 (3H), 7.18 (1H), 7.31 - 7.46 (3H), 7.46 - 7.60 (2H), 8.21 (1H), 8.51 (1H).

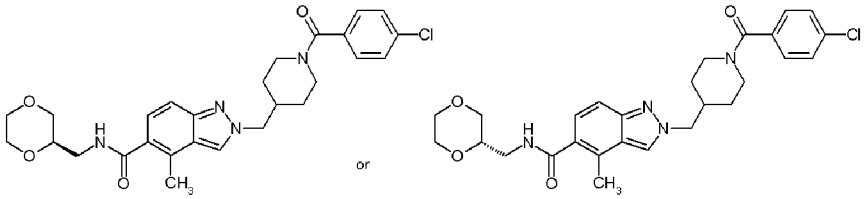
Example 414: (R or S)-2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-(1,4-dioxan-2-ylmethyl)-4-methyl-2H-indazol-5-carboxamide



From 185 mg of the racemate prepared in Example 413, 51 mg of the title compound together with 58 mg of the slower-eluting enantiomer (Example 415) were obtained by racemate separation by means of preparative chiral HPLC (Method D).

Analytical chiral HPLC: 12.62 min.

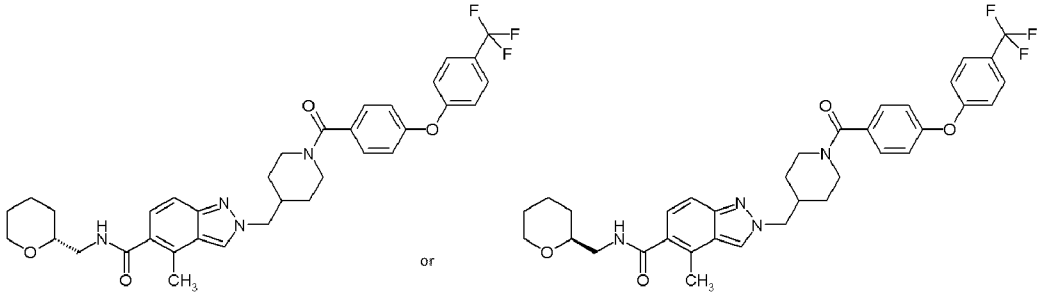
Example 415: (S or R)-2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-(1,4-dioxan-2-ylmethyl)-4-methyl-2H-indazol-5-carboxamide



From 185 mg of the racemate prepared in Example 413, 58 mg of the title compound together with 51 mg of the faster-eluting enantiomer (Example 414) were obtained by racemate separation by means of preparative chiral HPLC (Method D).

Analytical chiral HPLC: 13.68 min.

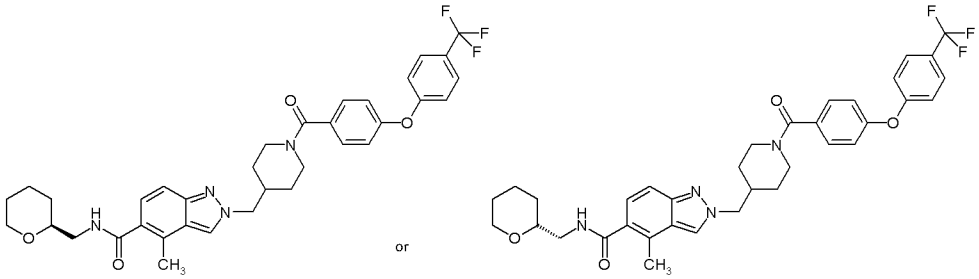
Example 416: (R or S)-4-methyl-N-(3,4,5,6-tetrahydro-2H-pyran-2-ylmethyl)-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



From 231 mg of the racemate prepared in Example 248, 24 mg of the title compound together with 24 mg of the slower-eluting enantiomer (Example 417) were obtained by racemate separation by means of preparative chiral HPLC (Method E).

Analytical chiral HPLC: 7.08 min.

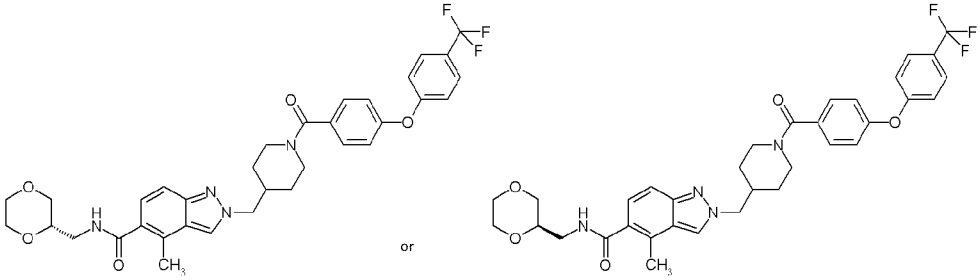
Example 417: (S or R)-4-methyl-N-(3,4,5,6-tetrahydro-2H-pyran-2-ylmethyl)-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



From 231 mg of the racemate prepared in Example 248, 24 mg of the title compound together with 24 mg of the faster-eluting enantiomer (Example 416) were obtained by racemate separation by means of preparative chiral HPLC (Method E).

Analytical chiral HPLC: 8.98 min.

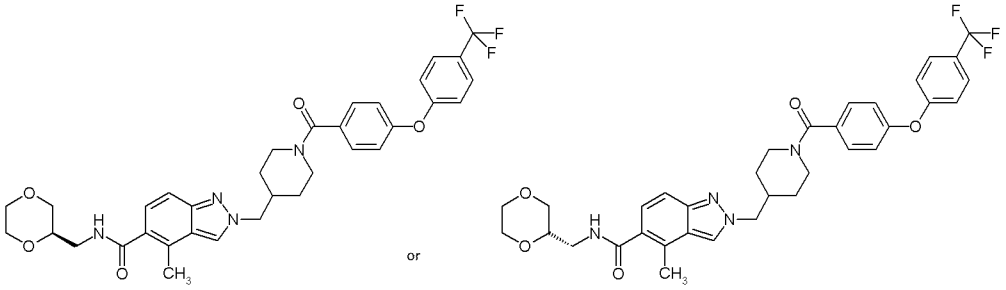
Example 418: (R or S)-N-(1,4-dioxan-2-ylmethyl)-4-methyl-2-[(1-{4-[4-(trifluoromethyl)-phenoxy]benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



From 280 mg of the racemate prepared in Example 249, 65 mg of the title compound together with 75 mg of the slower-eluting enantiomer (Example 419) were obtained by racemate separation by means of preparative chiral HPLC (Method D (injection volume: 0.1 ml; detection: UV 210 nM)).

Analytical chiral HPLC: 13.66 min.

Example 419: (R or S)-N-(1,4-dioxan-2-ylmethyl)-4-methyl-2-[(1-{4-[4-(trifluoromethyl)-phenoxy]benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide



From 280 mg of the racemate prepared in Example 249, 75 mg of the title compound together with 65 mg of the faster-eluting enantiomer (Example 418) were obtained by racemate separation by means of preparative chiral HPLC (Method D (injection volume: 0.1 ml; Detection: UV 210 nM)).

Analytical chiral HPLC: 14.90 min.

Biological Examples:

1. Detection of antagonism to the human prostaglandin E_2 (subtype EP2) receptor signal

1. 1 Detection principle

The binding of PGE_2 to the EP_2 subtype of the human PGE_2 receptor induces the activation of membrane-located adenylate cyclases and leads to the formation of cAMP. In the presence of the phosphodiesterase inhibitor IBMX, the cAMP accumulated owing to this stimulation and released by cell lysis is used in a competitive detection method. In this test, the cAMP present in the lysate competes with a fluorescence-labelled cAMP (cAMP-d2) for binding to an Eu cryptate-labelled anti-cAMP antibody.

In the absence of cellular cAMP, a maximal signal is produced, which is attributable to the binding of this cAMP-d2 molecule to the antibody. After excitation of the cAMP-d2 molecule at 337 nm, there is a fluorescence resonance energy transfer (FRET) to the Eu cryptate molecules of the anti-cAMP antibody (labelled therewith), followed by a long-lasting emission signal at 665 nm (and at 620 nM). Both signals are measured in a suitable measurement instrument with a time delay, i.e. after decay of the background fluorescence. Any increase in the low FRET signal caused by prostaglandin E_2 administration (measured as well ratio change = $emission_{665nm}/emission_{620nm}$ * 10000) indicates the action of antagonists.

1.2. Detection method

1.2.1. Test for antagonism (data per well of a 384-well plate):

To a test plate with the substance solutions already added (0.05 µ1; 100% DMSO, concentration range from 0.8 nM – 16.5 µM) were added 4 µl of a cAMP-d2/cell suspension (625000 cells/ml). After a 20-minute preincubation at room temperature (RT), 2 µl of a 3xPGE2 solution (1.5 nM, in PBS-IBMX) were added and incubated in the presence of the agonist for a further 60 mins at RT (volume: ~ 6 µl). Next the reaction was stopped by addition of 2 µl of lysis buffer and incubated for a further 20 mins at RT before the actual measurement (volume: ~ 8 µl).

2. Detection of antagonism to the human prostaglandin E_2 (subtype EP4) receptor signal

2. 1 Detection principle

The binding of PGE_2 to the EP_4 subtype of the human PGE_2 receptor induces the activation of membrane-located adenylate cyclases and leads to the formation of cAMP. In the presence of the phosphodiesterase inhibitor IBMX, the cAMP accumulated owing to this stimulation and released by cell lysis is used in a competitive detection method. In this test, the cAMP present in the lysate competes with a fluorescence-labelled cAMP (cAMP-d2) for binding to an Eu cryptate-labelled anti-cAMP antibody.

In the absence of cellular cAMP a maximal signal is produced, which is attributable to the binding of this cAMP-d2 molecule to the antibody. After excitation of the cAMP-d2 molecule at 337 nm, there is a fluorescence resonance energy transfer (FRET) to the Eu cryptate molecules of the anti-cAMP antibody (labelled therewith), followed by a long-lasting emission signal at 665 nm (and at 620 nM). Both signals are measured in a suitable measurement instrument with a time delay, i.e. after decay of the background fluorescence. Any increase in the low FRET signal caused by prostaglandin E_2 administration (measured as well ratio change = $emission_{665nm}/emission_{620nm}$ * 10000) indicates the action of antagonists.

2.2. Detection method

2.2.1. Test for antagonism (data per well of a 384-well plate):

To a test plate with the substance solutions already added (0.05 µl; 100% DMSO, concentration range from 0.8 nM - 16.5 µM) were added 4 µl of a cAMP-d2/cell suspension (312500 cells/ml). After a 20-minute preincubation at room temperature (RT), 2 µl of a 3xPGE2 solution (0.3 nM, in PBS-IBMX) were added and incubated in the presence of the agonist for a further 60 mins at RT (volume: ~ 6 µl). Next the reaction was stopped by addition of 2 µl of lysis buffer and incubated for a further 20 mins at RT before the actual measurement (volume: ~ 8 µl).

3. Detection of antagonism to the human prostaglandin D receptor signal

3. 1 Detection principle

The binding of prostaglandin D_2 to the human PGD receptor induces the activation of membrane-located adenylate cyclases and leads to the formation of cAMP. In the presence of the phosphodiesterase inhibitor IBMX, the cAMP accumulated owing to this stimulation and released by cell lysis is used in a competitive detection method. In this test, the cAMP present in the lysate competes with a fluorescence-labelled cAMP (cAMP-d2) for binding to an Eu cryptate-labelled anti-cAMP antibody.

In the absence of cellular cAMP, a maximal signal is produced, which is attributable to the binding of this cAMP-d2 molecule to the antibody. After excitation of the cAMP-d2 molecule at 337 nm, there is a fluorescence resonance energy transfer (FRET) to the Eu cryptate molecules of the anti-cAMP antibody (labelled therewith), followed by a long-lasting emission signal at 665 nm (and at 620 nM). Both signals are measured in a suitable measurement instrument with a time delay, i.e. after decay of the background fluorescence. Any increase in the low FRET signal caused by prostaglandin E_2 administration (measured as well ratio change = $emission_{665nm}/emission_{620nm}$ * 10000) indicates the action of antagonists.

3.2. Detection method

3.2.1. Test for antagonism (data per well of a 384-well plate):

To a test plate with the substance solutions already added (0.05 µ1; 100% DMSO, concentration range from 0.8 nM – 16.5 µM) were added 4 µl of a cAMP-d2/cell suspension (625000 cells/ml). After a 20-minute preincubation at room temperature (RT), 2 µl of a 3xPGD2 solution (6 nM, in PBS-IBMX) were added and incubated in the presence of the agonist for a further 30 mins at RT (volume: ~ 6 µl). Next the reaction was stopped by addition of 2 µl of lysis buffer and incubated for a further 20 mins at RT before the actual measurement (volume: ~ 8 µl).

4. The EP_2 subtype of the PGE_2 receptor and the pre-ovulatory cumulus expansion

4.1. Background:

In the pre-ovulatory antral follicle, the oocyte is surrounded by cumulus cells, which form a dense cell crown around the oocyte. After the LH peak (luteinizing hormone), a series of processes is activated, which results in a marked morphological change in this cell crown of cumulus cells. During this, the cumulus cells form an extracellular matrix, which leads to the so-called cumulus expansion (Vanderhyden *et al.* Dev Biol. 1990 Aug;140(2): 307-317) This cumulus expansion is an important component of the ovulatory process and the subsequent possibility of fertilization.

During the cumulus expansion, prostaglandins and here prostaglandin E_2, synthesis whereof is induced by the LH peak, are of decisive importance. Prostanoid EP_2 knockout mice (Hizaki *et al.*, 1999, Proc Natl Acad Sci U S A., Aug 31;96(18):10501-6.) show a markedly decreased cumulus expansion and severe subfertility, which demonstrates the importance of the prostanoid EP_2 receptor for this process.

4.2. Cumulus expansions test *in vitro*

In immature female mice (strain: B6D2F1 from Charles River), at an age of 14 - 18 days, the folliculogenesis was induced by a single administration (intraperitoneal) of 10 IU of PMSG (pregnant mare serum gonadotropin; Sigma G-4877, Lot 68H0909). 47-50 hours after the injection, the ovaries were removed and the cumulus-oocyte complexes removed. At this stage, the cumulus complex is not yet expanded.

The cumulus-oocyte complexes were now incubated for 20-24 hours with prostaglandin E_2 (PGE_2) (0.3 µM), vehicle control (ethanol) or test substances. Medium: alpha-MEM medium with 0.1 mM IBMX, pyruvate (0.23 mM), glutamine (2 mM), pen/strep 100 IU/ml pen. and 100 µg/ml strep.), HSA (8 mg/ml) and foetal bovine serum (FBS, 10%). The cumulus expansion was then established through the subdivision into four stages (after Vanderhyden *et al.* Dev Biol. 1990 Aug;140(2):307-317).

4.3 *In-vivo action on* post-ovulatory *in-vitro* fertilization :

Substances can exert an influence on fertility by decreasing the fertilizability of oocytes or cumulus-oocyte complexes. In order to study such effects, substances can be administered *in vivo* and subjected to *in vitro* fertilization after ovulation of cumulus-oocyte complexes has taken place. The *in-vitro* fertilization rate, where no test substance is any longer present, allows conclusions as to the *in-vivo* effects of the test substances.

Immature female mice (strain: B6D2F1, Charles River, Suelzfeld, age: 19-25 days) were kept in Macrolon cages in rooms with controlled illumination (12 hrs darkness: 12 hrs light), fed with a standard diet and provided with drinking water ad libitum.

The mice were primed with PMSG (pregnant mare serum gonadotropin) (10 IU/animal i.p.). After 48 hours, a stimulus triggering ovulation was created in the animals by one administration of 10 IU/animal i.p. (hCG, human chorionic gonadotropin). The test substances were dissolved in benzyl benzoate/castor oil (1+4 v/v) and administered in a volume of 0.1 ml s.c. 1 hour before hCG (n=5 animals per group). Fourteen hours after hCG administration, the animals were killed. Ovulated oocytes and cumulus-oocyte complexes were obtained from the bursa ovarii and/or oviduct and subjected to *in-vitro* fertilization, wherein for the fertilization a sperm count of 40000 sperms/0.5 ml was used for 1 hour. Twenty-four hours after the incubation with the sperms, the number of fertilized oocytes is established and the percentage fertilization rate determined.

The results in Table 4 show that Example 17 according to the invention has a dose-dependent influence on the fertilizability of ovulated cumulus-oocyte complexes.

4.4 *In-vivo* action on fertility in non-human primates (Cynomolgus):

In order to study the effect of substances on fertility, mating studies can be performed in monkeys (Jensen *et al.* Contraception 81 (2010) 165–171). For this, the test substances are administered to female cynomolgus monkeys (Macaca Fascicularis) which are being kept in groups, then the animals are mated with a male animal. Matings are checked for by sperm detection in daily vaginal smears. Pregnancies resulting therefrom are identified by hormone determinations and ultrasound examinations. Through the changes in the serum oestradiol concentrations during the cycle, (rise before the midcycle LH peak), the fertile phase within a cycle of the individual animals can be determined. Matings in this fertile period are described as "timed matings" (matings in the fertile phase). Apart from the absolute number of pregnancies occurring, the effect on the fertility can also be expressed as pregnancies per "timed matings".

To test the action of EP_2 receptor antagonists on fertility in monkeys, Examples 17 and 56 according to the invention were administered over 6 months, dissolved in 0.5 ml castor oil. Example 17 was administered once daily at a dosage of 10 mg/kg (n= 10 animals), while Example 56 was administered twice daily at a dosage of 10 mg/kg (n=9 animals). Only the vehicle was administered to a control group (n=10 animals). In the first month of the treatment, no male animal was placed with the female animals. After this, female and male animals were kept together over 5 months, with detection of pregnancies and cycle monitoring.

Table 5 shows that both substances result in a marked reduction in the number of pregnancies occurring. These data for the first time show the strong contraceptive effect of EP_2 receptor

antagonists in the primate. Further results of the study show that the substances have no effects on hormone levels and cycle length. This confirms that the substances produce a contraceptive effect by non-hormonal mechanisms. The reversibility of the fertility was demonstrated on some animals after discontinuation of the treatment.

5. Determination of the pharmacokinetic parameters after intravenous administration

5.1. Intravenous administration:

For this, the substances were administered in dissolved form, compatible solubilizers such as PEG400 and/or ethanol being used in tolerable quantity. The substances were administered at a dosage of 0.1 -1 mg/kg. The administration was effected in the female rat as a bolus injection. Here, at various times after bolus injection ca. 100-150 µl blood samples were withdrawn from the jugular vein via a catheter. The blood samples were treated with lithium-heparin as anticoagulant and stored refrigerated until further work-up. After centrifugation of the samples for 15 mins at 3000 rpm, an aliquot of 100 µl was withdrawn from the supernatant (plasma) and precipitated by addition of 400 µl of cold acetonitrile or methanol (absolute). The precipitated samples were frozen overnight at -20°C, then centrifuged once again for 15 mins at 3000 rpm, before 150 µl of the clear supernatant was withdrawn for the concentration determination. The analysis was performed with an Agilent 1200 HPLC system with attached LCMS/MS detection.

5.2 Calculation of the PK parameters

The calculation was performed by means of the PK calculation software WinNonLin®, where $t_{1/2}$ means half-life within a specified interval (here: terminal $t_{1/2}$, in hrs).

Table 1: Examples for the biological activity of the compounds according to the invention on the hEP_2 receptor (IC_{50} measured by cAMP antagonism test), selectivity towards hDP & hEP_4 (IC_{50} measured by cAMP antagonism test): x: 1 - 10, xx: 10 - 100, xxx > 100 :

Example	Antagonism hEP2 IC_{50} [M]	Selectivity hEP2/hDP	Selectivity hEP2/hEP4
1	1.03E-07	xxx	xxx
2	2.17E-08	xxx	xxx
3	4.91E-09	xxx	xxx
4	6.81E-08	xxx	xxx
5	5.11E-09	xxx	xxx
6	3.13E-07	xx	xx
7	2.58E-08	xxx	xxx
8	9.37E-09	xxx	xxx
9	1.72E-08	xxx	xxx
10	8.67E-09	xxx	xxx
11	8.14E-09	xxx	xxx
12	2.03E-08	xxx	xxx
13	3.59E-08	xxx	xxx
14	3.67E-09	xxx	xxx
15	4.17E-09	xxx	xxx
16	5.85E-09	xxx	xxx
17	3.44E-09	xxx	xxx
18	7.66E-09	xxx	xxx
19	8.57E-09	xxx	xxx
20	7.33E-09	xxx	xxx
21	3.58E-08	xxx	xxx
22	3.03E-08	xxx	xxx
23	1.61E-08	xxx	xxx
24	6.01E-08	xxx	xxx
25	2.52E-08	xxx	xxx
26	2.42E-08	xxx	xxx
27	1.93E-08	xxx	xxx
28	3.39E-08	xxx	xxx
29	9.31E-09	xxx	xxx

Example	Antagonism hEP2 IC_{50} [M]	Selectivity hEP2/hDP	Selectivity hEP2/hEP4
30	6.43E-08	xxx	xxx
31	3.08E-09	xxx	xxx
32	1.04E-08	xxx	xxx
33	3.42E-08	xxx	xxx
34	1.34E-07	xxx	xxx
35	6.92E-08	xxx	xxx
36	6.16E-08	xxx	xxx
37	1.04E-07	xxx	xxx
38	2.81E-08	xxx	xxx
39	1.13E-07	xxx	xxx
40	1.15E-08	xxx	xxx
41	5.62E-09	xxx	xxx
42	4.75E-09	xxx	xxx
43	4.82E-09	xxx	xxx
44	3.85E-09	xxx	xxx
45	5.51E-09	xxx	xxx
46	4.91E-09	xxx	xxx
47	5.61E-09	xxx	xxx
48	5.59E-09	xxx	xxx
49	6.44E-09	xxx	xxx
50	3.18E-09	xxx	xxx
51	6E-08	xxx	xxx
52	8.3E-07	xx	xx
53	4.42E-08	xxx	xxx
54	4.74E-09	xxx	xxx
55	9.67E-09	xxx	xxx
56	1.31E-08	xxx	xxx
57	5.29E-09	xxx	xxx
58	1.08E-06	xx	xx
59	7.58E-07	xx	xx
60	1.75E-07	xx	xx
61	1.5E-06	xx	xx
62	6.74E-07	xx	xx

Example	Antagonism hEP2 IC_{50} [M]	Selectivity hEP2/hDP	Selectivity hEP2/hEP4
63	1.44E-06	xx	xx
64	4.13E-06	x	x
65	2.79E-06	x	x
66	3.21E-07	xx	xx
67	4.05E-07	xx	xx
68	1.77E-08	xxx	xxx
69	2.9E-08	xxx	
70	4.9E-08	xxx	
71	8.29E-08	xxx	xxx
72	1.2E-07	xxx	xxx
73	7.78E-08	xxx	xxx
74	9.54E-08	xxx	xxx
75	6.7E-08	xxx	xxx
76	1.79E-07	xx	xx
77	5.39E-08	xxx	xxx
78	3.17E-08	xxx	xxx
79	1.25E-07	xxx	xxx
80	8.59E-08	xxx	xxx
81	5.13E-07	xx	xx
82	2.18E-07	xx	xx
83	3.26E-08	xxx	xxx
84	1.92E-08	xxx	xxx
85	3.55E-08	xxx	xxx
86	1.54E-08	xxx	xxx
87	2.4E-08	xxx	xxx
88	1.62E-08	xxx	xxx
89	9.4E-09	xxx	xxx
90	1.48E-08	xxx	xxx
91	2.03E-08	xxx	xxx
92	1.27E-08	xxx	xxx
93	1.15E-08	xxx	xxx
94	1.28E-08	xxx	xxx
95	6.18E-09	xxx	xxx

Example	Antagonism hEP2 IC_{50} [M]	Selectivity hEP2/hDP	Selectivity hEP2/hEP4
96	9.42E-09	xxx	xxx
97	1.27E-08	xxx	xxx
98	7.07E-09	xxx	xxx
99	1.04E-08	xxx	xxx
100	6.21E-09	xxx	xxx
101	6.58E-09	xxx	xxx
102	4.1E-07	xx	xx
103	5.95E-07	xx	xx
104	5.13E-07	xx	xx
105	2.85E-07	xx	xx
106	1.5E-07	xxx	xxx
107	1.14E-08	xxx	xxx
108	6.46E-09	xxx	xxx
109	9.53E-09	xxx	xxx
110	4.4E-09	xxx	xxx
111	1.37E-08	xxx	xxx
112	1.19E-08	xxx	xxx
113	1.39E-08	xxx	xxx
114	6.08E-09	xxx	xxx
115	9.05E-09	xxx	xxx
116	5.52E-09	xxx	xxx
117	1.78E-08	xxx	xxx
118	8.17E-09	xxx	
119	1.32E-08	xxx	
120	1.55E-08	xxx	
121	1.55E-08	xxx	xxx
122	2.86E-08	xxx	xxx
123	8.92E-09	xxx	xxx
124	7.99E-09	xxx	xxx
125	3.66E-09	xxx	xxx
126	2.12E-08	xxx	xxx
127	5.56E-08	xxx	xxx
128	4.71E-07	xx	xx

Example	Antagonism hEP2 IC_{50} [M]	Selectivity hEP2/hDP	Selectivity hEP2/hEP4
129	3.09E-07	xx	xx
130	2.41E-07	xx	xx
131	2.28E-07	xx	xx
132	1.09E-07	xxx	xxx
133	4.19E-08	xxx	xxx
134	5.65E-08	xxx	xxx
135	1.95E-08	xxx	xxx
136	6.59E-09	xxx	xxx
137	7.65E-09	xxx	xxx
138	1.6E-07	xxx	xxx
139	4.19E-07	xx	xx
140	5.53E-08	xxx	xxx
141	1.43E-07	xxx	xxx
142	7.13E-07	xx	xx
143	3.68E-08	xxx	xxx
144	5.08E-08	xxx	xxx
145	1.88E-08	xxx	xxx
146	5.26E-08	xxx	xxx
147	5.74E-08	xxx	xxx
148	2.74E-08	xxx	xxx
149	2.96E-08	xxx	xxx
150	1.28E-08	xxx	xxx
151	4.85E-08	xxx	xxx
152	3.33E-08	xxx	xxx
153	6.08E-08	xxx	xxx
154	8.08E-08	xxx	xxx
155	2.94E-08	xxx	xxx
156	1.84E-07	xx	xx
157	1.36E-08	xxx	xxx
158	6.21E-09	xxx	xxx
159	6.24E-09	xxx	xxx
160	8.29E-08	xxx	xxx
161	9.82E-08	xxx	xxx

Example	Antagonism hEP2 IC_{50} [M]	Selectivity hEP2/hDP	Selectivity hEP2/hEP4
162	9.33E-09	xxx	xxx
163	6.8E-09	xxx	xxx
164	1.09E-08	xxx	xxx
165	3.34E-08	xxx	xxx
166	2.87E-09	xxx	xxx
167	1.35E-08	xxx	xxx
168	2.93E-08	xxx	xxx
169	2.77E-08	xxx	xxx
170	4.25E-09	xxx	xxx
171	3.88E-09	xxx	xxx
172	3.16E-09	xxx	xxx
173	2.71E-09	xxx	xxx
174	6.58E-09	xxx	xxx
175	8.05E-09	xxx	xxx
176	7.77E-09	xxx	xxx
177	1.18E-07	xxx	xxx
178	6.83E-08	xxx	xxx
179	2.61E-06	x	x
180	1.73E-08	xxx	xxx
181	3.52E-08	xxx	xxx
182	6.42E-08	xxx	xxx
183	4.66E-08	xxx	xxx
184	7.68E-08	xxx	xxx
185	2.48E-08	xxx	xxx
186	5.19E-08	xxx	xxx
187	2.35E-08	xxx	xxx
188	1.49E-07	xxx	xxx
189	3.36E-08	xxx	xxx
190	2.72E-07	xx	xx
191	4.71E-08	xxx	xxx
192	2.06E-07	xx	xx
193	1.45E-07	xxx	xxx
194	4.09E-08	xxx	xxx

Example	Antagonism hEP2 IC_{50} [M]	Selectivity hEP2/hDP	Selectivity hEP2/hEP4
195	2.27E-07	xx	xx
196	5.08E-08	xxx	xxx
197	6.32E-08	xxx	xxx
198	1.53E-07	xxx	xxx
199	9.71E-08	xxx	xxx
200	1.51E-08	xxx	xxx
201	2.49E-08	xxx	xxx
202	5.06E-09	xxx	xxx
203	8.57E-08	xxx	xxx
204	1E-08	xxx	xxx
205	4.33E-08	xxx	xxx
206	4.13E-08	xxx	xxx
207	3.03E-08	xxx	xxx
208	8.06E-08	xxx	xxx
209	2.51E-08	xxx	xxx
210	1.95E-08	xxx	xxx
211	5.01E-08	xxx	xxx
212	1.06E-07	xxx	xxx
213	8.24E-08	xxx	xxx
214	6.49E-08	xxx	xxx
215	3.9E-08	xxx	xxx
216	8.61E-08	xxx	xxx
217	1.14E-07	xxx	xxx
218	1.28E-07	xxx	xxx
219	2.73E-07	xx	xx
220	1.47E-07	xxx	xxx
221	2.35E-07	xx	xx
222	4.09E-08	xxx	xxx
223	2E-08	xxx	xxx
224	5.62E-09	xxx	xxx
225	1.43E-08	xxx	xxx
226	1.19E-08	xxx	xxx
227	9.89E-09	xxx	xxx

Example	Antagonism hEP2 IC_{50} [M]	Selectivity hEP2/hDP	Selectivity hEP2/hEP4
228	8.09E-09	xxx	xxx
229	1.02E-08	xxx	xxx
230	1.37E-08	xxx	xxx
231	1.32E-08	xxx	xxx
232	3.83E-08	xxx	xxx
233	3.97E-08	xxx	xxx
234	4.77E-08	xxx	xxx
235	1.67E-08	xxx	xxx
236	5.75E-08	xxx	xxx
237	3.1E-08	xxx	xxx
238	3.24E-08	xxx	xxx
239	2.7E-08	xxx	xxx
240	2.51E-08	xxx	xxx
241	9.03E-09	xxx	xxx
242	3.05E-07	xx	xx
243	3.35E-07	xx	xx
244	4.42E-08	xxx	xxx
245	7.79E-09	xxx	xxx
246	9.23E-09	xxx	xxx
247	1.26E-08	xxx	xxx
248	1.47E-08	xxx	xxx
249	1.12E-08	xxx	xxx
250	3.06E-08	xxx	xxx
251	3.81E-06	x	x
252	2.95E-07	xx	xx
253	1.68E-07	xx	xx
254	5.52E-08	xxx	xxx
255	8.35E-08	xxx	xxx
256	1.07E-07		xxx
257	1.02E-07	xxx	xxx
258	1.09E-07	xxx	xxx
259	2.56E-08	xxx	xxx
260	8.02E-09	xxx	xxx

Example	Antagonism hEP2 IC_{50} [M]	Selectivity hEP2/hDP	Selectivity hEP2/hEP4
261	8.1E-08	xxx	xxx
262	3.34E-08	xxx	xxx
263	1.81E-07	xx	xx
264	1.37E-08	xxx	xxx
265	3.15E-08	xxx	xxx
266	1.89E-08	xxx	xxx
267	4.55E-08	xxx	xxx
268	2.29E-08	xxx	xxx
269	7.54E-09	xxx	xxx
270	5.31E-08	xxx	xxx
271	3.35E-08	xxx	xxx
272	2.37E-08	xxx	xxx
273	1.85E-08	xxx	xxx
274	4.46E-08	xxx	xxx
275	3.45E-08	xxx	xxx
276	2.26E-07	xx	xx
277	4.79E-08	xxx	xxx
278	1.04E-07	xxx	xxx
279	5.74E-08	xxx	xxx
280	3.07E-08	xxx	xxx
281	2.3E-08	xxx	xxx
282	2.01E-08	xxx	xxx
283	6.55E-08	xxx	xxx
284	5.64E-08	xxx	xxx
285	1E-07	xxx	xxx
286	1E-07	xxx	xxx
287	1.05E-06	xx	xx
288	4E-08	xxx	xxx
289	5.16E-08	xxx	xxx
290	4.26E-08	xxx	xxx
291	5.94E-09	xxx	xxx
292	2E-08	xxx	xxx
293	2.83E-08	xxx	xxx

Example	Antagonism hEP2 IC_{50} [M]	Selectivity hEP2/hDP	Selectivity hEP2/hEP4
294	1.32E-08	xxx	xxx
295	7.08E-08	xxx	xxx
296	2.97E-08	xxx	xxx
297	4.6E-07	xx	xx
298	3.45E-07	xx	xx
299	5.41E-07	xx	xx
300	7.98E-08	xxx	xxx
301	2.45E-08	xxx	xxx
302	1.31E-07	xxx	xxx
303	1.39E-08	xxx	xxx
304	9.98E-08	xxx	xxx
305	3.01E-07	xx	xx
306	7.66E-08	xxx	xxx
307	3.06E-08	xxx	xxx
308	2.22E-08	xxx	xxx
309	6.6E-08	xxx	xxx
310	8.06E-07	xx	xx
311	8.41E-08	xxx	xxx
312	1.58E-07	xxx	xxx
313	8.94E-08	xxx	xxx
314	2.78E-08	xxx	xxx
315	4.3E-08	xxx	xxx
316	7.9E-08	xxx	xxx
317	1.81E-07	xx	xx
318	2.63E-08	xxx	xxx
319	3.15E-07	xx	xx
320	1.56E-08	xxx	xxx
321	1.01E-07	xxx	xxx
322	7.62E-08	xxx	xxx
323	1.28E-07	xxx	xxx
324	4.6E-07	xx	xx
325	3.21E-07	xx	xx
326	4.85E-07	xx	xx

Example	Antagonism hEP2 IC_{50} [M]	Selectivity hEP2/hDP	Selectivity hEP2/hEP4
327	1.21E-06	xx	xx
328	2.56E-07	xx	xx
329	2.32E-07	xx	xx
330	9.53E-09	xxx	xxx
331	9.47E-09	xxx	xxx
332	5.47E-09	xxx	xxx
333	6.42E-09	xxx	xxx
334	7.42E-08	xxx	xxx
335	5.09E-09	xxx	xxx
336	5.59E-09	xxx	xxx
337	1.81E-08	xxx	xxx
338	2.8E-08	xxx	xxx
339	7.15E-09	xxx	xxx
340	1.99E-08	xxx	xxx
341	5.53E-08	xxx	xxx
342	1.03E-07	xxx	xxx
343	4.24E-08	xxx	xxx
344	1.03E-08	xxx	xxx
345	6.26E-09	xxx	xxx
346	1.49E-08	xxx	xxx
347	7.88E-09	xxx	xxx
348	8.88E-09	xxx	xxx
349	4.82E-09	xxx	xxx
350	8.41E-09	xxx	xxx
351	6.84E-09	xxx	xxx
352	2.17E-08	xxx	xxx
353	5.02E-08	xxx	xxx
354	5.87E-09	xxx	xxx
355	5.39E-09	xxx	xxx
356	6.36E-08	xxx	xxx
357	7.36E-09	xxx	xxx
358	8.01E-09	xxx	xxx
359	6.99E-09	xxx	xxx

Example	Antagonism hEP2 IC_{50} [M]	Selectivity hEP2/hDP	Selectivity hEP2/hEP4
360	6.27E-09	xxx	xxx
361	5.11E-09	xxx	xxx
362	1.51E-08	xxx	xxx
363	5.48E-09	xxx	xxx
364	6.61E-09	xxx	xxx
365	5.3E-09	xxx	xxx
366	1.89E-08	xxx	xxx
367	5.84E-09	xxx	xxx
368	1.2E-08	xxx	xxx
369	5.66E-09	xxx	xxx
370	3.07E-09	xxx	xxx
371	6.11E-09	xxx	xxx
372	7.29E-09	xxx	xxx
373	4.07E-08	xxx	xxx
374	6.58E-09	xxx	xxx
375	5.8E-09	xxx	xxx
376	3.59E-09	xxx	xxx
377	2.73E-08	xxx	xxx
378	7.77E-09	xxx	xxx
379	6.26E-08	xxx	xxx
380	5.35E-09	xxx	xxx
381	5.84E-09	xxx	xxx
382	1.94E-08	xxx	xxx
383	5.78E-09	xxx	xxx
384	3.95E-09	xxx	xxx
385	1.31E-08	xxx	xxx
386	2.57E-08	xxx	xxx
387	1.32E-08	xxx	xxx
388	2.05E-08	xxx	xxx
389	4.51E-09	xxx	xxx
390	3.14E-09	xxx	xxx
391	6.07E-09	xxx	xxx
392	2.18E-08	xxx	xxx

Example	Antagonism hEP2 IC_{50} [M]	Selectivity hEP2/hDP	Selectivity hEP2/hEP4
393	5E-08	xxx	xxx
394	5.7E-09	xxx	xxx
395	3.04E-08	xxx	xxx
396	1.8E-08	xxx	xxx
397	1.25E-08	xxx	xxx
398	1.82E-08	xxx	xxx
399	5.93E-07	xx	xx
400	5.61E-08	xxx	xxx
401	1.55E-07	xxx	xxx
402	7.77E-08	xxx	xxx
403	9.59E-09	xxx	xxx
404	2.02E-08	xxx	xxx
405	2.14E-06	x	x
406	8.19E-09	xxx	xxx
407	1.16E-08	xxx	xxx
408	2.35E-08	xxx	xxx
409	3.18E-08	xxx	xxx
410	9.04E-08	xxx	xxx
411	1.65E-08	xxx	xxx
412	6.35E-08	xxx	xxx
413	3.78E-08	xxx	xxx
414	2.23E-07	xx	xx
415	2.13E-08	xxx	xxx
416	1.07E-08	xxx	xxx
417	9.75E-09	xxx	xxx
418	1.58E-08	xxx	xxx
419	1.09E-08	xxx	xxx

Table 2: Reduction in the cumulus expansion in percent with use of 0.3 µM PGE2 for stimulation, reference 1: example 62 from DE102009049662A1

Example	% reduction at 1 µM	% reduction at 0.5 µm
Reference 1*	79% (*reduction at 10 µM)	

Example 5	59	56
Example 17	76	71
Example 42	79	48
Example 117	54	30
Example 283	26	25
Example 291	73	76
Example 303	47	38
Example 345	36	18

Table 3: Terminal half-life ($t_{1/2}$) after intravenous administration in the female rat, reference 1: example 62 from DE102009049662A1

Example	$t_{1/2}$ [hr]
Reference 1	0.4
Example 17	2.5
Example 42	3.2
Example 117	2.0
Example 283	5.8

Table 4: Reduction in *in-vitro* fertilization rate after *in-vivo* administration of the test substance:

Example	% fertilization with vehicle	% fertilization with 1 mg/kg	% fertilization with 5 mg/kg	% fertilization with 10 mg/kg
Example 17	30 ± 9	20 ± 10	9 ± 1	8 ± 4

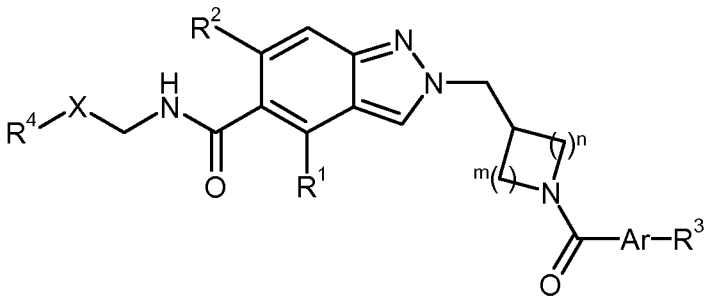
Table 5: Reduction in the pregnancy rates in the non-human primate (Cynomolgus)

Group	Animals per group	Number of "timed matings"*	Pregnancies	% Pregnancies/ "timed mating"
Control	10	21	8	38
Example 17	10	25	3	6
Example 56	9	34	2	12

*Detection of vaginal sperms in the fertile phase of the cycle

Claims:

1. Compounds of the general formula (I)



wherein

R^1: means H, C_1-C_2 alkyl or C_1-C_2 alkyloxy;

R^2: H or methyl;

subject to the proviso that one of the two residues R^1 or R^2 equals H;

X: $-(CH_2)_l-$, $-(CH_2)_k-O-$, $-CH_2-S-$, $CH_2-S(O)_2-$, $-CH(CH_3)-$, $-CH(CH_3)-O-$ or $-C(CH_3)_2-O-$;

k: 1 or 2;

l: 0, 1 or 2;

R^4: H, C_1-C_4 alkyl, C_3-C_4 cycloalkyl or CH_2-C_3-C_4 cycloalkyl;

and in the case of X: $-CH_2-$ or $-CH(CH_3)-$

R^4: additionally means a 4-6-membered heterocyclyl residue;

and in the case of X: $-(CH_2)_l-$ or $-CH(CH_3)-$

R^4: additionally means CN;

or

X together with R^4 form a 4-6-membered heterocyclyl residue via a ring carbon linkage;

m: 1 or 2;

n: 1 or 2;

Ar: a 6-10-membered aryl or 5-10-membered hetaryl residue,

R^3: halogen, CN, SF_5, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_4-C_6 heterocyclyl, O-C_1-C_4 alkyl, O-C_3-C_6 cycloalkyl, O-C_4-C_6 heterocyclyl, S-C_1-C_4 alkyl, $S(O)_2$-C_1-C_4 alkyl, Ar′, O-Ar′, $C(CH_3)_2$-CN or $C(CH_3)_2$-OH; and

Ar′: an optionally singly or doubly substituted 6-membered aryl or 5-6-membered heteroaryl residue;
wherein the substituents are selected from F, Cl, CN, C_1-C_4 alkyl, O-C_1-C_4 alkyl, $C(CH_3)_2$-CN, $C(CH_3)_2$-OH and $C(O)NH_2$;

and isomers, diastereomers, enantiomers and salts or cyclodextrin clathrates thereof.

2. Compounds according to Claim 1, wherein

R^1, R^2: mean H or methyl;

subject to the proviso that one of the two residues R^1 or R^2 equals H;

X: $-(CH_2)_l-$ or $-(CH_2)_k-O-$;

k: 1 or 2;

l: 0, 1 or 2;

R^4: C_1-C_4 alkyl, C_3-C_4 cycloalkyl or CH_2-C_3-C_4 cycloalkyl; and

m, n: 2;

and isomers, diastereomers, enantiomers and salts or cyclodextrin clathrates thereof and R^3, Ar and Ar´ have the meanings stated in Claim 1.

3. Compounds according to Claim 1 - 2, wherein

R^1, R^2: mean H or methyl;

subject to the proviso that one of the two residues R^1 or R^2 equals H;

X: $-(CH_2)_l-$ or $-(CH_2)_k-O-$;

k: 1 or 2;

l: 0, 1 or 2;

R^4: C_1-C_4 alkyl, C_3-C_4 cycloalkyl or CH_2-C_3-C_4 cycloalkyl; and

m, n: 1;

and isomers, diastereomers, enantiomers and salts or cyclodextrin clathrates thereof and R^3, Ar and Ar´ have the meanings stated in Claim 1.

4. Compounds according to Claim 1 - 3, wherein

R^1: means methyl;

R^2: H;

X: $-(CH_2)_l-$ or $-(CH_2)_k-O-$;

k: 1;

l: 0 or 1;

R^4: C_1-C_4 alkyl, C_3-C_4 cycloalkyl or CH_2-C_3-C_4 cycloalkyl;

m, n: 2; and

Ar: a phenyl residue;

and isomers, diastereomers, enantiomers and salts or cyclodextrin clathrates thereof and R^3 and Ar′ have the meanings stated in Claim 1.

5. Compounds according to Claim 1 - 4, wherein

R^1: means a methyl group;

R^2: H;

X: $-(CH_2)_l-$ or $-(CH_2)_k-O-$;

k: 1;

l: 0 or 1;

R^4: C_1-C_4 alkyl, C_3-C_4 cycloalkyl or CH_2-C_3-C_4 cycloalkyl;

m, n: 1; and

Ar: a phenyl residue;

and isomers, diastereomers, enantiomers and salts or cyclodextrin clathrates thereof and R^3 and Ar′ have the aforesaid meanings.

6. Compounds according to Claim 4 and 5 selected from a group which contains the following compounds:

1. 2-{[1-(4-cyano-2-fluorobenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
2. 2-{[1-(4-tert-butoxybenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
3. 2-({1-[4-(4-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
4. N-(2-methoxyethyl)-4-methyl-2-{[1-(4-morpholinobenzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide
5. 2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
6. 2-{[1-(2-fluoro-4-mesylbenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
7. 2-{[1-(2-fluoro-4-methoxybenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
8. 2-{[1-(4-bromo-2-fluorobenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
9. 2-{[1-(2-fluoro-4-methylbenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
10. 2-({1-[2-fluoro-4-(trifluoromethyl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
11. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(pentafluoro-λ^6-sulphanyl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide
12. N-(2-methoxyethyl)-4-methyl-2-{[1-(4-methylbenzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide
13. 2-({1-[4-(4-chlorophenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
14. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(4-methylphenoxy)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide
15. 2-({1-[4-(4-tert-butylphenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
16. N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
17. N-(2-methoxyethyl)-2-({1-[4-(4-methoxyphenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-2H-indazol-5-carboxamide
18. N-(2-methoxyethyl)-4-methyl-2-{[1-(4-phenoxybenzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide

19. 2-{[1-(4-cyclopropylbenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
20. 2-{[1-(4-methoxybenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
21. 2-{[1-(4-fluorobenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
22. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(trifluoromethyl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide
23. 2-{[1-(2-methoxybenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
24. N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[(trifluoromethyl)sulphonyl]benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
25. N-(2-methoxyethyl)-4-methyl-2-({1-[3-(trifluoromethyl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide
26. N-(2-methoxyethyl)-4-methyl-2-{[1-(3-methylbenzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide
27. 2-{[1-(3-chlorobenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
28. 2-({1-[4-(4-carbamoylphenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
29. 2-({1-[4-(cyclopentyloxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
30. 2-({1-[4-(difluoromethyl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
31. 2-{[1-(4-cyanobenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
32. 2-({1-[4-(1H-imidazol-1-yl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
33. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(oxazol-2-yl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide
34. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(oxazol-5-yl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide
35. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(isoxazol-5-yl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide
36. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(1H-pyrazol-1-yl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide

37. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(1H-1,2,4-triazol-1-yl)benzoyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide
38. 2-({1-[4-(difluoromethoxy)-2-fluorobenzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
39. 2-({1-[2-fluoro-4-(pyrrolidin-1-yl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
40. 2-({1-[(3,4'-difluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
41. 2-({1-[(3-fluoro-4'-methoxybiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
42. 2-({1-[(3-fluoro-4'-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
43. 2-[(1-{[3-fluoro-3'-(trifluoromethyl)biphenyl-4-yl]carbonyl}piperidin-4-yl)methyl]-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
44. 2-[(1-{[3-fluoro-2'-(trifluoromethoxy)biphenyl-4-yl]carbonyl}piperidin-4-yl)methyl]-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
45. 2-({1-[(2'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
46. 2-({1-[(2',4'-difluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
47. 2-({1-[(2-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
48. N-(2-methoxyethyl)-4-methyl-2-({1-[(2'-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide
49. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(4-pyridyloxy)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide
50. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(4H-1,2,4-triazol-4-yl)benzoyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide
51. 2-{[1-(2-fluoro-4-morpholinobenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
52. 2-{[1-(4-bromobenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
53. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(trifluoromethoxy)benzoyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide
54. 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

55. N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[(trifluoromethyl)sulphanyl]benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
56. 4-methyl-2-({1-[4-(pentafluoro-λ^6-sulphanyl)benzoyl]piperidin-4-yl}methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
57. 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
58. 4-methyl-N-(2,2,2-trifluoroethyl)-2-({1-[4-(trifluoromethoxy)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide
59. 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-[2-(cyclopropylmethoxy)ethyl]-4-methyl-2H-indazole-5-carboxamide
60. N-[2-(cyclopropylmethoxy)ethyl]-4-methyl-2-{[1-(4-methylbenzoyl)piperidin-4-yl]-methyl}-2H-indazol-5-carboxamide
61. N-[2-(cyclopropylmethoxy)ethyl]-2-({1-[4-(4-fluorophenoxy)benzoyl]piperidin-4-yl}-methyl)-4-methyl-2H-indazol-5-carboxamide
62. N-[2-(cyclopropylmethoxy)ethyl]-4-methyl-2-({1-[4-(trifluoromethyl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide
63. N-[2-(cyclopropylmethoxy)ethyl]-2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-4-methyl-2H-indazol-5-carboxamide
64. 2-{[1-(4-cyclopropylbenzoyl)piperidin-4-yl]methyl}-N-[2-(cyclopropylmethoxy)ethyl]-4-methyl-2H-indazol-5-carboxamide
65. 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methyl-N-[2-(2,2,2-trifluoroethoxy)-ethyl]-2H-indazol-5-carboxamide
66. 4-methyl-2-{[1-(4-methylbenzoyl)piperidin-4-yl]methyl}-N-[2-(2,2,2-trifluoroethoxy)-ethyl]-2H-indazol-5-carboxamide
67. 2-({1-[4-(4-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-[2-(2,2,2-trifluoroethoxy)ethyl]-2H-indazol-5-carboxamide
68. 4-methyl-N-[2-(2,2,2-trifluoroethoxy)ethyl]-2-({1-[4-(trifluoromethyl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide
69. 2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-4-methyl-N-[2-(2,2,2-trifluoroethoxy)ethyl]-2H-indazol-5-carboxamide
70. 2-{[1-(4-cyclopropylbenzoyl)piperidin-4-yl]methyl}-4-methyl-N-[2-(2,2,2-trifluoro-ethoxy)ethyl]-2H-indazol-5-carboxamide
71. 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-(2-isopropoxyethyl)-4-methyl-2H-indazol-5-carboxamide
72. N-(2-isopropoxyethyl)-4-methyl-2-{[1-(4-methylbenzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide

73. 2-({1-[4-(4-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-isopropoxyethyl)-4-methyl-2H-indazol-5-carboxamide
74. N-(2-isopropoxyethyl)-4-methyl-2-({1-[4-(trifluoromethyl)benzoyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide
75. 2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-isopropoxyethyl)-4-methyl-2H-indazol-5-carboxamide
76. 2-{[1-(4-cyclopropylbenzoyl)piperidin-4-yl]methyl}-N-(2-isopropoxyethyl)-4-methyl-2H-indazol-5-carboxamide
77. 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methyl-N-[2-(trifluoromethoxy)ethyl]-2H-indazol-5-carboxamide
78. 2-({1-[4-(4-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-[2-(trifluoro-methoxy)ethyl]-2H-indazol-5-carboxamide
79. 2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-4-methyl-N-[2-(trifluoro-methoxy)ethyl]-2H-indazol-5-carboxamide
80. 4-methyl-N-[2-(trifluoromethoxy)ethyl]-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
81. N-(2-tert-butoxyethyl)-2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methyl-2H-indazol-5-carboxamide
82. N-(2-tert-butoxyethyl)-2-({1-[4-(4-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-2H-indazol-5-carboxamide
83. N-(2-tert-butoxyethyl)-2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-4-methyl-2H-indazol-5-carboxamide
84. N-(2-tert-butoxyethyl)-4-methyl-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
85. 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-4-methyl-N-{2-[(^{2}H3)methyloxy]-(^{2}H4)ethyl}-2H-indazol-5-carboxamide
86. 2-({1-[4-(4-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-{2-[(^{2}H3)methyloxy](^{2}H4)ethyl}-2H-indazol-5-carboxamide
87. 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
88. N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[(trifluoromethyl)sulphanyl]benzoyl}azetidin-3-yl)methyl]-2H-indazol-5-carboxamide
89. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(trifluoromethoxy)benzoyl]azetidin-3-yl}methyl)-2H-indazol-5-carboxamide
90. 2-({1-[2-fluoro-4-(trifluoromethyl)benzoyl]azetidin-3-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

91. 2-{[1-(4-chloro-2-fluorobenzoyl)azetidin-3-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
92. 2-({1-[3-fluoro-4-(trifluoromethyl)benzoyl]azetidin-3-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
93. 2-({1-[4-chloro-3-(trifluoromethyl)benzoyl]azetidin-3-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
94. 2-{[1-(4-cyclopropylbenzoyl)azetidin-3-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
95. N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}azetidin-3-yl)methyl]-2H-indazol-5-carboxamide
96. 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
97. 4-methyl-N-(2,2,2-trifluoroethyl)-2-({1-[4-(trifluoromethoxy)benzoyl]azetidin-3-yl}-methyl)-2H-indazol-5-carboxamide
98. 2-({1-[2-fluoro-4-(trifluoromethyl)benzoyl]azetidin-3-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
99. 4-methyl-2-({1-[4-(pentafluoro-λ^6-sulphanyl)benzoyl]azetidin-3-yl}methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
100. N-[2-(cyclopropyloxy)ethyl]-4-methyl-2-({1-[4-(trifluoromethoxy)benzoyl]azetidin-3-yl}methyl)-2H-indazol-5-carboxamide
101. N-[2-(cyclobutyloxy)ethyl]-4-methyl-2-({1-[4-(trifluoromethoxy)benzoyl]azetidin-3-yl}methyl)-2H-indazol-5-carboxamide
102. 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-N-[2-(cyclopropylmethoxy)ethyl]-4-methyl-2H-indazol-5-carboxamide
103. N-[2-(cyclopropylmethoxy)ethyl]-2-({1-[4-(4-fluorophenoxy)benzoyl]azetidin-3-yl}-methyl)-4-methyl-2H-indazol-5-carboxamide
104. N-[2-(cyclopropylmethoxy)ethyl]-4-methyl-2-{[1-(4-methylbenzoyl)azetidin-3-yl]-methyl}-2H-indazol-5-carboxamide
105. 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-4-methyl-N-[2-(trifluoromethoxy)ethyl]-2H-indazol-5-carboxamide
106. N-(2-tert-butoxyethyl)-2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-4-methyl-2H-indazol-5-carboxamide
107. N-[2-(cyclopropylmethoxy)ethyl]-2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]azetidin-3-yl}methyl)-4-methyl-2H-indazol-5-carboxamide
108. 2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]azetidin-3-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

109. 2-({1-[4-(4-fluorophenoxy)benzoyl]azetidin-3-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
110. 2-({1-[4-(4-fluorophenoxy)benzoyl]azetidin-3-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
111. 2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]azetidin-3-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
112. 2-{[1-(4-chlorobenzoyl)azetidin-3-yl]methyl}-4-methyl-N-[2-(2,2,2-trifluoroethoxy)-ethyl]-2H-indazol-5-carboxamide
113. 4-methyl-N-[2-(2,2,2-trifluoroethoxy)ethyl]-2-[(1-{4-[4-(trifluoromethyl)phenoxy]-benzoyl}azetidin-3-yl)methyl]-2H-indazol-5-carboxamide
114. 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}-azetidin-3-yl)methyl]-2H-indazol-5-carboxamide
115. 2-({1-[4-(4-chlorophenoxy)benzoyl]azetidin-3-yl}methyl)-4-methyl-N-(2,2,2-trifluoro-ethyl)-2H-indazol-5-carboxamide
116. 2-({1-[4-(4-chlorophenoxy)benzoyl]azetidin-3-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
117. N-(2-methoxyethyl)-4-methyl-2-{[1-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}benzoyl)-azetidin-3-yl]methyl}-2H-indazol-5-carboxamide
118. 4-methyl-N-(2,2,2-trifluoroethyl)-2-{[1-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}-benzoyl)azetidin-3-yl]methyl}-2H-indazol-5-carboxamide
119. 2-{[1-(4-chlorobenzoyl)piperidin-4-yl]methyl}-N-ethyl-4-methyl-2H-indazol-5-carboxamide
120. 2-({1-[4-(4-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
121. 2-({1-[4-(4-chlorophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
122. 4-methyl-2-({1-[4-(4-methylphenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
123. 2-({1-[(4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
124. 4-methyl-2-{[1-(4-morpholinobenzoyl)piperidin-4-yl]methyl}-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
125. 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{4-[(trifluoromethyl)sulphanyl]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
126. 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{4-[4-(trifluoromethyl)phenoxy]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide

127. 4-methyl-N-(2,2,2-trifluoroethyl)-2-{[1-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}-benzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide
128. 4-methyl-N-(2,2,2-trifluoroethyl)-2-{[1-(4-{[6-(trifluoromethyl)pyridin-3-yl]oxy}-benzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide
129. 4-methyl-N-(2,2,2-trifluoroethyl)-2-{[1-(4-{[6-(trifluoromethyl)pyridin-2-yl]oxy}-benzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide
130. 2-({1-[4-(4-cyanophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
131. 2-({1-[4-(3-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
132. 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{4-[3-(trifluoromethyl)phenoxy]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
133. 2-[(1-{4-[(5-cyanopyridin-2-yl)oxy]benzoyl}piperidin-4-yl)methyl]-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
134. 2-[(1-{4-[(5-chloropyridin-2-yl)oxy]benzoyl}piperidin-4-yl)methyl]-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
135. 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{4-[5-(trifluoromethyl)pyridin-2-yl]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
136. 2-({1-[4-(2,4-difluorophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
137. 2-({1-[4-(3,4-difluorophenoxy)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
138. 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{[4'-(trifluoromethyl)biphenyl-4-yl]carbonyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
139. 2-{[1-(4-bromobenzoyl)piperidin-4-yl]methyl}-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
140. 2-({1-[4-(5-chloropyridin-2-yl)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
141. 2-({1-[(4'-methoxy-2'-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
142. 4-methyl-2-({1-[4-(6-methylpyridin-3-yl)benzoyl]piperidin-4-yl}methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
143. 2-({1-[(4'-fluoro-2'-methoxybiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
144. 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{4-[6-(trifluoromethyl)pyridin-3-yl]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide

145. 2-({1-[4-(6-methoxypyridin-3-yl)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
146. 2-({1-[4-(6-methoxypyridin-2-yl)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
147. 4-methyl-2-({1-[4-(5-methylpyridin-2-yl)benzoyl]piperidin-4-yl}methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
148. 2-({1-[4-(5-fluoropyridin-2-yl)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
149. 2-({1-[4-(5-methoxypyridin-2-yl)benzoyl]piperidin-4-yl}methyl)-4-methyl-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
150. 4-methyl-2-({1-[4-(2-methylpyrimidin-5-yl)benzoyl]piperidin-4-yl}methyl)-N-(2,2,2-trifluoroethyl)-2H-indazol-5-carboxamide
151. 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{4-[2-(trifluoromethyl)pyrimidin-5-yl]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
152. 4-methyl-N-(2,2,2-trifluoroethyl)-2-[(1-{4-[6-(trifluoromethyl)pyridin-2-yl]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
153. 2-({1-[4-(4-cyanophenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
154. 2-{[1-(4-bromo-3-methylbenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
155. 2-{[1-(4-tert-butylbenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
156. 2-({1-[4-(1-hydroxy-1-methylethyl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
157. 2-{[1-(4-cyclohexylbenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
158. 2-({1-[4-(1-cyano-1-methylethyl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
159. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(pyrimidin-2-yloxy)benzoyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide
160. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(3-pyridyloxy)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide
161. N-(2-methoxyethyl)-4-methyl-2-{[1-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}benzoyl)-piperidin-4-yl]methyl}-2H-indazol-5-carboxamide
162. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(2-pyridyloxy)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide

163. N-(2-methoxyethyl)-4-methyl-2-{[1-(4-{[4-(trifluoromethyl)pyrimidin-2-yl]oxy}-benzoyl)piperidin-4-yl]methyl}-2H-indazol-5-carboxamide
164. N-(2-methoxyethyl)-4-methyl-2-{[1-(4-{[6-(trifluoromethyl)pyridin-3-yl]oxy}benzoyl)-piperidin-4-yl]methyl}-2H-indazol-5-carboxamide
165. N-(2-methoxyethyl)-4-methyl-2-{[1-(4-{[6-(trifluoromethyl)pyridin-2-yl]oxy}benzoyl)-piperidin-4-yl]methyl}-2H-indazol-5-carboxamide
166. 2-({1-[(4'-methoxybiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
167. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(3,4,5,6-tetrahydro-2H-pyran-4-yloxy)benzoyl]-piperidin-4-yl}methyl)-2H-indazol-5-carboxamide
168. N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[3-(trifluoromethyl)phenoxy]benzoyl}piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
169. 2-[(1-{4-[(5-cyanopyridin-2-yl)oxy]benzoyl}piperidin-4-yl)methyl]-N-(2-methoxy-ethyl)-4-methyl-2H-indazol-5-carboxamide
170. 2-[(1-{4-[(5-chloropyridin-2-yl)oxy]benzoyl}piperidin-4-yl)methyl]-N-(2-methoxy-ethyl)-4-methyl-2H-indazol-5-carboxamide
171. 2-({1-[4-(2,4-difluorophenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
172. 2-({1-[4-(3,4-difluorophenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
173. N-(2-methoxyethyl)-4-methyl-2-[(1-{[4'-(trifluoromethyl)biphenyl-4-yl]carbonyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
174. 2-({1-[4-(3-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
175. 2-{[1-(2-fluoro-4-isopropoxybenzoyl)piperidin-4-yl]methyl}-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
176. 2-({1-[(3-fluoro-3',4'-dimethylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
177. 2-({1-[(2',3-difluoro-4'-methoxybiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
178. 2-({1-[4-(difluoromethoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
179. 2-({1-[4-(2-fluorophenoxy)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
180. 2-({1-[(4'-cyano-2'-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

181. 2-({1-[4-(5-chloropyridin-2-yl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
182. N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[6-(trifluoromethyl)pyridin-2-yl]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
183. N-(2-methoxyethyl)-2-({1-[(4'-methoxy-2'-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-4-methyl-2H-indazol-5-carboxamide
184. 2-({1-[(4'-chloro-2'-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
185. 2-[(1-{[4'-(1-cyano-1-methylethyl)biphenyl-4-yl]carbonyl}piperidin-4-yl)methyl]-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
186. N-(2-methoxyethyl)-2-({1-[4-(5-methoxypyridin-2-yl)benzoyl]piperidin-4-yl}methyl)-4-methyl-2H-indazol-5-carboxamide
187. N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[6-(trifluoromethyl)pyridin-3-yl]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
188. N-(2-methoxyethyl)-2-({1-[4-(6-methoxypyridin-3-yl)benzoyl]piperidin-4-yl}methyl)-4-methyl-2H-indazol-5-carboxamide
189. 2-({1-[(4'-fluoro-2'-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
190. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(6-methylpyridin-3-yl)benzoyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide
191. N-(2-methoxyethyl)-2-({1-[4-(6-methoxypyridin-2-yl)benzoyl]piperidin-4-yl}methyl)-4-methyl-2H-indazol-5-carboxamide
192. N-(2-methoxyethyl)-4-methyl-2-({1-[4-(2-methylpyrimidin-5-yl)benzoyl]piperidin-4-yl}methyl)-2H-indazol-5-carboxamide
193. 2-({1-[(4'-fluoro-2'-methoxybiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
194. 2-({1-[(4'-chloro-2'-methoxybiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
195. N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[2-(trifluoromethyl)pyrimidin-5-yl]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
196. 2-({1-[(4'-chloro-2'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
197. 2-({1-[(2'-chloro-4'-fluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
198. 2-({1-[4-(5-chloropyridin-3-yl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide

199. 2-({1-[4-(5-fluoropyridin-3-yl)benzoyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
200. N-(2-methoxyethyl)-4-methyl-2-[(1-{4-[5-(trifluoromethyl)pyridin-3-yl]benzoyl}-piperidin-4-yl)methyl]-2H-indazol-5-carboxamide
201. 2-[(1-{[4'-(1-hydroxy-1-methylethyl)biphenyl-4-yl]carbonyl}piperidin-4-yl)methyl]-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
202. 2-({1-[(3',5'-difluorobiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxy-ethyl)-4-methyl-2H-indazol-5-carboxamide
203. 2-({1-[(4'-fluoro-2-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxy-ethyl)-4-methyl-2H-indazol-5-carboxamide
204. 2-({1-[(3',5'-difluoro-2-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}methyl)-N-(2-methoxyethyl)-4-methyl-2H-indazol-5-carboxamide
205. N-(2-methoxyethyl)-4-methyl-2-({1-[3-methyl-4-(3-pyridyl)benzoyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide
206. N-(2-methoxyethyl)-4-methyl-2-({1-[3-methyl-4-(4-pyridyl)benzoyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide and
207. N-(2-methoxyethyl)-4-methyl-2-({1-[(2-methylbiphenyl-4-yl)carbonyl]piperidin-4-yl}-methyl)-2H-indazol-5-carboxamide

7. Use of the compounds according to formula I for the production of a drug containing suitable formulation and carrier substances.

8. Use of the drugs according to Claim 7, characterized in that the drug is used for the prophylaxis and treatment of diseases.

9. Use of the compounds according to Claim 1 - 6 and the drugs according to Claim 7 for fertility control/contraception.

10. Use of the drugs according to Claim 7, for the prophylaxis and direct treatment of diseases which are causally linked with the EP_2 receptor, or of diseases which can be treated by influencing the EP_2 receptor.

11. Use of the drugs according to Claim 7 for the prophylaxis and treatment of endometriosis.

12. Use of the drugs according to Claim 7 for the prophylaxis and treatment of menstrual complaints, where the menstrual problems can be severe and persistent bleeding, irregular bleeding and pains.

13. Use of the drugs according to Claim 7 for the prophylaxis and treatment of fibroids (myomas).

14. Use of the drugs according to Claim 7 for the prophylaxis and treatment of cancer, where the cancer diseases can be lung, intestinal, breast, skin, prostate or oesophageal cancer and leukaemia.

15. Use of the drugs according to Claim 7 for the prophylaxis and treatment of arteriosclerosis.

16. Use of the drugs according to Claim 7 for the prophylaxis and treatment of neurodegenerative, neuroinflammatory and ischaemic diseases, where the diseases can be Alzheimer's disease, Parkinson's disease, ALS, stroke and multiple sclerosis.

17. Use of the drugs according to Claim 7 for the prophylaxis and treatment of polycystic kidney diseases.

18. Use of the drugs according to Claim 7 for the prophylaxis and treatment of pain, where the pain can be inflammatory hyperalgesia.

19. Use of the drugs according to Claim 7 for the prophylaxis and treatment of infectious diseases of the lung.

20. Use of the drugs according to Claim 7 for the prophylaxis and treatment of chronic obstructive pulmonary diseases.

21. Use of the drugs according to Claim 7 for the prophylaxis and treatment of intestinal inflammatory diseases, where the intestinal inflammatory diseases can be Crohn's disease and ulcerative colitis.

22. Use of the drugs according to Claim 7 for the prophylaxis and treatment in bone marrow transplantation operations.

23. Use of the drugs according to Claim 7 for the prophylaxis and treatment of pathological eye diseases, where the pathological eye diseases can be Graves' disease.

24. Use of the drugs according to Claim 7 for the prophylaxis and treatment of aneurysms.

25. Use of the drugs according to Claim 7 for the prophylaxis and treatment of vascular damage and the Kawasaki syndrome.

26. Use of the drugs according to Claim 7 for the prophylaxis and treatment of arthritis.

27. Drug containing a compound of the general formula (I) in combination with a COX inhibitor for the treatment of diseases, wherein the COX inhibitors can be selected from the following list: aspirin, naproxen, indomethacin, meloxicam, ibuprofen, ketoprofen, piroxicam, tenoxicam, nimesulide, mefanemic acid, ketoralac, celecoxib (4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulphonamide), parecoxib (N-[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulphonylpropionamide), rofecoxib (4-(4-mesylphenyl)-3-phenylfuran-(5H)-one), valdecoxib (4-[5-methyl-3-phenyl-4-isoxazoyl)benzenesulphonamide), NS-398 (N-methyl-2-cyclohexanoxy-4-nitrobenzene-sulphonamide), lumiracoxib [2-(2'-chloro-6'-fluorophenyl)-amino-5-methylbenzene-acetic acid], ceracoxib and etoricoxib.

28. Drug according to Claim 27, where the diseases are infectious diseases, cancer, cardiovascular diseases, angiogenic diseases, uterine contraction disorders, pain, inflammatory diseases, neuroinflammatory diseases, neurodegenerative diseases, autoimmune diseases, immunodependent diseases/therapies, nephrological diseases and ophthalmological diseases and where the drugs can also be used for the treatment of pain and in transplantation and for fertility control.

29. Use of the compounds of the general formula I, according to Claims 1 - 6, in the form of a pharmaceutical preparation for enteral, parenteral, vaginal, intrauterine and oral administration.

30. Method for the preparation of the compounds of the general formula (I), characterized in that a compound of the general formula (VIII) is reacted with an amine of the general formula (XI), where R^1, R^2, R^3, R^4, X, Ar, m and n have the meaning stated in Claim 1.

31. Method for the preparation of the compounds of the general formula (I), characterized in that a compound of the general formula (VI) is reacted with an amine of the general formula (XI), where R^1, R^2, R^3, R^4, X, Ar, m and n have the meaning stated in Claim 1, and carbon monoxide or a carbon monoxide source such as for example molybdenum hexacarbonyl, under palladium(0) catalysis.

32. Method for the preparation of the compounds of the general formula (I), characterized in that a compound of the general formula (XV) is reacted with a carboxylic acid (Y = OH), a carboxylic acid chloride (Y = Cl) or anhydride (Y = O-C(O)-O-$CH_2(CH_3)CH_3$) of the general formula (IX), where R^1, R^2, R^3, R^4, X, Ar, m, n have the meaning stated in Claim 1.

33. Method for the preparation of the compounds of the general formula (I), characterized in that a compound of the general formula (XVI), wherein LG′ for example means Br or I, is reacted with a boronic acid or a boronic acid ester of the general formula (XVIII), where R^1, R^2, R^3, R^4, X, Ar, m and n have the meaning stated in Claim 1.

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A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/06 C07D401/14 C07D403/06 C07D403/14 C07D407/14
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A61K31/506 A61K31/5377 A61P15/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

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	DE 10 2009 049662 A1 (BAYER SCHERING PHARMA AG [DE]) 14 April 2011 (2011-04-14) cited in the application claims 1, 8-26	1-33
A	WO 2009/063365 A1 (PFIZER LTD [GB]; SKERRATT SARAH ELIZABETH [GB]; DACK KEVIN NEIL [GB]) 22 May 2009 (2009-05-22) cited in the application claims 1-14	1-33

☐ 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
14 January 2013	22/01/2013

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	Sotoca Usina, E

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2012/073556

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 102009049662 A1	14-04-2011	NONE	
WO 2009063365 A1	22-05-2009	CA 2705368 A1	22-05-2009
		EP 2222665 A1	01-09-2010
		JP 2011503169 A	27-01-2011
		US 2010256109 A1	07-10-2010
		WO 2009063365 A1	22-05-2009

NUEVOS *2H*–INDAZOLES COMO ANTAGONISTAS DEL RECEPTOR EP_2

La presente invención se refiere a nuevos antagonistas del receptor EP_2, su producción y su uso como fármacos y preparaciones farmacéuticas que contienen los nuevos *2H*–indazoles.

Se sabe desde hace tiempo que las prostaglandinas son moléculas clave en los procesos de la biología reproductiva femenina como, por ejemplo, la regulación de la ovulación y la fertilización. Los efectos sobre las contracciones uterinas, implantación, deciduación (por ejemplo, formación de la placenta) y menstruación también fueron descritos o son objeto de estudios científicos. Las prostaglandinas también desempeñan un papel importante en los cambios patológicos en el tracto reproductivo, incluyendo menorragia, dismenorrea, endometriosis, fibromas (miomas) y cáncer y, en general, se conocen en inflamación (por ejemplo, enfermedad de Crohn), infecciones (por ejemplo, infecciones bacterianas) y procesos neurodegenerativos (por ejemplo, Alzheimer, ALS) y funciones en la defensa inmunológica, angiogénesis, dolor, curación de heridas e interacciones con el sistema endócrino (por ejemplo, inducción de aromatasa). Hasta la fecha, el mecanismo a través del cual las prostaglandinas efectúan los cambios no se ha dilucidado por completo. Hallazgos

recientes indican que las prostaglandinas, sus receptores y sus vías de transducción de señales están incluidos en procesos tales como angiogénesis, apoptosis, proliferación y en procesos inflamatorios/antiinflamatorios.

Los efectos de las prostaglandinas son mediados a través de sus receptores acoplados con la proteína G, que están ubicados en la membrana celular. La prostaglandina E_2 (PGE_2) es de interés particular, la cual efectúa una gran variedad de acciones celulares por unión con subtipos de receptores funcionalmente diferentes, a saber, los receptores EP_1, EP_2, EP_3 y EP_4. Los subtipos de receptores a los que se une la prostaglandina E_2 parecen ser de particular importancia para las acciones mediadas por receptores que están implicados en la regulación de la fertilidad. De esta manera, se podría mostrar que las funciones reproductivas están alteradas en los ratones *knockout* EP_2 ($EP_2^{-/-}$), por ejemplo, en ratones que ya no tienen un receptor funcional de PGE_2 subtipo EP_2 y que estos animales tienen una "camada" más pequeña (Matsumoto y col., 2001, Biology of Reproduction 64, 1557–1565). Del mismo modo, se pudo demostrar que estos ratones knockout EP_2 (Hizaki y col., 1999, Proc Natl Acad Sci U. S. A, 31 de agosto; 96(18):10501–10506) desempeñan

una expansión del cumulus marcadamente menor y una subfertilidad severa, que se ha de considerar como causalmente ligada a procesos reproductivos reducido tales como ovulación y fertilización.

Conforme a ello, el receptor EP_2 es un blanco importante para el desarrollo de fármacos para la regulación de fertilidad femenina. La existencia de las 4 subclases del receptor PGE_2 abre la posibilidad de un desarrollo dirigido de compuestos selectivamente activos. Previamente, sin embargo, no se conocía casi ningún antagonista selectivo del receptor EP_2, dado que la mayoría de los compuestos conocidos también se unen con los otros subtipos de receptor PGE_2, tales como, por ejemplo, el receptor EP_4 u otros receptores de prostaglandina tal como el receptor DP.

Los antagonistas del receptor EP_2 se describen, por ejemplo, en la solicitud US 2005059742 y la solicitud EP 1467738 (Jabbour, Medical Research Council). Se reivindica un método en el que se puede usar un antagonista de EP_2 y/o EP_4 para el tratamiento de menorragia y dismenorrea. Se describe AH6809 como un antagonista del receptor EP_2 o EP_4 y no se describen otros antagonistas específicos ni nuevos compuestos.

En la solicitud WO 03/016254, Ono Pharmaceutical reivindica la producción de ácidos arilcarboxílicos o

derivados saturados de ácido carboxílico que son grupo arilo o o sustituidos con heterociclo, entre otros, como antagonistas del receptor PGE_2. Los compuestos descritos se reivindican para el tratamiento de una gran cantidad de enfermedades, incluyendo también enfermedades alérgicas, enfermedad de Alzheimer, dolor, aborto, problemas menstruales, menorragia y dismenorrea, endometriosis, enfermedades óseas, isquemia, etc. Sin embargo, los compuestos descritos se caracterizan por una afinidad particularmente alta por el receptor EP_3. En otra solicitud (WO 04/032964), se describen nuevos compuestos que también se caracterizan por una afinidad particularmente alta para el receptor EP_3, pero también se usan como antagonistas de EP_2, para el tratamiento y la prevención de enfermedades alérgicas.

En las solicitudes de la empresa Applied Research Systems WO 03/053923 (pirrolidinas sustituidas) o WO 03/035064 (pirazolidionas sustituidas), se reivindican compuestos para el tratamiento de enfermedades que se asocian con prostaglandinas, tales como, por ejemplo, infertilidad, hipertensión y osteoporosis. Los compuestos se unen con los subtipos de receptores EP_4 y EP_2.

En la solicitud WO 03/064391 (Pfizer Products), se

describen metabolitos de ácido [3-[[N-(4-*tert*-butilbencil)-(piridin-3-ilsulfonil)amino]metil]acético, que inhiben la unión de la [^{3}H] prostaglandina E_2 con el receptor EP_2. Se describe el uso de estos metabolitos para el tratamiento de osteoporosis.

En la solicitud US 2005124577, Tani y col. reivindican derivados de 8-azaprostaglandina para el tratamiento de enfermedades inmunológicas, enfermedades alérgicas, parto prematuro, aborto, etc. Los compuestos se unen con el receptor EP_2 y EP_4.

En las solicitudes de patente de Bayer Schering Pharma AG (WO 2007/057232, WO 2007/071456, WO 2008/028689, WO 2008/028690 WO 2008/028691, WO 2008/0152099, WO 2008/0152097, WO 2008/0152094, WO 2009/007421, WO 2009/007422) y DE 10 2009 049 662 A1, se reivindican por primera vez antagonistas selectivos de los receptores EP_2.

En las solicitudes de Summit Corporation PLC (documento WO 2007/091107) y CM Sun y col. (WO 2008/070599), se describen *2H*-indazoles, pero no para el tratamiento de trastornos de la fertilidad.

En las solicitudes de Pfizer WO 2009/063365 y WO 2008/139287, se reivindican azetidinas y en la solicitud WO 2010/052625, se reivindican pirrolidonas como antagonistas del receptor EP_2 y su uso para el

tratamiento de condiciones mediadas por EP_2 tales como endometriosis y leiomiomatos.

En una publicación (British Journal of Pharmacology (2011), 164, 1847–1856), Forselles y col. (Pfizer) describen antagonistas selectivos de los receptores EP_2. Los compuestos son azetidinas que desempeñan una influencia *in vivo* sobre el flujo sanguíneo. Los compuestos desempeñan una alta unión de proteínas.

En una publicación de P. M. Roveto y col. (239. ACS National Meeting of the Division of Medicinal Chemistry, 21–25 de marzo de 2010, San Francisco, Estados Unidos; MEDI 173), se describen nuevos tiazoles como antagonistas de EP_2.

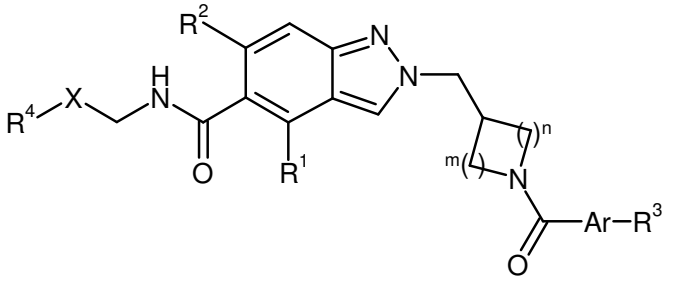
También se describen antagonistas del receptor EP_2 en la solicitud de Ligand Pharmaceuticals Inc. (documento WO 2010/008777). Estos compuestos son derivados bicíclicos de piridina. Los compuestos se reivindican para el tratamiento de dolor, pero también para el tratamiento de enfermedad de Alzheimer, esclerosis múltiple y trastornos de la fertilidad.

Para la regulación de los procesos que son responsables por último de la ovulación y fertilización y que, así, contribuyen con la inhibición de la fertilidad, se requieren otros antagonistas activos in

vivo del receptor EP_2 con mejores propiedades.

Así, la finalidad de la presente invención consistía en proporcionar otros antagonistas del receptor EP_2 con mejores propiedades que están disponibles in vivo y, así, son efectivos y estables.

Este problema se resolvió por medio de los compuestos de la fórmula general I,



(I),

en donde

R^1: significa H, alquilo C_1–C_2 o alquil C_1–C_2–oxi;

R^2: es H o metilo;

siempre que uno de los dos residuos R^1 o R^2 sea H;

X: es $-(CH_2)_1-$, $-(CH_2)_k-O-$, $-CH_2-S-$, $CH_2-S(O)_2-$, $-CH(CH_3)-$, $-CH(CH_3)-O-$ o $-C(CH_3)_2-O-$;

k: es 1 ó 2;

l: es 0, 1 ó 2;

R^4: es H, alquilo C_1–C_4, cicloalquilo C_3–C_4 o CH_2–cicloalquilo C_3–C_4;

y en el caso de que X: $-CH_2-$ o $-CH(CH_3)-$

R^4: es adicionalmente un residuo de heterociclilo de 4–6 miembros;

y en el caso de que X: $-(CH_2)_1-$ o $-CH(CH_3)-$

R^4: es adicionalmente CN;

o

X junto con R^4 forman un residuo de heterociclilo de 4–6 miembros por medio de una ligación de carbono de anillo;

m: es 1 ó 2;

n: es 1 ó 2;

Ar: es un residuo de arilo de 6–10 miembros o de hetarilo de 5–10 miembros,

R^3: es halógeno, CN, SF_5, alquilo C_1–C_4, cicloalquilo C_3–C_6, heterociclilo C_4–C_6, O–alquilo C_1–C_4, O–cicloalquilo C_3–C_6, O–heterociclilo C_4–C_6, S–alquilo C_1–C_4, $S(O)_2$–alquilo C_1–C_4, Ar´, O–Ar´, $C(CH_3)_2$–CN o $C(CH_3)_2$–OH;

Ar´: un residuo de arilo de 6 miembros o residuo de heteroarilo de 5–6 miembros opcionalmente mono– o disustituido;

en donde los sustituyentes están seleccionados de F, Cl, CN, alquilo C_1–C_4, O–alquilo C_1–C_4, $C(CH_3)_2$–CN, $C(CH_3)_2$–OH y $C(O)NH_2$;

y sus isómeros, diastereómeros, enantiómeros y sales o clatratos de ciclodextrina, para la producción de fármacos que superan las desventajas conocidas y tienen mejores propiedades tales como buena actividad, buena solubilidad y estabilidad *in vivo*.

Los compuestos de acuerdo con la invención tienen una acción antagonista sobre el receptor EP_2 y, así, entre otros, sirven para el control de la fertilidad femenina.

El alquilo C_1–C_2 o alquilo C_1–C_4 deberían entenderse cada uno como un residuo de alquilo lineal o ramificado tales como, por ejemplo, metilo, etilo, propilo, isopropilo, butilo, isobutilo, *sec*–butilo o *tert*–butilo.

Los residuos de alquilo pueden ser opcionalmente mono– o polisustituidos con flúor.

Los átomos de hidrógeno se pueden reemplazar opcionalmente por deuterio.

Alcoxi C_1–C_2 o alcoxi C_1–C_4 se ha de entender como residuo lineal o ramificado de la fórmula alquil–O–, tales como, por ejemplo, metoxi, etoxi, n–propoxi, isopropoxi, n–butoxi, *sec*–butoxi, isobutoxi o *tert*–butiloxi.

Los residuos de alcoxi pueden ser mono– o polisustituidos con flúor.

Cicloalquilo C_3–C_6 se ha de entender como anillos alquilo monocíclicos tales como ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo.

Los residuos de cicloalquilo pueden ser mono– o polisustituidos con flúor.

Heterociclilo de 4-6 miembros se ha de entender como anillos monocíclicos que, en lugar de los átomos de carbono, contienen uno o varios heteroátomos tales como oxígeno, azufre y/o nitrógeno o un grupo hetero tales como -S(O)- o $-SO_2-$. El enlace de unión puede estar en cualquier átomo de carbono o en un átomo de nitrógeno.

Por ejemplo, se pueden mencionar azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, 1,4-diazepanilo, morfolinilo, tiomorfolinilo, oxetanilo, tetrahidrofuranilo, tetrahidropiranilo, 1,4-dioxanilo y 2-oxo-oxazolidinilo.

Los residuos de heterociclilo pueden ser mono- o polisustituidos con flúor, hidroxi, metoxi o con oxo.

Halógeno se ha de entender en cada caso como flúor, cloro, bromo o yodo.

El residuo de arilo de C_6-C_{10} miembros en cada caso comprende 6 - 10 átomos de carbono y puede ser benzocondensado. Se pueden mencionar fenilo y naftilo.

El residuo de arilo de C_6-C_{10} miembros puede ser monosustituido opcionalmente con flúor, cloro o un grupo metilo.

El residuo de heteroarilo C_5-C_{10} se ha de entender como sistemas de anillos mono- o bicíclicos que contienen cada uno 5 - 10 átomos de anillo y que, en

lugar del carbono, pueden contener uno o varios heteroátomos iguales o diferentes, tales como oxígeno, azufre o nitrógeno. El enlace de ligación puede estar en cualquier átomo de carbono o en un átomo de nitrógeno.

Por ejemplo, se pueden mencionar tienilo, tiazolilo, furilo, pirrolilo, oxazolilo, imidazolilo, pirazolilo, isoxazolilo, isotiazolilo, oxadiazolilo, triazolilo, tiadiazolilo, tetrazolilo, piridilo, piridazinilo, pirimidinilo, pirazinilo, triazinilo, ftalidilo, tioftalidilo, indolilo, isoindolilo, indazolilo, benzotiazolilo, benzofurilo, benzotienilo, bencimidazolilo, benzoxazolilo, azocinilo, indolizinilo, purinilo, isoquinolinilo, quinolinilo, quinolizinilo, quinazolinilo, quinoxalinilo, cinolinilo, ftalazinilo, 1,7- o 1,8-naftiridinilo y pteridinilo.

El residuo de heteroarilo de C_5-C_{10} miembros puede ser monosustituido opcionalmente con flúor, cloro o un grupo metilo.

Si está contenido un grupo funcional básico, son apropiadas las sales fisiológicamente compatibles de ácidos orgánicos e inorgánicos tales como, entre otros, ácido clorhídrico, ácido sulfúrico, ácido fosfórico, ácido cítrico y ácido tartárico.

Se prefieren compuestos de la fórmula I, en donde

R^1, R^2: son H o metilo;

siempre que uno de los dos residuos R^1 o R^2 sea H;

X: es $-(CH_2)_l-$ o $-(CH_2)_k-O-$;

k: es 1 ó 2;

l: es 0, 1 ó 2;

R^4: es alquilo C_1–C_4, cicloalquilo C_3–C_4 o CH_2–cicloalquilo C_3–C_4;

m, n: es 2;

y sus isómeros, diastereómeros, enantiómeros y sales o clatratos de ciclodextrina y R^3, Ar y Ar´ tienen los significados antes mencionados.

También se prefieren los compuestos de la fórmula I, en donde

R^1, R^2: significan H o metilo;

siempre que uno de los dos residuos R^1 o R^2 sea H;

X: es $-(CH_2)_l-$ o $-(CH_2)_k-O-$;

k: es 1 ó 2;

l: es 0, 1 ó 2;

R^4: es alquilo C_1–C_4, -cicloalquilo C_3–C_4 o CH_2–cicloalquilo C_3–C_4;

m, n: es 1;

y sus isómeros, diastereómeros, enantiómeros y sales o clatratos de ciclodextrina y R^3, Ar y Ar´ tienen los significados antes mencionados.

También se prefieren los compuestos de la fórmula I, en donde

R^1: significa un grupo metilo;

R^2: es H;

X: es $-(CH_2)_l-$ o $-(CH_2)_k-O-$;

k: es 1;

l: es 0 ó 1;

R^4: es alquilo C_1-C_4, cicloalquilo C_3-C_4 o CH_2-cicloalquilo C_3-C_4;

m, n: es 2;

Ar: es un residuo de fenilo;

y sus isómeros, diastereómeros, enantiómeros y sales o clatratos de ciclodextrina y R^3 y Ar´ tienen los significados antes mencionados.

Además, se prefieren los compuestos de la fórmula I, en donde

R^1: significa un grupo metilo;

R^2: es H;

X: es $-(CH_2)_l-$ o $-(CH_2)_k-O-$;

k: es 1;

l: es 0 ó 1;

R^4: es alquilo C_1-C_4, cicloalquilo C_3-C_4 o CH_2-cicloalquilo C_3-C_4;

m, n: es 1;

Ar: es un residuo de fenilo;

y sus isómeros, diastereómeros, enantiómeros y sales o clatratos de ciclodextrina y R^3 y Ar´ tienen los significados antes mencionados.

Los siguientes compuestos de acuerdo con la presente invención son particularmente preferidos:

1. 2-{[1-(4-ciano-2-fluorobenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
2. 2-{[1-(4-*tert*-butoxibenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
3. 2-({1-[4-(4-fluorofenoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
4. N-(2-metoxietil)-4-metil-2-{[1-(4-morfolinobenzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida
5. 2-({1-[(4'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
6. 2-{[1-(2-fluoro-4-mesilbenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
7. 2-{[1-(2-fluoro-4-metoxibenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

8. 2-{[1-(4-bromo-2-fluorobenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
9. 2-{[1-(2-fluoro-4-metilbenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
10. 2-({1-[2-fluoro-4-(trifluorometil)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
11. N-(2-metoxietil)-4-metil-2-({1-[4-(pentafluoro-λ^6-sulfanil)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida
12. N-(2-metoxietil)-4-metil-2-{[1-(4-metilbenzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida
13. 2-({1-[4-(4-clorofenoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
14. N-(2-metoxietil)-4-metil-2-({1-[4-(4-metilfenoxi)benzoil]piperidin-4-il}-metil)-2H-indazol-5-carboxamida
15. 2-({1-[4-(4-*tert*-butilfenoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
16. N-(2-metoxietil)-4-metil-2-[(1-{4-[4-

(trifluorometil)fenoxi]benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida

17. N-(2-metoxietil)-2-({1-[4-(4-metoxifenoxi)benzoil]piperidin-4-il}metil)-4-metil-2H-indazol-5-carboxamida
18. N-(2-metoxietil)-4-metil-2-{[1-(4-fenoxibenzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida
19. 2-{[1-(4-ciclopropilbenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
20. 2-{[1-(4-metoxibenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
21. 2-{[1-(4-fluorobenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
22. N-(2-metoxietil)-4-metil-2-({1-[4-(trifluorometil)benzoil]piperidin-4-il}-metil)-2H-indazol-5-carboxamida
23. 2-{[1-(2-metoxibenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
24. N-(2-metoxietil)-4-metil-2-[(1-{4-[(trifluorometil)sulfonil]benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida
25. N-(2-metoxietil)-4-metil-2-({1-[3-(trifluorometil)benzoil]piperidin-4-il}-metil)-2H-indazol-5-carboxamida

26. N-(2-metoxietil)-4-metil-2-{[1-(3-metilbenzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida
27. 2-{[1-(3-clorobenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
28. 2-({1-[4-(4-carbamoilfenoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
29. 2-({1-[4-(ciclopentiloxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
30. 2-({1-[4-(difluorometil)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
31. 2-{[1-(4-cianobenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
32. 2-({1-[4-(1H-imidazol-1-il)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
33. N-(2-metoxietil)-4-metil-2-({1-[4-(oxazol-2-il)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida
34. N-(2-metoxietil)-4-metil-2-({1-[4-(oxazol-5-il)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida

35. N-(2-metoxietil)-4-metil-2-({1-[4-(isoxazol-5-il)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida
36. N-(2-metoxietil)-4-metil-2-({1-[4-(1H-pirazol-1-il)benzoil]piperidin-4-il}-metil)-2H-indazol-5-carboxamida
37. N-(2-metoxietil)-4-metil-2-({1-[4-(1H-1,2,4-triazol-1-il)benzoil]piperidin-4-il}-metil)-2H-indazol-5-carboxamida
38. 2-({1-[4-(difluorometoxi)-2-fluorobenzoil]piperidin-4-il}metil)-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida
39. 2-({1-[2-fluoro-4-(pirrolidin-1-il)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
40. 2-({1-[(3,4'-difluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
41. 2-({1-[(3-fluoro-4'-metoxibifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
42. 2-({1-[(3-fluoro-4'-metilbifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
43. 2-[(1-{[3-fluoro-3'-(trifluorometil)bifenil-4-

il]carbonil}piperidin-4-il)metil]-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

44. 2-[(1-{[3-fluoro-2'-(trifluorometoxi)bifenil-4-il]carbonil}piperidin-4-il)metil]-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
45. 2-({1-[(2'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
46. 2-({1-[(2',4'-difluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida
47. 2-({1-[(2-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
48. N-(2-metoxietil)-4-metil-2-({1-[(2'-metilbifenil-4-il)carbonil]piperidin-4-il}-metil)-2H-indazol-5-carboxamida
49. N-(2-metoxietil)-4-metil-2-({1-[4-(4-piridiloxi)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida
50. N-(2-metoxietil)-4-metil-2-({1-[4-(4H-1,2,4-triazol-4-il)benzoil]piperidin-4-il}-metil)-2H-indazol-5-carboxamida
51. 2-{[1-(2-fluoro-4-morfolinobenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-

carboxamida

52. 2-{[1-(4-bromobenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
53. N-(2-metoxietil)-4-metil-2-({1-[4-(trifluorometoxi)benzoil]piperidin-4-il}-metil)-2H-indazol-5-carboxamida
54. 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
55. N-(2-metoxietil)-4-metil-2-[(1-{4-[(trifluorometil)sulfanil]benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida
56. 4-metil-2-({1-[4-(pentafluoro-λ^6-sulfanil)benzoil]piperidin-4-il}metil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida
57. 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida
58. 4-metil-N-(2,2,2-trifluoroetil)-2-({1-[4-(trifluorometoxi)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida
59. 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-[2-(ciclopropilmetoxi)etil]-4-metil-2H-indazol-5-carboxamida
60. N-[2-(ciclopropilmetoxi)etil]-4-metil-2-{[1-(4-metilbenzoil)piperidin-4-il]-metil}-2H-indazol-5-

carboxamida

61. N-[2-(ciclopropilmetoxi)etil]-2-({1-[4-(4-fluorofenoxi)benzoil]piperidin-4-il}-metil)-4-metil-2H-indazol-5-carboxamida
62. N-[2-(ciclopropilmetoxi)etil]-4-metil-2-({1-[4-(trifluorometil)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida
63. N-[2-(ciclopropilmetoxi)etil]-2-({1-[(4'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-4-metil-2H-indazol-5-carboxamida
64. 2-{[1-(4-ciclopropilbenzoil)piperidin-4-il]metil}-N-[2-(ciclopropilmetoxi)etil]-4-metil-2H-indazol-5-carboxamida
65. 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metil-N-[2-(2,2,2-trifluoroetoxi)-etil]-2H-indazol-5-carboxamida
66. 4-metil-2-{[1-(4-metilbenzoil)piperidin-4-il]metil}-N-[2-(2,2,2-trifluoroetoxi)-etil]-2H-indazol-5-carboxamida
67. 2-({1-[4-(4-fluorofenoxi)benzoil]piperidin-4-il}metil)-4-metil-N-[2-(2,2,2-trifluoroetoxi)etil]-2H-indazol-5-carboxamida
68. 4-metil-N-[2-(2,2,2-trifluoroetoxi)etil]-2-({1-[4-(trifluorometil)benzoil]-piperidin-4-il}metil)-2H-indazol-5-carboxamida

69. 2-({1-[(4'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-4-metil-N-[2-(2,2,2-trifluoroetoxi)etil]-2H-indazol-5-carboxamida
70. 2-{[1-(4-ciclopropilbenzoil)piperidin-4-il]metil}-4-metil-N-[2-(2,2,2-trifluoro-etoxi)etil]-2H-indazol-5-carboxamida
71. 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-(2-isopropoxietil)-4-metil-2H-indazol-5-carboxamida
72. N-(2-isopropoxietil)-4-metil-2-{[1-(4-metilbenzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida
73. 2-({1-[4-(4-fluorofenoxi)benzoil]piperidin-4-il}metil)-N-(2-isopropoxietil)-4-metil-2H-indazol-5-carboxamida
74. N-(2-isopropoxietil)-4-metil-2-({1-[4-(trifluorometil)benzoil]piperidin-4-il}-metil)-2H-indazol-5-carboxamida
75. 2-({1-[(4'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-isopropoxietil)-4-metil-2H-indazol-5-carboxamida
76. 2-{[1-(4-ciclopropilbenzoil)piperidin-4-il]metil}-N-(2-isopropoxietil)-4-metil-2H-indazol-5-carboxamida
77. 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metil-N-[2-(trifluorometoxi)etil]-2H-indazol-5-

carboxamida

78. 2-({1-[4-(4-fluorofenoxi)benzoil]piperidin-4-il}metil)-4-metil-N-[2-(trifluoro-metoxi)etil]-2H-indazol-5-carboxamida
79. 2-({1-[(4'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-4-metil-N-[2-(trifluorometoxi)etil]-2H-indazol-5-carboxamida
80. 4-metil-N-[2-(trifluorometoxi)etil]-2-[(1-{4-[4-(trifluorometil)fenoxi]-benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida
81. N-(2-*tert*-butoxietil)-2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metil-2H-indazol-5-carboxamida
82. N-(2-*tert*-butoxietil)-2-({1-[4-(4-fluorofenoxi)benzoil]piperidin-4-il}metil)-4-metil-2H-indazol-5-carboxamida
83. N-(2-*tert*-butoxietil)-2-({1-[(4'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-4-metil-2H-indazol-5-carboxamida
84. N-(2-*tert*-butoxietil)-4-metil-2-[(1-{4-[4-(trifluorometil)fenoxi]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida
85. 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metil-N-{2-[(^{2}H3)metiloxi]-(^{2}H4)etil}-2H-indazol-5-carboxamida

86. 2-({1-[4-(4-fluorofenoxi)benzoil]piperidin-4-il}metil)-4-metil-N-{2-[(^{2}H3)metiloxi](^{2}H4)etil}-2H-indazol-5-carboxamida
87. 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
88. N-(2-metoxietil)-4-metil-2-[(1-{4-[(trifluorometil)sulfanil]benzoil}azetidin-3-il)metil]-2H-indazol-5-carboxamida
89. N-(2-metoxietil)-4-metil-2-({1-[4-(trifluorometoxi)benzoil]azetidin-3-il}-metil)-2H-indazol-5-carboxamida
90. 2-({1-[2-fluoro-4-(trifluorometil)benzoil]azetidin-3-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
91. 2-{[1-(4-cloro-2-fluorobenzoil)azetidin-3-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
92. 2-({1-[3-fluoro-4-(trifluorometil)benzoil]azetidin-3-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
93. 2-({1-[4-cloro-3-(trifluorometil)benzoil]azetidin-3-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
94. 2-{[1-(4-ciclopropilbenzoil)azetidin-3-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

95. N-(2-metoxietil)-4-metil-2-[(1-{4-[4-(trifluorometil)fenoxi]benzoil}azetidin-3-il)metil]-2H-indazol-5-carboxamida
96. 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida
97. 4-metil-N-(2,2,2-trifluoroetil)-2-({1-[4-(trifluorometoxi)benzoil]azetidin-3-il}-metil)-2H-indazol-5-carboxamida
98. 2-({1-[2-fluoro-4-(trifluorometil)benzoil]azetidin-3-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida
99. 4-metil-2-({1-[4-(pentafluoro-λ^6-sulfanil)benzoil]azetidin-3-il}metil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida
100. N-[2-(ciclopropiloxi)etil]-4-metil-2-({1-[4-(trifluorometoxi)benzoil]azetidin-3-il}metil)-2H-indazol-5-carboxamida
101. N-[2-(ciclobutiloxi)etil]-4-metil-2-({1-[4-(trifluorometoxi)benzoil]azetidin-3-il}metil)-2H-indazol-5-carboxamida
102. 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-N-[2-(ciclopropilmetoxi)etil]-4-metil-2H-indazol-5-carboxamida

103. N-[2-(ciclopropilmetoxi)etil]-2-({1-[4-(4-fluorofenoxi)benzoil]azetidin-3-il}-metil)-4-metil-2H-indazol-5-carboxamida
104. N-[2-(ciclopropilmetoxi)etil]-4-metil-2-{[1-(4-metilbenzoil)azetidin-3-il]-metil}-2H-indazol-5-carboxamida
105. 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-4-metil-N-[2-(trifluorometoxi)etil]-2H-indazol-5-carboxamida
106. N-(2-*tert*-butoxietil)-2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-4-metil-2H-indazol-5-carboxamida
107. N-[2-(ciclopropilmetoxi)etil]-2-({1-[(4'-fluorobifenil-4-il)carbonil]azetidin-3-il}metil)-4-metil-2H-indazol-5-carboxamida
108. 2-({1-[(4'-fluorobifenil-4-il)carbonil]azetidin-3-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
109. 2-({1-[4-(4-fluorofenoxi)benzoil]azetidin-3-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
110. 2-({1-[4-(4-fluorofenoxi)benzoil]azetidin-3-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida
111. 2-({1-[(4'-fluorobifenil-4-il)carbonil]azetidin-3-

il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

112. 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-4-metil-N-[2-(2,2,2-trifluoroetoxi)-etil]-2H-indazol-5-carboxamida
113. 4-metil-N-[2-(2,2,2-trifluoroetoxi)etil]-2-[(1-{4-[4-(trifluorometil)fenoxi]-benzoil}azetidin-3-il)metil]-2H-indazol-5-carboxamida
114. 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{4-[4-(trifluorometil)fenoxi]benzoil}-azetidin-3-il)metil]-2H-indazol-5-carboxamida
115. 2-({1-[4-(4-clorofenoxi)benzoil]azetidin-3-il}metil)-4-metil-N-(2,2,2-trifluoro-etil)-2H-indazol-5-carboxamida
116. 2-({1-[4-(4-clorofenoxi)benzoil]azetidin-3-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
117. N-(2-metoxietil)-4-metil-2-{[1-(4-{[5-(trifluorometil)piridin-2-il]oxi}benzoil)-azetidin-3-il]metil}-2H-indazol-5-carboxamida
118. 4-metil-N-(2,2,2-trifluoroetil)-2-{[1-(4-{[5-(trifluorometil)piridin-2-il] oxi}benzoil)azetidin-3-il]metil}-2H-indazol-5-carboxamida
119. 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-

etil-4-metil-2H-indazol-5-carboxamida

120. 2-({1-[4-(4-fluorofenoxi)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoro-etil)-2H-indazol-5-carboxamida
121. 2-({1-[4-(4-clorofenoxi)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoro-etil)-2H-indazol-5-carboxamida
122. 4-metil-2-({1-[4-(4-metilfenoxi)benzoil]piperidin-4-il}metil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida
123. 2-({1-[(4'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida
124. 4-metil-2-{[1-(4-morfolinobenzoil)piperidin-4-il]metil}-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida
125. 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{4-[(trifluorometil)sulfanil]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida
126. 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{4-[4-(trifluorometil)fenoxi]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida
127. 4-metil-N-(2,2,2-trifluoroetil)-2-{[1-(4-{[5-(trifluorometil)piridin-2-il]oxi}-benzoil)piperidin-4-il]metil}-2H-indazol-5-

carboxamida

128. 4-metil-N-(2,2,2-trifluoroetil)-2-{[1-(4-{[6-(trifluorometil)piridin-3-il]oxi}-benzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida
129. 4-metil-N-(2,2,2-trifluoroetil)-2-{[1-(4-{[6-(trifluorometil)piridin-2-il]oxi}-benzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida
130. 2-({1-[4-(4-cianofenoxi)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoro-etil)-2H-indazol-5-carboxamida
131. 2-({1-[4-(3-fluorofenoxi)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoro-etil)-2H-indazol-5-carboxamida
132. 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{4-[3-(trifluorometil)fenoxi]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida
133. 2-[(1-{4-[(5-cianopiridin-2-il)oxi]benzoil}piperidin-4-il)metil]-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida
134. 2-[(1-{4-[(5-cloropiridin-2-il)oxi]benzoil}piperidin-4-il)metil]-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida
135. 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{4-[5-

(trifluorometil)piridin-2-il]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida

136. 2-({1-[4-(2,4-difluorofenoxi)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida
137. 2-({1-[4-(3,4-difluorofenoxi)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida
138. 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{[4'-(trifluorometil)bifenil-4-il]carbonil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida
139. 2-{[1-(4-bromobenzoil)piperidin-4-il]metil}-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida
140. 2-({1-[4-(5-cloropiridin-2-il)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida
141. 2-({1-[(4'-metoxi-2'-metilbifenil-4-il)carbonil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida
142. 4-metil-2-({1-[4-(6-metilpiridin-3-il)benzoil]piperidin-4-il}metil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida
143. 2-({1-[(4'-fluoro-2'-metoxibifenil-4-il)carbonil]piperidin-4-il}metil)-4-metil-N-

(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

144. 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{4-[6-(trifluorometil)piridin-3-il]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida

145. 2-({1-[4-(6-metoxipiridin-3-il)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

146. 2-({1-[4-(6-metoxipiridin-2-il)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

147. 4-metil-2-({1-[4-(5-metilpiridin-2-il)benzoil]piperidin-4-il}metil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

148. 2-({1-[4-(5-fluoropiridin-2-il)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

149. 2-({1-[4-(5-metoxipiridin-2-il)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

150. 4-metil-2-({1-[4-(2-metilpirimidin-5-il)benzoil]piperidin-4-il}metil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

151. 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{4-[2-(trifluorometil)pirimidin-5-il]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida

152. 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{4-[6-(trifluorometil)piridin-2-il]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida
153. 2-({1-[4-(4-cianofenoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
154. 2-{[1-(4-bromo-3-metilbenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
155. 2-{[1-(4-*tert*-butilbenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
156. 2-({1-[4-(1-hidroxi-1-metiletil)benzoil]piperidin-4-il}metil)-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida
157. 2-{[1-(4-ciclohexilbenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
158. 2-({1-[4-(1-ciano-1-metiletil)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
159. N-(2-metoxietil)-4-metil-2-({1-[4-(pirimidin-2-iloxi)benzoil]piperidin-4-il}-metil)-2H-indazol-5-carboxamida
160. N-(2-metoxietil)-4-metil-2-({1-[4-(3-piridiloxi)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida

161. N-(2-metoxietil)-4-metil-2-{[1-(4-{[5-(trifluorometil)piridin-2-il]oxi}benzoil)-piperidin-4-il]metil}-2H-indazol-5-carboxamida
162. N-(2-metoxietil)-4-metil-2-({1-[4-(2-piridiloxi)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida
163. N-(2-metoxietil)-4-metil-2-{[1-(4-{[4-(trifluorometil)pirimidin-2-il]oxi}-benzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida
164. N-(2-metoxietil)-4-metil-2-{[1-(4-{[6-(trifluorometil)piridin-3-il]oxi}benzoil)-piperidin-4-il]metil}-2H-indazol-5-carboxamida
165. N-(2-metoxietil)-4-metil-2-{[1-(4-{[6-(trifluorometil)piridin-2-il]oxi}benzoil)-piperidin-4-il]metil}-2H-indazol-5-carboxamida
166. 2-({1-[(4'-metoxibifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
167. N-(2-metoxietil)-4-metil-2-({1-[4-(3,4,5,6-tetrahidro-2H-piran-4-iloxi)benzoil]-piperidin-4-il}metil)-2H-indazol-5-carboxamida
168. N-(2-metoxietil)-4-metil-2-[(1-{4-[3-(trifluorometil)fenoxi]benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida

169. 2-[(1-{4-[(5-cianopiridin-2-il)oxi]benzoil}piperidin-4-il)metil]-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida
170. 2-[(1-{4-[(5-cloropiridin-2-il)oxi]benzoil}piperidin-4-il)metil]-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida
171. 2-({1-[4-(2,4-difluorofenoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
172. 2-({1-[4-(3,4-difluorofenoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
173. N-(2-metoxietil)-4-metil-2-[(1-{[4'-(trifluorometil)bifenil-4-il]carbonil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida
174. 2-({1-[4-(3-fluorofenoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
175. 2-{[1-(2-fluoro-4-isopropoxibenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
176. 2-({1-[(3-fluoro-3',4'-dimetilbifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
177. 2-({1-[(2',3-difluoro-4'-metoxibifenil-4-

il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

178. 2-({1-[4-(difluorometoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
179. 2-({1-[4-(2-fluorofenoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
180. 2-({1-[(4'-ciano-2'-metilbifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
181. 2-({1-[4-(5-cloropiridin-2-il)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
182. N-(2-metoxietil)-4-metil-2-[(1-{4-[6-(trifluorometil)piridin-2-il]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida
183. N-(2-metoxietil)-2-({1-[(4'-metoxi-2'-metilbifenil-4-il)carbonil]piperidin-4-il}metil)-4-metil-2H-indazol-5-carboxamida
184. 2-({1-[(4'-cloro-2'-metilbifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
185. 2-[(1-{[4'-(1-ciano-1-metiletil)bifenil-4-il]carbonil}piperidin-4-il)metil]-N-(2-

metoxietil)-4-metil-2H-indazol-5-carboxamida

186. N-(2-metoxietil)-2-({1-[4-(5-metoxipiridin-2-il)benzoil]piperidin-4-il}metil)-4-metil-2H-indazol-5-carboxamida

187. N-(2-metoxietil)-4-metil-2-[(1-{4-[6-(trifluorometil)piridin-3-il]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida

188. N-(2-metoxietil)-2-({1-[4-(6-metoxipiridin-3-il)benzoil]piperidin-4-il}metil)-4-metil-2H-indazol-5-carboxamida

189. 2-({1-[(4'-fluoro-2'-metilbifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

190. N-(2-metoxietil)-4-metil-2-({1-[4-(6-metilpiridin-3-il)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida

191. N-(2-metoxietil)-2-({1-[4-(6-metoxipiridin-2-il)benzoil]piperidin-4-il}metil)-4-metil-2H-indazol-5-carboxamida

192. N-(2-metoxietil)-4-metil-2-({1-[4-(2-metilpirimidin-5-il)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida

193. 2-({1-[(4'-fluoro-2'-metoxibifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

194. 2-({1-[(4'-cloro-2'-metoxibifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
195. N-(2-metoxietil)-4-metil-2-[(1-{4-[2-(trifluorometil)pirimidin-5-il]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida
196. 2-({1-[(4'-cloro-2'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida
197. 2-({1-[(2'-cloro-4'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida
198. 2-({1-[4-(5-cloropiridin-3-il)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
199. 2-({1-[4-(5-fluoropiridin-3-il)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
200. N-(2-metoxietil)-4-metil-2-[(1-{4-[5-(trifluorometil)piridin-3-il]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida
201. 2-[(1-{[4'-(1-hidroxi-1-metiletil)bifenil-4-il]carbonil}piperidin-4-il)metil]-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
202. 2-({1-[(3',5'-difluorobifenil-4-

il)carbonil]piperidin-4-il}metil)-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida

203. 2-({1-[(4'-fluoro-2-metilbifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

204. 2-({1-[(3',5'-difluoro-2-metilbifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

205. N-(2-metoxietil)-4-metil-2-({1-[3-metil-4-(3-piridil)benzoil]piperidin-4-il}-metil)-2H-indazol-5-carboxamida

206. N-(2-metoxietil)-4-metil-2-({1-[3-metil-4-(4-piridil)benzoil]piperidin-4-il}-metil)-2H-indazol-5-carboxamida

207. N-(2-metoxietil)-4-metil-2-({1-[(2-metilbifenil-4-il)carbonil]piperidin-4-il}-metil)-2H-indazol-5-carboxamida

Un objeto de la presente invención es el uso de los compuestos de acuerdo con la invención para la producción de fármacos que contienen por lo menos uno de los compuestos de acuerdo con la fórmula I.

Otro objeto de la presente invención consiste en fármacos que contienen los compuestos de acuerdo con la invención, con una adecuada formulación y sustancias transportadoras.

En comparación con los conocidos antagonistas EP_2 de prostaglandina, los nuevos antagonistas de EP_2 se caracterizan por propiedades mejoradas tales como una mejor disponibilidad y estabilidad.

Un objeto de la presente invención son fármacos para el control de la fertilidad o para anticoncepción y para el tratamiento y prevención de enfermedades que incluyen enfermedades infecciosas, cáncer, enfermedades cardiovasculares, enfermedades angiogénicas, trastornos de contracción uterina, dolor, enfermedades inflamatorias, enfermedades neuroinflamatorias, enfermedades neurodegenerativas, enfermedades autoinmunológicas, enfermedades/terapias inmunodependientes, enfermedades nefrológicas y enfermedades oftalmológicas.

Debe entenderse que la expresión enfermedades infecciosas se refiere a enfermedades causadas por parásitos unicelulares (por ejemplo, Klebsiella o Streptococcus). Con las enfermedades infecciosas, los fármacos pueden tener una acción inmunomoduladora de manera tal que es posible tratar las enfermedades profilácticamente (disminución del riesgo de infección tal como, por ejemplo, en los implantes de médula ósea) o por vía terapéutica. Debe entenderse que el término “cáncer” se refiere a los tumores sólidos y las

leucemias; las infecciones virales como, por ejemplo, las infecciones por cytomegalus, hepatitis, hepatitis B y C y enfermedades por VI; enfermedades cardiovasculares, enfermedad de reperfusión isquémica, estenosis, arteriosclerosis, restenosis, artritis, síndrome de Kawasaki y aneurismas; enfermedades angiogénicas como, por ejemplo, endometriosis y fibrosis y fibromas en el útero; enfermedades de contracción uterina como, por ejemplo, enfermedades de contracción, por ejemplo problemas menstruales; dolor; por ejemplo enfermedad inflamatoria, hiperalgesia y artritis, enfermedades inflamatorias, por ejemplo enfermedades intestinales inflamatorias; enfermedades neuroinflamatorias y degenerativas, por ejemplo esclerosis múltiple, Alzheimer, Parkinson, ALS y accidente cerebrovascular; enfermedades/terapias inmunodependientes, por ejemplo trasplantes en los que la inmumodulación aumenta el éxito terapéutico; enfermedades autoinmunes por ejemplo la enfermedad oftalmológica de Graves, y las enfermedades de riñón poliquístico y la glomerulonefritis.

Otro objeto de la presente invención son fármacos para el tratamiento y prevención de las enfermedades mencionadas anteriormente, que contienen al menos un compuesto de acuerdo con la fórmula general I, y

fármacos con formulación adecuada y sustancias transportadoras.

Para el uso de los compuestos de acuerdo con la invención como fármacos, los mismos se convierten en la forma de una preparación farmacéutica que, además de la sustancia activa contiene productos farmacéuticos, materiales portadores o vehículo inertes orgánicos o inorgánicos adecuados para las administración enteral o parenteral, tales como, por ejemplo, agua, gelatina, goma arábiga, lactosa, almidón, estearato de magnesio, talco, aceites vegetales, polialquilenglicoles, etc. Las preparaciones farmacéuticas pueden estar en forma sólida, por ejemplo como comprimidos, comprimidos recubiertos o cápsulas; en forma semisólida, por ejemplo en forma de ungüentos o pomadas, cremas, geles o supositorios; o en forma líquida, por ejemplo como soluciones, suspensiones o emulsiones.

Opcionalmente contienen aditivos, que están destinados, por ejemplo, para actuar como agentes de relleno de carga, aglutinantes, desintegrantes, lubricantes, solventes, mediadores de solución, aromas enmascarantes, colorantes, o emulsionantes. Los tipos de aditivos en el sentido de la invención abarcan por ejemplo los sacáridos (mono-, di-, tri-, oligo- y/o polisacáridos), grasas, ceras, aceites, hidrocarburos,

aniónicos, surfactantes aniónicos, no iónicos, catiónicos, naturales, sintéticos o semisintéticos. Además, opcionalmente contienen aditivos tales como agentes conservantes, agentes estabilizantes, agentes humectantes o agentes emulsionantes, sales para la modificación de la presión osmótica o sustancias tampón.

Estas preparaciones farmacéuticas son también un objeto de la presente invención.

Para la inhalación, se preparan de manera ventajosa soluciones de aerosol, o bien preparaciones adecuadas de sustancias sólidas para su inhalación.

Para uso oral, los comprimidos, comprimidos recubiertos o cápsulas con vehículos o aglutinantes, talco y/o hidrocarburo, tales como, por ejemplo, lactosa, maíz o almidón de papa, son particularmente adecuados. También es posible el uso en forma líquida, tal como, por ejemplo, en forma de jarabe, al que opcionalmente se añade un edulcorante. Del mismo modo, para el uso oral de tales compuestos, también son adecuados los clatratos, por ejemplo los clatratos con ciclodextrina alfa, beta o gamma; también puede mencionarse la beta-hidroxipropilciclodextrina.

Para la administración parenteral, se utilizan soluciones estériles, inyectables, acuosas u oleosas.

Las soluciones o suspensiones de inyección son particularmente adecuadas, en particular las soluciones acuosas de los compuestos activos en aceite de ricino polietoxilado.

Para la aplicación vaginal, son adecuados y se utilizan habitualmente por ejemplo supositorios, tampones, geles, espumas o pesarios intrauterinos.

Para la inyección intraarticular, pueden utilizarse suspensiones de cristales preparadas.

Para la inyección intramuscular, es posible utilizar soluciones o suspensiones inyectables acuosas y oleosas y las preparaciones de deposición correspondientes.

Para la aplicación rectal, los nuevos compuestos se pueden utilizar en la forma de supositorios, cápsulas, soluciones (por ejemplo en forma de enemas) y ungüentos tanto para terapia sistémica como también para terapia local.

Para la aplicación pulmonar de los nuevos compuestos, éstos se pueden utilizar en forma de aerosoles y formulaciones de inhalación.

Para uso local en los ojos, en el canal auditivo externo, el oído medio, fosas nasales y senos paranasales, los nuevos compuestos se pueden utilizar como gotas, ungüentos o pomadas y tinturas apropiadas

en preparaciones farmacéuticas.

Para aplicación tópica, son posibles las formulaciones en geles, ungüentos, ungüentos grasos, cremas, pastas, polvos, leche y tinturas. La dosificación de los compuestos de la fórmula general I en estas preparaciones debería ser de 0,01% – 20% a efectos de lograr una acción farmacológica adecuada.

La dosificación de las sustancias activas puede variar en función de la vía de administración, la edad y el peso del paciente, la naturaleza y la gravedad de la enfermedad a tratar y factores similares. El tratamiento puede efectuarse mediante dosis individuales o mediante un gran número de dosis durante un período más prolongado. La dosis diaria es de 0,5 – 1000 mg, con preferencia, de 50 a 200 mg, y la dosis puede administrarse como una dosis individual para la administración de una vez o subdividirse en 2 o más dosis diarias.

Como sistemas portadores, también pueden utilizarse aditivos tensioactivos tales como sales de los ácidos biliares o fosfolípidos animales o vegetales, pero también mezclas de los mismos y sus liposomas o componentes.

Las formulaciones y las presentaciones descritas anteriormente son también un objeto de la presente

invención.

La administración de los compuestos de acuerdo con la invención se puede efectuar mediante cualquier método convencional, inclusive la vía oral y parenteral, por ejemplo, por inyecciones subcutáneas o intramusculares, y diversas técnicas de inhalación. Las aplicaciones enterales, parenterales, vaginales, intrauterinas y orales son también un objeto de la presente invención.

Los compuestos de acuerdo con la invención de la fórmula general I se unen al receptor EP_2 y tienen una acción antagonista. La acción antagonista puede ser determinada mediante una prueba de antagonismo (véase el Ejemplo 1.2.1 de los ejemplos biológicos).

Debe entenderse que el término “antagonistas” se refiere a moléculas que se unen a sus receptores apropiados y que inhiben la iniciación de la(s) vía(s) de transducción de las señales acopladas al receptor a través del o de los ligandos de presentación natural. Normalmente, los antagonistas competen con el ligando de presentación natural de los receptores en cuanto a la unión al receptor. Sin embargo, otras modificaciones del receptor por las moléculas que impiden que las vías de transducción de señales acopladas con el receptor sean activadas por el o los ligandos de presentación

natural, también son posibles (por ejemplo, modificaciones estéricas, no competitivas, del receptor).

Es más preferible que los antagonistas se unan reversiblemente a sus correspondientes receptores.

El antagonista del receptor EP_2 tiene una afinidad preferencial para el receptor EP_2 en comparación con cualquier otro receptor EP. El antagonismo se mide en la presencia del agonista natural (PGE_2).

Para la determinación de la selectividad, es posible determinar la acción del antagonista EP_2 en un receptor EP_4 humano (Ejemplo 2.2.1) o en el receptor de PGD (Ejemplo 3.2.1) (Tabla 1).

Además, las sustancias de acuerdo con la invención son más estables *in vivo* que los antagonistas de los receptores EP_2 que se describen en el estado más cercano de la técnica (DE 10 2009 049 662 A1), y esto tiene como resultado mayores vidas medias (ver Tabla 3).

Otro objeto de la presente invención es el uso de las sustancias de acuerdo con la invención como antagonistas de los receptores EP_2 para el tratamiento de enfermedades que son causadas por trastornos en la cadena de transducción de señales en las que está implicado el receptor EP_2, tales como, por ejemplo, el

dolor y los trastornos de la fertilidad. Los antagonistas del receptor EP_2 también son adecuados para el control de la fertilidad.

En el folículo antral preovulatorio, el oocito está rodeado por células del cumulus que forman una corona celular densa alrededor del oocito. Después del pico de la hormona luteinizante (LH pico), se activa una serie de procesos que resultan en un marcado cambio morfológico en esta corona celular de las células del cumulus. Durante esto, las células del cumulus forman una matriz extracelular, lo que conduce a la denominada expansión del cumulus (Vanderhyden y col. 1990, Dev. Biol., Aug; 140 (2) :307-317). Esta expansión del cumulus es un componente importante del proceso ovulatorio y de la posibilidad subsiguiente de fertilización.

Durante la expansión del cumulus, las prostaglandinas y en este caso la prostaglandina E_2, cuya síntesis es inducida por el pico de LH, son de importancia decisiva. Los ratones prostanoides *knockout* EP_2 (Hizaki y col, 1999, Proc Natl Acad Sci U.S.A., Aug. 31; 96 (18):10501-6) muestran una expansión del cumulus marcadamente disminuida y una subfertilidad grave, lo que demuestra la importancia de los receptores EP_2 de prostanoide para este proceso.

La acción de un antagonista de EP_2 sobre la expansión del cumulus se puede medir en una prueba de expansión del cumulus (véase el Ejemplo 4.2).

Las sustancias de acuerdo con la invención tienen efectos inhibidores en las pruebas de expansión del cumulus y una influencia en la posibilidad de fertilización de los complejos cumulus-ovocito ovulados (véase el Ejemplo 4,3 y la Tabla 4). Las sustancias según la invención tienen un efecto anticonceptivo en primates no humanos (cinomólogo), en los cuales provocan una tasa de embarazo notablemente disminuida sin tener una influencia en el ciclo (duración del ciclo y hormonas) (véase el Ejemplo 4.4 y la Tabla 5). Esto demuestra por primera vez un efecto anticonceptivo de los antagonistas de los receptores EP_2 en primates no humanos. Este efecto se basa en mecanismos no hormonales, lo que demuestra la posibilidad de una anticoncepción, libre de hormonas, con las sustancias de acuerdo con la invención.

Un objeto de la presente invención es el uso de las sustancias de acuerdo con la invención para el control de la fertilidad.

Si bien el AH6809 antagonista del receptor EP_2 primero suprime la expansión del cumulus, en solo aproximadamente 30%, con una concentración de 100 a 200

µM, en la presencia de la sustancia de acuerdo con la invención, de acuerdo con el Ejemplo 17, puede lograrse una supresión de aproximadamente el 70% de la expansión del cumulus ya con una concentración 100–200 veces menor (0,5 µM; IC_{50}: 3,4 nM, véase la Tabla 1). En estos experimentos, las sustancias de ensayo compiten con el agonista PGE_2 del receptor natural EP_2 (0,3 µM).

Mediante la administración de la sustancia del Ejemplo 62 de la solicitud DE 10 2009 049 662 A1, puede lograrse de manera similar una supresión de la expansión del cumulus de aproximadamente el 70%; sin embargo para ello es necesaria una concentración de 10 µm, lo representa una concentración de 10–20 veces menor en comparación con AH6809. Sin embargo, esto es marcadamente superior a la concentración de 0,5 µm para el Ejemplo 17 de la presente invención (véase la Tabla 2).

El Ejemplo 17 de acuerdo con la presente invención también se caracteriza también por una mejor vida media terminal. Si bien el Ejemplo 62 de la solicitud DE 10 2009 049 662 A1 tiene un $t_{1/2}$ de 0,4 horas, para el Ejemplo 17 se trata de 2,5 horas (véase la Tabla 3).

En consecuencia, la sustancia 17 de la presente invención es marcadamente superior a este compuesto conocido del estado de la técnica.

Un objeto de la presente invención es el uso de las sustancias de acuerdo con la invención para la inhibición de la expansión del cumulus y, por lo tanto, de la ovulación y la fertilización para la anticoncepción.

Una forma particular de anticoncepción es la protección de emergencia (también conocida como la "píldora del día después"). Esto se debe entender en el sentido de la toma de una o más sustancias con el objeto de prevenir un posible embarazo después del coito sin protección y en el caso de una presumible falla del método de protección.

Un objeto de la presente invención es el uso de las sustancias según la invención para la protección de emergencia.

Otro objeto de la presente invención es el uso de las sustancias de acuerdo con la invención como antagonistas de los receptores EP_2 para la prevención y tratamiento directo de enfermedades que están vinculadas causalmente con el receptor EP_2 o de enfermedades que pueden ser tratadas por el hecho de influir en el receptor EP_2.

Las prostaglandinas desempeñan un papel importante en la angiogénesis (Sales, Jabbour, 2003, Reproduction 126, 559 a 567; Kuwano y col, 2004, FASEB J. 18, 300-

310; Kamiyama y col, 2006, Oncogene 25, 7019-7028; Chang y col, 2005, prostaglandins & Other Lipid Mediators 76, 48-58).

La endometriosis es una enfermedad crónica en la que intervienen procesos inflamatorios, inmunomoduladores y angiogénicos. Junto con otros factores, las prostaglandinas y aquí en particular la PGE_2 y el receptor EP_2 son de importancia particular (Banu y col, 2009, Molecular Endocrinology 23: 1291-1305; Bulun 2009, N Engl J Med, 360, 268-279).

Cerca del 10% de las mujeres sufren regularmente de sangrados intensos durante la menstruación, causados por cambios en los vasos sanguíneos del endometrio. Además, se han observado diferencias estructurales en los vasos sanguíneos, tales como, por ejemplo, la formación incompleta de la capa de músculo liso (Abberton y col., 1999, Hum. Reprod. 14, 1072-1079, Rogers y col. 2003, Res. Microsc Tech. 60 (4), 412-419). Dado que la pérdida sanguínea durante la menstruación está parcialmente regulada por la constricción de los vasos sanguíneos, es evidente que los defectos en la musculatura lisa contribuyen sustancialmente al sangrado.

Un objeto de la presente invención es el uso de las sustancias de la fórmula general I para la

prevención y tratamiento de la endometriosis.

Las prostaglandinas desempeñan un papel importante en la contracción uterina, y las contracciones excesivamente fuertes son responsables de los problemas menstruales (Sales, Jabbour, 2003, Reproduction 126, 559 – 567). Las prostaglandinas y en este caso en especial la EP_2 y el receptor EP_4 se han relacionado con sangrado menstrual grave (Smith y col., 2007 (Human Reproduction, Vol. 22, No.5 pp 1450–1456).

Un objeto de la presente invención es el uso de las sustancias de la fórmula general I para la prevención y el tratamiento de los problemas menstruales y del sangrado menstrual severo y de los dolores durante la menstruación.

Los fibromas (miomas) son tumores benignos en el útero con una elevada tasa de difusión. A través de la estimulación de la aromatasa por una vía de señales mediada por PGE_2/cAMP, y por intermedio de otros mecanismos posibles, existe un vínculo con el metabolismo de las prostaglandinas (Imir y col., 2007, J Clin Endocrinol Metab 92, 1979–1982).

Un objeto de la presente invención es el uso de las sustancias de la fórmula general I para la prevención y el tratamiento de los fibromas (miomas).

Un número creciente de resultados de investigación

también confirma la importancia de los receptores EP, y en particular también de los receptores EP_2 en un gran número de tipos de cáncer (por ejemplo, cáncer de mama, carcinoma de colon, cáncer de pulmón, cáncer de próstata, leucemia y cáncer piel), lo que apunta a posibilidades futuras para el uso de moduladores (antagonistas o agonistas) del receptor EP_2 para el tratamiento y la prevención (prevención y/o adyuvante) de cáncer (Fulton y col., 2006, Cancer Res; 66(20): 9794-7; Castellone y col., 2005, Science Vol 310, 1504-1510; Chang y col., 2005, Cancer Res; 65(11): 4496-9); Hull y col., 2004, Mol Cancer Ther; 3(8):1031-9; Richards y col., 2003, J Clin Endocrinol Metab 88: 2810-2816,; Sinha y col., 2007, Cancer Res; 67(9): 4507-13; Wang y col., 2004, Seminars in Oncology, Vol 31, No 1, Suppl 3: pp 64-73), Yu y col., 2008; JPET publicado el 26 de junio como DOI:10.1124/jpet.108.141275, Denizot y col., 2005, Int. J. Cancer: 115, 499-501; Fiancette y col., 2011, J Oncol. pii: 389021, Chun y col., 2011, Mol Carcinog. 50(6): 439-48).

Un objeto de la presente invención es el uso de las sustancias de la fórmula general I para el tratamiento y prevención de enfermedades de cáncer.

La activación de las células endoteliales

desempeña un papel importante en el proceso patogénico de la arteriosclerosis. En este caso, los productos de oxidación de la lipoproteína de baja densidad (LDL) son importantes en la aparición y desarrollo de enfermedades arterioscleróticas. Investigaciones más recientes indican que en ello interviene el receptor EP_2 (Li y col, 2006; Circ Res. 98:642-650).

Un objeto de la presente invención es el uso de las sustancias de la fórmula general I para el tratamiento y prevención de la arteriosclerosis.

Las publicaciones científicas más recientes muestran que en las enfermedades neurodegenerativas, neuroinflamatorias e isquémicas (Alzheimer, Parkinson, ALS y accidente cerebrovascular), las prostaglandinas y el receptor EP_2 son componentes importantes del proceso patológico (Hoshino y col, 2007, J Biol Chem,; 282 (45): 32676-88; Liang y col, 2005, The Journal of Neuroscience, 25 (44): 10180 -10187, Jin y col, 2007, J Neuroinflammation Jan 4;4:2; Liang y col., 2008, Ann Neurol; 64: 304-314; Cimino y col, 2008, Current Medicinal Chemistry, 1863-1869).

La esclerosis múltiple es una inflamación crónica del sistema nervioso. Las prostaglandinas, especialmente PGE_2, y los efectos mediados por el receptor EP_2 tienen una relación causal con los

procesos patológicos en la esclerosis múltiple (Palumbo y col., 2011, Prostaglandins, Leukotrienes and Essential Fatty Acids 85: 29–35; Palumbo y col., 2011, J. Neurochem. 10.1111/j.1471–4159, Kihara y col., 2009, Proc Natl Acad Sci U. S. A, 106, No. 51: 21807–21812).

Un objeto de la presente invención es el uso de las sustancias de la fórmula general I para el tratamiento y prevención de enfermedades neurodegenerativas, neuroinflamatorias e isquémicas, tales como, por ejemplo, la enfermedad de Alzheimer, de Parkinson, ALS y los accidentes cerebrovasculares y para el tratamiento de la esclerosis múltiple.

Las enfermedades de riñón poliquístico también están vinculadas con el receptor EP_2 (Song y col, 2009, Human Molecular Genetics, 18, N.º 13: 2328–2343; Elberg y col, 2007, Am J Physiol Renal Physiol 293: F1622–F1632.)

Un objeto de la presente invención es el uso de las sustancias de la fórmula I general para el tratamiento y prevención de las enfermedades de riñón poliquístico.

Reinold y col. (J. Clin. Invest. 115, 673–679 (2005)) describen receptores PGE_2 del subtipo EP_2 como los elementos señal claves en la hiperalgesia inflamatoria. Los ratones que ya no portan este

receptor (EP_2-/ -) no sienten dolor espinal inflamatorio. Hay indicios de que una sensibilidad inflamatoria aumentada al dolor puede ser tratada mediante la modulación específica de receptores EP_2. Además, el receptor EP_2 está ligado con otros tipos de dolor (Zeilhofer, 2007, Biochemical Pharmacology 73; 165 - 174), entre otros, en los nervios faciales (Patwardhan y col (J Dent Res 87(3): 262-266, 2008)).

Un objeto de la presente invención es el uso de las sustancias de acuerdo con la invención para el tratamiento y la prevención de los dolores de orígenes diversos, tales como, por ejemplo, la hiperalgesia inflamatoria.

Las publicaciones científicas recientes se refieren al uso de inhibidores de EP_2 para la prevención y/o tratamiento de infecciones del tracto respiratorio. Serezani y col. (Am Respir Cell Mol Biol. Vol. 37. pp 562-570, 2007) afirma que la capacidad de los macrófagos del tracto respiratorio para destruir las bacterias, se deteriora a través de la activación del receptor EP_2 por PGE_2. Las infecciones bacterianas conducen a una mayor producción de prostaglandinas, entre otras cosas, del PG_2, que a través de este mecanismo debilita la defensa endógena contra las bacterias. Como se muestra en dicha publicación, esta

capacidad para luchar contra las bacterias puede ser restaurada por la inactivación del receptor EP_2 (y del receptor EP_4). Otras publicaciones relevantes que explican estas conexiones son: Sadikot y col., 2007, Eur. J. Immunol. 37: 1001–1009; Aronoff y col., 2004, The Journal of Immunology, 173: 559–565 y Medeiros y col., 2009, J Exp Med. 206(1):61–68.

Un objeto de la presente invención es el uso de las sustancias según la invención para la prevención y tratamiento de enfermedades infecciosas del pulmón.

Los fibroblastos y en este caso en particular sus funciones en la restauración de los tejidos dañados desempeñan un papel decisivo en la enfermedad pulmonar obstructiva crónica. Durante la misma, un exceso de PGE_2 suprime importantes funciones de reparación de los fibroblastos (Togo y col, 2008, Am J Respir Crit Care Med, 178: 248–260).

Un objeto de la presente invención es el uso de las sustancias de acuerdo con la invención para la prevención y el tratamiento de enfermedades pulmonares obstructivas crónicas.

Las enfermedades inflamatorias intestinales (por ejemplo, la enfermedad de Crohn) también están también relacionadas con el receptor de prostaglandinas EP2 (Sheibanie y col, 2007, The Journal of Immunology, 178:

8138-8147).

Un objeto de la presente invención es el uso de las sustancias según la invención para la prevención y el tratamiento de enfermedades inflamatorias intestinales.

Durante el trasplante de médula ósea, a menudo se producen complicaciones por infecciones, en las que un exceso de producción de PGE_2 está vinculada con una disminución de las defensas inmunológicas (Ballinger y col, 2006, The Journal of Immunology, 177: 5499 - 5508).

Un objeto de la presente invención es el uso de las sustancias según la invención para la prevención y el tratamiento en el trasplante de médula ósea.

La enfermedad de Graves es una enfermedad autoinmune de la tiroides, en la que el cuadro clínico también puede incluir cambios patológicos en el ojo (orbitopatía endocrina; protrusión de los globos oculares (exoftalmia)). Durante dicha enfermedad, los linfocitos invasores activan los fibroblastos que están presentes, lo que conduce, entre otras cosas a una acumulación de mucopolisacáridos. Las posibles consecuencias son el deterioro de la visión que llega hasta la ceguera. Los estudios muestran que la interleuquina-6 es de importancia decisiva para los

mecanismos patológicos y que la interleuquina-6 es inducida a través de PGE_2 y del receptor EP_2. (Raychaudhuri y col., 2010, PloS ONE, 5: e15296; Wang y col., 1995, J Clin Endocrinol Metab 80: 3553-3560).

Un objeto de la presente invención es el uso de las sustancias de acuerdo con la invención para la prevención y el tratamiento en la orbitopatía en conexión con la enfermedad de Graves u otras enfermedades patológicas de los ojos.

Los aneurismas son dilataciones vasculares con el riesgo de conducir a rupturas vasculares con hemorragias de efectos graves que amenazan la vida, como, por ejemplo, parálisis, pérdida o deterioro del lenguaje, limitaciones cognitivas y otras consecuencias neurológicas en caso de hemorragias cerebrales. Incluso sin rupturas, los aneurismas cerebrales pueden causar síntomas neurológicos graves a través de la presión sobre las fibras nerviosas. Los aneurismas cerebrales se encuentran en aproximadamente el 1 al 5% de la población, existiendo una mayor incidencia en las mujeres. Las rupturas de aneurismas en los vasos sanguíneos periféricos implican un alto riesgo de trombosis, infartos cardiacos, dolor y un número de otros cuadros clínicos. Las terapias farmacológicas incluyen principalmente la limitación de los factores

de riesgo como la hipertensión.

Estudios científicos recientes pudieron demostrar que el receptor EP_2 desempeña una parte importante en la patogénesis de los aneurismas cerebrales. En este caso, a través de la cascada de COX-2- PGE_2-EP_2-NF-**κ**-β se crea un estado inflamatorio que está causalmente involucrado en la formación de los aneurismas. (Aoki y col., 2011, British Journal of Pharmacology 163: 1237-1249; Aoki y col. 2007, 116:2830-2840).

Un objeto de la presente invención es el uso de las sustancias de acuerdo con la invención para la prevención y el tratamiento de los aneurismas.

El síndrome de Kawasaki es una enfermedad aguda, febril y sistémica, que afecta principalmente niños menores de 5 años. Los daños a largo plazo pueden incluir cambios en los vasos sanguíneos, en particular, los vasos sanguíneos coronarios (por ejemplo, formación de aneurismas) y enfermedades relacionadas con el mismo, tales como trastornos del ritmo cardíaco y el infarto cardíaco. La incidencia varía regionalmente, así por ejemplo 185 de 100.000 niños menores de 5 años en Japón y cerca de 9 de cada 100.000 niños en Alemania. La prostaglandina E_2 es elevada en la fase aguda de la enfermedad (Lee y col., 1988, Prostaglandins Leukot Essent Fatty Acids, 31 (2):53-

57). A través de estudios recientes de investigación se pudo demostrar que la integrina β1 es activado por PGE_2 y mediada a través del receptor EP_2, que está causalmente relacionado con el daño vascular (Kajimoto y col, 2009, Inflamm Res 58: 224-228).

Un objeto de la presente invención es el uso de las sustancias de acuerdo con la invención para la prevención y el tratamiento del síndrome de Kawasaki, en particular también para la prevención de los daños vasculares, y para evitarlos.

Investigaciones recientes indican que el receptor EP_2 tiene un papel importante en la artritis y que en este caso influye en la patogénesis de esta enfermedad a través de mecanismos inmunomodulatorios (Harizi y col., 2010, Inmunología y Biología Celular, 1-8).

Un objeto de la presente invención es el uso de las sustancias de acuerdo con la invención para la prevención y el tratamiento de la artritis.

El ligando natural (agonista) del receptor EP_2 es PGE_2, cuya síntesis es mediada por enzimas de ciclooxigenasas (COX) (COX-1, COX-2). Estas enzimas participan principalmente en dichos cuadros clínicos y en las indicaciones y la aparición de los mismos a través de un aumento de la expresión y actividad. Por tanto, en todas las posibilidades de uso mencionadas,

es posible una combinación de un inhibidor de COX (COX-2 y/o COX-1), con el objetivo de

a) el logro de una mayor actividad farmacológica, más efectiva, que con una sola clase de sustancias y

b) permitir una dosificación más baja de una o de ambas clases de sustancias, lo que conduce a una reducción de los posibles efectos secundarios y a una mejor tolerancia.

Por lo tanto, los fármacos que contienen un compuesto de la fórmula general (I) en combinación con un inhibidor de COX para el tratamiento de enfermedades (preparaciones combinadas) son también un objeto de la presente invención. Como inhibidores de COX pueden mencionarse por ejemplo los inhibidores de COX no selectivos tales como aspirina, naproxeno, indometacina, ibuprofeno y los inhibidores de COx selectivos meloxicam, cetoprofeno, piroxicam, tenoxicam, nimesulide, ácido mefanémico, quetoralac, celecoxib (4-[5-(4-metilfenil)-3-(trifluorometil)-1H-pirazol-1-il]bencensulfonamioda) parecoxib (N-[4-(5-metil-3-fenil-4-isoxazolil)fenil] sulfonilpropionamida), rofecoxib (4-(4-mesilfenil)-3-fenil-furan-2(5H)-ona), valdecoxib (4-[5-metil-3-fenil-4-isoxazoil)bencensulfonamida), NS-398 (N-metil-2-ciclohexanoxi-4-nitrobenzensulfonamida), lumiracoxib

[ácido 2-(2'-cloro-6'-fluoro-fenil)-amino-5-metilbencenacético], ceracoxib y etoricoxib.

Estas preparaciones combinadas puede ser utilizadas para el tratamiento de las siguientes enfermedades: enfermedades infecciosas, cáncer, enfermedades cardiovasculares, enfermedades angiogénicas, trastornos de contracción uterina, dolor, enfermedades inflamatorias, enfermedades neuroinflamatorias, enfermedades neurodegenerativas, enfermedades autoinmunes, enfermedades/terapias inmunodependientes, enfermedades nefrológicas y enfermedades oftalmológicas.

También se las puede utilizar para el control de la fertilidad.

Además, la invención se refiere a un proceso para la producción de los compuestos de acuerdo con la invención de la fórmula general I.

Para ello, por ejemplo, un ácido carboxílico de la fórmula VIII se hace reaccionar con una amina de la fórmula general XI por medio de métodos conocidos por los expertos en el arte para dar los compuestos de acuerdo con la invención de la fórmula general I (Esquema 1).

La reacción tiene lugar, por ejemplo, convirtiendo un ácido carboxílico de la fórmula VIII con

cloroformiato de isobutilo en presencia de una amina terciaria, por ejemplo, trietilamina, en un anhídrido mixto que reacciona con una sal de metal alcalino de la amina XI apropiada en un solvente inerte o mezcla de solventes, por ejemplo, tetrahidrofurano, N,N-dimetilformamida o dimetoxietano a temperaturas de entre –30 °C y +60 °C para dar los compuestos objeto de la fórmula I.

También es posible activar un ácido carboxílico VIII con reactivos tales como, por ejemplo, diciclohexilcarbodiimida (DCC), 1-(3-dimetilaminopropil)-3-etilcarbodiimida (EDCI), N-hidroxibenzotriazol (HOBT) o hexafluorofosfato de N-[(dimetilamino)-(3H-[1,2,3]triazolo[4,5-b]piridin-3-iloxi)metiliden]-N-metilmetanaminio (HATU). Por ejemplo, la reacción con HATU tiene lugar en un solvente inerte, por ejemplo, N,N-dimetilformamida o dimetilsulfóxido en presencia de la amina XI apropiada y una amina terciaria, por ejemplo, trietilamina o diisopropilamina, a temperaturas de entre –30 °C y +60 °C.

También es posible convertir un ácido carboxílico de la fórmula VIII en el correspondiente cloruro de ácido carboxílico con un cloruro de ácido inorgánico, por ejemplo, pentacloruro de fósforo, tricloruro de

fósforo o cloruro de tionilo y luego en los compuestos objeto de la fórmula general I en piridina o un solvente inerte, tales como, por ejemplo, N,N-dimetilformamida, en presencia de la amina XI apropiada y una amina terciaria, por ejemplo, trietilamina, a temperaturas de entre −30 °C y +60 °C.

Los compuestos de acuerdo con la invención de la fórmula general I también se pueden obtener de bromoindazoles de la fórmula general VI bajo catálisis de paladio (0) por reacción con una amina XI apropiada y monóxido de carbono (CO) o una fuente de monóxido de carbono, tales como, por ejemplo, hexacarbonilmolibdeno en un solvente apropiado o mezcla de solventes, por ejemplo, 1,4-dioxano/agua o tetrahidrofurano, adición de una base como, por ejemplo, carbonato de sodio o 1,8-diazabiciclo(5,4,0)undec-7-eno (DBU) y una mezcla de catalizador-ligando, por ejemplo, acetato de paladio (II) o transbis(acetato)bis[o-(di-o-tolilfosfino)bencil]-dipaladio (II) / tri-*tert*-butilfosfinotetrafluoroborato a temperaturas de entre 80 °C y 160 °C (opcionalmente con irradiación de microondas de entre 80-200 watts) y en el caso del uso de monóxido de carbono a una presión de CO de 5-15 bar (Esquema 1).

Los compuestos de acuerdo con la invención de la

fórmula general I también se pueden obtener a partir de aminas de la fórmula general XV por reacción con ácidos carboxílicos (Y = OH), cloruros (Y = Cl) o anhídridos (por ejemplo, Y = O-C(O)-O-$CH_2(CH)_3CH_3$) de la fórmula IX de la manera descrita para la producción de los compuestos I a partir de los compuestos VIII y XI (Esquema 2).

Del mismo modo, los compuestos de la fórmula general I se pueden obtener a partir de los compuestos de la fórmula general XVI, en donde LG´, por ejemplo, significa Br o I, por reacción con los compuestos de la fórmula XVIII (Esquema 2).

Los compuestos de la fórmula XVIII son, por ejemplo, ácidos (Het)arilborónicos (R^3-Met = (Het)Ar-$B(OH)_2$) o ésteres pinacólicos de ácido borónico (R^3-Met= (Het)Ar-BPin), que se convierten en compuestos de biarilo de la fórmula I por medio de métodos conocidos por los expertos en el arte en un solvente apropiado, por ejemplo, N,N-dimetilformamida, tetrahidrofurano, dimetoxietano y opcionalmente agua y adición de una base, por ejemplo, trietilamina, carbonato de potasio, carbonato de cesio y una mezcla de catalizador-ligando, por ejemplo, de acetato de paladio (II) / trifenilfosfina, bis(difenilfosfino)ferrocenodicloropaladio (II) (/

1,1'-bis(difenilfosfino)ferroceno/ Cu(I)Cl) a temperaturas de entre 20 °C y 120 °C.

Los compuestos de la fórmula XVIII también pueden ser alcoholes de (Het)arilo (R^3-Met = (Het)ArO-H), que se convierten en éteres de biarilo de la fórmula I por medio de métodos conocidos por los expertos en el arte en un solvente apropiado, por ejemplo, N,N-dimetilformamida o dimetilsulfóxido con adición de una base, por ejemplo, carbonato de potasio, carbonato de cesio bajo catálisis de cobre (I), por ejemplo, con bromuro de cobre (I) a temperaturas de entre 60 °C y 120 °C.

Los ácidos carboxílicos de la fórmula general VIII se pueden obtener, por ejemplo, a partir de ésteres de la fórmula VII por saponificación de ésteres en un solvente apropiado o mezcla de solventes, por ejemplo, metanol, etanol o tetrahidrofurano, agua con adición de una solución acuosa de un hidróxido de metal alcalino, por ejemplo, hidróxido de sodio o hidróxido de litio a temperaturas de entre 20 °C y 60 °C (Esquema 1).

De la misma manera, los ácidos carboxílicos XIII se pueden obtener a partir de los ésteres XII (Esquema 2, PG: por ejemplo, Boc (*tert*-butiloxicarbonilo) y los ácidos carboxílicos XXI a partir de los ésteres XX (Esquema 3, LG´: por ejemplo, Br o I).

Los ésteres de la fórmula general VII se pueden obtener a partir de bromoindazoles de la fórmula general VI bajo catálisis de paladio (0) por reacción con monóxido de carbono o una fuente de monóxido de carbono, tales como, por ejemplo, hexacarbonilo de molibdeno y metanol en un solvente apropiado, por ejemplo, dimetilsulfóxido, N,N-dimetilformamida o tetrahidrofurano y adición de una base, por ejemplo, trietilamina o 1,8-diazabiciclo(5,4,0)undec-7-eno y una mezcla de catalizador-ligando, por ejemplo, de acetato de paladio (II) / bis-1,3-difenilfosfino-propano o transbis(acetato)bis[o-(di-o-tolilfosfino)bencil]dipaladio (II) / tri-*tert*-butilfosfinotetrafluoroborato a temperaturas de entre 20 °C y 140 °C (opcionalmente con irradiación de microondas de entre 80 – 200 watts) y en el caso de usar monóxido de carbono a una presión de CO de 5 – 15 bar (Esquema 1).

Este método no está restringido a ésteres metílicos, es decir, al uso de metanol, pero se puede extender también a otros ésteres. De esta manera, por ejemplo, al usar etanol en lugar de metanol de esta manera, se pueden sintetizar los correspondientes ésteres de etilo.

De la misma manera, los ésteres XII se pueden

obtener a partir de los bromuros IV (Esquema 2, –PG: por ejemplo, –Boc).

Las amidas de la fórmula general VII también se pueden obtener a partir de las aminas de la fórmula general XIX por reacción con compuestos de la fórmula general IX (Esquema 3), análogamente a la síntesis de los compuestos I a partir de los compuestos XV (Esquema 2).

Los compuestos de la fórmula general VII también se pueden obtener a partir de compuestos de la fórmula XX y reacción con compuestos de la fórmula XVIII (Esquema 3), análogamente a la conversión descrita de los compuestos XVI en los compuestos de la fórmula I (Esquema 2).

Las amidas de la fórmula general VI se pueden obtener de las aminas de la fórmula general V por reacción con ácidos carboxílicos (Y = OH), cloruros (Y = Cl) o anhídridos (por ejemplo, Y = O–C(O)–O–$CH_2(CH)_3CH_3$) de la fórmula IX (Esquema 1), tal como se describe para la conversión de aminas XV en amidas I (Esquema 2).

Las amidas de la fórmula general XVI se pueden obtener de una manera análoga a partir de aminas XV y ácidos carboxílicos o derivados de ácido carboxílico XVII (Y: por ejemplo, OH, Cl u O–C(O)–O–$CH_2(CH)_3CH_3$;

LG´: por ejemplo, Br o I) (Esquema 2).

De forma análoga, las aminas XX (LG´: por ejemplo, Br o I) se pueden obtener de las aminas XIX y ácidos carboxílicos o derivados de ácido carboxílico XVII (Y: por ejemplo, OH, Cl u O–C(O)–O–$CH_2(CH)_3CH_3$; LG´: por ejemplo, Br o I) (Esquema 3).

Del mismo modo, los ácidos carboxílicos XIII (PG: por ejemplo, Boc) se pueden convertir con aminas XI en amidas XIV (Esquema 2) y ácidos carboxílicos XXI (LG´: por ejemplo, Br, I) con aminas XI a amidas XVI (Esquema 3) de esta manera.

Las aminas secundarias V se pueden obtener a partir de los correspondientes carbamatos IV (PG: por ejemplo, Boc) por medio de métodos conocidos por los expertos en el arte (Esquema 1).

De esta manera, por ejemplo, los carbamatos de *tert*-butilo se pueden convertir en las aminas V en un medio ácido con el uso, por ejemplo, de ácido trifluoroacético o ácido clorhídrico en un solvente apropiado o mezcla de solventes como, por ejemplo, diclorometano, dioxano o acetona/agua. En un medio anhidro, las aminas V se forman como las correspondientes sales.

De forma análoga, las aminas XV se pueden obtener a partir de los carbamatos XIV (Esquema 2) y las aminas

XIX a partir de los carbamatos XII (Esquema 3).

Los *2H*-indazoles de las fórmulas generales IV y VI se pueden producir en diversas vías.

Por ejemplo, los *2H*-indazoles IV se pueden obtener de los *1H*-indazoles de la fórmula general II por alquilación con compuestos de la fórmula general III (PG: por ejemplo, Boc, LG: por ejemplo, Br, I, O-Ts (tosiloxi) u O-Ms (mesiloxi)) en un solvente apropiado, por ejemplo, N,N-dimetilformamida, N,N-dimetilacetamida, dimetilsulfóxido o incluso THF, 1,4-dioxano y adición de una base como, por ejemplo, carbonato de potasio o carbonato de cesio (opcionalmente con adición de yoduro de tetrabutilamonio) o incluso bis(trimetilsilil)amida de sodio, a temperaturas de entre 25 °C y 100 °C o incluso en caso de usar bis(trimetilsilil)amida de sodio 0 °C y 25 °C (Esquema 1).

De forma análoga, los *2H*-indazoles de la fórmula general VI se pueden obtener a partir de los *1H*-indazoles de la fórmula general II y compuestos de la fórmula general X (LG: por ejemplo, Br, I, O-Ts u O-Ms) (Esquema 1).

Los *2H*-indazoles de la fórmula general IV también se pueden obtener a partir de orto-nitrobenzaldehídos de la fórmula general XXVII por reacción con una amina

XXVIII apropiada (PG: por ejemplo, Boc) en un solvente apropiado, por ejemplo, 1,4-dioxano y adición de un agente de reducción como, por ejemplo, trietilfosfito, posiblemente con adición de carbonato de potasio o carbonato de cesio o tamiz molecular en polvo, a temperaturas de entre 100 °C y 160 °C (Esquema 4).

Análogamente, los *2H*-indazoles de la fórmula general VI se pueden obtener a partir de los orto-nitrobenzaldehídos XXVII por reacción con las aminas XXIX (Esquema 4).

Los compuestos de la fórmula general XIV (PG: por ejemplo, Boc) también se pueden obtener a partir de bromo-indazoles de la fórmula general IV (PG: por ejemplo, Boc) bajo catálisis de paladio (0) por reacción con una amina XI apropiada y monóxido de carbono o una fuente de monóxido de carbono, tales como, por ejemplo, hexacarbonilmolibdeno (Esquema 2), análogamente al proceso descrito para la conversión de los bromoindazoles VI en los compuestos de la fórmula general I, (Esquema 1).

Los orto-nitrobenzaldehídos de la fórmula general XXVII se pueden producir a partir de los orto-nitrotoluenos de la fórmula general XXVI por medio de métodos conocidos por los expertos en el arte en dos etapas de reacción (Esquema 4).

Para ello, se disuelve un orto-nitrotolueno XXVI en un solvente apropiado como N,N-dimetilformamida y se convierte con N,N-dimetilformamida dimetilacetal a temperaturas de entre 100 - 140 °C en la correspondiente enamina, que inmediatamente se oxida a temperaturas entre 0 °C y 20 °C en el correspondiente orto-nitrobenzaldehído con un agente oxidante apropiado como, por ejemplo, $NaIO_4$ en una mezcla de solventes acuosos apropiados como agua/N,N-dimetilformamida y opcionalmente con adición de una base como, por ejemplo, trietilamina, N,N-diisopropil-etilamina, bicarbonato de sodio o carbonato de sodio.

Los orto-nitrotoluenos de la fórmula general XXVI se pueden producir a partir de las orto-metilanilinas de la fórmula general XXV por medio de métodos conocidos por los expertos en el arte (Esquema 4).

Para ello, se disuelve una orto-metilanilina XXV en un solvente apropiado como diclorometano o cloroformo, se trata con *tert*-butóxido de zirconio (IV), tamiz molecular molido 3Å e hidroperóxido de *tert*-butilo y se hizo reaccionar a temperaturas de 20-40 °C.

Los *1H*-indazoles de la fórmula general II se puede liberar de las acetamidas de la fórmula general XXIV por medio de métodos conocidos por los expertos en el

arte (Esquema 4).

Para ello, por ejemplo, una acetamida XXIV se hace reaccionar en un solvente apropiado como metanol o etanol y adición de ácido clorhídrico al 37% a temperaturas de 40 – 80 °C.

De forma análoga, las anilinas de la fórmula XXV se pueden liberar de las acetanilidas de la fórmula XXIII (Esquema 4).

Las acetamidas de la fórmula general XXIV se pueden producir a partir de las orto-metilacetanilidas de la fórmula general XXIII por medio de métodos conocidos por los expertos en el arte (Esquema 4).

Para ello, las orto-metilacetanilidas XXIII se disuelven en un solvente apropiado como cloroformo o tolueno, se tratan con anhídrido acético, isopentilo o nitrito de *tert*-butilo y opcionalmente acetato de potasio y 18-corona-6 y se hacen reaccionar a temperaturas de 60 – 100 °C.

Las orto-metilacetanilidas XXIII se pueden producir a partir de las acetanilidas de la fórmula general XXII por bromination por medio de métodos conocidos por los expertos en el arte (Esquema 4).

Para ello, las acetanilidas XXII, que se pueden obtener, por ejemplo, a partir de las correspondientes anilinas por reacción con anhídrido acético en un

solvente apropiado (por ejemplo, tolueno) a temperaturas de 80–110 °C, se hace reaccionar con bromo en ácido acético glacial a temperaturas de 10–25 °C.

Los compuestos de la fórmula general III, en donde LG significa –OTs u –OMs, se pueden producir por medio de métodos conocidos por los expertos en el arte a partir de los correspondientes alcoholes.

Para ello, los alcoholes se hacen reaccionar con cloruro de p-toluensulfonilo o cloruro de metansulfonilo a temperaturas de entre 0 °C y 40 °C en un solvente apropiado, por ejemplo, diclorometano o tetrahidrofurano o tolueno y adición de una base apropiada, por ejemplo, piridina o trietilamina.

Los compuestos de la fórmula general X, en donde LG significa –OTs u –OMs, se pueden producir a partir de los correspondientes aminoalcoholes XXX por medio de métodos conocidos por los expertos en el arte (Esquema 4).

Para ello, en una primera etapa, los aminoalcoholes XXX se convierten en las correspondientes amidas XXXI en un solvente apropiado, por ejemplo, diclorometano, con cloruros de ácido arilcarboxílico de la fórmula Cl–C(O)–Ar–R^3 y adición de una base apropiada, por ejemplo, trietilamina, a temperaturas de entre 0 °C y 25 °C. Opcionalmente, los

correspondientes ésteres formados como subproductos se pueden separar o incluso saponificar en los correspondientes alcoholes XXXI en condiciones estándar, por ejemplo, con uso de una base, por ejemplo, hidróxido de potasio, en una mezcla de solventes apropiada, por ejemplo, etanol/agua, a temperaturas de entre 20 °C y 40 °C

Los alcoholes N-protegidos XXXI así obtenidos se pueden convertir en los compuestos de la fórmula X con LG: -OTs u -OMs análogamente al proceso descrito para la síntesis de los compuestos III. Los compuestos de la fórmula X con LG: -Br se pueden obtener a partir de los correspondientes alcoholes XXXI por medio de métodos conocidos por los expertos en el arte por reacción con un agente de bromination como, por ejemplo, CBr_4 con adición de PPh_3 como un oxófilo en un solvente apropiado, por ejemplo, cloroformo, a temperaturas de entre 20 °C y 40 °C.

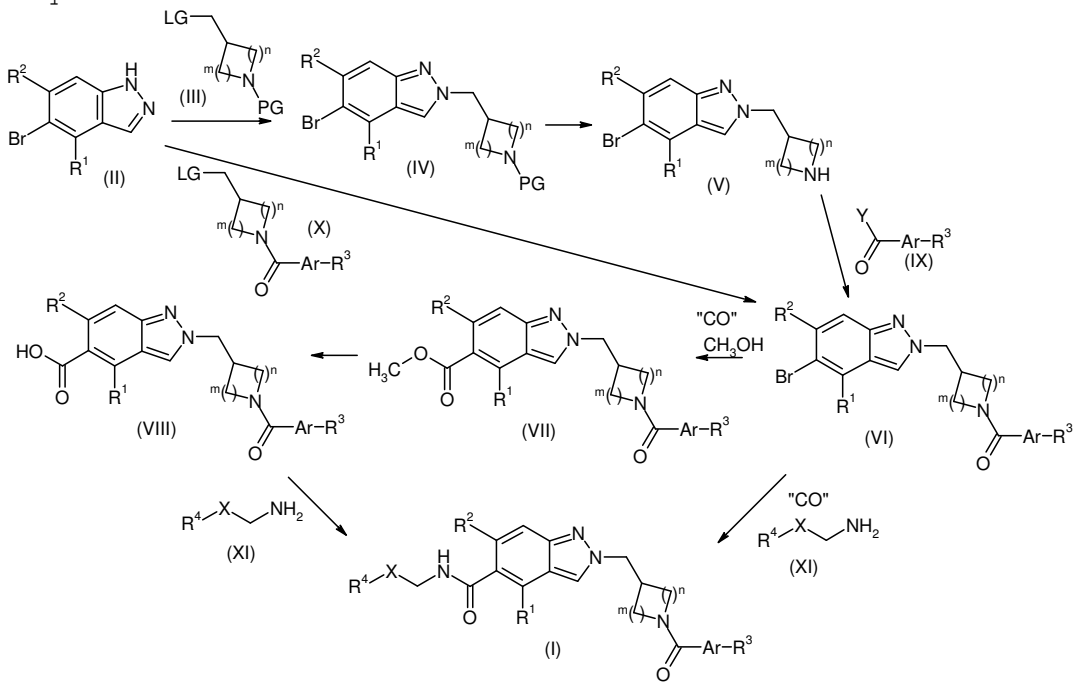
Los compuestos de la fórmula general XXIX se pueden producir por medio de métodos conocidos por los expertos en el arte, por ejemplo, a partir de las aminas de la fórmula XXXII (Esquema 4).

Para ello, en una primera etapa, las aminas XXXII se convierten en las correspondientes amidas XXXIII análogamente a la síntesis de los compuestos I partir

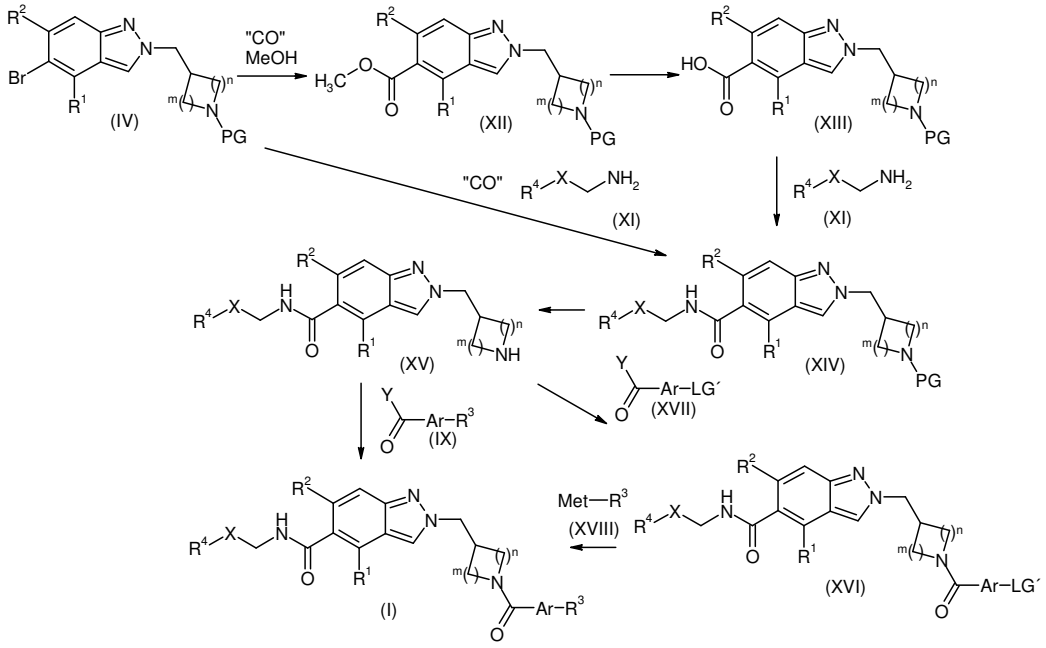
de los compuestos XV.

El grupo *tert*-butiloxicarbonilo en los compuestos de la fórmula XXXIII se cliva análogamente a la conversión de los compuestos IV en los compuestos V, así, se pueden obtener los compuestos de la fórmula XXIX.

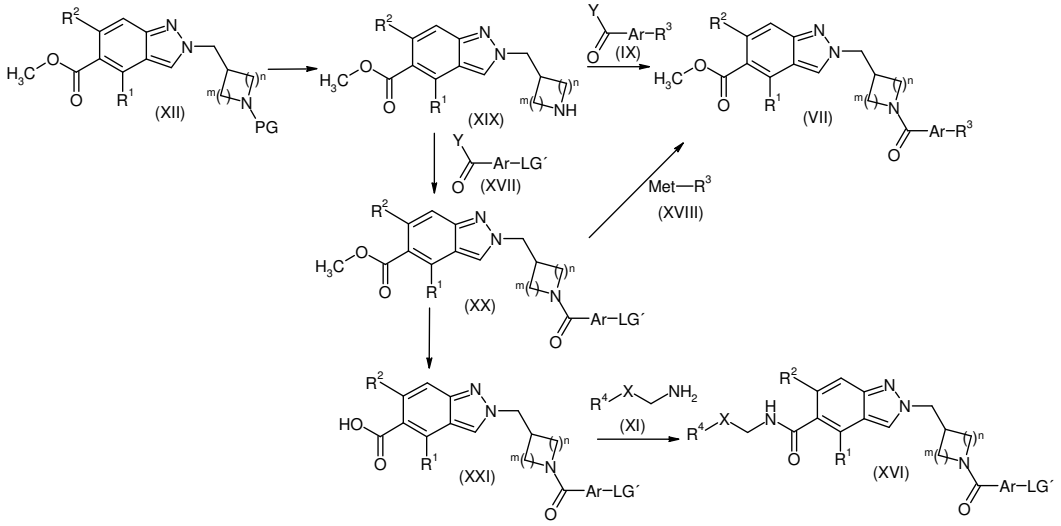
Esquema 1



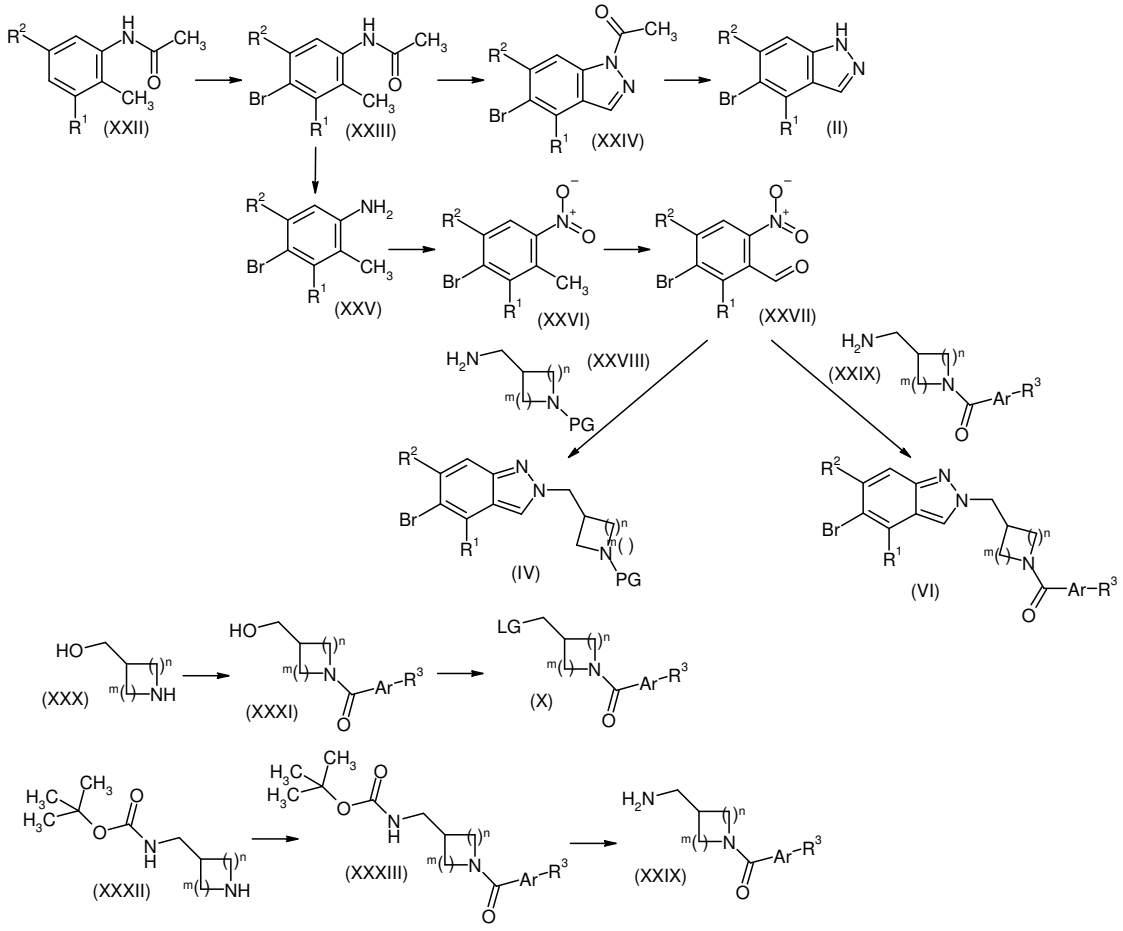
Esquema 2



Esquema 3



Esquema 4



Producción de los compuestos de acuerdo con la invención

Los siguientes ejemplos ilustran la producción de los compuestos de acuerdo con la invención de la fórmula general (I), sin limitar el rango de los compuestos reivindicados a estos ejemplos.

Los compuestos de acuerdo con la invención de la fórmula general (I) se pueden producir y caracterizar tal como se describe más abajo.

LC-MS: Waters Acquity HPLC / MS 100-800 Daltons; 20 V

(Micromasa / Waters ZQ 4000); columna: BEHC 18 (Waters), 2,1 x 50 mm, BEH 1,7 µm; fase móvil: A: H_2O/0,05% de HCOOH, B: CH_3CN/0,05% de HCOOH. Gradiente: 10–90% de B en 1,7 min, 90% de B durante 0,2 min, 98–2% de B en 0,6 min; tasa de flujo: 1,3 ml / min, detección: UV = 200 – 400 nm.

Método de separación de HPLC quiral A:

PLC quiral preparativa: sistema: Dionex: bomba P 580, Gilson: Liquid Handler 215, Knauer: detector UV K-2501 columna: Chiralpak AD-H 5 µm 250x20 mm; solvente: hexano / etanol 50:50; tasa de flujo: 15 ml/min; volumen de inyección: 0,5 ml; detección: UV 254 nm.

PLC quiral analítica: sistema: Waters: Alliance 2695, DAD 996, ESA: corona; columna: Chiralpak AD-H 5 µm 150x4,6 mm solvente: hexano / etanol 50:50; tasa de flujo: 1,0 ml/min; temperatura: 25 °C; inyección: 5 µl; detección: DAD 254 nm.

Método de separación de HPLC quiral B:

HPLC quiral preparativa: sistema: Dionex: bomba P 580, Gilson: Liquid Handler 215, Knauer: detector UV K-2501 columna: Chiralpak IC 5 µm 250x30 mm; solvente: etanol / metanol 50:50; tasa de flujo: 30 ml/min; volumen de inyección: 0,5 ml; detección: UV 254 nm.

HPLC quiral analítico: sistema: Waters: Alliance 2695, DAD 996, ESA: Corona; columna: Chiralpak IC 5 µm

150x4,6 mm solvente: etanol / metanol 50:50; tasa de flujo: 1,0 ml/min; temperatura: 25 °C; inyección: 5 µl; detección: DAD 254 nm.

Método de separación de HPLC quiral C:

HPLC quiral preparativa: sistema: Dionex: bomba P 580, Gilson: Liquid Handler 215, Knauer: detector UV K-2501 columna: Chiralpak AD-H 5 µm 250x20 mm; solvente: hexano / 2-propanol 50:50; tasa de flujo: 15 ml/min; volumen de inyección: 0,25 ml; detección: UV 254 nm.

PLC quiral analítico: sistema: Waters: Alliance 2695, DAD 996, ESA: Corona; columna: Chiralpak AD-H 5 µm 150x4,6 mm solvente: hexano / 2-propanol 50:50; tasa de flujo: 1,0 ml/min; temperatura: 25 °C; inyección: 5 µl; detección: DAD 254 nm.

Método de separación de HPLC quiral D:

HPLC quiral preparativa: sistema: Dionex: bomba P 580, Gilson: Liquid Handler 215, Knauer: detector UV K-2501 columna: Chiralpak IB 5 µm 250x20 mm; solvente: hexano / etanol 70:30; tasa de flujo: 20 ml/min; volumen de inyección: 0,1 ml; detección: UV 210 nm.

HPLC quiral analítica: sistema: Waters: Alliance 2695, DAD 996, ESA: Corona; columna: Chiralpak IB 5 µm 150x4,6 mm solvente: hexano / etanol 70:30; tasa de flujo: 1,0 ml/min; temperatura: 25 °C; inyección: 5 µl; detección: DAD 230 nm.

Método de separación de HPLC quiral E:

HPLC quiral preparativa: sistema: Dionex: bomba P 580, Gilson: Liquid Handler 215, Knauer: detector UV K-2501 columna: Chiralpak IC 5 µm 250x20 mm; solvente: etanol / metanol 50:50; tasa de flujo: 15 ml/min; volumen de inyección: 0,3 ml; detección: UV 230 nm.

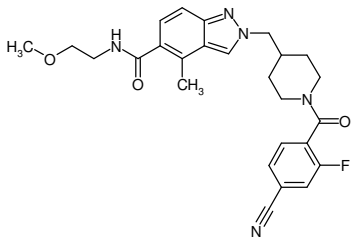
HPLC quiral analítica: sistema: Waters: Alliance 2695, DAD 996, ESA: Corona; columna: Chiralpak IC 5 µm 150x4,6 mm solvente: etanol / metanol 50:50; tasa de flujo: 1,0 ml/min; temperatura: 25 °C; inyección: 5 µl; detección: DAD 230 nm.

Abreviaturas

Boc	*tert*-butoxicarbonilo
CO	monóxido de carbono
DBU	1,8-diazabiciclo[5,4,0]undec-7-eno
DCM	diclorometano
DMF	N,N-dimetilformamida
DMSO	dimetilsulfóxido
ESI; ES+	ionización por electronebulización (en MS); traza iónica de carga positiva
hr(s)	hora(s)
HATU	N-óxido de hexafluorofosfato de N-[(dimetilamino)-1H-1,2,3-triazolo[4,5-b]piridin-1-ilmetilen]-N-metilmetanaminio
HPLC	*cromatografía líquida de alta presión, de*

	alto rendimiento
conc.	concentrado
LC–MS	cromatografía líquida–espectroscopia de masa acoplada
M	molar
min(s)	minuto(s)
MS	espectroscopia de masa
N	normal
RMN	espectroscopia de resonancia magnética
R_t	tiempo de retención (en HPLC y LC)
RT	temperatura ambiente
tert	terciario
THF	tetrahidrofurano

Ejemplo 1: 2-{[1-(4-ciano-2-fluorobenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



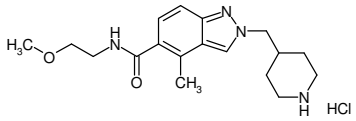
A una solución de 33,7 mg de ácido 4-ciano-2-fluorobenzoico en 1,0 ml de dimetilsulfóxido se añadieron 85,5 mg de HATU, 75 mg de la amina preparada en el Ejemplo 1a y 0,071 ml de N,N-diisopropiletilamina y esto se agitó durante 1 hora a 25 °C. La mezcla se

concentró al vacío y el residuo así obtenido se purificó por HPLC. Rendimiento: 43,3 mg del compuesto del título.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,07 - 1,28 (2H), 1,30 - 1,44 (1H), 1,47 - 1,61 (1H), 2,18 - 2,34 (1H), 2,49 (3H), 2,71 - 2,83 (1H), 2,92 - 3,08 (1H), 3,32 (4H), 3,36 (2H), 3,42 (2H), 4,31 (2H), 4,39 - 4,51 (1H), 7,14 (1H), 7,38 (1H), 7,50 - 7,63 (1H), 7,71 - 7,79 (1H), 7,95 (1H), 8,09 - 8,15 (1H), 8,47 (1H).

El material de partida para el compuesto del título anterior se preparó de la siguiente manera:

Ejemplo 1a: clorhidrato de N-(2-metoxietil)-4-metil-2-(4-piperidilmetil)-2H-indazol-5-carboxamida

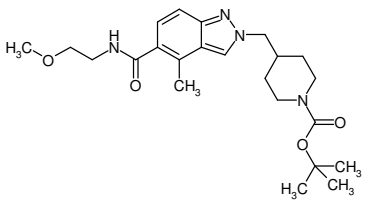


A 855,1 mg de 1b se añadieron 4,5 ml de ácido clorhídrico 4 M en dioxano y 1 ml de dioxano. Se formó una masa oleosa, que se disolvió en agitación vigorosa y calentamiento moderado. La mezcla se agitó durante 1 hr a aproximadamente 30 °C. La mezcla de reacción se concentró. Rendimiento: 764,7 mg del compuesto del título, que luego se hizo reaccionar sin ulterior purificación.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,33 - 1,50 (2H), 1,52 - 1,62 (2H), 2,17 - 2,31 (1H), 2,32 - 2,38 (1H),

2,49 (3H), 2,67 – 2,86 (2H), 3,13 – 3,28 (5H), 3,31 – 3,46 (4H), 4,33 (2H), 7,16 (1H), 7,38 (1H), 8,13 (1H), 8,53 (1H), 8,71 – 8,88 (1H), 8,99 – 9,11 (1H).

Ejemplo 1b: 4-({5-[N-(2-metoxietil)carbamoil]-4-metil-2H-indazol-2-il}-metil)piperidin-1-carboxilato de *tert*-butilo

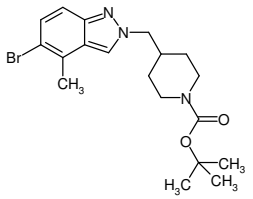


Versión A: 2820 mg de 1c, 1556 mg de 2-metoxietilamina, 1823 mg de hexa-carbonilo de molibdeno, 200,4 mg de tetrafluoroborato de tri-*tert*-butilfosfina y 647,5 mg de *trans*-bis(acetato)-bis[o-(di-o-tolilfosfino)bencil]dipaladio (II) se colocaron en porciones en tres tubos de microondas y se suspendieron con 56 ml de THF. A continuación, 3,1 ml de DBU se añadieron y la mezcla se agitó durante 20 min a 125 °C y 200 watts en el microondas. Las mezclas de reacción se combinaron, se filtraron y se diluyeron con algo de acetato de etilo y la fase orgánica se lavó dos veces con agua y una vez con solución saturada de cloruro de sodio. Esto se secó sobre sulfato de sodio, se filtró y se concentró. El residuo se cromatografió en el Biotage SP4. Gradiente: acetato de etilo/metanol 0-10%. Rendimiento: 885,1 mg del compuesto del título.

Versión B: 780 mg de 1d y 1747 mg de HATU se disolvieron primero en 10 ml de DMSO. A continuación, se añadieron 314 mg de 2-metoxietilamina y 1080 mg de N,N-diisopropiletilamina. La mezcla se agitó durante 1 hr a temperatura ambiente. La mezcla de reacción se vertió en agua y se extrajo tres veces con acetato de etilo. Las fases orgánicas combinadas se lavaron con solución saturada de cloruro de sodio, se secaron sobre sulfato de sodio, se filtraron y se concentraron. El residuo se purificó por cromatografía en el Biotage SP4. Gradiente: acetato de etilo/metanol 0-10%. Rendimiento: 740 mg del compuesto del título.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,01 - 1,13 (2H), 1,34 (9H), 1,36 - 1,43 (2H), 2,06 - 2,19 (1H), 2,49 (3H), 2,59 - 2,70 (2H), 3,29 (3H), 3,33 - 3,39 (2H), 3,40 - 3,45 (2H), 3,82 - 3,93 (2H), 4,28 (2H), 7,14 (1H), 7,38 (1H), 8,09 - 8,14 (1H), 8,46 (1H).

Ejemplo 1c: 4-[(5-bromo-4-metil-2H-indazol-2-il)metil]piperidin-1-carboxilato de *tert*-butilo

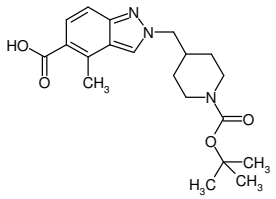


5 g de 5-bromo-4-metil-1H-indazol se disolvió en 110 ml de DMF y se trataron con 11,5 g de carbonato de

cesio y 7,9 g de N-Boc-4-(bromometil)piperidina. La mezcla se agitó durante 3 hrs a 60 °C y durante la noche a temperatura ambiente. La mezcla de reacción se diluyó luego con acetato de etilo y la fase orgánica se lavó dos veces con agua, se secó sobre sulfato de sodio, se filtró y se concentró. El residuo se purificó por cromatografía en el Biotage SP4 a través de una columna 65i-Si. Gradiente: hexano/acetato de etilo 0-100%. Rendimiento: 3,53 g del compuesto del título.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 0,99 - 1,12 (2H), 1,34 (9H), 1,36 - 1,44 (2H), 2,04 - 2,19 (1H), 2,47 (3H), 2,54 - 2,72 (2H), 3,82 - 3,93 (2H), 4,27 (2H), 7,29 (1H), 7,34 (1H), 8,46 (1H).

Ejemplo 1d: ácido 2-{[1-(*tert*-butoxicarbonil)piperidin-4-il]metil}-4-metil-2H-indazol-5-carboxílico

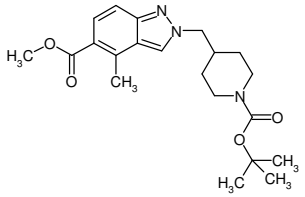


1080 mg de 1e se disolvieron en 8 ml de metanol y se trataron con 1235 mg de hidróxido de litio en 10 ml de agua. Otros 2 ml de THF se añadieron como solubilizante. La mezcla se agitó durante 24 hrs a temperatura ambiente. A continuación, se destiló el metanol y THF. El residuo acuoso se diluyó con agua y se lavó una vez con acetato de etilo. La fase acuosa se

acidificó con ácido sulfúrico al 10% y se extrajo dos veces con acetato de etilo. Las fases orgánicas combinadas se secaron sobre sulfato de sodio, se filtraron y se concentraron. Rendimiento: 880 mg del compuesto del título.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 0,99 - 1,18 (2H), 1,37 - 1,48 (2H), 1,34 (9H), 2,05 - 2,21 (1H), 2,53 - 2,70 (2H), 2,73 (3H), 3,81 - 3,94 (2H), 4,29 (2H), 7,39 (1H), 7,62 (1H), 8,62 (1H), 11,92 - 12,31 (1H).

Ejemplo 1e: 2-{[1-(*tert*-butoxicarbonil)piperidin-4-il]metil)}-4-metil-2H-indazol-5-carboxilato de metilo

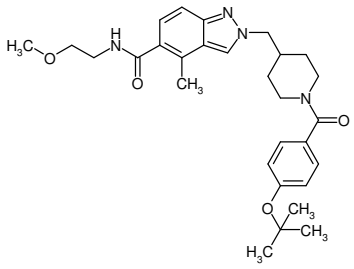


666 mg de 1c, 156,8 mg de metanol, 645,8 mg de hexacarbonilo de molibdeno, 47,3 mg de tetrafluoroborato de tri-*tert*-butilfosfina y 123,5 mg de *trans*-bis(acetato)-bis[o-(di-o-tolil-fosfino)bencil]dipaladio (II) se colocaron en un tubo de microondas y se suspendieron en 15 ml de THF. A continuación, 0,7 ml de DBU se añadieron y la mezcla se agitó durante 20 min a 125 °C y 150 watts en el microondas. A continuación, se concentró, se extrajo en acetato de etilo y la fase orgánica se lavó dos veces con agua y una vez con solución saturada de cloruro de

sodio. Se secó sobre sulfato de sodio, se filtró y se concentró. El residuo se cromatografió en el Biotage SP4. Gradiente: hexano/acetato de etilo 0-100%. Rendimiento: 363 mg del compuesto del título.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,01 - 1,12 (2H), 1,34 (9H), 1,37 - 1,45 (2H), 2,08 - 2,19 (1H), 2,53 - 2,69 (2H), 2,73 (3H), 3,79 (3H), 3,83 - 3,93 (2H), 4,30 (2H), 7,42 (1H), 7,62 (1H), 8,67 (1H).

Ejemplo 2: 2-({1-[4-*tert*-(butoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

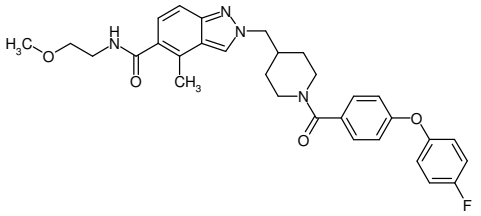


De forma análoga al Ejemplo 1, se obtuvieron 35,9 mg del compuesto del título a partir de 75 mg de la amina preparada en el Ejemplo 1a y 39,7 mg de ácido 4-(*tert*-butoxi)benzoico.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,09 - 1,26 (2H), 1,29 (9H), 1,35 - 1,58 (2H), 2,15 - 2,35 (1H), 2,49 (3H), 2,69 - 2,97 (2H), 3,24 (3H), 3,32 - 3,47 (4H), 4,23 - 4,40 (2H), 6,98 (2H), 7,14 (1H), 7,23 (2H), 7,38 (1H), 8,10 (1H), 8,47 (1H).

Ejemplo 3: 2-({1-[4-(4-fluorofenoxi)benzoil]piperidin-

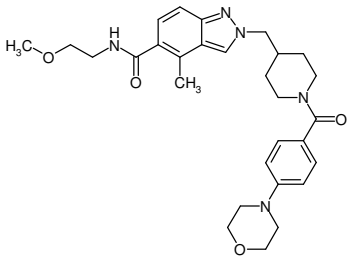
4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 51,6 mg del compuesto del título a partir de 75 mg de la amina preparada en el Ejemplo 1a y 47,5 mg de ácido 4-(4-fluorofenoxi)benzoico.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,10 - 1,30 (2H), 1,32 - 1,58 (2H), 2,19 - 2,35 (1H), 2,49 (3H), 2,71 - 3,02 (2H), 3,25 (3H), 3,32 - 3,39 (2H), 3,40 - 3,47 (2H), 4,32 (2H), 6,95 (2H), 7,06 - 7,14 (3H), 7,15 - 7,27 (3H), 7,31 - 7,42 (3H), 8,07 - 8,15 (1H), 8,47 (1H).

Ejemplo 4: N-(2-metoxietil)-4-metil-2-{[1-(4-morfolinobenzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida

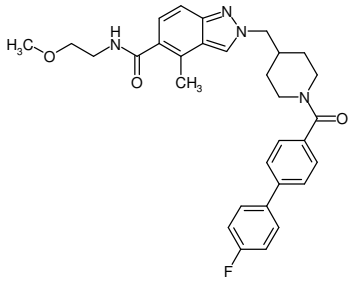


De forma análoga al Ejemplo 1, se obtuvieron 48,1 mg del compuesto del título a partir de 75 mg de la amina preparada en el Ejemplo 1a y 42,3 mg de ácido 4-

morfolinobenzoico.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,09 – 1,29 (2H), 1,36 – 1,53 (2H), 2,16 – 2,34 (1H), 2,49 (3H), 2,72 – 2,94 (2H), 3,13 (4H), 3,24 (3H), 3,42 (4H), 3,64 – 3,75 (4H), 3,92 – 4,15 (1H), 4,32 (2H), 6,92 (2H), 7,14 (1H), 7,20 (2H), 7,38 (1H), 8,07 – 8,15 (1H), 8,47 (1H).

Ejemplo 5: 2-({1-[(4'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida

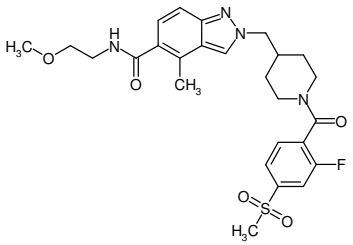


De forma análoga al Ejemplo 1, se obtuvieron 50,1 mg del compuesto del título a partir de 75 mg de la amina preparada en el Ejemplo 1a y 44,2 mg de ácido 4-(4-fluorofenil)benzoico.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,11 – 1,32 (2H), 1,32 – 1,64 (2H), 2,20 – 2,36 (1H), 2,49 (3H), 2,63 – 3,08 (2H), 3,24 (3H), 3,42 (4H), 3,50 – 3,73 (1H), 4,24 – 4,55 (3H), 7,10 – 7,20 (1H), 7,27 2H), 7,41 (3H), 7,67 (4H), 8,03 – 8,16 (1H), 8,48 (1H).

Ejemplo 6: 2-{[1-(2-fluoro-4-mesilbenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-

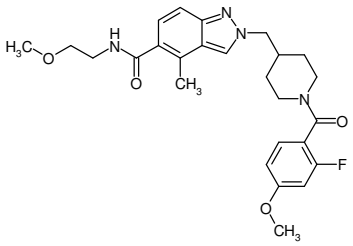
carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 40,1 mg del compuesto del título a partir de 75 mg de la amina preparada en el Ejemplo 1a y 44,6 mg de ácido 2-fluoro-4-mesilbenzoico.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,06 - 1,30 (2H), 1,31 - 1,45 (1H), 1,51 - 1,64 (1H), 2,20 - 2,37 (1H), 2,49 (3H), 2,71 - 2,85 (1H), 2,91 - 3,10 (1H), 3,24 (3H), 3,26 (3H), 3,33 - 3,39 (2H), 3,42 (2H), 4,24 - 4,39 (2H), 4,40 - 4,51 (1H), 7,14 (1H), 7,38 (1H), 7,59 - 7,69 (1H), 7,76 - 7,89 (2H), 8,07 - 8,14 (1H), 8,47 (1H).

Ejemplo 7: 2-{[1-(2-fluoro-4-metoxibenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

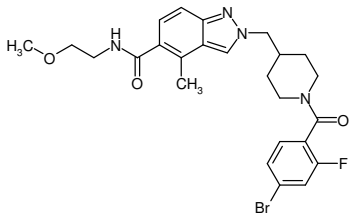


De forma análoga al Ejemplo 1, se obtuvieron 43,1 mg del compuesto del título a partir de 75 mg de la

amina preparada en el Ejemplo 1a y 34,8 mg de ácido 2-fluoro-4-metoxibenzoico.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,05 - 1,25 (2H), 1,32 - 1,44 (1H), 1,48 - 1,61 (1H), 2,18 - 2,33 (1H), 2,49 (3H), 2,63 - 2,79 (1H), 2,88 - 3,05 (1H), 3,24 (3H), 3,42 (d, 5H), 3,75 (3H), 4,27 - 4,35 (2H), 4,37 - 4,49 (1H), 6,77 - 6,89 (2H), 7,14 (1H), 7,24 (1H), 7,38 (1H), 8,07 - 8,15 (1H), 8,47 (1H).

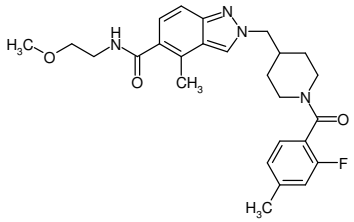
Ejemplo 8: 2-{[1-(4-bromo-2-fluorobenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 51,8 mg del compuesto del título a partir de 75 mg de la amina preparada en el Ejemplo 1a y 44,7 mg de ácido 4-bromo-2-fluorobenzoico.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,04 - 1,27 (2H), 1,32 - 1,43 (1H), 1,49 - 1,61 (1H), 2,20 - 2,33 (1H), 2,48 (3H), 2,67 - 2,80 (1H), 2,91 - 3,05 (1H), 3,24 (3H), 3,33 - 3,46 (5H), 4,24 - 4,36 (2H), 4,38 - 4,49 (1H), 7,15 (1H), 7,27 - 7,34 (1H), 7,35 - 7,41 (1H), 7,44 - 7,50 (1H), 7,60 - 7,66 (1H), 8,07 - 8,15 (1H), 8,47 (1H).

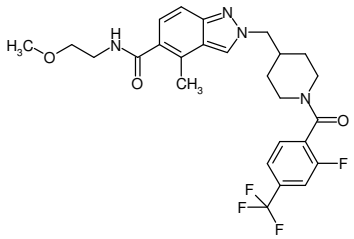
Ejemplo 9: 2-{[1-(2-fluoro-4-metilbenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 38,3 mg del compuesto del título a partir de 75 mg de la amina preparada en el Ejemplo 1a y 31,5 mg de ácido 2-fluoro-4-metilbenzoico.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,04 – 1,26 (2H), 1,31 – 1,43 (1H), 1,48 – 1,60 (1H), 2,18 – 2,35 (4H), 2,48 (3H), 2,64 – 2,79 (1H), 2,89 – 3,04 (1H), 3,24 (3H), 3,33 – 3,39 (3H), 3,39 – 3,45 (2H), 4,23 – 4,36 (2H), 4,39 – 4,49 (1H), 7,01 – 7,10 (2H), 7,13 (1H), 7,16 – 7,24 (1H), 7,38 (1H), 8,07 – 8,14 (1H), 8,47 (1H).

Ejemplo 10: 2-({1-[2-fluoro-4-(trifluorometil)benzoil]piperidin-4-il}metil)-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida

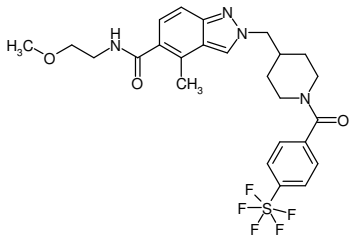


De forma análoga al Ejemplo 1, se obtuvieron 57,8

mg del compuesto del título a partir de 75 mg de la amina preparada en el Ejemplo 1a y 42,5 mg de ácido 2-fluoro-4-(trifluorometil)benzoico.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,07 - 1,29 (2H), 1,32 - 1,44 (1H), 1,52 - 1,62 (1H), 2,20 - 2,36 (1H), 2,49 (3H), 2,67 - 2,84 (1H), 2,93 - 3,07 (1H), 3,24 (3H), 3,32 - 3,39 (3H), 3,39 - 3,46 (2H), 4,24 - 4,39 (2H), 4,40 - 4,51 (1H), 7,14 (1H), 7,38 (1H), 7,56 - 7,68 (2H), 7,76 (1H), 8,07 - 8,14 (1H), 8,47 (1H).

Ejemplo 11: N-(2-metoxietil)-4-metil-2-({1-[4-(pentafluoro-λ^6-sulfanil)benzoil] piperidin-4-il}metil)-2H-indazol-5-carboxamida

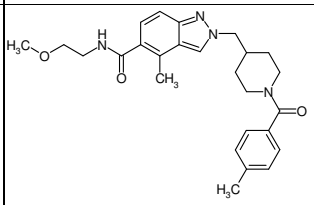
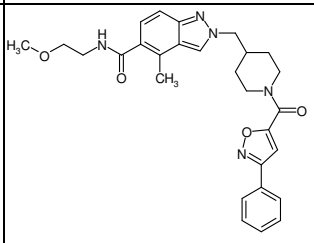


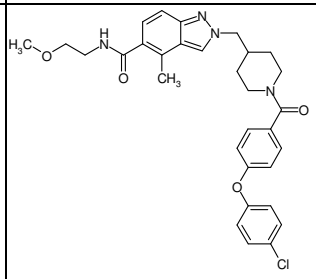
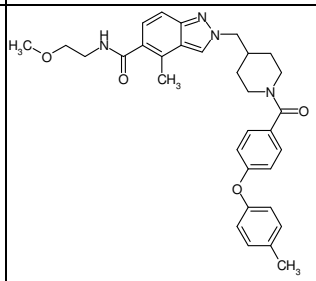
De forma análoga al Ejemplo 1, se obtuvieron 135,1 mg del compuesto del título a partir de 150 mg de la amina preparada en el Ejemplo 1a y 101,5 mg de ácido 4-(pentafluoro-λ^6-sulfanil)benzoico.

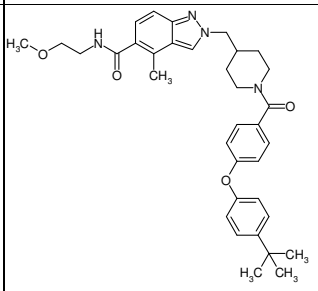
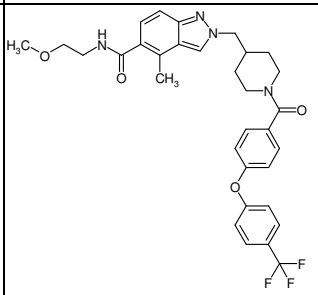
^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,10 - 1,30 (2H), 1,31 - 1,42 (1H), 1,50 - 1,62 (1H), 2,20 - 2,33 (1H), 2,49 (3H), 2,67 - 2,83 (1H), 2,91 - 3,06 (1H), 3,24 (3H), 3,32 - 3,39 (2H), 3,41 (3H), 4,32 (2H), 4,37 - 4,48 (1H), 7,14 (1H), 7,38 (1H), 7,55 (2H), 7,94

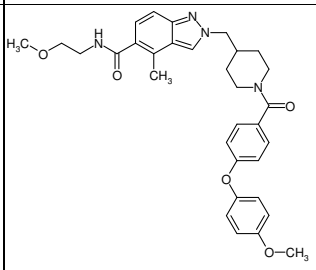
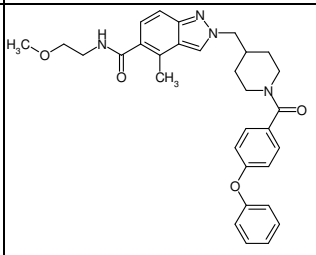
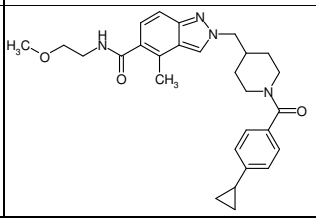
(2H), 8,12 (1H), 8,47 (1H).

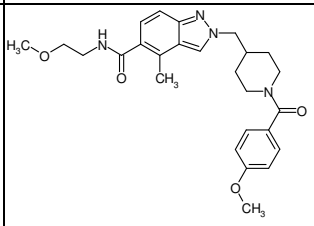
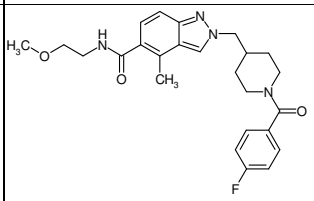
Los siguientes compuestos se prepararon de forma análoga:

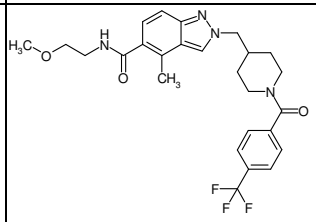
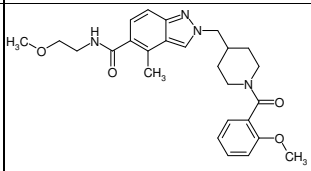
Ej.	Estructura	Nombre IUPAC	Análisis
12		N-(2-metoxietil)-4-metil-2-{[1-(4-metilbenzoil)-piperidin-4-il]-metil}-2H-indazol-5-carboxamida	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,20 (2H), 1,42 (2H), 2,29 (4H), 2,49 (3H), 2,73 (1H), 2,93 (1H), 3,25 (3H), 3,37 (2H), 3,43 (2H), 3,57 (1H), 4,31 (2H), 4,40 (1H), 7,14 (1H), 7,21 (4H), 7,38 (1H), 8,09 (1H), 8,46 (1H).
13		N-(2-metoxietil)-4-metil-2-({1-[(3-fenilisoxazol-5-il)carbonil]piperidin-4-il}metil)-2H-	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,25 (2H), 1,55 (2H), 2,34 (1H), 2,49 (3H), 2,83 (1H), 3,15 (1H), 3,24 (3H), 3,40 (4H), 3,87 (1H), 4,35 (3H), 7,15 (1H), 7,40 (1H), 7,46 (1H), 7,50 (3H), 7,90

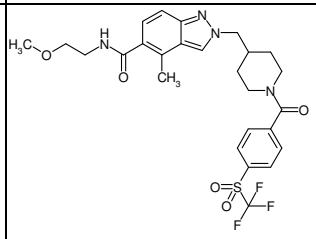
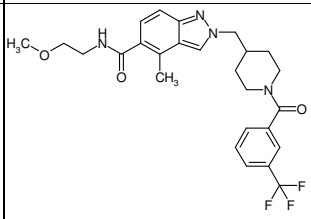
Ej.	Estructura	Nombre IUPAC	Análisis
		indazol-5-carboxamida	(2H), 8,13 (1H), 8,49 (1H).
14		2-({1-[4-(4-cloro-fenoxi)benzoil]-piperidin-4-il}-metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,21 (2H), 1,45 (2H), 2,26 (1H), 2,49 (3H), 2,76 (1H), 2,94 (1H), 3,24 (3H), 3,40 (4H), 3,62 (1H), 4,33 (3H), 7,04 (4H), 7,15 (1H), 7,40 (5H), 8,12 (1H), 8,47 (1H).
15		N-(2-metoxietil)-4-metil-2-({1-[4-(4-metilfenoxi)-benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,20 (2H), 1,43 (2H), 2,26 (4H), 2,48 (3H), 2,76 (1H), 2,90 (1H), 3,24 (3H), 3,38 (4H), 3,62 (1H), 4,32 (3H), 6,92 (4H), 7,71 (3H), 7,34 (3H), 8,12 (1H), 8,47 (1H).

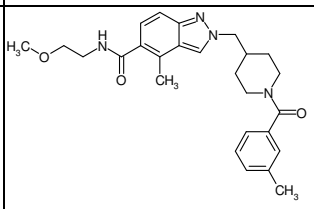
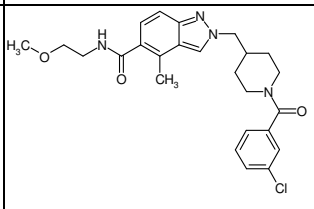
Ej.	Estructura	Nombre IUPAC	Análisis
16		2-({1-[4-(4-*tert*-butilfenoxi)-benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,21 (2H), 1,25 (9H), 1,44 (2H), 2,26 (1H), 2,48 (3H), 2,77 (1H), 2,291 (1H), 3,24 (3H), 3,39 (4H), 3,64 (1H), 4,32 (3H), 6,95 (4H), 7,14 (1H), 7,36 (5H), 8,12 (1H), 8,47 (1H).
17		N-(2-metoxietil)-4-metil-2-[(1-{4-[4-(trifluorometil)-fenoxi]benzoil}-piperidin-4-il)-metil]-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,22 (2H), 1,45 (2H), 2,27 (1H), 2,49 (3H), 2,77 (1H), 2,97 (1H), 3,24 (3H), 3,39 (4H), 3,61 (1H), 4,33 (3H), 7,15 (5H), 7,39 (3H), 7,73 (2H), 8,12 (1H), 8,48 (1H).

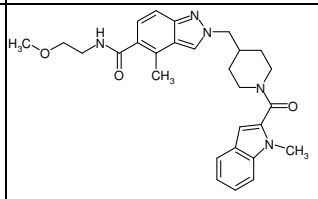
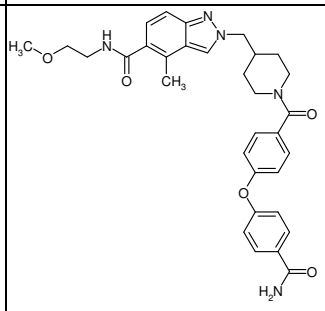
Ej.	Estructura	Nombre IUPAC	Análisis
18		N-(2-metoxietil)-2-({1-[4-(4-metoxi-fenoxi)benzoil]-piperidin-4-il}-metil)-4-metil-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,19 (2H), 1,44 (2H), 2,25 (1H), 2,48 (3H), 2,86 (2H), 3,24 (3H), 3,40 (4H), 3,64 (1H), 3,72 (3H), 4,32 (3H), 6,88 (2H), 6,95 (2H), 7,02 (2H), 7,14 (1H), 7,31 (2H), 7,38 (1H), 8,12 (1H), 8,47 (1H).
19		N-(2-metoxietil)-4-metil-2-{[1-(4-fenoxibenzoil)-piperidin-4-il]-metil}-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,21 (2H), 1,44 (2H), 2,26 (1H), 2,49 (3H), 2,77 (1H), 2,92 (1H), 3,24 (3H), 3,38 (4H), 3,64 (1H), 4,32 (3H), 6,97 (2H), 7,04 (2H), 7,16 (2H), 7,26 (5H), 8,12 (1H), 8,47 (1H).
20		2-{[1-(4-ciclopropil-benzoil)piperi	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 0,65 (2H), 0,93 (2H), 1,19

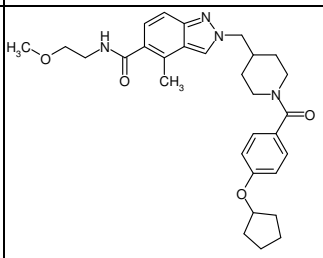
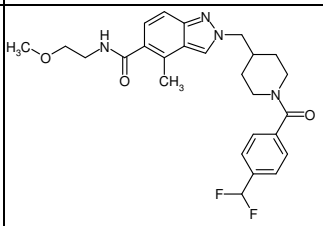
Ej.	Estructura	Nombre IUPAC	Análisis
		din-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida	(2H), 1,43 (2H), 1,90 (1H), 2,25 (1H), 2,48 (3H), 2,73 (1H), 2,92 (1H), 3,24 (3H), 3,39 (4H), 3,59 (1H), 4,32 (3H), 7,14 (5H), 7,38 (1H), 8,12 (1H), 8,47 (1H).
21		2-{[1-(4-metoxi-benzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,19 (2H), 1,44 (2H), 2,26 (1H), 2,49 (3H), 2,82 (2H), 3,24 (3H), 3,36 (2H), 3,42 (2H), 3,50 (1H), 3,74 (3H), 4,31 (3H), 6,93 (2H), 7,14 (1H), 7,29 (2H), 7,38 (1H), 8,12 (1H), 8,47 (1H).
22		2-{[1-(4-fluoro-benzoil)piperidin-4-il]metil}-N-	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,20 (2H), 1,37 (1H), 1,51 (1H), 2,27 (1H), 2,49 (3H), 2,72 (1H), 2,97

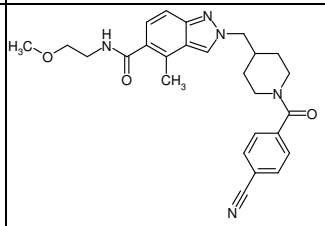
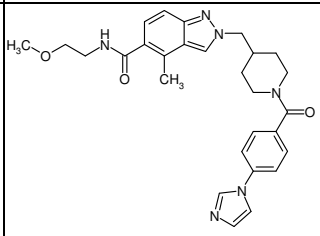
Ej.	Estructura	Nombre IUPAC	Análisis
		(2-metoxietil)-4-metil-2H-indazol-5-carboxamida	(1H), 3,24 (3H), 3,36 (2H), 3,42 (2H), 3,52 (1H), 4,31 (2H), 4,40 (1H), 7,14 (1H), 7,23 (2H), 7,39 (3H), 8,12 (1H), 8,47 (1H).
23		N-(2-metoxietil)-4-metil-2-({1-[4-(trifluorometil)-benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,22 (2H), 1,34 (1H), 1,56 (1H), 2,28 (1H), 2,49 (3H), 2,75 (1H), 2,99 (1H), 3,24 (3H), 3,35 (2H), 3,42 (3H), 4,32 (2H), 4,44 (1H), 7,14 (1H), 7,38 (1H), 7,55 (2H), 7,77 (2H), 8,12 (1H), 8,47 (1H).
24		2-{[1-(2-metoxi-benzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,11 (2H), 1,35 (1H), 1,52 (1H), 2,23 (1H), 2,49 (3H), 2,66 (1H), 2,87 (1H), 3,22 (1H), 3,24 (3H), 3,35 (2H), 3. 42

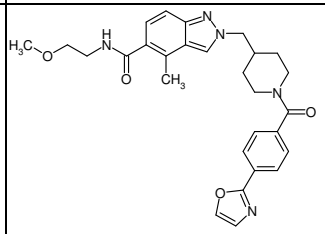
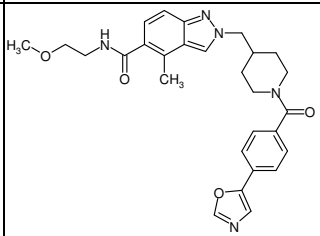
Ej.	Estructura	Nombre IUPAC	Análisis
		metil-2H-indazol-5-carboxamida	(2H), 3,71 (3H), 4,29 (1H), 4,33 (1H), 4,45 (1H), 6. 94 (1H), 7,07 (3H), 7,33 (1H), 7,39 (1H), 8,12 (1H), 8,48 (1H).
25		N-(2-metoxietil)-4-metil-2-[(1-{4-[(trifluorometil)-sulfonil]benzoil}-piperidin-4-il)-metil]-2H-indazol-5-carboxamida	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,23 (2H), 1,36 (1H), 1,57 (1H), 2,29 (1H), 2,49 (3H), 2,77 (1H), 3,01 (1H), 3,24 (3H), 3,35 (3H), 3,42 (2H), 4,32 (2H), 4,44 (1H), 7,14 (1H), 7,38 (1H), 7,77 (2H), 8,15 (3H), 8,47 (1H).
26		N-(2-metoxietil)-4-metil-2-({1-[3-(trifluorometil)-benzoil]piperi	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,24 (2H), 1,37 (1H), 1,55 (1H), 2,28 (1H), 2,49 (3H), 2,75 (1H), 3,01 (1H), 3,24 (3H), 3,36 (2H), 3,42 (3H), 4. 32

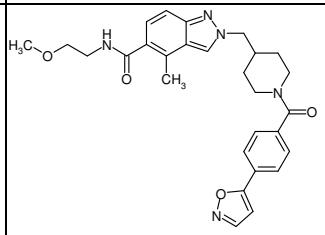
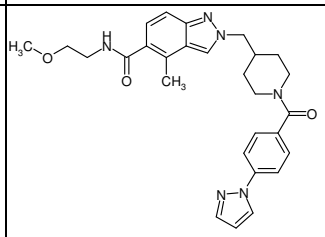
Ej.	Estructura	Nombre IUPAC	Análisis
		din-4-il}metil)-2H-indazol-5-carboxamida	(2H), 4. 43 (1H), 7,14 (1H), 7,38 (1H), 7,65 (3H), 7,78 (1H), 8,12 (1H), 8,47 (1H).
27		N-(2-metoxietil)-4-metil-2-{[1-(3-metilbenzoil)-piperidin-4-il]-metil}-2H-indazol-5-carboxamida	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,20 (2H), 1,36 (1H), 1,52 (1H), 2,29 (4H), 2,49 (3H), 2,69 (1H), 2,95 (1H), 3,24 (3H), 3,36 (2H), 3,42 (2H), 3,53 (1H), 4,31 (2H), 4,41 (1H), 7,12 (3H), 7,21 (1H), 7,27 (1H), 7,38 (1H), 8,12 (1H), 8,47 (1H).
28		2-{[1-(3-cloro-benzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,21 (2H), 1,36 (1H), 1,53 (1H), 2,27 (1H), 2,49 (3H), 2,72 (1H), 2,98 (1H), 3,24 (3H), 3,35 (2H), 3,42 (3H), 4,31 (2H), 4,40 (1H), 7,14

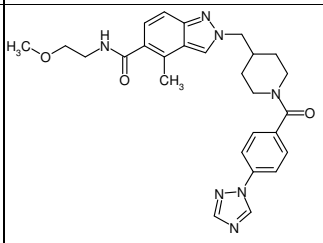
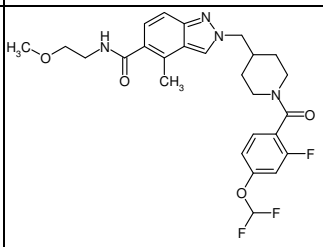
Ej.	Estructura	Nombre IUPAC	Análisis
		indazol-5-carboxamida	(1H), 7,28 (1H), 7,43 (4H), 8,12 (1H), 8,47 (1H).
29		N-(2-metoxietil)-4-metil-2-({1-[(1-metil-1H-indol-2-il)carbonil]-piperidin-4-il}metil)-2H-indazol-5-carboxamida	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,25 (2H), 1,50 (2H), 2,31 (1H), 2,49 (3H), 2,82 (1H), 3,05 (1H), 3,24 (3H), 3,36 (2H), 3,42 (2H), 3,69 (3H), 3,98 (1H), 4,34 (2H), 4,44 (1H), 6,57 (1H), 7,05 (1H), 7,15 (1H), 7,20 (1H), 7,39 (1H), 7,46 (1H), 7,56 (1H), 8,12 (1H), 8,49 (1H).
30		2-({1-[4-(4-carbamoilfenoxi)-benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,22 (2H), 1,49 (2H), 2,31 (1H), 2,52 (3H), 2,82 (1H), 2,98 (1H), 3,27 (3H), 3,39 (2H), 3,45 (2H), 3,65 (1H), 4,35 (2H), 4,43 (1H), 7,08

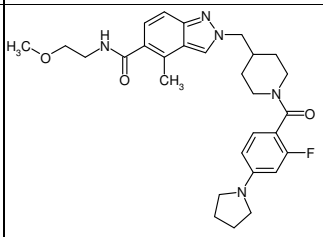
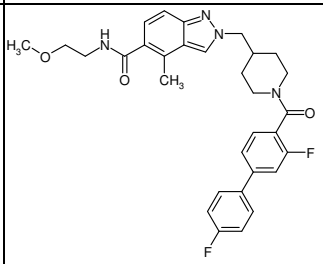
Ej.	Estructura	Nombre IUPAC	Análisis
		metil-2H-indazol-5-carboxamida	(4H), 7,17 (1H), 7,29 (1H), 7,41 (3H), 7,91 (3H), 8,12 (1H), 8,50 (1H).
31		2-({1-[4-(ciclopentiloxi)benzoil]-piperidin-4-il}-metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,23 (2H), 1,47 (2H), 1,57 (2H), 1,68 (4H), 1,90 (2H), 2,28 (1H), 2,52 (3H), 2,86 (2H), 3,27 (3H), 3,39 (2H), 3,45 (2H), 3,85 (2H), 4,34 (2H), 4,83 (1H), 6,91 (2H), 7,17 (1H), 7,28 (2H), 7,41 (1H), 8,12 (1H), 8,49 (1H).
32		2-({1-[4-(difluorometil)benzoil]-piperidin-4-il}-metil)-N-(2-metoxietil)-4-metil-2H-	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,24 (2H), 1,39 (1H), 1,57 (1H), 2,30 (1H), 2,52 (3H), 2,76 (1H), 3,01 (1H), 3,27 (3H), 3,39 (2H), 3,45 (3H), 4,35 (2H), 4,45 (1H), 7,18

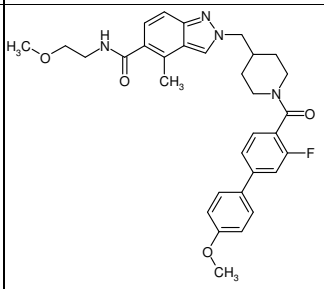
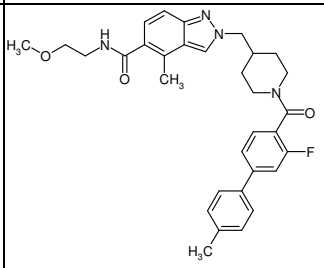
Ej.	Estructura	Nombre IUPAC	Análisis
		indazol-5-carboxamida	(2H), 7,41 (1H), 7,49 (2H), 7,62 (2H), 8,12 (1H), 8,49 (1H).
33		2-{[1-(4-ciano-benzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,24 (2H), 1,39 (1H), 1,58 (1H), 2,30 (1H), 2,52 (3H), 2,77 (1H), 3,01 (1H), 3,27 (3H), 3,39 (3H), 3,45 (2H), 4,34 (2H), 4,44 (1H), 7,17 (1H), 7,41 (1H), 7,54 (2H), 7,90 (2H), 8,12 (1H), 8,49 (1H).
34		2-({1-[4-(1H-imidazol-1-il)-benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,24 (2H), 1,39 (1H), 156 (1H), 2,29 (1H), 2,49 (3H), 2,76 (1H), 3,04 (1H), 3,24 (3H), 3,37 (3H), 3,42 (3H), 4,33 (2H), 4,44 (1H), 7,15 (1H), 7,39 (1H), 7,61 (2H), 7,84 (3H), 8,11

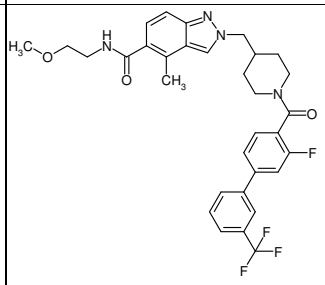
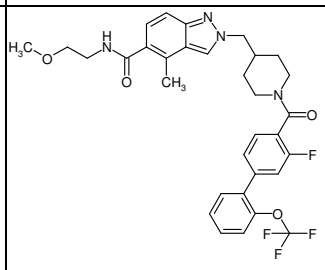
Ej.	Estructura	Nombre IUPAC	Análisis
		carboxamida	(1H), 8,26 (1H), 8,48 (1H).
35		N-(2-metoxietil)-4-metil-2-({1-[4-(oxazol-2-il)-benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,24 (2H), 1,37 (1H), 1,54 (1H), 2,27 (1H), 2,49 (3H), 2,75 (1H), 3,00 (1H), 3,24 (3H), 3,36 (2H), 3,42 (2H), 3,53 (1H), 4,32 (2H), 4,43 (1H), 7,14 (1H), 7,38 (2H), 7,48 (2H), 8,00 (2H), 8,12 (1H), 8,23 (1H), 8,48 (1H).
36		N-(2-metoxietil)-4-metil-2-({1-[4-(oxazol-5-il)-benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,22 (2H), 1,38 (1H), 1,53 (1H), 2,28 (1H), 2,49 (3H), 2,74 (1H), 2,98 (1H), 3,24 (3H), 3,36 (2H), 3,41 (2H), 3,55 (1H), 4,32 (2H), 4,41 (1H), 7,15 (1H), 7,42 (3H), 7,74 (3H), 8,12

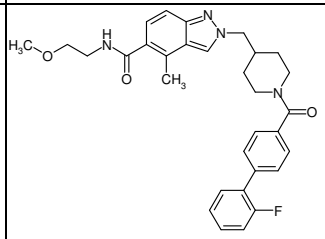
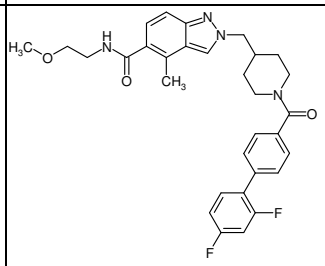
Ej.	Estructura	Nombre IUPAC	Análisis
			(1H), 8,47 (2H).
37		N-(2-metoxietil)-4-metil-2-({1-[4-(isoxazol-5-il)-benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,22 (2H), 1,36 (1H), 1,55 (1H), 2,28 (1H), 2,49 (3H), 2,74 (1H), 2,99 (1H), 3,24 (3H), 3,39 (5H), 4,31 (2H), 4,43 (1H), 4,74 (2H), 7,14 (1H), 7,38 (1H), 7,50 (2H), 7,95 (2H), 8,12 (1H), 8,47 (1H).
38		N-(2-metoxietil)-4-metil-2-({1-[4-(1H-pirazol-1-il)-benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,22 (2H), 1,46 (2H), 2,28 (1H), 2,49 (3H), 2,76 (1H), 2,99 (1H), 3,24 (3H), 3,39 (4H), 3,61 (1H), 4,32 (2H), 4,41 (1H), 6,54 (1H), 7,15 (1H), 7,39 (1H), 7,46 (2H), 7,74 (1H), 7,87 (2H), 8,12 (1H), 8,50 (2H).

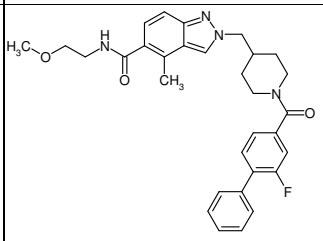
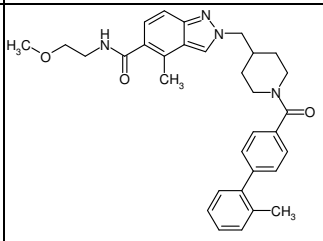
Ej.	Estructura	Nombre IUPAC	Análisis
39		N-(2-metoxietil)-4-metil-2-({1-[4-(1H-1,2,4-triazol-1-il)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,22 (2H), 1,39 (1H), 1,53 (1H), 2,27 (1H), 2,49 (3H), 2,76 (1H), 3,00 (1H), 3,24 (3H), 3,39 (4H), 3,54 (1H), 4,32 (2H), 4,43 (1H), 7,15 (1H), 7,39 (1H), 7,53 (2H), 7,90 (2H), 8,12 (1H), 8,24 (1H), 8,48 (1H), 9,32 (1H).
40		2-({1-[4-(difluoro-metoxi)-2-fluoro-benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,16 (2H), 1,38 (1H), 1,55 (1H), 2,26 (1H), 2,48 (3H), 2,73 (1H), 2,98 (1H), 3,24 (3H), 3,38 (5H), 4,31 (2H), 4,44 (1H), 7,12 (3H), 7,31 (1H), 7,40 (2H), 8,12 (1H), 8,47 (1H).

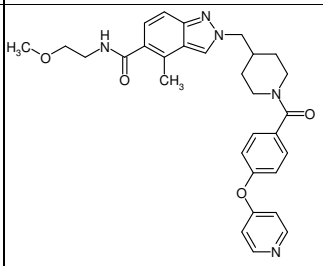
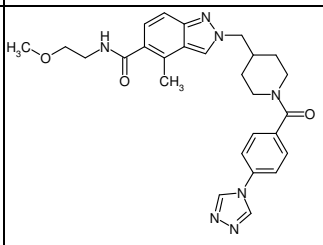
Ej.	Estructura	Nombre IUPAC	Análisis
41		2-({1-[2-fluoro-4-(pirrolidin-1-il)-benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,14 (2H), 1,43 (2H), 1,90 (4H), 2,23 (1H), 2,48 (3H), 2,68 (1H), 2,94 (1H), 3,19 (4H), 3,24 (3H), 3,36 (2H), 3,42 (3H), 4,31 (2H), 4,39 (1H), 6,29 (2H), 7,10 (2H), 7,38 (1H), 8,12 (1H), 8,47 (1H).
42		2-({1-[(3,4'-difluoro-bifenil-4-il)-carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,19 (2H), 1,39 (1H), 1,57 (1H), 2,28 (1H), 2,49 (3H), 2,76 (1H), 3,01 (1H), 3,24 (3H), 3,38 (5H), 4,32 (2H), 4,47 (1H), 7,15 (1H), 7,28 (2H), 7,40 (2H), 7,56 (2H), 7,76 (2H), 8,12 (1H), 8,48 (1H).

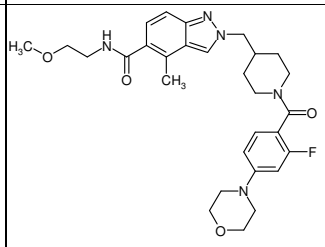
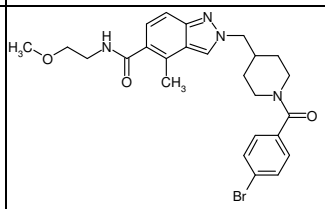
Ej.	Estructura	Nombre IUPAC	Análisis
43		2-({1-[(3-fluoro-4'-metoxibifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,19 (2H), 1,39 (1H), 1,57 (1H), 2,28 (1H), 2,49 (3H), 2,76 (1H), 3,01 (1H), 3,24 (3H), 3,38 (5H), 4,32 (2H), 4,47 (1H), 7,15 (1H), 7,28 (2H), 7,40 (2H), 7,56 (2H), 7,76 (2H), 8,12 (1H), 8,48 (1H).
44		2-({1-[(3-fluoro-4'-metilbifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,19 (2H), 1,39 (1H), 1,57 (1H), 2,31 (4H), 2,49 (3H), 2,75 (1H), 3,01 (1H), 3,24 (3H), 3,36 (2H), 3,42 (3H), 4,32 (2H), 4,48 (1H), 7,14 (1H), 7,26 (2H), 7,39 (2H), 7,56 (4H), 8,12 (1H), 8,48 (1H).

Ej.	Estructura	Nombre IUPAC	Análisis
45		2-[(1-{[3-fluoro-3'-(trifluorometil)-bifenil-4-il]-carbonil}-piperidin-4-il)-metil]-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,20 (2H), 1,40 (1H), 1,57 (1H), 2,29 (1H), 2,49 (3H), 2,76 (1H), 3,03 (1H), 3,24 (3H), 3,36 (2H), 3,41 (3H), 4,33 (2H), 4,48 (1H), 7,15 (1H), 7,39 (1H), 7,45 (1H), 7,69 (4H), 8,03 (2H), 8,12 (1H), 8,49 (1H).
46		2-[(1-{[3-fluoro-2'-(trifluorometoxi)-bifenil-4-il]-carbonil}piperidin-4-il)metil]-N-(2-metoxietil)-4-metil-2H-indazol-5-	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,20 (2H), 1,42 (1H), 1,57 (1H), 2,29 (1H), 2,49 (3H), 2,76 (1H), 3,04 (1H), 3,24 (3H), 3,36 (5H), 4,32 (2H), 4,48 (1H), 7,15 (1H), 7,44 (8H), 8,12 (1H), 8,49 (1H).

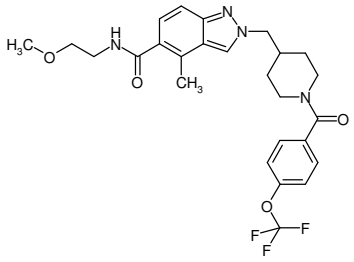
Ej.	Estructura	Nombre IUPAC	Análisis
		carboxamida	
47		2-({1-[(2'-fluoro-bifenil-4-il)-carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,23 (2H), 1,41 (1H), 1,53 (1H), 2,29 (1H), 2,49 (3H), 2,74 (1H), 3,01 (1H), 3,24 (3H), 3,36 (4H), 3,60 (1H), 4,33 (2H), 4,44 (1H), 7,15 (1H), 7,29 (2H), 7,40 (4H), 7,55 (3H), 8,12 (1H), 8,48 (1H).
48		2-({1-[(2',4'-difluoro-bifenil-4-il)-carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,23 (2H), 1,39 (1H), 1,53 (1H), 2,28 (1H), 2,49 (3H), 2,75 (1H), 3,01 (1H), 3,24 (3H), 3,39 (4H), 3,60 (1H), 4,33 (2H), 4,43 (1H), 7,16 (2H), 7,40 (4H), 7,56 (3H), 8,12 (1H), 8,48 (1H).

Ej.	Estructura	Nombre IUPAC	Análisis
49		2-({1-[(2-fluoro-bifenil-4-il)-carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,24 (2H), 1,39 (1H), 1,56 (1H), 2,29 (1H), 2,49 (3H), 2,74 (1H), 3,02 (1H), 3,25 (3H), 3,37 (2H), 3,42 (2H), 3,59 (1H), 4,33 (2H), 4,43 (1H), 7,15 (1H), 7,28 (2H), 7,40 (2H), 7,46 (2H), 7,54 (3H), 8,12 (1H), 8,48 (1H).
50		N-(2-metoxietil)-4-metil-2-({1-[(2'-metilbifenil-4-il)carbonil]piperidin-4-il}metil)-2H-indazol-5-carboxamida	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,24 (2H), 1,42 (1H), 1,55 (1H), 2,20 (3H), 2,29 (1H),,249 (3H), 2,75 (1H), 3,02 (1H), 3,25 (3H), 3,37 (2H), 3,42 (2H), 3,64 (1H), 4,33 (2H), 4,42 (1H), 7,21 (5H), 7,38 (5H), 8,12 (1H), 8,49 (1H).

Ej.	Estructura	Nombre IUPAC	Análisis
51		N-(2-metoxietil)-4-metil-2-({1-[4-(piridiloxi)benzoil]piperidin-4-il}-metil)-2H-indazol-5-carboxamida	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,24 (2H), 1,42 (1H), 1,55 (1H), 2,29 (1H), 2,49 (3H), 2,76 (1H), 3,02 (1H), 3,25 (3H), 3,37 (2H), 3,43 (2H), 3,60 (1H), 4,33 (2H), 4,44 (1H), 7,15 (1H), 7,37 (3H), 7,48 (2H), 7,53 (2H), 8,12 (1H), 8,48 (1H), 8,75 (2H).
52		N-(2-metoxietil)-4-metil-2-({1-[4-(4H-1,2,4-triazol-4-il)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,23 (2H), 1,38 (1H), 1,54 (1H), 2,28 (1H), 2,49 (3H), 2,74 (1H), 3,02 (1H), 3,24 (3H), 3,36 (2H), 3,42 (2H), 3,53 (1H), 4,32 (2H), 4,42 (1H), 7,14 (1H), 7,38 (1H), 7,55 (2H), 7,75 (2H), 8,14 (1H), 8,48 (1H), 9,15 (2H).

Ej.	Estructura	Nombre IUPAC	Análisis
53		2-{[1-(2-fluoro-4-morfolinobenzoil)-piperidin-4-il]-metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida	^{1}H-RMN (600 MHz, DMSO-d_6): δ [ppm] = 1,01 (1H), 1,21 (1H), 1,36 (1H), 1,48 (1H), 1,57 (1H), 2,08 (1H), 2,53 (3H), 2,96 (7H), 3,29 (3H), 3,41 (2H), 3,47 (2H), 3,67 (4H), 4,34 (2H), 4,50 (1H), 6,86 (2H), 7,14 (2H), 7,41 (1H), 8,11 (1H), 8,47 (1H), 8,56 (1H).
54		2-{[1-(4-bromo-benzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm]=1,22 (2H), 1,36 (1H), 1,52 (1H), 2,26 (1H), 2,49 (3H), 2,72 (1H), 2,97 (1H), 3,24 (3H), 3,36 (2H), 3,42 (2H), 3,49 (1H), 4,31 (2H), 4,40 (1H), 7,14 (1H), 7,29 (2H), 7,38 (1H), 7,60 (2H), 8,12 (1H), 8,47 (1H).

Ejemplo 55: N-(2-metoxietil)-4-metil-2-({1-[4-(trifluorometoxi)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida

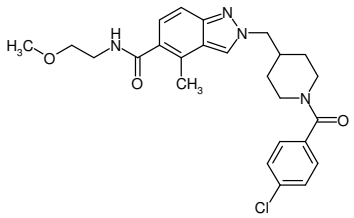


150 mg de la amina preparada en el Ejemplo 1a se disolvieron primero en 1,5 ml de piridina. 101 mg de cloruro de 4-(trifluorometoxi)benzoílo luego se añadieron y la mezcla se agitó durante 30 min a temperatura ambiente. La mezcla de reacción luego se trató con un poco de tolueno y se concentró. El residuo se extrajo en acetato de etilo y se lavó dos veces con agua, dos veces con solución saturada de bicarbonato de sodio (pH 9) y una vez con solución saturada de cloruro de sodio. La fase orgánica se secó sobre sulfato de sodio, se filtró y se concentró. El residuo se purificó por cromatografía en el Biotage SP4. Gradiente: acetato de etilo/metanol 0-10%. Rendimiento: 118,2 mg del compuesto del título.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,17 - 1,30 (2H), 1,30 - 1,45 (1H), 1,45 - 1,62 (1H), 2,19 - 2,35 (1H), 2,49 (3H), 2,64 - 2,86 (1H), 2,86 - 3,07 (1H), 3,24 (3H), 3,31 - 3,56 (5H), 4,31 (2H), 4,36 - 4,49

(1H), 7,14 (1H), 7,35 – 7,42 (3H), 7,43 – 7,50 (2H), 8,11 (1H), 8,47 (1H).

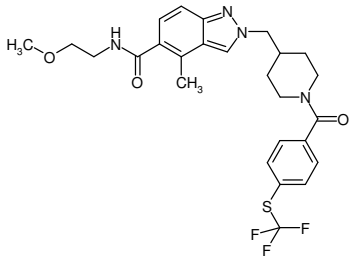
Ejemplo 56: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 183 mg del compuesto del título a partir de 300 mg de la amina preparada en el Ejemplo 1a y 157,4 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,10 – 1,29 (2H), 1,29 – 1,43 (1H), 1,44 – 1,61 (1H), 2,20 – 2,34 (1H), 2,49 (3H), 2,66 – 2,83 (1H), 2,84 – 3,06 (1H), 3,25 (3H), 3,32 – 3,39 (2H), 3,40 – 3,45 (2H), 3,45 – 3,55 (1H), 4,26 – 4,35 (2H), 4,35 – 4,46 (1H), 7,14 (1H), 7,32 – 7,41 (3H), 7,47 (2H), 8,09 – 8,15 (1H), 8,47 (1H).

Ejemplo 57: N-(2-metoxietil)-4-metil-2-[(1-{4-[(trifluorometil)sulfanil]benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida

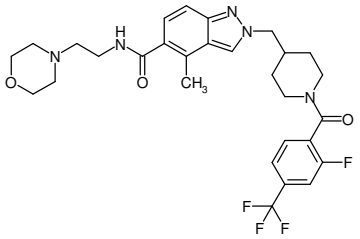


60 mg de la amina preparada en el Ejemplo 1a se disolvieron primero en 2 ml de DCM a 0 °C. 0,034 ml de trietilamina y 43,2 mg de cloruro de 4-[(trifluorometil)sulfanil]benzoílo luego se añadieron y la mezcla se agitó durante 2 hrs a 0 °C. La mezcla de reacción luego se diluyó con DCM y se lavó con ácido clorhídrico 1 molar, solución saturada de bicarbonato de sodio (pH 9) y solución saturada de cloruro de sodio. La fase orgánica se secó sobre sulfato de sodio, se filtró y se concentró. El residuo se purificó por cromatografía en el Biotage SP4. Gradiente: DCM/Metanol 0-10%. La fracción de producto se extrajo en acetato de etilo y se extrajo dos veces con solución saturada de bicarbonato de sodio. La fase orgánica se concentró y el residuo otra vez se purificó por HPLC. Rendimiento: 26,5 mg del compuesto del título.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,14 – 1,30 (2H), 1,31 – 1,42 (1H), 1,49 – 1,61 (1H), 2,21 – 2,32 (1H), 2,49 (3H), 2,67 – 2,80 (1H), 2,93 – 3,05 (1H), 3,25 (3H), 3,36 (2H), 3,42 (3H), 4,27 – 4,36 (2H), 4,38 – 4,48 (1H), 7,14 (1H), 7,38 (1H), 7,48 (2H), 7,75

(2H), 8,09 – 8,14 (1H), 8,47 (1H).

Ejemplo 58: 2-({1-[2-fluoro-4-(trifluorometil)benzoil]piperidin-4-il}metil)-4-metil-N-(2-morfolinoetil)-2H-indazol-5-carboxamida

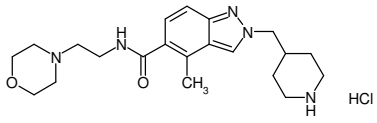


De forma análoga al Ejemplo 1, se obtuvieron 34,6 mg del compuesto del título a partir de 75 mg de la amina preparada en el Ejemplo 58a y 37,0 mg de ácido 2-fluoro-4-(trifluorometil)benzoico.

^{1}H-RMN (400 MHz, metanol-d_4): δ [ppm] = 1,24 – 1,43 (2H), 1,50 – 1,59 (1H), 1,65 – 1,73 (1H), 2,33 – 2,45 (1H), 2,65 (3H), 2,80 – 2,91 (1H), 3,05 – 3,18 (1H), 3,19 – 3,26 (2H), 3,39 – 3,44 (2H), 3,45 – 3,52 (1H), 3,63 – 3,70 (2H), 3,71 – 3,82 (4H), 4,06 – 4,14 (2H), 4,39 (2H), 4,62 – 4,70 (1H), 7,39 (1H), 7,47 (1H), 7,54 – 7,62 (3H), 8,45 (1H).

El material de partida se preparó de la siguiente manera:

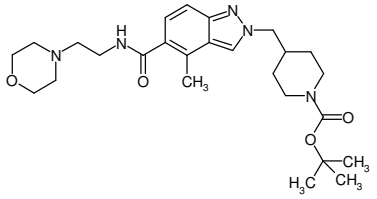
Ejemplo 58a: clorhidrato de 4-metil-N-(2-morfolinoetil)-2-(4-piperidilmetil)-2H-indazol-5-carboxamida



A 624,4 mg de 58b se añadieron 2,9 ml de ácido clorhídrico 4 M en dioxano y 0,5 ml de dioxano. Se formó una masa oleosa, que se disolvió en agitación vigorosa y calentamiento moderado. La mezcla se agitó durante 1 hr a aproximadamente 30 °C. La mezcla de reacción se concentró. Rendimiento: 980 mg del compuesto del título, que luego se hizo reaccionar sin ulterior purificación.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,33 - 1,51 (2H), 1,58 - 1,64 (1H), 2,17 - 2,31 (1H), 2,55 (3H), 2,70 - 2,86 (2H), 3,02 - 3,31 (7H), 3,43 - 3,51 (2H), 3,61 - 3,71 (2H), 3,72 - 3,88 (3H), 3,89 - 3,99 (2H), 4,30 - 4,36 (2H), 7,29 (1H), 7,40 (1H), 8,46 - 8,52 (1H), 8,54 - 8,58 (1H), 8,69 - 8,85 (1H), 8,96 - 9,10 (1H).

Ejemplo 58b: 4-({4-metil-5-[N-(2-morfolinoetil)carbamoil]-1H-indazol-2-il}-metil)piperidin-1-carboxilato de *tert*-butilo

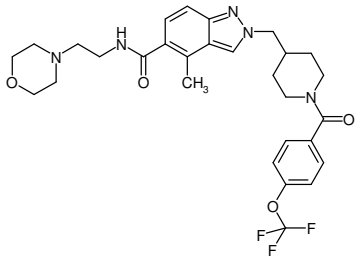


896 mg de 1c, 857 mg de 2-morfolinoetilamina, 579,3 mg de hexacarbonilo de molibdeno, 63,6 mg de

tetrafluoroborato de tri-*tert*-butilfosfina y 205,8 mg de *trans*-bis(acetato)-bis[o-(di-o-tolilfosfino)bencil]dipaladio (II) se colocaron en un tubo de microondas y se suspendieron en 18 ml de THF. Luego se añadió 1,0 ml de DBU y la mezcla se agitó durante 20 min a 125 °C y 200 watts en el microondas. La mezcla de reacción se diluyó con cierta cantidad de acetato de etilo y primero se filtró a través de Celite. El filtrado se diluyó con acetato de etilo y la fase orgánica se lavó dos veces con agua y una vez con solución saturada de cloruro de sodio. Luego se secó sobre sulfato de sodio, se filtró y se concentró. El residuo se cromatografió en el Biotage SP4. Gradiente: acetato de etilo/metanol 0-10%. Rendimiento: 624,4 mg del compuesto del título.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 0,98 - 1,13 (2H), 1,34 (11H), 2,05 - 2,27 (2H), 2,33 - 2,41 (5H), 2,51 (3H), 2,56 - 2,73 (2H), 3,25 - 3,37 (2H), 3,51 - 3,57 (4H), 3,81 - 3,93 (2H), 4,28 (2H), 7,14 (1H), 7,36 - 7,41 (1H), 7,95 - 8,02 (1H), 8,46 (1H).

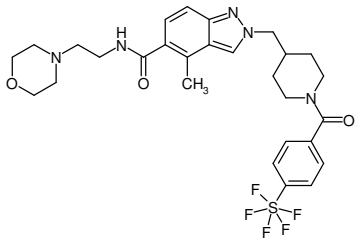
Ejemplo 59: 4-metil-N-(2-morfolinoetil)-2-({1-[4-(trifluorometoxi)benzoil] piperidin-4-il}metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 10,1 mg del compuesto del título a partir de 75 mg de la amina preparada en el Ejemplo 58a y 43,9 mg de cloruro de 4-(trifluorometoxi)benzoílo.

^{1}H-RMN (400 MHz, metanol-d_4): δ [ppm] = 1,24 - 1,44 (2H), 1,44 - 1,58 (1H), 1,59 - 1,74 (1H), 2,32 - 2,44 (1H), 2,51 - 2,58 (4H), 2,59 - 2,65 (5H), 2,77 - 2,90 (1H), 3,02 - 3,17 (1H), 3,53 (2H), 3,62 - 3,72 (5H), 4,35 - 4,41 (2H), 4,55 - 4,67 (1H), 7,29 (1H), 7,34 (2H), 7,43 (1H), 7,49 (2H), 8,39 (1H).

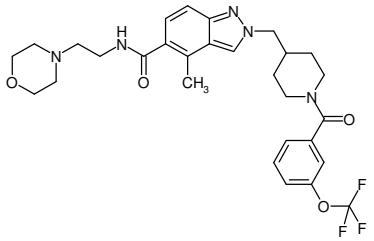
Ejemplo 60: 4-metil-N-(2-morfolinoetil)-2-({1-[4-(pentafluoro-λ^6-sulfanil)benzoil]-piperidin-4-il}metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 14,0 mg del compuesto del título a partir de 75 mg de la amina preparada en el Ejemplo 58a y 44,1 mg de ácido 4-(pentafluoro-λ^6-sulfanil)benzoico.

^{1}H-RMN (400 MHz, cloroformo-d): δ [ppm] = 1,16 - 1,32 (1H), 1,33 - 1,48 (1H), 1,50 - 1,63 (1H), 1,71 - 1,83 (1H), 1,84 - 2,08 (2H), 2,44 (1H), 2,55 (4H), 2,60 - 2,71 (5H), 2,72 - 2,85 (1H), 2,96 - 3,10 (1H), 3,60 (2H), 3,67 - 3,78 (4H), 4,33 (2H), 4,71 - 4,81 (1H), 6,45 (1H), 7,34 (1H), 7,47 (2H), 7,54 (1H), 7,79 (2H), 7,96 (1H).

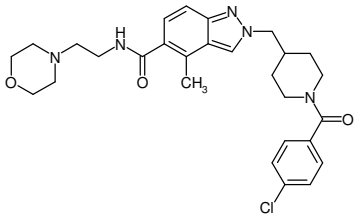
Ejemplo 61: 4-metil-N-(2-morfolinoetil)-2-({1-[3-(trifluorometoxi)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 18,1 mg del compuesto del título a partir de 75 mg de la amina preparada en el Ejemplo 58a y 43,9 mg de cloruro de 3-(trifluorometoxi)benzoílo.

^{1}H-RMN (400 MHz, cloroformo-d): δ [ppm] = 1,18 - 1,46 (2H), 1,49 - 1,63 (1H), 1,66 - 1,82 (1H), 2,37 - 2,49 (1H), 2,62 (3H), 2,67 (3H), 2,70 - 2,78 (4H), 2,79 - 2,86 (2H), 2,93 - 3,09 (1H), 3,66 - 3,74 (2H), 3,83 (4H), 4,32 (2H), 4,66 - 4,82 (1H), 6,83 - 6,96 (1H), 7,23 - 7,29 (2H), 7,29 - 7,34 (1H), 7,39 (1H), 7,43 (1H), 7,54 (1H), 7,96 (1H).

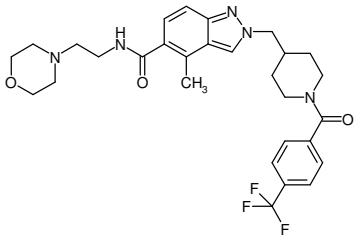
Ejemplo 62: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metil-N-(2-morfolinoetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 14,9 mg del compuesto del título a partir de 75 mg de la amina preparada en el Ejemplo 58a y 34,2 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (400 MHz, metanol-d_4): δ [ppm] = 1,24 - 1,42 (2H), 1,46 - 1,58 (1H), 1,58 - 1,71 (1H), 2,31 - 2,43 (1H), 2,63 (5H), 2,65 (3H), 2,73 - 2,91 (1H), 3,00 - 3,15 (1H), 3,25 - 3,33 (2H), 3,63 - 3,77 (3H), 3,79 - 4,03 (3H), 4,38 (2H), 4,54 - 4,67 (1H), 7,38 (3H), 7,42 - 7,49 (3H), 8,44 (1H).

Ejemplo 63: 4-metil-N-(2-morfolinoetil)-2-({1-[4-(trifluorometil)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida

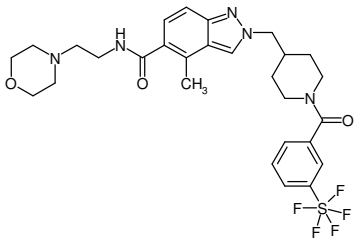


De forma análoga al Ejemplo 1, se obtuvieron 31,7 mg del compuesto del título a partir de 75 mg de la

amina preparada en el Ejemplo 58a y 33,8 mg de ácido 4-(trifluorometil)benzoico.

^{1}H-RMN (400 MHz, metanol-d_4): δ [ppm] = 1,24 - 1,43 (2H), 1,45 - 1,57 (1H), 1,63 - 1,73 (1H), 2,33 - 2,45 (1H), 2,66 (3H), 2,79 - 2,90 (1H), 3,04 - 3,17 (1H), 3,18 - 3,27 (2H), 3,39 - 3,45 (2H), 3,56 - 3,70 (3H), 3,76 (4H), 4,06 - 4,14 (2H), 4,36 - 4,42 (2H), 4,59 - 4,68 (1H), 7,39 (1H), 7,47 (1H), 7,57 (2H), 7,73 (2H), 8,45 (1H).

Ejemplo 64: 4-metil-N-(2-morfolinoetil)-2-({1-[4-(pentafluoro-λ^6-sulfanil)benzoil]-piperidin-4-il}metil)-2H-indazol-5-carboxamida

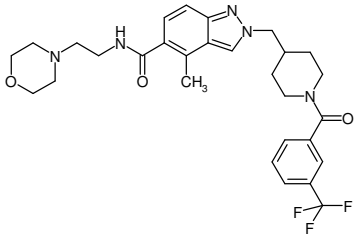


De forma análoga al Ejemplo 1, se obtuvieron 24,7 mg del compuesto del título a partir de 75 mg de la amina preparada en el Ejemplo 58a y 44,1 mg de ácido 3-(pentafluoro-λ^6-sulfanil)benzoico.

^{1}H-RMN (400 MHz, metanol-d_4): δ [ppm] = 1,27 - 1,47 (2H), 1,48 - 1,60 (1H), 1,60 - 1,74 (1H), 2,31 - 2,46 (1H), 2,66 (3H), 2,78 - 2,93 (1H), 3,04 - 3,18 (1H), 3,18 - 3,26 (2H), 3,39 - 3,43 (2H), 3,57 - 3,70 (3H), 3,72 - 3,82 (4H), 4,06 - 4,14 (2H), 4,39 (2H),

4,55 – 4,67 (1H), 7,38 (1H), 7,47 (1H), 7,60 – 7,67 (2H), 7,82 – 7,86 (1H), 7,89 – 7,94 (1H), 8,45 (1H).

Ejemplo 65: 4-metil-N-(2-morfolinoetil)-2-({1-[3-(trifluorometil)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida

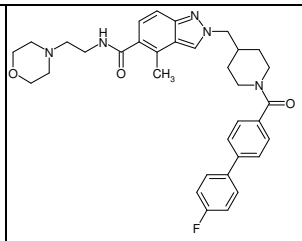
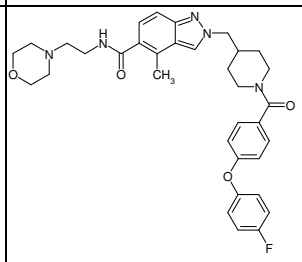


De forma análoga al Ejemplo 1, se obtuvieron 14,0 mg del compuesto del título a partir de 75 mg de la amina preparada en el Ejemplo 58a y 33,8 mg de ácido 3-(trifluorometil)benzoico.

^{1}H-RMN (400 MHz, metanol-d_4): δ [ppm] = 1,28 – 1,45 (2H), 1,47 – 1,59 (1H), 1,59 – 1,73 (1H), 2,32 – 2,45 (1H), 2,66 (3H), 2,79 – 2,93 (1H), 3,05 – 3,18 (1H), 3,19 – 3,27 (2H), 3,39 – 3,45 (2H), 3,58 – 3,70 (3H), 3,72 – 3,82 (4H), 4,06 – 4,14 (2H), 4,39 (2H), 4,57 – 4,68 (1H), 7,39 (1H), 7,47 (1H), 7,64 (2H), 7,67 – 7,70 (1H), 7,73 – 7,78 (1H), 8,45 (1H).

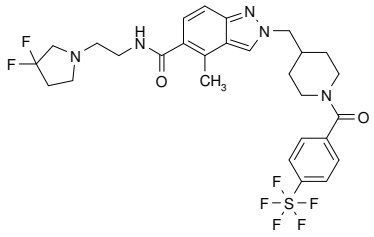
Los siguientes compuestos se prepararon de forma análoga:

Ej.	Estructura	Nombre IUPAC	Análisis

66		2-({1-[(4'-fluoro-bifenil-4-il)-carbonil]piperidin-4-il}metil)-4-metil-N-(2-morfolino-etil)-2H-indazol-5-carboxamida	1H-RMN (400 MHz, metanol-d_4): δ [ppm] = 1,35 (2H), 1,53 (1H), 1,66 (1H), 2,40 (1H), 2,66 (3H), 2,85 (1H), 3,11 (1H), 3,24 (2H), 3,42 (2H), 3,65 (2H), 3,76 (5H), 4,08 (2H), 4,40 (2H), 4,63 (1H), 7,17 (2H), 7,38 (1H), 7,47 (3H), 7,65 (4H), 8,45 (1H).
67		2-({1-[4-(4-fluoro-fenoxi)benzoil]-piperidin-4-il}-metil)-4-metil-N-(2-morfolinoetil)-2H-indazol-5-carboxamida	1H-RMN (400 MHz, metanol-d_4): δ [ppm] = 1,33 (2H), 1,68 (2H), 2,38 (1H), 2,66 (3H), 2,84 (1H), 3,11 (1H), 3,25 (2H), 3,42 (2H), 3,65 (2H), 3,76 (5H), 4,11 (2H), 4,38 (2H), 4,59 (1H), 6,98 (2H), 7,04 (2H), 7,11 (2H), 7,38 (3H), 7,47 (1H), 8,44 (1H).

Ejemplo 68: N-[2-(3,3-difluoropirrolidin-1-il)etil]-4-

metil-2-({1-[4-(pentafluoro-λ^6-sulf-anil)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida

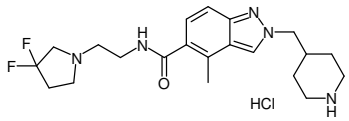


De forma análoga al Ejemplo 57, se obtuvieron 61,7 mg del compuesto del título a partir de 266,5 mg de la amina preparada en el Ejemplo 68a y 150,3 mg de cloruro de 4-(pentafluoro-λ^6-sulfanil)benzoílo.

^{1}H-RMN (300 MHz, cloroformo-d): δ [ppm] = 1,13 - 1,46 (2H), 1,48 - 1,65 (1H), 1,66 - 1,87 (1H), 2,26 - 2,50 (3H), 2,66 (3H), 2,71 - 3,23 (8H), 3,57 - 3,72 (3H), 4,25 - 4,42 (2H), 4,67 - 4,84 (1H), 6,40 - 6,61 (1H), 7,38 (1H), 7,47 (2H), 7,53 (1H), 7,79 (2H), 7,96 (1H).

El material de partida se preparó de la siguiente manera:

Ejemplo 68a: clorhidrato de *N*-[2-(3,3-difluoropirrolidin-1-il)etil]-4-metil-2-(4-piperidilmetil)-2H-indazol-5-carboxamida

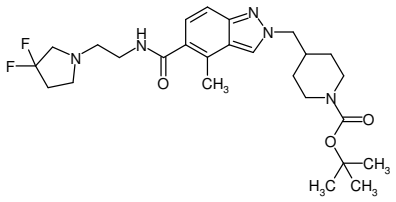


A 416,6 mg de 68b se añadieron 1,85 ml de ácido clorhídrico 4 M en dioxano y 0,5 ml de dioxano. Se

formó una masa oleosa, que se disolvió en agitación vigorosa y calentamiento moderado. La mezcla se agitó durante 1 hr a aproximadamente 30 °C. La mezcla de reacción se concentró. Rendimiento: 439,2 mg del compuesto del título, que luego se hizo reaccionar sin ulterior purificación.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,36 - 1,48 (2H), 1,54 - 1,63 (2H), 2,18 - 2,28 (1H), 2,40 - 2,45 (2H), 2,55 (3H), 2,72 - 2,83 (2H), 3,14 - 3,22 (2H), 3,38 - 3,44 (2H), 3,56 - 3,63 (2H), 3,65 - 3,95 (2H), 4,11 - 4,21 (2H), 7,32 (1H), 7,40 (1H), 8,43 - 8,48 (1H), 8,57 (1H), 8,68 - 8,82 (1H), 8,96 - 9,07 (1H).

Ejemplo 68b: 4-[(5-{N-[2-(3,3-difluoropirrolidin-1-il)etil]carbamoil}-4-metil-2H-indazol-2-il)metil]-piperidin-1-carboxilato de *tert*-butilo

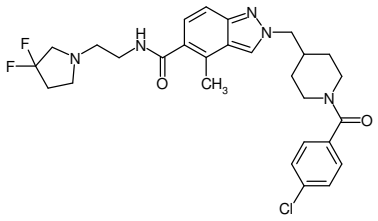


220 mg de 1c, 242,7 mg de 2-(3,3-difluoro-pirrolidin-1-il)etilamina, 142,2 mg de hexacarbonilo de molibdeno, 15,6 mg de tetrafluoroborato de tri-*tert*-butilfosfina y 50,5 mg de *trans*-bis(acetato)-bis-[o-(di-o-tolilfosfino)bencil]dipaladio (II) se colocaron en un tubo de microondas y se suspendieron en 4,4 ml de THF. 0,24 ml de DBU luego se añadieron y la mezcla se

agitó durante 20 min a 125 °C y 200 watts en el microondas. La mezcla de reacción se diluyó con un poco de acetato de etilo y primero se filtró a través de Celite. El filtrado se diluyó con acetato de etilo y la fase orgánica se lavó dos veces con agua y una vez con solución saturada de cloruro de sodio. Se secó sobre sulfato de sodio, se filtró y se concentró. El residuo (209,3 mg) se cromatografió en el Biotage SP4. Gradiente: DCM/metanol 0–10%. Rendimiento: 53,4 mg del compuesto del título.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,00 – 1,12 (2H), 1,32 – 1,42 (2H), 1,34 (9H), 2,07 – 2,25 (3H), 2,50 (3H), 2,57 (2H), 2,60 – 2,68 (2H), 2,72 (2H), 2,91 (2H), 3,30 – 3,35 (2H), 3,83 – 3,92 (2H), 4,28 (2H), 7,15 (1H), 7,39 (1H), 8,04 – 8,09 (1H), 8,47 (1H).

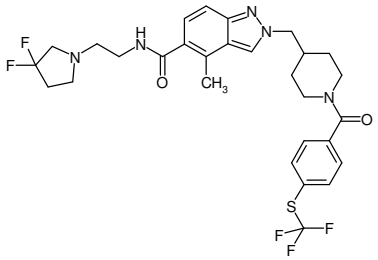
Ejemplo 69: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-[2-(3,3-difluoropirrolidin-1-il)etil]-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 57, se obtuvieron 79,9 mg del compuesto del título a partir de 125,0 mg de la amina preparada en el Ejemplo 68a y 54,5 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, cloroformo-d): δ [ppm] = 1,13 - 1,35 (2H), 1,46 - 1,84 (2H), 2,27 - 2,50 (3H), 2,66 (3H), 2,80 - 3,26 (8H), 3,59 - 3,83 (3H), 4,25 - 4,39 (2H), 4,62 - 4,85 (1H), 6,41 - 6,69 (1H), 7,30 - 7,40 (6H), 7,55 (1H), 7,96 (1H).

Ejemplo 70: N-[2-(3,3-difluoropirrolidin-1-il)etil]-4-metil-2-[(1-{4-[(trifluorometil) sulfanil]benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida

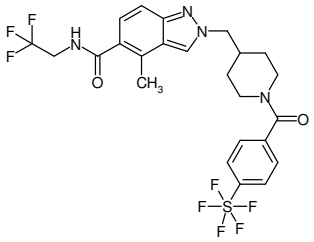


De forma análoga al Ejemplo 55, se obtuvieron 15,2 mg del compuesto del título a partir de 23,4 mg de la amina preparada en el Ejemplo 68a y 14,0 mg de cloruro de 4-[(trifluorometil)sulfanil]benzoílo.

^{1}H-RMN (400 MHz, cloroformo-d): δ [ppm] = 1,23 - 1,26 (1H), 1,33 - 1,46 (1H), 1,48 - 1,61 (1H), 1,77 (1H), 2,20 - 2,35 (2H), 2,36 - 2,49 (1H), 2,64 (3H), 2,73 - 2,85 (5H), 2,90 - 3,10 (3H), 3,56 (2H), 3,63 - 3,76 (1H), 4,26 - 4,39 (2H), 4,70 - 4,82 (1H), 6,28 (1H), 7,33 (1H), 7,42 (2H), 7,53 (1H), 7,68 (2H), 7,96 (1H).

Ejemplo 71: 4-metil-2-({1-[4-(pentafluoro-λ^6-

sulfanil)benzoil]piperidin-4-il}metil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

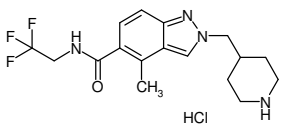


De forma análoga al Ejemplo 1, se obtuvieron 124,8 mg del compuesto del título a partir de 146,9 mg de la amina preparada en el Ejemplo 71a y 93,3 mg de ácido 4-(pentafluoro-λ^6-sulfanil)benzoico.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,12 – 1,31 (2H), 1,31 – 1,45 (1H), 1,47 – 1,63 (1H), 2,20 – 2,36 (1H), 2,50 (3H), 2,67 – 2,83 (1H), 2,91 – 3,07 (1H), 3,36 – 3,47 (1H), 3,96 – 4,10 (2H), 4,29 – 4,37 (2H), 4,37 – 4,48 (1H), 7,17 (1H), 7,43 (1H), 7,56 (2H), 7,94 (2H), 8,50 – 8,54 (1H), 8,75 – 8,83 (1H).

El material de partida se preparó de la siguiente manera:

Ejemplo 71a: clorhidrato de 4-metil-2-(4-piperidilmetil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

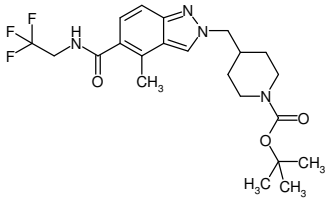


A 425,2 mg de 71b se añadieron 2,35 ml de ácido clorhídrico 4 M en dioxano y 0,5 ml de dioxano. Se

formó una masa oleosa, que se disolvió en agitación vigorosa y calentamiento moderado. La mezcla se agitó durante 1 hr a aproximadamente 30 °C. La mezcla de reacción se concentró. Rendimiento: 440,6 mg del compuesto del título, que luego se hizo reaccionar sin ulterior purificación.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,35 – 1,49 (2H), 1,53 – 1,62 (2H), 2,20 – 2,32 (1H), 2,51 (3H), 2,72 – 2,85 (2H), 3,14 – 3,23 (2H), 3,97 – 4,09 (2H), 4,34 (2H), 7,18 (1H), 7,43 (1H), 8,58 (1H), 8,64 – 8,77 (1H), 8,78 – 8,85 (1H), 8,93 – 9,08 (1H).

Ejemplo 71b: 4-({4-metil-5-[N-(2,2,2-trifluoroetil)carbamoil]-2H-indazol-2-il}-metil)piperidin-1-carboxilato de *tert*-butilo

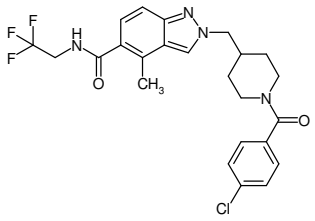


2820 mg de 1c, 2052 mg de 2,2,2-trifluoroetilamina, 1823,2 mg de hexacarbonilo de molibdeno, 200,4 mg de tetrafluoroborato de tri-*tert*-butilfosfina y 647,5 mg de *trans*-bis(acetato)-bis[o-(di-o-tolilfosfino)-bencil]dipaladio (II) se colocaron en un tubo de microondas y se suspendieron en 56 ml de THF. 3,1 ml de DBU luego se añadieron y la mezcla se agitó durante 20 min a 125 °C y 200 watts en el

microondas. La mezcla de reacción se diluyó con un poco de acetato de etilo, se lavó dos veces con agua y una vez con solución saturada de cloruro de sodio. Se secó sobre sulfato de sodio, se filtró y se concentró. El residuo se cromatografió en el Biotage SP4. Gradiente: hexano/acetato de etilo 0–100%. Rendimiento: 475,2 mg del compuesto del título.

^{1}H–RMN (300 MHz, DMSO–d_6): δ [ppm] = 0,99 – 1,17 (2H), 1,30 – 1,44 (11H), 2,05 – 2,21 (1H), 2,50 (3H), 2,54 – 2,73 (2H), 3,81 – 3,94 (2H), 3,95 – 4,10 (2H), 4,29 (2H), 7,18 (1H), 7,43 (1H), 8,51 (1H), 8,74 – 8,83 (1H).

Ejemplo 72: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

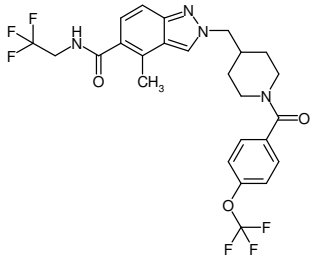


De forma análoga al Ejemplo 1, se obtuvieron 97,8 mg del compuesto del título a partir de 146,9 mg de la amina preparada en el Ejemplo 71a y 58,8 mg de ácido 4-clorobenzoico.

^{1}H–RMN (300 MHz, DMSO–d_6): δ [ppm] = 1,11 – 1,29 (2H), 1,31 – 1,45 (1H), 1,45 – 1,61 (1H), 2,20 – 2,35 (1H), 2,50 (3H), 2,63 – 2,84 (1H), 2,85 – 3,08 (1H),

3,42 – 3,59 (1H), 3,96 – 4,10 (2H), 4,29 – 4,47 (3H), 7,17 (1H), 7,36 (2H), 7,40 – 7,50 (3H), 8,52 (1H), 8,75 – 8,82 (1H).

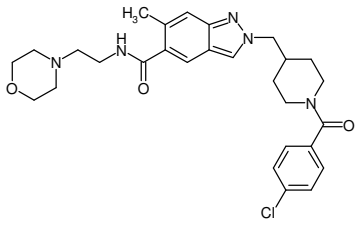
Ejemplo 73: 4-metil-N-(2,2,2-trifluoroetil)-2-({1-[4-(trifluorometoxi)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 105,4 mg del compuesto del título a partir de 146,9 mg de la amina preparada en el Ejemplo 71a y 77,5 mg de ácido 4-(trifluorometoxi)benzoico.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,12 – 1,30 (2H), 1,31 – 1,46 (1H), 1,47 – 1,64 (1H), 2,20 – 2,36 (1H), 2,50 (3H), 2,66 – 2,85 (1H), 2,86 – 3,09 (1H), 3,40 – 3,55 (1H), 3,96 – 4,10 (2H), 4,29 – 4,48 (3H), 7,17 (1H), 7,36 – 7,50 (5H), 8,52 (1H), 8,75 – 8,82 (1H).

Ejemplo 74: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-6-metil-N-(2-morfolinoetil)-2H-indazol-5-carboxamida

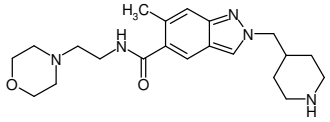


De forma análoga al Ejemplo 55, se obtuvieron 30 mg del compuesto del título a partir de 79 mg de la amina preparada en el Ejemplo 74a y 26 mg de cloruro de 4-clorobenzoílo.

^{1}RMN (400 MHz, metanol-d_4): δ [ppm] = 1,31 (2H), 1,50 (1H), 1,65 (1H), 2,35 (1H), 2,47 (3H), 2,63 (6H), 2,81 (1H), 3,07 (1H), 3,53 (2H), 3,71 (5H), 4,34 (2H), 4,59 (1H), 7,36 (2H), 7,43 (3H), 7,75 (1H), 8,24 (1H).

El material de partida se preparó de la siguiente manera:

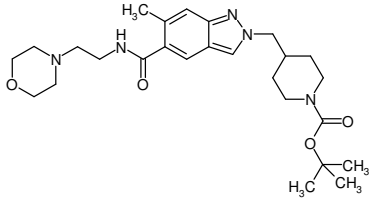
Ejemplo 74a: 6-metil-N-(2-morfolinoetil)-2-(4-piperidilmetil)-2H-indazol-5-carboxamida



768 mg de (1,58 mmol) de carbamato de *tert*-butilo 74b se disolvieron en 4,0 ml ácido clorhídrico 4 M en dioxano y se agitó bajo nitrógeno a temperatura ambiente. Otros 0,8 ml de ácido clorhídrico 4 M en dioxano se añadieron y la mezcla se agitó a temperatura ambiente. La solución de reacción se concentró y dio 760 mg del compuesto del título, que se usó en la siguiente reacción sin ulterior purificación.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,34 – 1,50 (2H), 1,53 – 1,67 (2H), 2,21 – 2,30 (1H), 2,41 (3H), 2,74 – 2,89 (2H), 3,07 – 3,33 (8H), 3,62 – 3,71 (2H), 3,77 – 3,90 (2H), 3,90 – 4,03 (2H), 4,35 (2H), 7,39 (1H), 7,88 (1H), 8,44 (1H), 8,57 (1H), 8,62 – 8,79 (1H), 8,87 – 9,02 (1H), 11,17 (1H).

Ejemplo 74b: 4-({6-metil-5-[N-(2-morfolinoetil)carbamoil]-2H-indazol-2-il}-metil)piperidin-1-carboxilato de *tert*-butilo

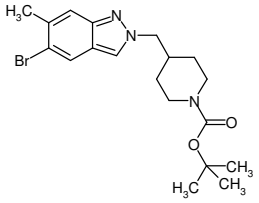


3,00 g (7,35 mmol) de 5-bromoindazol 74c y 2,87 g (22,04 mmol) de 2-morfolino-etilamina se disolvieron en 134 ml de dioxano y se añadieron 1,94 g (7,35 mmol) de hexacarbonilo de molibdeno, 167 mg (1,47 mmol) de acetato de paladio, 213 mg (0,74 mmol) de tetrafluoroborato de tributilfosfonio, 2,34 g (22,0 mmol) de carbonato de sodio y 2 gotas de agua. La mezcla de reacción se calentó hasta 125 °C bajo nitrógeno y se agitó a esta temperatura durante 2,5 hrs. Para la elaboración, la suspensión se filtró sobre Celite, se volvió a lavar con dioxano, se concentró al vacío y se secó. El producto crudo se separó por cromatografía en columna. Rendimiento: 518 mg del

compuesto del título.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 0,93 – 1,16 (2H), 1,26–1,37 (2H), 1,34 (9H), 1,99 – 2,17 (1H), 2,32 – 2,43 (10H), 2,54 – 2,72 (2H), 3,34 (1H), 3,48 – 3,59 (4H), 3,86 (2H), 4,26 (2H), 7,35 (1H), 7,63 (1H), 8,09 (1H), 8,32 (1H).

Ejemplo 74c: 4-[(5-bromo-6-metil-2H-indazol-2-il)metil]piperidin-1-carboxilato de *tert*-butilo

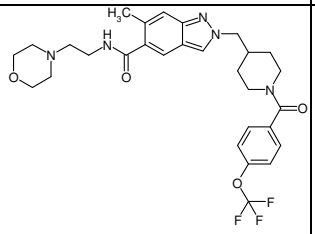


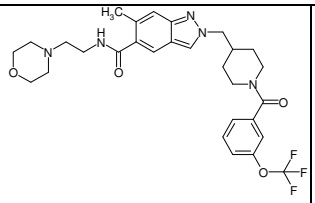
10,0 g (47,4 mmol) de 5-bromo-4-metil-1H-indazol y 21,0 g (56,9 mmol) de 4-[(tosiloxi)metil]piperidin-1-carboxilato de *tert*-butilo se disolvieron en 726 ml de DMF. A ello se añadieron 21,0 g (56,9 mmol) de yoduro de tetrabutilamonio y 18,5 g (56,9 mmol) de carbonato de cesio y la mezcla de reacción se calentó bajo nitrógeno a 80 °C durante 1,5 hrs. Para la elaboración, se trató con agua y acetato de etilo, la fase orgánica se separó y la fase acuosa se extrajo varias veces con acetato de etilo. Las fases orgánicas se lavaron con solución saturada de cloruro de sodio, se secaron sobre sulfato de sodio y se concentraron al vacío. Después de purificar por cromatografía en columna, esto dio como

resultado el compuesto del título en 5 g de rendimiento.

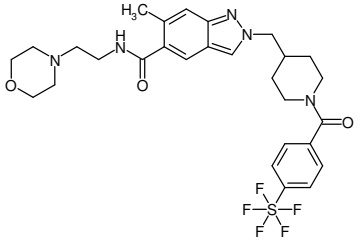
^{1}H-RMN (600 MHz, cloroformo-d): δ [ppm] = 1,16 – 1,30 (2H), 1,45 (9H), 1,54 (2H), 2,22 – 2,33 (1H), 2,51 (3H), 2,67 (2H), 4,03 – 4,17 (2H), 4,27 – 4,32 (2H), 7,60 (1H), 7,81 (1H), 7,90 (1H).

Los siguientes compuestos se prepararon de forma análoga:

Ej.	Estructura	Nombre IUPAC	Análisis
75		6-metil-N-(2-morfolinoetil)-2-({1-[4-(trifluorometoxi)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida	^{1}H-RMN (400 MHz, metanol-d_4): δ [ppm] = 1,32 (2H), 1,51 (1H), 1,65 (1H), 2,36 (1H), 2,47 (3H), 2,60 (6H), 2,83 (1H), 3,10 (1H), 3,52 (2H), 3,70 (5H), 4,35 (2H), 4,61 (1H), 7,37 (3H), 7,49 (2H), 7,74 (1H), 8,24 (1H).

76		6-metil-N-(2-morfolinoetil)-2-({1-[3-(trifluorometoxi)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida	^{1}H-RMN (400 MHz, metanol-d_4): δ [ppm] = 1,32 (2H), 1,49 (1H), 1,65 (1H), 2,36 (1H), 2,46 (3H), 2,59 (6H), 2,83 (1H), 3,10 (1H), 3,51 (2H), 3,69 (5H), 4,35 (2H), 4,60 (1H), 7,33 (2H), 7,40 (2H), 7,54 (1H), 7,74 (1H), 8,24 (1H).

Ejemplo 77: 6-metil-N-(2-morfolinoetil)-2-({1-[4-(pentafluoro-λ^6-sulfanil)benzoil] piperidin-4-il}metil)-2H-indazol-5-carboxamida

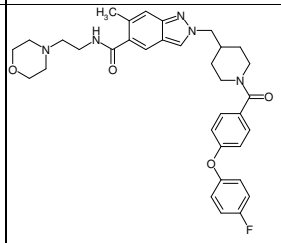
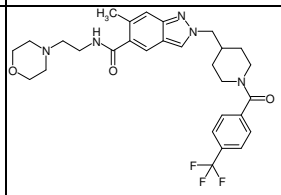


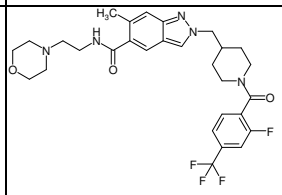
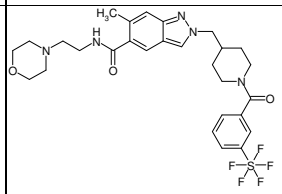
De forma análoga al Ejemplo 1, se obtuvieron 23 mg del compuesto del título a partir de 79 mg de la amina preparada en el Ejemplo 74a y 47 mg del ácido.

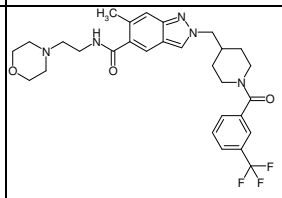
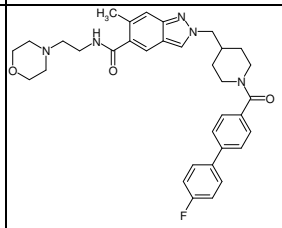
^{1}H-RMN (400 MHz, metanol-d_4): δ [ppm] = 1,34 (2H),

1,52 (1H), 1,66 (1H), 2,37 (1H), 2,49 (3H), 2,84 (1H), 3,10 (1H), 3,25 (2H), 3,42 (2H), 3,63 (3H), 3,75 (4H), 4,10 (2H), 4,36 (2H), 4,62 (1H), 7,43 (1H), 7,56 (2H), 7,89 (3H), 8,28 (1H).

Los siguientes compuestos se prepararon de forma análoga:

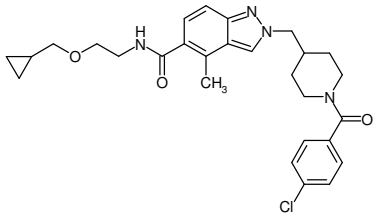
Ej.	Estructura	Nombre IUPAC	Análisis
78		2-({1-[4-(4-fluoro-fenoxi)benzoil]-piperidin-4-il}-metil)-6-metil-N-(2-morfolinoetil)-2H-indazol-5-carboxamida	^{1}H-RMN (400 MHz, metanol-d_4): δ [ppm] = 1,31 (2H), 1,58 (2H), 2,35 (1H), 2,49 (3H), 2,40-4,20 (15H), 4,35 (2H), 4,58 (1H), 6,97 (2H), 7,04 (2H), 7,11 (2H), 7,37 (2H), 7,43 (1H), 7,87 (1H), 8,27 (1H).
79		6-metil-N-(2-morfolinoetil)-2-({1-[4-(trifluoro-metil)benzoil]-piperidin-4-il}-metil)-2H-indazol-5-	^{1}H-RMN (300 MHz, metanol-d_4): δ [ppm] = 1,34 (2H), 1,51 (1H), 1,67 (1H), 2,38 (1H), 2,50 (3H), 2,85 (1H), 3,10 (1H), 3,25 (2H), 3,43 (2H), 3,64 (3H), 3,76 (4H), 4,10 (2H),

Ej.	Estructura	Nombre IUPAC	Análisis
		carboxamida	4,38 (2H), 4,64 (1H), 7,44 (1H), 7,57 (2H), 7,76 (2H), 7,89 (1H), 8,31 (1H).
80		2-({1-[2-fluoro-4-(trifluorometil)benzoil]piperidin-4-il}-metil)-6-metil-N-(2-morfolinoetil)-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, metanol-d_4): δ [ppm] = 1,34 (2H), 1,54 (1H), 1,68 (1H), 2,38 (1H), 2,50 (3H), 2,86 (1H), 3,12 (1H), 3,26 (2H), 3,43 (3H), 3,66 (2H), 3,76 (4H), 4,11 (2H), 4,37 (2H), 4,67 (1H), 7,44 (1H), 7,59 (3H), 7,89 (1H), 8,31 (1H).
81		6-metil-N-(2-morfolinoetil)-2-({1-[3-(pentafluoro-λ^6-sulfanil)benzoil]-piperidin-4-il}-metil)-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, metanol-d_4): δ [ppm] = 1,35 (2H), 1,53 (1H), 1,65 (1H), 2,38 (1H), 2,50 (3H), 2,86 (1H), 3,14 (1H), 3,26 (2H), 3,43 (2H), 3,66 (3H), 3,76 (4H), 4,11 (2H), 4,37 (2H), 4,62 (1H),

Ej.	Estructura	Nombre IUPAC	Análisis
			7,44 (1H), 7,63 (2H), 7,89 (3H), 8,30 (1H).
82		6-metil-N-(2-morfolinoetil)-2-({1-[3-(trifluorometil)-benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, metanol-d_4): δ [ppm] = 1,35 (2H), 1,53 (1H), 1,65 (1H), 2,38 (1H), 2,50 (3H), 2,85 (1H), 3,12 (1H), 3,26 (2H), 3,43 (2H), 3,66 (3H), 3,76 (4H), 4,11 (2H), 4,38 (2H), 4,63 (1H), 7,45 (1H), 7,66 (3H), 7,77 (1H), 7,90 (1H), 8,33 (1H).
83		2-({1-[(4'-fluoro-bifenil-4-il)-carbonil]piperidin-4-il}metil)-6-metil-N-(2-morfolinoetil)-2H-indazol-5-	^{1}H-RMN (300 MHz, metanol-d_4): δ [ppm] = 1,35 (2H), 1,53 (1H), 1,65 (1H), 2,39 (1H), 2,50 (3H), 2,85 (1H), 3,12 (1H), 3,26 (2H), 3,42 (2H), 3,63 (3H), 3,74 (4H), 4,08 (2H), 4,37 (2H), 4,64 (1H), 7,18 (2H), 7,46 (3H),

Ej.	Estructura	Nombre IUPAC	Análisis
		carboxamida	7,66 (4H), 7,88 (1H), 8,30 (1H).

Ejemplo 84: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-[2-(ciclopropilmetoxi)etil]-4-metil-2H-indazol-5-carboxamida

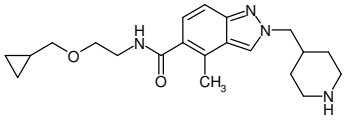


De forma análoga al Ejemplo 1, se obtuvieron 38 mg del compuesto del título a partir de 75 mg de la amina preparada en el Ejemplo 84a y 29 mg de ácido 4-clorobenzoico.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 0,14 (2H), 0,42 (2H), 0,97 (1H), 1,21 (2H), 1,36 (1H), 1,52 (1H), 2,27 (1H), 2,50 (3H), 2,72 (1H), 2,97 (1H), 3,23 (2H), 3,36 (2H), 3,48 (3H), 4,31 (2H), 4,40 (1H), 7,14 (1H), 7,36 (3H), 7,46 (2H), 8,12 (1H), 8,47 (1H).

El material de partida se preparó de la siguiente manera:

Ejemplo 84a: N-[2-(ciclopropilmetoxi)etil]-4-metil-2-(4-piperidilmetil)-2H-indazol-5-carboxamida

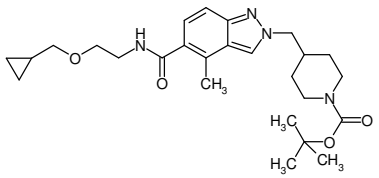


A 781 mg de 84b se añadieron 3,7 ml de ácido

clorhídrico 4 M en dioxano y 0,5 ml de dioxano. La mezcla se agitó durante 30 min a aproximadamente 30 °C. La mezcla de reacción se concentró, se extrajo en un poco de tolueno y se concentró nuevamente. Rendimiento: 751 mg del compuesto del título, que luego se hizo reaccionar sin ulterior purificación.

^{1}H-RMN (400 MHz, DMSO-d6): δ [ppm] = 0,14 (2H), 0,42 (2H), 0,97 (1H), 1,43 (2H), 1,58 (2H), 2,26 (1H), 2,50 (3H), 2,65 (1H), 2,78(2H), 3,18 (2H), 3,22 (2H), 3,36 (2H), 3,49 (2H), 4,33 (2H), 7,16 (2H), 7,38 (1H), 8,11 (1H), 8,53 (1H), 8,80 (1H), 9,06 (1H).

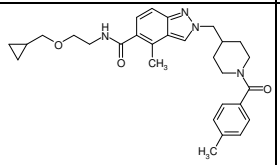
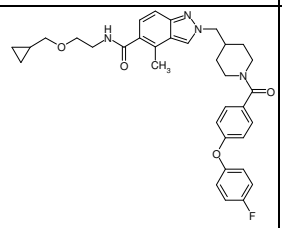
Ejemplo 84b: 4-[(5-{N-[2-(ciclopropilmetoxi)etil]carbamoil}-4-metil-2H-indazol-2-il)metil]piperidin-1-carboxilato de *tert*-butilo

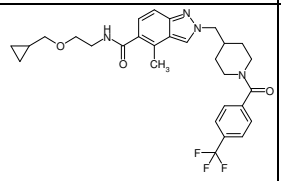
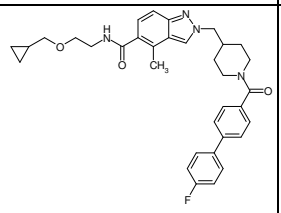


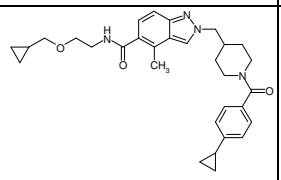
500 mg de 1d se hizo reaccionar con 203 mg de amina análogamente al 1b versión B. Rendimiento: 781 mg del compuesto del título.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 0,98 – 1,13 (2H), 1,34 (11H), 2,05 – 2,27 (2H), 2,33 – 2,41 (5H), 2,51 (3H), 2,56 – 2,73 (2H), 3,25 – 3,37 (2H), 3,51 – 3,57 (4H), 3,81 – 3,93 (2H), 4,28 (2H), 7,14 (1H), 7,36 – 7,41 (1H), 7,95 – 8,02 (1H), 8,46 (1H).

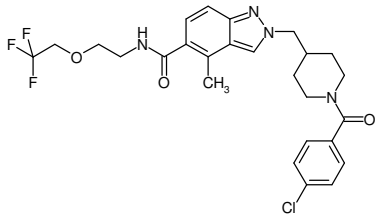
Los siguientes compuestos se prepararon de forma análoga:

Ej.	Estructura	Nombre IUPAC	Análisis
85		N-[2-(ciclopropil-metoxi)etil]-4-metil-2-{[1-(4-metilbenzoil)-piperidin-4-il]-metil}-2H-indazol-5-carboxamida	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 0,14 (2H), 0,42 (2H), 0,97 (1H), 1,19 (2H), 1,37 (1H), 1,50 (1H), 2,26 (1H), 2,29 (3H), 2,50 (3H), 2,72 (1H), 2,94 (1H), 3,23 (2H), 3,36 (2H), 3,48 (2H), 3,57 (1H), 4,30 (2H), 4,39 (1H), 7,14 (1H), 7,21 (4H), 7,38 (1H), 8,12 (1H), 8,47 (1H).
86		N-[2-(ciclopropil-metoxi)etil]-2-({1-[4-(4-fluorofenoxi)-benzoil]piperidin-4-il}metil)-4-	^{1}H-RMN (400 MHz, DMSO-d6): δ [ppm] = 0,14 (2H), 0,42 (2H), 0,97 (1H), 1,19 (2H), 1,45 (2H), 2,26 (1H), 2,50 (3H), 2,75 (1H), 2,96 (1H), 3,23 (2H), 3,36 (2H), 3,48 (2H), 3,62

Ej.	Estructura	Nombre IUPAC	Análisis
		metil-2H-indazol-5-carboxamida	(1H), 4,31 (2H), 4,39 (1H), 6,95 (2H), 7,12 (3H), 7,23 (2H), 7,36 (3H), 8,12 (1H), 8,47 (1H).
87		N-[2-(ciclopropil-metoxi)etil]-4-metil-2-({1-[4-(tri-fluorometil)benzoil]piperidin-4-il}-metil)-2H-indazol-5-carboxamida	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 0,14 (2H), 0,42 (2H), 0,96 (1H), 1,22 (2H), 1,36 (1H), 1,56 (1H), 2,28 (1H), 2,50 (3H), 2,74 (1H), 2,99 (1H), 3,23 (2H), 3,36 (2H), 2,43 (1H), 3,48 (2H), 4,31 (2H), 4,43 (1H), 7,15 (1H), 7,38 (1H), 7,55 (2H), 7,77 (2H), 8,12 (1H), 8,47 (1H).
88		N-[2-(ciclopropil-metoxi)etil]-2-({1-[(4'-fluorobifenil-4-	^{1}H-RMN (400 MHz, DMSO-d6): δ [ppm] = 0,14 (2H), 0,42 (2H), 0,96 (1H), 1,23 (2H), 1,39 (1H), 1,55 (1H), 2,28 (1H), 2,50 (3H), 2,74

Ej.	Estructura	Nombre IUPAC	Análisis
		il)carbonil]pi peridin-4- il}metil)-4- metil-2H- indazol-5- carboxamida	(1H), 3,01 (1H), 3,23 (2H), 3,36 (2H), 3,48 (2H), 3,61 (1H), 4,33 (2H), 4,44 (1H), 7,15 (1H), 7,28 (2H), 7,40 (3H), 7,69 (4H), 8,12 (1H), 8,48 (1H).
89		2-{[1-(4- ciclopropil- benzoil)piperi din-4- il]metil}-N- [2- (ciclopropilme toxi)etil]-4- metil-2H- indazol-5- carboxamida	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 0,17 (2H), 0,45 (2H), 0,69 (2H), 0,97 (3H), 1,21 (2H), 1,47 (2H), 1,93 (1H), 2,27 (1H), 2,52 (3H), 2,78 (1H), 2,93 (1H), 3,26 (2H), 3,37 (2H), 3,51 (2H), 3,62 (1H), 4,34 (2H), 4,41 (1H), 7,10 (2H), 7,17 (1H), 7,22 (2H), 7,41 (1H), 8,11 (1H), 8,49 (1H).

Ejemplo 90: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metil-N-[2-(2,2,2-trifluoro-etoxi)etil]-2H-indazol-5-carboxamida

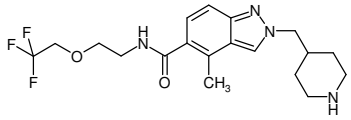


De forma análoga al Ejemplo 1, se obtuvieron 40 mg del compuesto del título a partir de 75 mg de la amina preparada en el Ejemplo 90a y 27 mg de ácido 4-clorobenzoico.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,20 (2H), 1,36 (1H), 1,53 (1H), 2,27 (1H), 2,49 (3H), 2,72 (1H), 2,97 (1H), 3,40 (2H), 3,49 (1H), 3,69 (2H), 4,07 (2H), 4,31 (2H), 4,40 (1H), 7,15 (1H), 7,37 (3H), 7,46 (2H), 8,19 (1H), 8,48 (1H).

El material de partida se preparó de la siguiente manera:

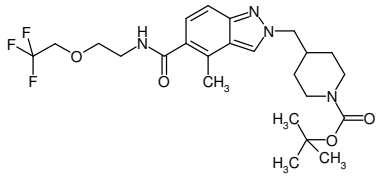
Ejemplo 90a: 4-metil-2-(4-piperidilmetil)-N-[2-(2,2,2-trifluoroetoxi)etil]-2H-indazol-5-carboxamida



A 610 mg de 90b se añadieron 3,0 ml de ácido clorhídrico 4 M en dioxano y 0,5 ml de dioxano. La mezcla se agitó durante 30 min a aproximadamente 30 °C. La mezcla de reacción se concentró, se extrajo en un poco de tolueno y se concentró nuevamente. Rendimiento: 619 mg del compuesto del título, que luego se hizo reaccionar sin ulterior purificación.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,42 (2H), 1,59 (2H), 2,26 (1H), 2,50 (3H), 2,64 (1H), 2,79 (2H), 3,20 (2H), 3,40 (2H), 3,70 (2H), 4,07 (2H), 4,33 (2H), 5,67(1H), 7,16 (1H), 7,39 (1H), 8,18 (1H), 8,53 (1H), 8,69 (1H), 8,94 (1H).

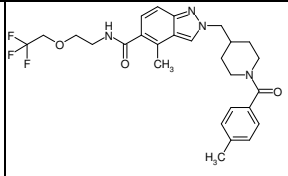
Ejemplo 90b: 4-[(4-metil-5-{N-[2-(2,2,2-trifluoroetoxi)etil]carbamoil}-2H-indazol-2-il)metil]piperidin-1-carboxilato de *tert*-butilo

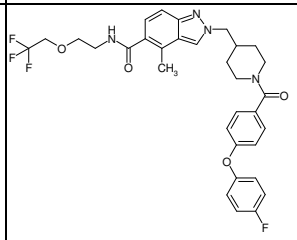
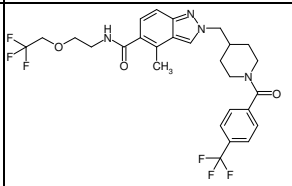


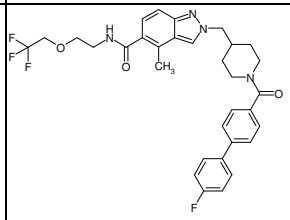
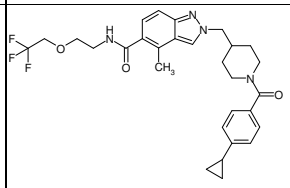
500 mg de 1d se hizo reaccionar con 240 mg de amina análogamente al 1b versión B. Rendimiento: 670 mg del compuesto del título.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,07 (2H), 1,34 (9H), 1,37 (2H), 2,14 (1H), 2,49 (3H), 2,63 (2H), 3,40 (2H), 3,70 (2H), 3,88 (2H), 4,06 (2H), 4,29 (2H), 7,15 (1H), 7,39 (1H), 8,16 (1H), 8,47 (1H).

Los siguientes compuestos se prepararon de forma análoga:

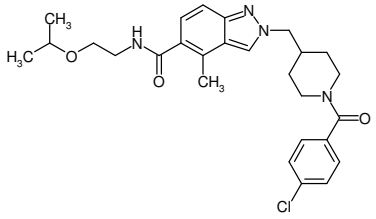
Ej.	Estructura	Nombre IUPAC	Análisis
91		4-metil-2-{[1-(4-metilbenzoil)-piperidin-4-	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,19 (2H), 1,36 (1H), 1,49 (1H), 2,25 (1H), 2,29

Ej.	Estructura	Nombre IUPAC	Análisis
		il]-metil}-N-[2-(2,2,2-trifluoro-etoxi)etil]-2H-indazol-5-carboxamida	(3H), 2,49 (3H), 2,71 (1H), 2,93 (1H), 3,40 (2H), 3,56 (1H), 3,69 (2H), 4,07 (2H), 4,31 (2H), 4,40 (1H), 7,15 (1H), 7,21 (4H), 7,39 (1H), 8,19 (1H), 8,48 (1H).
92		2-({1-[4-(4-fluoro-fenoxi)ben-zoil]-piperidin-4-il}-metil)-4-metil-N-[2-(2,2,2-tri-fluoroetoxi)etil]-2H-indazol-5-carboxamida	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,19 (2H), 1,44 (2H), 2,26 (1H), 2,49 (3H), 2,73 (1H), 2,95 (1H), 3,40 (2H), 3,60 (1H), 3,69 (2H), 4,07 (2H), 4,31 (2H), 4,38 (1H), 6,95 (2H), 7,12 (3H), 7,22 (2H), 7,37 (3H), 8,19 (1H), 8,48 (1H).
93		4-metil-N-[2-(2,2,2-trifluoro-etoxi)etil]-2-	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,22 (2H), 1,36 (1H), 1,56 (1H), 2,28 (1H), 2,49

Ej.	Estructura	Nombre IUPAC	Análisis
		({1-[4-(trifluoro-metil)benzoil]-piperidin-4-il}-metil)-2H-indazol-5-carboxamida	(3H), 2,74 (1H), 2,99 (1H), 3,40 (3H), 3,69 (2H), 4,07 (2H), 4,32 (2H), 4,43 (1H), 7,15 (1H), 7,39 (1H), 7,55 (2H), 7,77 (2H), 8,19 (1H), 8,48 (1H).
94		2-({1-[(4'-fluoro-bifenil-4-il)-car-bonil]piperidin-4-il}metil)-4-metil-N-[2-(2,2,2-trifluoroetoxi)-etil]-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,23 (2H), 1,39 (1H), 1,52 (1H), 2,28 (1H), 2,49 (3H), 2,75 (1H), 3,00 (1H), 3,39 (2H), 3,60 (1H), 3,69 (2H), 4,07 (2H), 4,33 (2H), 4,43 (1H), 7,15 (1H), 7,27 (2H), 7,40 (3H), 7,68 (4H), 8,19 (1H), 8,49 (1H).
95		2-{[1-(4-ciclo-propilbenzoil)-piperidin-4-il]-metil}-4-	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 0,69 (2H), 0,96 (2H), 1,21 (2H), 1,47 (2H), 1,93 (1H), 2,28 (1H), 2,52

Ej.	Estructura	Nombre IUPAC	Análisis
		metil-N-[2-(2,2,2-trifluoroetoxi)etil]-2H-indazol-5-carboxamida	(3H), 2,77 (1H), 2,94 (1H), 3,43 (2H), 3,61 (1H), 3,72 (2H), 4,09 (2H), 4,34 (2H), 4,42 (1H), 7,10 (2H), 7,17 (1H), 7,22 (2H), 7,41 (1H), 8,18 (1H).

Ejemplo 96: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-(2-isopropoxietil)-4-metil-2H-indazol-5-carboxamida

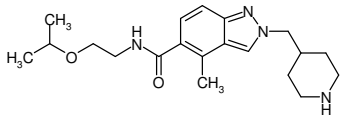


De forma análoga al Ejemplo 1, se obtuvieron 36 mg del compuesto del título a partir de 75 mg de la amina preparada en el Ejemplo 96a y 30 mg de ácido 4-clorobenzoico.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,07 (6H), 1,22 (2H), 1,39 (1H), 1,51 (1H), 2,26 (1H), 2,50 (3H), 2,75 (1H), 2,97 (1H), 3,33 (2H), 3,45 (3H), 3,55 (1H), 4,31 (2H), 4,39 (1H), 7,14 (1H), 7,36 (3H), 7,47 (2H), 8,05 (1H), 8,46 (1H).

El material de partida se preparó de la siguiente manera:

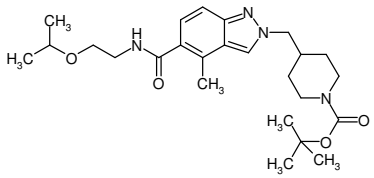
Ejemplo 96a: N-(2-isopropoxietil)-4-metil-2-(4-piperidilmetil)-2H-indazol-5-carboxamida



A 650 mg de 96b se añadieron 3,2 ml de ácido clorhídrico 4 M en dioxano y 0,5 ml de dioxano. La mezcla se agitó durante 30 min a aproximadamente 30°C. La mezcla de reacción se concentró, se extrajo en un poco de tolueno y se concentró nuevamente. Rendimiento: 529 mg del compuesto del título, que luego se hizo reaccionar sin ulterior purificación.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,06 (3H), 1,07 (3H), 1,42 (2H), 1,57 (2H), 2,25 (1H), 2,50 (3H), 2,65 (1H), 2,78 (2H), 3,19 (2H), 3,32 (2H), 3,45 (2H), 3,55 (1H), 4,32 (1H), 6,61 (1H), 7,15 (1H), 7,38 (1H), 8,11 (1H), 8,53 (1H), 8,78 (1H), 9,04 (1H).

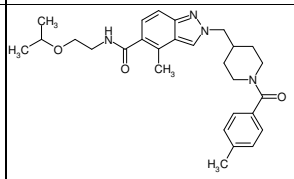
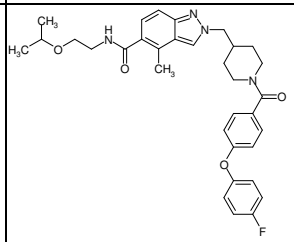
Ejemplo 96b: 4-({5-[N-(2-isopropoxietil)carbamoil]-4-metil-2H-indazol-2-il}-metil)piperidin-1-carboxilato de *tert*-butilo

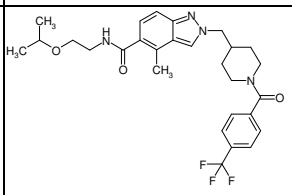
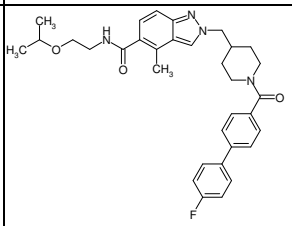


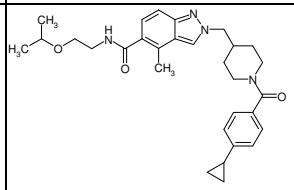
500 mg de 1d se hicieron reaccionar con 138 mg de amina análogamente al 1b versión B. Rendimiento: 650 mg del compuesto del título.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,07 (8H), 1,34 (9H), 1,38 (2H), 2,13 (1H), 2,50 (3H), 2,63 (2H), 3,33 (2H), 3,46 (2H), 3,55 (1H), 3,87 (2H), 4,28 (2H), 7,14 (1H), 7,38 (1H), 8,05 (1H), 8,46 (1H).

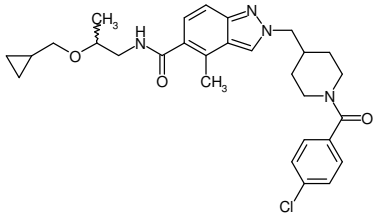
Los siguientes compuestos se prepararon de forma análoga:

Ej.	Estructura	Nombre IUPAC	Análisis
97		N-(2-isopropoxi-etil)-4-metil-2-{[1-(4-metil-benzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,07 (6H), 1,19 (2H), 1,45 (2H), 2,29 (4H), 2,50 (3H), 2,75 (1H), 2,92 (1H), 3,33 (2H), 3,45 (2H), 3,55 (2H), 4,31 (2H), 4,40 (1H), 7,14 (1H), 7,20 (4H), 7,38 (1H), 8,05 (1H), 8,46 (1H).
98		2-({1-[4-(4-fluoro-fenoxi)benzoil]-piperidin-4-il}-metil)-N-(2-isopropo-xietil)-4-	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,07 (6H), 1,21 (2H), 1,45 (2H), 2,25 (1H), 2,49 (3H), 2,85 (2H), 3,31 (2H), 3,45 (2H), 3,55 (2H), 4,31 (2H), 4,40

Ej.	Estructura	Nombre IUPAC	Análisis
		metil-2H-indazol-5-carboxamida	(1H), 6,95 (2H), 7,10 (3H), 7,22 (2H), 7,36 (3H), 8,05 (1H), 8,46 (1H).
99		N-(2-isopropoxi-etil)-4-metil-2-({1-[4-(trifluoro-metil)benzoil]-piperidin-4-il}-metil)-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,06 (6H), 1,22 (2H), 1,37 (1H), 1,56 (1H), 2,28 (1H), 2,50 (3H), 2,75 (1H), 2,99 (1H), 3,33 (2H), 3,45 (3H), 3,55 (1H), 4,32 (2H), 4,43 (1H), 7,15 (1H), 7,38 (1H), 7,55 (2H), 7,77 (2H), 8,05 (1H), 8,46 (1H).
100		2-({1-[(4'-fluoro-bifenil-4-il)-carbonil]piperidin-4-il}metil)-N-(2-isopropoxietil	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,06 (6H), 1,23 (2H), 1,47 (2H), 2,28 (1H), 2,50 (3H), 2,76 (1H), 2,98 (1H), 3,33 (2H), 3,45 (2H), 3,55 (2H), 4,33 (2H), 4,43 (1H), 7,15

Ej.	Estructura	Nombre IUPAC	Análisis
		)-4-metil-2H-indazol-5-carboxamida	(1H), 7,27 (2H), 7,39 (3H), 7,68 (4H), 8,05 (1H), 8,47 (1H).
101		2-{[1-(4-ciclopropil-benzoil)piperidin-4-il]metil}-N-(2-isopropoxietil)-4-metil-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 0,66 (2H), 0,94 (2H), 1,06 (6H), 1,20 (2H), 1,44 (2H), 1,90 (1H), 2,24 (1H), 2,49 (3H), 2,82 (2H), 3,32 (2H), 3,45 (2H), 3,55 (2H), 4,31 (2H), 4,39 (1H), 7,12 (5H), 7,38 (1H), 8,05 (1H), 8,46 (1H).

Ejemplo 102: (+/-)-2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-[2-(ciclopropilmetoxi) propil]-4-metil-2H-indazol-5-carboxamida

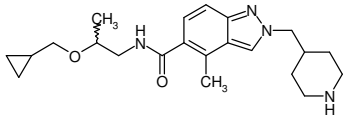


De forma análoga al Ejemplo 1, se obtuvieron 41 mg del compuesto del título a partir de 100 mg de la amina preparada en el Ejemplo 102a y 37 mg de ácido 4-clorobenzoico.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 0,16 (2H), 0,43 (2H), 0,97 (1H), 1,10 (3H), 1,23 (2H), 1,40 (1H), 1,55 (1H), 2,29 (1H), 2,53 (3H), 2,75 (1H), 2,99 (1H), 3,23 (2H), 3,20 (2H), 3,51 (1H), 3,59 (1H), 4,34 (2H), 4,43 (1H), 7,17 (1H), 7,39 (3H), 7,49 (2H), 8,09 (1H), 8,49 (1H).

El material de partida se preparó de la siguiente manera:

Ejemplo 102a: (+/-)-N-[2-(ciclopropilmetoxi)propil]-4-metil-2-(4-piperidilmetil)-2H-indazol-5-carboxamida

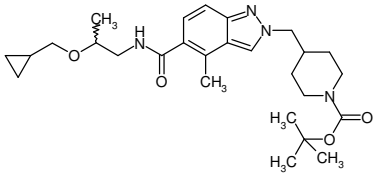


A 632 mg de 102b se añadieron 2,9 ml de ácido clorhídrico 4 M en dioxano y 0,5 ml de dioxano. La mezcla se agitó durante 30 min a aproximadamente 30 °C. La mezcla de reacción se concentró, se extrajo en un poco de tolueno y se concentró nuevamente. Rendimiento: 561 mg del compuesto del título, que luego se hizo reaccionar sin ulterior purificación.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 0,13 (2H), 0,40 (2H), 0,94 (1H), 1,07 (3H), 1,44 (2H), 1,57 (2H), 2,26 (1H), 2,50 (3H), 2,77 (2H), 3,20 (6H), 3,57 (1H), 4,33 (2H), 6,33 (1H), 7,16 (1H), 7,39 (1H), 8,11 (1H), 8,53 (1H), 8,79 (1H), 9,06 (1H).

Ejemplo 102b: 4-[(5-{N-[2-

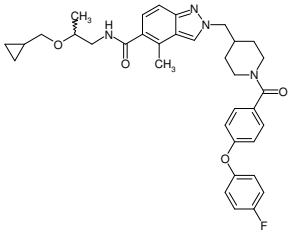
(ciclopropilmetoxi)propil]carbamoil}-4-metil-2H-indazol-2-il)metil]piperidin-1-carboxilato de (+/-)-*tert*-butilo

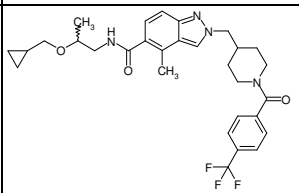
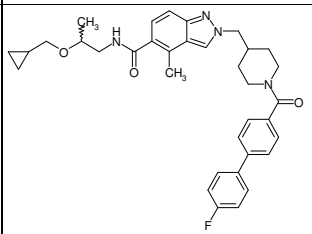


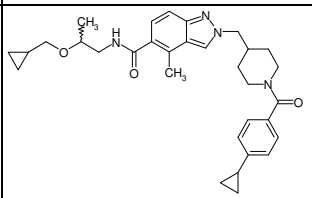
500 mg de 1d se hizo reaccionar con 222 mg de amina análogamente al 1b versión B. Rendimiento: 631 mg del compuesto del título.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 0,13 (2H), 0,40 (2H), 0-94 (1H), 1,07 (3H), 1,14 (2H), 1,34 (9H), 1,38 (2H), 2,13 (1H), 2,50 (3H), 3,24 (6H), 3,57 (1H), 3,87 (2H), 4,28 (2H), 7,15 (1H), 7,39 (1H), 8,09 (1H), 8,46 (1H).

Los siguientes compuestos se prepararon de forma análoga:

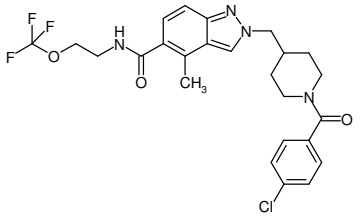
Ej.	Estructura	Nombre IUPAC	Análisis
103		(+/-)-N-[2-(ciclo-propilmetoxi)-propil]-2-({1-[4-(4-fluo-rofenoxi)-benzoil]pi-peridin-4-il}-	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 0,16 (2H), 0,43 (2H), 0,97 (1H), 1,10 (3H), 1,22 (2H), 1,48 (2H), 2,29 (1H), 2,53 (3H), 2,81 (1H), 2,92 (1H), 3,23 (2H), 3,28 (2H),

Ej.	Estructura	Nombre IUPAC	Análisis
		metil)-4-metil-2H-indazol-5-carboxamida	3,60 (1H), 3,70 (1H), 4,34 (2H), 4,42 (1H), 6,98 (2H), 7,14 (3H), 7,25 (2H), 7,39 (3H), 8,09 (1H), 8,49 (1H).
104		(+/-)-N-[2-(ciclo-propilmetoxi)-propil]-4-metil-2-({1-[4-(trifluoro-metil)benzoil]-piperidin-4-il}-metil)-2H-indazol-5-carboxamida	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 0,16 (2H), 0,43 (2H), 0,97 (1H), 1,10 (3H), 1,24 (2H), 1,38 (1H), 1,59 (1H), 2,30 (1H), 2,53 (3H), 2,78 (1H), 3,02 (1H), 3,23 (2H), 3,28 (2H), 3,45 (1H), 3,60 (1H), 4,34 (2H), 4,46 (1H), 7,17 (1H), 7,41 (1H), 7,57 (2H), 7,80 (2H), 8,09 (1H), 8,49 (1H).
105		(+/-)-N-[2-(ciclo-propilmetoxi)-propil]-2-({1-[(4'-	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 0,16 (2H), 0,42 (2H), 0,97 (1H), 1,10 (3H), 1,26 (2H), 1,45 (1H),

Ej.	Estructura	Nombre IUPAC	Análisis
		fluorobifenil-4-il)carbonil]-piperidin-4-il}-metil)-4-metil-2H-indazol-5-carboxamida	1,55 (1H), 2,32 (1H), 2,53 (3H), 2,7 9(1H), 3,03 (1H), 3,23 (2H), 3,27 (2H), 3,60 (2H), 4,36 (2H), 4,46 (1H), 7,17 (1H), 7,30 (2H), 7,42 (3H), 7,71 (4H), 8,09 (1H), 8,50 (1H).
106		(+/-)-2-{[1-(4-ciclopropilbenzoil) piperidin-4-il]-metil}-N-[2-(ciclopropil-metoxi)propil]-4-metil-2H-indazol-5-carboxamida	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 0,16 (2H), 0,43 (2H), 0,69 (2H), 0,96 (3H), 1,10 (3H), 1,20 (2H), 1,47 (2H), 1,93 (1H), 2,28 (1H), 2,53 (3H), 2,77 (1H), 2,93 (1H), 3,23 (2H), 3,28 (2H), 3,59 (2H), 4,34 (2H), 4,40 (1H), 7,10 (2H), 7,17 (1H), 7,22 (2H), 7,41 (1H), 8,09 (1H), 8,49 (1H).

Ejemplo 107: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metil-N-[2-(trifluorometoxi)

etil]-2H-indazol-5-carboxamida

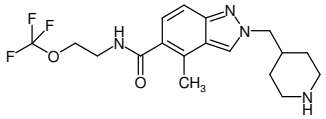


De forma análoga al Ejemplo 1, se obtuvieron 26 mg del compuesto del título a partir de 75 mg de la amina preparada en el Ejemplo 107a y 28 mg de ácido 4-clorobenzoico.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,20 (2H), 1,36 (1H), 1,52 (1H), 2,27 (1H), 2,49 (3H), 2,72 (1H), 2,97 (1H), 3,51 (3H), 4,17 (2H), 4,33 (3H), 7,15 (1H), 7,41 (5H), 8,37 (1H), 8,49 (1H).

El material de partida se preparó de la siguiente manera:

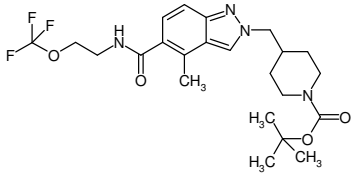
Ejemplo 107a: 4-metil-2-(4-piperidilmetil)-N-[2-(trifluorometoxi)etil]-2H-indazol-5-carboxamida



A 648 mg de 107b se añadieron 3,0 ml de ácido clorhídrico 4 M en dioxano y 0,5 ml de dioxano. La mezcla se agitó durante 30 min a aproximadamente 30 °C. La mezcla de reacción se concentró, se extrajo en un poco de tolueno y se concentró nuevamente. Rendimiento: 766 mg del compuesto del título, que luego se hizo reaccionar sin ulterior purificación.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,43 (2H), 1,57 (2H), 2,24 (1H), 2,50 (3H), 2,78 (2H), 3,19 (2H), 3,50 (1H), 4,17 (2H), 4,33 (2H), 6,49 (1H), 7,17 (2H), 7,40 (1H), 8,39 (1H), 8,55 (1H), 8,70 (1H), 8,98 (1H).

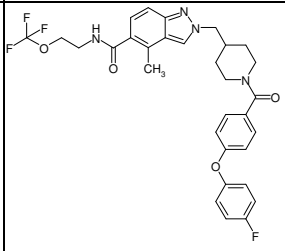
Ejemplo 107b: 4-[(4-metil-5-{N-[2-(trifluorometoxi)etil]carbamoil}-2H-indazol-2-il)metil]piperidin-1-carboxilato de *tert*-butilo

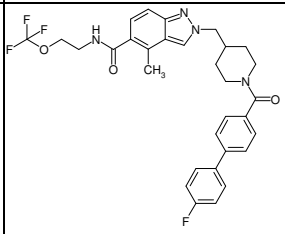
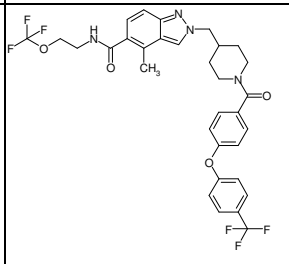


500 mg de 1d se hizo reaccionar con 293 mg de amina análogamente al 1b versión B. Rendimiento: 748 mg del compuesto del título.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,07 (2H), 1,34 (9H), 1,37 (2H), 2,12 (1H), 2,50 (3H), 2,63 (1H), 3,52 (2H), 3,87 (2H), 4,17 (2H), 4,29 (2H), 7,16 (2H), 7,41 (1H), 8,37 (1H), 8,48 (1H).

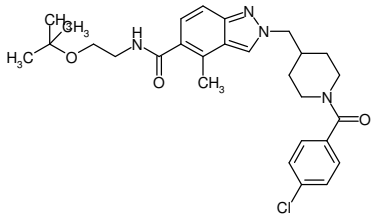
Los siguientes compuestos se prepararon de forma análoga:

Ej.	Estructura	Nombre IUPAC	Análisis
108		2-({1-[4-(4-fluoro-fenoxi)benzoil]-piperidin-4-il}metil)-4-	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,19 (2H), 1,46 (2H), 2,26 (1H), 2,49 (3H), 2,87

		metil-N-[2-(tri-fluorometoxi)etil]-2H-indazol-5-carboxamida	(2H), 3,51 (3H), 4,17 (2H), 4,33 (3H), 6,95 (2H), 7,16 (5H), 7,38 (3H), 8,36 (1H), 8,49 (1H).
109		2-({1-[(4'-fluoro-bifenil-4-il)-carbonil]piperidin-4-il}-metil)-4-metil-N-[2-(trifluoro-metoxi)etil]-2H-indazol-5-carboxamida	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,23 (2H), 1,47 (2H), 2,28 (1H), 2,50 (3H), 2,74 (1H), 2,99 (1H), 3,51 (2H), 3,61 (1H), 4,17 (2H), 4,34 (3H), 7,16 (1H), 7,27 (2H), 7,40 (3H), 7,68 (4H), 8,37 (1H), 8,50 (1H).
110		4-metil-N-[2-(trifluorometoxi)etil]-2-[(1-{4-[4-(trifluoro-metil)fenoxi]-benzoil}piperidi	^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,21 (2H), 1,46 (2H), 2,27 (1H), 2,50 (3H), 2,76 (1H), 2,98 (1H),

		n-4-il)-metil]-2H-indazol-5-carboxamida	3,51 (2H), 3,61 (1H), 4,17 (2H), 4,33 (2H), 4,43 (1H), 7,14 (5H), 7,41 (3H), 7,73 (2H), 8,37 (1H), 8,49 (1H).

Ejemplo 111: N-(2-*tert*-butoxietil)-2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metil-2H-indazol-5-carboxamida



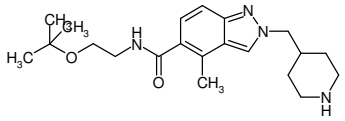
De forma análoga al Ejemplo 1, se obtuvieron 8 mg del compuesto del título a partir de 75 mg de la amina preparada en el Ejemplo 111a y 28 mg de ácido 4-clorobenzoico.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,12 (9H), 1,21 (2H), 1,36 (1H), 1,53 (1H), 2,27 (1H), 2,50 (3H), 2,72 (1H), 2,97 (1H), 3,29 (2H), 3,43 (3H), 4,31 (2H), 4,40 (1H), 7,14 (1H), 7,36 (3H), 7,46 (2H), 8,04 (1H), 8,46 (1H).

El material de partida se preparó de la siguiente manera:

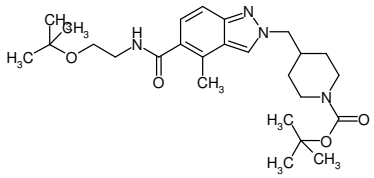
Ejemplo 111a: N-(2-*tert*-butoxietil)-4-metil-2-(4-

piperidilmetil)-2H-indazol-5-carboxamida



A 743 mg de 111b se añadieron 3,5 ml de ácido clorhídrico 4 M en dioxano y 0,5 ml de dioxano. La mezcla se agitó durante 30 min a aproximadamente 30 °C. La mezcla de reacción se concentró, se extrajo en un poco de tolueno y se concentró nuevamente. Rendimiento: 677 mg del compuesto del título en una mezcla con N-(2-hidroxietil)-4-metil-2-(4-piperidilmetil)-2H-indazol-5-carboxamida, que luego se hizo reaccionar sin ulterior purificación.

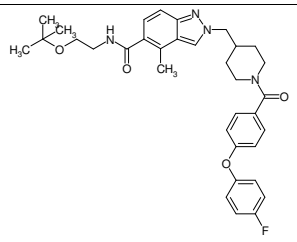
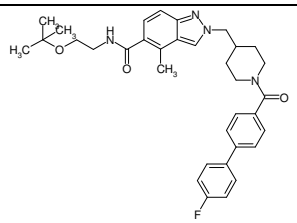
Ejemplo 111b: 4-({5-[N-(2-*tert*-butoxietil)carbamoil]-4-metil-2H-indazol-2-il}metil)piperidin-1-carboxilato de *tert*-butilo

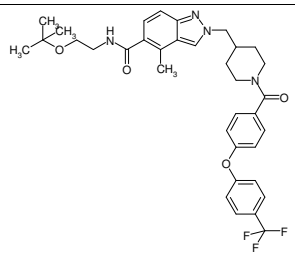


500 mg de 1d se hizo reaccionar con 206 mg de amina análogamente al 1b versión B. Rendimiento: 743 mg del compuesto del título.

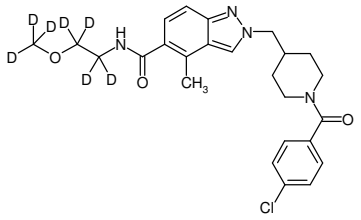
^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,06 (2H), 1,11 (9H), 1,34 (9H), 1,39 (2H), 2,13 (1H), 2,50 (3H), 2,65 (2H), 3,27 (2H), 3,40 (2H), 3,87 (2H), 4,28 (2H), 7,14 (1H), 7,38 (1H), 8,05 (1H), 8,46 (1H).

Los siguientes compuestos se prepararon de forma análoga:

Ej.	Estructura	Nombre IUPAC	Análisis
112		N-(2-*tert*-butoxietil)-2-({1-[4-(4-fluoro-fenoxi)benzoil]-piperidin-4-il}metil)-4-metil-2H-indazol-5-carboxamida	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,12 (9H), 1,20 (2H), 1,44 (2H), 2,26 (1H), 2,50 (3H), 2,76 (1H), 2,93 (1H), 3,30 (2H), 3,40 (2H), 3,57 (1H), 4,31 (2H), 4,39 (1H), 6,95 (2H), 7,12 (3H), 7,23 (2H), 7,36 (3H), 8,04 (1H), 8,46 (1H).
113		N-(2-*tert*-butoxietil)-2-({1-[(4'-fluoro-bifenil-4-il)-carbonil]piperidin-4-il}metil)-4-	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,11 (9H), 1,23 (2H), 1,40 (1H), 1,54 (1H), 2,29 (1H), 2,50 (3H), 2,75 (1H), 3,00 (1H), 3,29 (2H),

		metil-2H-indazol-5-carboxamida	3,40 (2H), 3,65 (1H), 4,32 (2H), 4,43 (1H), 7,15 (1H), 7,28 (2H), 7,40 (3H), 7,69 (4H), 8,05 (1H), 8,47 (1H).
114		N-(2-*tert*-butoxietil)-4-metil-2-[(1-{4-[4-(trifluorometil)-fenoxi]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida	^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,12 (9H), 1,21 (2H), 1,40 (1H), 1,52 (1H), 2,27 (1H), 2,50 (3H), 2,75 (1H), 2,99 (1H), 3,28 (2H), 3,40 (2H), 3,60 (1H), 4,32 (2H), 4,40 (1H), 7,15 (5H), 7,40 (3H), 7,73 (2H), 8,04 (1H), 8,47 (1H).

Ejemplo 115: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-(2-[$^{2}H_3$]metoxi[$^{2}H_4$]etil)-4-metil-2H-indazol-5-carboxamida

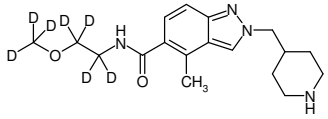


De forma análoga al Ejemplo 1, se obtuvieron 1 mg del compuesto del título a partir de 54 mg de la amina preparada en el Ejemplo 115a y 22 mg de ácido 4-clorobenzoico.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,20 (2H), 1,40 (1H), 1,51 (1H), 2,27 (1H), 2,49 (3H), 2,75 (1H), 2,96 (1H), 3,50 (1H), 4,31 (2H), 4,40 (1H), 7,15 (1H), 7,36 (3H), 7,47 (2H), 8,07 (1H), 8,46 (1H).

El material de partida se preparó de la siguiente manera:

Ejemplo 115a: 4-metil-N-(2-[^{2}H$_3$]metiloxi[^{2}H$_4$]etil)-2-(4-piperidilmetil)-2H-indazol-5-carboxamida

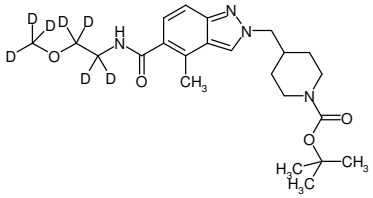


A 131 mg de 115b se añadieron 0,7 ml de ácido clorhídrico 4 M en dioxano y 0,5 ml de dioxano. La mezcla se agitó durante 30 min a aproximadamente 30 °C. La mezcla de reacción se concentró, se extrajo en un poco de tolueno y se concentró nuevamente. Rendimiento: 108 mg del compuesto del título, que luego se hizo reaccionar sin ulterior purificación.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,42 (2H),

1,58 (2H), 2,26 (1H), 2,49 (3H), 2,78 (2H), 3,19 (2H), 4,33 (2H), 5,55 (1H), 7,16 (1H), 7,38 (1H), 8,12 (1H), 8,53 (1H), 8,70 (1H), 8,97 (1H).

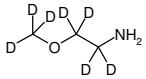
Ejemplo 115b: 4-({4-metil-5-[N-(2-[$^2H_3$]metiloxi[$^2H_4$]etil)carbamoil]-2H-indazol-2-il}metil)piperidin-1-carboxilato de *tert*-butilo



500 mg de 1d se hizo reaccionar análogamente al 1b versión B con 110 mg de amina preparada en 115c. Rendimiento: 131 mg del compuesto del título.

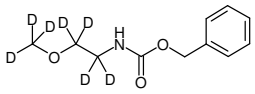
^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,07 (2H), 1,34 (9H), 1,37 (2H), 2,13 (1H), 2,49 (3H), 2,62 (2H), 3,88 (2H), 4,28 (2H), 7,15 (1H), 7,38 (1H), 8,07 (1H), 8,46 (1H).

Ejemplo 115c: 2-[$^2H_3$]metiloxi[$^2H_4$]etan-1-amina



110 mg de (0,51 mmol) de 115d se colocaron primero en 2,2 ml de tolueno. Después de la adición de 11 mg de paladio/carbón (10%) e hidrógeno a presión normal, la mezcla se agitó durante 50 min a temperatura ambiente. La mezcla de reacción se filtró a través de Celite y se volvió a lavar con tolueno. El filtrado incoloro se usó como solución en la posterior reacción.

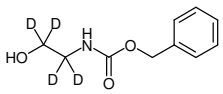
Ejemplo 115d: *N*-(2-[$^2H_3$]metiloxi[$^2H_4$]etil)carbamato de bencilo



1,32 g (6,6 mmol) de 115e) se disolvieron en 23 ml acetonitrilo. Luego se añadieron 2,3 g (9,9 mmol) de óxido de plata y 1,64 ml (3,8 g, 26 mmol) de yodometano deuterado. La mezcla de reacción se agitó durante 1,5 hrs a 40 °C, 7,5 hrs a 72 °C y luego durante la noche a temperatura ambiente. Se añadieron 2,3 g (9,9 mmol) adicionales de óxido de plata y la mezcla se agitó durante 1,5 hrs a 72 °C. Para la elaboración, el sólido negro se filtró en la bomba y el filtrado claro se concentró. El residuo se purificó por cromatografía en columna (hexano/acetato de etilo 0-10%). Rendimiento: 1,13 g del compuesto del título.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 4,97 (2H), 7,31 (5H).

Ejemplo 115e: *N*-(2-hidroxi[$^2H_4$]etil)carbamato de bencilo

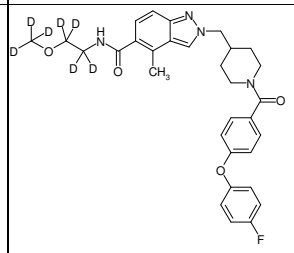


1,0 g (15 mmol) de aminoetanol deuterado se disolvió primero en 29 ml de diclorometano. A continuación, se añadieron 2,5 ml (1,8 g, 18 mmol) de trietilamina y la mezcla de reacción se enfrió hasta 0

°C. A esta temperatura, se añadieron cuidadosamente gota a gota 2,75 ml (3,34 g, 19,6 mmol) de cloroformiato de bencilo. Después de completar la adición, la mezcla se agitó durante 1 hr más sin baño de hielo y en el proceso se calentó hasta temperatura ambiente. La mezcla de reacción se diluyó una vez con cierta cantidad de diclorometano y se lavó una vez con solución saturada de cloruro de sodio. La fase orgánica se secó sobre sulfato de sodio, se filtró y se concentró. El producto crudo se purificó dos veces por cromatografía en columna (diclorometano/metanol 0–10% y acetato de etilo). Rendimiento: 1,32 g del compuesto del título.

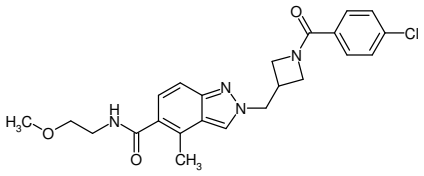
^{1}H–RMN (300 MHz, DMSO–d_6): δ [ppm] = 4,54 (1H), 4,97 (2H), 7,12 (1H), 7,81 (5H).

El siguiente compuesto se preparó de forma análoga:

Ej.	Estructura	Nombre IUPAC	Análisis
116		2-({1-[4-(4-fluoro-fenoxi)benzoil]-piperidin-4-il}metil)-4-metil-N-(2-[$^2H_3$]-metil	^{1}H–RMN (300 MHz, DMSO–d_6): δ [ppm] = 1,19 (2H), 1,46 (2H), 2,25 (1H), 2,49 (3H), 2,85 (2H), 3,66 (1H),

		metiloxi[$^2H_4$]etil)-2H-indazol-5-carboxamida	4,31 (2H), 4,38 (1H), 6,95 (2H), 7,16 (5H), 7,36 (3H), 8,07 (1H), 8,46 (1H).

Ejemplo 117: 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

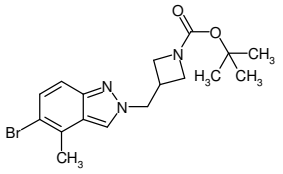


De forma análoga al Ejemplo 55, se obtuvieron 471 mg del compuesto del título a partir de 500 mg del compuesto preparado en el Ejemplo 117e) y 287 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,49 (3H), 3,22 (1H), 3,25 (3H), 3,32-3,46 (4H), 3,89 (1H), 4,09 (1H), 4,19 (1H), 4,37 (1H), 4,67 (2H), 7,15 (1H), 7,38 (1H), 7,48 (2H), 7,59 (2H), 8,12 (1H), 8,54 (1H).

El material de partida se preparó de la siguiente manera:

Ejemplo 117a: 3-[(5-bromo-4-metil-2H-indazol-2-il)metil]-azetidin-1-carboxilato de *tert*-butilo

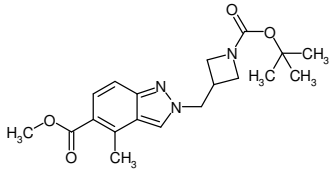


A una solución de 21,1 g de 5-bromo-4-metil-1H-indazol y 37,6 g de 3-[(tosiloxi)-metil]azetidin-1-carboxilato de *tert*-butilo en 100 ml de dioxano se añadieron 150 ml de una solución 1 M de bis(trimetilsilil)amida de sodio en tetrahidrofurano a 25 °C y esto se agitó durante 6 h a 90 °C. Después de enfriar, la mezcla de reacción se trató con acetato de etilo y agua, las fases orgánicas se separaron y la fase acuosa se extrajo dos veces con 100 ml porciones de acetato de etilo. Las fases orgánicas combinadas se lavaron con solución saturada de cloruro de sodio, se secaron sobre sulfato de sodio y se concentró al vacío después de triturar.

El residuo así obtenido se purificó por cromatografía en el Flashmaster (hexano/acetato de etilo 1:0-0:1). Se obtuvieron 15,0 g del compuesto del título.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,32 (9H), 2,48 (3H), 3,07 (1H), 3,69 (2H), 3,87 (2H), 4,59 (2H), 7,28 (1H), 7,35 (1H), 8,53 (1H).

Ejemplo 117b: 2-{[1-(*tert*-butoxicarbonil)azetidin-3-il]metil}-4-metil-2H-indazol-5-carboxilato de metilo

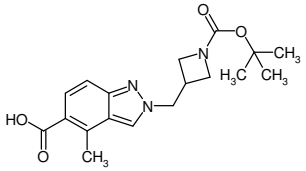


A una solución de 8,16 g del bromuro preparado en

el Ejemplo 117a en 65,4 ml de metanol, se añadieron 6,5 g de dicloruro de 1,1-bis(difenilfosfino)ferrocen-paladio (II) y 15 g de acetato de potasio a 25 °C y la mezcla se agitó bajo CO a 10,15 bar y 120 °C durante 24 horas en un autoclave. La mezcla de reacción luego se enfrió, se filtró a través de Celite en la bomba y el filtrado se concentró al vacío. El residuo así obtenido se purificó por cromatografía en el Flashmaster (hexano/acetato de etilo 1:0-0:1). Se obtuvieron 6,97 g del compuesto del título.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,32 (9H), 2,73 (3H), 3,09 (1H), 3,71 (2H), 3,79 (3H), 3,87 (2H), 4,62 (2H), 7,42 (1H), 7,63 (1H), 8,74 (1H).

Ejemplo 117c: ácido 2-{[1-(*tert*-butoxicarbonil)azetidin-3-il]metil}-4-metil-2H-indazol-5-carboxílico

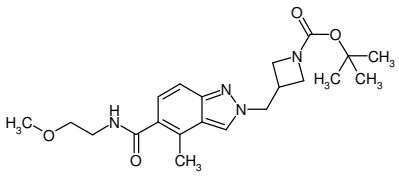


De forma análoga al Ejemplo 1d, se obtuvieron 5,2 g del compuesto del título a partir de 15,1 g del éster preparado en el Ejemplo 117b.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,32 (9H), 2,73 (3H), 3,09 (1H), 3,71 (2H), 3,87 (2H), 4,61 (2H), 7,39 (1H), 7,64 (1H), 8,70 (1H), 12,57 (1H).

Ejemplo 117d: 3-({5-[N-(2-metoxietil)carbamoil]-4-

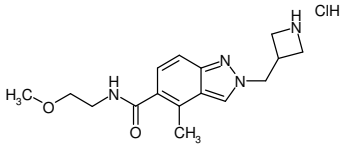
metil-2H-indazol-2-il}-metil)azetidin-1-carboxilato de *tert*-butilo



De forma análoga al Ejemplo 1, se obtuvieron de 2,5 g del ácido preparado en el Ejemplo 117c y 0,54 g de 2-metoxietilamina, se obtuvo un producto crudo por medio de purificación en una unidad Biotage (acetato de etilo: 0 a 30% de metanol) dio 2,69 g del compuesto del título.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,32 (9H), 2,49 (3H), 3,08 (1H), 3,25 (3H), 3,32-3,46 (4H), 3,70 (2H), 3,86 (2H), 4,60 (2H), 7,15 (1H), 7,38 (1H), 8,11 (1H), 8,54 (1H).

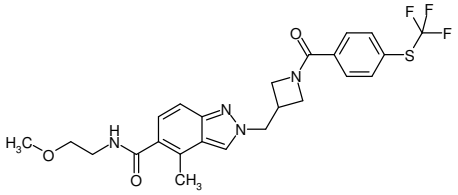
Ejemplo 117e: clorhidrato de 2-(azetidin-3-ilmetil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 2,69 g de la amida preparada en el Ejemplo 117d, se obtuvieron 2,59 g del compuesto del título que se hizo reaccionar sin ulterior purificación.

Ejemplo 118: N-(2-metoxietil)-4-metil-2-[(1-{4-[(trifluorometil)sulfanil]benzoil} azetidin-3-

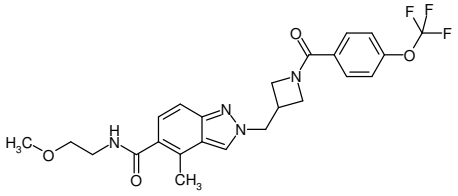
il)metil]-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 29 mg del compuesto del título a partir de 55 mg del compuesto preparado en el Ejemplo 117e y 43 mg de cloruro de 4-[(trifluorometil)sulfanil]benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,49 (3H), 3,22 (1H), 3,25 (3H), 3,36 (2H), 3,42 (2H), 3,92 (1H), 4,11 (1H), 4,20 (1H), 4,39 (1H), 4,67 (2H), 7,15 (1H), 7,38 (1H), 7,69 (2H), 7,76 (2H), 8,12 (1H), 8,54 (1H).

Ejemplo 119: N-(2-metoxietil)-4-metil-2-({1-[4-(trifluorometoxi)benzoil]azetidin-3-il}metil)-2H-indazol-5-carboxamida

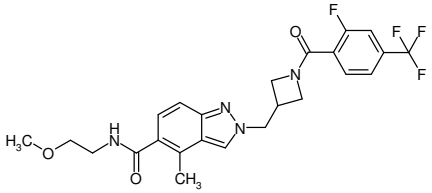


De forma análoga al Ejemplo 55, se obtuvieron 27 mg del compuesto del título a partir de 55 mg del compuesto preparado en el Ejemplo 117e y 40 mg de cloruro de 4-(trifluorometoxi)benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,49 (3H), 3,20 (1H), 3,24 (3H), 3,32-3,46 (4H), 3,91 (1H), 4,10 (1H), 4,20 (1H), 4,39 (1H), 4,67 (2H), 7,15 (1H), 7,35-7,44

(3H), 7,70 (2H), 8,12 (1H), 8,54 (1H).

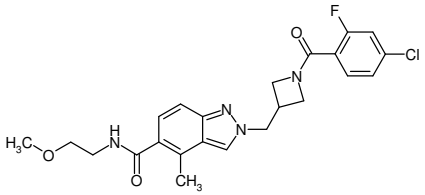
Ejemplo 120: 2-({1-[2-fluoro-4-(trifluorometil)benzoil]azetidin-3-il}metil)-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 17 mg del compuesto del título a partir de 55 mg del compuesto preparado en el Ejemplo 117e y 41 mg de cloruro de 2-fluoro-4-(trifluorometil)benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,48 (3H), 3,23 (1H), 3,25 (3H), 3,36 (2H), 3,42 (2H), 3,94 (2H), 4,11 (2H), 4,66 (2H), 7,15 (1H), 7,38 (1H), 7,64 (2H), 7,79 (1H), 8,12 (1H), 8,54 (1H).

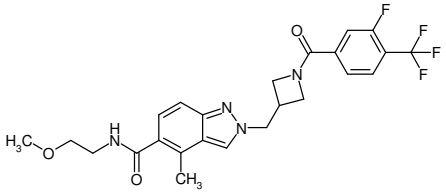
Ejemplo 121: 2-{[1-(4-cloro-2-fluorobenzoil)azetidin-3-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 19 mg del compuesto del título a partir de 42 mg del compuesto preparado en el Ejemplo 117e y 26 mg de cloruro de 4-cloro-2-fluorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,48 (3H), 3,21 (1H), 3,24 (3H), 3,33-3,46 (4H), 3,86-3,97 (2H), 4,08 (2H), 4,65 (2H), 7,15 (1H), 7,34 (1H), 7,37 (1H), 7,44 (1H), 7,52 (1H), 8,12 (1H), 8,53 (1H).

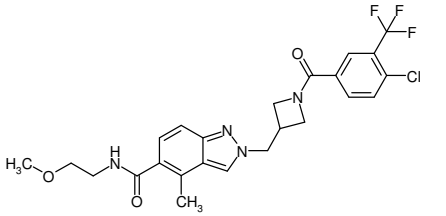
Ejemplo 122: 2-({1-[3-fluoro-4-(trifluorometil)benzoil]azetidin-3-il}metil)-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 15 mg del compuesto del título a partir de 42 mg del compuesto preparado en el Ejemplo 117e y 31 mg de cloruro de 3-fluoro-4-(trifluorometil)benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,49 (3H), 3,21 (1H), 3,25 (3H), 3,36 (2H), 3,42 (2H), 3,93 (1H), 4,12 (1H), 4,22 (1H), 4,40 (1H), 4,67 (2H), 7,15 (1H), 7,37 (1H), 7,57 (1H), 7,64 (1H), 7,85 (1H), 8,12 (1H), 8,54 (1H).

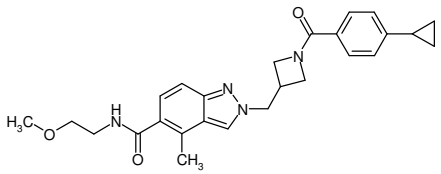
Ejemplo 123: 2-({1-[4-cloro-3-(trifluorometil)benzoil]azetidin-3-il}metil)-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 6 mg del compuesto del título a partir de 42 mg del compuesto preparado en el Ejemplo 117e y 33 mg de cloruro de 4-cloro-3-(trifluorometil)benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,49 (3H), 3,21 (1H), 3,25 (3H), 3,31-3,46 (4H), 3,92 (1H), 4,11 (1H), 4,22 (1H), 4,41 (1H), 4,67 (2H), 7,15 (1H), 7,37 (1H), 7,79 (1H), 7,86 (1H), 7,94 (1H), 8,12 (1H), 8,53 (1H).

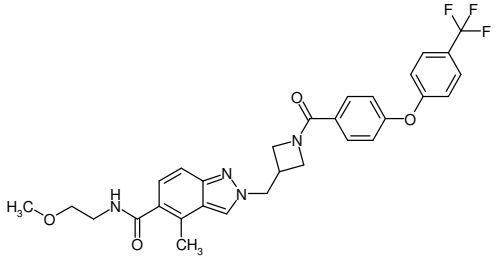
Ejemplo 124: 2-{[1-(4-ciclopropilbenzoil)azetidin-3-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 76 mg del compuesto del título a partir de 163 mg del compuesto preparado en el Ejemplo 117e y 78 mg de ácido 4-ciclopropilbenzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,71 (2H), 0,99 (2H), 1,95 (1H), 2,52 (3H), 3,24 (1H), 3,34-3,41 (5H), 3,45 (2H), 3,90 (1H), 4,09 (1H), 4,20 (1H), 4,38 (1H), 4,68 (2H), 7,12 (2H), 7,18 (1H), 7,41 (1H), 7,48 (2H), 8,12 (1H), 8,57 (1H).

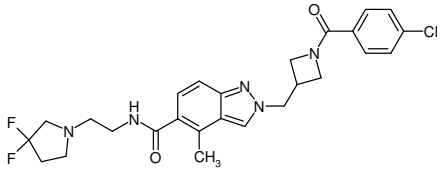
Ejemplo 125: N-(2-metoxietil)-4-metil-2-[(1-{4-[4-(trifluorometil)fenoxi]benzoil} azetidin-3-il)metil]-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 478 mg del compuesto del título a partir de 1,20 g del compuesto preparado en el Ejemplo 117e y 850 mg de ácido 4-[4-(trifluorometil)fenoxi]benzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,52 (3H), 3,25 (1H), 3,27 (3H), 3,39 (2H), 3,45 (2H), 3,94 (1H), 4,12 (1H), 4,24 (1H), 4,42 (1H), 4,70 (2H), 7,14 (2H), 7,18 (1H), 7,22 (2H), 7,41 (1H), 7,69 (2H), 7,77 (2H), 8,12 (1H), 8,57 (1H).

Ejemplo 126: 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-N-[2-(3,3-difluoropirrolidin-1-il)etil]-4-metil-2H-indazol-5-carboxamida

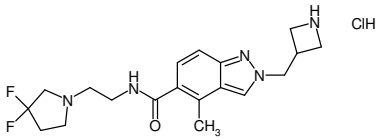


De forma análoga al Ejemplo 55, se obtuvieron 38 mg del compuesto del título a partir de 43 mg del compuesto preparado en el Ejemplo 126a y 20 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,10-2,27 (3H), 2,49 (3H), 2,57 (2H), 2,72 (2H), 2,91 (2H), 3,17-3,36

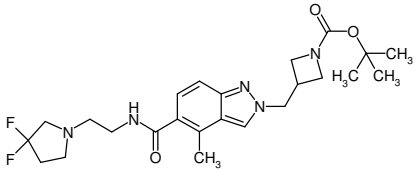
(2H), 3,89 (1H), 4,08 (1H), 4,19 (1H), 4,36 (1H), 4,67 (2H), 7,14 (1H), 7,38 (1H), 7,48 (2H), 7,59 (2H), 8,05 (1H), 8,54 (1H).

Ejemplo 126a: clorhidrato de 2-(azetidin-3-ilmetil)-N-[2-(3,3-difluoropirrolidin-1-il)etil]-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 50 mg del compuesto preparado en el Ejemplo 126b, se obtuvieron 43 mg del compuesto del título que se hizo reaccionar sin ulterior purificación.

Ejemplo 126b: 3-[(5-{N-[2-(3,3-difluoropirrolidin-1-il)etil]carbamoil}-4-metil-2H-indazol-2-il)metil]azetidin-1-carboxilato de *tert*-butilo

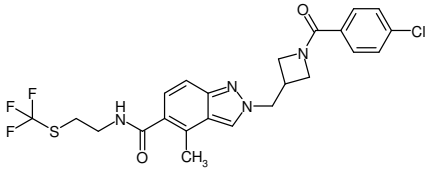


De forma análoga al Ejemplo 1b, se obtuvieron 71 mg del compuesto del título a partir de 70 mg del compuesto preparado en el Ejemplo 117a y 83 mg de 2-(3,3-difluoropirrolidin-1-il)etilamina.

^{1}H-RMN (300 MHz, DMSO-d6): 1,32 (9H), 2,10-2,28 (2H), 2,50 (3H), 2,57 (2H), 2,66-2,77 (2H), 2,84-2,98 (2H), 3,08 (1H), 3,23-3,36 (2H), 3,69 (2H), 3,86 (2H),

4,60 (2H), 7,14 (1H), 7,39 (1H), 8,05 (1H), 8,55 (1H).

Ejemplo 127: 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-4-metil-N-{2-[(trifluorometil) sulfanil]etil}-2H-indazol-5-carboxamida

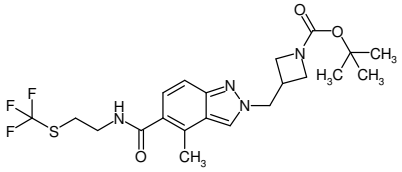


De forma análoga al Ejemplo 55, se obtuvieron 143 mg del compuesto del título a partir de 130 mg del compuesto preparado en el Ejemplo 127b y 61 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,51 (3H), 3,13-3,29 (3H), 3,50 (2H), 3,90 (1H), 4,09 (1H), 4,19 (1H), 4,37 (1H), 4,67 (2H), 7,19 (1H), 7,40 (1H), 7,48 (2H), 7,59 (2H), 8,38 (1H), 8,57 (1H).

El material de partida se preparó de la siguiente manera:

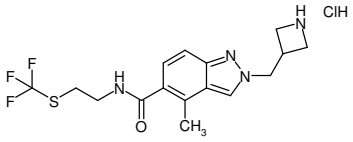
Ejemplo 127a: 3-{[4-metil-5-(N-{2-[(trifluorometil)sulfanil]etil}carbamoil)-indazol-2-il]metil}azetidin-1-carboxilato de *tert*-butilo



De forma análoga al Ejemplo 1, se obtuvieron 674 mg del compuesto del título a partir de 500 mg del compuesto preparado en el Ejemplo 117c.

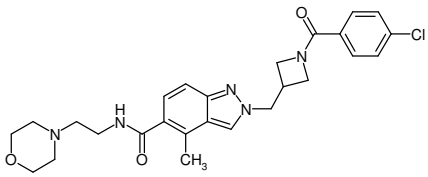
^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,32 (9H), 2,52 (3H), 3,08 (1H), 3,17 (2H), 3,50 (2H), 3,69 (2H), 3,86 (2H), 4,61 (2H), 7,19 (1H), 7,41 (1H), 8,38 (1H), 8,57 (1H).

Ejemplo 127b: clorhidrato de 2-(azetidin-3-ilmetil)-4-metil-N-{2-[(trifluorometil)sulfanil]etil}-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 150 mg del compuesto preparado en el Ejemplo 127a, se obtuvieron 130 mg del compuesto del título, que luego se hizo reaccionar sin purificación.

Ejemplo 128: 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-4-metil-N-(2-morfolinoetil)-2H-indazol-5-carboxamida



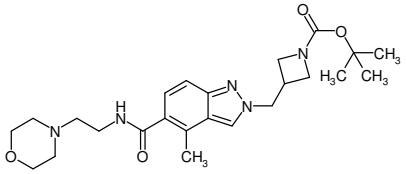
De forma análoga al Ejemplo 55, se obtuvieron 30 mg del compuesto del título a partir de 50 mg del compuesto preparado en el Ejemplo 128b y 24 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,34-2,45 (6H), 2,51 (3H), 3,22 (1H), 3,33 (2H), 3,54 (4H), 3,89 (1H),

4,08 (1H), 4,19 (1H), 4,36 (1H), 4,67 (2H), 7,15 (1H), 7,38 (1H), 7,48 (2H), 7,59 (2H), 7,99 (1H), 8,54 (1H).

El material de partida se preparó de la siguiente manera:

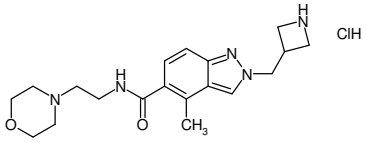
Ejemplo 128a: 3-({4-metil-5-[N-(2-morfolinoetil)carbamoil]-2H-indazol-2-il}metil)azetidin-1-carboxilato de *tert*-butilo



De forma análoga al Ejemplo 1b, se obtuvieron 59 mg del compuesto del título a partir de 200 mg del compuesto preparado en el Ejemplo 117a y 205 mg de 2-morfolinoetilamina.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,32 (9H), 2,34-2,44 (6H), 2,52 (3H), 3,08 (1H), 3,33 (2H), 3,54 (4H), 3,69 (2H), 3,86 (2H), 4,61 (2H), 7,15 (1H), 7,39 (1H), 7,98 (1H), 8,55 (1H).

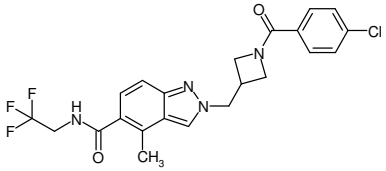
Ejemplo 128b: clorhidrato de 2-(azetidin-3-ilmetil)-4-metil-N-(2-morfolinoetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 59 mg del compuesto preparado en el Ejemplo 128a, se obtuvieron 63 mg del compuesto del título, que luego se

hizo reaccionar sin purificación.

Ejemplo 129: 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

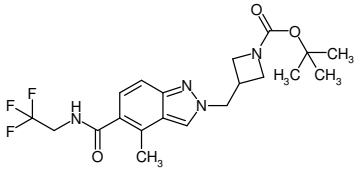


De forma análoga al Ejemplo 55, se obtuvieron 127 mg del compuesto del título a partir de 128 mg del compuesto preparado en el Ejemplo 129b y 68 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,50 (3H), 3,22 (1H), 3,90 (1H), 3,96-4,13 (3H), 4,19 (1H), 4,37 (1H), 4,68 (2H), 7,18 (1H), 7,42 (1H), 7,48 (2H), 7,59 (2H), 8,59 (1H), 8,79 (1H).

El material de partida se preparó de la siguiente manera:

Ejemplo 129a: 3-({4-metil-5-[N-(2,2,2-trifluoroetil)carbamoil]-2H-indazol-2-il}metil)azetidin-1-carboxilato de *tert*-butilo

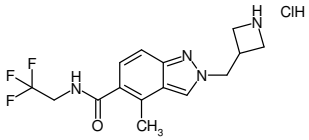


De forma análoga al Ejemplo 1, se obtuvieron 1,02 g del compuesto del título a partir de 1,0 g del compuesto preparado en el Ejemplo 117c y 287 mg de

2,2,2-trifluoroetilamina.

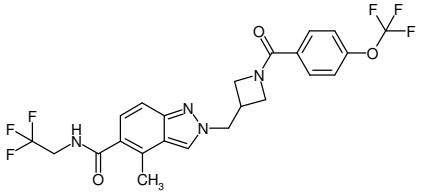
^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,32 (9H), 2,51 (3H), 3,09 (1H), 3,70 (2H), 3,86 (2H), 4,03 (2H), 4,62 (2H), 7,17 (1H), 7,43 (1H), 8,60 (1H), 8,79 (1H).

Ejemplo 129b: clorhidrato de 2-(azetidin-3-ilmetil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 1,0 g del compuesto preparado en el Ejemplo 129a, se obtuvieron 852 mg del compuesto del título, que luego se hizo reaccionar sin purificación.

Ejemplo 130: 4-metil-N-(2,2,2-trifluoroetil)-2-({1-[4-(trifluorometoxi)benzoil]azetidin-3-il}metil)-2H-indazol-5-carboxamida

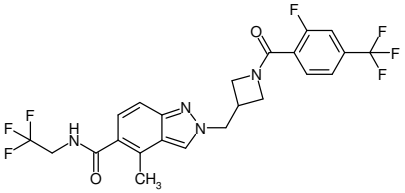


De forma análoga al Ejemplo 55, se obtuvieron 113 mg del compuesto del título a partir de 128 mg del compuesto preparado en el Ejemplo 129b y 87 mg de cloruro de 4-(trifluorometoxi)benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,50 (3H), 3,23 (1H), 3,92 (1H), 3,96-4,14 (3H), 4,20 (1H), 4,39 (1H), 4,68 (2H), 7,18 (1H), 7,36-7,46 (3H), 7,70 (2H), 8,59

(1H), 8,79 (1H).

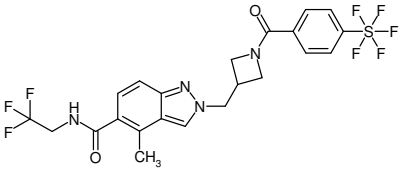
Ejemplo 131: 2-({1-[2-fluoro-4-(trifluorometil)benzoil]azetidin-3-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 128 mg del compuesto del título a partir de 128 mg del compuesto preparado en el Ejemplo 129b y 88 mg de cloruro de 2-fluoro-4-(trifluorometil)benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,49 (3H), 3,23 (1H), 3,89-4,16 (6H), 4,67 (2H), 7,17 (1H), 7,42 (1H), 7,60-7,67 (2H), 7,79 (1H), 8,58 (1H), 8,80 (1H).

Ejemplo 132: 4-metil-2-({1-[4-(pentafluoro-λ^6-sulfanil)benzoil]azetidin-3-il}metil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

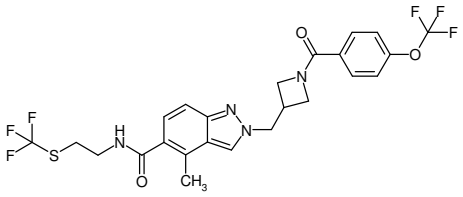


De forma análoga al Ejemplo 1, se obtuvieron 121 mg del compuesto del título a partir de 128 mg del compuesto preparado en el Ejemplo 129b y 96 mg de ácido 4-(pentafluoro-λ^6-sufanil)benzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,50 (3H), 3,24

(1H), 3,94 (1H), 3,98-4,08 (2H), 4,12 (1H), 4,20 (1H), 4,39 (1H), 4,69 (2H), 7,18 (1H), 7,42 (1H), 7,76 (2H), 7,95 (2H), 8,59 (1H), 8,80 (1H).

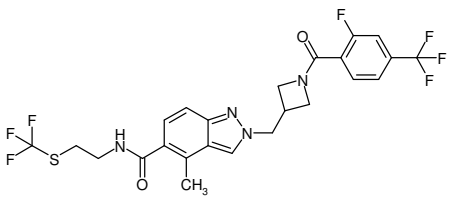
Ejemplo 133: 4-metil-2-({1-[4-(trifluorometoxi)benzoil]azetidin-3-il}metil)-N-{2-[(trifluorometil)sulfanil]etil}-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 178 mg del compuesto del título a partir de 130 mg del compuesto preparado en el Ejemplo 127b y 78 mg de cloruro de 4-(trifluorometoxi)benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,51 (3H), 3,13-3,28 (3H), 3,51 (2H), 3,91 (1H), 4,10 (1H), 4,20 (1H), 4,39 (1H), 4,67 (2H), 7,19 (1H), 7,40 (3H), 7,70 (2H), 8,38 (1H), 8,57 (1H).

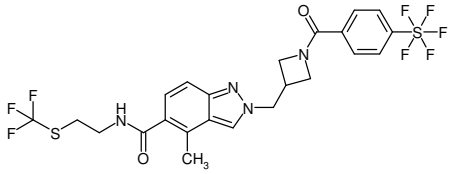
Ejemplo 134: 2-({1-[2-fluoro-4-(trifluorometil)benzoil]azetidin-3-il}metil)-4-metil-N-{2-[(trifluorometil)sulfanil]etil}-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 128 mg del compuesto del título a partir de 130 mg del compuesto preparado en el Ejemplo 127b y 79 mg de cloruro de 2-fluoro-4-(trifluorometil)benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,51 (3H), 3,12-3,25 (3H), 3,50 (2H), 3,89-3,98 (2H), 4,06-4,16 (2H), 4,67 (2H), 7,19 (1H), 7,40 (1H), 7,64 (2H), 7,79 (1H), 8,39 (1H), 8,56 (1H).

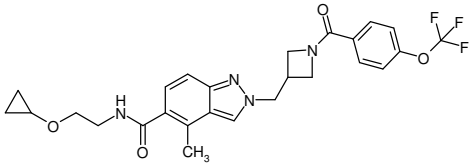
Ejemplo 135: 4-metil-2-({1-[4-(pentafluoro-λ^6-sulfanil)benzoil]azetidin-3-il}metil)-N-{2-[(trifluorometil)sulfanil]etil}-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 84 mg del compuesto del título a partir de 130 mg del compuesto preparado en el Ejemplo 127b y 87 mg de ácido 4-(pentafluoro-λ^6-sulfanil)benzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,51 (3H), 3,18 (2H), 3,23 (1H), 3,51 (2H), 3,94 (1H), 4,12 (1H), 4,20 (1H), 4,39 (1H), 4,68 (2H), 7,19 (1H), 7,41 (1H), 7,76 (2H), 7,95 (2H), 8,39 (1H), 8,56 (1H).

Ejemplo 136: N-[2-(ciclopropiloxi)etil]-4-metil-2-({1-[4-(trifluorometoxi)benzoil] azetidin-3-il}metil)-2H-indazol-5-carboxamida

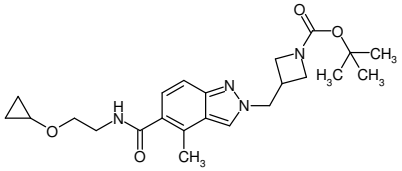


De forma análoga al Ejemplo 55, se obtuvieron 172 mg del compuesto del título a partir de 161 mg del compuesto preparado en el Ejemplo 136b y 109 mg de cloruro de 4-(trifluorometoxi)benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,36-0,48 (4H), 2,48 (3H), 3,22 (1H), 3,27 (1H), 3,35 (2H), 3,53 (2H), 3,91 (1H), 4,10 (1H), 4,20 (1H), 4,39 (1H), 4,67 (2H), 7,14 (1H), 7,35-7,44 (3H), 7,71 (2H), 8,11 (1H), 8,54 (1H).

El material de partida se preparó de la siguiente manera:

Ejemplo 136a: 3-[(5-{N-[2-(ciclopropiloxi)etil]carbamoil}-4-metil-2H-indazol-2-il)metil]azetidin-1-carboxilato de *tert*-butilo

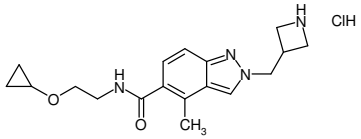


De forma análoga al Ejemplo 1, se obtuvieron 189 mg del compuesto del título a partir de 150 mg del compuesto preparado en el Ejemplo 118c y 140 mg de trifluoroacetato de 2-ciclopropoxi-etilamonio (que puede prepararse de acuerdo con el Ejemplo 154a) y 154b) a partir de ciclopropanol y bromoacetamida

seguido de clivaje de Boc con ácido trifluoroacético análogamente al Ejemplo 1a)).

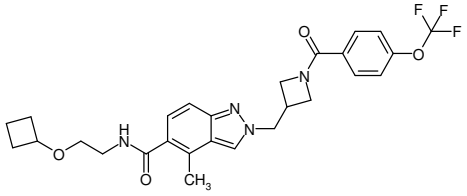
^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,36-0,48 (4H), 1,33 (9H), 2,49 (3H), 3,08 (1H), 3,25-3,39 (3H), 3,53 (2H), 3,70 (2H), 3,87 (2H), 4,61 (2H), 7,14 (1H), 7,38 (1H), 8,10 (1H), 8,54 (1H).

Ejemplo 136b: clorhidrato de 2-(azetidin-3-ilmetil)-N-[(2-ciclopropiloxi)etil]-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 189 mg del compuesto preparado en el Ejemplo 136a, se obtuvieron 161 mg del compuesto del título, que luego se hizo reaccionar sin purificación.

Ejemplo 137: N-[2-(ciclobutiloxi)etil]-4-metil-2-({1-[4-(trifluorometoxi)benzoil] azetidin-3-il}metil)-2H-indazol-5-carboxamida

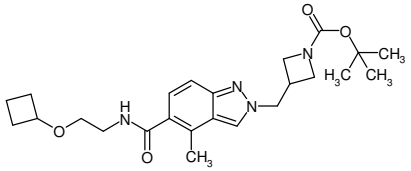


De forma análoga al Ejemplo 55, se obtuvieron 207 mg del compuesto del título a partir de 254 mg del compuesto preparado en el Ejemplo 137b y 166 mg de cloruro de 4-(trifluorometoxi)benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,42 (1H), 1,59 (1H), 1,80 (2H), 2,11 (2H), 2,50 (3H), 3,17-3,28 (1H), 3,31-3,41 (4H), 3,85-3,95 (2H), 4,10 (1H), 4,20 (1H), 4,39 (1H), 4,67 (2H), 7,15 (1H), 7,35-7,44 (3H), 7,71 (2H), 8,11 (1H), 8,54 (1H).

El material de partida se preparó de la siguiente manera:

Ejemplo 137a: 3-[(5-{N-[2-(ciclobutiloxi)etil]carbamoil}-4-metil-2H-indazol-2-il)metil]azetidin-1-carboxilato de *tert*-butilo

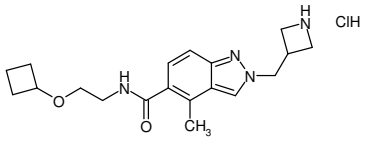


De forma análoga al Ejemplo 1, se obtuvieron 297 mg del compuesto del título a partir de 220 mg del compuesto preparado en el Ejemplo 117c y 143 mg de trifluoroacetato de 2-(ciclobutiloxi)etilamonio (que puede prepararse de acuerdo con Ejemplo 154a) y 154b) a partir de ciclobutanol y bromoacetamida seguido de clivaje de Boc con ácido trifluoroacético análogamente al Ejemplo 1a)).

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,33 (9H), 1,35-1,49 (1H), 1,59 (1H), 1,80 (2H), 2,11 (2H), 2,50 (3H), 3,08 (1H), 3,30-3,41 (4H), 3,69 (2H), 3,82-3,95 (3H), 4,61 (2H), 7,15 (1H), 7,38 (1H), 8,10 (1H), 8,54 (1H).

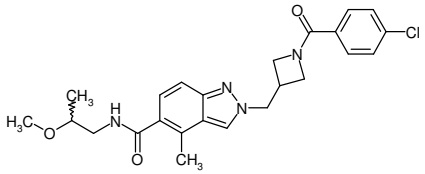
Ejemplo 137b: clorhidrato de 2-(azetidin-3-ilmetil)-N-

[(2-(ciclobutiloxi)etil]-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 297 mg del compuesto preparado en el Ejemplo 137a, se obtuvieron 254 mg del compuesto del título, que luego se hizo reaccionar sin purificación.

Ejemplo 138: (+/-)-2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-N-(2-metoxipropil)-4-metil-2H-indazol-5-carboxamida



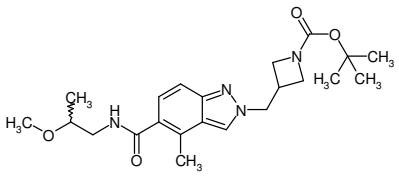
De forma análoga al Ejemplo 55, se obtuvieron 166 mg del compuesto del título a partir de 237 mg del compuesto preparado en el Ejemplo 138b y 129 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,07 (3H), 2,49 (3H), 3,14-3,28 (3H), 3,43 (1H), 3,89 (1H), 4,08 (1H), 4,19 (1H), 4,36 (1H), 4,67 (2H), 7,15 (1H), 7,38 (1H), 7,48 (2H), 7,59 (2H), 8,11 (1H), 8,54 (1H).

El material de partida se preparó de la siguiente manera:

Ejemplo 138a: 3-({5-[N-(2-metoxipropil)carbamoil]-4-

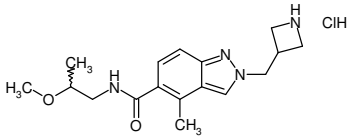
metil-2H-indazol-2-il}metil)azetidin-1-carboxilato de (+/-)-*tert*-butilo



De forma análoga al Ejemplo 1, se obtuvieron 331 mg del compuesto del título a partir de 323 mg del compuesto preparado en el Ejemplo 117c y 117 mg de 2-metoxipropilamina.

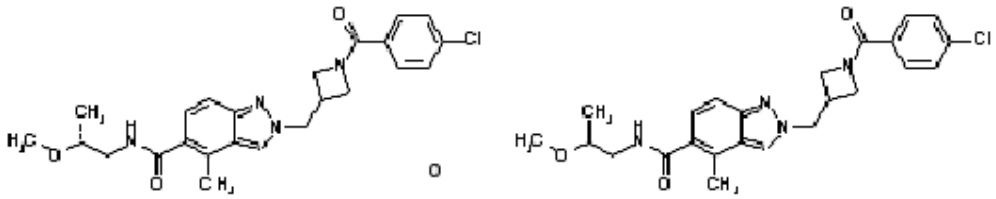
^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,08 (3H), 1,33 (9H), 2,50 (3H), 3,09 (1H), 3,16-3,31 (2H), 3,44 (1H), 3,69 (2H), 3,85 (2H), 4,61 (2H), 7,15 (1H), 7,39 (1H), 8,08 (1H), 8,54 (1H).

Ejemplo 138b: clorhidrato de (+/-)-2-(azetidin-3-ilmetil)-N-(2-metoxipropil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 280 mg del compuesto preparado en el Ejemplo 138a, se obtuvieron 247 mg del compuesto del título, que luego se hizo reaccionar sin purificación.

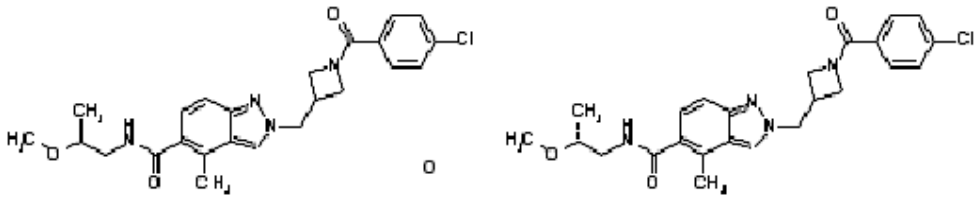
Ejemplo 139: (R o S)-2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-N-(2-metoxipropil)-4-metil-2H-indazol-5-carboxamida



A partir de 158 mg del racemato preparado en el Ejemplo 138, se obtuvieron 52 mg del compuesto del título junto con 48 mg del enantiómero de elución más lenta (Ejemplo 140) por separación de racematos por medio de HPLC quiral preparativa (Método A).

HPLC quiral analítica: 14,5 min.

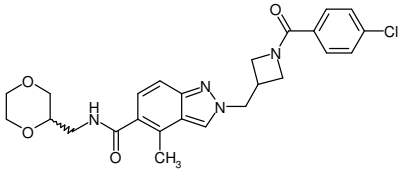
Ejemplo 140: (S o R)-2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-N-(2-metoxipropil)-4-metil-2H-indazol-5-carboxamida



A partir de 158 mg del racemato preparado en el Ejemplo 138, se obtuvieron 48 mg del compuesto del título junto con 52 mg del enantiómero de elución más rápida (Ejemplo 139) por separación de racematos por medio de HPLC quiral preparativa (Método A).

HPLC quiral analítica: 17,1 min.

Ejemplo 141: (+/-)-2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-N-(1,4-dioxan-2-ilmetil)-4-metil-2H-indazol-5-carboxamida

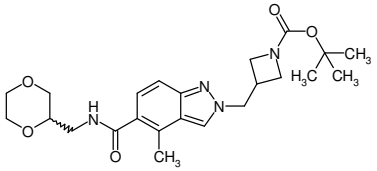


De forma análoga al Ejemplo 55, se obtuvieron 177 mg del compuesto del título a partir de 269 mg del compuesto preparado en el Ejemplo 141b y 136 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,49 (3H), 3,13-3,28 (4H), 3,38-3,66 (4H), 3,67-3,77 (2H), 3,89 (1H), 4,08 (1H), 4,19 (1H), 4,37 (1H), 4,67 (2H), 7,15 (1H), 7,38 (1H), 7,48 (2H), 7,59 (2H), 8,17 (1H), 8,55 (1H).

El material de partida se preparó de la siguiente manera:

Ejemplo 141a: 3-({5-[N-(1,4-dioxan-2-ilmetil)carbamoil]-4-metil-2H-indazol-2-il}metil)azetidin-1-carboxilato de (+/-)-*tert*-butilo

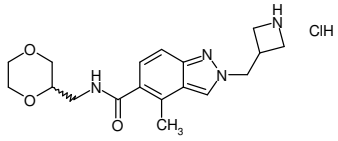


De forma análoga al Ejemplo 1, se obtuvieron 364 mg del compuesto del título a partir de 323 mg del compuesto preparado en el Ejemplo 117c y 110 mg de 1,4-dioxan-2-ilmetilamina.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,33 (9H), 2,50 (3H), 3,09 (1H), 3,16-3,29 (3H), 3,40-3,77 (8H), 3,86 (2H), 4,61 (2H), 7,16 (1H), 7,39 (1H), 8,14 (1H), 8,55

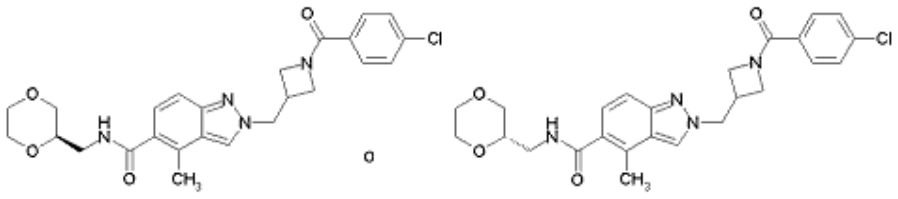
(1H).

Ejemplo 141b: clorhidrato de (+/-)-2-(azetidin-3-ilmetil)-N-(1,4-dioxan-2-ilmetil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 314 mg del compuesto preparado en el Ejemplo 141a, se obtuvieron 274 mg del compuesto del título, que luego se hizo reaccionar sin purificación.

Ejemplo 142: (R o S)-2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-N-(1,4-dioxan-2-il-metil)-4-metil-2H-indazol-5-carboxamida

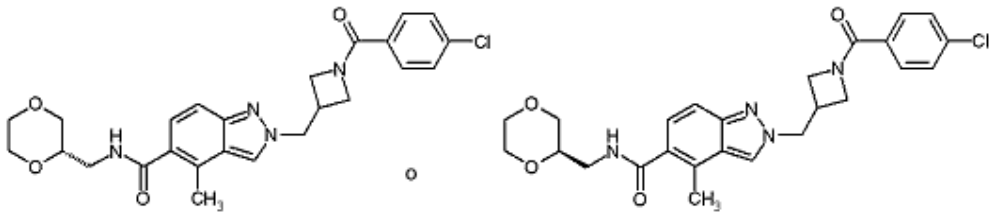


A partir de 172 mg del racemato preparado en el Ejemplo 141, se obtuvieron 60 mg del compuesto del título junto con 60 mg del enantiómero de elución más lenta (Ejemplo 143) por separación de racematos por medio de HPLC quiral preparativa (Método B).

HPLC quiral analítica: 5,84 min.

Ejemplo 143: (S o R)-2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-N-(1,4-dioxan-2-il-metil)-4-metil-2H-indazol-

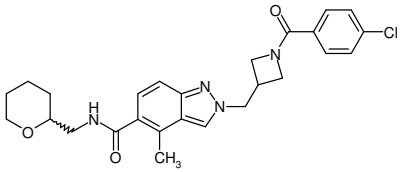
5-carboxamida



A partir de 172 mg del racemato preparado en el Ejemplo 141, se obtuvieron 60 mg del compuesto del título junto con 60 mg del enantiómero de elución más rápida (Ejemplo 142) por separación de racematos por medio de HPLC quiral preparativa (Método B).

HPLC quiral analítica: 6,28 min.

Ejemplo 144: (+/-)-2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-4-metil-N-(3,4,5,6-tetra-hidro-2H-piran-2-ilmetil)-2H-indazol-5-carboxamida

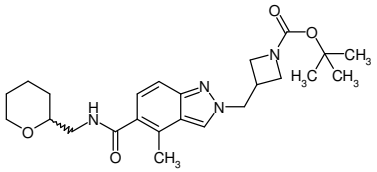


De forma análoga al Ejemplo 55, se obtuvieron 144 mg del compuesto del título a partir de 255 mg del compuesto preparado en el Ejemplo 144b y 130 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,10-1,23 (1H), 1,35-1,47 (3H), 1,61 (1H), 1,71-1,81 (1H), 2,48 (3H), 3,15-3,27 (4H), 3,37 (1H), 3,80-3,93 (2H), 4,08 (1H), 4,19 (1H), 4,36 (1H), 4,66 (2H), 7,14 (1H), 7,37 (1H), 7,48 (2H), 7,59 (2H), 8,09 (1H), 8,54 (1H).

El material de partida se preparó de la siguiente manera:

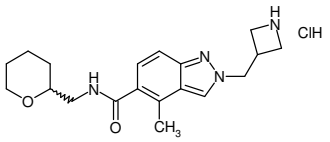
Ejemplo 144a: 3-({4-metil-5-[N-(3,4,5,6-tetrahidro-2H-piran-2-ilmetil)-carbamoil]-2H-indazol-2-il}metil)azetidin-1-carboxilato de (+/-)-*tert*-butilo



De forma análoga al Ejemplo 1, se obtuvieron 342 mg del compuesto del título a partir de 323 mg del compuesto preparado en el Ejemplo 117c y 141 mg de clorhidrato de 3,4,5,6-tetrahidro-2H-piran-2-ilmetil-amina.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,14-1,21 (1H), 1,33 (9H), 1,37-1,49 (3H), 1,61 (1H), 1,71-1,80 (1H), 2,49 (3H), 3,09 (1H), 3,21 (2H), 3,27-3,43 (2H), 3,69 (2H), 3,81-3,91 (3H), 4,61 (2H), 7,15 (1H), 7,38 (1H), 8,06 (1H), 8,53 (1H).

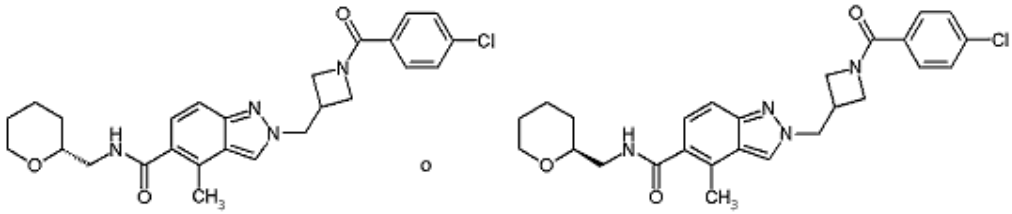
Ejemplo 144b: clorhidrato de (+/-)-2-(azetidin-3-ilmetil)-4-metil-N-(3,4,5,6-tetrahidro-2H-piran-2-il-metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 298 mg del compuesto preparado en el Ejemplo 144a, se

obtuvieron 261 mg del compuesto del título, que luego se hizo reaccionar sin purificación.

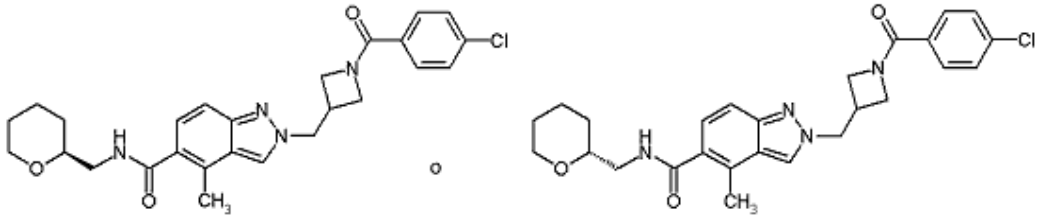
Ejemplo 145: (R o S)-2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-4-metil-N-(3,4,5,6-tetrahidro-2H-piran-2-ilmetil)-2H-indazol-5-carboxamida



A partir de 140 mg del racemato preparado en el Ejemplo 144, se obtuvieron 43 mg del compuesto del título junto con 35 mg del enantiómero de elución más lenta (Ejemplo 146) por separación de racematos por medio de HPLC quiral preparativa (Método C).

HPLC quiral analítica: 4,38 min.

Ejemplo 146: (S o R)-2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-4-metil-N-(3,4,5,6-tetrahidro-2H-piran-2-ilmetil)-2H-indazol-5-carboxamida

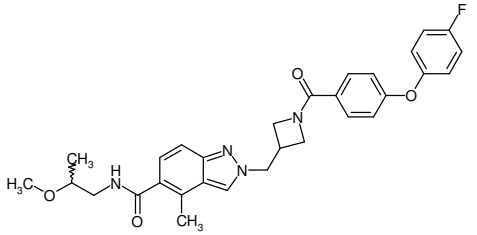


A partir de 140 mg del racemato preparado en el Ejemplo 144, se obtuvieron 35 mg del compuesto del título junto con 43 mg del enantiómero de elución más rápida (Ejemplo 145) por separación de racematos por

medio de HPLC quiral preparativa (Método C).

HPLC quiral analítica: 4,88 min.

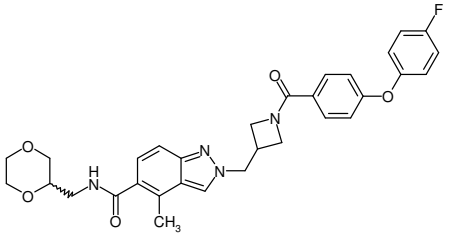
Ejemplo 147: (+/-)-2-({1-[4-(4-fluorofenoxi)benzoil]azetidin-3-il}metil)-N-(2-metoxi-propil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron de 42 mg del compuesto preparado en el Ejemplo 138b y 28 mg de ácido 4-(4-fluorofenoxi)benzoico, un material aún contaminado después de purificación por HPLC, que luego se purificó por una cromatografía de capa delgada preparativa adicional con acetato de etilo / metanol en la relación 9:1 como fase móvil. Rendimiento de esta manera: 15 mg del compuesto del título.

^{1}H-RMN (300 MHz, CDCl3): δ = 1,22 (3H), 2,64 (3H), 3,28 (1H), 3,36 (3H), 3,40 (1H), 3,57 (1H), 3,76 (1H), 3,97-4,46 (4H), 4,66 (2H), 6,14 (1H), 6,93 (2H), 6,97-7,11 (4H), 7,32 (1H), 7,51 (1H), 7,60 (2H), 8,00 (1H).

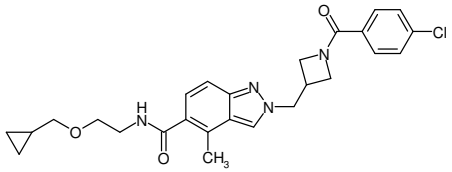
Ejemplo 148: (+/-)-N-(1,4-dioxan-2-ilmetil)-2-({1-[4-(4-fluorofenoxi)benzoil]azetidin-3-il}metil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 18 mg del compuesto del título a partir de 43 mg del compuesto preparado en el Ejemplo 141b y 26 mg de ácido 4-(4-fluorofenoxi)benzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,49 (3H), 3,13-3,28 (4H), 3,38-3,66 (4H), 3,67-3,77 (2H), 3,89 (1H), 4,07 (1H), 4,19 (1H), 4,37 (1H), 4,66 (2H), 6,94 (2H), 7,08-7,18 (3H), 7,24 (2H), 7,38 (1H), 7,60 (2H), 8,17 (1H), 8,55 (1H).

Ejemplo 149: 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-N-[2-(ciclopropilmetoxi)etil]-4-metil-2H-indazol-5-carboxamida



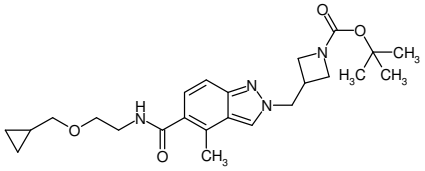
De forma análoga al Ejemplo 55, se obtuvieron 72 mg del compuesto del título a partir de 127 mg del compuesto preparado en el Ejemplo 149b y 65 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,17 (2H), 0,45 (2H), 0,99 (1H), 2,51-2,54 (3H), 3,20-3,28 (3H), 3,38 (2H), 3,51 (2H), 3,92 (1H), 4,11 (1H), 4,21 (1H), 4,39

(1H), 4,69 (2H), 7,18 (1H), 7,40 (1H), 7,50 (2H), 7,62 (2H), 8,12 (1H), 8,56 (1H).

El material de partida se preparó de la siguiente manera:

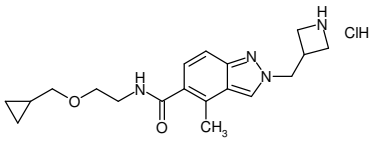
Ejemplo 149a: 3-[(5-{N-[2-(ciclopropilmetoxi)etil]carbamoil}-4-metil-2H-indazol-2-il)metil]azetidin-1-carboxilato de *tert*-butilo



De forma análoga al Ejemplo 1, se obtuvieron 448 mg del compuesto del título a partir de 400 mg del compuesto preparado en el Ejemplo 117c y 133 mg de clorhidrato de 2-(ciclopropilmetoxi)etilamina.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,14 (2H), 0,42 (2H), 0,97 (1H), 1,33 (9H), 2,50 (3H), 3,09 (1H), 3,24 (2H), 3,36 (2H), 3,49 (2H), 3,69 (2H), 3,86 (2H), 4,61 (2H), 7,15 (1H), 7,38 (1H), 8,08 (1H), 8,54 (1H).

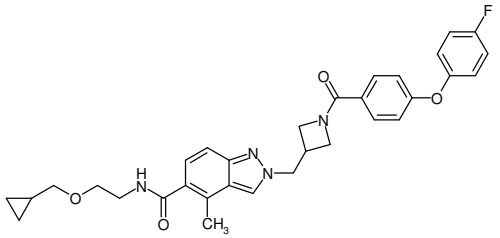
Ejemplo 149b: clorhidrato de 2-(azetidin-3-ilmetil)-N-[2-(ciclopropilmetoxi)etil]-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 448 mg del compuesto preparado en el Ejemplo 149a, se

obtuvieron 390 mg del compuesto del título, que luego se hizo reaccionar sin purificación.

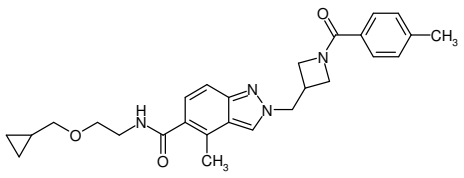
Ejemplo 150: N-[2-(ciclopropilmetoxi)etil]-2-({1-[4-(4-fluorofenoxi)benzoil]azetidin-3-il}metil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 48 mg del compuesto del título a partir de 102 mg del compuesto preparado en el Ejemplo 149b y 63 mg de ácido 4-(4-fluorofenoxi)benzoico.

^{1}H-RMN (300 MHz, CDCl3): δ = 0,20 (2H), 0,54 (2H), 1,05 (1H), 2,65 (3H), 3,32 (2H), 3,35-3,45 (1H), 3,63-3,75 (4H), 3,99-4,50 (4H), 4,66 (2H), 6,22 (1H), 6,93 (2H), 6,97-7,11 (4H), 7,34 (1H), 7,51 (1H), 7,61 (2H), 8,00 (1H).

Ejemplo 151: N-[2-(ciclopropilmetoxi)etil]-4-metil-2-{[1-(4-metilbenzoil)azetidin-3-il]metil}-2H-indazol-5-carboxamida

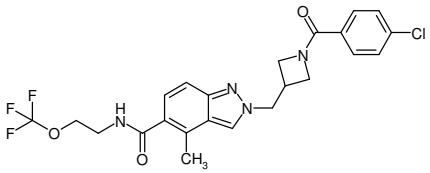


De forma análoga al Ejemplo 1, se obtuvieron 55 mg del compuesto del título a partir de 127 mg del

compuesto preparado en el Ejemplo 149b y 46 mg de ácido 4-metilbenzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,17 (2H), 0,45 (2H), 0,99 (1H), 2,33 (3H), 2,53 (3H), 3,19-3,28 (3H), 3,38 (2H), 3,51 (2H), 3,90 (1H), 4,09 (1H), 4,20 (1H), 4,38 (1H), 4,69 (2H), 7,18 (1H), 7,24 (2H), 7,41 (1H), 7,50 (2H), 8,11 (1H), 8,57 (1H).

Ejemplo 152: 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-4-metil-N-[2-(trifluorometoxi) etil]-2H-indazol-5-carboxamida

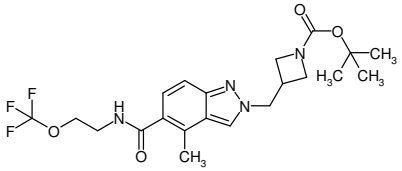


De forma análoga al Ejemplo 55, se obtuvieron 122 mg del compuesto del título a partir de 234 mg del compuesto preparado en el Ejemplo 152b y 115 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,52 (3H), 3,25 (1H), 3,54 (2H), 3,93 (1H), 4,11 (1H), 4,17-4,25 (3H), 4,40 (1H), 4,70 (2H), 7,19 (1H), 7,43 (1H), 7,50 (2H), 7,61 (2H), 8,38 (1H), 8,58 (1H).

El material de partida se preparó de la siguiente manera:

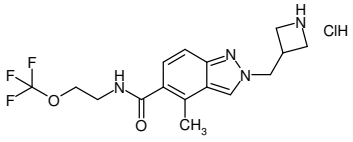
Ejemplo 152a: 3-[(4-metil-5-{N-[2-(trifluorometoxi)etil]carbamoil}-2H-indazol-2-il)metil]azetidin-1-carboxilato de *tert*-butilo



De forma análoga al Ejemplo 1, se obtuvieron 272 mg del compuesto del título a partir de 250 mg del compuesto preparado en el Ejemplo 117c y 120 mg de clorhidrato de 2-(trifluorometoxi)etilamina.

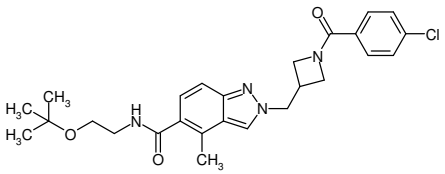
^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,32 (9H), 2,50 (3H), 3,08 (1H), 3,51 (2H), 3,70 (2H), 3,86 (2H), 4,17 (2H), 4,61 (2H), 7,16 (1H), 7,41 (1H), 8,36 (1H), 8,56 (1H).

Ejemplo 152b: clorhidrato de 2-(azetidin-3-ilmetil)-4-metil-N-[2-(trifluorometoxi)etil]-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 272 mg del compuesto preparado en el Ejemplo 152a, se obtuvieron 240 mg del compuesto del título, que luego se hizo reaccionar sin purificación.

Ejemplo 153: N-(2-*tert*-butoxietil)-2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-4-metil-2H-indazol-5-carboxamida

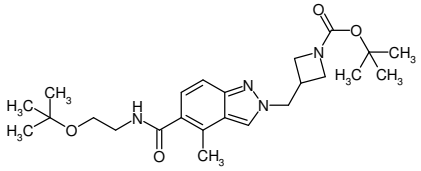


De forma análoga al Ejemplo 55) 12 mg del compuesto del título a partir de 160 mg del compuesto preparado en el Ejemplo 153b) y 81 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,14 (9H), 2,53 (3H), 3,19-3,34 (3H), 3,43 (2H), 3,92 (1H), 4,11 (1H), 4,21 (1H), 4,39 (1H), 4,69 (2H), 7,18 (1H), 7,40 (1H), 7,50 (2H), 7,62 (2H), 8,05 (1H), 8,56 (1H).

El material de partida se preparó de la siguiente manera:

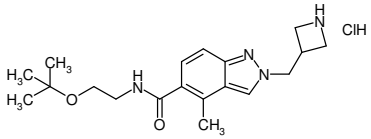
Ejemplo 153a: 3-({5-[N-(2-*tert*-butoxietil)carbamoil]-4-metil-2H-indazol-2-il}-metil)azetidin-1-carboxilato de *tert*-butilo



De forma análoga al Ejemplo 1, se obtuvieron 284 mg del compuesto del título a partir de 250 mg del compuesto preparado en el Ejemplo 117c y 111 mg de clorhidrato de 2-*tert*-butoxietilamina.

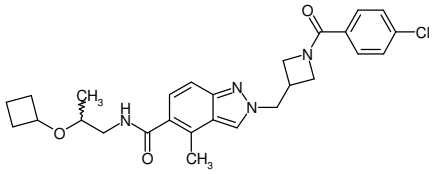
^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,11 (9H), 1,32 (9H), 2,50 (3H), 3,08 (1H), 3,27 (2H), 3,40 (2H), 3,69 (2H), 3,86 (2H), 4,60 (2H), 7,15 (1H), 7,38 (1H), 8,04 (1H), 8,54 (1H).

Ejemplo 153b: clorhidrato de 2-(azetidin-3-ilmetil)-N-(2-*tert*-butoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 284 mg del compuesto preparado en el Ejemplo 153a, se obtuvieron 240 mg del compuesto del título, que luego se hizo reaccionar sin purificación.

Ejemplo 154: (+/-)-2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-N-[2-(ciclobutiloxi)propil]-4-metil-2H-indazol-5-carboxamida

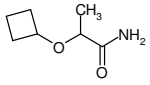


De forma análoga al Ejemplo 55, se obtuvieron 135 mg del compuesto del título a partir de 222 mg del compuesto preparado en el Ejemplo 154d y 109 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,05 (3H), 1,39 (1H), 1,55 (1H), 1,80 (2H), 2,11 (2H), 2,50 (3H), 3,08-3,23 (3H), 3,55 (1H), 3,89 (1H), 4,03-4,13 (1H), 4,19 (1H), 4,37 (1H), 4,67 (2H), 7,15 (1H), 7,38 (1H), 7,48 (2H), 7,59 (2H), 8,07 (1H), 8,53 (1H).

El material de partida se preparó de la siguiente manera:

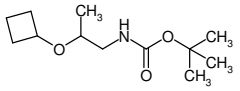
Ejemplo 154a: (+/-)-2-(ciclobutiloxi)-propanamida



A una suspensión de 732 mg de hidruro de sodio en 15 ml de THF, 2,0 g de ciclobutanol en 0,5 ml de THF se añadieron gota a gota y se agitó durante 30 minutos a 25 °C. La mezcla de reacción luego se enfrió hasta 0 °C y 2,11 g de (+/-) 2-bromopropanamida en 0,5 ml de tetrahidrofurano se añadieron gota a gota y luego se agitó durante 18 horas a 25 °C. La mezcla de reacción se vertió en agua helada y se extrajo una vez con 75 ml diclorometano. La fase orgánica se lavó con solución saturada de cloruro de sodio, se secó sobre sulfato de sodio y se concentró al vacío después de triturar. El producto crudo así obtenido se purificó por cromatografía en columna en gel de sílice con hexano / 0-50% de acetato de etilo. Rendimiento: 0,79 g del compuesto del título.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,14 (3H), 1,38 (1H), 1,56 (1H), 1,83 (2H), 2,08 (2H), 3,62 (1H), 3,90 (1H), 7,07 (2H).

Ejemplo 154b: N-[2-(ciclobutiloxi)propil]carbamato de (+/-)-*tert*-butilo



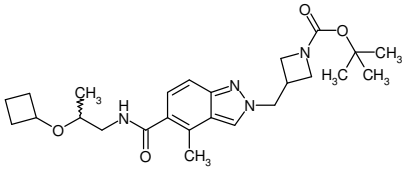
A una suspensión de 6,9 g de hidruro de litio y aluminio en 250 ml de THF, se añadieron cuidadosamente 6,5 g de la amida preparada en el Ejemplo 154a en 81 ml de THF gota a gota a 0 °C. La mezcla se agitó primero

durante 30 minutos a 0 °C y luego se calentó durante 5 horas a reflujo. Después de enfriar, la mezcla se trató cuidadosamente con 20 g de sulfato de sodio decahidrato y 20 g de fluoruro de potasio y materia sólida se eliminó por filtración después brevemente. El filtrado se concentró al vacío. El residuo así obtenido (5,8 g) se disolvió sin ulterior purificación en 174 ml de diclorometano y se trató con 11,9 g de bicarbonato de di-*tert*-butilo. Después de agitar durante 16 horas a 25 °C, se concentró al vacío y el residuo así obtenido se purificó por cromatografía doble en columna en gel de sílice con hexano / 0-40% de acetato de etilo.

Rendimiento: 8,54 g del compuesto del título.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,94 (3H), 1,28-1,42 (10H), 1,53 (1H), 1,76 (2H), 2,07 (2H), 2,76 (1H), 2,90 (1H), 3,34 (1H), 3,92 (1H), 6,72 (1H).

Ejemplo 154c: 3-[(5-{N-[2-(ciclobutiloxi)propil]carbamoil}-4-metil-2H-indazol-2-il)metil]azetidin-1-carboxilato de (+/-)-*tert*-butilo

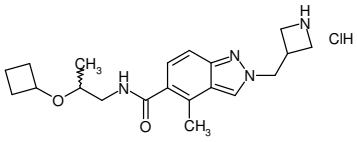


De forma análoga al Ejemplo 1a, a partir de 200 mg del compuesto preparado en el Ejemplo 154b), se obtuvo 2-(ciclobutiloxi)propilamina como el clorhidrato que, sin purificación ulterior junto con 250 mg del

compuesto preparado en el Ejemplo 117c análogamente al Ejemplo 1, dio como resultado 259 mg del compuesto del título.

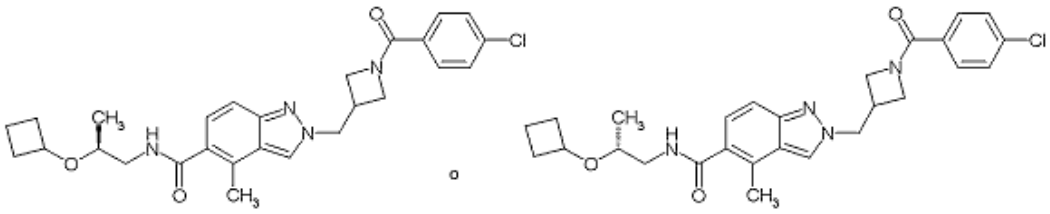
^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,05 (3H), 1,32 (9H), 1,39 (1H), 1,55 (1H), 1,80 (2H), 2,11 (2H), 2,50 (3H), 3,02-3,17 (2H), 3,22 (1H), 3,54 (1H), 3,69 (2H), 3,86 (2H), 3,99 (1H), 4,61 (2H), 7,15 (1H), 7,39 (1H), 8,09 (1H), 8,55 (1H).

Ejemplo 154d: clorhidrato de (+/-)-2-(azetidin-3-ilmetil)-N-[2-(ciclobutiloxi)propil]-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 259 mg del compuesto preparado en el Ejemplo 154c, se obtuvieron 225 mg del compuesto del título, que luego se hizo reaccionar sin purificación.

Ejemplo 155: (S o R)-2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-N-[2-(ciclobutiloxi)-propil]-4-metil-2H-indazol-5-carboxamida

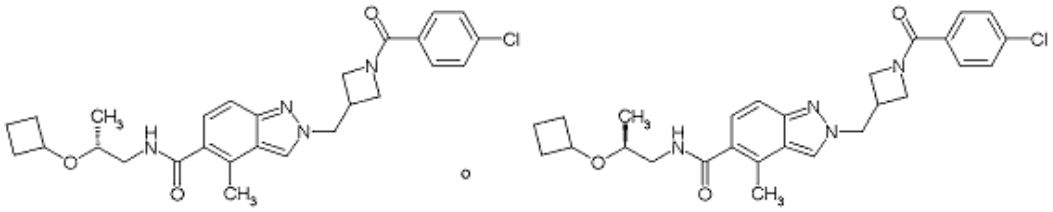


A partir de 135 mg del racemato preparado en el Ejemplo 154, se obtuvieron 41 mg del compuesto del

título junto con 21 mg del enantiómero de elución más lenta (Ejemplo 156) por separación de racematos por medio de HPLC quiral preparativa (Método A).

HPLC quiral analítica: 10,05 min.

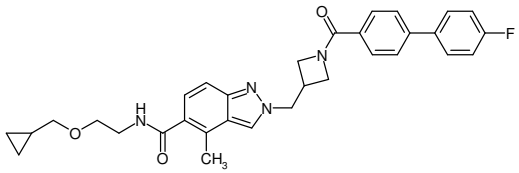
Ejemplo 156: (R o S)-2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-N-[2-(ciclobutiloxi)-propil]-4-metil-2H-indazol-5-carboxamida



A partir de 135 mg del racemato preparado en el Ejemplo 154, se obtuvieron 21 mg del compuesto del título junto con 41 mg del enantiómero de elución más rápida (Ejemplo 155) por separación de racematos por medio de HPLC quiral preparativa (Método A).

HPLC quiral analítica: 13,14 min.

Ejemplo 157: N-[2-(ciclopropilmetoxi)etil]-2-({1-[(4'-fluorobifenil-4-il)carbonil] azetidin-3-il}metil)-4-metil-2H-indazol-5-carboxamida

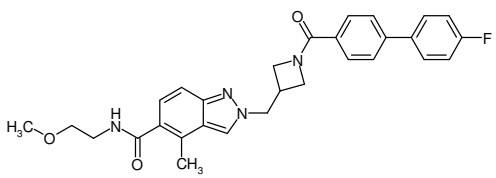


De forma análoga al Ejemplo 1, se obtuvieron 54 mg del compuesto del título a partir de 102 mg del compuesto preparado en el Ejemplo 149b y 58 mg de ácido

4'-fluorobifenil-4-carboxílico.

^{1}H-RMN (300 MHz, CDCl3): δ = 0,20 (2H), 0,54 (2H), 1,05 (1H), 2,66 (3H), 3,32 (2H), 3,42 (1H), 3,61-3,73 (4H), 4,09 (1H), 4,28 (1H), 4,38 (1H), 4,49 (1H), 4,69 (2H), 6,22 (1H), 7,10-7,18 (2H), 7,26 (2H), 7,35 (1H), 7,50-7,59 (3H), 7,70 (2H), 8,01 (1H).

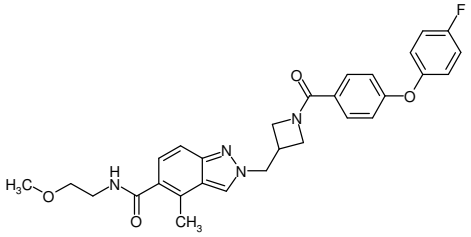
Ejemplo 158: 2-({1-[(4'-fluorobifenil-4-il)carbonil]azetidin-3-il}metil)-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 54 mg del compuesto del título a partir de 108 mg del compuesto preparado en el Ejemplo 117e y 69 mg de ácido 4'-fluorobifenil-4-carboxílico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,49 (3H), 3,17-3,29 (4H), 3,36 (2H), 3,43 (2H), 3,92 (1H), 4,11 (1H), 4,24 (1H), 4,42 (1H), 4,68 (2H), 7,15 (1H), 7,29 (2H), 7,39 (1H), 7,63-7,78 (6H), 8,12 (1H), 8,56 (1H).

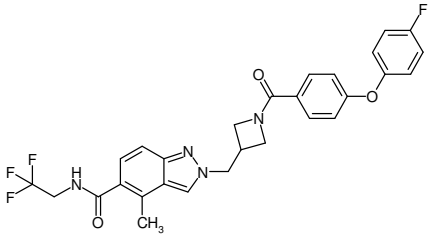
Ejemplo 159: 2-({1-[4-(4-fluorofenoxi)benzoil]azetidin-3-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 28 mg del compuesto del título a partir de 108 mg del compuesto preparado en el Ejemplo 117e y 74 mg de ácido 4-(4-fluorofenoxi)benzoico.

^{1}H-RMN (300 MHz, CDCl3): δ = 2,65 (3H), 3,31-3,46 (4H), 3,58 (2H), 3,67 (2H), 4,06 (1H), 4,24 (1H), 4,40 (2H), 4,66 (2H), 6,15 (1H), 6,89-7,13 (6H), 7,33 (1H), 7,51 (1H), 7,61 (2H), 8,00 (1H).

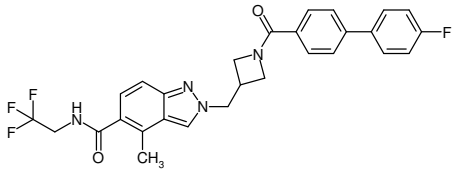
Ejemplo 160: 2-({1-[4-(4-fluorofenoxi)benzoil]azetidin-3-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 47 mg del compuesto del título a partir de 115 mg del compuesto preparado en el Ejemplo 129b y 74 mg de ácido 4-(4-fluorofenoxi)benzoico.

^{1}H-RMN (300 MHz, CDCl3): δ = 2,65 (3H), 3,39 (1H), 3,97-4,52 (6H), 4,67 (2H), 6,04 (1H), 6,89-7,12 (6H), 7,31 (1H), 7,53 (1H), 7,60 (2H), 8,03 (1H).

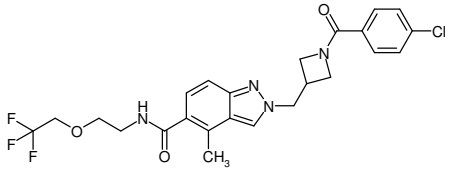
Ejemplo 161: 2-({1-[(4'-fluorobifenil-4-il)carbonil]azetidin-3-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 28 mg del compuesto del título a partir de 115 mg del compuesto preparado en el Ejemplo 129b y 69 mg de ácido 4'-fluorobifenil-4-carboxílico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,65 (3H), 3,42 (1H), 4,01-4,54 (6H), 4,69 (2H), 6,02 (1H), 7,15 (2H), 7,32 (1H), 7,51-7,62 (5H), 7,69 (2H), 8,04 (1H).

Ejemplo 162: 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-4-metil-N-[2-(2,2,2-trifluoro-etoxi)etil]-2H-indazol-5-carboxamida



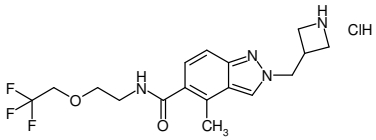
De forma análoga al Ejemplo 55, se obtuvieron 197 mg del compuesto del título a partir de 252 mg del compuesto preparado en el Ejemplo 162a y 108 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,49 (3H), 3,22 (1H), 3,40 (2H), 3,69 (2H), 3,90 (1H), 4,03-4,13 (3H), 4,19 (1H), 4,37 (1H), 4,67 (2H), 7,15 (1H), 7,38 (1H),

7,48 (2H), 7,59 (2H), 8,19 (1H), 8,55 (1H).

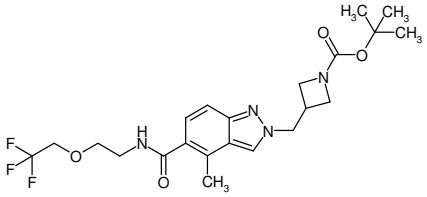
El material de partida se preparó de la siguiente manera:

Ejemplo 162a: clorhidrato de 2-(azetidin-3-ilmetil)-4-metil-N-[2-(2,2,2-trifluoroetoxi)etil]-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 583 mg del compuesto preparado en el Ejemplo 162b, se obtuvieron 505 mg del compuesto del título, que luego se hizo reaccionar sin purificación.

Ejemplo 162b: 3-[(4-metil-5-{N-[2-(2,2,2-trifluoroetoxi)etil]carbamoil}-2H-indazol-2-il)metil]azetidin-1-carboxilato de *tert*-butilo

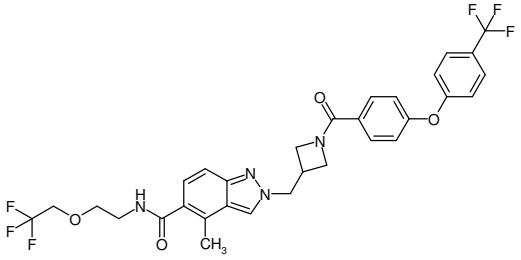


De forma análoga al Ejemplo 1, se obtuvieron 580 mg del compuesto del título a partir de 500 mg del compuesto preparado en el Ejemplo 117c y 260 mg de clorhidrato de 2-(2,2,2-trifluoroetoxi)etilamina.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,32 (9H), 2,50 (3H), 3,08 (1H), 3,40 (2H), 3,61-3,76 (4H), 3,86 (2H), 4,07 (2H), 4,61 (2H), 7,15 (1H), 7,39 (1H), 8,18 (1H),

8,55 (1H).

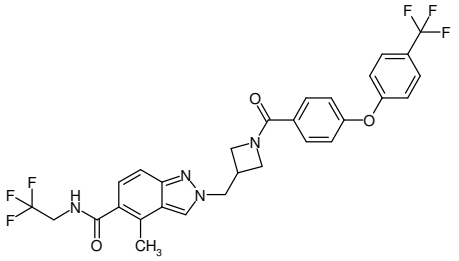
Ejemplo 163: 4-metil-N-[2-(2,2,2-trifluoroetoxi)etil]-2-[(1-{4-[4-(trifluorometil) fenoxi]benzoil}azetidin-3-il)metil]-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 89 mg del compuesto del título a partir de 252 mg del compuesto preparado en el Ejemplo 162a y 175 mg de ácido 4-[4-(trifluorometil)fenoxi]benzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,49 (3H), 3,23 (1H), 3,40 (2H), 3,69 (2H), 3,90 (1H), 4,01-4,14 (3H), 4,21 (1H), 4,40 (1H), 4,68 (2H), 7,11 (2H), 7,15 (1H), 7,20 (2H), 7,39 (1H), 7,66 (2H), 7,75 (2H), 8,19 (1H), 8,56 (1H).

Ejemplo 164: 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{4-[4-(trifluorometil)fenoxi] benzoil}azetidin-3-il)metil]-2H-indazol-5-carboxamida

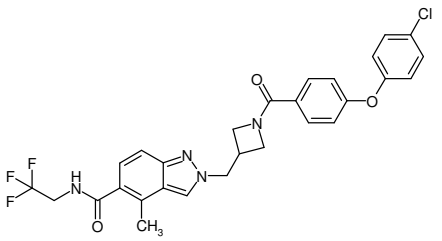


De forma análoga al Ejemplo 1, se obtuvieron 64 mg

del compuesto del título a partir de 225 mg del compuesto preparado en el Ejemplo 129b y 149 mg de ácido 4-[4-(trifluorometil)fenoxi]benzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,50 (3H), 3,24 (1H), 3,91 (1H), 3,95-4,15 (3H), 4,22 (1H), 4,40 (1H), 4,69 (2H), 7,11 (2H), 7,15-7,23 (3H), 7,43 (1H), 7,66 (2H), 7,75 (2H), 8,60 (1H), 8,79 (1H).

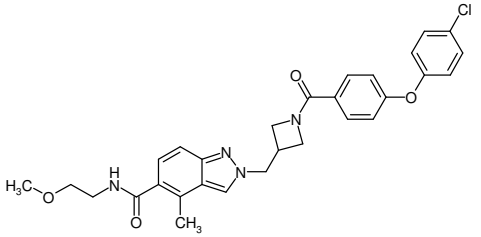
Ejemplo 165: 2-({1-[4-(4-clorofenoxi)benzoil]azetidin-3-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 97 mg del compuesto del título a partir de 225 mg del compuesto preparado en el Ejemplo 129b y 131 mg de ácido 4-(4-clorofenoxi)benzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,50 (3H), 3,23 (1H), 3,90 (1H), 3,96-4,12 (3H), 4,20 (1H), 4,38 (1H), 4,68 (2H), 7,00 (2H), 7,09 (2H), 7,18 (1H), 7,40-7,48 (3H), 7,62 (2H), 8,60 (1H), 8,79 (1H).

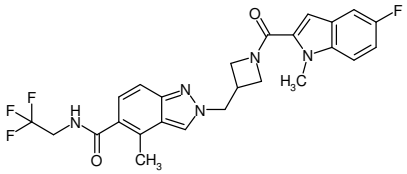
Ejemplo 166: 2-({1-[4-(4-clorofenoxi)benzoil]azetidin-3-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 99 mg del compuesto del título a partir de 225 mg del compuesto preparado en el Ejemplo 117e y 140 mg de ácido 4-(4-clorofenoxi)benzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,49 (3H), 3,16-3,27 (4H), 3,36 (2H), 3,42 (2H), 3,89 (1H), 4,08 (1H), 4,19 (1H), 4,38 (1H), 4,67 (2H), 7,00 (2H), 7,09 (2H), 7,15 (1H), 7,38 (1H), 7,45 (2H), 7,62 (2H), 8,12 (1H), 8,55 (1H).

Ejemplo 167: 2-({1-[(5-fluoro-1-metil-1H-indol-2-il)carbonil]azetidin-3-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

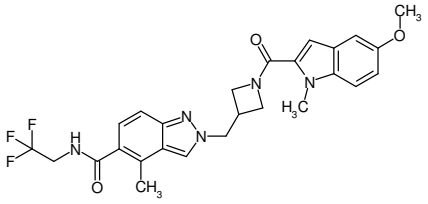


De forma análoga al Ejemplo 1, se obtuvieron 48 mg del compuesto del título a partir de 180 mg del compuesto preparado en el Ejemplo 129b y 82 mg de ácido 5-fluoro-1-metil-1H-indol-2-carboxílico.

^{1}H-RMN (300 MHz, CDCl3): δ = 2,66 (3H), 2,80 (3H), 3,36-3,51 (1H), 4,01 (3H), 4,04-4,63 (6H), 4,70 (2H), 6,03 (1H), 6,68 (1H), 7,08 (1H), 7,22-7,36 (3H), 7,55

(1H), 8,05 (1H).

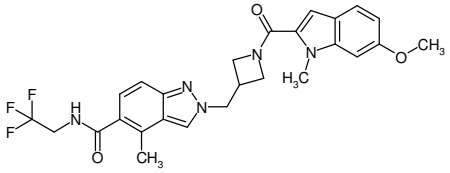
Ejemplo 168: 2-({1-[(5-metoxi-1-metil-1H-indol-2-il)carbonil]azetidin-3-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 15 mg del compuesto del título a partir de 180 mg del compuesto preparado en el Ejemplo 129b y 87 mg de ácido 5-metoxi-1-metil-1H-indol-2-carboxílico.

^{1}H-RMN (300 MHz, CDCl3): δ = 2,66 (3H), 3,43 (1H), 3,84 (3H), 4,00 (3H), 4,03-4,59 (6H), 4,70 (2H), 6,02 (1H), 6,66 (1H), 7,02 (1H), 7,27-7,35 (3H), 7,56 (1H), 8,06 (1H).

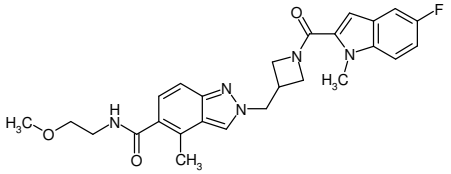
Ejemplo 169: 2-({1-[(6-metoxi-1-metil-1H-indol-2-il)carbonil]azetidin-3-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 57 mg del compuesto del título a partir de 180 mg del compuesto preparado en el Ejemplo 129b y 87 mg de ácido 6-metoxi-1-metil-1H-indol-2-carboxílico.

^{1}H-RMN (300 MHz, CDCl3): δ = 2,66 (3H), 3,43 (1H), 3,89 (3H), 3,99 (3H), 4,05-4,60 (6H), 4,70 (2H), 6,01 (1H), 6,69 (1H), 6,77 (1H), 6,81 (1H), 7,32 (1H), 7,48 (1H), 7,56 (1H), 8,05 (1H).

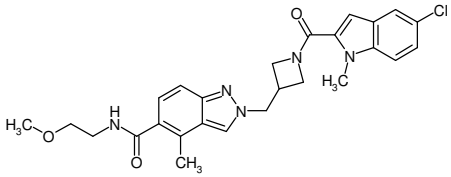
Ejemplo 170: 2-({1-[(5-fluoro-1-metil-1H-indol-2-il)carbonil]azetidin-3-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 95 mg del compuesto del título a partir de 180 mg del compuesto preparado en el Ejemplo 117e y 87 mg de ácido 5-fluoro-1-metil-1H-indol-2-carboxílico.

^{1}H RMN (300 MHz, CDCl3): δ = 2,65 (3H), 3,35-3,51 (4H), 3,58 (2H), 3,67 (2H), 4,01 (3H), 4,02-4,62 (4H), 4,69 (2H), 6,15 (1H), 6,68 (1H), 7,08 (1H), 7,21-7,38 (3H), 7,53 (1H), 8,02 (1H).

Ejemplo 171: 2-({1-[(5-cloro-1-metil-1H-indol-2-il)carbonil]azetidin-3-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

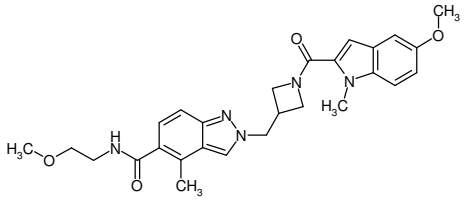


De forma análoga al Ejemplo 1, se obtuvieron 90 mg del compuesto del título a partir de 180 mg del

compuesto preparado en el Ejemplo 117e y ácido 95 mg de 5-cloro-1-metil-1H-indol-2-carboxílico.

^{1}H-RMN (300 MHz, CDCl3): δ = 2,66 (3H), 3,37-3,49 (4H), 3,58 (2H), 3,67 (2H), 4,00 (3H), 4,08 (1H), 4,37 (2H), 4,56 (1H), 4,70 (2H), 6,15 (1H), 6,66 (1H), 7,27-7,38 (3H), 7,53 (1H), 7,58 (1H), 8,02 (1H).

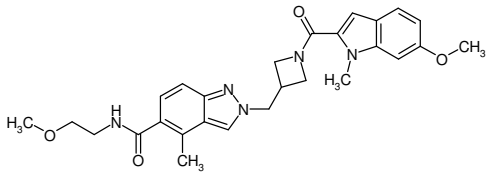
Ejemplo 172: N-(2-metoxietil)-2-({1-[(5-metoxi-1-metil-1H-indol-2-il)carbonil] azetidin-3-il}metil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 86 mg del compuesto del título a partir de 180 mg del compuesto preparado en el Ejemplo 117e y 93 mg de ácido 5-metoxi-1-metil-1H-indol-2-carboxílico.

^{1}H-RMN (300 MHz, CDCl3): δ = 2,65 (3H), 3,36-3,50 (4H), 3,58 (2H), 3,67 (2H), 3,84 (3H), 4,00 (3H), 4,07 (1H), 4,35 (2H), 4,55 (1H), 4,69 (2H), 6,15 (1H), 6,66 (1H), 6,97-7,06 (2H), 7,28 (1H), 7,34 (1H), 7,53 (1H), 8,02 (1H).

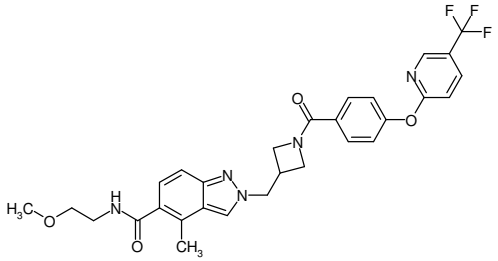
Ejemplo 173: N-(2-metoxietil)-2-({1-[(6-metoxi-1-metil-1H-indol-2-il)carbonil] azetidin-3-il}metil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 97 mg del compuesto del título a partir de 180 mg del compuesto preparado en el Ejemplo 117e y 93 mg de ácido 6-metoxi-1-metil-1H-indol-2-carboxílico.

^{1}H-RMN (300 MHz, CDCl3): δ = 2,66 (3H), 3,37-3,47 (4H), 3,58 (2H), 3,67 (2H), 3,89 (3H), 3,99 (3H), 4,02-4,60 (4H), 4,69 (2H), 6,15 (1H), 6,69 (1H), 6,77 (1H), 6,81 (1H), 7,34 (1H), 7,48 (1H), 7,53 (1H), 8,02 (1H).

Ejemplo 174: N-(2-metoxietil)-4-metil-2-{[1-(4-{[5-(trifluorometil)piridin-2-il]oxi} benzoil)azetidin-3-il]metil}-2H-indazol-5-carboxamida

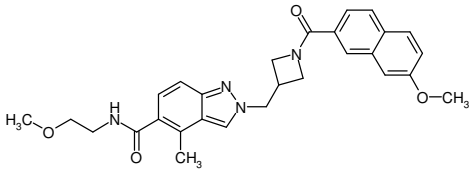


De forma análoga al Ejemplo 1, se obtuvieron 66 mg del compuesto del título a partir de 135 mg del compuesto preparado en el Ejemplo 117e y 96 mg de ácido 4-{[5-(trifluorometil)piridin-2-il]oxi}-benzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,50 (3H), 3,18-3,27 (4H), 3,36 (2H), 3,42 (2H), 3,91 (1H), 4,10 (1H), 4,24 (1H), 4,42 (1H), 4,68 (2H), 7,15 (1H), 7,24 (2H),

7,28 (1H), 7,39 (1H), 7,67 (2H), 8,12 (1H), 8,24 (1H), 8,56 (2H).

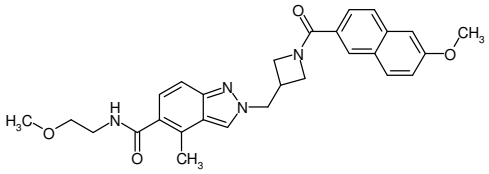
Ejemplo 175: N-(2-metoxietil)-2-{[1-(7-metoxi-2-naftoil)azetidin-3-il]metil}-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 72 mg del compuesto del título a partir de 135 mg del compuesto preparado en el Ejemplo 117e y 69 mg de ácido 7-metoxi-naftalen-2-carboxílico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,50 (3H), 3,21-3,28 (4H), 3,36 (2H), 3,42 (2H), 3,85 (3H), 3,93-3,99 (1H), 4,14 (1H), 4,26 (1H), 4,47 (1H), 4,69 (2H), 7,15 (1H), 7,22 (1H), 7,38 (1H), 7,43 (1H), 7,50 (1H), 7,81-7,88 (2H), 8,05 (1H), 8,12 (1H), 8,56 (1H).

Ejemplo 176: N-(2-metoxietil)-2-{[1-(6-metoxi-2-naftoil)azetidin-3-il]metil}-4-metil-2H-indazol-5-carboxamida

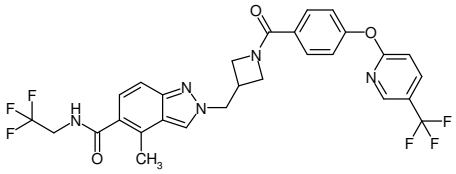


De forma análoga al Ejemplo 1, se obtuvieron 72 mg del compuesto del título a partir de 135 mg del compuesto preparado en el Ejemplo 117e y 69 mg de ácido

6-metoxinaftalen-2-carboxílico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,49 (3H), 3,21-3,28 (4H), 3,33-3,39 (2H), 3,42 (2H), 3,86 (3H), 3,91-3,98 (1H), 4,13 (1H), 4,27 (1H), 4,48 (1H), 4,69 (2H), 7,15 (1H), 7,19 (1H), 7,34 (1H), 7,38 (1H), 7,63 (1H), 7,82 (1H), 7,92 (1H), 8,08-8,14 (2H), 8,56 (1H).

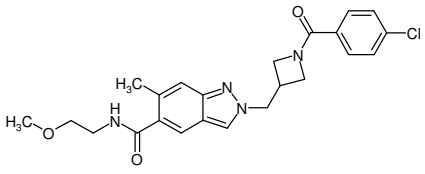
Ejemplo 177: 4-metil-N-(2,2,2-trifluoroetil)-2-{[1-(4-{[5-(trifluorometil)piridin-2-il] oxi}benzoil)azetidin-3-il]metil}-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 68 mg del compuesto del título a partir de 170 mg del compuesto preparado en el Ejemplo 129b y 113 mg de ácido 4-{[5-(trifluorometil)piridin-2-il]oxi}benzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,35 (3H), 3,21 (1H), 3,89 (1H), 3,96-4,13 (3H), 4,21 (1H), 4,40 (1H), 4,68 (2H), 7,24 (2H), 7,28 (1H), 7,40 (1H), 7,66 (2H), 7,72 (1H), 8,24 (1H), 8,48 (1H), 8,56 (1H), 8,89 (1H).

Ejemplo 178: 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-N-(2-metoxietil)-6-metil-2H-indazol-5-carboxamida

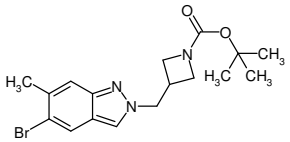


De forma análoga al Ejemplo 55, se obtuvieron 154 mg del compuesto del título a partir de 210 mg del compuesto preparado en el Ejemplo 178e y 119 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,34 (3H), 3,19 (1H), 3,24 (3H), 3,34 (2H), 3,42 (2H), 3,87 (1H), 4,07 (1H), 4,16 (1H), 4,34 (1H), 4,65 (2H), 7,35 (1H), 7,48 (2H), 7,59 (2H), 7,63 (1H), 8,21 (1H), 8,41 (1H).

El material de partida se preparó de la siguiente manera:

Ejemplo 178a: 3-[(5-bromo-6-metil-2H-indazol-2-il)metil]azetidin-1-carboxilato de *tert*-butilo



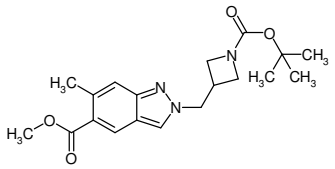
A una solución de 6,18 g de 5-bromo-6-metil-1H-indazol y 15 g de 3-[(tosil-oxi)metil]azetidin-1-carboxilato de *tert*-butilo en 200 ml de DMF se añadieron 9,54 g de carbonato de cesio y 10,8 g de yoduro de tetrabutilamonio a 25 °C y esto luego se calentó a reflujo durante 1,5 hrs. Después de enfriar, la mezcla de reacción se trató con 1:1 hexano / éter y agua, las fases se separaron y la fase acuosa se extrajo dos veces con porciones de 250 ml de 1:1 hexano / éter. Las fases orgánicas combinadas se lavaron con solución saturada de cloruro de sodio, se secaron sobre

sulfato de sodio y se concentraron al vacío después de triturar.

El residuo así obtenido se purificó por cromatografía doble en columna en gel de sílice con hexano / 0–20% de acetato de etilo. Se obtuvieron 2,88 g del compuesto del título.

^{1}H–RMN (300 MHz, DMSO–d6): δ = 1,32 (9H), 2,37 (3H), 3,05 (1H), 3,67 (2H), 3,85 (2H), 4,59 (2H), 7,56 (1H), 7,97 (1H), 8,33 (1H).

Ejemplo 178b: 2–{[1–(*tert*–butoxicarbonil)azetidin–3–il]metil}–6–metil–2H–indazol–5–carboxilato de metilo

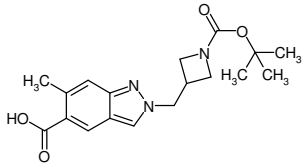


A una solución de 730 mg del bromuro preparado en el Ejemplo 178a en 17,5 ml de tetrahidrofurano se añadieron 0,23 ml de metanol, 145 mg de *trans*–bis(acetato)–bis[o–(di–o–tolilfosfino)–bencil]dipaladio (II), 877 mg de DBU y 760 mg de hexacarbonilo de molibdeno. Esta mezcla de reacción se calentó luego en el microondas (120 watts) durante 20 minutos a 125 °C. Siete preparaciones más se realizaron de la misma manera y todo se elaboró en conjunto. Para ello, se concentraron al vacío y el residuo se extrajo en agua y acetato de etilo. Después de la separación de fases, la fase acuosa se extrajo tres veces con porciones de 75

ml de acetato de etilo y las fases orgánicas combinadas se lavaron con solución saturada de cloruro de sodio, se secaron sobre sulfato de sodio y se concentraron al vacío después de triturar. El residuo así obtenido se purificó por cromatografía doble en columna en gel de sílice con hexano / 0–30% de acetato de etilo. Rendimiento: 4,0 g del compuesto del título.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,32 (9H), 2,52 (3H), 3,07 (1H), 3,69 (2H), 3,86 (2H), 3,78 (3H), 4,62 (2H), 7,43 (1H), 8,33 (1H), 8,53 (1H).

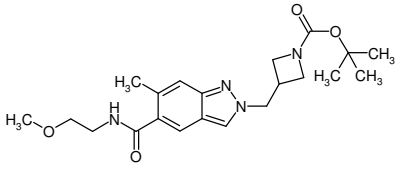
Ejemplo 178c: ácido 2-{[1-(*tert*-butoxicarbonil)azetidin-3-il]metil}-6-metil-2H-indazol-5-carboxílico



De forma análoga al Ejemplo 1d, se obtuvieron 3,2 g del compuesto del título a partir de 4,0 g del éster preparado en el Ejemplo 178b.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,32 (9H), 2,53 (3H), 3,07 (1H), 3,69 (2H), 3,86 (2H), 4,61 (2H), 7,39 (1H), 8,31 (1H), 8,50 (1H), 12,48 (1H).

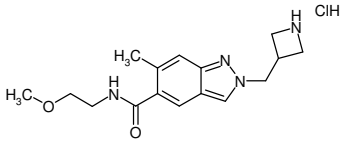
Ejemplo 178d: 3-({5-[N-(2-metoxietil)carbamoil]-6-metil-2H-indazol-2-il}-metil)azetidin-1-carboxilato de *tert*-butilo



De forma análoga al Ejemplo 1, se obtuvieron 603 mg del compuesto del título a partir de 500 mg del ácido preparado en el Ejemplo 178c y 109 mg de 2-metoxietilamina.

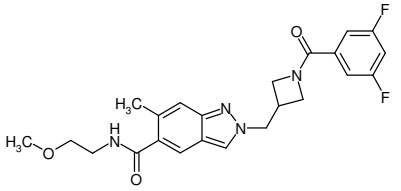
^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,32 (9H), 2,34 (3H), 3,06 (1H), 3,25 (3H), 3,32-3,45 (4H), 3,67 (2H), 3,84 (2H), 4,59 (2H), 7,35 (1H), 7,64 (1H), 8,21 (1H), 8,41 (1H).

Ejemplo 178e: clorhidrato de 2-(azetidin-3-ilmetil)-N-(2-metoxietil)-6-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 250 mg de la amida preparada en el Ejemplo 178d, se obtuvieron 275 mg del compuesto del título, que se hizo reaccionar sin ulterior purificación.

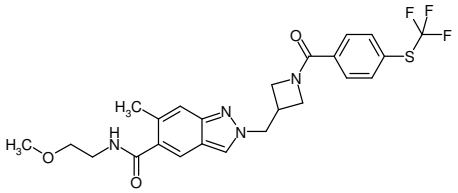
Ejemplo 179: 2-{[1-(3,5-Difluorobenzoil)azetidin-3-il]metil}-N-(2-metoxietil)-6-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 51 mg del compuesto del título a partir de 77 mg del compuesto preparado en el Ejemplo 178e y 44 mg de cloruro de 3,5-difluorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,33 (3H), 3,18 (1H), 3,24 (3H), 3,34 (2H), 3,42 (2H), 3,87 (1H), 4,03-4,11 (1H), 4,20 (1H), 4,38 (1H), 4,65 (2H), 7,20-7,28 (2H), 7,34 (1H), 7,36-7,45 (2H), 7,64 (1H), 8,22 (1H), 8,42 (1H).

Ejemplo 180: N-(2-metoxietil)-6-metil-2-[(1-{4-[(trifluorometil)sulfanil]benzoil} azetidin-3-il)metil]-2H-indazol-5-carboxamida

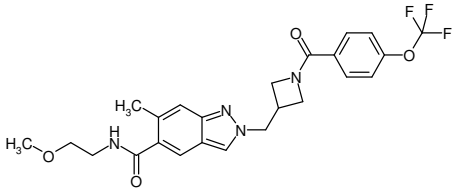


De forma análoga al Ejemplo 55, se obtuvieron 30 mg del compuesto del título a partir de 43 mg del compuesto preparado en el Ejemplo 178e y 34 mg de cloruro de 4-[(trifluorometil)sulfanil]benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,34 (3H), 3,20 (1H), 3,24 (3H), 3,34 (2H), 3,42 (2H), 3,89 (1H), 4,09 (1H), 4,17 (1H), 4,36 (1H), 4,65 (2H), 7,34 (1H), 7,63 (1H), 7,69 (2H), 7,76 (2H), 8,21 (1H), 8,41 (1H).

Ejemplo 181: N-(2-metoxietil)-6-metil-2-({1-[4-(trifluorometoxi)benzoil]azetidin-3-il}metil)-2H-

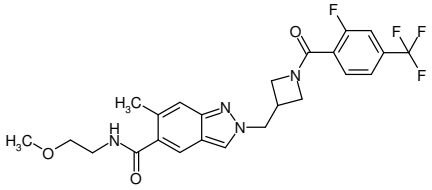
indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 221 mg del compuesto del título a partir de 294 mg del compuesto preparado en el Ejemplo 178e y 214 mg de cloruro de 4-(trifluorometoxi)benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,34 (3H), 3,20 (1H), 3,25 (3H), 3,34 (2H), 3,42 (2H), 3,89 (1H), 4,08 (1H), 4,18 (1H), 4,36 (1H), 4,65 (2H), 7,35 (1H), 7,40 (2H), 7,64 (1H), 7,70 (2H), 8,21 (1H), 8,42 (1H).

Ejemplo 182: 2-({1-[2-fluoro-4-(trifluorometil)benzoil]azetidin-3-il}metil)-N-(2-metoxi-etil)-6-metil-2H-indazol-5-carboxamida

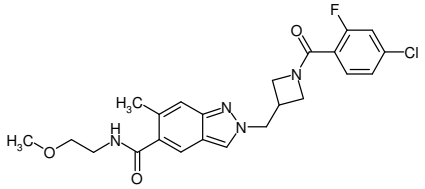


De forma análoga al Ejemplo 55, se obtuvieron 11 mg del compuesto del título a partir de 43 mg del compuesto preparado en el Ejemplo 178e y 32 mg de cloruro de 2-fluoro-4-(trifluorometil)benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,33 (3H), 3,20 (1H), 3,24 (3H), 3,35 (2H), 3,42 (2H), 3,86- 3,95 (2H), 4,02-4,16 (2H), 4,65 (2H), 7,34 (1H), 7,61-7,69 (3H),

7,79 (1H), 8,21 (1H), 8,41 (1H).

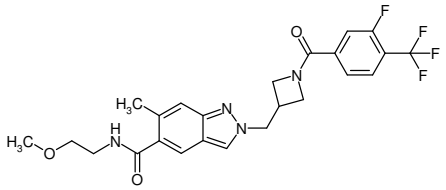
Ejemplo 183: 2-{[1-(4-cloro-2-fluorobenzoil)azetidin-3-il]metil}-N-(2-metoxietil)-6-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron de 70 mg del compuesto preparado en el Ejemplo 178e y 44 mg de cloruro de 4-cloro-2-fluorobenzoílo, se obtuvo un material aún contaminado después de la purificación por HPLC, que luego se purificó por cromatografía de capa delgada preparativa adicional con acetato de etilo / metanol en la relación 9:1 como fase móvil. Esto dio 12 mg del compuesto del título.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,34 (3H), 3,19 (1H), 3,25 (3H), 3,34 (2H), 3,42 (2H), 3,84-3,93 (2H), 4,02-4,10 (2H), 4,64 (2H), 7,32-7,36 (2H), 7,46 (1H), 7,53 (1H), 7,63 (1H), 8,22 (1H), 8,41 (1H).

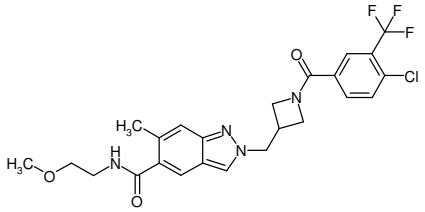
Ejemplo 184: 2-({1-[3-fluoro-4-(trifluorometil)benzoil]azetidin-3-il}metil)-N-(2-metoxi-etil)-6-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 32 mg del compuesto del título a partir de 70 mg del compuesto preparado en el Ejemplo 178e y 52 mg de cloruro de 3-fluoro-4-(trifluorometil)benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,34 (3H), 3,20 (1H), 3,24 (3H), 3,30-3,38 (2H), 3,42 (2H), 3,90 (1H), 4,10 (1H), 4,19 (1H), 4,38 (1H), 4,66 (2H), 7,34 (1H), 7,57 (1H), 7,60-7,67 (2H), 7,85 (1H), 8,21 (1H), 8,41 (1H).

Ejemplo 185: 2-({1-[4-cloro-3-(trifluorometil)benzoil]azetidin-3-il}metil)-N-(2-metoxi-etil)-6-metil-2H-indazol-5-carboxamida

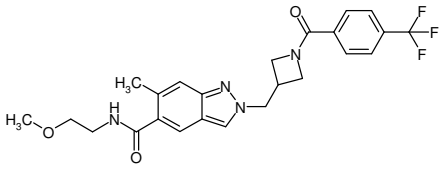


De forma análoga al Ejemplo 55, se obtuvieron 30 mg del compuesto del título a partir de 70 mg del compuesto preparado en el Ejemplo 178e y 55 mg de cloruro de 4-cloro-3-(trifluorometil)benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,34 (3H), 3,19 (1H), 3,24 (3H), 3,34 (2H), 3,42 (2H), 3,89 (1H), 4,10 (1H), 4,20 (1H), 4,35-4,43 (1H), 4,65 (2H), 7,33 (1H), 7,64 (1H), 7,78 (1H), 7,85 (1H), 7,93 (1H), 8,21 (1H), 8,40 (1H).

Ejemplo 186: N-(2-metoxietil)-6-metil-2-({1-[4-

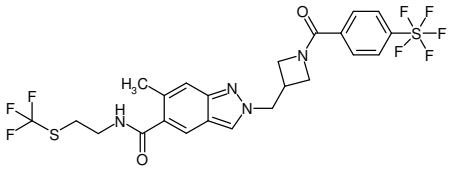
(trifluorometil)benzoil]azetidin-3-il}metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 31 mg del compuesto del título a partir de 70 mg del compuesto preparado en el Ejemplo 178e y 47 mg de cloruro de 4-(trifluorometil)benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,34 (3H), 3,20 (1H), 3,24 (3H), 3,35 (2H), 3,42 (2H), 3,90 (1H), 4,06-4,21 (2H), 4,35 (1H), 4,66 (2H), 7,34 (1H), 7,63 (1H), 7,73-7,82 (4H), 8,21 (1H), 8,41 (1H).

Ejemplo 187: 6-metil-2-({1-[4-(pentafluoro-λ^6-sulfanil)benzoil]azetidin-3-il}metil)-N-{2-[(trifluorometil)sulfanil]etil}-2H-indazol-5-carboxamida



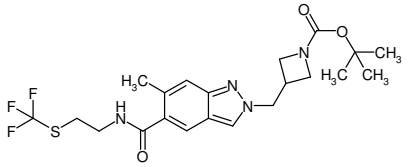
De forma análoga al Ejemplo 1, se obtuvieron 35 mg del compuesto del título a partir de 170 mg del compuesto preparado en el Ejemplo 187b y 103 mg de ácido 4-(pentafluoro-λ^6-sulfanil)benzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,36 (3H), 3,12-3,23 (3H), 3,49 (2H), 3,91 (1H), 4,06-4,21 (2H), 4,36

(1H), 4,66 (2H), 7,36 (1H), 7,69 (1H), 7,76 (2H), 7,95 (2H), 8,44 (1H), 8,46 (1H).

El material de partida se preparó de la siguiente manera:

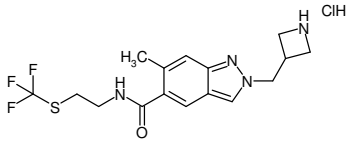
Ejemplo 187a: 3-{[6-metil-5-(N-{2-[(trifluorometil)sulfanil]etil}carbamoil)-2H-indazol-2-il]metil}azetidin-1-carboxilato de *tert*-butilo



De forma análoga al Ejemplo 1, se obtuvieron 998 mg del compuesto del título a partir de 800 mg del ácido preparado en el Ejemplo 178c y 336 mg de 2-[(trifluorometil)sulfanil]etilamina.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,32 (9H), 2,36 (3H), 3,06 (1H), 3,13-3,21 (2H), 3,49 (2H), 3,67 (2H), 3,84 (2H), 4,59 (2H), 7,37 (1H), 7,70 (1H), 8,44 (1H), 8,47 (1H).

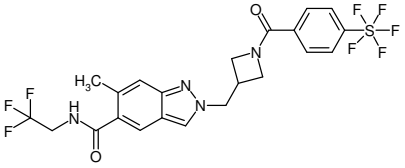
Ejemplo 187b: clorhidrato de 2-(azetidin-3-ilmetil)-6-metil-N-{2-[(trifluorometil)sulfanil]etil}-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a), a partir de 395 mg de la amida preparada en el Ejemplo 187a), se

obtuvieron 402 mg del compuesto del título que se hizo reaccionar sin ulterior purificación.

Ejemplo 188: 6-metil-2-({1-[4-(pentafluoro-λ^6-sulfanil)benzoil]azetidin-3-il}metil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

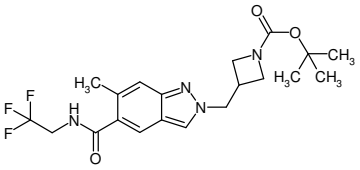


De forma análoga al Ejemplo 1, se obtuvieron 25 mg del compuesto del título a partir de 136 mg del compuesto preparado en el Ejemplo 188b y 93 mg de ácido 4-(pentafluoro-λ^6-sulfanil)benzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,34 (3H), 3,20 (1H), 3,91 (1H), 3,95-4,21 (4H), 4,36 (1H), 4,67 (2H), 7,38 (1H), 7,71 (1H), 7,76 (2H), 7,95 (2H), 8,45 (1H), 8,86 (1H).

El material de partida se preparó de la siguiente manera:

Ejemplo 188a: 3-({6-metil-5-[N-(2,2,2-trifluoroetil)carbamoil]-2H-indazol-2-il}metil)azetidin-1-carboxilato de *tert*-butilo

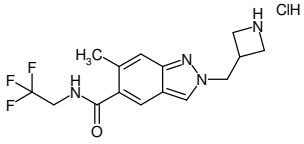


De forma análoga al Ejemplo 1, se obtuvieron 550 mg del compuesto del título a partir de 560 mg del

ácido preparado en el Ejemplo 178c y 160 mg de 2,2,2-trifluoroetilamina.

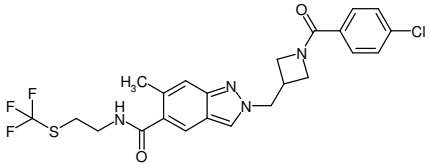
^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,32 (9H), 2,34 (3H), 3,06 (1H), 3,67 (2H), 3,84 (2H), 3,93-4,10 (2H), 4,60 (2H), 7,40 (1H), 7,71 (1H), 8,46 (1H), 8,88 (1H).

Ejemplo 188b: clorhidrato de 2-(azetidin-3-ilmetil)-6-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 550 mg de la amida preparada en el Ejemplo 188a, se obtuvieron 530 mg del compuesto del título, que se hizo reaccionar sin ulterior purificación.

Ejemplo 189: 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-6-metil-N-{2-[(trifluorometil) sulfanil]etil}-2H-indazol-5-carboxamida

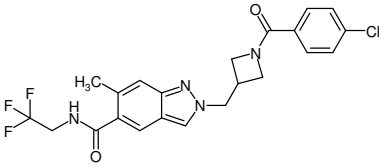


De forma análoga al Ejemplo 55, se obtuvieron 45 mg del compuesto del título a partir de 170 mg del compuesto preparado en el Ejemplo 187b y 80 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,39 (3H), 3,17-3,27 (3H), 3,52 (2H), 3,90 (1H), 4,10 (1H), 4,19 (1H),

4,37 (1H), 4,68 (2H), 7,39 (1H), 7,50 (2H), 7,61 (2H), 7,72 (1H), 8,47 (1H), 8,49 (1H).

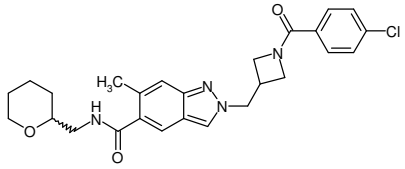
Ejemplo 190: 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-6-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 60 mg del compuesto del título a partir de 136 mg del compuesto preparado en el Ejemplo 188b y 72 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,34 (3H), 3,20 (1H), 3,87 (1H), 3,94-4,11 (3H), 4,16 (1H), 4,35 (1H), 4,66 (2H), 7,39 (1H), 7,48 (2H), 7,59 (2H), 7,71 (1H), 8,46 (1H), 8,89 (1H).

Ejemplo 191: (+/-)-2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-6-metil-N-(3,4,5,6-tetrahidro-2H-piran-2-ilmetil)-2H-indazol-5-carboxamida

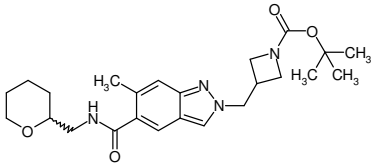


De forma análoga al Ejemplo 55, se obtuvieron 49 mg del compuesto del título a partir de 120 mg del compuesto preparado en el Ejemplo 191b y 61 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,08-1,23 (1H), 1,36-1,49 (3H), 1,62 (1H), 1,72-1,80 (1H), 2,34 (3H), 3,10-3,43 (5H), 3,80-3,92 (2H), 4,07 (1H), 4,16 (1H), 4,34 (1H), 4,65 (2H), 7,34 (1H), 7,47 (2H), 7,59 (2H), 7,63 (1H), 8,16 (1H), 8,40 (1H).

El material de partida se preparó de la siguiente manera:

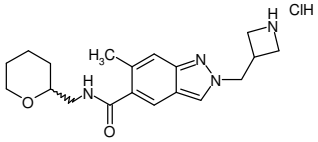
Ejemplo 191a: 3-({6-metil-5-[N-(3,4,5,6-tetrahidro-2H-piran-2-ilmetil)-carbamoil]-2H-indazol-2-il}metil)azetidin-1-carboxilato de (+/-)-*tert*-butilo



De forma análoga al Ejemplo 1, se obtuvieron 140 mg del compuesto del título a partir de 300 mg del ácido preparado en el Ejemplo 178c y 105 mg de 3,4,5,6-tetrahidro-2H-piran-2-ilmetilamina.

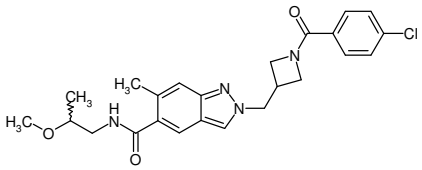
^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,07-1,24 (1H), 1,27-1,49 (12H), 1,62 (1H), 1,76 (1H), 2,33 (3H), 3,06 (1H), 3,20 (2H), 3,29-3,45 (2H), 3,67 (2H), 3,78-3,90 (3H), 4,59 (2H), 7,35 (1H), 7,63 (1H), 8,16 (1H), 8,40 (1H).

Ejemplo 191b: clorhidrato de (+/-)-2-(azetidin-3-ilmetil)-6-metil-N-(3,4,5,6-tetrahidro-2H-piran-2-ilmetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 140 mg de la amida preparada en el Ejemplo 191a, se obtuvieron 132 mg del compuesto del título, que se hizo reaccionar sin ulterior purificación.

Ejemplo 192: (+/-)-2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-N-(2-metoxipropil)-6-metil-2H-indazol-5-carboxamida

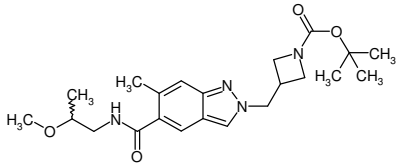


De forma análoga al Ejemplo 55, se obtuvieron 89 mg del compuesto del título a partir de 151 mg del compuesto preparado en el Ejemplo 192b y 82 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,08 (3H), 2,34 (3H), 3,13-3,32 (6H), 3,43 (1H), 3,87 (1H), 4,07 (1H), 4,16 (1H), 4,34 (1H), 4,65 (2H), 7,35 (1H), 7,48 (2H), 7,59 (2H), 7,63 (1H), 8,18 (1H), 8,41 (1H).

El material de partida se preparó de la siguiente manera:

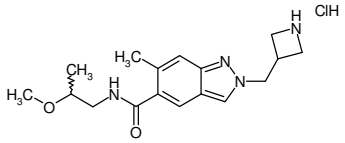
Ejemplo 192a: 3-({5-[N-(2-metoxipropil)carbamoil]-6-metil-2H-indazol-2-il}metil)azetidin-1-carboxilato de (+/-)-*tert*-butilo



De forma análoga al Ejemplo 1, se obtuvieron 358 mg del compuesto del título a partir de 300 mg del ácido preparado en el Ejemplo 178c y 77 mg de 2-metoxipropan-1-amina.

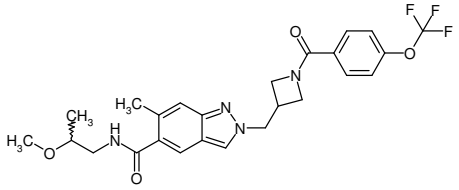
^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,08 (3H), 1,32 (9H), 2,34 (3H), 3,06 (1H), 3,13-3,31 (5H), 3,43 (1H), 3,67 (2H), 3,84 (2H), 4,59 (2H), 7,35 (1H), 7,64 (1H), 8,18 (1H), 8,40 (1H).

Ejemplo 192b: clorhidrato de (+/-)-2-(azetidin-3-ilmetil)-N-(2-metoxipropil)-6-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a), a partir de 358 mg de la amida preparada en el Ejemplo 192a), se obtuvieron 319 mg del compuesto del título, que se hizo reaccionar sin ulterior purificación.

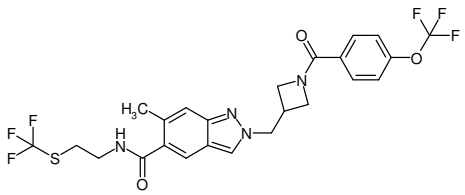
Ejemplo 193: (+/-)-N-(2-metoxipropil)-6-metil-2-({1-[4-(trifluorometoxi)benzoil]-azetidin-3-il}metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 87 mg del compuesto del título a partir de 151 mg del compuesto preparado en el Ejemplo 192b y 106 mg de cloruro de 4-(trifluorometoxi)benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,08 (3H), 2,34 (3H), 3,13-3,31 (6H), 3,43 (1H), 3,88 (1H), 4,08 (1H), 4,17 (1H), 4,36 (1H), 4,65 (2H), 7,35 (1H), 7,40 (2H), 7,64 (1H), 7,70 (2H), 8,18 (1H), 8,41 (1H).

Ejemplo 194: 6-metil-2-({1-[4-(trifluorometoxi)benzoil]azetidin-3-il}metil)-N-{2-[(trifluorometil)sulfanil]etil}-2H-indazol-5-carboxamida

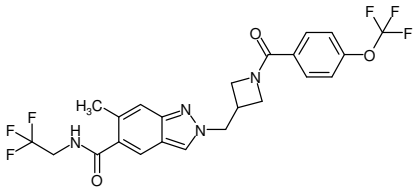


De forma análoga al Ejemplo 55, se obtuvieron 87 mg del compuesto del título a partir de 173 mg del compuesto preparado en el Ejemplo 187b y 105 mg de cloruro de 4-(trifluorometoxi)benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,36 (3H), 3,11-3,24 (3H), 3,49 (2H), 3,89 (1H), 4,09 (1H), 4,17 (1H), 4,36 (1H), 4,66 (2H), 7,36 (1H), 7,40 (2H), 7,66-7,74

(3H), 8,44 (1H), 8,46 (1H).

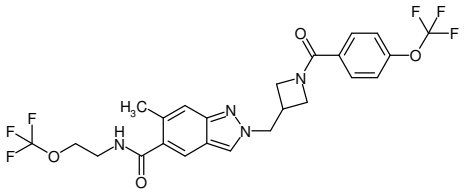
Ejemplo 195: 6-metil-N-(2,2,2-trifluoroetil)-2-({1-[4-(trifluorometoxi)benzoil]azetidin-3-il}metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 70 mg del compuesto del título a partir de 170 mg del compuesto preparado en el Ejemplo 188b y 116 mg de cloruro de 4-(trifluorometoxi)benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,35 (3H), 3,21 (1H), 3,89 (1H), 3,95-4,13 (3H), 4,18 (1H), 4,36 (1H), 4,67 (2H), 7,40 (3H), 7,66-7,75 (3H), 8,45 (1H), 8,86 (1H).

Ejemplo 196: 6-metil-2-({1-[4-(trifluorometoxi)benzoil]azetidin-3-il}metil)-N-[2-(trifluorometoxi)etil]-2H-indazol-5-carboxamida

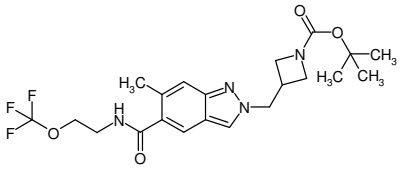


De forma análoga al Ejemplo 55, se obtuvieron 22 mg del compuesto del título a partir de 179 mg del compuesto preparado en el Ejemplo 196b y 113 mg de cloruro de 4-(trifluorometoxi)benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,34 (3H), 3,20 (1H), 3,50 (2H), 3,89 (1H), 4,08 (1H), 4,14-4,21 (3H), 4,36 (1H), 4,66 (2H), 7,36 (1H), 7,40 (2H), 7,66 (1H), 7,70 (2H), 8,44 (1H), 8,46 (1H).

El material de partida se preparó de la siguiente manera:

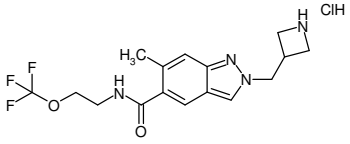
Ejemplo 196a: 3-[(6-metil-5-{N-[2-(trifluorometoxi)etil]carbamoil}-2H-indazol-2-il)metil]azetidin-1-carboxilato de *tert*-butilo



De forma análoga al Ejemplo 1, se obtuvieron 417 mg del compuesto del título a partir de 300 mg del ácido preparado en el Ejemplo 178c y 144 mg de clorhidrato de 2-(trifluorometoxi)etilamina.

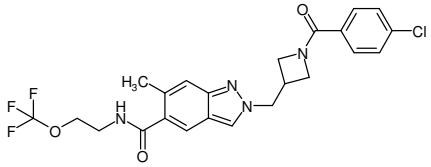
^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,32 (9H), 2,34 (3H), 3,06 (1H), 3,50 (2H), 3,68 (2H), 3,84 (2H), 4,16 (2H), 4,59 (2H), 7,37 (1H), 7,66 (1H), 8,44 (1H), 8,46 (1H).

Ejemplo 196b: clorhidrato de 2-(azetidin-3-ilmetil)-6-metil-N-[2-(trifluorometoxi)etil]-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 417 mg de la amida preparada en el Ejemplo 196a, se obtuvieron 369 mg del compuesto del título, que se hizo reaccionar sin ulterior purificación.

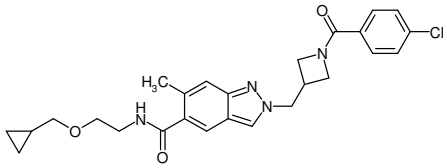
Ejemplo 197: 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-6-metil-N-[2-(trifluorometoxi) etil]-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 41 mg del compuesto del título a partir de 179 mg del compuesto preparado en el Ejemplo 196b y 88 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,34 (3H), 3,19 (1H), 3,50 (2H), 3,87 (1H), 4,07 (1H), 4,13-4,21 (3H), 4,34 (1H), 4,65 (2H), 7,36 (1H), 7,48 (2H), 7,59 (2H), 7,66 (1H), 8,44 (1H), 8,46 (1H).

Ejemplo 198: 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-N-[2-(ciclopropilmetoxi)etil]-6-metil-2H-indazol-5-carboxamida



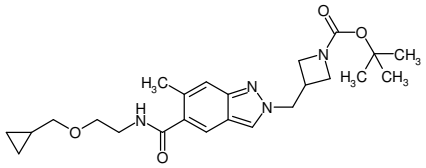
De forma análoga al Ejemplo 55, se obtuvieron 107 mg del compuesto del título a partir de 214 mg del

compuesto preparado en el Ejemplo 198b y 109 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,14 (2H), 0,42 (2H), 0,97 (1H), 2,34 (3H), 3,12-3,26 (3H), 3,34 (2H), 3,47 (2H), 3,87 (1H), 4,07 (1H), 4,16 (1H), 4,34 (1H), 4,65 (2H), 7,35 (1H), 7,48 (2H), 7,59 (2H), 7,63 (1H), 8,21 (1H), 8,42 (1H).

El material de partida se preparó de la siguiente manera:

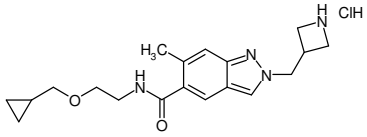
Ejemplo 198a: 3-[(5-{N-[2-(ciclopropilmetoxi)etil]carbamoil}-6-metil-2H-indazol-2-il)metil]azetidin-1-carboxilato de *tert*-butilo



De forma análoga al Ejemplo 1, se obtuvieron 247 mg del compuesto del título a partir de 245 mg del ácido preparado en el Ejemplo 178c y 82 mg de clorhidrato de 2-(ciclopropilmetoxi)etilamina.

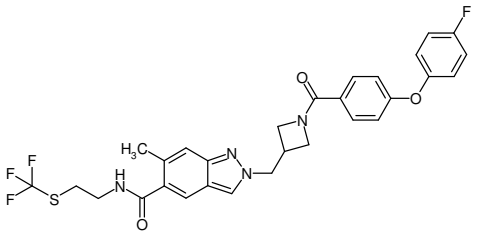
^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,14 (2H), 0,43 (2H), 0,97 (1H), 1,32 (9H), 2,35 (3H), 3,06 (1H), 3,23 (2H), 3,34 (2H), 3,48 (2H), 3,67 (2H), 3,85 (2H), 4,59 (2H), 7,35 (1H), 7,64 (1H), 8,18 (1H), 8,41 (1H).

Ejemplo 198b: clorhidrato de 2-(azetidin-3-ilmetil)-N-[2-(ciclopropilmetoxi)etil]-6-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 247 mg de la amida preparada en el Ejemplo 198a, se obtuvieron 214 mg del compuesto del título, que se hizo reaccionar sin ulterior purificación.

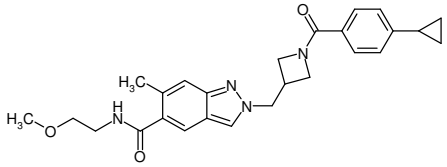
Ejemplo 199: 2-({1-[4-(4-fluorofenoxi)benzoil]azetidin-3-il}metil)-6-metil-N-{2-[(trifluorometil)sulfanil]etil}-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 56 mg del compuesto del título a partir de 173 mg del compuesto preparado en el Ejemplo 187b y 98 mg de ácido 4-(4-fluorofenoxi)benzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,38 (3H), 3,16-3,27 (3H), 3,52 (2H), 3,90 (1H), 4,08 (1H), 4,19 (1H), 4,38 (1H), 4,68 (2H), 6,97 (2H), 7,14 (2H), 7,27 (2H), 7,39 (1H), 7,62 (2H), 7,72 (1H), 8,47 (1H), 8,49 (1H).

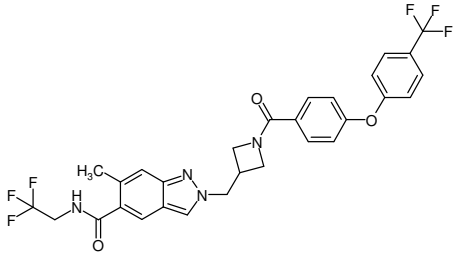
Ejemplo 200: 2-{[1-(4-ciclopropilbenzoil)azetidin-3-il]metil}-N-(2-metoxietil)-6-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 86 mg del compuesto del título a partir de 168 mg del compuesto preparado en el Ejemplo 178e y 80 mg de ácido 4-ciclopropilbenzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,71 (2H), 0,99 (2H), 1,95 (1H), 2,37 (3H), 3,21 (1H), 3,27 (3H), 3,37 (2H), 3,45 (2H), 3,88 (1H), 4,07 (1H), 4,17 (1H), 4,35 (1H), 4,67 (2H), 7,12 (2H), 7,38 (1H), 7,47 (2H), 7,66 (1H), 8,22 (1H), 8,44 (1H).

Ejemplo 201: 6-metil-N-(2,2,2-trifluoroetil)-2-[(1-{4-[4-(trifluorometil)fenoxi] benzoil}azetidin-3-il)metil]-2H-indazol-5-carboxamida

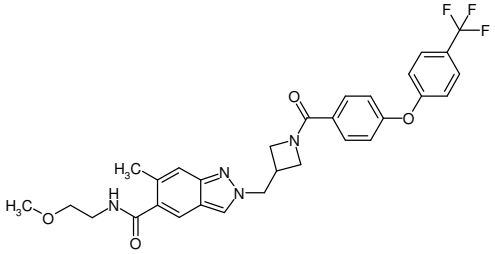


De forma análoga al Ejemplo 1, se obtuvieron 71 mg del compuesto del título a partir de 180 mg del compuesto preparado en el Ejemplo 188b y 95 mg de ácido 4-[4-(trifluorometil)fenoxi]benzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,34 (3H), 3,21 (1H), 3,88 (1H), 3,95-4,13 (3H), 4,19 (1H), 4,37 (1H),

4,67 (2H), 7,11 (2H), 7,19 (2H), 7,39 (1H), 7,65 (2H), 7,69–7,79 (3H), 8,47 (1H), 8,88 (1H).

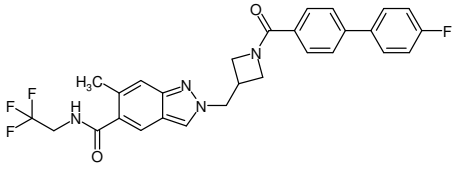
Ejemplo 202: N-(2-metoxietil)-6-metil-2-[(1-{4-[4-(trifluorometil)fenoxi]benzoil}-azetidin-3-il)metil]-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 108 mg del compuesto del título a partir de 180 mg del compuesto preparado en el Ejemplo 178e y 102 mg de ácido 4-[4-(trifluorometil)fenoxi]benzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,34 (3H), 3,14-3,26 (4H), 3,34 (2H), 3,42 (2H), 3,88 (1H), 4,07 (1H), 4,19 (1H), 4,37 (1H), 4,66 (2H), 7,11 (2H), 7,19 (2H), 7,35 (1H), 7,61–7,68 (3H), 7,75 (2H), 8,21 (1H), 8,42 (1H).

Ejemplo 203: 2-({1-[(4'-fluorobifenil-4-il)carbonil]azetidin-3-il}metil)-6-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

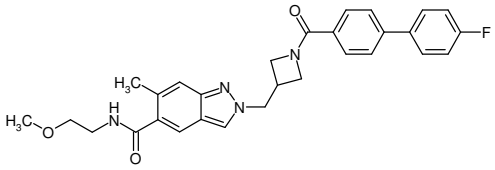


De forma análoga al Ejemplo 1, se obtuvieron 104 mg del compuesto del título a partir de 180 mg del

compuesto preparado en el Ejemplo 188b y 73 mg de ácido 4'-fluorobifenil-4-carboxílico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,34 (3H), 3,22 (1H), 3,90 (1H), 3,95-4,14 (3H), 4,21 (1H), 4,40 (1H), 4,68 (2H), 7,28 (2H), 7,40 (1H), 7,60-7,77 (7H), 8,48 (1H), 8,89 (1H).

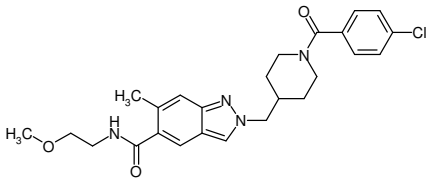
Ejemplo 204: 2-({1-[(4'-fluorobifenil-4-il)carbonil]azetidin-3-il}metil)-N-(2-metoxi-etil)-6-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 73 mg del compuesto del título a partir de 180 mg del compuesto preparado en el Ejemplo 178e y 78 mg de ácido 4'-fluorobifenil-4-carboxílico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,34 (3H), 3,14-3,26 (4H), 3,34 (2H), 3,41 (2H), 3,89 (1H), 4,09 (1H), 4,21 (1H), 4,39 (1H), 4,66 (2H), 7,28 (2H), 7,35 (1H), 7,61-7,77 (7H), 8,21 (1H), 8,43 (1H).

Ejemplo 205: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-6-metil-2H-indazol-5-carboxamida

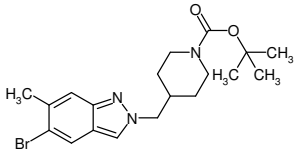


De forma análoga al Ejemplo 55, se obtuvieron de 85 mg del compuesto preparado en el Ejemplo 205c y 45 mg de cloruro de 4-clorobenzoílo, se obtuvo un material aún contaminado después de cromatografía en columna que luego se purificó por cromatografía de capa fina preparativa adicional con diclorometano / metanol en la relación 95:5 as fase móvil. Rendimiento: 48 mg del compuesto del título.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,09-1,53 (4H), 2,24 (1H), 2,34 (3H), 2,71 (1H), 2,97 (1H), 3,24 (3H), 3,34 (2H), 3,38-3,54 (3H), 7,31-7,37 (3H), 7,46 (2H), 7,63 (1H), 8,21 (1H), 8,33 (H).

El material de partida se preparó de la siguiente manera:

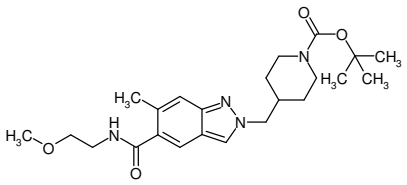
Ejemplo 205a: 4-[(5-bromo-6-metil-2H-indazol-2-il)metil]piperidin-1-carboxilato de ter-butilo



De forma análoga al Ejemplo 1c, se obtuvieron 2,99 g del compuesto del título a partir de 5,7 g de 5-bromo-6-metil-1H-indazol y 15,0 g de 4-[(tosiloxi)metil]piperidin-1-carboxilato de ter-butilo.

^{1}H-RMN (300 MHz, $CDCl_3$): δ = 1,14-1,30 (2H), 1,44 (9H), 1,53 (2H), 2,24 (1H), 2,50 (3H), 2,66 (2H), 4,11 (2H), 4,23 (2H), 7,55 (1H), 7,77 (1H), 7,87 (1H).

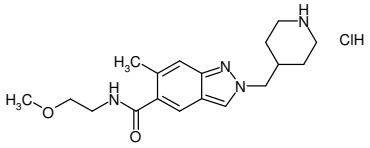
Ejemplo 205b: 4-({5-[N-(2-metoxietil)carbamoil]-6-metil-2H-indazol-2-il}-metil)piperidin-1-carboxilato de ter-butilo



De forma análoga al Ejemplo 1b, se obtuvieron 3,56 g del compuesto del título a partir de 600 mg del bromuro preparado en el Ejemplo 205a y 331 mg de 2-metoxietilamina después de cuatro corridas y purificación doble por cromatografía.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,96-1,15 (2H), 1,29-1,42 (10H), 2,03-2,18 (1H), 2,34 (3H), 2,51-2,73 (3H), 3,25 (3H), 3,31-3,45 (4H), 3,86 (2H), 4,26 (2H), 7,35 (1H), 7,63 (1H), 8,21 (1H), 8,32 (1H).

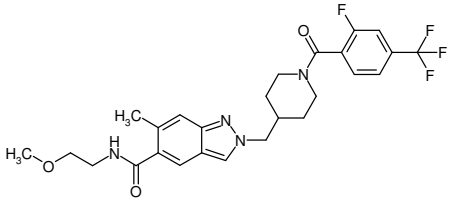
Ejemplo 205c: clorhidrato de N-(2-metoxietil)-6-metil-2-(4-piperidilmetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 100 mg de la amida preparada en el Ejemplo 205b, se obtuvieron 85 mg del compuesto del título, que se hizo reaccionar sin ulterior purificación.

Ejemplo 206: 2-({1-[2-fluoro-4-(trifluorometil)benzoil]piperidin-4-il}metil)-N-(2-

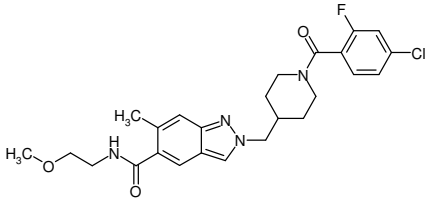
metoxi-etil)-6-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron de 85 mg del compuesto preparado en el Ejemplo 205c y 58 mg de cloruro de 2-fluoro-4-(trifluorometil)benzoílo, se obtuvo un material aún contaminado después de cromatografía en columna que luego se purificó por cromatografía de capa fina preparativa adicional con diclorometano / metanol en la relación 95:5 como fase móvil. Rendimiento: 40 mg del compuesto del título.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,03-1,28 (2H), 1,37 (1H), 1,53 (1H), 2,23 (1H), 2,34 (3H), 2,77 (1H), 3,00 (1H), 3,26-3,49 (11H), 4,30 (2H), 4,44 (1H), 7,35 (1H), 7,54-7,67 (3H), 7,78 (1H), 8,21 (1H), 8,34 (1H).

Ejemplo 207: 2-{[1-(4-cloro-2-fluorobenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-6-metil-2H-indazol-5-carboxamida

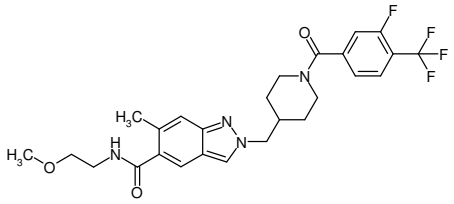


De forma análoga al Ejemplo 55, se obtuvieron 68 mg del compuesto del título a partir de 85 mg del compuesto preparado en el Ejemplo 205c y 49 mg de

cloruro de 4-cloro-2-fluorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,04-1,25 (2H), 1,37 (1H), 1,51 (1H), 2,23 (1H), 2,34 (3H), 2,73 (1H), 2,98 (1H), 3,21-3,48 (3H), 3,30-3,38 (3H), 3,42 (2H), 4,29 (2H), 4,42 (1H), 7,29-7,42 (3H), 7,51 (1H), 7,63 (1H), 8,21 (1H), 8,33 (1H).

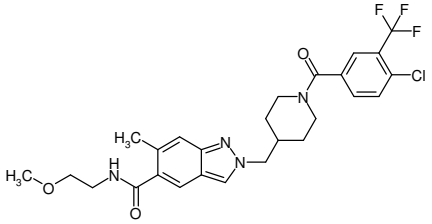
Ejemplo 208: 2-({1-[3-fluoro-4-(trifluorometil)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-6-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 70 mg del compuesto del título a partir de 85 mg del compuesto preparado en el Ejemplo 205c y 58 mg de cloruro de 3-fluoro-4-(trifluorometil)benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,13-1,27 (2H), 1,35 (1H), 1,51 (1H), 2,23 (1H), 2,34 (3H), 2,74 (1H), 2,98 (1H), 3,22-3,45 (8H), 4,29 (2H), 4,40 (1H), 7,32-7,38 (2H), 7,52 (1H), 7,63 (1H), 7,82 (1H), 8,21 (1H), 8,33 (1H).

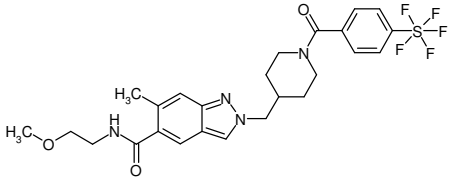
Ejemplo 209: 2-({1-[4-cloro-3-(trifluorometil)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-6-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 92 mg del compuesto del título a partir de 85 mg del compuesto preparado en el Ejemplo 205c y 62 mg de cloruro de 4-cloro-3-(trifluorometil)benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,14-1,28 (2H), 1,35 (1H), 1,44-1,53 (1H), 2,25 (1H), 2,34 (3H), 2,74 (1H), 3,01 (1H), 3,24 (3H), 3,34 (2H), 3,39-3,50 (3H), 4,29 (2H), 4,39 (1H), 7,35 (1H), 7,61-7,68 (2H), 7,74-7,80 (2H), 8,21 (1H), 8,33 (1H).

Ejemplo 210: N-(2-metoxietil)-6-metil-2-({1-[4-(pentafluoro-λ^6-sulfanil)benzoil]-piperidin-4-il}metil)-2H-indazol-5-carboxamida

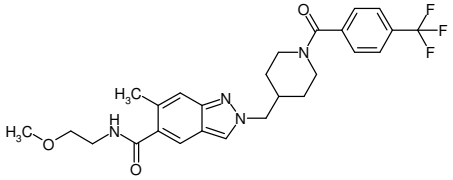


De forma análoga al Ejemplo 1, se obtuvieron 126 mg del compuesto del título a partir de 85 mg del compuesto preparado en el Ejemplo 205c y 58 mg de ácido 4-(pentafluoro-λ^6-sulfanil)benzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,12-1,27 (2H), 1,35 (1H), 1,51 (1H), 2,24 (1H), 2,34 (3H), 2,74 (1H), 2,99 (1H), 3,24 (3H), 3,34-3,46 (5H), 4,30 (2H), 4,41

(1H), 7,35 (1H), 7,55 (2H), 7,63 (1H), 7,94 (2H), 8,21 (1H), 8,33 (1H).

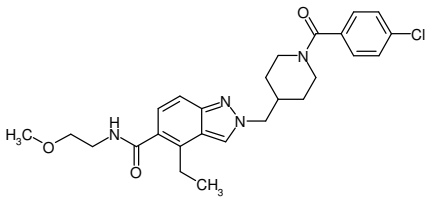
Ejemplo 211: N-(2-metoxietil)-6-metil-2-({1-[4-(trifluorometil)benzoil]piperidin-4-il}-metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 69 mg del compuesto del título a partir de 85 mg del compuesto preparado en el Ejemplo 205c y 53 mg de cloruro de 4-(trifluorometil)benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,10-1,26 (2H), 1,35 (1H), 1,51 (1H), 2,19-2,30 (1H), 2,34 (3H), 2,74 (1H), 2,98 (1H), 3,21-3,47 (8H), 4,30 (2H), 4,42 (1H), 7,35 (1H), 7,54 (2H), 7,63 (1H), 7,77 (2H), 8,21 (1H), 8,33 (1H).

Ejemplo 212: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-etil-N-(2-metoxietil)-2H-indazol-5-carboxamida



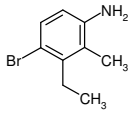
De forma análoga al Ejemplo 55, se obtuvieron 61 mg del compuesto del título a partir de 91 mg del

compuesto preparado en el Ejemplo 212i y 46 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,14-1,28 (5H), 1,31-1,60 (2H), 2,27 (1H), 2,63-3,04 (4H), 3,24 (3H), 3,31-3,56 (5H), 4,31 (2H), 4,39 (1H), 7,10 (1H), 7,32-7,41 (3H), 7,46 (2H), 8,11 (1H), 8,50 (1H).

El material de partida se preparó de la siguiente manera:

Ejemplo 212a: 4-bromo-3-etil-2-metilanilina

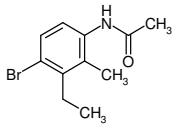


Una suspensión de 3 g de clorhidrato de 3-etil-2-metilanilina en 200 ml de acetato de etilo se lavó dos veces con 30 ml porciones de solución saturada de carbonato de sodio y dos veces con porciones de 20 ml de solución saturada de cloruro de sodio, se secó sobre sulfato de sodio y se concentró al vacío después de triturar. Esto dio 2,69 g de etil-2-metilanilina, que luego se hizo reaccionar sin purificación.

A una solución de 2,36 g de la amina preparada anteriormente en 29 ml de DMF, una solución de 3,1 g de N-bromosuccinimida en 14,5 ml de DMF se añadió gota a gota a 0 °C y se agitó durante 30 minutos a 0 °C. A continuación, la mezcla de reacción se diluyó con 400 ml de acetato de etilo y se lavó una vez con 30 ml de

una solución acuosa al 10% de carbonato de sodio y una vez con 30 ml de agua. Después de secar sobre sulfato de sodio y filtrar, se concentró al vacío. El producto crudo así obtenido (3,86 g) se usó en la siguiente etapa sin purificación.

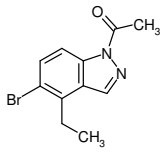
Ejemplo 212b: N-(4-bromo-3-etil-2-metilfenil)acetamida



A una solución de 3,86 g del bromuro preparado en el Ejemplo 212a en 48 ml de piridina, se añadieron 2,04 ml de anhídrido acético gota a gota a 0°C y se agitaron durante 20 horas a 25 °C. La mezcla de reacción se concentró al vacío y el producto crudo así obtenido se purificó por cromatografía en columna en gel de sílice con hexano / 0-100% de acetato de etilo. De esta manera, se obtuvieron 3,73 g del compuesto del título.

^{1}H-RMN (300 MHz, CDCl3): δ = 1,13 (3H), 2,20 (3H), 2,25 (3H), 2,86 (2H), 6,91 (1H), 7,33 (1H), 7,40 (1H).

Ejemplo 212c: 1-(5-bromo-4-etil-1H-indazol-1-il)etan-1-ona

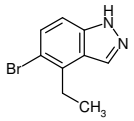


A una solución de 3,72 g de la acetamida preparada en el Ejemplo 212b en 31,5 ml de cloroformo se añadieron 4,1 ml de anhídrido acético y 2,85 g de

acetato de potasio y 192 mg de 18-corona-6 y 3,4 g de nitrilo de isopentilo luego se añadieron gota a gota. La mezcla de reacción se calentó durante 20 horas a reflujo y después de agitar se diluyó con 200 ml de acetato de etilo. La fase orgánica se lavó con 20 ml de solución de carbonato de sodio y una vez con solución saturada de cloruro de sodio. Después de secar sobre sulfato de sodio y filtrar, se concentró al vacío y el producto crudo así obtenido se purificó por cromatografía en columna en gel de sílice con hexano / 0-50% de acetato de etilo. Rendimiento: 3,78 g del compuesto del título.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,18 (3H), 2,68 (3H), 3,04 (2H), 7,73 (1H), 8,03 (1H), 8,64 (1H).

Ejemplo 212d: 5-bromo-4-etil-1H-indazol

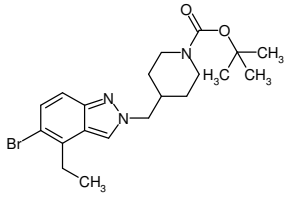


Una mezcla de 3,78 g del compuesto preparado en el Ejemplo 212c en 7,3 ml de metanol y 26,3 ml de ácido clorhídrico al 37% se calentó a reflujo durante 2 horas. Esto luego se diluyó con 400 ml de acetato de etilo. La fase orgánica se lavó tres veces con porciones de 50 ml de solución de bicarbonato de sodio y una vez con 50 ml de solución saturada de cloruro de sodio, se secó sobre sulfato de sodio y se concentró al

vacío. El producto crudo así obtenido se purificó por cromatografía en columna en gel de sílice con hexano / 0-50% de acetato de etilo. Rendimiento: 2,97 g del compuesto del título.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,17 (3H), 2,98 (2H), 7,30 (1H), 7,41 (1H), 8,16 (1H), 13,17 (1H).

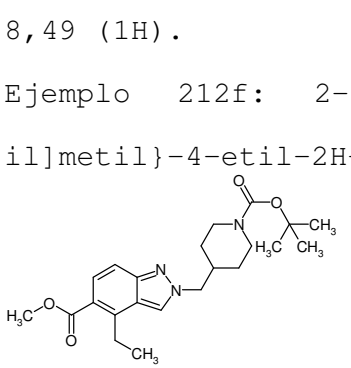
Ejemplo 212e: 4-[(5-bromo-4-etil-2H-indazol-2-il)metil]piperidin-1-carboxilato de ter-butilo



De forma análoga al Ejemplo 1c, se obtuvieron 961 mg del compuesto del título a partir de 2,97 g del indazol preparado en el Ejemplo 212d y 7,3 g de 4-[(tosiloxi)metil]piperidin-1-carboxilato de ter-butilo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,01-1,13 (2H), 1,16 (3H), 1,34 (9H), 1,41 (2H), 2,12 (1H), 2,63 (2H), 2,90 (2H), 3,87 (2H), 4,27 (2H), 7,27 (1H), 7,35 (1H), 8,49 (1H).

Ejemplo 212f: 2-{[1-(ter-butoxicarbonil)piperidin-4-il]metil}-4-etil-2H-indazol-5-carboxilato de metilo

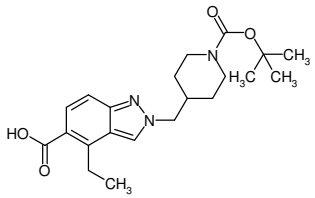


De forma análoga al Ejemplo 1e, después de dos

corridas, se obtuvieron 571 mg del compuesto del título de 347 mg del bromuro preparado en el Ejemplo 212e y 0,1 ml de metanol.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,02-1,15 (2H), 1,17-1,24 (3H), 1,34 (9H), 1,42 (2H), 2,14 (1H), 2,63 (2H), 3,17 (2H), 3,79 (3H), 3,88 (2H), 4,30 (2H), 7,43 (1H), 7,60 (1H), 8,68 (1H).

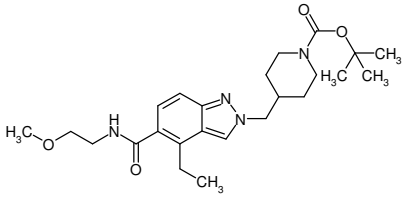
Ejemplo 212g: ácido 2-{[1-(ter-butoxicarbonil)piperidin-4-il]metil}-4-etil-2H-indazol-5-carboxílico



De forma análoga al Ejemplo 1d, se obtuvieron 427 mg del compuesto del título a partir de 371 mg del éster en el Ejemplo 212f.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,00-1,15 (2H), 1,20 (3H), 1,34 (9H), 1,42 (2H), 2,14 (1H), 2,64 (2H), 3,19 (2H), 3,88 (2H), 4,29 (2H), 7,39 (1H), 7,61 (1H), 8,63 (1H), 12,33 (1H).

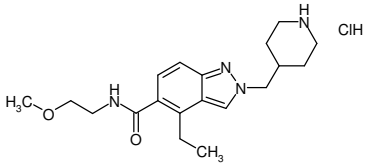
Ejemplo 212h: 4-({4-etil-5-[N-(2-metoxietil)carbamoil]-2H-indazol-2-il}-metil)piperidin-1-carboxilato de ter-butilo



De forma análoga al Ejemplo 1, se obtuvieron 215 mg del compuesto del título a partir de 427 mg del ácido preparado en el Ejemplo 212g y 83 mg de 2-metoxi-etilamina.

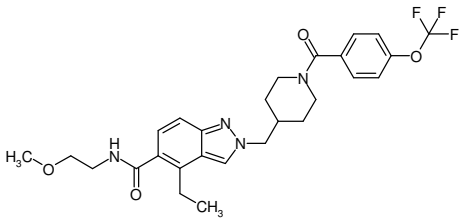
^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,98-1,14 (2H), 1,19 (3H), 1,30-1,47 (11H), 2,13 (1H), 2,65 (2H), 2,90 (2H), 3,24 (3H), 3,32-3,45 (4H), 3,87 (2H), 4,28 (2H), 7,10 (1H), 7,38 (1H), 8,12 (1H), 8,50 (1H).

Ejemplo 212i: clorhidrato de 4-etil-N-(2-metoxietil)-2-(4-piperidilmetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 215 mg de la amida preparada en el Ejemplo 212h, se obtuvieron 258 mg del compuesto del título, que se hizo reaccionar sin ulterior purificación.

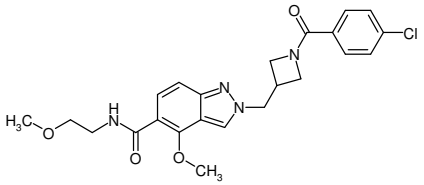
Ejemplo 213: 4-Etil-N-(2-metoxietil)-2-({1-[4-(trifluorometoxi)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 32 mg del compuesto del título a partir de 91 mg del compuesto preparado en el Ejemplo 212i y 59 mg de cloruro de 4-(trifluorometoxi)benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,14-1,29 (5H), 1,31-1,61 (2H), 2,20-2,35 (1H), 2,66-3,06 (4H), 3,24 (3H), 3,30-3,56 (5H), 4,31 (2H), 4,41 (1H), 7,10 (1H), 7,34-7,43 (3H), 7,47 (2H), 8,11 (1H), 8,50 (1H).

Ejemplo 214: 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-4-metoxi-N-(2-metoxietil)-2H-indazol-5-carboxamida

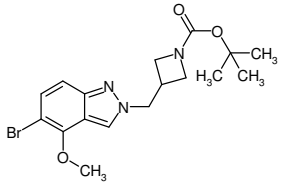


De forma análoga al Ejemplo 55, se obtuvieron 691 mg del compuesto del título a partir de 68 mg del compuesto preparado en el Ejemplo 214c y 37 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 3,22 (1H), 3,27 (3H), 3,40-3,47 (4H), 3,92 (1H), 4,10 (1H), 4,16 (3H), 4,19 (1H), 4,38 (1H), 4,66 (2H), 7,21 (1H), 7,48 (2H), 7,55-7,67 (3H), 8,18 (1H), 8,87 (1H).

El material de partida se preparó de la siguiente manera:

Ejemplo 214a: 3-[(5-bromo-4-metoxi-2H-indazol-2-il)metil]azetidin-1-carboxilato de ter-butilo



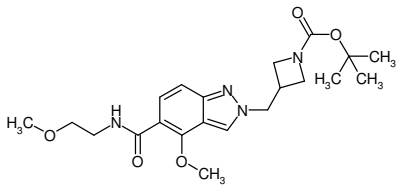
A una solución de 1,94 g de 3-[(tosiloxi)metil]azetidin-1-carboxilato de ter-butilo en 15,5 ml acetona se añadieron 837 mg de yoduro de litio y la mezcla de reacción se agitó durante 16 horas a 35 °C. Después de enfriar, se diluyó con 200 ml de acetato de etilo y la fase orgánica se lavó dos veces con porciones de 30 ml de agua y una vez con 20 ml de solución saturada de cloruro de sodio. Después de secar sobre sulfato de sodio y filtrar, se concentró al vacío. De esta manera, se obtuvieron 1,6 g de 3-(iodometil)azetidin-1-carboxilato de ter-butilo, que luego se hizo reaccionar sin purificación.

A una solución de 620 mg de 5-bromo-7-metoxi-1H-indazol en 24 ml de DMF se añadieron 1,11 g de carbonato de potasio y la mezcla se agitó a 25 °C durante 30 minutos. A continuación, se añadieron 1,25 g del yoduro preparado con anterioridad y la mezcla de reacción se agitó durante 3 horas a 60 °C. Después de

enfriar, se diluyó con 200 ml de 1:1 éter ter-butilmetílico / hexano, se lavó una vez con porciones de 20 ml de agua y solución saturada de cloruro de sodio, se secó sobre sulfato de sodio y se concentró al vacío y el producto crudo así obtenido se purificó por cromatografía en columna en gel de sílice con un gradiente de hexano / acetato de etilo. Rendimiento: 263 mg del compuesto del título.

^{1}H-RMN (300 MHz, CDCl3): δ = 1,43 (9H), 3,23 (1H), 3,78 (2H), 4,07 (2H), 4,10 (3H), 4,59 (2H), 7,28 (1H), 7,36 (1H), 8,03 (1H).

Ejemplo 214b: 3-({4-metoxi-5-[N-(2-metoxietil)carbamoil]-2H-indazol-2-il}metil)azetidin-1-carboxilato de ter-butilo

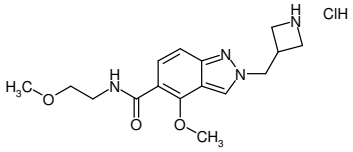


De forma análoga al Ejemplo 1b, se obtuvo un total de 193 mg del compuesto del título de 110 y 252 mg, respectivamente, del compuesto preparado en el Ejemplo 214a y 63 y 143 mg, respectivamente, de 2-metoxietilamina.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,32 (9H), 3,10 (1H), 3,27 (3H), 3,38-3,48 (4H), 3,72 (2H), 3,82-3,94

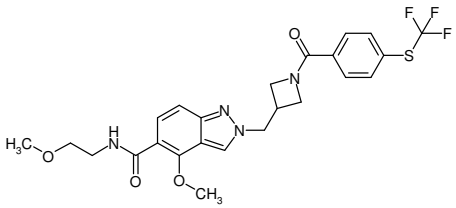
(2H), 4,17 (3H), 4,60 (2H), 7,21 (1H), 7,63 (1H), 8,18 (1H), 8,87 (1H).

Ejemplo 214c: clorhidrato de 2-(azetidin-3-ilmetil)-4-metoxi-N-(2-metoxietil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 50 mg del compuesto preparado en el Ejemplo 214b, se obtuvieron 42 mg del compuesto del título, que luego se hizo reaccionar sin purificación.

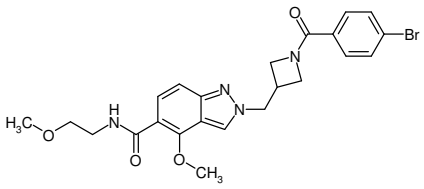
Ejemplo 215: 4-metoxi-N-(2-metoxietil)-2-[(1-{4-[(trifluorometil)sulfanil]benzoil} azetidin-3-il)metil]-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 56 mg del compuesto del título a partir de 42 mg del compuesto preparado en el Ejemplo 214c y 32 mg de cloruro de 4-[(trifluorometil)sulfani]benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 3,21 (1H), 3,27 (3H), 3,38-3,49 (4H), 3,95 (1H), 4,12 (1H), 4,16 (3H), 4,21 (1H), 4,40 (1H), 4,67 (2H), 7,20 (1H), 7,63 (1H), 7,69 (2H), 7,76 (2H), 8,18 (1H), 8,87 (1H).

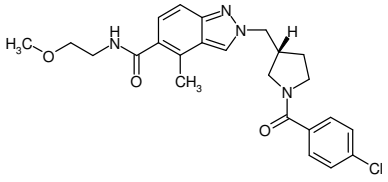
Ejemplo 216: 2-{[1-(4-bromobenzoil)azetidin-3-il]metil}-4-metoxi-N-(2-metoxietil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 48 mg del compuesto del título a partir de 42 mg del compuesto preparado en el Ejemplo 214c y 29 mg de cloruro de 4-bromobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 3,23 (1H), 3,26 (3H), 3,38-3,48 (4H), 3,92 (1H), 4,09 (1H), 4,16 (3H), 4,19 (1H), 4,38 (1H), 4,66 (2H), 7,20 (1H), 7,51 (2H), 7,58-7,68 (3H), 8,18 (1H), 8,86 (1H).

Ejemplo 217: 2-{[(R)-1-(4-clorobenzoil)pirrolidin-3-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



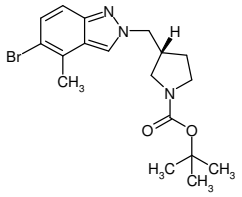
De forma análoga al Ejemplo 55, se obtuvieron 50 mg del compuesto del título a partir de 106 mg del compuesto preparado en el Ejemplo 217e y 58 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,57-1,73 (1H),

1,81–1,97 (1H), 2,47 / 2,51 (3H), 2,78–2,93 (1H), 3,25 (3H), 3,19–3,61 (8H), 4,39 / 4,51 (2H), 7,11–7,18 (1H), 7,33–7,43 (1H), 7,45 (2H), 7,50 (2H), 8,09–8,16 (1H), 8,47 / 8,55 (1H).

El material de partida se preparó de la siguiente manera:

Ejemplo 217a: 3-[(5-bromo-4-metil-2H-indazol-2-il)metil]pirrolidin-1-carboxilato de (R)-ter-butilo



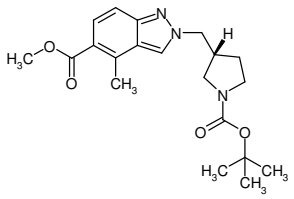
A una solución de 9,0 g de 3-(hidroximetil)pirrolidin-1-carboxilato de (R)-ter-butilo en 100 ml de piridina se añadieron 12,8 g de cloruro de p-toluenosulfonilo a 0 °C bajo nitrógeno y se agitó durante 3 horas a 25 °C. La mezcla de reacción se diluyó con acetato de etilo y se agitó durante 30 minutos con bicarbonato de sodio. Las fases se separaron luego y la fase orgánica se lavó con solución saturada de cloruro de sodio, se secó sobre sulfato de sodio y se concentró al vacío después de triturar. El residuo así obtenido se purificó por cromatografía en columna en gel de sílice con hexano / 0–100% de acetato de etilo. Rendimiento: 11,4 g de 3-[(tosiloxi)metil]pirrolidin-1-carboxilato de (R)-ter-

butilo.

De forma análoga al Ejemplo 1c, se obtuvieron 1,97 g del compuesto del título a partir de 4,53 g de 5-bromo-4-metil-1H-indazol y 11,4 g de 3-[(tosiloxi)metil]pirrolidin-1-carboxilato de (R)-ter-butilo preparado con anterioridad con adición de 7,9 g de yoduro de tetrabutilamonio.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,34 (9H), 1,50-1,66 (1H), 1,81 (1H), 2,48 (3H), 2,78 (1H), 3,01 (1H), 3,16 (1H), 3,25-3,37 (2H), 4,41 (2H), 7,29 (1H), 7,36 (1H), 8,51 (1H).

Ejemplo 217b: 2-{[(R)-1-(ter-butoxicarbonil)pirrolidin-3-il]metil}-4-metil-2H-indazol-5-carboxilato de metilo

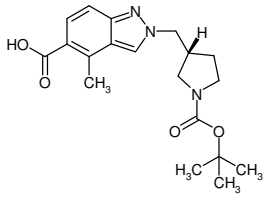


De forma análoga al Ejemplo 1e, después de dos corridas, se obtuvieron 820 mg del compuesto del título de 563 mg del bromuro preparado en el Ejemplo 217a y 0,17 ml de metanol.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,34 (9H), 1,58 (1H), 1,83 (1H), 2,73 (3H), 2,80 (1H), 3,03 (1H), 3,17 (1H), 3,25-3,37 (2H), 3,79 (3H), 4,37-4,49 (2H), 7,44

(1H), 7,64 (1H), 8,72 (1H).

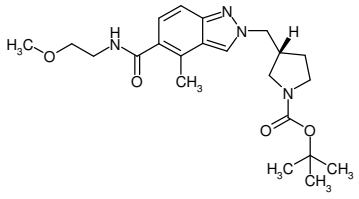
Ejemplo 217c: ácido 2-{[(R)-1-(ter-butoxicarbonil)pirrolidin-3-il]metil}-4-metil-2H-indazol-5-carboxílico



De forma análoga al Ejemplo 1d, se obtuvieron 701 mg del compuesto del título a partir de 620 mg del éster preparado en el Ejemplo 217b.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,34 (9H), 1,50-1,69 (1H), 1,82 (1H), 1,75-1,86 (1H), 2,69-2,88 (4H), 3,03 (1H), 3,17 (1H), 3,24-3,38 (1H), 4,42 (2H), 7,40 (1H), 7,65 (1H), 8,68 (1H), 12,28 (1H).

Ejemplo 217d: 3-({5-[N-(2-metoxietil)carbamoil]-4-metil-2H-indazol-2-il}metil)pirrolidin-1-carboxilato de (R)-ter-butilo

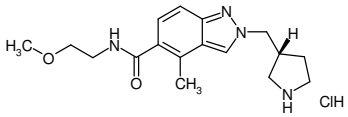


De forma análoga al Ejemplo 1, se obtuvieron 376 mg del compuesto del título a partir de 350 mg del ácido preparado en el Ejemplo 217c y 73 mg de 2-metoxietilamina.

^{1}H-RMN (300 MHz, DMSO-d_6): δ = 1,35 (9H), 1,57

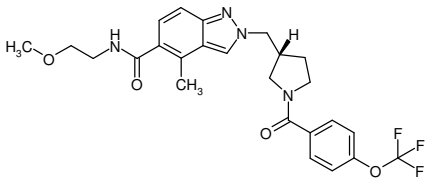
(1H), 1,80 (1H), 2,50 (3H), 2,73–2,86 (1H), 3,01 (1H), 3,11–3,22 (1H), 3,25 (3H), 3,26–3,39 (3H), 3,39–3,46 (2H), 4,42 (2H), 7,15 (1H), 7,39 (1H), 8,13 (1H), 8,52 (1H).

Ejemplo 217e: clorhidrato de N-(2-metoxietil)-4-metil-2-[(R)-pirrolidin-3-ilmetil]-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 376 mg de la amida preparada en el Ejemplo 217d, se obtuvieron 465 mg del compuesto del título, que se hizo reaccionar sin ulterior purificación.

Ejemplo 218: N-(2-metoxietil)-4-metil-2-({(R)-1-[4-(trifluorometoxi)benzoil]-pirrolidin-3-il}metil)-2H-indazol-5-carboxamida

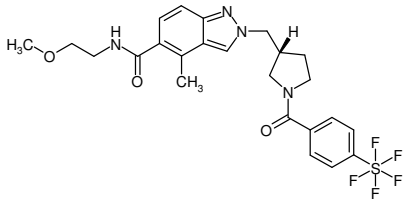


De forma análoga al Ejemplo 55, se obtuvieron 61 mg del compuesto del título a partir de 106 mg del compuesto preparado en el Ejemplo 217e y 74 mg de cloruro de 4-(trifluorometoxi)benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,57–1,74 (1H), 1,81–1,97 (1H), 2,47 / 2,51 (3H), 2,77–2,94 (1H), 3,25–3,62 (11H), 4,40 / 4,51 (2H), 7,09–7,19 (1H), 7,31–7,44

(3H), 7,61 (2H), 8,08-8,16 (1H), 8,47 / 8,55 (1H).

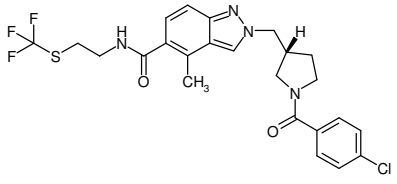
Ejemplo 219: N-(2-metoxietil)-4-metil-2-({(3R)-1-[4-(pentafluoro-λ^6-sulfanil)benzoil]-pirrolidin-3-il}metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 29 mg del compuesto del título a partir de 106 mg del compuesto preparado en el Ejemplo 217e y 75 mg de ácido 4-(pentafluoro-λ^6-sulfanil)benzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,57-1,76 (1H), 1,81-1,99 (1H), 2,50 (3H), 2,77-2,94 (1H), 3,16-3,62 (11H), 4,39 / 4,52 (2H), 7,09-7,19 (1H), 7,32-7,44 (1H), 7,68 (2H), 7,90-7,97 (2H), 8,10-8,17 (1H), 8,46 / 8,55 (1H).

Ejemplo 220: 2-{[(R)-1-(4-clorobenzoil)pirrolidin-3-il]metil}-4-metil-N-{2-[(trifluoro-metil)sulfanil]etil}-2H-indazol-5-carboxamida



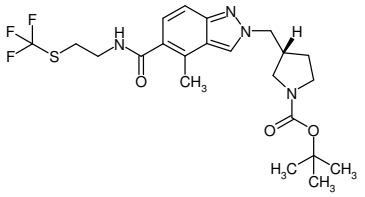
De forma análoga al Ejemplo 55, se obtuvieron 29 mg del compuesto del título a partir de 106 mg del compuesto preparado en el Ejemplo 220b y 48 mg de

cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,57-1,73 (1H), 1,81-1,96 (1H), 2,48 / 2,53 (3H), 2,79-2,93 (1H), 3,13-3,60 (8H), 4,40 / 4,51 (2H), 7,14-7,23 (1H), 7,33-7,53 (5H), 8,35-8,42 (1H), 8,49 / 8,58 (1H).

El material de partida se preparó de la siguiente manera:

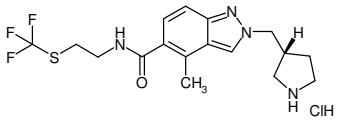
Ejemplo 220a: 3-{[4-metil-5-(N-{2-[(trifluorometil)sulfanil]etil}-carbamoil)-2H-indazol-2-il]metil}pirrolidin-1-carboxilato de (R)-ter-butilo



De forma análoga al Ejemplo 1, se obtuvieron 245 mg del compuesto del título a partir de 350 mg del ácido preparado en el Ejemplo 217c y 141 mg de 2-[(trifluorometil)sulfanil]etilamina.

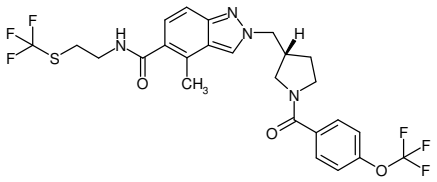
^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,35 (9H), 1,52-1,64 (1H), 1,81 (1H), 2,52 (3H), 2,71-2,96 (2H), 2,97-3,05 (12H), 3,18 (2H), 3,23-3,28 (1H), 3,51 (2H), 4,42 (2H), 7,19 (1H), 7,42 (1H), 8,39 (1H), 8,54 (1H).

Ejemplo 220b: clorhidrato de 4-metil-2-[(R)-pirrolidin-3-ilmetil]-N-{2-[(trifluorometil)sulfanil]-etil}-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 245 mg de la amida preparada en el Ejemplo 220a, se obtuvieron 410 mg del compuesto del título, que se hizo reaccionar sin ulterior purificación.

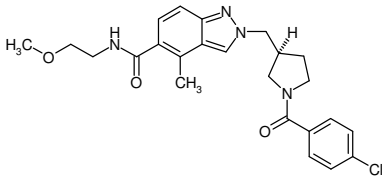
Ejemplo 221: 4-metil-2-({(R)-1-[4-(trifluorometoxi)benzoil]pirrolidin-3-il}metil)-N-{2-[(trifluorometil)sulfanil]etil}-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 55, se obtuvieron 49 mg del compuesto del título a partir de 106 mg del compuesto preparado en el Ejemplo 220b y 62 mg de cloruro de 4-(trifluorometoxi)benzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,58-1,74 (1H), 1,81-1,98 (1H), 2,48 / 2,53 (3H), 2,78-2,94 (1H), 3,12-3,62 (8H), 4,40 / 4,52 (2H), 7,14-7,23 (1H), 7,32-7,49 (3H), 7,61 (2H), 8,35-8,43 (1H), 8,49 / 8,58 (1H).

Ejemplo 222: 2-{[(S)-1-(4-clorobenzoil)pirrolidin-3-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

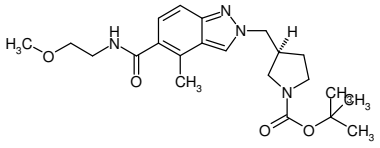


De forma análoga al Ejemplo 55, se obtuvieron 67 mg del compuesto del título a partir de 134 mg del compuesto preparado en el Ejemplo 222a y 73 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, CDCl3): δ = 1,72-1,86 (1H), 1,99-2,20 (1H), 2,64 (3H), 2,93-3,13 (1H), 3,29-3,36 (1H), 3,39 (3H), 3,45-3,71 (6H), 3,76-3,86 (1H), 4,31-4,57 (2H), 6,12-6,20 (1H), 7,30-7,42 (3H), 7,43-7,56 (3H), 7,90 / 8,02 (1H).

El material de partida se preparó de la siguiente manera:

Ejemplo 222a: 3-({5-[N-(2-metoxietil)carbamoil]-4-metil-2H-indazol-2-il}metil)pirrolidin-1-carboxilato de (S)-ter-butilo

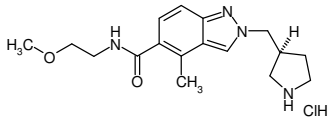


De forma análoga a los Ejemplos 217a a 217d, este compuesto del título se preparó en una cantidad de 760 mg a partir de 3-(hidroximetil)pirrolidin-1-carboxilato de (S)-ter-butilo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,35 (9H), 1,52-1,64 (1H), 1,77-1,87 (1H), 1,76-1,82 (1H), 2,50 (3H),

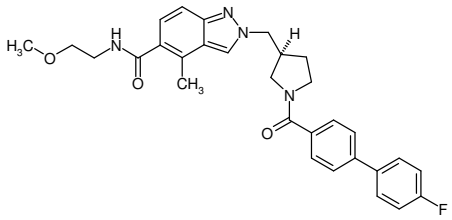
2,74-2,86 (1H), 3,02 (1H), 3,12-3,20 (1H), 3,25 (3H), 3,31 (1H), 3,36 (2H), 3,43 (2H), 4,42 (2H), 7,16 (1H), 7,39 (1H), 8,10 (1H), 8,51 (1H).

Ejemplo 222b: clorhidrato de N-(2-metoxietil)-4-metil-2-[(S)-pirrolidin-3-ilmetil]-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 159 mg de la amida preparada en el Ejemplo 222a, se obtuvieron 134 mg del compuesto del título, que se hizo reaccionar sin ulterior purificación.

Ejemplo 223: 2-({(S)-1-[(4'-fluorobifenil-4-il)carbonil]pirrolidin-3-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

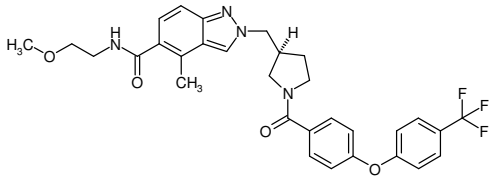


De forma análoga al Ejemplo 1, se obtuvieron 128 mg del compuesto del título a partir de 230 mg del compuesto preparado en el Ejemplo 222b y 141 mg de ácido 4'-fluorobifenil-4-carboxílico.

^{1}H-RMN (300 MHz, CDCl3): δ = 1,73-1,89 (1H), 1,98-2,24 (1H), 2,60 / 2,67 (3H), 2,94-3,18 (1H), 3,37 / 3,39 (3H), 3,49-3,76 (6H), 3,79-3,91 (2H), 4,32-4,61 (2H), 6,08-6,21 (1H), 7,09-7,20 (2H), 7,28-7,38 (1H),

7,46-7,62 (7H), 7,91 / 8,04 (1H).

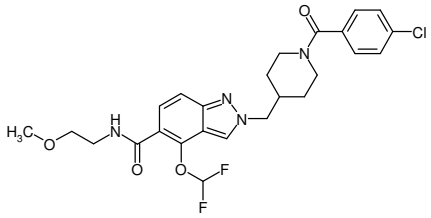
Ejemplo 224: N-(2-metoxietil)-4-metil-2-{[(S)-1-{4-[4-(trifluorometil)fenoxi] benzoil}pirrolidin-3-il]metil}-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 102 mg del compuesto del título a partir de 230 mg del compuesto preparado en el Ejemplo 222b y 184 mg de ácido 4-[4-(trifluorometil)fenoxi]benzoico.

^{1}H-RMN (300 MHz, CDCl3): δ = 1,70-2,25 (2H), 2,63 / 2,66 (3H), 2,94-3,17 (1H), 3,39 (3H), 3,47-3,92 (8H), 4,33-4,59 (2H), 6,15 (1H), 7,00-7,11 (4H), 7,30-7,40 (1H), 7,47-7,65 (5H), 7,91 / 8,03 (1H).

Ejemplo 225: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-(difluorometoxi)-N-(2-metoxietil)-2H-indazol-5-carboxamida

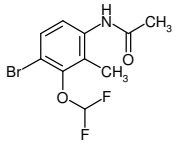


De forma análoga al Ejemplo 55, se obtuvieron 90 mg del compuesto del título a partir de 106 mg del compuesto preparado en el Ejemplo 225h y 49 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,14-1,58 (4H), 2,19-2,34 (1H), 2,67-2,81 (1H), 2,97 (1H), 3,22-3,53 (9H), 4,37 (2H), 7,13 (1H), 7,31-7,39 (3H), 7,47 (2H), 7,54 (1H), 8,21 (1H), 8,50 (1H).

El material de partida se preparó de la siguiente manera:

Ejemplo 225a: N-[4-bromo-3-(difluorometoxi)-2-metilfenil]acetamida



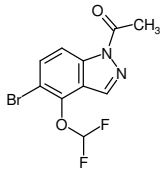
A una solución de 5,0 g de 3-difluorometoxi-2-metilanilina en 48 ml de DMF, una solución de 5,1 g de N-bromosuccinimida en 24 ml de DMF se añadió gota a gota a 0 °C y se agitó durante 1 hora a 0 °C. A continuación, la mezcla de reacción se diluyó con 400 ml hexano / acetato de etilo y se lavó una vez con 50 ml de una solución acuosa al 10% de carbonato de sodio y tres veces con porciones de 50 ml de agua. Después de secar sobre sulfato de sodio y filtrar, se concentró al vacío. El producto crudo así obtenido (6,68 g) se usó en la siguiente etapa sin purificación.

A una solución de 6,39 g del bromuro preparado con anterioridad en 70 ml de piridina, se añadieron 3,0 ml de anhídrido acético gota a gota a 0 °C y se agitaron durante 20 horas a 25 °C. La mezcla de reacción se

concentró al vacío y el producto crudo así obtenido se purificó por cromatografía en columna en gel de sílice con hexano / 0–100% de acetato de etilo. La sustancia luego se recristalizó en hexano. De esta manera, se obtuvieron 6,39 g del compuesto del título.

^{1}H–RMN (300 MHz, CDCl3): δ = 2,22 (3H), 2,27 (3H), 6,51 (1H), 6,95 (1H), 7,46 (1H), 7,71 (1H).

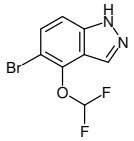
Ejemplo 225b: 1–[5–bromo–4–(difluorometoxi)–1H–indazol–1–il]etan–1–ona



De forma análoga al Ejemplo 212c, se obtuvieron se obtuvieron 5,32 g del compuesto del título a partir de 6,38 g de la amida preparada en el Ejemplo 225a.

^{1}H–RMN (300 MHz, DMSO–d6): δ = 2,70 (3H), 7,34 (1H), 7,90 (1H), 8,16 (1H), 8,46 (1H).

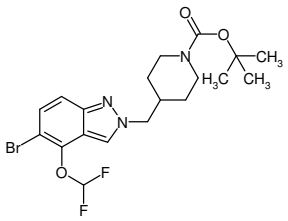
Ejemplo 225c: 5–bromo–4–(difluorometoxi)–1H–indazol



De forma análoga al Ejemplo 212d, se obtuvieron 4,12 g del compuesto del título a partir de 5,32 g del indazol preparado en el Ejemplo 225b.

^{1}H–RMN (300 MHz, DMSO–d6): δ = 7,30 (1H), 7,44 (1H), 7,56 (1H), 8,06 (1H), 13,54 (1H).

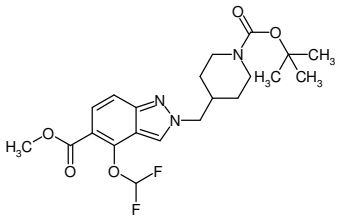
Ejemplo 225d: 4-{[5-bromo-4-(difluorometoxi)-2H-indazol-2-il]metil}-piperidin-1-carboxilato de ter-butilo



De forma análoga al Ejemplo 212e, se obtuvieron 2,06 g del compuesto del título a partir de 4,1 g del indazol preparado en el Ejemplo 225c y 8,7 g de 4-[(tosiloxi)metil]piperidin-1-carboxilato de ter-butilo.

^{1}H-RMN (300 MHz, CDCl3): δ = 1,19-1,28 (2H), 1,45 (9H), 1,51-1,59 (2H), 2,25 (1H), 2,68 (2H), 4,12 (2H), 4,27 (2H), 6,61 (1H), 7,41 (1H), 7,50 (1H), 7,95 (1H).

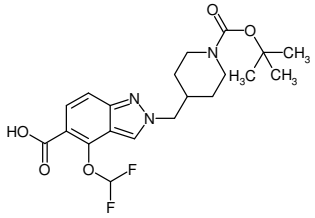
Ejemplo 225e: 2-{[1-(ter-butoxicarbonil)piperidin-4-il]metil}-4-(difluorometoxi)-2H-indazol-5-carboxilato de metilo



De forma análoga al Ejemplo 1e, después de tres corridas se obtuvieron 1,28 g del compuesto del título a partir de 683 mg del bromuro preparado en el Ejemplo 225d y 0,18 ml de metanol.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,96-1,22 (2H), 1,28-1,47 (11H), 2,14 (1H), 2,54-2,74 (2H), 3,81 (3H), 3,87 (2H), 4,36 (2H), 7,17 (1H), 7,58 (1H), 7,65 (1H), 8,62 (1H).

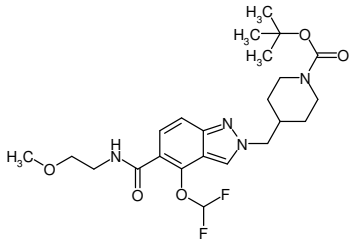
Ejemplo 225f: ácido 2-{[1-(ter-butoxicarbonil)piperidin-4-il]metil}-4-(difluorometoxi)-2H-indazol-5-carboxílico



De forma análoga al Ejemplo 1d, se obtuvieron 1,05 g del compuesto del título a partir de 1,28 g del éster preparado en el Ejemplo 225e.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,97-1,16 (2H), 1,28-1,47 (11H), 2,13 (1H), 2,63 (2H), 3,87 (2H), 4,35 (2H), 7,14 (1H), 7,54 (1H), 7,65 (1H), 8,58 (1H), 13,05 (1H).

Ejemplo 225g: 4-({4-(difluorometoxi)-5-[N-(2-metoxietil)carbamoil]-2H-indazol-2-il}metil)piperidin-1-carboxilato de ter-butilo

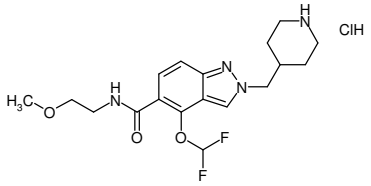


De forma análoga al Ejemplo 1, se obtuvieron 503

mg del compuesto del título a partir de 520 mg del compuesto preparado en el Ejemplo 225f y 92 mg de 2-metoxietilamina.

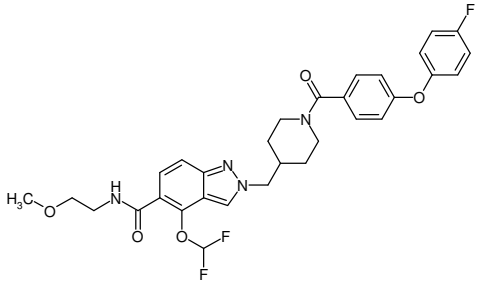
^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,01-1,13 (2H), 1,34 (9H), 1,38 (2H), 2,13 (1H), 2,59-2,71 (6H), 3,24 (3H), 3,34-3,44 (2H), 3,87 (2H), 4,34 (2H), 7,14 (1H), 7,33 (1H), 7,54 (1H), 8,21 (1H), 8,50 (1H).

Ejemplo 225h: clorhidrato de 4-(difluorometoxi)-N-(2-metoxietil)-2-(4-piperidilmetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 122 mg de la amida preparada en el Ejemplo 225g, se obtuvieron 106 mg del compuesto del título, que se hizo reaccionar sin ulterior purificación.

Ejemplo 226: 4-(difluorometoxi)-2-({1-[4-(4-fluorofenoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-2H-indazol-5-carboxamida

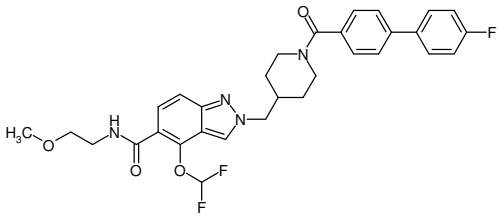


De forma análoga al Ejemplo 1, se obtuvieron 11 mg

del compuesto del título a partir de 106 mg del compuesto preparado en el Ejemplo 225h y 59 mg de ácido 4-(4-fluorofenoxi)benzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,10-1,59 (4H), 2,23-2,33 (1H), 2,75-3,01 (2H), 3,24 (3H), 3,33-3,51 (5H), 3,51-3,72 (1H), 4,37 (2H), 6,95 (2H), 7,07-7,12 (2H), 7,13 (1H), 7,17-7,26 (2H), 7,28-7,39 (3H), 7,54 (1H), 8,21 (1H), 8,50 (1H).

Ejemplo 227: 4-(difluorometoxi)-2-({1-[(4'-fluorobifenil-4-il)carbonil]piperidin-4-il} metil)-N-(2-metoxietil)-2H-indazol-5-carboxamida

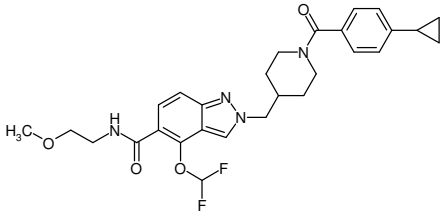


De forma análoga al Ejemplo 1, se obtuvieron 38 mg del compuesto del título a partir de 106 mg del compuesto preparado en el Ejemplo 225h y 55 mg de ácido 4'-fluorobifenil-4-carboxílico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,14-1,62 (4H), 2,23-2,35 (1H), 2,68-2,85 (1H), 2,91-3,09 (1H), 3,24 (3H), 3,32-3,48 (5H), 3,50-3,70 (1H), 4,38 (2H), 7,14 (1H), 7,28 (2H), 7,33 (1H), 7,40 (2H), 7,55 (1H), 7,64-7,75 (4H), 8,21 (1H), 8,51 (1H).

Ejemplo 228: 2-{[1-(4-ciclopropilbenzoil)piperidin-4-il]metil}-4-(difluorometoxi)-N-(2-metoxietil)-2H-

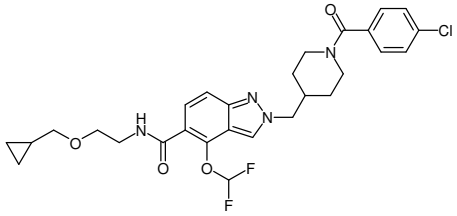
indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 75 mg del compuesto del título a partir de 106 mg del compuesto preparado en el Ejemplo 225h y 41 mg de ácido 4-ciclopropilbenzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,66 (2H), 0,94 (2H), 1,10-1,54 (4H), 1,90 (1H), 2,14-2,31 (1H), 2,72-3,02 (2H), 3,03-3,18 (1H), 3,24 (3H), 3,33-3,47 (4H), 3,49-3,68 (1H), 4,37 (2H), 7,07 (2H), 7,13 (1H), 7,19 (2H), 7,33 (1H), 7,54 (1H), 8,21 (1H), 8,50 (1H).

Ejemplo 229: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-[2-(ciclopropilmetoxi)-etil]-4-(difluorometoxi)-2H-indazol-5-carboxamida



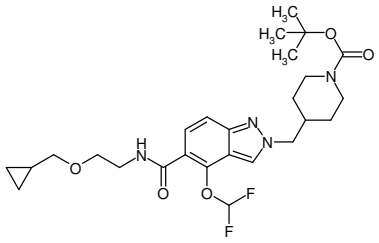
De forma análoga al Ejemplo 55, se obtuvieron 170 mg del compuesto del título a partir de 127 mg del compuesto preparado en el Ejemplo 229b y 53 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,14 (2H), 0,42

(2H), 0,96 (1H), 1,10-1,27 (2H), 1,37 (1H), 1,51 (1H), 2,26 (1H), 2,71 (1H), 2,97 (1H), 3,20-3,55 (8H), 4,37 (2H), 7,14 (1H), 7,31-7,38 (3H), 7,47 (2H), 7,55 (1H), 8,21 (1H), 8,51 (1H).

El material de partida se preparó de la siguiente manera:

Ejemplo 229a: 4-{[5-{N-[2-(ciclopropilmetoxi)etil]carbamoil}-4-(difluoro-metoxi)-2H-indazol-2-il]metil}piperidin-1-carboxilato de ter-butilo

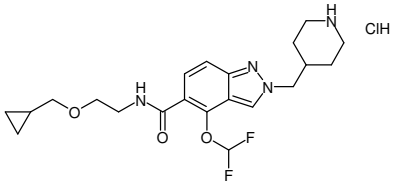


De forma análoga al Ejemplo 1, se obtuvieron 453 mg del compuesto del título a partir de 520 mg del compuesto preparado en el Ejemplo 225f y 185 mg de 2-(ciclopropilmetoxi)etilamina.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,14 (2H), 0,42 (2H), 0,97 (1H), 1,07 (2H), 1,34 (9H), 1,39 (2H), 2,13 (1H), 2,56-2,72 (2H), 3,23 (2H), 3,37 (2H), 3,48 (2H), 3,87 (2H), 4,34 (2H), 7,15 (1H), 7,34 (1H), 7,55 (1H), 8,21 (1H), 8,50 (1H).

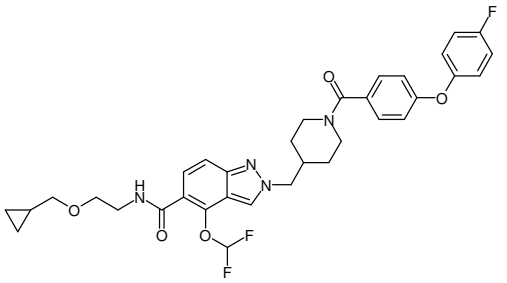
Ejemplo 229b: clorhidrato de N-[(2-ciclopropilmetoxi)etil]-4-(difluorometoxi)-2-(4-

piperidilmetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 145 mg de la amida preparada en el Ejemplo 229a, se obtuvieron 127 mg del compuesto del título, que se hizo reaccionar sin ulterior purificación.

Ejemplo 230: N-[2-(ciclopropilmetoxi)etil]-4-(difluorometoxi)-2-({1-[4-(4-fluoro-fenoxi)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida

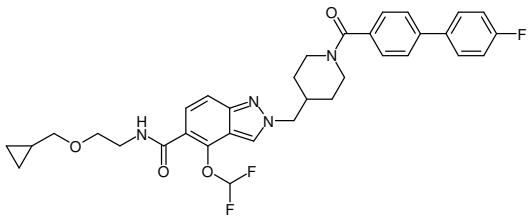


De forma análoga al Ejemplo 1, se obtuvieron 156 mg del compuesto del título a partir de 127 mg del compuesto preparado en el Ejemplo 229b y 64 mg de ácido 4-(4-fluorofenoxi)benzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,14 (2H), 0,42 (2H), 0,96 (1H), 1,10-1,54 (4H), 2,18-2,33 (1H), 2,71-3,02 (2H), 3,03-3,16 (1H), 3,22 (2H), 3,37 (2H), 3,47 (2H), 3,55-3,68 (1H), 4,37 (2H), 6,95 (2H), 7,10 (2H),

7,14 (1H), 7,22 (2H), 7,34 (3H), 7,55 (1H), 8,21 (1H), 8,51 (1H).

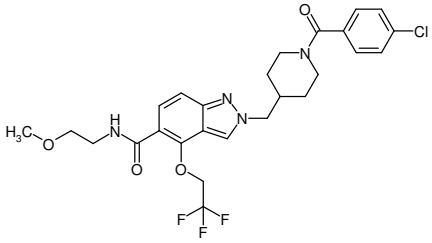
Ejemplo 231: N-[2-(ciclopropilmetoxi)etil]-4-(difluorometoxi)-2-({1-[(4'-fluoro-bifenil-4-il)carbonil]piperidin-4-il}metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 164 mg del compuesto del título a partir de 127 mg del compuesto preparado en el Ejemplo 229b y 60 mg de ácido 4'-fluorobifenil-4-carboxílico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,14 (2H), 0,42 (2H), 0,96 (1H), 1,14-1,60 (4H), 2,27 (1H), 2,70-3,04 (1H), 2,87 (1H), 3,03-3,15 (1H), 3,22 (2H), 3,37 (2H), 3,47 (2H), 3,60 (1H), 4,38 (2H), 7,14 (1H), 7,28 (2H), 7,34 (1H), 7,41 (2H), 7,55 (1H), 7,64-7,75 (4H), 8,21 (1H), 8,52 (1H).

Ejemplo 232: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-(2,2,2-trifluoroetoxi)-2H-indazol-5-carboxamida

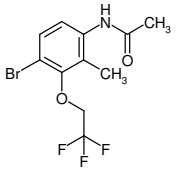


De forma análoga al Ejemplo 55, se obtuvieron 113 mg del compuesto del título a partir de 109 mg del compuesto preparado en el Ejemplo 232h y 46 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,12-1,61 (3H), 2,19-2,34 (1H), 2,67-3,07 (2H), 3,23 (3H), 3,33-3,56 (4H), 4,28-4,47 (3H), 4,95 (2H), 7,31-7,39 (3H), 7,40-7,50 (3H), 7,99 (1H), 8,65 (1H).

El material de partida se preparó de la siguiente manera:

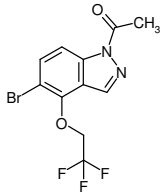
Ejemplo 232a: N-[4-bromo-2-metil-3-(2,2,2-trifluoroetoxi)fenil]acetamida



De forma análoga al Ejemplo 225a, 6,13 g del compuesto del título a partir de 5,0 g de 2-metil-3-(2,2,2-trifluoroetoxi)anilina.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,07 (3H), 2,18 (3H), 4,55 (2H), 7,29 (1H), 7,45 (1H), 9,42 (1H).

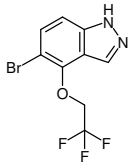
Ejemplo 232b: 1-[5-bromo-4-(2,2,2-trifluoroetoxi)-1H-indazol-1-il]etan-1-ona



De forma análoga al Ejemplo 212c, se obtuvieron 5,08 g del compuesto del título a partir de 6,13 g de la amida preparada en el Ejemplo 232a.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 2,69 (3H), 5,14 (2H), 7,80 (1H), 7,99 (1H), 8,64 (1H).

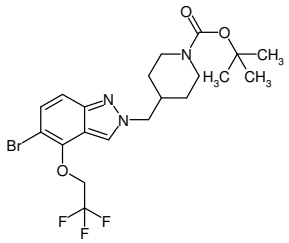
Ejemplo 232c: 5-bromo-4-(2,2,2-trifluoroetoxi)-1H-indazol



De forma análoga al Ejemplo 212d, se obtuvieron 3,57 g del compuesto del título a partir de 5,08 g del indazol preparado en el Ejemplo 232b.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 5,05 (2H), 7,24 (1H), 7,45 (1H), 8,26 (1H), 13,38 (1H).

Ejemplo 232d: 4-{[5-bromo-4-(2,2,2-trifluoroetoxi)-2H-indazol-2-il]metil}-piperidin-1-carboxilato de ter-butilo

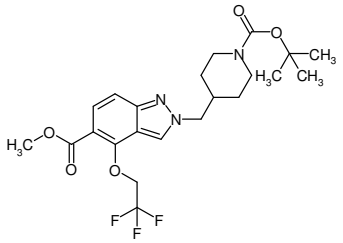


De forma análoga al Ejemplo 212e, se obtuvieron

1,77 g del compuesto del título a partir de 3,57 g del indazol preparado en el Ejemplo 232c y 6,7 g de 4-[(tosiloxi)metil]piperidin-1-carboxilato de ter-butilo.

^{1}H-RMN (300 MHz, CDCl3): δ = 1,16-1,31 (2H), 1,45 (9H), 1,54 (2H), 2,25 (1H), 2,68 (2H), 4,05-4,21 (2H), 4,27 (2H), 4,54 (2H), 7,35 (1H), 7,41 (1H), 7,91 (1H).

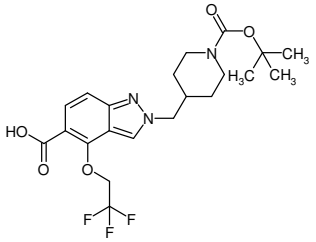
Ejemplo 232e: 2-{[1-(ter-butoxicarbonil)piperidin-4-il]metil}-4-(2,2,2-trifluoro-etoxi)-2H-indazol-5-carboxilato de metilo



De forma análoga al Ejemplo 1e, después de tres corridas, se obtuvieron 857 mg del compuesto del título a partir de 590 mg del bromuro preparado en el Ejemplo 232d y 0,15 ml de metanol.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,00-1,17 (2H), 1,34 (9H), 1,37-1,47 (2H), 2,13 (1H), 2,55-2,74 (2H), 3,79 (3H), 3,87 (2H), 4,32 (2H), 4,89 (2H), 7,39 (1H), 7,56 (1H), 8,67 (1H).

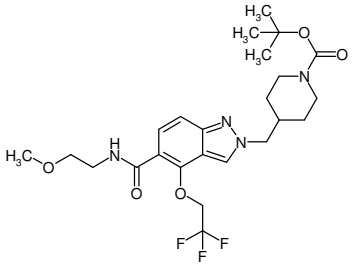
Ejemplo 232f: ácido 2-{[1-(ter-butoxicarbonil)piperidin-4-il]metil}-4-(2,2,2-trifluoroetoxi)-2H-indazol-5-carboxílico



De forma análoga al Ejemplo 1d, se obtuvieron 724 mg del compuesto del título a partir de 854 mg del éster preparado en el Ejemplo 232e.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,01-1,17 (2H), 1,34 (9H), 1,40 (2H), 2,13 (1H), 2,53-2,75 (2H), 3,87 (2H), 4,32 (2H), 4,84 (2H), 7,37 (1H), 7,58 (1H), 8,60 (1H), 12,74 (1H).

Ejemplo 232g: 4-({5-[N-(2-metoxietil)carbamoil]-4-(2,2,2-trifluoroetoxi)-2H-indazol-2-il}metil)piperidin-1-carboxilato de ter-butilo

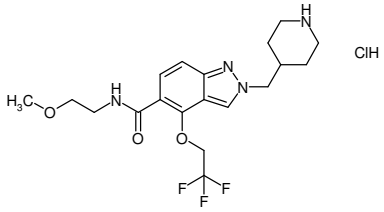


De forma análoga al Ejemplo 1, se obtuvieron 386 mg del compuesto del título a partir de 360 mg del compuesto preparado en el Ejemplo 232f y 59 mg de 2-metoxietilamina.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,98-1,18 (2H), 1,34 (9H), 1,43 (2H), 2,14 (1H), 2,65 (2H), 3,23 (3H), 3,35-3,47 (4H), 3,88 (2H), 4,30 (2H), 4,96 (2H), 7,35

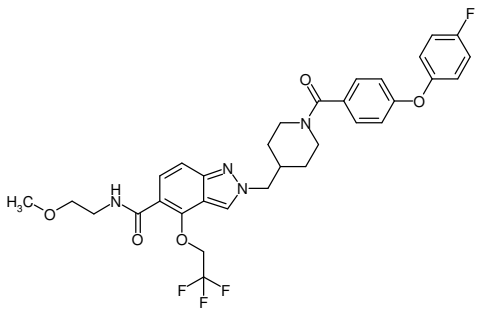
(1H), 7,43 (1H), 7,99 (1H), 8,65 (1H).

Ejemplo 232h: clorhidrato de N-(2-metoxietil)-2-(4-piperidilmetil)-4-(2,2,2-trifluoroetoxi)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 109 mg de la amida preparada en el Ejemplo 232g, se obtuvieron 113 mg del compuesto del título, que se hizo reaccionar sin ulterior purificación.

Ejemplo 233: 2-({1-[4-(4-fluorofenoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-(2,2,2-trifluoroetoxi)-2H-indazol-5-carboxamida

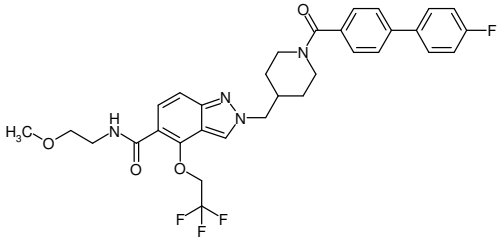


De forma análoga al Ejemplo 1, se obtuvieron 51 mg del compuesto del título a partir de 109 mg del compuesto preparado en el Ejemplo 232h y 56 mg de ácido 4-(4-fluorofenoxi)benzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,10-1,31 (1H),

1,48 (2H), 2,18-2,37 (1H), 2,69-3,04 (2H), 3,23 (3H), 3,37-3,48 (4H), 3,56-3,71 (1H), 4,33 (2H), 4,95 (2H), 6,95 (2H), 7,06-7,15 (2H), 7,18-7,27 (2H), 7,31-7,38 (3H), 7,40-7,47 (1H), 7,99 (1H), 8,66 (1H).

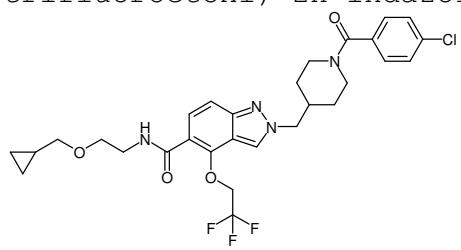
Ejemplo 234: 2-({1-[(4'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxi-etil)-4-(2,2,2-trifluoroetoxi)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 61 mg del compuesto del título a partir de 109 mg del compuesto preparado en el Ejemplo 232h y 52 mg de ácido 4-(4-fluorofenil)benzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,14-1,63 (3H), 2,19-2,37 (1H), 2,68-3,09 (2H), 3,23 (3H), 3,34-3,48 (4H), 3,62 (1H), 4,28-4,42 (2H), 4,96 (2H), 7,22-7,47 (6H), 7,64-7,76 (4H), 7,99 (1H), 8,66 (1H).

Ejemplo 235: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-[2-(ciclopropilmetoxi)-etil]-4-(2,2,2-trifluoroetoxi)-2H-indazol-5-carboxamida

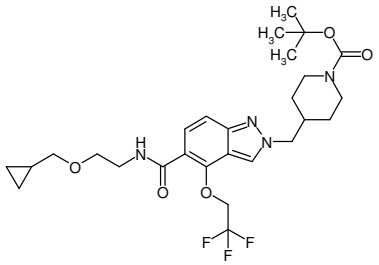


De forma análoga al Ejemplo 55, se obtuvieron 122 mg del compuesto del título a partir de 122 mg del compuesto preparado en el Ejemplo 235b y 48 mg de cloruro de 4-clorobenzoílo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,13 (2H), 0,41 (2H), 0,95 (1H), 1,11-1,62 (3H), 2,19-2,34 (1H), 2,73 (1H), 2,98 (1H), 3,21 (2H), 3,33-3,57 (5H), 4,33 (2H), 4,95 (2H), 7,31-7,51 (6H), 8,00 (1H), 8,65 (1H).

El material de partida se preparó de la siguiente manera:

Ejemplo 235a: 4-{[5-{N-[2-(ciclopropilmetoxi)etil]carbamoil}-4-(2,2,2-trifluoroetoxi)-2H-indazol-2-il]metil}piperidin-1-carboxilato de ter-butilo

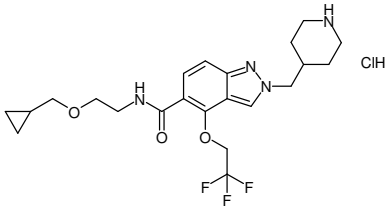


De forma análoga al Ejemplo 1, se obtuvieron 429 mg del compuesto del título a partir de 360 mg del compuesto preparado en el Ejemplo 232f y 119 mg de 2-(ciclopropilmetoxi)etilamina.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,13 (2H), 0,42 (2H), 0,95 (1H), 1,08 (2H), 1,34 (9H), 1,41 (2H), 2,14 (1H), 3,22 (2H), 3,41 (2H), 3,48 (2H), 3,88 (2H), 4,30

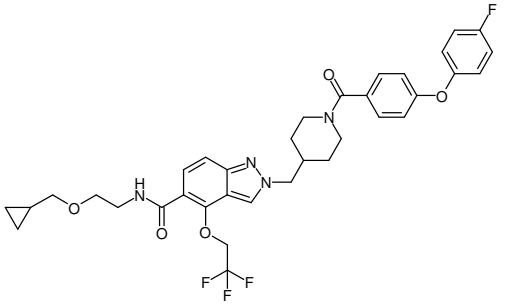
(2H), 4,95 (2H), 7,35 (1H), 7,42 (1H), 8,00 (1H), 8,65 (1H).

Ejemplo 235b: clorhidrato de N-[2-(ciclopropilmetoxi)etil]-2-(4-piperidilmetil)-4-(2,2,2-trifluoro-etoxi)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 138 mg de la amida preparada en el Ejemplo 235a, se obtuvieron 122 mg del compuesto del título, que se hizo reaccionar sin ulterior purificación.

Ejemplo 236: N-[2-(ciclopropilmetoxi)etil]-2-({1-[4-(4-fluorofenoxi)benzoil]piperidin-4-il}metil)-4-(2,2,2-trifluoroetoxi)-2H-indazol-5-carboxamida

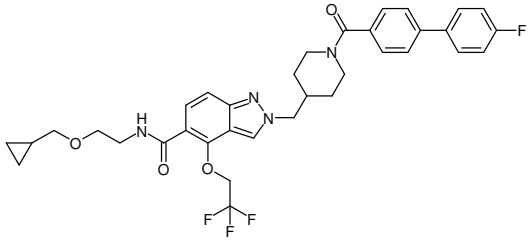


De forma análoga al Ejemplo 1, se obtuvieron 95 mg del compuesto del título a partir de 122 mg del compuesto preparado en el Ejemplo 235b y 58 mg de ácido 4-(4-fluorofenoxi)benzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,13 (2H), 0,41

(2H), 0,95 (1H), 1,09-1,60 (3H), 2,17-2,36 (1H), 2,68-3,06 (2H), 3,22 (2H), 3,34-3,76 (5H), 4,33 (2H), 4,95 (2H), 6,95 (2H), 7,06-7,14 (2H), 7,17-7,27 (2H), 7,30-7,38 (3H), 7,42 (1H), 7,99 (1H), 8,65 (1H).

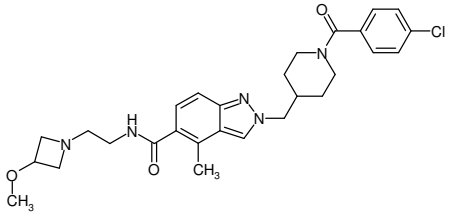
Ejemplo 237: N-[2-(ciclopropilmetoxi)etil]-2-({1-[(4'-fluorobifenil-4-il)carbonil] piperidin-4-il}metil)-4-(2,2,2-trifluoroetoxi)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 98 mg del compuesto del título a partir de 122 mg del compuesto preparado en el Ejemplo 235b y 54 mg de ácido 4-(4-fluorofenoxi)benzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,12 (2H), 0,41 (2H), 0,95 (1H), 1,15-1,64 (3H), 2,21-2,36 (1H), 2,70-3,10 (2H), 3,21 (2H), 3,35-3,69 (5H), 4,35 (2H), 4,95 (2H), 7,22-7,46 (6H), 7,63-7,77 (4H), 7,99 (1H), 8,66 (1H).

Ejemplo 238: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-[2-(3-metoxiazetidin-1-il) etil]-4-metil-2H-indazol-5-carboxamida

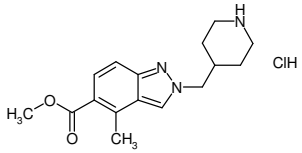


De forma análoga al Ejemplo 1, se obtuvieron 33 mg del compuesto del título a partir de 120 mg del compuesto preparado en el Ejemplo 238c y 40 mg de 2-(3-metoxiazetidin-1-il)etilamina (preparada análogamente al documento WO 2006/104406).

^{1}H-RMN (300 MHz, CDCl3): δ = 0,83 (1H), 1,20-2,01 (4H), 2,38 (1H), 2,66 (3H), 2,69-3,09 (2H), 3,31 (3H), 3,43 (2H), 3,56-3,90 (5H), 4,18-4,32 (3H), 4,43 (2H), 6,91 (1H), 7,30-7,41 (5H), 7,52 (1H), 7,95 (1H).

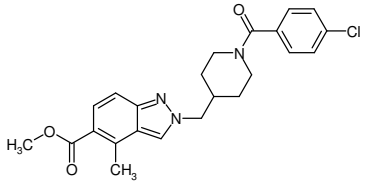
El material de partida se preparó de la siguiente manera:

Ejemplo 238a: clorhidrato de 4-metil-2-(4-piperidilmetil)-2H-indazol-5-carboxilato de metilo



De forma análoga al Ejemplo 1a, a partir de 3,0 g del éster preparado en el Ejemplo 1e, se obtuvieron 2,51 g del compuesto del título, que se hizo reaccionar sin ulterior purificación.

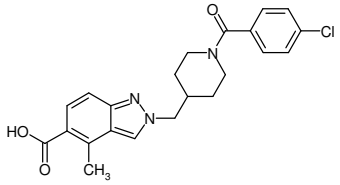
Ejemplo 238b: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metil-2H-indazol-5-carboxilato de metilo



De forma análoga al Ejemplo 55, se obtuvieron 3,27 g del compuesto del título a partir de 2,5 g del compuesto preparado en el Ejemplo 238a y 1,5 g de cloruro de 4-clorobenzoílo.

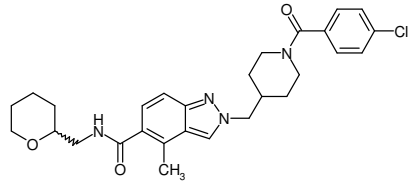
^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,16-1,63 (4H), 2,21-2,33 (1H), 2,73 (4H), 2,90-3,05 (1H), 3,44-3,55 (1H), 3,79 (3H), 4,32 (2H), 4,36-4,47 (1H), 7,36 (2H), 7,42 (1H), 7,46 (2H), 7,63 (1H), 8,67 (1H).

Ejemplo 238c: ácido 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metil-2H-indazol-5-carboxílico



De forma análoga al Ejemplo 1d, se obtuvieron 470 mg del compuesto del título a partir de 485 mg del éster preparado en el Ejemplo 238b.

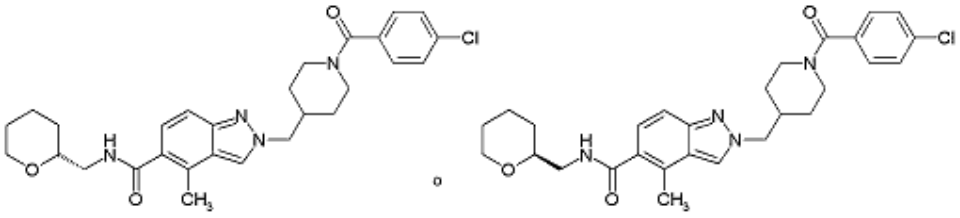
Ejemplo 239: (+/-)-2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metil-N-(3,4,5,6-tetra-hidro-2H-piran-2-ilmetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 188 mg del compuesto del título a partir de 300 mg del compuesto preparado en el Ejemplo 238c y 92 mg de clorhidrato de 3,4,5,6-tetrahidro-2H-piran-2-ilmetil-amina.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,01-1,27 (3H), 1,29-1,64 (7H), 2,19-2,32 (1H), 2,48 (3H), 2,66-2,80 (1H), 2,89-3,00 (1H), 3,00-3,08 (1H), 3,16-3,25 (2H), 3,34-3,42 (1H), 3,43-3,55 (1H), 3,77-3,88 (1H), 4,31 (2H), 4,39 (1H), 7,14 (1H), 7,32-7,40 (2H), 7,46 (2H), 7,83 (1H), 8,09 (1H), 8,46 (1H).

Ejemplo 240: (R o S)-2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metil-N-(3,4,5,6-tetrahidro-2H-piran-2-ilmetil)-2H-indazol-5-carboxamida

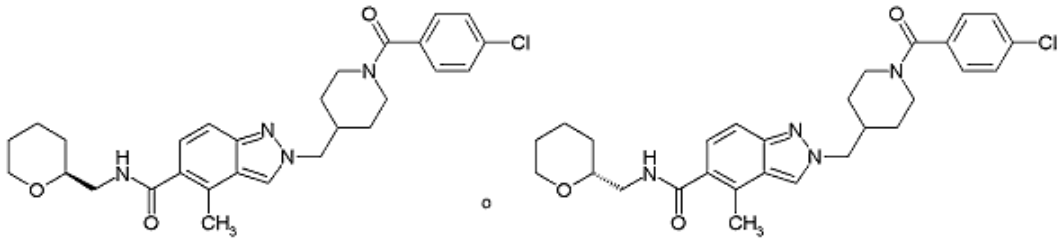


A partir de 185 mg del racemato preparado en el Ejemplo 239, se obtuvieron 51 mg del compuesto del título junto con 53 mg del enantiómero de elución más lenta (Ejemplo 241) por separación de racematos por medio de HPLC quiral preparativa (Método B).

HPLC quiral analítica: 7,02 min.

Ejemplo 241: (S o R)-2-{[1-(4-clorobenzoil)piperidin-4-

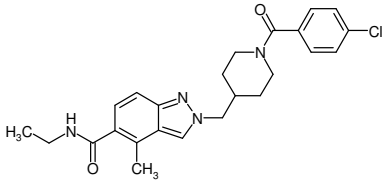
il]metil}-4-metil-N-(3,4,5,6-tetrahidro-2H-piran-2-ilmetil)-2H-indazol-5-carboxamida



A partir de 185 mg del racemato preparado en el Ejemplo 239, se obtuvieron 53 mg del compuesto del título junto con 51 mg del enantiómero de elución más rápida (Ejemplo 240) por separación de racematos por medio de HPLC quiral preparativa (Método B).

HPLC quiral analítica: 8,24 min.

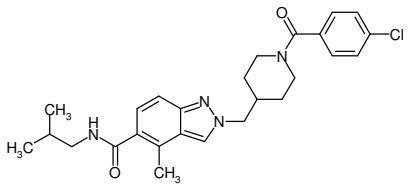
Ejemplo 242: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-etil-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 85 mg del compuesto del título a partir de 300 mg del compuesto preparado en el Ejemplo 238c y 43 mg de etilamina 2 M en THF.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,08 (3H), 1,16-1,60 (4H), 2,20-2,33 (1H), 2,48 (3H), 2,63-3,07 (2H), 3,22 (2H), 3,48 (1H), 4,24-4,46 (3H), 7,14 (1H), 7,31-7,42 (3H), 7,46 (2H), 8,08 (1H), 8,46 (1H).

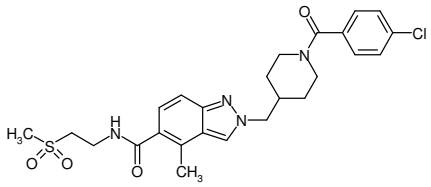
Ejemplo 243: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-isobutil-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 92 mg del compuesto del título a partir de 300 mg del compuesto preparado en el Ejemplo 238c y 69 mg de isobutilamina.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,85-0,90 (6H), 1,13-1,57 (4H), 1,75-1,83 (1H), 2,21-2,34 (1H), 2,49 (3H), 3,03 (4H), 3,48 (1H), 4,27-4,45 (3H), 7,14 (1H), 7,31-7,41 (3H), 7,46 (2H), 8,11 (1H), 8,47 (1H).

Ejemplo 244: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-(2-mesiletil)-4-metil-2H-indazol-5-carboxamida

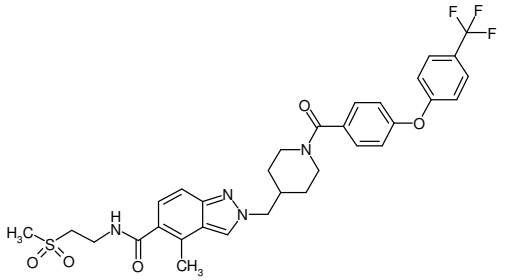


De forma análoga al Ejemplo 1, se obtuvieron 132 mg del compuesto del título a partir de 300 mg del compuesto preparado en el Ejemplo 238c y 151 mg de clorhidrato de 2-mesiletilamina.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,19-1,62 (4H), 2,24-2,36 (1H), 2,54 (3H), 2,70-3,05 (2H), 3,05 (3H),

3,38 (2H), 3,52 (1H), 3,65 (2H), 4,30-4,49 (3H), 7,22 (1H), 7,38 (2H), 7,42 (1H), 7,49 (2H), 8,33 (1H), 8,52 (1H).

Ejemplo 245: N-(2-mesiletil)-4-metil-2-[(1-{4-[4-(trifluorometil)fenoxi]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida

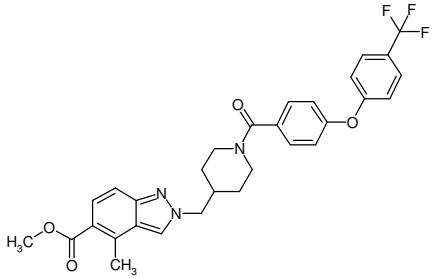


De forma análoga al Ejemplo 1, se obtuvieron 67 mg del compuesto del título a partir de 137 mg del compuesto preparado en el Ejemplo 245b y 41 mg de clorhidrato de 2-mesiletilamina.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,15-1,62 (4H), 2,22-2,33 (1H), 2,50 (3H), 2,68-3,01 (2H), 3,02 (2H), 3,35 (1H), 3,52-3,69 (3H), 4,28-4,47 (2H), 7,12 (1H), 7,15-7,22 (2H), 7,37-7,44 (2H), 7,73 (1H), 8,32 (1H), 8,50 (1H).

El material de partida se preparó de la siguiente manera:

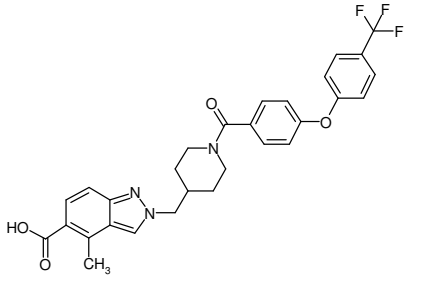
Ejemplo 245a: 4-metil-2-[(1-{4-[4-(trifluorometil)fenoxi]benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxilato de metilo



De forma análoga al Ejemplo 1, se obtuvieron 2,73 g del compuesto del título a partir de 3,76 g del compuesto preparado en el Ejemplo 238a y 3,28 g de ácido 4-[4-(trifluorometil)fenoxi]benzoico.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,25 (2H), 1,35-1,70 (2H), 2,20-2,37 (1H), 2,65-2,70 (3H), 2,75-3,10 (2H), 3,52-3,72 (1H), 3,82 (4H), 4,36 (2H), 7,14 (2H), 7,20 (2H), 7,39-7,48 (3H), 7,66 (1H), 7,75 (2H), 8,70 (1H).

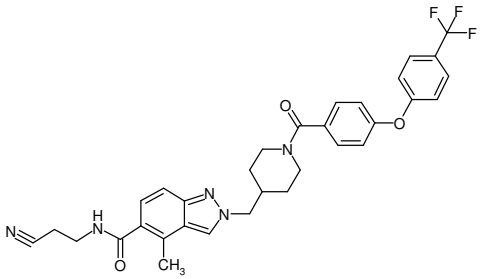
Ejemplo 245b: ácido 4-metil-2-[(1-{4-[4-(trifluorometil)fenoxi]benzoil}piperidin-4-il)-metil]-2H-indazol-5-carboxílico



De forma análoga al Ejemplo 1d, se obtuvieron 1,1 g del compuesto del título a partir de 2,73 g del éster preparado en el Ejemplo 245a.

Ejemplo 246: N-(2-cianoetil)-4-metil-2-[(1-{4-[4-

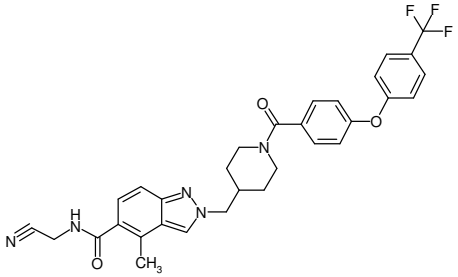
(trifluorometil)fenoxi]benzoil} piperidin-4-il)metil]-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 144 mg del compuesto del título a partir de 137 mg del compuesto preparado en el Ejemplo 245b y 18 mg de 3-aminopropanonitrilo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,13-1,58 (4H), 2,21-2,33 (1H), 2,52 (3H), 2,75 (2H), 2,80-3,16 (2H), 3,44 (2H), 3,59 (1H), 4,27-4,50 (3H), 7,12 (2H), 7,15-7,21 (3H), 7,37-7,44 (3H), 7,73 (2H), 8,46 (1H), 8,51 (1H)

Ejemplo 247: N-(cianometil)-4-metil-2-[(1-{4-[4-(trifluorometil)fenoxi]benzoil} piperidin-4-il)metil]-2H-indazol-5-carboxamida

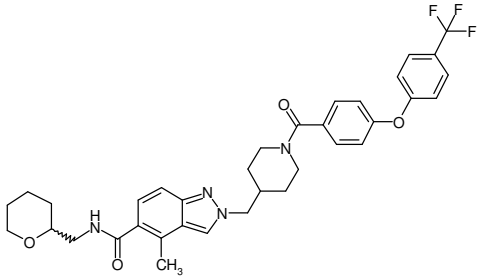


De forma análoga al Ejemplo 1, se obtuvieron 125 mg del compuesto del título a partir de 137 mg del

compuesto preparado en el Ejemplo 245b y 24 mg de clorhidrato de 2-aminoacetonitrilo.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,16-1,60 (4H), 2,23-2,34 (1H), 2,53 (3H), 2,69-3,06 (2H), 3,59 (1H), 4,26 (2H), 4,29-4,50 (3H), 7,08-7,23 (5H), 7,38-7,46 (3H), 7,73 (2H), 8,54 (1H), 8,83 (1H).

Ejemplo 248: (+/-)-4-metil-N-(3,4,5,6-tetrahidro-2H-piran-2-ilmetil)-2-[(1-{4-[4-(trifluorometil)fenoxi]benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida

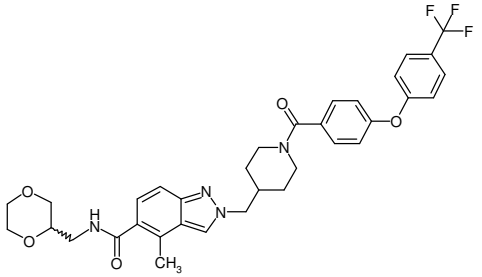


De forma análoga al Ejemplo 1, se obtuvieron 231 mg del compuesto del título a partir de 254 mg del compuesto preparado en el Ejemplo 245b y 72 mg de 3,4,5,6-tetrahidro-2H-piran-2-ilmetil-amina.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,01-1,66 (10H), 2,24-2,32 (1H), 2,70-3,15 (4H), 3,21 (3H), 3,34-3,43 (1H), 3,54-3,64 (1H), 3,76-3,89 (2H), 4,32 (3H), 7,09-7,21 (5H), 7,35-7,44 (3H), 7,73 (2H), 8,09 (1H), 8,47 (1H).

Ejemplo 249: (+/-)-N-(1,4-dioxan-2-ilmetil)-4-metil-2-[(1-{4-[4-(trifluorometil)fenoxi] benzoil}piperidin-4-

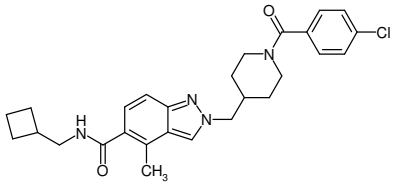
il)metil]-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 280 mg del compuesto del título a partir de 254 mg del compuesto preparado en el Ejemplo 245b y 73 mg de 1,4-dioxan-2-ilmetilamina.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,13-1,61 (4H), 2,23-2,32 (1H), 2,49 (3H), 2,75 (1H), 2,94-3,27 (4H), 3,38-3,77 (8H), 4,32 (2H), 7,09-7,21 (5H), 7,36-7,44 (3H), 7,73 (2H), 8,16 (1H), 8,48 (1H).

Ejemplo 250: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-(ciclobutilmetil)-4-metil-2H-indazol-5-carboxamida

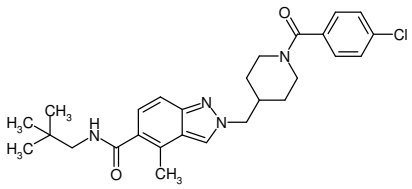


De forma análoga al Ejemplo 1, se obtuvieron 79 mg del compuesto del título a partir de 300 mg del compuesto preparado en el Ejemplo 238c y 115 mg de clorhidrato de ciclobutilmetilamina.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,16-1,58 (4H), 1,64-1,86 (4H), 1,90-2,01 (2H), 2,19-2,32 (1H), 2,48

(3H), 2,50 (1H), 2,66-3,05 (2H), 3,19-3,25 (2H), 3,48 (1H), 4,27-4,47 (3H), 7,12 (1H), 7,31-7,40 (3H), 7,46 (2H), 8,09 (1H), 8,46 (1H).

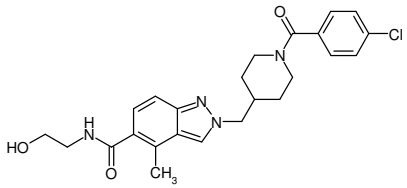
Ejemplo 251: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-(2,2-dimetilpropil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 108 mg del compuesto del título a partir de 300 mg del compuesto preparado en el Ejemplo 238c y 83 mg de 2,2-dimetilpropan-1-amina.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 0,91 (9H), 1,17-1,63 (4H), 2,24-2,36 (1H), 2,52 (3H), 2,70-3,04 (2H), 3,07 (2H), 3,52 (1H), 4,30-4,50 (3H), 7,17 (1H), 7,38 (2H), 7,42 (1H), 7,49 (2H), 8,07 (1H), 8,49 (1H).

Ejemplo 252: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-(2-hidroxietil)-4-metil-2H-indazol-5-carboxamida

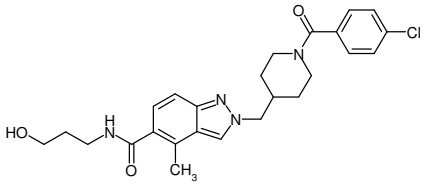


De forma análoga al Ejemplo 1, se obtuvieron 84 mg del compuesto del título a partir de 370 mg del

compuesto preparado en el Ejemplo 238c y 54 mg de 2-aminoetanol.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,14-1,64 (4H), 2,24-2,35 (1H), 2,53 (3H), 2,69-3,09 (2H), 3,30 (2H), 3,43-3,58 (3H), 4,27-4,50 (3H), 4,67 (1H), 7,20 (1H), 7,35-7,43 (3H), 7,49 (2H), 8,02 (1H), 8,49 (1H).

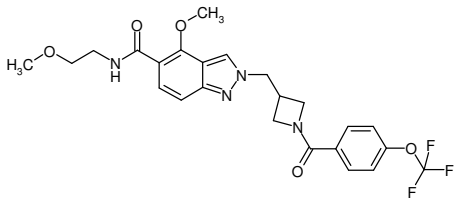
Ejemplo 253: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-(3-hidroxipropil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 95 mg del compuesto del título a partir de 370 mg del compuesto preparado en el Ejemplo 238c y 66 mg de 3-aminopropan-1-ol.

^{1}H-RMN (300 MHz, DMSO-d6): δ = 1,17-1,60 (4H), 1,66 (2H), 2,22-2,35 (1H), 2,53 (3H), 2,70-3,09 (2H), 3,27 (2H), 3,47 (2H), 3,47-3,67 (1H), 4,34 (2H), 4,41 (1H), 4,45 (1H), 7,17 (1H), 7,35-7,43 (3H), 7,49 (2H), 8,07 (1H), 8,49 (1H).

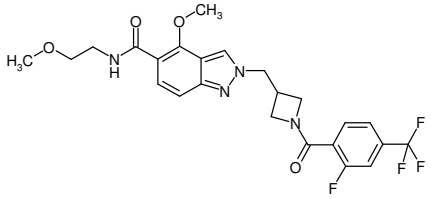
Ejemplo 254: 4-metoxi-N-(2-metoxietil)-2-({1-[4-(trifluorometoxi)benzoil]azetidin-3-il}metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 90 mg del compuesto del título a partir de 100 mg del compuesto preparado en el Ejemplo 214c y 97 mg de ácido 4-(trifluorometoxi)benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 3,24 - 3,29 (1H), 3,29 - 3,32 (3H), 3,43 - 3,51 (4H), 3,91 - 4,04 (1H), 4,10 - 4,18 (1H), 4,20 (3H), 4,22 - 4,29 (1H), 4,44 (1H), 4,70 (2H), 7,24 (1H), 7,37 - 7,51 (2H), 7,66 (1H), 7,70 - 7,80 (2H), 8,22 (1H), 8,91 (1H).

Ejemplo 255: 2-({1-[2-fluoro-4-(trifluorometil)benzoil]azetidin-3-il}metil)-4-metoxi-N-(2-metoxietil)-2H-indazol-5-carboxamida

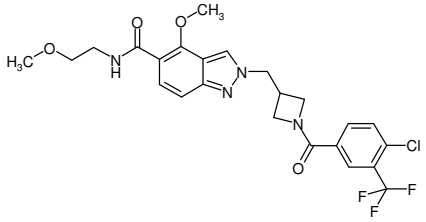


De forma análoga al Ejemplo 1, se obtuvieron 40 mg del compuesto del título a partir de 100 mg del compuesto preparado en el Ejemplo 214c y 98 mg de ácido 2-fluoro-4-(trifluorometil)benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 3,30 (4H), 3,44 - 3,50 (4H), 3,94 - 4,04 (2H), 4,15 (2H), 4,20 (3H), 4,70 (2H), 7,24 (1H), 7,60 - 7,75 (3H), 7,78 -

7,89 (1H), 8,16 - 8,27 (1H), 8,90 (1H).

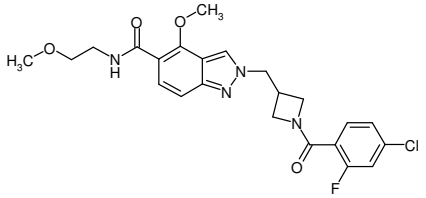
Ejemplo 256: 2-({1-[4-cloro-3-(trifluorometil)benzoil]azetidin-3-il}metil)-4-metoxi-N-(2-metoxietil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1, se obtuvieron 40 mg del compuesto del título a partir de 100 mg del compuesto preparado en el Ejemplo 214c y 106 mg de ácido 4-cloro-3-(trifluorometil)benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 3,30 (4H), 3,43 - 3,53 (4H), 3,95 - 4,05 (1H), 4,20 (4H), 4,23 - 4,31 (1H), 4,47 (1H), 4,71 (2H), 7,23 (1H), 7,67 (1H), 7,78 - 7,85 (1H), 7,86 - 7,93 (1H), 7,96 (1H), 8,22 (1H), 8,90 (1H).

Ejemplo 257: 2-{[1-(4-cloro-2-fluorobenzoil)azetidin-3-il]metil}-4-metoxi-N-(2-metoxietil)-2H-indazol-5-carboxamida

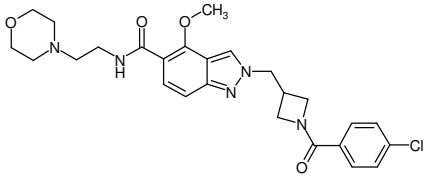


De forma análoga al Ejemplo 1, se obtuvieron 20 mg del compuesto del título a partir de 100 mg del compuesto preparado en el Ejemplo 214c y 82 mg de ácido

4-cloro-2-fluorobenzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 3,30 (4H), 3,42 - 3,51 (4H), 3,98 (2H), 4,14 (2H), 4,20 (3H), 4,69 (2H), 7,24 (1H), 7,38 (1H), 7,48 (1H), 7,56 (1H), 7,66 (1H), 8,15 - 8,30 (1H), 8,90 (1H).

Ejemplo 258: 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-4-metoxi-N-(2-morfolino-etil)-2H-indazol-5-carboxamida

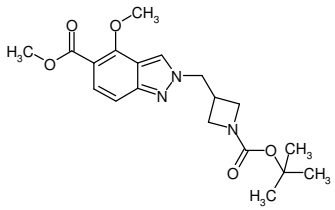


De forma análoga al Ejemplo 1b Versión B, 67 mg del compuesto del título a partir de 66 mg del compuesto preparado en el Ejemplo 258d y 32 mg de 2-morfolinoetilamina en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 2,44 (4H), 3,21 - 3,36 (3H), 3,42 (2H), 3,61 (4H), 3,88 - 4,04 (1H), 4,07 - 4,18 (1H), 4,23 (4H), 4,35 - 4,50 (1H), 4,70 (2H), 7,25 (1H), 7,41 - 7,56 (2H), 7,59 - 7,66 (2H), 7,70 (1H), 8,32 (1H), 8,91 (1H).

El material de partida se preparó de la siguiente manera:

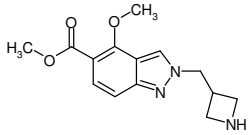
Ejemplo 258a: 2-{[1-(ter-butoxicarbonil)azetidin-3-il]metil}-4-metoxi-2H-indazol-5-carboxilato de metilo



De forma análoga al Ejemplo 1e, 448 mg del compuesto del título a partir de 750 mg del compuesto preparado en el Ejemplo 214a y 546 mg de metanol.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,27 - 1,44 (9H), 3,01 - 3,22 (1H), 3,78 (5H), 3,85 - 3,99 (2H), 4,14 (3H), 4,64 (2H), 7,24 (1H), 7,51 (1H), 8,94 (1H).

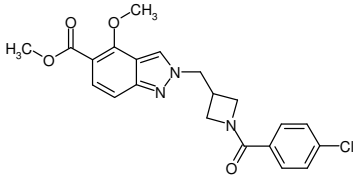
Ejemplo 258b: 2-(azetidin-3-ilmetil)-4-metoxi-2H-indazol-5-carboxilato de metilo



Primero se colocaron 800 mg de 258a en 40 ml de acetona, se trataron con 40 ml de ácido clorhídrico semi concentrado, se agitó hasta una completa conversión y se concentró hasta sequedad. Rendimiento: 414 mg del compuesto del título.

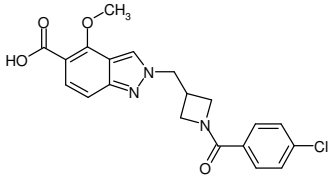
^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 3,39 (1H), 3,79 (3H), 3,84 - 3,95 (2H), 3,96 - 4,07 (2H), 4,15 (3H), 4,72 (2H), 7,25 (1H), 7,52 (1H), 8,92 (1H).

Ejemplo 258c: 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-4-metoxi-2H-indazol-5-carboxilato de metilo



Primero se colocaron 404 mg de 258b en 30 ml de DCM a 0 °C, se trataron con 0,21 ml de cloruro de 4-cloro-benzoílo y 0,75 ml de N-etildiisopropilamina y se agitó a temperatura ambiente hasta la conversión completa. Para la elaboración, la solución de reacción se trató con solución saturada de bicarbonato de sodio, se extrajo con DCM y las fases orgánicas combinadas se secaron con sulfato de sodio y se concentraron hasta sequedad. Esto dio 608 mg del compuesto del título, que se usó en la siguiente etapa sin ulterior purificación.

Ejemplo 258d: ácido 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-4-metoxi-2H-indazol-5-carboxílico

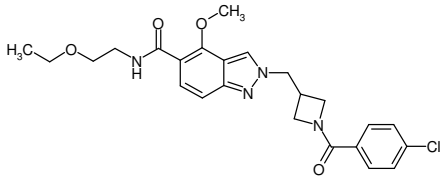


Primero se colocaron 550 mg de 258c en 20 ml de etanol, se trataron con 20 ml de hidróxido de sodio 2 N y se agitaron hasta la conversión completa. Para la elaboración, la solución de reacción se ajustó a un pH de 3 con ácido clorhídrico 1 N, se extrajo con acetato de etilo y las fases orgánicas combinadas se secaron con sulfato de sodio y se concentraron hasta sequedad. Rendimiento después de purificación por cromatografía

en columna en gel de sílice con un gradiente de hexano/ acetato de etilo: 213 mg del compuesto del título.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 3,27 (1H), 3,97 (1H), 4,07 – 4,17 (4H), 4,24 (1H), 4,42 (1H), 4,70 (2H), 7,22 (1H), 7,46 – 7,57 (3H), 7,59 – 7,68 (2H), 8,88 (1H), 12,61 (m, 1H).

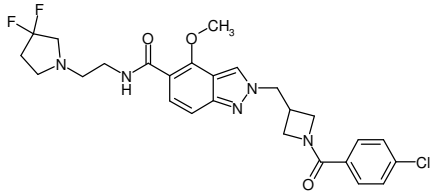
Ejemplo 259: 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-N-(2-etoxietil)-4-metoxi-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b Versión B, se obtuvieron 30 mg del compuesto del título a partir de 66 mg del compuesto preparado en el Ejemplo 258d y 22 mg de 2-etoxietilamina en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,07 – 1,21 (3H), 3,30 (1H), 3,40 – 3,57 (6H), 3,90 – 4,02 (1H), 4,08 – 4,17 (1H), 4,21 (4H), 4,34 – 4,48 (1H), 4,70 (2H), 7,24 (1H), 7,45 – 7,57 (2H), 7,60 – 7,74 (3H), 8,24 (1H), 8,91 (1H).

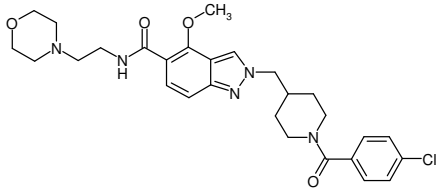
Ejemplo 260: 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-N-[2-(3,3-difluoropirrolidin-1-il)etil]-4-metoxi-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b Versión B, se obtuvieron 58 mg del compuesto del título a partir de 66 mg del compuesto preparado en el Ejemplo 258d y 37 mg de 2-(3,3-difluoropirrolidin-1-il)etil-amina en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 2,27 (2H), 2,64 (2H), 2,77 (2H), 2,96 (2H), 3,22 – 3,30 (1H), 3,41 (2H), 3,92 – 4,01 (1H), 4,11 (1H), 4,19 (4H), 4,35 – 4,48 (1H), 4,70 (2H), 7,24 (1H), 7,51 (2H), 7,57 – 7,75 (3H), 8,32 (1H), 8,90 (1H).

Ejemplo 261: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metoxi-N-(2-morfolino-etil)-2H-indazol-5-carboxamida



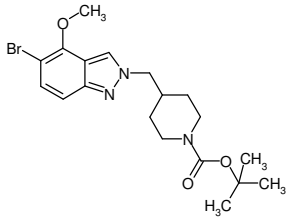
De forma análoga al Ejemplo 1b, Versión B, se obtuvieron se obtuvieron 77 mg del compuesto del título a partir de 100 mg del compuesto preparado en el Ejemplo 261e y 46 mg de 2-morfolinoetilamina en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,11 – 1,33 (2H), 1,35 – 1,75 (2H), 2,18 – 2,39 (1H), 2,65 – 2,88 (2H), 2,90 – 3,23 (3H), 3,41 – 3,82 (8H), 3,84 – 4,12

(2H), 4,24 (3H), 4,35 (3H), 7,26 (1H), 7,33 – 7,44 (2H), 7,46 – 7,58 (2H), 7,69 (1H), 8,27 – 8,52 (1H), 8,87 (1H).

El material de partida se preparó de la siguiente manera:

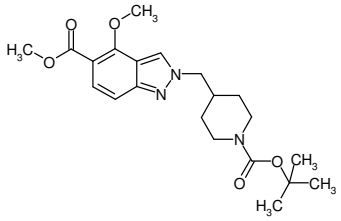
Ejemplo 261a: 4-[(5-bromo-4-metoxi-2H-indazol-2-il)metil]piperidin-1-carboxilato de ter-butilo



De forma análoga al Ejemplo 1c, se obtuvieron 5,57 g del compuesto del título a partir de 9,65 g de 5-bromo-4-metoxi-1H-indazol y 23,55 g de 4-[(tosiloxi)metil]piperidin-1-carboxilato de ter-butilo.

^{1}H-RMN (400 MHz, cloroformo-d): δ [ppm] = 1,16 – 1,31 (2H), 1,39 – 1,49 (9H), 1,52 – 1,64 (2H), 2,16 – 2,36 (1H), 2,56 – 2,80 (2H), 4,11 (5H), 4,26 (2H), 7,28 – 7,33 (1H), 7,34 – 7,39 (1H), 7,99 (1H).

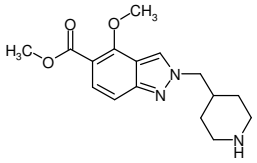
Ejemplo 261b: 2-{[1-(ter-butoxicarbonil)piperidin-4-il]metil}-4-metoxi-2H-indazol-5-carboxilato de metilo



De forma análoga al Ejemplo 1e, se obtuvieron 1,1

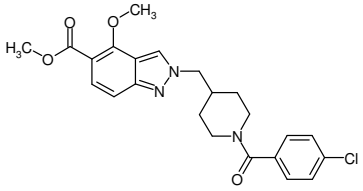
g del compuesto del título a partir de 2,4 g del compuesto preparado en el Ejemplo 261a y 1,63 g de metanol.

Ejemplo 261c: 4-metoxi-2-(4-piperidilmetil)-2H-indazol-5-carboxilato de metilo



De forma análoga al Ejemplo 258b, a partir de 1,1 g del compuesto preparado en el Ejemplo 261b, se obtuvieron 1,1 g del compuesto del título, que se hizo reaccionar en la siguiente etapa sin ulterior purificación.

Ejemplo 261d: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metoxi-2H-indazol-5-carboxilato de metilo

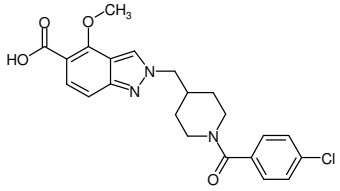


De forma análoga al Ejemplo 258c, a partir de 1,1 g del compuesto preparado en el Ejemplo 261c y 762 mg de cloruro de 4-clorobenzoílo, se obtuvieron 980 mg del compuesto del título después de purificación por cromatografía en columna en gel de sílice con un gradiente de hexano/acetato de etilo.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,24 (2H), 1,36 - 1,76 (2H), 2,18 - 2,40 (1H), 2,65 - 2,88 (1H),

2,91 – 3,12 (1H), 3,42 – 3,67 (1H), 3,78 (3H), 4,05 – 4,21 (3H), 4,35 (3H), 7,24 (1H), 7,34 – 7,43 (2H), 7,45 – 7,56 (3H), 8,86 (1H).

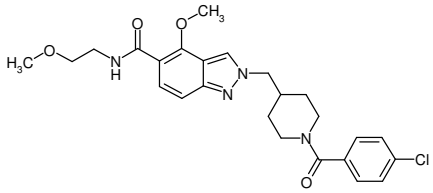
Ejemplo 261e: ácido 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metoxi-2H-indazol-5-carboxílico



De forma análoga al Ejemplo 258d, 547 mg del compuesto del título a partir de 980 mg del compuesto preparado en el Ejemplo 261d.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,12 – 1,35 (2H), 1,35 – 1,73 (2H), 2,21 – 2,40 (1H), 2,63 – 3,12 (2H), 3,14 – 3,70 (3H), 4,34 (3H), 5,76 (s, 1H), 7,21 (1H), 7,32 – 7,45 (2H), 7,46 – 7,58 (3H), 8,76 (1H).

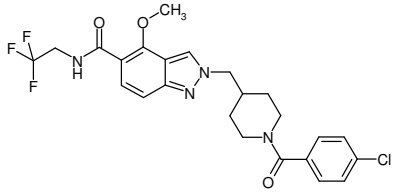
Ejemplo 262: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metoxi-N-(2-metoxietil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 50 mg del compuesto del título a partir de 100 mg del compuesto preparado en el Ejemplo 261e y 26 mg de 2-metoxietilamina en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,11 – 1,35 (2H), 1,35 – 1,72 (2H), 2,21 – 2,39 (1H), 2,69 – 2,88 (1H), 2,92 – 3,11 (1H), 3,30 (s, 3H), 3,38 – 3,64 (5H), 4,20 (3H), 4,34 (3H), 7,25 (1H), 7,34 – 7,43 (2H), 7,45 – 7,57 (2H), 7,66 (1H), 8,22 (1H), 8,83 (1H).

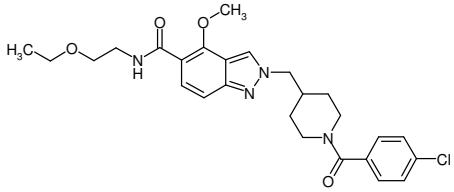
Ejemplo 263: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metoxi-N-(2,2,2-trifluoro-etil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 68 mg del compuesto del título a partir de 100 mg del compuesto preparado en el Ejemplo 261e y 35 mg de 2,2,2-trifluoroetilamina en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,09 – 1,35 (2H), 1,37 – 1,75 (2H), 2,21 – 2,41 (1H), 2,69 – 2,88 (1H), 2,92 – 3,19 (1H), 3,42 – 3,69 (1H), 4,13 (2H), 4,23 (3H), 4,35 (3H), 7,26 (1H), 7,34 – 7,45 (2H), 7,46 – 7,55 (2H), 7,61 (1H), 8,59 (1H), 8,88 (1H).

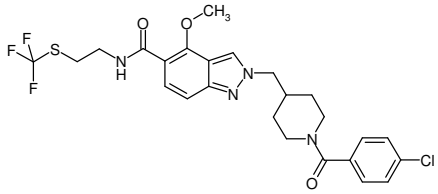
Ejemplo 264: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-(2-etoxietil)-4-metoxi-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 60 mg del compuesto del título a partir de 100 mg del compuesto preparado en el Ejemplo 261e y 31 mg de 2-etoxietilamina en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,14 (3H), 1,19 - 1,35 (2H), 1,37 - 1,72 (2H), 2,23 - 2,43 (1H), 2,68 - 2,88 (1H), 2,91 - 3,15 (1H), 3,41 - 3,56 (m, 7H), 4,20 (3H), 4,34 (3H), 7,25 (1H), 7,33 - 7,45 (2H), 7,46 - 7,55 (2H), 7,67 (1H), 8,23 (1H), 8,83 (1H).

Ejemplo 265: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metoxi-N-{2-[(trifluoro-metil)sulfanil]etil}-2H-indazol-5-carboxamida

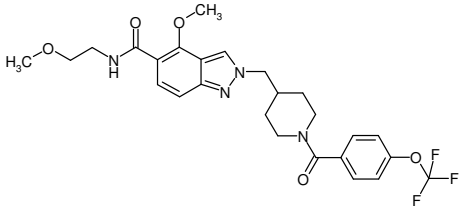


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 68 mg del compuesto del título a partir de 100 mg del compuesto preparado en el Ejemplo 261e y 51 mg de 2-[(trifluorometil)sulfanil]-etilamina en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,14 - 1,35 (2H), 1,36 - 1,72 (2H), 2,18 - 2,40 (1H), 2,66 - 2,87 (1H), 2,91 - 3,11 (1H), 3,21 (2H), 3,42 - 3,70 (3H),

4,22 (3H), 4,34 (3H), 7,24 (1H), 7,32 – 7,45 (2H), 7,46 – 7,55 (2H), 7,64 (1H), 8,45 (1H), 8,85 (1H).

Ejemplo 266: 4-metoxi-N-(2-metoxietil)-2-({1-[4-(trifluorometoxi)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida

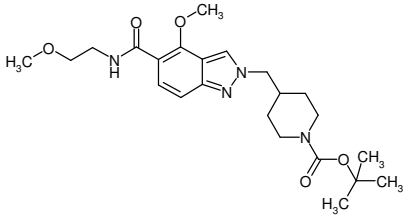


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 84 mg del compuesto del título a partir de 100 mg del compuesto preparado en el Ejemplo 266b y 89 mg de ácido 4-(trifluorometoxi)benzoico en DMF.

LC-MS: R_t = 1,16 min, MS (ES+): m/z = 435 $(M+H)^+$.

El material de partida se preparó de la siguiente manera:

Ejemplo 266a: 4-({4-metoxi-5-[N-(2-metoxietil)carbamoil]-2H-indazol-2-il}metil)piperidin-1-carboxilato de ter-butilo

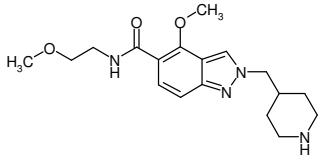


3 g de compuesto 261a, 1,59 g de 2-metoxietilamina, 1,87 g de hexacarbonilo de molibdeno, 204 mg de tetrafluoroborato de tri-ter-butilfosfina y

316 mg de acetato de paladio (II) se suspendieron primero en 100 ml de 1,4-dioxano. A continuación, se añadieron 2,25 g de carbonato de sodio y algunas gotas de agua y la mezcla se agitó durante 25 min a 140°C y 150 watts en el microondas. La mezcla de reacción se concentró y el residuo se purificó por cromatografía en columna en gel de sílice usando un gradiente de hexano/ acetato de etilo/ metanol. Rendimiento: 1,3 g del compuesto del título.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 0,99 - 1,22 (2H), 1,29 - 1,55 (11H), 2,03 - 2,33 (1H), 2,60 - 2,83 (2H), 3,28 - 3,31 (3H), 3,43 - 3,52 (4H), 3,82 - 4,03 (2H), 4,20 (3H), 4,31 (2H), 7,25 (1H), 7,66 (1H), 8,21 (1H), 8,82 (1H).

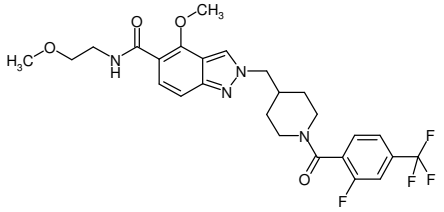
Ejemplo 266b: 4-metoxi-N-(2-metoxietil)-2-(4-piperidilmetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 258b, a partir de 1,3 g del compuesto preparado en el Ejemplo 266a, se obtuvieron 1,48 g del compuesto del título, que se usó en las posteriores reacciones sin ulterior purificación.

Ejemplo 267: 2-({1-[2-fluoro-4-(trifluorometil)benzoil]piperidin-4-il}metil)-4-metoxi-

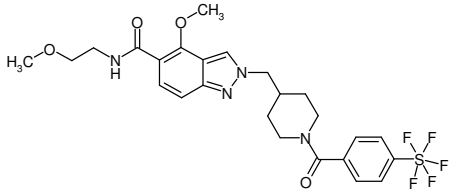
N-(2-metoxietil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 20 mg del compuesto del título a partir de 100 mg del compuesto preparado en el Ejemplo 266b y 90 mg de ácido 2-fluoro-4-(trifluorometil)benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,05 - 1,36 (2H), 1,39 - 1,53 (1H), 1,56 - 1,72 (1H), 2,21 - 2,40 (1H), 2,75 - 2,90 (1H), 2,92 - 3,15 (1H), 3,27 - 3,35 (4H), 3,44 - 3,53 (4H), 4,20 (3H), 4,27 - 4,43 (2H), 4,44 - 4,58 (1H), 7,25 (1H), 7,54 - 7,74 (3H), 7,81 (1H), 8,20 (1H), 8,83 (1H).

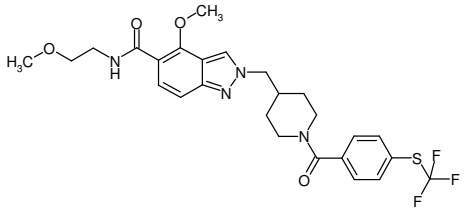
Ejemplo 268: 4-metoxi-N-(2-metoxietil)-2-({1-[4-(pentafluoro-λ^6-sulfanil)benzoil]-piperidin-4-il}metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 39 mg del compuesto del título a partir de 100 mg del compuesto preparado en el Ejemplo 266b y 107 mg de ácido 4-(pentafluoro-λ^6-sulfanil)benzoico en DMF.

LC-MS: R_t = 1,18 min, MS (ES+): m/z = 577 $(M+H)^+$.

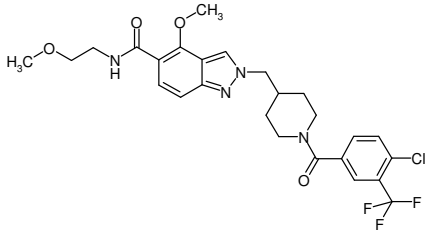
Ejemplo 269: 4-metoxi-N-(2-metoxietil)-2-[(1-{4-[(trifluorometil)sulfanil]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 25 mg del compuesto del título a partir de 100 mg del compuesto preparado en el Ejemplo 266b y 96 mg de ácido 4-[(trifluorometil)sulfanil]benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,09 - 1,37 (2H), 1,38 - 1,72 (2H), 2,23 - 2,39 (1H), 2,70 - 2,93 (1H), 2,95 - 3,16 (1H), 3,30 (3H), 3,40 - 3,55 (5H), 4,20 (3H), 4,35 (d, 3H), 7,25 (1H), 7,46 - 7,58 (2H), 7,66 (1H), 7,78 (2H), 8,20 (1H), 8,82 (1H).

Ejemplo 270: 2-({1-[4-cloro-3-(trifluorometil)benzoil]piperidin-4-il}metil)-4-metoxi-N-(2-metoxietil)-2H-indazol-5-carboxamida

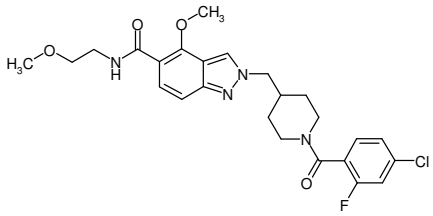


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 27 mg del compuesto del título a partir de

100 mg del compuesto preparado en el Ejemplo 266b y 97 mg de ácido 4-cloro-3-(trifluorometil)benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,15 - 1,37 (2H), 1,38 - 1,73 (2H), 2,14 - 2,41 (1H), 2,70 - 2,88 (1H), 2,95 - 3,18 (1H), 3,30 (3H), 3,39 - 3,62 (5H), 4,20 (3H), 4,35 (3H), 7,25 (1H), 7,59 - 7,73 (2H), 7,75 - 7,86 (2H), 8,20 (1H), 8,82 (1H).

Ejemplo 271: 2-{[1-(4-cloro-2-fluorobenzoil)piperidin-4-il]metil}-4-metoxi-N-(2-metoxietil)-2H-indazol-5-carboxamida

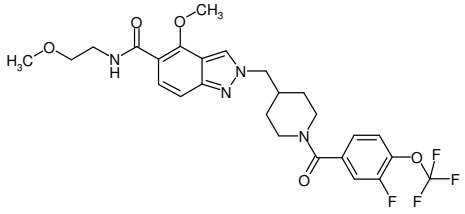


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 17 mg del compuesto del título a partir de 100 mg del compuesto preparado en el Ejemplo 266b y 75 mg de ácido 4-cloro-2-fluorobenzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,08 - 1,33 (2H), 1,37 - 1,52 (1H), 1,53 - 1,70 (1H), 2,20 - 2,42 (1H), 2,72 - 2,88 (1H), 2,94 - 3,12 (1H), 3,30 (3H), 3,37 (1H), 3,43 - 3,51 (4H), 4,20 (3H), 4,34 (2H), 4,42 - 4,55 (1H), 7,25 (1H), 7,31 - 7,48 (2H), 7,55 (1H), 7,66 (1H), 8,20 (1H), 8,83 (1H).

Ejemplo 272: 2-({1-[3-fluoro-4-(trifluorometoxi)benzoil]piperidin-4-il}metil)-4-

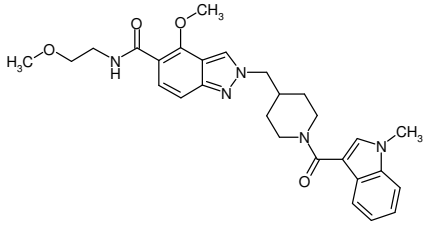
metoxi-N-(2-metoxietil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 12 mg del compuesto del título a partir de 100 mg del compuesto preparado en el Ejemplo 266b y 97 mg de ácido 3-fluoro-4-(trifluorometoxi)benzoico en DMF.

LC-MS: R_t = 1,18 min, MS (ES+): m/z = 553 $(M+H)^+$.

Ejemplo 273: 4-metoxi-N-(2-metoxietil)-2-({1-[(1-metil-1H-indol-3-il)carbonil]-piperidin-4-il}metil)-2H-indazol-5-carboxamida

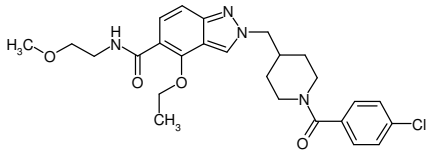


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 19 mg del compuesto del título a partir de 100 mg del compuesto preparado en el Ejemplo 266b y 76 mg de ácido 1-metil-1H-indol-3-carboxílico en DMF.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,11 - 1,40 (2H), 1,54 (2H), 2,18 - 2,42 (1H), 2,93 (2H), 3,30 (3H), 3,40 - 3,45 (4H), 3,70 - 3,91 (3H), 4,12 - 4,48 (7H), 7,00 - 7,34 (3H), 7,48 (1H), 7,66 (3H), 8,22

(1H), 8,84 (1H).

Ejemplo 274: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-etoxi-N-(2-metoxietil)-2H-indazol-5-carboxamida

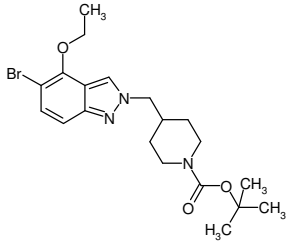


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 47 mg del compuesto del título a partir de 110 mg del compuesto preparado en el Ejemplo 274c y 72 mg de ácido 4-clorobenzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,10 - 1,33 (2H), 1,44 (5H), 2,20 - 2,39 (1H), 2,68 - 2,85 (1H), 2,92 - 3,12 (1H), 3,32 (7H), 3,51 - 3,62 (1H), 4,20 - 4,59 (5H), 7,26 (1H), 7,33 - 7,44 (2H), 7,47 - 7,55 (2H), 7,70 (1H), 8,30 (1H), 8,79 (1H).

El material de partida se preparó de la siguiente manera:

Ejemplo 274a: 4-[(5-bromo-4-etoxi-2H-indazol-2-il)metil]piperidin-1-carboxilato de ter-butilo

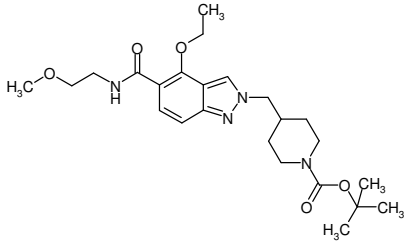


De forma análoga al Ejemplo 74c, se obtuvieron 285 mg del compuesto del título a partir de 484 mg de 5-

bromo-4-etoxi-1H-indazol y 1,11 g de 4-[(5-bromo-4-etoxi-2H-indazol-2-il)-metil]piperidin-1-carboxilato de ter-butilo.

^{1}H-RMN (400 MHz, cloroformo-d): δ [ppm] = 1,13 - 1,34 (2H), 1,46 (9H), 1,49 (3H), 1,56 - 1,63 (2H), 2,16 - 2,37 (1H), 2,54 - 2,80 (2H), 4,02 - 4,21 (2H), 4,26 (2H), 4,33 (2H), 7,28 - 7,43 (2H), 7,93 (1H).

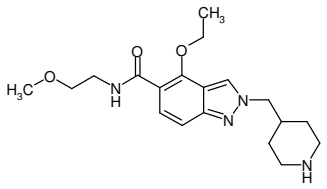
Ejemplo 274b: 4-({4-etoxi-5-[N-(2-metoxietil)carbamoil]-2H-indazol-2-il}-metil)piperidin-1-carboxilato de ter-butilo



De forma análoga al Ejemplo 266a, se obtuvieron 235 mg del compuesto del título a partir de 285 mg del compuesto preparado en el Ejemplo 274a y 146 mg de 2-metoxietilamina.

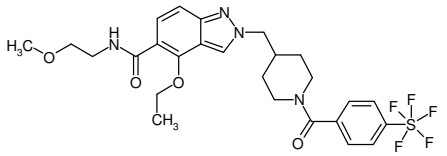
^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 0,97 - 1,22 (2H), 1,29 - 1,56 (14H), 2,06 - 2,31 (1H), 2,59 - 2,86 (2H), 3,33 (3H), 3,49 (4H), 3,80 - 4,02 (2H), 4,30 (2H), 4,51 (2H), 7,26 (1H), 7,71 (1H), 8,31 (1H), 8,79 (1H).

Ejemplo 274c: 4-etoxi-N-(2-metoxietil)-2-(4-piperidilmetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 258b, a partir de 235 mg del compuesto preparado en el Ejemplo 274b, se obtuvieron 237 mg del compuesto del título, que se hizo reaccionar en la siguiente etapa sin ulterior purificación.

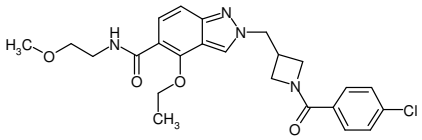
Ejemplo 275: 4-etoxi-N-(2-metoxietil)-2-({1-[4-(pentafluoro-λ^6-sulfanil)benzoil]-piperidin-4-il}metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 30 mg del compuesto del título a partir de 110 mg del compuesto preparado en el Ejemplo 274c y 113 mg de ácido 4-(pentafluoro-λ^6-sulfanil)benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d$_6$): δ [ppm] = 1,10 - 1,36 (2H), 1,44 (4H), 1,54 - 1,69 (1H), 2,22 - 2,40 (1H), 2,70 - 2,87 (1H), 2,93 - 3,13 (1H), 3,30 (3H), 3,48 (5H), 4,34 (2H), 4,41 - 4,63 (3H), 7,26 (1H), 7,59 (2H), 7,70 (1H), 7,98 (2H), 8,30 (1H), 8,79 (1H).

Ejemplo 276: 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-4-etoxi-N-(2-metoxietil)-2H-indazol-5-carboxamida

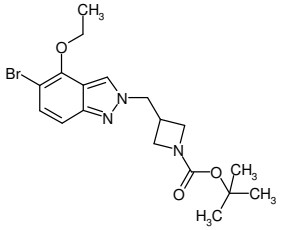


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 25 mg del compuesto del título a partir de 50 mg del compuesto preparado en el Ejemplo 276c y 35 mg de ácido 4-clorobenzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,44 (3H), 3,21 - 3,29 (1H), 3,31 (3H), 3,49 (4H), 3,96 (1H), 4,06 - 4,30 (2H), 4,34 - 4,59 (3H), 4,69 (2H), 7,25 (1H), 7,51 (2H), 7,62 (2H), 7,71 (1H), 8,30 (1H), 8,86 (1H).

El material de partida se preparó de la siguiente manera:

Ejemplo 276a: 3-[(5-bromo-4-etoxi-2H-indazol-2-il)metil]azetidin-1-carboxilato de ter-butilo

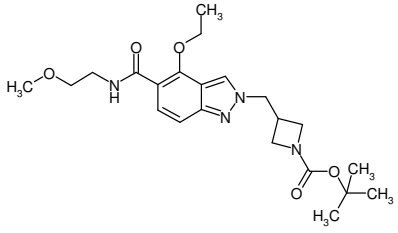


De forma análoga al Ejemplo 74c, se obtuvieron 204 mg del compuesto del título a partir de 500 mg de 5-bromo-4-etoxi-1H-indazol y 1,06 g de 3-[(tosiloxi)metil]azetidin-1-carboxilato de ter-butilo.

^{1}H-RMN (600 MHz, cloroformo-d): δ [ppm] = 1,44 (9H), 1,49 (3H), 3,14 - 3,30 (1H), 3,72 - 3,83 (2H), 4,07 (2H), 4,33 (2H), 4,59 (2H), 7,29 (1H), 7,37 (1H),

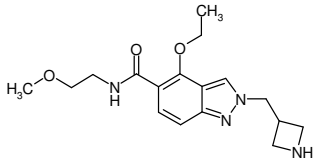
7,98 (1H).

Ejemplo 276b: 3-({4-etoxi-5-[N-(2-metoxietil)carbamoil]-2H-indazol-2-il}-metil)azetidin-1-carboxilato de ter-butilo



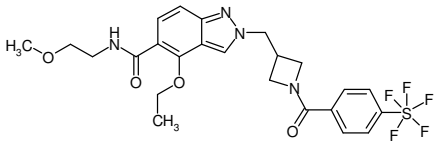
De forma análoga al Ejemplo 266a, se obtuvieron de 191 mg del compuesto preparado en el Ejemplo 276a y 105 mg de 2-metoxietilamina, 121 mg del compuesto del título, que se hizo reaccionar en la siguiente etapa sin ulterior purificación.

Ejemplo 276c: 2-(azetidin-3-ilmetil)-4-etoxi-N-(2-metoxietil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 258b, a partir de 121 mg del compuesto preparado en el Ejemplo 276b, se obtuvieron 93 mg del compuesto del título, que se hizo reaccionar en la siguiente etapa sin ulterior purificación.

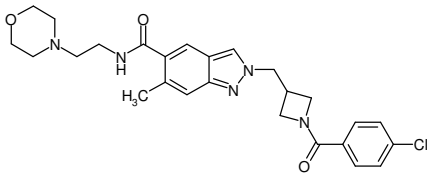
Ejemplo 277: 4-etoxi-N-(2-metoxietil)-2-({1-[4-(pentafluoro-λ^6-sulfanil)benzoil]-azetidin-3-il}metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 35 mg del compuesto del título a partir de 50 mg de 276c y 56 mg de ácido 4-(pentafluoro-λ⁶-sulfanil)benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,37 - 1,50 (3H), 3,26 (1H), 3,31 (3H), 3,43 - 3,57 (4H), 3,92 - 4,05 (1H), 4,10 - 4,31 (2H), 4,38 - 4,57 (3H), 4,70 (2H), 7,25 (1H), 7,66 - 7,87 (3H), 7,98 (2H), 8,30 (1H), 8,86 (1H).

Ejemplo 278: 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-6-metil-N-(2-morfolinoetil)-2H-indazol-5-carboxamida



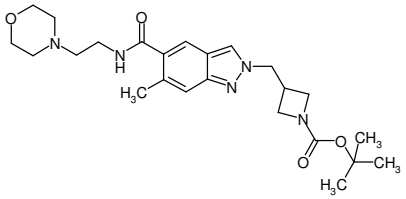
De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 23 mg del compuesto del título a partir de 100 mg de 278b y 66 mg de ácido 4-clorobenzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 2,42 (s, 3H), 3,09 - 3,27 (m, 3H), 3,29 - 3,33 (2H), 3,49 - 3,73 (m, 6H), 3,84 - 3,96 (m, 1H), 3,97 - 4,15 (m, 3H), 4,16 - 4,27 (m, 1H), 4,31 - 4,45 (m, 1H), 4,62 - 4,80 (m, 2H), 7,36 - 7,47 (1H), 7,48 - 7,57 (2H), 7,58 - 7,70 (2H),

7,77 – 7,89 (1H), 8,41 – 8,58 (2H).

El material de partida se preparó de la siguiente manera:

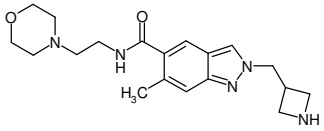
Ejemplo 278a: 3-({6-metil-5-[N-(2-morfolinoetil)carbamoil]-2H-indazol-2-il}metil)azetidin-1-carboxilato de ter-butilo



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 418 mg del compuesto del título a partir de 410 mg de 178c y 232 mg de 2-morfolinoetilamina en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,36 (9H), 2,39 (3H), 2,44 (4H), 2,95 – 3,17 (1H), 3,24 – 3,43 (4H), 3,58 (4H), 3,64 – 3,79 (2H), 3,88 (2H), 4,62 (2H), 7,39 (1H), 7,68 (1H), 8,04 – 8,22 (1H), 8,45 (1H).

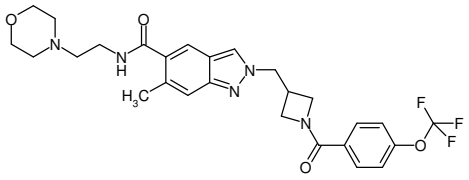
Ejemplo 278b: 2-(azetidin-3-ilmetil)-6-metil-N-(2-morfolinoetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 258b, a partir de 400 mg del compuesto preparado en el Ejemplo 278a, se obtuvieron 372 mg del compuesto del título, que se hizo reaccionar en la siguiente etapa sin ulterior

purificación.

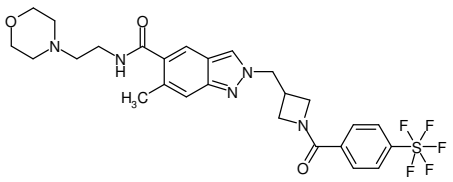
Ejemplo 279: 6-metil-N-(2-morfolinoetil)-2-({1-[4-(trifluorometoxi)benzoil]azetidin-3-il}metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 44 mg del compuesto del título a partir de 100 mg de 278b y 86 mg de ácido 4-(trifluorometoxi)benzoico en DMF.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 2,42 (3H), 3,07 - 3,27 (5H), 3,48 - 3,74 (6H), 3,85 - 4,17 (4H), 4,18 - 4,29 (1H), 4,33 - 4,48 (1H), 4,61 - 4,82 (2H), 7,30 - 7,54 (3H), 7,68 - 7,78 (2H), 7,79 - 7,88 (1H), 8,43 - 8,60 (2H).

Ejemplo 280: 6-metil-N-(2-morfolinoetil)-2-({1-[4-(pentafluoro-λ^6-sulfanil)benzoil]-azetidin-3-il}metil)-2H-indazol-5-carboxamida

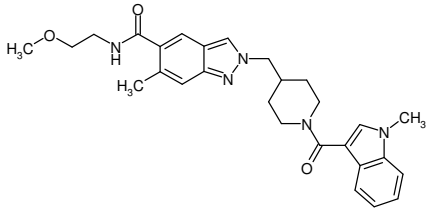


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 37 mg del compuesto del título a partir de

100 mg de 278b y 104 mg de ácido 4-(pentafluoro-λ^6-sulfanil)benzoico en DMF.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 2,42 (3H), 3,06 - 3,27 (5H), 3,47 - 3,75 (6H), 3,87 - 4,08 (3H), 4,09 - 4,29 (2H), 4,33 - 4,49 (1H), 4,61 - 4,80 (2H), 7,34 - 7,52 (1H), 7,71 - 7,88 (3H), 7,92 - 8,07 (2H), 8,39 - 8,59 (2H).

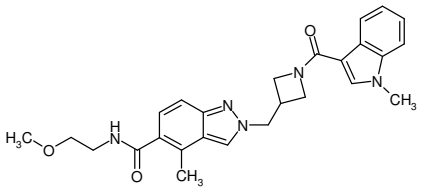
Ejemplo 281: N-(2-metoxietil)-6-metil-2-({1-[(1-metil-1H-indol-3-il)carbonil]-piperidin-4-il}metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 4,2 mg del compuesto del título a partir de 150 mg de 205c y 119 mg de ácido 1-metil-1H-indol-3-carboxílico en DMF.

LC-MS: R_t = 1,01 min, MS (ES+): m/z = 489 $(M+H)^+$.

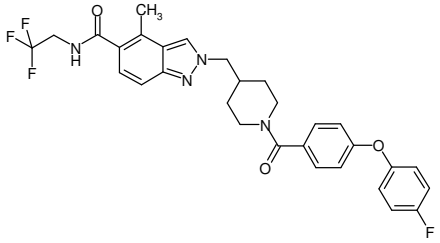
Ejemplo 282: N-(2-metoxietil)-4-metil-2-({1-[(1-metil-1H-indol-3-il)carbonil]azetidin-3-il}metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 35 mg del compuesto del título a partir de 175 mg de 117e y 122 mg de ácido 1-metil-1H-indol-3-carboxílico en DMF.

LC-MS: R_t = 0,95 min, MS (ES+): m/z = 460 $(M+H)^+$.

Ejemplo 283: 2-({1-[4-(4-fluorofenoxi)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

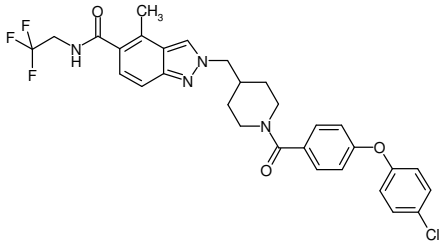


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 267 mg del compuesto del título a partir de 250 mg de 71a y 246 mg de ácido 4-(4-fluorofenoxi)benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,16 - 1,32 (2H), 1,35 - 1,69 (2H), 2,20 - 2,39 (1H), 2,54 (3H), 2,70 - 3,15 (2H), 3,50 - 3,83 (1H), 4,07 (2H), 4,36 (3H), 6,91 - 7,05 (2H), 7,08 - 7,31 (5H), 7,34 - 7,42 (2H), 7,46 (1H), 8,56 (1H), 8,83 (1H).

Ejemplo 284: 2-({1-[4-(4-clorofenoxi)benzoil]piperidin-

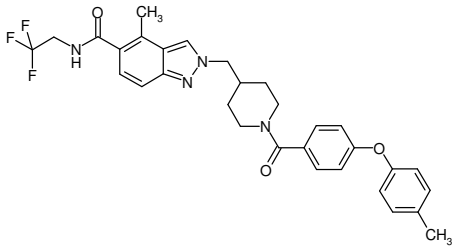
4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 55 mg del compuesto del título a partir de 100 mg de 71a y 105 mg de 4-(4-clorofenoxi)benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,23 (2H), 1,34 - 1,72 (2H), 2,21 - 2,41 (1H), 2,54 (3H), 2,67 - 3,20 (2H), 3,51 - 3,83 (1H), 4,07 (2H), 4,36 (3H), 6,92 - 7,15 (4H), 7,20 (1H), 7,35 - 7,53 (5H), 8,56 (1H), 8,84 (1H).

Ejemplo 285: 4-metil-2-({1-[4-(4-metilfenoxi)benzoil]piperidin-4-il}metil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

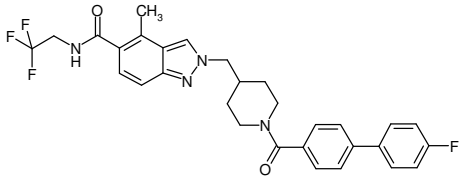


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 60 mg del compuesto del título a partir de 100 mg de 71a y 97 mg de ácido 4-(4-

metilfenoxi)benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,23 (2H), 1,36 – 1,71 (2H), 2,30 (4H), 2,54 (3H), 2,64 – 3,17 (2H), 3,49 – 3,82 (1H), 4,07 (2H), 4,36 (3H), 6,85 – 7,04 (4H), 7,21 (3H), 7,29 – 7,41 (2H), 7,46 (1H), 8,56 (1H), 8,84 (s1H).

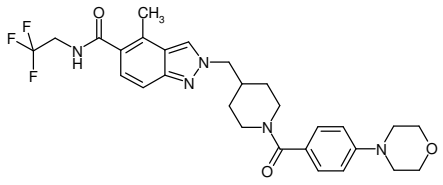
Ejemplo 286: 2-({1-[(4'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 39 mg del compuesto del título a partir de 100 mg de 71a y 92 mg de ácido 4-(4-fluorofenil)benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,14 – 1,36 (2H), 1,36 – 1,73 (2H), 2,18 – 2,41 (1H), 2,54 (3H), 2,70 – 3,16 (2H), 3,51 – 3,82 (1H), 4,07 (2H), 4,38 (3H), 7,21 (1H), 7,31 (2H), 7,40 – 7,53 (3H), 7,64 – 7,85 (4H), 8,56 (1H), 8,81 (1H).

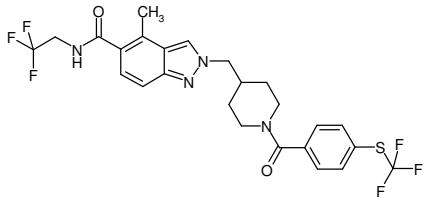
Ejemplo 287: 4-metil-2-{[1-(4-morfolinobenzoil)piperidin-4-il]metil}-N-(2,2,2-trifluoro-etil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 45 mg del compuesto del título a partir de 100 mg de 71a y 88 mg de ácido 4-morfolinobenzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,24 (2H), 1,40 - 1,60 (2H), 2,20 - 2,40 (1H), 2,54 (3H), 2,73 - 3,01 (2H), 3,38 (4H), 3,64 - 3,81 (5H), 4,07 (3H), 4,36 (2H), 6,94 (2H), 7,16 - 7,30 (3H), 7,46 (1H), 8,55 (1H), 8,81 (1H).

Ejemplo 288: 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{4-[(trifluorometil)sulfanil]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida

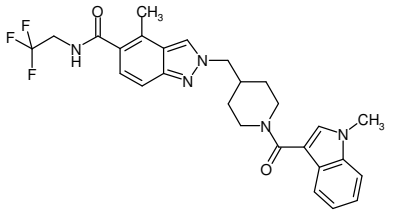


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 67 mg del compuesto del título a partir de 100 mg de 71a y 94 mg de ácido 4-[(trifluorometil)sulfanil]benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,12 - 1,35 (2H), 1,35 - 1,70 (2H), 2,21 - 2,40 (1H), 2,54 (3H), 2,70 - 2,88 (1H), 2,94 - 3,12 (1H), 3,38 - 3,61 (1H),

4,07 (2H), 4,36 (3H), 7,21 (1H), 7,37 – 7,60 (3H), 7,78 (2H), 8,55 (1H), 8,81 (1H).

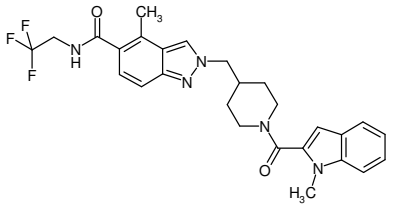
Ejemplo 289: 4-metil-2-({1-[(1-metil-1H-indol-3-il)carbonil]piperidin-4-il}metil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 43 mg del compuesto del título a partir de 100 mg de 71a y 74 mg de ácido 1-metil-1H-indol-3-carboxílico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,27 (2H), 1,52 (2H), 2,20 – 2,40 (1H), 2,54 (3H), 2,92 (2H), 3,82 (3H), 4,07 (2H), 4,27 (2H), 4,38 (2H), 6,92 – 7,33 (3H), 7,47 (2H), 7,61 – 7,76 (2H), 8,56 (1H), 8,81 (1H).

Ejemplo 290: 4-metil-2-({1-[(1-metil-1H-indol-2-il)carbonil]piperidin-4-il}metil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

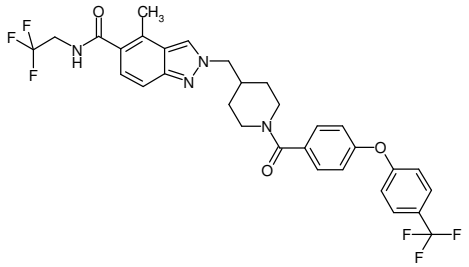


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 51 mg del compuesto del título a partir de

100 mg de 71a y 74 mg de ácido 1-metil-1H-indol-2-carboxílico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,17 - 1,41 (2H), 1,43 - 1,73 (2H), 2,19 - 2,43 (1H), 2,54 (3H), 2,74 - 3,23 (2H), 3,73 (3H), 4,07 (3H), 4,39 (3H), 6,60 (s, 1H), 7,03 - 7,14 (1H), 7,16 - 7,30 (2H), 7,48 (2H), 7,59 (1H), 8,57 (1H), 8,81 (1H).

Ejemplo 291: 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{4-[4-(trifluorometil)fenoxi]-benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida

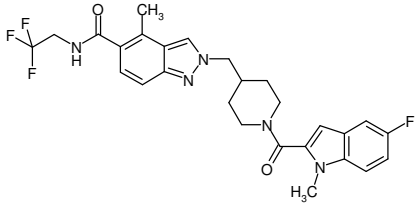


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 156 mg del compuesto del título de 150 mg de 71a y 179 mg de ácido 4-[4-(trifluorometil)fenoxi]benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,23 (2H), 1,36 - 1,68 (2H), 2,20 - 2,43 (1H), 2,54 (3H), 2,68 - 3,17 (2H), 3,50 - 3,79 (1H), 4,07 (2H), 4,37 (3H), 7,09 - 7,28 (5H), 7,35 - 7,51 (3H), 7,76 (2H), 8,56 (1H), 8,83 (1H).

Ejemplo 292: 2-({1-[(5-fluoro-1-metil-1H-indol-2-il)carbonil]piperidin-4-il}metil)-4-metil-N-(2,2,2-

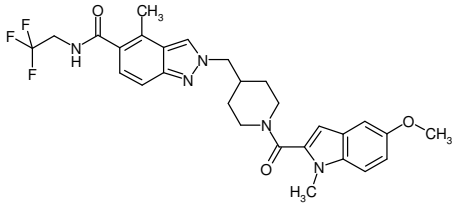
trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 28 mg del compuesto del título a partir de 100 mg de 71a y 82 mg de ácido 5-fluoro-1-metil-1H-indol-2-carboxílico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,18 - 1,38 (2H), 1,39 - 1,72 (2H), 2,25 - 2,42 (1H), 2,54 (3H), 2,74 - 3,25 (2H), 3,73 (3H), 4,07 (3H), 4,38 (3H), 6,58 (1H), 7,09 (1H), 7,21 (1H), 7,36 (1H), 7,47 (2H), 8,57 (1H), 8,83 (1H).

Ejemplo 293: 2-({1-[(5-metoxi-1-metil-1H-indol-2-il)carbonil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

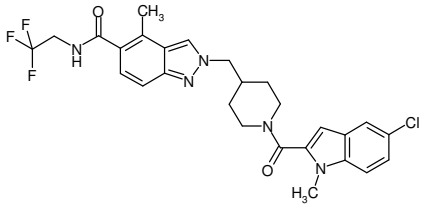


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 37 mg del compuesto del título a partir de 100 mg de 71a y 87 mg de ácido 5-metoxi-1-metil-1H-indol-2-carboxílico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,30 (2H), 1,41 - 1,71 (2H), 2,26 - 2,43 (1H), 2,54 (3H), 2,71 -

3,22 (2H), 3,69 (3H), 3,75 (3H), 4,07 (3H), 4,39 (3H), 6,51 (1H), 6,88 (1H), 7,07 (1H), 7,21 (1H), 7,34 – 7,54 (2H), 8,57 (1H), 8,83 (1H).

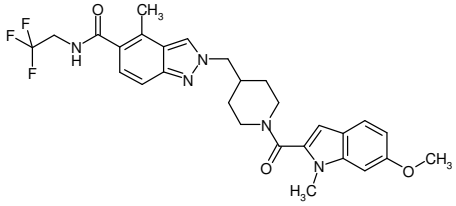
Ejemplo 294: 2-({1-[(5-cloro-1-metil-1H-indol-2-il)carbonil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 43 mg del compuesto del título a partir de 100 mg de 71a y 89 mg de ácido 5-cloro-1-metil-1H-indol-2-carboxílico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,29 (2H), 1,38 – 1,72 (2H), 2,26 – 2,43 (1H), 2,54 (3H), 2,71 – 3,21 (2H), 3,73 (3H), 3,84 – 4,18 (3H), 4,38 (3H), 6,59 (1H), 7,15 – 7,28 (2H), 7,47 (1H), 7,55 (1H), 7,65 (1H), 8,57 (1H), 8,83 (1H).

Ejemplo 295: 2-({1-[(6-metoxi-1-metil-1H-indol-2-il)carbonil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

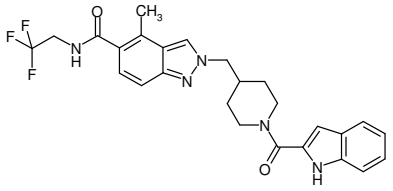


De forma análoga al Ejemplo 1b, Versión B, se

obtuvieron 36 mg del compuesto del título a partir de 100 mg de 71a y 87 mg de ácido 6-metoxi-1-metil-1H-indol-2-carboxílico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,28 (2H), 1,52 (2H), 2,25 - 2,43 (1H), 2,54 (3H), 2,78 - 3,16 (2H), 3,70 (3H), 3,82 (3H), 3,97 - 4,63 (6H), 6,54 (1H), 6,73 (1H), 7,01 (1H), 7,21 (1H), 7,39 - 7,53 (2H), 8,57 (1H), 8,83 (t1H).

Ejemplo 296: 2-{[1-(1H-Indol-2-ilcarbonil)piperidin-4-il]metil}-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

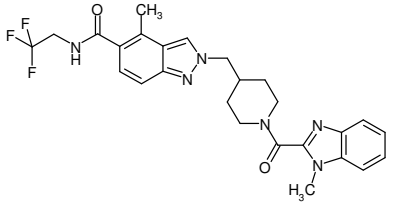


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 43 mg del compuesto del título a partir de 100 mg de 71a y 68 mg de ácido indol-2-carboxílico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,16 - 1,40 (2H), 1,58 (2H), 2,27 - 2,44 (1H), 2,55 (3H), 2,77 - 3,24 (2H), 4,07 (2H), 4,30 - 4,59 (4H), 6,74 (1H), 6,95 - 7,08 (1H), 7,10 - 7,26 (2H), 7,40 (1H), 7,48 (1H), 7,59 (1H), 8,58 (1H), 8,84 (1H), 11,54 (1H).

Ejemplo 297: 4-metil-2-({1-[(1-metil-1H-benzimidazol-2-il)carbonil]piperidin-4-il}-metil)-N-(2,2,2-

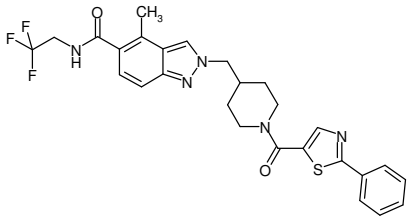
trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 26 mg del compuesto del título a partir de 100 mg de 71a y 75 mg de ácido 1-metil-1H-benzimidazol-2-carboxílico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,17 - 1,42 (2H), 1,46 (1H), 1,57 - 1,75 (1H), 2,27 - 2,44 (1H), 2,54 (3H), 2,87 (1H), 3,11 (1H), 3,83 (3H), 4,07 (3H), 4,40 (2H), 4,48 - 4,62 (1H), 7,13 - 7,41 (3H), 7,47 (1H), 7,58 - 7,76 (2H), 8,58 (1H), 8,83 (1H).

Ejemplo 298: 4-metil-2-({1-[(2-feniltiazol-5-il)carbonil]piperidin-4-il}metil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

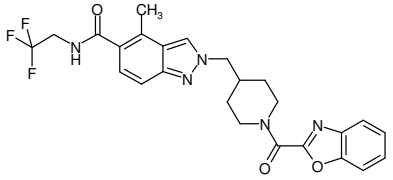


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 53 mg del compuesto del título a partir de 100 mg de 71a y 87 mg de ácido 2-feniltiazol-5-carboxílico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,18 - 1,41

(2H), 1,56 (2H), 2,27 – 2,44 (1H), 2,54 (3H), 2,73 – 3,29 (2H), 3,93 – 4,53 (6H), 7,21 (1H), 7,42 – 7,61 (4H), 7,93 – 8,03 (2H), 8,14 (1H), 8,57 (1H), 8,83 (1H).

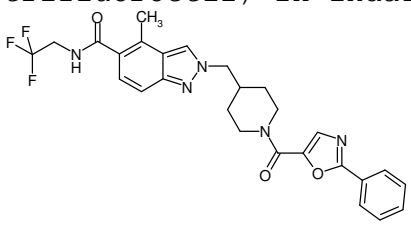
Ejemplo 299: 2-{[1-(benzoxazol-2-ilcarbonil)piperidin-4-il]metil}-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 20 mg del compuesto del título a partir de 100 mg de 71a y 69 mg de ácido benzoxazol-2-carboxílico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,19 – 1,44 (2H), 1,48 – 1,72 (2H), 2,29 – 2,46 (1H), 2,54 (3H), 2,82 – 3,01 (1H), 3,12 – 3,31 (1H), 4,07 (2H), 4,40 (4H), 7,21 (1H), 7,42 – 7,61 (3H), 7,78 – 7,95 (2H), 8,58 (1H), 8,83 (1H).

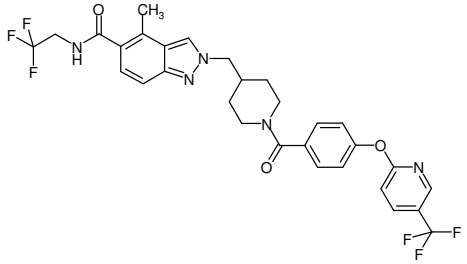
Ejemplo 300: 4-metil-2-({1-[(2-feniloxazol-5-il)carbonil]piperidin-4-il}metil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 20 mg del compuesto del título a partir de 100 mg de 71a y 80 mg de ácido 2-feniloxazol-5-carboxílico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,15 - 1,43 (2H), 1,59 (2H), 2,31 - 2,45 (1H), 2,55 (3H), 2,70 - 3,35 (2H), 4,07 (2H), 4,39 (4H), 7,21 (1H), 7,48 (1H), 7,53 - 7,67 (3H), 7,80 (1H), 7,94 - 8,07 (2H), 8,58 (1H), 8,83 (1H).

Ejemplo 301: 4-metil-N-(2,2,2-trifluoroetil)-2-{[1-(4-{[5-(trifluorometil)piridin-2-il]-oxi}benzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida

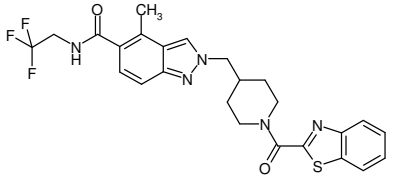


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 23 mg del compuesto del título a partir de 75 mg de 71a y 90 mg de ácido 4-{[5-(trifluorometil)piridin-2-il]oxi}benzoico en DMF.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,13 - 1,35 (2H), 1,37 - 1,72 (2H), 2,19 - 2,42 (1H), 2,54 (3H), 2,69 - 3,17 (2H), 3,55 - 3,82 (1H), 3,91 - 4,18 (2H), 4,26 - 4,60 (3H), 7,28 (4H), 7,38 - 7,56 (3H), 8,16 -

8,33 (1H), 8,49 - 8,63 (2H), 8,75 - 8,91 (1H).

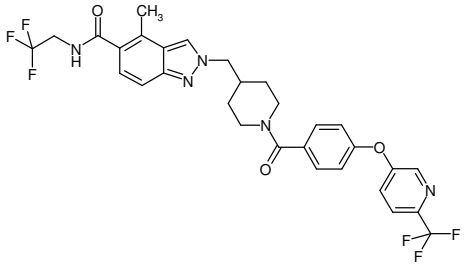
Ejemplo 302: 2-{[1-(benzotiazol-2-ilcarbonil)piperidin-4-il]metil}-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 35 mg del compuesto del título a partir de 75 mg de 71a y 57 mg de ácido benzotiazol-2-carboxílico en DMF.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,36 (2H), 1,59 (2H), 2,31 - 2,46 (1H), 2,55 (3H), 2,91 (1H), 3,26 (1H), 4,07 (2H), 4,31 - 4,61 (3H), 4,95 - 5,23 (1H), 7,21 (1H), 7,41 - 7,69 (3H), 8,05 - 8,28 (2H), 8,58 (1H), 8,83 (1H).

Ejemplo 303: 4-metil-N-(2,2,2-trifluoroetil)-2-{[1-(4-{[6-(trifluorometil)piridin-3-il]-oxi}benzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida



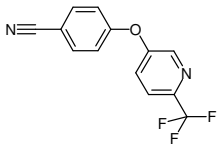
De forma análoga al Ejemplo 1b, Versión B, se

obtuvieron 42 mg del compuesto del título a partir de 75 mg de 71a y 90 mg del ácido carboxílico preparado en el Ejemplo 303b) en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,16 – 1,33 (2H), 1,34 – 1,67 (2H), 2,21 – 2,39 (1H), 2,54 (3H), 2,68 – 3,16 (2H), 3,52 – 3,76 (1H), 3,95 – 4,16 (2H), 4,28 – 4,61 (3H), 7,13 – 7,31 (3H), 7,46 (3H), 7,59 – 7,71 (1H), 7,92 (1H), 8,52 – 8,65 (2H), 8,84 (1H).

El material de partida se preparó de la siguiente manera:

Ejemplo 303a: 4-{[6-(trifluorometil)piridin-3-il]oxi}benzonitrilo

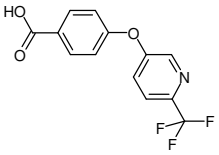


2,5 g de 5-bromo-2-(trifluorometil)piridina, 5,8 g de 4-hidroxibenzonitrilo, 10,8 g de carbonato de cesio y 1,87 g de hexacarbonilmolibdeno en 100 ml de 1,4-dioxano se calentaron a reflujo hasta la conversión completa. La mezcla de reacción se diluyó con agua, se extrajo varias veces con acetato de etilo y las fases orgánicas combinadas se lavaron con solución saturada de cloruro de sodio, se secaron sobre sulfato de sodio y se concentraron. El residuo se purificó por cromatografía en columna en gel de sílice usando un gradiente de hexano/ acetato de etilo. Rendimiento:

1,35 g del compuesto del título.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 7,35 (2H), 7,75 - 7,84 (1H), 7,89 - 8,03 (3H), 8,66 (1H).

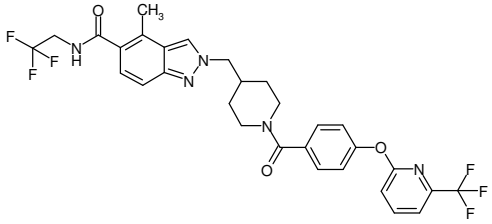
Ejemplo 303b: ácido 4-{[6-(trifluorometil)piridin-2-il]oxi}benzoico



1,33 g del compuesto preparado en el Ejemplo 303a en 64 ml de etanol se trataron con 32 ml de solución al 40% de hidróxido de potasio y se calentó a reflujo hasta la conversión completa. La mezcla de reacción se diluyó con agua y se extrajo con acetato de etilo. La fase orgánica se lavó con solución saturada de cloruro de sodio, se secó sobre sulfato de sodio y se concentró. Rendimiento: 1,32 g del compuesto del título.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 7,19 - 7,33 (2H), 7,68 - 7,81 (1H), 7,90 - 8,08 (3H), 8,64 (1H), 12,71 - 13,28 (1H).

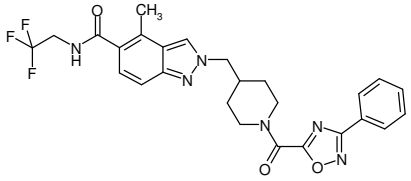
Ejemplo 304: 4-metil-N-(2,2,2-trifluoroetil)-2-{[1-(4-{[6-(trifluorometil)piridin-2-il]-oxi}benzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 48 mg del compuesto del título a partir de 75 mg de 71a y 90 mg de ácido 4-{[6-(trifluorometil)piridin-2-il]oxi}benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,15 - 1,34 (2H), 1,35 - 1,71 (2H), 2,23 - 2,41 (1H), 2,54 (3H), 2,67 - 3,17 (2H), 3,51 - 3,77 (1H), 3,97 - 4,18 (2H), 4,22 - 4,65 (3H), 7,13 - 7,31 (3H), 7,37 (1H), 7,41 - 7,53 (3H), 7,67 (1H), 8,07 - 8,20 (1H), 8,57 (1H), 8,75 - 8,92 (1H).

Ejemplo 305: 4-metil-2-({1-[(3-fenil-1,2,4-oxadiazol-5-il)carbonil]piperidin-4-il}metil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

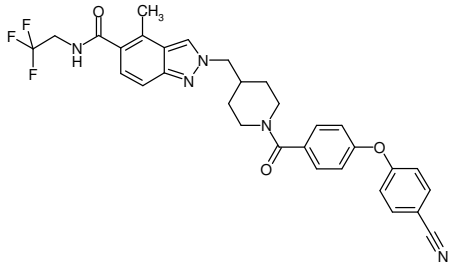


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 40 mg del compuesto del título a partir de 90 mg de 71a y 73 mg de ácido 3-fenil-1,2,4-oxadiazol-5-carboxílico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,18 - 1,43 (2H), 1,48 - 1,72 (2H), 2,33 - 2,47 (1H), 2,54 (3H),

2,95 (1H), 3,24 (1H), 3,94 – 4,17 (3H), 4,33 – 4,53 (3H), 7,21 (1H), 7,47 (1H), 7,55 – 7,70 (3H), 7,96 – 8,12 (2H), 8,57 (1H), 8,83 (1H).

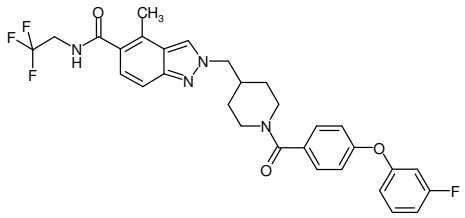
Ejemplo 306: 2-({1-[4-(4-cianofenoxi)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 59 mg del compuesto del título a partir de 110 mg de 71a y 101 mg de ácido 4-(4-cianofenoxi)benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,17 – 1,34 (2H), 1,35 – 1,70 (2H), 2,18 – 2,41 (1H), 2,54 (3H), 2,70 – 3,18 (2H), 3,54 – 3,79 (1H), 4,07 (2H), 4,37 (3H), 7,10 – 7,28 (5H), 7,41 – 7,52 (3H), 7,79 – 7,94 (2H), 8,56 (s1H), 8,81 (s1H).

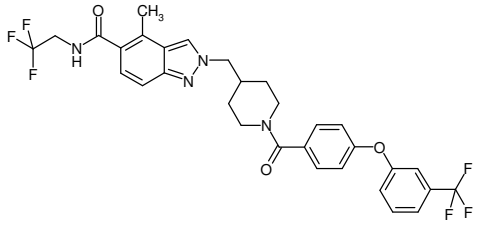
Ejemplo 307: 2-({1-[4-(3-fluorofenoxi)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 40 mg del compuesto del título a partir de 100 mg de 71a y 89 mg de ácido 4-(3-fluorofenoxi)benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,14 - 1,34 (2H), 1,36 - 1,70 (2H), 2,22 - 2,44 (1H), 2,54 (3H), 2,70 - 3,13 (2H), 3,52 - 3,86 (1H), 4,07 (2H), 4,37 (3H), 6,79 - 7,12 (5H), 7,21 (1H), 7,35 - 7,52 (4H), 8,55 (1H), 8,81 (1H).

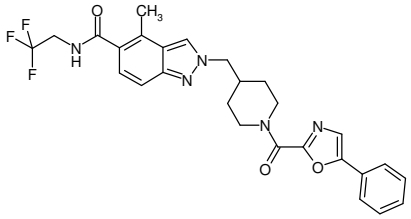
Ejemplo 308: 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{4-[3-(trifluorometil)fenoxi]-benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 47 mg del compuesto del título a partir de 100 mg de 71a y 119 mg de ácido 4-[3-(trifluorometil)fenoxi]benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,16 - 1,34 (2H), 1,37 - 1,66 (2H), 2,22 - 2,38 (1H), 2,54 (3H), 2,69 - 3,14 (2H), 3,50 - 3,83 (1H), 4,07 (2H), 4,37 (3H), 7,10 (2H), 7,21 (1H), 7,36 (1H), 7,39 - 7,50 (4H), 7,54 (1H), 7,61 - 7,75 (1H), 8,55 (1H), 8,81 (1H).

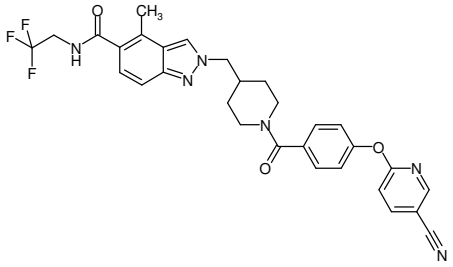
Ejemplo 309: 4-metil-2-({1-[(5-feniloxazol-2-il)carbonil]piperidin-4-il}metil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 10 mg del compuesto del título a partir de 100 mg de 71a y 73 mg de ácido 5-feniloxazol-2-carboxílico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,24 (2H), 1,58 (2H), 2,29 – 2,45 (1H), 2,55 (3H), 2,86 (1H), 3,21 (1H), 4,07 (2H), 4,31 – 4,52 (3H), 4,62 (1H), 7,21 (1H), 7,39 – 7,57 (4H), 7,74 – 7,83 (2H), 7,88 (1H), 8,57 (1H), 8,81 (1H).

Ejemplo 310: 2-[(1-{4-[(5-cianopiridin-2-il)oxi]benzoil}piperidin-4-il)metil]-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

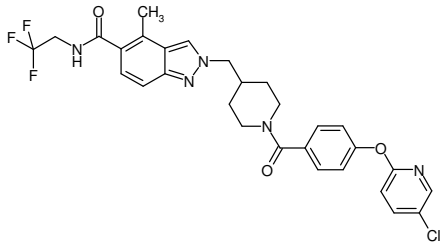


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 47 mg del compuesto del título a partir de 100 mg de 71a y 119 mg de ácido 4-[3-

(trifluorometil)fenoxi]benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,16 - 1,34 (2H), 1,37 - 1,66 (2H), 2,22 - 2,38 (1H), 2,54 (3H), 2,69 - 3,14 (2H), 3,50 - 3,83 (1H), 4,07 (2H), 4,37 (3H), 7,10 (2H), 7,21 (1H), 7,36 (1H), 7,39 - 7,50 (4H), 7,54 (1H), 7,61 - 7,75 (1H), 8,55 (1H), 8,81 (1H).

Ejemplo 311: 2-[(1-{4-[(5-cloropiridin-2-il)oxi]benzoil}piperidin-4-il)metil]-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

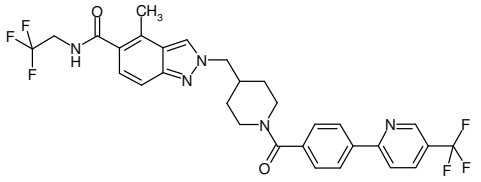


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 72 mg del compuesto del título a partir de 100 mg de 71a y 96 mg de ácido 4-[(5-cloropiridin-2-il)oxi]benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,17 - 1,34 (2H), 1,36 - 1,73 (2H), 2,22 - 2,41 (1H), 2,54 (3H), 2,69 - 3,18 (2H), 3,47 - 3,88 (1H), 4,07 (2H), 4,37 (3H), 7,06 - 7,28 (4H), 7,34 - 7,52 (3H), 7,99 (1H), 8,22 (1H), 8,56 (1H), 8,81 (1H).

Ejemplo 312: 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{4-[5-(trifluorometil)piridin-2-il]-benzoil}piperidin-4-

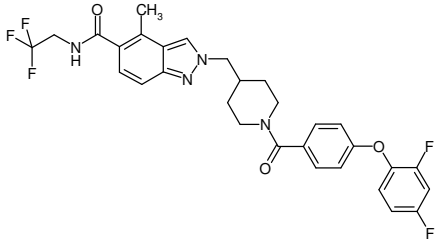
il)metil]-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 83 mg del compuesto del título a partir de 100 mg de 71a y 103 mg de ácido 4-[5-(trifluorometil)piridin-2-il]benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,28 (2H), 1,36 - 1,73 (2H), 2,33 (1H), 2,54 (3H), 2,70 - 3,18 (2H), 3,47 - 3,76 (1H), 3,96 - 4,16 (2H), 4,38 (3H), 7,21 (1H), 7,41 - 7,60 (3H), 8,17 - 8,40 (4H), 8,56 (1H), 8,81 (1H), 9,07 (1H).

Ejemplo 313: 2-({1-[4-(2,4-difluorofenoxi)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

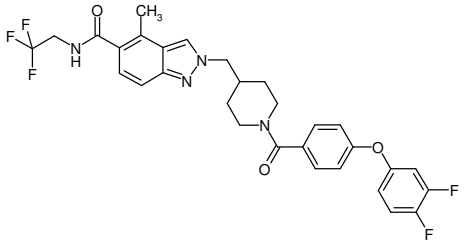


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 87 mg del compuesto del título a partir de 100 mg de 71a y 96 mg de ácido 4-(2,4-

difluorofenoxi)benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,23 (2H), 1,34 - 1,72 (2H), 2,18 - 2,42 (1H), 2,52 - 2,58 (3H), 2,69 - 3,20 (2H), 3,43 - 3,84 (1H), 4,07 (2H), 4,36 (3H), 6,92 - 7,06 (2H), 7,09 - 7,25 (2H), 7,28 - 7,42 (3H), 7,43 - 7,61 (2H), 8,55 (1H), 8,81 (1H).

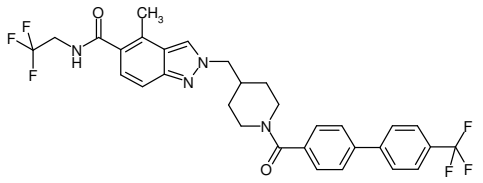
Ejemplo 314: 2-({1-[4-(3,4-difluorofenoxi)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 48 mg del compuesto del título a partir de 100 mg de 71a y 96 mg de ácido 4-(3,4-difluorofenoxi)benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,24 (2H), 1,36 - 1,72 (2H), 2,19 - 2,42 (1H), 2,54 (3H), 2,70 - 3,17 (2H), 3,44 - 3,86 (1H), 3,99 - 4,17 (2H), 4,36 (3H), 6,86 - 6,97 (1H), 7,01 - 7,11 (2H), 7,21 (1H), 7,29 (1H), 7,35 - 7,55 (4H), 8,55 (1H), 8,81 (1H).

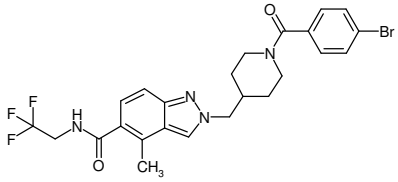
Ejemplo 315: 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{[4'-(trifluorometil)bifenil-4-il]-carbonil}piperidin-4-il)metil]-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 32 mg del compuesto del título a partir de 100 mg de 71a y 102 mg de ácido 4'-(trifluorometil)bifenil-4-carboxílico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,27 (2H), 1,37 - 1,71 (2H), 2,24 - 2,39 (1H), 2,53 (3H), 2,70 - 3,18 (2H), 3,43 - 3,51 (2H), 3,54 - 3,86 (1H), 4,37 (3H), 7,18 (1H), 7,38 - 7,57 (3H), 7,72 - 7,88 (4H), 7,89 - 7,98 (2H), 8,13 (1H), 8,51 (1H).

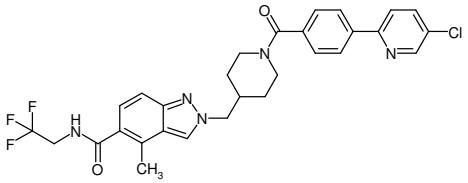
Ejemplo 316: 2-{[1-(4-bromobenzoil)piperidin-4-il]metil}-4-metil-N-(2,2,2-trifluoro-etil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 6,96 g del compuesto del título a partir de 5,61 g 71a y 2,89 g de ácido 4-bromobenzoico.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,17 - 1,32 (2H), 1,34 - 1,74 (2H), 2,19 - 2,41 (1H), 2,54 (3H), 2,88 - 3,22 (2H), 3,42 - 3,74 (1H), 3,94 - 4,18 (2H), 4,36 (3H), 7,20 (1H), 7,32 (2H), 7,46 (1H), 7,64 (2H), 8,55 (1H), 8,83 (1H).

Ejemplo 317: 2-({1-[4-(5-cloropiridin-2-il)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

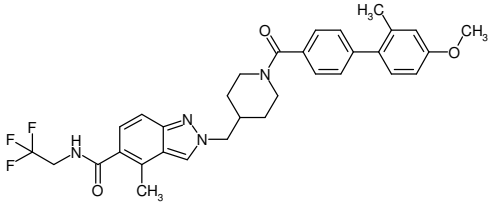


80 mg del bromuro de arilo preparado en el Ejemplo 316 junto con 32 mg de ácido (5-cloropiridin-2-il)borónico se colocaron primero en 1 ml de tetrahidrofurano, se trataron con 17,3 mg de 1,1'-bis(difenilfosfino)ferrocenodicloropaladio (II) y 0,17 ml de solución 1 M de carbonato de potasio y se calentaron en el microondas durante 10 minutos a 120 °C (100 watts). Después de la adición fresca de 11 mg de ácido (5-cloropiridin-2-il)borónico y 17,3 mg de catalizador de paladio (II), la mezcla de reacción se calentó otra vez en el microondas durante 10 minutos a 120 °C (100 watts) hasta la conversión completa. La mezcla de reacción se concentró. Después de la purificación por HPLC, esto dio como resultado 15 mg del compuesto del título.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,18 – 1,36 (2H), 1,37 – 1,75 (2H), 2,28 – 2,38 (1H), 2,54 (3H), 2,73 – 3,18 (2H), 3,49 – 3,74 (1H), 3,95 – 4,16 (2H), 4,28 – 4,62 (3H), 7,22 (1H), 7,33 – 7,65 (5H), 7,98 –

8,22 (3H), 8,56 (1H), 8,77 – 8,91 (1H).

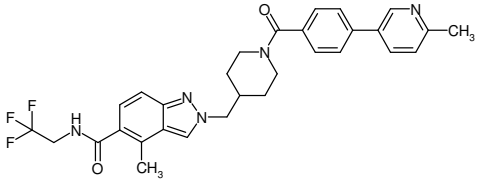
Ejemplo 318: 2-({1-[(4'-metoxi-2'-metilbifenil-4-il)carbonil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 317, se obtuvieron 50 mg del compuesto del título a partir de 125 mg de 316 y 53 mg de ácido (4-metoxi-2-metil-fenil)borónico.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,16 – 1,36 (2H), 1,37 – 1,74 (2H), 2,23 (3H), 2,29 – 2,38 (1H), 2,54 (3H), 2,72 – 3,12 (2H), 3,77 (4H), 3,97 – 4,17 (2H), 4,38 (3H), 6,75 – 6,94 (2H), 7,07 – 7,26 (2H), 7,29 – 7,56 (5H), 8,56 (1H), 8,81 (1H).

Ejemplo 319: 4-metil-2-({1-[4-(6-metilpiridin-3-il)benzoil]piperidin-4-il}metil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

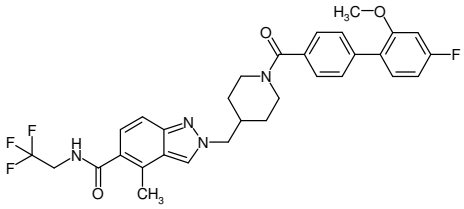


De forma análoga al Ejemplo 317, se obtuvieron 37 mg del compuesto del título a partir de 125 mg de 316 y 44 mg de ácido (6-metilpiridin-3-il)borónico a reflujo.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,15 – 1,35

(2H), 1,37 – 1,71 (2H), 2,20 – 2,40 (1H), 2,52 (3H), 2,54 (3H), 2,74 – 3,15 (2H), 3,52 – 3,82 (1H), 4,07 (2H), 4,38 (3H), 7,20 (1H), 7,37 (1H), 7,47 (3H), 7,77 (2H), 8,01 (1H), 8,57 (1H), 8,72 – 8,92 (2H).

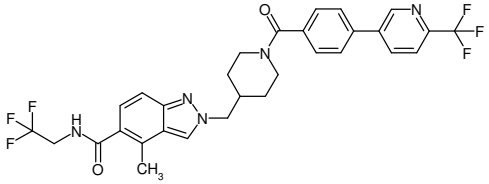
Ejemplo 320: 2-({1-[(4'-fluoro-2'-metoxibifenil-4-il)carbonil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 317, se obtuvieron 60 mg del compuesto del título a partir de 125 mg de 316 y 75 g de ácido (4-fluoro-2-metoxifenil)borónico a reflujo.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,16 – 1,37 (2H), 1,38 – 1,75 (2H), 2,25 – 2,37 (1H), 2,54 (3H), 2,72 – 3,17 (2H), 3,79 (4H), 4,07 (2H), 4,38 (3H), 6,87 (1H), 7,04 (1H), 7,21 (1H), 7,27 – 7,58 (6H), 8,56 (1H), 8,81 (1H).

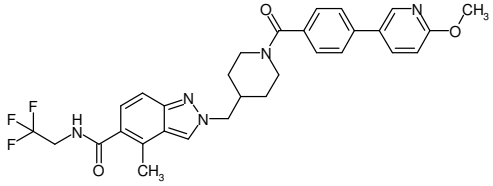
Ejemplo 321: 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{4-[6-(trifluorometil)piridin-3-il]-benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 317, se obtuvieron 45 mg del compuesto del título a partir de 125 mg de 316 y 84 mg de ácido [6-(trifluorometil)piridin-3-il]borónico a reflujo.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,15 - 1,37 (2H), 1,37 - 1,71 (2H), 2,22 - 2,41 (1H), 2,54 (3H), 2,73 - 3,20 (2H), 3,45 - 3,74 (1H), 3,93 - 4,17 (2H), 4,29 - 4,62 (3H), 7,21 (1H), 7,39 - 7,62 (4H), 7,89 (2H), 8,01 (1H), 8,57 (1H), 8,73 - 8,92 (1H), 9,13 (1H).

Ejemplo 322: 2-({1-[4-(6-metoxipiridin-3-il)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

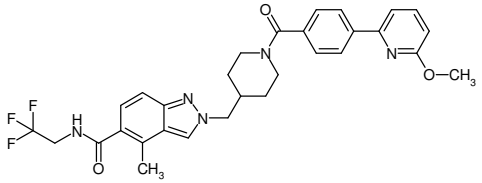


De forma análoga al Ejemplo 317, se obtuvieron 54 mg del compuesto del título a partir de 125 mg de 316 y 68 mg de ácido (6-metoxipiridin-3-il)borónico a reflujo.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,13 - 1,35 (2H), 1,36 - 1,71 (2H), 2,20 - 2,40 (1H), 2,54 (3H), 2,73 - 3,16 (2H), 3,51 - 3,77 (1H), 3,90 (3H), 3,96 - 4,19 (2H), 4,37 (3H), 6,93 (1H), 7,20 (1H), 7,39 - 7,52 (3H), 7,73 (2H), 8,05 (1H), 8,47 - 8,63 (2H), 8,83

(1H).

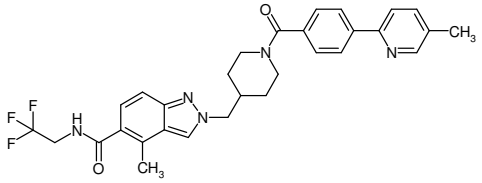
Ejemplo 323: 2-({1-[4-(6-metoxipiridin-2-il)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 317, se obtuvieron 55 mg del compuesto del título a partir de 125 mg de 316 y 49 mg de ácido (6-metoxipiridin-2-il)borónico a reflujo.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,16 - 1,36 (2H), 1,37 - 1,69 (2H), 2,20 - 2,41 (1H), 2,54 (3H), 2,74 - 3,16 (2H), 3,47 - 3,81 (1H), 3,96 (3H), 4,06 (2H), 4,38 (3H), 6,81 (1H), 7,21 (1H), 7,47 (3H), 7,60 (1H), 7,74 - 7,90 (1H), 8,15 (2H), 8,56 (1H), 8,81 (1H).

Ejemplo 324: 4-metil-2-({1-[4-(5-metilpiridin-2-il)benzoil]piperidin-4-il}metil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

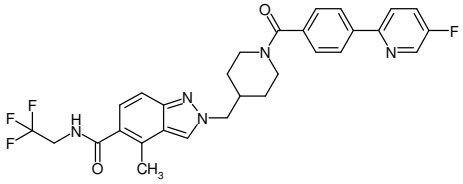


De forma análoga al Ejemplo 317, se obtuvieron 9 mg del compuesto del título a partir de 125 mg de 316 y

44 mg de ácido (5-metilpiridin-2-il)borónico a reflujo.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,16 - 1,36 (2H), 1,37 - 1,71 (2H), 2,24 - 2,30 (1H), 2,34 (3H), 2,54 (3H), 2,74 - 3,16 (2H), 3,52 - 3,79 (1H), 3,93 - 4,17 (2H), 4,38 (3H), 7,20 (1H), 7,37 - 7,54 (3H), 7,66 - 7,78 (1H), 7,89 (1H), 8,11 (2H), 8,45 - 8,61 (2H), 8,74 - 8,88 (1H).

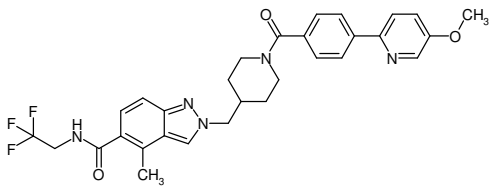
Ejemplo 325: 2-({1-[4-(5-fluoropiridin-2-il)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 317, se obtuvieron 35 mg del compuesto del título a partir de 125 mg de 316 y 45 mg de ácido (5-fluoropiridin-2-il)borónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,17 - 1,34 (2H), 1,35 - 1,69 (2H), 2,22 - 2,41 (1H), 2,54 (3H), 2,69 - 3,19 (2H), 3,51 - 3,78 (1H), 4,07 (2H), 4,38 (3H), 7,20 (1H), 7,40 - 7,53 (3H), 7,85 (1H), 8,04 - 8,17 (3H), 8,57 (1H), 8,68 (1H), 8,83 (1H).

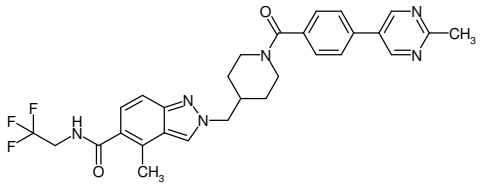
Ejemplo 326: 2-({1-[4-(5-metoxipiridin-2-il)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 317, se obtuvieron 94 mg del compuesto del título a partir de 125 mg de 316 y 49 mg de ácido (5-metoxipiridin-2-il)borónico a reflujo.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,19 - 1,36 (2H), 1,37 - 1,69 (2H), 2,28 - 2,40 (1H), 2,54 (3H), 2,73 - 3,19 (2H), 3,48 - 3,79 (1H), 3,88 (3H), 4,07 (2H), 4,38 (3H), 7,20 (1H), 7,38 - 7,55 (4H), 7,96 (1H), 8,07 (2H), 8,39 (1H), 8,57 (1H), 8,82 (1H).

Ejemplo 327: 4-metil-2-({1-[4-(2-metilpirimidin-5-il)benzoil]piperidin-4-il}metil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

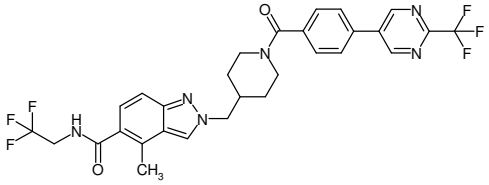


De forma análoga al Ejemplo 317, se obtuvieron 46 mg del compuesto del título a partir de 125 mg de 316 y 102 mg de éster pinacólico de ácido (2-metilpirimidin-5-il)borónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,16 - 1,35 (2H), 1,35 - 1,67 (2H), 2,21 - 2,42 (1H), 2,54 (3H), 2,67 (3H), 2,71 - 2,89 (1H), 2,93 - 3,20 (1H), 3,50 -

3,73 (1H), 4,07 (2H), 4,37 (3H), 7,20 (1H), 7,40 – 7,57 (3H), 7,85 (2H), 8,57 (1H), 8,84 (1H), 9,05 (2H).

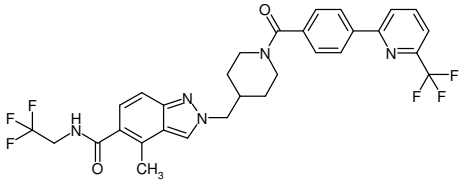
Ejemplo 328: 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{4-[2-(trifluorometil)pirimidin-5-il]-benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 317, se obtuvieron 34 mg del compuesto del título a partir de 125 mg de 316 y 89 mg de ácido [2-(trifluorometil)pirimidin-5-il]borónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,21 – 1,35 (2H), 1,36 – 1,71 (2H), 2,23 – 2,41 (1H), 2,54 (3H), 2,71 – 2,89 (1H), 2,94 – 3,17 (1H), 3,48 – 3,72 (1H), 4,05 (2H), 4,28 – 4,61 (3H), 7,21 (1H), 7,47 (1H), 7,57 (2H), 7,98 (2H), 8,57 (1H), 8,84 (1H), 9,44 (2H).

Ejemplo 329: 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{4-[6-(trifluorometil)piridin-2-il]-benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida

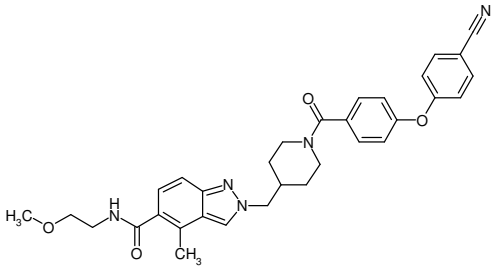


De forma análoga al Ejemplo 317, se obtuvieron 70 mg del compuesto del título a partir de 125 mg de 316 y

121 mg de éster pinacólico de ácido [6-(trifluorometil)piridin-2-il]borónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,19 - 1,36 (2H), 1,37 - 1,72 (2H), 2,23 - 2,39 (1H), 2,54 (3H), 2,68 - 2,90 (1H), 2,92 - 3,16 (1H), 3,50 - 3,73 (1H), 4,06 (2H), 4,38 (3H), 7,20 (1H), 7,41 - 7,60 (3H), 7,89 (1H), 8,11 - 8,27 (3H), 8,33 (1H), 8,56 (1H), 8,81 (1H).

Ejemplo 330: 2-({1-[4-(4-cianofenoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

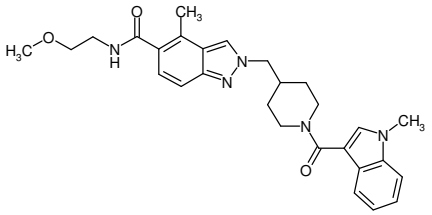


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 151 mg del compuesto del título a partir de 213 mg de 71a y 153 mg de ácido 4-(4-cianofenoxi)benzoico en DMF.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,22 (2H), 1,31 - 1,66 (2H), 2,15 - 2,36 (1H), 2,49 (3H), 2,70 - 3,12 (2H), 3,24 (3H), 3,36 (2H), 3,39 - 3,46 (2H), 3,50 - 3,79 (1H), 4,32 (3H), 7,00 - 7,23 (5H), 7,30 - 7,49 (3H), 7,75 - 7,91 (2H), 8,12 (1H), 8,48 (1H).

Ejemplo 331: N-(2-metoxietil)-4-metil-2-({1-[(1-metil-

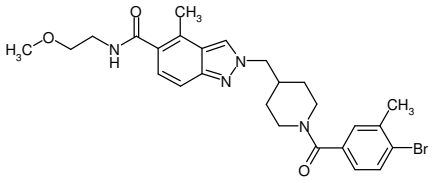
1H-indol-3-il)carbonil]-piperidin-4-il}metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 26 mg del compuesto del título a partir de 38 mg de 71a y 36 mg de ácido 1-metil-1H-indol-3-carboxílico en DMF.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,23 (2H), 1,43 - 1,64 (2H), 2,20 - 2,39 (1H), 2,53 (3H), 2,80 - 3,03 (2H), 3,28 (3H), 3,37 - 3,50 (4H), 3,81 (3H), 4,37 (4H), 7,18 (3H), 7,36 - 7,53 (2H), 7,67 (2H), 8,04 - 8,25 (1H), 8,52 (1H).

Ejemplo 332: 2-{[1-(4-bromo-3-metilbenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

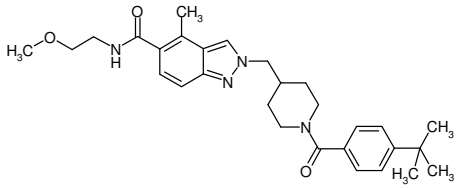


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 498 mg del compuesto del título a partir de 807 mg de 71a y 788 mg de ácido 4-bromo-3-metilbenzoico en DMF.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,20 - 1,32

(2H), 1,33 – 1,67 (2H), 2,24 – 2,33 (1H), 2,36 (3H), 2,52 (3H), 2,73 (1H), 2,91 – 3,13 (1H), 3,28 (3H), 3,35 – 3,63 (5H), 4,34 (3H), 7,03 – 7,23 (2H), 7,30 – 7,49 (2H), 7,63 (1H), 8,15 (1H), 8,51 (1H).

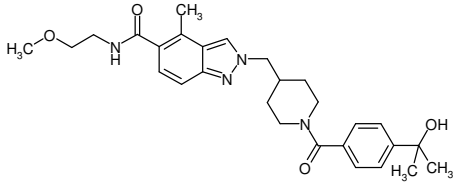
Ejemplo 333: 2-{[1-(4-ter-butilbenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 50 mg del compuesto del título a partir de 100 mg de 71a y 81 mg de ácido 4-ter-butilbenzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,20 – 1,33 (11H), 1,33 – 1,67 (2H), 2,21 – 2,37 (1H), 2,52 (3H), 2,68 – 3,10 (2H), 3,28 (3H), 3,36 – 3,43 (2H), 3,45 (2H), 3,52 – 3,74 (1H), 4,35 (3H), 7,18 (1H), 7,25 – 7,35 (2H), 7,36 – 7,52 (3H), 8,15 (1H), 8,50 (1H).

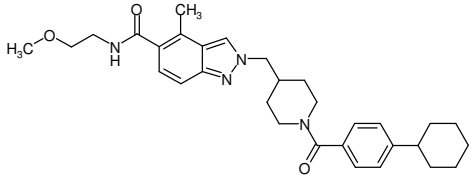
Ejemplo 334: 2-({1-[4-(1-hidroxi-1-metiletil)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 28 mg del compuesto del título a partir de 100 mg de 71a y 82 mg de ácido 4-(1-hidroxi-1-metiletil)benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,24 (2H), 1,42 (8H), 2,20 - 2,40 (1H), 2,52 (3H), 2,64 - 3,11 (2H), 3,28 (3H), 3,34 - 3,43 (2H), 3,43 - 3,51 (2H), 3,53 - 3,71 (1H), 4,35 (3H), 4,76 - 5,43 (1H), 7,18 (1H), 7,28 (2H), 7,42 (1H), 7,46 - 7,56 (2H), 8,15 (1H), 8,51 (1H).

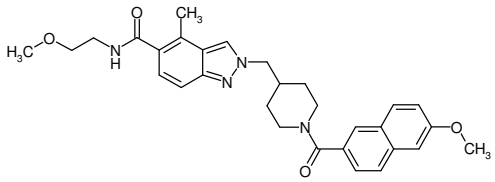
Ejemplo 335: 2-{[1-(4-ciclohexilbenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 75 mg del compuesto del título a partir de 100 mg de 71a y 93 mg de ácido 4-ciclohexilbenzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,10 - 1,63 (9H), 1,64 - 1,89 (5H), 2,17 - 2,40 (1H), 2,52 (3H), 2,69 - 3,08 (2H), 3,28 (3H), 3,38 - 3,43 (2H), 3,43 - 3,49 (2H), 3,53 - 3,73 (1H), 4,35 (3H), 7,18 (1H), 7,27 (4H), 7,42 (1H), 8,15 (1H), 8,50 (1H).

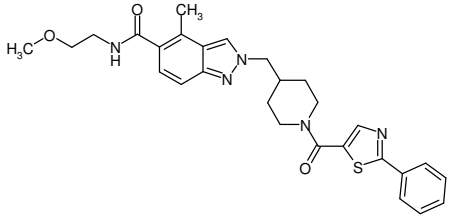
Ejemplo 336: N-(2-metoxietil)-2-{[1-(6-metoxi-2-naftoil)piperidin-4-il]metil}-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 23 mg del compuesto del título a partir de 100 mg de 71a) y 92 mg de ácido 6-metoxi-naftalen-2-carboxílico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,23 (2H), 1,37 – 1,72 (2H), 2,23 – 2,39 (1H), 2,52 (3H), 2,72 – 3,12 (2H), 3,28 (3H), 3,36 – 3,42 (2H), 3,43 – 3,49 (2H), 3,59 – 3,81 (1H), 3,89 (3H), 4,36 (3H), 7,09 – 7,27 (2H), 7,33 – 7,49 (3H), 7,79 – 7,95 (3H), 8,15 (1H), 8,51 (1H).

Ejemplo 337: N-(2-metoxietil)-4-metil-2-({1-[(2-feniltiazol-5-il)carbonil]piperidin-4-il}metil)-2H-indazol-5-carboxamida

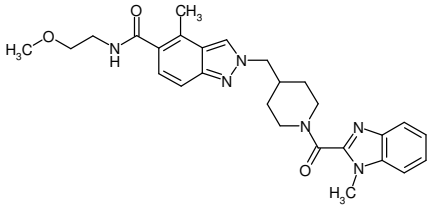


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 36 mg del compuesto del título a partir de 100 mg de 71a y 93 mg de ácido 2-feniltiazol-5-

carboxílico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,23 (2H), 1,55 (2H), 2,19 – 2,45 (1H), 2,52 – 2,56 (3H), 2,70 – 3,24 (2H), 3,28 (3H), 3,36 – 3,43 (2H), 3,44 – 3,49 (2H), 4,37 (4H), 7,19 (1H), 7,43 (1H), 7,49 – 7,62 (3H), 7,90 – 8,03 (2H), 8,08 – 8,25 (2H), 8,52 (1H).

Ejemplo 338: N-(2-metoxietil)-4-metil-2-({1-[(1-metil-1H-benzimidazol-2-il)carbonil]-piperidin-4-il}metil)-2H-indazol-5-carboxamida

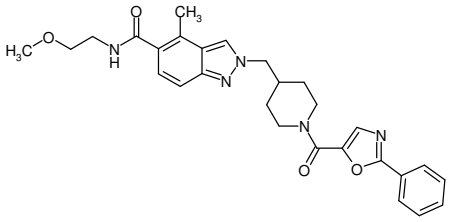


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 39 mg del compuesto del título a partir de 100 mg de 71a y 80 mg de ácido 1-metil-1H-benzimidazol-2-carboxílico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,22 – 1,43 (2H), 1,43 – 1,53 (1H), 1,59 – 1,70 (1H), 2,27 – 2,44 (1H), 2,53 (3H), 2,87 (1H), 3,11 (1H), 3,28 (3H), 3,36 – 3,42 (2H), 3,43 – 3,48 (2H), 3,83 (3H), 4,00 – 4,14 (1H), 4,39 (2H), 4,48 – 4,61 (1H), 7,18 (1H), 7,23 – 7,46 (3H), 7,58 – 7,74 (2H), 8,10 – 8,20 (1H), 8,53 (1H).

Ejemplo 339: N-(2-metoxietil)-4-metil-2-({1-[(2-feniloxazol-5-il)carbonil]piperidin-4-il}metil)-2H-

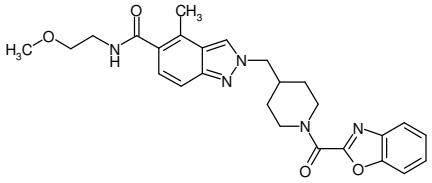
indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 30 mg del compuesto del título a partir de 100 mg de 71a y 86 mg de ácido 2-feniloxazol-5-carboxílico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,14 - 1,48 (2H), 1,59 (2H), 2,24 - 2,46 (1H), 2,52 - 2,56 (3H), 2,71 - 3,01 (1H), 3,11 - 3,26 (1H), 3,28 (3H), 3,36 - 3,43 (2H), 3,43 - 3,50 (2H), 4,38 (4H), 7,19 (1H), 7,43 (1H), 7,52 - 7,67 (3H), 7,80 (1H), 7,97 - 8,05 (2H), 8,16 (1H), 8,53 (1H).

Ejemplo 340: 2-{[1-(benzoxazol-2-ilcarbonil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

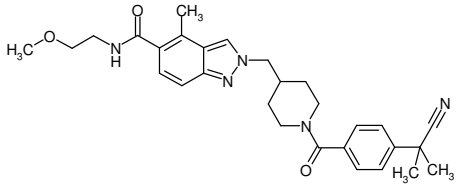


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 37 mg del compuesto del título a partir de 100 mg de 71a y 84 mg de ácido benzoxazol-2-carboxílico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,19 - 1,43

(2H), 1,48 – 1,73 (2H), 2,28 – 2,45 (1H), 2,53 (3H), 2,91 (1H), 3,22 (1H), 3,33 – 3,57 (m, 7H), 4,25 – 4,60 (4H), 7,18 (1H), 7,36 – 7,62 (3H), 7,78 – 7,95 (2H), 8,16 (1H), 8,53 (1H).

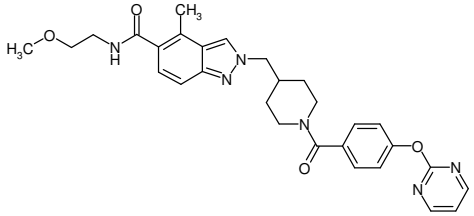
Ejemplo 341: 2-({1-[4-(1-ciano-1-metiletil)benzoil]piperidin-4-il}metil)-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 20 mg del compuesto del título a partir de 100 mg de 71a y 86 mg de ácido 4-(1-ciano-1-metiletil)benzoico en DMF.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,17 – 1,34 (2H), 1,35 – 1,64 (2H), 1,70 (6H), 2,16 – 2,40 (1H), 2,52 (3H), 2,64 – 3,13 (2H), 3,28 (3H), 3,40 (2H), 3,43 – 3,49 (2H), 3,49 – 3,67 (1H), 4,35 (3H), 7,18 (1H), 7,42 (3H), 7,58 (2H), 8,15 (1H), 8,50 (1H).

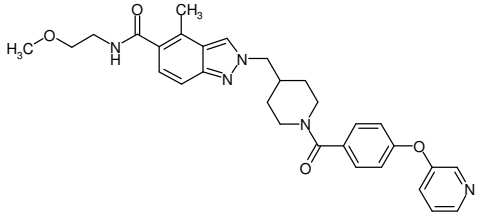
Ejemplo 342: N-(2-metoxietil)-4-metil-2-({1-[4-(pirimidin-2-iloxi)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 37 mg del compuesto del título a partir de 100 mg de 71a y 98 mg de ácido 4-(2-pirimidiniloxi)benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,26 (2H), 1,38 - 1,66 (2H), 2,20 - 2,40 (1H), 2,52 - 2,56 (3H), 2,70 - 3,16 (2H), 3,28 (3H), 3,36 - 3,43 (2H), 3,43 - 3,49 (2H), 3,64 - 3,77 (m, 1H), 4,36 (3H), 7,18 (1H), 7,22 - 7,33 (3H), 7,39 - 7,49 (3H), 8,15 (1H), 8,43 - 8,57 (1H), 8,66 (2H).

Ejemplo 343: N-(2-metoxietil)-4-metil-2-({1-[4-(3-piridiloxi)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida

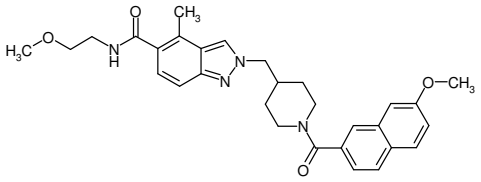


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 7 mg del compuesto del título a partir de 75 mg de 71a y 73 mg de ácido 4-(3-piridiloxi)benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,17 - 1,32 (2H), 1,35 - 1,69 (2H), 2,19 - 2,38 (1H), 2,52 (3H), 2,70 - 3,14 (2H), 3,28 (3H), 3,34 - 3,43 (2H), 3,43 - 3,51 (2H), 3,55 - 3,70 (1H), 4,35 (3H), 7,04 - 7,13 (2H), 7,18 (1H), 7,37 - 7,46 (3H), 7,47 - 7,54 (1H),

7,58 (1H), 8,15 (1H), 8,38 – 8,55 (3H).

Ejemplo 344: N-(2-metoxietil)-2-{[1-(7-metoxi-2-naftoil)piperidin-4-il]metil}-4-metil-2H-indazol-5-carboxamida

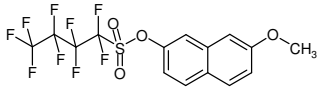


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 28 mg del compuesto del título a partir de 75 mg de 71a y 69 mg del ácido carboxílico preparado en el Ejemplo 344c) en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,21 – 1,35 (2H), 1,37 – 1,75 (2H), 2,23 – 2,39 (1H), 2,52 (3H), 2,73 – 3,13 (2H), 3,28 (3H), 3,35 – 3,42 (2H), 3,45 (2H), 3,53 – 3,74 (1H), 3,88 (3H), 4,37 (3H), 7,13 – 7,25 (2H), 7,29 (1H), 7,36 – 7,48 (2H), 7,77 – 7,93 (3H), 8,15 (1H), 8,52 (1H).

El material de partida se preparó de la siguiente manera:

Ejemplo 344a: 7-metoxinaftalen-2-il-1,1,2,2,3,3,4,4,4-nonafluorobutan-1-sulfonato

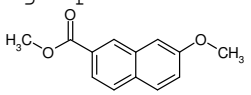


5,12 g de 7-metoxi-2-naftol se disolvieron en 50 ml de tolueno y enfriado hasta 0°C. 30,7 ml de N,N-diisopropiletilamina y 17,6 ml de fluoruro de

nonafluorobutansulfonilo se añadieron sucesivamente gota a gota y la mezcla de reacción luego se agitó a temperatura ambiente hasta la conversión completa. La mezcla de reacción se vertió en 600 ml de solución saturada de cloruro de amonio, el aceite marrón depositado se separó y la fase acuosa se extrajo varias veces con acetato de etilo. Las fases orgánicas combinadas se lavaron con agua y solución saturada de cloruro de sodio, se secó y se concentró. El residuo se purificó por cromatografía en columna en gel de sílice usando un gradiente de hexano/ acetato de etilo. Rendimiento: 11,45 g del compuesto del título.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 3,89 (3H), 7,28 (1H), 7,41 (1H), 7,52 (1H), 7,90 - 8,00 (2H), 8,05 (1H).

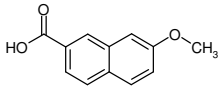
Ejemplo 344b: 7-metoxinaftalen-2-carboxilato de metilo



De forma análoga al Ejemplo 1e, 2,34 g del compuesto del título a partir de 11,0 g de 344a y 8,8 ml de metanol.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 3,89 (3H), 3,91 (3H), 7,31 (1H), 7,57 (1H), 7,82 (1H), 7,94 (2H), 8,54 (1H).

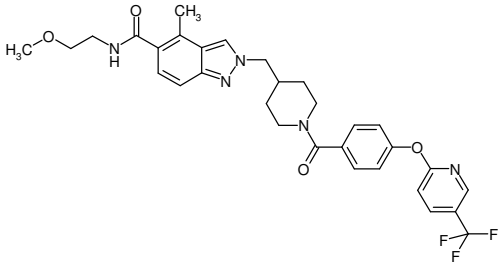
Ejemplo 344c: ácido 7-metoxinaftalen-2-carboxílico



De forma análoga al Ejemplo 258d, 1,27 g del compuesto del título a partir de 2,0 g de 344b.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 3,89 (3H), 7,30 (1H), 7,53 (1H), 7,78 - 7,86 (1H), 7,87 - 8,01 (2H), 8,50 (1H), 12,99 (1H).

Ejemplo 345: N-(2-metoxietil)-4-metil-2-{[1-(4-{[5-(trifluorometil)piridin-2-il]oxi}-benzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida

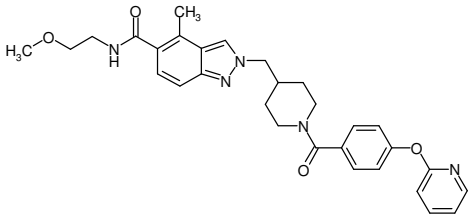


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 221 mg del compuesto del título a partir 200 mg de 71a y 232 mg de ácido 4-{[5-(trifluorometil)piridin-2-il]oxi}benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,21 - 1,34 (2H), 1,36 - 1,72 (2H), 2,23 - 2,39 (1H), 2,53 (3H), 2,89 (2H), 3,31 (3H), 3,36 - 3,43 (2H), 3,43 - 3,50 (2H), 3,53 - 3,86 (1H), 4,36 (3H), 7,18 (1H), 7,23 - 7,33 (3H), 7,37 - 7,50 (3H), 8,13 (1H), 8,25 (1H), 8,51 (1H), 8,55 - 8,63 (1H).

Ejemplo 346: N-(2-metoxietil)-4-metil-2-({1-[4-(2-piridiloxi)benzoil]piperidin-4-il}-metil)-2H-indazol-5-

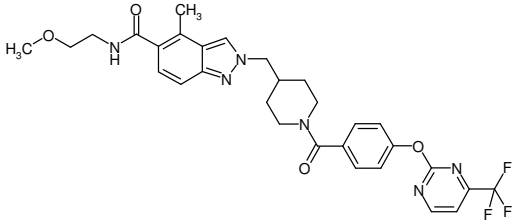
carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 29 mg del compuesto del título a partir de 100 mg de 71a y 98 mg de ácido 4-(2-piridiloxi)benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,23 (2H), 1,39 - 1,68 (2H), 2,24 - 2,39 (1H), 2,52 - 2,56 (3H), 2,71 - 3,13 (2H), 3,28 (3H), 3,36 - 3,43 (2H), 3,45 (2H), 3,53 - 3,87 (1H), 4,36 (3H), 7,08 (1H), 7,13 - 7,26 (4H), 7,34 - 7,52 (3H), 7,88 (1H), 8,07 - 8,23 (2H), 8,51 (1H).

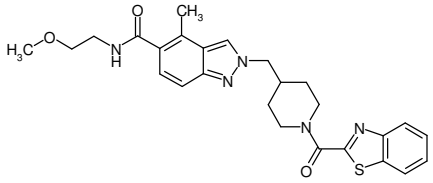
Ejemplo 347: N-(2-metoxietil)-4-metil-2-{[1-(4-{[4-(trifluorometil)pirimidin-2-il]-oxi}benzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 11 mg del compuesto del título a partir de 75 mg de 71a y 97 mg de ácido 4-{[4-(trifluorometil)pirimidin-2-il]oxi}benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,23 (2H), 1,37 – 1,69 (2H), 2,19 – 2,39 (1H), 2,53 (3H), 2,68 – 3,18 (2H), 3,28 (3H), 3,36 – 3,43 (2H), 3,45 (2H), 3,51 – 3,79 (1H), 4,36 (3H), 7,18 (1H), 7,31 – 7,39 (2H), 7,39 – 7,53 (3H), 7,81 (1H), 8,15 (1H), 8,51 (1H), 9,00 (1H).

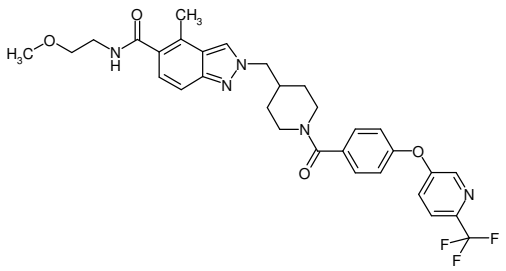
Ejemplo 348: 2-{[1-(benzotiazol-2-ilcarbonil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 28 mg del compuesto del título a partir de 75 mg de 71a y 61 mg de ácido benzotiazol-2-carboxílico en DMF.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,34 (2H), 1,62 (2H), 2,32 – 2,45 (1H), 2,53 (3H), 2,82 – 3,00 (1H), 3,26 (1H), 3,28 (3H), 3,40 (2H), 3,43 – 3,50 (2H), 4,38 (3H), 4,98 – 5,23 (1H), 7,19 (1H), 7,43 (1H), 7,59 (2H), 8,01 – 8,30 (3H), 8,53 (1H).

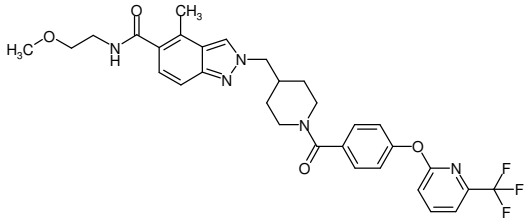
Ejemplo 349: N-(2-metoxietil)-4-metil-2-{[1-(4-{[6-(trifluorometil)piridin-3-il]oxi}-benzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 34 mg del compuesto del título a partir de 75 mg de 71a y 96 mg de 303b en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,24 (2H), 1,37 – 1,68 (2H), 2,22 – 2,38 (1H), 2,53 (3H), 2,71 – 3,14 (2H), 3,28 (3H), 3,36 – 3,43 (2H), 3,44 – 3,49 (2H), 3,52 – 3,84 (1H), 4,36 (3H), 7,09 – 7,29 (3H), 7,35 – 7,53 (3H), 7,65 (1H), 7,92 (1H), 8,13 (1H), 8,51 (1H), 8,60 (1H).

Ejemplo 350: N-(2-metoxietil)-4-metil-2-{[1-(4-{[6-(trifluorometil)piridin-2-il]oxi}-benzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida

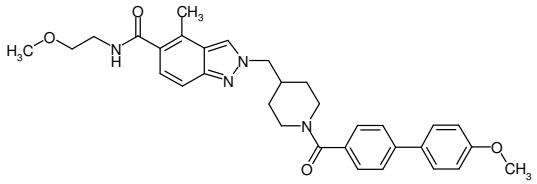


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 36 mg del compuesto del título a partir de 100 mg de 71a y 129 mg de ácido 4-{[6-(trifluorometil)piridin-2-il]oxi}benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,20 – 1,34

(2H), 1,36 – 1,66 (2H), 2,24 – 2,39 (1H), 2,53 (3H), 2,70 – 3,16 (2H), 3,28 (3H), 3,36 – 3,43 (2H), 3,44 – 3,49 (2H), 3,53 – 3,82 (1H), 4,36 (3H), 7,18 (1H), 7,22 – 7,30 (2H), 7,32 – 7,50 (4H), 7,67 (1H), 8,06 – 8,21 (2H), 8,51 (1H).

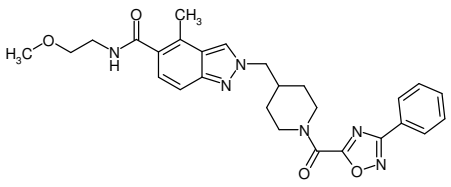
Ejemplo 351: 2-({1-[(4'-metoxibifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 15 mg del compuesto del título a partir de 100 mg de 71a y 104 mg de ácido 4'-metoxi-bifenil-4-carboxílico en DMF.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,24 (2H), 1,37 – 1,64 (2H), 2,19 – 2,32 (1H), 2,53 (3H), 2,74 – 3,10 (2H), 3,28 (3H), 3,40 (2H), 3,45 (2H), 3,67 – 3,91 (4H), 4,21 – 4,64 (3H), 7,04 (2H), 7,19 (1H), 7,41 (2H), 7,66 (5H), 8,04 – 8,22 (1H), 8,51 (1H).

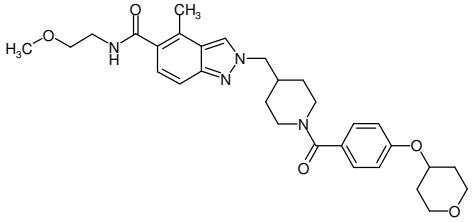
Ejemplo 352: N-(2-metoxietil)-4-metil-2-({1-[(3-fenil-1,2,4-oxadiazol-5-il)carbonil]-piperidin-4-il}metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 12 mg del compuesto del título a partir de 100 mg de 71a y 78 mg de ácido 3-fenil-1,2,4-oxadiazol-5-carboxílico en DMF.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,33 (2H), 1,50 - 1,72 (2H), 2,31 - 2,45 (1H), 2,53 (3H), 2,86 - 3,04 (1H), 3,16 - 3,26 (1H), 3,28 (3H), 3,41 (2H), 3,43 - 3,51 (2H), 3,94 - 4,13 (1H), 4,28 - 4,55 (3H), 7,19 (1H), 7,43 (1H), 7,52 - 7,72 (3H), 7,96 - 8,09 (2H), 8,13 (1H), 8,52 (1H).

Ejemplo 353: N-(2-metoxietil)-4-metil-2-({1-[4-(3,4,5,6-tetrahidro-2H-piran-4-iloxi)-benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida

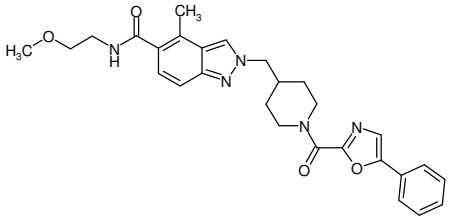


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 21 mg del compuesto del título a partir de 100 mg de 71a y 91 mg de ácido 4-(3,4,5,6-tetrahidro-2H-piran-4-iloxi)benzoico en DMF.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,23 (2H), 1,38 - 1,70 (4H), 1,97 (2H), 2,18 - 2,41 (1H), 2,53

(3H), 2,75 – 3,02 (2H), 3,28 (3H), 3,35 – 3,54 (8H), 3,84 (2H), 4,35 (2H), 4,52 – 4,77 (1H), 7,00 (2H), 7,18 (1H), 7,30 (2H), 7,42 (1H), 8,13 (1H), 8,50 (1H).

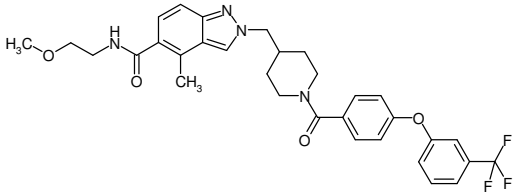
Ejemplo 354: N-(2-metoxietil)-4-metil-2-({1-[(5-feniloxazol-2-il)carbonil]piperidin-4-il}metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 10 mg del compuesto del título a partir de 100 mg de 71a y 77 mg de ácido 5-fenil-oxazol-2-carboxílico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,17 – 1,41 (2H), 1,59 (2H), 2,28 – 2,45 (1H), 2,52 – 2,56 (3H), 2,85 (1H), 3,20 (1H), 3,28 (3H), 3,36 – 3,43 (2H), 3,44 – 3,50 (2H), 4,38 (3H), 4,57 – 4,74 (1H), 7,19 (1H), 7,39 – 7,57 (4H), 7,74 – 7,82 (2H), 7,88 (1H), 8,13 (1H), 8,52 (1H).

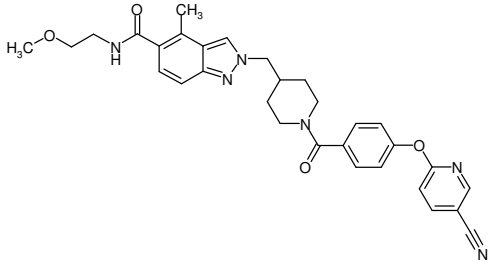
Ejemplo 355: N-(2-metoxietil)-4-metil-2-[(1-{4-[3-(trifluorometil)fenoxi]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 40 mg del compuesto del título a partir de 100 mg de 71a y 115 mg de ácido 4-[(3-(trifluorometil)fenoxi]benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,23 (2H), 1,35 - 1,65 (2H), 2,19 - 2,38 (1H), 2,52 - 2,56 (3H), 2,71 - 3,12 (2H), 3,28 (3H), 3,36 - 3,43 (2H), 3,43 - 3,50 (2H), 3,53 - 3,87 (1H), 4,35 (3H), 7,07 - 7,15 (2H), 7,18 (1H), 7,30 - 7,48 (5H), 7,54 (1H), 7,64 (1H), 8,13 (1H), 8,50 (1H).

Ejemplo 356: 2-[(1-{4-[(5-cianopiridin-2-il)oxi]benzoil}piperidin-4-il)metil]-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

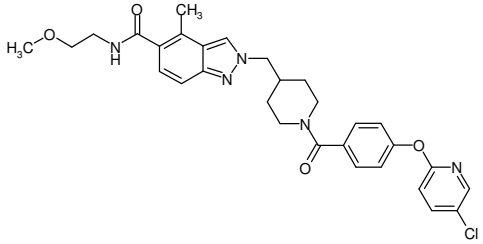


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 15 mg del compuesto del título a partir de 100 mg de 71a y 98 mg de ácido 4-[(5-cianopiridin-2-il)oxi]benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,21 - 1,35 (2H), 1,36 - 1,75 (2H), 2,23 - 2,39 (1H), 2,53 (3H), 2,69 - 3,19 (2H), 3,28 (3H), 3,36 - 3,43 (2H), 3,46 (2H), 3,53 - 3,85 (1H), 4,36 (3H), 7,18 (1H), 7,23 -

7,33 (3H), 7,36 – 7,53 (3H), 8,13 (1H), 8,34 (1H), 8,51 (1H), 8,66 (1H).

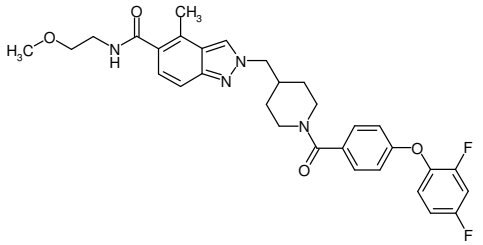
Ejemplo 357: 2-[(1-{4-[(5-cloropiridin-2-il)oxi]benzoil}piperidin-4-il)metil]-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 40 mg del compuesto del título a partir de 100 mg de 71a y 102 mg de ácido 4-[(5-cloropiridin-2-il)oxi]benzoico en DMF.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,25 (2H), 1,36 – 1,70 (2H), 2,20 – 2,39 (1H), 2,53 (3H), 2,66 – 3,15 (2H), 3,28 (3H), 3,40 (2H), 3,43 – 3,50 (2H), 3,55 – 3,90 (1H), 4,36 (3H), 7,08 – 7,28 (4H), 7,42 (3H), 7,99 (1H), 8,10 – 8,30 (2H), 8,51 (1H).

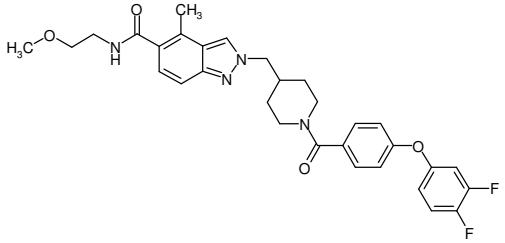
Ejemplo 358: 2-({1-[4-(2,4-difluorofenoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 22 mg del compuesto del título a partir de 100 mg de 71a y 102 mg de ácido 4-(2,4-difluorofenoxi)benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,21 (2H), 1,33 - 1,76 (2H), 2,20 - 2,39 (1H), 2,52 (3H), 2,69 - 3,13 (2H), 3,28 (3H), 3,36 - 3,43 (2H), 3,43 - 3,50 (2H), 3,53 - 3,90 (1H), 4,35 (3H), 6,91 - 7,04 (2H), 7,11 - 7,22 (2H), 7,30 - 7,46 (4H), 7,51 (1H), 8,13 (1H), 8,50 (1H).

Ejemplo 359: 2-({1-[4-(3,4-difluorofenoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida

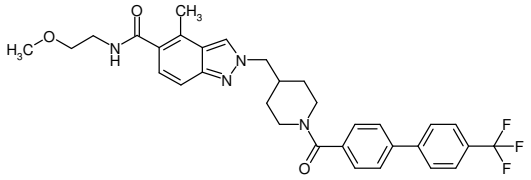


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 23 mg del compuesto del título a partir de 100 mg de 71a y 102 mg de ácido 4-(3,4-difluorofenoxi)benzoico en DMF.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,17 - 1,30 (2H), 1,35 - 1,70 (2H), 2,20 - 2,40 (1H), 2,52 (3H), 2,74 - 3,14 (2H), 3,28 (3H), 3,40 (2H), 3,43 - 3,51 (2H), 3,52 - 3,89 (1H), 4,35 (3H), 6,94 (1H), 7,05

(2H), 7,18 (1H), 7,30 (1H), 7,36 - 7,59 (4H), 8,15 (1H), 8,51 (1H).

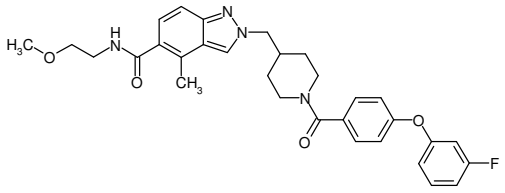
Ejemplo 360: N-(2-metoxietil)-4-metil-2-[(1-{[4'-(trifluorometil)bifenil-4-il]-carbonil}piperidin-4-il)metil]-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 44 mg del compuesto del título a partir de 100 mg de 71a y 109 mg de ácido 4'-(trifluorometil)bifenil-4-carboxílico en DMF

LC-MS: R_t = 1,28 min, MS (ES+): m/z = 579 $(M+H)^+$.

Ejemplo 361: 2-({1-[4-(3-fluorofenoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

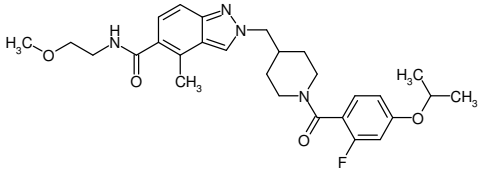


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 43 mg del compuesto del título a partir de 100 mg de 71a y 95 mg de ácido 4-(3-fluorofenoxi)benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,17 - 1,31 (2H), 1,33 - 1,69 (2H), 2,19 - 2,38 (1H), 2,52 (3H),

2,70 – 3,11 (2H), 3,28 (3H), 3,36 – 3,43 (2H), 3,43 – 3,49 (2H), 3,54 – 3,85 (1H), 4,35 (3H), 6,85 – 7,13 (5H), 7,18 (1H), 7,35 – 7,55 (4H), 8,15 (1H), 8,51 (1H).

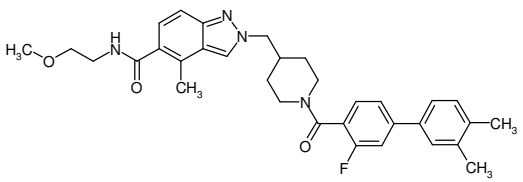
Ejemplo 362: 2-{[1-(2-fluoro-4-isopropoxibenzoil)piperidin-4-il]metil}-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 31 mg del compuesto del título a partir de 75 mg de 71a y 41 mg de ácido 2-fluoro-4-isopropoxibenzoico.

^{1}H-RMN (300 MHz, cloroformo-d): δ [ppm] = 1,21 – 1,42 (8H), 1,51 (1H), 1,69 (1H), 2,38 (1H), 2,56 – 2,80 (4H), 2,87 – 3,08 (1H), 3,36 (3H), 3,48 – 3,73 (4H), 4,28 (2H), 4,51 (1H), 4,74 (1H), 5,28 (1H), 6,19 (1H), 6,54 (1H), 6,67 (1H), 7,13 – 7,38 (2H), 7,50 (1H), 7,94 (1H).

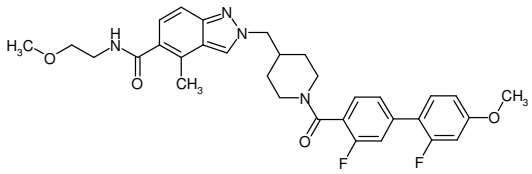
Ejemplo 363: 2-({1-[(3-fluoro-3',4'-dimetilbifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 35 mg del compuesto del título a partir de 75 mg de 71a y 50 mg de ácido 3-fluoro-3',4'-dimetilbifenil-4-carboxílico.

^{1}H-RMN (300 MHz, cloroformo-d): δ [ppm] = 1,25 - 1,51 (2H), 1,57 (1H), 1,76 (1H), 2,25 - 2,37 (6H), 2,45 (1H), 2,61 - 2,71 (3H), 2,79 (1H), 3,06 (1H), 3,40 (3H), 3,53 - 3,77 (5H), 4,34 (2H), 4,83 (1H), 6,04 - 6,30 (1H), 7,15 - 7,47 (7H), 7,55 (1H), 7,98 (1H).

Ejemplo 364: 2-({1-[(2',3-difluoro-4'-metoxibifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

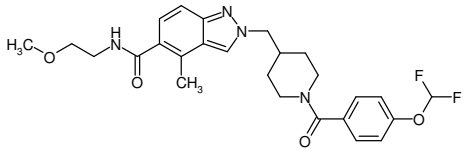


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 28 mg del compuesto del título a partir de 90 mg de 71a y 65 mg de ácido 3,2'-difluoro-4'-metoxibifenil-4-carboxílico.

^{1}H-RMN (300 MHz, cloroformo-d): δ [ppm] = 1,25 - 1,50 (2H), 1,50 - 1,84 (2H), 2,44 (1H), 2,66 (3H), 2,78 (1H), 3,03 (1H), 3,39 (3H), 3,53 - 3,76 (5H), 3,85 (3H), 4,23 - 4,45 (2H), 4,83 (1H), 6,17 (1H), 6,64 - 6,92 (2H), 7,18 - 7,48 (5H), 7,54 (1H), 7,97 (1H).

Ejemplo 365: 2-({1-[4-

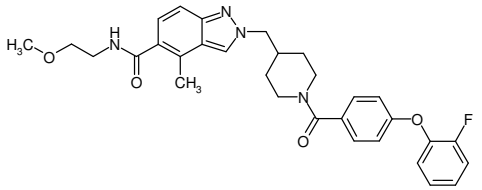
(difluorometoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 23 mg del compuesto del título a partir de 75 mg de 71a y 38 mg de ácido 4-(difluorometoxi)benzoico.

^{1}H-RMN (300 MHz, cloroformo-d): δ [ppm] = 1,26 (2H), 1,59 (2H), 2,26 - 2,49 (1H), 2,62 (3H), 2,84 (2H), 3,36 (3H), 3,43 (1H), 3,50 - 3,96 (4H), 4,29 (2H), 4,46 - 5,02 (1H), 6,13 - 6,25 (1H), 6,26 - 6,82 (1H), 7,11 (2H), 7,22 - 7,43 (3H), 7,50 (1H), 7,93 (1H).

Ejemplo 366: 2-({1-[4-(2-fluorofenoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

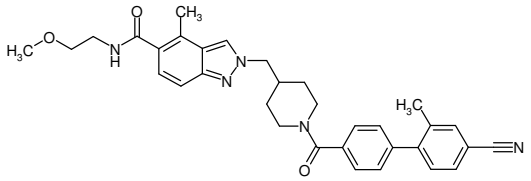


120 mg de compuesto 54, 26 mg de o-fluorofenol, 152 mg de carbonato de cesio, 6,7 mg de bromuro de cobre (I) y 3,2 mg de (2-piridil)acetona se suspendieron en 6 ml de dimetilsulfóxido y se agitaron durante 3 días a 80 °C. La mezcla de reacción se

filtró, la torta filtrante se lavó con agua y acetato de etilo y la fase acuosa se extrajo varias veces con acetato de etilo. Las fases orgánicas combinadas se secaron con sulfato de sodio y se concentraron. El residuo se purificó por HPLC y se obtuvieron 12 mg del compuesto del título.

^{1}H-RMN (300 MHz, cloroformo-d): δ [ppm] = 1,16 - 1,47 (2H), 1,62 (2H), 2,43 (1H), 2,66 (3H), 2,85 (2H), 3,39 (3H), 3,53 - 3,74 (4H), 3,79 - 4,19 (1H), 4,33 (2H), 4,47 - 5,02 (1H), 6,15 (1H), 6,96 (2H), 7,07 - 7,23 (3H), 7,30 - 7,45 (3H), 7,54 (1H), 7,96 (1H).

Ejemplo 367: 2-({1-[(4'-ciano-2'-metilbifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

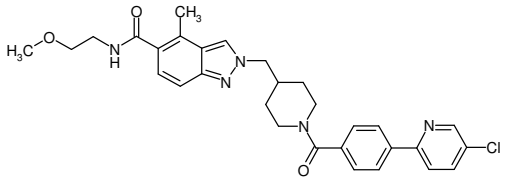


De forma análoga al Ejemplo 317, se obtuvieron 40 mg del compuesto del título a partir de 80 mg de 54 y 38 mg de ácido (2-metil-4-cianofenil)borónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,20 - 1,34 (2H), 1,36 - 1,69 (2H), 2,28 (4H), 2,53 (3H), 2,69 - 3,19 (2H), 3,28 (3H), 3,36 - 3,43 (2H), 3,43 - 3,50 (2H), 3,54 - 3,77 (1H), 4,37 (3H), 7,18 (1H), 7,37 -

7,50 (6H), 7,74 (1H), 7,83 (1H), 8,15 (1H), 8,52 (1H).

Ejemplo 368: 2-({1-[4-(5-cloropiridin-2-il)benzoil]piperidin-4-il}metil)-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida

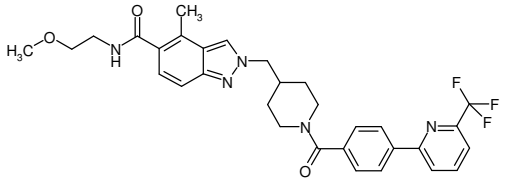


200 mg del bromuro de arilo preparado en el Ejemplo 54 junto con 187 mg de éster pinacólico del ácido (5-cloropiridin-2-il)-2-borónico se colocaron primero en 3 ml de DMF, se trataron con 48 mg de 1,1'-bis(difenilfosfino)ferrocenodicloropaladio (II), 39 mg de cloruro de cobre (I), 254 mg de carbonato de cesio y 22 mg de 1,1'-bis(difenilfosfino)ferroceno y se calentaron durante aproximadamente 1 día a 70 °C, hasta no observar más un progreso de la reacción. La mezcla de reacción se trató con agua y solución saturada de bicarbonato de sodio, se trató varias veces con acetato de etilo y las fases orgánicas combinadas se secaron con sulfato de sodio y se concentraron. Después de purificación por HPLC, esto dio como resultado 92 mg del compuesto del título.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,19 – 1,36 (2H), 1,37 – 1,72 (2H), 2,23 – 2,41 (1H), 2,52 – 2,57 (3H), 2,70 – 3,13 (2H), 3,28 (3H), 3,39 (2H), 3,45

(2H), 3,51 – 3,80 (1H), 4,36 (3H), 7,18 (1H), 7,36 – 7,52 (3H), 8,05 (2H), 8,09 – 8,22 (3H), 8,51 (1H), 8,73 (1H).

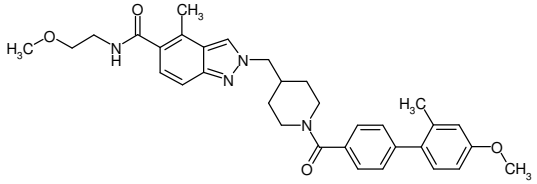
Ejemplo 369: N-(2-metoxietil)-4-metil-2-[(1-{4-[6-(trifluorometil)piridin-2-il]-benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 317, se obtuvieron 33 mg del compuesto del título a partir de 100 mg de 54 y 80 mg de éster pinacólico del ácido [6-(trifluorometil)piridin-2-il]borónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,18 – 1,35 (2H), 1,36 – 1,67 (2H), 2,25 – 2,41 (1H), 2,53 (3H), 2,70 – 3,15 (2H), 3,28 (3H), 3,35 – 3,43 (2H), 3,43 – 3,51 (2H), 3,53 – 3,73 (1H), 4,37 (3H), 7,18 (1H), 7,42 (1H), 7,53 (2H), 7,89 (1H), 8,06 – 8,26 (4H), 8,33 (1H), 8,51 (1H).

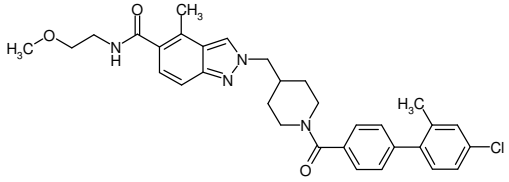
Ejemplo 370: N-(2-metoxietil)-2-({1-[(4'-metoxi-2'-metilbifenil-4-il)carbonil]-piperidin-4-il}metil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 317, se obtuvieron 52 mg del compuesto del título a partir de 100 mg de 54 y 48 mg de ácido (4-metoxi-2-metilfenil)borónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,16 - 1,35 (2H), 1,37 - 1,67 (2H), 2,23 (3H), 2,26 - 2,42 (1H), 2,53 (3H), 2,70 - 3,12 (2H), 3,28 (3H), 3,36 - 3,43 (2H), 3,43 - 3,50 (2H), 3,77 (4H), 4,36 (3H), 6,77 - 6,92 (2H), 7,10 - 7,22 (2H), 7,39 (5H), 8,15 (1H), 8,52 (1H).

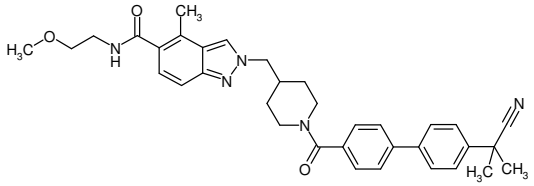
Ejemplo 371: 2-({1-[(4'-cloro-2'-metilbifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 317, se obtuvieron 43 mg del compuesto del título a partir de 100 mg de 54 y 50 mg de ácido (4-cloro-2-metilfenil)borónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,27 (2H), 1,38 - 1,70 (2H), 2,23 (4H), 2,53 (3H), 2,70 - 3,15 (2H), 3,28 (3H), 3,36 - 3,43 (2H), 3,43 - 3,49 (2H), 3,55 - 3,84 (1H), 4,36 (3H), 7,12 - 7,27 (2H), 7,28 - 7,35 (1H), 7,36 - 7,47 (6H), 8,15 (1H), 8,52 (1H).

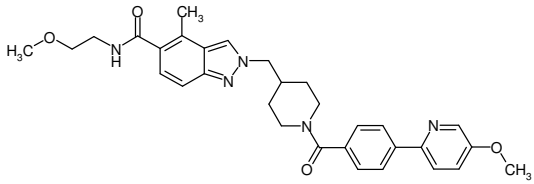
Ejemplo 372: 2-[(1-{[4'-(1-ciano-1-metiletil)bifenil-4-il]carbonil}piperidin-4-il)-metil]-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 317, se obtuvieron 67 mg del compuesto del título a partir de 100 mg de 54 y 55 mg de ácido [4-(1-ciano-1-metiletil)fenil]borónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,28 (2H), 1,36 - 1,65 (2H), 1,72 (6H), 2,24 - 2,40 (1H), 2,53 (3H), 2,70 - 3,14 (2H), 3,28 (3H), 3,36 - 3,43 (2H), 3,43 - 3,49 (2H), 3,54 - 3,77 (1H), 4,36 (3H), 7,18 (1H), 7,38 - 7,50 (3H), 7,62 (2H), 7,75 (4H), 8,15 (1H), 8,52 (1H).

Ejemplo 373: N-(2-metoxietil)-2-({1-[4-(5-metoxipiridin-2-il)benzoil]piperidin-4-il}-metil)-4-metil-2H-indazol-5-carboxamida

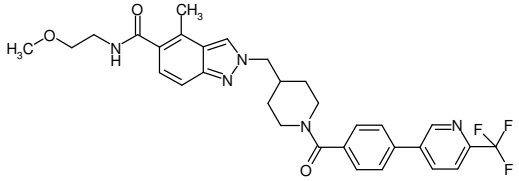


De forma análoga al Ejemplo 368, se obtuvieron 12 mg del compuesto del título a partir de 200 mg de 54 y 183 mg de éster pinacólico del ácido (5-metoxipiridin-

2-il)borónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,22 - 1,33 (2H), 1,36 - 1,66 (2H), 2,23 - 2,38 (1H), 2,53 (3H), 2,68 - 3,12 (2H), 3,28 (3H), 3,35 - 3,42 (2H), 3,43 - 3,50 (2H), 3,54 - 3,78 (1H), 3,88 (3H), 4,36 (3H), 7,18 (1H), 7,36 - 7,55 (4H), 7,96 (1H), 8,07 (2H), 8,13 (1H), 8,39 (1H), 8,51 (1H).

Ejemplo 374: N-(2-metoxietil)-4-metil-2-[(1-{4-[6-(trifluorometil)piridin-3-il]-benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida

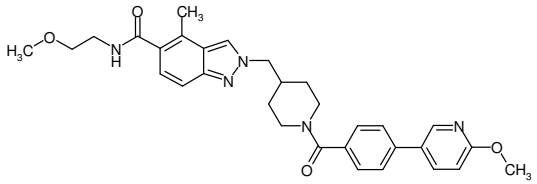


De forma análoga al Ejemplo 317, se obtuvieron 37 mg del compuesto del título a partir de 100 mg de 54 y 56 mg de ácido [2-(trifluorometil)piridin-5-il]borónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,19 - 1,36 (2H), 1,36 - 1,69 (2H), 2,21 - 2,42 (1H), 2,53 (3H), 2,70 - 3,14 (2H), 3,28 (3H), 3,36 - 3,43 (2H), 3,43 - 3,50 (2H), 3,53 - 3,72 (1H), 4,36 (3H), 7,18 (1H), 7,42 (1H), 7,53 (2H), 7,89 (2H), 8,01 (1H), 8,15 (1H), 8,41 (1H), 8,52 (1H), 9,13 (1H).

Ejemplo 375: N-(2-metoxietil)-2-({1-[4-(6-metoxipiridin-3-il)benzoil]piperidin-4-il}-metil)-4-

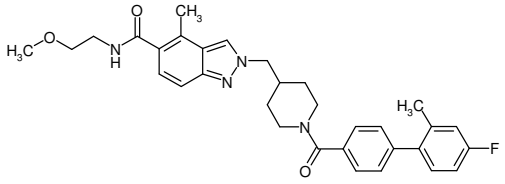
metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 317, se obtuvieron 50 mg del compuesto del título a partir de 100 mg de 54 y 47 mg de ácido (2-metoxipiridin-5-il)borónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,26 (2H), 1,34 - 1,70 (2H), 2,21 - 2,40 (1H), 2,53 (3H), 2,69 - 3,15 (2H), 3,28 (3H), 3,36 - 3,43 (2H), 3,43 - 3,49 (2H), 3,51 - 3,79 (1H), 3,90 (3H), 4,36 (3H), 6,93 (1H), 7,18 (1H), 7,36 - 7,52 (3H), 7,72 (2H), 8,05 (1H), 8,15 (1H), 8,46 - 8,57 (2H).

Ejemplo 376: 2-({1-[(4'-fluoro-2'-metilbifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

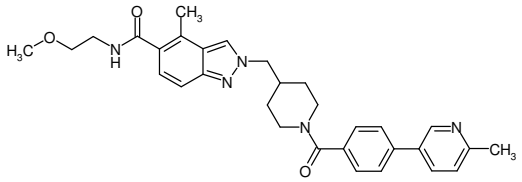


De forma análoga al Ejemplo 317, se obtuvieron 261 mg del compuesto del título a partir de 300 mg de 54 y 135 mg de ácido (4-fluoro-2-metilfenil)borónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,27 (2H),

1,37 – 1,70 (2H), 2,24 (4H), 2,53 (3H), 2,71 – 3,14 (2H), 3,28 (3H), 3,36 – 3,43 (2H), 3,43 – 3,50 (2H), 3,55 – 3,83 (1H), 4,37 (3H), 7,05 – 7,12 (1H), 7,18 (2H), 7,22 – 7,30 (1H), 7,40 (5H), 8,14 (1H), 8,52 (1H).

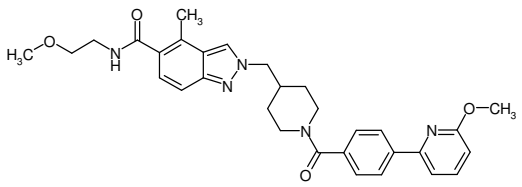
Ejemplo 377: N-(2-metoxietil)-4-metil-2-({1-[4-(6-metilpiridin-3-il)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 317, se obtuvieron 45 mg del compuesto del título a partir de 80 mg de 54 y 32 mg de ácido (2-metilpiridin-5-il)borónico a reflujo.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,26 (2H), 1,37 – 1,71 (2H), 2,18 – 2,39 (1H), 2,52 – 2,58 (3H), 2,73 – 3,16 (2H), 3,28 (3H), 3,36 – 3,43 (2H), 3,45 (2H), 3,54 – 3,79 (1H), 4,36 (3H), 7,18 (1H), 7,30 – 7,54 (4H), 7,76 (2H), 8,00 (1H), 8,15 (1H), 8,51 (1H), 8,78 (1H).

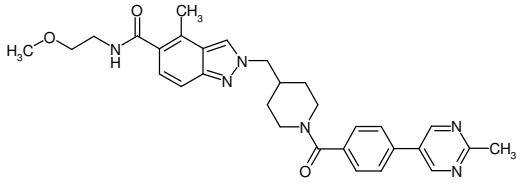
Ejemplo 378: N-(2-metoxietil)-2-({1-[4-(6-metoxipiridin-2-il)benzoil]piperidin-4-il}metil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 317, se obtuvieron 30 mg del compuesto del título a partir de 100 mg de 54 y 45 mg de ácido (6-metoxipiridin-2-il)borónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,26 (2H), 1,35 - 1,68 (2H), 2,32 (1H), 2,52 (3H), 2,70 - 3,13 (2H), 3,28 (3H), 3,36 - 3,43 (2H), 3,43 - 3,50 (2H), 3,53 - 3,74 (1H), 3,96 (3H), 4,36 (3H), 6,81 (1H), 7,18 (1H), 7,37 - 7,67 (4H), 7,81 (1H), 8,15 (3H), 8,51 (1H).

Ejemplo 379: N-(2-metoxietil)-4-metil-2-({1-[4-(2-metilpirimidin-5-il)benzoil]-piperidin-4-il}metil)-2H-indazol-5-carboxamida

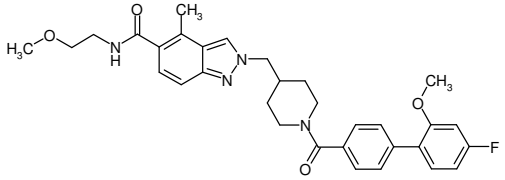


De forma análoga al Ejemplo 317, se obtuvieron 36 mg del compuesto del título a partir de 100 mg de 54 y 64 mg de éster pinacólico del ácido (2-metilpirimidin-5-il)borónico a reflujo.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,27 (2H), 1,38 - 1,70 (2H), 2,21 - 2,40 (1H), 2,53 (3H), 2,67

(3H), 2,73 – 3,16 (2H), 3,28 (3H), 3,40 (2H), 3,43 – 3,50 (2H), 3,53 – 3,76 (1H), 4,36 (3H), 7,18 (1H), 7,42 (1H), 7,51 (2H), 7,84 (2H), 8,13 (1H), 8,51 (1H), 9,05 (2H).

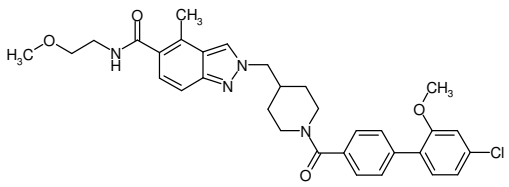
Ejemplo 380: 2-({1-[(4'-fluoro-2'-metoxibifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 317, se obtuvieron 47 mg del compuesto del título a partir de 100 mg de 54 y 50 mg de ácido (4-fluoro-2-metoxifenil)borónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,19 – 1,34 (2H), 1,37 – 1,71 (2H), 2,22 – 2,40 (1H), 2,53 (3H), 2,70 – 3,15 (2H), 3,28 (3H), 3,36 – 3,43 (2H), 3,43 – 3,50 (2H), 3,56 – 3,75 (1H), 3,79 (3H), 4,36 (3H), 6,87 (1H), 6,99 – 7,10 (1H), 7,18 (1H), 7,30 – 7,46 (4H), 7,50 (2H), 8,13 (1H), 8,51 (1H).

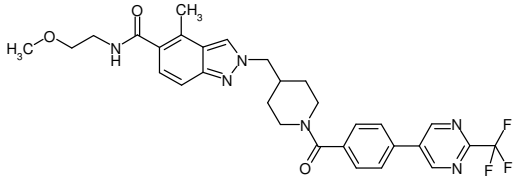
Ejemplo 381: 2-({1-[(4'-cloro-2'-metoxibifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 317, se obtuvieron 87 mg del compuesto del título a partir de 100 mg de 54 y 54 mg de ácido (4-fluoro-2-metoxifenil)borónico a reflujo.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,26 (2H), 1,39 - 1,69 (2H), 2,19 - 2,39 (1H), 2,53 (3H), 2,75 - 3,14 (2H), 3,28 (3H), 3,40 (2H), 3,45 (2H), 3,57 - 3,74 (1H), 3,81 (3H), 4,36 (3H), 7,04 - 7,25 (3H), 7,28 - 7,62 (6H), 8,13 (1H), 8,51 (1H).

Ejemplo 382: N-(2-metoxietil)-4-metil-2-[(1-{4-[2-(trifluorometil)pirimidin-5-il]-benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida

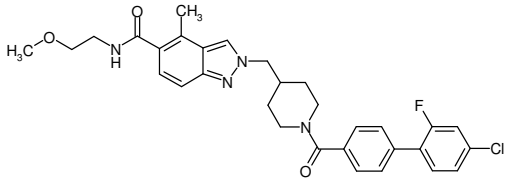


De forma análoga al Ejemplo 317, se obtuvieron 14 mg del compuesto del título a partir de 100 mg de 54 y 56 mg de ácido [2-(trifluorometil)pirimidin-5-il]borónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,24 (2H), 1,38 - 1,73 (2H), 2,22 - 2,41 (1H), 2,53 (3H), 2,70 - 2,89 (1H), 2,94 - 3,18 (1H), 3,28 (3H), 3,36 - 3,43

(2H), 3,44 – 3,49 (2H), 3,51 – 3,70 (1H), 4,37 (3H), 7,18 (1H), 7,42 (1H), 7,57 (2H), 7,97 (2H), 8,13 (1H), 8,51 (1H), 9,43 (2H).

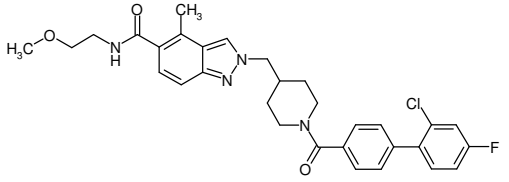
Ejemplo 383: 2-({1-[(4'-cloro-2'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 317, se obtuvieron 51 mg del compuesto del título a partir de 100 mg de 54 y 51 mg de ácido (4-cloro-2-fluorofenil)borónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,27 (2H), 1,38 – 1,68 (2H), 2,32 (1H), 2,53 (3H), 2,71 – 2,91 (1H), 2,93 – 3,16 (1H), 3,28 (3H), 3,40 (2H), 3,45 (2H), 3,53 – 3,78 (m, 1H), 4,37 (3H), 7,18 (1H), 7,33 – 7,52 (4H), 7,53 – 7,74 (4H), 8,13 (1H), 8,51 (1H).

Ejemplo 384: 2-({1-[(2'-cloro-4'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

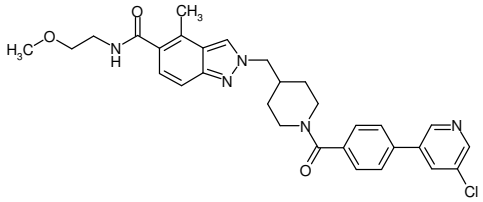


De forma análoga al Ejemplo 317, se obtuvieron 26

mg del compuesto del título a partir de 100 mg de 54 y 51 mg de ácido (2-cloro-4-fluorofenil)borónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,28 (2H), 1,38 - 1,67 (2H), 2,23 - 2,39 (1H), 2,53 (3H), 2,71 - 2,91 (1H), 2,94 - 3,15 (1H), 3,28 (3H), 3,36 - 3,43 (2H), 3,43 - 3,50 (2H), 3,54 - 3,74 (1H), 4,37 (3H), 7,18 (1H), 7,33 (1H), 7,39 - 7,63 (7H), 8,13 (1H), 8,51 (1H).

Ejemplo 385: 2-({1-[4-(5-cloropiridin-3-il)benzoil]piperidin-4-il}metil)-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida

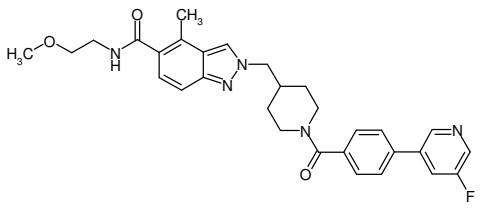


De forma análoga al Ejemplo 317, se obtuvieron 22 mg del compuesto del título a partir de 100 mg de 54 y 46 mg de ácido (5-cloropiridin-3-il)borónico a reflujo.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,21 - 1,35 (2H), 1,36 - 1,69 (2H), 2,23 - 2,40 (1H), 2,53 (3H), 2,69 - 2,90 (1H), 2,92 - 3,16 (1H), 3,28 (3H), 3,40 (2H), 3,45 (2H), 3,53 - 3,73 (1H), 4,36 (3H), 7,18 (1H), 7,35 - 7,57 (3H), 7,86 (2H), 8,15 (1H), 8,30 (1H), 8,52 (1H), 8,65 (1H), 8,90 (1H).

Ejemplo 386: 2-({1-[4-(5-fluoropiridin-3-

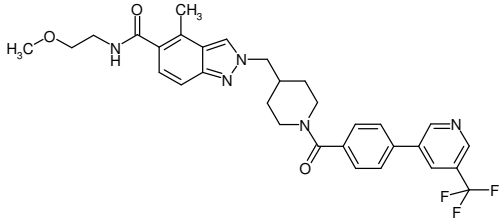
il)benzoil]piperidin-4-il}metil)-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 317, se obtuvieron 57 mg del compuesto del título a partir de 100 mg de 54 y 41 mg de ácido (5-fluoropiridin-3-il)borónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,27 (2H), 1,37 - 1,70 (2H), 2,24 - 2,40 (1H), 2,52 - 2,55 (3H), 2,70 - 2,89 (1H), 2,93 - 3,15 (1H), 3,28 (3H), 3,36 - 3,43 (2H), 3,43 - 3,50 (2H), 3,53 - 3,73 (1H), 4,36 (3H), 7,18 (1H), 7,42 (1H), 7,50 (2H), 7,86 (2H), 8,07 - 8,18 (2H), 8,51 (1H), 8,61 (1H), 8,84 (1H).

Ejemplo 387: N-(2-metoxietil)-4-metil-2-[(1-{4-[5-(trifluorometil)piridin-3-il]-benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida

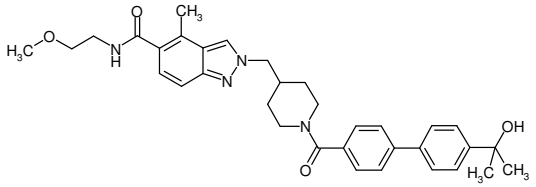


De forma análoga al Ejemplo 317, se obtuvieron 73

mg del compuesto del título a partir de 100 mg de 54 y 56 mg de ácido [5-(trifluorometil)piridin-3-il]borónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,20 - 1,35 (2H), 1,36 - 1,67 (2H), 2,23 - 2,40 (1H), 2,53 (3H), 2,69 - 2,92 (1H), 2,93 - 3,17 (1H), 3,28 (3H), 3,35 - 3,43 (2H), 3,43 - 3,49 (2H), 3,53 - 3,75 (1H), 4,37 (3H), 7,18 (1H), 7,42 (1H), 7,52 (2H), 7,93 (2H), 8,07 - 8,20 (1H), 8,45 - 8,58 (2H), 9,00 (1H), 9,24 (1H).

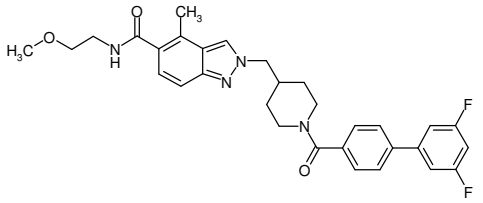
Ejemplo 388: 2-[(1-{[4'-(1-hidroxi-1-metiletil)bifenil-4-il]carbonil}piperidin-4-il)-metil]-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 317, se obtuvieron 46 mg del compuesto del título a partir de 100 mg de 54 y 77 mg de éster pinacólico del ácido (4-hidroxi-ter-butilfenil)borónico a reflujo.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,26 (2H), 1,45 (8H), 2,22 - 2,42 (1H), 2,53 (3H), 2,71 - 2,90 (1H), 2,91 - 3,14 (1H), 3,28 (3H), 3,40 (2H), 3,43 - 3,50 (2H), 3,56 - 3,80 (1H), 4,36 (3H), 5,06 (1H), 7,18 (d, 1H), 7,37 - 7,50 (3H), 7,50 - 7,67 (4H), 7,71 (2H), 8,15 (1H), 8,52 (1H).

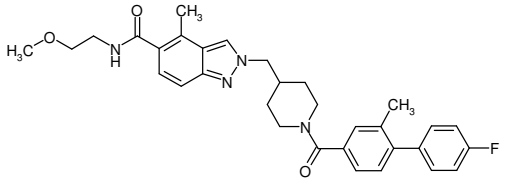
Ejemplo 389: 2-({1-[(3',5'-difluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 317, se obtuvieron 22 mg del compuesto del título a partir de 100 mg de 54 y 46 mg de ácido (3,5-difluorofenil)borónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,18 - 1,35 (2H), 1,36 - 1,70 (2H), 2,19 - 2,39 (1H), 2,52 - 2,56 (3H), 2,71 - 2,92 (1H), 2,93 - 3,17 (1H), 3,28 (3H), 3,36 - 3,43 (2H), 3,43 - 3,49 (2H), 3,52 - 3,71 (1H), 4,36 (3H), 7,11 - 7,33 (2H), 7,37 - 7,54 (5H), 7,81 (2H), 8,13 (1H), 8,51 (1H).

Ejemplo 390: 2-({1-[(4'-fluoro-2-metilbifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

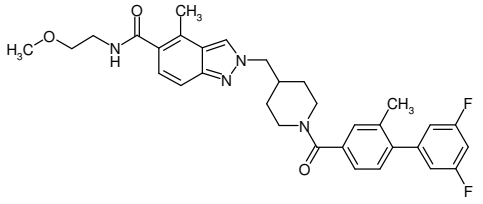


De forma análoga al Ejemplo 317, se obtuvieron 25 mg del compuesto del título a partir de 60 mg de 332 y

19 mg de ácido (4-fluorofenil)borónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,25 (2H), 1,37 - 1,67 (2H), 2,24 (4H), 2,53 (3H), 2,69 - 2,87 (1H), 2,92 - 3,14 (1H), 3,28 (3H), 3,36 - 3,43 (2H), 3,43 - 3,50 (2H), 3,56 - 3,81 (1H), 4,36 (3H), 7,11 - 7,34 (6H), 7,36 - 7,46 (3H), 8,15 (1H), 8,52 (1H).

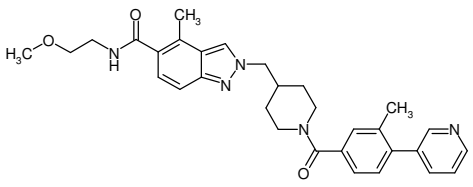
Ejemplo 391: 2-({1-[(3',5'-difluoro-2-metilbifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 317, se obtuvieron 30 mg del compuesto del título a partir de 60 mg de 332 y 27 mg de ácido (3,5-difluorofenil)borónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,23 (2H), 1,36 - 1,69 (2H), 2,27 (4H), 2,53 (3H), 2,69 - 2,90 (1H), 2,92 - 3,15 (1H), 3,28 (3H), 3,36 - 3,43 (2H), 3,45 (2H), 3,53 - 3,76 (1H), 4,36 (3H), 7,08 - 7,21 (3H), 7,22 - 7,34 (4H), 7,42 (1H), 8,15 (1H), 8,52 (1H).

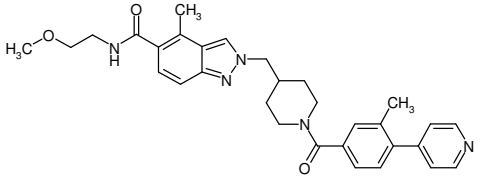
Ejemplo 392: N-(2-metoxietil)-4-metil-2-({1-[3-metil-4-(3-piridil)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 317, se obtuvieron 19 mg del compuesto del título a partir de 60 mg de 332 y 21 mg de ácdo piridin-3-ilborónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,20 - 1,33 (2H), 1,37 - 1,71 (2H), 2,26 (4H), 2,53 (3H), 2,70 - 2,88 (1H), 2,94 - 3,17 (1H), 3,28 (3H), 3,36 - 3,43 (2H), 3,43 - 3,49 (2H), 3,56 - 3,82 (1H), 4,36 (3H), 7,18 (1H), 7,23 - 7,37 (3H), 7,39 - 7,56 (2H), 7,83 (1H), 8,15 (1H), 8,52 (1H), 8,56 - 8,65 (2H).

Ejemplo 393: N-(2-metoxietil)-4-metil-2-({1-[3-metil-4-(4-piridil)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida

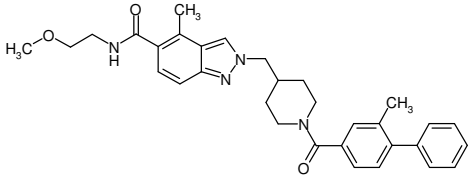


De forma análoga al Ejemplo 317, se obtuvieron 19 mg del compuesto del título a partir de 60 mg de 332 y 21 mg de ácido piridin-4-ilborónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,18 - 1,33 (2H), 1,37 - 1,67 (2H), 2,27 (4H), 2,52 - 2,56 (3H), 2,70 - 2,86 (1H), 2,93 - 3,13 (1H), 3,28 (3H), 3,36 - 3,43 (2H), 3,43 - 3,49 (2H), 3,55 - 3,75 (1H), 4,36 (3H), 7,18 (1H), 7,23 - 7,36 (3H), 7,38 - 7,48 (3H),

8,15 (1H), 8,52 (1H), 8,60 – 8,69 (2H).

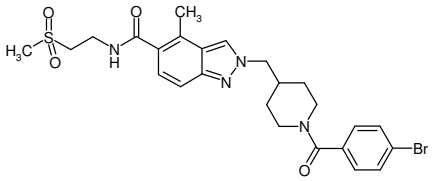
Ejemplo 394: N-(2-metoxietil)-4-metil-2-({1-[(2-metilbifenil-4-il)carbonil]piperidin-4-il}metil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 317, se obtuvieron 57 mg del compuesto del título a partir de 60 mg de 332 y 21 mg de ácido fenilborónico a reflujo.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,19 – 1,34 (2H), 1,37 – 1,67 (2H), 2,25 (4H), 2,53 (3H), 2,68 – 2,88 (1H), 2,92 – 3,17 (1H), 3,28 (3H), 3,36 – 3,43 (2H), 3,45 (2H), 3,59 – 3,81 (1H), 4,36 (3H), 7,13 – 7,32 (4H), 7,33 – 7,50 (6H), 8,15 (1H), 8,52 (1H).

Ejemplo 395: 2-{[1-(4-bromobenzoil)piperidin-4-il]metil}-N-(2-mesiletil)-4-metil-2H-indazol-5-carboxamida



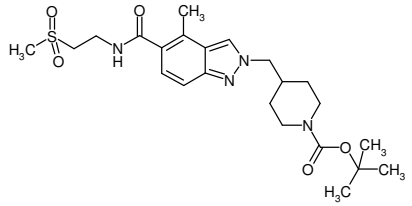
De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 383 mg del compuesto del título a partir de 1 g de 395b y 797 mg de ácido 4-bromobenzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,21 – 1,32 (2H), 1,34 – 1,67 (2H), 2,21 – 2,38 (1H), 2,55 (3H),

2,68 – 2,87 (1H), 3,05 (4H), 3,39 (2H), 3,45 – 3,59 (1H), 3,66 (2H), 4,35 (3H), 7,23 (1H), 7,28 – 7,37 (2H), 7,43 (1H), 7,59 – 7,70 (2H), 8,34 (1H), 8,52 (1H).

El material de partida se preparó de la siguiente manera:

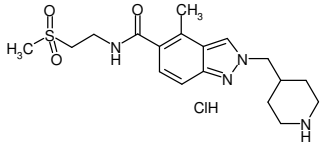
Ejemplo 395a: 4-({5-[N-(2-mesiletil)carbamoil]-4-metil-2H-indazol-2-il}-metil)piperidin-1-carboxilato de ter-butilo



De forma análoga al Ejemplo 266a, se obtuvieron 1,26 g del compuesto del título a partir de 2,506 g de 1c y 3,022 g de clorhidrato de 2-mesiletilamina.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,02 – 1,17 (2H), 1,34 – 1,54 (11H), 2,08 – 2,24 (1H), 2,55 (3H), 2,73 (2H), 3,06 (3H), 3,34 – 3,47 (2H), 3,57 – 3,76 (2H), 3,91 (2H), 4,32 (2H), 7,23 (1H), 7,43 (1H), 8,33 (1H), 8,52 (1H).

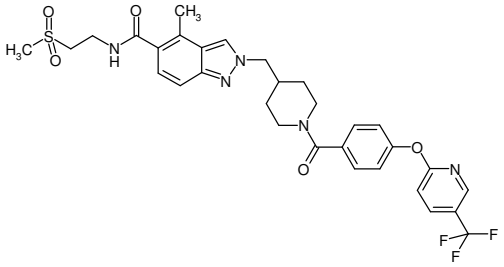
Ejemplo 395b: clorhidrato de N-(2-mesiletil)-4-metil-2-(4-piperidilmetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 258b a partir de 1,26

g de compuesto 395a, se obtuvieron 1,29 g del compuesto del título, que se hizo reaccionar sin ulterior purificación.

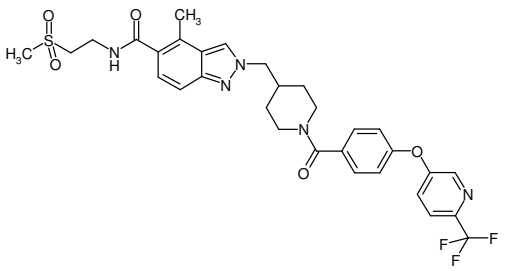
Ejemplo 396: N-(2-mesiletil)-4-metil-2-{[1-(4-{[5-(trifluorometil)piridin-2-il]oxi}-benzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 30 mg del compuesto del título a partir de 80 mg de 395b y 90 mg de ácido 4-{[5-(trifluorometil)piridin-2-il]oxi}benzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,19 - 1,35 (2H), 1,36 - 1,72 (2H), 2,22 - 2,41 (1H), 2,55 (3H), 3,06 (5H), 3,39 (2H), 3,49 - 3,89 (3H), 4,37 (3H), 7,20 - 7,32 (4H), 7,40 - 7,49 (3H), 8,25 (1H), 8,34 (1H), 8,53 (1H), 8,58 (1H).

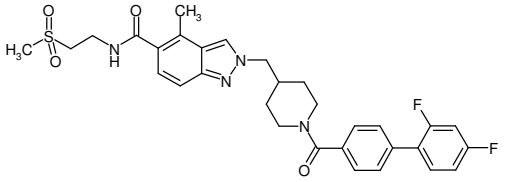
Ejemplo 397: N-(2-mesiletil)-4-metil-2-{[1-(4-{[6-(trifluorometil)piridin-3-il]oxi}-benzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 30 mg del compuesto del título a partir de 80 mg de 395b y 90 mg de 303b en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,24 (2H), 1,35 – 1,70 (2H), 2,22 – 2,40 (1H), 2,55 (3H), 3,06 (5H), 3,39 (2H), 3,55 – 3,75 (3H), 4,36 (3H), 7,20 – 7,28 (3H), 7,40 – 7,49 (3H), 7,65 (1H), 7,92 (1H), 8,34 (1H), 8,53 (1H), 8,60 (1H).

Ejemplo 398: 2-({1-[(2',4'-difluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-mesil-etil)-4-metil-2H-indazol-5-carboxamida

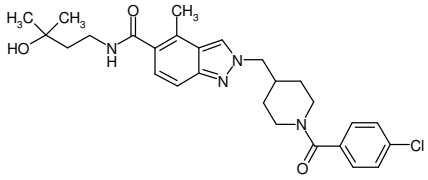


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 25 mg del compuesto del título a partir de 80 mg de 395b y 74 mg de ácido 2',4'-difluoro-bifenil-4-carboxílico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,21 – 1,35 (2H), 1,37 – 1,70 (2H), 2,22 – 2,41 (1H), 2,55 (3H), 3,05 (5H), 3,38 (2H), 3,50 – 3,83 (3H), 4,37 (3H), 7,15

– 7,29 (2H), 7,31 – 7,52 (4H), 7,55 – 7,73 (3H), 8,34 (1H), 8,53 (1H).

Ejemplo 399: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-(3-hidroxi-3-metilbutil)-4-metil-2H-indazol-5-carboxamida

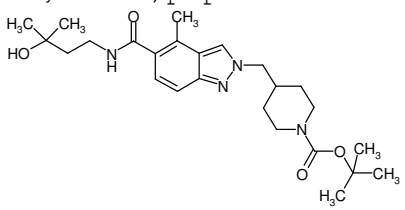


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 37 mg del compuesto del título a partir de 160 mg de 399b y 105 mg de ácido 4-clorobenzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,14 (6H), 1,17 – 1,32 (2H), 1,33 – 1,71 (4H), 2,23 – 2,37 (1H), 2,51 (3H), 2,68 – 2,87 (1H), 2,87 – 3,13 (1H), 3,31 (2H), 3,47 – 3,55 (1H), 4,34 (s, 4H), 7,17 (1H), 7,33 – 7,45 (3H), 7,50 (2H), 7,97 – 8,09 (1H), 8,50 (1H).

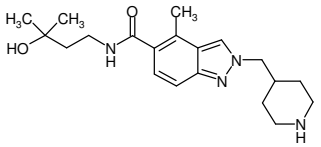
El material de partida se preparó de la siguiente manera:

Ejemplo 399a: 4-({5-[N-(3-hidroxi-3-metilbutil)carbamoil]-4-metil-2H-indazol-2-il}metil)piperidin-1-carboxilato de ter-butilo



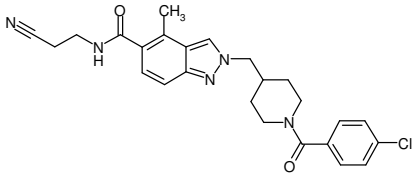
De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 150 mg de 1d y 69 mg de 4-amino-2-metilbutan-2-ol en DMF se hicieron reaccionar a 60 °C. Después de la separación de fases y la extracción, las fases orgánicas combinadas se lavaron adicionalmente con ácido clorhídrico 0,1 N y solución saturada de bicarbonato de sodio. Esto dio 132 mg del compuesto del título, que se usó en la siguiente etapa sin ulterior purificación.

Ejemplo 399b: N-(3-hidroxi-3-metilbutil)-4-metil-2-(4-piperidilmetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 258b, a partir de 132 mg de 399a, se obtuvieron 162 mg del compuesto del título, que se usó en la siguiente etapa sin ulterior purificación.

Ejemplo 400: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-(2-cianoetil)-4-metil-2H-indazol-5-carboxamida



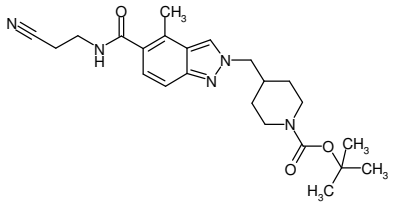
De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 55 mg del compuesto del título a partir de

177 mg de 400b y 128 mg de ácido 4-clorobenzoico en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,23 (2H), 1,33 – 1,70 (2H), 2,20 – 2,38 (1H), 2,56 (3H), 2,78 (3H), 2,90 – 3,11 (1H), 3,47 (3H), 4,35 (3H), 7,22 (1H), 7,34 – 7,56 (5H), 8,44 – 8,57 (2H).

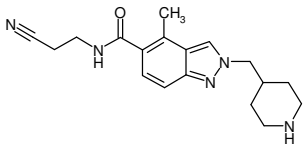
El material de partida se preparó de la siguiente manera:

Ejemplo 400a: 4-({5-[N-(2-cianoetil)carbamoil]-4-metil-2H-indazol-2-il}-metil)-piperidin-1-carboxilato de ter-butilo



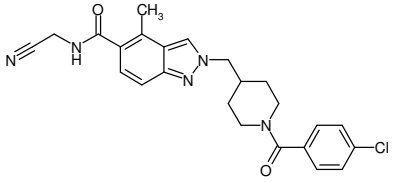
De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 150 mg de 1d y 42 mg de 3-aminopropannitrilo en DMF se hicieron reaccionar a 60 °C. Después de la separación de fases y la extracción, las fases orgánicas combinadas se lavaron adicionalmente con ácido clorhídrico 0,1 N y solución saturada de bicarbonato de sodio. Esto dio 137 mg del compuesto del título, que se usó en la siguiente etapa sin ulterior purificación.

Ejemplo 400b: N-(2-cianoetil)-4-metil-2-(4-piperidilmetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 258b, a partir de 137 mg de 400a, se obtuvieron 177 mg del compuesto del título, que se usó en la siguiente etapa sin ulterior purificación.

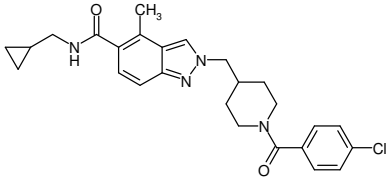
Ejemplo 401: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-(cianometil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 75 mg del compuesto del título a partir de 90 mg de 238c y 29 mg de aminoacetonitrilo en DMF.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,21 - 1,33 (23H), 1,34 - 1,69 (2H), 2,15 - 2,41 (1H), 2,57 (3H), 2,75 - 2,86 (1H), 2,93 - 3,14 (1H), 3,39 - 3,69 (1H), 4,29 (2H), 4,33 - 4,55 (3H), 7,18 - 7,28 (1H), 7,39 (2H), 7,43 - 7,55 (3H), 8,57 (1H), 8,77 - 8,90 (1H).

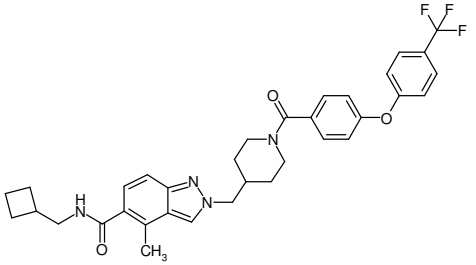
Ejemplo 402: 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-(ciclopropilmetil)-4-metil-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 44 mg del compuesto del título a partir de 90 mg de 238c) y 19 mg de ciclopropilmetilamina en DMF.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 0,23 (2H), 0,33 – 0,53 (2H), 0,94 – 1,11 (1H), 1,20 – 1,33 (2H), 1,34 – 1,68 (2H), 2,21 – 2,41 (1H), 2,54 (3H), 2,69 – 2,85 (1H), 2,93 – 3,08 (1H), 3,13 (2H), 3,44 – 3,68 (1H), 4,35 (3H), 7,18 (1H), 7,33 – 7,46 (3H), 7,47 – 7,60 (2H), 8,07 – 8,30 (1H), 8,51 (1H).

Ejemplo 403: N-(ciclobutilmetil)-4-metil-2-[(1-{4-[4-(trifluorometil)fenoxi]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida



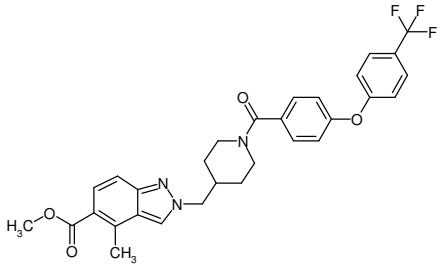
De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 48 mg del compuesto del título a partir de 137 mg de 403b y 31 mg de clorhidrato de (ciclobutilamino)metilamina.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,17 – 1,32 (2H), 1,35 – 1,64 (2H), 1,67 – 1,90 (4H), 1,93 – 2,08

(2H), 2,22 – 2,38 (1H), 2,51 – 2,52 (3H), 2,69 – 2,88 (1H), 2,90 – 3,13 (1H), 3,20 – 3,30 (2H), 3,51 – 3,83 (1H), 4,36 (3H), 7,09 – 7,27 (5H), 7,35 – 7,52 (3H), 7,76 (2H), 8,13 (1H), 8,51 (1H).

El material de partida se preparó de la siguiente manera:

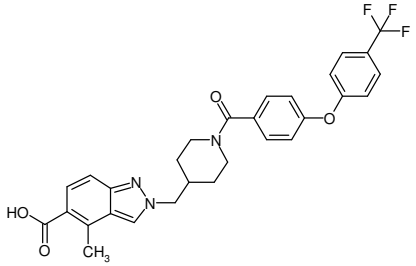
Ejemplo 403a: 4-metil-2-[(1-{4-[4-(trifluorometil)fenoxi]benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxilato de metilo



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 2,73 g del compuesto del título a partir de 3,76 g de 238a y 3,28 g de ácido 4-[4-(trifluorometil)fenoxi]benzoico.

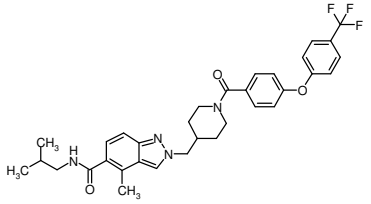
^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,19 – 1,35 (2H), 1,38 – 1,74 (2H), 2,17 – 2,41 (1H), 2,76 (3H), 2,78 – 3,14 (2H), 3,44 – 3,76 (1H), 3,82 (3H), 4,37 (3H), 7,06 – 7,28 (4H), 7,38 – 7,50 (3H), 7,67 (1H), 7,76 (2H), 8,71 (1H).

Ejemplo 403b: ácido 4-metil-2-[(1-{4-[4-(trifluorometil)fenoxi]benzoil}piperidin-4-il)-metil]-2H-indazol-5-carboxílico



De forma análoga al Ejemplo 1d, a partir de 1,05 g de 403a, se obtuvieron 970 mg del compuesto del título, que se usó en la siguiente etapa sin ulterior purificación.

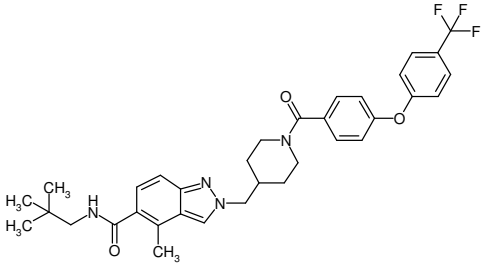
Ejemplo 404: N-isobutil-4-metil-2-[(1-{4-[4-(trifluorometil)fenoxi]benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 35 mg del compuesto del título a partir de 100 mg de 403b y 14 mg de isobutilamina.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 0,91 (6H), 1,24 (2H), 1,34 - 1,69 (2H), 1,82 (1H), 2,19 - 2,42 (1H), 2,52 (3H), 2,71 - 2,90 (1H), 3,06 (3H), 3,51 - 3,85 (1H), 4,36 (3H), 7,05 - 7,27 (5H), 7,37 - 7,52 (3H), 7,76 (2H), 8,16 (1H), 8,51 (1H).

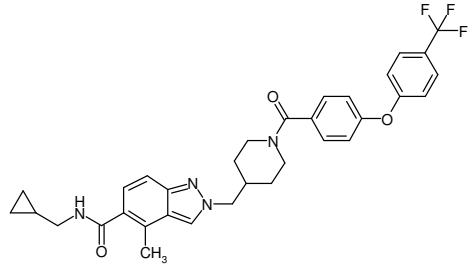
Ejemplo 405: 4-metil-N-neopentil-2-[(1-{4-[4-(trifluorometil)fenoxi]benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 36 mg del compuesto del título a partir de 100 mg de 403b y 16 mg de neopentilamina.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 0,92 (9H), 1,17 - 1,32 (2H), 1,34 - 1,69 (2H), 2,21 - 2,38 (1H), 2,52 - 2,57 (3H), 2,70 - 2,88 (1H), 3,08 (3H), 3,53 - 3,85 (1H), 4,36 (3H), 7,04 - 7,28 (5H), 7,35 - 7,52 (3H), 7,76 (2H), 8,12 (1H), 8,51 (1H).

Ejemplo 406: N-(ciclopropilmetil)-4-metil-2-[(1-{4-[4-(trifluorometil)fenoxi]-benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida

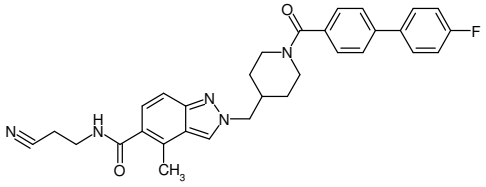


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 33 mg del compuesto del título a partir de 100 mg de 403b y 26 mg de ciclopropilmetilamina.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 0,23 (2H), 0,35 - 0,54 (2H), 0,93 - 1,11 (1H), 1,23 (2H), 1,36 - 1,67 (2H), 2,18 - 2,41 (1H), 2,54 (3H), 2,66 - 3,22

(4H), 3,47 – 3,85 (1H), 4,36 (3H), 7,03 – 7,29 (5H), 7,35 – 7,53 (3H), 7,76 (2H), 8,22 (1H), 8,52 (1H).

Ejemplo 407: N-(2-cianoetil)-2-({1-[(4'-fluorobifenil-4-il)carbonil]piperidin-4-il}-metil)-4-metil-2H-indazol-5-carboxamida

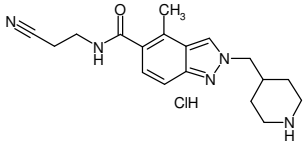


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 37 mg del compuesto del título a partir de 140 mg de 407a y 84 mg de ácido 4'-fluorobifenil-4-carboxílico.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,18 – 1,37 (2H), 1,37 – 1,68 (2H), 2,22 – 2,41 (1H), 2,56 (3H), 2,78 (4H), 3,39 – 3,53 (2H), 3,56 – 3,82 (1H), 4,37 (3H), 7,14 – 7,37 (3H), 7,39 – 7,53 (3H), 7,63 – 7,83 (4H), 8,36 – 8,60 (2H).

El material de partida se preparó de la siguiente manera:

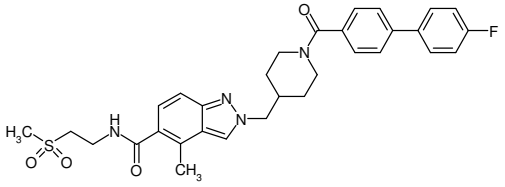
Ejemplo 407a: clorhidrato de N-(2-cianoetil)-4-metil-2-(4-piperidilmetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 165 mg de 400a, se obtuvieron 140 mg del compuesto del título,

que se usó en la siguiente etapa sin ulterior purificación.

Ejemplo 408: 2-({1-[(4'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-mesil-etil)- 4-metil-2H-indazol-5-carboxamida

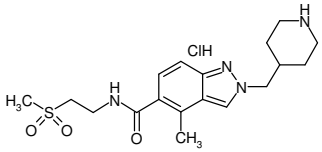


De forma análoga al Ejemplo 1b), Versión B, se obtuvieron 126 mg del compuesto del título a partir de 300 mg de 408a) y 156 mg de ácido 4'-fluorobifenil-4-carboxílico.

LC-MS: R_t = 1,20 min, MS (ES+): m/z = 577 $(M+H)^+$.

El material de partida se preparó de la siguiente manera:

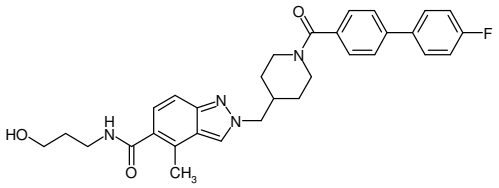
Ejemplo 408a: clorhidrato de N-(2-mesiletil)-4-metil-2-(4-piperidilmetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 346 mg de 395a, se obtuvieron 300 mg del compuesto del título, que se usó en la siguiente etapa sin ulterior purificación.

Ejemplo 409: 2-({1-[(4'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(3-hidroxi-propil)-

4-metil-2H-indazol-5-carboxamida

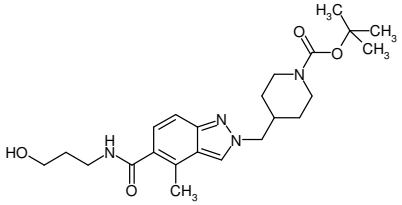


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 20 mg del compuesto del título a partir de 124 mg de 409b) y 73 mg de ácido 4'-fluorobifenil-4-carboxílico.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,26 (2H), 1,38 - 1,59 (2H), 1,67 (2H), 2,23 - 2,42 (1H), 2,52 - 2,57 (3H), 2,69 - 3,17 (2H), 3,19 - 3,94 (6H), 4,36 (3H), 7,18 (1H), 7,31 (2H), 7,38 - 7,51 (3H), 7,63 - 7,86 (4H), 8,08 (1H), 8,51 (1H).

El material de partida se preparó de la siguiente manera:

Ejemplo 409a: 4-({5-[N-(3-hidroxipropil)carbamoil]-4-metil-2H-indazol-2-il}-metil)piperidin-1-carboxilato de ter-butilo

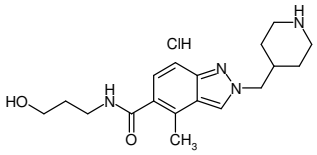


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 151 mg del compuesto del título a partir de 150 mg de 1d y 30 mg de 3-amino-propan-1-ol.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,01 - 1,30

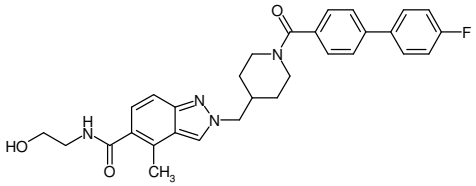
(3H), 1,32 – 1,49 (10H), 1,67 (2H), 2,08 – 2,27 (1H), 2,52 (3H), 2,57 – 2,80 (2H), 3,29 (2H), 3,41 – 3,54 (2H), 3,81 – 4,00 (2H), 4,32 (2H), 4,48 (1H), 7,18 (1H), 7,42 (1H), 8,10 (1H), 8,50 (1H).

Ejemplo 409b: N-(3-hidroxipropil)-4-metil-2-(4-piperidilmetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 246 mg de 409a, se obtuvieron 124 mg del compuesto del título, que se usó en la siguiente etapa sin ulterior purificación.

Ejemplo 410: 2-({1-[(4'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-hidroxi-etil)-4-metil-2H-indazol-5-carboxamida



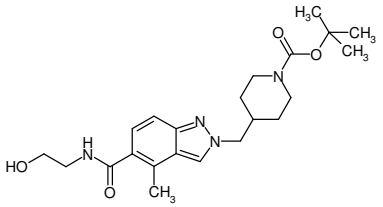
De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 36 mg del compuesto del título a partir de 117 mg de 410b y 72 mg de ácido 4'-fluorobifenil-4-carboxílico.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,26 (2H), 1,39 – 1,74 (2H), 2,21 – 2,40 (1H), 2,53 (3H), 2,75 – 3,16 (2H), 3,20 – 3,37 (2H), 3,43 – 3,74 (4H), 4,36

(3H), 7,21 (1H), 7,31 (2H), 7,38 – 7,52 (3H), 7,65 – 7,81 (4H), 8,03 (1H), 8,51 (1H).

El material de partida se preparó de la siguiente manera:

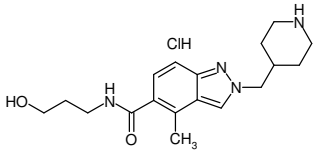
Ejemplo 410a: 4-({5-[N-(2-hidroxietil)carbamoil]-4-metil-2H-indazol-2-il}-metil)piperidin-1-carboxilato de ter-butilo



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 143 mg del compuesto del título a partir de 150 mg de 1d) y 25 mg de 2-aminoetan-1-ol.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,01 – 1,30 (3H), 1,32 – 1,51 (10H), 2,07 – 2,26 (1H), 2,52 – 2,55 (3H), 2,58 – 2,82 (2H), 3,30 (2H), 3,45 – 3,58 (2H), 3,83 – 3,98 (2H), 4,32 (2H), 4,69 (1H), 7,21 (1H), 7,41 (1H), 8,05 (1H), 8,50 (1H).

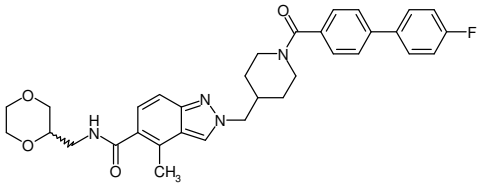
Ejemplo 410b: clorhidrato de N-(3-hidroxipropil)-4-metil-2-(4-piperidilmetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a) a partir de 138 mg de 410a, se obtuvieron 117 mg del compuesto del título obtained, que se usó en la siguiente etapa sin ulterior

purificación.

Ejemplo 411: (+/-)-N-(1,4-dioxan-2-ilmetil)-2-({1-[(4'-fluorobifenil-4-il)carbonil]-piperidin-4-il}metil)-4-metil-2H-indazol-5-carboxamida

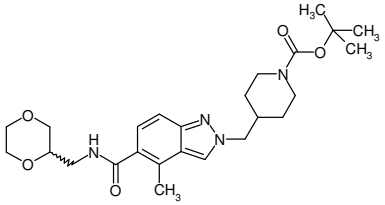


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 62 mg del compuesto del título a partir de 226 mg de 411b) y 119 mg de ácido 4'-fluorobifenil-4-carboxílico.

^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 1,19 - 1,34 (2H), 1,37 - 1,73 (2H), 2,23 - 2,42 (1H), 2,53 (3H), 2,69 - 2,90 (1H), 2,90 - 3,14 (1H), 3,17 - 3,30 (3H), 3,47 (1H), 3,58 (1H), 3,59 - 3,70 (3H), 3,71 - 3,82 (2H), 4,37 (3H), 7,19 (1H), 7,31 (2H), 7,38 - 7,53 (3H), 7,66 - 7,81 (4H), 8,18 (1H), 8,52 (1H).

El material de partida se preparó de la siguiente manera:

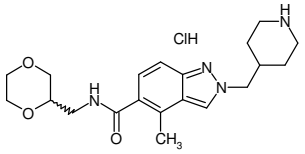
Ejemplo 411a: 4-({5-[N-(1,4-dioxan-2-ilmetil)carbamoil]-4-metil-2H-indazol-2-il}metil)piperidin-1-carboxilato de (+/-)-ter-butilo



De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 267 mg del compuesto del título a partir de 250 mg de 1d y 78 mg de (+/-)-1,4-dioxan-2-ilmetilamina.

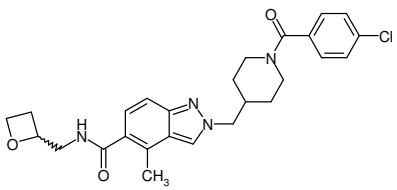
^{1}H-RMN (400 MHz, DMSO-d_6): δ [ppm] = 0,99 - 1,18 (2H), 1,38 (11H), 2,09 - 2,24 (1H), 2,53 (3H), 3,10 - 3,29 (4H), 3,41 - 3,52 (1H), 3,53 - 3,70 (4H), 3,70 - 3,81 (2H), 3,84 - 3,98 (2H), 4,32 (2H), 7,18 (1H), 7,41 (1H), 8,12 - 8,24 (1H), 8,51 (1H).

Ejemplo 411b: clorhidrato de (+/-)-N-(1,4-dioxan-2-ilmetil)-4-metil-2-(4-piperidilmetil)-2H-indazol-5-carboxamida



De forma análoga al Ejemplo 1a, a partir de 261 mg de 411a, se obtuvieron 226 mg del compuesto del título, que se usó en la siguiente etapa sin ulterior purificación.

Ejemplo 412: (+/-)-2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metil-N-(oxetan-2-il-metil)-2H-indazol-5-carboxamida

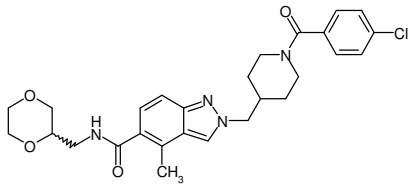


De forma análoga al Ejemplo 1b, Versión B, se

obtuvieron 55 mg del compuesto del título a partir de 350 mg de 238c) y 83 mg de (+/-)-oxetan-2-ilmetilamina.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,16 - 1,31 (2H), 1,33 - 1,69 (2H), 2,19 - 2,38 (2H), 2,53 (3H), 2,58 - 2,66 (1H), 2,66 - 2,86 (1H), 2,90 - 3,14 (1H), 3,38 - 3,64 (3H), 4,35 (5H), 4,71 - 4,96 (1H), 7,19 (1H), 7,33 - 7,45 (3H), 7,47 - 7,55 (2H), 8,21 - 8,37 (1H), 8,51 (1H).

Ejemplo 413: (+/-)-2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-(1,4-dioxan-2-ilmetil)-4-metil-2H-indazol-5-carboxamida

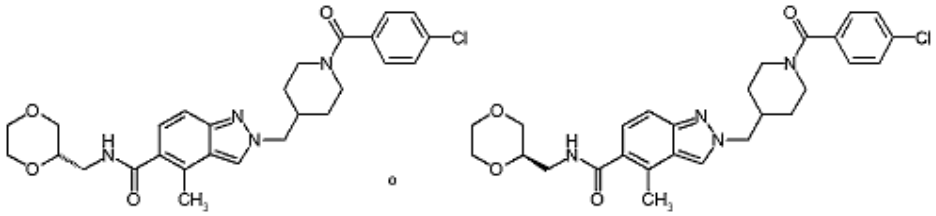


De forma análoga al Ejemplo 1b, Versión B, se obtuvieron 185 mg del compuesto del título a partir de 376 mg de 238c y 111 mg de clorhidrato de (+/-)-1,4-dioxan-2-ilmetilamina.

^{1}H-RMN (300 MHz, DMSO-d_6): δ [ppm] = 1,19 - 1,32 (2H), 1,33 - 1,66 (2H), 2,20 - 2,40 (1H), 2,53 (3H), 2,71 - 2,86 (1H), 2,90 - 3,11 (1H), 3,16 - 3,32 (3H), 3,40 - 3,59 (3H), 3,60 - 3,70 (2H), 3,71 - 3,83 (2H), 4,35 (3H), 7,18 (1H), 7,31 - 7,46 (3H), 7,46 - 7,60 (2H), 8,21 (1H), 8,51 (1H).

Ejemplo 414: (R o S)-2-{[1-(4-clorobenzoil)piperidin-4-

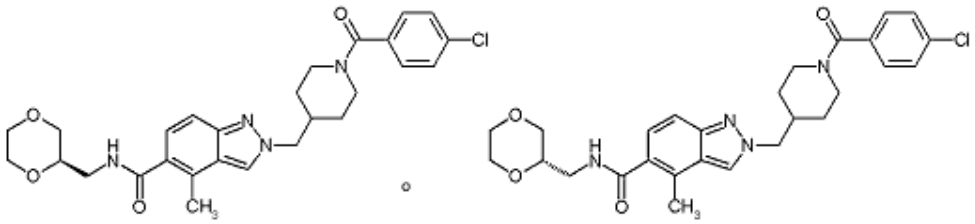
il]metil}-N-(1,4-dioxan-2-il-metil)-4-metil-2H-indazol-5-carboxamida



A partir de 185 mg del racemato preparado en el Ejemplo 413, se obtuvieron 51 mg del compuesto del título junto con 58 mg del enantiómero de elución más lenta (Ejemplo 415) por separación de racematos por medio de HPLC quiral preparativa (Método D).

HPLC quiral analítica: 12,62 min.

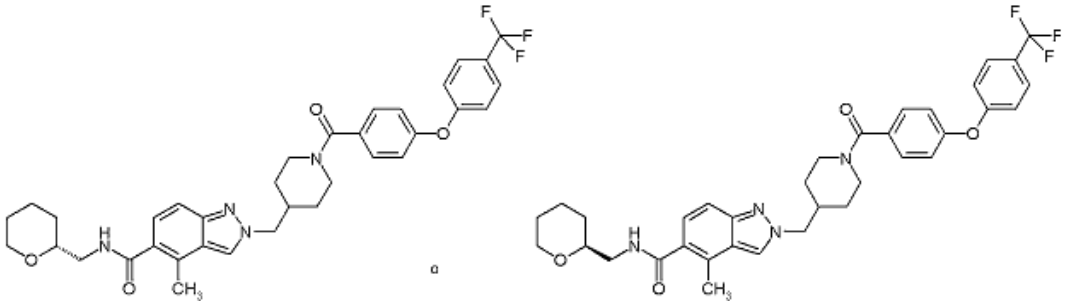
Ejemplo 415: (S o R)-2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-(1,4-dioxan-2-il-metil)-4-metil-2H-indazol-5-carboxamida



A partir de 185 mg del racemato preparado en el Ejemplo 413, se obtuvieron 58 mg del compuesto del título junto con 51 mg del enantiómero de elución más rápida (Ejemplo 414) por separación de racematos por medio de HPLC quiral preparativa (Método D).

HPLC quiral analítica: 13,68 min.

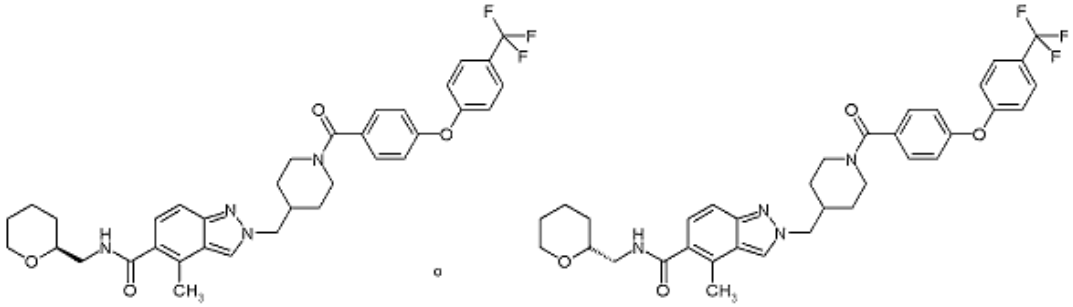
Ejemplo 416: (R o S)-4-metil-N-(3,4,5,6-tetrahidro-2H-piran-2-ilmetil)-2-[(1-{4-[4-(trifluorometil)fenoxi]benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida



A partir de 231 mg del racemato preparado en el Ejemplo 248, se obtuvieron 24 mg del compuesto del título junto con 24 mg del enantiómero de elución más lenta (Ejemplo 417) por separación de racematos por medio de HPLC quiral preparativa (Método E).

HPLC quiral analítica: 7,08 min.

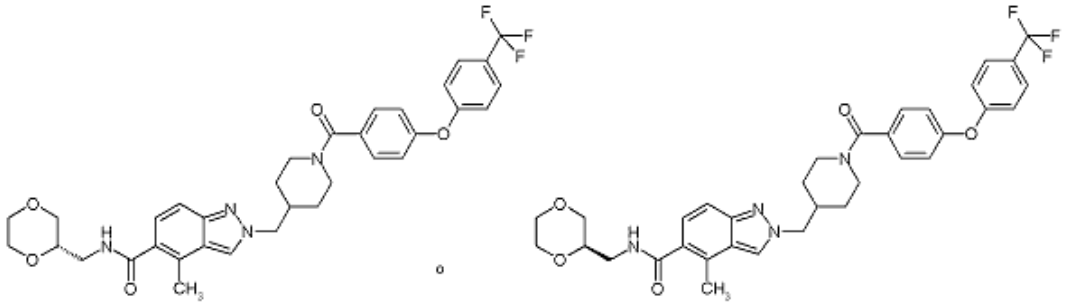
Ejemplo 417: (S o R)-4-metil-N-(3,4,5,6-tetrahidro-2H-piran-2-ilmetil)-2-[(1-{4-[4-(trifluorometil)fenoxi]benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida



A partir de 231 mg del racemato preparado en el Ejemplo 248, se obtuvieron 24 mg del compuesto del título junto con 24 mg del enantiómero de elución más rápida (Ejemplo 416) por separación de racematos por medio de HPLC quiral preparativa (Método E).

HPLC quiral analítica: 8,98 min.

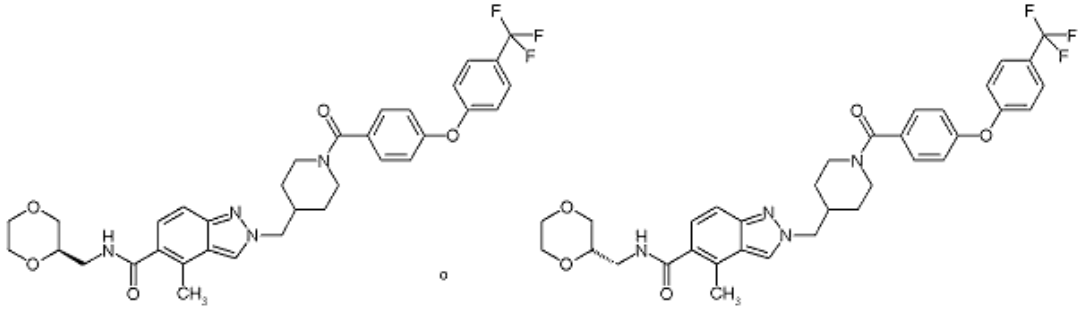
Ejemplo 418: (R o S)-N-(1,4-dioxan-2-ilmetil)-4-metil-2-[(1-{4-[4-(trifluorometil)-fenoxi]benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida



A partir de 280 mg del racemato preparado en el Ejemplo 249, se obtuvieron 65 mg del compuesto del título junto con 75 mg del enantiómero de elución más lenta (Ejemplo 419) por separación de racematos por medio de HPLC quiral preparativa (Método D (volumen de inyección: 0,1 ml; detección: UV 210 nM)).

HPLC quiral analítica: 13,66 min.

Ejemplo 419: (R o S)-N-(1,4-dioxan-2-ilmetil)-4-metil-2-[(1-{4-[4-(trifluorometil)-fenoxi]benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida



A partir de 280 mg del racemato preparado en el Ejemplo 249, se obtuvieron 75 mg del compuesto del título junto con 65 mg del enantiómero de elución más rápida (Ejemplo 418) por separación de racematos por medio de HPLC quiral preparativa (Método D (volumen de inyección: 0,1 ml; detección: UV 210 nM)).

HPLC quiral analítica: 14,90 min.

Ejemplos biológicos:

1. Detección de antagonismo a la señal del receptor de prostaglandina humana E_2 (subtipo EP2)

1. 1 Principio de detección

La unión de PGE_2 al subtipo EP_2 del receptor humano PGE_2 induce la activación de las adenilato ciclasas situadas en membrana, y conduce a la formación de cAMP. En presencia del inhibidor de la fosfodiesterasa IBMX, el cAMP acumulado debido a esta estimulación y liberado por la lisis celular, se emplea en un método de detección competitivo. En este ensayo, el cAMP presente en el lisado compite con un cAMP marcado con fluorescencia (cAMP-d2) para su unión a un anticuerpo

etiquetado con Eu-criptato.

En ausencia de cAMP celular, se produce una señal máxima, que es atribuible a la unión de esta molécula cAMP-d2 al anticuerpo. Después de la excitación de la molécula cAMP-d2 a 337 nm, se produce una transferencia de energía de resonancia de fluorescencia (FRET, fluorescence resonance energy transfer) a las moléculas Eu-criptato del anticuerpo anti-cAMP (etiquetado con el mismo), seguido de una señal de emisión de larga duración a 665 nm (y a 620 nM). Ambas señales se miden en un instrumento de medición adecuado con un retardo de tiempo, es decir, después de la desintegración o descomposición de la fluorescencia de fondo. Cualquier aumento en la baja señal de FRET causado por la administración de prostaglandina E_2 (medido como cambio de la relación = $\text{emisión}_{665nm}/\text{emisión}_{620nm}$ * 10.000) indica la acción de antagonistas.

1.2 Método de detección

1.2.1. Ensayo de antagonismo (datos por cavidad de una placa de 384 cavidades):

En una placa de ensayo con las soluciones de sustancias ya añadidas (0,05 µl; 100% de DMSO, intervalo de concentración de entre 0,8 nM y 16,5 µM), se agregaron 4 µl de una suspensión de cAMP-d2/células (625.000 células/ml). Después de una preincubación de

20 minutos a temperatura ambiente (TA), se añadieron 2 µl de una solución 3xPGE2 (1,5 nM, en PBS-IBMX) y se incubó en la presencia del agonista durante otros 60 min a temperatura ambiente (volumen: ~ 6 µl). A continuación, se detuvo la reacción mediante la adición de 2 µl de tampón de lisis y se incubó durante otros 20 minutos a temperatura ambiente antes de la medición real (volumen: ~ 8 µl).

2. Detección de antagonismo con respecto a la señal del receptor de prostaglandina humana E_2 (subtipo EP4)

2. 1 Principio de detección

La unión de PGE_2 al subtipo EP_4 del receptor humano PGE_2 induce la activación de las adenilato ciclasas situadas en membranas y conduce a la formación de cAMP. En la presencia del inhibidor de la fosfodiesterasa IBMX, el cAMP acumulado debido a esta estimulación y liberado por la lisis celular se emplea en un método de detección competitivo. En este ensayo, el cAMP presente en el lisado compite con un cAMP marcado con fluorescencia (cAMP-d2) para su unión a un anticuerpo anti-cAMP etiquetado con Eu-criptato.

En ausencia de cAMP celular, se produce una señal máxima, que es atribuible a la unión de esta molécula cAMP-d2 al anticuerpo. Después de la excitación de la molécula cAMP-d2 a 337 nm, se produce una transferencia

de energía de resonancia de fluorescencia (FRET, fluorescence resonance energy transfer) a las moléculas Eu-criptato del anticuerpo anti-cAMP (etiquetado con el mismo), seguido de una señal de emisión de larga duración a 665 nm (y a 620 nM). Ambas señales se miden en un instrumento de medición adecuado con un retardo de tiempo, es decir, después de la desintegración o descomposición de la fluorescencia de fondo. Cualquier aumento en la baja señal de FRET causado por la administración de prostaglandina E_2 (medido como cambio de la relación = $\text{emisión}_{665nm}/\text{emisión}_{620nm}$ * 10.000) indica la acción de antagonistas.

2.2. Método de detección

2.2.1. Ensayo de antagonismo (datos por cavidad de una placa de 384 cavidades):

En una placa de ensayo con las soluciones de sustancias ya añadidas (0,05 µl; 100% de DMSO, intervalo de concentración de entre 0,8 nM y 16,5 µM), se agregaron 4 µl de una suspensión de cAMP-d2/células (312.500 células/ml). Después de una preincubación de 20 minutos a temperatura ambiente (TA), se añadieron 2 µl de una solución 3xPGE2 (0,3 nM, en PBS-IBMX) y se incubó en la presencia del agonista durante otros 60 min a temperatura ambiente (volumen: ~ 6 µl). A continuación, se detuvo la reacción mediante la adición

de 2 µl de tampón de lisis y se incubó durante otros 20 minutos a temperatura ambiente antes de la medición real (volumen: ~ 8 µl).

3. Detección de antagonismo con respecto a la señal del receptor de prostaglandina humana D

3. 1 Principio de detección

La unión de prostaglandina D_2 al receptor PGD humano induce la activación de las adenilato ciclasas situadas en membranas y conduce a la formación de cAMP. En la presencia del inhibidor de la fosfodiesterasa IBMX, el cAMP acumulado debido a esta estimulación y liberado por la lisis celular se emplea en un método de detección competitivo. En este ensayo, el cAMP presente en el lisado compite con un cAMP marcado con fluorescencia (cAMP-d2) para su unión a un anticuerpo anti-cAMP etiquetado con Eu -criptato.

En ausencia de cAMP celular, se produce una señal máxima, que es atribuible a la unión de esta molécula cAMP-d2 al anticuerpo. Después de la excitación de la molécula cAMP-d2 a 337 nm, se produce una transferencia de energía de resonancia de fluorescencia (FRET, fluorescence resonance energy transfer) a las moléculas Eu-criptato del anticuerpo anti-cAMP (etiquetado con el mismo), seguido de una señal de emisión de larga duración a 665 nm (y a 620 nM). Ambas señales se miden

en un instrumento de medición adecuado con un retardo de tiempo, es decir, después de la desintegración o descomposición de la fluorescencia de fondo. Cualquier aumento en la baja señal de FRET causado por la administración de prostaglandina E_2 (medido como cambio de la relación de cavidad = $emisión_{665nm}/emisión_{620nm}$ * 10.000) indica la acción de antagonistas.

3.2. Método de detección

3.2.1. Ensayo de antagonismo (datos por cavidad de una placa de 384 cavidades):

En una placa de ensayo con las soluciones de sustancias ya añadidas (0,05 µl; 100% de DMSO, intervalo de concentración de entre 0,8 nM y 16,5 µM), se agregaron 4 µl de una suspensión de cAMP-d2/células (62.500 células/ml). Después de una preincubación de 20 minutos a temperatura ambiente (TA), se añadieron 2 µl de una solución 3xPGE2 (6 nM, en PBS-IBMX) y se incubó en la presencia del agonista durante otros 30 min a temperatura ambiente (volumen: ~ 6 µl). A continuación, se detuvo la reacción mediante la adición de 2 µl de tampón de lisis y se incubó durante otros 20 minutos a temperatura ambiente antes de la medición real (volumen: ~ 8 µl).

4. El subtipo EP_2 del receptor PGE_2, y la expansión preovulatoria del cúmulo

4.1. Antecedentes:

En el folículo antral preovulatorio, el oocito está rodeado por células del cúmulo, que forman una corona celular densa alrededor del oocito. Después del pico de LH (luteinizing hormone, hormona luteinizante), se activa una serie de procesos que resultan en un marcado cambio morfológico en esta corona celular de las células del cúmulo. Durante esto, las células del cúmulo forman una matriz extracelular, lo que conduce a la denominada expansión del cúmulo (Vanderhyden et al Dev. Biol. 19890 Aug; 140 (2): 307-317) Esta expansión del cúmulo es un componente importante del proceso ovulatorio y de la subsiguiente posibilidad de fertilización.

Durante la expansión del cúmulo, las prostaglandinas y en este caso la prostaglandina E_2, cuya síntesis es inducida por el pico de LH, son de importancia decisiva. Los ratones knockout para prostanoide EP_2 (Hizaki y col., 1999, Proc Natl Acad Sci U.S.A., Aug 31, 96 (18): 10501-6) muestran una expansión del cúmulo marcadamente disminuida y una subfertilidad grave, lo que demuestra la importancia del receptor EP_2 de prostanoide para este proceso.

4.2. Ensayo de expansiones de cúmulo *in vitro*

En unos ratones hembra no adultas (cepa: B6D2F1 de

Charles River), con una edad de 14 – 18 días, se indujo la foliculogénesis mediante una única administración (intraperitoneal) de 10 UI de PMSG (pregnant mare serum gonadotropin, gonadotropina sérica de yegua preñada; Sigma G-4877, Lote 68H0909). 47-50 horas después de la inyección, se retiraron los ovarios y se eliminaron los complejos cúmulo-ovocito. En esta etapa, el complejo del cúmulo todavía no está expandido.

Los complejos cúmulo-ovocito se incubaron ahora durante 20-24 horas con prostaglandina E_2 (PGE_2) (0,3 µM), vehículo de control (etanol) o sustancias de ensayo. Medio: medio alfa-MEM con IBMX 0,1 mM, piruvato (0,23 mM), glutamina (2 mM), penicilina / estreptomicina 100 UI / ml de penicilina y 100 mg/ml de estreptomicina.), HSA (8 mg/ml) y suero fetal bovino (FBS, foetal bovine serum, 10%). Seguidamente se determinó la expansión del cúmulo por medio de la subdivisión en cuatro etapas (según Vanderhyden y col. Dev Biol. 1990 Aug; 140 (2) :307-317).

4.3 Acción in vivo sobre la fertilización posovulatoria *in-vitro* :

Las sustancias pueden ejercer una influencia sobre la fertilidad, mediante la disminución de la posibilidad de fertilizar los oocitos o los complejos cúmulo-oocito. Con el fin de estudiar tales efectos,

las sustancias pueden administrarse in vivo y se somete a fertilización in vitro después de haber tenido lugar la ovulación de los complejos cúmulo-oocito ha tenido lugar. La tasa de fertilización in vitro, donde ya no hay ninguna sustancia presente, permite sacar conclusiones sobre los efectos in vivo de las sustancias de ensayo.

Unos ratones hembra no adultas (cepa: B6D2F1, Charles River, Suelzfeld, edad: entre 19 y 25 días) se mantuvieron en jaulas Macrolon en habitaciones con iluminación controlada (12 horas oscuridad: 12 horas de luz), se los alimentó con una dieta estándar y se los proveyó con agua potable ad libitum. Los ratones fueron cebados con PMSG (pregnant mare serum gonadotropin, gonadotropina sérica de yegua preñada) (10 UI/animal ip). Después de 48 horas, se creó una ovulación desencadenante de estímulo en los animales mediante una administración de 10 UI/animal ip (hCG, human chorionic gonadotropin, gonadotropina coriónica humana). Las sustancias de ensayo se disolvieron en benzoato de bencilo/aceite de ricino (1 +4 v(v) y se administraron en un volumen de 0,1 ml s.c. 1 hora antes de la hCG (n = 5 animales por grupo). Catorce horas después de la administración de hCG, los animales fueron sacrificados. Se obtuvieron los oocitos ovulados y los

complejos cúmulo-oocito de las bolsas de ovarios y de sometieron a fertilización in vitro, y durante 1 hora se utilizó un recuento de espermatozoides de 40.000 espermas/0,5 ml. Veinticuatro horas después de la incubación con los espermatozoides, se determinó el número de oocitos fertilizados y se estableció el índice porcentual de fertilización.

Los resultados de la Tabla 4 muestran que el Ejemplo 17 de acuerdo con la invención tiene una influencia dependiente de la dosis, sobre posibilidad de fertilizar los complejos cúmulo-oocito ovulados.

4.4 Acción i*n vivo* sobre la fertilidad en primates no humanos (Cynomolgus):

Con el fin de estudiar el efecto de las sustancias sobre la fertilidad, es posible llevar a cabo estudios de apareamiento en monos (Jensen y col.. Contraception 81 (2010) 165-171). Para esto, las sustancias de ensayo se administran a hembras de monos cynomolgus (Macaca fascicularis) que se mantienen en grupos, y a continuación, los animales se aparean con un animal macho. Los apareamientos se comprueban mediante la detección de esperma en los frotis vaginales diarios. Las preñeces resultantes de ello se identifican mediante determinaciones hormonales y ecografías. A través de los cambios en las concentraciones séricas de

estradiol durante el ciclo, (subida antes del pico de LH a mitad del ciclo), es posible determinar la fase fértil dentro de un ciclo de los animales individuales. Los apareamientos en este periodo fértil se describen como “apareamientos en tiempo oportuno” (apareamientos en la fase fértil). Aparte del número absoluto de preñeces que ocurren, el efecto sobre la fertilidad también puede ser expresado como “preñeces por apareamientos en tiempo oportuno”.

Para probar la acción de los antagonistas del receptor EP_2 sobre la fertilidad en monos, se administraron los Ejemplos 17 y 56 de acuerdo con la invención durante 6 meses, disueltos en 0,5 ml de aceite de ricino. El Ejemplo 17 se administró una vez al día con una dosis de 10 mg/kg (n = 10 animales), mientras que el Ejemplo 56 se administró dos veces al día con una dosis de 10 mg / kg (n = 9 animales). El vehículo sólo se administró a un grupo de control (n = 10 animales). En el primer mes del tratamiento, ningún animal macho fue colocado con los animales hembra. Después de esto, se mantuvieron las hembras y los machos juntos durante 5 meses, con la detección de las preñeces y la supervisión del ciclo.

La Tabla 5 muestra que ambas sustancias resultan en una marcada reducción en el número de preñeces que

se presentan. Estos datos muestran por primera vez el fuerte efecto anticonceptivo de los antagonistas del receptor EP_2 en el primate. Otros resultados del estudio muestran que las sustancias no tienen efectos sobre los niveles hormonales ni sobre la duración del ciclo. Esto confirma que las sustancias producen un efecto anticonceptivo mediante mecanismos no hormonales. La reversibilidad de la fertilidad se demostró en algunos animales después de la interrupción del tratamiento.

5. Determinación de los parámetros farmacocinéticos después de la administración intravenosa

5.1. Administración intravenosa:

Para ello, las sustancias se administraron en forma disuelta, para lo cual se utilizaron solubilizadores compatibles tales como PEG400 y/o etanol en una cantidad tolerable. Las sustancias se administraron con una dosis de 0,1–1 mg/kg. La administración se efectuó en la rata hembra como una inyección en bolo. En este caso, en diversos momentos después de la inyección de bolo se extrajeron aproximadamente entre 100 y 150 µl de muestras de sangre de la vena yugular mediante un catéter. Las muestras de sangre fueron tratadas con litio-heparina como anticoagulante y se almacenaron refrigeradas hasta

un tratamiento posterior. Después de la centrifugación de las muestras durante 15 minutos a 3.000 rpm, se retiró una parte alícuota de 100 µl del material sobrenadante (plasma) y se la precipitó mediante la adición de 400 µl de acetonitrilo o metanol frío (absoluta). Las muestras precipitadas se congelaron durante la noche a 20 °C, después se centrifugaron de nuevo durante 15 minutos a 3.000 rpm, antes de retirarse 150 µl del material sobrenadante claro, para determinar la concentración. El análisis se llevó a cabo con un sistema Agilent 1200 HPLC con detección de LCMS/MS adjunta.

5.2 Cálculo de los parámetros de PK

El cálculo se realizó por medio de software de cálculo de PK WinNonLin ®, donde $t_{1/2}$ significa semivida dentro de un intervalo especificado (aquí: $t_{1/2}$ terminal, en horas).

Tabla 1: Ejemplos para la actividad biológica de los compuestos de acuerdo con la invención en el receptor HEp_2 (IC_{50} medido mediante el ensayo de antagonismo de cAMP). Selectividad con respecto a HDP & hEP_4 (IC_{50} medido mediante el ensayo de antagonismo de cAMP): x: 1 a 10, xx: 10 a 100, xxx> 100:

Ejemplo	Antagonismo hEP2 IC_{50} [M]	Selectividad hEP2/hDP	Selectividad hEP2/hEP4
1	1,03E-07	xxx	xxx
2	2,17E-08	xxx	xxx
3	4,91E-09	xxx	xxx
4	6,81E-08	xxx	xxx
5	5,11E-09	xxx	xxx
6	3,13E-07	xx	xx
7	2,58E-08	xxx	xxx
8	9,37E-09	xxx	xxx
9	1,72E-08	xxx	xxx
10	8,67E-09	xxx	xxx
11	8,14E-09	xxx	xxx
12	2,03E-08	xxx	xxx
13	3,59E-08	xxx	xxx
14	3,67E-09	xxx	xxx
15	4,17E-09	xxx	xxx
16	5,85E-09	xxx	xxx
17	3,44E-09	xxx	xxx
18	7,66E-09	xxx	xxx
19	8,57E-09	xxx	xxx
20	7,33E-09	xxx	xxx
21	3,58E-08	xxx	xxx
22	3,03E-08	xxx	xxx

Ejemplo	Antagonismo hEP2 IC_{50} [M]	Selectividad hEP2/hDP	Selectividad hEP2/hEP4
23	1,61E-08	xxx	xxx
24	6,01E-08	xxx	xxx
25	2,52E-08	xxx	xxx
26	2,42E-08	xxx	xxx
27	1,93E-08	xxx	xxx
28	3,39E-08	xxx	xxx
29	9,31E-09	xxx	xxx
30	6,43E-08	xxx	xxx
31	3,08E-09	xxx	xxx
32	1,04E-08	xxx	xxx
33	3,42E-08	xxx	xxx
34	1,34E-07	xxx	xxx
35	6,92E-08	xxx	xxx
36	6,16E-08	xxx	xxx
37	1,04E-07	xxx	xxx
38	2,81E-08	xxx	xxx
39	1,13E-07	xxx	xxx
40	1,15E-08	xxx	xxx
41	5,62E-09	xxx	xxx
42	4,75E-09	xxx	xxx
43	4,82E-09	xxx	xxx
44	3,85E-09	xxx	xxx

Ejemplo	Antagonismo hEP2 IC_{50} [M]	Selectividad hEP2/hDP	Selectividad hEP2/hEP4
45	5,51E-09	xxx	xxx
46	4,91E-09	xxx	xxx
47	5,61E-09	xxx	xxx
48	5,59E-09	xxx	xxx
49	6,44E-09	xxx	xxx
50	3,18E-09	xxx	xxx
51	6E-08	xxx	xxx
52	8,3E-07	xx	xx
53	4,42E-08	xxx	xxx
54	4,74E-09	xxx	xxx
55	9,67E-09	xxx	xxx
56	1,31E-08	xxx	xxx
57	5,29E-09	xxx	xxx
58	1,08E-06	xx	xx
59	7,58E-07	xx	xx
60	1,75E-07	xx	xx
61	1,5E-06	xx	xx
62	6,74E-07	xx	xx
63	1,44E-06	xx	xx
64	4,13E-06	x	x
65	2,79E-06	x	x
66	3,21E-07	xx	xx

Ejemplo	Antagonismo hEP2 IC_{50} [M]	Selectividad hEP2/hDP	Selectividad hEP2/hEP4
67	4,05E-07	xx	xx
68	1,77E-08	xxx	xxx
69	2,9E-08	xxx	
70	4,9E-08	xxx	
71	8,29E-08	xxx	xxx
72	1,2E-07	xxx	xxx
73	7,78E-08	xxx	xxx
74	9,54E-08	xxx	xxx
75	6,7E-08	xxx	xxx
76	1,79E-07	xx	xx
77	5,39E-08	xxx	xxx
78	3,17E-08	xxx	xxx
79	1,25E-07	xxx	xxx
80	8,59E-08	xxx	xxx
81	5,13E-07	xx	xx
82	2,18E-07	xx	xx
83	3,26E-08	xxx	xxx
84	1,92E-08	xxx	xxx
85	3,55E-08	xxx	xxx
86	1,54E-08	xxx	xxx
87	2,4E-08	xxx	xxx
88	1,62E-08	xxx	xxx

Ejemplo	Antagonismo hEP2 IC_{50} [M]	Selectividad hEP2/hDP	Selectividad hEP2/hEP4
89	9,4E-09	xxx	xxx
90	1,48E-08	xxx	xxx
91	2,03E-08	xxx	xxx
92	1,27E-08	xxx	xxx
93	1,15E-08	xxx	xxx
94	1,28E-08	xxx	xxx
95	6,18E-09	xxx	xxx
96	9,42E-09	xxx	xxx
97	1,27E-08	xxx	xxx
98	7,07E-09	xxx	xxx
99	1,04E-08	xxx	xxx
100	6,21E-09	xxx	xxx
101	6,58E-09	xxx	xxx
102	4,1E-07	xx	xx
103	5,95E-07	xx	xx
104	5,13E-07	xx	xx
105	2,85E-07	xx	xx
106	1,5E-07	xxx	xxx
107	1,14E-08	xxx	xxx
108	6,46E-09	xxx	xxx
109	9,53E-09	xxx	xxx
110	4,4E-09	xxx	xxx

Ejemplo	Antagonismo hEP2 IC_{50} [M]	Selectividad hEP2/hDP	Selectividad hEP2/hEP4
111	1,37E-08	xxx	xxx
112	1,19E-08	xxx	xxx
113	1,39E-08	xxx	xxx
114	6,08E-09	xxx	xxx
115	9,05E-09	xxx	xxx
116	5,52E-09	xxx	xxx
117	1,78E-08	xxx	xxx
118	8,17E-09	xxx	
119	1,32E-08	xxx	
120	1,55E-08	xxx	
121	1,55E-08	xxx	xxx
122	2,86E-08	xxx	xxx
123	8,92E-09	xxx	xxx
124	7,99E-09	xxx	xxx
125	3,66E-09	xxx	xxx
126	2,12E-08	xxx	xxx
127	5,56E-08	xxx	xxx
128	4,71E-07	xx	xx
129	3,09E-07	xx	xx
130	2,41E-07	xx	xx
131	2,28E-07	xx	xx
132	1,09E-07	xxx	xxx

Ejemplo	Antagonismo hEP2 IC_{50} [M]	Selectividad hEP2/hDP	Selectividad hEP2/hEP4
133	4,19E-08	xxx	xxx
134	5,65E-08	xxx	xxx
135	1,95E-08	xxx	xxx
136	6,59E-09	xxx	xxx
137	7,65E-09	xxx	xxx
138	1,6E-07	xxx	xxx
139	4,19E-07	xx	xx
140	5,53E-08	xxx	xxx
141	1,43E-07	xxx	xxx
142	7,13E-07	xx	xx
143	3,68E-08	xxx	xxx
144	5,08E-08	xxx	xxx
145	1,88E-08	xxx	xxx
146	5,26E-08	xxx	xxx
147	5,74E-08	xxx	xxx
148	2,74E-08	xxx	xxx
149	2,96E-08	xxx	xxx
150	1,28E-08	xxx	xxx
151	4,85E-08	xxx	xxx
152	3,33E-08	xxx	xxx
153	6,08E-08	xxx	xxx
154	8,08E-08	xxx	xxx

Ejemplo	Antagonismo hEP2 IC_{50} [M]	Selectividad hEP2/hDP	Selectividad hEP2/hEP4
155	2,94E-08	xxx	xxx
156	1,84E-07	xx	xx
157	1,36E-08	xxx	xxx
158	6,21E-09	xxx	xxx
159	6,24E-09	xxx	xxx
160	8,29E-08	xxx	xxx
161	9,82E-08	xxx	xxx
162	9,33E-09	xxx	xxx
163	6,8E-09	xxx	xxx
164	1,09E-08	xxx	xxx
165	3,34E-08	xxx	xxx
166	2,87E-09	xxx	xxx
167	1,35E-08	xxx	xxx
168	2,93E-08	xxx	xxx
169	2,77E-08	xxx	xxx
170	4,25E-09	xxx	xxx
171	3,88E-09	xxx	xxx
172	3,16E-09	xxx	xxx
173	2,71E-09	xxx	xxx
174	6,58E-09	xxx	xxx
175	8,05E-09	xxx	xxx
176	7,77E-09	xxx	xxx

Ejemplo	Antagonismo hEP2 IC_{50} [M]	Selectividad hEP2/hDP	Selectividad hEP2/hEP4
177	1,18E-07	xxx	xxx
178	6,83E-08	xxx	xxx
179	2,61E-06	x	x
180	1,73E-08	xxx	xxx
181	3,52E-08	xxx	xxx
182	6,42E-08	xxx	xxx
183	4,66E-08	xxx	xxx
184	7,68E-08	xxx	xxx
185	2,48E-08	xxx	xxx
186	5,19E-08	xxx	xxx
187	2,35E-08	xxx	xxx
188	1,49E-07	xxx	xxx
189	3,36E-08	xxx	xxx
190	2,72E-07	xx	xx
191	4,71E-08	xxx	xxx
192	2,06E-07	xx	xx
193	1,45E-07	xxx	xxx
194	4,09E-08	xxx	xxx
195	2,27E-07	xx	xx
196	5,08E-08	xxx	xxx
197	6,32E-08	xxx	xxx
198	1,53E-07	xxx	xxx

Ejemplo	Antagonismo hEP2 IC_{50} [M]	Selectividad hEP2/hDP	Selectividad hEP2/hEP4
199	9,71E-08	xxx	xxx
200	1,51E-08	xxx	xxx
201	2,49E-08	xxx	xxx
202	5,06E-09	xxx	xxx
203	8,57E-08	xxx	xxx
204	1E-08	xxx	xxx
205	4,33E-08	xxx	xxx
206	4,13E-08	xxx	xxx
207	3,03E-08	xxx	xxx
208	8,06E-08	xxx	xxx
209	2,51E-08	xxx	xxx
210	1,95E-08	xxx	xxx
211	5,01E-08	xxx	xxx
212	1,06E-07	xxx	xxx
213	8,24E-08	xxx	xxx
214	6,49E-08	xxx	xxx
215	3,9E-08	xxx	xxx
216	8,61E-08	xxx	xxx
217	1,14E-07	xxx	xxx
218	1,28E-07	xxx	xxx
219	2,73E-07	xx	xx
220	1,47E-07	xxx	xxx

Ejemplo	Antagonismo hEP2 IC_{50} [M]	Selectividad hEP2/hDP	Selectividad hEP2/hEP4
221	2,35E-07	xx	xx
222	4,09E-08	xxx	xxx
223	2E-08	xxx	xxx
224	5,62E-09	xxx	xxx
225	1,43E-08	xxx	xxx
226	1,19E-08	xxx	xxx
227	9,89E-09	xxx	xxx
228	8,09E-09	xxx	xxx
229	1,02E-08	xxx	xxx
230	1,37E-08	xxx	xxx
231	1,32E-08	xxx	xxx
232	3,83E-08	xxx	xxx
233	3,97E-08	xxx	xxx
234	4,77E-08	xxx	xxx
235	1,67E-08	xxx	xxx
236	5,75E-08	xxx	xxx
237	3,1E-08	xxx	xxx
238	3,24E-08	xxx	xxx
239	2,7E-08	xxx	xxx
240	2,51E-08	xxx	xxx
241	9,03E-09	xxx	xxx
242	3,05E-07	xx	xx

Ejemplo	Antagonismo hEP2 IC_{50} [M]	Selectividad hEP2/hDP	Selectividad hEP2/hEP4
243	3,35E-07	xx	xx
244	4,42E-08	xxx	xxx
245	7,79E-09	xxx	xxx
246	9,23E-09	xxx	xxx
247	1,26E-08	xxx	xxx
248	1,47E-08	xxx	xxx
249	1,12E-08	xxx	xxx
250	3,06E-08	xxx	xxx
251	3,81E-06	x	x
252	2,95E-07	xx	xx
253	1,68E-07	xx	xx
254	5,52E-08	xxx	xxx
255	8,35E-08	xxx	xxx
256	1,07E-07		xxx
257	1,02E-07	xxx	xxx
258	1,09E-07	xxx	xxx
259	2,56E-08	xxx	xxx
260	8,02E-09	xxx	xxx
261	8,1E-08	xxx	xxx
262	3,34E-08	xxx	xxx
263	1,81E-07	xx	xx
264	1,37E-08	xxx	xxx

Ejemplo	Antagonismo hEP2 IC_{50} [M]	Selectividad hEP2/hDP	Selectividad hEP2/hEP4
265	3,15E-08	xxx	xxx
266	1,89E-08	xxx	xxx
267	4,55E-08	xxx	xxx
268	2,29E-08	xxx	xxx
269	7,54E-09	xxx	xxx
270	5,31E-08	xxx	xxx
271	3,35E-08	xxx	xxx
272	2,37E-08	xxx	xxx
273	1,85E-08	xxx	xxx
274	4,46E-08	xxx	xxx
275	3,45E-08	xxx	xxx
276	2,26E-07	xx	xx
277	4,79E-08	xxx	xxx
278	1,04E-07	xxx	xxx
279	5,74E-08	xxx	xxx
280	3,07E-08	xxx	xxx
281	2,3E-08	xxx	xxx
282	2,01E-08	xxx	xxx
283	6,55E-08	xxx	xxx
284	5,64E-08	xxx	xxx
285	1E-07	xxx	xxx
286	1E-07	xxx	xxx

Ejemplo	Antagonismo hEP2 IC_{50} [M]	Selectividad hEP2/hDP	Selectividad hEP2/hEP4
287	1,05E-06	xx	xx
288	4E-08	xxx	xxx
289	5,16E-08	xxx	xxx
290	4,26E-08	xxx	xxx
291	5,94E-09	xxx	xxx
292	2E-08	xxx	xxx
293	2,83E-08	xxx	xxx
294	1,32E-08	xxx	xxx
295	7,08E-08	xxx	xxx
296	2,97E-08	xxx	xxx
297	4,6E-07	xx	xx
298	3,45E-07	xx	xx
299	5,41E-07	xx	xx
300	7,98E-08	xxx	xxx
301	2,45E-08	xxx	xxx
302	1,31E-07	xxx	xxx
303	1,39E-08	xxx	xxx
304	9,98E-08	xxx	xxx
305	3,01E-07	xx	xx
306	7,66E-08	xxx	xxx
307	3,06E-08	xxx	xxx
308	2,22E-08	xxx	xxx

Ejemplo	Antagonismo hEP2 IC_{50} [M]	Selectividad hEP2/hDP	Selectividad hEP2/hEP4
309	6,6E-08	xxx	xxx
310	8,06E-07	xx	xx
311	8,41E-08	xxx	xxx
312	1,58E-07	xxx	xxx
313	8,94E-08	xxx	xxx
314	2,78E-08	xxx	xxx
315	4,3E-08	xxx	xxx
316	7,9E-08	xxx	xxx
317	1,81E-07	xx	xx
318	2,63E-08	xxx	xxx
319	3,15E-07	xx	xx
320	1,56E-08	xxx	xxx
321	1,01E-07	xxx	xxx
322	7,62E-08	xxx	xxx
323	1,28E-07	xxx	xxx
324	4,6E-07	xx	xx
325	3,21E-07	xx	xx
326	4,85E-07	xx	xx
327	1,21E-06	xx	xx
328	2,56E-07	xx	xx
329	2,32E-07	xx	xx
330	9,53E-09	xxx	xxx

Ejemplo	Antagonismo hEP2 IC_{50} [M]	Selectividad hEP2/hDP	Selectividad hEP2/hEP4
331	9,47E-09	xxx	xxx
332	5,47E-09	xxx	xxx
333	6,42E-09	xxx	xxx
334	7,42E-08	xxx	xxx
335	5,09E-09	xxx	xxx
336	5,59E-09	xxx	xxx
337	1,81E-08	xxx	xxx
338	2,8E-08	xxx	xxx
339	7,15E-09	xxx	xxx
340	1,99E-08	xxx	xxx
341	5,53E-08	xxx	xxx
342	1,03E-07	xxx	xxx
343	4,24E-08	xxx	xxx
344	1,03E-08	xxx	xxx
345	6,26E-09	xxx	xxx
346	1,49E-08	xxx	xxx
347	7,88E-09	xxx	xxx
348	8,88E-09	xxx	xxx
349	4,82E-09	xxx	xxx
350	8,41E-09	xxx	xxx
351	6,84E-09	xxx	xxx
352	2,17E-08	xxx	xxx

Ejemplo	Antagonismo hEP2 IC_{50} [M]	Selectividad hEP2/hDP	Selectividad hEP2/hEP4
353	5,02E-08	xxx	xxx
354	5,87E-09	xxx	xxx
355	5,39E-09	xxx	xxx
356	6,36E-08	xxx	xxx
357	7,36E-09	xxx	xxx
358	8,01E-09	xxx	xxx
359	6,99E-09	xxx	xxx
360	6,27E-09	xxx	xxx
361	5,11E-09	xxx	xxx
362	1,51E-08	xxx	xxx
363	5,48E-09	xxx	xxx
364	6,61E-09	xxx	xxx
365	5,3E-09	xxx	xxx
366	1,89E-08	xxx	xxx
367	5,84E-09	xxx	xxx
368	1,2E-08	xxx	xxx
369	5,66E-09	xxx	xxx
370	3,07E-09	xxx	xxx
371	6,11E-09	xxx	xxx
372	7,29E-09	xxx	xxx
373	4,07E-08	xxx	xxx
374	6,58E-09	xxx	xxx

Ejemplo	Antagonismo hEP2 IC_{50} [M]	Selectividad hEP2/hDP	Selectividad hEP2/hEP4
375	5,8E-09	xxx	xxx
376	3,59E-09	xxx	xxx
377	2,73E-08	xxx	xxx
378	7,77E-09	xxx	xxx
379	6,26E-08	xxx	xxx
380	5,35E-09	xxx	xxx
381	5,84E-09	xxx	xxx
382	1,94E-08	xxx	xxx
383	5,78E-09	xxx	xxx
384	3,95E-09	xxx	xxx
385	1,31E-08	xxx	xxx
386	2,57E-08	xxx	xxx
387	1,32E-08	xxx	xxx
388	2,05E-08	xxx	xxx
389	4,51E-09	xxx	xxx
390	3,14E-09	xxx	xxx
391	6,07E-09	xxx	xxx
392	2,18E-08	xxx	xxx
393	5E-08	xxx	xxx
394	5,7E-09	xxx	xxx
395	3,04E-08	xxx	xxx
396	1,8E-08	xxx	xxx

Ejemplo	Antagonismo hEP2 IC_{50} [M]	Selectividad hEP2/hDP	Selectividad hEP2/hEP4
397	1,25E-08	xxx	xxx
398	1,82E-08	xxx	xxx
399	5,93E-07	xx	xx
400	5,61E-08	xxx	xxx
401	1,55E-07	xxx	xxx
402	7,77E-08	xxx	xxx
403	9,59E-09	xxx	xxx
404	2,02E-08	xxx	xxx
405	2,14E-06	x	x
406	8,19E-09	xxx	xxx
407	1,16E-08	xxx	xxx
408	2,35E-08	xxx	xxx
409	3,18E-08	xxx	xxx
410	9,04E-08	xxx	xxx
411	1,65E-08	xxx	xxx
412	6,35E-08	xxx	xxx
413	3,78E-08	xxx	xxx
414	2,23E-07	xx	xx
415	2,13E-08	xxx	xxx
416	1,07E-08	xxx	xxx
417	9,75E-09	xxx	xxx
418	1,58E-08	xxx	xxx

Ejemplo	Antagonismo hEP2 IC_{50} [M]	Selectividad hEP2/hDP	Selectividad hEP2/hEP4
419	1,09E-08	xxx	xxx

Tabla 2: Reducción en la expansión del cúmulo en porcentaje con uso de 0,3 µM de PGE2 para la estimulación, referencia 1: ejemplo 62 del documento DE 102009049662A1

Ejemplo	% de reducción a 1 µM	% reducción a 0,5 µm
Referencia 1*	79% (*reducción a 10 µM)	
Ejemplo 5	59	56
Ejemplo 17	76	71
Ejemplo 42	79	48
Ejemplo 117	54	30
Ejemplo 283	26	25
Ejemplo 291	73	76
Ejemplo 303	47	38
Ejemplo 345	36	18

Tabla 3: Vida media terminal ($t_{1/2}$) después de la administración intravenosa en la rata hembra, referencia 1: ejemplo 62 del documento DE 102009049662A1

Ejemplo	$t_{1/2}$ [hr]

Referencia 1	0,4
Ejemplo 17	2,5
Ejemplo 42	3,2
Ejemplo 117	2,0
Ejemplo 283	5,8

Tabla 4: Reducción en la tasa de fertilización in vitro después de la administración *in vivo* de la sustancia de ensayo:

Ejemplo	% de fertilización con vehículo	% de fertilización con 1 mg/kg	% de fertilización con 5 mg/kg	% de fertilización con 10 mg/kg
Ejemplo 17	30 ± 9	20 ± 10	9 ± 1	8 ± 4

Tabla 5: Reducción en las tasas de preñez en el primate no humano (Cynomolgus)

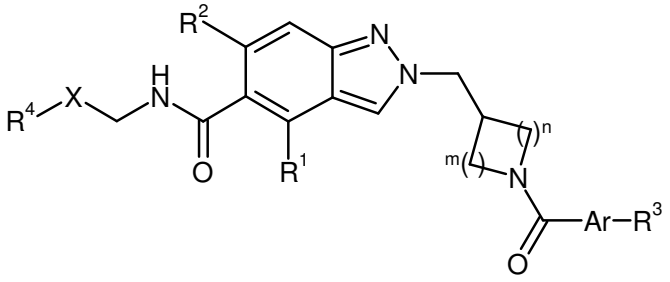
Grupo	Animales por grupo	Cantidad de “apareamientos en tiempo oportuno”*	Preñez	% de preñez/ “apareamiento en tiempo oportuno”
Control	10	21	8	38
Ejemplo 17	10	25	3	6
Ejemplo 56	9	34	2	12

*detección de espermas vaginales en la fase fértil del

ciclo

REIVINDICACIONES

1. Compuestos de la fórmula general (I)



CARACTERIZADOS porque

R^1: significa H, alquilo C_1-C_2 o alquil C_1-C_2-oxilo;

R^2: es H o metilo;

siempre que uno de los dos residuos R^1 o R^2 sea H;

X: es $-(CH_2)_1-$, $-(CH_2)_k-O-$, $-CH_2-S-$, $CH_2-S(O)_2-$, $-CH(CH_3)-$, $-CH(CH_3)-O-$ o $-C(CH_3)_2-O-$;

k: es 1 ó 2;

l: es 0, 1 ó 2;

R^4: H, alquilo C_1-C_4, cicloalquilo C_3-C_4 o CH_2-cicloalquilo C_3-C_4;

y en el caso de que X: $-CH_2-$ o $-CH(CH_3)-$

R^4: significa adicionalmente un residuo de heterociclilo de 4-6 miembros;

y en el caso de que X: $-(CH_2)_1-$ o $-CH(CH_3)-$

R^4: significa adicionalmente CN;

o

X junto con R^4 forman un residuo de heterociclilo de 4-6 miembros por medio de una ligación de carbono

de anillo;

m: es 1 ó 2;

n: es 1 ó 2;

Ar: es un residuo de arilo de 6-10 miembros o residuo de hetarilo de entre 5 y 10 miembros,

R^3: es halógeno, CN, SF_5, alquilo C_1-C_4, cicloalquilo C_3-C_6, heterociclilo C_4-C_6, O-alquilo C_1-C_4, O-cicloalquilo C_3-C_6, O-heterociclilo C_4-C_6, S-alquilo C_1-C_4, $S(O)_2$-alquilo C_1-C_4, Ar´, O-Ar´, $C(CH_3)_2$-CN o $C(CH_3)_2$-OH; y

Ar´: un residuo de arilo de 6 miembros o residuo de heteroarilo de 5-6 miembros opcionalmente mono- o disustituido;

en donde los sustituyentes están seleccionados de F, Cl, CN, alquilo C_1-C_4, O-alquilo C_1-C_4, $C(CH_3)_2$-CN, $C(CH_3)_2$-OH y $C(O)NH_2$;

y sus isómeros, diasteroisómeros, enantiómeros y sales o clatratos de ciclodextrina.

2. Compuestos de acuerdo a la reivindicación 1, CARACTERIZADOS porque

R^1, R^2: son H o metilo;

siempre que uno de los dos residuos R^1 o R^2 sea H;

X: es $-(CH_2)_1-$ o $-(CH_2)_k-O-$;

k: es 1 ó 2;

l: es 0, 1 ó 2;

R^4: es alquilo C_1-C_4, cicloalquilo C_3-C_4 o CH_2-cicloalquilo C_3-C_4; y

m, n: es 2;

y sus isómeros, diasteroisómeros, enantiómeros y sales o clatratos de ciclodextrina y R^3, Ar y Ar´ tienen los significados establecidos en la reivindicación 1.

3. Compuestos de acuerdo a la reivindicación 1 a 2, CARACTERIZADOS porque

R^1, R^2: mean H o metilo;

siempre que uno de los dos residuos R^1 o R^2 sea H;

X: es $-(CH_2)_l-$ o $-(CH_2)_k-O-$;

k: es 1 ó 2;

l: es 0, 1 ó 2;

R^4: es alquilo C_1-C_4, cicloalquilo C_3-C_4 o CH_2-cicloalquilo C_3-C_4; y

m, n: 1;

y sus isómeros, diasteroisómeros, enantiómeros y sales o clatratos de ciclodextrina y R^3, Ar y Ar´ tienen los significados establecidos en la reivindicación 1.

4. Compuestos de acuerdo a la reivindicación 1 a 3, CARACTERIZADOS porque

R^1: significa metilo;

R^2: es H;

X: es $-(CH_2)_l-$ o $-(CH_2)_k-O-$;

k: es 1;

l: es 0 ó 1;

R^4: es alquilo C_1–C_4, cicloalquilo C_3–C_4 o CH_2–cicloalquilo C_3–C_4;

m, n: es 2; y

Ar: un residuo de fenilo;

y sus isómeros, diasteroisómeros, enantiómeros y sales o clatratos de ciclodextrina y R^3 y Ar´ tienen los significados establecidos en la reivindicación 1.

5. Compuestos de acuerdo a la reivindicación 1 a 4, CARACTERIZADOS porque

R^1: significa un grupo metilo;

R^2: es H;

X: es $-(CH_2)_l-$ o $-(CH_2)_k-O-$;

k: es 1;

l: es 0 ó 1;

R^4: es alquilo C_1–C_4, cicloalquilo C_3–C_4 o CH_2–cicloalquilo C_3–C_4;

m, n: es 1; y

Ar: es un residuo de fenilo;

y sus isómeros, diasteroisómeros, enantiómeros y sales o clatratos de ciclodextrina y R^3 y Ar´ tienen los significados antes mencionados.

6. Compuestos de acuerdo a la reivindicación 4 y 5 CARACTERIZADOS porque se seleccionan de un grupo que contiene los siguientes compuestos:

1. 2-{[1-(4-ciano-2-fluorobenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
2. 2-{[1-(4-ter-butoxibenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
3. 2-({1-[4-(4-fluorofenoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
4. N-(2-metoxietil)-4-metil-2-{[1-(4-morfolinobenzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida
5. 2-({1-[(4'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
6. 2-{[1-(2-fluoro-4-mesilbenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
7. 2-{[1-(2-fluoro-4-metoxibenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
8. 2-{[1-(4-bromo-2-fluorobenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
9. 2-{[1-(2-fluoro-4-metilbenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-

carboxamida

10. 2-({1-[2-fluoro-4-(trifluorometil)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
11. N-(2-metoxietil)-4-metil-2-({1-[4-(pentafluoro-λ⁶-sulfanil)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida
12. N-(2-metoxietil)-4-metil-2-{[1-(4-metilbenzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida
13. 2-({1-[4-(4-clorofenoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
14. N-(2-metoxietil)-4-metil-2-({1-[4-(4-metilfenoxi)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida
15. 2-({1-[4-(4-ter-butilfenoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
16. N-(2-metoxietil)-4-metil-2-[(1-{4-[4-(trifluorometil)fenoxi]benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida
17. N-(2-metoxietil)-2-({1-[4-(4-metoxifenoxi)benzoil]piperidin-4-il}metil)-4-metil-2H-indazol-5-carboxamida

18. N-(2-metoxietil)-4-metil-2-{[1-(4-fenoxibenzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida
19. 2-{[1-(4-ciclopropilbenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
20. 2-{[1-(4-metoxibenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
21. 2-{[1-(4-fluorobenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
22. N-(2-metoxietil)-4-metil-2-({1-[4-(trifluorometil)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida
23. 2-{[1-(2-metoxibenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
24. N-(2-metoxietil)-4-metil-2-[(1-{4-[(trifluorometil)sulfonil]benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida
25. N-(2-metoxietil)-4-metil-2-({1-[3-(trifluorometil)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida
26. N-(2-metoxietil)-4-metil-2-{[1-(3-metilbenzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida
27. 2-{[1-(3-clorobenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

28. 2-({1-[4-(4-carbamoilfenoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
29. 2-({1-[4-(ciclopentiloxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
30. 2-({1-[4-(difluorometil)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
31. 2-{[1-(4-cianobenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
32. 2-({1-[4-(1H-imidazol-1-il)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
33. N-(2-metoxietil)-4-metil-2-({1-[4-(oxazol-2-il)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida
34. N-(2-metoxietil)-4-metil-2-({1-[4-(oxazol-5-il)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida
35. N-(2-metoxietil)-4-metil-2-({1-[4-(isoxazol-5-il)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida
36. N-(2-metoxietil)-4-metil-2-({1-[4-(1H-pirazol-1-il)benzoil]piperidin-4-il}metil)-2H-indazol-5-

carboxamida

37. N-(2-metoxietil)-4-metil-2-({1-[4-(1H-1,2,4-triazol-1-il)benzoil]piperidin-4-il}-metil)-2H-indazol-5-carboxamida

38. 2-({1-[4-(difluorometoxi)-2-fluorobenzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

39. 2-({1-[2-fluoro-4-(pirrolidin-1-il)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

40. 2-({1-[(3,4'-difluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

41. 2-({1-[(3-fluoro-4'-metoxibifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

42. 2-({1-[(3-fluoro-4'-metilbifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida

43. 2-[(1-{[3-fluoro-3'-(trifluorometil)bifenil-4-il]carbonil}piperidin-4-il)metil]-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

44. 2-[(1-{[3-fluoro-2'-(trifluorometoxi)bifenil-4-il]carbonil}piperidin-4-il)metil]-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

45. 2-({1-[(2'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
46. 2-({1-[(2',4'-difluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
47. 2-({1-[(2-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
48. N-(2-metoxietil)-4-metil-2-({1-[(2'-metilbifenil-4-il)carbonil]piperidin-4-il}-metil)-2H-indazol-5-carboxamida
49. N-(2-metoxietil)-4-metil-2-({1-[4-(4-piridiloxi)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida
50. N-(2-metoxietil)-4-metil-2-({1-[4-(4H-1,2,4-triazol-4-il)benzoil]piperidin-4-il}-metil)-2H-indazol-5-carboxamida
51. 2-{[1-(2-fluoro-4-morfolinobenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
52. 2-{[1-(4-bromobenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
53. N-(2-metoxietil)-4-metil-2-({1-[4-(trifluorometoxi)benzoil]piperidin-4-il}-metil)-2H-

indazol-5-carboxamida

54. 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

55. N-(2-metoxietil)-4-metil-2-[(1-{4-[(trifluorometil)sulfanil]benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida

56. 4-metil-2-({1-[4-(pentafluoro-λ^6-sulfanil)benzoil]piperidin-4-il}metil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

57. 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

58. 4-metil-N-(2,2,2-trifluoroetil)-2-({1-[4-(trifluorometoxi)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida

59. 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-[2-(ciclopropilmetoxi)etil]-4-metil-2H-indazol-5-carboxamida

60. N-[2-(ciclopropilmetoxi)etil]-4-metil-2-{[1-(4-metilbenzoil)piperidin-4-il]-metil}-2H-indazol-5-carboxamida

61. N-[2-(ciclopropilmetoxi)etil]-2-({1-[4-(4-fluorofenoxi)benzoil]piperidin-4-il}-metil)-4-metil-2H-indazol-5-carboxamida

62. N-[2-(ciclopropilmetoxi)etil]-4-metil-2-({1-[4-

(trifluorometil)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida

63. N-[2-(ciclopropilmetoxi)etil]-2-({1-[(4'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-4-metil-2H-indazol-5-carboxamida

64. 2-{[1-(4-ciclopropilbenzoil)piperidin-4-il]metil}-N-[2-(ciclopropilmetoxi)etil]-4-metil-2H-indazol-5-carboxamida

65. 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metil-N-[2-(2,2,2-trifluoroetoxi)-etil]-2H-indazol-5-carboxamida

66. 4-metil-2-{[1-(4-metilbenzoil)piperidin-4-il]metil}-N-[2-(2,2,2-trifluoroetoxi)-etil]-2H-indazol-5-carboxamida

67. 2-({1-[4-(4-fluorofenoxi)benzoil]piperidin-4-il}metil)-4-metil-N-[2-(2,2,2-trifluoroetoxi)etil]-2H-indazol-5-carboxamida

68. 4-metil-N-[2-(2,2,2-trifluoroetoxi)etil]-2-({1-[4-(trifluorometil)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida

69. 2-({1-[(4'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-4-metil-N-[2-(2,2,2-trifluoroetoxi)etil]-2H-indazol-5-carboxamida

70. 2-{[1-(4-ciclopropilbenzoil)piperidin-4-il]metil}-4-metil-N-[2-(2,2,2-trifluoro-etoxi)etil]-2H-

indazol-5-carboxamida

71. 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-(2-isopropoxietil)-4-metil-2H-indazol-5-carboxamida

72. N-(2-isopropoxietil)-4-metil-2-{[1-(4-metilbenzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida

73. 2-({1-[4-(4-fluorofenoxi)benzoil]piperidin-4-il}metil)-N-(2-isopropoxietil)-4-metil-2H-indazol-5-carboxamida

74. N-(2-isopropoxietil)-4-metil-2-({1-[4-(trifluorometil)benzoil]piperidin-4-il}-metil)-2H-indazol-5-carboxamida

75. 2-({1-[(4'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-isopropoxietil)-4-metil-2H-indazol-5-carboxamida

76. 2-{[1-(4-ciclopropilbenzoil)piperidin-4-il]metil}-N-(2-isopropoxietil)-4-metil-2H-indazol-5-carboxamida

77. 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metil-N-[2-(trifluorometoxi)etil]-2H-indazol-5-carboxamida

78. 2-({1-[4-(4-fluorofenoxi)benzoil]piperidin-4-il}metil)-4-metil-N-[2-(trifluoro-metoxi)etil]-2H-indazol-5-carboxamida

79. 2-({1-[(4'-fluorobifenil-4-il)carbonil]piperidin-

4-il}metil)-4-metil-N-[2-(trifluoro-metoxi)etil]-2H-indazol-5-carboxamida

80. 4-metil-N-[2-(trifluorometoxi)etil]-2-[(1-{4-[4-(trifluorometil)fenoxi]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida

81. N-(2-ter-butoxietil)-2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metil-2H-indazol-5-carboxamida

82. N-(2-ter-butoxietil)-2-({1-[4-(4-fluorofenoxi)benzoil]piperidin-4-il}metil)-4-metil-2H-indazol-5-carboxamida

83. N-(2-ter-butoxietil)-2-({1-[(4'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-4-metil-2H-indazol-5-carboxamida

84. N-(2-ter-butoxietil)-4-metil-2-[(1-{4-[4-(trifluorometil)fenoxi]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida

85. 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-4-metil-N-{2-[(^{2}H3)metiloxi]-(^{2}H4)etil}-2H-indazol-5-carboxamida

86. 2-({1-[4-(4-fluorofenoxi)benzoil]piperidin-4-il}metil)-4-metil-N-{2-[(^{2}H3)metiloxi](^{2}H4)etil}-2H-indazol-5-carboxamida

87. 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

88. N-(2-metoxietil)-4-metil-2-[(1-{4-[(trifluorometil)sulfanil]benzoil}azetidin-3-il)metil]-2H-indazol-5-carboxamida
89. N-(2-metoxietil)-4-metil-2-({1-[4-(trifluorometoxi)benzoil]azetidin-3-il}metil)-2H-indazol-5-carboxamida
90. 2-({1-[2-fluoro-4-(trifluorometil)benzoil]azetidin-3-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
91. 2-{[1-(4-cloro-2-fluorobenzoil)azetidin-3-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
92. 2-({1-[3-fluoro-4-(trifluorometil)benzoil]azetidin-3-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
93. 2-({1-[4-cloro-3-(trifluorometil)benzoil]azetidin-3-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
94. 2-{[1-(4-ciclopropilbenzoil)azetidin-3-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
95. N-(2-metoxietil)-4-metil-2-[(1-{4-[4-(trifluorometil)fenoxi]benzoil}azetidin-3-il)metil]-2H-indazol-5-carboxamida
96. 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-

carboxamida

97. 4-metil-N-(2,2,2-trifluoroetil)-2-({1-[4-(trifluorometoxi)benzoil]azetidin-3-il}-metil)-2H-indazol-5-carboxamida

98. 2-({1-[2-fluoro-4-(trifluorometil)benzoil]azetidin-3-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

99. 4-metil-2-({1-[4-(pentafluoro-λ^6-sulfanil)benzoil]azetidin-3-il}metil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

100. N-[2-(ciclopropiloxi)etil]-4-metil-2-({1-[4-(trifluorometoxi)benzoil]azetidin-3-il}metil)-2H-indazol-5-carboxamida

101. N-[2-(ciclobutiloxi)etil]-4-metil-2-({1-[4-(trifluorometoxi)benzoil]azetidin-3-il}metil)-2H-indazol-5-carboxamida

102. 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-N-[2-(ciclopropilmetoxi)etil]-4-metil-2H-indazol-5-carboxamida

103. N-[2-(ciclopropilmetoxi)etil]-2-({1-[4-(4-fluorofenoxi)benzoil]azetidin-3-il}-metil)-4-metil-2H-indazol-5-carboxamida

104. N-[2-(ciclopropilmetoxi)etil]-4-metil-2-{[1-(4-metilbenzoil)azetidin-3-il]-metil}-2H-indazol-5-

carboxamida

105. 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-4-metil-N-[2-(trifluorometoxi)etil]-2H-indazol-5-carboxamida

106. N-(2-ter-butoxietil)-2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-4-metil-2H-indazol-5-carboxamida

107. N-[2-(ciclopropilmetoxi)etil]-2-({1-[(4'-fluorobifenil-4-il)carbonil]azetidin-3-il}metil)-4-metil-2H-indazol-5-carboxamida

108. 2-({1-[(4'-fluorobifenil-4-il)carbonil]azetidin-3-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

109. 2-({1-[4-(4-fluorofenoxi)benzoil]azetidin-3-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

110. 2-({1-[4-(4-fluorofenoxi)benzoil]azetidin-3-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

111. 2-({1-[(4'-fluorobifenil-4-il)carbonil]azetidin-3-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

112. 2-{[1-(4-clorobenzoil)azetidin-3-il]metil}-4-metil-N-[2-(2,2,2-trifluoroetoxi)-etil]-2H-indazol-5-carboxamida

113. 4-metil-N-[2-(2,2,2-trifluoroetoxi)etil]-2-[(1-{4-[4-(trifluorometil)fenoxi]-benzoil}azetidin-3-il)metil]-2H-indazol-5-carboxamida
114. 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{4-[4-(trifluorometil)fenoxi]benzoil}-azetidin-3-il)metil]-2H-indazol-5-carboxamida
115. 2-({1-[4-(4-clorofenoxi)benzoil]azetidin-3-il}metil)-4-metil-N-(2,2,2-trifluoro-etil)-2H-indazol-5-carboxamida
116. 2-({1-[4-(4-clorofenoxi)benzoil]azetidin-3-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
117. N-(2-metoxietil)-4-metil-2-{[1-(4-{[5-(trifluorometil)piridin-2-il]oxi}benzoil)-azetidin-3-il]metil}-2H-indazol-5-carboxamida
118. 4-metil-N-(2,2,2-trifluoroetil)-2-{[1-(4-{[5-(trifluorometil)piridin-2-il]oxi}-benzoil)azetidin-3-il]metil}-2H-indazol-5-carboxamida
119. 2-{[1-(4-clorobenzoil)piperidin-4-il]metil}-N-etil-4-metil-2H-indazol-5-carboxamida
120. 2-({1-[4-(4-fluorofenoxi)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida
121. 2-({1-[4-(4-clorofenoxi)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-

indazol-5-carboxamida

122. 4-metil-2-({1-[4-(4-metilfenoxi)benzoil]piperidin-4-il}metil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

123. 2-({1-[(4'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

124. 4-metil-2-{[1-(4-morfolinobenzoil)piperidin-4-il]metil}-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

125. 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{4-[(trifluorometil)sulfanil]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida

126. 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{4-[4-(trifluorometil)fenoxi]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida

127. 4-metil-N-(2,2,2-trifluoroetil)-2-{[1-(4-{[5-(trifluorometil)piridin-2-il]oxi}-benzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida

128. 4-metil-N-(2,2,2-trifluoroetil)-2-{[1-(4-{[6-(trifluorometil)piridin-3-il]oxi}-benzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida

129. 4-metil-N-(2,2,2-trifluoroetil)-2-{[1-(4-{[6-(trifluorometil)piridin-2-il]oxi}-benzoil)piperidin-4-il]metil}-2H-indazol-5-carboxamida

130. 2-({1-[4-(4-cianofenoxi)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoro-etil)-2H-indazol-5-carboxamida
131. 2-({1-[4-(3-fluorofenoxi)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoro-etil)-2H-indazol-5-carboxamida
132. 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{4-[3-(trifluorometil)fenoxi]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida
133. 2-[(1-{4-[(5-cianopiridin-2-il)oxi]benzoil}piperidin-4-il)metil]-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida
134. 2-[(1-{4-[(5-cloropiridin-2-il)oxi]benzoil}piperidin-4-il)metil]-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida
135. 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{4-[5-(trifluorometil)piridin-2-il]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida
136. 2-({1-[4-(2,4-difluorofenoxi)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida
137. 2-({1-[4-(3,4-difluorofenoxi)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida
138. 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{[4'-

(trifluorometil)bifenil-4-il]carbonil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida

139. 2-{[1-(4-bromobenzoil)piperidin-4-il]metil}-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

140. 2-({1-[4-(5-cloropiridin-2-il)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

141. 2-({1-[(4'-metoxi-2'-metilbifenil-4-il)carbonil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

142. 4-metil-2-({1-[4-(6-metilpiridin-3-il)benzoil]piperidin-4-il}metil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

143. 2-({1-[(4'-fluoro-2'-metoxibifenil-4-il)carbonil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

144. 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{4-[6-(trifluorometil)piridin-3-il]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida

145. 2-({1-[4-(6-metoxipiridin-3-il)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

146. 2-({1-[4-(6-metoxipiridin-2-il)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-

indazol-5-carboxamida

147. 4-metil-2-({1-[4-(5-metilpiridin-2-il)benzoil]piperidin-4-il}metil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

148. 2-({1-[4-(5-fluoropiridin-2-il)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

149. 2-({1-[4-(5-metoxipiridin-2-il)benzoil]piperidin-4-il}metil)-4-metil-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

150. 4-metil-2-({1-[4-(2-metilpirimidin-5-il)benzoil]piperidin-4-il}metil)-N-(2,2,2-trifluoroetil)-2H-indazol-5-carboxamida

151. 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{4-[2-(trifluorometil)pirimidin-5-il]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida

152. 4-metil-N-(2,2,2-trifluoroetil)-2-[(1-{4-[6-(trifluorometil)piridin-2-il]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida

153. 2-({1-[4-(4-cianofenoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

154. 2-{[1-(4-bromo-3-metilbenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

155. 2-{[1-(4-ter-butilbenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
156. 2-({1-[4-(1-hidroxi-1-metiletil)benzoil]piperidin-4-il}metil)-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida
157. 2-{[1-(4-ciclohexilbenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
158. 2-({1-[4-(1-ciano-1-metiletil)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
159. N-(2-metoxietil)-4-metil-2-({1-[4-(pirimidin-2-iloxi)benzoil]piperidin-4-il}-metil)-2H-indazol-5-carboxamida
160. N-(2-metoxietil)-4-metil-2-({1-[4-(3-piridiloxi)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida
161. N-(2-metoxietil)-4-metil-2-{[1-(4-{[5-(trifluorometil)piridin-2-il]oxi}benzoil)-piperidin-4-il]metil}-2H-indazol-5-carboxamida
162. N-(2-metoxietil)-4-metil-2-({1-[4-(2-piridiloxi)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida
163. N-(2-metoxietil)-4-metil-2-{[1-(4-{[4-(trifluorometil)pirimidin-2-il]oxi}-benzoil)piperidin-4-il]metil}-2H-indazol-5-

carboxamida

164. N-(2-metoxietil)-4-metil-2-{[1-(4-{[6-(trifluorometil)piridin-3-il]oxi}benzoil)-piperidin-4-il]metil}-2H-indazol-5-carboxamida

165. N-(2-metoxietil)-4-metil-2-{[1-(4-{[6-(trifluorometil)piridin-2-il]oxi}benzoil)-piperidin-4-il]metil}-2H-indazol-5-carboxamida

166. 2-({1-[(4'-metoxibifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

167. N-(2-metoxietil)-4-metil-2-({1-[4-(3,4,5,6-tetrahidro-2H-piran-4-iloxi)benzoil]-piperidin-4-il}metil)-2H-indazol-5-carboxamida

168. N-(2-metoxietil)-4-metil-2-[(1-{4-[3-(trifluorometil)fenoxi]benzoil}piperidin-4-il)metil]-2H-indazol-5-carboxamida

169. 2-[(1-{4-[(5-cianopiridin-2-il)oxi]benzoil}piperidin-4-il)metil]-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida

170. 2-[(1-{4-[(5-cloropiridin-2-il)oxi]benzoil}piperidin-4-il)metil]-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida

171. 2-({1-[4-(2,4-difluorofenoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

172. 2-({1-[4-(3,4-difluorofenoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
173. N-(2-metoxietil)-4-metil-2-[(1-{[4'-(trifluorometil)bifenil-4-il]carbonil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida
174. 2-({1-[4-(3-fluorofenoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
175. 2-{[1-(2-fluoro-4-isopropoxibenzoil)piperidin-4-il]metil}-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
176. 2-({1-[(3-fluoro-3',4'-dimetilbifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
177. 2-({1-[(2',3-difluoro-4'-metoxibifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
178. 2-({1-[4-(difluorometoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
179. 2-({1-[4-(2-fluorofenoxi)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida
180. 2-({1-[(4'-ciano-2'-metilbifenil-4-

il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

181. 2-({1-[4-(5-cloropiridin-2-il)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

182. N-(2-metoxietil)-4-metil-2-[(1-{4-[6-(trifluorometil)piridin-2-il]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida

183. N-(2-metoxietil)-2-({1-[(4'-metoxi-2'-metilbifenil-4-il)carbonil]piperidin-4-il}metil)-4-metil-2H-indazol-5-carboxamida

184. 2-({1-[(4'-cloro-2'-metilbifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

185. 2-[(1-{[4'-(1-ciano-1-metiletil)bifenil-4-il]carbonil}piperidin-4-il)metil]-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

186. N-(2-metoxietil)-2-({1-[4-(5-metoxipiridin-2-il)benzoil]piperidin-4-il}metil)-4-metil-2H-indazol-5-carboxamida

187. N-(2-metoxietil)-4-metil-2-[(1-{4-[6-(trifluorometil)piridin-3-il]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida

188. N-(2-metoxietil)-2-({1-[4-(6-metoxipiridin-3-il)benzoil]piperidin-4-il}metil)-4-metil-2H-

indazol-5-carboxamida

189. 2-({1-[(4'-fluoro-2'-metilbifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

190. N-(2-metoxietil)-4-metil-2-({1-[4-(6-metilpiridin-3-il)benzoil]piperidin-4-il}-metil)-2H-indazol-5-carboxamida

191. N-(2-metoxietil)-2-({1-[4-(6-metoxipiridin-2-il)benzoil]piperidin-4-il}metil)-4-metil-2H-indazol-5-carboxamida

192. N-(2-metoxietil)-4-metil-2-({1-[4-(2-metilpirimidin-5-il)benzoil]piperidin-4-il}metil)-2H-indazol-5-carboxamida

193. 2-({1-[(4'-fluoro-2'-metoxibifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

194. 2-({1-[(4'-cloro-2'-metoxibifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

195. N-(2-metoxietil)-4-metil-2-[(1-{4-[2-(trifluorometil)pirimidin-5-il]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida

196. 2-({1-[(4'-cloro-2'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida

197. 2-({1-[(2'-cloro-4'-fluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida

198. 2-({1-[4-(5-cloropiridin-3-il)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

199. 2-({1-[4-(5-fluoropiridin-3-il)benzoil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

200. N-(2-metoxietil)-4-metil-2-[(1-{4-[5-(trifluorometil)piridin-3-il]benzoil}-piperidin-4-il)metil]-2H-indazol-5-carboxamida

201. 2-[(1-{[4'-(1-hidroxi-1-metiletil)bifenil-4-il]carbonil}piperidin-4-il)metil]-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

202. 2-({1-[(3',5'-difluorobifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida

203. 2-({1-[(4'-fluoro-2-metilbifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxi-etil)-4-metil-2H-indazol-5-carboxamida

204. 2-({1-[(3',5'-difluoro-2-metilbifenil-4-il)carbonil]piperidin-4-il}metil)-N-(2-metoxietil)-4-metil-2H-indazol-5-carboxamida

205. N-(2-metoxietil)-4-metil-2-({1-[3-metil-4-(3-

piridil)benzoil]piperidin-4-il}-metil)-2H-indazol-5-carboxamida

206. N-(2-metoxietil)-4-metil-2-({1-[3-metil-4-(4-piridil)benzoil]piperidin-4-il}-metil)-2H-indazol-5-carboxamida and

207. N-(2-metoxietil)-4-metil-2-({1-[(2-metilbifenil-4-il)carbonil]piperidin-4-il}-metil)-2H-indazol-5-carboxamida

7. Uso de los compuestos de acuerdo con la fórmula I CARACTERIZADO porque es para la producción de un fármaco que contiene una formulación apropiada y sustancias portadoras.

8. Uso de los fármacos de acuerdo a la reivindicación 7, CARACTERIZADO porque el fármaco se usa para la prevención y el tratamiento de enfermedades.

9. Uso de los compuestos de acuerdo a la reivindicación 1 a 6 y los fármacos de acuerdo a la reivindicación 7 CARACTERIZADO porque es para control de la fertilidad/anticoncepción.

10. Uso de los fármacos de acuerdo a la reivindicación 7, CARACTERIZADO porque es para la prevención y el tratamiento directo de enfermedades que se ligan causalmente con el receptor EP_2 o enfermedades que se pueden tratar influyendo sobre el receptor EP_2.

11. Uso de los fármacos de acuerdo a la reivindicación 7 CARACTERIZADO porque es para la prevención y el tratamiento de endometriosis.

12. Uso de los fármacos de acuerdo a la reivindicación 7 CARACTERIZADO porque es para la prevención y el tratamiento de molestias menstruales, donde los problemas menstruales pueden ser sangrado severo y persistente, sangrado irregular y dolores.

13. Uso de los fármacos de acuerdo a la reivindicación 7 CARACTERIZADO porque es para la prevención y el tratamiento de fibromas (miomas).

14. Uso de los fármacos de acuerdo a la reivindicación 7 CARACTERIZADO porque es para la prevención y el tratamiento de cáncer, donde las enfermedades cancerosas pueden ser cáncer de pulmón, intestinal, de mama, de piel, de próstata o de esófago y leucemia.

15. Uso de los fármacos de acuerdo a la reivindicación 7 CARACTERIZADO porque es para la prevención y el tratamiento de arteriosclerosis.

16. Uso de los fármacos de acuerdo a la reivindicación 7 CARACTERIZADO porque es para la prevención y el tratamiento de enfermedades neurodegenerativas, neuroinflamatorias e isquémicas, donde las enfermedades pueden ser enfermedad de

Alzheimer, enfermedad de Parkinson, ALS, apoplejía y esclerosis múltiple.

17. Uso de los fármacos de acuerdo a la reivindicación 7 CARACTERIZADO porque es para la prevención y el tratamiento de enfermedades de riñón poliquístico.

18. Uso de los fármacos de acuerdo a la reivindicación 7 CARACTERIZADO porque es para la prevención y el tratamiento de dolor, donde el dolor puede ser hiperalgesia inflamatoria.

19. Uso de los fármacos de acuerdo a la reivindicación 7 CARACTERIZADO porque es para la prevención y el tratamiento de enfermedades infecciosas del pulmón.

20. Uso de los fármacos de acuerdo a la reivindicación 7 CARACTERIZADO porque es para la prevención y el tratamiento de enfermedades pulmonares obstructivas crónicas.

21. Uso de los fármacos de acuerdo a la reivindicación 7 CARACTERIZADO porque es para la prevención y el tratamiento de enfermedades inflamatorias intestinales, donde las enfermedades inflamatorias intestinales pueden ser enfermedad de Crohn y colitis ulcerativa.

22. Uso de los fármacos de acuerdo a la

reivindicación 7 CARACTERIZADO porque es para la prevención y el tratamiento en operaciones de trasplante de médula ósea.

23. Uso de los fármacos de acuerdo a la reivindicación 7 CARACTERIZADO porque es para la prevención y el tratamiento de enfermedades oftálmicas patológicas, donde las enfermedades oftálmicas patológicas pueden ser enfermedad de Graves.

24. Uso de los fármacos de acuerdo a la reivindicación 7 CARACTERIZADO porque es para la prevención y el tratamiento de aneurismas.

25. Uso de los fármacos de acuerdo a la reivindicación 7 CARACTERIZADO porque es para la prevención y el tratamiento de daño vascular y el síndrome de Kawasaki.

26. Uso de los fármacos de acuerdo a la reivindicación 7 CARACTERIZADO porque es para la prevención y el tratamiento de artritis.

27. Fármaco CARACTERIZADO porque contiene un compuesto de la fórmula general (I) en combinación con un inhibidor de COX para el tratamiento de enfermedades, en donde los inhibidores de COX pueden estar seleccionados de la siguiente lista: aspirina, naproxeno, indometacina, meloxicam, ibuprofeno, cetoprofeno, piroxicam, tenoxicam, nimesulide, ácido

mefanémico, quetoralac, celecoxib (4-[5-(4-metilfenil)-3-(trifluorometil)-1H-pirazol-1-il]bencensulfonamida), parecoxib (N-[4-(5-metil-3-fenil-4-isoxazolil)fenil]sulfonilpropionamida), rofecoxib (4-(4-mesilfenil)-3-fenilfuran-(5H)-ona), valdecoxib (4-[5-metil-3-fenil-4-isoxazoil)bencensulfonamida), NS-398 (N-metil-2-ciclohexanoxi-4-nitrobencensulfonamida), lumiracoxib [ácido 2-(2'-cloro-6'-fluorofenil)-amino-5-metilbencen-acético], ceracoxib y etoricoxib.

28. Fármaco de acuerdo a la reivindicación 27, CARACTERIZADO porque las enfermedades son enfermedades infecciosas, cáncer, enfermedades cardiovasculares, enfermedades angiogénicas, trastornos de contracción uterina, dolor, enfermedades inflamatorias, enfermedades neuroinflamatorias, enfermedades neurodegenerativas, enfermedades autoinmunes, enfermedades inmunodependientes/terapias, enfermedades nefrológicas y enfermedades oftalmológicas y donde los fármacos también se pueden usar para el tratamiento de dolor y en el trasplante y el control de la fertilidad.

29. Uso de los compuestos de la fórmula general I, de acuerdo con las reivindicaciones 1 - 6, CARACTERIZADO porque es en la forma de una preparación farmacéutica para administración enteral, parenteral, vaginal, intrauterina y oral.

30. Método para la preparación de los compuestos de la fórmula general (I), CARACTERIZADO porque un compuesto de la fórmula general (VIII) se hace reaccionar con una amina de la fórmula general (XI), donde R^1, R^2, R^3, R^4, X, Ar, m y n tienen el significado establecido en la reivindicación 1.

31. Método para la preparación de los compuestos de la fórmula general (I), CARACTERIZADO porque un compuesto de la fórmula general (VI) se hace reaccionar con una amina de la fórmula general (XI), donde R^1, R^2, R^3, R^4, X, Ar, m y n tienen el significado establecido en la reivindicación 1 y monóxido de carbono o una fuente de monóxido de carbono tales como, por ejemplo, hexacarbonilo de molibdeno, bajo catálisis de paladio (0).

32. Método para la preparación de los compuestos de la fórmula general (I), CARACTERIZADO porque un compuesto de la fórmula general (XV) se hace reaccionar con un ácido carboxílico (Y = OH), un cloruro de ácido carboxílico (Y = Cl) o anhídrido (Y = $O-C(O)-O-CH_2(CH_3)CH_3$) de la fórmula general (IX), donde R^1, R^2, R^3, R^4, X, Ar, m, n tienen el significado establecido en la reivindicación 1.

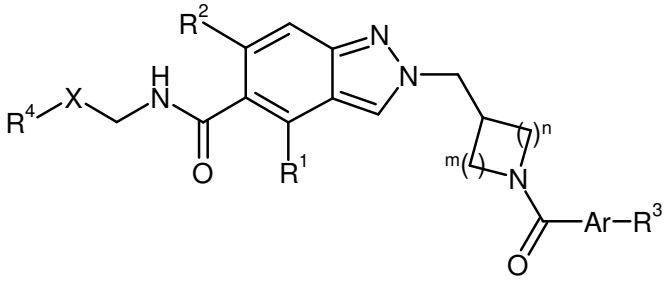
33. Método para la preparación de los compuestos de la fórmula general (I), CARACTERIZADO

porque un compuesto de la fórmula general (XVI), en donde LG´ por ejemplo, significa Br o I, se hace reaccionar con un ácido borónico o un éster de ácido borónico de la fórmula general (XVIII), donde R^1, R^2, R^3, R^4, X, Ar, m y n tienen el significado establecido en la reivindicación 1.

NUEVOS *2H*–INDAZOLES COMO ANTAGONISTAS DEL RECEPTOR EP_2

RESUMEN

Nuevos *2H*–indazoles de la fórmula general (I), métodos para su preparación y su uso para la producción de agentes farmacéuticos para el tratamiento de enfermedades e indicaciones que están ligadas con el receptor de EP_2.



(I)

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.
BHC113005-WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2012/073556	26/11/2012	28/11/2011
Applicant		
BAYER INTELLECTUAL PROPERTY GMBH		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2, 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/EP2012/073556

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/06 C07D401/14 C07D403/06 C07D403/14 C07D407/14
C07D413/14 C07D417/14 A61K31/416 A61K31/4439 A61K31/4545
A61K31/506 A61K31/5377 A61P15/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

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	DE 10 2009 049662 A1 (BAYER SCHERING PHARMA AG [DE]) 14 April 2011 (2011-04-14) cited in the application claims 1, 8-26	1-33
A	WO 2009/063365 A1 (PFIZER LTD [GB]; SKERRATT SARAH ELIZABETH [GB]; DACK KEVIN NEIL [GB]) 22 May 2009 (2009-05-22) cited in the application claims 1-14	1-33

☐ 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
14 January 2013	22/01/2013

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2012/073556

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 102009049662 A1	14-04-2011	NONE	
WO 2009063365 A1	22-05-2009	CA 2705368 A1	22-05-2009
		EP 2222665 A1	01-09-2010
		JP 2011503169 A	27-01-2011
		US 2010256109 A1	07-10-2010
		WO 2009063365 A1	22-05-2009