SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 13-040959- -00000-0000

Fecha: 2013-02-28 16:28:45 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve. 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 5

Industria y Comercio
SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL
DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: NUEVOS COMPUESTOS.

SOLICITANTE: BOEHRINGER INGELHEIM INTERNATIONAL GMBH

DIRECCIÓN: Binger Strasse. 173, 55216 Ingelheim am Rhein
Alemania

APODERADO: CARLOS R. OLARTE

BOGOTÁ 28 de Febrero de 2013

P2013/000002

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Alemania

APODERADO: CARLOS R. OLARTE

BOGOTÁ 28 de Febrero de 2013

P2013/000002

OLARTEMOURE

OLARTE MOURE & ASOCI

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2013/000002**

SOLICITUD DE:

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

[ ] Capítulo I. [X] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**
Dirección: Corporate Patents, Binger Str. 173, 55216 Ingelheim am Rhein
Nacionalidad o Domicilio: Alemania
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, Colombia
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/EP2011/064258 Fecha Agosto 19, 2011

Publicación Internacional No. WO 2012/022793 A1 Fecha Febrero 23, 2012

(6) **Título (54)** **NUEVOS COMPUESTOS.**

Clasificación Internacional (51) C07D 235/30; A61K 31/4184; A61P 11/00; A61P 29/00.

Prioridad

SI [X] **NO** [ ]

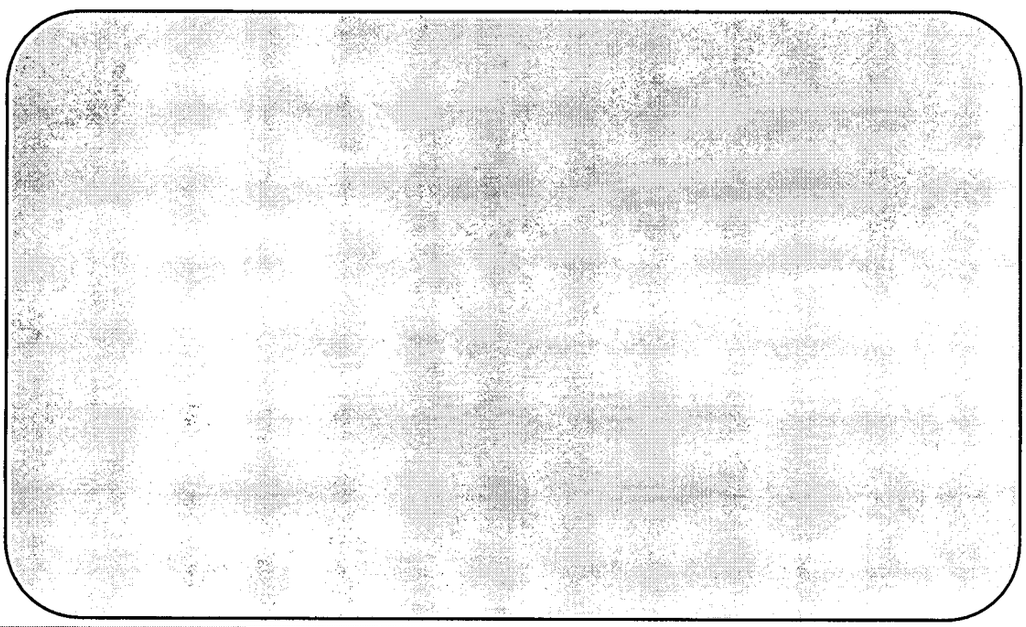
(33) País de Origen	(32) Fecha	(31) Número de Solicitud
EP	Agosto 20, 2010	10173501.7

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

(10) **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones. Declaración bajo la Regla 4.17 (ii) del PCT.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**



(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

LISTA DE INVENTORES

PCT/EP2011/064258

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Boehringer Ingelheim GmbH,
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Binger Strasse 173,
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55216 Ingelheim Am Rhein
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Nacionalidad: Neerlandés

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Suecia
Nacionalidad: Sueco

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 13 - 0020742

Bogotá D.C., Febrero 28 de 2013 - 16:07:32

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	181982212	28/02/2013	9.174.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	112 PTC CAP-I EXAMEN DE PATENTIBILIDAD DE INVENSION	505.000.00	505.000.00
				$505.000.00

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

Responsable: _____
-*****-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 13-040959- -00000-0000
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Industria y Comercio
SUPERINTENDENCIA

PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA
RELACIÓN DE ANEXOS

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

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

Radicador

Planilla:

ID	*No. Radicación*	*Consecutivo*	*Item*
1	[illegible]		
2	[illegible]		
3			
4			
5			
6			
7	13-40959		
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			

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

Observaciones:

[illegible] CD

ANEXO CD

Industria y Comercio
SUPERINTENDENCIA

ADM

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 13-040959- -00000-0000

Fecha: 2013-02-28 16:20:45 Dep. 2020 DIR.NUEVASCR
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PATENTE DE INVENCIÓN ☐ MODELO DE UTILIDAD ☐ Art 33 Decisión 486/00

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

Completa ☐ Incompleta ☐

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

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

Completa ☒ Incompleta ☐

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

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

Completa ☐ Incompleta ☐

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

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

Completa ☐ Incompleta ☐

TESTIMONIO

ESCRITURA: 001416
MINUTA: 000657

K: 007735

DELEGACION DE PODER
QUE OTORGA
BOEHRINGER INGELHEIM INTERNATIONAL GMBH
REPRESENTADO POR
JANNE IVETTE LUQUE CARDENAS
A FAVOR DE
CARLOS REINALDO OLARTE
&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&

I N T R O D U C C I O N ==

EN LA CIUDAD DE LIMA AL VEINTISEIS DE JULIO DEL DOS MIL DIEZ, ANTE MI; MARIO GINO BENVENUTO MURGUIA, NOTARIO DE ESTA CAPITAL. ==

C O M P A R E C E N: ==

JANNE IVETTE LUQUE CARDENAS, QUIEN MANIFIESTA SER DE NACIONALIDAD: PERUANA, DE ESTADO CIVIL CASADA, DE PROFESION U OCUPACIÓN: ABOGADA Y DOMICILIAR EN AVENIDA REPUBLICA DE PANAMA 3531, OFICINA 1203, DISTRITO DE SAN ISIDRO PROVINCIA Y DEPARTAMENTO DE LIMA, DEBIDAMENTE IDENTIFICADA CON DOCUMENTO NACIONAL DE IDENTIDAD NUMERO 29562321, QUIEN PROCEDE EN REPRESENTACION DE **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**, CUYAS FACULTADES CONSTAN EN EL PODER OTORGADO CON FECHA QUINCE DE JULIO DEL DOS MIL DIEZ, DEBIDAMENTE LEGALIZADO POR EL MINISTERIO DE RELACIONES ESTERIORES CON FECHA VEINTITRES DE JULIO DEL DOS MIL DIEZ, QUE SE INSERTA. ==== LA COMPARECIENTE ES INTELIGENTE EN EL IDIOMA CASTELLANO, QUIEN SE OBLIGA CON CAPACIDAD, LIBERTAD Y CONOCIMIENTO SUFICIENTE DE CONFORMIDAD CON EL EXAMEN QUE LE HE EFECTUADO DE LO QUE DOY FE; Y ME ENTREGÓ UNA MINUTA QUE ARCHIVO EN SU LEGAJO RESPECTIVO BAJO EL NUMERO DE ORDEN CORRESPONDIENTE Y CUYO TENOR LITERAL ES COMO SIGUE: ==

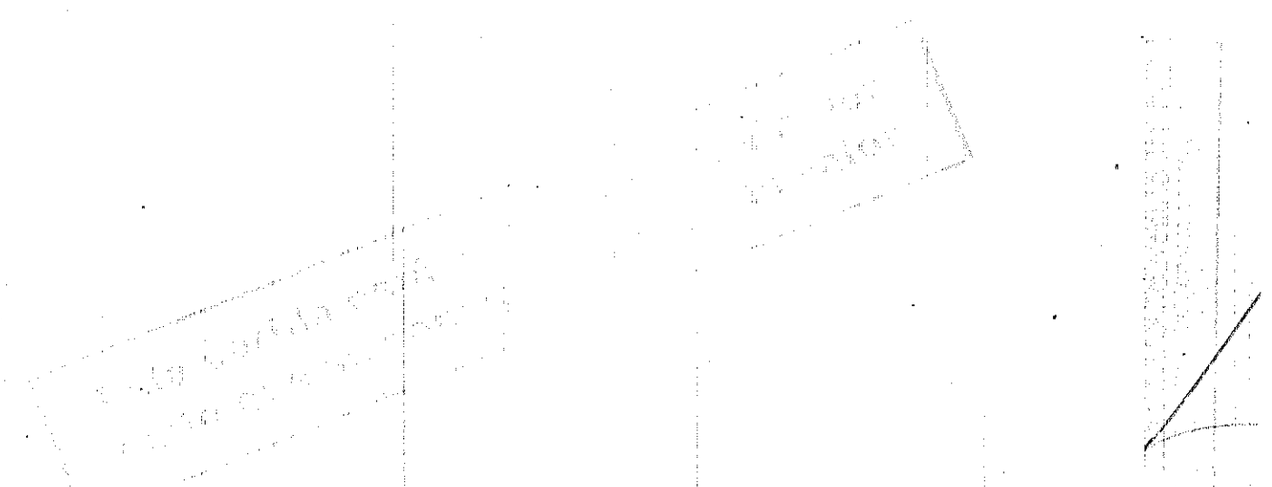
M I N U T A: ==

SEÑOR NOTARIO: ==

SÍRVASE EXTENDER EN SU REGISTRO DE ESCRITURAS PÚBLICAS UNA DE **DELEGACION DE PODER** QUE OTORGA LA SEÑORA **IVETTE LUQUE CARDENAS**, IDENTIFICADA CON DNI N° 29562321, DE NACIONALIDAD PERUANA, ESTADO CIVIL CASADA, OCUPACIÓN ABOGADO Y CON DOMICILIO EN AV. REPÚBLICA DE PANAMÁ N° 3531, OFICINA 1203, SAN ISIDRO, QUIEN ACTÚA EN REPRESENTACIÓN DE **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**, UNA EMPRESA CONSTITUIDA Y EXISTENTE BAJO LAS LEYES DE ALEMANIA, CON DOMICILIO EN BINGER STRASSE 173, 55216 INGELHEIM AM RHEIN, ALEMANIA, SEGÚN PODER OTORGADO CON FECHA 13 DE OCTUBRE DE 2009, Y A QUIEN EN ADELANTE SE LE DENOMINARÁ **EL PODERDANTE**; A FAVOR DEL SEÑOR **CARLOS REINALDO OLARTE**, IDENTIFICADO CON CÉDULA N° 79.782.747, A QUIEN EN ADELANTE SE LE DENOMINARÁ **EL APODERADO**; EN LOS SIGUIENTES TÉRMINOS Y CONDICIONES: ==

PRIMERO: CON FECHA 15 DE JULIO DE 2010, LA EMPRESA **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**, UNA EMPRESA CONSTITUIDA Y EXISTENTE BAJO LAS LEYES DE ALEMANIA, CON DOMICILIO EN BINGER STRASSE 173, 55216 INGELHEIM AM RHEIN, ALEMANIA, OTORGÓ PODER A FAVOR DE **EL PODERDANTE**, EL CUAL USTED SEÑOR NOTARIO SE SERVIRÁ INSERTAR. ==

SEGUNDO: POR EL PRESENTE DOCUMENTO, **EL PODERDANTE** DELEGA PODER A FAVOR DE **EL APODERADO** PARA QUE REPRESENTE EN LA REPÚBLICA DE COLOMBIA A LA SOCIEDAD **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**, TAL COMO CONSTA EN EL PODER ADJUNTO, ANTE CUALQUIER AUTORIDAD ADMINISTRATIVA O JUDICIAL, INCLUYENDO LA SECRETARÍA Y TRIBUNAL DE JUSTICIA DE LA COMUNIDAD ANDINA, PARA EL INICIO, TRAMITACIÓN, OBTENCIÓN, DEFENSA Y HACER RESPETAR TODAS Y CUALQUIERA DE LAS PATENTES DE INVENCIÓN, MODELOS DE UTILIDAD, DISEÑOS INDUSTRIALES, MARCAS, LEMAS COMERCIALES, NOMBRES COMERCIALES, PROTECCIÓN DE DATOS DE PRUEBA, PROTECCIÓN DE SECRETOS EMPRESARIALES, DERECHOS DE AUTOR, REGISTRO DE NOMBRES DE DOMINIO, O SEGUIMIENTO DE PROCEDIMIENTOS EN MATERIAS TALES COMO PROPIEDAD INTELECTUAL. ==



TESTIMONIO

EL APODERADO ACTUANDO EN FORMA INDIVIDUAL PODRÁ DEMANDAR, RECONVENIR, CONTESTAR DEMANDAS Y RECONVENCIONES, PRESENTAR TODO TIPO DE SOLICITUDES, RECURSOS, RESPUESTAS U OPOSICIONES, PRESENTAR TODO TIPO DE RECURSOS DE IMPUGNACIÓN, PRESENTAR DECLARACIONES, JURADAS O NO, PRESENTAR CUALQUIER OTRO RECURSO O REMEDIO PROCESAL PERMITIDO POR LEY, PAGAR IMPUESTOS Y ANUALIDADES, SOLICITAR TESTIMONIOS, RENUNCIAR A LOS DERECHOS DE REGISTRO SOBRE UN ELEMENTO DE LA PROPIEDAD INDUSTRIAL, DESISTIRSE DEL PROCESO Y DE LA PRETENSIÓN, ALLANARSE A LA PRETENSIÓN, CONCILIAR, TRANSIGIR, SOMETER A ARBITRAJE LAS PRETENSIONES CONTROVERTIDAS EN EL PROCESO, SOLICITAR Y EJECUTAR MEDIDAS CAUTELARES ASÍ COMO VISITAS INSPECTIVAS, RATIFICAR LOS ACTOS JURÍDICOS PROCESALES SUSCRITOS CON ANTERIORIDAD AL OTORGAMIENTO Y/O PRESENTACIÓN DEL PRESENTE PODER, SUSTITUIR O DELEGAR LA REPRESENTACIÓN, REVOCAR LOS PODERES OTORGADOS, RECIBIR NOTIFICACIONES EN NOMBRE DE LA COMPAÑÍA Y LOS DEMÁS ACTOS QUE EXPRESE LA LEY. ==========
AGREGUE USTED SEÑOR NOTARIO, LAS CLÁUSULAS DE LEY, E INSERTE EL PODER AL QUE SE HA HECHO REFERENCIA. =======
LIMA, 21 DE JULIO DE 2010. ==========
FIRMADO.- UNA FIRMA ILEGIBLE.- ==========
ABOGADO QUE AUTORIZA.-UN SELLO QUE DICE.- JURGEN STROBACH FLORIAN.- ABOGADO.- C.A.L. 30548.- UNA FIRMA ILEGIBLE.-
INSERTO UNO: TRADUCCION OFICIAL ==========
MARIO GINO BENVENUTO MURGUIA, ABOGADO NOTARIO DE LIMA, CERTIFICO QUE HE TENIDO A LA VISTA **LA TRADUCCION OFICIAL DEL PODER ESPECIAL,** DEBIDAMENTE LEGALIZADO POR EL MINISTERIO DE RELACIONES EXTERIORES CON FECHA VEINTITRES DE JULIO DEL DOS MIL DIEZ, CUYO TENOR LITERAL ES COMO SIGUE: ==========

TRADUCCIÓN OFICIAL

TRA. N° TOI.0077.10

Primera página del documento original:

PODER ESPECIAL de fecha 15 de julio de 2010 redactado en idioma castellano e inglés

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Segunda página del documento original:

UR. Nr: 1446/2010

Por la presente se certifica que las firmas que anteceden de:

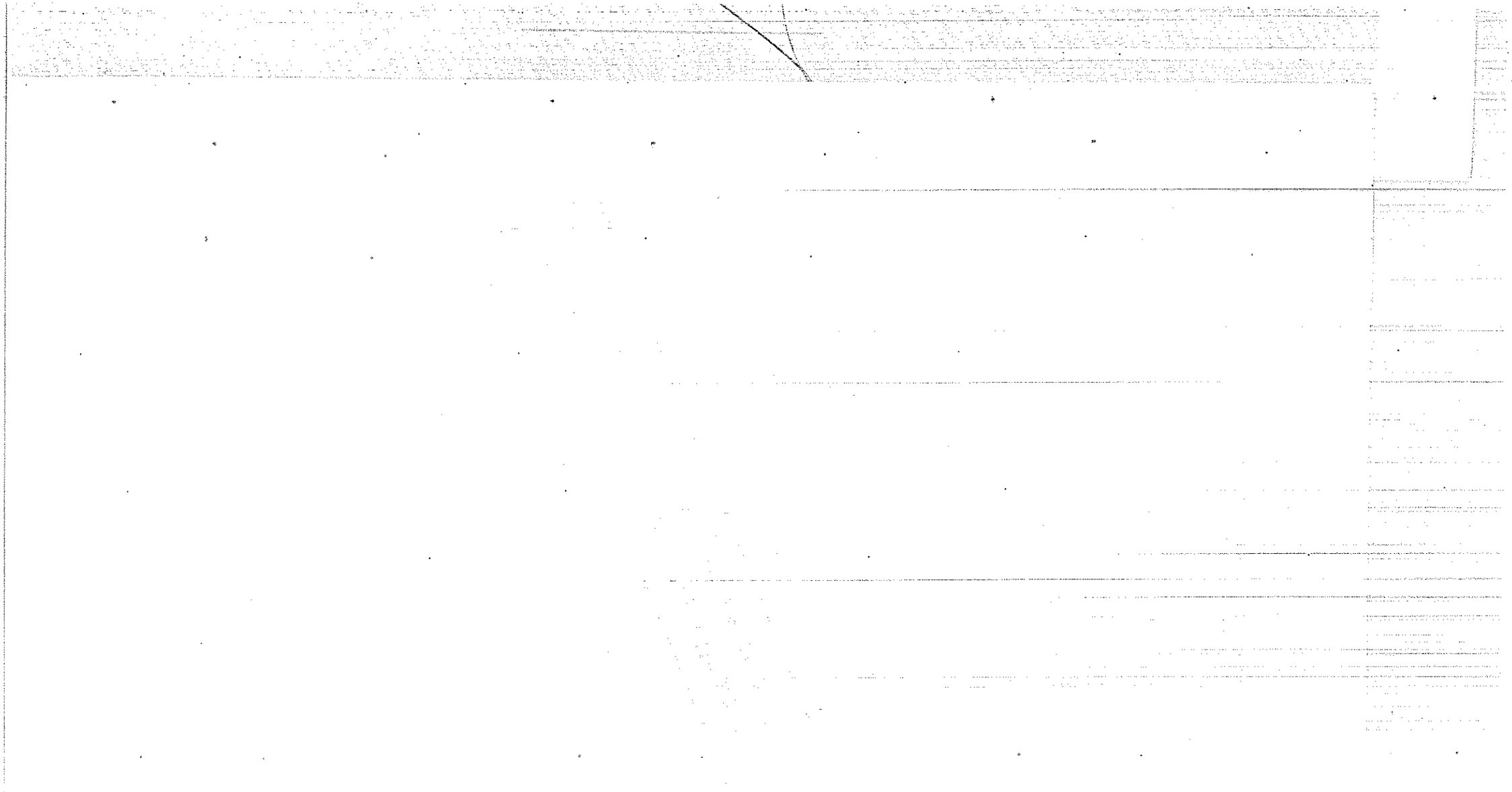
- Dr. Michael Kompter, nacido el 11 de mayo de 1955, con domicilio en 55216 Ingelheim am Rhein, Binger Straße 173.
- Dr. Christian Hauke, nacido el 31 de agosto de 1947, con domicilio en 55216 Ingelheim am Rhein, Binger Straße 173.

a quienes he conocido en persona,
han sido estampadas en mi presencia

Asimismo, certifico que Boehringer Ingelheim International GmbH es una sociedad debidamente constituida bajo las leyes de la República Federal de

Mary Ann Montagudo Medina
Traductora Pública Juramentada
Registro JUT N°105

Estados Unidos 888 - Lima 11 - Perú - Telfs. (511) 460-1659 • (511) 463-1167 • Fax: (511) 463-4548
maeinm@terra.com.pe



Mario Cesar Benavente Mayer
Notario Público de Lima

TESTIMONIO

TRA. N° TOI.0077.10

Alemania, con domicilio en Binger Strasse 173, 55216 Ingelheim am Rhein, Alemania.

Dicha sociedad se encuentra inscrita en el Registro Mercantil del Juzgado de Distrito de Bingen, bajo el número HR B 1063 desde el 14 de mayo de 1968. Dicha inscripción ha sido transferida por ley al Registro Mercantil del Juzgado de Distrito de Mainz, donde se encuentra inscrita bajo el número HR B 21063 desde el 28 de diciembre de 2005.

Asimismo, certifico que los doctores Michael Kompter y Christian Hauke, han sido autorizados para firmar el documento que antecede y actualmente se encuentran debidamente autorizados para firmar a nombre de Boehringer Ingelheim International GmbH en calidad de apoderados.

Ingelheim am Rhein, 15 de julio de 2010

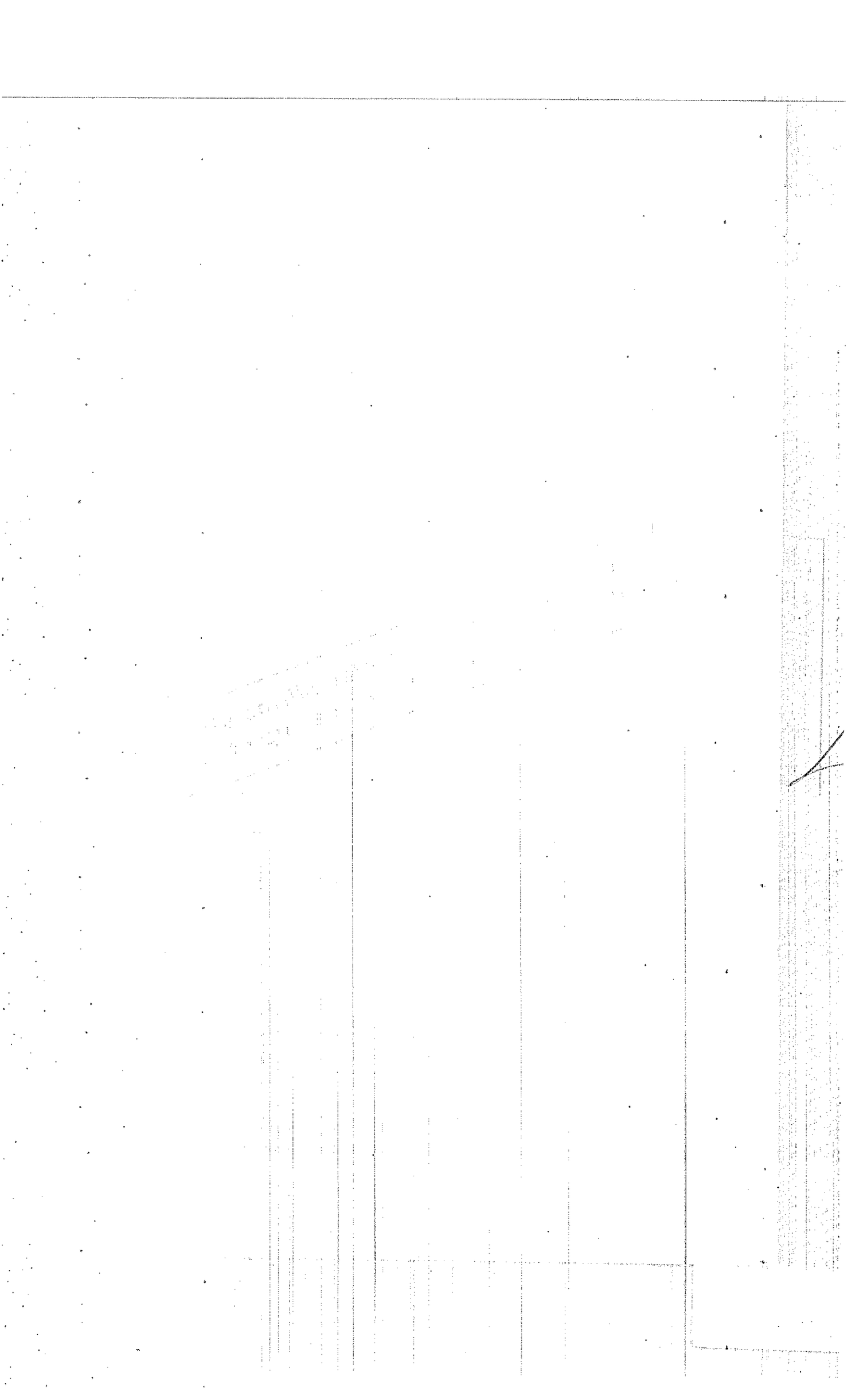
(firmado ilegible)

Notario Público

Mary Ann Montesinos Medina
Traductora Pública Juramentada
Registro N° 105

Estados Unidos 888 - Lima 11 - Perú - Telfs. (511) 460-1859 • (511) 463-1167 • Fax (511) 463-4548
maerm@terra.com.pe

Av. Juan de Arona N° 545 Altura Cdra. 31 de la Av. Arequipa – San Isidro
Central: 719 – 1667 / 719 – 1668 / 719 – 1669 / Telefax.: 717 – 1031
www.notariabenvenuto.com / e-mail: notario@notariabenvenuto.com



Pedro Alejandro Benvenuto Murgia
ABOGADO NOTARIADO DE LIMA

TESTIMONIO

TRA. N° TOI.0077.10

Reverso de la segunda página del documento original:

(sello en idioma extranjero distinto al inglés, de fecha 16 de julio de 2010)

(sello en idioma castellano del Consulado del Perú, de fecha 20 de julio de 2010)

(sello) **MINISTERIO DE RELACIONES EXTERIORES**

DIRECCIÓN GENERAL DE POLÍTICA CONSULAR

Legalización N° 092720

Se legaliza la firma que antecede del Sr.(a) Alfredo Arecco-Sablich sin juzgar el contenido del documento

Lima, 23 de julio de 2010

(fdo.) Maribel del Rosario LUYO JAVIER

Departamento de Legalizaciones

Dirección de Trámites Consulares/sello

La infrascrita, Traductora Pública Juramentada, certifica que la presente traducción es fiel y correcta del texto original en idioma Castellano..... adjunto. Esta traducción no debe interpretarse como reconocimiento de la autenticidad del documento traducido.
En fe de lo cual, firmo y sello en.....Lima.....
a los...26....días del mes de...julio.....de 2010..

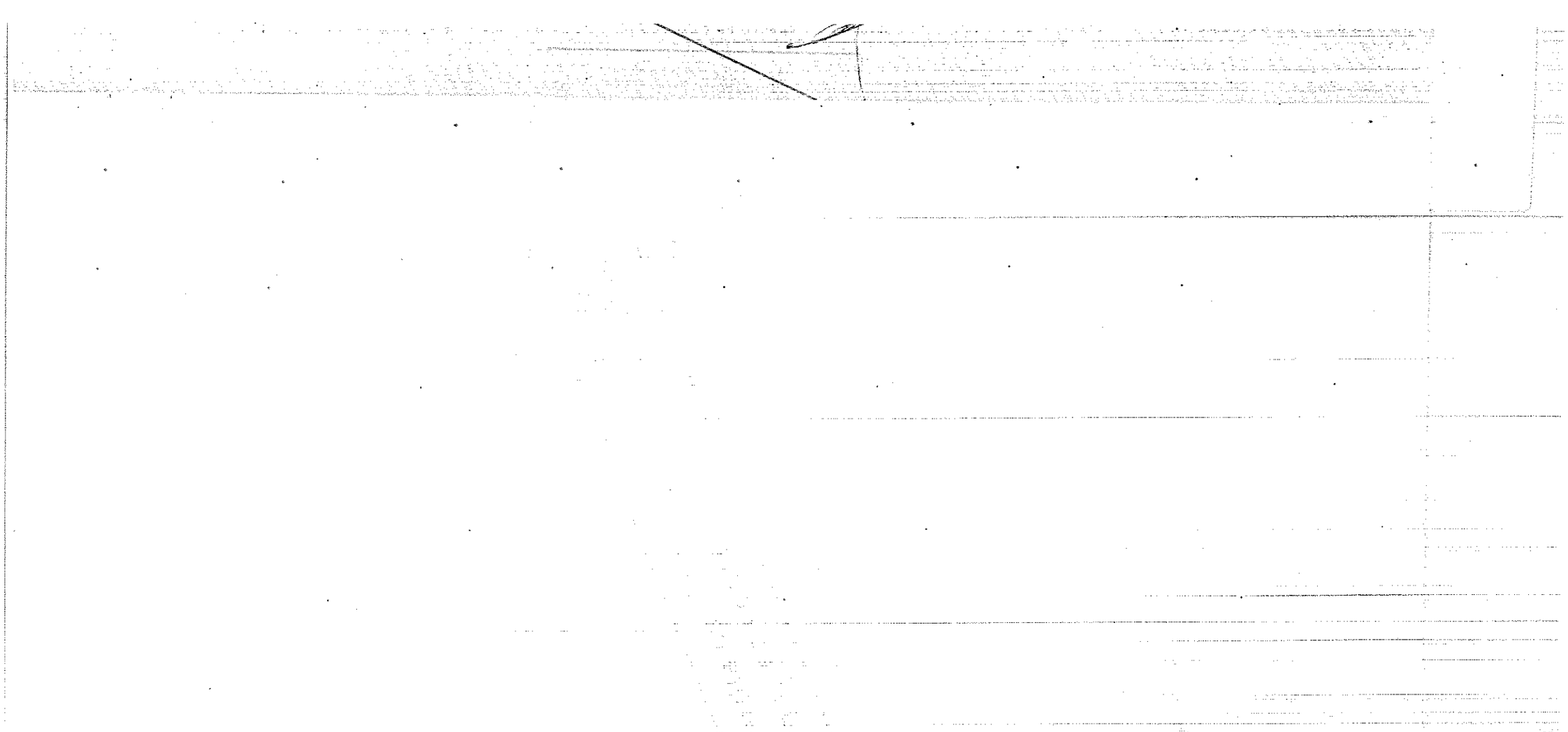
MINISTERIO DE RELACIONES EXTERIORES
DIRECCIÓN GENERAL DE POLÍTICA CONSULAR
Legalización N°
Se legaliza la firma que antecede del Sr.(a)

SIN JUZGAR EL CONTENIDO DEL DOCUMENTO

Julia Adela Moreano de Dueñas
Departamento de Legalizaciones
Dirección de Trámites Consulares
LIMA 27 JUL. 2010

Mary Ann Montesinos Medina
Traductora Pública Juramentada
Registro JVT N° 105

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maemm@terra.com.pe



TESTIMONIO

FERNÁNDEZ - DÁVILA & BUENO
ABOGADOS

PODER ESPECIAL

Conste por el presente documento el Poder Especial que otorga *[insertar nombre de poderdante]*, domiciliada en *[insertar domicilio]* constituida de acuerdo a las leyes de *[insertar país de constitución]*, representada por su *[insertar cargo en la cía.]* Sr.(a) *[insertar nombre del representante de la cía.]*, a favor de FERNÁNDEZ-DÁVILA ABOGADOS SAC, CARLOS FERNÁNDEZ DAVILA WINKLER, ROSA BUENO MERA, JULIETA DEL PILAR TIJERO MARTINO, DIEGO CORDOVA FLORES, IVETTE LUQUE CARDENAS y/o CLARISA SILES VASCONES, domiciliados en Av. República de Panamá 3531, Oficina 1203, San Isidro, Lima, Perú, para que la representen en la República de Perú, República de Bolivia, República de Chile, República de Colombia, República de Ecuador y República Bolivariana de Venezuela, ante cualquier autoridad administrativa o judicial, incluyendo la Secretaría y Tribunal de Justicia de la Comunidad Andina, para el inicio, tramitación, obtención, defensa y hacer respetar todas y cualquiera de las patentes de invención, modelos de utilidad, diseños industriales, marcas, lemas comerciales, nombres comerciales, protección de datos de prueba, protección de secretos empresariales, derechos de autor, registro de nombres de dominio, o seguimiento de procedimientos en materias tales como Propiedad Intelectual.

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Suscrito en..... el ..... de ..... de 2010

ESTE PODER REQUIERE DE LEGALIZACIÓN NOTARIAL (PRECISANDO QUE EL REPRESENTANTE TIENE LAS FACULTADES PARA OTROGARLO Y QUE ESTUVO PRESENTE AL MOMENTO DE HACERLO) Y DE CONSUL PERUANO (CUANDO ES OTORGADO EN EL EXTRANJERO)

SPECIAL POWER OF ATTORNEY

By means of this Special Power of Attorney *Boehringer Ingelheim International GmbH* with address in *Binger Strasse 173, 55216 Ingelheim am Rhein, Germany* and incorporated under the laws of *Germany* duly represented by its *Authorized Signatories* Dr. Michael KOMPTER and Dr. Christian HAUKE, grants to FERNÁNDEZ-DÁVILA ABOGADOS SAC, CARLOS FERNÁNDEZ DAVILA WINKLER, ROSA BUENO MERA, JULIETA DEL PILAR TIJERO MARTINO, DIEGO CORDOVA FLORES, IVETTE LUQUE CARDENAS and/or CLARISA SILES VASCONES, with address at Av. República de Panamá 3531, Oficina 1203, San Isidro, Lima, Perú, the powers to represent in the Republic of Perú, the Republic of Bolivia, Republic of Chile, Republic of Colombia, Republic of Ecuador and the Bolivarian Republic of Venezuela before any administrative or judicial authority of any class, including the Andean Secretariat and the Andean Court of Justice to initiate, prosecution, obtain, defend and enforce any and all of the company's Patents for Invention, Utility Models, Industrial Designs, Trademarks, Trade Names, Commercial Emblems, Test Data Protection, Protection of Trade Secrets, Copyrights, Registration of Domain names and handle proceedings related to Intellectual Property.

The empowered representatives will exert this power of attorney acting individually and indistinctively with the following powers, having authority to claim, to counter-claim, to answer complaints and counter-claims, to file petitions, recourses, replies and oppositions, to withdraw the registration of an industrial property element, to abandon the action and the requested relief, to defend a suit, to file standard or sworn declarations, to file all sort of petitions, appeal and motions permitted by law, pay taxes and annuities, request testimonies, to accept in total or part the demanded pretensions, conciliate, settle, submit to arbitration the contradicted pretensions in the process, to require and execute precautionary measures and inspections among others, to ratify all the acts in regular procedures and proceedings entered into before the granting and/or presentation of this document, substitute or delegate the representation, revoke such substitutions, receive notifications on behalf of the Company and for the rest of the acts which the law provides.

Executed in Ingelheim, on 15th July of 2010

BOEHRINGER INGELHEIM INTERNATIONAL GMBH

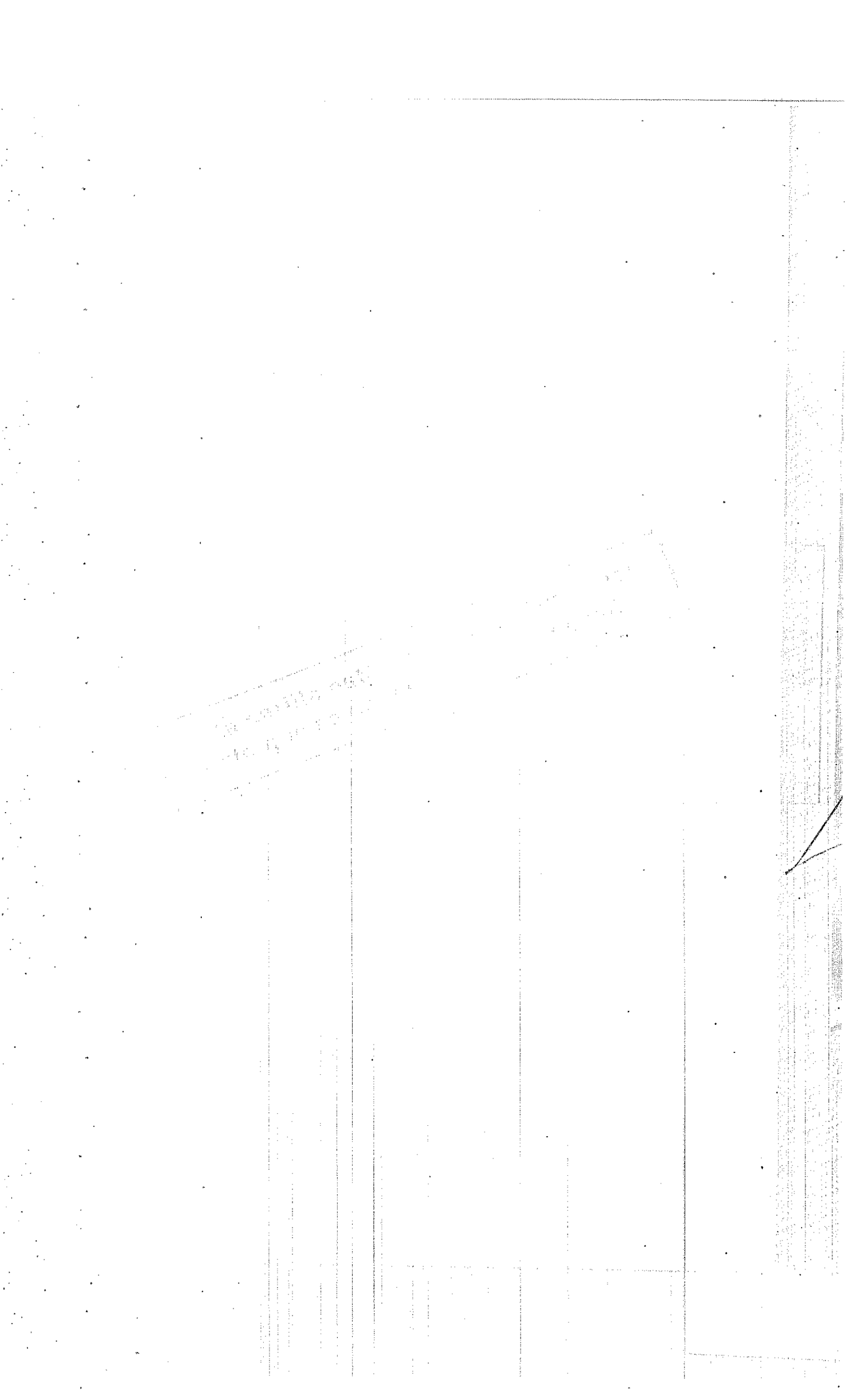
ppa.

Dr. Michael KOMPTER
Authorized Signatory

ppa.

Dr. Christian HAUKE
Authorized Signatory

THIS POWER OF ATTORNEY REQUIRES LEGALIZATION OF A NOTARY (STATING THAT THE REPRESENTATIVE HAS ENOUGH POWERS TO GRANT IT AND APPEARED AND EXECUTED IT PERSONALLY) AND OF A PERUVIAN CONSUL (WHEN GRANTED ABROAD)



TESTIMONIO

UR.Nr. 1446/2010

It is herewith certified that above signatures of:

- Dr. Michael **K o m p t e r**, born 11th day of May 1955, with its business address at 55216 Ingelheim am Rhein, Binger Straße 173,
- Dr. Christian **H a u k e**, born 31st day of August 1947, with its business address at 55216 Ingelheim am Rhein, Binger Straße 173,

personally known,
were duly given in my presence.

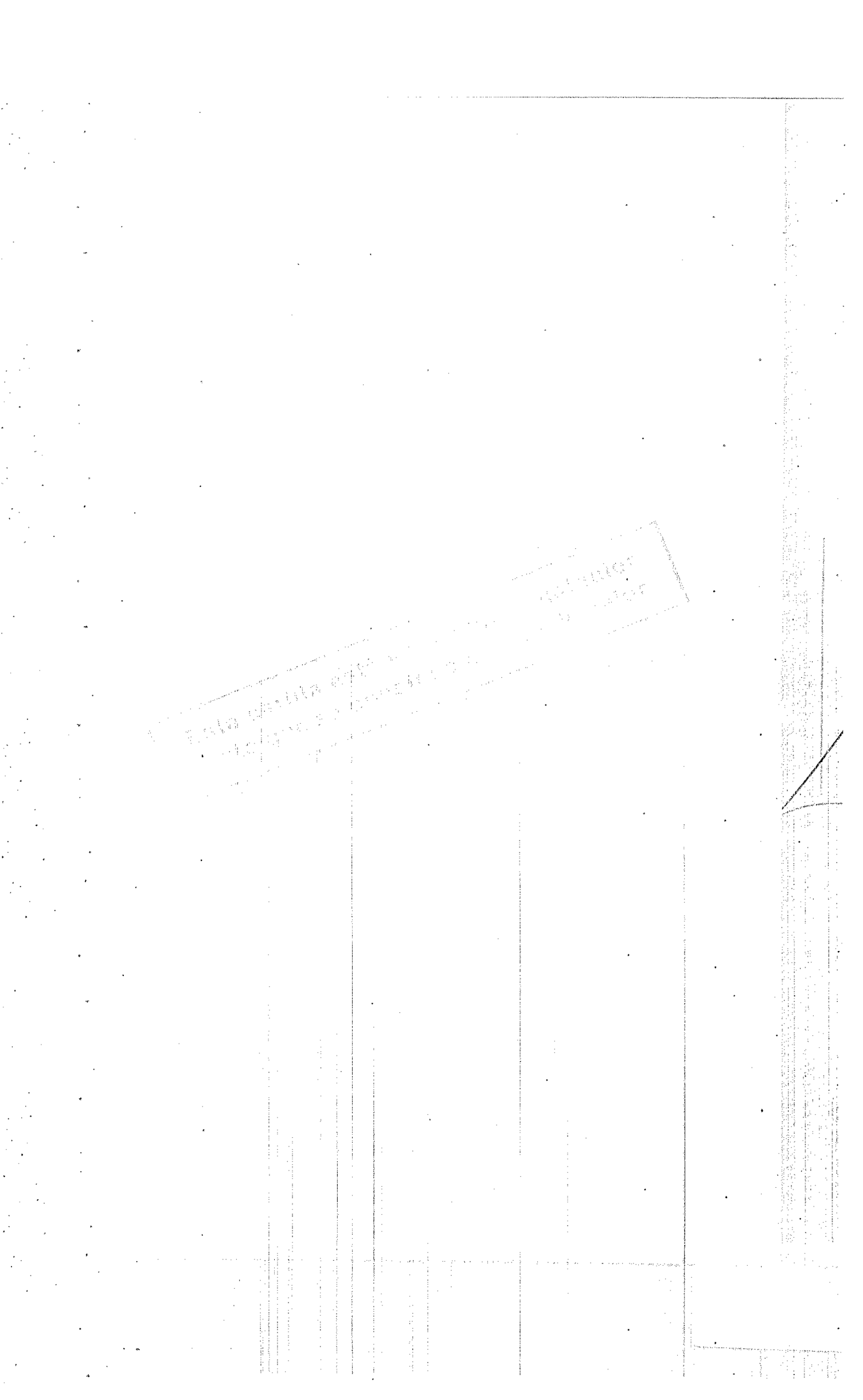
It is herewith certified that **Boehringer Ingelheim International GmbH** is a corporation duly organized and existing under the laws of the Federal Republic of Germany having its principal place of business at Binger Strasse 173, 55216 Ingelheim am Rhein, Germany.

It had been entered into the Commercial Register of the District Court of Bingen under HR B 1063 as of 14th day of May 1968. This registration was transferred by law to the Commercial Register of the District Court of Mainz, where it has been registered under HR B 21063 since 28th day of December 2005.

Furthermore, I certify that Dr. Michael Kompter and Dr. Christian Hauke were authorized to sign the foregoing document and still are duly authorized to sign on behalf as procurists of **Boehringer Ingelheim International GmbH**.

Ingelheim am Rhein, the 15th day of July 2010/Ge

Notary public



TESTIMONIO

AL DORSO: ==========

910 E 1

Die Echtheit vorstehender Unterschrift des
Notars Horst Heintskill in Ingelheim am Rhein
und die Echtheit des beigedrückten Dienstsiegels
werden hierdurch bestätigt. Zugleich wird bescheinigt, dass der
Vorgenannte zur Vornahme der Amtshandlung gesetzlich befugt war.

Präsidentin des Landgerichts 2 Mainz

Kostenrechnung:
Gebühr für die Erteilung
der Legalisation
Wert: 50.000,00 €
JVKostO v. 26.7.1957
i.V.m. § 45 KostO
Gebühr: 33,00 €
Mainz, 16.07.10
Heppes-Schwarz
Amtsinspektorin

Präsidentin des Landgerichts 2 Mainz

Mainz, den 16. Juli 2010
Die Präsidentin des Landgerichts
In Vertretung
Dr. Matthias Friedrich
Vorsitzender Richter am Landgericht

CONSULADO GENERAL DEL PERU
FRANCFORT DEL MENO

Se legaliza la firma de:
DR. MATTHIAS FRIEDRICH

Quien desempeña el cargo de:
REPRASENTANTE DEL PRESIDENTE
DEL JUZGADO REGIONAL
EN MAINZ

Nº de Orden: 0363
Nº de Actuación: 1171
Nº de Tarifa: 22 a
Derechos percibidos: S/C: 80.00
e: 72.00

Francfort del Meno, 20 de Julio de 2010

ALFREDO ARECCO-SABLICH
Cónsul General del Perú

CONSULADO GENERAL DEL PERU FRANCFORT DEL MENO

MINISTERIO DE RELACIONES EXTERIORES
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Se legaliza la firma que antecede del Sr.(a)
Alfredo Arecco - Sablich
SIN JUZGAR EL CONTENIDO DEL DOCUMENTO

Maribel del Rosario Llaya Jaylar
Departamento de Legalizaciones
Dirección de Trámites Consulares
LIMA, 23 JUL 2010

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DE NOT
y sellos
al (la)
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ma del N

Mario Gino Benvenuto Murguía
ABOGADO NOTARIO DE LIMA

TESTIMONIO

INSERTO. ==========

DE CONFORMIDAD CON LA LEY DEL NOTARIADO, ARTICULO 59, INCISO D), TRANSCRIBO: ==========

CÓDIGO PROCESAL CIVIL: "ARTÍCULO 74º.- FACULTADES GENERALES.- LA REPRESENTACIÓN JUDICIAL CONFIERE AL REPRESENTANTE LAS ATRIBUCIONES Y POTESTADES GENERALES QUE CORRESPONDEN AL REPRESENTADO, SALVO AQUELLAS PARA LAS QUE LA LEY EXIGE FACULTADES EXPRESAS. LA REPRESENTACIÓN SE ENTIENDE OTORGADA PARA TODO EL PROCESO, INCLUSO PARA LA EJECUCIÓN DE LA SENTENCIA Y EL COBRO DE COSTAS Y COSTOS, LEGITIMANDO AL REPRESENTANTE PARA SU INTERVENCIÓN EN EL PROCESO Y REALIZACIÓN DE TODOS LOS ACTOS DEL MISMO, SALVO AQUELLOS QUE REQUIERAN LA INTERVENCIÓN PERSONAL Y DIRECTA DEL REPRESENTADO." ==========

CÓDIGO PROCESAL CIVIL: "ARTÍCULO 75º.- FACULTADES ESPECIALES.- SE REQUIERE EL OTORGAMIENTO DE FACULTADES ESPECIALES PARA REALIZAR TODOS LOS ACTOS DE DISPOSICIÓN DE DERECHOS SUSTANTIVOS Y PARA DEMANDAR, RECONVENIR, CONTESTAR DEMANDAS Y RECONVENCIONES, DESISTIRSE DEL PROCESO Y DE LA PRETENSIÓN, ALLANARSE A LA PRETENSIÓN, CONCILIAR, TRANSIGIR, SOMETER A ARBITRAJE LAS PRETENSIONES CONTROVERTIDAS EN EL PROCESO, SUSTITUIR O DELEGAR LA REPRESENTACIÓN PROCESAL Y PARA LOS DEMÁS ACTOS QUE EXPRESE LA LEY. EL OTORGAMIENTO DE FACULTADES ESPECIALES SE RIGE POR EL PRINCIPIO DE LITERALIDAD. NO SE PRESUME LA EXISTENCIA DE FACULTADES ESPECIALES NO CONFERIDAS EXPLÍCITAMENTE." ==========

CONCLUSION: ==========

FORMALIZADO EL INSTRUMENTO LA COMPARECIENTE LE DIO LECTURA, DESPUES DE LO CUAL SE AFIRMA Y RATIFICA EN SU CONTENIDO, DECLARANDO QUE SE TRATA DE UN ACTO VALIDO Y NO SIMULADO, MANIFESTANDO IGUALMENTE CONOCER LOS ANTECEDENTES Y/O TITULOS QUE SE ORIGINAN POR EL PRESENTE INSTRUMENTO Y DECLARANDO RECONOCER COMO SUYA LA FIRMA DE LA MINUTA QUE LA ORIGINA. ==========

DEJO CONSTANCIA DE HABER ADVERTIDO A LA INTERESADA DE LOS EFECTOS LEGALES DEL PRESENTE INSTRUMENTO NOTARIAL. ==========

LA PRESENTE ESCRITURA PUBLICA SE INICIA EN LA FOJA DE PAPEL NOTARIAL CON NUMERO DE SERIE B Nº0706090 Y CONCLUYE EN LA FOJA DE PAPEL NOTARIAL CON NUMERO DE SERIE B Nº0706093(VUELTA), DE LO QUE DOY FE. ==========

FIRMADO: JANNE IVETTE LUQUE CARDENAS.- UNA HUELLA DIGITAL.- UNA FIRMA ILEGIBLE.- FIRMÓ EL VEINTISEIS DE JULIO DEL AÑO DOS MIL DIEZ.- ==========

EL PROCESO DE FIRMAS CONCLUYO EL: VEINTISEIS DE JULIO DEL DOS MIL DIEZ.- ==========

FIRMADO: DR. MARIO GINO BENVENUTO MURGUIA. ABOGADO - NOTARIO DE LIMA. ==========

ES TRANSCRIPCION DE LA ESCRITURA PUBLICA QUE CORRE EN EL REGISTRO CON FECHA VEINTISEIS DIAS DEL MES DE JULIO DEL AÑO DOS MIL DIEZ DE FOJAS 004590 A FOJAS 004593(VUELTA), Y A SOLICITUD DE PARTE INTERESADA EXPIDO EL PRESENTE, DE ACUERDO A LEY EL QUE RUBRICO EN CADA UNA DE SUS HOJAS, SELLO, SIGNO Y FIRMO EN LIMA, VEINTISEIS DE JULIO DEL AÑO DOS MIL DIEZ. ==========

MARIO GINO BENVENUTO MURGUIA
ABOGADO
NOTARIO DE LIMA

O DE NOTARIOS DE LIMA CERTIFICA:
a y sellos que anteceden en esta foja
en al (la) Notario(a) de Lima,
Benvenuto Murguia
Nº 116766 Fecha: 26 JUL 2010
irma del Notario(a) más no el contenido

Juan Gutiérrez Adriazola
FISCAL

Av. Juan de Arona N° 545 Altura Cdra. 31 de la Av. Arequipa – San Isidro
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Julia Adela Morenaú de Dueñas
Departamento de Legalizaciones
Dirección de Trámites Consulares

LIMA 27 JUL. 2010

CONSULADO GENERAL DE COLOMBIA
Lima – Perú

No. 1793

Lima, 02 Agosto 2010

El suscrito Cónsul General Consulares hace constar que el(a) señor (a) JULIA ADELA MOREANO DE DUEÑAS - DIRECION DE TRAMITES CONSULARES. Cuya firma aparece al pie del presente documento desempeñaba las funciones allí indicadas.

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JAIRO MONTES MORENO
Cónsul General

Dirección: Jorge Basadre 1580 TEL. (511) 4410530- 4410954 Fax: 2213661-4416922-4218029
Sitio Web: http://www.embajadacolombia.org.pe/html/ - consuladogeneral@embajadacolombia.org.pe

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JAIRO MONTES
CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

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JEFE DE LEGALIZACIONES
BOGOTA D.C.

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(74) Agents: **HAMMANN, Heinz** et al.; Binger Str. 173, 55216 Ingelheim Am Rhein (DE).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

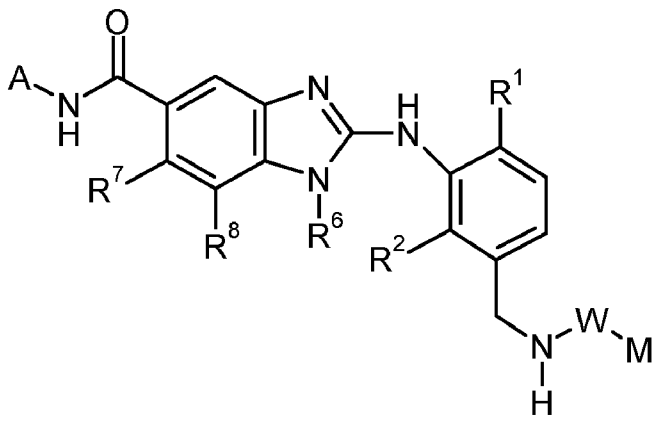
Declarations under Rule 4.17:

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

Published:

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

(54) **Title**: NEW COMPOUNDS



(I)

(57) **Abstract**: This invention relates to compounds of formula (I) their use as inhibitors of the microsomal prostaglandin E_2 synthase-1 (mPGES-1), pharmaceutical compositions containing them, and their use as medicaments for the treatment and/or prevention of inflammatory diseases and associated conditions. A, M, W, R^1, R^2, R^6, R^7, R^8 have meanings given in the description.

WO 2012/022793 A1

NEW COMPOUNDS

Field of the Invention

This invention relates to novel compounds, which are inhibitors of the microsomal prostaglandin E_2 synthase-1 (mPGES-1), pharmaceutical compositions containing them, and their use as medicaments for the treatment and/or prevention of inflammatory diseases and associated conditions such as inflammatory/nociceptive pain.

Background of the Invention

There are many acute and chronic diseases/disorders that are inflammatory in their nature including but not limited to rheumatoid diseases e.g. rheumatoid arthritis, osteoarthritis, diseases of the visceral system e.g. inflammatory bowel syndrome, autoimmune diseases, e.g. lupus erythematodes, lung diseases like asthma and COPD. Current treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase (COX)-2 inhibitors are efficacious, but show a prevalence for gastrointestinal and cardiovascular side effects. There is a high need for new treatment options showing equivalent efficacy with an improved side effect profile.

mPGES inhibitors may show such an improved side effect profile because they block the generation of PGE_2 in a more specific manner as described below.

NSAIDs and COX-2 inhibitors reduce inflammation and pain through inhibition of one or both isoformes of COX enzymes. The cyclooxygenase (COX) enzyme exists in two forms, one that is constitutively expressed in many cells and tissues (COX-1), and one that in most cells and tissues is induced by pro-inflammatory stimuli, such as cytokines, during an inflammatory response (COX-2). COXs metabolise arachidonic acid to the unstable intermediate prostaglandin H_2 (PGH_2). PGH_2 is further metabolized to other prostaglandins including PGE_2, $PGF_{2\alpha}$, PGD_2, prostacyclin and thromboxane A_2. These arachidonic acid metabolites are known to have pronounced physiological and pathophysiological activity including pro-inflammatory effects. PGE_2 in particular is known to be a strong pro-inflammatory mediator, and is also known to induce fever, inflammation and pain. Consequently, numerous drugs were developed with a view to inhibiting the formation of PGE_2, including “NSAIDs” (non-steroidal antiinflammatory drugs) and “coxibs” (selective COX-2 inhibitors). These drugs act predominantly by inhibition of COX-1 and/or COX-2, thereby reducing the formation of PGE_2.

However, the inhibition of COXs has the disadvantage that it results in the reduction of the formation of all metabolites downstream of PGH_2, some of which are known to have beneficial properties. In view of this, drugs which act by inhibition of COXs are therefore known/suspected to cause adverse biological effects.

For example, the non-selective inhibition of COXs by NSAIDs may give rise to gastrointestinal side-effects and affect platelet and renal function. Even the selective inhibition of COX-2 by coxibs, whilst reducing such gastrointestinal side-effects, is believed to give rise to cardiovascular problems.

An alternative treatment of inflammatory diseases that does not give rise to the above-mentioned side effects would thus be of real benefit in the clinic. In particular, a drug that preferably inhibits the transformation of PGH_2 to the pro-inflammatory mediator PGE_2 selectively might be expected to reduce the inflammatory response in the absence of a corresponding reduction of the formation of other, beneficial arachidonic acid metabolites. Such inhibition would accordingly be expected to alleviate the undesirable side-effects mentioned above.

PGH_2 may be transformed to PGE_2 by prostaglandin E synthases (PGES). Two microsomal prostaglandin E synthases (mPGES-1 and mPGES-2), and one cytosolic prostaglandin E synthase (cPGES) have been described. mPGES-1 is proposed to be closely linked to COX-2 and both enzyme's are upregulated during e.g. inflammation. Thus agents that are capable of inhibiting the action of mPGES-1 and thereby reducing the formation of PGE_2 are likely to be of benefit for the treatment of inflammation and more general acute and chronic pain conditions

Benzimidazole and imidazopyridine derivatives with mPGES-1 inhibitory activity are disclosed in WO 2010/034796, WO 2010/034797, WO 2010/034798, WO 2010/034799. PCT/EP2010/052799 describes a broad class of different 2-arylamino benzimidazoles in which the aryl group bears a particular side chain.

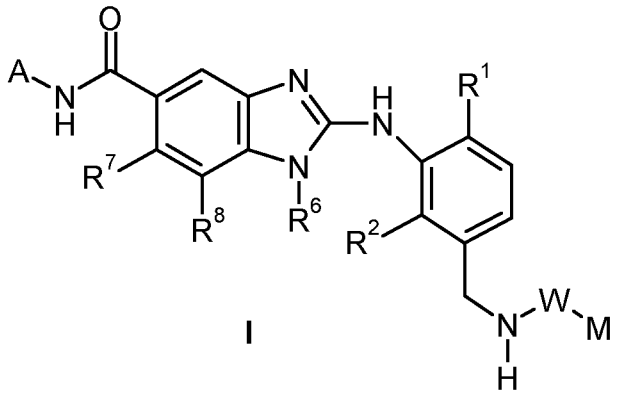
DETAILED DESCRIPTION OF THE INVENTION

The present invention is a selection from the general formula of PCT/EP2010/052799 providing compounds that unexpectedly show improved activity in a cell based pharmacological assay.

Compounds with a similar affinity for the mPGES-1 enzyme as measured in the enzyme assay may have different potencies in the cell-based assay.

Data from a cell based pharmacological assay when compared with data from an enzyme assay are considered to allow for a better predictibility and estimation of therapeutic effective concentrations/doses. Compounds of the present invention show high potency in both assays. Consequently, they are likely to be more suitable for the in-vivo use.

The present invention provides a compound of formula **I,**



I

in which

R^1 and **R^2** independently represent halo, -C_{1-3}alkyl, which latter alkyl group is optionally substituted by one or more fluorine atoms;

W represents -C(O)-, -C(O)O-, which groups are bound to the nitrogen of the –NH- moiety via the carbon atom;

M represents

-C_{1-6}alkyl, -C_{3-7}cycloalkyl, both of which groups are optionally substituted by one or more groups selected from -F, -OH, -CN, -NH_2, -NH(C_{1-2}alkyl), -N (C_{1-2}alkyl)$_2$, -OC_{1-3}alkyl, -C_{1-5}alkyl, -C_{3-4}cycloalkyl, in which latter three groups the alkyl or cycloalkyl groups are optionally substituted by one or more fluorine atoms;

or

oxetanyl-, tetrahydrofuranyl-, tetrahydropyranyl-, azetidinyl-, pyrrolidinyl-, piperidinyl-, all of which groups are optionally substituted by one or more substituents selected from fluoro, -CN, -C_{1-3} alkyl, which latter alkyl group is optionally substituted by one or more fluorine atoms;

or

phenyl-, pyridyl-, thienyl-, pyrrolyl-, pyrazolyl-, imidazolyl-, thiazolyl-, oxazolyl-, or isoxazolyl-, all of which groups are optionally substituted by one or more substituents selected from halo, -CN or -C_{1-3}alkyl, which latter alkyl group is optionally further substituted by one or more fluorine atoms;

R^8 represents –H, halogen, -C_{1-3}alkyl, which latter alkyl group is optionally substituted by one or more fluorine atoms;

R^6 represents –H, -C_{1-5}alkyl, -C_{3-5}cycloalkyl-C_{0-2}alkyl, in which latter three groups the alkyl or cycloalkyl fragments are optionally substituted by one or more fluorine atoms;

R^7 represents halo, C_{1-5}alkyl-O-, C_{3-7}cycloalkyl-C_{0-2}alkyl-O-, 4-7-membered heterocycloalkyl-C_{0-2}alkyl-O-, in which latter three groups the alkyl, cycloalkyl or heterocycloalkyl fragments are optionally substituted by one or more substituents selected from -F and -OC_{1-3}alkyl which latter alkyl group is optionally further substituted by one or more fluorine atoms;

A represents C_{1-8} alkyl-, phenyl-, indanyl-, naphthyl-, 1,2,3,4-tetrahydronaphthyl-, pyridyl-, thienyl-, benzothienyl-, pyrrolyl-, indolyl-pyrazolyl-, indazolyl-, thiazolyl-, benzothiazolyl-, oxazolyl-, benzoxazolyl-, isoxazolyl-, benzisoxazolyl-, phenyl-C_{1-3}alkyl-, thienyl-C_{1-3}alkyl-, pyridyl-C_{1-3}alkyl-, C_{3-7}cycloalkyl-C_{0-3}alkyl-, oxetanyl-C_{0-3}alkyl-, tetrahydrofuranyl-C_{0-3}alkyl, tetrahydropyranyl-C_{0-3}alkyl, in which groups the alkyl-, cycloalkyl- and heterocycloalkyl fragments are optionally substituted by one or more substituents selected from **R^{9a}** and the aryl and heteroaryl fragments are optionally substituted by one or more substituents selected from **R^{9b}**;

each **R^{9a}** independently represents -F, -Cl, -C_{1-3}alkyl which is optionally substituted by one or more substituents selected from -F, -OC_{1-3} alkyl;

each **R^{9b}** represents independently -halo, -CN; -C_{1-3} alkyl which is optionally substituted by one or more fluorine atoms;

or a salt thereof, particularly a physiologically acceptable salt thereof.

In second embodiment, in the general formula **I, A, M, W, R^1, R^2, R^6, R^7** have the same meaning as defined in any of the preceding embodiments, and

R^8 represents –H or fluoro.

In another embodiment, in the general formula **I, A, M, W, R^1, R^2, R^7, R^8** have the same meaning as defined in any of the preceding embodiments, and

R^6 represents -H, $-CH_3$, cyclopropyl.

In another embodiment, in the general formula **I, A, M, W, R^6, R^7, R^8** have the same meaning as defined in any of the preceding embodiments, and

R^1 and R^2 independently represent chloro, fluoro, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$.

In another embodiment, in the general formula **I, A, M, W, R^1, R^2, R^6, R^8** have the same meaning as defined in any of the preceding embodiments, and

R^7 represents fluoro, $-OCHF_2$, $-OCF_3$, $-OCH_2CH_2F$, $-OCH_2CHF_2$, $-OCH_2CF_3$, -O-tetrahydrofuran-3-yl, $-O-CH_2$-cyclopropyl.

In another embodiment, in the general formula **I, M, W, R^1, R^2, R^6, R^7, R^8** have the same meaning as defined in any of the preceding embodiments, and

A represents C_{1-4} alkyl-, C_{3-7}cycloalkyl-C_{0-2}alkyl-, tetrahydrofuranyl-methyl-, phenyl-C_{1-2} alkyl-, pyridyl-methyl-, phenyl-, indanyl-, pyridyl-, thienyl-, thiazolyl-, benzothiazolyl-, in which groups the alkyl-, cycloalkyl- and heterocycloalkyl-fragments are optionally substituted by one or more substituents selected from -F, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, and the aryl and heteroaryl fragments are optionally substituted by -F, -Cl, -Br, -CN, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$.

In another embodiment, in the general formula **I, A, W, R^1, R^2, R^6, R^7, R^8** have the same meaning as defined in any of the preceding embodiments, and

M represents

$-C_{1-4}$ alkyl, $-C_{3-5}$ cycloalkyl, both of which groups are optionally substituted by one or more groups selected from -F, -OH, -CN, $-NH_2$, $-OCH_3$, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, cyclopropyl;

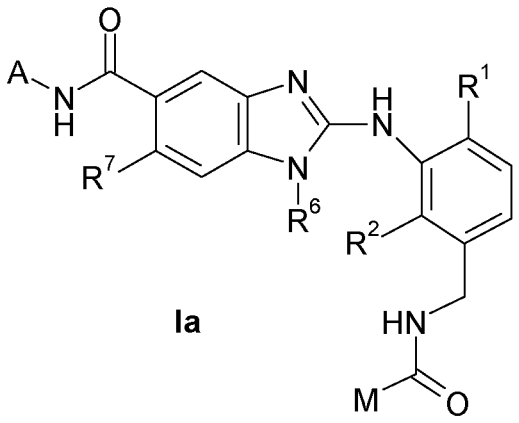
or

oxetanyl-, tetrahydrofuranyl-, azetidinyl- or pyrrolidinyl-, all of which groups are optionally substituted by one or more substituents selected from -F, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$;

or

phenyl-, indanyl-, thienyl-, pyrrolyl-, pyrazolyl-, imidazolyl-, thiazolyl-, or isoxazolyl-, all of which groups are optionally substituted by one or more substituents selected from –F, -Cl, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$.

Another embodiment of the present invention comprises compounds of formula **Ia**

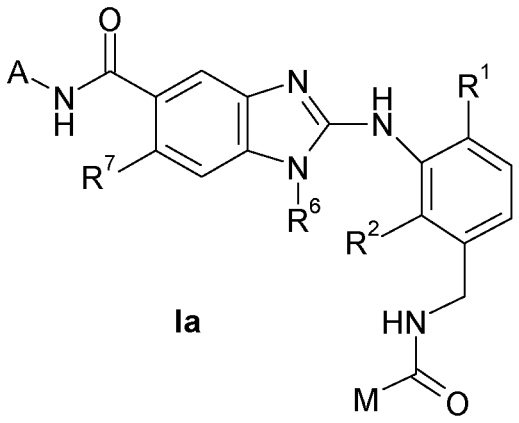


Ia

in which

A, M, R^1, R^2, R^6, R^7 have the same meaning as defined in any of the preceding embodiments.

A further embodiment of the present invention comprises compounds of formula **Ia**



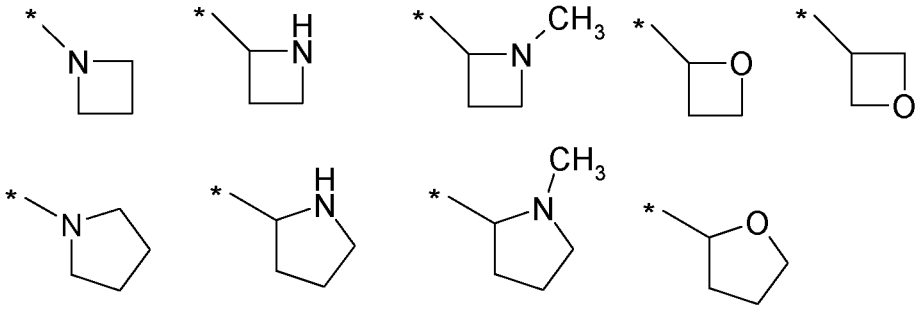
Ia

in which

M represents

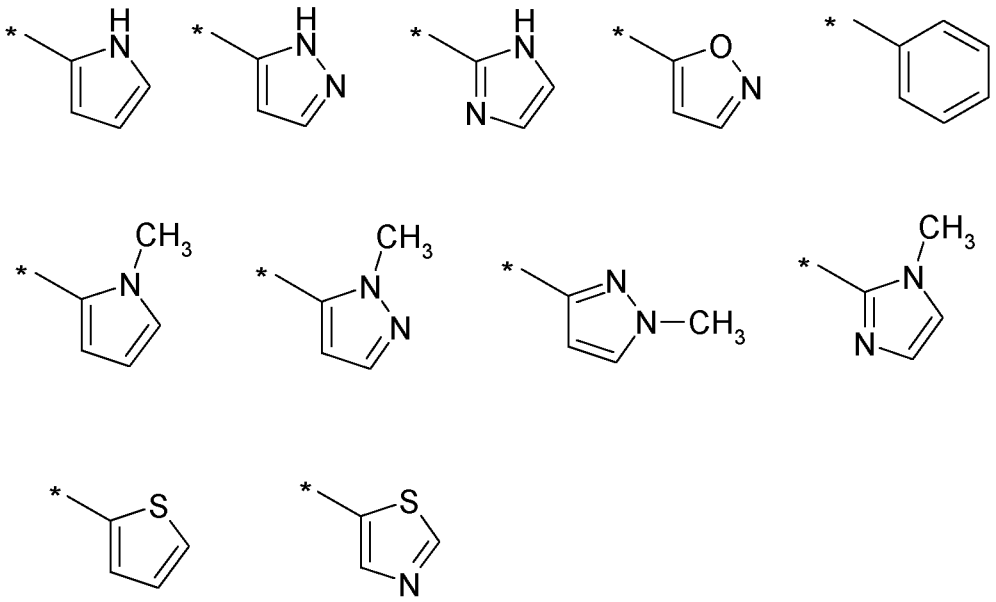
methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *s*-butyl, *t*-butyl, -CH_2-cyclopropyl, cyclopropyl, cyclobutyl, cyclopentyl, all of which groups are optionally substituted by one or more groups selected from -F, -OH, -CN, -NH_2, -OCH_3, -CH_3, -CF_3;

or is selected from the following groups



which latter nine groups are optionally substituted by one or more substituents selected from -F, -CH_3, -CF_3;

or is selected from the following groups



which latter eleven groups are optionally substituted by one or more substituents selected from -F, -Cl, -CH_3, -CF_3;

and

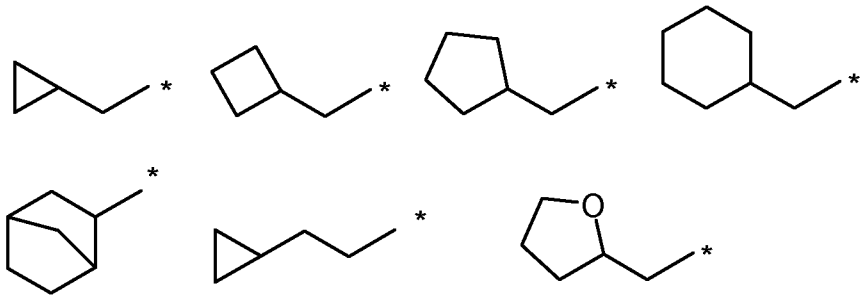
A, R^1, R^2, R^6, R^7 have the same meaning as defined in any of the preceding embodiments.

A further embodiment of the present invention comprises compounds of formula **Ia** in which

A represents methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *s*-butyl, *t*-butyl, which latter seven groups are optionally substituted by one or more fluorine atoms,

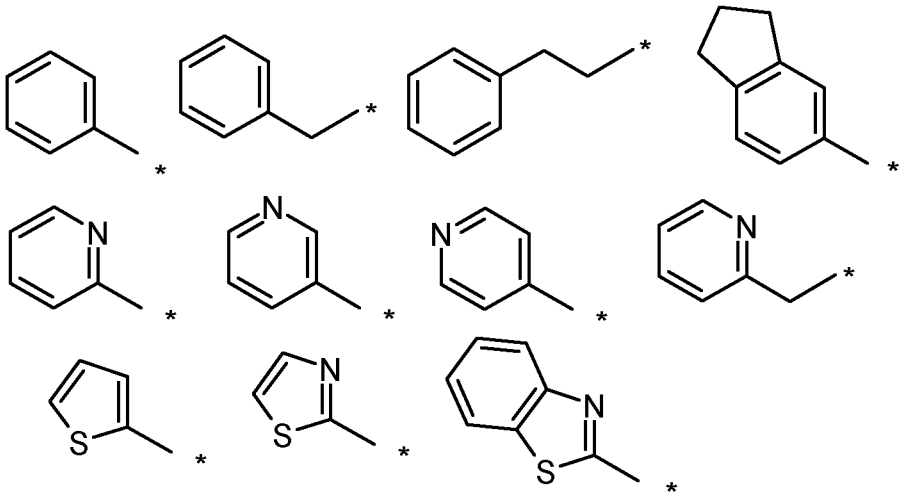
or cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, which latter four groups are optionally substituted by one or more substituents selected from -F, -CH_3, -CHF_2, -CF_3;

or is selected from the following groups:



which latter seven groups are optionally substituted by one or more substituents selected from -F, -CH_3, -CHF_2, -CF_3;

or is selected from the following groups:

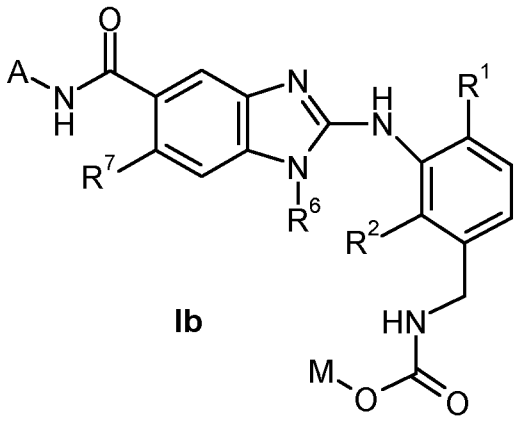


in which latter eleven groups the aryl and heteroaryl fragments are optionally substituted by one or more substituents selected from -F, -Cl, -Br, -CN, -CH_3, -CF_3;

and

M, $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^6}$, $\mathbf{R^7}$ have the same meaning as defined in any of the preceding embodiments.

A further embodiment of the present invention comprises compounds of formula **Ib**



Ib

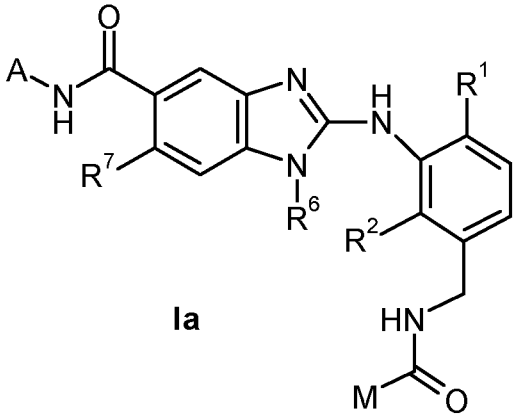
in which

M is tert-butyl;

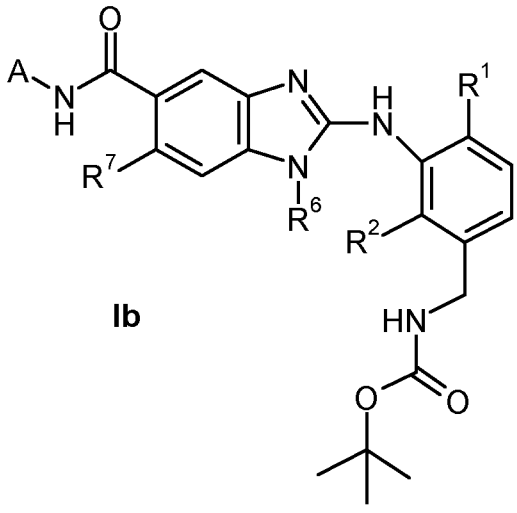
and

A, R^1, R^2, R^6, R^7 have the same meaning as defined in any of the preceding embodiments.

A further embodiment of the present invention comprises compounds of formula **Ia or Ib**



Ia



Ib

in which

R^1 and R^2 independently represent chloro, fluoro, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$;

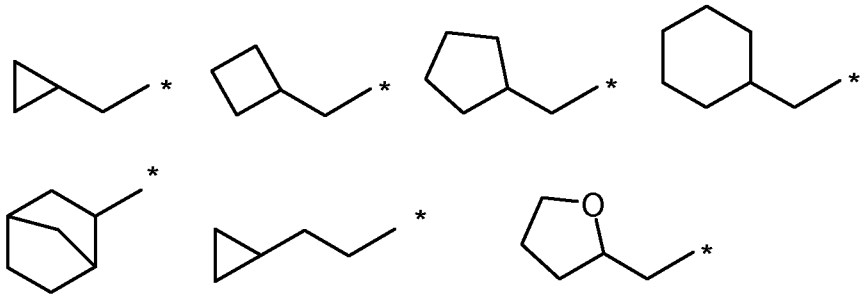
R^6 represents -H, $-CH_3$, cyclopropyl;

R^7 represents fluoro, $-OCHF_2$, $-OCF_3$, $-OCH_2CH_2F$, $-OCH_2CHF_2$, $-OCH_2CF_3$, tetrahydrofuran-3-yl-O-, -O-CH_2-cyclopropyl;

A represents methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *s*-butyl, *t*-butyl, which latter seven groups are optionally substituted by one or more fluorine atoms,

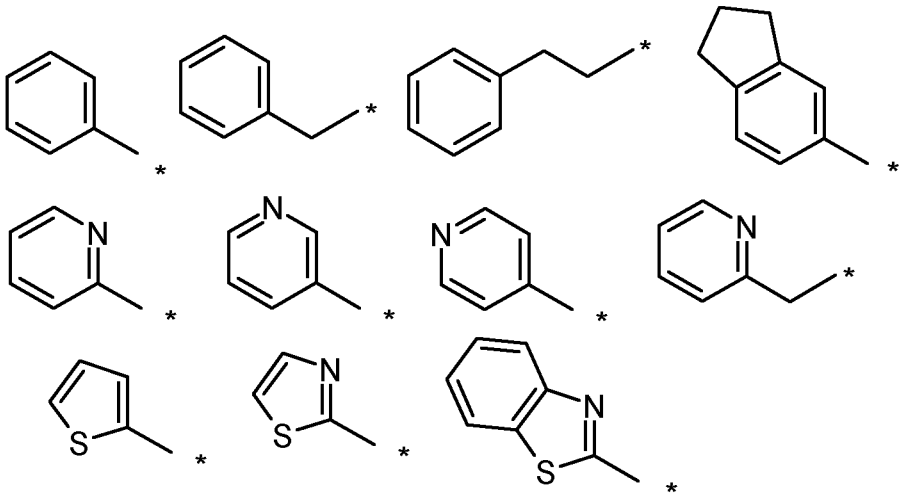
or cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, which latter four groups are optionally substituted by one or more substituents selected from -F, -CH_3, -CHF_2, -CF_3;

or is selected from the following groups:



which latter seven groups are optionally substituted by one or more substituents selected from -F, -CH_3, -CHF_2, -CF_3;

or is selected from the following groups:

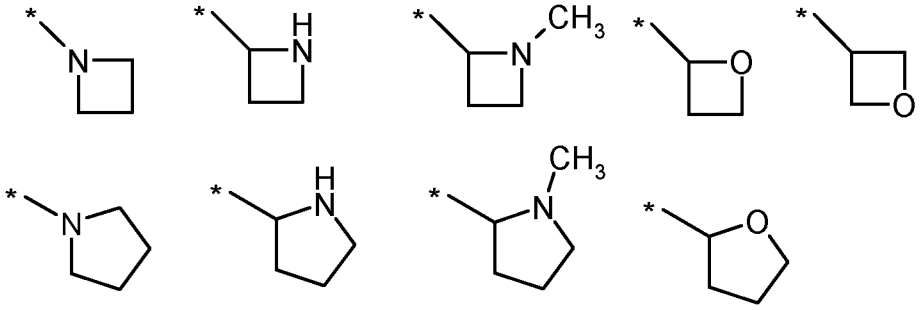


in which latter eleven groups the aryl and heteroaryl fragments are optionally substituted by one or more substituents selected from -F, -Cl, -Br, -CN, -CH_3, -CF_3;

M represents

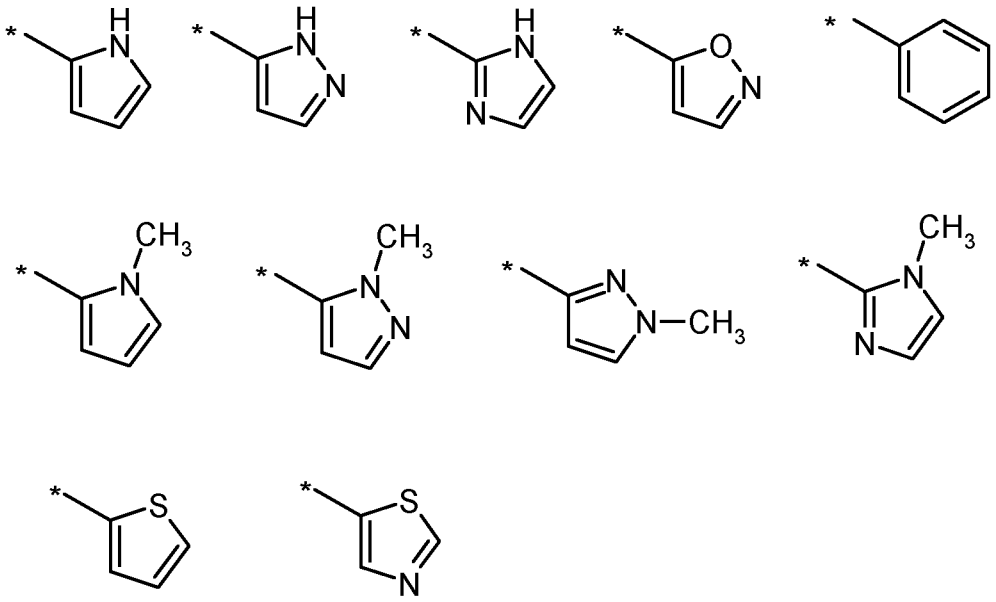
methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *s*-butyl, *t*-butyl, cyclopropyl, -CH_2-cyclopropyl, cyclobutyl, cyclopentyl, all of which groups are optionally substituted by one or more groups selected from -F, -OH, -CN, -NH_2, -OCH_3, -CH_3, -CF_3;

or is selected from the following groups



which latter nine groups are optionally substituted by one or more substituents selected from -F, -CH_3, -CF_3;

or is selected from the following groups



which latter eleven groups are optionally substituted by one or more substituents selected from -F, -Cl, -CH_3, -CF_3;

or salts thereof, particularly physiologically acceptable salts thereof.

TERMS AND DEFINITIONS USED

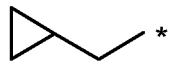
General definitions:

Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. As used in the specification, however, unless specified to the contrary, the following terms have the meaning indicated and the following conventions are adhered to.

In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, C_{1-6}-alkyl means an alkyl group or radical having 1 to 6 carbon atoms. In general, for groups comprising two or more subgroups, the last named subgroup is the radical attachment point, for example, the substituent "aryl-C_{1-3}-alkyl-" means an aryl group which is bound to a C_{1-3}-alkyl-group, the latter of which is bound to the core or to the group to which the substituent is attached.

In case a compound of the present invention is depicted in form of a chemical name and as a formula in case of any discrepancy the formula shall prevail.

An asterisk is may be used in sub-formulas to indicate the bond which is connected to the core molecule as defined, for example a cyclopropylmethyl- group would be represented by the following drawing:



Stereochemistry/solvates/hydrates:

Unless specifically indicated, throughout the specification and the appended claims, a given chemical formula or name shall encompass tautomers (e.g. *1H-benzimidazole* may be considered to be identical to a corresponding compound containing a *3H-benzimidazole*) and all stereo, optical and geometrical isomers (e.g. enantiomers, diastereomers, E/Z isomers etc...) and racemates thereof as well as mixtures in different proportions of the separate enantiomers, mixtures of diastereomers, or mixtures of any of the foregoing forms where such isomers and enantiomers exist, as well as salts, including pharmaceutically acceptable salts thereof and solvates thereof such as for instance hydrates including solvates of the free compounds or solvates of a salt of the compound.

Salts:

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, and commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. For example, such salts include salts from ammonia, L-arginine, betaine, benethamine, benzathine, calcium hydroxide, choline, deanol, diethanolamine (2,2'-iminobis(ethanol)), diethylamine, 2-(diethylamino)-ethanol, 2-aminoethanol, ethylenediamine, N-ethyl-glucamine, hydrabamine, 1H-imidazole, lysine, magnesium hydroxide, 4-(2-hydroxyethyl)-morpholine, piperazine, potassium hydroxide, 1-(2-hydroxyethyl)-pyrrolidine, sodium hydroxide, triethanolamine (2,2',2"-nitrilotris(ethanol)), trometh-amine, zinc hydroxide, acetic acid, 2.2-dichloro-acetic acid, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 2,5-dihydroxybenzoic acid, 4-acetamido-benzoic acid, (+)-camphoric acid, (+)-camphor-10-sulfonic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, decanoic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, ethylenediamonotetraacetic acid, formic acid, fumaric acid, galacaric acid, gentisic acid, D-glucoheptonic acid, D-gluconic acid, D-glucuronic acid, glutamic acid, glutantic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycine, glycolic acid, hexanoic acid, hippuric acid, hydrobromic acid, hydrochloric acid isobutyric acid, DL-lactic acid, lactobionic acid, lauric acid, lysine, maleic acid, (-)-L-malic acid, malonic acid, DL-mandelic acid, methanesulfonic acid, galactaric acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, octanoic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid (embonic acid), phosphoric acid, propionic acid, (-)-L-pyroglutamic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid and undecylenic acid. Further pharmaceutically acceptable salts can be formed with cations from metals like aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and the like. (also see Pharmaceutical salts, Berge, S.M. et al., J. Pharm. Sci., (1977), 66, 1-19).

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these

compounds with a sufficient amount of the appropriate base or acid in water or in an organic diluent like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile, or a mixture thereof.

Salts of other acids than those mentioned above which for example are useful for purifying or isolating the compounds of the present invention (e.g. trifluoro acetate salts) also comprise a part of the invention.

Halogen:

The term halogen generally denotes fluorine, chlorine, bromine and iodine.

Alkyl:

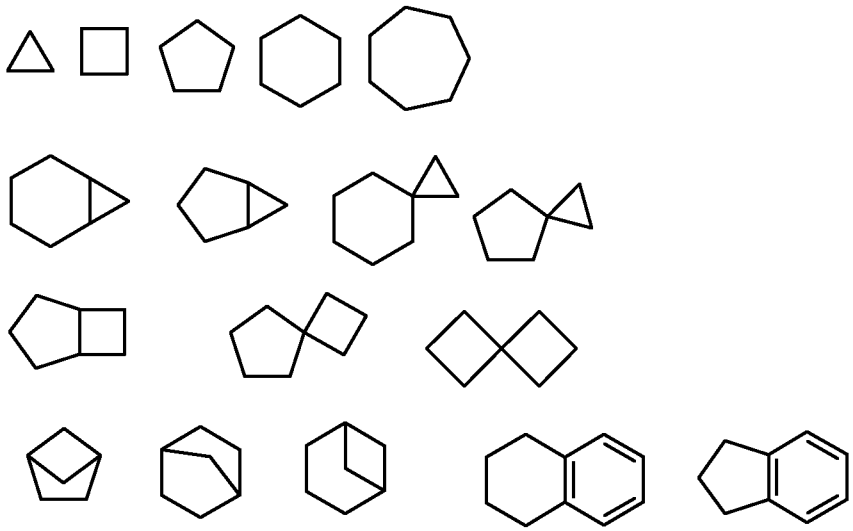
The term "C_{1-n}-alkyl", wherein n is an integer from 2 to n, either alone or in combination with another radical denotes an acyclic, saturated, branched or linear hydrocarbon radical with 1 to n C atoms. For example the term C_{1-5}-alkyl embraces the radicals H_3C-, H_3C-CH_2-, H_3C-CH_2-CH_2-, H_3C-$CH(CH_3)$-, H_3C-CH_2-CH_2-CH_2-, H_3C-CH_2-$CH(CH_3)$-, H_3C-$CH(CH_3)$-CH_2-, H_3C-$C(CH_3)_2$-, H_3C-CH_2-CH_2-CH_2-CH_2-, H_3C-CH_2-CH_2-$CH(CH_3)$-, H_3C-CH_2-$CH(CH_3)$-CH_2-, H_3C-$CH(CH_3)$-CH_2-CH_2-, H_3C-CH_2-$C(CH_3)_2$-, H_3C-$C(CH_3)_2$-CH_2-, H_3C-$CH(CH_3)$-$CH(CH_3)$- and H_3C-CH_2-$CH(CH_2CH_3)$-.

Cycloalkyl:

The term "C_{3-n}-cycloalkyl", wherein n is an integer > 3, either alone or in combination with another radical denotes a cyclic, saturated, hydrocarbon radical with 3 to n C atoms. For example the term C_{3-7}-cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "cycloalkyl" also includes bi-, tri- or tetra-cyclic ring structures consisting only of carbon and containing between one and four rings wherein such rings may be attached together in a pendent manner or may be fused. The term "cycloalkyl" additionally encompasses spiro systems, and bridged systems. The cyclic hydrocarbon radical may also be fused to an phenyl ring.

Thus, the term "cycloalkyl" includes the following exemplary structures which are not depicted as radicals as each form may be attached through a covalent bond to any atom of the cyclalkyl ring fragment as long as appropriate valencies are maintained:

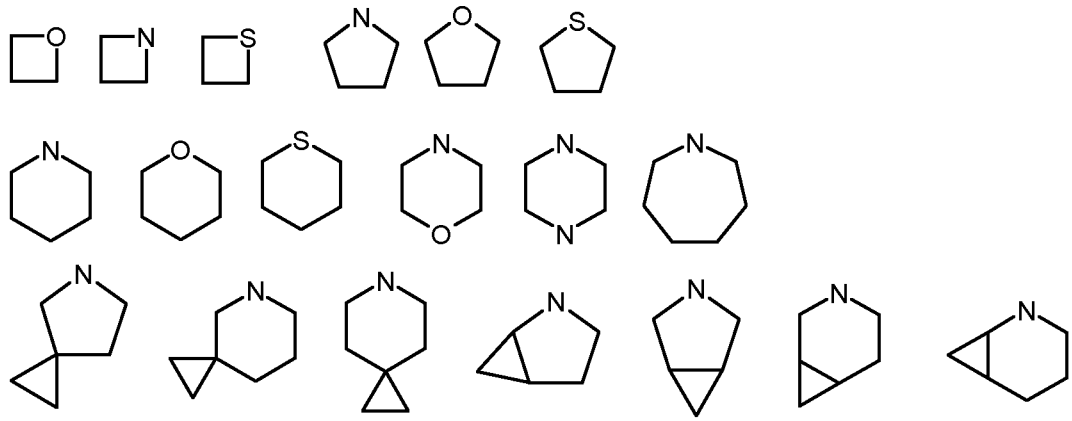


Heterocycloalkyl:

The term "C_{3-n}-heterocycloalkyl", wherein n is an integer > 3, either alone or in combination with another radical denotes a cyclic non-aromatic mono-, bi-, tri- or spirocyclic radical with 3 to n ring atoms wherein at least one ring atom is selected from N, O or S and wherein n is the upper limit of ring atoms. The cyclic hydrocarbon radical may also be fused to an phenyl ring. Substituents on heterocycloalkyl groups may, where appropriate, be located on any atom in the ring system including a heteroatom.

The point of attachment of heterocycloalkyl radicals may be *via* any atom in the non-aromatic ring system including (where appropriate) a heteroatom (such as a nitrogen atom) and also including an atom on any fused non-aromatic *carbo*cyclic ring fragment that may be present as part of the ring system.

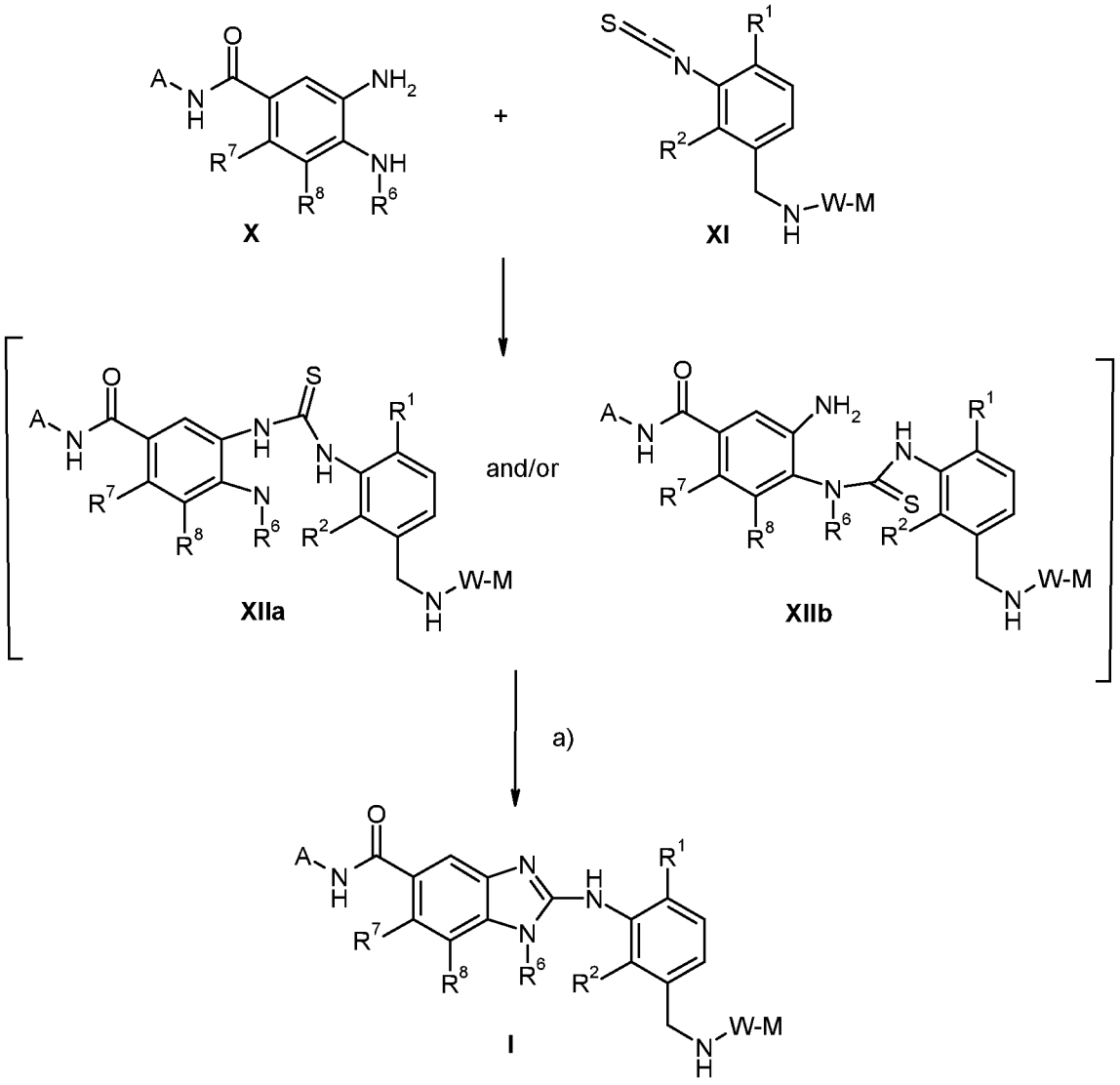
Thus, the term "heterocycloalkyl" includes the following exemplary structures which are not depicted as radicals as each form may be attached through a covalent bond to any atom as long as appropriate valencies are maintained:



METHODS OF PREPARATION

Compounds of the present invention can be prepared in accordance with techniques that are well known to those skilled in the art, for example as described hereinafter and in the experimental section or in analogy to methods described in WO2010/034796 and WO2010/034797. According to a further aspect of the invention there is provided a process for the preparation of a compound of formula **I**, which process can be performed for example according to the following schemes A-C.

Scheme A *(all variable groups are as defined in claim 1):*

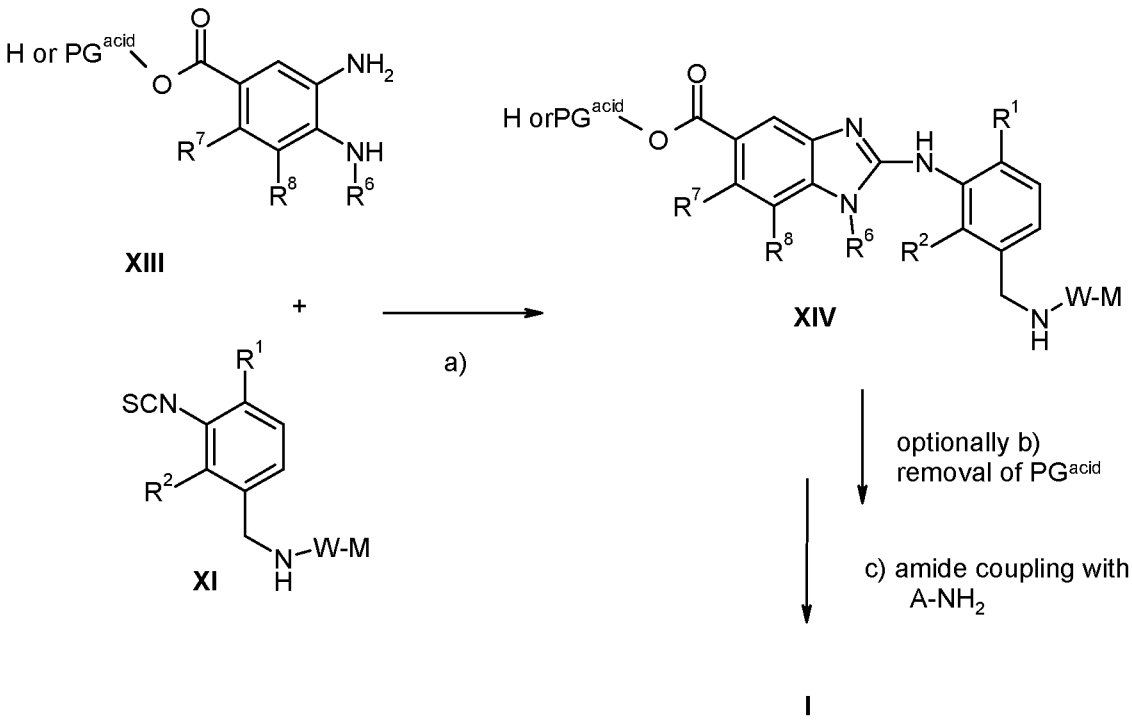


The reaction between phenylenediamine **X** and the thioisocyanate **XI** (Step a) can be performed under standard conditions known to those skilled in the art - for example in analogy to the process described in WO2010/034796 - in presence of a suitable solvent such

as diethyl ether (Et_2O), dimethylformamide (DMF), dichloromethane (DCM), acetonitrile (MeCN) and/or tetrahydrofuran (THF). The reaction is preferably performed in the presence of a suitable reagent which enhances the cyclisation step as for instance CH_3-I or a carbodiimide based compound such as N,N'-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI, or its salt, e.g. hydrochloride) or N,N'-diisopropylcarbodiimide (DIC). The reaction may proceed at any suitable temperature between 0°C to 200°C, preferably between room temperature and 100°C. **Step a** can be performed in a step-wise reaction under isolation of the thiourea intermediates **XIIa** and/or **XIIb** or in a one-pot procedure.

Alternatively the compounds of formula **I** can be synthesized according to scheme B.

Scheme B (all variable groups are as defined in claim 1 and PG^{acid} is a protecting group of a carboxylic acid function)*:*



The protecting group PG^{acid} is a literature known protecting group of a carboxylic acid, well known to those skilled in the art as for example described in "*Protective Groups in Organic Synthesis*", 3rd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999), for example a C_{1-5}-alkyl-, allyl- or a benzyl-group.

Step a) can be performed as described in **scheme A**, but may also be performed in the presence of an additive (such as 2,2,2-trifluoro-N,O-bis-(trimethylsilyl)-acetamide) when an unprotected carboxylic acid moiety is present in **XIII**.

Step b) can be performed under known saponification conditions, for example with aqueous LiOH, NaOH or KOH in ethanol (EtOH), methanol (MeOH), DMF, MeCN, THF or dioxane or with Pd/C in MeOH.

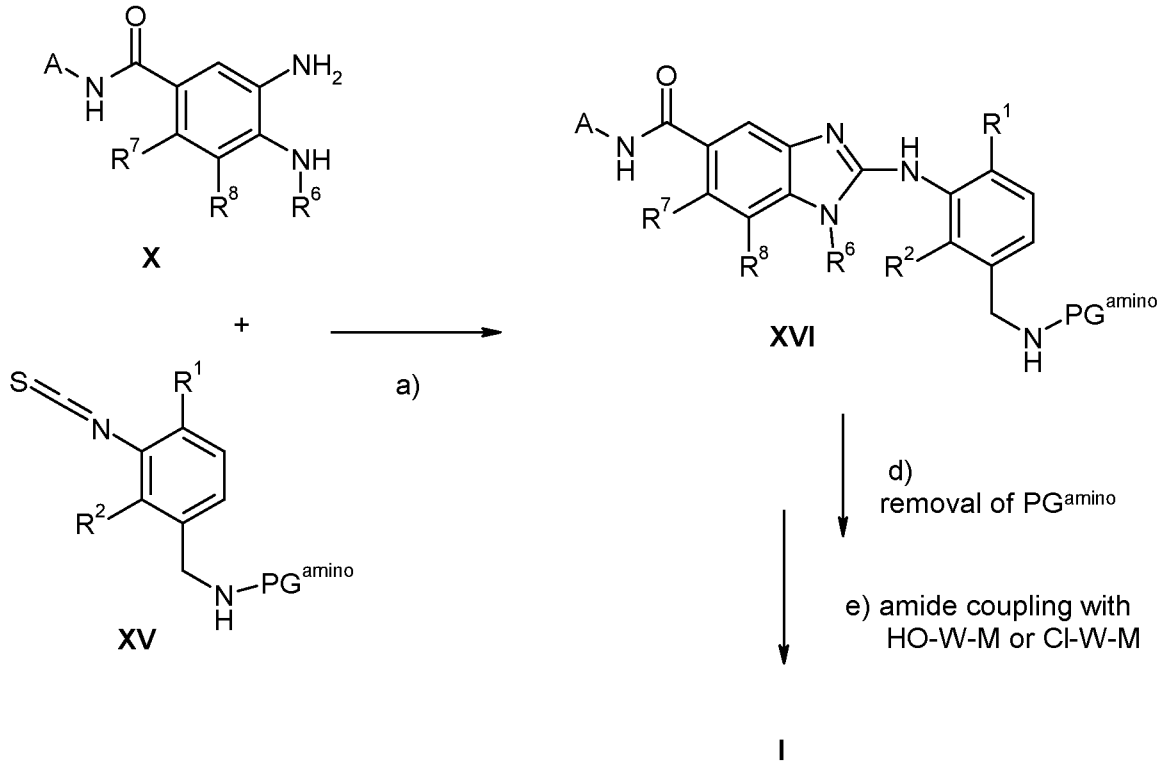
The amide formation in **step c**) can be performed with an additional *in-situ* activating agent like 1-propylphosphonic acid cyclic anhydride (PPA), *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyl-uronium tetrafluoroborate (TBTU), *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyl-uronium hexafluorophosphate (HBTU), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium-hexafluorophosphate (HATU), DCC , EDCI, carbonyldiimidazole (CDI), carbonylditriazole (CDT), 1-chloro-2-methyl-propenyl-dimethylamine, oxalyl chloride or other activating agents of the state of the art.

The coupling reaction is preferably performed in the presence of a base such as NaOH, KOH, $NaHCO_3$, triethylamine (TEA), N-ethyldiisopropylamine (DIPEA), pyridine, N,N,-dimethylaminopyridine (DMAP) or other appropriate bases of the state of the art and for example described in Houben-Weyl, "Methods in Organic Synthesis", Vol. E22a, p 425ff. The coupling reactions are performed in an appropriate solvent for example DCM, dioxane, THF, MeCN, DMF, dimethylacetamide (DMA), N-methylpyrrolidone (NMP) or in mixtures of the above mentioned solvents at any suitable temperature between 0°C to 100°C.

When PG^{acid} is a methyl or ethyl group the conversion of **XIV** to **I** can also be carried out in a one-pot procedure for example with trimethylaluminium or triethylaluminium in hexane, dioxane, THF at 20-80°C.

Alternatively the compounds of formula **I** can be synthesized according to scheme C.

Scheme C (all variable groups are as defined in claim 1 and PG^{amino} is a protecting group of the benzylic amino group)*:*



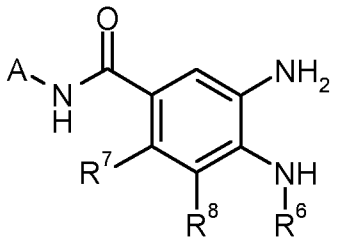
The protecting group PG^{amino} in **XV** is a literature known protecting group of an amino group well known to those skilled in the art as for example described in "*Protective Groups in Organic Synthesis*", 3rd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999), for example a tert-butoxycarbonyl-, benzyloxycarbonyl-, ethoxycarbonyl-, methoxycarbonyl-, allyloxycarbonyl- or trifluormethylcarbonyl group.

Step a) can be performed as described in Scheme 1..

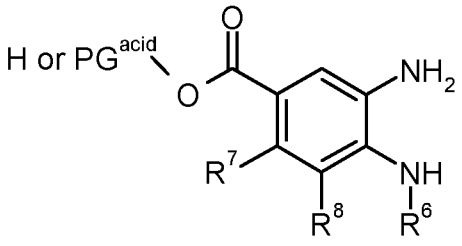
Step d) PG^{amino} in **XVI** can be removed in accordance with techniques that are well known to those skilled in the art and which are exemplified hereinafter. For example **XVI** can be deprotected using an appropriate agent (depending on the prtecting group) such as for example trifluoro acetic acid, HCl or H_2SO_4 solutions, KOH; $Ba(OH)_2$, Pd on carbon (Pd/C), trimethylsilyl iodide or other conditions as described in "*Protective Groups in Organic Synthesis*", 3rd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999). Appropriate co-solvent for this step is for example DCM, THF, MeCN, DMF, DMA, NMP or mixtures of the above mentioned solvents at any suitable temperature between 0°C to 100°C.

The amide formation in **step e**) can be performed with the acids **HO-W-M** and an additional *in-situ* activating agent like PPA, TBTU, HBTU, HATU, DCC, EDCI, CDI, CTI, 1-chloro-2-methyl-propenyl-dimethylamine, oxalyl chloride or other activating agents of the state of the art in analogy to Scheme B, step c; or directly with the corresponding acid chloride **Cl-W-M** under analogous conditions without an additional in situ activating agent.

The coupling reaction is preferably performed in the presence of a base such as NaOH, KOH, $NaHCO_3$, TEA, DIPEA, pyridine, DMAP or other appropriate bases of the state of the art and for example described in described in Houben-Weyl, "Methods in Organic Synthesis", Vol. E22a, p 425ff. The coupling reactions are performed in an appropriate solvent for example DCM, dioxane, THF, MeCN, DMF, DMA, NMP or in mixtures of the above mentioned solvents.

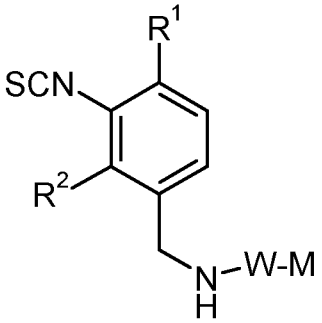


X

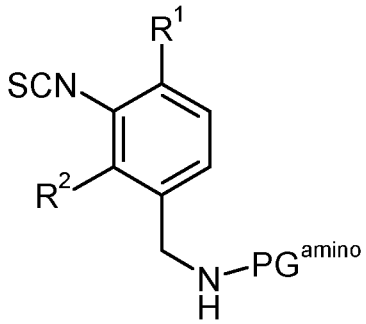


XIII

The synthesis of building blocks **X** and **XIII** wherein **A**, **R^6-R^8** have the meaning as defined in claim 1 and PG^{acid} is a literature known carboxylic acid protecting group as described above, can be performed in analogy to literature procedures which are well known to those skilled in the art, as for example in analogy to methods described in WO2010/034796 and WO2010/034797.



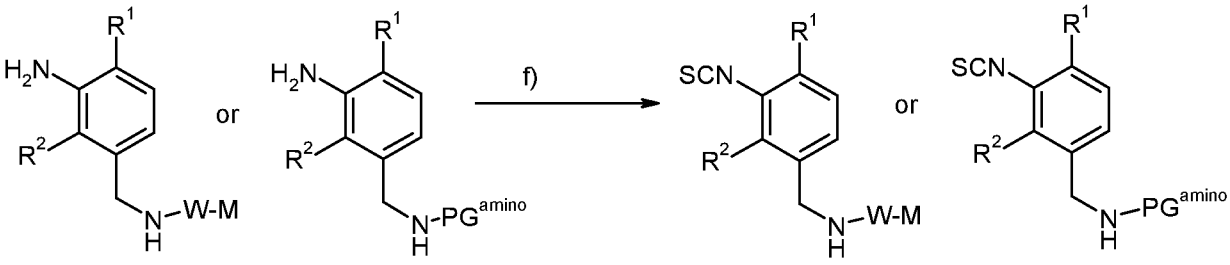
XI



XV

The synthesis of the building blocks **XI** and **XV** - wherein all variable groups are as defined in claim 1 and PG^{amino} is a protecting group of the benzylic amino group - is employing standard reaction conditions according to scheme D known to those skilled in the art which are examplified in the experimental part in detail.

Scheme D (all variable groups are as defined in claim 1 and PG^{amino} is a protecting group of the benzylic amino group)*:*

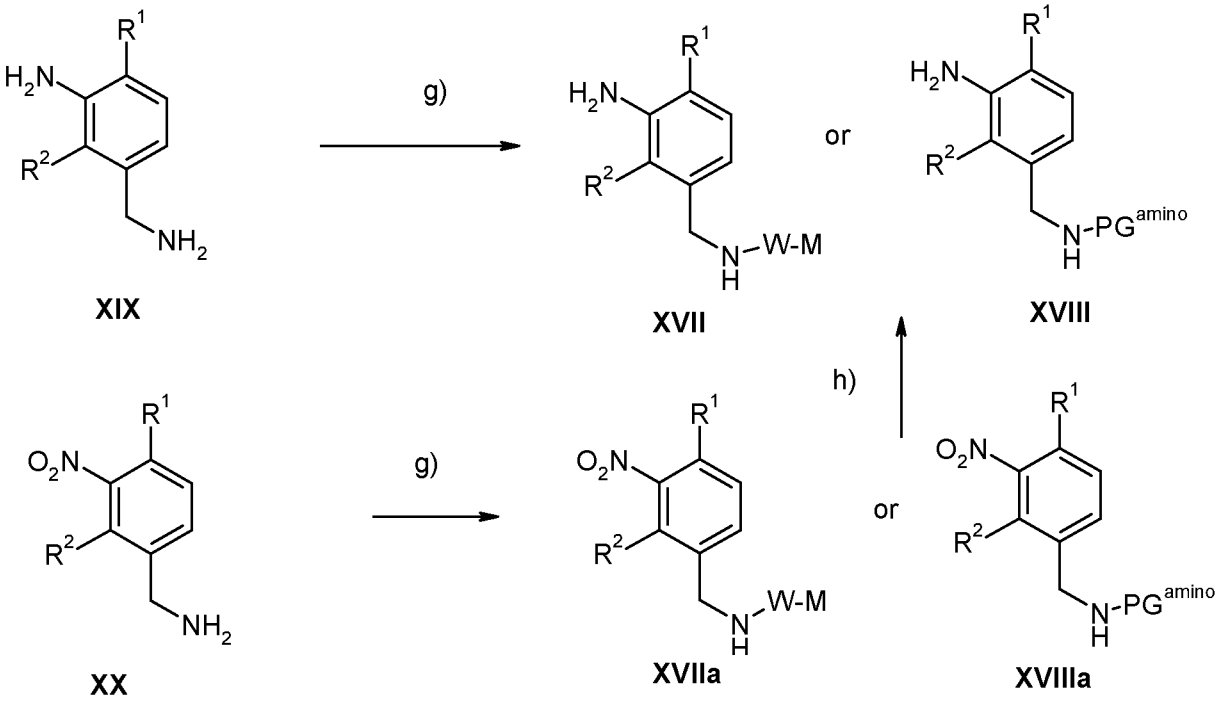


XVII **XVIII** **XI** **XV**

Step f) can be performed according to standard literature procedures for example with reagents such as 1,1'-thiocarbonyldi-2-pyridone, O,O'-di-2-pyridylthiocarbonate, 1,1'-thiocarbonyldiimidazole or with thiophosgene in a solvent as for example DCM, dioxane or DMF at temperatures between 0-150°C and optionally under addition of a base like DMAP or TEA.

The building blocks **XVII** and **XVIII** can be prepared according to scheme E:

Scheme E (all variable groups are as defined in claim 1 and PG^{amino} is a protecting group of the benzylic amino group)*:*



XIX **XVII** **XVIII**

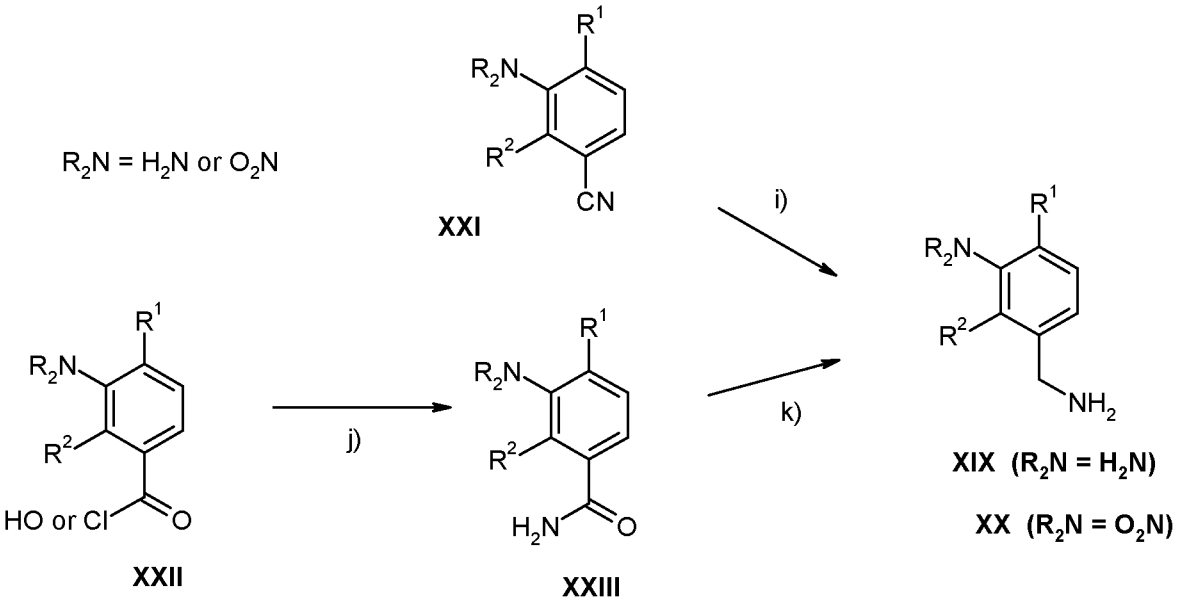
XX **XVIIa** **XVIIIa**

The amide formation in **step g)** can be performed in analogy to **step c) or step e)** to synthesize compound **XVII** or by using common reagents for amino group protection for example di-tert-butyl-dicarbonate, methyl-, ethyl-, benzyl or allyl-chloroformate under standard reaction conditions as described in "*Protective Groups in Organic Synthesis*", 3rd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999) to synthesize compounds **XVIII.**

The nitro group in precursor **XVIIa or XVIIIa** can be reduced to the amino group in **step h)** under literature known reduction conditions for example via hydrogenation (preferably at 1-5 bar) in presence of Pd/C or RaNi in MeOH, EtOH or THF optionally under acidic conditions in presence of HCl, or by using $SnCl_2$/HCl, $Na_2S_2O_4$, Zn/HCl, Fe/HCl, Fe-powder/aqueous NH_4Cl solution or according to procedures described in the literature for example R. Larock, *Comprehensive Organic Transformations*, VCH Verlagsgemeinschaft, Weinheim (1989). Appropriate solvent for this step is for example DCM, THF, MeCN, DMF, DMA, NMP, EtOH, MeOH or mixtures of the above mentioned solvents at any suitable temperature between 0°C to 100°C.

The building blocks **XIX** and **XX** can be prepared according to scheme F-G:

Scheme F (all variable groups are as defined in claim 1)*:*



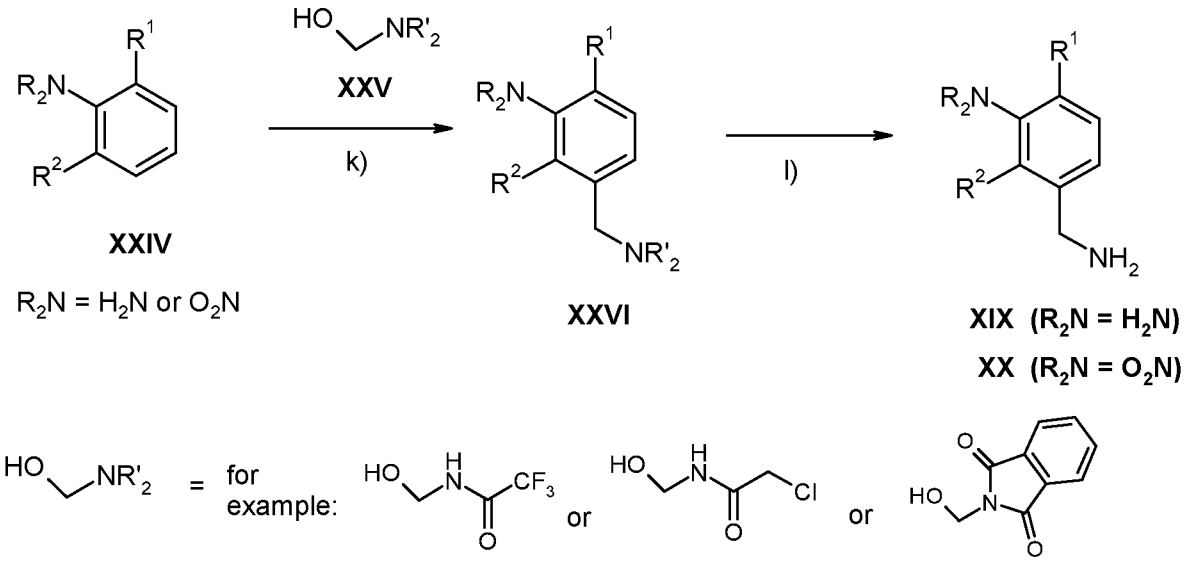
Step i) can be performed via hydrogenation (1-5 bar) with a catalyst like Pd/C, PtO_2 or RaNi in a suitable solvent like MeOH or EtOH optionally using HCl or NH_3 as additive at temperatures between 0-60°C or via reduction with $LiAlH_4$ or BH_3-containing reagents under literature-known conditions.

Step j) can be performed under the amide coupling conditions described for step e) and using NH_3 as coupling partner, for example 1-chloro-2-methyl-propenyl-dimethylamine in THF can be used as activating agent.

Step k) can be performed using $LiAlH_4$ or BH_3-containing reagents under literature known conditions as for example compiled in R.C.Larock, Comprehensive Organic Transformations, VCH, 1989, p.432-433, preferably with $LiAlH_4$ in THF at 0-80°C.

Alternatively compounds **XIX** and **XX** can be prepared according to scheme G

Scheme G (all variable groups are as defined in claim 1)*:*

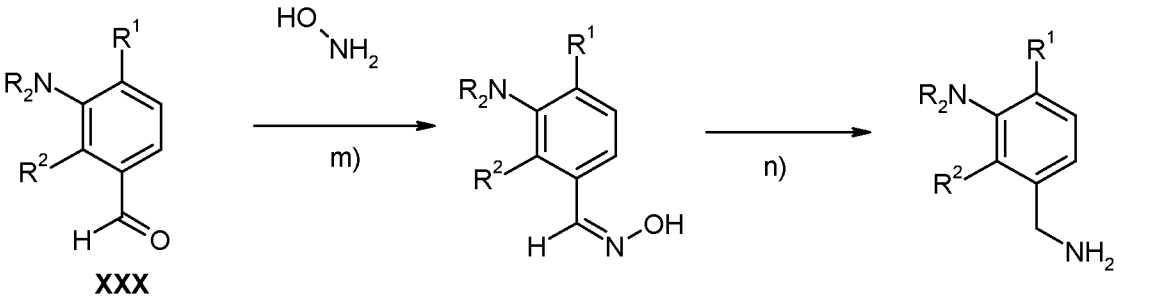


Step k) can be performed mixing **XXIV** with reagent **XXV** in concentrated H_2SO_4 or F_3C-SO_3H at temperatures between 0-150°C, preferably between 20-80°C.

Step l) can be performed using literature known deprotection procedures for the corresponding nitrogen protecting groups for example treatment of the phthalimide with hydrazine or cleavage of the amide bond using bases like NaOH in MeOH or EtOH at temperatures between 20-80°C or under acidic conditions using aqeous HCl solution or HCl in dioxane at temperatures between 20-80°C

Alternatively compounds **XIX** and **XX** can be prepared according to scheme H

Scheme H (all variable groups are as defined in claim 1)*:*



XXX

$R_2N = H_2N$ or O_2N

XXXI

XIX ($R_2N = H_2N$)

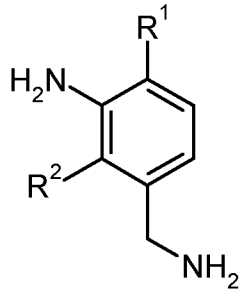
XX ($R_2N = O_2N$)

Step m) can be performed mixing **XXX** with HO-NH_2 in an appropriate solvent for example MeCN, DCM, THF, optionally using HCl as additive at temperatures between 0-60°C.

Step n) can be performed applying literature known reduction conditions for example via hydrogenation preferably at 1-5 bar H_2 pressure in presence of Pd/C or Ra-Ni in MeOH, EtOH or THF optionally using HCl or HOAc as catalyst, or by using $SnCl_2$/HCl, Zn/HCl, Fe/HCl, Fe-powder/aqueous NH_4Cl solution or according to procedures described in the literature for example R. Larock, *Comprehensive Organic Transformations*, VCH Verlagsgemeinschaft, Weinheim (1989).

Therefore, a further aspect of the present invention is a process for preparing compounds of formula **I** comprising the following steps:

(1) reacting a compound of formula **XIX**



XIX

in which

R^1 and **R^2** independently represent halo, -C_{1-3}alkyl, which latter alkyl group is optionally substituted by one or more fluorine atoms;

with an acid chloride of formula **Cl-W-M**

in which

W represents -C(O)-, -C(O)O-, which groups are bound to the nitrogen of the –NH- moiety via the carbon atom;

M represents

$-C_{1-6}$alkyl, $-C_{3-7}$cycloalkyl, both of which groups are optionally substituted by one or more groups selected from -F, -OH, -CN, $-NH_2$, $-NH(C_{1-2}alkyl)$, $-N(C_{1-2}alkyl)_2$, $-OC_{1-3}$alkyl, $-C_{1-5}$alkyl, $-C_{3-4}$cycloalkyl, in which latter three groups the alkyl or cycloalkyl groups are optionally substituted by one or more fluorine atoms;

or

oxetanyl-, tetrahydrofuranyl-, tetrahydropyranyl-, azetidinyl-, pyrrolidinyl-, piperidinyl-, all of which groups are optionally substituted by one or more substituents selected from fluoro, -CN, $-C_{1-3}$ alkyl, which latter alkyl group is optionally substituted by one or more fluorine atoms;

or

phenyl-, pyridyl-, thienyl-, pyrrolyl-, pyrazolyl-, imidazolyl-, thiazolyl-, oxazolyl-, or isoxazolyl-, all of which groups are optionally substituted by one or more substituents selected from halo, -CN or $-C_{1-3}$alkyl, which latter alkyl group is optionally further substituted by one or more fluorine atoms;

or

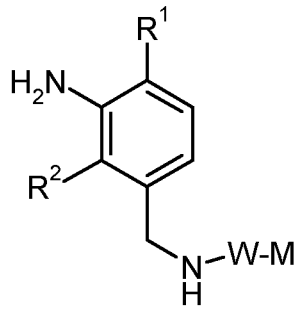
with an acid of formula **HO-W-M** in the presence of a *in situ* activating agent selected from the group of 1-propylphosphonic acid cyclic anhydride (PPA), *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyl-uronium tetrafluoroborate (TBTU), *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyl-uronium hexafluorophosphate (HBTU), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium-hexafluorophosphate (HATU), DCC, EDCI, carbonyldiimidazole (CDI), carbonylditriazole (CDT), 1-chloro-2-methyl-propenyl-dimethylamine and oxalyl chloride;

and

in the presence of a base selected from the group of NaOH, KOH, $NaHCO_3$, triethylamine (TEA), N-ethyldiisopropylamine (DIPEA), pyridine, N,N,-dimethylaminopyridine (DMAP) in a solvent selected from the group of dichloromethane, dioxane, THF, MeCN, dimethylformamide, dimethylacetamide (DMA), N-methylpyrrolidone (NMP) or in mixtures thereof;

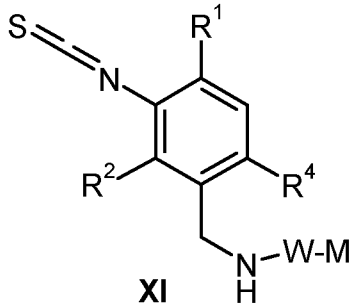
at a temperature between 0°C to 100°C

to obtain a compound of formula **XVII**



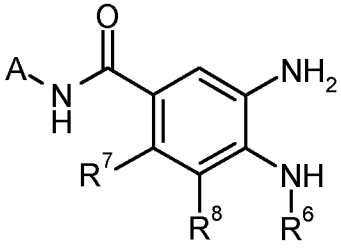
XVII ;

(2) reacting the compound of formula **XVII**
with a reagent selected from the group of 1,1'-thiocarbonyldi-2-pyridone, O,O'-di-2-pyridylthiocarbonate, 1,1'-thiocarbonyldiimidazole and thiophosgene
in a solvent selected from the group of dichloromethane, dioxane and DMF
at temperatures between 0-150°C and optionally in the presence of a base which is preferably DMAP or TEA
to obtain a compound of formula **XI**



XI

(3) reacting the compound of formula **XI**
with a compound of formula **XIII**

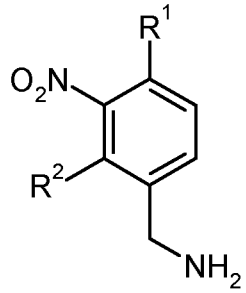


X

in the presence of a reagent selected from the group of CH_3-I, N,N'-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI, or its hydrochloride) and N,N'-diisopropylcarbodiimide (DIC);
in a solvent selected from the group of diethyl ether (Et_2O), dimethylformamide (DMF), dichloromethane (DCM), acetonitrile (MeCN) and tetrahydrofuran (THF)
preferably at a temperature between 0°C and 100°C.

An alternative process for preparing compounds of formula **I** comprises the following steps:

(1) reacting a compound of formula **XX**



XX

in which

R^1 and **R^2** independently represent halo, -C_{1-3}alkyl, which latter alkyl group is optionally substituted by one or more fluorine atoms;

with an acid chloride of formula **Cl-W-M**
in which

W represents -C(O)-, -C(O)O-, which groups are bound to the nitrogen of the –NH- moiety via the carbon atom;

M represents
-C_{1-6}alkyl, -C_{3-7}cycloalkyl, both of which groups are optionally substituted by one or more groups selected from -F, -OH, -CN, -NH_2, -NH(C_{1-2}alkyl), -N (C_{1-2}alkyl)$_2$, -OC_{1-3}alkyl, -C_{1-5}alkyl, -C_{3-4}cycloalkyl, in which latter three groups the alkyl or cycloalkyl groups are optionally substituted by one or more fluorine atoms;
or

oxetanyl-, tetrahydrofuranyl-, tetrahydropyranyl-, azetidinyl-, pyrrolidinyl-, piperidinyl-, all of which groups are optionally substituted by one or more substituents selected from fluoro, -CN, -C_{1-3} alkyl, which latter alkyl group is optionally substituted by one or more fluorine atoms;

or

phenyl-, pyridyl-, thienyl-, pyrrolyl-, pyrazolyl-, imidazolyl-, thiazolyl-, oxazolyl-, or isoxazolyl-, all of which groups are optionally substituted by one or more substituents selected from halo, -CN or -C_{1-3}alkyl, which latter alkyl group is optionally further substituted by one or more fluorine atoms.

or

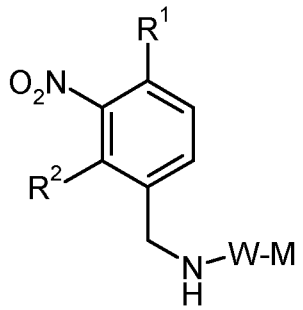
with an acid of formula **HO-W-M** in the presence of a *in situ* activating agent selected from the group of 1-propylphosphonic acid cyclic anhydride (PPA), *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyl-uronium tetrafluoroborate (TBTU), *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyl-uronium hexafluorophosphate (HBTU), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium-hexafluorophosphate (HATU), DCC, EDCI, carbonyldiimidazole (CDI), carbonylditriazole (CDT), 1-chloro-2-methyl-propenyl-dimethylamine and oxalyl chloride;

and

in the presence of a base selected from the group of NaOH, KOH, $NaHCO_3$, triethylamine (TEA), N-ethyldiisopropylamine (DIPEA), pyridine, N,N,-dimethylaminopyridine (DMAP) in a solvent selected from the group of dichloromethane, dioxane, THF, MeCN, dimethylformamide, dimethylacetamide (DMA), N-methylpyrrolidone (NMP) or in mixtures thereof;

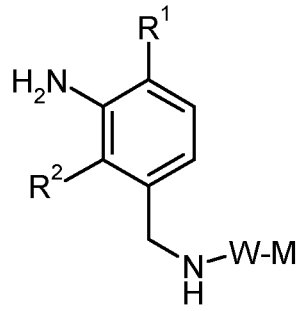
at a temperature between 0°C to 100°C

to obtain a compound of formula **XVIIa**



XVIIa ;

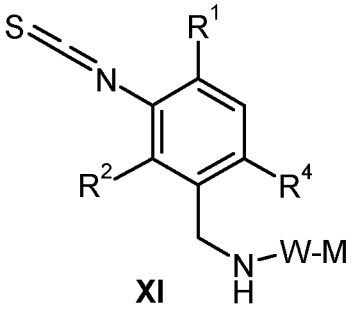
(2) converting the compound of formula **XVIIa** into a compound of formula **XVII**



XVII

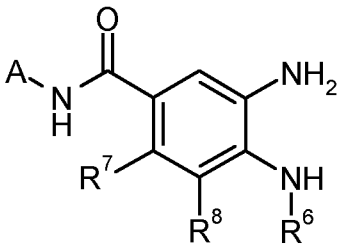
by catalytic hydrogenation (preferably at 1-5 bar) in presence of Pd/C or RaNi in MeOH, EtOH or THF, optionally under acidic conditions in presence of HCl,
or
by reduction with a reagent selected from the group of $SnCl_2$/HCl, $Na_2S_2O_4$, Zn/HCl, Fe/HCl, Fe-powder/aqueous NH_4Cl solution in a solvent selected from the group of DCM, THF, MeCN, DMF, DMA, NMP, EtOH, MeOH or mixtures thereof at a temperature between 0°C to 100°C;

(3) reacting the compound of formula **XVII**
with a reagent selected from the group of 1,1'-thiocarbonyldi-2-pyridone, O,O'-di-2-pyridylthiocarbonate, 1,1'-thiocarbonyldiimidazole and thiophosgene
in a solvent selected from the group of dichloromethane, dioxane and DMF
at temperatures between 0-150°C and optionally in the presence of a base which is preferably DMAP or TEA
to obtain a compound of formula **XI**



XI

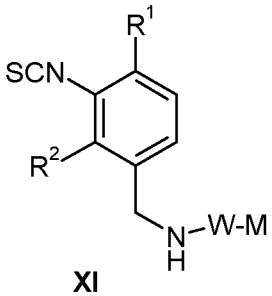
(4) reacting the compound of formula **XI**
with a compound of formula **XIII**



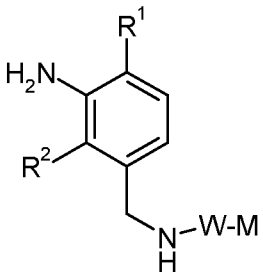
X

in the presence of a reagent selected from the group of CH_3-I, N,N'-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI, or its hydrochloride) and N,N'-diisopropylcarbodiimide (DIC);
in a solvent selected from the group of diethyl ether (Et_2O), dimethylformamide (DMF), dichloromethane (DCM), acetonitrile (MeCN) and tetrahydrofuran (THF)
preferably at a temperature between 0°C and 100°C.

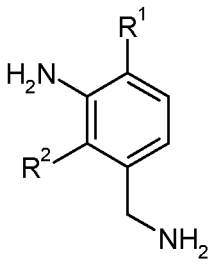
A further aspect of the present invention is the intermediates of the formulae **XI, XVII, XIX and XX**



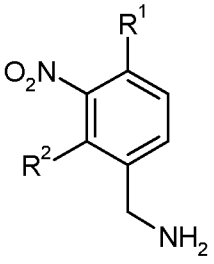
XI



XVII



XIX



XX

in which

R^1 and **R^2** independently represent halo, -C_{1-3}alkyl, which latter alkyl group is optionally substituted by one or more fluorine atoms;

W represents -C(O)-, -C(O)O-, which groups are bound to the nitrogen of the –NH- moiety via the carbon atom;

M represents

$-C_{1-6}$alkyl, $-C_{3-7}$cycloalkyl, both of which groups are optionally substituted by one or more groups selected from -F, -OH, -CN, $-NH_2$, $-NH(C_{1-2}alkyl)$, $-N(C_{1-2}alkyl)_2$, $-OC_{1-3}$alkyl, $-C_{1-5}$alkyl, $-C_{3-4}$cycloalkyl, in which latter three groups the alkyl or cycloalkyl groups are optionally substituted by one or more fluorine atoms;

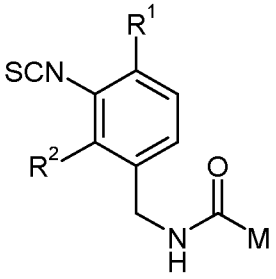
or

oxetanyl-, tetrahydrofuranyl-, tetrahydropyranyl-, azetidinyl-, pyrrolidinyl-, piperidinyl-, all of which groups are optionally substituted by one or more substituents selected from fluoro, -CN, $-C_{1-3}$ alkyl, which latter alkyl group is optionally substituted by one or more fluorine atoms;

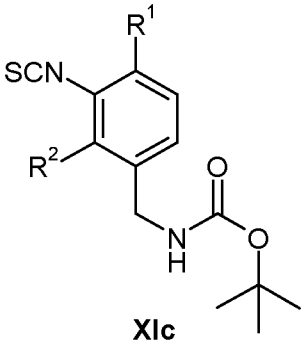
or

phenyl-, pyridyl-, thienyl-, pyrrolyl-, pyrazolyl-, imidazolyl-, thiazolyl-, oxazolyl-, or isoxazolyl-, all of which groups are optionally substituted by one or more substituents selected from halo, -CN or $-C_{1-3}$alkyl, which latter alkyl group is optionally further substituted by one or more fluorine atoms.

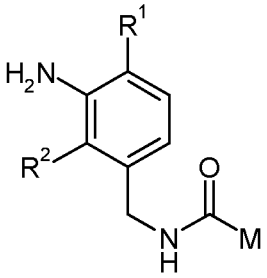
A second embodiment comprises as preferred intermediates compounds of formulae **XIb, XIc, XVIIb, XVIIc, XIX and XX**



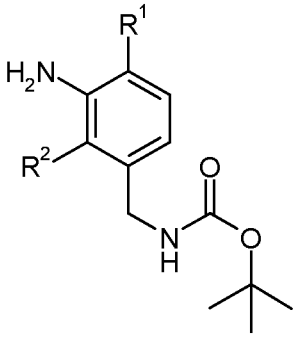
XIb



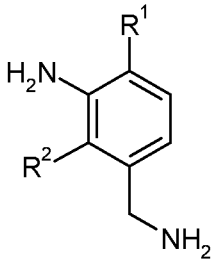
XIc



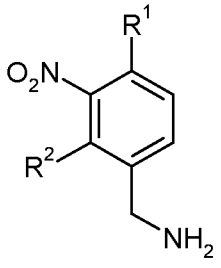
XVIIb



XVIIc



XIX



XX

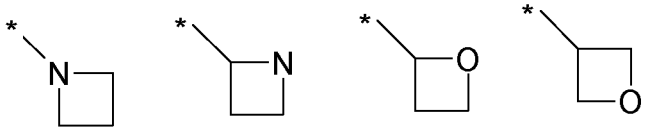
in which

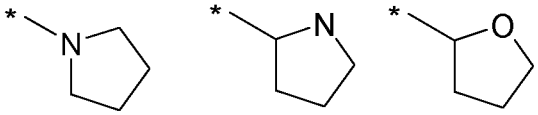
R^1 and R^2 independently represent –chloro, fluoro or $–CH_3$;

M represents

methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *s*-butyl, *t*-butyl, cyclopropyl, $-CH_2$-cyclopropyl, cyclobutyl, cyclopentyl, all of which groups are optionally substituted by one or more groups selected from -F, -OH, -CN, $-NH_2$, $-OCH_3$, $-CH_3$, $-CF_3$;

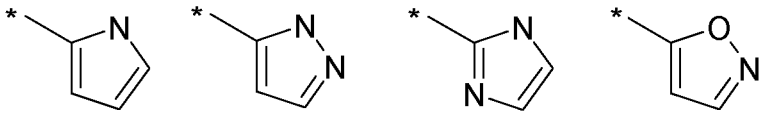
or is selected from the following groups

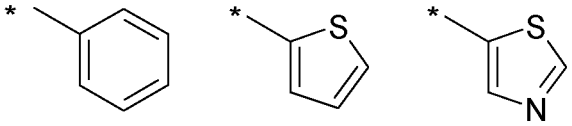




all of which groups are optionally substituted by one or more substituents selected from -F, $-CH_3$, or $-CF_3$;

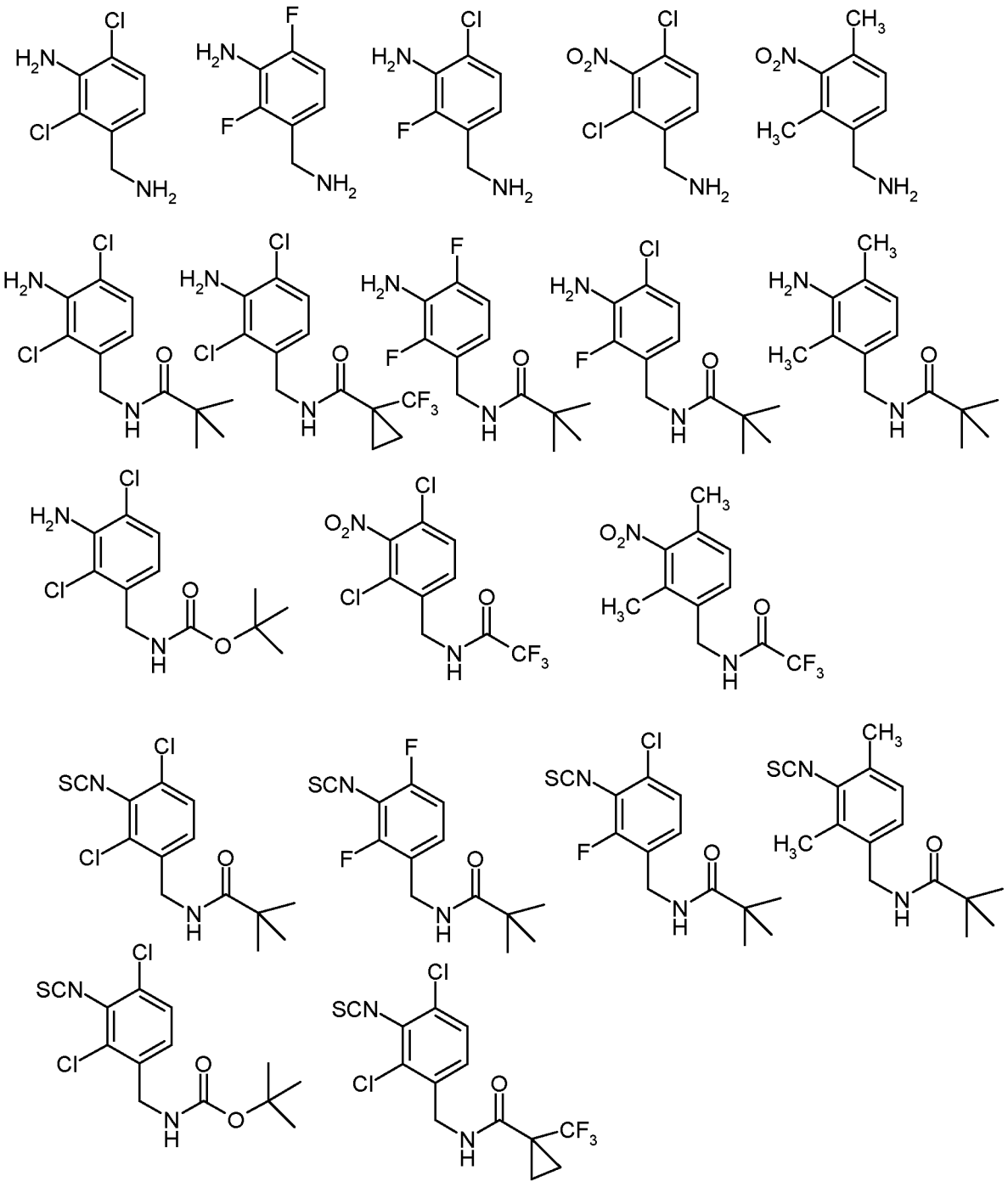
or is selected from the following groups





all of which groups are optionally substituted by one or more substituents selected from -F, -Cl, $-CH_3$, or $-CF_3$.

A further embodiment comprises, as more preferred intermediates, compounds of formulae **XIb, XIc, XVIIb, XVIIc, XIX and XX**, namely



5

Biological Assays

mPGES protein production

Microsomes from Rosetta E.coli bacteria expressing recombinant human mPGES-1 can be derived as described below:

Inoculate 5ml LB with Ampicilin (50 µg/ml) and Chloramphenicol (34 µg/ml) with bacteria from freeze culture. Incubate 8h at 37 ºC with 200rpm. Thereafter, inoculate 500-1000 ml LB containing Amp and Chloro with the 5 ml on culture and grow to OD640 of 0.8-1.0. Chill the culture to +4°C before induction. Induce the culture with IPTG at a final concentration of 400µM. Express the protein at room temp 18-23 ºC with 200 rpm shaking over night.

The following steps can be performed on the following day:

1. Spin down the cells in 250ml centrifuge flasks for 15min at 7000rpm (Beckmann Coulte Avanti J-E centrifuge)
2. Dissolve the pellet from 250ml culture in 12.5 ml homogenization buffer
3. (15mM Tris-HCL pH8, 1mM EDTA pH8, 0.25mM Sucrose, 2.5mM GSH, 1Tablet Protease inhibitor per 50ml buffer)
4. Disintegrate the cells by sonication, 5X10 seconds at 48% amplitude of a 750W sonifier
5. Add 2.5ml $MgCl_2$ (100mM) and DNase 12.5µl (0.8mg/ml) and incubate on ice for 30 min
6. Spin down the bacteria debris and save the supernatant, 7000 rpm for 15 min
7. Isolate the protein containing membranes in the supernatant by ultracentrifugation 120000 x g for 2hour at 4°C (Sorvall T880 rotor).
8. Discard the supernatant and dissolve the pellet in 20mM Potassium phosphate buffer pH7.4 (KH_2PO_4 and K_2HPO_4) buffer by sonication (5x10s, 30% of a 50W sonifier) and aliquot the enzyme and store aliquots at -80°C.

Before each experiment is performed an aliquot of the enzyme is thawed and it can then be dissolved in 0.1 M Potassium phosphate buffer pH7.4 (KH_2PO_4 and K_2HPO_4) buffer containing 2,5 mM GSH.

mPGES-1 enzyme assay

The aim of this assay is to determine the affinity of a test compound for the mPGES-1 enzyme.

47µl of recombinant human mPGES-1 (~ 0.5 µg protein/well) containing microsomal suspension in a buffer containing GSH, (2.5 mmol/L L-Glutathione reduced, dissolved in 0.1mol/L Phosphat Buffer pH 7.4) is dispensed in a 384-well plate and thereafter 1 µl of the test compound(s) is/are added and incubated for 25 minutes at room temperature. The enzyme reaction is started by the addition of 2ul PGH2 (final conc. 2 µM) disolved in water-free Diglyme. After 60 seconds the reaction is terminated by addition of a stop solution containing $FeCl_2$ (10µL 0.074mol/l $FeCl_2$). The samples are diluted between 1:25 in PBS (Phosphate Buffered Saline). 10µl of the diluted samples are transferred to 384-well low volume plate. In order to quantify the amount of PGE_2 that has been formed, a homogenous time resolved fluorescent (HTRF) detecting of PGE_2 has been performed using a commercially available kit from Cisbio according to the manufactures recommendation. This HTRF –based assay has been described in detail (see: Goedken et al., J Biomol Screen, 2008, 13(7), 619-625). Briefly, the diluted samples are mixed with 5µl PGE_2-d2 conjungate and 5µl anti-PGE_2 cryptate conjungate. After an incubation period of the plates over night, the fluorescence is measured by the use of an appropriate microplate reader.
The fluorescence of Europium cryptate (maxex = 307 nm, maxem = 620 nm) and d2-PGE_2 (maxex = 620 nm, maxem = 665 nm) are measured.
The extent of the specific HTRF is measured as a ratio of the emission intensity at 665 nm vs. that at 620 nm at an excitation puls of 320 nm. The quantification plate contains also wells with different concentrations of PGE_2 as calibration curve for the calculation of the PGE_2 concentrations from the HTRF ratio values.

From all mPGES enzyme assay the background is subtracted and the IC_{50} is calculated over a nonlinear regression with conventional software.

Table A. mPGES-1 inhibitory effect (IC_{50} values in nM) of compounds in the enzyme assay

example	IC50 [nM]	example	IC50 [nM]	example	IC50 [nM]	example	IC50 [nM]
1	2	**26**	2	**51**	3	**76**	3
2	2	**27**	4	**52**	4	**77**	2
3	4	**28**	3	**53**	4	**78**	2
4	4	**29**	4	**54**	3	**79**	2
5	2	**30**	4	**55**	4	**80**	1
6	2	**31**	3	**56**	4	**81**	3
7	2	**32**	3	**57**	4	**82**	1
8	3	**33**	4	**58**	3		
9	4	**34**	4	**59**	4		
10	7	**35**	4	**60**	3	**85**	1
11	4	**36**	4	**61**	4	**177**	1
12	4	**37**	5	**62**	2	**178**	1
13	3	**38**	3	**63**	3	**179**	1
14	1	**39**	4	**64**	2	**180**	2
15	3	**40**	4	**65**	4		
16	5	**41**	4	**66**	4		
17	1	**42**	4	**67**	2		
18	1	**43**	4	**68**	2		
19	1	**44**	3	**69**	2		
20	3	**45**	4	**70**	4		
21	3	**46**	3	**71**	2		
22	2	**47**	3	**72**	1		
23	1	**48**	3	**73**	2		
24	3	**49**	4	**74**	9		
25	2	**50**	4	**75**	2		

A549 cell-based assay

Although the enzymatic assay is a high throughput assay the disadvantage is that it uses a recombinant protein which is not in its natural enviroment. Accordingly a cellular assay was established in which a cell line of human origin (A549) expressing the mPGES-1 protein was used. In addtion in order to mimic the situation in humans in which compounds can be bound to plasma proteins 50% human serum is added in the assay. By having the combination of testing mPGES-1 in a cellular enviroment and the presence of 50% human serum this assay has a higher relevance to judge the therapeutic potential of a mPGES-inhibitor than the pure enzyme assay.

A549 cells (ATCC: CCL-185) are grown to about 90% confluence in F-12K Nutrient Mixture (Kaighn's Mod. Gibco) containing 10% FBS in a humified incubator at 37°C and 5% CO_2. Cells were detached using Trypsin-EDTA. A549 cells were seeded in a 384-well collagene plate at a density of 7000 cells/well (50µl) in F-12 medium containing 1% Penicillin-Streptomycin and 50% human serum. The cells were allowed to attach for 3-4h. After that the cells were incubated for 20-24h in F-12k medium supplemented with 50 % human serum, 1% Penicillin-Streptomycin and containing IL-1β at a final concentration of 5 ng/ml as well as 10 nM arachidonic acid in the presence of a vehicle or a test compound. The total volume is 100 µl.

Concentrations of PGE_2 in the cell free medium (10 µl) were measured using a commercially available HTRF kit from Cisbio (as described above). The PGE_2 formation in the absence of test compound was taken as 100%.

IC_{50} values were derived from at 6-8 point titrations using conventional software.

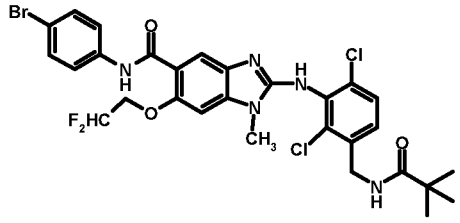
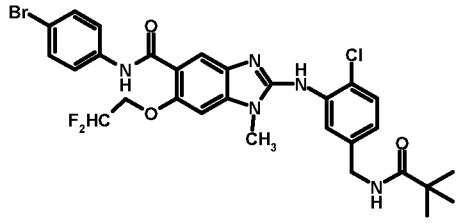
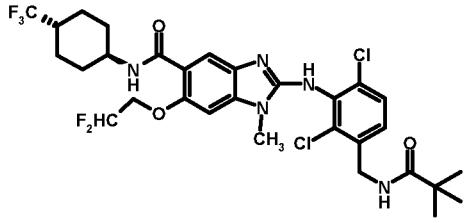
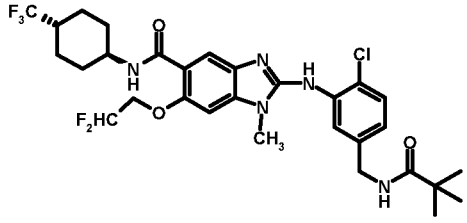
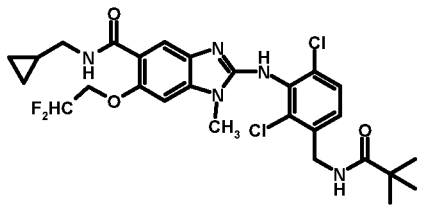
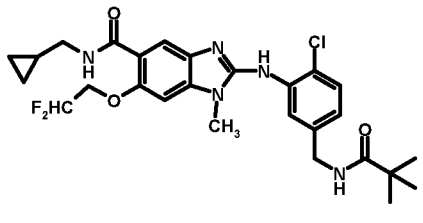
The compounds listed in table B are efficacious to block the generation of PGE_2. Compounds of formula I may therefore be expected to have therapeutic potential to treat inflammatory diseases and associated conditions such as inflammatory/nociceptive pain.

Table B. mPGES-1 inhibitory effect (IC_{50} values in nM) of compounds in the cell assay

example	IC50 [nM]	example	IC50 [nM]	example	IC50 [nM]	example	IC50 [nM]
1	<1	**26**	11	**51**	<1	**76**	2
2	3	**27**	124	**52**	<1	**77**	12
3	1	**28**	1	**53**	1	**78**	8
4	2	**29**	<1	**54**	<1	**79**	1
5	<1	**30**	<1	**55**	<1	**80**	7
6	2	**31**	1	**56**	3	**81**	50
7	1	**32**	1	**57**	<1	**82**	43
8	<1	**33**	<1	**58**	2		
9	79	**34**	1	**59**	<1	**84**	<1
10	4	**35**	<1	**60**	<1	**85**	4
11	4	**36**	<1	**61**	<1	**86**	<1
12	7	**37**	9	**62**	1	**87**	221
13	28	**38**	<1	**63**	1	**88**	68
14	5	**39**	<1	**64**	<1		
15	11	**40**	<1	**65**	6	**90**	36
16	106	**41**	1	**66**	<1	**91**	10
17	1	**42**	<1	**67**	1	**92**	9
18	4	**43**	4	**68**	1	**93**	66
19	2	**44**	1	**69**	3		
20	14	**45**	<1	**70**	16	**95**	13
21	36	**46**	1	**71**	16	**96**	14
22	1	**47**	<1	**72**	9		
23	<1	**48**	1	**73**	1	**98**	2
		49	1	**74**	1		
25	9	**50**	1	**75**	<1	**100**	52

example	IC50 [nM]	example	IC50 [nM]	example	IC50 [nM]	example	IC50 [nM]
101	11	**126**	72	**151**	1	**176**	<1
102	15	**127**	85	**152**	<1	**177**	<1
103	18	**128**	26	**153**	3	**178**	<1
				154	36	**179**	<1
		130	3	**155**	2	**180**	93
		131	1	**156**	10		
107	106	**132**	2				
108	59	**133**	1	**158**	<1		
109	57	**134**	8	**159**	1		
110	8	**135**	<1	**160**	<1		
111	7	**136**	17	**161**	2		
112	19	**137**	4	**162**	<1		
113	25	**138**	49	**163**	5		
		139	27	**164**	15		
115	300			**165**	<1		
16	3	**141**	<1	**166**	7		
17	20	**142**	2.5	**167**	6		
18	11			**168**	<1		
		144	2	**169**	1		
20	9	**145**	7	**170**	<1		
21	119	**146**	2	**171**	4		
22	4	**147**	4	**172**	2		
23	3	**148**	2				
24	28	**149**	1	**174**	<1		
25	220	**150**	1				

Table C. Comparison of enzym and cell IC50 (nM) of selected benzimidazoles

Structure	Enzym IC50	Cell IC50
	2	<1
 of PCT/EP2010/052799	3	10
	2	<1
 of PCT/EP2010/052799	3	17
	4	1
 of PCT/EP2010/052799	2	>200

Tables A, B and C demonstrate that compounds with a similar affinity for the mPGES-1 enzyme as measured in the enzyme assay may have different potencies in the cell based assay.

Data from a cell based pharmacological assay when compared with data from an enzyme assay are considered to allow for a better predictibility and estimation of therapeutic effective concentrations/doses. Compounds of the present invention show high potency in both assays. Consequently, they are likely to be more suitable for the in-vivo use.

METHOD OF TREATMENT

The present invention relates to compounds of formula **I** which are useful in the prevention and/or treatment of a disease and/or condition in which the inhibition of prostaglandin E synthases, in particular that of the microsomal prostaglandin E_2 synthase-1 (mPGES-1) is of therapeutic benefit, including but not limited to the treatment and/or prevention of inflammatory diseases and/or associated conditions.

The term “inflammation” will be understood to include any inflammatory disease, disorder or condition *per se*, any condition that has an inflammatory component associated with it, and/or any condition characterised by inflammation as a symptom, including *inter alia* acute, chronic, ulcerative, specific, allergic and necrotic inflammation, and other forms of inflammation known to those skilled in the art. The term thus also includes, for the purposes of this invention, inflammatory pain, pain generally and/or fever.

Where a condition has an inflammatory component associated with it, or a condition characterised by inflammation as a symptom, the skilled person will appreciate that compounds of the invention may be useful in the treatment of the inflammatory symptoms and/or the inflammation associated with the condition.

Compounds of the invention may also have effects that are not linked to inflammatory mechanisms, such as in the reduction of bone loss in a subject. Such conditions include osteoporosis, osteoarthritis, Paget’s disease and/or periodontal diseases.

A further aspect of the present invention relates to a compound of formula **I** as a medicament.

Another aspect of the present invention is the use of compounds of formula **I** for the treatment and/or prevention of a disease and/or condition in which the inhibition of the mPGES-1 is of therapeutic benefit.

A further aspect of the present invention is the use of a compound of formula **I** for the treatment and/or prevention of inflammatory diseases and/or associated conditions.

The present invention also relates to the use of compounds of formula I for the treatment and/or prevention of the following diseases and conditions:

1. Rheumatic diseases or autoimmune diseases or muscoskeletal diseases: all forms of rheumatic diseases including e.g. soft tissue rheumatism, rheumatoid arthritis, polymyalgia rheumatica, reactive arthritis, tenosynovitis, gout or metabolic arthritis, bursitis, tendonitis, juvenile arthritis, spondyloarthropathies like e.g. spondylitis, ankylosing spondylitis, psoriatric arthropathy; sarcoidosis, fibromyalgia, myositis, polymyositis, osteoarthritis, traumatic arthritis, collagenoses of any origin e.g. systemic lupus erythematosus, scleroderma, dermatomyositis, Still's Disease, Sjögren syndrome, Felty syndrome; rheumatic fever and rheumatic heart disease, diseases of blood vessels like vasculitis, polyarthritis nodosa, Behcet's syndrome, giant cell arthritis, Wegener´s granulomatosis, Henoch-Schönlein purpura; psoriatic arthritis, fungal arthritis, in particular including pain associated with any of the aforementioned conditions;

2. Headaches such as migraines with and without aura, tension-type headaches, cluster headaches and headaches with different origins;

3. Sympathetically maintained pain like complex regional pain syndrome Type I and II;

4. Neuropathic pain such as low back pain, hip pain, leg pain, non-herpetic neuralgia, post herpetic neuralgia, diabetic neuropathy, nerve injury-induced pain, acquired immune deficiency syndrome (AIDS) related neuropathic pain, head trauma, toxin and chemotherapy caused nerve injuries, phantom limb pain, multiple sclerosis, root avulsions, painful traumatic mononeuropathy, painful polyneuropathy, thalamic pain syndrome, post-stroke pain, central nervous system injury, post surgical pain, carpal tunnel syndrome, trigeminal neuralgia, post mastectomy syndrome, postthoracotomy syndrome, stump pain, repetitive motion pain, neuropathic pain associated hyperalgesia and allodynia, alcoholism and other drug-induced pain;

5. Cancer pain induced by or associated with tumors such as bone tumors, lymphatic leukemia; Hodgkin's disease, malignant lymphoma; lymphogranulomatoses; lymphosarcoma; solid malignant tumors; extensive metastases;

6. Visceral disorders such as chronic pelvic pain, pancreatitis, peptic ulcer, interstitial cystitis, cystitis, renal colic, angina, dysmenorrhoea, menstruation, gynaecological pain, irritable bowel disease (IBS), inflammatory bowel disease, Crohn's disease and ulcerative colitis, nephritis, prostatitis, vulvodynia, non-ulcer dyspepsia, non-cardiac chest pain, myocardial ischemia;

7. Inflammation associated diseases of ear, nose, mouth and throat like influenza and viral/bacterial infections such as the common cold, allergic rhinitis (seasonal and perennial),

pharyngitis, tonsillitis, gingivitis, larhyngitis, sinusitis, and vasomotor rhinitis, fever, hay fever, thyroiditis, otitis, dental conditions like toothache, perioperative and post-operative conditions, trigeminal neuralgia, uveitis; iritis, allergic keratitis, conjunctivitis, blepharitis, neuritis nervi optici, choroiditis, glaucoma and sympathetic opthalmia, as well as pain thereof;

8. Neurological diseases such as cerebral oedema and angioedema, cerebral dementia like e.g. Parkinson's and Alzheimers disease, senile dementia; multiple sclerosis, epilepsy, drug resistant epilepsy, stroke, myasthenia gravis, brain and meningeal infections like encephalomyelitis, meningitis, including HIV as well as schizophrenia, delusional disorders, autism, affective disorders and tic disorders;

9. Work-related diseases like pneumoconiosis, including aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis;

10. Lung diseases such as asthma including allergic asthma (atopic or non-atopic) as well as exercise-induced bronchoconstriction, occupational asthma, viral- or bacterial exacerbation of asthma, other non-allergic asthmas and "wheezy-infant syndrome", Chronic obstructive pulmonary disease (COPD) including emphysema, adult respiratory distress syndrome, bronchitis, pneumonia, adult respiratory distress syndrome (ARDS), pigeon fancier's disease, farmers lung;

11. Skin diseases such as psoriasis and eczema, dermatitis, sunburn, burns as well as aprains and strains and tissue trauma;

12. Vascular and heart diseases which are inflammation- related like artheriosclerosis including cardiac transplant atherosclerosis, panarteritis nodosa, periarteritis nodosa, arteritis temporalis, Wegner granulomatosis, giant cell arthritis, reperfusion injury and erythema nodosum, thrombosis (e.g. deep vein thrombosis, renal, hepathic, portal vein thrombosis); coronary artery disease, aneurysm, vascular rejection, myocardial infarction, embolism, stroke, thrombosis including venous thrombosis, angina including unstable angina, coronary plaque inflammation, bacterial-induced inflammation including Chlamydia-induced inflammation, viral induced inflammation, and inflammation associated with surgical procedures such as vascular grafting including coronary artery bypass surgery, revascularization procedures including angioplasty, stent placement, endarterectomy, or other invasive procedures involving arteries, veins and capillaries, artery restenosis;

13. Diabetes-associated symptoms such as diabetic vasculopathy, diabetic neuropathy, diabetic retinopathy, post capillary resistance or diabetic symptoms associated with insulitis (e.g. hyperglycemia, diuresis, proteinuria and increased nitrite and kallikrein urinary excretion);

14. Benign and malignant tumors and neoplasia including cancer, such as colorectal cancer, brain cancer, bone cancer, epithelial cell-derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophageal cancer, small bowel cancer, stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer, skin cancer such as squamous cell and basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers effecting epithelial cells throughout the body; neoplasias like gastrointestinal cancer, Barrett's esophagus, liver cancer, bladder cancer, pancreatic cancer, ovarian cancer, prostate cancer, cervical cancer, lung cancer, breast cancer and skin cancer; adenomatous polyps, including familial adenomatous polyposis (FAP) as well preventing polyps from forming in patients at risk of FAP.

15. Various other disease states and conditions like epilepsy, septic shock e.g. as antihypovolemic and/or antihypotensive agents, sepsis, osteoporosis, benign prostatic hyperplasia and hyperactive bladder, nephritis, pruritis, vitiligo, disturbances of visceral motility at respiratory, genitourinary, gastrointestinal or vascular regions, wounds, allergic skin reactions, mixed-vascular and non-vascular syndromes, septic shock associated with bacterial infections or with trauma, central nervous system injury, tissue damage and postoperative fever, syndromes associated with itching.

Preferred according to the present invention is the use of a compound of formula I for the treatment and/or prevention of pain; in particular pain that is associated with any one of the diseases or conditions listed above.

Another aspect of the present invention is a method for the treatment and/or prevention of above mentioned diseases and conditions, which method comprises the administration of an effective amount of a compound of formula I to a human being.

DOSAGE

The dose range of the compounds of formula I applicable per day is usually from 0.01 to 5000 mg, preferably from 1 to 2000 mg, more preferably from 5 to 500 mg, most preferably 10 to 250 mg. Each dosage unit may conveniently contain from 2 to 500 mg, preferably 5 to 250 mg.

The actual pharmaceutically effective amount or therapeutic dosage will of course depend on factors known by those skilled in the art such as age and weight of the patient, route of administration and severity of disease. In any case the combination will be administered at dosages and in a manner which allows a pharmaceutically effective amount to be delivered based upon patient's unique condition.

PHARMACEUTICAL FORMULATIONS

Suitable preparations for administering the compounds of formula will be apparent to those with ordinary skill in the art and include for example tablets, pills, capsules, suppositories, lozenges, troches, solutions, syrups, elixirs, sachets, injectables, inhalatives and powders etc. The content of the pharmaceutically active compound(s) should be in the range from 1 to 99 wt.-%, preferably 10 to 90 wt.-%, more preferably 20 to 70 wt.-%, of the composition as a whole.

Suitable tablets may be obtained, for example, by mixing one or more compounds according to formula I with known excipients, for example inert diluents, carriers, disintegrants, adjuvants, surfactants, binders and/or lubricants . The tablets may also consist of several layers. A further aspect of the invention is a pharmaceutical formulation including a compound of formula I in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

COMBINATION THERAPY

The compounds according to the present invention can be combined with other treatment options known to be used in the art in connection with a treatment of any of the indications the treatment of which is in the focus of the present invention.

Among such treatment options that are considered suitable for combination with the treatment according to the present inventions are:

- non-steroidal antiinfiammatory drugs (NSAIDs) including COX-2 inhibitors;
- opiate receptor agonists;
- Cannabionoid agonists or inhibitors of the endocannabinoid pathway
- Sodium channel blockers;
- N-type calcium channel blockers;
. serotonergic and noradrenergic modulators;
- corticosteroids;
- histamine H1 receptor antagonists;
- histamine H2 receptor antagonists;
- proton pump inhibitors;
- leukotriene antagonists and 5-lipoxygenase inhibitors;
- local anesthetics;
- VR1 agonists and antagonists;
- Nicotinic acetylcholine receptor agonists;

- P2X3 receptor antagonists;
- NGF agonists and antagonists or anti-NGF antibodies;
- NK1 and NK2 antagonists;
- Bradykinin B1 antagonists
- CCR2 antagonists
- iNOS or nNOS or eNOS inhibitors
- NMDA antagonist;
- potassium channel modulators;
- GABA modulators;
- serotonergic and noradrenergic modulators;
- anti-migraine drugs;

-neuropathic pain drugs such as pregabaline or duloxetine.

Said list is not considered to have a limiting character.

In the following representative examples of such treatment options shall be given.

- Non-steroidal antiinfiammatory drugs (NSAIDs) including COX-2 inhibitors: propionic acid derivatives (alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenhufen, fenoprofen, flubiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid, and tioxaprofen), acetic acid derivatives (indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac), fenamic acid derivatives (meclofenamic acid, mefenamic acid, and tolfenamic acid), biphenyl-carboxylic acid derivatives, oxicams (isoxicam, meloxicam, piroxicam, sudoxicam and tenoxican), salicylates (acetyl salicylic acid, sulfasalazine) and the pyrazolones (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone), and the coxibs (celecoxib, valecoxib, rofecoxib and etoricoxib) and the like;
- Antiviral drugs like acyclovir, tenovir, pleconaril, peramivir, pocosanol and the like.
- Antibiotic drugs like gentamicin, streptomycin, geldanamycin, doripenem, cephalexin, cefaclor, ceftazichine, cefepime, erythromycin, vancomycin, aztreonam, amoxicillin, bacitracin, enoxacin, mafenide, doxycycline, chloramphenicol and the like;
- Opiate receptor agonists: morphine, propoxyphene (Darvon), tramadol, buprenorphin and the like;

- Glucocorticosteroids such as bethamethasone, budesonide, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone and deflazacort; immunosuppressive, immunomodulatory, or cytsostatic drugs inlcuding but not limited to hydroxychlorquine, D-penicillamine, sulfasalizine, auranofin, gold mercaptopurine, tacrolimus, sirolimus, mycophenolate mofetil, cyclosporine, leflunomide, methotrexate, azathioprine, cyclophosphamide and glatiramer acetate and novantrone, fingolimod (FTY720), minocycline and thalidomide and the like;
- anti-TNF antibodies or TNF-receptor antagonists such as but not limited to Etanercept, Infliximab, Adalimumab (D2E7), CDP 571, and Ro 45-2081 (Lenercept), or biologic agents directed against targets such as but not limited to CD-4, CTLA-4, LFA-1, IL-6, ICAM-1, C5 and Natalizumab and the like;
- IL-1 receptor antagonists such as but not limited to Kineret;
- Sodium channel blockers: carbamazepine, mexiletine, lamotrigine, tectin, lacosamide and the like.
- N-type calcium channel blockers: Ziconotide and the like.
- Serotonergic and noradrenergic modulators: paroxetine, duloxetine, clonidine, amitriptyline, citalopram;
- Histamine H1 receptor antagonists: bromophtniramint, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripelennamine, hydroxyzine, methdiJazine, promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine pyrilamine, astemizole, terfenadine, loratadine, cetirizine, deslo- ratadine, fexofenadine and levocetirizine and the like;
- Histamine H2 receptor antagonists: cimetidine, famotidine and ranitidine and the like;
- Proton pump inhibitors: omeprazole, pantoprazole and esomeprazole and the like;
- Leukotriene antagonists and 5-lipoxygenase inhibitors: zafirlukast, mon- telukast, pranlukast and zileuton and the like;
- Local anesthetics such as ambroxol, lidocaine and the like;
- Potassium channel modulators:like retigabine;
- GABA modulators: lacosamide, pregabalin, gabapentin and the like;
- Anti-migraine drugs: sumatriptan, zolmitriptan, naratriptan, eletriptan, telcegepant and the like;
- NGF antibodies such as RI-724 and the like.

Combination therapy is also possible with new principles for the treatment of pain e.g. P2X3 antagonists, VR1 antagonists, NK1 and NK2 antagonists, NMDA antagonists, mGluR antagonists and the like.

The combination of compounds is preferably a synergistic combination. Synergy, as described for example by Chou and Talalay, Adv. Enzyme Regul. 22:27-55 (1984), occurs when the effect of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at suboptimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased pharmacological effect, or some other beneficial effect of the combination compared with the individual components.

EXPERIMENTAL SECTION

Preparation of examples for compounds of the general formula I

Unless otherwise stated, one or more tautomeric forms of compounds of the examples described hereinafter may be prepared in *situ* and/or isolated. All tautomeric forms of compounds of the examples described hereinafter should be considered to be disclosed.

The invention is illustrated by way of the following examples, in which the following abbreviations may be employed:

Abbreviations:

AcOH	acetic acid
aq	aqueous
BSTFA	N,O-bis (trimethylsilyl) trifluoroacetamide
Boc	tert-butoxycarbonyl
Boc_2O	di-tert-butyl-dicarbonate
CDT	carbonylditriazole
CE	chromatography equipment
CH	cyclohexane
conc	concentrated
DCM	dichloromethane
DIC	N,N-diisopropylcarbodiimide
DIPEA	*N*-ethyldiisopropylamine

DMAP	*N,N*-dimethylaminopyridine
DMSO	dimethylsulphoxide
DMF	*N,N*-dimethylformamide
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EtOAc	ethyl acetate
Et_2O	diethyl ether
EtOH	ethanol
HBTU	*O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HPLC	high performance liquid chromatography
i-PrOH	isopropanol
KHMDS	Potassium hexamethyldisilazane
MeCN	acetonitrile
MeOH	methanol
MS	mass spectrometry
MTBE	methyl-*tert*-butyl ether
PE	petrol ether
PPA	1-propylphosphonic-acid cyclic anhydride
Pd/C	10% Palladium on carbon
RP	reversed phase
rt	room temperature
R_f	retention factor
R_t	retention time
sat	saturated
TBTU	*O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate
TCDI	thiocarbonyl diimidazole
TEA	triethylamine
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TLC	thin layer chromatography

Analytical methods

All compounds specified in the examples below gave the correct mass spectra matching the theoretical isotope pattern. For practical reasons, only one of the major isotope peaks is given as representative data for the mass spectrum.

The TLC data is obtained by using the following tlc plates

a) Silica gel plates 60 F254 Merck No 1.05714.0001 abbreviated in the experimental part as "silica gel"

b) Reversed phase plates: RP-8 F 254s Merck No: 1.15684.0001 abbreviated in the experimental part as "RP-8".

c) Aluminiumoxide plates 60 F254 Merck 1.05713.0001 abbreviated in the experimental part as "Alox"

The R_f values given are determined without chamber saturation.

Flash chromatography purifications are performed using silica gel from Millipore (MATREX™, 35 bis 70 µm) or Alox (E. Merck, Darmstadt, Aluminiumoxid 90 standardisiert, 63 bis 200 µm, Artikel-Nr: 1.01097.9050).

The HPLC/MS data, where specified, are obtained under the following conditions:

CE 1:

Agilent HP 1200 with binary pump, Agilent MS 6140, HiPALS1367C

The diode array detection is measured in a wavelength range of 190-400 nm.

Range of mass-spectrometric detection: m/z 100 to m/z 1000.

CE 2:

Waters SQD MS, Acquity UPLC.

The diode array detection is measured in a wavelength range from 210-500 nm

Range of mass-spectrometric detection: m/z 120 to m/z 820

CE 3:

Agilent LC/MSD SL 61956B; Agilent 1100; quarternary. pump;.

The diode array detection is measured in a wavelength range from 190-400 nm

Range of mass-spectrometric detection: m/z 100 to m/z 1000

CE 4:

Agilent HP 100 with binary pump, Waters ZQ2000,

The diode array detection is measured in a wavelength of 210-500 nm.

Range of mass-spectrometric detection: m/z 120 to m/z 820.

CE 5:

Acquity UPLC, Waters SQD MS,

The diode array detection is measured in a wavelength of 210-500 nm.

Range of mass-spectrometric detection: m/z 120 to m/z 820.

The following methods are used (if not stated otherwise the column temperature is 25°C):

Method A (CE 2):

Stationary phase (column temperature: constant at 60°C): Sunfire C18, 2.5. µm, 2.1x50 mm

Mobile phase: E1: water with 0.1% HCOOH, E2: MeCN with 0.1% HCOOH

Eluent gradient:

time in min	%E1	%E2	flow rate in mL/min
0.0	95	5	1.5
1.20	70	30	1.5
2.40	0	100	1.5
2.60	0	100	1.5
2.70	95	5	1.5

Method B (CE 1):

Stationary phase: Zorbax Stable Bond C18, 1.8 µm, 3.0x30 mm

Mobile phase: E1: water with 0.15% HCOOH, E2: MeCN

Eluent gradient:

time in min	%E1	%E2	flow rate in mL/min
0.00	95	5	1.6
1.00	10	90	1.6
2.50	10	90	1.6
2.75	95	5	1.6

Method C (CE 1):

Stationary phase:: As described in method B.

Eluent gradient:

time in min	%E1	%E2	flow rate in mL/min
0.00	95	5	1.6
2.25	10	90	1.6
2.50	10	90	1.6
2.75	95	5	1.6

Method D (CE 4):

Stationary phase (column temperature: constant at 40°C): XBridge C18, 3.5 µm, 4.6x50 mm

Mobile phase: E1: water with 0.032% NH_4OH, E2: MeOH

Eluent gradient:

time in min	%E1	%E2	flow rate in mL/min
0.00	95	5	1.5
2.00	0	100	1.5

Method E (CE 1):

Stationary phase (column temperature: constant at 40°C): Waters XBridge C18, 2.5 µm, 3.0x30 mm

Mobile phase: E1: water with 0.15% HCOOH, E2: MeCNEluent gradient:

time in min	%E1	%E2	flow rate in mL/min
0.00	95	5	1.6
2.25	10	90	1.6
2.50	10	90	1.6
2.75	95	5	1.6

Method F (CE 3)::

Stationary phase (column temperature: constant at 40°C): Zorbax Stable bond C18, 5 µm, 30x100 mm; Mobile phase: E1: water with 0.15% HCOOH, E2: MeCN

Eluent gradient:

time in min	%E1	%E2	flow rate in mL/min
0.00	95	5	50
2.00	95	5	50
11.00	10	90	50
12.00	10	90	50
13.00	90	10	50

Method G (CE 3):

Stationary phase: Zorbax Stable Bond C18, 3.5 µm, 4.6x75 mm

Mobile phase: E1: water with 0.15% HCOOH, E2: MeCN

Eluent gradient:

time in min	%E1	%E2	flow rate in mL/min
0.00	95	5	1.6
2.00	10	90	1.6
5.00	10	90	1.6
5.50	95	5	1.6

Method H (CE 5)

Stationary phase (column temperature: constant at 60°C): XBridge C18, 1.7 µm, 2.1x50 mm

Mobile phase: E1: water with 0.1% NH_4OH, E2: MeCN

Eluent gradient:

time in min	%E1	%E2	flow rate in mL/min
0.0	95	5	1.5
0.70	0	100	1.5
0.80	0	100	1.5
0.81	95	5	1.5
1.90	95	5	0.2
2.00	0	100	0.2
3.00	0	5	0.2

Method I (CE 4):

Stationary phase (column temperature: constant at 60°C): Sunfire C18, 3.5. µm, 4.6x50 mm

Mobile phase: E1: water with 0.1% TFA, E2: MeCN with 0.1% TFA

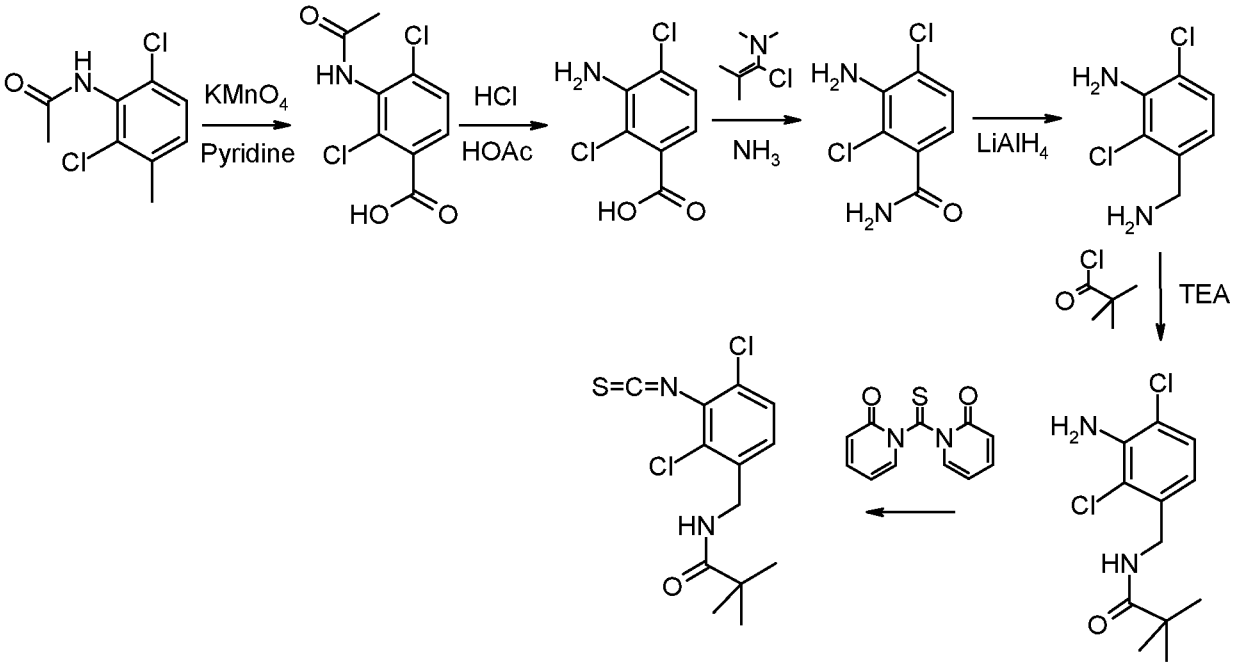
Eluent gradient:

time in min	%E1	%E2	flow rate in mL/min
0.0	95	5	1.5
2.00	0	100	1.5
2.50	0	100	1.5
2.60	95	5	1.5

Synthesis of building blocks of the 2,3,4-trisubstituted benzylamine-type:

Building block A:

N-(2,4-Dichloro-3-isothiocyanato-benzyl)- 2,2-dimethyl-propionamide



(a) 3-Acetylamino-2,4-dichloro-benzoic acid

Water (110 mL) is added to *N*-(2,6-dichloro-3-methyl-phenyl)-acetamide (13 g, 59 mmol) in pyridine (30 mL). The mixture is heated to 70°C and $KMnO_4$ (47 g, 298 mmol) is cautiously added portionwise. After 6 h at reflux the reaction mixture is filtered through a pad of celite and washed with hot water. The filtrate is cooled to rt, concentrated and slowly acidified with 6 M aq. HCl solution. The mixture is cooled in an ice bath, filtered and the filtercake is washed with cold water and dried to give the sub-title compound.

Yield: 11.6 g (78%). R_f = 0.1(silica gel, DCM:EtOH 9:1). MS m/z: 248 $[M+H]^+$.

(b) 3-Amino-2,4-dichloro-benzoic acid

3-Acetylamino-2,4-dichloro-benzoic acid (21.0 g, 84.6 mmol) is stirred in 6 M aq. HCl-solution (120 mL) and acetic acid (250 mL) at reflux for 24 h. The reaction mixture is cooled, concentrated, diluted with water and concentrated again. The residue is diluted with water, stirred under cooling and filtered. The filtercake is washed and dried to give the sub-title compound.

Yield: 16.8 g (96%). MS m/z: 204 $[M-H]^-$. HPLC-method C: R_t= 1.46 min.

(c) 3-Amino-2,4-dichloro-benzamide

(1-Chloro-2-methyl-propenyl)-dimethyl-amine (16.1 mL, 116 mmol) is added to 3-amino-2,4-dichloro-benzoic acid (20.0 g, 97.1 mmol) in THF (320 mL). After 4 h at rt the mixture is added dropwise to conc. NH_3 (320 mL) and stirred at rt overnight. The reaction mixture is concentrated, cooled and filtered. The filtercake is dried to give the sub-title compound.
Yield: 17.4 g (87%). MS m/z: 205 $[M+H]^+$. HPLC-method C: R_t= 1.19 min.

(d) 3-Amino-2,4-dichloro-benzylamine

3-Amino-2,4-dichloro-benzamide (2.00 g, 9.8 mmol) in THF (45 mL) is added dropwise to $LiAlH_4$ (1 M in THF, 24.4 mL) in THF (45 mL). The reaction mixture is stirred for 1 h at rt and 10 h at reflux. Excess $LiAlH_4$ is destroyed under cooling as described by L.F.Fieser & M. Fieser Vol 1, p 584 Wiley 1967. After 30 min the mixture is filtered and the filtrate is concentrated to give the sub-title compound.
Yield: 1.85 g (99%). R_f = 0.12 (silica gel, DCM:EtOH 95:5). MS m/z: 191 $[M+H]^+$.

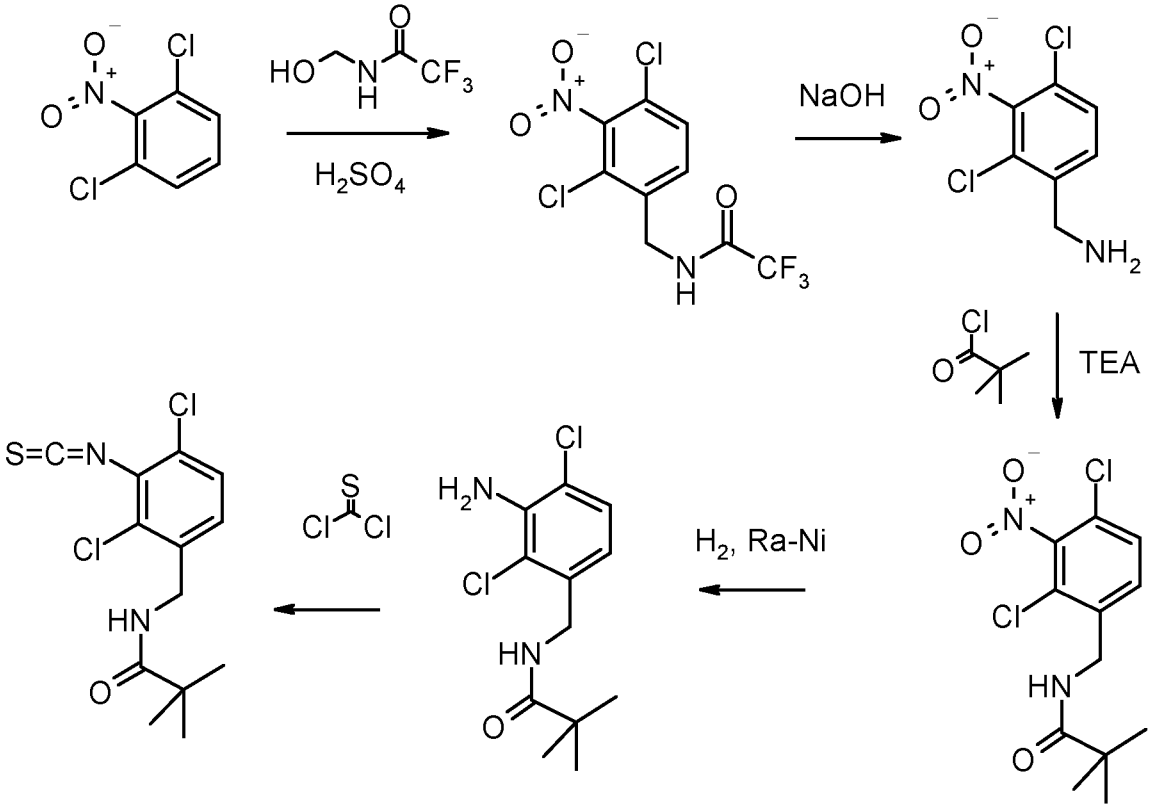
(e) *N*-(3-Amino-2,4-dichloro-benzyl)- 2,2-dimethyl-propionamide

3-Amino-2,4-dichloro-benzylamine (2.28 g, 11.9 mmol) is added to a mixture of 2,2-dimethyl-propionic acid chloride (1.47 mL, 11.9 mmol) and TEA (4.14 mL, 29.8 mmol) in THF (90 mL) and it is stirred for 3 h. The reaction mixture is concentrated, diluted with EtOAc, washed with 5% aq. $NaHCO_3$ solution and water, dried with Na_2SO_4 filtered and concentrated to give the sub-title compound.
Yield: 3.1 g (94%). R_f = 0.61 (silica gel, DCM:EtOH 95:5).

(f) *N*-(2,4-Dichloro-3-isothiocyanato-benzyl)- 2,2-dimethyl-propionamide

1,1'-Thiocarbonyldi-2-pyridone (4.87 g, 21 mmol) is added to a mixture of *N*-(3-amino-2,4-dichloro-benzyl)- 2,2-dimethyl-propionamide (5.50 g, 20 mmol) and dioxane (200 mL) and stirred at rt for 2 h and at reflux for 8 h. The mixture is concentrated, diluted with DCM and filtered over silica gel. The filtrate is concentrated to give the sub-title compound.
Yield: 6.00 g (95%). HPLC-method B: R_t= 1.58 min. MS m/z: 318 $[M+H]^+$.

Alternatively, building block A can also be prepared acording to the following scheme:



(g) *N*-(3-Nitro-2,4-dichloro-benzyl)- 2,2,2-trifluoroacetamide

N-(Hydroxymethyl)trifluoroacetamide (6.6 mmol; 0.946 g) is added to a mixture of 2,6-dichloro-nitrobenzene (0.899 mL; 6.6 mmol) and conc. H_2SO_4 (15 mL) at 75°C. The mixture is stirred at 75°C overnight, poured into ice water and stirred for 1 h. The precipitate is collected by filtration and dried. Yield 0.32 g (15%). MS $[M-H]^-$ = 315, HPLC-method B: R_t = 1.43 min.

(h) 3-Nitro-2,4-dichloro-benzylamine

A mixture of *N*-(3-nitro-2,4-dichloro-benzyl)- 2,2,2-trifluoroacetamide (0.66 g, impure, content ~50%), 4M NaOH-solution (1.3 mL, 5.2 mmol) and MeOH (15 mL) is refluxed for 4 h. Then the mixture is concentrated, diluted with water, acidified with 4M HCl, filtered, 4M NaOH-solution is added and it is extracted with EtOAc. The organic phase is dried with Na_2SO_4, filtered and concentrated. Yield 0.17 g

MS m/z: 221 $[M+H]^+$. HPLC-method B: R_t = 1.02 min.

(i) *N*-(3-Nitro-2,4-dichloro-benzyl)- 2,2-dimethyl-propionamide

2,2-Dimethyl-propionic acid chloride (0.124 mL, 1.01 mmol) is added to a mixture of 3-nitro-2,4-dichloro-benzylamine (0.28 g, 1.01 mmol) and TEA (0.35 mL, 2.52 mmol) in THF (10 mL) and it is stirred overnight. The reaction mixture is concentrated, diluted with EtOAc, washed

successively with 5% aq. $NaHCO_3$ solution and brine, dried with Na_2SO_4 filtered and concentrated.

Yield: 0.29 g. MS m/z: 306 $[M+H]^+$. HPLC-method B: R_t = 1.42 min.

(g) *N*-(3-Amino-2,4-dichloro-benzyl)- 2,2-dimethyl-propionamide

A mixture of 3-nitro-2,4-dichloro-benzylamine (290 mg, 0.95 mmol), Ra-Ni (50 mg) and THF (15 mL) is stirred for 7 h under a hydrogen atmosphere (50 psi). The catalyst is removed by filtration and the filtrate is concentrated.

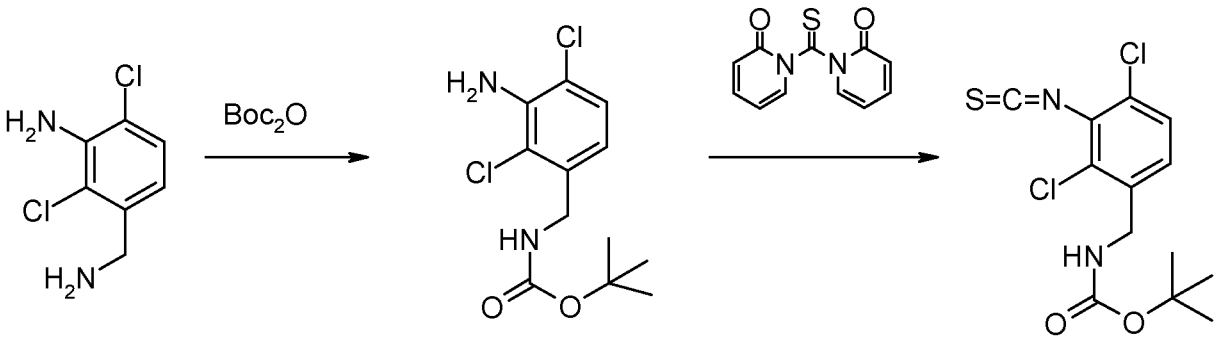
Yield: 0.26 g. MS m/z: 276 $[M+H]^+$. HPLC-method B: R_t= 1.32 min.

(h) *N*-(2,4-Dichloro-3-isothiocyanato-benzyl)- 2,2-dimethyl-propionamide

A mixture of *N*-(3-amino-2,4-dichloro-benzyl)- 2,2-dimethyl-propionamide (0.95 g, 3.4 mmol) in 4.0 mL dioxane is added to thiophosgene (0.45 mL, 5.8 mmol) in 2.5 mL water. The mixture is stirred overnight, extracted with DCM and the organic phase is washed with 5% aq NaHCO3 solution and water and dried with Na_2SO_4. After fltration and concentration, the crude product is diluted with DCM, filtered through a pad of silica gel and concentrated.

Building block B:

(2,4-Dichloro-3-isothiocyanato-benzyl)-carbamic acid tert-butyl ester



(a) (3-Amino-2,4-dichloro-benzyl)-carbamic acid tert-butyl ester

Boc_2O (1.48 g, 6.68 mmol) in 3.3 mL DCM is added at 0°C to a mixture of 3-amino-2,4-dichloro-benzylamine (1.16 g, 6.07 mmol), 6.7 mL DCM and 12.1 mL 1 N NaOH-solution. The mixture is stirred vigourously for 2d and diluted with 5% aq NH_3-solution. The organic phase is separated and the aq. phase is washed 2 x with DCM. The combined organic phase is washed with brine, dried with Na_2SO_4, filtered and concentrated to give the sub-title compound.

Yield: 1.71 g (97%). R_f = 0.65 (silica gel, DCM:EtOH 95:5). MS m/z: 291 $[M+H]^+$.

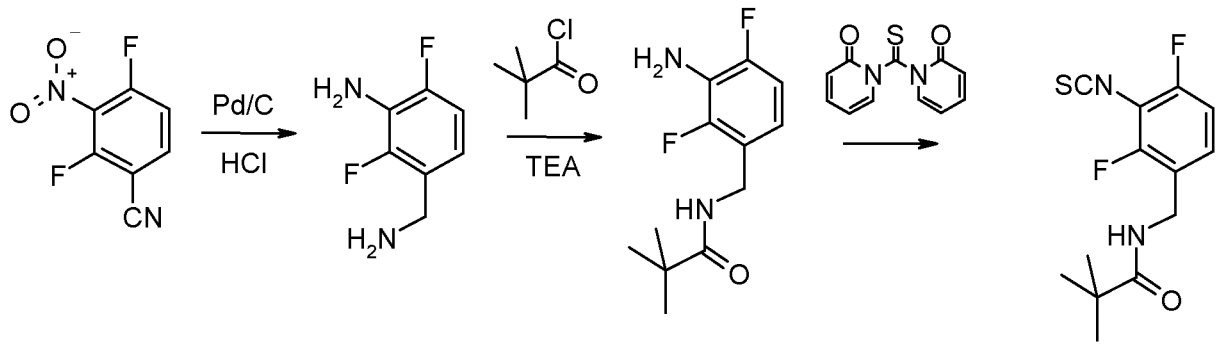
(b) (2,4-Dichloro-3-isothiocyanato-benzyl)-carbamic acid tert-butyl ester

1,1'-Thiocarbonyldi-2-pyridone (0.42 g, 1.8 mmol) is added to a mixture of (3-amino-2,4-dichloro-benzyl)-carbamic acid tert-butyl ester (0.50 g, 1.7 mmol) and dioxane (25 mL) and stirred at rt for 2 h and at reflux for 2 d. The mixture is concentrated, diluted with DCM and filtered over silica gel. The filtrate is concentrated to give the title compound.

Yield: 0.49 g (86%). R_f = 0.83 (silica gel, DCM:EtOH 95:5).

Building block C:

N-(2,4-Difluoro-3-isothiocyanato-benzyl)-2,2-dimethyl-propionamide



(a) 3-Aminomethyl-2,6-difluoro-aniline

A mixture of 3-nitro-2,4-difluoro-benzonitrile (500 mg, 2.72 mmol), Pd/C (200 mg), conc. HCl (1.50 mL, 18.0 mmol) and MeOH (25 mL) is stirred at rt overnight under a hydrogen atmosphere (3.2 bar). The catalyst is removed by filtration, the filtrate is concentrated and evaporated twice from EtOH to give the sub-title compound as HCl salt.

Yield: 580 mg. MS m/z: 159 $[M+H]^+$.

(b) *N*-(3-Amino-2,4-difluoro-benzyl)-2,2-dimethyl-propionamide

TEA (400 µL, 2.86 mmol) followed by pivaloyl chloride (60 µL, 0.52 mmol) are added to 3-aminomethyl-2,6-difluoro-aniline (120 mg as HCl salt) in THF (10 mL) and stirred at rt overnight. The reaction mixture is diluted with EtOAc and sat. $NaHCO_3$-solution, the organic layer is washed with water and brine, dried and concentrated to give the sub-title compound.

Yield: 110 mg. HPLC-method B: R_t= 1.19 min. MS m/z: 243 $[M+H]^+$. R_f = 0.45 (silica gel, DCM:EtOH 95:5).

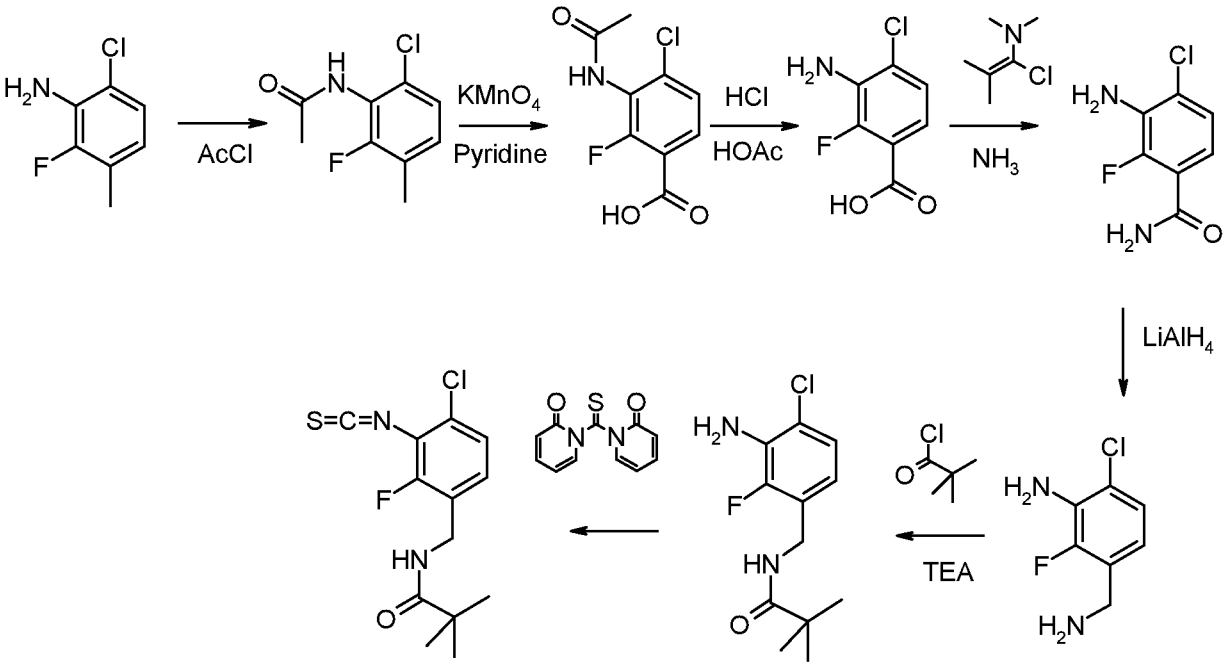
(c) *N*-(2,4-Difluoro-3-isothiocyanato-benzyl)-2,2-dimethyl-propionamide

A mixture of *N*-(3-amino-2,4-difluoro-benzyl)-2,2-dimethyl-propionamide (570 mg, 2.35 mmol), 1,1'-thiocarbonyldi-2(1H)-pyridone (550 mg, 2.35 mmol) and dioxane (20 mL) is stirred at reflux overnight. The reaction mixture is concentrated, diluted with DCM, filtered through a pad of silica gel and the filtrate is concentrated to give the title compound.

Yield: 440 mg (65%). R_f = 0.80 (silica gel, DCM:EtOH 95:5).

Building block D:

N-(4-Chloro-fluoro-3-isothiocyanato-benzyl)- 2,2-dimethyl-propionamide



(a) *N*-(6-Chloro-2-fluoro-3-methyl-phenyl)-acetamide

Acetylchloride (2.56 mL, 36.0 mmol) is added to a mixture of 6-chloro-2-fluoro-3-methyl-aniline (5.00 g, 31.3 mmol) and toluene (200 mL), additional toluene (50 mL) is added and the mixture is heated to reflux for 3 h. Then it is cooled with an ice bath and the formed precipitate is filtered off, washed with cold toluene and dried.

Yield: 4.75 g (75%). HPLC-method B: R_t= 1.12 min. MS m/z: 202 $[M+H]^+$.

(b) 3-Acetylamino-4-chloro-2-fluoro-benzoic acid

The sub-title compound is prepared from *N*-(6-chloro-2-fluoro-3-methyl-phenyl)-acetamide and $KMnO_4$ in pyridine in analogy to step Aa.

Yield: 49%. R_f = 0.2 (silica gel, DCM/EtOH 4:1). HPLC R_t = 0.93 min (method B). MS m/z: 232 $[M+H]^+$.

(c) 3-Amino-4-chloro-2-fluoro-benzoic acid

The sub-title compound is prepared from 3-acetylamino-4-chloro-2-fluoro-benzoic acid and 6 M HCl-solution in analogy to step Ab.

Yield: 96%. HPLC R_t = 1.10 min (method B). MS m/z: 190 $[M+H]^+$.

(d) 3-Amino-4-chloro-2-fluoro-benzamide

The sub-title compound is prepared from 3-amino-4-chloro-2-fluoro-benzoic acid, (1-chloro-2-methyl-propenyl)-dimethyl-amine and conc. NH_3 in analogy to step Ac.

Yield: 69%. R_f = 0.3 (silica gel, PE:EtOAc 4:6). HPLC-method B: R_t= 0.97 min. MS m/z: 189 $[M+H]^+$.

(e) 3-Amino-4-chloro-2-fluoro-benzylamine

The crude sub-title compound is prepared from 3-amino-4-chloro-2-fluoro-benzamide and $LiAlH_4$ in analogy to step Ad.

HPLC-method B: R_t= 0.37 min. MS m/z: 175 $[M+H]^+$.

(f) *N*-(3-Amino-4-chloro-2-fluoro-benzyl)- 2,2-dimethyl-propionamide

The sub-title compound is prepared from crude 3-amino-4-chloro-2-fluoro-benzylamine, 2,2-dimethyl-propionic acid chloride and TEA in analogy to example Ae.

Yield: 36% (side product in 29%: *N*-(3-Amino-4-chloro-benzyl)- 2,2-dimethyl-propionamide). Rf = 0.6 (silica gel, PE:EtOAc 6:4). HPLC-method B: R_t= 1.27 min. MS m/z: 259 $[M+H]^+$.

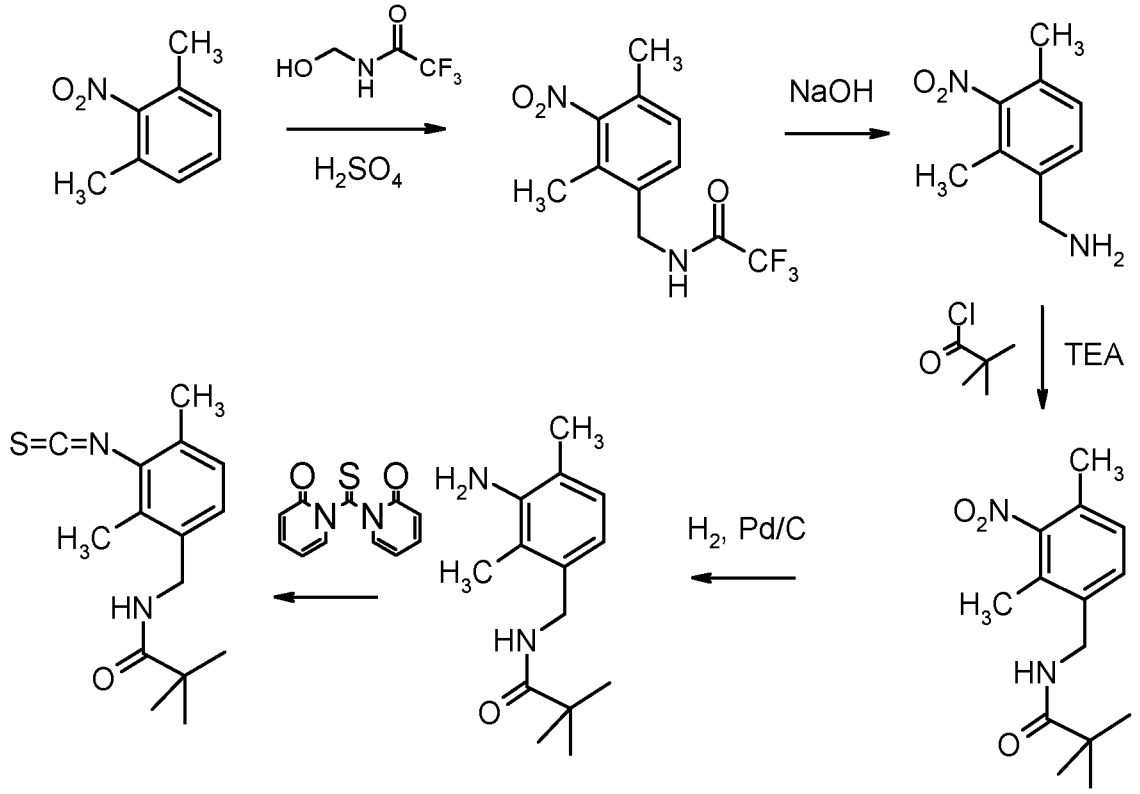
(g) *N*-(4-Chloro-2-fluoro-3-isothiocyanato-benzyl)- 2,2-dimethyl-propionamide

The title compound is prepared from *N*-(3-amino-4-chloro-2-fluoro-benzyl)- 2,2-dimethyl-propionamide, 1,1'-thiocarbonyldi-2-pyridone in analogy to step Af.

Yield: 65%. R_f = 0.9 (silica gel, DCM:EtOH 95:5).

Building block E:

N-(2,4-Dimethyl-3-isothiocyanato-benzyl)- 2,2-dimethyl-propionamide



(a) *N*-(3-Nitro-2,4-dimethyl-benzyl)- 2,2,2-trifluoroacetamide

N-(Hydroxymethyl)trifluoroacetamide (6.6 mmol; 0.946 g) is added to a mixture of 2,6-dimethyl-nitrobenzene (0.899 mL; 6.6 mmol) and conc. H_2SO_4 (15 mL). The mixture is stirred at rt overnight, poured into ice water and stirred for 2 h. The precipitate is collected by filtration and dried. Yield 1.5 g (84%). MS $[M-H]^-$ = 275, TLC: R_f = 0.67 (silica gel, DCM:EtOH 95:5)).

(b) 3-Nitro-2,4-dimethyl-benzylamine

A mixture of *N*-(3-nitro-2,4-dimethyl-benzyl)- 2,2,2-trifluoroacetamide (1.53 g, 5.54 mmol), 4M NaOH-solution (6.9 mL, 28 mmol) and MeOH (30 mL) is refluxed for 2 h. Then the mixture is concentrated, diluted with water and extracted with EtOAc. The organic phase is dried with Na_2SO_4, filtered and concentrated.

MS m/z: 181 $[M+H]^+$. HPLC-method C: R_t = 1.13 min.

(c) *N*-(3-Nitro-2,4-dimethyl-benzyl)- 2,2-dimethyl-propionamide

3-Nitro-2,4-dimethyl-benzylamine (1.40 g, crude) is added to a mixture of 2,2-dimethyl-propionic acid chloride (0.682 mL, 5.5 mmol) and TEA (1.92 mL, 13.8 mmol) in THF (30 mL) and it is stirred overnight. The reaction mixture is concentrated, diluted with EtOAc, washed

sucessively with 2 M aq. HCl-solution, 5% aq. $NaHCO_3$ solution and water, dried with Na_2SO_4 filtered and concentrated.

Yield: 1.41 g. MS m/z: 265 $[M+H]^+$. HPLC-method B: R_t = 1.37 min.

(d) *N*-(3-Amino-2,4-dimethyl-benzyl)- 2,2-dimethyl-propionamide

A mixture of *N*-(3-nitro-2,4-dimethyl-benzyl)- 2,2-dimethyl-propionamide (500 mg, 1.89 mmol), Pd/C (50 mg) and MeOH (20 mL) is stirred for 9 h under a hydrogen atmosphere (50 psi). The catalyst is removed by filtration and the filtrate is concentrated.

Yield: 0.42 g. MS m/z: 235 $[M+H]^+$. HPLC-method B: R_t= 1.32 min.

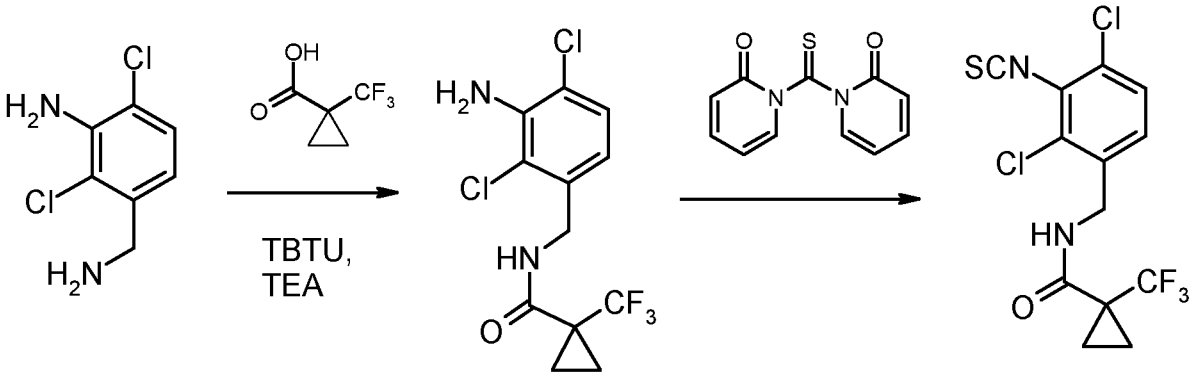
(e) *N*-(2,4-Dimethyl-3-isothiocyanato-benzyl)- 2,2-dimethyl-propionamide

The title compound is prepared from *N*-(3-amino-2,4-dimethyl-benzyl)- 2,2-dimethyl-propionamide, 1,1'-thiocarbonyldi-2-pyridone in analogy to step Af.

Yield: 65%. R_f = 0.81 (silica gel, DCM:EtOH 95:5).

Building block F:

N-(2,4-Dichloro-3-isothiocyanato-benzyl)-1-trifluoromethyl-cyclopropane carboxamide



(a) N-(2,4-Dichloro-3-amino-benzyl)-1-trifluoromethyl-cyclopropane carboxamide

The sub-title compound is prepared from 3-amino-2,4-dichloro-benzylamine (0.310 g, 1.01 mmol), 1-trifluoromethyl-cyclopropane carboxylic acid (0.17 g, 1.1 mmol), TBTU (0.39 g, 1.2 mmol) and TEA (0.71 mL) in DMF in analogy to step 1d.

Yield: 289 mg (83%). MS m/z: 327 $[M+H]^+$.

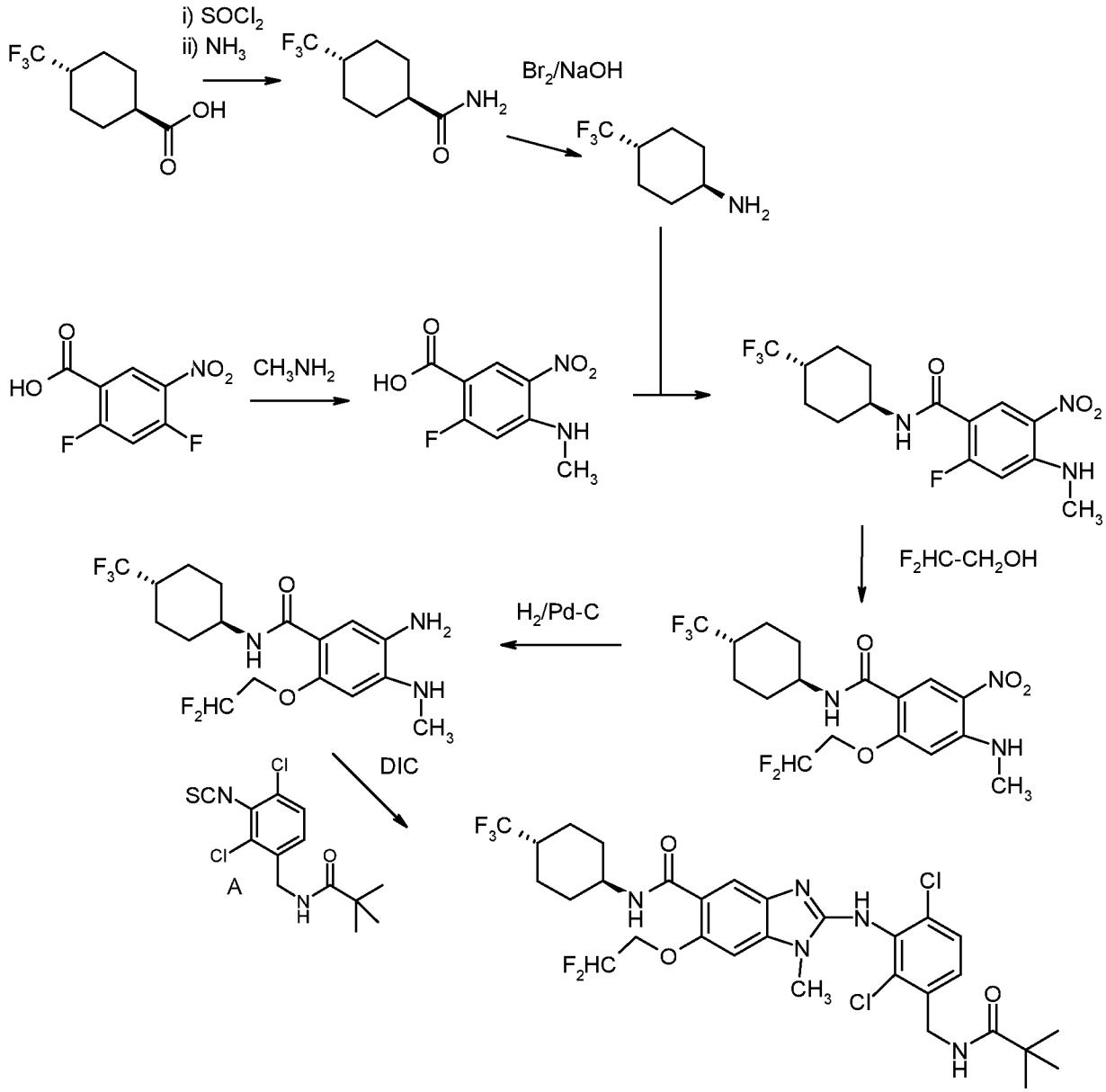
(b) N-(2,4-Dichloro-3-isothiocyanato-benzyl)-1-trifluoromethyl-cyclopropane carboxamide

The title compound is prepared from N-(2,4-dichloro-3-amino-benzyl)-1-trifluoromethyl-cyclopropane carboxamide (150 mg, 0.45 mmol) and 1,1'-thiocarbonyldi-2-pyridone (89 mg, 0.38 mmol) in analogy to step Af.

Yield: 92 mg (crude).

Example 1

N-(*trans*-4-Trifluoromethyl-cyclohex-1-yl)- 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-(2,2-difluoro-ethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid amide



(a) trans-4-Trifluormethyl-cyclohexyl-carboxylic acid amide

A mixture of trans-4-trifluoromethyl-cyclohexane-carboxylic acid (10.4 g, 53.1 mmol), $SOCl_2$ (10 mL, 137 mmol), DCM (100 mL) and DMF (200 µl) is heated to reflux for 1.5 h and concentrated. The crude acid chloride is diluted with 100 mL THF and conc. NH_3 (350 mL) is slowly added. It is stirred for 5 min and the mixture is concentrated and dried at 40°.

Yield: 9.7 g.

(b) trans-4-Trifluormethyl-cyclohexyl-amine

Bromine (2.85 mL, 55 mmol) is stirred for 10 min in 1N aq. NaOH-solution (200 mL), then trans-4-trifluormethyl-cyclohexyl-carboxylic acid amide is added and it is stirred for 45 min at rt and for 3 h at reflux. After cooling to rt the mixture is extracted with Et_2O, the organic phase is dried with $MgSO_4$, filtered, treated with 2N HCl in Et_2O and concentrated to give the sub-title compound as HCl-salt.

Yield: 8.5 g MS *m/z*: 168 [M+H]+.

(c) 2-Fluoro-4-methylamino-5-nitro-benzoic acid

Methylamine (13.5 mL, 40% in water) is added to an ice-cooled mixture of 2,4-difluoro-5-nitro-benzoic acid (10.0 g, 49 mmol) in water (100 mL) and it is stirred for 30 min at rt. The mixture is acidified with 6N aq. HCl-solution and the precipitate is fitered, washed with water and dried at 60°C. The crude material was recrystallized from MeOH. The final product was slightly contaminated by its regioisomer 4-fluoro-2-methylamino-5-nitro-benzoic acid.

(d) *N*-(*trans*-4-Trifluoromethyl-cyclohex-1-yl)-2-fluoro-4-methylamino-5-nitro-benzoic acid amide

A mixture of crude 2-fluoro-4-methylamino-5-nitro-benzoic acid (4.88 g containing traces of regioisomer), DIPEA (11.7 mL, 68.3 mmol), TBTU (8.05 g, 25.1 mmol) and THF (100 mL) is stirred for 15 min, then trans-4-trifluormethyl-cyclohexyl-amine (4.64 g, HCl salt) is added and it is stirred overnight. The mixture is concentrated, aq $NaHCO_3$ is added and the resulting precipitate is filtered, washed and dried.

Yield: 8.14 g. R_f = 0.3 (silica gel, DCM:EtOH 98:2). HPLC R_t = 1.44 min (method B). MS m/z: 364 $[M+H]^+$.

(e) *N*-(*trans*-4-Trifluoromethyl-cyclohex-1-yl)-2-(2,2-difluoro-ethoxy)-4-methylamino-5-nitro-benzoic acid amide

A mixture of 2,2-difluoroethanol (2.12 mL, 33,6 mmol), KOtBu (3.84 g, 32.4 mmol) and THF (100 mL) is stirred for 15 min, then *N*-(*trans*-4-trifluoromethyl-cyclohex-1-yl)-2-fluoro-4-methylamino-5-nitro-benzoic acid amide (8.14 g, 22.4 mmol) is added and it is stirred for 1.5 h. Water is added to the mixture and THF is destilled off. The resulting precipitate is filtered, washed with water and dried.

Yield: 8.60 g. R_f = 0.35 (silica gel, PE:Et_2O 1:1). HPLC R_t = 1.47 min (method B). MS m/z: 426 $[M+H]^+$.

(f) *N*-(*trans*-4-Trifluoromethyl-cyclohex-1-yl)-2-(2,2-difluoro-ethoxy)-4-methylamino-5-amino-benzoic acid amide

A mixture of *N*-(*trans*-4-trifluoromethyl-cyclohex-1-yl)-2-(2,2-difluoro-ethoxy)-4-methylamino-5-nitro-benzoic acid amide (6.38 g, 15.0 mmol), Pd/C (0.50 g) and MeOH (100 mL) is stirred under 50 psi H_2-atmosphere for 4 h. The mixture is filtered, the catalyst is washed with THF and the combined filtrate is concentrated. The crude mixture is purified by flash chromatography (silica gel; DCM/EtOH 97/3).

Yield: 5.38 g (91%). R_f = 0.3 (DCM/EtOH 95:5). HPLC R_t = 1.25 min (method B). MS m/z: 396 $[M+H]^+$.

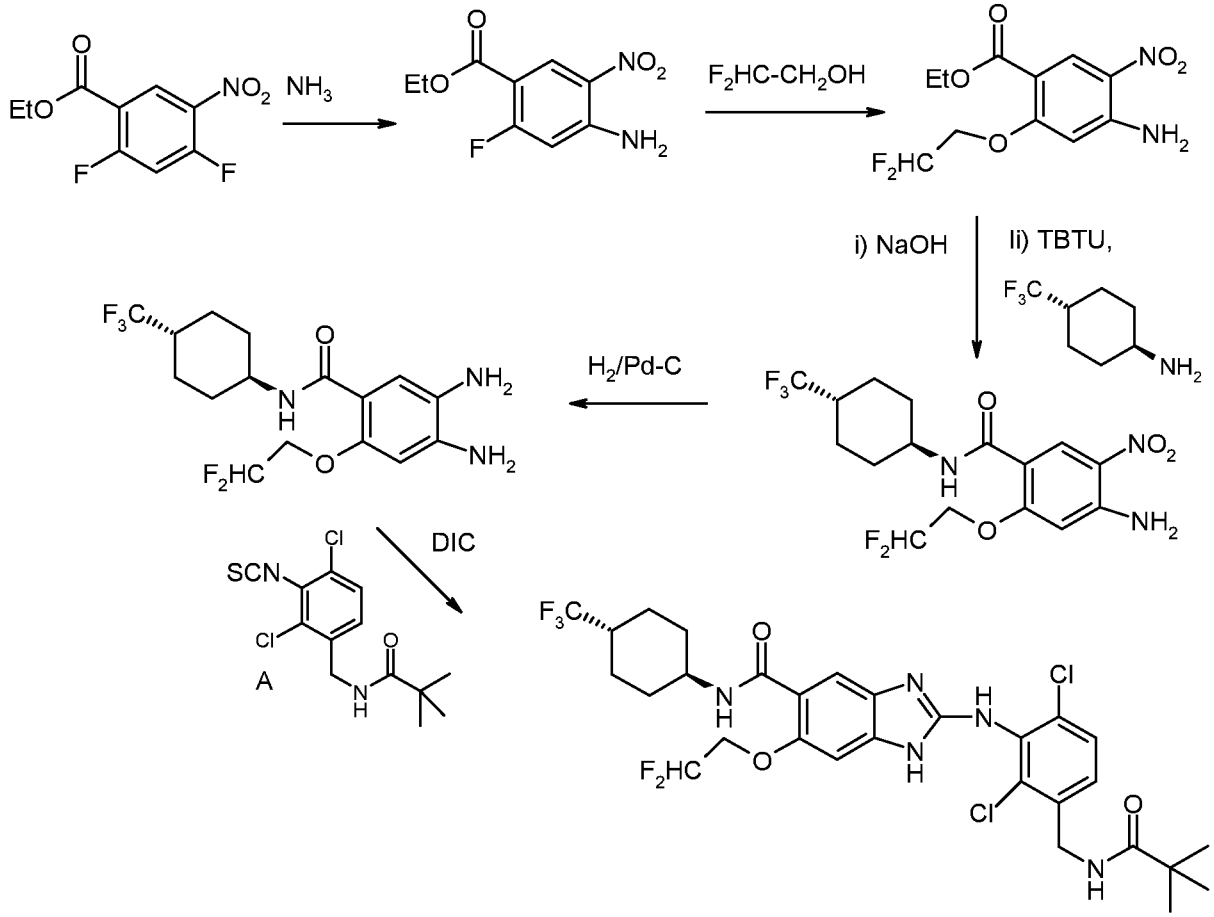
(g) *N*-(*trans*-4-Trifluoromethyl-cyclohex-1-yl)-2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-(2,2-difluoro-ethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid amide

A mixture of *N*-(*trans*-4-trifluoromethyl-cyclohex-1-yl)-2-(2,2-difluoro-ethoxy)-4-methylamino-5-amino-benzoic acid amide (200 mg, 0.506 mmol), *N*-(2,4-dichloro-3-isothiocyanato-benzyl)-2,2-dimethyl-propionamide (160 mg, 0.505 mmol) and DMF (2.0 mL) is stirred for 3h, then DIC (102 µl, 0,658 mmol) is added and it is stirred at 80°C for 2 h. The crude mixture is concentrated and purified by flash chromatography (silica gel; DCM/EtOH 98:2 -> 97:3.

Yield: 0.320 g (93%). Rf = 0.35 (DCM/EtOH 95:5). HPLC R_t = 1.42 min (method B). MS m/z: 678 $[M+H]^+$.

Example 2

N-(*trans*-4-Trifluoromethyl-cyclohex-1-yl)- 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-(2,2-difluoro-ethoxy)-1H-benzimidazole-5-carboxylic acid amide



(a) Ethyl 2-fluoro-4-amino-5-nitro-benzoate

A mixture of ethyl 2,4-difluoro-5-nitro-benzoate (5.0 g, 21 mmol), 5.2 mL conc. NH_3 and THF (25 mL) is stirred for 30 min in an ice bath and overnight at rt. The mixture is concentrated and diluted with water. The precipitate is filtered, washed with water and dried at 55°C to furnish the crude sub-title compound.

Yield: 4.58 g. R_f = 0.57 (silica gel, PE/EtOAc 3:2). MS m/z: 227 $[M-H]^-$.

(b) Ethyl 2-(2,2-difluoro-ethoxy)-4-amino-5-nitro-benzoate

A mixture of 2,2-difluoroethanol (0.062 mL, 0.97 mmol), KOtBu (0.108 g, 0.964 mmol) and THF (5 mL) is stirred for 15 min, then ethyl 2-fluoro-4-amino-5-nitro-benzoate (0.200 g) is added and it is stirred for 15 h. Water is added to the mixture and it is extracted with EtOAc. The organic phase is washed with water and brine, dried with Na_2SO_4 and concentrated.

Yield: 0.24 g. R_f = 0.7 (silica gel, DCM/EtOH 95:5). HPLC R_t = 1.34 min (method B). MS m/z: 291 $[M+H]^+$.

(c) 2-(2,2-Difluoro-ethoxy)-4-amino-5-nitro-benzoic acid

A mixture of ethyl 2-(2,2-difluoro-ethoxy)-4-amino-5-nitro-benzoate (0.24 g, 0.827 mmol), 4 N aq.NaOH-solution (0.845 mL) and MeOH (10 mL) is stirred for 1.5 h at 70°C, The mixture is concentrated and the residue is diluted with water and acidified with 4N aq. HCl-solution. The precipitate is filtered off, washed with water and dried at 50°C.

Yield: 0.17 g (78%). R_f = 0.4 (silica gel, DCM/EtOH 9:1). HPLC R_t = 1.14 min (method B). MS m/z: 263 $[M+H]^+$.

(d) *N*-(*trans*-4-Trifluoromethyl-cyclohex-1-yl)-2-(2,2-difluoro-ethoxy)-4-amino-5-nitro-benzoic acid amide

The subtitle compound is prepared from 2-(2,2-difluoro-ethoxy)-4-amino-5-nitro-benzoic acid and trans-4-trifluoromethyl-cyclohexyl-amine with TBTU and DIPEA in analogy to example 1d.

Yield: 100%. R_f = 0.7 (silica gel, DCM:EtOH 9:1). HPLC R_t = 1.43 min (method B). MS m/z: 412 $[M+H]^+$.

(e) *N*-(*trans*-4-Trifluoromethyl-cyclohex-1-yl)-2-(2,2-difluoro-ethoxy)-4,5-diamino-benzoic acid amide

The subtitle compound is prepared from *N*-(*trans*-4-trifluoromethyl-cyclohex-1-yl)-2-(2,2-difluoro-ethoxy)-4-amino-5-nitro-benzoic acid amide with Pd/C and H_2 in analogy to example 1f.

Yield: quantitative. R_f = 0.4 (DCM/EtOH 9:1). HPLC R_t = 1.19 min (method B). MS m/z: 382 $[M+H]^+$.

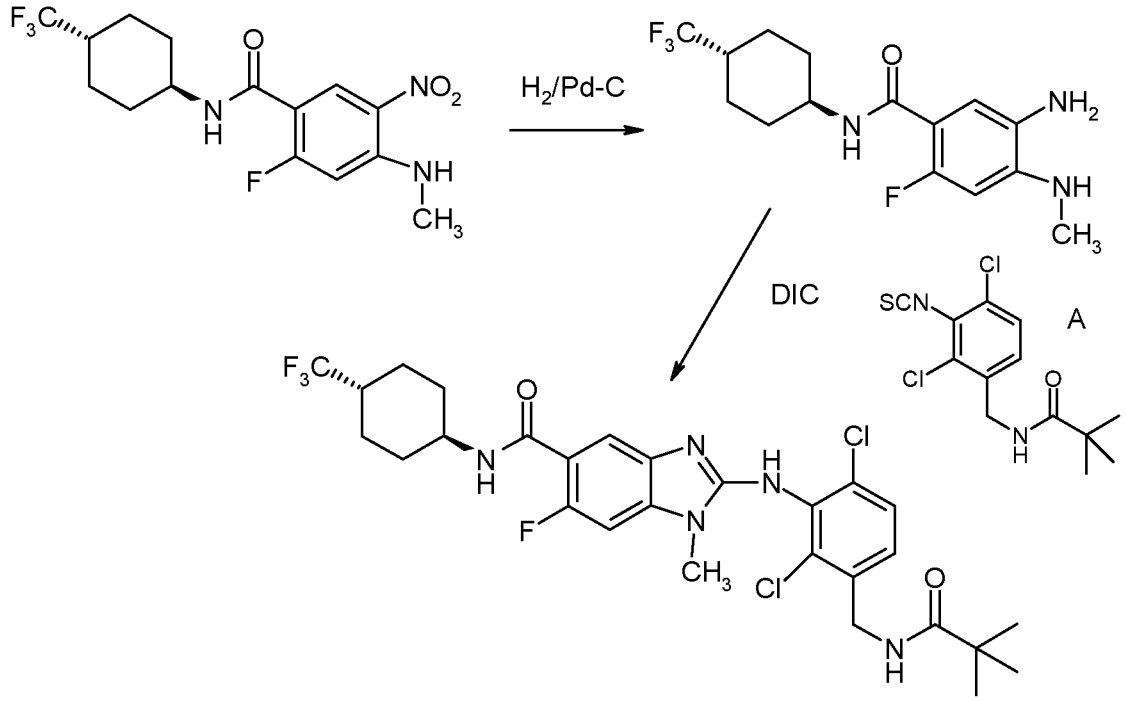
(f) *N*-(*trans*-4-Trifluoromethyl-cyclohex-1-yl)- 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-(2,2-difluoro-ethoxy)-1H-benzimidazole-5-carboxylic acid amide

The title compound is prepared from *N*-(*trans*-4-trifluoromethyl-cyclohex-1-yl)-2-(2,2-difluoro-ethoxy)-4,5-diamino-benzoic acid amide and *N*-(2,4-dichloro-3-isothiocyanato-benzyl)- 2,2-dimethyl-propionamide with DIC in analogy to example 1g.

Yield: 43%. R_f = 0.2 (DCM/EtOH 95:5). HPLC R_t = 1.34 min (method B). MS m/z: 664 $[M+H]^+$

Example 3

N-(*trans*-4-Trifluoromethyl-cyclohex-1-yl)- 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-fluoro-1-methyl-1H-benzimidazole-5-carboxylic acid amide



(a) *N*-(*trans*-4-Trifluoromethyl-cyclohex-1-yl)-2-fluoro-4-methylamino-5-amino-benzoic acid amide

The subtitle compound is prepared from *N*-(*trans*-4-trifluoromethyl-cyclohex-1-yl)-2-fluoro-4-methylamino-5-nitro-benzoic acid amide with Pd/C and H_2 in analogy to example 1f.

Yield: 98%. R_f = 0.25 (DCM/EtOH 95:5). HPLC R_t = 1.32 min (method B). MS m/z: 334 $[M+H]^+$.

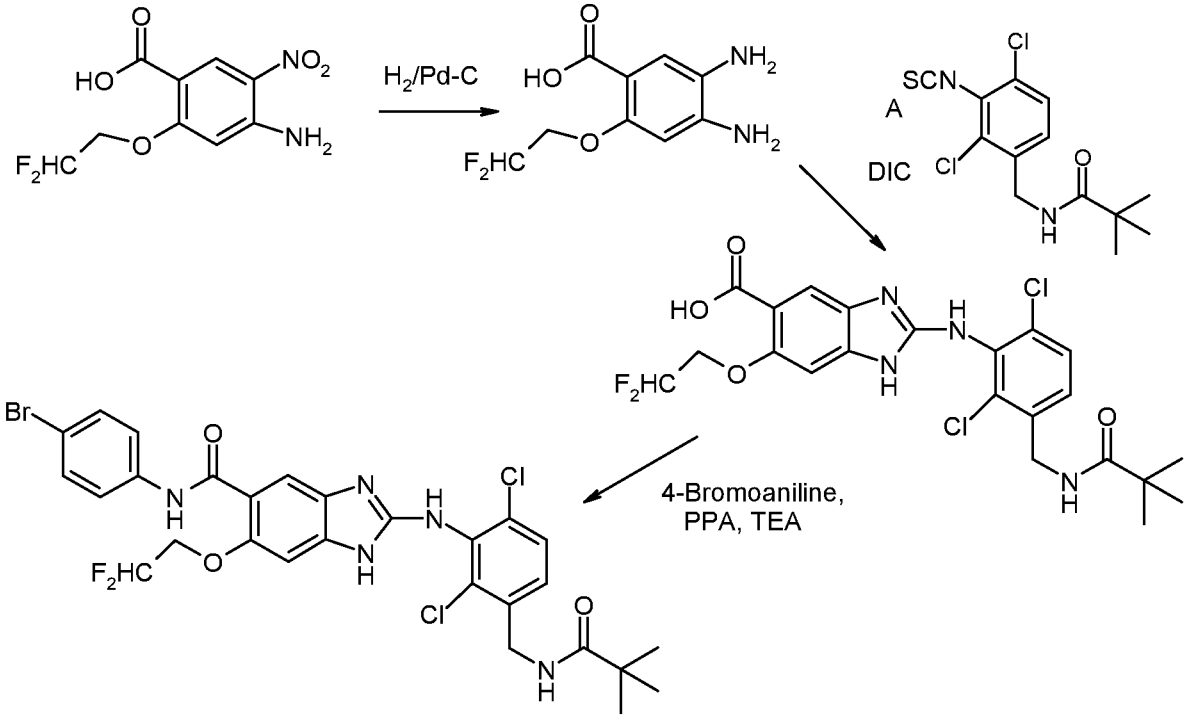
(b) *N*-(*trans*-4-Trifluoromethyl-cyclohex-1-yl)-2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-fluoro-1-methyl-1H-benzimidazole-5-carboxylic acid amide

The title compound is prepared from *N*-(*trans*-4-trifluoromethyl-cyclohex-1-yl)-2-fluoro-4-methylamino-5-amino-benzoic acid amide and *N*-(2,4-dichloro-3-isothiocyanato-benzyl)- 2,2-dimethyl-propionamide with DIC in analogy to example 1g.

Yield: 60%. R_f = 0.4 (DCM/EtOH 95:5). HPLC R_t = 1.36 min (method B). MS m/z: 616 $[M+H]^+$

Example 4

N-(4-Bromo-phenyl)- 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-(2,2-difluoro-ethoxy)-1H-benzimidazole-5-carboxylic acid amide



(a) 2-(2,2-Difluoro-ethoxy)-4,5-diamino-benzoic acid

The subtitle compound is prepared from 2-(2,2-difluoro-ethoxy)-4-amino-5-nitro-benzoic acid (example 2c) with Pd/C and H_2 in analogy to example 1f.

Yield: 99%. R_f = 0.3 (DCM/EtOH 9:1).

(b) 2-{2,6-Dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-(2,2-difluoro-ethoxy)-1H-benzimidazole-5-carboxylic acid

A mixture of 2-(2,2-difluoro-ethoxy)-4,5-diamino-benzoic acid (732 mg, 3.15 mmol), *N*-(2,4-dichloro-3-isothiocyanato-benzyl)- 2,2-dimethyl-propionamide (1.00 g, 3.15 mmol) and MeCN (15 mL) is stirred for 48h, then BSTFA (1.03 mL, 3.15 mmol) is added and it is stirred at reflux for 10 min. Then DIC (0.494 mL, 3.15 mmol) is added and it is stirred for another 4 h. The mixture is cooled to rt, diluted with HOAc and concentrated. The residue is stirred with 1N NaOH, filtered and the filtrate is acidified with 4N HCl, extracted with EtOAc and purified via chromatography [DCM -> DCM + 10% EtOH/HOAc (95:5)] to give the subtitle compound.

Yield: 0.720 g (44%). R_f = 0.13 (DCM/EtOH 95:5 + few drops HOAc). MS m/z: 515 $[M+H]^+$.

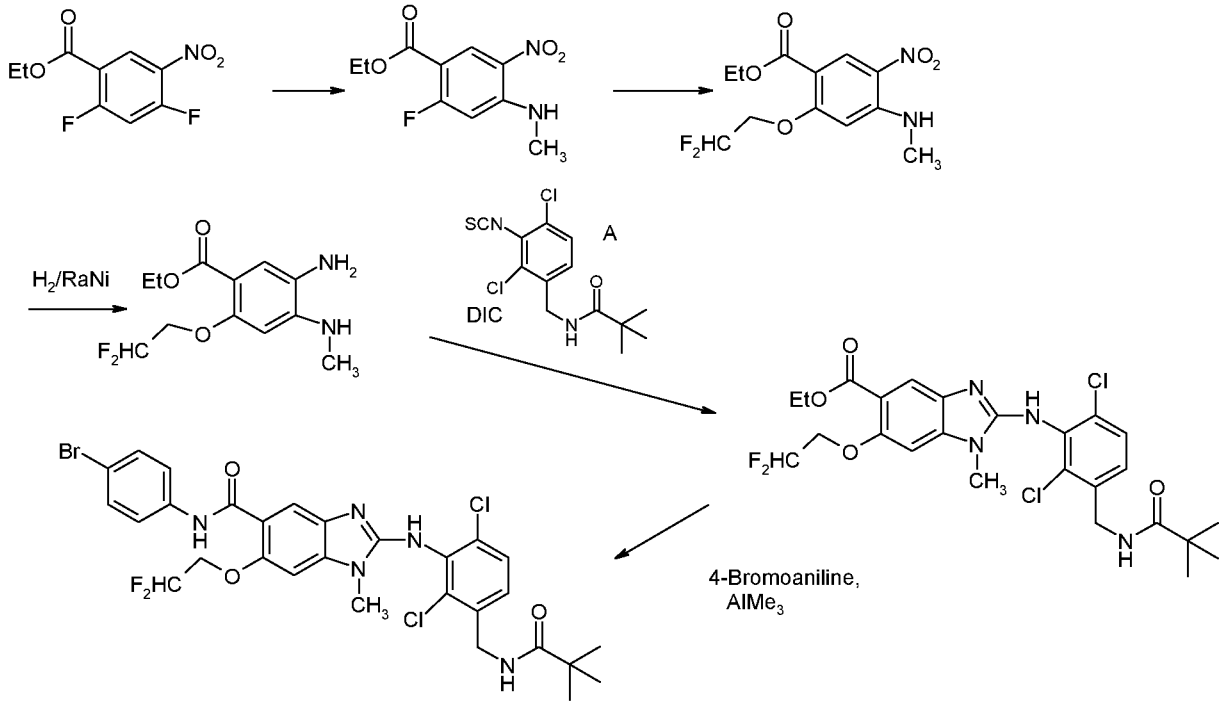
(c) *N*-(4-Bromo-phenyl)- 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-(2,2-difluoro-ethoxy)-1H-benzimidazole-5-carboxylic acid amide

PPA (0.223 mL, 50% in EtOAc, ~0.38 mmol) is slowly added to a mixture of 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-(2,2-difluoro-ethoxy)-1H-benzimidazole-5-carboxylic acid (0.150 g, 0.291 mmol), 4-bromoaniline (50 mg, 0.291 mmol), TEA (0.101 mL, 0.728 mmol) and THF (10 mL). The mixture is refluxed for 3 d, concentrated and purified via prep. HPLC (column: Zorbax stable bond C18, 5 µm, 30x100mm, gradient: water +0.15% HCOOH/MeOH 95:5 ->10:90) to furnish the title compound.

Yield: 0.043 g (22%). HPLC R_t = 1.67 min (method B). MS m/z: 668 $[M+H]^+$.

Example 5

N-(4-Bromo-phenyl)- 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-(2,2-difluoro-ethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid amide



(a) Ethyl 2-fluoro-4-(methylamino)-5-nitrobenzoate

A 2M solution of $MeNH_2$ in THF (21.6 mL; 43.3 mmol) is added dropwise to a solution of ethyl 2,4-difluoro-5-nitrobenzoate (5.0 g; 21.6 mmol) in THF (70 mL) at -5 °C. The mixture is left overnight at rt whereafter an additional portion of 2M $MeNH_2$ in THF (10.0 mL; 2 M; 21.6 mmol) is added at 0 °C. After 3 h at rt, water is added and the mixture is concentrated. The resulting precipitate is filtered off and dried to give the sub-title compound. Yield: 5.0 g (96%).

(b) Ethyl 2-(2,2-difluoroethoxy)-4-(methylamino)-5-nitrobenzoate

A solution of 2,2-difluoroethanol (1.7 g; 20.6 mmol) in THF (50 mL) is added to a solution of ethyl 2-fluoro-4-(methylamino)-5-nitrobenzoate (5.0 g; 20.6 mmol) in DMF (100 mL). Sodium hydride (0.824 g; 60%; 20.6 mmol) is added in portions and the mixture is stirred overnight at rt. A solution of TFA (30 mL; 0.45 M aq) is added and the mixture is concentrated. The resulting precipitate is filtered off, washed with water, dried and recrystallized from EtOH/water to give the sub-title compound. Yield: 4.8 g (76%).

(c) Ethyl 5-amino-2-(2,2-difluoroethoxy)-4-(methylamino)benzoate

A mixture of ethyl 2-(2,2-difluoroethoxy)-4-(methylamino)-5-nitrobenzoate (2.0 g; 6.57 mmol), Ra-Ni (1.0 g) and THF (100 mL) is stirred under H_2-atmosphere (8 atm) overnight at rt. Na_2SO_4 is added and the mixture is stirred another 30 min under H_2-atmosphere. The mixture is filtered through celite and concentrated and the sub-title compound is used in the next step without further purification.

(d) Ethyl 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-(2,2-difluoro-ethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid ester

A mixture of ethyl 5-amino-2-(2,2-difluoroethoxy)-4-(methylamino)benzoate (0.942 g; 3.44 mmol), *N*-(2,4-dichloro-3-isothiocyanato-benzyl)- 2,2-dimethyl-propionamide (1.09 g, 3.44 mmol) and DMF (5 mL) is stirred overnight at rt. Then DIC (0.695 mL, 4.44 mmol) is added and the mixture is heated for 6 h to 80°C. The mixture is concentrated, diluted with EtOAc, washed with water and the resulting organic phase is dried with Na_2SO_4. After concentration and purification via column chromatography (silica gel, DCM -> DCM/EtOH 97:3) the sub-title compound is obtained

Yield: 1.35 g (71%). R_f = 0.42 (DCM/EtOH 95:5). MS m/z: 557 $[M+H]^+$.

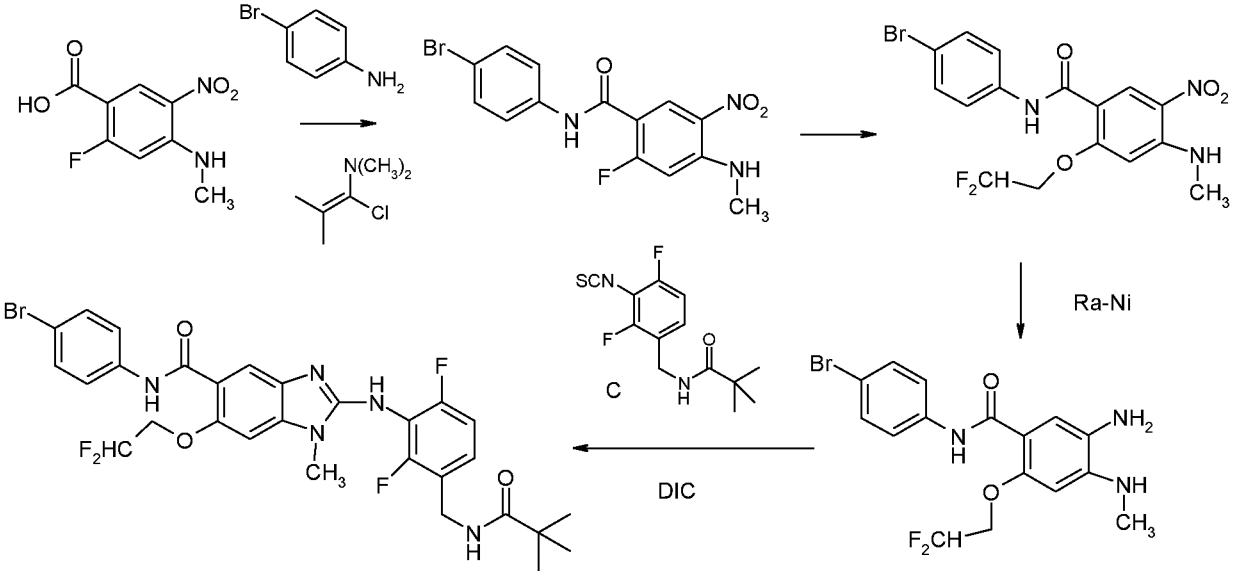
(e) *N*-(4-Bromo-phenyl)- 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-(2,2-difluoro-ethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid amide

Me_3Al in heptane (1.08 mL; 1 M; 1.08 mmol) is added to a solution of 4-bromoaniline (0.139 g; 0.807 mmol) in 1,4-dioxane (5 mL) and the mixture is stirred for 30 min at rt. Then ethyl 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-(2,2-difluoro-ethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid ester in 5 mL 1,4-dioxane is added slowly and the mixture is stirred for 10 h at 60°C, cooled and MeOH is added carefully. The crude mixture is acidified with HOAc, concentrated and purified via chromatography (silica gel, DCM -> DCM/EtOH 95:5).

Yield: 85 mg (46%). HPLC R_t = 2.80 min (method G). MS m/z: 682 $[M+H]^+$.

Example 6

N-(4-Bromo-phenyl)- 2-{2,6-difluoro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-(2,2-difluoro-ethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid amide



(a) *N*-(4-Bromophenyl)-2-fluoro-4-methylamino-5-nitro-benzamide

A mixture of 2-fluoro-4-methylamino-5-nitro-benzoic acid (0.500 g, 2.34 mmol), (1-chloro-2-methyl-propenyl)-dimethylamine (0.371 mL, 2.80 mmol) and DCM (50 mL) is stirred for 30 min, then 4-bromoaniline (0.402 mg, 2.34 mmol) and DIPEA (0.549 mL, 3.15 mmol) are added and it is stirred for 2 h. The mixture is concentrated, water is added and the precipitate is filtered, washed with water and dried to give the subtitle compound.

Yield: 0.820 g (95%). HPLC R_t = 1.47 min (method B). MS m/z: 368 $[M+H]^+$.

(b) *N*-(4-Bromophenyl)-2-(2,2-difluoro-ethoxy)-4-methylamino-5-nitro-benzamide

The subtitle compound is prepared from *N*-(4-bromophenyl)-2-fluoro-4-methylamino-5-nitro-benzamide, 2,2-difluoroethanol and KOtBu in analogy to example 1e.

Yield: 0.94 g (98%). HPLC R_t = 1.54 min (method B). MS m/z: 430 $[M+H]^+$.

(c) *N*-(4-Bromophenyl)-2-(2,2-difluoro-ethoxy)-4-methylamino-5-amino-benzamide

The subtitle compound is prepared from *N*-(4-bromophenyl)-2-(2,2-difluoro-ethoxy)-4-methylamino-5-nitro-benzamide, Ra-Ni and H_2 in analogy to example 5c.

Yield: 0.86 g (98%). R_f = 0.40 (DCM/EtOH 95:5). MS m/z: 400 $[M+H]^+$.

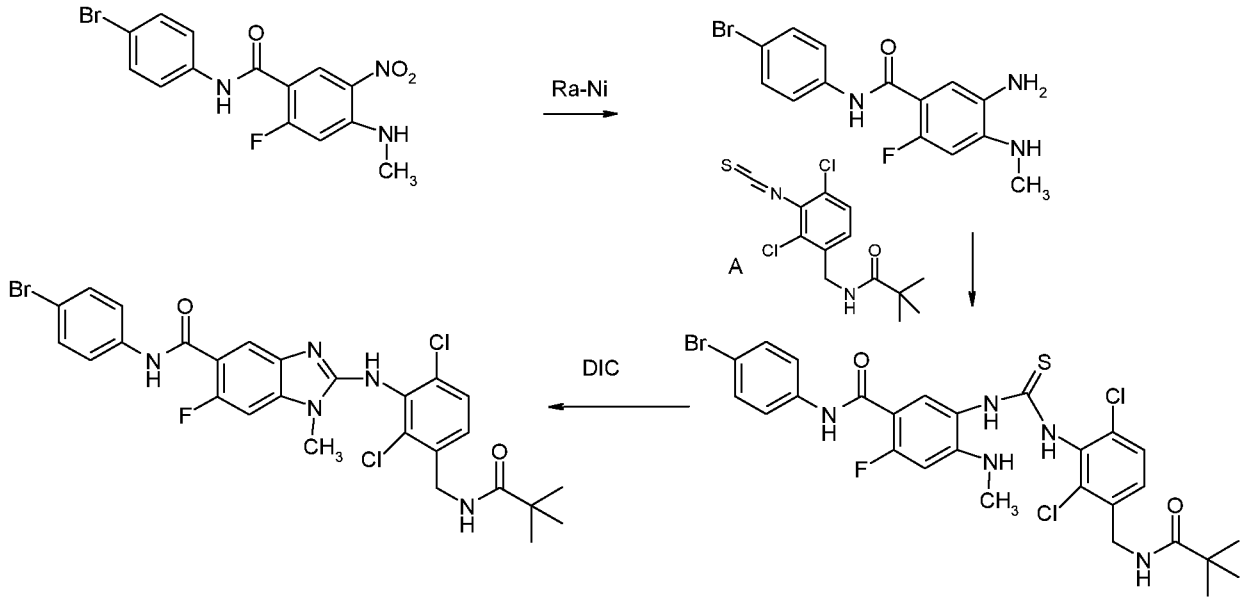
(d) *N*-(4-Bromo-phenyl)- 2-{2,6-difluoro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-(2,2-difluoro-ethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid amide

The title compound is prepared from *N*-(4-bromophenyl)-2-(2,2-difluoro-ethoxy)-4-methylamino-5-amino-benzamide and *N*-(2,4-difluoro-3-isothiocyanato-benzyl)-2,2-dimethyl-propionamide with DIC in analogy to example 1g.

Yield: 0.12 g (52%). R_f = 0.35 (DCM/EtOH 95:5). HPLC R_t = 1.52 min (method B). MS m/z: 650 $[M+H]^+$.

Example 7

N-(4-Bromo-phenyl)- 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-fluoro-1-methyl-1H-benzimidazole-5-carboxylic acid amide



(a) *N*-(4-Bromophenyl)-2-fluoro-4-methylamino-5-amino-benzamide

The subtitle compound is prepared from *N*-(4-bromophenyl)-2-fluoro-4-methylamino-5-nitro-benzamide, Ra-Ni and H_2 in analogy to example 5c.

Yield: quantitative. HPLC R_t = 1.34 min (method B). MS m/z: 339 $[M+H]^+$.

(b) *N*-(4-Bromophenyl)-5-(3-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenyl}-thioureido)-2-fluoro-4-methylamino-benzamide

A mixture of *N*-(4-bromophenyl)-2-fluoro-4-methylamino-5-amino-benzamide (220 mg, 0.543 mmol), *N*-(2,4-Dichloro-3-isothiocyanato-benzyl)- 2,2-dimethyl-propionamide (0.172 mg, 0.543 mmol) and DMF (5 mL) is stirred for 3 d, diluted with water, and extracted with EtOAc. The organic phase is washed with water, dried with Na_2SO_4 and concentrated to give the crude product.

HPLC R_t = 1.48 min (method B). MS m/z: 656 $[M+H]^+$.

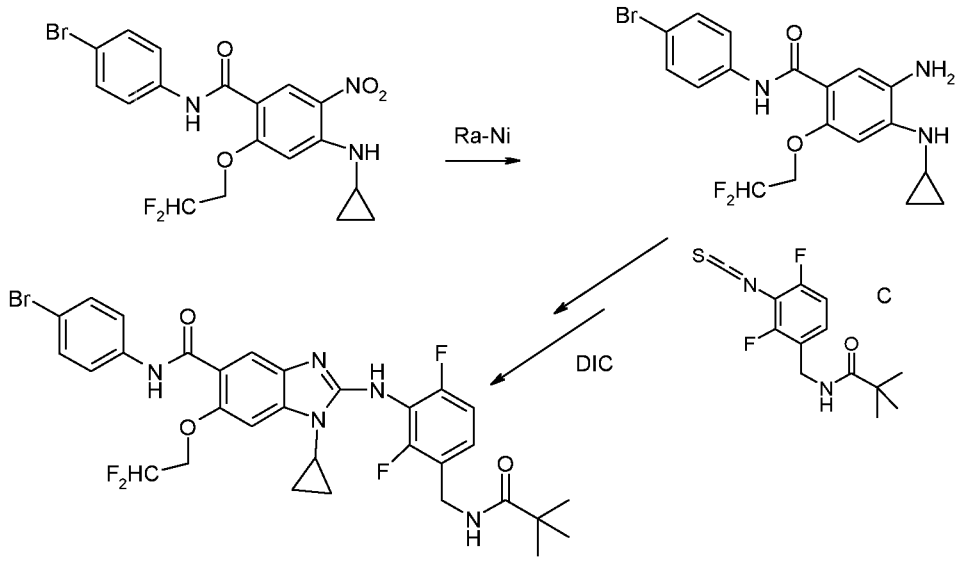
(c) *N*-(4-Bromo-phenyl)- 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-fluoro-1-methyl-1H-benzimidazole-5-carboxylic acid amide

A mixture of crude *N*-(4-Bromophenyl)-5-(3-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenyl}-thioureido)-2-fluoro-4-methylamino-benzamide (400 mg), DIC (111 µl, 0.700 mmol) and DMF (5 mL) is stirred at 80°C for 8 h. The crude mixture is concentrated and purified by flash chromatography (silica gel; DCM -> DCM/EtOH 97:3) to give the title compound.

Yield: 0.230 g (68%). R_f = 0.34 (DCM/EtOH 95:5). MS m/z: 620 $[M+H]^+$.

Example 11

N-(4-Bromo-phenyl)- 2-{2,6-difluoro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-(2,2-difluoroethoxy-1-cyclopropyl-1H-benzimidazole-5-carboxylic acid amide



(a) *N*-(4-Bromophenyl)-2-(2,2-difluoroethoxy)-4-cyclopropylamino-5-amino-benzamide

The subtitle compound is prepared from *N*-(4-bromophenyl)-2-(2,2-difluoroethoxy)-4-cyclopropylamino-5-nitro-benzamide (prepared from 2,4-difluoro-5-nitrobenzoic acid, cyclopropylamine, 4-bromoaniline and 2,2-difluoroethanol in analogy to the examples 1c, 6a, 1e) and Ra-Ni/H_2 in analogy to example 5c.

HPLC R_t = 1.4 min (method B). MS m/z: 427 $[M+H]^+$.

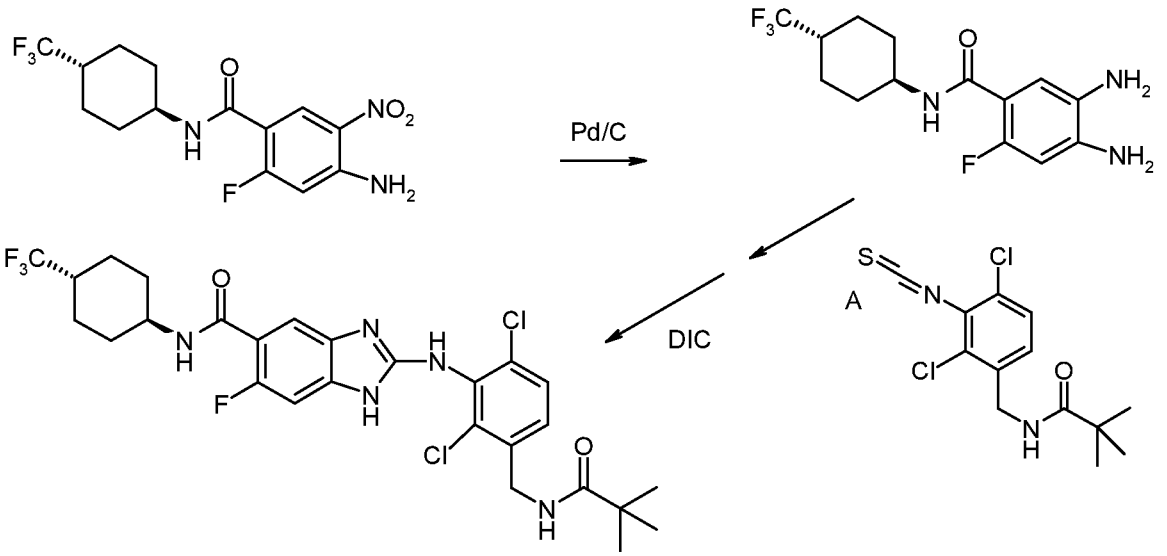
(b) *N*-(4-Bromo-phenyl)- 2-{2,6-difluoro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-(2,2-difluoroethoxy-1-cyclopropyl-1H-benzimidazole-5-carboxylic acid amide

The title compound is prepared from *N*-(4-Bromophenyl)-2-(2,2-difluoroethoxy)-4-cyclopropylamino-5-amino-benzamide and *N*-(2,4-difluoro-3-isothiocyanato-benzyl)-2,2-dimethyl-propionamide with DIC in analogy to the examples 7b/7c.

R_f = 0.36 (DCM/EtOH 95:5). MS m/z: 676 $[M+H]^+$.

Example 12

N-(*trans*-4-Trifluoromethyl-cyclohex-1-yl)- 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-fluoro-1H-benzimidazole-5-carboxylic acid amide



(a) *N*-(*trans*-4-Trifluoromethyl-cyclohex-1-yl)-2-fluoro-4,5-diamino-benzoic acid amide

The subtitle compound is prepared from *N*-(*trans*-4-trifluoromethyl-cyclohex-1-yl)-2-fluoro-4-amino-5-nitro-benzoic acid amide (prepared from 2-fluoro-4-amino-5-nitro-benzoic acid, *trans*-4-trifluoromethyl-cyclohexylamine in analogy to the example 2d) with Pd/C and H_2 in analogy to example 1f.

HPLC R_t = 1.58 min (method B). MS m/z: 320 $[M+H]^+$.

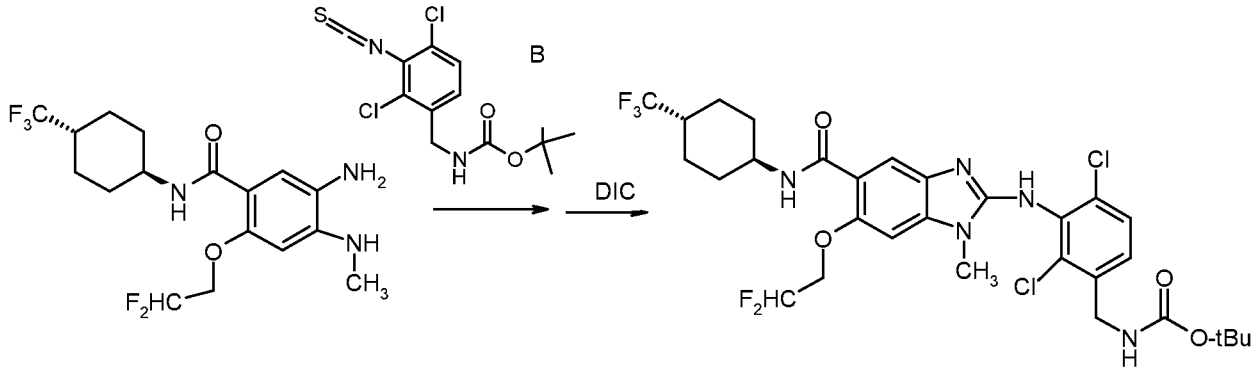
(b) *N*-(*trans*-4-Trifluoromethyl-cyclohex-1-yl)- 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-fluoro-1H-benzimidazole-5-carboxylic acid amide

The title compound is prepared from *N*-(*trans*-4-trifluoromethyl-cyclohex-1-yl)-2-fluoro-4,5-diamino-benzoic acid amide and *N*-(2,4-dichloro-3-isothiocyanato-benzyl)-2,2-dimethyl-propionamide with DIC in analogy to examples 7b/7c.

HPLC R_t = 2.52 min (method G). MS m/z: 602 $[M+H]^+$.

Example 13

N-(*trans*-4-Trifluoromethyl-cyclohex-1-yl)- 2-{2,6-dichloro-3-[(tert-butoxy-carbonylamino)-methyl]-phenylamino}-6-(2,2-difluoroethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid amide

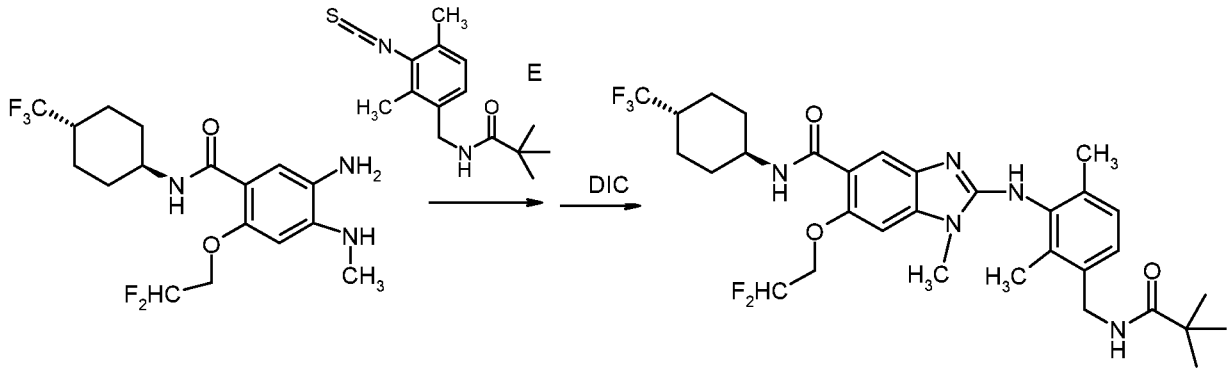


The title compound is prepared from *N*-(*trans*-4-trifluoromethyl-cyclohex-1-yl)-2-(2,2-difluoro-ethoxy)-4-methylamino-5-amino-benzoic acid amide and (2,4-dichloro-3-isothiocyanato-benzyl)-carbamic acid tert-butyl ester with DIC in analogy to examples 7b/7c.

R_f = 0.25 (DCM/EtOH 95:5). MS m/z: 694 $[M+H]^+$.

Example 14

N-(*trans*-4-Trifluoromethyl-cyclohex-1-yl)- 2-{2,6-dimethyl-3-[(2,2-dimethyl-propionylamino)-methyl]- phenylamino}-6-(2,2-difluoroethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid amide

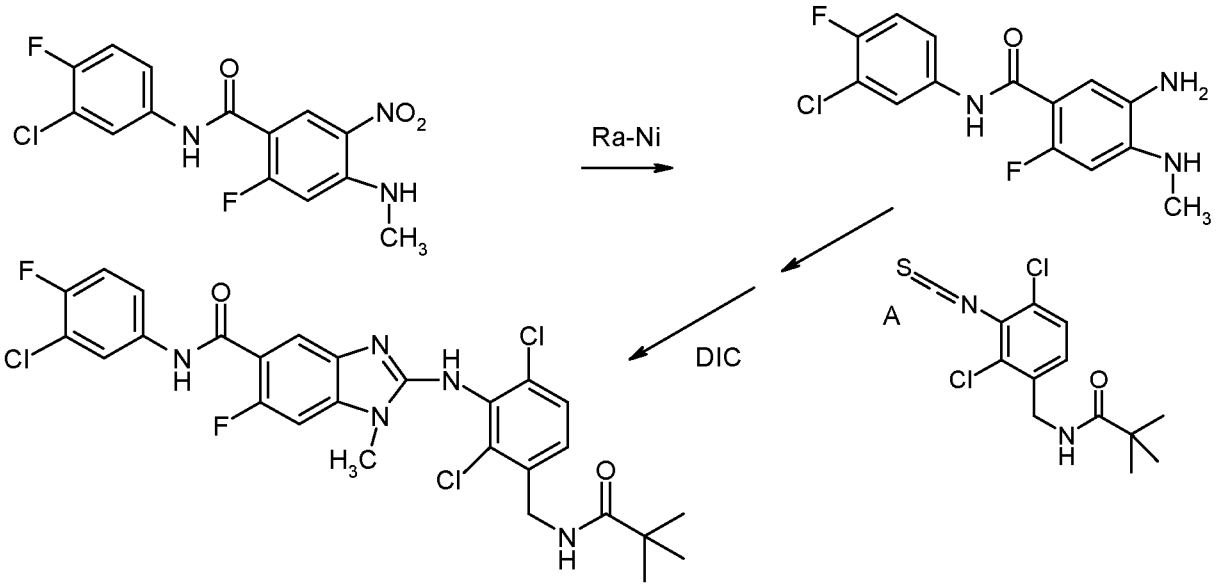


The title compound is prepared from *N*-(*trans*-4-trifluoromethyl-cyclohex-1-yl)-2-(2,2-difluoro-ethoxy)-4-methylamino-5-amino-benzoic acid amide and *N*-(2,4-dimethyl-3-isothiocyanato-benzyl)- 2,2-dimethyl-propionamide with DIC in analogy to examples 7b/7c.

R_f = 0.15 (DCM/EtOH 95:5). MS m/z: 638 $[M+H]^+$.

Example 17

N-(4-Fluoro-3-chloro-phenyl)- 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-fluoro-1-methyl-1H-benzimidazole-5-carboxylic acid amide



(a) *N*-(4-Fluoro-3-chloro-phenyl)-2-fluoro-4-methylamino-5-amino-benzoic acid amide

The subtitle compound is prepared from *N*-(4-fluoro-3-chloro-phenyl)-2-fluoro-4-methylamino-5-nitro-benzoic acid amide (prepared from 2-fluoro-4-methylamino-5-nitro-benzoic acid, 4-fluoro-3-chloro-aniline in analogy to the step 6a) with Ra-Ni and H_2 in analogy to example 5c.

MS m/z: 312 $[M+H]^+$.

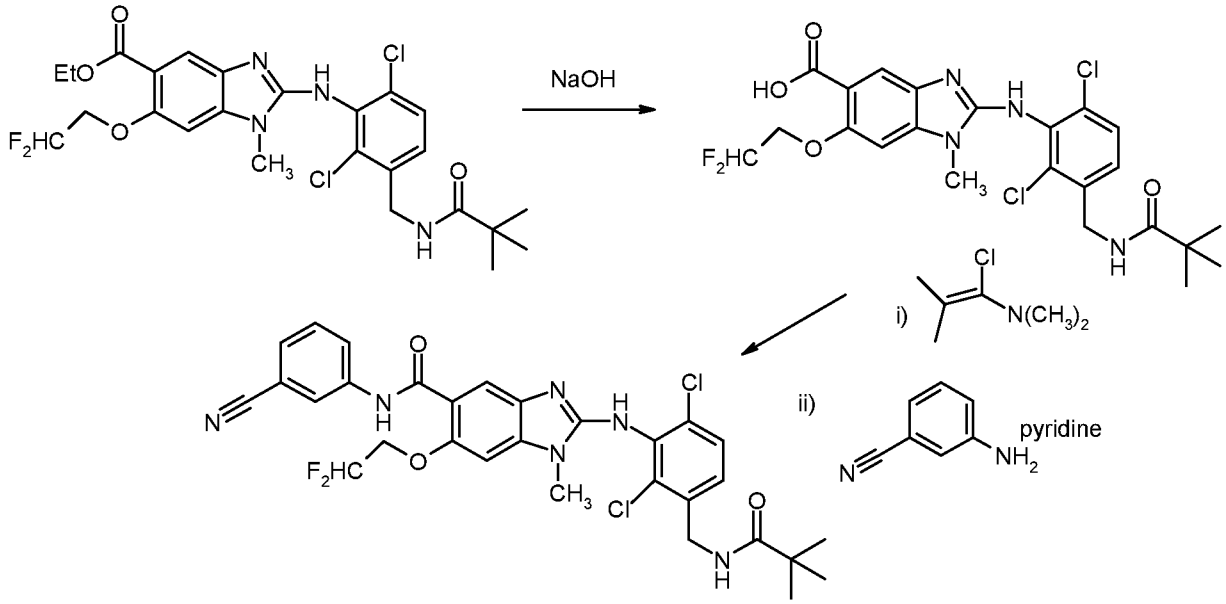
(b) *N*-(4-Fluoro-3-chloro-phenyl)- 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-fluoro-1-methyl-1H-benzimidazole-5-carboxylic acid amide

The title compound is prepared from *N*-(4-fluoro-3-chloro-phenyl)-2-fluoro-4-methylamino-5-amino-benzoic acid amide and *N*-(2,4-dichloro-3-isothiocyanato-benzyl)-2,2-dimethyl-propionamide with DIC in analogy to examples 7b/7c.

HPLC R_t = 2.52 min (method G). MS m/z: 594 $[M+H]^+$.

Example 28

N-(3-Cyano-phenyl)- 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-(2,2-difluoro-ethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid amide



(a) 2-{2,6-Dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-(2,2-difluoro-ethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid

A mixture of ethyl 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-(2,2-difluoro-ethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid ester (1.170 g; 2.10 mmol), 4 N aq. NaOH-solution (2.10 mL, 8.4 mmol) and EtOH (30 mL) is stirred for 4 d. Then, the mixture is concentrated, diluted with water and acidified with 4 N aq. HCl-solution. The precipitate is filtered, washed with water and dried to give 0.60 g of the product. The filtrate is extracted with EtOAc, the organic phase is dried with Na_2SO_4, and concentrated to give additional 0.23 g of the sub-title compound.

Yield: 0.83 g (75%). HPLC R_t = 1.16 min (method C). MS m/z: 529 $[M+H]^+$.

(b) *N*-(3-Cyano-phenyl)- 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-(2,2-difluoro-ethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid amide

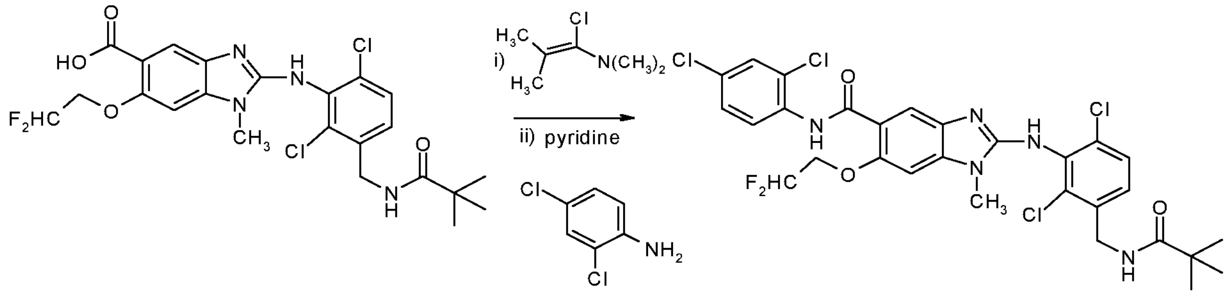
(1-Chloro-2-methyl-propenyl)-dimethylamine (20 µl) is added to a mixture of 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-(2,2-difluoro-ethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid (53 mg, 0.10 mmol) in 2.0 mL acetonitrile and it is stirred 10 min at rt. Additional (1-chloro-2-methyl-propenyl)-dimethylamine (20 µl) is added and the mixture is stirred for additional 20 min at rt. The crude acid chloride solution is added to a mixture of 3-aminobenzonitrile (12 mg, 0.10 mmol), pyridine (24 µL, 0.30 mmol) and acetonitrile (1.0 mL) and it is stirred for 15 min at rt and additional 5 h at 55°C. The solvent is

removed *in vacuo* and the residue is dissolved in 2 mL of a 19:1 DMF/water-solution and is purified *via* preparative HPLC to furnish the title compound.

Yield: 26 mg (42%). HPLC R_t = 1.65 min (method A). MS m/z: 629 $[M+H]^+$.

Example 60

N-(2,4-dichloro-phenyl)- 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-(2,2-difluoro-ethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid amide

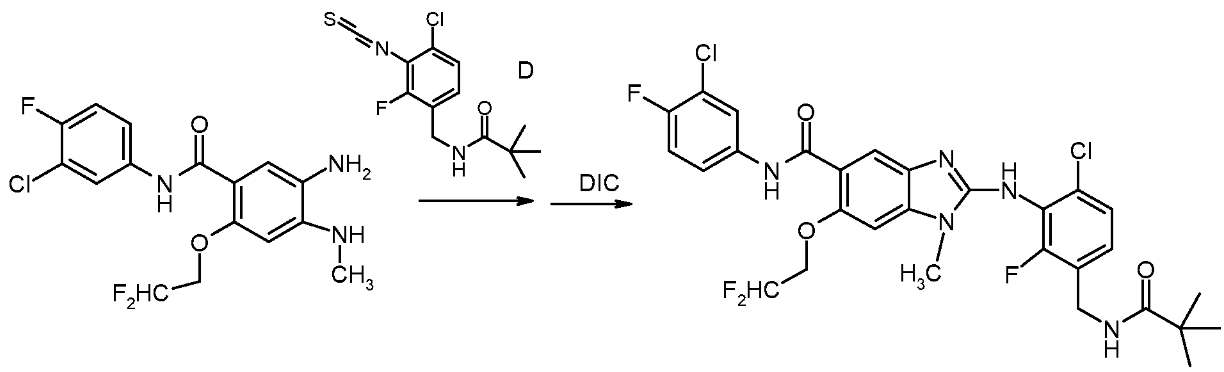


(1-Chloro-2-methyl-propenyl)-dimethylamine (20 µl) is added to a mixture of 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-(2,2-difluoro-ethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid (53 mg, 0.10 mmol) in 1.0 mL acetonitrile and it is stirred 15 min at rt. The crude acid chloride solution is added to a mixture of 2,4-dichloroaniline (16 mg, 0.10 mmol), pyridine (24 µL, 0.30 mmol) and acetonitrile (1.0 mL) and it is stirred over the weekend at 60°C. The solvent is removed *in vacuo* and the residue is dissolved in 2 mL of a 9:1 DMF/water-solution and is purified *via* preparative HPLC.

Yield: 53 mg (79%). HPLC R_t = 2.83 min (method D). MS m/z: 672 $[M+H]^+$.

Example 75

N-(3-Chloro-4-fluoro-phenyl)- 2-{6-chloro-2-fluoro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-(2,2-difluoroethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid amide

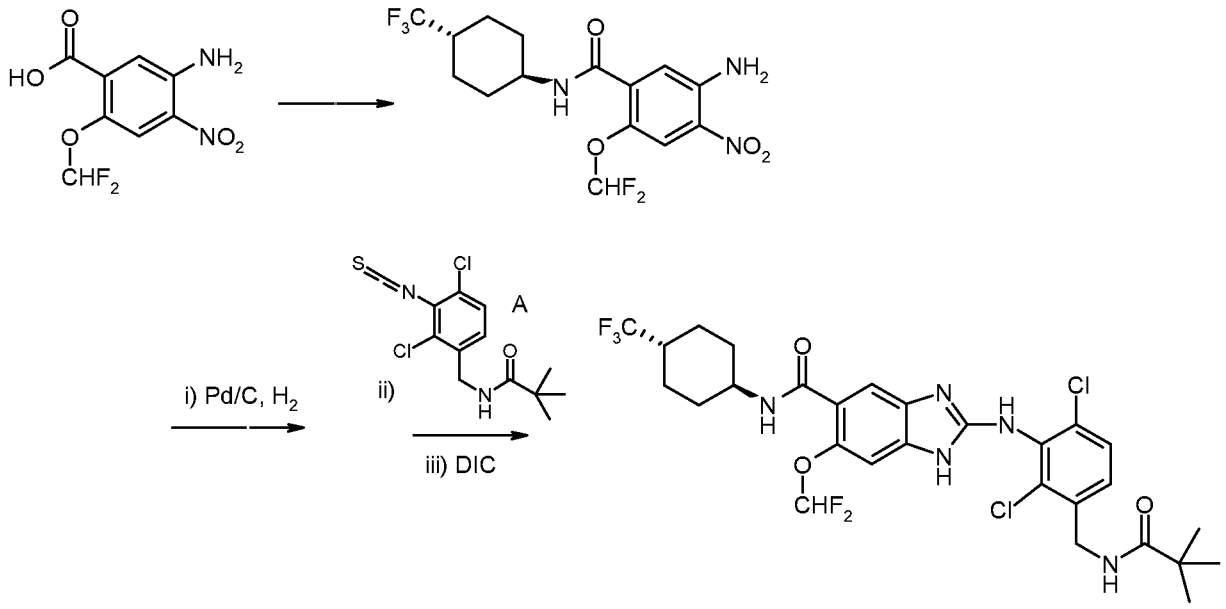


A mixture of *N*-(3-chloro-4-fluorophenyl)-2-(2,2-difluoroethoxy)-4-methylamino-5-amino-benzamide (60 mg, 0.161 mmol, prepared from 3-chloro-4-fluoro-aniline, 2,2-difluoroethanol and 2-fluoro-4-methylamino-5-nitro benzoic acid according to the sequence 1d-1f), *N*-(4-chloro-2-fluoro-3-isothiocyanato-benzyl)- 2,2-dimethyl-propionamide (0.48 mg, 0.161 mmol) and DMF (2 mL) is stirred for 3 h. Then DIC (25 µl, 0.16 mmol) is added and it is stirred at 80°C overnight. The crude mixture is concentrated and purified by flash chromatography (silica gel; DCM -> DCM/EtOH 98:2).

Yield: 80 mg (78%). R_f = 0.45 (DCM/EtOH 95:5). HPLC R_t = 1.48 min (method B). MS m/z: 640 $[M+H]^+$.

Example 78

N-(*trans*-4-Trifluoromethyl-cyclohex-1-yl)- 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]- phenylamino}-6-(difluoromethoxy)-1H-benzimidazole-5-carboxylic acid amide



a) *N*-(*trans*-4-Trifluoromethyl-cyclohex-1-yl)-2-(difluoromethoxy)-5-amino-4-nitro-benzoic acid amide

(1-Chloro-2-methyl-propenyl)-dimethylamine (102 µl) is added to a mixture of 2-(difluoro-methoxy)-5-amino-4-nitro-benzoic acid (175 mg, 0.705 mmol, prepared in analogy to WO2010/034797), 5 mL THF and 10 mL DCM and it is stirred for 5 h. Then *trans*-4-trifluoromethyl-cyclohexylamine (158 mg, 0.776 mmol) and pyridine (139 µL, 1.77 mmol) are added and it is.stirred overnight. The solvent is removed *i. vac.,* half-saturated aq.$NaHCO_3$ – solution is added and it is extracted with DCM. The organic layers are dried with Na_2SO_4, filtered, concentrated and purified *via* preparative HPLC (Method F).

Yield: 70 mg (25%). HPLC R_t = 2.06 min (method E). MS m/z: 398 $[M+H]^+$.

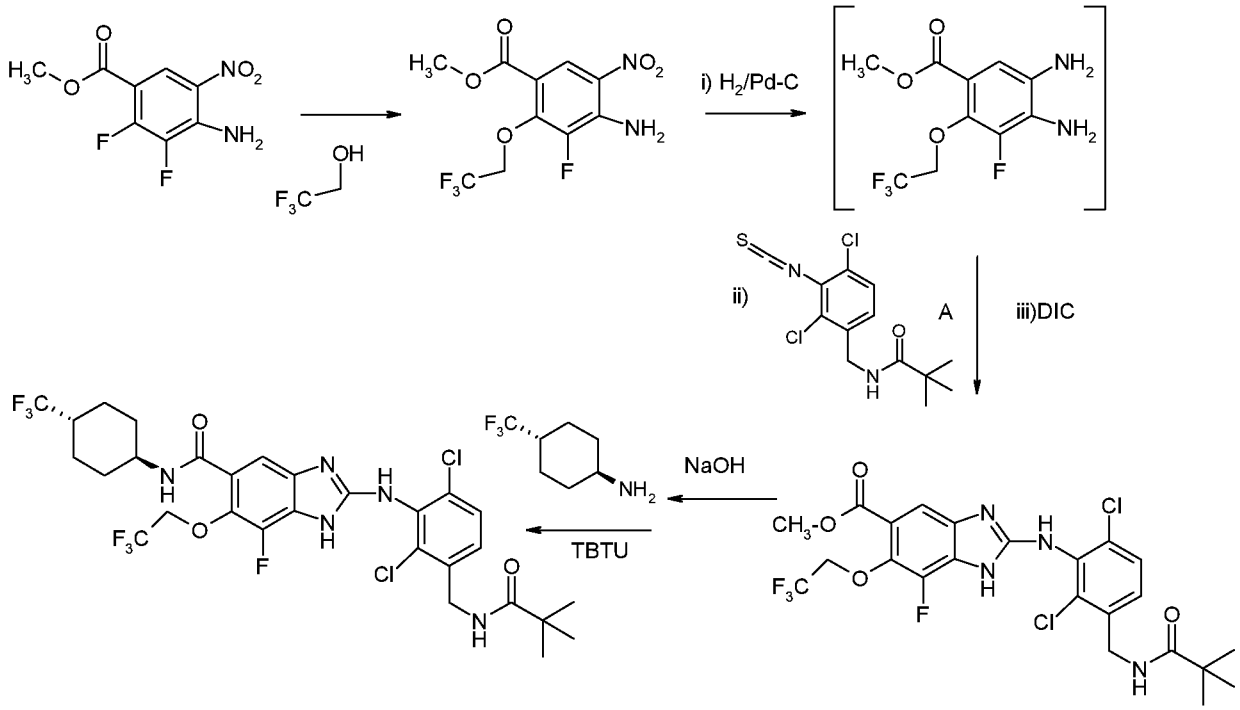
b) *N*-(*trans*-4-Trifluoromethyl-cyclohex-1-yl)- 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]- phenylamino}-6-(difluoromethoxy)-1H-benzimidazole-5-carboxylic acid amide

A mixture of *N*-(*trans*-4-trifluoromethyl-cyclohex-1-yl)-2-(difluoromethoxy)-5-amino-4-nitro-benzoic acid amide (70 mg, 0.176 mmol), Pd/C (15 mg) and 10 mL THF is stirred under a H_2-atmosphere (3 bar) for 2h. The crude mixture is filtered into a flask charged with *N*-(2,4-dichloro-3-isothiocyanato-benzyl)- 2,2-dimethyl-propionamide (59 mg, 0.185 mmol) and the filter cake is washed with 40 mL THF. The mixture is stirred for 4 h at rt and overnight at 60°C. Then the reaction mixture is concentrated to ~10 mL and stirred for additional 8 h at 60°C. Then it is concentrated i.vac., diluted with MeCN (2.0 mL) and DIC (29 µl, 0.186 mmol) is added and it is stirred for 4 d. Then the mixture is concentrated, diluted with DMF and THFand purified via HPLC.

Yield: 34 mg (30%). HPLC R_t = 2.00 min (method E). MS m/z: 650 $[M+H]^+$.

Example 79

N-(*trans*-4-Trifluoromethyl-cyclohex-1-yl)- 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]- phenylamino}-6-(2,2,2-trifluoroethoxy)-7-fluoro-1H-benzimidazole-5-carboxylic acid amide



(a) 2-(2,2,3-Trifluoro-ethoxy)-3-fluoro-4-amino-5-nitro-benzoic acid methyl ester

A mixture of 2,2,2-triifluoroethanol (0.377 mL, 5.2 mmol), KOtBu (0.580 g, 0.5.2 mmol) and THF (20 mL) is stirred for 15 min at 0°C, then methyl 2,3-difluoro-4-amino-5-nitro-benzoate (1.00 g) in THF (20 mL) is added and it is stirred for 15 h at rt. Water is added to the mixture and the mixture is concentrated. The resulting precipitate is filtered, washed with water and dried at 50°C.

Yield:1.15 g (86%). HPLC R_t = 1.95 min (method E). MS m/z: 313 $[M+H]^+$.

(b) 2-{2,6-Dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]- phenylamino}-6-(2,2,2-trifluoroethoxy)-7-fluoro-1H-benzimidazole-5-carboxylic acid methyl ester

The subtitle compound is prepared from 2-(2,2,3-trifluoro-ethoxy)-3-fluoro-4-amino-5-nitro-benzoic acid methyl ester in analogy to 78b using i) Pd/C and H_2; ii) *N*-(2,4-dichloro-3-isothiocyanato-benzyl)- 2,2-dimethyl-propionamide and iii) DIC.

Yield: 90 mg (45%). HPLC R_t = 2.01 min (method E). MS m/z: 565 $[M+H]^+$.

(c) 2-{2,6-Dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]- phenylamino}-6-(2,2,2-trifluoroethoxy)-7-fluoro-1H-benzimidazole-5-carboxylic acid

The subtitle compound is prepared from 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]- phenylamino}-6-(2,2,2-trifluoroethoxy)-7-fluoro-1H-benzimidazole-5-carboxylic acid methyl ester and NaOH in analogy to example 28a.

Yield: 60 mg (62%). HPLC R_t = 1.81 min (method E). MS m/z: 551 $[M+H]^+$.

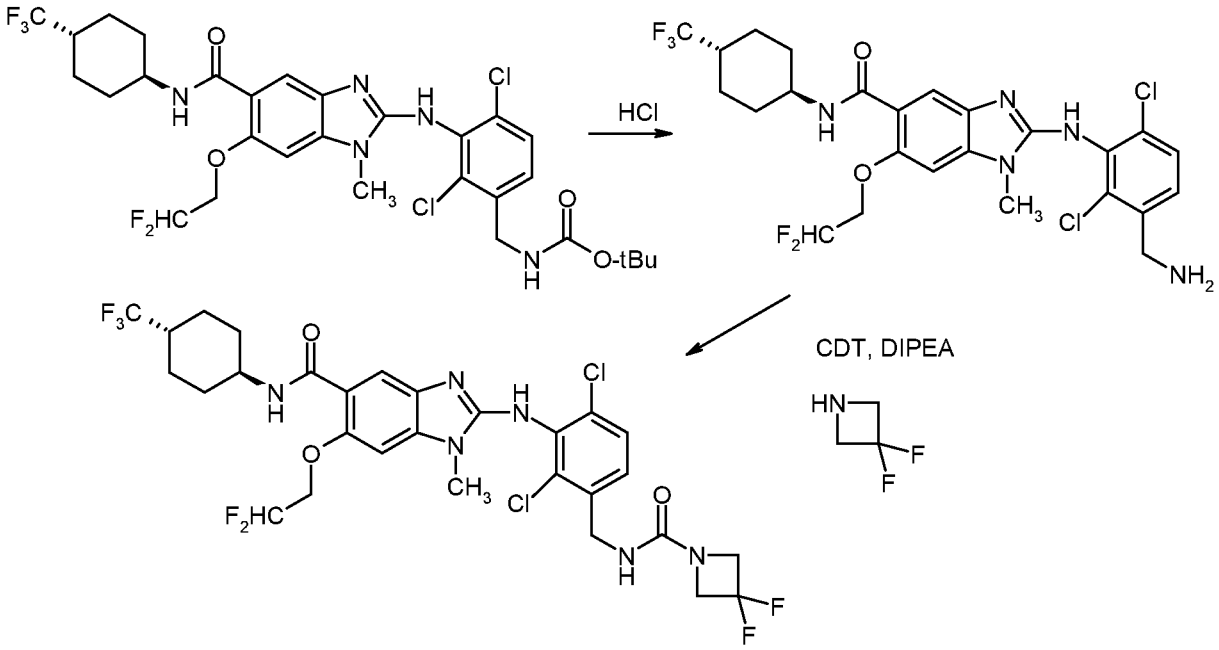
(d) *N*-(*trans*-4-Trifluoromethyl-cyclohex-1-yl)- 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]- phenylamino}-6-(2,2,2-trifluoroethoxy)-7-fluoro-1H-benzimidazole-5-carboxylic acid amide

A mixture of 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]- phenylamino}-6-(2,2,2-trifluoroethoxy)-7-fluoro-1H-benzimidazole-5-carboxylic acid (60 mg, 0.109 mmol), TBTU (36.7 mg, 0.114 mmol), DIPEA (66µl, 0.38 mmol) and DMF (1 mL) is stirred for 30 min, then *trans*-4-trifluoromethyl-cyclohexylamine (24 mg, HCl salt) is added and it is stirred for 1 h. The mixture is diluted with EtOAc, washed with satd. aq. $NaHCO_3$-solution, dried with Na_2SO_4 and concentrated to give the title compound.

Yield: 76 mg (100%). HPLC R_t = 2.24 min (method E). MS m/z: 700 $[M+H]^+$.

Example 80

N-(*trans*-4-Trifluoromethyl-cyclohex-1-yl)- 2-{2,6-dichloro-3-[(3,3-difluoro-azetidine-1-carbonylamino)-methyl]-phenylamino}-6-(2,2-difluoroethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid amide



(a) *N*-(*trans*-4-Trifluoromethyl-cyclohex-1-yl)- 2-(2,6-dichloro-3-aminomethyl-phenylamino)-6-(2,2-difluoroethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid amide

A mixture of *N*-(*trans*-4-trifluoromethyl-cyclohex-1-yl)- 2-{2,6-dichloro-3-[(tert-butoxy-carbonylamino)-methyl]-phenylamino}-6-(2,2-difluoroethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid amide (350 mg, 0.504 mmol), 6 M aq.HCl-solution (15 mL) and THF (15 mL) is stirred overnight, the mixture is concentrated and directly used in the next step.

Yield: 320 mg (quantitative). HPLC R_t = 1.23 min (method B). MS m/z: 594 $[M+H]^+$.

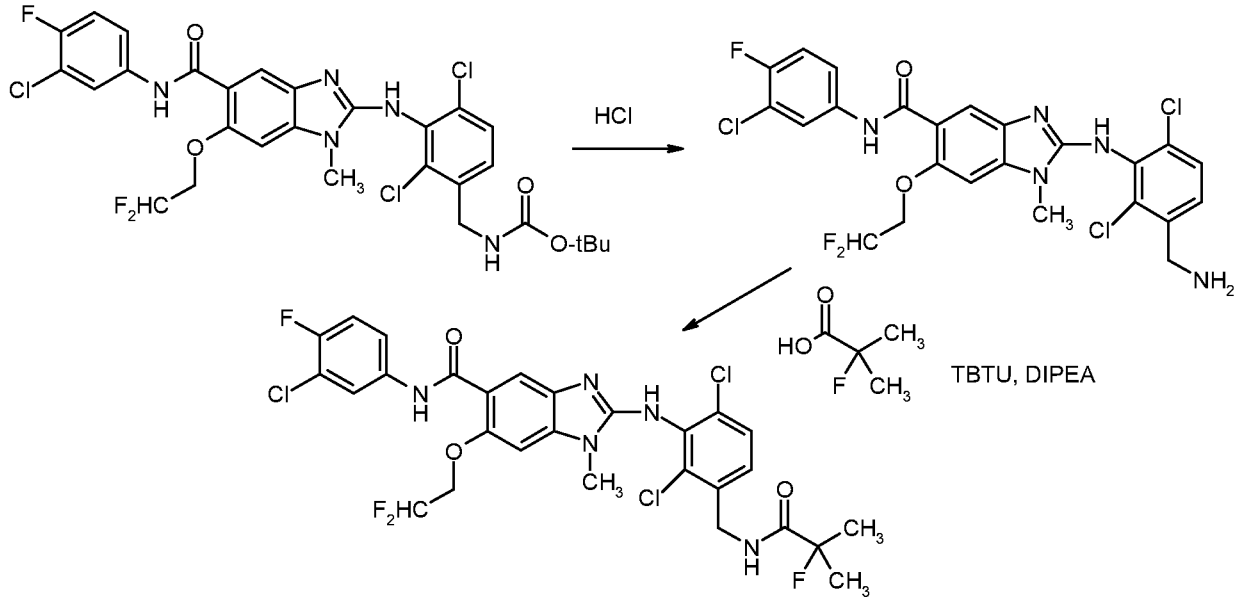
(b) *N*-(*trans*-4-Trifluoromethyl-cyclohex-1-yl)- 2-{2,6-dichloro-3-[(3,3-difluoro-azetidine-1-carbonylamino)-methyl]-phenylamino}-6-(2,2-difluoroethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid amide

CDT (45 mg, 90%) is added to an ice-cooled mixture of crude *N*-(*trans*-4-trifluoromethyl-cyclohex-1-yl)- 2-(2,6-dichloro-3-aminomethyl-phenylamino)-6-(2,2-difluoroethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid amide (140 mg), DIPEA (0.12 mL, 0.68 mmol) and THF (5.0 mL) and it is stirred for 30 min. Then 3,3-difluoroazetidine x HCl (30 mg, 0.22 mmol) is added and the mixture is heated to 60°C for 4 d (every day another 30 mg of the azetidine is added). The reaction mixture is concentrated and purified via chromatography (silica gel, DCM->DCM/EtOH 95:5).

Yield: 60 mg (38%). R_f(TLC): 0.26 (DCM/EtOH 95:5). MS m/z: 713 $[M+H]^+$.

Example 84

N-(3-Chloro-4-fluoro-phenyl)- 2-{2,6-dichloro-3-[(2-fluoro-2-methyl-propionylamino)-methyl]-phenylamino}-6-(2,2-difluoroethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid amide



(a) *N*-(3-Chloro-4-fluoro-phenyl)-2-(2,6-dichloro-3-aminomethyl-phenylamino)-6-(2,2-difluoroethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid amide

A mixture of *N*-(3-chloro-4-fluoro-phenyl)-2-{2,6-dichloro-3-[(tert-butoxy-carbonylamino)-methyl]-phenylamino}-6-(2,2-difluoroethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid amide (4.0 g, 5.9 mmol, prepared in analogy to example 75 from *N*-(3-chloro-4-fluorophenyl)-2-(2,2-difluoroethoxy)-4-methylamino-5-amino-benzamide with building block B), 4 M HCl in dioxane (50 mL) and dioxane (200 mL) is stirred for 2 h. The precipitate is filtered off, washed with water and diluted with 10 mL conc. aq. NH_3. The mixture is extracted with EtOAc, the organic phase is dried with Na_2SO_4 and concentrated.

Yield: 2.62 g (77%). MS m/z: 572 $[M+H]^+$.

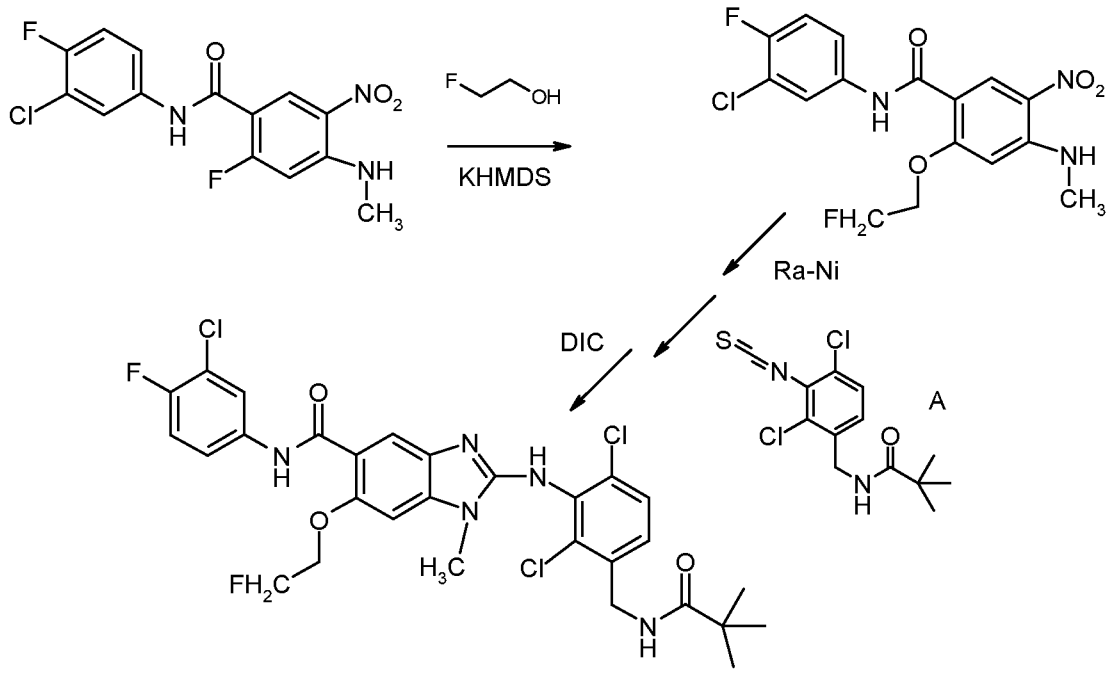
(b) *N*-(3-Chloro-4-fluoro-phenyl)- 2-{2,6-dichloro-3-[(2-fluoro-2-methyl-propionylamino)-methyl]- phenylamino}-6-(2,2-difluoroethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid amide

TBTU (1.0 mL of a 0.11 M solution in DMF) was added to a mixture of *N*-(3-chloro-4-fluoro-phenyl)-2-(2,6-dichloro-3-aminomethyl-phenylamino)-6-(2,2-difluoroethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid amide (1.0 mL of a 0.10 M solution in DMF), DIPEA (52 µl, 0.3 mmol) and 2-fluoro-2-methylpropionic acid (1.0 mL of a 0.13 M solution in DMF) and it was stirred for 3 d and the mixture was purified by prep. HPLC.

Yield: 38 mg (57%). HPLC R_t = 1.69 min (method I). MS m/z: 661 $[M+H]^+$.

Example 177

N-(3-Chloro-4-fluoro-phenyl)- 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]-phenylamino}-6-(2-fluoroethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid amide



a) *N*-(3-chloro-4-fluorophenyl)-2-(2-fluoroethoxy)-4-methylamino-5-nitro-benzamide KHMDS (0.320 g, 1.60 mmol) is added to an ice-cooled mixture of *N*-(4-fluoro-3-chloro-phenyl)-2-fluoro-4-methylamino-5-nitro-benzoic acid amide (500 mg, 1.46 mmol), 2-fluoroethanol (0.129 ml, 2.19 mmol) and 30 ml THF. After 30 min the temperature is raised to 60°C for 4.5 h, then it is stirred at rt overnight. Additional 2-fluoroethanol (0.129 ml, 2.19 mmol) and KHMDS (0.160 g, 0.80 mmol) are added and it is stirred for 4.5 h at 60°C. Then the mixture is diluted with satd. aq. $NaHCO_3$-solution and the precipitate is filtered off, washed with water and dried.

Yield: 360 mg (64%). HPLC R_t = 2.28 min (method E). MS m/z: 386 $[M+H]^+$.

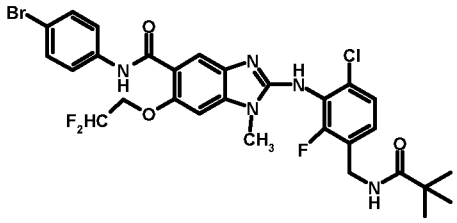
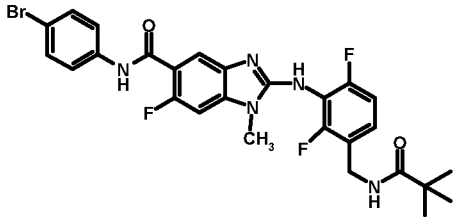
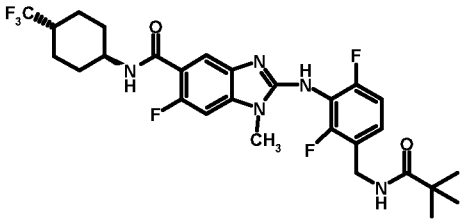
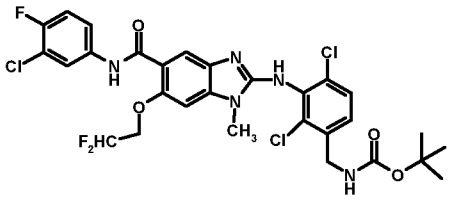
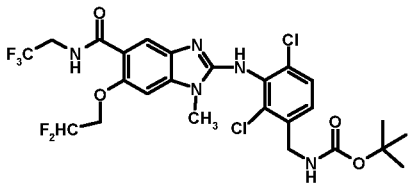
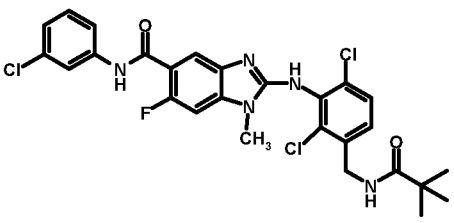
b) *N*-(3-Chloro-4-fluoro-phenyl)- 2-{2,6-dichloro-3-[(2,2-dimethyl-propionylamino)-methyl]- phenylamino}-6-(2-fluoroethoxy)-1-methyl-1H-benzimidazole-5-carboxylic acid amide

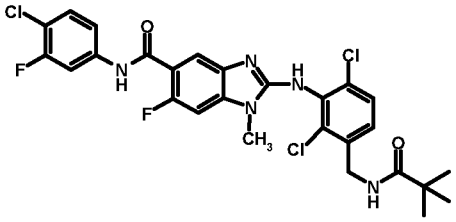
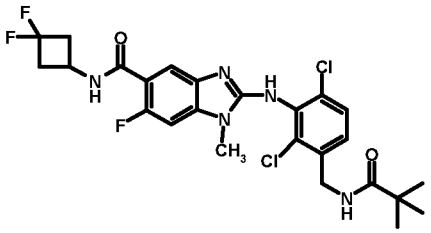
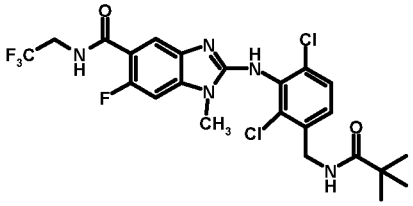
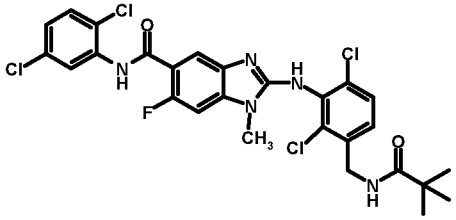
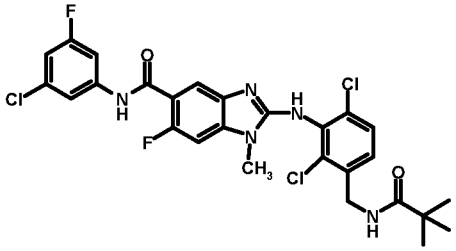
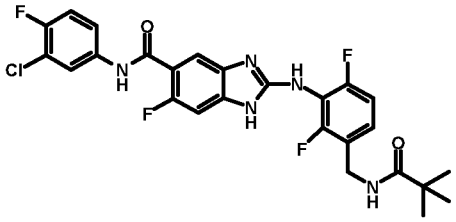
A mixture of *N*-(3-chloro-4-fluorophenyl)-2-(2-fluoroethoxy)-4-methylamino-5-nitro-benzamide (67.9 mg, 0.176 mmol), Pd/C (15 mg) and 10 mL THF is stirred under a H_2-atmosphere (3 bar) for 8h. The crude mixture is filtered into a flask charged with *N*-(2,4-dichloro-3-isothiocyanato-benzyl)-2,2-dimethyl-propionamide (59 mg, 0.185 mmol) and concentrated to ~5 mL. The mixture is stirred for 2 h at rt and concentrated i.vac.. The mixture is diluted with MeCN (2.0 mL), DIC (29 µl, 0.186 mmol) is added and it is stirred overnight at rt and 2 h at 60°C. The mixture is cooled to rt and the resulting precipitate is filtered off, washed with MeCN, redissolved in dioxane/MeCN and a few drops of HCOOH and lyophilized.

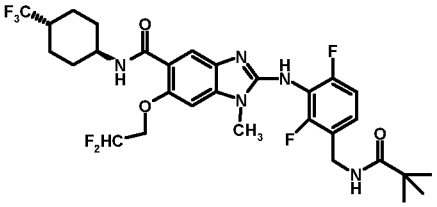
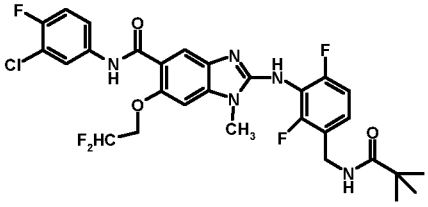
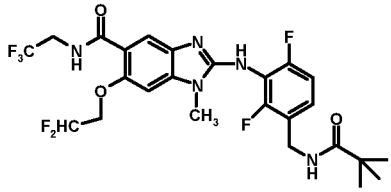
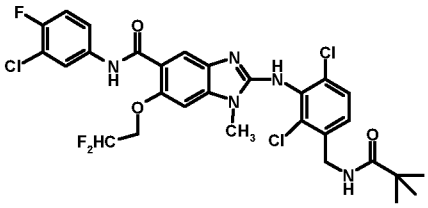
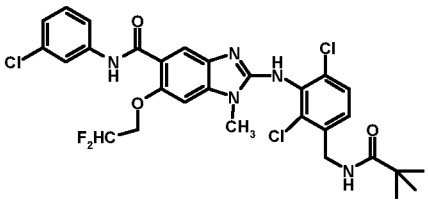
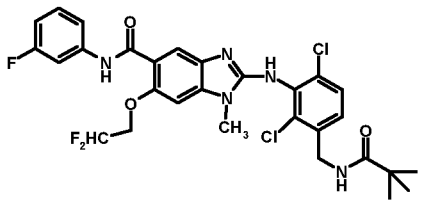
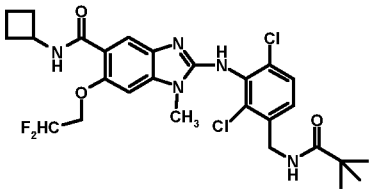
Yield: 29 mg (26%). HPLC R_t = 2.09 min (method E). MS m/z: 638 $[M+H]^+$.

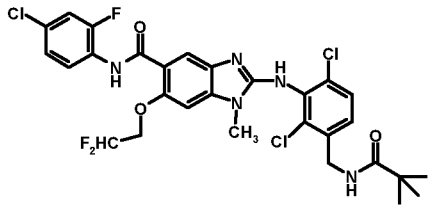
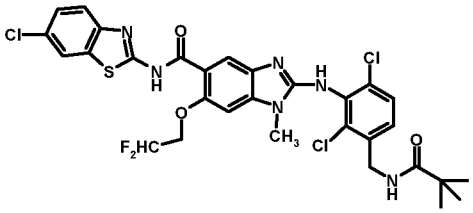
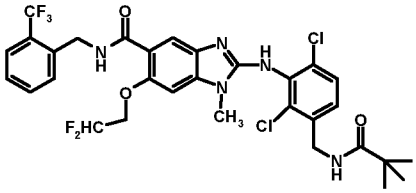
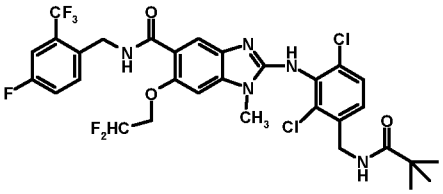
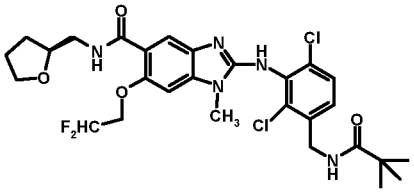
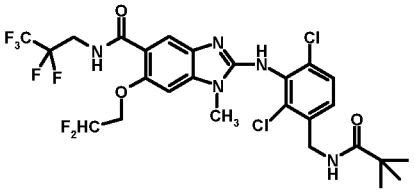
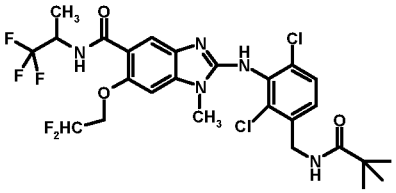
The following examples in Table 1 are prepared in analogy to the methods described above.

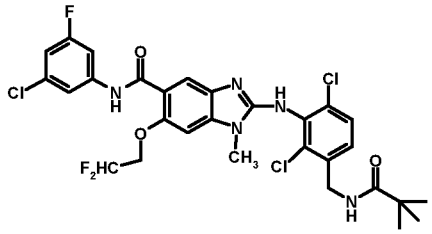
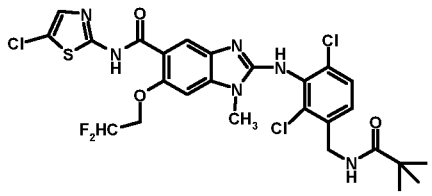
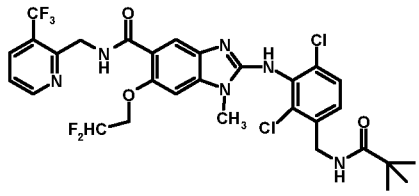
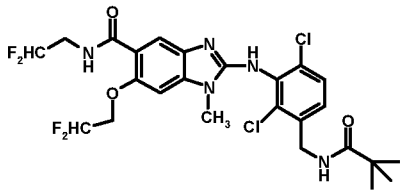
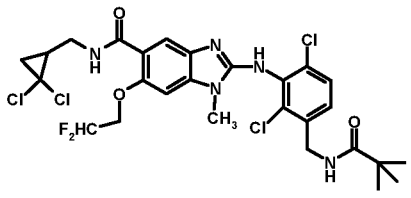
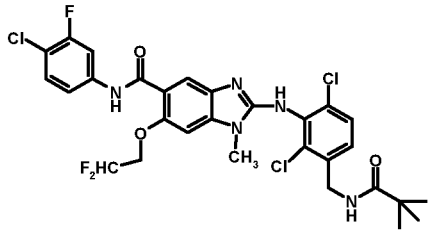
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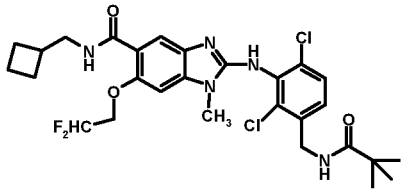
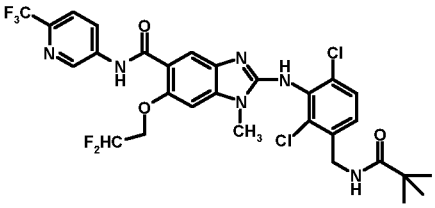
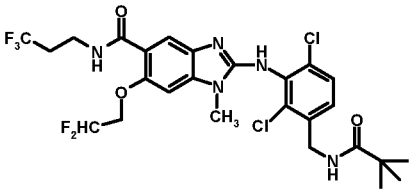
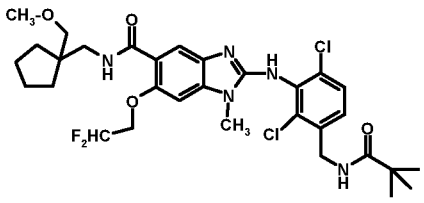
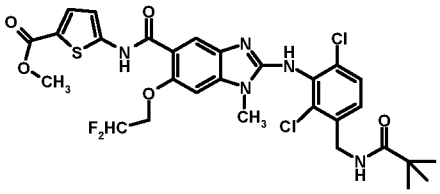
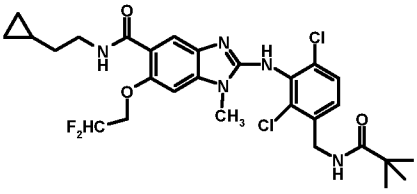
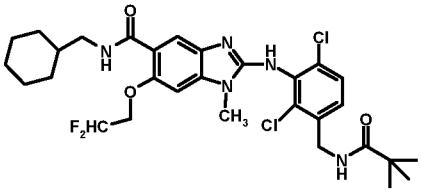
Ex.	Structure	Formula/ Mw.	MS* *m/z* $[M+H]^+$	R_f (TLC, silica gel) or R_t [min] (HPLC-method)	Prepared in analogy to example
8		$C_{29}H_{28}BrClF_3N_5O_3$ 666.916	666	R_t = 1.44 (method B)	**6**
9		$C_{27}H_{25}BrF_3N_5O_2$ 588.419	589	R_t = 1.39 (method B)	**7**
10		$C_{28}H_{31}F_6N_5O_2$ 583.569	584	R_f = 0.25 (DCM/EtOH 95:5)	**3**
15		$C_{29}H_{37}Cl_3F_3N_5O_4$ 672.909	672	R_t = 2.21 (method E)	**13**
16		$C_{25}H_{26}Cl_2F_5N_5O_4$ 626.403	626	R_f = 0.36 (PE/EtOAc 1:1)	**13**
18		$C_{27}H_{25}Cl_3FN_5O_2$ 576.876	576	R_f = 0.35 (DCM/EtOH 95:5)	**17**

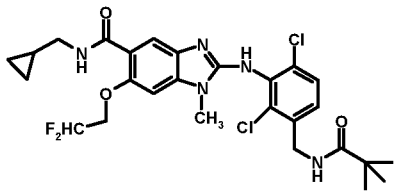
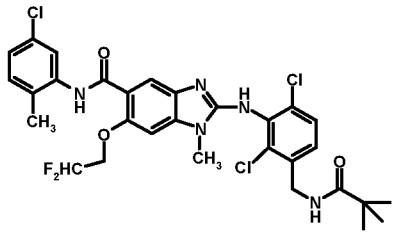
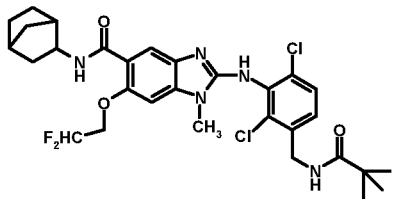
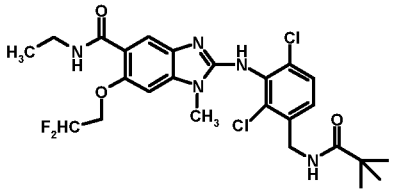
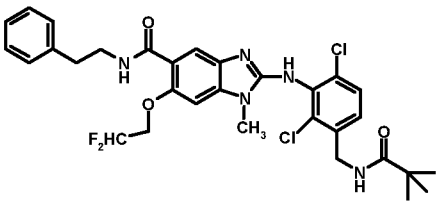
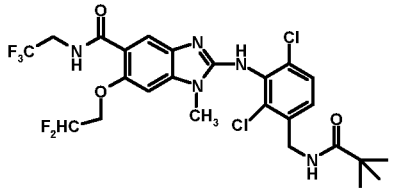
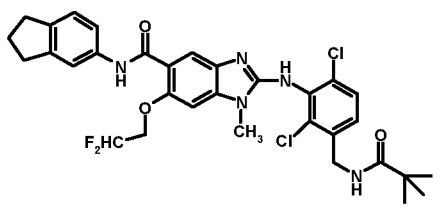
Ex.	Structure	Formula/ Mw.	MS* *m/z* $[M+H]^+$	R_f (TLC, silica gel) or R_t [min] (HPLC-method)	Prepared in analogy to example
19		$C_{27}H_{24}Cl_3F_2N_5O_2$ 594.867	594	R_f = 0.27 (DCM/EtOH 95:5)	17
20		$C_{25}H_{26}Cl_2F_3N_5O_2$ 556.407	556	R_f = 0.22 (DCM/EtOH 95:5)	17
21		$C_{23}H_{23}Cl_2F_4N_5O_2$ 548.360	548	R_f = 0.24 (DCM/EtOH 95:5)	17
22		$C_{27}H_{24}Cl_4FN_5O_2$ 611.321	610	R_f = 0.35 (DCM/EtOH 95:5)	17
23		$C_{27}H_{24}Cl_3F_2N_5O_2$ 594.867	594	R_f = 0.29 (DCM/EtOH 95:5)	17
24		$C_{26}H_{22}Cl_3F_2N_5O_2$ 547.932	548	R_f = 0.19 (DCM/EtOH 95:5)	17

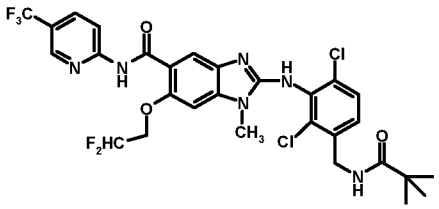
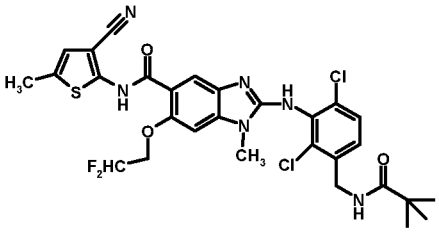
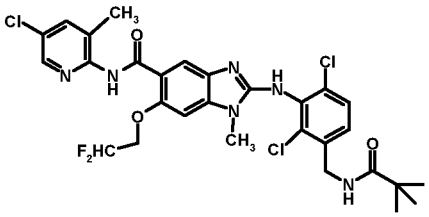
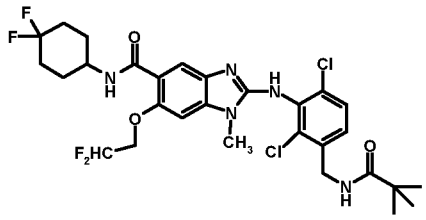
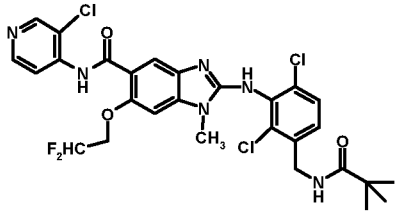
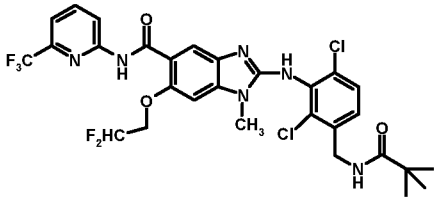
Ex.	Structure	Formula/ Mw.	MS* *m/z* $[M+H]^+$	R_f (TLC, silica gel) or R_t [min] (HPLC-method)	Prepared in analogy to example
25		$C_{30}H_{34}F_7N_5O_3$ 645.612	646	R_f = 0.22 (DCM/EtOH 95:5)	**1**
26		$C_{29}H_{27}ClF_5N_5O_3$ 624.001	624	R_f = 0.27 (DCM/EtOH 95:5)	**11**
27		$C_{25}H_{26}F_7N_5O_3$ 577.495	578	R_f = 0.19 (DCM/EtOH 95:5)	**11**
29		$C_{29}H_{27}Cl_3F_3N_5O_3$ 656.917	656	R_t = 1.78 (method A)	**28**
30		$C_{29}H_{28}Cl_3F_2N_5O_3$ 638.927	638	R_t = 1.76 (method A)	**28**
31		$C_{29}H_{28}Cl_2F_3N_5O_3$ 622.472	622	R_t = 1.69 (method A)	**28**
32		$C_{27}H_{31}Cl_2F_2N_5O_3$ 582.476	582	R_t = 1.51 (method A)	**28**

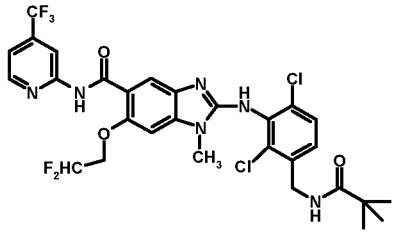
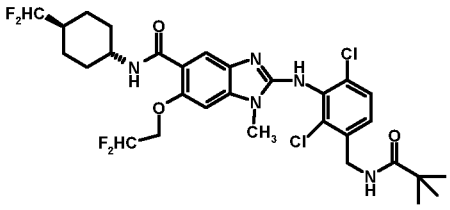
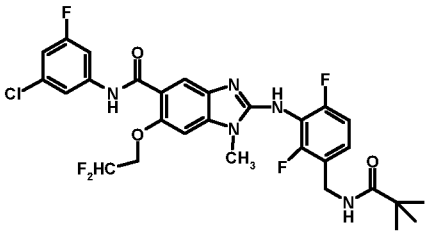
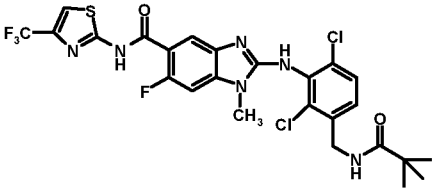
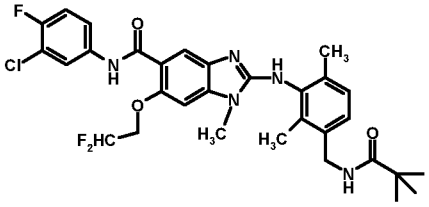
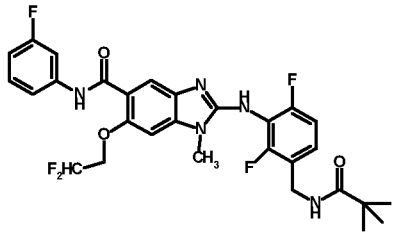
Ex.	Structure	Formula/ Mw.	MS* *m/z* $[M+H]^+$	R_f (TLC, silica gel) or R_t [min] (HPLC-method)	Prepared in analogy to example
33		$C_{29}H_{27}Cl_3F_3N_5O_3$ 656.917	656	R_t = 1.82 (method A)	**28**
34		$C_{30}H_{27}Cl_3F_3N_6O_3S$ 696.003	695	R_t = 1.93 (method A)	**28**
35		$C_{31}H_{30}Cl_2F_5N_5O_3$ 686.506	686	R_t = 1.70 (method A)	**28**
36		$C_{31}H_{29}Cl_2F_6N_5O_3$ 704.496	704	R_t = 1.72 (method A)	**28**
37		$C_{28}H_{33}Cl_2F_2N_5O_4$ 612.502	612	R_t = 1.42 (method A)	**28**
38		$C_{26}H_{26}Cl_2F_7N_5O_3$ 660.415	660	R_t = 1.65 (method A)	**28**
39		$C_{26}H_{28}Cl_2F_5N_5O_3$ 624.435	624	R_t = 1.60 (method A)	**28**

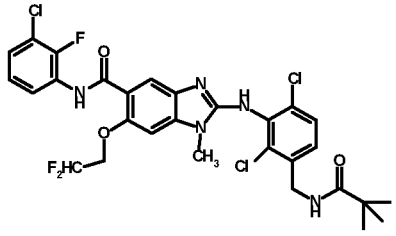
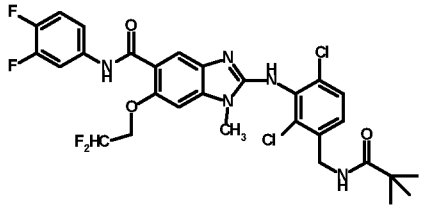
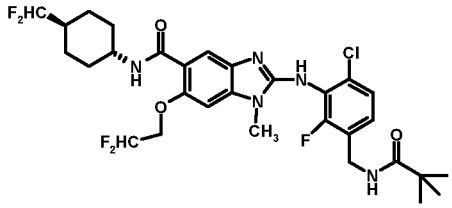
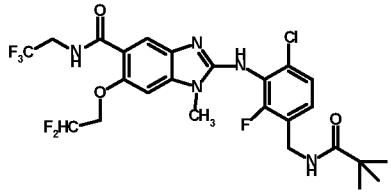
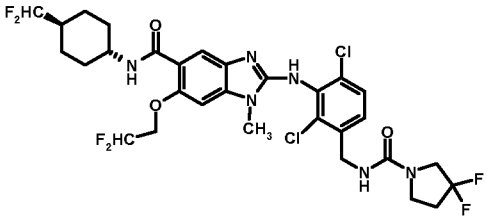
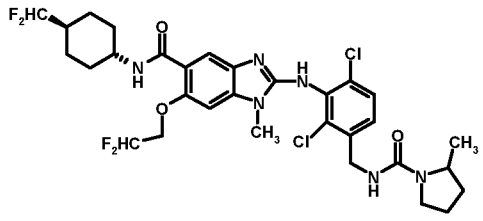
Ex.	Structure	Formula/ Mw.	MS* *m/z* $[M+H]^+$	R_f (TLC, silica gel) or R_t [min] (HPLC-method)	Prepared in analogy to example
40		$C_{29}H_{27}Cl_3F_3N_5O_3$ 656.917	656	R_t = 1.83 (method A)	**28**
41		$C_{26}H_{25}Cl_3F_2N_6O_3S$ 645.943	645	R_t = 1.79 (method A)	**28**
42		$C_{30}H_{29}Cl_2F_5N_6O_3$ 687.494	687	R_t = 1.62 (method A)	**28**
43		$C_{25}H_{27}Cl_2F_4N_5O_3$ 592.418	592	R_t = 1.44 (method A)	**28**
44		$C_{27}H_{29}Cl_4F_2N_5O_3$ 651.366	650	R_t = 1.62 (method A)	**28**
45		$C_{29}H_{27}Cl_3F_3N_5O_3$ 656.917	656	R_t = 1.81 (method A)	**28**

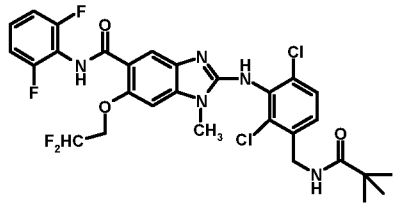
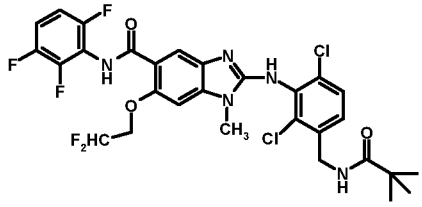
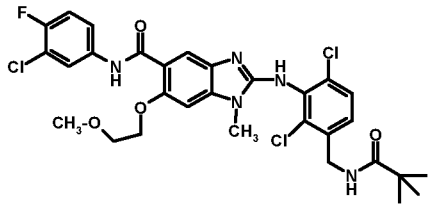
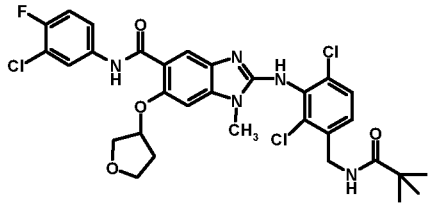
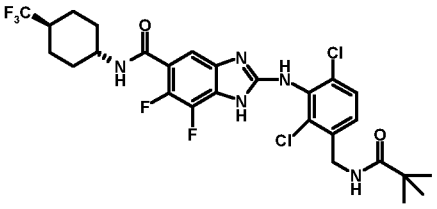
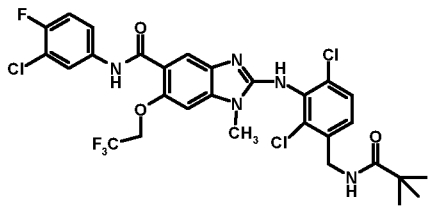
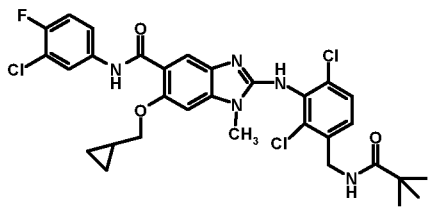
Ex.	Structure	Formula/ Mw.	MS* *m/z* $[M+H]^+$	R_f (TLC, silica gel) or R_t [min] (HPLC-method)	Prepared in analogy to example
46		$C_{28}H_{33}Cl_2F_2N_5O_3$ 596.503	596	R_t = 1.58 (method A)	**28**
47		$C_{29}H_{27}Cl_2F_5N_6O_3$ 673.467	673	R_t = 1.74 (method A)	**28**
48		$C_{26}H_{28}Cl_2F_5N_5O_3$ 624.435	624	R_t = 1.54 (method A)	**28**
49		$C_{31}H_{39}Cl_2F_2N_5O_4$ 654.582	654	R_t = 1.66 (method A)	**28**
50		$C_{29}H_{29}Cl_2F_2N_5O_5S$ 668.546	668	R_t = 1.70 (method A)	**28**
51		$C_{28}H_{33}Cl_2F_2N_5O_3$ 596.503	596	R_t = 1.56 (method A)	**28**
52		$C_{30}H_{37}Cl_2F_2N_5O_3$ 624.556	624	R_t = 1.69 (method A)	**28**

Ex.	Structure	Formula/ Mw.	MS* *m/z* $[M+H]^+$	R_f (TLC, silica gel) or R_t [min] (HPLC-method)	Prepared in analogy to example
53		$C_{27}H_{31}Cl_2F_2N_5O_3$ 582.476	582	R_t = 1.50 (method A)	**28**
54		$C_{30}H_{30}Cl_3F_2N_5O_3$ 652.954	652	R_t = 1.77 (method A)	**28**
55		$C_{30}H_{35}Cl_2F_2N_5O_3$ 622.541	622	R_t = 1.65 (method A)	**28**
56		$C_{25}H_{29}Cl_2F_2N_5O_3$ 556.438	556	R_t = 1.36 (method A)	**28**
57		$C_{31}H_{33}Cl_2F_2N_5O_3$ 632.536	632	R_t = 1.62 (method A)	**28**
58		$C_{25}H_{26}Cl_2F_5N_5O_3$ 610.408	610	R_t = 1.54 (method A)	**28**
59		$C_{32}H_{33}Cl_2F_2N_5O_3$ 644.647	644	R_t = 1.77 (method A)	**28**

Ex.	Structure	Formula/ Mw.	MS* *m/z* $[M+H]^+$	R_f (TLC, silica gel) or R_t [min] (HPLC-method)	Prepared in analogy to example
61		$C_{29}H_{27}Cl_2F_5N_6O_3$ 673.461	673	R_t = 2.74 (method D)	**60**
62		$C_{29}H_{28}Cl_2F_2N_6O_3S$ 649.539	649	R_t = 2.73 (method D)	**60**
63		$C_{29}H_{29}Cl_3F_5N_6O_3$ 653.934	653	R_t = 2.63 (method D)	**60**
64		$C_{29}H_{33}Cl_2F_4N_5O_3$ 646.503	646	R_t = 2.61 (method D)	**60**
65		$C_{29}H_{27}Cl_3F_2N_6O_3$ 639.908	639	R_t = 2.65 (method D)	**60**
66		$C_{29}H_{27}Cl_2F_5N_6O_3$ 673.461	673	R_t = 2.70 (method D)	**60**

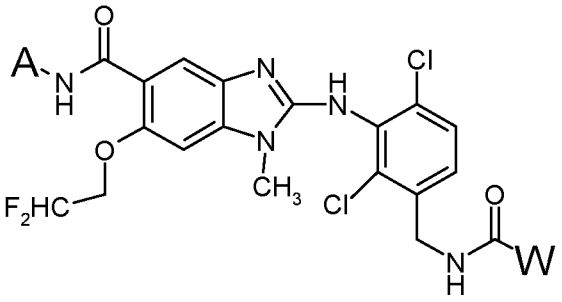
Ex.	Structure	Formula/ Mw.	MS* *m/z* $[M+H]^+$	R_f (TLC, silica gel) or R_t [min] (HPLC-method)	Prepared in analogy to example
67		$C_{29}H_{27}Cl_2F_5N_6O_3$ 673.461	673	R_t = 2.72 (method D)	**60**
68		$C_{30}H_{35}Cl_2F_4N_5O_3$ 660.530	660	R_t = 2.64 (method D)	**60**
69		$C_{29}H_{27}ClF_5N_5O_3$ 624.001	624	R_f = 0.26 (DCM/EtOH 95:5)	**11**
70		$C_{25}H_{22}Cl_2F_4N_6O_2S$ 617.446	617	R_f = 0.26 (DCM/EtOH 95:5)	**17**
71		$C_{31}H_{33}ClF_3N_5O_3$ 616.074	616	R_f = 0.19 (DCM/EtOH 95:5)	**14**
72		$C_{29}H_{28}F_5N_5O_3$ 589.557	590	R_f = 0.27 (DCM/EtOH 95:5)	**6**

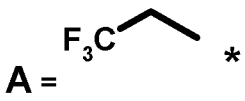
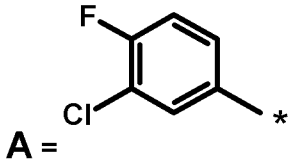
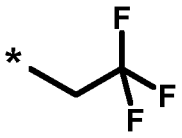
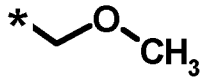
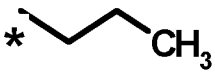
Ex.	Structure	Formula/ Mw.	MS* *m/z* $[M+H]^+$	R_f (TLC, silica gel) or R_t [min] (HPLC-method)	Prepared in analogy to example
73		$C_{29}H_{27}Cl_3F_3N_5O_3$ 656.910	656	R_f = 0.28 (DCM/EtOH 95:5)	**7**
74		$C_{29}H_{27}Cl_2F_4N_5O_3$ 640.456	640	R_t = 1.45 (method B)	**7**
76		$C_{30}H_{34}ClF_6N_5O_3$ 662.066	662	R_t = 1.42 (method B)	**75**
77		$C_{25}H_{26}ClF_6N_5O_3$ 593.949	594	R_t = 1.31 (method B)	**75**
81		$C_{30}H_{31}Cl_2F_7N_6O_3$ 727.500	727	R_f = 0.28 (DCM/EtOH 95:5)	**80**
82		$C_{30}H_{31}Cl_2F_7N_6O_3$ 705.546	705	R_f = 0.23 (DCM/EtOH 95:5)	**80**

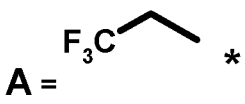
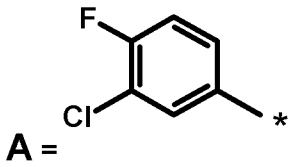
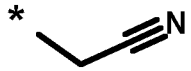
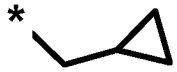
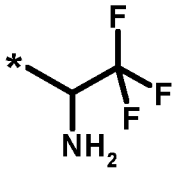
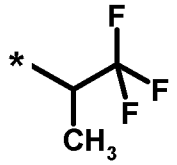
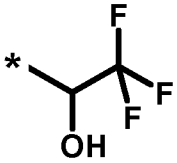
Ex.	Structure	Formula/ Mw.	MS* *m/z* $[M+H]^+$	R_f (TLC, silica gel) or R_t [min] (HPLC-method)	Prepared in analogy to example
83		$C_{29}H_{27}Cl_2F_4N_5O_3$ 640.456	640	R_f = 0.28 (DCM/EtOH 95:5)	**7**
85		$C_{29}H_{26}Cl_2F_5N_5O_3$ 658.446	658	R_f = 0.25 (DCM/EtOH 95:5)	**7**
178		$C_{30}H_{31}Cl_3FN_5O_4$ 650.955	650	R_t = 2.08 (method E)	**177**
179		$C_{31}H_{31}Cl_3FN_5O_4$ 662.966	662	R_t = 2.01 (method E)	**177**
180		$C_{27}H_{28}Cl_2F_5N_5O_2$ 620.441	620	R_t = 2.10 (method E)	**79**
181		$C_{29}H_{26}Cl_3F_4N_5O_3$ 674.900	674	R_t = 2.18 (method E)	**177**
182		$C_{31}H_{31}Cl_3FN_5O_3$ 646.966	646	Rt = 2.23 (method E)	**177**

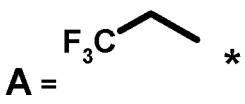
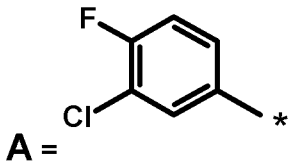
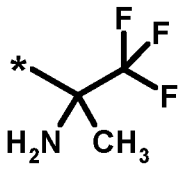
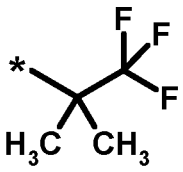
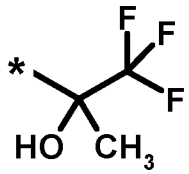
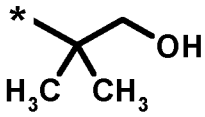
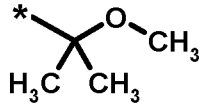
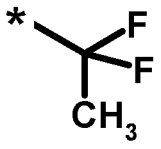
The following examples in Table 2 are prepared in analogy to example 84 (A and W are as defined in the table).

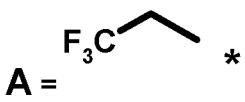
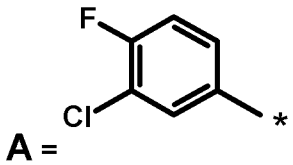
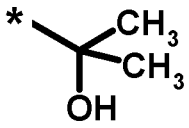
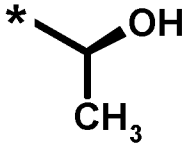
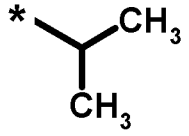
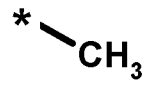
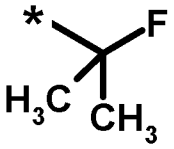
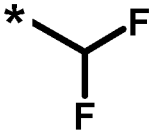
Table 2

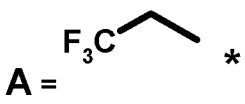
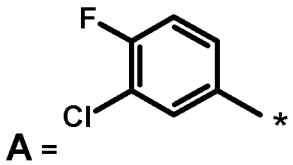
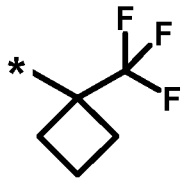
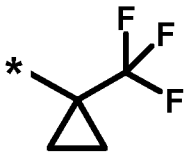
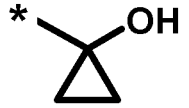
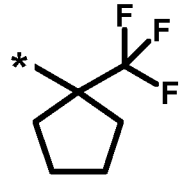


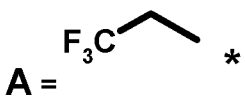
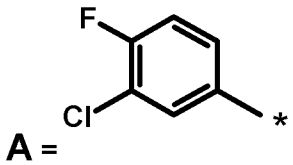
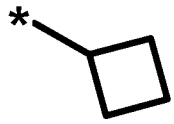
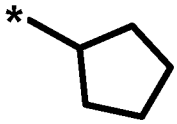
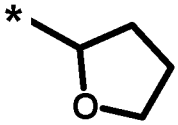
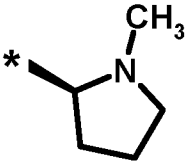
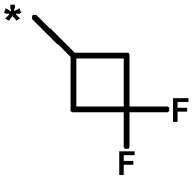
Ex.	A = 	Ex.	A = 	W =
128	$C_{23}H_{19}Cl_2F_8N_5O_3$ MW: 636,325 MS* *m/z* $[M+H]^+$ = 636 R_t = 1,5 (method I)	**131**	$C_{27}H_{20}Cl_3F_6N_5O_3$ MW: 682,834 MS* *m/z* $[M+H]^+$ = 682 R_t = 1,70 (method I)	
101	$C_{23}H_{22}Cl_2F_5N_5O_4$ MW: 598,354 MS* *m/z* $[M+H]^+$ = 598 Rt = 1,40 (method I)	**163**	$C_{27}H_{23}Cl_3F_3N_5O_4$ MW: 644,863 MS* *m/z* $[M+H]^+$ = 644 Rt = 1,61 (method I)	
104	$C_{22}H_{20}Cl_2F_5N_5O_4$ MW: 584,33 MS* *m/z* $[M+H]^+$ = 584 Rt = 1,34 (method I)	**139**	$C_{26}H_{21}Cl_3F_3N_5O_4$ MW: 630,836 MS* *m/z* $[M+H]^+$ = 630 Rt = 1,54 (method I)	
106	$C_{24}H_{24}Cl_2F_5N_5O_3$ MW: 596,382 MS* *m/z* $[M+H]^+$ = 596 Rt = 0,47 (method H)	**132**	$C_{28}H_{25}Cl_3F_3N_5O_3$ MW: 642,89 MS* *m/z* $[M+H]^+$ = 642 Rt = 1,67(method I)	

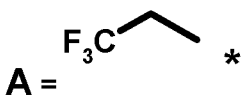
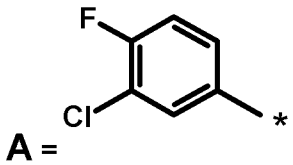
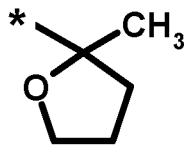
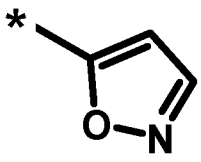
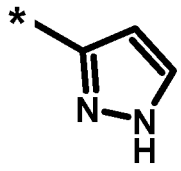
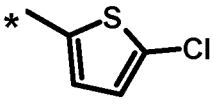
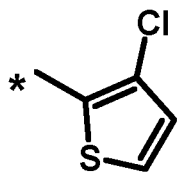
Ex.	A = 	Ex.	A = 	W =
111	$C_{23}H_{22}Cl_2F_5N_5O_3$ MW: 582,355 MS* *m/z* $[M+H]^+$ = 582 Rt = 1,42 (method I)	**146**	$C_{27}H_{23}Cl_3F_3N_5O_3$ MW: 628,864 MS* *m/z* $[M+H]^+$ = 528 Rt = 1,63 (method I)	
112	$C_{23}H_{19}Cl_2F_5N_6O_3$ MW: 593,338 MS* *m/z* $[M+H]^+$ = 593 Rt = 1,41 (method I)	**154**	$C_{27}H_{20}Cl_3F_3N_6O_3$ MW: 639,847 MS* *m/z* $[M+H]^+$ = 639 Rt = 0,52 (method H)	
88	$C_{25}H_{24}Cl_2F_5N_5O_3$ MW: 608,393 MS* *m/z* $[M+H]^+$ = 608 Rt = 1,48 (method I)	**144**	$C_{29}H_{25}Cl_3F_3N_5O_3$ MW: 654,902 MS* *m/z* $[M+H]^+$ = 654 Rt = 1,68 (method I)	
87	$C_{23}H_{20}Cl_2F_8N_6O_3$ MW: 651,34 MS* *m/z* $[M+H]^+$ = 651 Rt = 0,46 (method H)	**164**	$C_{27}H_{21}Cl_3F_6N_6O_3$ MW: 697,849 MS* *m/z* $[M+H]^+$ = 697 Rt = 0,54 (method H)	
89	$C_{24}H_{21}Cl_2F_8N_5O_3$ MW: 650,352 MS* *m/z* $[M+H]^+$ = 650 Rt = 0,50 (method H)	**141**	$C_{28}H_{22}Cl_3F_6N_5O_3$ MW: 696,861 MS* *m/z* $[M+H]^+$ = 696 Rt = 0,58 (method H)	
96	$C_{23}H_{19}Cl_2F_8N_5O_4$ MW: 652,324 MS* *m/z* $[M+H]^+$ = 652 Rt = 1,47 (method I)	**161**	$C_{27}H_{20}Cl_3F_6N_5O_4$ MW: 698,833 MS* *m/z* $[M+H]^+$ = 698 Rt = 1,66 (method I)	

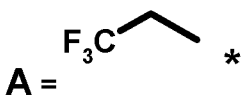
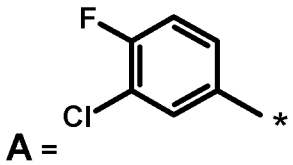
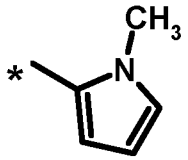
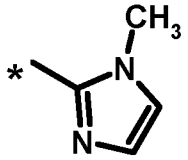
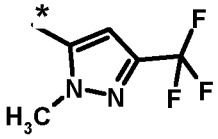
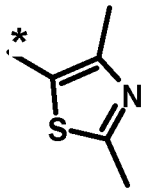
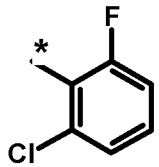
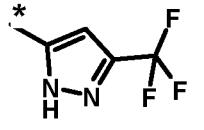
Ex.	A = 	Ex.	A = 	W =
98	$C_{24}H_{22}Cl_2F_8N_6O_3$ MW: 665,367 MS* *m/z* $[M+H]^+$ = 665 Rt = 0,48 (method H)	**152**	$C_{28}H_{23}Cl_3F_6N_6O_3$ MW: 711,876 MS* *m/z* $[M+H]^+$ = 711 Rt = 0,56 (method H)	
116	$C_{25}H_{23}Cl_2F_8N_5O_3$ MW: 664,379 MS* *m/z* $[M+H]^+$ = 664 Rt = 0,52 (method H)	**176**	$C_{29}H_{24}Cl_3F_6N_5O_3$ MW: 710,88 MS* *m/z* $[M+H]^+$ = 710 Rt = 1,78 (method I)	
123	$C_{24}H_{21}Cl_2F_8N_5O_4$ MW: 666,351 MS* *m/z* $[M+H]^+$ = 666 Rt = 1,49 (method I)	**149**	$C_{28}H_{22}Cl_3F_6N_5O_4$ MW: 712,86 MS* *m/z* $[M+H]^+$ = 712 Rt = 0,56 (method H)	
126	$C_{25}H_{26}Cl_2F_5N_5O_4$ MW: 626,407 MS* *m/z* $[M+H]^+$ = 626 Rt = 1,41 (method I)	**155**	$C_{29}H_{27}Cl_3F_3N_5O_4$ MW: 672,916 MS* *m/z* $[M+H]^+$ = 672 Rt = 0,53 (method H)	
130	$C_{25}H_{26}Cl_2F_5N_5O_4$ MW: 626,407 MS* *m/z* $[M+H]^+$ = 626 Rt = 1,48 (method I)	**135**	$C_{29}H_{27}Cl_3F_3N_5O_4$ MW: 672,916 MS* *m/z* $[M+H]^+$ = 672 Rt = 1,68 (method I)	
95	$C_{23}H_{20}Cl_2F_7N_5O_3$ MW: 618,335 MS* *m/z* $[M+H]^+$ = 618 Rt = 0,48 (method H)	**162**	$C_{27}H_{21}Cl_3F_3N_5O_3$ MW: 664,844 MS* *m/z* $[M+H]^+$ = 664 Rt = 1,70 (method I)	

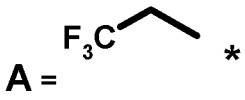
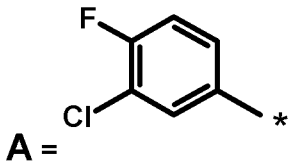
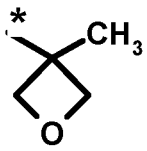
Ex.	A = 	Ex.	A = 	W =
108	$C_{24}H_{24}Cl_2F_5N_5O_4$ MW: 612,381 MS* *m/z* $[M+H]^+$ = 612 Rt = 0,44 (method H)	**175**	$C_{28}H_{25}Cl_3F_3N_5O_4$ MW: 658,89 MS* *m/z* $[M+H]^+$ = 658 Rt = 1,60 (method I)	
109	$C_{23}H_{22}Cl_2F_5N_5O_4$ MW: 598,354 MS* *m/z* $[M+H]^+$ = 598 Rt = 1,36 (method I)	**147**	$C_{27}H_{23}Cl_3F_3N_5O_4$ MW: 644,863 MS* *m/z* $[M+H]^+$ = 644 Rt = 0,51 (method H)	
110	$C_{24}H_{24}Cl_2F_5N_5O_3$ MW: 596,382 MS* *m/z* $[M+H]^+$ = 596 Rt = 1,47 (method I)	**151**	$C_{28}H_{25}Cl_3F_3N_5O_3$ MW: 642,89 MS* *m/z* $[M+H]^+$ = 642 Rt = 0,55 (method H)	
115	$C_{22}H_{20}Cl_2F_5N_5O_3$ MW: 568,328 MS* *m/z* $[M+H]^+$ = 568 Rt = 1,37 (method I)	**173**	$C_{26}H_{21}Cl_3F_3N_5O_3$ MW: 614,837 MS* *m/z* $[M+H]^+$ = 614 Rt = 1,58 (method I)	
118	$C_{24}H_{23}Cl_2F_6N_5O_3$ MW: 614,372 MS* *m/z* $[M+H]^+$ = 614 Rt = 0,49 (method H)			
124	$C_{22}H_{18}Cl_2F_7N_5O_3$ MW: 604,308 MS* *m/z* $[M+H]^+$ = 604 Rt = 1,45 (method I)	**159**	$C_{26}H_{19}Cl_3F_5N_5O_3$ MW: 650,817 MS* *m/z* $[M+H]^+$ = 650 Rt = 0,55 (method H)	

Ex.	A = 	Ex.	A = 	W =
86	$C_{26}H_{23}Cl_2F_8N_5O_3$ MW: 676,39 MS* *m/z* $[M+H]^+$ = 676 Rt = 0,53 (method H)	**157**	$C_{30}H_{24}Cl_3F_6N_5O_3$ MW: 722,899 MS* *m/z* $[M+H]^+$ = 722 Rt = 1,78 (method I)	
99	$C_{25}H_{21}Cl_2F_8N_5O_3$ MW: 662,363 MS* *m/z* $[M+H]^+$ = 662 Rt = 0,52 (method H)	**174**	$C_{29}H_{22}Cl_3F_6N_5O_3$ MW: 708,872 MS* *m/z* $[M+H]^+$ = 708 Rt = 1,76 (method I)	
103	$C_{25}H_{24}Cl_2F_5N_5O_3$ MW: 608,393 MS* *m/z* $[M+H]^+$ = 608 Rt = 1,50 (method I)	**133**	$C_{29}H_{25}Cl_3F_3N_5O_3$ MW: 654,902 MS* *m/z* $[M+H]^+$ = 654 Rt = 0,57 (method H)	
93	$C_{24}H_{22}Cl_2F_5N_5O_4$ MW: 610,365 MS* *m/z* $[M+H]^+$ = 610 Rt = 0,43 (method H)	**171**	$C_{28}H_{23}Cl_3F_3N_5O_4$ MW: 656,874 MS* *m/z* $[M+H]^+$ = 656 Rt = 1,60 (method I)	
97	$C_{27}H_{25}Cl_2F_8N_5O_3$ MW: 690,417 MS* *m/z* $[M+H]^+$ = 690 Rt = 0,55 (method H)	**165**	$C_{31}H_{26}Cl_3F_6N_5O_3$ MW: 736,925 MS* *m/z* $[M+H]^+$ = 736 Rt = 1,84 (method I)	
113	$C_{25}H_{21}Cl_2F_5N_6O_3$ MW: 619,378 MS* *m/z* $[M+H]^+$ = 619 Rt = 0,47 (method H)	**145**	$C_{29}H_{22}Cl_3F_3N_6O_3$ MW: 665,885 MS* *m/z* $[M+H]^+$ = 665 Rt = 0,56 (method H)	

Ex.	A = 	Ex.	A = 	W =
100	$C_{24}H_{22}Cl_2F_5N_5O_3$ MW: 594,366 MS* *m/z* $[M+H]^+$ = 594 Rt = 1,45 (method I)	**148**	$C_{28}H_{23}Cl_3F_3N_5O_3$ MW: 640,875 MS* *m/z* $[M+H]^+$ = 640 Rt = 0,55 (method H)	
91	$C_{25}H_{24}Cl_2F_5N_5O_3$ MW: 608,393 MS* *m/z* $[M+H]^+$ = 608 Rt = 1,49 (method I)	**172**	$C_{29}H_{25}Cl_3F_3N_5O_3$ MW: 654,902 MS* *m/z* $[M+H]^+$ = 654 Rt = 0,56 (method H)	
120	$C_{26}H_{26}Cl_2F_5N_5O_3$ MW: 622,419 MS* *m/z* $[M+H]^+$ = 622 Rt = 1,54 (method I)	**160**	$C_{30}H_{27}Cl_3F_3N_5O_3$ MW: 668,928 MS* *m/z* $[M+H]^+$ = 668 Rt = 1,74 (method I)	
90	$C_{25}H_{24}Cl_2F_5N_5O_4$ MW: 624,392 MS* *m/z* $[M+H]^+$ = 624 Rt = 0,46 (method H)	**137**	$C_{29}H_{25}Cl_3F_3N_5O_4$ MW: 670,9 MS* *m/z* $[M+H]^+$ = 670 Rt = 0,54 (method H)	
94	$C_{26}H_{27}Cl_2F_5N_6O_3$ MW: 637,434 MS* *m/z* $[M+H]^+$ = 637 Rt = 0,49 (method H)	**169**	$C_{30}H_{28}Cl_3F_3N_6O_3$ MW: 683,943 MS* *m/z* $[M+H]^+$ = 683 Rt = 0,57 (method H)	
102	$C_{25}H_{22}Cl_2F_7N_5O_3$ MW: 644,373 MS* *m/z* $[M+H]^+$ = 644 Rt = 0,49 (method H)	**167**	$C_{29}H_{23}Cl_3F_5N_5O_3$ MW: 690,882 MS* *m/z* $[M+H]^+$ = 690 Rt = 0,57 (method H)	

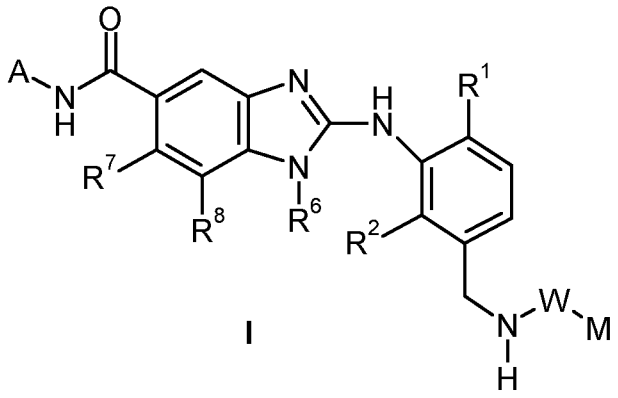
Ex.	A = 	Ex.	A = 	W =
119	$C_{24}H_{20}Cl_2F_7N_5O_3$ MW: 630,346 MS* *m/z* $[M+H]^+$ = 630 Rt = 0,48 (method H)	**153**	$C_{28}H_{21}Cl_3F_5N_5O_3$ MW: 676,855 MS* *m/z* $[M+H]^+$ = 676 Rt = 1,69 (method I)	
122	$C_{26}H_{26}Cl_2F_5N_5O_4$ MW: 638,418 MS* *m/z* $[M+H]^+$ = 638 Rt = 1,48 (method I)	**170**	$C_{30}H_{27}Cl_3F_3N_5O_4$ MW: 684,927 MS* *m/z* $[M+H]^+$ = 684 Rt = 0,56 (method H)	
107	$C_{24}H_{19}Cl_2F_5N_6O_4$ MW: 621,348 MS* *m/z* $[M+H]^+$ = 621 Rt = 1,44 (method I)	**166**	$C_{28}H_{20}Cl_3F_3N_6O_4$ MW: 667,857 MS* *m/z* $[M+H]^+$ = 667 Rt = 0,54 (method H)	
127	$C_{24}H_{20}Cl_2F_5N_7O_3$ MW: 620,364 MS* *m/z* $[M+H]^+$ = 620 Rt = 0,44 (method H)	**134**	$C_{28}H_{21}Cl_3F_3N_7O_3$ MW: 666,873 MS* *m/z* $[M+H]^+$ = 666 Rt = 0,54 (method H)	
92	$C_{25}H_{19}Cl_3F_5N_5O_3S$ MW: 670,872 MS* *m/z* $[M+H]^+$ = 670 Rt = 0,54 (method H)	**140**	$C_{29}H_{20}Cl_4F_3N_5O_3S$ MW: 717,381 MS* *m/z* $[M+H]^+$ = 717 Rt = 1,82 (method I)	
117	$C_{25}H_{19}Cl_3F_5N_5O_3S$ MW: 670,872 MS* *m/z* $[M+H]^+$ = 670 Rt = 0,53 (method H)	**168**	$C_{29}H_{20}Cl_4F_3N_5O_3S$ MW: 717,381 MS* *m/z* $[M+H]^+$ = 717 Rt = 1,76 (method I)	

Ex.	A = 	Ex.	A = 	W =
114	$C_{26}H_{23}Cl_2F_5N_6O_3$ MW: 633,403 MS* *m/z* $[M+H]^+$ = 633 Rt = 1,53 (method I)	**142**	$C_{30}H_{24}Cl_3F_3N_6O_3$ MW: 679,912 MS* *m/z* $[M+H]^+$ = 679 Rt = 0,54 (method H)	
121	$C_{25}H_{22}Cl_2F_5N_7O_3$ MW: 634,391 MS* *m/z* $[M+H]^+$ = 634 Rt = 1,35 (method I)	**156**	$C_{29}H_{23}Cl_3F_3N_7O_3$ MW: 680,9 MS* *m/z* $[M+H]^+$ = 680 Rt = 0,55 (method H)	
125	$C_{26}H_{21}Cl_2F_8N_7O_3$ MW: 702,388 MS* *m/z* $[M+H]^+$ = 702 Rt = 0,54 (method H)	**143**	$C_{30}H_{22}Cl_3F_6N_7O_3$ MW: 748,897 MS* *m/z* $[M+H]^+$ = 748 Rt = 1,81 (method I)	
129	$C_{26}H_{23}Cl_2F_5N_6O_3S$ MW: 665,469 MS* *m/z* $[M+H]^+$ = 665 Rt = 0,47 (method H)	**138**	$C_{30}H_{24}Cl_3F_3N_6O_3S$ MW: 711,978 MS* *m/z* $[M+H]^+$ = 711 Rt = 1,64 (method I)	
105	$C_{27}H_{20}Cl_3F_6N_5O_3$ MW: 682,834 MS* *m/z* $[M+H]^+$ = 682 Rt = 0,47 (method H)	**158**	$C_{31}H_{21}Cl_4F_4N_5O_3$ MW: 729,343 MS* *m/z* $[M+H]^+$ = 729 Rt = 1,74 (method I)	
		136	$C_{29}H_{20}Cl_3F_6N_7O_3$ MW: 734,87 MS* *m/z* $[M+H]^+$ = 734 Rt = 1,74 (method I)	

Ex.	A = 	Ex.	A = 	W =
		150	$C_{29}H_{25}Cl_3F_3N_5O_4$ MW: 670,9 MS* *m/z* $[M+H]^+$ = 670 Rt = 1,60 (method I)	

Claims

1. A compound of formula **I**



I

in which

R^1 and **R^2** independently represent halo, -C_{1-3}alkyl, which latter alkyl group is optionally substituted by one or more fluorine atoms;

W represents -C(O)-, -C(O)O-, which groups are bound to the nitrogen of the –NH- moiety via the carbon atom;

M represents

-C_{1-6}alkyl, -C_{3-7}cycloalkyl, both of which groups are optionally substituted by one or more groups selected from -F, -OH, -CN, -NH_2, -NH(C_{1-2}alkyl), -N (C_{1-2}alkyl)$_2$, -OC_{1-3}alkyl, -C_{1-5}alkyl, -C_{3-4}cycloalkyl, in which latter three groups the alkyl or cycloalkyl groups are optionally substituted by one or more fluorine atoms;

or

oxetanyl-, tetrahydrofuranyl-, tetrahydropyranyl-, azetidinyl-, pyrrolidinyl-, piperidinyl-, all of which groups are optionally substituted by one or more substituents selected from fluoro, -CN, -C_{1-3} alkyl, which latter alkyl group is optionally substituted by one or more fluorine atoms;

or

phenyl-, pyridyl-, thienyl-, pyrrolyl-, pyrazolyl-, imidazolyl-, thiazolyl-, oxazolyl-, or isoxazolyl-, all of which groups are optionally substituted by one or more substituents selected from halo, -CN or -C_{1-3}alkyl, which latter alkyl group is optionally further substituted by one or more fluorine atoms;

R^8 represents –H, halogen, -C_{1-3}alkyl, which latter alkyl group is optionally substituted by one or more fluorine atoms;

R^6 represents –H, -C_{1-5}alkyl, -C_{3-5}cycloalkyl-C_{0-2}alkyl, in which latter three groups the alkyl or cycloalkyl fragments are optionally substituted by one or more fluorine atoms;

R^7 represents halo, C_{1-5}alkyl-O-, C_{3-7}cycloalkyl-C_{0-2}alkyl-O-, 4-7-membered heterocycloalkyl-C_{0-2}alkyl-O-, in which latter three groups the alkyl, cycloalkyl or heterocycloalkyl fragments are optionally substituted by one or more substituents selected from -F and -OC_{1-3}alkyl which latter alkyl group is optionally further substituted by one or more fluorine atoms;

A represents C_{1-8} alkyl-, phenyl-, indanyl-, naphthyl-, 1,2,3,4-tetrahydronaphthyl-, pyridyl-, thienyl-, benzothienyl-, pyrrolyl-, indolyl-pyrazolyl-, indazolyl-, thiazolyl-, benzothiazolyl-, oxazolyl-, benzooxazolyl-, isoxazolyl-, benzisoxazolyl-, phenyl-C_{1-3}alkyl-, thienyl-C_{1-3}alkyl-, pyridyl-C_{1-3}alkyl-, C_{3-7}cycloalkyl-C_{0-3}alkyl-, oxetanyl-C_{0-3}alkyl-, tetrahydrofuranyl-C_{0-3}alkyl, tetrahydropyranyl-C_{0-3}alkyl, in which groups the alkyl-, cycloalkyl- and heterocycloalkyl fragments are optionally substituted by one or more substituents selected from R^{9a} and the aryl and heteroaryl fragments are optionally substituted by one or more substituents selected from R^{9b};

each R^{9a} independently represents -F, -Cl, -C_{1-3}alkyl which is optionally substituted by one or more substituents selected from -F, -OC_{1-3} alkyl;

each R^{9b} represents independently -halo, -CN; -C_{1-3} alkyl which is optionally substituted by one or more fluorine atoms;

or a salt thereof.

2. A compound according to claim 1, wherein

R^8 represents –H or fluoro.

3. A compound according to claim 1 or 2, wherein

R^6 represents -H, $-CH_3$, cyclopropyl.

4. A compound according to any one of the preceding claims, wherein

R^1 and **R^2** independently represent chloro, fluoro, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$.

5. A compound according to any one of the preceding claims, wherein

R^7 represents fluoro, $-OCHF_2$, $-OCF_3$, $-OCH_2CH_2F$, $-OCH_2CHF_2$, $-OCH_2CF_3$, -O-tetrahydrofuran-3-yl, -O-CH_2-cyclopropyl.

6. A compound according to any one of the preceding claims, wherein

A represents C_{1-4} alkyl-, C_{3-7}cycloalkyl-C_{0-2}alkyl-, tetrahydrofuranyl-methyl-, phenyl-C_{1-2} alkyl-, pyridyl-methyl-, phenyl-, indanyl-, pyridyl-, thienyl-, thiazolyl-, benzothiazolyl-, in which groups the alkyl-, cycloalkyl- and heterocycloalkyl-fragments are optionally substituted by one or more substituents selected from -F, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, and the aryl and heteroaryl fragments are optionally substituted by -F, -Cl, -Br, -CN, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$.

7. A compound according to any one of the preceding claims, wherein

M represents

$-C_{1-4}$ alkyl, $-C_{3-5}$ cycloalkyl, both of which groups are optionally substituted by one or more groups selected from -F, -OH, -CN, $-NH_2$, $-OCH_3$, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, cyclopropyl;

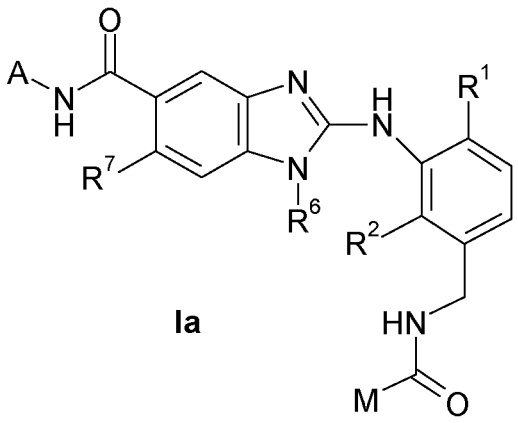
or

oxetanyl-, tetrahydrofuranyl-, azetidinyl- or pyrrolidinyl-, all of which groups are optionally substituted by one or more substituents selected from -F, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$;

or

phenyl-, indanyl-, thienyl-, pyrrolyl-, pyrazolyl-, imidazolyl-, thiazolyl-, or isoxazolyl-, all of which groups are optionally substituted by one or more substituents selected from –F, -Cl, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$.

8. A compound according to any one of the preceding claims, namely a compound of formula **Ia**



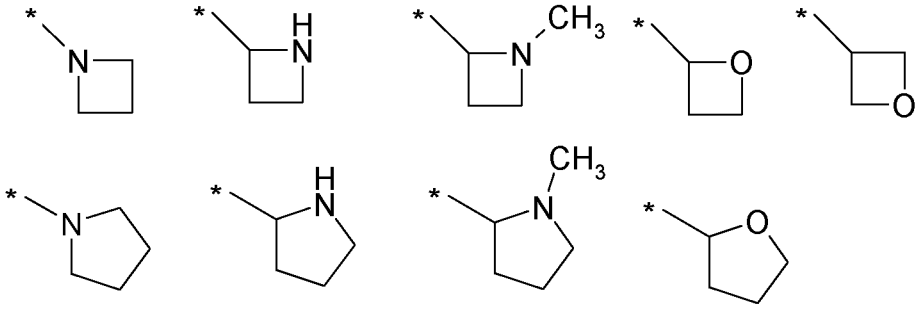
Ia

in which

M represents

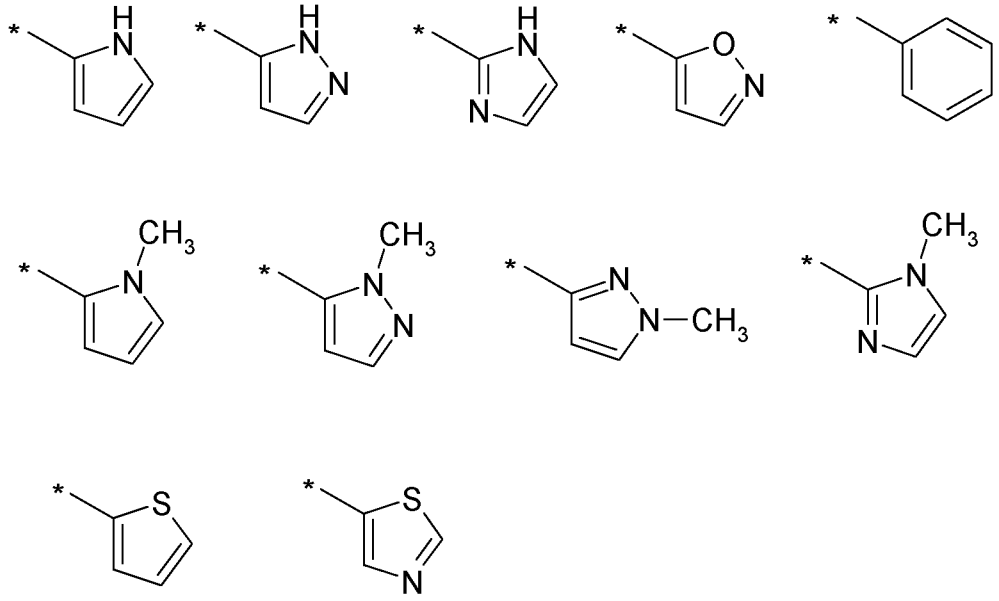
methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *s*-butyl, *t*-butyl, cyclopropyl, $-CH_2$-cyclopropyl, cyclobutyl, cyclopentyl, all of which groups are optionally substituted by one or more groups selected from -F, -OH, -CN, $-NH_2$, $-OCH_3$, $-CH_3$, $-CF_3$;

or is selected from the following groups



which latter nine groups are optionally substituted by one or more substituents selected from -F, $-CH_3$, $-CF_3$;

or is selected from the following groups



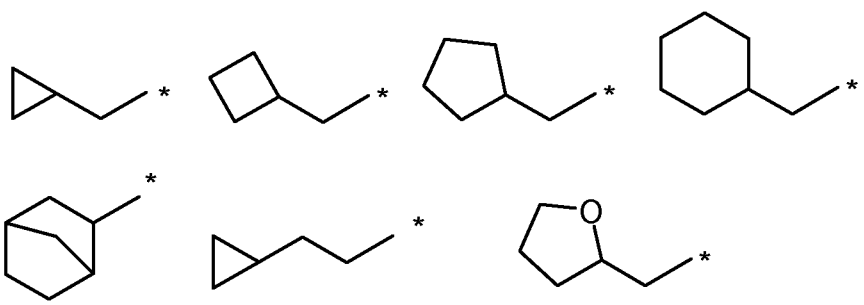
which latter eleven groups are optionally substituted by one or more substituents selected from -F, -Cl, $-CH_3$, $-CF_3$;

and

A, R^1, R^2, R^6, R^7 have the same meaning as defined in any of the preceding claims.

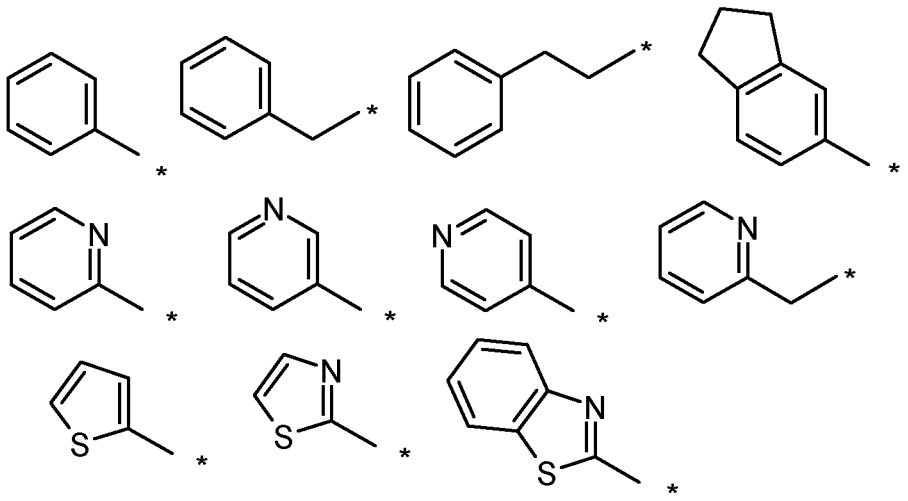
9. A compound according to claim 8, wherein

A represents methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *s*-butyl, *t*-butyl, which latter seven groups are optionally substituted by one or more fluorine atoms,
or cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, which latter four groups are optionally substituted by one or more substituents selected from -F, $-CH_3$, $-CHF_2$, $-CF_3$;
or is selected from the following groups:



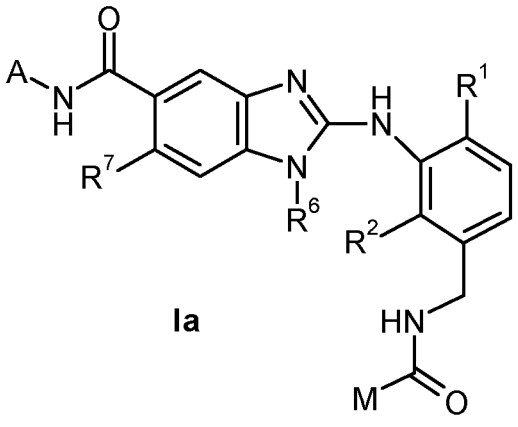
which latter seven groups are optionally substituted by one or more substituents selected from -F, -CH_3, -CHF_2, -CF_3;

or is selected from the following groups:

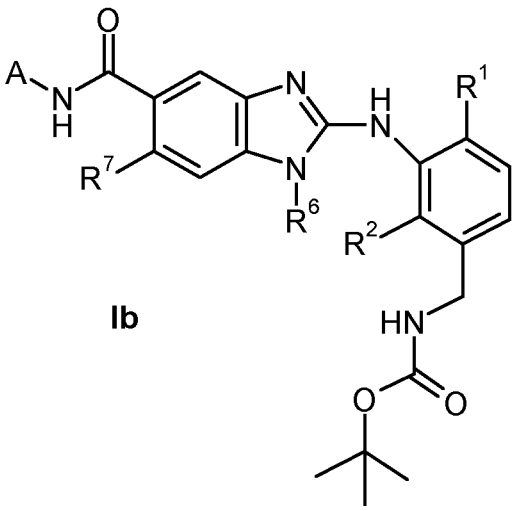


in which latter eleven groups the aryl and heteroaryl fragments are optionally substituted by one or more substituents selected from -F, -Cl, -Br, -CN, -CH_3, -CF_3.

10. A compound according to any one of the preceding claims, namely a compound of formula **Ia** or **Ib**



Ia



Ib

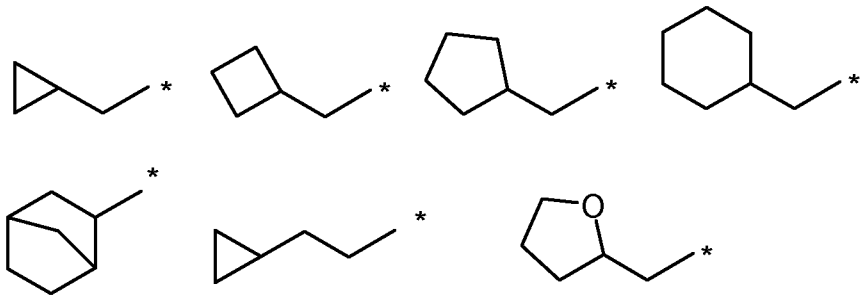
in which

R^1 and R^2 independently represent –chloro, fluoro, -CH_3, -CH_2F, -CHF_2, -CF_3;

R^6 represents -H, -CH_3, cyclopropyl;

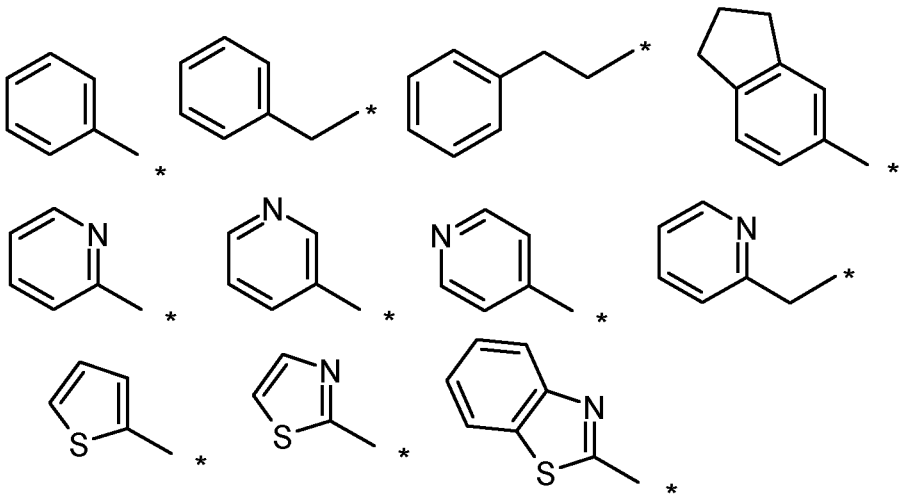
R^7 represents fluoro, $-OCHF_2$, $-OCF_3$, $-OCH_2CH_2F$, $-OCH_2CHF_2$, $-OCH_2CF_3$, tetrahydrofuran-3-yl-O-, -O-CH_2-cyclopropyl;

A represents methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *s*-butyl, *t*-butyl, which latter seven groups are optionally substituted by one or more fluorine atoms,
or cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, which latter four groups are optionally substituted by one or more substituents selected from -F, -CH_3, $-CHF_2$, $-CF_3$;
or is selected from the following groups:



which latter seven groups are optionally substituted by one or more substituents selected from -F, $-CH_3$, $-CHF_2$, $-CF_3$;

or is selected from the following groups:

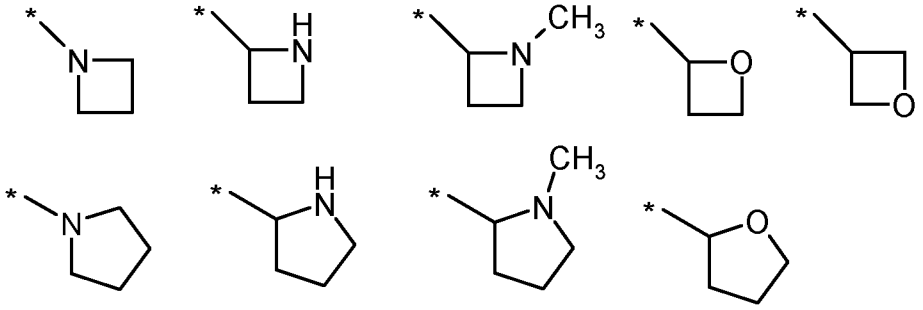


in which latter eleven groups the aryl and heteroaryl fragments are optionally substituted by one or more substituents selected from -F, -Cl, -Br, -CN, $-CH_3$, $-CF_3$;

M represents

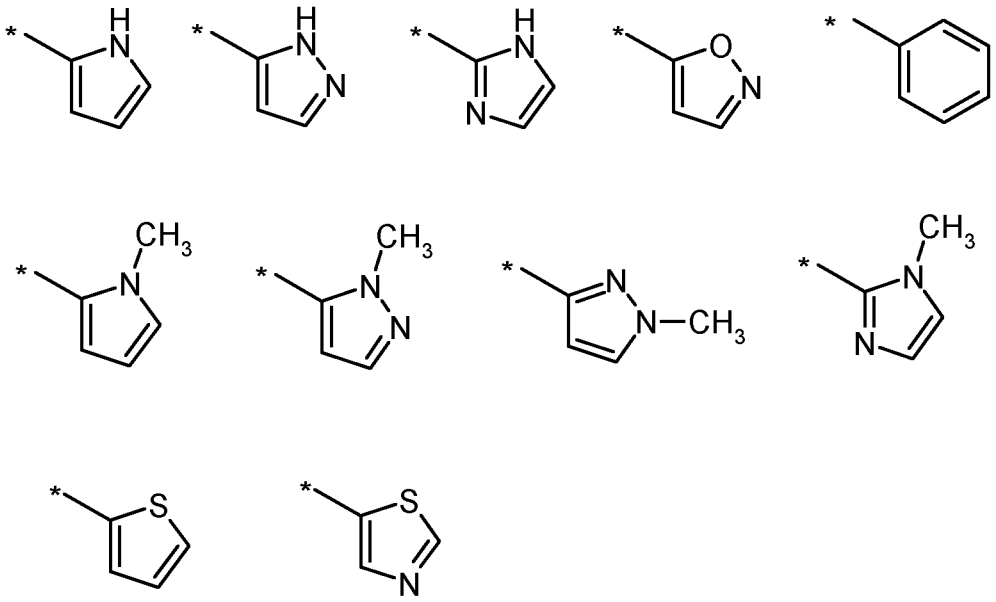
methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *s*-butyl, *t*-butyl, cyclopropyl, -CH_2-cyclopropyl, cyclobutyl, cyclopentyl, all of which groups are optionally substituted by one or more groups selected from -F, -OH, -CN, -NH_2, -OCH_3, -CH_3, -CF_3;

or is selected from the following groups



which latter nine groups are optionally substituted by one or more substituents selected from -F, -CH_3, -CF_3;

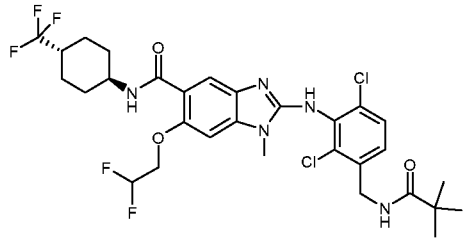
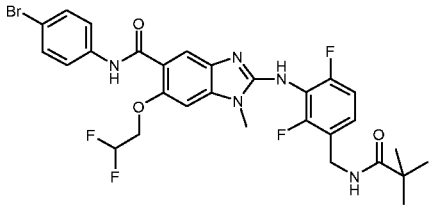
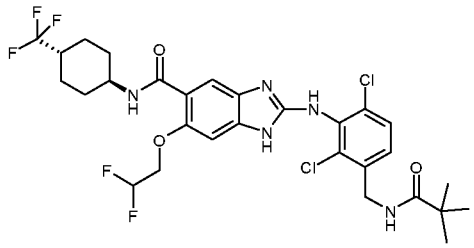
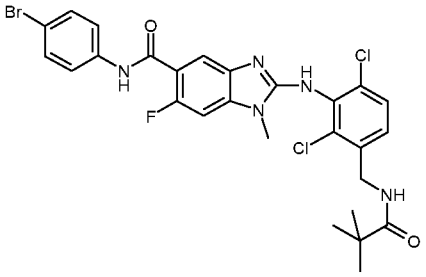
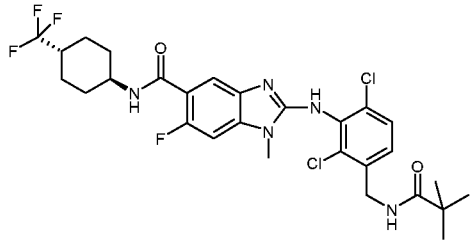
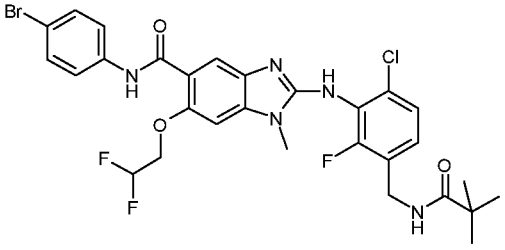
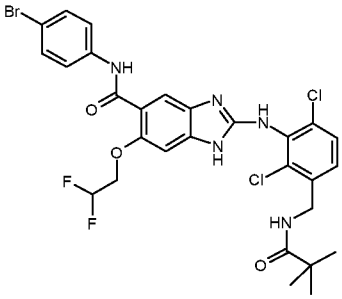
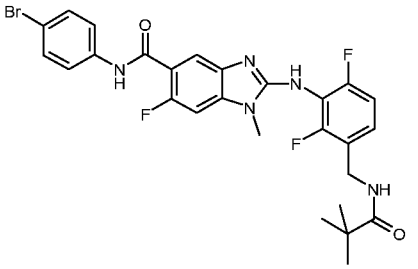
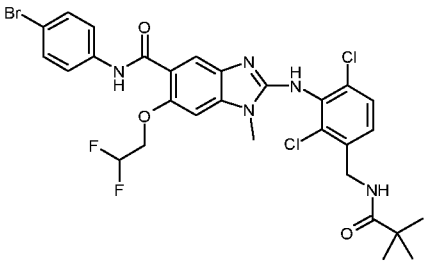
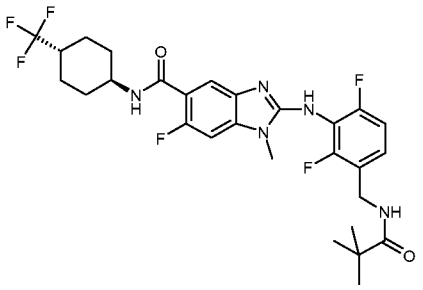
or is selected from the following groups

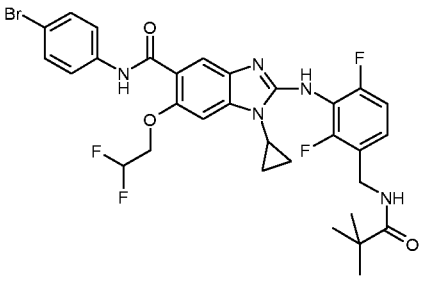
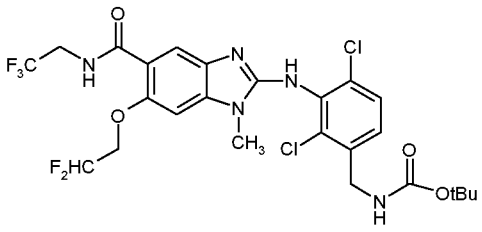
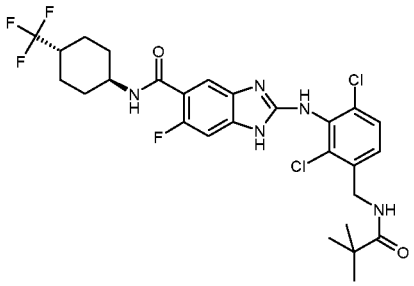
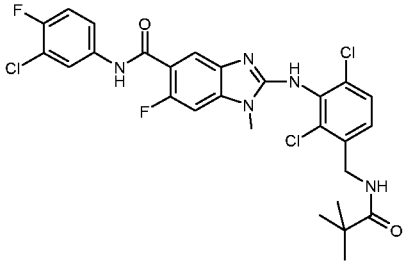
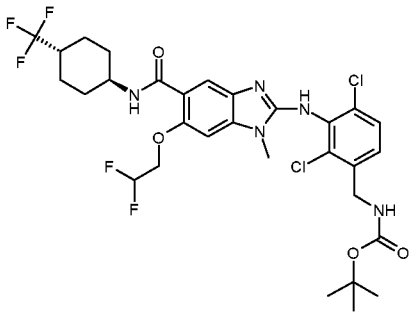
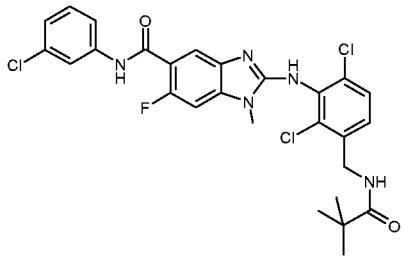
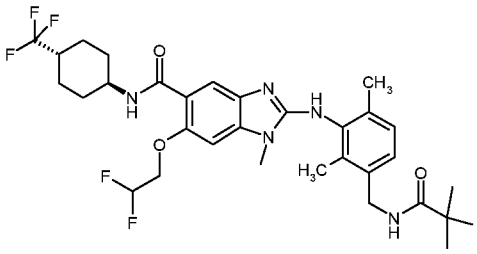
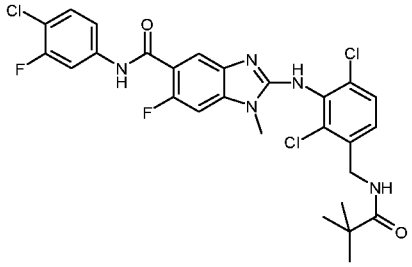
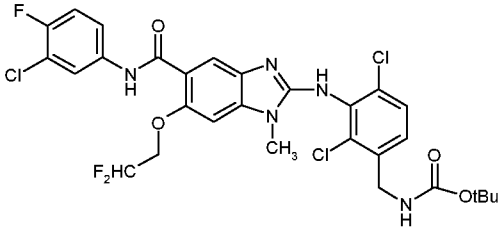
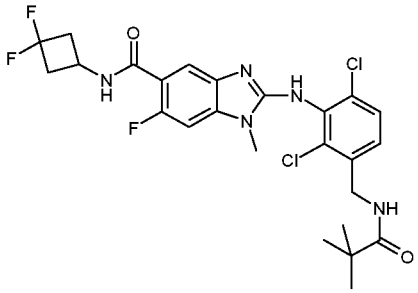


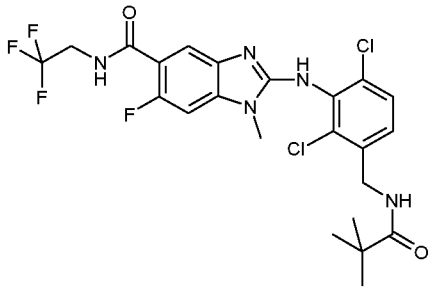
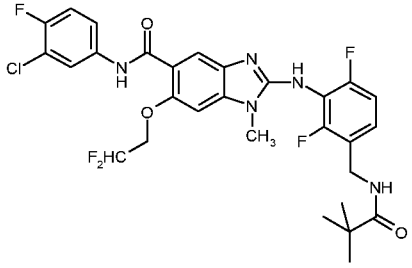
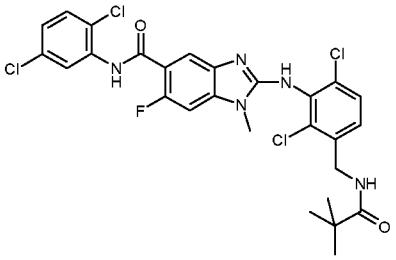
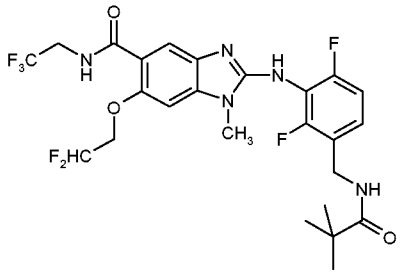
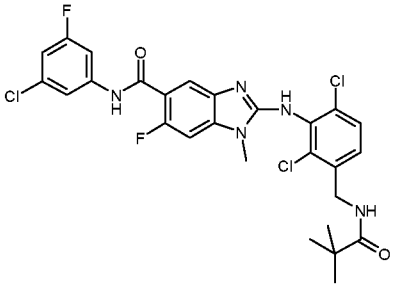
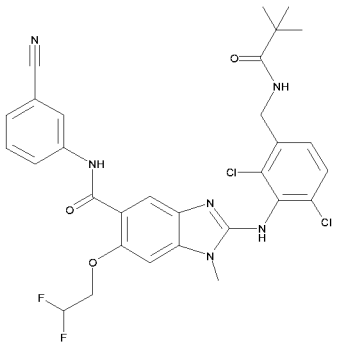
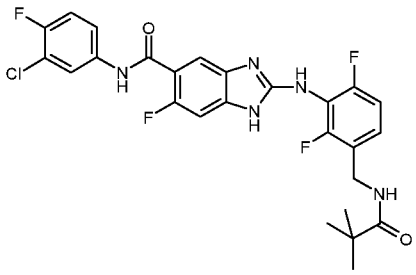
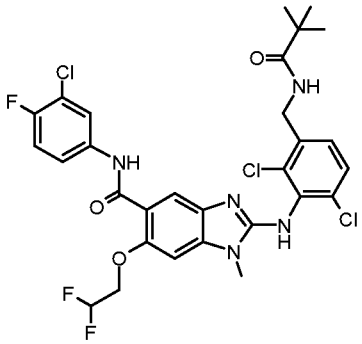
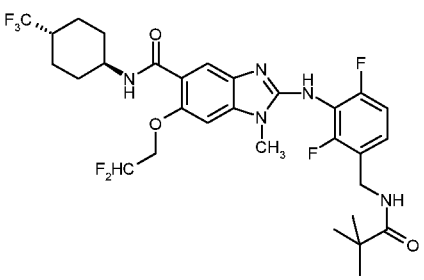
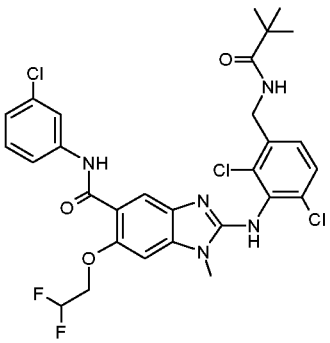
which latter eleven groups are optionally substituted by one or more substituents selected from -F, -Cl, -CH_3, -CF_3;

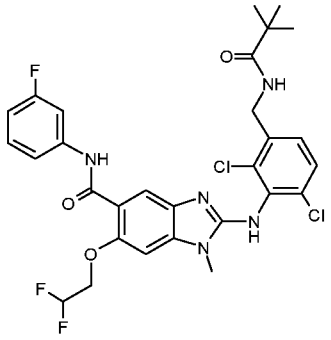
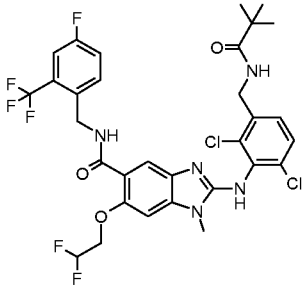
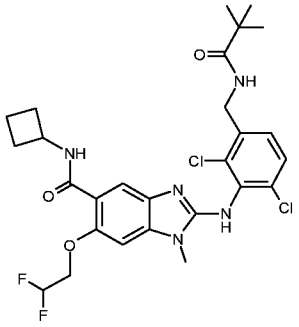
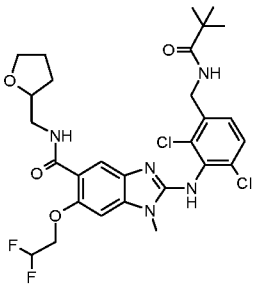
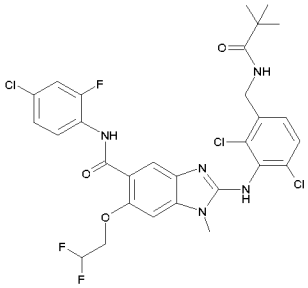
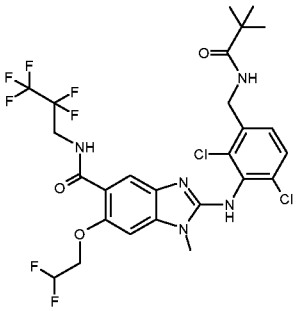
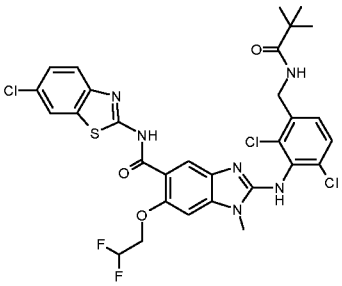
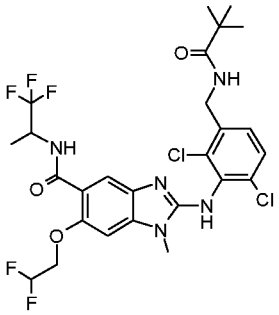
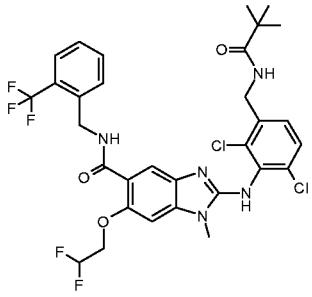
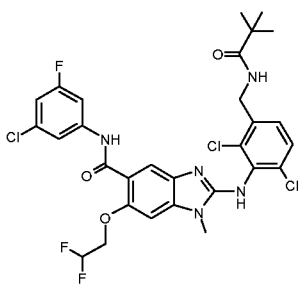
or a salt thereof.

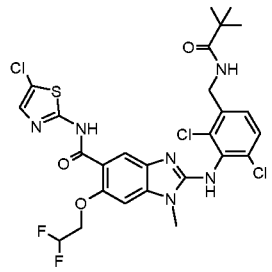
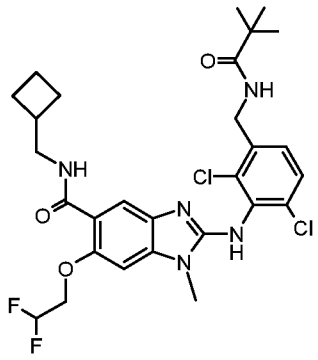
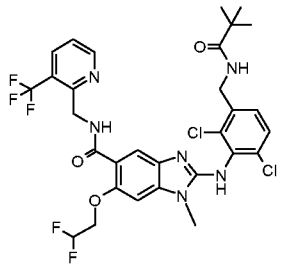
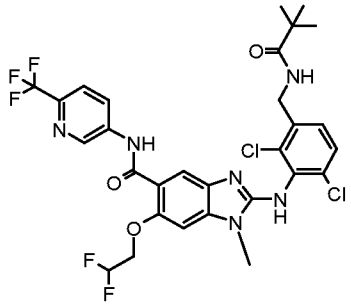
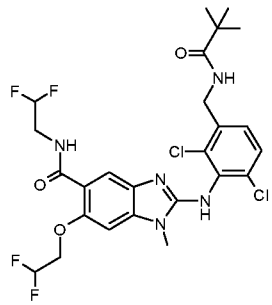
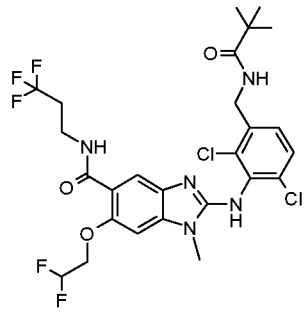
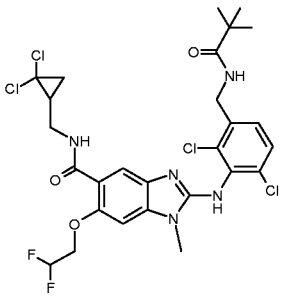
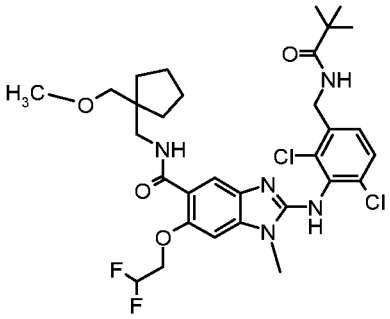
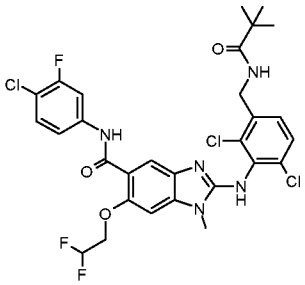
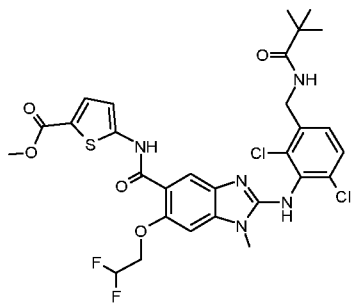
11. A compound according to any one of the preceding claims selected from the group comprising

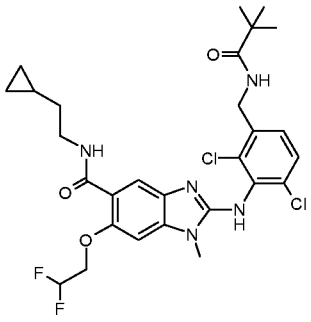
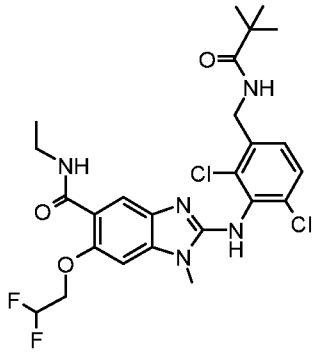
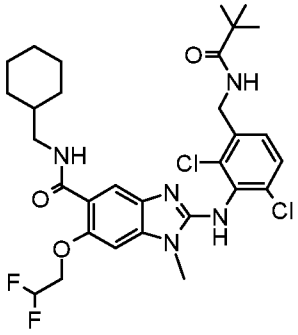
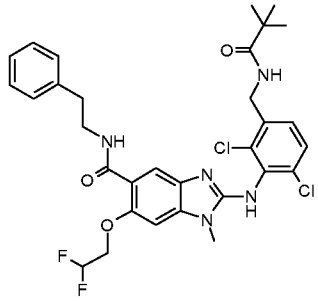
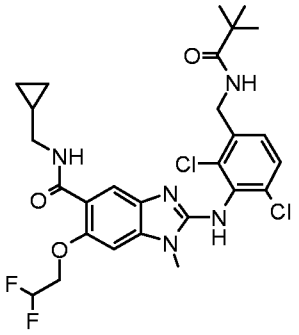
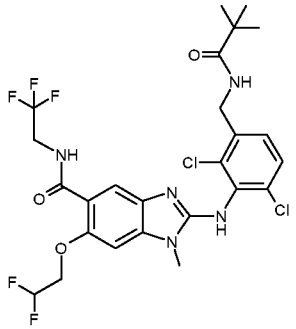
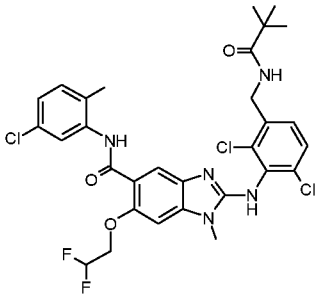
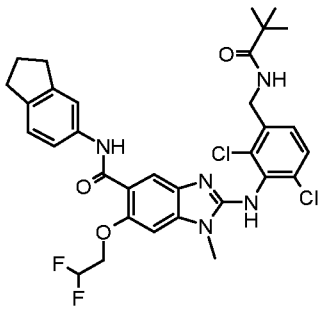
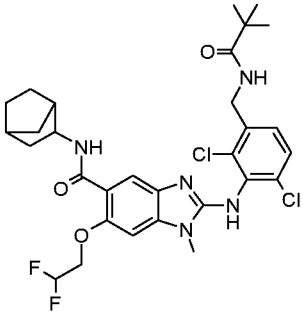
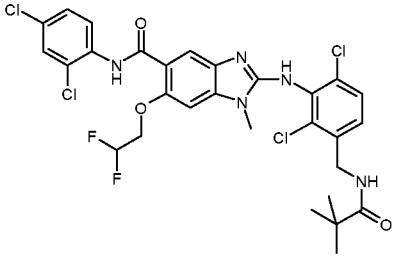
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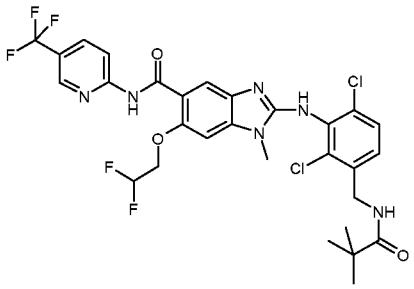
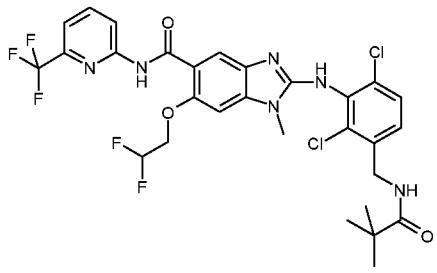
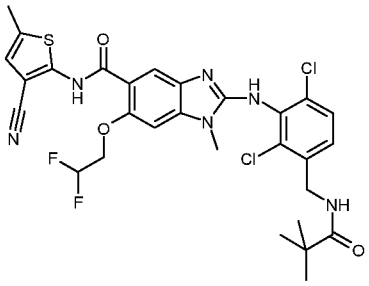
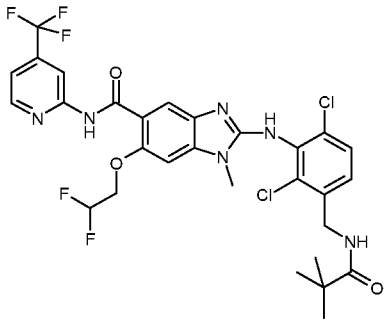
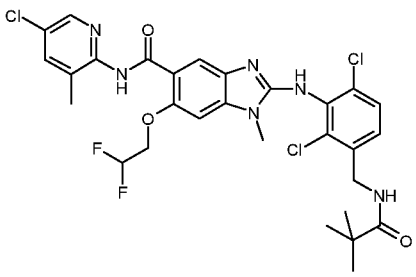
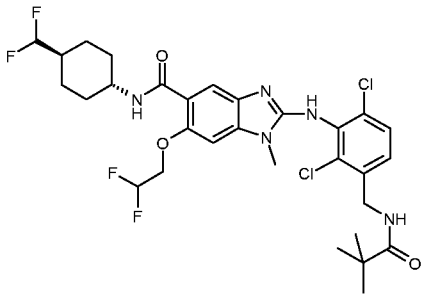
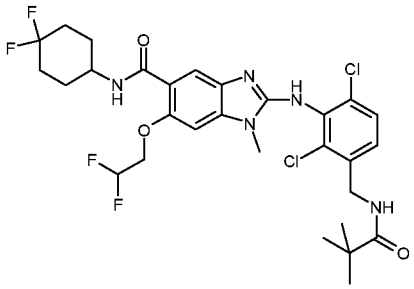
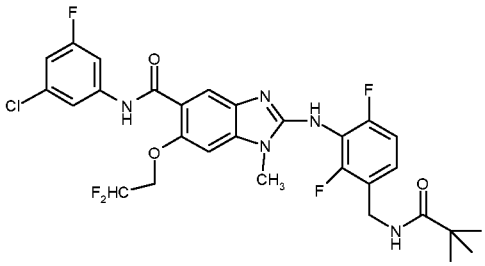
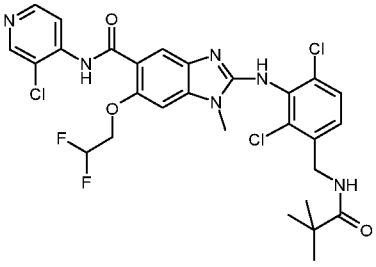
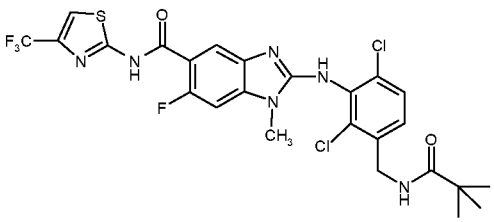
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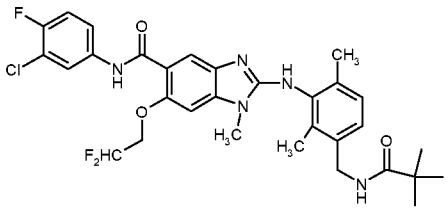
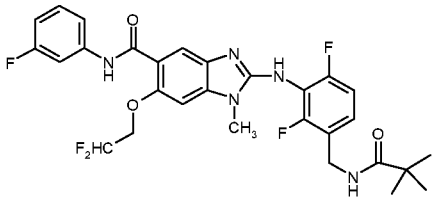
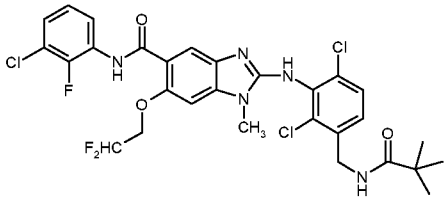
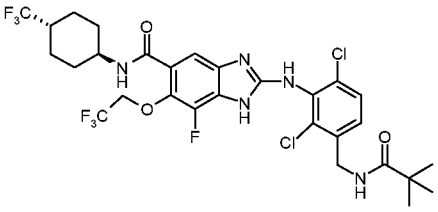
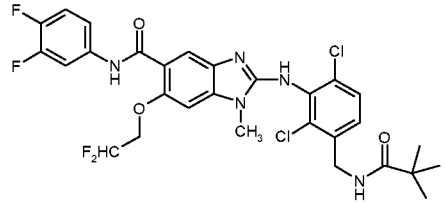
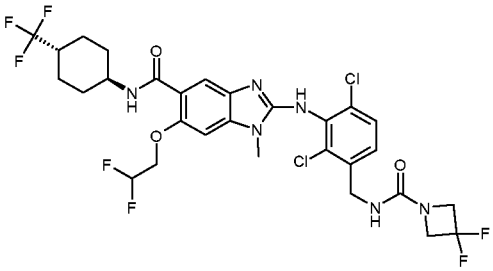
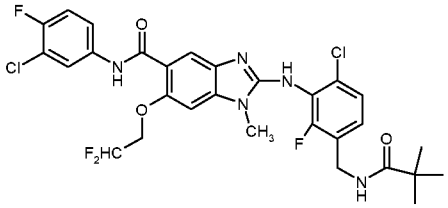
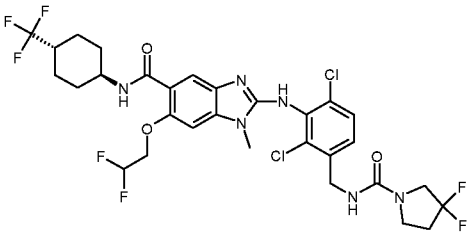
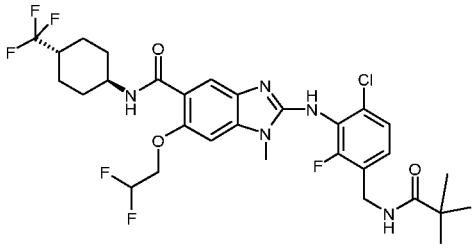
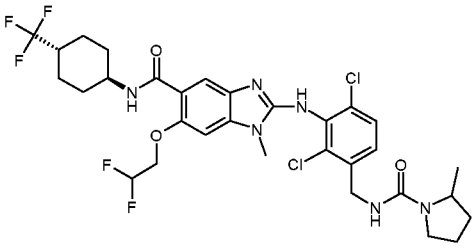
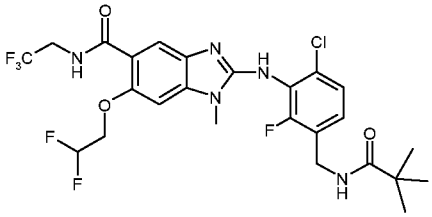
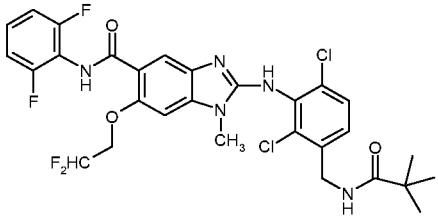
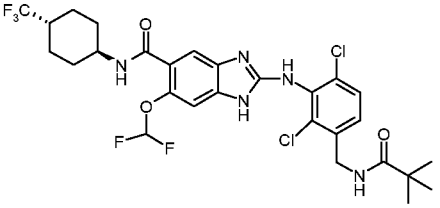
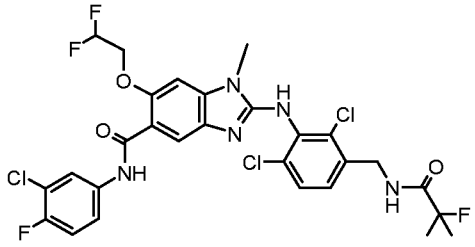
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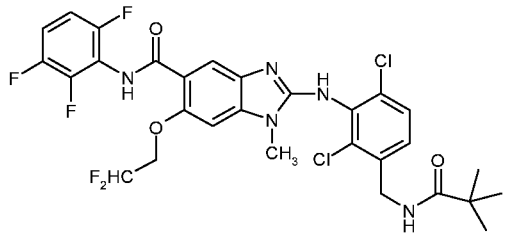
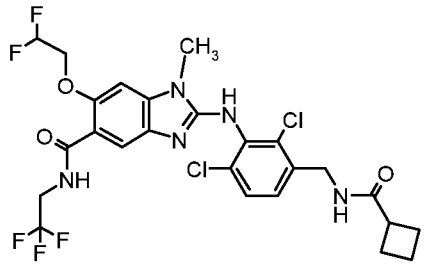
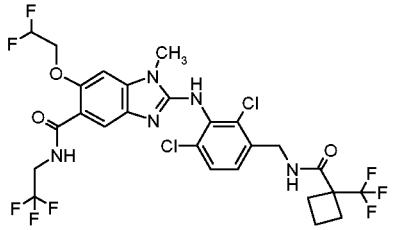
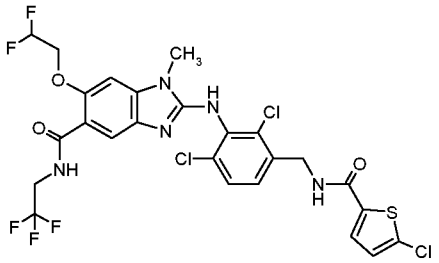
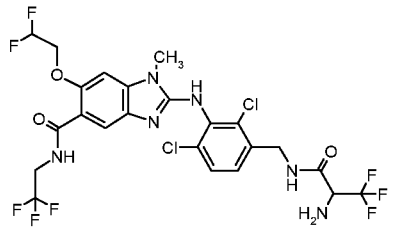
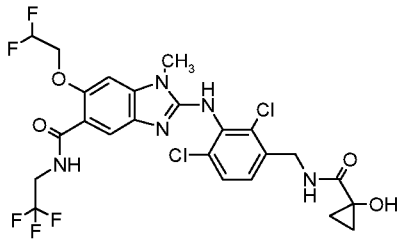
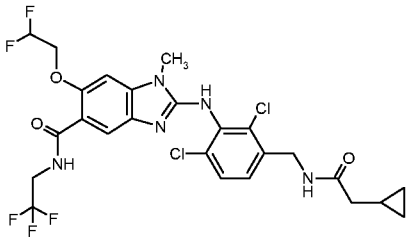
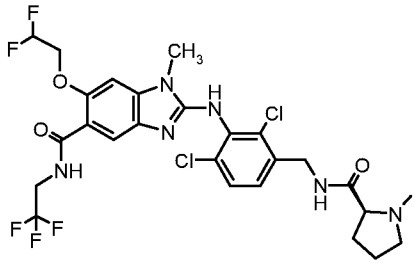
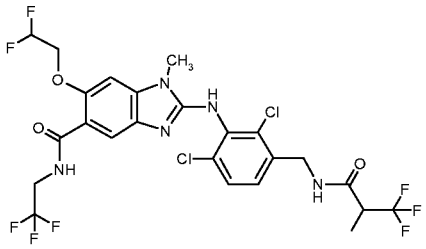
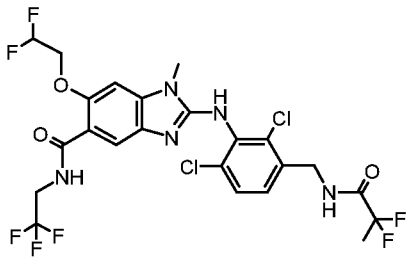
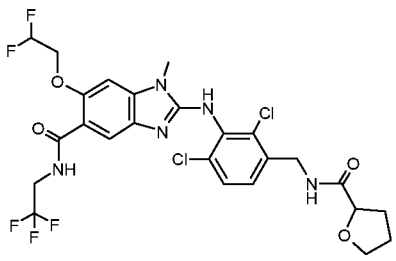
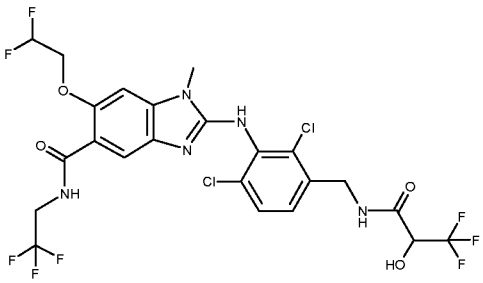
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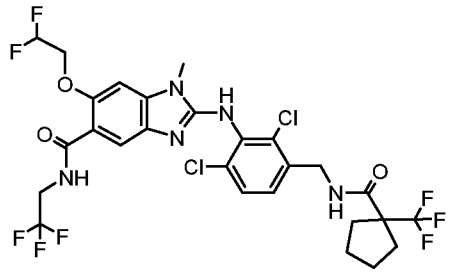
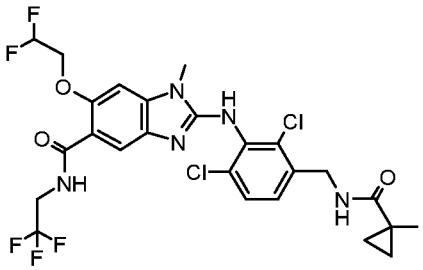
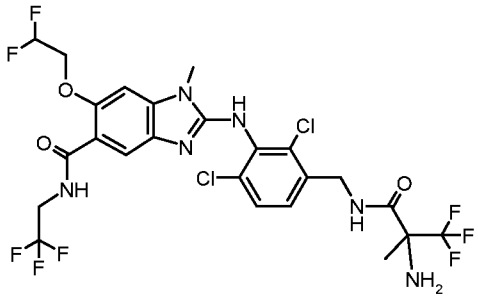
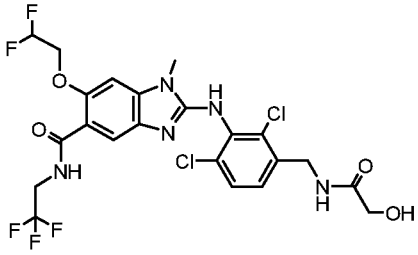
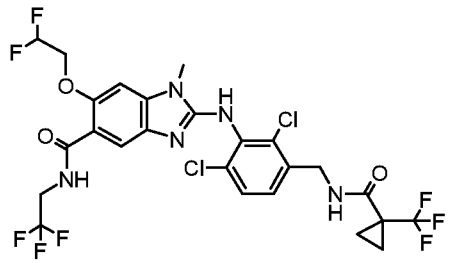
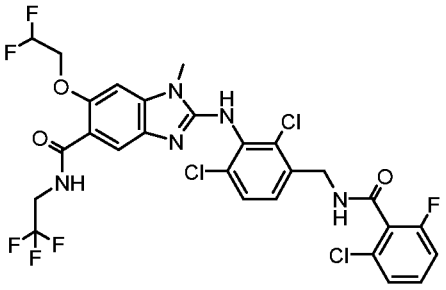
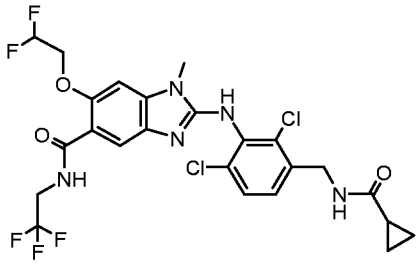
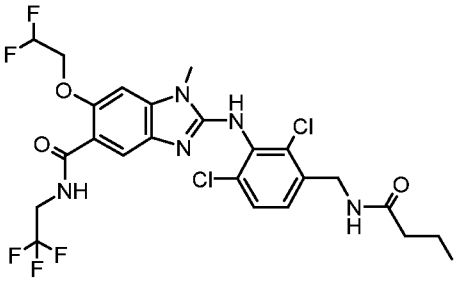
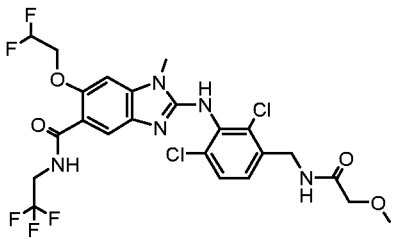
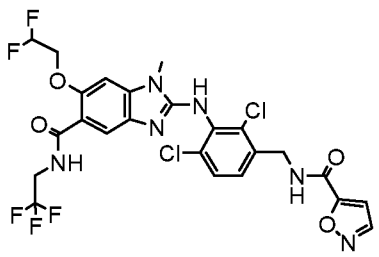
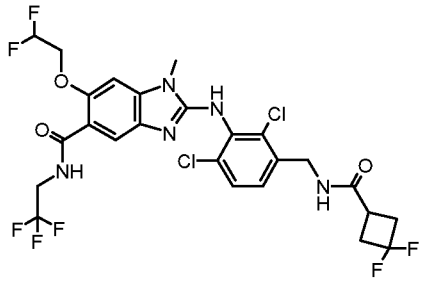
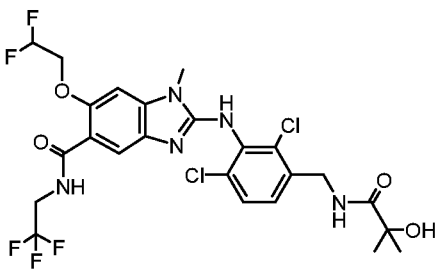
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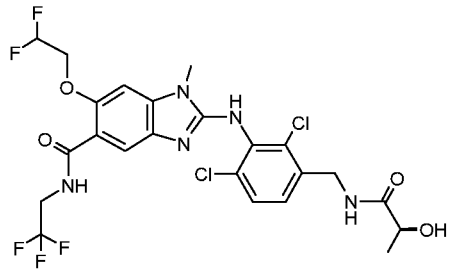
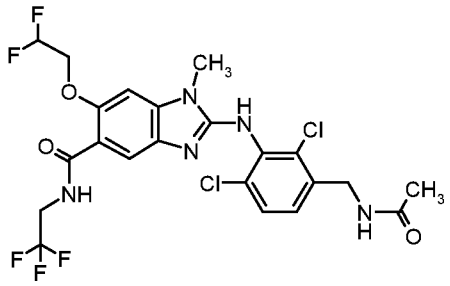
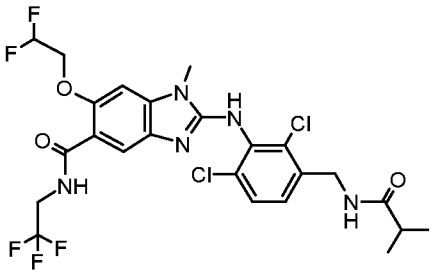
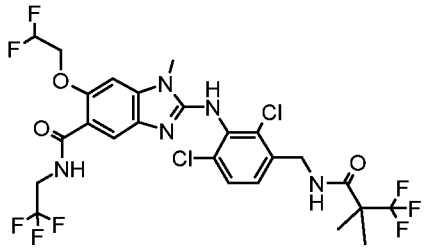
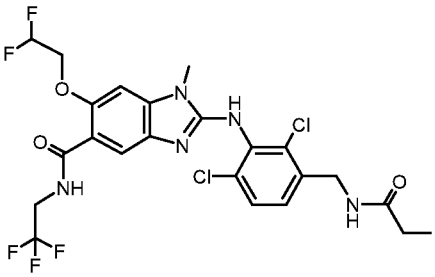
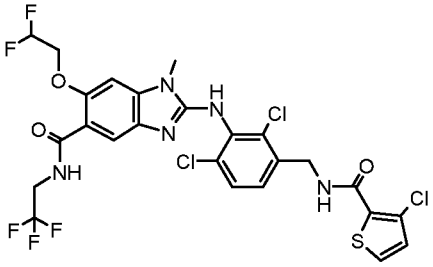
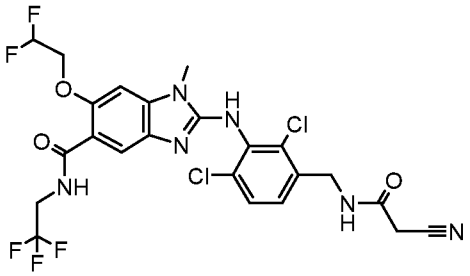
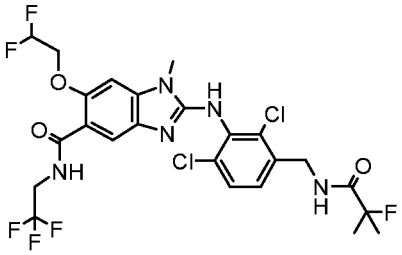
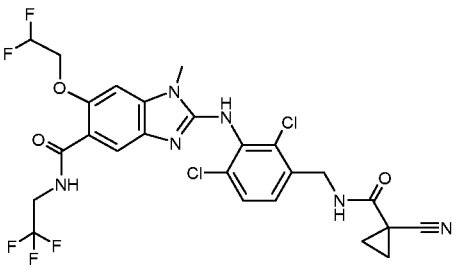
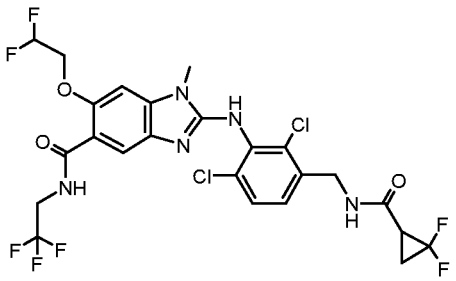
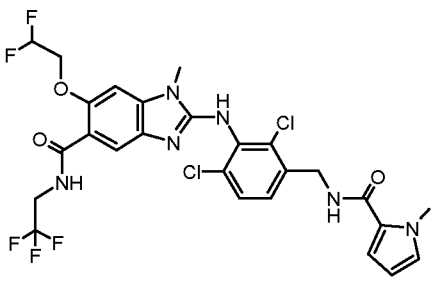
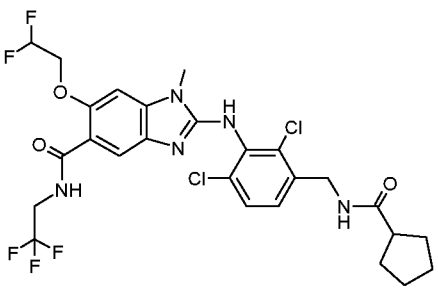
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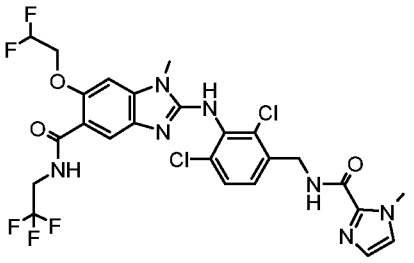
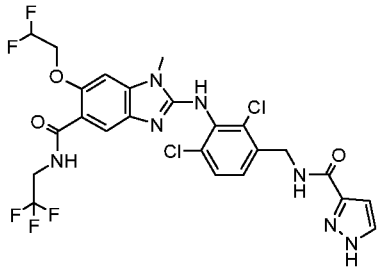
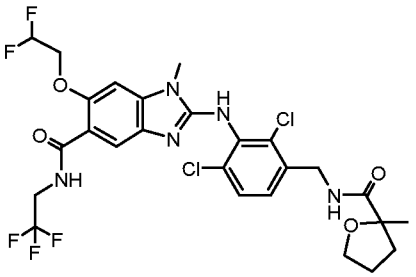
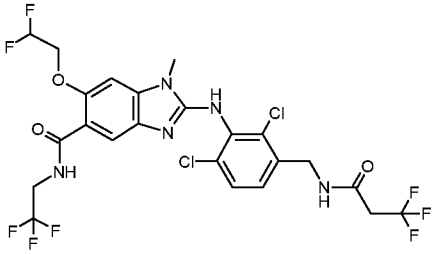
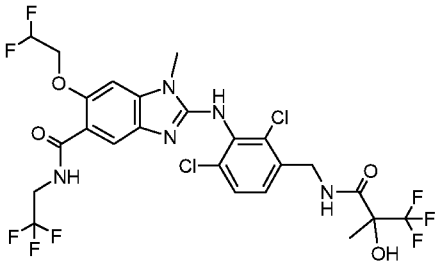
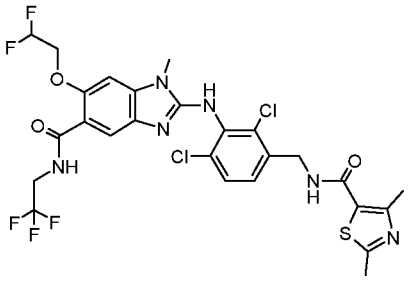
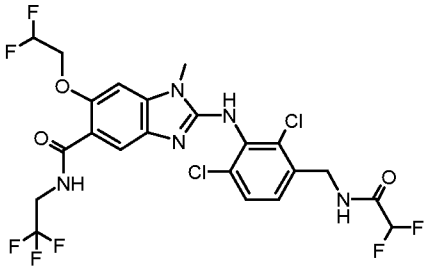
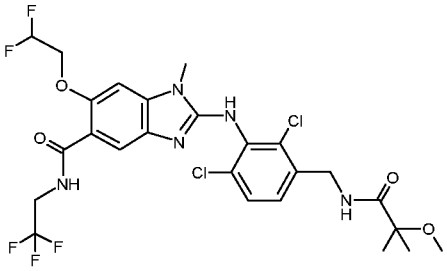
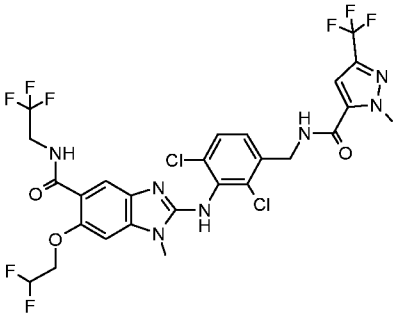
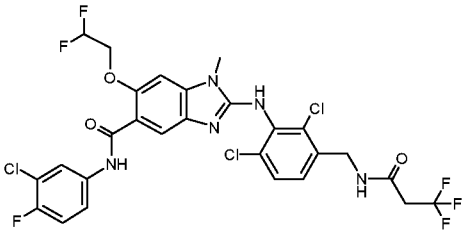
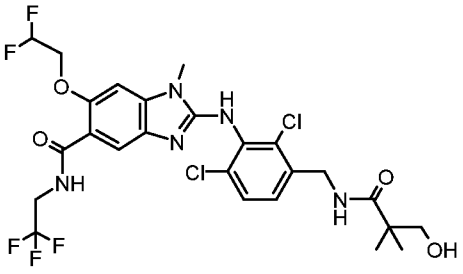
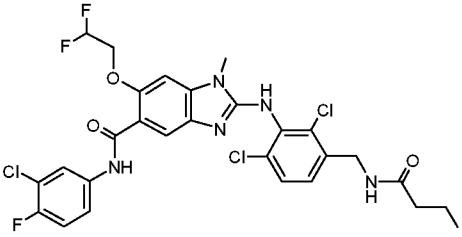
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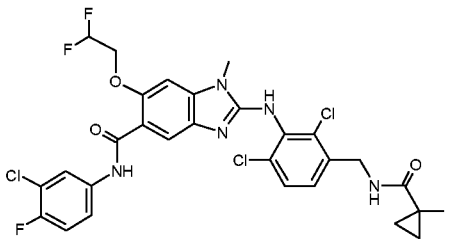
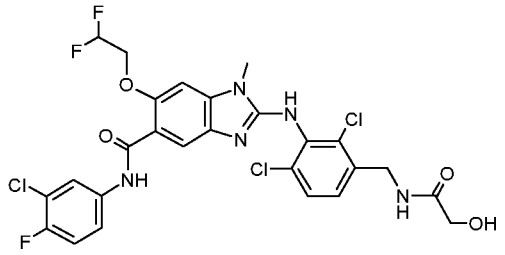
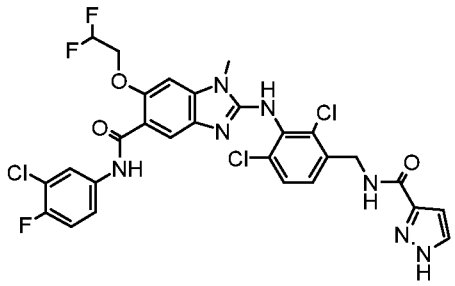
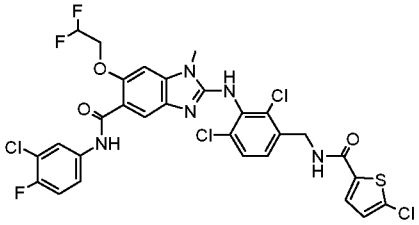
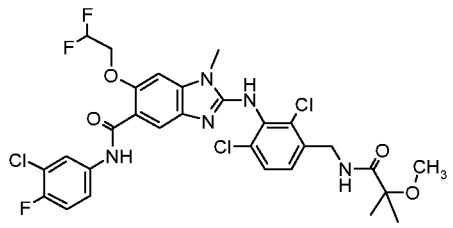
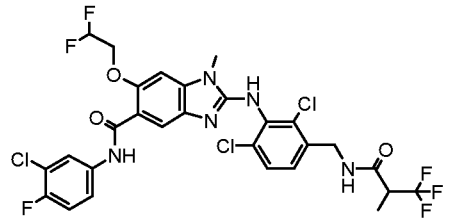
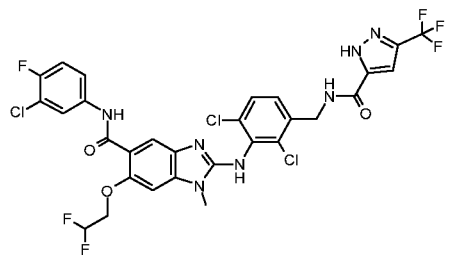
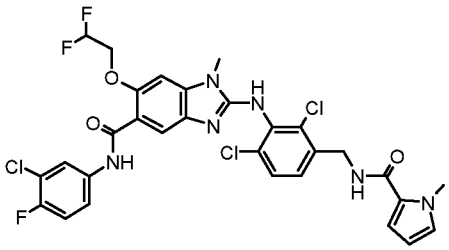
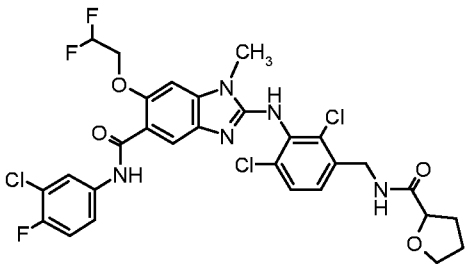
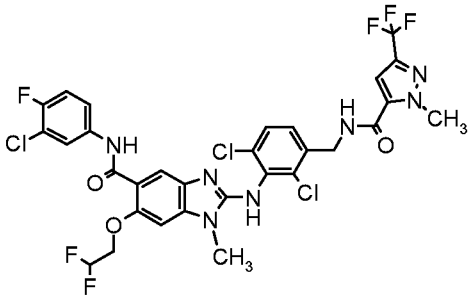
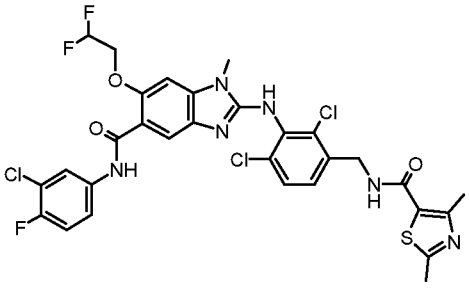
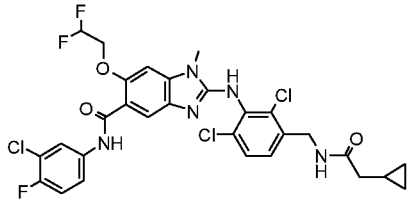
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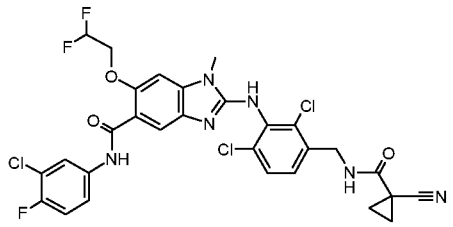
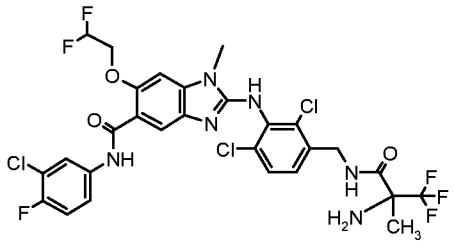
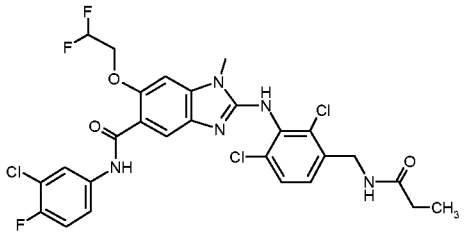
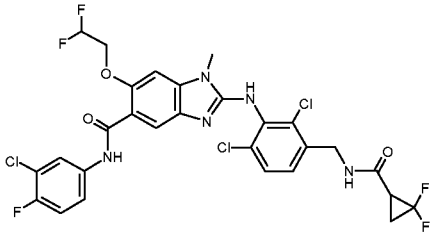
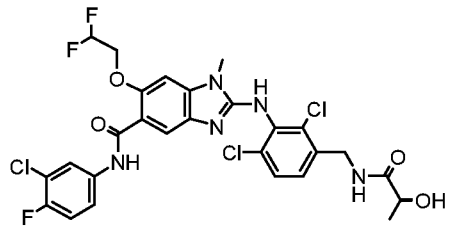
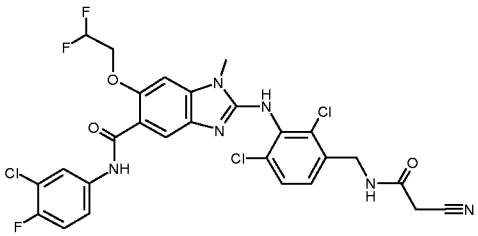
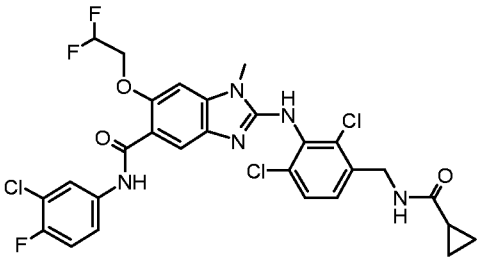
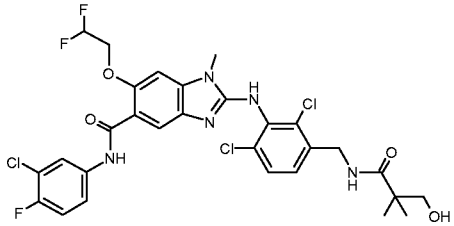
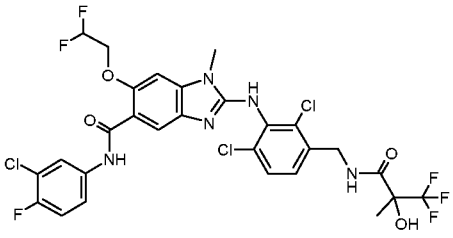
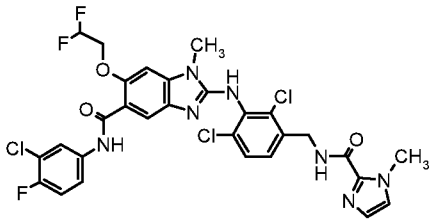
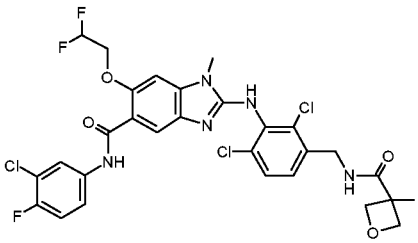
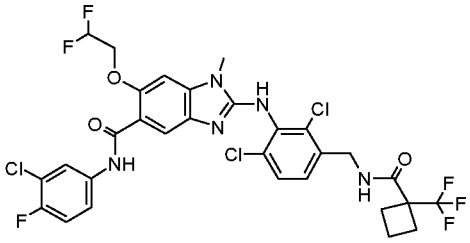
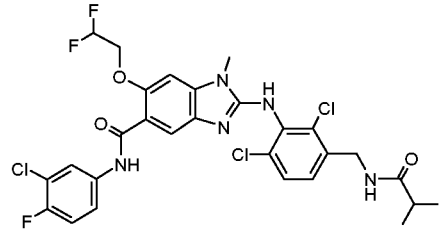
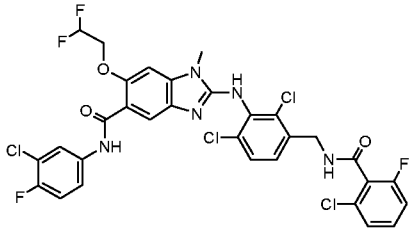
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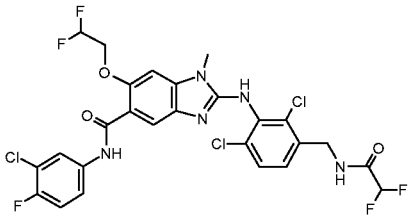
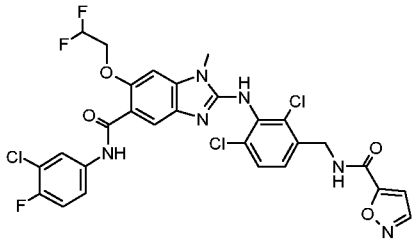
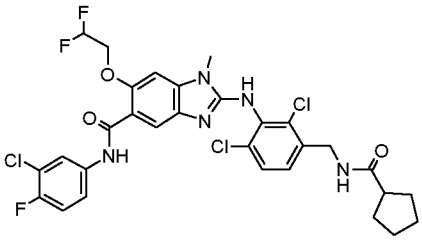
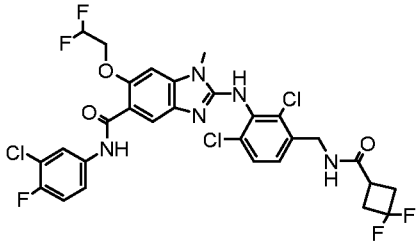
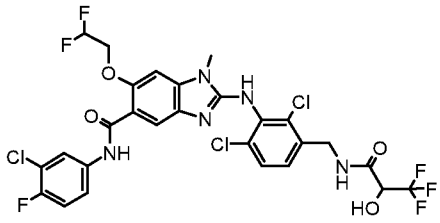
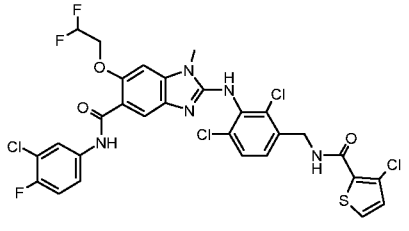
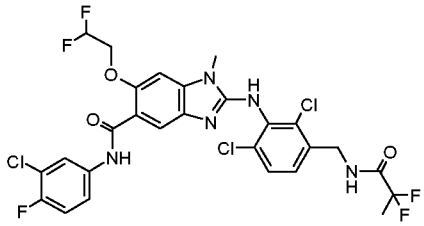
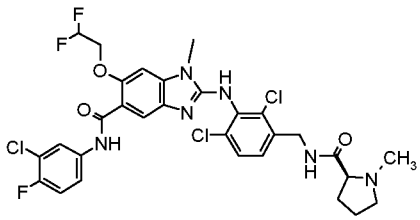
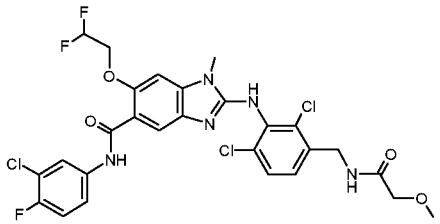
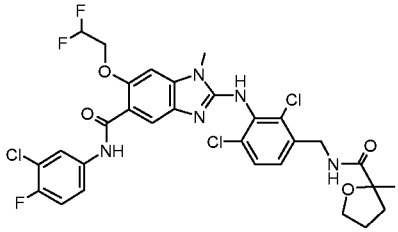
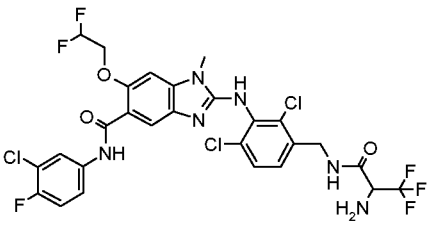
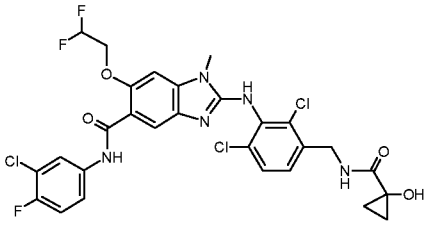
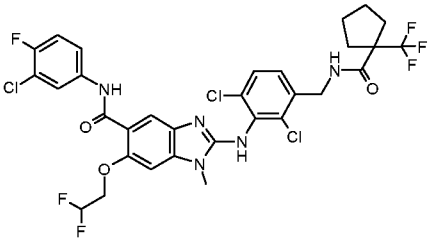
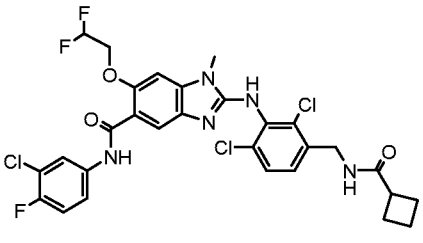
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100		106	
101		107	
102		108	

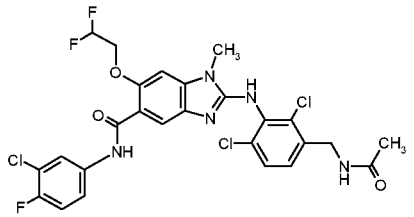
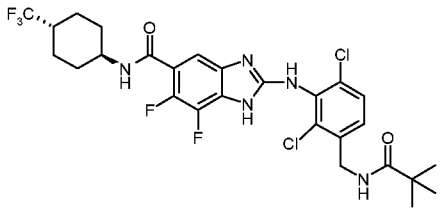
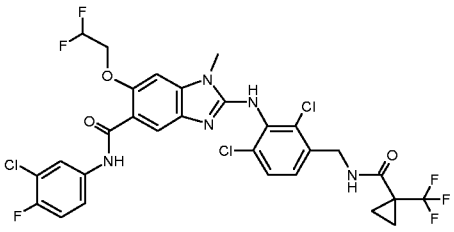
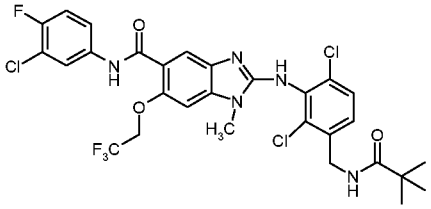
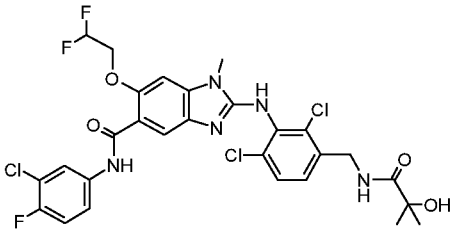
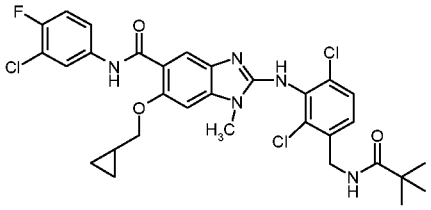
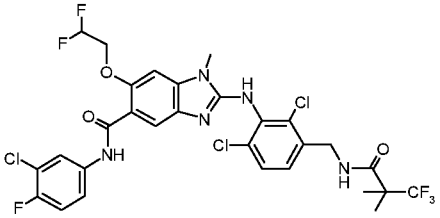
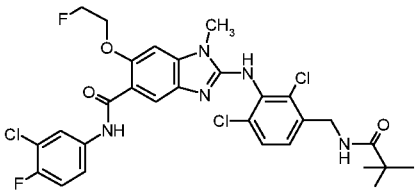
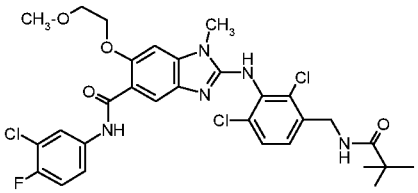
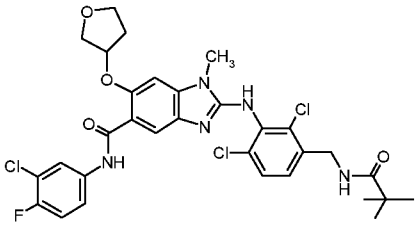
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113		119	
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	Structure		Structure
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122		128	
123		129	
124		130	
125		131	
126		132	

	Structure		Structure
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134		140	
135		141	
136		142	
137		143	
138		144	

	Structure		Structure
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146		153	
147		154	
148		155	
149		156	
150		157	
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	Structure		Structure
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164		171	
165		172	

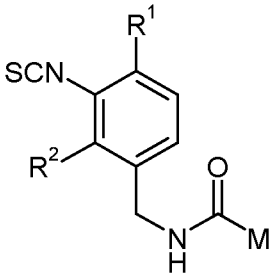
	Structure		Structure
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174		181	
175		182	
176			
177			
178			
179			

12. A compound according to any of the preceding claims for use as a medicament.

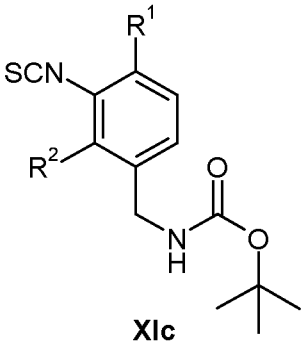
13. A pharmaceutical composition comprising at least one compound according to any of claims 1 to 11 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable adjuvant, diluent and/or carrier.

14. A compound according to any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof for use in the treatment and/or prevention of inflammatory diseases and/or associated conditions, in particular pain.

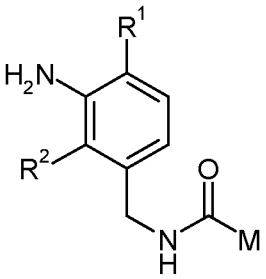
15. An intermediate of formula **XIb, XIc, XVIIb, XVIIc, XIX or XX**



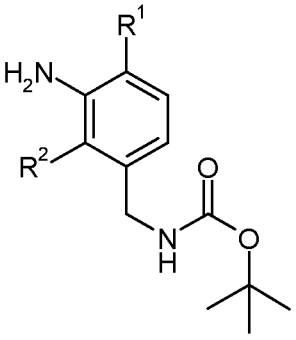
XIb



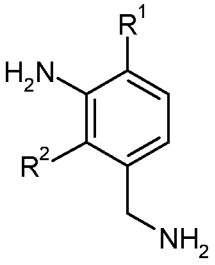
XIc



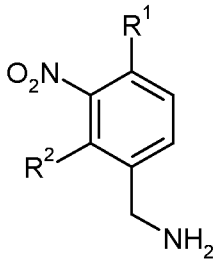
XVIIb



XVIIc



XIX



XX

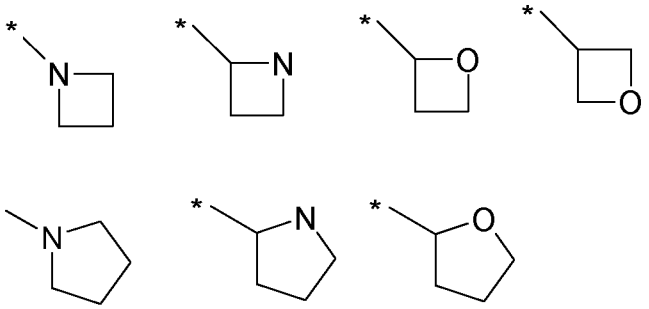
in which

R^1 and R^2 independently represent –chloro, fluoro or $–CH_3$;

M represents

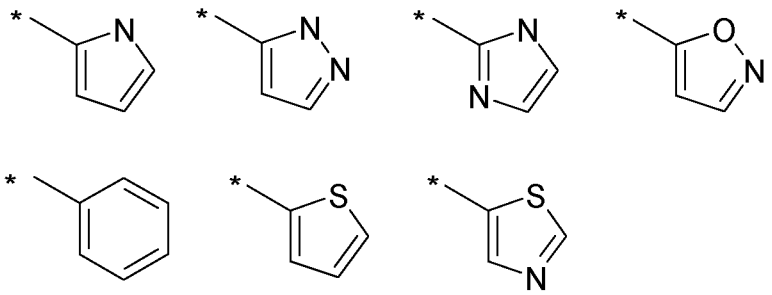
methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *s*-butyl, *t*-butyl, cyclopropyl, $-CH_2$-cyclopropyl, cyclobutyl, cyclopentyl, all of which groups are optionally substituted by one or more groups selected from -F, -OH, -CN, $-NH_2$, $-OCH_3$, $-CH_3$, $-CF_3$;

or is selected from the following groups



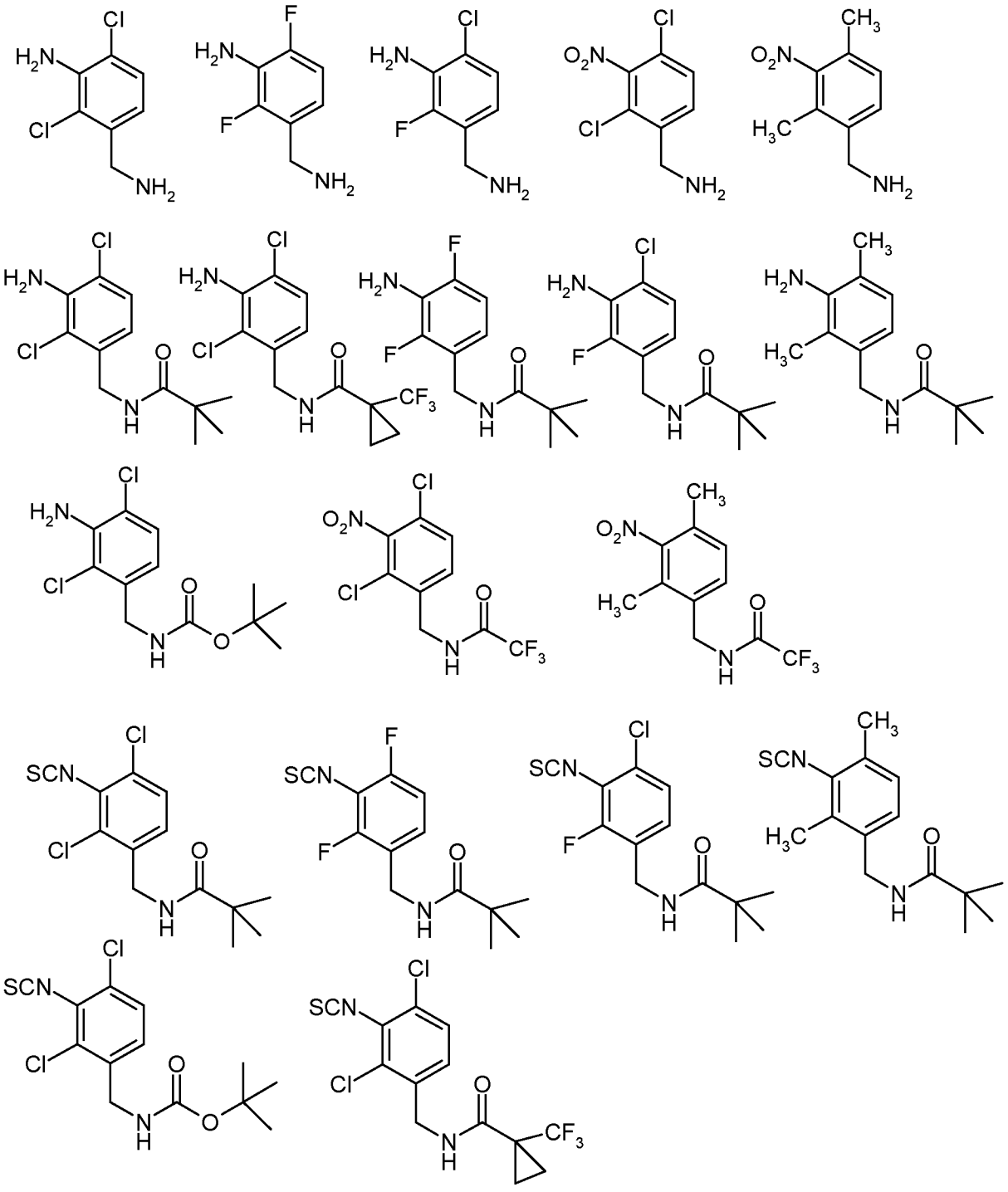
all of which groups are optionally substituted by one or more substituents selected from -F, -CH_3, or -CF_3;

or is selected from the following groups



all of which groups are optionally substituted by one or more substituents selected from -F, -Cl, -CH_3, or -CF_3.

16. An intermediate according to claim 15, selected from the group of compounds comprising



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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/064258

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D235/30 A61K31/4184 A61P11/00 A61P29/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN 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.
Y	WO 2005/070906 A (NOVARTIS PHARMA GMBH) 4 August 2005 (2005-08-04) claims 1-13	1-16
Y	WO 2010/034796 A1 (BOEHRINGER INGELHEIM INT [DE]; PFAU ROLAND [DE]; ARNDT KIRSTEN [DE]; D) 1 April 2010 (2010-04-01) claims 1-18	1-16
A	WO 2007/095124 A (TRANSTECH PHARMA, INC.) 23 August 2007 (2007-08-23) * Examples *claims 1-40; tables 1-11	1-16

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 September 2011	10/10/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Herz, Claus

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	R. D. CARPENTER ET AL.: "Carbodiimide-based benzimidazole library method", JOURNAL OF COMBINATORIAL CHEMISTRY, vol. 8, no. 6, 27 October 2006 (2006-10-27), pages 907-914, XP002557183, * Scheme 4: Compounds of formula 10e & Figure 1 *	1-16
A	FR 2 851 563 A (SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES) 27 August 2004 (2004-08-27) claims 1-10	1-16
A	WO 2008/009924 A2 (BIOLIPOX AB [SE]; BOEHRINGER INGELHEIM INT [DE]; PELCMAN BENJAMIN [SE]) 24 January 2008 (2008-01-24) claims 1-48	1-16
A	WO 2008/071944 A1 (BOEHRINGER INGELHEIM INT [DE]; BIOLIPOX AB [SE]; PELCMAN BENJAMIN [SE]) 19 June 2008 (2008-06-19) claims 1-43	1-16
A	D. J. GALE, J. F. K. WILSHIRE: "The Amidomethylation of Some N,N-Dialkylanilines (Tscherniac-Einhorn Reaction)", AUST. J. CHEM., vol. 28, 1975, pages 2447-2458, XP002615311, table 3	15,16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2011/064258

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International application No
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NUEVOS COMPUESTOS

Campo de la Invención

Esta invención se refiere a nuevos compuestos, que son inhibidores de la prostaglandina E_2 sintasa-1 microsómica (mPGES-1), a composiciones farmacéuticas que los contienen, y a su uso como medicamentos para el tratamiento y/o prevención de enfermedades inflamatorias y afecciones asociadas, tales como el dolor inflamatorio/nociceptivo.

Antecedentes de la invención

Existen muchas enfermedades/trastornos agudos y crónicos que son inflamatorios por naturaleza incluyendo, aunque sin limitarse a ellas, enfermedades reumáticas, p.ej. artritis reumatoide, artrosis, enfermedades del sistema visceral, p.ej. síndrome inflamatorio del intestino, enfermedades autoinmunes, p.ej. lupus eritematoso, enfermedades pulmonares como el asma y la enfermedad pulmonar obstructiva crónica (EPOC). El tratamiento actual con fármacos antiinflamatorios no esteroideos (los AINE) y con inhibidores de la ciclooxigenasa (COX)-2 es eficaz, pero presenta una prevalencia de efectos colaterales gastrointestinales y cardiovasculares. Existe una gran necesidad de nuevas opciones de tratamiento que muestren una eficacia equivalente con un mejor perfil de efectos colaterales.

Los inhibidores de la mPGES pueden presentar dicho mejor perfil de efectos colaterales porque bloquean la generación de PGE_2 de una manera más específica como se describe más adelante.

Los AINE y los inhibidores de la COX-2 reducen la inflamación y el dolor a través de la inhibición de una o ambas isoformas de las enzimas COX. La enzima ciclooxigenasa (COX) existe en dos formas, una que se expresa constitutivamente en muchas células y tejidos (COX-1), y otra que en la mayoría de las células y tejidos se induce por estímulos proinflamatorios tales como citocinas, durante una respuesta inflamatoria (COX-2). Las COX metabolizan el ácido araquidónico en el intermedio inestable prostaglandina H_2 (PGH_2). La PGH_2 es metabolizada posteriormente hasta otras prostaglandinas incluyendo PGE_2, $PGF_{2\alpha}$, PGD_2, prostaciclina y tromboxano A_2. Se sabe que estos metabolitos del ácido araquidónico tienen una actividad fisiológica y fisiopatológica pronunciada, que incluye efectos proinflamatorios. Se conoce que la PGE_2 en particular es un fuerte mediador proinflamatorio y también se sabe que induce fiebre, inflamación y dolor. Por consiguiente, se han desarrollado numerosos fármacos con vistas a inhibir la formación de la PGE_2, incluyendo los “AINE” (fármacos antiinflamatorios no esteroideos) y los “coxibs” (inhibidores selectivos de la COX-2). Estos fármacos actúan predominantemente por inhibición de la COX-1 y/o COX-2, reduciendo de este modo la formación de PGE_2.

Sin embargo, la inhibición de las COX tiene el inconveniente de que ocasiona la reducción de la formación de todos los metabolitos situados más abajo de la PGH_2, de los que se sabe que algunos tienen propiedades beneficiosas. En vista de esto, se sabe o se sospecha que los fármacos que actúan por medio de la inhibición de las COX producen efectos biológicos adversos.

Por ejemplo, la inhibición no selectiva de las COX por los AINE puede producir efectos colaterales gastrointestinales y afectar la función de las plaquetas y la función renal. Incluso se cree que la inhibición selectiva de la COX-2 por los coxibs, aunque reduce tales efectos colaterales gastrointestinales, da lugar a problemas cardiovasculares.

Un tratamiento alternativo de las enfermedades inflamatorias que no dé lugar a los efectos colaterales mencionados antes, sería por tanto un beneficio real en clínica. En particular, un fármaco que inhiba preferiblemente la transformación de la PGH_2 en el mediador proinflamatorio PGE_2 de manera selectiva, se podría esperar que reduzca la respuesta inflamatoria en ausencia de una reducción correspondiente de la formación de otros metabolitos de ácido araquidónico beneficiosos. Se podría esperar por tanto que dicha inhibición alivie los efectos colaterales indeseables mencionados antes.

La PGH_2 puede ser transformada en PGE_2 por las prostaglandinas E sintasas (PGES). Se han descrito dos prostaglandinas E sintasas microsómicas (mPGES-1 y mPGES-2), y una prostaglandina E sintasa citosólica (cPGES). Se piensa que la mPGES-1 está estrechamente ligada a la COX-2 y ambas enzimas aumentan p.ej. durante la inflamación. Por tanto los agentes que son capaces de inhibir la acción de la mPGES-1 y con ello reducir la formación de PGE_2 son probablemente beneficiosos para el tratamiento de la inflamación y afecciones dolorosas agudas y crónicas más generales.

Los derivados de bencimidazol e imidazopiridina con actividad inhibidora de la mPGES-1 están descritos en los documentos WO 2010/034796, WO 2010/034797, WO 2010/034798 y WO 2010/034799.

El documento PCT/EP2010/052799 describe una clase amplia de diferentes 2-arilamino-bencimidazoles en los que el grupo arilo lleva una cadena lateral particular.

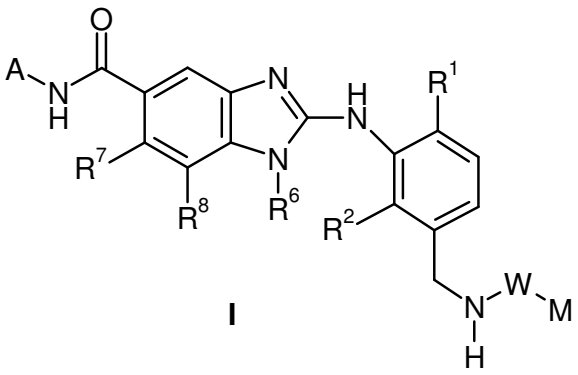
DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

La presente invención es una selección a partir de la fórmula general del documento PCT/EP2010/052799 que proporciona compuestos que presentan de forma inesperada mejor actividad en un ensayo farmacológico basado en células.

Los compuestos con una afinidad similar para la enzima mPGES-1 medida en el ensayo enzimático, pueden tener diferentes potencias en el ensayo basado en células.

Los datos procedentes de un ensayo farmacológico basado en células cuando se comparan con los datos procedentes de un ensayo enzimático se considera que permiten una mejor predicción y estimación de las concentraciones/dosis terapéuticas eficaces. Los compuestos de la presente invención muestran una potencia alta en ambos ensayos. Por consiguiente, es probable que sean más adecuados para el uso *in-vivo*.

La presente invención proporciona un compuesto de la fórmula **I,**



I

en la que

R^1 y **R^2** representan independientemente halo, -alquilo C_{1-3}, y este último grupo alquilo está opcionalmente sustituido con uno o más átomos de flúor;

W representa -C(O)-, -C(O)O-, y estos grupos están unidos al nitrógeno del resto –NH- por medio del átomo de carbono;

M representa

-alquilo C_{1-6}, -cicloalquilo C_{3-7}, y ambos grupos están opcionalmente sustituidos con uno o más grupos seleccionados de -F, -OH, -CN, $-NH_2$, -NH(alquilo C_{1-2}), -N(alquil $C_{1-2})_2$, -O-alquilo C_{1-3}, -alquilo C_{1-5}, -cicloalquilo C_{3-4}, en cuyos tres últimos grupos los grupos alquilo o cicloalquilo están opcionalmente sustituidos con uno o más átomos de flúor;

o

oxetanilo-, tetrahidrofuranilo-, tetrahidropiranilo-, azetidinilo-, pirrolidinilo-, piperidinilo-, y todos estos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de fluoro, -CN, -alquilo C_{1-3}, y este último grupo alquilo está opcionalmente sustituido con uno o más átomos de flúor;

o

fenilo-, piridilo-, tienilo-, pirrolilo-, pirazolilo-, imidazolilo-, tiazolilo-, oxazolilo-, o isoxazolilo-, y todos estos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de halo, -CN o -

alquilo C_{1-3}, y este último grupo alquilo está opcionalmente sustituido además con uno o más átomos de flúor;

R^8 representa –H, halógeno, -alquilo C_{1-3}, y este último grupo alquilo está opcionalmente sustituido con uno o más átomos de flúor;

R^6 representa –H, -alquilo C_{1-5}, -cicloalquil C_{3-5}-alquilo C_{0-2}, en cuyos tres últimos grupos los fragmentos alquilo o cicloalquilo están opcionalmente sustituidos con uno o más átomos de flúor;

R^7 representa halo, alquil C_{1-5}-O-, cicloalquil C_{3-7}-alquil C_{0-2}-O-, (heterocicloalquil de 4-7-miembros)-alquil C_{0-2}-O-, en cuyos tres últimos grupos los fragmentos alquilo, cicloalquilo o heterocicloalquilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F y -O-alquilo C_{1-3} y este último grupo alquilo está opcionalmente sustituido además con uno o más átomos de flúor;

A representa alquilo C_{1-8}-, fenilo-, indanilo-, naftilo-, 1,2,3,4-tetrahidronaftilo-, piridilo-, tienilo-, benzotienilo-, pirrolilo-, indolil-pirazolilo-, indazolilo-, tiazolilo-, benzotiazolilo-, oxazolilo-, benzoxazolilo-, isoxazolilo-, bencisoxazolilo-, fenil-alquilo C_{1-3}-, tienil-alquilo C_{1-3}-, piridil-alquilo C_{1-3}-, cicloalquil C_{3-7}-alquilo C_{0-3}-, oxetanil-alquilo C_{0-3}-, tetrahidrofuranil-alquilo C_{0-3}, tetrahidropiranil-alquilo C_{0-3}, en cuyos grupos los fragmentos alquilo-, cicloalquilo- y heterocicloalquilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de **R^{9a}** y los fragmentos arilo y heteroarilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de **R^{9b}**;

cada R^{9a} representa independientemente -F, -Cl, -alquilo C_{1-3} que está opcionalmente sustituido con uno o más sustituyentes seleccionados de -F, -O-alquilo C_{1-3} ;

cada R^{9b} representa independientemente -halo, -CN; -alquilo C_{1-3} que está opcionalmente sustituido con uno o más átomos de flúor;

o una de sus sales, particularmente una de sus sales fisiológicamente aceptables.

En una segunda realización, en la fórmula general **I, A, M**, **W, R^1**, **R^2, R^6, R^7** tienen el mismo significado que se ha definido en cualquiera de las realizaciones precedentes, y

R^8 representa –H o fluoro.

En otra realización, en la fórmula general **I, A, M**, **W, R^1**, **R^2, R^7, R^8** tienen el mismo significado que se ha definido en cualquiera de las realizaciones precedentes, y

R^6 representa -H, $-CH_3$, ciclopropilo.

En otra realización, en la fórmula general **I, A, M**, **W, R^6, R^7, R^8** tienen el mismo significado que se ha definido en cualquiera de las realizaciones precedentes, y

R^1 y R^2 representan independientemente cloro, fluoro, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$.

En otra realización, en la fórmula general **I, A, M, W, R^1, R^2, R^6, R^8** tienen el mismo significado que se ha definido en cualquiera de las realizaciones precedentes, y

R^7 representa fluoro, $-OCHF_2$, $-OCF_3$, $-OCH_2CH_2F$, $-OCH_2CHF_2$, $-OCH_2CF_3$, -O-tetrahidrofuran-3-ilo, -O-CH_2-ciclopropilo.

En otra realización, en la fórmula general **I, M, W, R^1, R^2, R^6, R^7, R^8** tienen el mismo significado que se ha definido en cualquiera de las realizaciones precedentes, y

A representa alquilo C_{1-4}-, cicloalquil C_{3-7}-alquilo C_{0-2}-, tetrahidrofuranil-metilo-, fenil-alquilo C_{1-2} -, piridil-metilo-, fenilo-, indanilo-, piridilo-, tienilo-, tiazolilo-, benzotiazolilo-, en cuyos grupos los fragmentos alquilo-, cicloalquilo- y heterocicloalquilo- están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, y los fragmentos arilo y heteroarilo están opcionalmente sustituidos con -F, -Cl, -Br, -CN, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$.

En otra realización, en la fórmula general **I, A, W, R^1, R^2, R^6, R^7, R^8** tienen el mismo significado que se ha definido en cualquiera de las realizaciones precedentes, y

M representa

-alquilo C_{1-4}, -cicloalquilo C_{3-5}, y ambos grupos están opcionalmente sustituidos con uno o más grupos seleccionados de -F, -OH, -CN, $-NH_2$, $-OCH_3$, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, ciclopropilo;

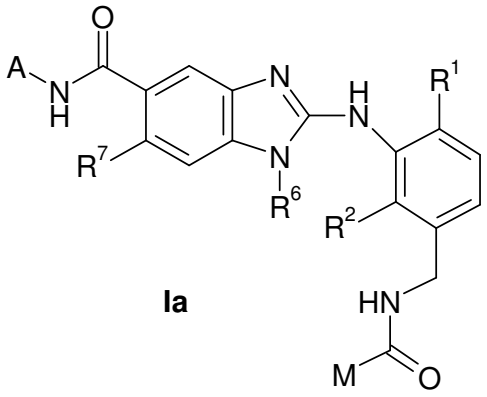
u

oxetanilo-, tetrahidrofuranilo-, azetidinilo- o pirrolidinilo-, y todos estos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$;

o

fenilo-, indanilo-, tienilo-, pirrolilo-, pirazolilo-, imidazolilo-, tiazolilo-, o isoxazolilo-, y todos estos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, -Cl, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$.

Otra realización de la presente invención comprende compuestos de la fórmula **Ia**

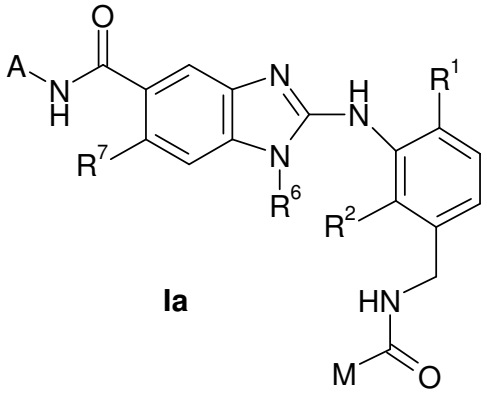


Ia

en la que

A, M, R^1, R^2, R^6, R^7 tienen el mismo significado que se ha definido en cualquiera de las realizaciones precedentes.

Una realización adicional de la presente invención comprende compuestos de la fórmula **Ia**



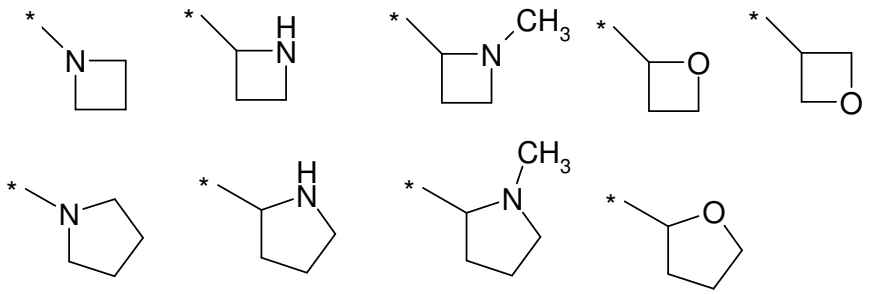
Ia

en la que

M representa

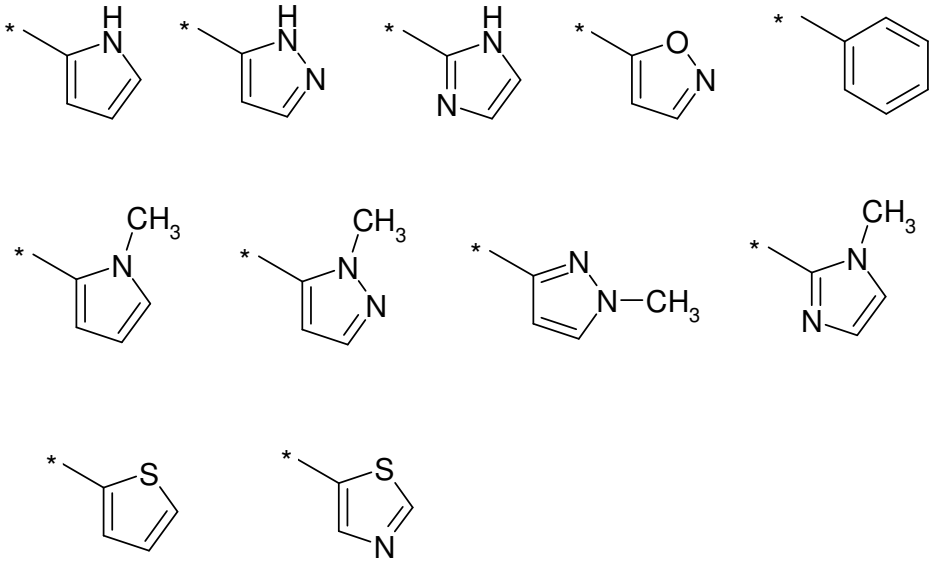
metilo, etilo, propilo, *i*-propilo, *n*-butilo, *s*-butilo, *t*-butilo, -CH_2-ciclopropilo, ciclopropilo, ciclobutilo, ciclopentilo, y todos estos grupos están opcionalmente sustituidos con uno o más grupos seleccionados de -F, -OH, -CN, -NH_2, -OCH_3, -CH_3, -CF_3;

o se selecciona de los siguientes grupos



y estos nueve últimos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, -CH_3, -CF_3;

o se selecciona de los siguientes grupos



y estos once últimos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, -Cl, -CH_3, -CF_3;

y

A, R^1, R^2, R^6, R^7 tienen el mismo significado que se ha definido en cualquiera de las realizaciones precedentes.

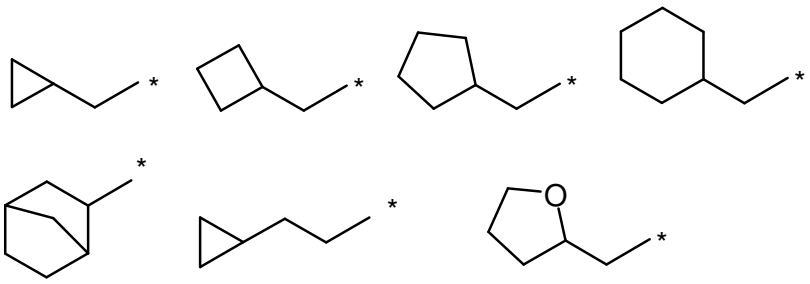
Una realización adicional de la presente invención comprende compuestos de la fórmula **Ia**

en la que

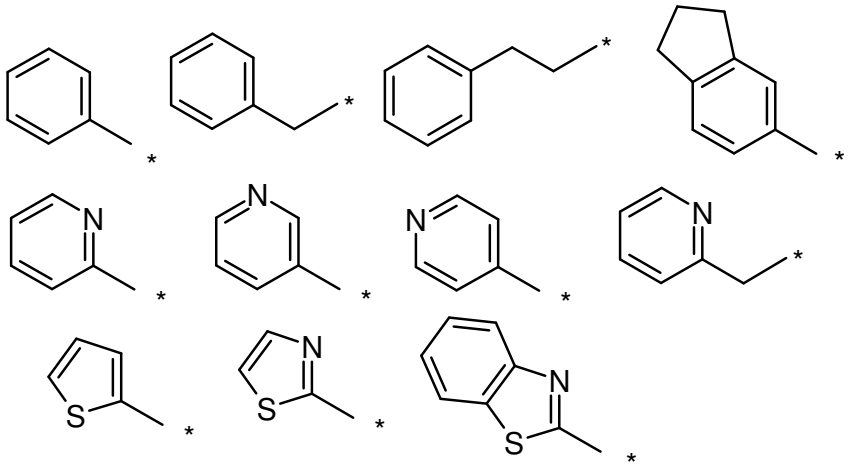
A representa metilo, etilo, propilo, *i*-propilo, *n*-butilo, *s*-butilo, *t*-butilo, y estos siete últimos grupos están opcionalmente sustituidos con uno o más átomos de flúor,

o ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, y estos cuatro últimos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, -CH_3, -CHF_2, -CF_3;

o se selecciona de los siguientes grupos:



y estos siete últimos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, $-CH_3$, $-CHF_2$, $-CF_3$;
o se selecciona de los siguientes grupos:

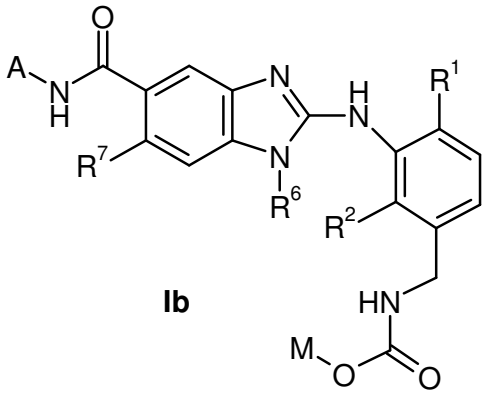


en cuyos once últimos grupos los fragmentos arilo y heteroarilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, -Cl, -Br, -CN, $-CH_3$, $-CF_3$;

y

M, R^1, R^2, R^6, R^7 tienen el mismo significado que se ha definido en cualquiera de las realizaciones precedentes.

Una realización adicional de la presente invención comprende compuestos de la fórmula **Ib**



Ib

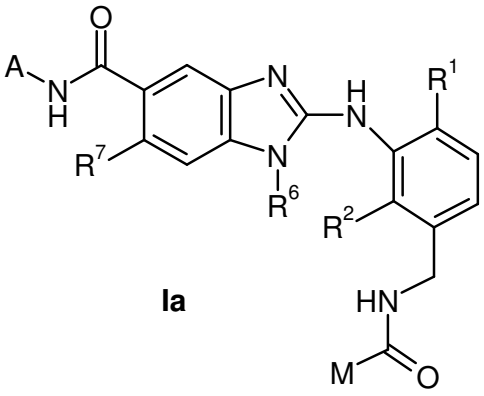
en la que

M es *terc*-butilo;

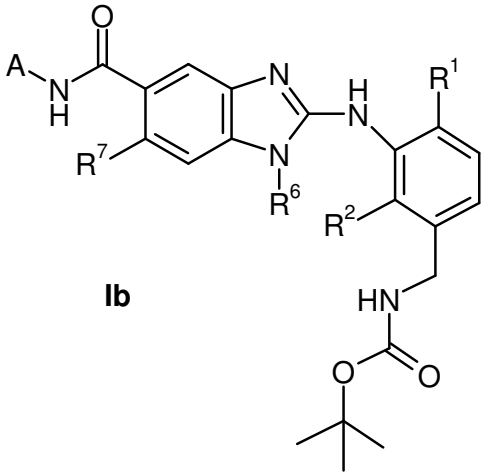
y

A, R^1, R^2, R^6, R^7 tienen el mismo significado que se ha definido en cualquiera de las realizaciones precedentes.

Una realización adicional de la presente invención comprende compuestos de la fórmula **Ia o Ib**



Ia



Ib

en las que

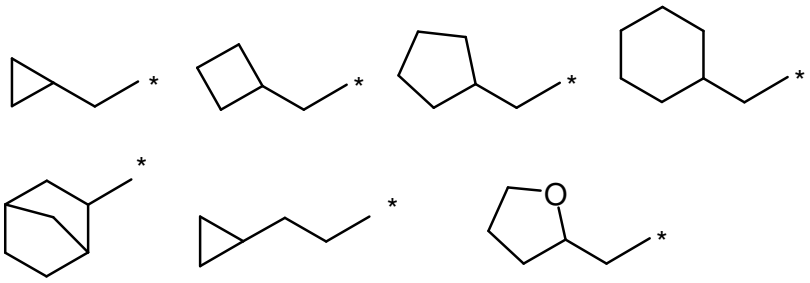
R^1 y R^2 representan independientemente cloro, fluoro, -CH_3, -CH_2F, -CHF_2, -CF_3;

R^6 representa -H, -CH_3, ciclopropilo;

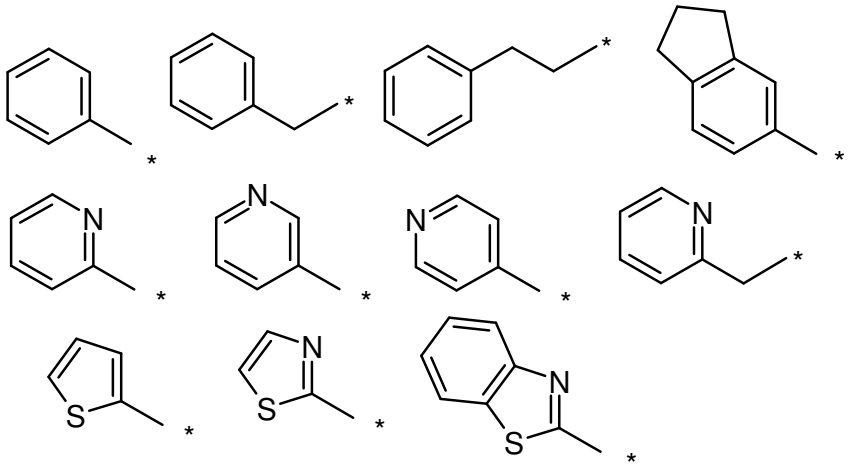
R^7 representa fluoro, -$OCHF_2$, -OCF_3, -OCH_2CH_2F, -OCH_2CHF_2, -OCH_2CF_3, tetrahidrofuran-3-il-O-, -O-CH_2-ciclopropilo;

A representa metilo, etilo, propilo, *i*-propilo, *n*-butilo, *s*-butilo, *t*-butilo, y estos siete últimos grupos están opcionalmente sustituidos con uno o más átomos de flúor,

o ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, y estos cuatro últimos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, -CH_3, -CHF_2, -CF_3;
o se selecciona de los siguientes grupos:



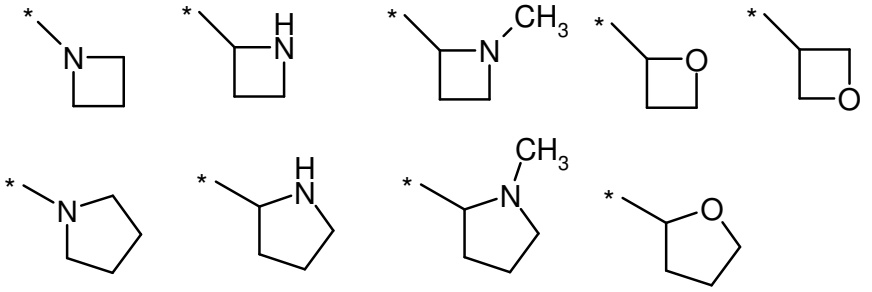
y estos siete últimos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, -CH_3, -CHF_2, -CF_3;
o se selecciona de los siguientes grupos:



en cuyos once últimos grupos los fragmentos arilo y heteroarilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, -Cl, -Br, -CN, -CH_3, -CF_3;

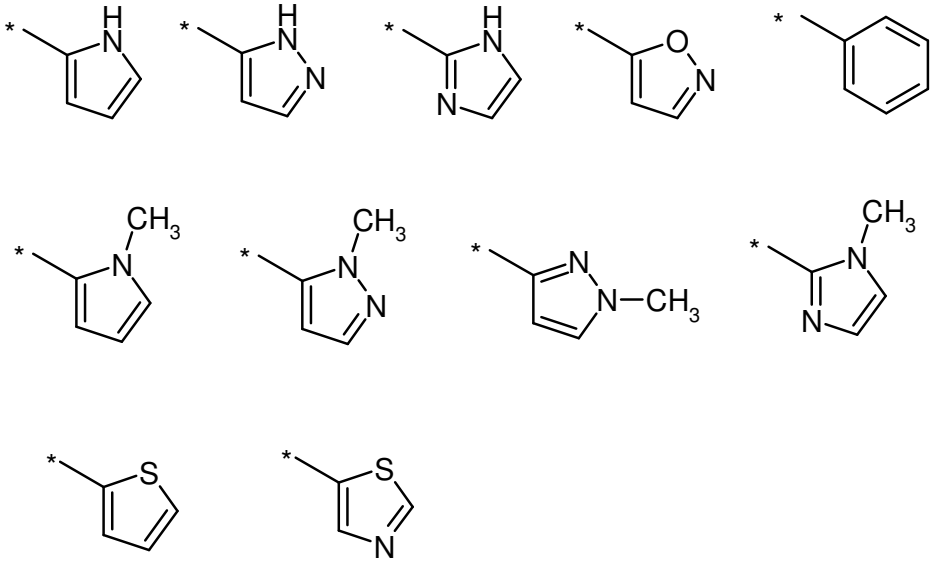
M representa

metilo, etilo, propilo, *i*-propilo, *n*-butilo, *s*-butilo, *t*-butilo, ciclopropilo, -CH_2-ciclopropilo, ciclobutilo, ciclopentilo, y todos estos grupos están opcionalmente sustituidos con uno o más grupos seleccionados de -F, -OH, -CN, -NH_2, -OCH_3, -CH_3, -CF_3;
o se selecciona de los siguientes grupos



y estos nueve últimos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, -CH_3, -CF_3;

o se selecciona de los siguientes grupos



y estos once últimos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, -Cl, -CH_3, -CF_3;

o las sales de los mismos, particularmente las sales de los mismos fisiológicamente aceptables.

TÉRMINOS Y DEFINICIONES USADOS

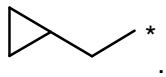
Definiciones generales:

Los términos que no se definen de forma específica en la presente memoria tendrán el significado que les den los expertos en la técnica a la luz de la descripción y el contexto. Sin embargo, tal y como se usan en la memoria descriptiva, a menos que se especifique lo contrario, los siguientes términos tienen el significado indicado y se adhieren a los siguientes convenios.

En los grupos, radicales o restos que se definen a continuación, el número de átomos de carbono se especifica a menudo detrás del grupo, por ejemplo, alquilo C_{1-6} significa un grupo o radical alquilo que tiene 1 a 6 átomos de carbono. En general, para grupos que comprenden dos o más subgrupos, el subgrupo nombrado en último lugar es el punto de unión del radical, por ejemplo, el sustituyente "aril-alquilo C_{1-3}-" significa un grupo arilo que está unido a un grupo alquilo C_{1-3}, estando este último unido al núcleo o al grupo al que se une el sustituyente.

En el caso en que un compuesto de la presente invención se represente en forma de un nombre químico y como una fórmula, en caso de cualquier discrepancia, prevalecerá la fórmula.

Se puede utilizar un asterisco en las sub-fórmulas para indicar el enlace que está conectado con el núcleo de la molécula como se ha definido, por ejemplo un grupo ciclopropilmetilo- se debe representar por la siguiente figura:



Estereoquímica/solvatos/hidratos:

A menos que se indique específicamente, a lo largo de la memoria descriptiva y de las reivindicaciones adjuntas, una fórmula química o un nombre químico dados englobarán los tautómeros (por ejemplo, *1H-bencimidazol* se puede considerar idéntico a un compuesto correspondiente que contiene un *3H-bencimidazol*) y todos los estereoisómeros, e isómeros ópticos y geométricos (por ejemplo, enantiómeros, diastereoisómeros, isómeros E/Z etc…) y sus racematos así como las mezclas en diferentes proporciones de los enantiómeros separados, mezclas de diastereoisómeros, o mezclas de cualquiera de las formas mencionadas en las que existen dichos isómeros y enantiómeros, así como las sales, incluyendo las sales de los mismos y los solvatos de los mismos farmacéuticamente aceptables tales como por ejemplo los hidratos incluyendo los solvatos de los compuestos libres o los solvatos de una sal del compuesto.

Sales:

La expresión "farmacéuticamente aceptable" se emplea en la presente memoria para hacer referencia a aquellos compuestos, materiales, composiciones y/o formas farmacéuticas que, basándose en el buen criterio médico, son adecuados para su uso en contacto con los tejidos de seres humanos y animales sin una toxicidad, irritación, respuesta alérgica excesivas, ni ningún otro problema o complicación, y en proporción con una relación beneficio/riesgo razonable.

Tal y como se usa en la presente memoria, las "sales farmacéuticamente aceptables" se refieren a derivados de los compuestos descritos, en los que el compuesto original se

modifica preparando sales de ácidos o bases de éste. Ejemplos de sales farmacéuticamente aceptables incluyen, pero sin limitarse a ellas, sales de ácidos minerales u orgánicos de restos de carácter básico, tales como aminas; sales alcalinas u orgánicas de restos de carácter ácido, tales como ácidos carboxílicos y similares. Por ejemplo, tales sales incluyen sales de amonio, L-arginina, betaina, benetamina, benzatina, hidróxido de calcio, colina, deanol, dietanolamina (2,2'-iminobis(etanol)), dietilamina, 2-(dietilamino)-etanol, 2-aminoetanol, etilendiamina, N-etil-glucamina, hidrabamina, 1H-imidazol, lisina, hidróxido de magnesio, 4-(2-hidroxietil)-morfolina, piperazina, hidróxido de potasio, 1-(2-hidroxietil)-pirrolidina, hidróxido de sodio, trietanolamina (2,2',2"-nitrilotris(etanol)), trometamina, hidróxido de cinc, ácido acético, ácido 2.2-dicloro-acético, ácido adípico, ácido algínico, ácido ascórbico, ácido L-aspártico, ácido bencenosulfónico, ácido benzoico, ácido 2,5-dihidroxibenzoico, ácido 4-acetamido-benzoico, ácido (+)-canfórico, ácido (+)-canfor-10-sulfónico, ácido carbónico, ácido cinámico, ácido cítrico, ácido ciclámico, ácido decanoico, ácido dodecilsulfúrico, ácido etano-1,2-disulfónico, ácido etanosulfónico, ácido 2-hidroxi-etanosulfónico, ácido etilendiaminotetraacético, ácido fórmico, ácido fumárico, ácido galactárico, ácido gentísico, ácido D-glucoheptónico, ácido D-glucónico, ácido D-glucurónico, ácido glutámico, ácido glutántico, ácido glutárico, ácido 2-oxo-glutárico, ácido glicerofosfórico, glicina, ácido glicólico, ácido hexanoico, ácido hipúrico, ácido bromhídrico, ácido clorhídrico, ácido isobutírico, ácido DL-láctico, ácido lactobiónico, ácido láurico, lisina, ácido maleico, ácido (-)-L-málico, ácido malónico, ácido DL-mandélico, ácido metanosulfónico, ácido galactárico, ácido naftaleno-1,5-disulfónico, ácido naftaleno-2-sulfónico, ácido 1-hidroxi-2-naftoico, ácido nicotínico, ácido nítrico, ácido octanoico, ácido oleico, ácido orótico, ácido oxálico, ácido palmítico, ácido pamoico (ácido embónico), ácido fosfórico, ácido propiónico, ácido (-)-L-piroglutámico, ácido salicílico, ácido 4-amino-salicílico, ácido sebácico, ácido esteárico, ácido succínico, ácido sulfúrico, ácido tánico, ácido (+)-L-tartárico, ácido tiociánico, ácido p-toluenosulfónico y ácido undecilénico. Se pueden formar otras sales farmacéuticamente aceptables con cationes de metales tales como aluminio, calcio, litio, magnesio, potasio, sodio, cinc y similares. (véase también Pharmaceutical salts, Berge, S.M. *et al.*, J. Pharm. Sci., (1977), 66, 1-19).

Las sales farmacéuticamente aceptables de la presente invención se pueden sintetizar a partir del compuesto original que contiene un resto básico o ácido por métodos químicos convencionales. En general, se pueden preparar sales de este tipo haciendo reaccionar las formas de ácido o base libre de estos compuestos con una cantidad suficiente de la base o ácido apropiado en agua o en un diluyente orgánico, tal como éter, acetato de etilo, etanol, isopropanol o acetonitrilo, o una mezcla de estos.

Las sales de otros ácidos distintos de los mencionados anteriormente que, por ejemplo, son útiles para purificar o aislar los compuestos de la presente invención (por ejemplo, sales trifluoroacetato) también forman parte de la invención.

Halógeno:

En general, el término halógeno indica flúor, cloro, bromo y yodo.

Alquilo:

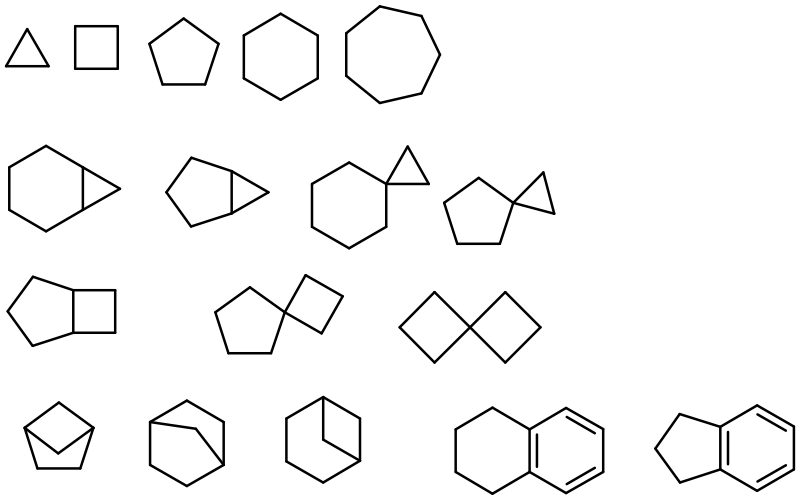
El término "alquilo-C_{1-n}", en el que n es un número entero de 2 a n, ya sea solo o en combinación con otro radical, indica un radical hidrocarbonado acíclico, saturado, lineal o ramificado, con 1 a n átomos de C. Por ejemplo, el término alquilo C_{1-5} incluye los radicales H_3C-, H_3C-CH_2-, H_3C-CH_2-CH_2-, H_3C-$CH(CH_3)$-, H_3C-CH_2-CH_2-CH_2-, H_3C-CH_2-$CH(CH_3)$-, H_3C-$CH(CH_3)$-CH_2-, H_3C-$C(CH_3)_2$-, H_3C-CH_2-CH_2-CH_2-CH_2-, H_3C-CH_2-CH_2-$CH(CH_3)$-, H_3C-CH_2-$CH(CH_3)$-CH_2-, H_3C-$CH(CH_3)$-CH_2-CH_2-, H_3C-CH_2-$C(CH_3)_2$-, H_3C-$C(CH_3)_2$-CH_2-, H_3C-$CH(CH_3)$-$CH(CH_3)$- y H_3C-CH_2-$CH(CH_2CH_3)$-.

Cicloalquilo:

El término " cicloalquilo C_{3-n}", en el que n es un número entero > 3, ya sea solo o en combinación con otro radical, indica un radical hidrocarbonado cíclico, saturado, con 3 a n átomos de C. Por ejemplo, el término cicloalquilo C_{3-7} incluye ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y cicloheptilo.

El término "cicloalquilo" incluye también estructuras de anillos bi-, tri- o tetra-cíclicos que consisten solamente en carbono y que contienen entre uno y cuatro anillos, cuyos anillos pueden estar unidos entre sí de una manera en pendiente o pueden estar condensados. El término "cicloalquilo" engloba adicionalmente sistemas espiro, y sistemas de puente. El radical hidrocarbonado cíclico también puede estar condensado con un anillo fenílico.

Por tanto, el término "cicloalquilo" incluye las siguientes estructuras a modo de ejemplo que no se representan como radicales ya que cada forma puede estar unida mediante un enlace covalente a cualquier átomo del fragmento de anillo cicloalquilo siempre que se mantengan las valencias apropiadas:



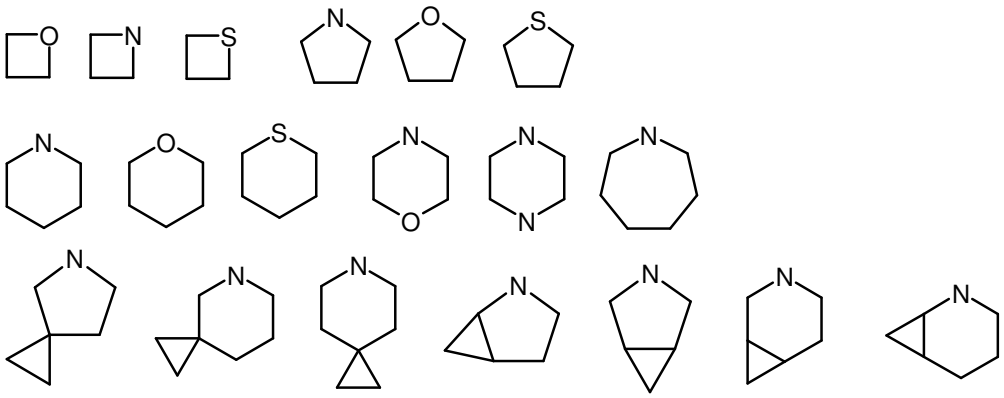
Heterocicloalquilo:

El término “heterocicloalquilo C_{3-n}”, en el que n es un número entero > 3, ya sea solo o en combinación con otro radical, indica un radical no aromático cíclico mono-, bi-, tri- o espirocíclico con 3 a n átomos en el anillo en el que al menos un átomo del anillo se selecciona de N, O o S y en el que n es el límite superior de átomos del anillo. El radical hidrocarbonado cíclico se puede condensar también con un anillo fenílico.

Los sustituyentes en los grupos heterocicloalquilo, cuando sea apropiado, se pueden situar sobre cualquier átomo del sistema de anillos incluyendo un heteroátomo.

El punto de unión de los radicales heterocicloalquilo puede ser a través de cualquier átomo del sistema de anillos no aromáticos incluyendo (cuando sea apropiado) un heteroátomo (tal como un átomo de nitrógeno) e incluyendo también un átomo en cualquier fragmento del anillo carbocíclico condensado no aromático, que pueda estar presente como parte del sistema de anillos.

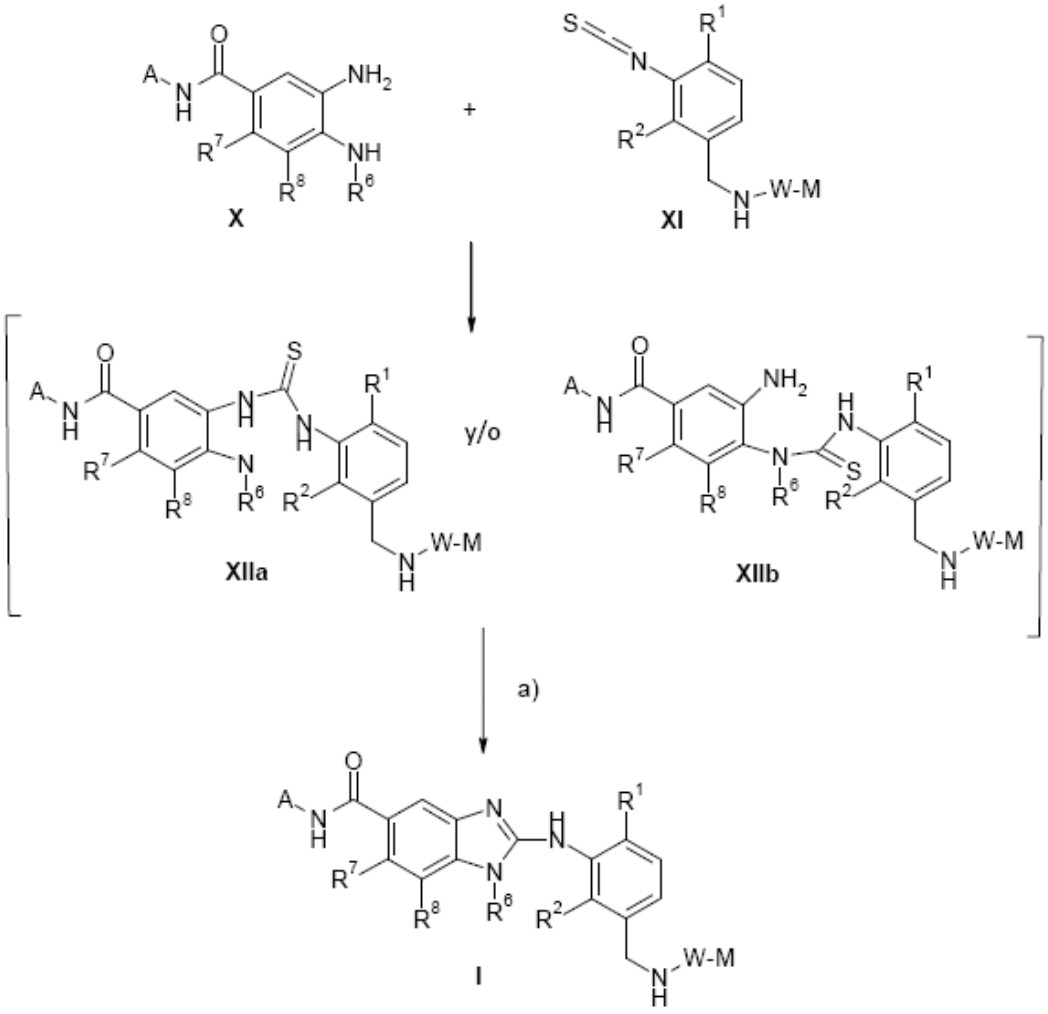
Así, el término “heterocicloalquilo” incluye las siguientes estructuras a modo de ejemplo que no se representan como radicales ya que cada forma puede estar unida mediante un enlace covalente a cualquier átomo siempre que se mantengan las valencias apropiadas:



MÉTODOS DE PREPARACIÓN

Los compuestos de la presente invención se pueden preparar de acuerdo con métodos que son bien conocidos por los expertos en la técnica, por ejemplo como se describen aquí más adelante y en la sección experimental o análogamente a los métodos descritos en los documentos WO2010/034796 y WO2010/034797. Según un aspecto adicional de la invención se proporciona un procedimiento para la preparación de un compuesto de la fórmula I, cuyo procedimiento se puede llevar a cabo, por ejemplo, según los siguientes esquemas A-C.

Esquema A *(todos los grupos variables son como se definen en la reivindicación 1):*

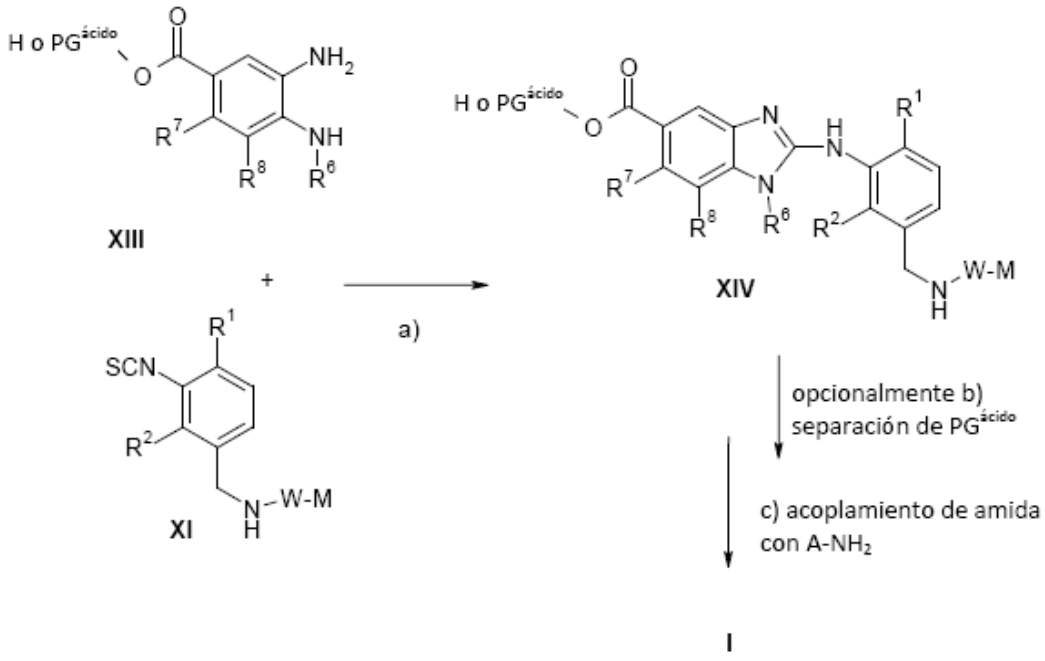


La reacción entre la fenilendiamina **X** y el tioisocianato **XI** (Etapa a) se puede llevar a cabo en condiciones estándar conocidas por los expertos en la técnica - por ejemplo

análogamente al procedimiento descrito en el documento WO2010/034796 - en presencia de un disolvente adecuado tal como éter dietílico (Et_2O), dimetilformamida (DMF), diclorometano (DCM), acetonitrilo (MeCN) y/o tetrahidrofurano (THF). La reacción se lleva a cabo preferiblemente en presencia de un reactivo adecuado que potencia la etapa de ciclación como por ejemplo CH_3-I o un compuesto basado en carbodiimida tal como N,N'-diciclohexilcarbodiimida (DCC), 1-etil-3-(3-dimetilaminopropil)carbodiimida (EDCI, o su sal, por ejemplo, hidrocloruro) o N,N'-diisopropilcarbodiimida (DIC). La reacción se puede realizar a cualquier temperatura adecuada entre 0 °C a 200 °C, preferiblemente entre la temperatura ambiente y 100 °C. La **etapa a** se puede realizar en una reacción por etapas con aislamiento de los intermedios de tiourea **XIIa** y/o **XIIb** o en un procedimiento de recipiente único.

Alternativamente los compuestos de la fórmula **I** se puede sintetizar según el esquema B.

Esquema B (todos los grupos variables son como se definen en la reivindicación 1 y $PG^{ácido}$ es un grupo protector de una función de ácido carboxílico)*:*



El grupo protector $PG^{ácido}$ es un grupo protector de ácido carboxílico conocido de las publicaciones científicas, bien conocido por los expertos en la técnica como por ejemplo los descritos en "*Protective Groups in Organic Synthesis*", 3rd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999), por ejemplo un grupo alquilo C_{1-5}, alilo o bencilo.

La **etapa a)** se puede llevar a cabo como se describe en el **esquema A**, pero también se puede llevar a cabo en presencia de un aditivo (tal como 2,2,2-trifluoro-N,O-bis-

(trimetilsilil)-acetamida) cuando está presente en **XIII** un resto de ácido carboxílico no protegido.

La **etapa b**) se puede llevar a cabo en condiciones de saponificación conocidas, por ejemplo con LiOH acuoso, NaOH o KOH en etanol (EtOH), metanol (MeOH), DMF, MeCN, THF o dioxano o con Pd/C en MeOH.

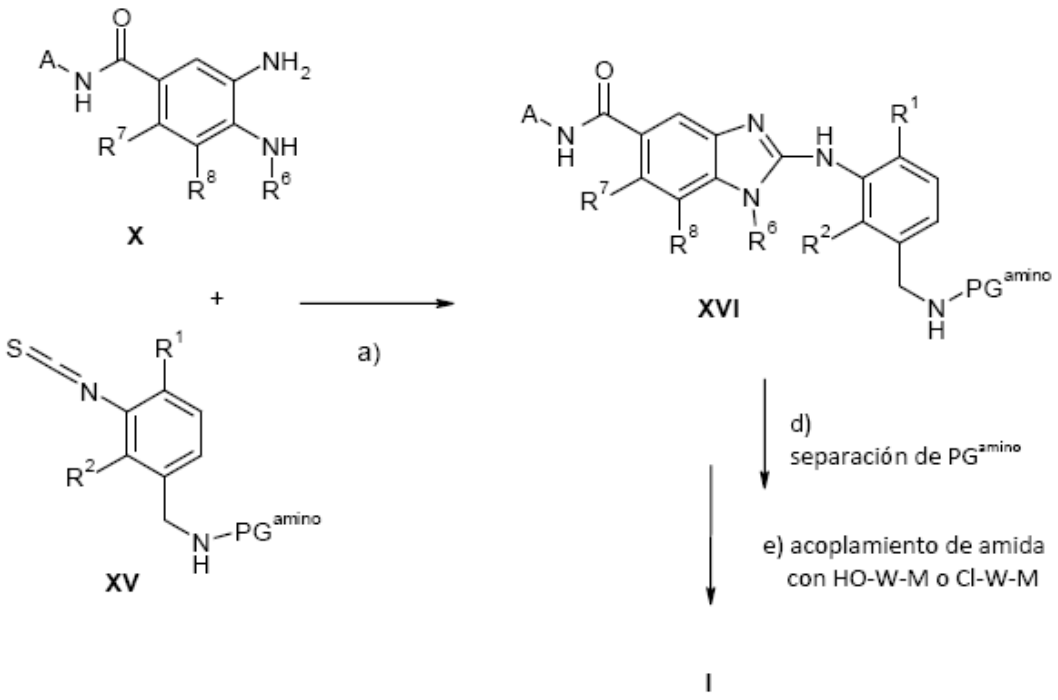
La formación de amida en la **etapa c**) se puede **r**ealizar con un agente activante adicional *in-situ* tal como anhídrido cíclico de ácido 1-propilfosfónico (PPA), tetrafluoroborato de *O*-(benzotriazol-1-il)-*N,N,N',N'*-tetrametil-uronio (TBTU), hexafluorofosfato de *O*-(benzotriazol-1-il)-*N,N,N',N'*-tetrametil-uronio (HBTU), hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (HATU), DCC, EDCI, carbonildiimidazol (CDI), carbonilditriazol (CDT), 1-cloro-2-metil-propenil-dimetilamina, cloruro de oxalilo o con otros agentes activantes según los conocimientos más avanzados de la técnica.

La reacción de acoplamiento se realiza preferiblemente en presencia de una base tal como NaOH, KOH, $NaHCO_3$, trietilamina (TEA), N-etildiisopropilamina (DIPEA), piridina, N,N,-dimetilaminopiridina (DMAP) u otras bases apropiadas de la técnica actual y por ejemplo las descritas en Houben-Weyl, "Methods in Organic Synthesis", Vol. E22a, p 425ff. Las reacciones de acoplamiento se realizan en un disolvente apropiado por ejemplo DCM, dioxano, THF, MeCN, DMF, dimetilacetamida (DMA), N-metilpirrolidona (NMP) o en mezclas de los disolventes mencionados a cualquier temperatura adecuada entre 0 °C a 100 °C.

Cuando el grupo protector de ácido ($PG^{ácido}$) es un grupo metilo o etilo se puede realizar también la conversión d**e XIV** a **I** en un procedimiento de recipiente único por ejemplo con trimetilaluminio o trietilaluminio en hexano, dioxano, THF a 20-80 °C.

Alternativamente los compuestos de la fórmula **I** se pueden sintetizar según el esquema C.

Esquema C (todos los grupos variables son como se definen en la reivindicación 1 y PG^{amino} es un grupo protector del grupo amino-bencílico)*:*



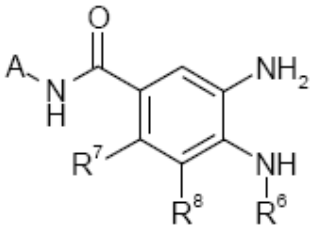
El grupo protector de amino (PG^{amino}) en **XV** es un grupo protector de un grupo amino conocido de las publicaciones científicas, bien conocido por los expertos en la técnica tal como por ejemplo los descritos en "*Protective Groups in Organic Synthesis*", 3rd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999), por ejemplo un grupo *terc*-butoxicarbonilo-, benciloxicarbonilo-, etoxicarbonilo-, metoxicarbonilo-, aliloxicarbonilo- o trifluorometilcarbonilo.

La **etapa a)** se puede llevar a cabo como se describe en el Esquema 1.

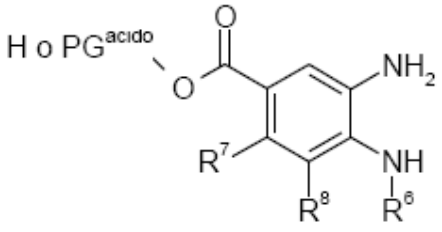
En la **etapa d**) el PG^{amino} de **XVI** se puede separar por métodos bien conocidos por los expertos en la técnica y de los que se dan ejemplos más adelante en esta memoria. Por ejemplo el compuesto **XVI** se puede desproteger usando un agente apropiado (que depende del grupo protector) tal como por ejemplo soluciones de ácido trifluoroacético, HCl o H_2SO_4, KOH; $Ba(OH)_2$, Pd sobre carbono (Pd/C), yoduro de trimetilsililo u otras condiciones como se describen en "*Protective Groups in Organic Synthesis*", 3rd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999). Un co-disolvente apropiado para esta etapa es por ejemplo DCM, THF, MeCN, DMF, DMA, NMP o mezclas de los disolventes mencionados a cualquier temperatura adecuada entre 0 °C a 100 °C.

La formación de amida en la **etapa e**) se puede realizar con los ácidos **HO-W-M** y un agente activante adicional *in-situ* tal como PPA, TBTU, HBTU, HATU, DCC, EDCI, CDI, CTI, 1-cloro-2-metil-propenil-dimetilamina, cloruro de oxalilo o con otros agentes activantes de la técnica actual análogamente al Esquema B, etapa c; o directamente con el correspondiente cloruro de ácido **Cl-W-M** en condiciones análogas sin ningún agente activante *in situ*.

La reacción de acoplamiento preferiblemente se realiza en presencia de una base tal como NaOH, KOH, $NaHCO_3$, TEA, DIPEA, piridina, DMAP u otras bases apropiadas de la técnica actual y por ejemplo las descritas en Houben-Weyl, "Methods in Organic Synthesis", Vol. E22a, p 425ff. Las reacciones de acoplamiento se realizan en un disolvente apropiado por ejemplo DCM, dioxano, THF, MeCN, DMF, DMA, NMP o en mezclas de los disolventes mencionados antes.

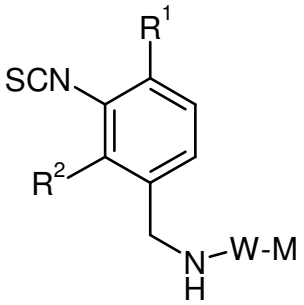


X

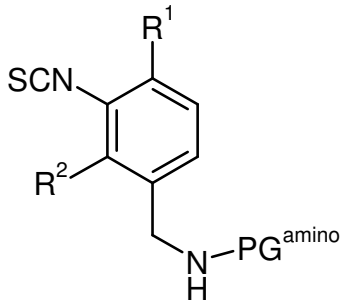


XIII

La síntesis de los bloques estructurales **X** y **XIII** en los que **A**, **R^6-R^8** tienen el significado definido en la reivindicación 1 y $PG^{ácido}$ es un grupo protector de ácido carboxílico conocido de las publicaciones científicas, como se ha descrito antes, se puede llevar a cabo análogamente a los procedimientos de las publicaciones científicas que son bien conocidos por los expertos en la técnica, como por ejemplo, análogamente a los métodos descritos en los documentos WO2010/034796 y WO2010/034797.



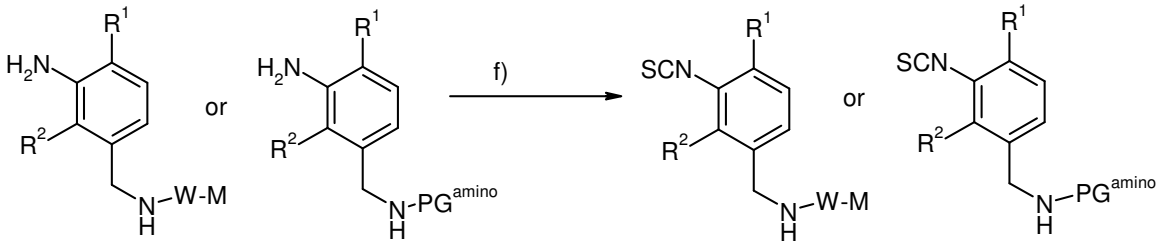
XI



XV

La síntesis de los bloques estructurales **XI** y **XV** - en los que todos los grupos variables son como se definen en la reivindicación 1 y PG^{amino} es un grupo protector del grupo amino-bencílico - emplea condiciones estándar de reacción según el esquema D conocido por los expertos en la técnica del cual se dan ejemplos en la parte experimental en detalle.

Esquema D (todos los grupos variables son como se definen en la reivindicación 1 y PG^{amino} es un grupo protector del grupo amino-bencílico)*:*

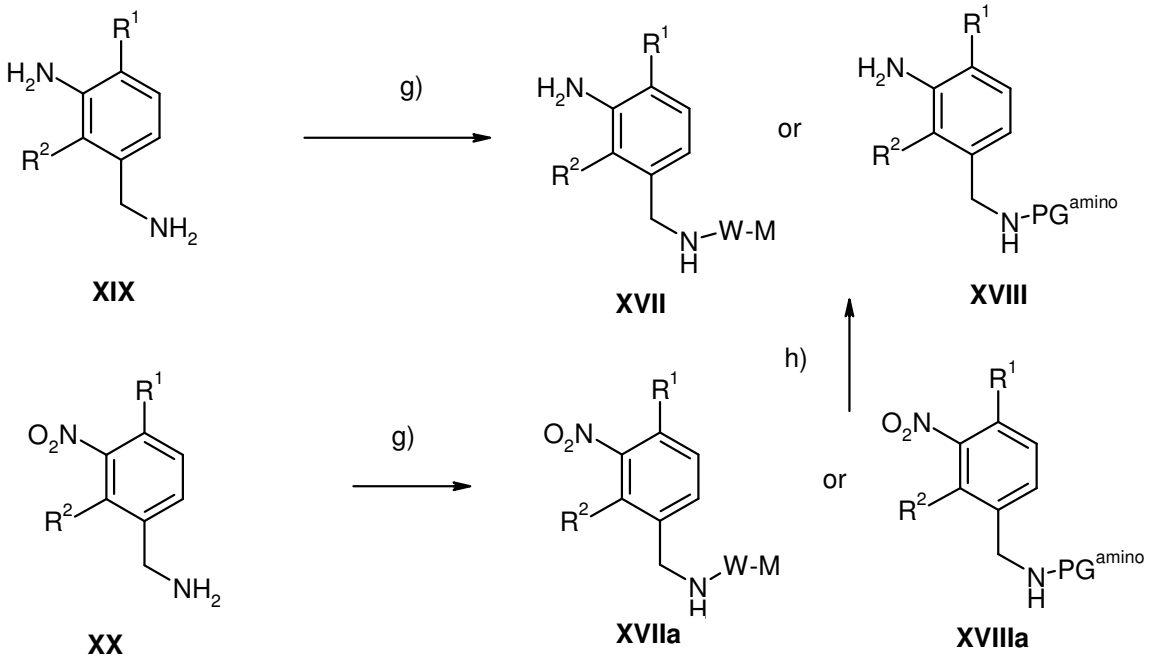


XVII **XVIII** **XI** **XV**

La **etapa f)** se puede llevar a cabo según los procedimientos estándar de las publicaciones científicas por ejemplo con reactivos tales como 1,1'-tiocarbonildi-2-piridona, O,O'-di-2-piridiltiocarbonato, 1,1'-tiocarbonildiimidazol o con tiofosgeno en un disolvente como por ejemplo DCM, dioxano o DMF a temperaturas entre 0-150 °C y opcionalmente con adición de una base tal como DMAP o TEA.

Los bloques estructurales **XVII** y **XVIII** se pueden preparar según el esquema E:

Esquema E (todos los grupos variables son como se definen en la reivindicación 1 y PG^{amino} es un grupo protector del grupo amino-bencílico)*:*



XIX **XVII** **XVIII**

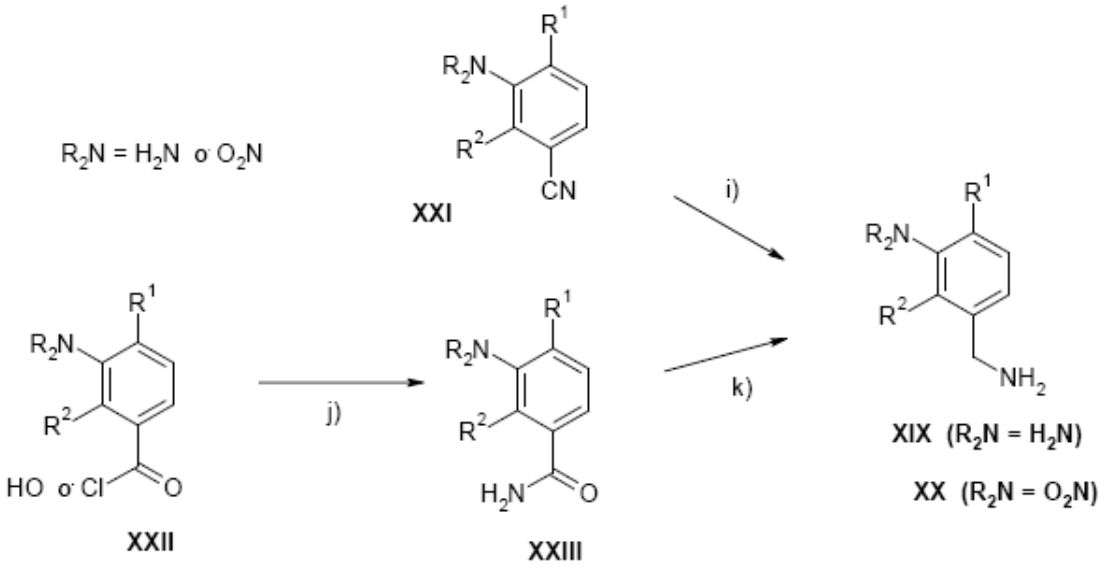
XX **XVIIa** **XVIIIa**

La formación de amida en la **etapa g)** se puede realizar análogamente a la **etapa c)** o **etapa e)** para sintetizar el compuesto **XVII** o utilizando reactivos comunes para la protección del grupo amino por ejemplo dicarbonato de di-*terc*-butilo, cloroformiato de metilo, etilo, bencilo o alilo en condiciones estándar de reacción como las descritas en "*Protective Groups in Organic Synthesis*", 3rd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999) para sintetizar los compuestos **XVIII.**

El grupo nitro en el precursor **XVIIa o XVIIIa** se puede reducir al grupo amino en la **etapa h)** en condiciones de reducción conocidas por las publicaciones científicas, por ejemplo mediante hidrogenación (preferiblemente a 1-5 bares) en presencia de Pd/C o RaNi en MeOH, EtOH o THF opcionalmente en condiciones ácidas en presencia de HCl, o utilizando $SnCl_2$/HCl, $Na_2S_2O_4$, Zn/HCl, Fe/HCl, Fe-polvo/solución acuosa de NH_4Cl o según los procedimientos descritos en las publicaciones científicas por ejemplo R. Larock, *Comprehensive Organic Transformations*, VCH Verlagsgemeinschaft, Weinheim (1989). Un disolvente apropiado para esta etapa es por ejemplo DCM, THF, MeCN, DMF, DMA, NMP, EtOH, MeOH o mezclas de los disolventes mencionados antes a cualquier temperatura adecuada entre 0 °C a 100 °C.

Los bloques estructurales **XIX** y **XX** se pueden preparar según los esquemas F-G:

Esquema F (todos los grupos variables son como se definen en la reivindicación 1)*:*



La **etapa i)** se puede llevar a cabo mediante hidrogenación (1-5 bares) con un catalizador tal como Pd/C, PtO_2 o RaNi en un disolvente adecuado tal como MeOH o EtOH utilizando opcionalmente HCl o NH_3 como aditivos a temperaturas entre 0-60 °C o mediante reducción con reactivos que contienen $LiAlH_4$ o BH_3 en condiciones conocidas por las publicaciones científicas.

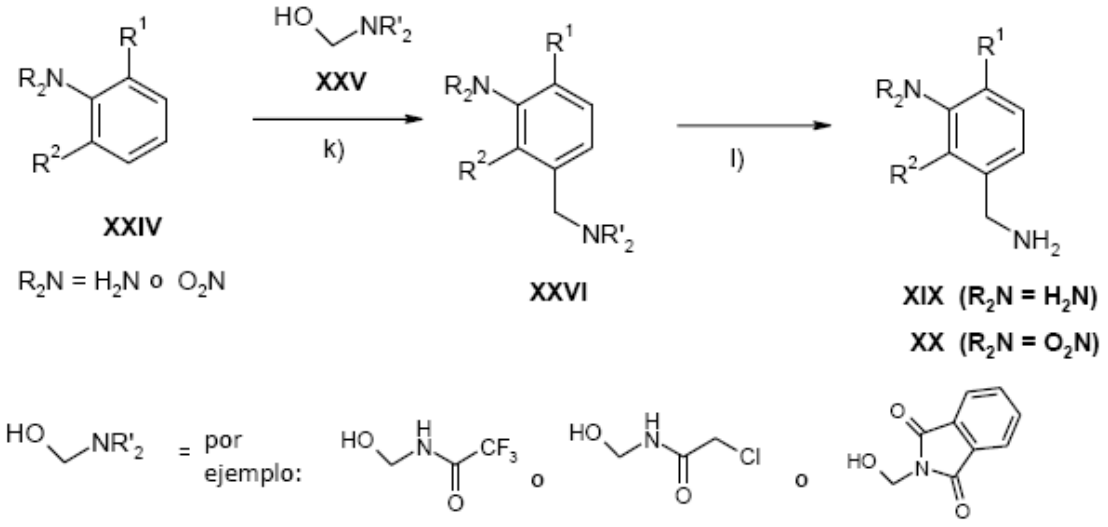
La **etapa j)** se puede llevar a cabo en las condiciones de acoplamiento de amida descritas para la etapa e) y utilizando NH_3 como copartícipe de acoplamiento, por ejemplo se puede usar como agente activante 1-cloro-2-metil-propenil-dimetilamina en THF.

La **etapa k)** se puede llevar a cabo utilizando reactivos que contienen $LiAlH_4$ o BH_3 en condiciones conocidas en las publicaciones científicas como por ejemplo las compiladas en

R.C.Larock, Comprehensive Organic Transformations, VCH, 1989, p.432-433, preferiblemente con $LiAlH_4$ en THF a 0-80 ºC.

Alternativamente, los compuestos **XIX** y **XX** se pueden preparar según el esquema G

Esquema G (todos los grupos variables son como se definen en la reivindicación 1)*:*

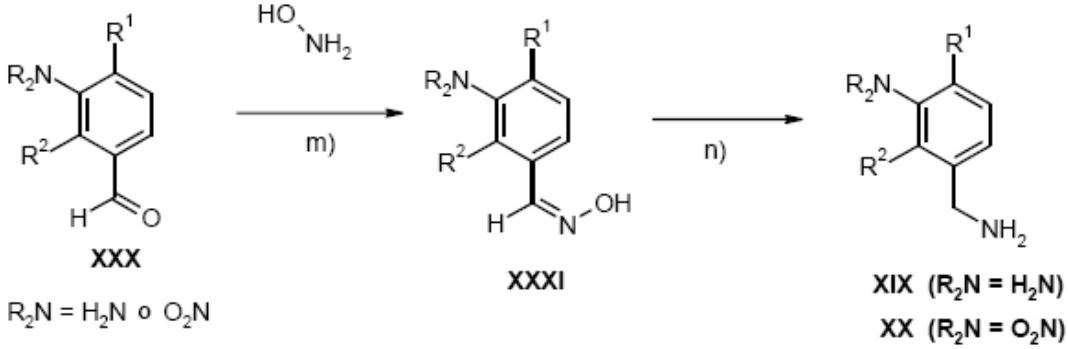


La **etapa k)** se puede llevar a cabo mezclando el compuesto **XXIV** con el reactivo **XXV** en H_2SO_4 concentrado o $F_3C\text{-}SO_3H$ a temperaturas entre 0-150 ºC, preferiblemente entre 20-80 ºC.

La **etapa l)** se puede llevar a cabo utilizando los procedimientos de desprotección conocidos de las publicaciones científicas para los correspondientes grupos protectores de nitrógeno por ejemplo tratamiento de la ftalimida con hidrazina o escisión del enlace amida utilizando bases como NaOH en MeOH o EtOH a temperaturas entre 20-80 ºC o en condiciones ácidas utilizando solución acuosa de HCl o HCl en dioxano a temperaturas entre 20-80 ºC

Alternativamente los compuestos **XIX** y **XX** se pueden preparar según el esquema H

Esquema H (todos los grupos variables son como se definen en la reivindicación 1)*:*

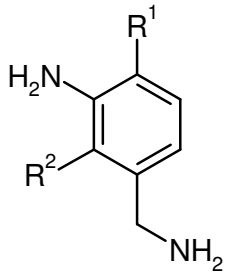


La **etapa m)** se puede llevar a cabo mezclando **XXX** con $HO-NH_2$ en un disolvente apropiado por ejemplo MeCN, DCM, THF, utilizando opcionalmente HCl como aditivo a temperaturas entre 0-60 °C.

La **etapa n)** se puede llevar a cabo aplicando las condiciones de reducción conocidas de las publicaciones científicas por ejemplo mediante hidrogenación preferiblemente a una presión de H_2 de 1-5 bares en presencia de Pd/C o Ra-Ni en MeOH, EtOH o THF, utilizando opcionalmente HCl o HOAc como catalizador, o utilizando $SnCl_2$/HCl, Zn/HCl, Fe/HCl, Fe-polvo/solución acuosa de NH_4Cl o según los procedimientos descritos en las publicaciones científicas por ejemplo R. Larock, *Comprehensive Organic Transformations*, VCH Verlagsgemeinschaft, Weinheim (1989).

Por lo tanto, un aspecto adicional de la presente invención es un procedimiento para preparar compuestos de la fórmula **I** que comprende las siguientes etapas:

(1) hacer reaccionar un compuesto de la fórmula **XIX**



XIX

en la que

R^1 y **R^2** representan independientemente halo, -alquilo C_{1-3}, y este último grupo alquilo está opcionalmente sustituido con uno o más átomos de flúor;

con un cloruro de ácido de la fórmula **Cl-W-M**

en la que

W representa -C(O)-, -C(O)O-, y estos grupos están unidos al nitrógeno del resto –NH- por medio del átomo de carbono;

M representa

-alquilo C_{1-6}, -cicloalquilo C_{3-7}, y ambos grupos están opcionalmente sustituidos con uno o más grupos seleccionados de -F, -OH, -CN, $-NH_2$, -NH(alquilo C_{1-2}), -N(alquil $C_{1-2})_2$, -O-alquilo C_{1-3}, -alquilo C_{1-5}, -cicloalquilo C_{3-4}, en cuyos tres últimos grupos los grupos alquilo o cicloalquilo están opcionalmente sustituidos con uno o más átomos de flúor;

o

oxetanilo-, tetrahidrofuranilo-, tetrahidropiranilo-, azetidinilo-, pirrolidinilo-, piperidinilo-, y todos estos grupos están opcionalmente sustituidos con uno

o más sustituyentes seleccionados de fluoro, -CN, -alquilo C_{1-3}, y este último grupo alquilo está opcionalmente sustituido con uno o más átomos de flúor;

o

fenilo-, piridilo-, tienilo-, pirrolilo-, pirazolilo-, imidazolilo-, tiazolilo-, oxazolilo-, o isoxazolilo-, y todos estos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de halo, -CN o -alquilo C_{1-3}, y este último grupo alquilo está opcionalmente sustituido además con uno o más átomos de flúor;

o

con un ácido de la fórmula **HO-W-M** en presencia de un agente activante *in situ* seleccionado del grupo de anhídrido cíclico de ácido 1-propilfosfónico (PPA), tetrafluoroborato de *O*-(benzotriazol-1-il)-*N,N,N',N'*-tetrametil-uronio (TBTU), hexafluorofosfato de *O*-(benzotriazol-1-il)-*N,N,N',N'*-tetrametil-uronio (HBTU), hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (HATU), DCC, EDCI, carbonildiimidazol (CDI), carbonilditriazol (CDT), 1-cloro-2-metil-propenil-dimetilamina y cloruro de oxalilo;

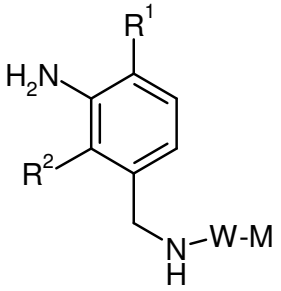
y

en la presencia de una base seleccionada del grupo de NaOH, KOH, $NaHCO_3$, trietilamina (TEA), N-etildiisopropilamina (DIPEA), piridina, N,N,-dimetilaminopiridina (DMAP)

en un disolvente seleccionado del grupo de diclorometano, dioxano, THF, MeCN, dimetilformamida, dimetilacetamida (DMA), N-metilpirrolidona (NMP) o en mezclas de los mismos;

a una temperatura entre 0 °C a 100 °C

para obtener un compuesto de la fórmula **XVII**



XVII ;

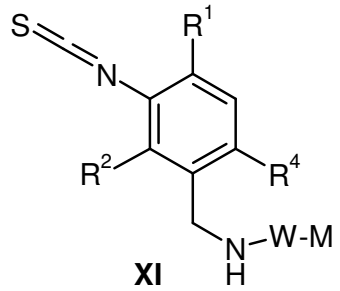
(2) hacer reaccionar el compuesto de la fórmula **XVII**

con un reactivo seleccionado del grupo de 1,1'-tiocarbonildi-2-piridona, O,O'-di-2-piridiltiocarbonato, 1,1'-tiocarbonildiimidazol y tiofosgeno

en un disolvente seleccionado del grupo de diclorometano, dioxano y DMF

a temperaturas entre 0-150 °C y opcionalmente en presencia de una base que es preferiblemente DMAP o TEA

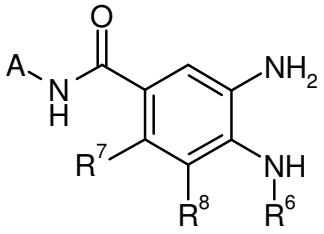
para obtener un compuesto de la fórmula **XI**



XI

(3) hacer reaccionar el compuesto de la fórmula **XI**

con un compuesto de la fórmula **XIII**



X

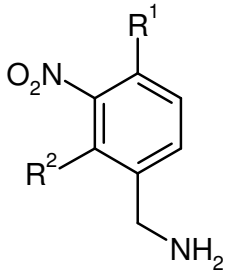
en presencia de un reactivo seleccionado del grupo de CH_3-I, N,N'-diciclohexilcarbodiimida (DCC), 1-etil-3-(3-dimetilaminopropil)carbodiimida (EDCI, o su hidrocloruro) y N,N'-diisopropilcarbodiimida (DIC);

en un disolvente seleccionado del grupo de éter dietílico (Et_2O), dimetilformamida (DMF), diclorometano (DCM), acetonitrilo (MeCN) y tetrahidrofurano (THF)

preferiblemente a una temperatura entre 0 °C y 100 °C.

Un procedimiento alternativo para preparar los compuestos de la fórmula **I** comprende las siguientes etapas:

(1) hacer reaccionar un compuesto de la fórmula **XX**



XX

en la que

R^1 y **R^2** representan independientemente halo, -alquilo C_{1-3}, y este último grupo alquilo está opcionalmente sustituido con uno o más átomos de flúor;

con un cloruro de ácido de la fórmula **Cl-W-M**

en la que

W representa -C(O)-, -C(O)O-, y estos grupos están unidos al nitrógeno del resto –NH- mediante el átomo de carbono;

M representa

-alquilo C_{1-6}, -cicloalquilo C_{3-7}, y ambos grupos están opcionalmente sustituidos con uno o más grupos seleccionados de -F, -OH, -CN, $-NH_2$, -NH(alquilo C_{1-2}), -N(alquil $C_{1-2})_2$, -O-alquilo C_{1-3}, -alquilo C_{1-5}, -cicloalquilo C_{3-4}, en cuyos tres últimos grupos los grupos alquilo o cicloalquilo están opcionalmente sustituidos con uno o más átomos de flúor;

o

oxetanilo-, tetrahidrofuranilo-, tetrahidropiranilo-, azetidinilo-, pirrolidinilo-, piperidinilo-, y todos estos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de fluoro, -CN, -alquilo C_{1-3}, y este último grupo alquilo está opcionalmente sustituido con uno o más átomos de flúor;

o

fenilo-, piridilo-, tienilo-, pirrolilo-, pirazolilo-, imidazolilo-, tiazolilo-, oxazolilo-, o isoxazolilo-, y todos estos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de halo, -CN o -alquilo C_{1-3}, y este último grupo alquilo está opcionalmente sustituido además con uno o más átomos de flúor.

o

con un ácido de la fórmula **HO-W-M** en presencia de un agente activante *in situ* seleccionado del grupo de anhídrido cíclico de ácido 1-propilfosfónico (PPA), tetrafluoroborato de *O*-(benzotriazol-1-il)-*N,N,N',N'*-tetrametil-uronio (TBTU), hexafluorofosfato de *O*-(benzotriazol-1-il)-*N,N,N',N'*-tetrametil-uronio (HBTU), hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (HATU), DCC, EDCI, carbonildiimidazol (CDI), carbonilditriazol (CDT), 1-cloro-2-metil-propenil-dimetilamina y cloruro de oxalilo;

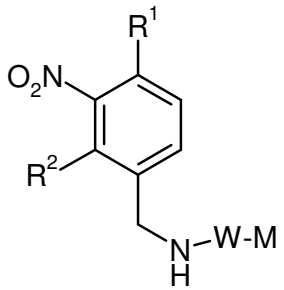
y

en la presencia de una base seleccionada del grupo de NaOH, KOH, $NaHCO_3$, trietilamina (TEA), N-etildiisopropilamina (DIPEA), piridina, N,N,-dimetilaminopiridina (DMAP)

en un disolvente seleccionado del grupo de diclorometano, dioxano, THF, MeCN, dimetilformamida, dimetilacetamida (DMA), N-metilpirrolidona (NMP) o en mezclas de los mismos;

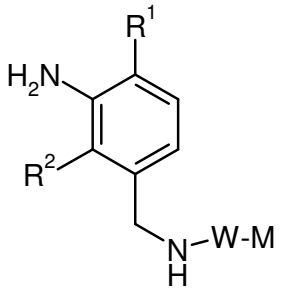
a una temperatura entre 0 °C y 100 °C

para obtener un compuesto de la fórmula **XVIIa**



XVIIa ;

(2) convertir el compuesto de la fórmula **XVIIa** en un compuesto de la fórmula **XVII**



XVII

por hidrogenación catalítica (preferiblemente a 1-5 bares) en presencia de Pd/C o RaNi en MeOH, EtOH o THF, opcionalmente en condiciones ácidas en presencia de HCl,

o

por reducción con un reactivo seleccionado del grupo de $SnCl_2$/HCl, $Na_2S_2O_4$, Zn/HCl, Fe/HCl, Fe-polvo/solución acuosa de NH_4Cl en un disolvente seleccionado del grupo de DCM, THF, MeCN, DMF, DMA, NMP, EtOH, MeOH o mezclas de los mismos a una temperatura entre 0 °C a 100 °C;

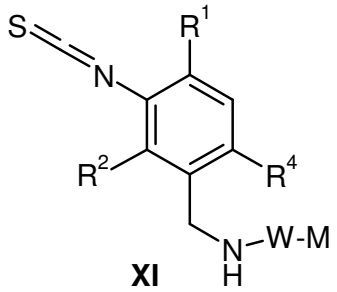
(3) hacer reaccionar el compuesto de la fórmula **XVII**

con un reactivo seleccionado del grupo de 1,1'-tiocarbonildi-2-piridona, O,O'-di-2-piridiltiocarbonato, 1,1'-tiocarbonildiimidazol y tiofosgeno

en un disolvente seleccionado del grupo de diclorometano, dioxano y DMF

a temperaturas entre 0-150 °C y opcionalmente en presencia de una base que es preferiblemente DMAP o TEA

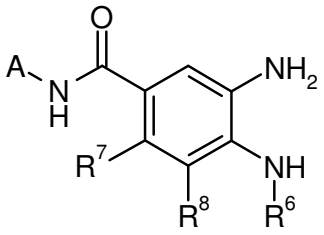
para obtener un compuesto de la fórmula **XI**



XI

(4) hacer reaccionar el compuesto de la fórmula **XI**

con un compuesto de la fórmula **XIII**



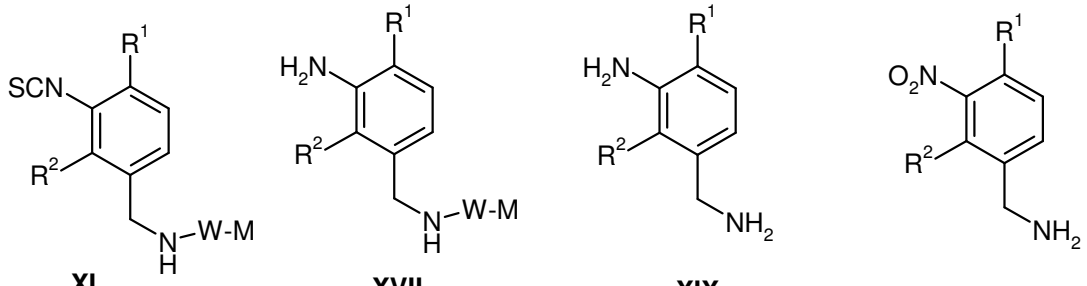
X

en presencia de un reactivo seleccionado del grupo de CH_3-I, N,N'-diciclohexilcarbodiimida (DCC), 1-etil-3-(3-dimetilaminopropil)carbodiimida (EDCI, o su hidrocloruro) y N,N'-diisopropilcarbodiimida (DIC);

en un disolvente seleccionado del grupo de éter dietílico (Et_2O), dimetilformamida (DMF), diclorometano (DCM), acetonitrilo (MeCN) y tetrahidrofurano (THF)

preferiblemente a una temperatura entre 0 °C y 100 °C.

Un aspecto adicional de la presente invención son los intermedios de las fórmulas **XI, XVII, XIX y XX**



XI **XVII** **XIX** **XX**

en las que

R^1 y **R^2** representan independientemente halo, -alquilo C_{1-3}, y este último grupo alquilo está opcionalmente sustituido con uno o más átomos de flúor;

W representa -C(O)-, -C(O)O-, y estos grupos están unidos al nitrógeno del resto –NH- por medio del átomo de carbono;

M representa

-alquilo C_{1-6}, -cicloalquilo C_{3-7}, y ambos grupos están opcionalmente sustituidos con uno o más grupos seleccionados de -F, -OH, -CN, $-NH_2$, -NH(alquilo C_{1-2}), -N(alquil $C_{1-2})_2$, -O-alquilo C_{1-3}, -alquilo C_{1-5}, -cicloalquilo C_{3-4}, en cuyos tres últimos grupos los grupos alquilo o cicloalquilo están opcionalmente sustituidos con uno o más átomos de flúor;

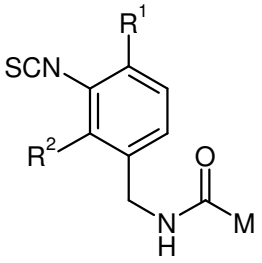
o

oxetanilo-, tetrahidrofuranilo-, tetrahidropiranilo-, azetidinilo-, pirrolidinilo-, piperidinilo-, y todos estos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de fluoro, -CN, -alquilo C_{1-3} , y este último grupo alquilo está opcionalmente sustituido con uno o más átomos de flúor;

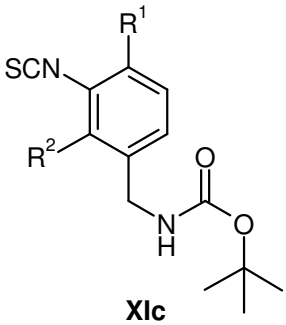
o

fenilo-, piridilo-, tienilo-, pirrolilo-, pirazolilo-, imidazolilo-, tiazolilo-, oxazolilo-, o isoxazolilo-, y todos estos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de halo, -CN o -alquilo C_{1-3}, y este último grupo alquilo está opcionalmente sustituido además con uno o más átomos de flúor.

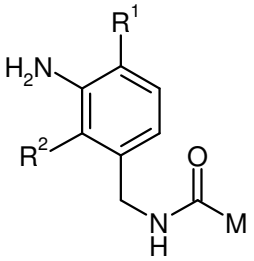
Una segunda realización comprende como intermedios preferidos los compuestos de las fórmulas **XIb, XIc, XVIIb, XVIIc, XIX y XX**



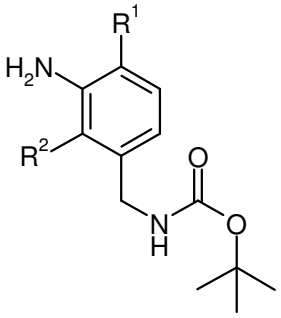
XIb



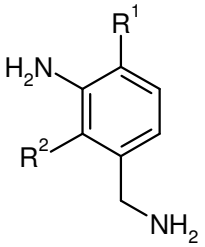
XIc



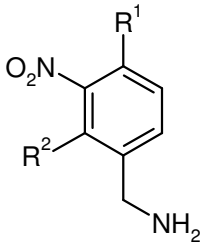
XVIIb



XVIIc



XIX



XX

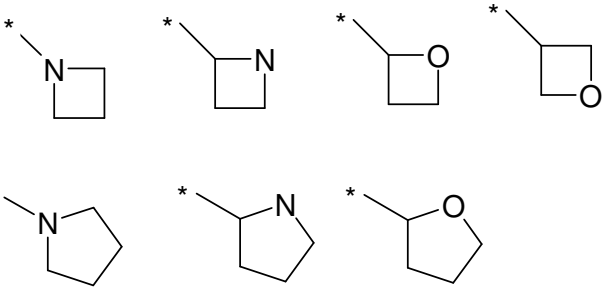
en las que

R^1 y R^2 representan independientemente –cloro, fluoro o $–CH_3$;

M representa

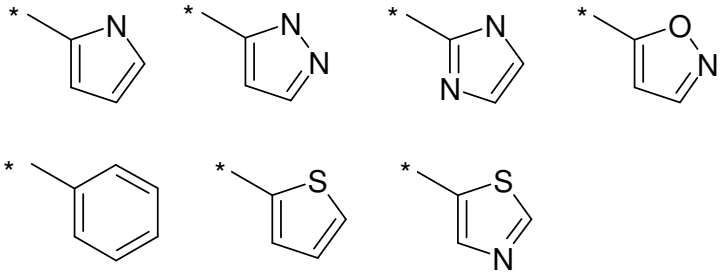
metilo, etilo, propilo, *i*-propilo, *n*-butilo, *s*-butilo, *t*-butilo, ciclopropilo, $-CH_2$-ciclopropilo, ciclobutilo, ciclopentilo, y todos estos grupos están opcionalmente sustituidos con uno o más grupos seleccionados de -F, -OH, -CN, $-NH_2$, $-OCH_3$, $-CH_3$, $-CF_3$;

o se selecciona de los siguientes grupos



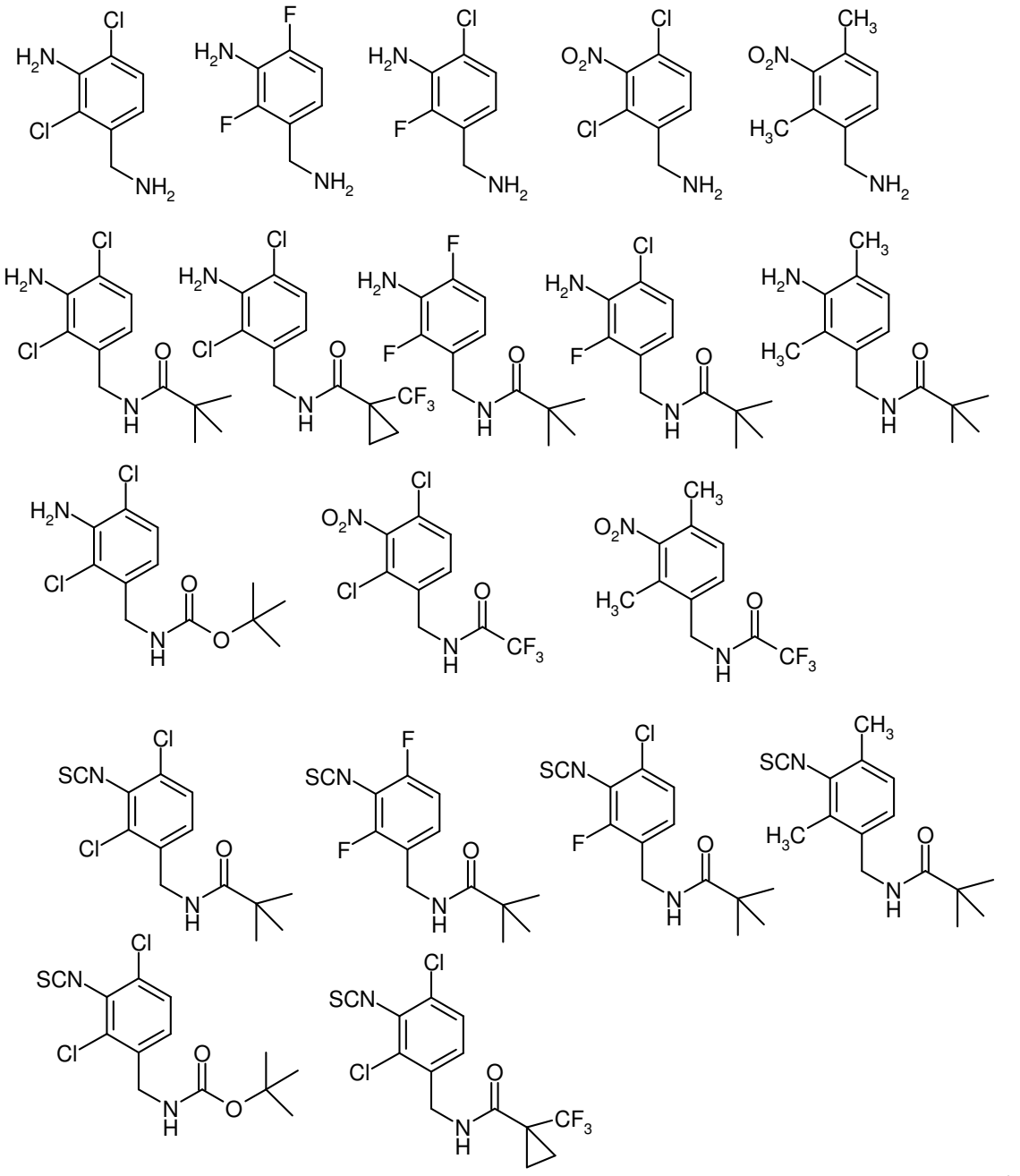
y todos estos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, $-CH_3$, o $-CF_3$;

o se selecciona de los siguientes grupos



y todos estos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, -Cl, $-CH_3$, o $-CF_3$.

Una realización adicional comprende, como intermedios más preferidos, los compuestos de las fórmulas **XIb, XIc, XVIIb, XVIIc, XIX y XX**, a saber



Ensayos biológicos

Producción de la proteína mPGES

Microsomas de la bacteria E.coli Rosetta que expresan la mPGES-1 humana recombinante se pueden obtener como se describe a continuación:

Se inoculan 5 ml de LB que contienen ampicilina (50 µg/ml) y cloranfenicol (34 µg/ml), con bacterias procedentes de cultivo congelado. Se incuban durante 8 h a 37 ºC a

200 rpm. Luego se inoculan 500-1000 ml de LB que contienen ampicilina y cloranfenicol con los 5 ml en el cultivo y se desarrollan hasta OD640 de 0,8-1,0. Se enfría el cultivo hasta +4 ºC antes de la inducción. Se induce el cultivo con IPTG a una concentración final de 400 µM. Se expresa la proteína a temperatura ambiente de 18-23 ºC con agitación a 200 rpm durante una noche.

Al día siguiente, se pueden llevar a cabo las siguientes etapas:

1. Se centrifugan las células en tubos de centrífuga de 250 ml durante 15 min a 7000 rpm (centrífuga Beckmann Coulte Avanti J-E)
2. Se disuelve el sedimento de 250 ml de cultivo en 12,5 ml de tampón de homogeneización
3. (Tris-HCl 15 mM pH 8, EDTA 1 mM pH 8, sacarosa 0,25 mM, GSH 2,5 mM, 1 comprimido de inhibidor de la proteasa por 50 ml de tampón)
4. Se desintegran las células por sonicación, 5 X 10 segundos a amplitud del 48 % de un sonificador a 750 W
5. Se añaden 2,5 ml de $MgCl_2$ (100 mM) y 12,5 µl de DNasa (0,8 mg/ml) y se incuba en hielo durante 30 min
6. Se centrifugan los restos de bacterias y se conserva el sobrenadante, 7000 rpm durante 15 min
7. Se aíslan las membranas que contienen la proteína en el sobrenadante por ultracentrifugación a 120000 x g durante 2 horas a 4 ºC (rotor Sorvall T880).
8. Se desprecia el sobrenadante y se disuelve el sedimento en tampón de fosfato de potasio 20 mM pH 7,4 (KH_2PO_4 y K_2HPO_4) por sonicación (5 x 10 s, 30 % de un sonificador a 50 W) y se divide la enzima en alícuotas y se conservan las alícuotas a -80 ºC.

Antes de llevar a cabo cada experimento se descongela una alícuota de la enzima y ésta se puede disolver después en tampón de fosfato de potasio 0,1 M pH 7,4 (KH_2PO_4 y K_2HPO_4) que contiene GSH 2,5 mM.

Ensayo de la enzima mPGES-1

El objetivo de este ensayo es determinar la afinidad de un compuesto de ensayo para la enzima mPGES-1.

Se dispensan 47 µl de mPGES-1 recombinante humana (~ 0,5 µg de proteína/pocillo) que contiene una suspensión microsómica en un tampón que contiene GSH, (2,5 mmol/L de L-Glutatión reducido, disuelto en 0,1 mol/L de tampón fosfato de pH 7,4) a una placa de 384 pocillos y se añade después 1 µl del compuesto o compuestos de ensayo y se incuba durante 25 minutos a temperatura ambiente. La reacción enzimática se empieza por la adición de 2 µl de PGH2 (concentración final 2 µM) disueltos en Diglyme exenta de agua.

Después de 60 segundos se termina la reacción por adición de una solución de parada que contiene $FeCl_2$ (10 µl, 0,074mol/l de $FeCl_2$). Se diluyen las muestras a 1:25 en PBS (solución salina tamponada con fosfato). Se transfieren 10 µl de las muestras diluidas a una placa de bajo volumen de 384 pocillos. Con el fin de cuantificar la cantidad de PGE_2 que se ha formado, se ha realizado una detección de la fluorescencia homogénea resuelta en el tiempo (HTRF) de la PGE_2 utilizando un kit comercialmente disponible de CisBio, según la recomendación del fabricante. Este ensayo basado en la HTRF ha sido descrito con detalle (véase: Goedken *et al.*, J Biomol Screen, 2008, 13(7), 619-625). En resumen, las muestras diluidas se mezclan con 5 µl de conjugado de PGE_2-d2 y 5 µl de conjugado de criptato anti-PGE_2. Después de un periodo de incubación de las placas de una noche, se mide la fluorescencia mediante el uso de un lector de microplacas apropiado.

Se mide la fluorescencia del criptato de europio (maxex = 307 nm, maxem = 620 nm) y de la d2-PGE_2 (maxex = 620 nm, maxem = 665 nm).

Se mide la extensión de la HTRF específica como una relación de la intensidad de emisión a 665 nm frente a la de 620 nm a unos pulsos de excitación de 320 nm. La placa de cuantificación contiene también pocillos con diferentes concentraciones de PGE_2 como una curva de calibración para el cálculo de las concentraciones de PGE_2 a partir de los valores de la relación de HTRF.

De todos los ensayos de la enzima mPGES se resta el ruido de fondo y se calcula la IC_{50} sobre una curva de regresión no lineal mediante un software convencional.

Tabla A. Efecto inhibidor de la mPGES-1 (valores de IC_{50} en nM) de los compuestos en el ensayo con enzima

Ejemplo	IC50 [nM]	Ejemplo	IC50 [nM]	Ejemplo	IC50 [nM]	Ejemplo	IC50 [nM]
1	2	**26**	2	**51**	3	**76**	3
2	2	**27**	4	**52**	4	**77**	2
3	4	**28**	3	**53**	4	**78**	2
4	4	**29**	4	**54**	3	**79**	2
5	2	**30**	4	**55**	4	**80**	1
6	2	**31**	3	**56**	4	**81**	3
7	2	**32**	3	**57**	4	**82**	1
8	3	**33**	4	**58**	3		
9	4	**34**	4	**59**	4		

Ejemplo	IC50 [nM]	Ejemplo	IC50 [nM]	Ejemplo	IC50 [nM]	Ejemplo	IC50 [nM]
10	7	**35**	4	**60**	3	**85**	1
11	4	**36**	4	**61**	4	**177**	1
12	4	**37**	5	**62**	2	**178**	1
13	3	**38**	3	**63**	3	**179**	1
14	1	**39**	4	**64**	2	**180**	2
15	3	**40**	4	**65**	4		
16	5	**41**	4	**66**	4		
17	1	**42**	4	**67**	2		
18	1	**43**	4	**68**	2		
19	1	**44**	3	**69**	2		
20	3	**45**	4	**70**	4		
21	3	**46**	3	**71**	2		
22	2	**47**	3	**72**	1		
23	1	**48**	3	**73**	2		
24	3	**49**	4	**74**	9		
25	2	**50**	4	**75**	2		

Ensayo basado en células A549

Aunque el ensayo enzimático es un ensayo de alto rendimiento, tiene la desventaja de que utiliza una proteína recombinante que no existe en un entorno natural. Por consiguiente se estableció un ensayo celular en el que se utilizó una línea de células de origen humano (A549) que expresa la proteína mPGES-1. Además con el fin de imitar la situación de los seres humanos en la que los compuestos se pueden unir a las proteínas plasmáticas se añade un 50 % de suero humano en el ensayo. Al tener la combinación de la mPGES-1 de análisis en un entorno celular y la presencia de un 50 % de suero humano, este ensayo tiene una relevancia más alta para juzgar el potencial terapéutico de un inhibidor de la mPGES que el ensayo enzimático puro.

Las células A549 (ATCC: CCL-185) se cultivan hasta aproximadamente un 90 % de confluencia en mezcla F-12K Nutrient (Kaighn's Mod. Gibco) que contiene un 10 % de FBS

en un incubador humidificado a 37 °C y 5 % de CO_2. Se separaron las células utilizando Tripsina-EDTA. Se sembraron las células A549 en una placa de colágeno de 384 pocillos a una densidad de 7000 células/pocillo (50 µl) en medio F-12 que contiene 1 % de penicilina-estreptomicina y 50 % de suero humano. Se dejó que se unieran las células durante 3-4 h. Después de esto se incubaron las células durante 20-24 h en medio F-12k suplementado con 50 % de suero humano, 1 % de penicilina-estreptomicina y que contenía IL-1β a una concentración final de 5 ng/ml así como ácido araquidónico 10 nM en presencia de un vehículo o de un compuesto de ensayo. El volumen total es 100 µl.

Se midieron las concentraciones de PGE_2 en el medio libre de células (10 µl) utilizando un kit HTRF comercialmente disponible de Cisbio (como se ha descrito antes). La formación de PGE_2 en ausencia de compuesto de ensayo fue considerada como el 100 %.

Los valores IC_{50} se derivaron de valoraciones en 6-8 puntos utilizando un software convencional.

Los compuestos listados en la tabla B son eficaces para bloquear la generación de PGE_2. Se puede esperar por tanto que los compuestos de la fórmula I tengan un potencial terapéutico para tratar las enfermedades inflamatorias y las afecciones asociadas tales como el dolor inflamatorio/nociceptivo.

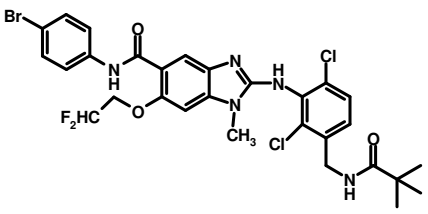
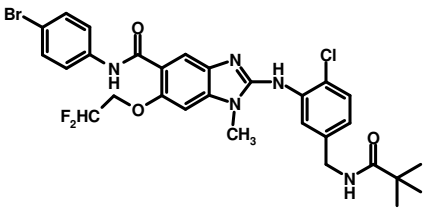
Tabla B. Efecto inhibidor de la mPGES-1 (valores de IC_{50} en nM) de los compuestos en el ensayo de células

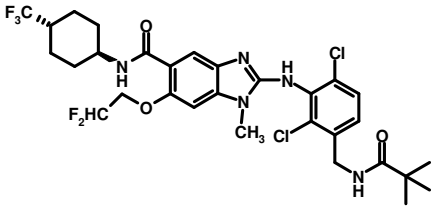
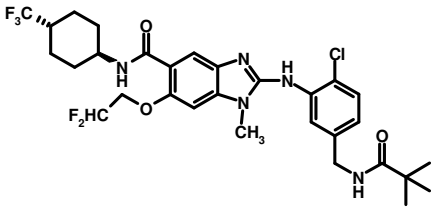
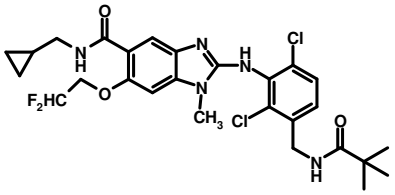
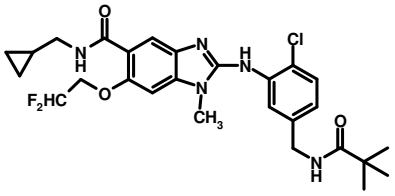
Ejemplo	IC50 [nM]	Ejemplo	IC50 [nM]	Ejemplo	IC50 [nM]	Ejemplo	IC50 [nM]
1	<1	**26**	11	**51**	<1	**76**	2
2	3	**27**	124	**52**	<1	**77**	12
3	1	**28**	1	**53**	1	**78**	8
4	2	**29**	<1	**54**	<1	**79**	1
5	<1	**30**	<1	**55**	<1	**80**	7
6	2	**31**	1	**56**	3	**81**	50
7	1	**32**	1	**57**	<1	**82**	43
8	<1	**33**	<1	**58**	2		
9	79	**34**	1	**59**	<1	**84**	<1
10	4	**35**	<1	**60**	<1	**85**	4
11	4	**36**	<1	**61**	<1	**86**	<1

Ejemplo	IC50 [nM]	Ejemplo	IC50 [nM]	Ejemplo	IC50 [nM]	Ejemplo	IC50 [nM]
12	7	**37**	9	**62**	1	**87**	221
13	28	**38**	<1	**63**	1	**88**	68
14	5	**39**	<1	**64**	<1		
15	11	**40**	<1	**65**	6	**90**	36
16	106	**41**	1	**66**	<1	**91**	10
17	1	**42**	<1	**67**	1	**92**	9
18	4	**43**	4	**68**	1	**93**	66
19	2	**44**	1	**69**	3		
20	14	**45**	<1	**70**	16	**95**	13
21	36	**46**	1	**71**	16	**96**	14
22	1	**47**	<1	**72**	9		
23	<1	**48**	1	**73**	1	**98**	2
		49	1	**74**	1		
25	9	**50**	1	**75**	<1	**100**	52
101	11	**126**	72	**151**	1	**176**	<1
102	15	**127**	85	**152**	<1	**177**	<1
103	18	**128**	26	**153**	3	**178**	<1
				154	36	**179**	<1
		130	3	**155**	2	**180**	93
		131	1	**156**	10		
107	106	**132**	2				
108	59	**133**	1	**158**	<1		
109	57	**134**	8	**159**	1		
110	8	**135**	<1	**160**	<1		
111	7	**136**	17	**161**	2		
112	19	**137**	4	**162**	<1		

Ejemplo	IC50 [nM]	Ejemplo	IC50 [nM]	Ejemplo	IC50 [nM]	Ejemplo	IC50 [nM]
113	25	**138**	49	**163**	5		
		139	27	**164**	15		
115	300			**165**	<1		
16	3	**141**	<1	**166**	7		
17	20	**142**	2,5	**167**	6		
18	11			**168**	<1		
		144	2	**169**	1		
20	9	**145**	7	**170**	<1		
21	119	**146**	2	**171**	4		
22	4	**147**	4	**172**	2		
23	3	**148**	2				
24	28	**149**	1	**174**	<1		
25	220	**150**	1				

Tabla C. Comparación de la IC50 (nM) enzimática y celular de bencimidazoles seleccionados

Estructura	Enzima IC_{50}	Célula IC_{50}
	2	<1
 del documento PCT/EP2010/052799	3	10

Estructura	Enzima IC_{50}	Célula IC_{50}
	2	<1
 del documento PCT/EP2010/052799	3	17
	4	1
 del documento PCT/EP2010/052799	2	> 200

Las tablas A, B y C demuestran que los compuestos con una afinidad similar para la enzima mPGES-1 medida en el ensayo enzimático pueden tener diferentes potencias en el ensayo basado en células.

Se considera que los datos procedentes de un ensayo farmacológico basado en células cuando se comparan con los datos procedentes de un ensayo enzimático permiten una mejor predicción y estimación de las concentraciones/dosis terapéuticas eficaces. Los compuestos de la presente invención muestran una potencia alta en ambos ensayos. Por consiguiente, es probable que sean más adecuados para el uso *in-vivo*.

MÉTODO DE TRATAMIENTO

La presente invención se refiere a compuestos de la fórmula **I** que son útiles en la prevención y/o tratamiento de una enfermedad y/o afección en la que la inhibición de las prostaglandinas E sintasas, en particular la de la prostaglandina E_2 sintasa-1 microsómica (mPGES-1) es de beneficio terapéutico, incluyendo pero sin limitarse a ellos, el tratamiento y/o prevención de enfermedades inflamatorias y/o afecciones asociadas.

Se entenderá que el término “inflamación” incluye cualquier enfermedad, trastorno o afección inflamatoria *per se*, cualquier afección que tenga asociado un componente inflamatorio, y/o cualquier afección caracterizada por la inflamación como síntoma, incluyendo, entre otras, la inflamación aguda, crónica, ulcerosa, específica, alérgica y necrótica, y otras formas de inflamación conocidas por los expertos en la técnica. De esta manera, el término incluye también, para los fines de esta invención, el dolor inflamatorio, el dolor en general y/o la fiebre.

Cuando una afección tiene un componente inflamatorio asociado con ella, o es una afección caracterizada por la inflamación como síntoma, los expertos apreciarán que los compuestos de la invención pueden ser útiles en el tratamiento de los síntomas inflamatorios y/o de la inflamación asociada con la afección.

Los compuestos de la invención pueden tener también efectos que no están ligados a los mecanismos inflamatorios, tales como en la reducción de la pérdida ósea en un sujeto. Dichas afecciones incluyen osteoporosis, artrosis, enfermedad de Paget y/o enfermedades periodontales.

Un aspecto adicional de la presente invención se refiere a un compuesto de la fórmula **I** como un medicamento.

Otro aspecto de la presente invención es el uso de los compuestos de la fórmula **I** para el tratamiento y/o prevención de una enfermedad y/o afección en la que la inhibición de la mPGES-1 es de beneficio terapéutico.

Otro aspecto de la presente invención es el uso de un compuesto de la fórmula **I** para el tratamiento y/o prevención de enfermedades inflamatorias y/o afecciones asociadas.

La presente invención se refiere también al uso de un compuesto de la fórmula **I** para el tratamiento y/o la prevención de las siguientes enfermedades y afecciones:

1. Enfermedades reumáticas o enfermedades autoinmunes o enfermedades musculoesqueléticas: todas las formas de enfermedades reumáticas, incluyendo por ejemplo reumatismo de tejidos blandos, artritis reumatoide, polimialgia reumática, artritis reactiva, tenosinovitis, gota o artritis metabólica, bursitis, tendinitis, artritis juvenil, espondiloartropatías como p.ej. espondilitis, espondilitis anquilosante, artropatía psoriásica; sarcoidosis, fibromialgia, miositis, polimiositis, artrosis, artritis traumática, colagenosis de cualquier origen, p.ej. lupus eritematoso sistémico, escleroderma, dermatomiositis, enfermedad de Still, síndrome de Sjögren, síndrome de Felty; fiebre reumática y cardiopatía reumática,

enfermedades de los vasos sanguíneos tales como vasculitis, poliartritis nudosa, síndrome de Behcet, artritis de células gigantes, granulomatosis de Wegener, púrpura de Henoch-Schönlein; artritis psoriásica, artritis fúngica, incluyendo en particular el dolor asociado con cualquiera de las afecciones antes mencionadas;

2. Cefaleas tales como migrañas con o sin aura, cefaleas de tipo tensión, cefaleas en racimos y cefaleas con diferente orígenes;

3. Dolor mantenido simpáticamente tal como el síndrome de dolor regional complejo de tipos I y II;

4. Dolor neuropático tal como lumbago, dolor de caderas, dolor de piernas, neuralgia no herpética, neuralgia post-herpética, neuropatía diabética, dolor inducido por lesiones nerviosas, dolor neuropático relacionado con el síndrome de inmunodeficiencia adquirida (SIDA), traumatismo craneal, lesiones nerviosas provocadas por toxinas y quimioterapia, dolor del miembro fantasma, esclerosis múltiple, avulsiones de la raíz del nervio, mononeuropatía traumática dolorosa, polineuropatía dolorosa, síndrome de dolor talámico, dolor post-ictus, lesión del sistema nervioso central, dolor post-quirúrgico, síndrome del túnel carpiano, neuralgia del trigémino, síndrome post-mastectomía, síndrome post-toracotomía, dolor de muñón, dolor de movimientos repetitivos, hiperalgesia y alodinia asociadas a dolor neuropático, alcoholismo y otros dolores inducidos por fármacos;

5. Dolor de cáncer inducido por tumores o asociado con tumores tales como tumores óseos, leucemia linfática; enfermedad de Hodgkin, linfoma maligno; linfogranulomatosis; linfosarcoma; tumores sólidos malignos; metástasis extensiva;

6. Trastornos viscerales como dolor pélvico crónico, pancreatitis, úlcera péptica, cistitis intersticial, cistitis, cólico renal, angina, dismenorrea, menstruación, dolor ginecológico, enfermedad del intestino irritable (IBS), enfermedad inflamatoria del intestino, enfermedad de Crohn y colitis ulcerosa, nefritis, prostatitis, vulvodinia, dispepsia no ulcerosa, dolor de pecho no cardiaco, isquemia de miocardio;

7. Enfermedades asociadas con inflamación de oídos, nariz, boca y garganta tales como gripe e infecciones víricas/bacterianas tales como resfriado común, rinitis alérgica (estacional y perenne), faringitis, amigdalitis, gingivitis, laringitis, sinusitis y rinitis vasomotora, fiebre, rinitis polínica, tiroiditis, otitis, afecciones odontológicas tales como dolor de dientes, afecciones perioperatorias y posoperatorias, neuralgia del trigémino, uveítis; iritis, queratitis alérgica, conjuntivitis, blefaritis, neuritis del nervio óptico, coroiditis, glaucoma y oftalmia simpática, así como el dolor asociado con las mismas;

8. Enfermedades neurológicas tales como edema cerebral y angioedema, demencia cerebral como por ejemplo enfermedad de Parkinson y de Alzheimer, demencia senil; esclerosis múltiple, epilepsia, epilepsia resistente a los fármacos, ictus, miastenia grave, infecciones del cerebro y de las meninges tales como encefalomielitis, meningitis, incluyendo

VIH así como esquizofrenia, trastornos delirantes, autismo, trastornos afectivos y trastornos de tic;

9. Enfermedades asociadas con el trabajo tales como neumoconiosis, incluyendo aluminosis, antracosis, asbestosis, calicosis, tilosis, siderosis, silicosis, tabacosis y bisinosis;

10. Enfermedades pulmonares tales como asma, incluyendo el asma alérgica (atópica o no atópica) así como la broncoconstricción inducida por ejercicio, asma ocupacional, exacerbación vírica o bacteriana del asma, otros tipos de asma no alérgica y síndrome del lactante sibilante ("wheezy-infant syndrome"), enfermedad pulmonar obstructiva crónica (EPOC) incluyendo enfisema, síndrome disneico agudo del adulto, bronquitis, neumonía, síndrome disneico agudo del adulto (ARDS), neumopatía de los avicultores, alveolitis alérgica de los avicultores;

11. Enfermedades de la piel tales como psoriasis y eczema, dermatitis, quemaduras solares, así como esguinces y distensiones musculares, y traumatismo de tejidos;

12. Enfermedades vasculares y cardiacas que están relacionadas con la inflamación, tales como arterioesclerosis incluyendo ateroesclerosis por trasplante cardiaco, panarteritis nudosa, periarteritis nudosa, arteritis temporal, granulomatosis de Wegner, artritis de células gigantes, lesión por reperfusión y eritema nudoso, trombosis (p.ej. trombosis venosa profunda, trombosis renal, hepática, trombosis de la vena porta); enfermedad de las arterias coronarias, aneurisma, rechazo vascular, infarto de miocardio, embolia, ictus, trombosis incluyendo trombosis venosa, angina incluyendo angina inestable, inflamación de la placa coronaria, inflamación inducida por bacterias incluyendo la inflamación inducida por clamidia, inflamación inducida por virus e inflamación asociada con procedimientos quirúrgicos tales como los injertos vasculares incluyendo cirugía de derivación de arterias coronarias, procedimientos de revascularización incluyendo angioplastia, colocación de endoprótesis vasculares, endarterectomía u otros procedimientos invasivos que comprometen arterias, venas y capilares, restenosis arterial;

13. Síntomas asociados con la diabetes tales como vasculopatía diabética, neuropatía diabética, retinopatía diabética, resistencia poscapilar o síntomas diabéticos asociados con insulitis (p.ej. hiperglucemia, diuresis, proteinuria y mayor excreción urinaria de nitrito y calicreína);

14. Tumores benignos y malignos y neoplasias incluyendo cáncer, tales como cáncer colorrectal, cáncer de cerebro, cáncer de huesos, neoplasia derivada de células epiteliales (carcinoma epitelial) tal como carcinoma de células basales, adenocarcinoma, cáncer gastrointestinal tal como cáncer labial, cáncer de la cavidad bucal, cáncer de esófago, cáncer del intestino delgado, cáncer de estómago, cáncer de colon, cáncer de hígado, cáncer de vejiga, cáncer de páncreas, cáncer de ovario, cáncer de cuello uterino, cáncer de pulmón, cáncer de mama, cáncer de piel tal como cáncer de células escamosas y cánceres

de células basales, cáncer de próstata, carcinoma de células renales y otros tipos de cáncer conocidos que afectan a las células epiteliales de todo el cuerpo; neoplasias tales como cáncer gastrointestinal, esófago de Barrett, cáncer de hígado, cáncer de vejiga, cáncer pancreático, cáncer de ovario, cáncer de próstata, cáncer de cuello uterino, cáncer de pulmón, cáncer de mama y cáncer de piel; pólipos adenomatosos, incluyendo poliposis adenomatosa familiar (FAP) así como en la prevención de formación de pólipos en pacientes con riesgo de FAP.

15. Otras diferentes patologías y afecciones tales como epilepsia, choque septicémico, p.ej. como agentes antihipovolémicos y/o agentes antihipotensivos, septicemia, osteoporosis, hiperplasia prostática benigna y vejiga hiperactiva, nefritis, pruritis, vitíligo, trastornos de movilidad visceral en regiones respiratorias, genitourinarias, gastrointestinales o vasculares, heridas, reacciones alérgicas en la piel, síndromes no vasculares y vasculares mixtos, choque septicémico asociado con infecciones bacterianas o con traumatismos, lesión del sistema nervioso central, daño de tejidos y fiebre posoperatoria, síndromes asociados con prurito.

Según la presente invención se prefiere el uso de un compuesto de la fórmula **I** para el tratamiento y/o prevención del dolor; en particular el dolor asociado con cualquiera de las enfermedades o afecciones mencionadas anteriormente.

Otro aspecto de la presente invención es un método para el tratamiento y/o prevención de las enfermedades y afecciones mencionadas antes, cuyo método comprende la administración de una cantidad eficaz de un compuesto de la fórmula I a un ser humano.

DOSIS

El intervalo de dosis de los compuestos de la fórmula I aplicable por día es usualmente de 0,01 a 5000 mg, preferiblemente de 1 a 2000 mg, más preferiblemente de 5 a 500 mg y lo más preferiblemente de 10 a 250 mg. Cada unidad de administración puede contener de forma conveniente de 2 a 500 mg, preferiblemente 5 a 250 mg.

La cantidad o dosificación terapéutica real, farmacéuticamente eficaz, dependerá naturalmente de factores conocidos por los expertos en la técnica tales como la edad y el peso del paciente, la vía de administración y la gravedad de la enfermedad. En cualquier caso, la combinación se administrará a dosificaciones y de una manera que permita suministrar una cantidad farmacéuticamente eficaz, basada en el estado singular del paciente.

FORMULACIONES FARMACÉUTICAS

Preparaciones adecuadas para administrar los compuestos de la fórmula I serán evidentes para los expertos habituales en la técnica e incluyen, por ejemplo, comprimidos, píldoras, cápsulas, supositorios, comprimidos para chupar, trociscos, soluciones, jarabes, elixires, sobres, inyectables, inhaladores y polvos etc. El contenido del compuesto o compuestos farmacéuticamente activos debe estar en el intervalo de 1 a 99 % en peso, preferiblemente de 10 a 90 % en peso, más preferiblemente de 20 a 70 % en peso de la composición en conjunto.

Comprimidos adecuados se pueden obtener, por ejemplo, mezclando uno o más compuestos según la fórmula I con excipientes conocidos, por ejemplo diluyentes inertes, vehículos, disgregantes, adyuvantes, tensioactivos, aglutinantes y/o lubricantes. Los comprimidos pueden comprender también varias capas. Otro aspecto de la invención es una formulación farmacéutica que incluye un compuesto de la fórmula I junto con un adyuvante, diluyente o vehículo farmacéuticamente aceptable.

TERAPIA DE COMBINACIÓN

Los compuestos según la presente invención se pueden combinar con otras opciones de tratamiento conocidas por su uso en la técnica en relación con el tratamiento de cualquiera de las afecciones, cuyo tratamiento es el foco de la presente invención.

Entre dichas opciones de tratamiento que se consideran adecuadas para combinación con el tratamiento según la presente invención, se encuentran las siguientes:

- fármacos antiinflamatorios no esteroideos (AINE) incluyendo los inhibidores de la COX-2;
- agonistas del receptor de opiáceos;
- agonistas cannabinoides o inhibidores de la ruta endocannabinoide
- bloqueantes del canal de sodio;
- bloqueantes del canal de calcio tipo N;
- moduladores serotonérgicos y noradrenérgicos;
- corticosteroides;
- antagonistas del receptor de histamina H1;
- antagonistas del receptor de histamina H2;
- inhibidores de la bomba de protones;
- antagonistas del leucotrieno e inhibidores de la 5-lipoxigenasa;
- anestésicos locales;
- agonistas y antagonistas de VR1;
- agonistas del receptor nicotínico de acetilcolina;
- antagonistas del receptor P2X3;
- agonistas y antagonistas de NGF o anticuerpos anti-NGF;
- antagonistas de NK1 y NK2;

- antagonistas de bradiquinina B1
- antagonistas de CCR2
- inhibidores de iNOS o de nNOS o de eNOS
- antagonista de NMDA;
- moduladores del canal de potasio;
- moduladores de GABA;
- moduladores serotonérgicos y noradrenérgicos;
- fármacos anti-migraña;
- fármacos para el dolor neuropático tales como pregabalina o duloxetina.

Esta lista no se considera de carácter limitativo.

A continuación, se ofrecen ejemplos representativos de dichas opciones de tratamiento.

- Fármacos antiinflamatorios no esteroideos (AINE) incluyendo los inhibidores de la COX-2: derivados de ácido propiónico (alminoprofeno, benoxaprofeno, ácido buclóxico, carprofeno, fenhufeno, fenoprofeno, flubiprofeno, ibuprofeno, indoprofeno, cetoprofeno, miroprofeno, naproxeno, oxaprozina, pirprofeno, pranoprofeno, suprofeno, ácido tiaprofénico y tioxaprofeno), derivados de ácido acético (indometacina, acemetacina, alclofenaco, clidanaco, diclofenaco, fenclofenaco, ácido fenclózico, fentiazaco, furofenaco, ibufenaco, isoxepaco, oxpinaco, sulindaco, tiopinaco, tolmetina, zidometacina y zomepirac), derivados de ácido fenámico (ácido meclofenámico, ácido mefenámico y ácido tolfenámico), derivados de ácido bifenilcarboxílico, oxicams (isoxicam, meloxicam, piroxicam, sudoxicam y tenoxican), salicilatos (ácido acetilsalicílico, sulfasalicina) y las pirazolonas (apazona, bezpiperilona, feprazona, mofebutazona, oxifenbutazona, fenilbutazona), y los coxibs (celecoxib, valecoxib, rofecoxib y etoricoxib) y similares;
- Fármacos antivíricos como aciclovir, tenovir, pleconaril, peramivir, pocosanol y similares.
- Fármacos antibióticos como gentamicina, estreptomicina, geldanamicina, doripenem, cefalexina, cefaclor, ceftaziquina, cefepima, eritromicina, vancomicina, aztreonam, amoxicilina, bacitracina, enoxacina, mafenida, doxiciclina, cloranfenicol y similares;
- Agonistas del receptor de opiáceos: morfina, propoxifeno (Darvon), tramadol, buprenorfina y similares.
- Glucocorticosteroides, tales como betametasona, budesonida, dexametasona, hidrocortisona, metilprednisolona, prednisolona, prednisona y deflazacort; fármacos inmunodepresores, inmunomoduladores o citostáticos, incluyendo pero sin limitarse a ellos, hidroxiclorquina, D-penicilamina, sulfasalizina, auranofina, mercaptopurina de oro, tacrolimus, sirolimus, micofenolato de mofetilo, ciclosporina, leflunomida,

metotrexato, azatioprina, ciclofosfamida y acetato de glatiramer y novantrona, fingolimod (FTY720), minociclina y talidomida y similares;

- Anticuerpos anti-TNF o antagonistas del receptor TNF tales como Etanercept, Infliximab, Adalimumab (D2E7), CDP 571 y Ro 45-2081 (Lenercept), pero sin limitarse a ellos, o agentes biológicos dirigidos directamente, aunque sin limitación, contra dianas tales como CD-4, CTLA-4, LFA-1, ilo-6, ICAM-1, C5 y Natalizumab y similares;
- Antagonistas del receptor IL-1 tales como Kineret, pero sin limitación;
- Bloqueantes del canal de sodio: carbamazepina, mexiletina, lamotrigina, tectina, lacosamida y similares.
- Bloqueantes del canal de calcio tipo N: Ziconotida y similares.
- Moduladores serotonérgicos y noradrenérgicos: paroxetina, duloxetina, clonidina, amitriptilina, citalopram;
- Antagonistas del receptor de histamina H1: bromfeniramina, clorfeniramina, dexclorfeniramina, triprolidina, clemastina, difenhidramina, difenilpiralina, tripelenamina, hidroxizina, metdilazina, prometazina, trimeprazina, azatadina, ciproheptadina, antazolina, feniramina, pirilamina, astemizol, terfenadina, loratadina, cetirizina, desloratadina, fexofenadina y levocetirizina y similares;
- Antagonistas del receptor de histamina H2: cimetidina, famotidina y ranitidina y similares;
- Inhibidores de la bomba de protones: omeprazol, pantoprazol y esomeprazol y similares;
- Antagonistas del leucotrieno e inhibidores de la 5-lipoxigenasa: zafirlukast, montelukast, pranlukast y zileuton y similares;
- Anestésicos locales tales como ambroxol, lidocaína y similares;
- Moduladores del canal de potasio: como retigabina;
- Moduladores de GABA: lacosamida, pregabalina, gabapentina y similares;
- Fármacos antimigraña: sumatriptan, zolmitriptan, naratriptan, eletriptan, telcagepant y similares;
- Anticuerpos NGF tales como RI-724 y similares.

La terapia de combinación es posible también con nuevos principios para el tratamiento del dolor, p.ej. antagonistas de P2X3, antagonistas de VR1, antagonistas de NK1 y NK2, antagonistas de NMDA, antagonistas de mGluR y similares.

La combinación de los compuestos es preferiblemente una combinación sinérgica. La sinergia, como se describe, por ejemplo, por Chou and Talalay, Adv. Enzyme Regul. 22:27-55 (1984), tiene lugar cuando el efecto de los compuestos que se administran en combinación es mayor que el efecto aditivo de los compuestos que se administran solos

como un agente individual. En general, un efecto sinérgico se demuestra más claramente en concentraciones subóptimas de los compuestos. La sinergia puede ser en términos de menor citotoxicidad, mayor efecto farmacológico o algún otro efecto beneficioso de la combinación, en comparación con los componentes individuales.

SECCIÓN EXPERIMENTAL

Preparación de ejemplos para los compuestos de la fórmula general I

A menos que se indique otra cosa, se pueden preparar *in situ* y/o se pueden aislar una o más formas tautoméricas de los compuestos de los ejemplos descritos más adelante en la presente memoria. Se deben considerar para exponer todas las formas tautoméricas de los compuestos de los ejemplos descritos a continuación.

La invención se ilustra por medio de los siguientes ejemplos en los que se pueden emplear las siguientes abreviaturas:

Abreviaturas:

AcOH	ácido acético
ac.	acuoso
BSTFA	N,O-bis (trimetilsilil)trifluoroacetamida
Boc	*terc*-butoxicarbonilo
Boc_2O	dicarbonato de di-*terc*-butilo
CDT	carbonilditriazol
CE	equipo de cromatografía
CH	ciclohexano
conc	concentrado
DCM	diclorometano
DIC	N,N-diisopropilcarbodiimida
DIPEA	*N*-etildiisopropilamina
DMAP	*N,N*-dimetilaminopiridina
DMSO	dimetilsulfóxido
DMF	N,N-dimetilformamida
EDC	hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida
EtOAc	acetato de etilo
Et_2O	éter dietílico
EtOH	etanol
HBTU	hexafluorofosfato de *O*-(benzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio

HPLC	cromatografía de líquidos de alta resolución
i-PrOH	isopropanol
KHMDS	hexametildisilazano de potasio
MeCN	acetonitrilo
MeOH	metanol
MS	espectrometría de masas
MTBE	éter metil-*terc*-butílico
PE	éter de petróleo
PPA	anhídrido cíclico de ácido 1-propilfosfónico
Pd/C	paladio al 10 % sobre carbono
RP	fase inversa
ta	temperatura ambiente
R_f	factor de retención
R_t	tiempo de retención
sat	saturado
TBTU	tetrafluoroborato de *O*-(benzotriazol-1-il)-N,N,N',N'-tetrametiluronio
TCDI	tiocarbonil diimidazol
TEA	trietilamina
THF	tetrahidrofurano
TFA	ácido trifluoroacético
TLC	cromatografía de capa fina

Métodos analíticos

Todos los compuestos especificados en los ejemplos que siguen dieron los espectros de masas correctos correspondientes a los modelos de isótopos teóricos. Por razones prácticas, se da solamente uno de los picos de los isótopos principales como dato representativo del espectro de masas.

Los datos de TLC se obtienen utilizando las siguientes placas de tlc

a) Placas de gel de sílice 60 F254 Merck No 1.05714.0001 abreviadas en la parte experimental como “gel de sílice”

b) Placas de fase inversa: RP-8 F 254s Merck No: 1.15684.0001 abreviadas en la parte experimental como “RP-8”.

c) Placas de óxido de aluminio 60 F254 Merck No 1.05713.0001 abreviadas en la parte experimental como “Alox”

Los valores de R_f dados se determinan sin saturación de la cámara.

Las purificaciones por cromatografía rápida se realizan utilizando gel de sílice de Millipore (MATREX™, 35 bis 70 µm) o Alox (E. Merck, Darmstadt, Aluminiumoxid 90 standardisiert, 63 bis 200 µm, nº de Artículo: 1.01097.9050).

Los datos de HPLC/MS, donde se especifiquen, se obtienen en las siguientes condiciones:

CE 1:
Agilent HP 1200 con bomba binaria, Agilent MS 6140, HiPALS1367C
La detección por la matriz de diodos se mide en un intervalo de longitud de onda de 190-400 nm.
Intervalo de detección espectrométrica de masas: m/z 100 a m/z 1000

CE 2:
Waters SQD MS, Acquity UPLC.
La detección por la matriz de diodos se mide en un intervalo de longitud de onda de 210-500 nm
Intervalo de detección espectrométrica de masas: m/z 120 a m/z 820

CE 3:
Agilent LC/MSD SL 61956B; Agilent 1100; bomba cuaternaria;.
La detección por la matriz de diodos se mide en un intervalo de longitud de onda de 190-400 nm
Intervalo de detección espectrométrica de masas: m/z 100 a m/z 1000

CE 4:
Agilent HP 100 con bomba binaria, Waters ZQ2000,
La detección por la matriz de diodos se mide en una longitud de onda de 210-500 nm.
Intervalo de detección espectrométrica de masas: m/z 120 a m/z 820

CE 5:
Acquity UPLC, Waters SQD MS,
La detección por la matriz de diodos se mide en una longitud de onda 210-500 nm.
Intervalo de detección espectrométrica de masas: m/z 120 a m/z 820

Se usan los siguientes métodos (si no se indica otra cosa la temperatura de la columna es de 25 °C):

Método A (CE 2):

Fase estacionaria (temperatura de la columna: constante a 60 °C): Sunfire C18, 2,5 µm, 2,1 x 50 mm

Fase móvil: E1: agua con 0,1 % de HCOOH, E2: MeCN con 0,1 % de HCOOH

Gradiente de eluyente:

tiempo en min	%E1	%E2	caudal en ml/min
0,0	95	5	1,5
1,20	70	30	1,5
2,40	0	100	1,5
2,60	0	100	1,5
2,70	95	5	1,5

Método B (CE 1):

Fase estacionaria: Zorbax Stable Bond C18, 1,8 µm, 3,0 x 30 mm

Fase móvil: E1: agua con 0,15 % de HCOOH, E2: MeCN

Gradiente de eluyente:

tiempo en min	%E1	%E2	caudal en ml/min
0,00	95	5	1,6
1,00	10	90	1,6
2,50	10	90	1,6
2,75	95	5	1,6

Método C (CE 1):

Fase estacionaria: Como se ha descrito en el método B.

Gradiente de eluyente:

tiempo en min	%E1	%E2	caudal en ml/min
0,00	95	5	1,6
2,25	10	90	1,6
2,50	10	90	1,6
2,75	95	5	1,6

Método D (CE 4):

Fase estacionaria (temperatura de la columna: constante a 40 °C): XBridge C18, 3,5 µm, 4,6 x 50 mm

Fase móvil: E1: agua con 0,032 % de NH_4OH, E2: MeOH

Gradiente de eluyente:

tiempo en min	%E1	%E2	caudal en ml/min

0,00	95	5	1,5
2,00	0	100	1,5

Método E (CE 1):

Fase estacionaria (temperatura de la columna: constante a 40 °C): Waters XBridge C18, 2,5 µm, 3,0 x 30 mm

Fase móvil: E1: agua con 0,15 % de HCOOH, E2: MeCN Gradiente del eluyente:

tiempo en min	%E1	%E2	caudal en ml/min
0,00	95	5	1,6
2,25	10	90	1,6
2,50	10	90	1,6
2,75	95	5	1,6

Método F (CE 3)::

Fase estacionaria (temperatura de la columna: constante a 40 °C): Zorbax Stable bond C18, 5 µm, 30 x100 mm; Fase móvil: E1: agua con 0,15 % de HCOOH, E2: MeCN

Gradiente de eluyente:

tiempo en min	%E1	%E2	caudal en ml/min
0,00	95	5	50
2,00	95	5	50
11,00	10	90	50
12,00	10	90	50
13,00	90	10	50

Método G (CE 3):

Fase estacionaria: Zorbax Stable Bond C18, 3,5 µm, 4,6 x 75 mm

Fase móvil: E1: agua con 0,15 % de HCOOH, E2: MeCN

Gradiente de eluyente:

tiempo en min	%E1	%E2	caudal en ml/min
0,00	95	5	1,6
2,00	10	90	1,6
5,00	10	90	1,6
5,50	95	5	1,6

Método H (CE 5)

Fase estacionaria (temperatura de la columna: constante a 60 °C): XBridge C18, 1,7 µm, 2,1 x 50 mm

Fase móvil: E1: agua con 0,1 % de NH_4OH, E2: MeCN

Gradiente de eluyente:

tiempo en min	%E1	%E2	caudal en ml/min
0,0	95	5	1,5
0,70	0	100	1,5
0,80	0	100	1,5
0,81	95	5	1,5
1,90	95	5	0,2
2,00	0	100	0,2
3,00	0	5	0,2

Método I (CE 4):

Fase estacionaria (temperatura de la columna: constante a 60 °C): Sunfire C18, 3,5 µm, 4,6 x 50 mm

Fase móvil: E1: agua con 0,1 % de TFA, E2: MeCN con 0,1 % de TFA

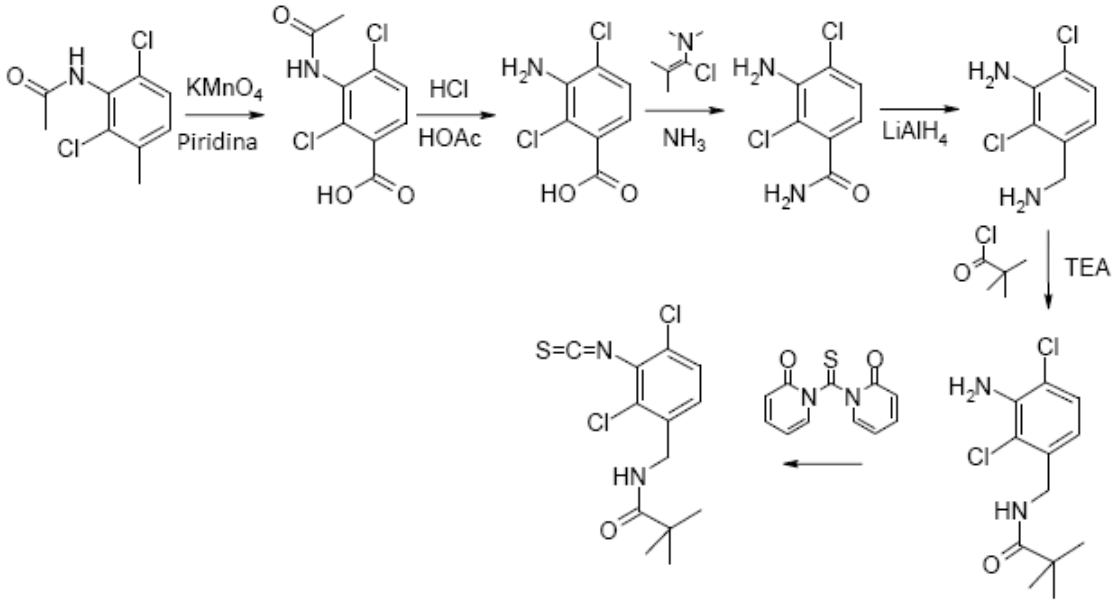
Gradiente de eluyente:

tiempo en min	%E1	%E2	caudal en ml/min
0,0	95	5	1,5
2,00	0	100	1,5
2,50	0	100	1,5
2,60	95	5	1,5

Síntesis de bloques estructurales del tipo de bencilamina 2,3,4-trisustituida:

Bloque estructural A:

N-(2,4-Dicloro-3-isotiocianato-bencil)-2,2-dimetil-propionamida



(a) Ácido 3-acetilamino-2,4-dicloro-benzoico

Se añade agua (110 mL) a *N*-(2,6-dicloro-3-metil-fenil)-acetamida (13 g, 59 mmol) en piridina (30 mL). Se calienta la mezcla a 70 °C y se añade cuidadosamente $KMnO_4$ (47 g, 298 mmol) en porciones. Después de 6 h a reflujo se filtra la mezcla de reacción a través de un lecho de celita y se lava con agua caliente. Se enfría el filtrado a temperatura ambiente, se concentra y se acidifica lentamente con solución acuosa 6 M de HCl. Se enfría la mezcla en un baño de hielo, se filtra y la torta del filtro se lava con agua fría y se seca para dar el compuesto del subtítulo.

Rendimiento: 11,6 g (78 %). R_f = 0,1 (gel de sílice, DCM:EtOH 9:1). MS m/z: 248 $[M+H]^+$.

(b) Ácido 3-amino-2,4-dicloro-benzoico

Se agita ácido 3-acetilamino-2,4-dicloro-benzoico (21,0 g, 84,6 mmol) en solución acuosa de HCl 6 M (120 mL) y ácido acético (250 mL) a reflujo durante 24 h. La mezcla de reacción se enfría, se concentra, se diluye con agua y se concentra de nuevo. Se diluye el residuo con agua, se agita con enfriamiento y se filtra. La torta del filtro se lava y se seca para dar el compuesto del subtítulo.

Rendimiento: 16,8 g (96 %). MS m/z: 204 $[M-H]^-$. HPLC-método C: R_t = 1,46 min

(c) 3-Amino-2,4-dicloro-benzamida

Se añade (1-cloro-2-metil-propenil)-dimetil-amina (16,1 mL, 116 mmol) a ácido 3-amino-2,4-dicloro-benzoico (20,0 g, 97,1 mmol) en THF (320 mL). Después de 4 h a temperatura ambiente se añade la mezcla gota a gota a NH_3 concentrado (320 mL) y se agita a temperatura ambiente durante la noche. Se concentra la mezcla de reacción, se enfría y se filtra. Se seca la torta del filtro para dar el compuesto del subtítulo.

Rendimiento: 17,4 g (87 %). MS m/z: 205 $[M+H]^+$. HPLC-método C: R_t = 1,19 min

(d) 3-Amino-2,4-dicloro-bencilamina

Se añade 3-amino-2,4-dicloro-benzamida (2,00 g, 9,8 mmol) en THF (45 mL) gota a gota a $LiAlH_4$ (1 M en THF, 24,4 mL) en THF (45 mL). Se agita la mezcla de reacción durante 1 h a temperatura ambiente y durante 10 h a reflujo. Se destruye el exceso de $LiAlH_4$ con enfriamiento como se ha descrito por L.F.Fieser & M. Fieser Vol 1, p 584 Wiley 1967. Después de 30 min se filtra la mezcla y se concentra el filtrado para dar el compuesto del subtítulo.

Rendimiento: 1,85 g (99 %). R_f = 0,12 (gel de sílice, DCM:EtOH 95:5). MS m/z: 191 [M+H]+.

(e) *N*-(3-Amino-2,4-dicloro-bencil)-2,2-dimetil-propionamida

Se añade 3-amino-2,4-dicloro-bencilamina (2,28 g, 11,9 mmol) a una mezcla de cloruro de ácido 2,2-dimetil-propiónico (1,47 mL, 11,9 mmol) y TEA (4,14 mL, 29,8 mmol) en THF (90 mL) y se agita durante 3 h. La mezcla de reacción se concentra, se diluye con EtOAc, se lava con solución acuosa de $NaHCO_3$ al 5 % y agua, se seca con Na_2SO_4, se filtra y se concentra para dar el compuesto del subtítulo.

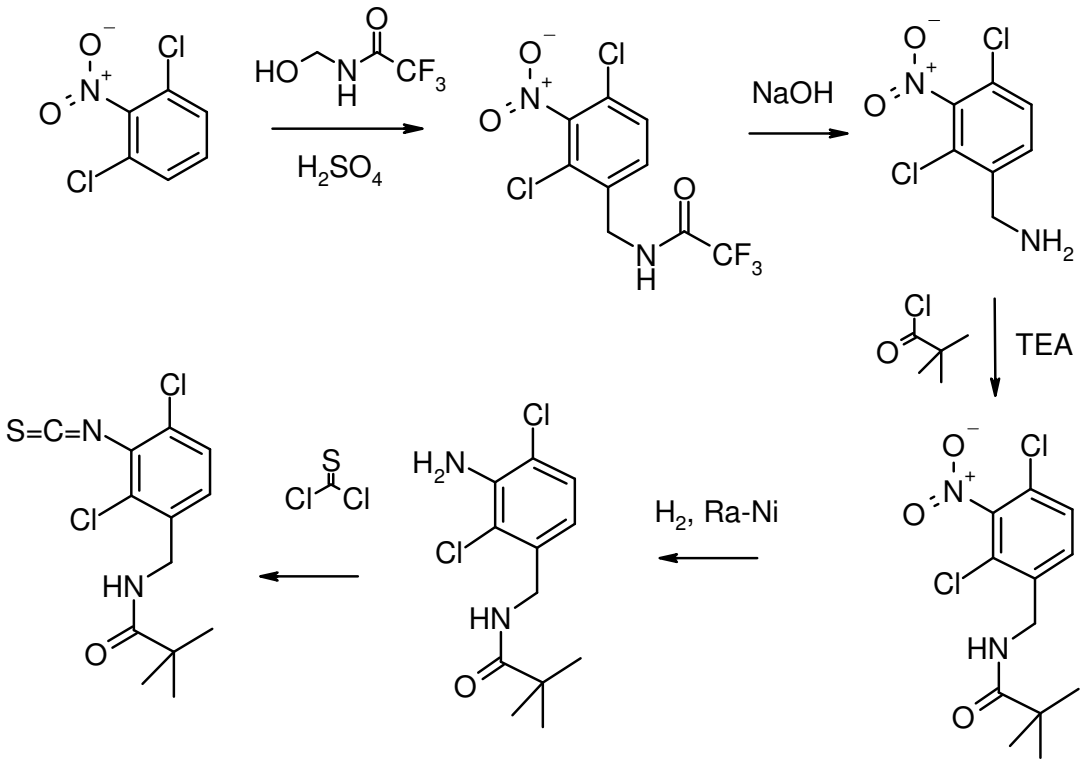
Rendimiento: 3,1 g (94 %). R_f = 0,61 (gel de sílice, DCM:EtOH 95:5).

(f) *N*-(2,4-Dicloro-3-isotiocianato-bencil)-2,2-dimetil-propionamida

Se añade 1,1'-tiocarbonildi-2-piridona (4,87 g, 21 mmol) a una mezcla de *N*-(3-amino-2,4-dicloro-bencil)-2,2-dimetil-propionamida (5,50 g, 20 mmol) y dioxano (200 mL) y se agita a temperatura ambiente durante 2 h y a reflujo durante 8 h. Se concentra la mezcla, se diluye con DCM y se filtra sobre gel de sílice. Se concentra el filtrado para dar el compuesto del subtítulo.

Rendimiento: 6,00 g (95 %). HPLC-método B: R_t= 1,58 min. MS m/z: 318 $[M+H]^+$.

Alternativamente, el bloque estructural A se puede preparar también según el siguiente esquema:



(g) *N*-(3-Nitro-2,4-dicloro-bencil)-2,2,2-trifluoroacetamida

Se añade *N*-(hidroximetil)trifluoroacetamida (6,6 mmol; 0,946 g) a una mezcla de 2,6-dicloro-nitrobenceno (0,899 mL; 6,6 mmol) y H_2SO_4 concentrado (15 mL) a 75 °C. Se agita la mezcla a 75 °C durante la noche, se vierte sobre hielo-agua y se agita durante 1 h. Se recoge el precipitado por filtración y se seca. Rendimiento 0,32 g (15 %). MS $[M-H]^-$ = 315, HPLC-método B: R_t = 1,43 min

(h) 3-Nitro-2,4-dicloro-bencilamina

Una mezcla de *N*-(3-nitro-2,4-dicloro-bencil)-2,2,2-trifluoroacetamida (0,66 g, impura, contenido ~50 %), solución de NaOH 4 M (1,3 mL, 5,2 mmol) y MeOH (15 mL) se mantiene a reflujo durante 4 h. Después se concentra la mezcla, se diluye con agua, se acidifica con HCl 4 M, se filtra, se añade solución de NaOH 4 M y se extrae con EtOAc. La fase orgánica se seca con Na_2SO_4, se filtra y se concentra. Rendimiento 0,17 g.
MS m/z: 221 $[M+H]^+$. HPLC-método B: R_t = 1,02 min

(i) *N*-(3-Nitro-2,4-dicloro-bencil)-2,2-dimetil-propionamida

Se añade cloruro de ácido 2,2-dimetil-propiónico (0,124 mL, 1,01 mmol) a una mezcla de 3-nitro-2,4-dicloro-bencilamina (0,28 g, 1,01 mmol) y TEA (0,35 mL, 2,52 mmol) en THF (10 mL) y se agita durante la noche. Se concentra la mezcla de reacción, se diluye con

EtOAc, se lava sucesivamente con solución acuosa de $NaHCO_3$ al 5 % y salmuera, se seca con Na_2SO_4, se filtra y se concentra.

Rendimiento: 0,29 g. MS m/z: 306 $[M+H]^+$. HPLC-método B: R_t = 1,42 min

(g) *N*-(3-Amino-2,4-dicloro-bencil)-2,2-dimetil-propionamida

Una mezcla de 3-nitro-2,4-dicloro-bencilamina (290 mg, 0,95 mmol), Ra-Ni (50 mg) y THF (15 mL) se agita durante 7 h en una atmósfera de hidrógeno (344,8 KPa). Se separa el catalizador por filtración y se concentra el filtrado.

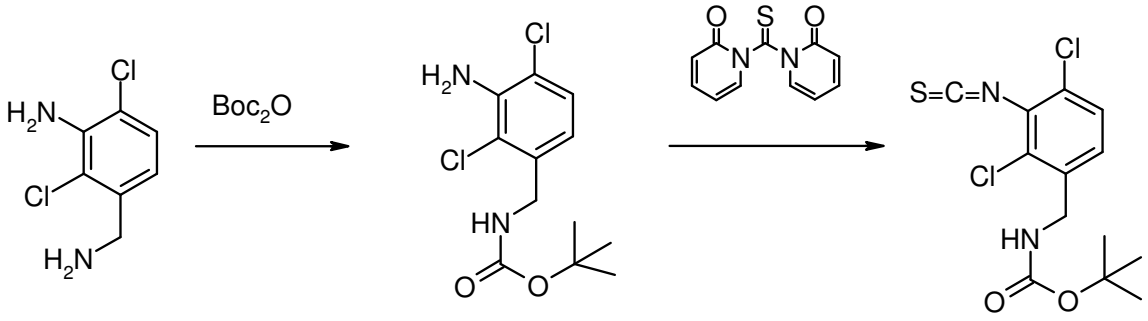
Rendimiento: 0,26 g. MS m/z: 276 $[M+H]^+$. HPLC-método B: R_t = 1,32 min

(h) *N*-(2,4-Dicloro-3-isotiocianato-bencil)-2,2-dimetil-propionamida

Se añade una mezcla de *N*-(3-amino-2,4-dicloro-bencil)-2,2-dimetil-propionamida (0,95 g, 3,4 mmol) en 4,0 mL de dioxano a tiofosgeno (0,45 mL, 5,8 mmol) en 2,5 mL de agua. Se agita la mezcla durante la noche, se extrae con DCM y la fase orgánica se lava con solución acuosa de NaHCO3 al 5 % y agua y se seca con Na_2SO_4. Después de filtración y concentración, se diluye el producto crudo con DCM, se filtra a través de un lecho de gel de sílice y se concentra.

Bloque estructural B:

Éster *terc*-butílico del ácido (2,4-dicloro-3-isotiocianato-bencil)-carbámico



(a) Éster *terc*-butílico del ácido (3-amino-2,4-dicloro-bencil)-carbámico

Se añade Boc_2O (1,48 g, 6,68 mmol) en 3,3 mL de DCM a 0 °C a una mezcla de 3-amino-2,4-dicloro-bencilamina (1,16 g, 6,07 mmol), 6,7 mL de DCM y 12,1 mL de solución de NaOH 1 N. Se agita la mezcla vigorosamente durante 2 días y se diluye con solución acuosa de NH_3 al 5 %. Se separa la fase orgánica y se lava la fase acuosa 2 x con DCM. La fase orgánica reunida se lava con salmuera, se seca con Na_2SO_4, se filtra y se concentra para dar el compuesto del subtítulo.

Rendimiento: 1,71 g (97 %). R_f = 0,65 (gel de sílice, DCM:EtOH 95:5). MS m/z: 291 $[M+H]^+$.

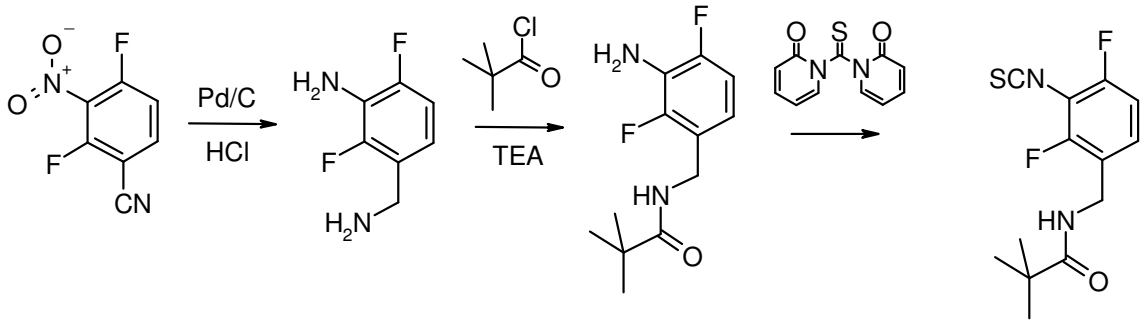
(b) Éster *terc*-butílico del ácido (2,4-dicloro-3-isotiocianato-bencil)-carbámico

Se añade 1,1'-tiocarbonildi-2-piridona (0,42 g, 1,8 mmol) a una mezcla de éster *terc*-butílico del ácido (3-amino-2,4-dicloro-bencil)-carbámico (0,50 g, 1,7 mmol) y dioxano (25 mL) y se agita a temperatura ambiente durante 2 h y a reflujo durante 2 días. Se concentra la mezcla, se diluye con DCM y se filtra sobre gel de sílice. Se concentra el filtrado para dar el compuesto del título.

Rendimiento: 0,49 g (86 %). R_f = 0,83 (gel de sílice, DCM:EtOH 95:5).

Bloque estructural C:

N-(2,4-Difluoro-3-isotiocianato-bencil)-2,2-dimetil-propionamida



(a) 3-Aminometil-2,6-difluoro-anilina

Una mezcla de 3-nitro-2,4-difluoro-benzonitrilo (500 mg, 2,72 mmol), Pd/C (200 mg), HCl conc. (1,50 mL, 18,0 mmol) y MeOH (25 mL) se agita a temperatura ambiente durante la noche en atmósfera de hidrógeno (3,2 bares). Se separa el catalizador por filtración, se concentra el filtrado y se evapora dos veces en EtOH para dar el compuesto del subtítulo como la sal HCl.

Rendimiento: 580 mg. MS m/z: 159 $[M+H]^+$.

(b) *N*-(3-Amino-2,4-difluoro-bencil)-2,2-dimetil-propionamida

Se añade TEA (400 µL, 2,86 mmol) seguido por cloruro de pivaloilo (60 µL, 0,52 mmol) a 3-aminometil-2,6-difluoro-anilina (120 mg como sal HCl) en THF (10 mL) y se agita a temperatura ambiente durante la noche. Se diluye la mezcla de reacción con EtOAc y solución saturada de $NaHCO_3$, se lava la capa orgánica con agua y salmuera, se seca y se concentra para dar el compuesto del subtítulo.

Rendimiento: 110 mg. HPLC-método B: R_t= 1,19 min. MS m/z: 243 $[M+H]^+$. R_f = 0,45 (gel de sílice, DCM:EtOH 95:5).

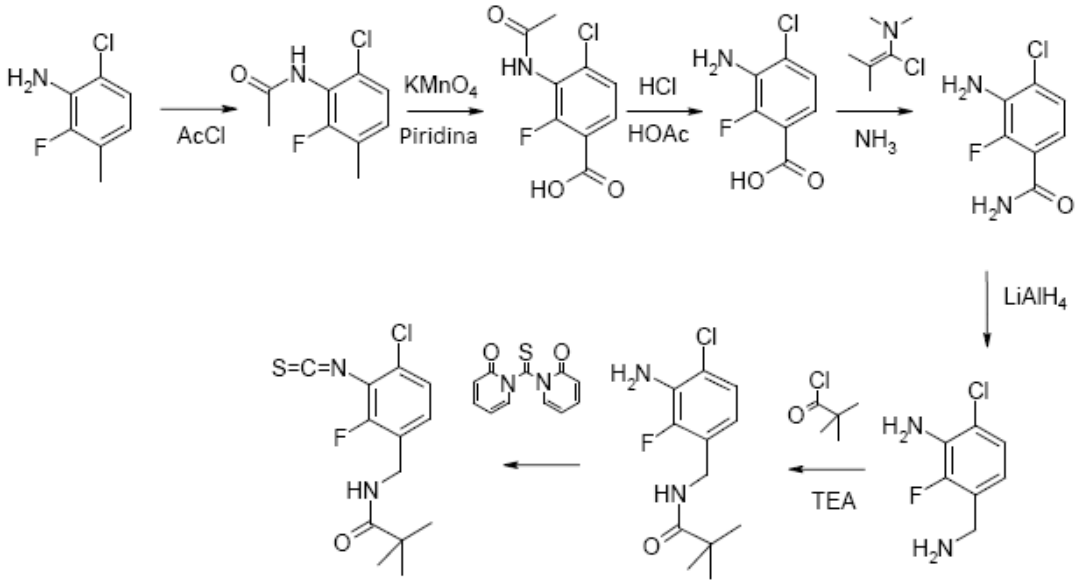
(c) *N*-(2,4-Difluoro-3-isotiocianato-bencil)-2,2-dimetil-propionamida

Una mezcla de *N*-(3-amino-2,4-difluoro-bencil)-2,2-dimetil-propionamida (570 mg, 2,35 mmol), 1,1'-tiocarbonildi-2(1H)-piridona (550 mg, 2,35 mmol) y dioxano (20 mL) se agita

a reflujo durante la noche. Se concentra la mezcla de reacción, se diluye con DCM, se filtra a través de un lecho de gel de sílice y se concentra el filtrado para dar el compuesto del título. Rendimiento: 440 mg (65 %). R_f = 0,80 (gel de sílice, DCM:EtOH 95:5).

Bloque estructural D:

N-(4-Cloro-fluoro-3-isotiocianato-bencil)-2,2-dimetil-propionamida



(a) *N*-(6-Cloro-2-fluoro-3-metil-fenil)-acetamida

Se añade cloruro de acetilo (2,56 mL, 36,0 mmol) a una mezcla de 6-cloro-2-fluoro-3-metil-anilina (5,00 g, 31,3 mmol) y tolueno (200 mL). Se añade tolueno adicional (50 mL) y se calienta la mezcla a reflujo durante 3 h. Después se enfría con un baño de hielo y se separa por filtración el precipitado formado, se lava con tolueno frío y se seca.

Rendimiento: 4,75 g (75 %). HPLC-método B: R_t= 1,12 min. MS m/z: 202 $[M+H]^+$.

(b) Ácido 3-acetilamino-4-cloro-2-fluoro-benzoico

El compuesto del subtítulo se prepara a partir de *N*-(6-cloro-2-fluoro-3-metil-fenil)-acetamida y $KMnO_4$ en piridina análogamente a la etapa Aa.

Rendimiento: 49 %. R_f = 0,2 (gel de sílice, DCM/EtOH 4:1). HPLC R_t = 0,93 min (método B). MS m/z: 232 $[M+H]^+$.

(c) Ácido 3-amino-4-cloro-2-fluoro-benzoico

El compuesto del subtítulo se prepara a partir del ácido 3-acetilamino-4-cloro-2-fluoro-benzoico y solución de HCl 6 M análogamente a la etapa Ab.

Rendimiento: 96 %. HPLC R_t = 1,10 min (método B). MS m/z: 190 $[M+H]^+$.

(d) 3-Amino-4-cloro-2-fluoro-benzamida

El compuesto del subtítulo se prepara a partir de ácido 3-amino-4-cloro-2-fluoro-benzoico, (1-cloro-2-metil-propenil)-dimetil-amina y NH_3 conc. análogamente a la etapa Ac.
Rendimiento: 69 %. R_f = 0,3 (gel de sílice, PE:EtOAc 4:6). HPLC-método B: R_t= 0,97 min. MS m/z: 189 $[M+H]^+$.

(e) 3-Amino-4-cloro-2-fluoro-bencilamina

El compuesto del subtítulo crudo se prepara a partir de 3-amino-4-cloro-2-fluoro-benzamida y $LiAlH_4$ análogamente a la etapa Ad.
HPLC-método B: R_t= 0,37 min. MS m/z: 175 $[M+H]^+$.

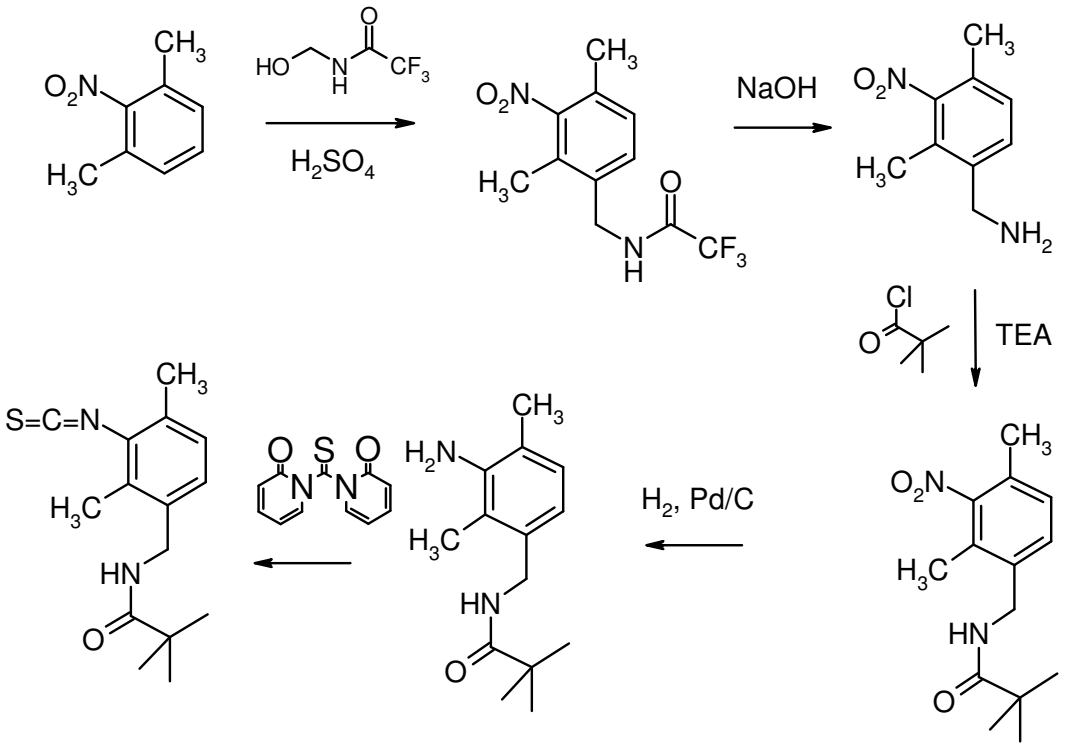
(f) *N*-(3-Amino-4-cloro-2-fluoro-bencil)-2,2-dimetil-propionamida

El compuesto del subtítulo se prepara a partir de 3-amino-4-cloro-2-fluoro-bencilamina cruda, cloruro de ácido 2,2-dimetil-propiónico y TEA análogamente al ejemplo Ae.
Rendimiento: 36 % (producto secundario en un 29 %: *N*-(3-Amino-4-cloro-bencil)-2,2-dimetil-propionamida). Rf = 0,6 (gel de sílice, PE:EtOAc 6:4). HPLC-método B: R_t= 1,27 min. MS m/z: 259 $[M+H]^+$.

(g) *N*-(4-Cloro-2-fluoro-3-isotiocianato-bencil)-2,2-dimetil-propionamida

El compuesto del título se prepara a partir de *N*-(3-amino-4-cloro-2-fluoro-bencil)-2,2-dimetil-propionamida, 1,1'-tiocarbonildi-2-piridona análogamente a la etapa Af.
Rendimiento: 65 %. R_f = 0,9 (gel de sílice, DCM:EtOH 95:5).

Bloque estructural E:
N-(2,4-Dimetil-3-isotiocianato-bencil)-2,2-dimetil-propionamida



(a) *N*-(3-Nitro-2,4-dimetil-bencil)-2,2,2-trifluoroacetamida

Se añade *N*-(hidroximetil)trifluoroacetamida (6,6 mmol; 0,946 g) a una mezcla de 2,6-dimetil-nitrobenceno (0,899 mL; 6,6 mmol) y H_2SO_4 conc. (15 mL). Se agita la mezcla a temperatura ambiente durante la noche, se vierte sobre hielo-agua y se agita durante 2 h. Se recoge el precipitado por filtración y se seca. Rendimiento 1,5 g (84 %). MS $[M-H]^-$ = 275, TLC: R_f = 0,67 (gel de sílice, DCM:EtOH 95:5)).

(b) 3-Nitro-2,4-dimetil-bencilamina

Una mezcla de *N*-(3-nitro-2,4-dimetil-bencil)-2,2,2-trifluoroacetamida (1,53 g, 5,54 mmol), solución de NaOH 4 M (6,9 mL, 28 mmol) y MeOH (30 mL) se mantiene a reflujo durante 2 h. Después se concentra la mezcla, se diluye con agua y se extrae con EtOAc. La fase orgánica se seca con Na_2SO_4, se filtra y se concentra.

MS m/z: 181 $[M+H]^+$. HPLC-método C: R_t = 1,13 min

(c) *N*-(3-Nitro-2,4-dimetil-bencil)-2,2-dimetil-propionamida

Se añade 3-nitro-2,4-dimetil-bencilamina (1,40 g, cruda) a una mezcla de cloruro de ácido 2,2-dimetil-propiónico (0,682 mL, 5,5 mmol) y TEA (1,92 mL, 13,8 mmol) en THF (30 mL) y se agita durante la noche. Se concentra la mezcla de reacción, se diluye con EtOAc, se lava sucesivamente con solución acuosa de HCl 2 M, solución acuosa de $NaHCO_3$ al 5 % y agua, se seca con Na_2SO_4 se filtra y se concentra.

Rendimiento: 1,41 g. MS m/z: 265 $[M+H]^+$. HPLC-método B: R_t = 1,37 min

(d) *N*-(3-Amino-2,4-dimetil-bencil)-2,2-dimetil-propionamida

Una mezcla de *N*-(3-nitro-2,4-dimetil-bencil)-2,2-dimetil-propionamida (500 mg, 1,89 mmol), Pd/C (50 mg) y MeOH (20 mL) se agita durante 9 h en atmósfera de hidrógeno (344,8 KPa). Se separa el catalizador por filtración y se concentra el filtrado.

Rendimiento: 0,42 g. MS m/z: 235 $[M+H]^+$. HPLC-método B: R_t = 1,32 min

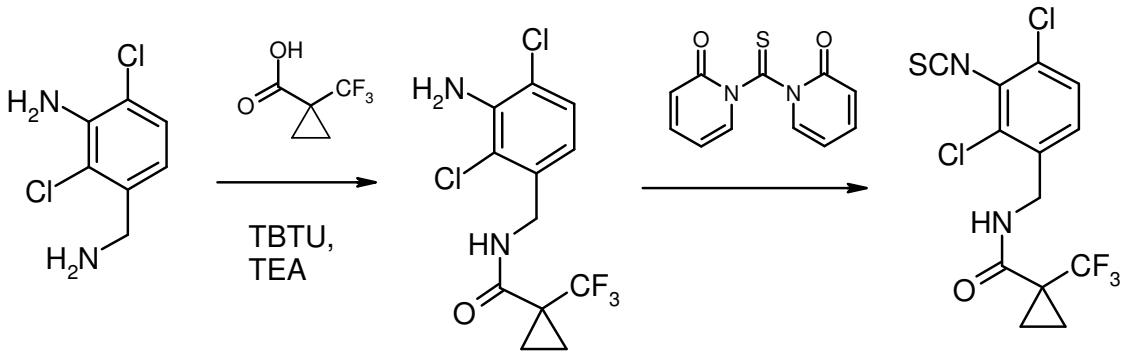
(e) *N*-(2,4-Dimetil-3-isotiocianato-bencil)-2,2-dimetil-propionamida

El compuesto del título se prepara a partir de *N*-(3-amino-2,4-dimetil-bencil)-2,2-dimetil-propionamida, 1,1'-tiocarbonildi-2-piridona análogamente a la etapa Af.

Rendimiento: 65 %. R_f = 0,81 (gel de sílice, DCM:EtOH 95:5).

Bloque estructural F:

N-(2,4-Dicloro-3-isotiocianato-bencil)-1-trifluorometil-ciclopropano-carboxamida



(a) N-(2,4-Dicloro-3-amino-bencil)-1-trifluorometil-ciclopropano-carboxamida

El compuesto del subtítulo se prepara a partir de 3-amino-2,4-dicloro-bencilamina (0,310 g, 1,01 mmol), ácido1-trifluorometil-ciclopropano-carboxílico (0,17 g, 1,1 mmol), TBTU (0,39 g, 1,2 mmol) y TEA (0,71 mL) en DMF análogamente a la etapa 1d.

Rendimiento: 289 mg (83 %). MS m/z: 327 $[M+H]^+$.

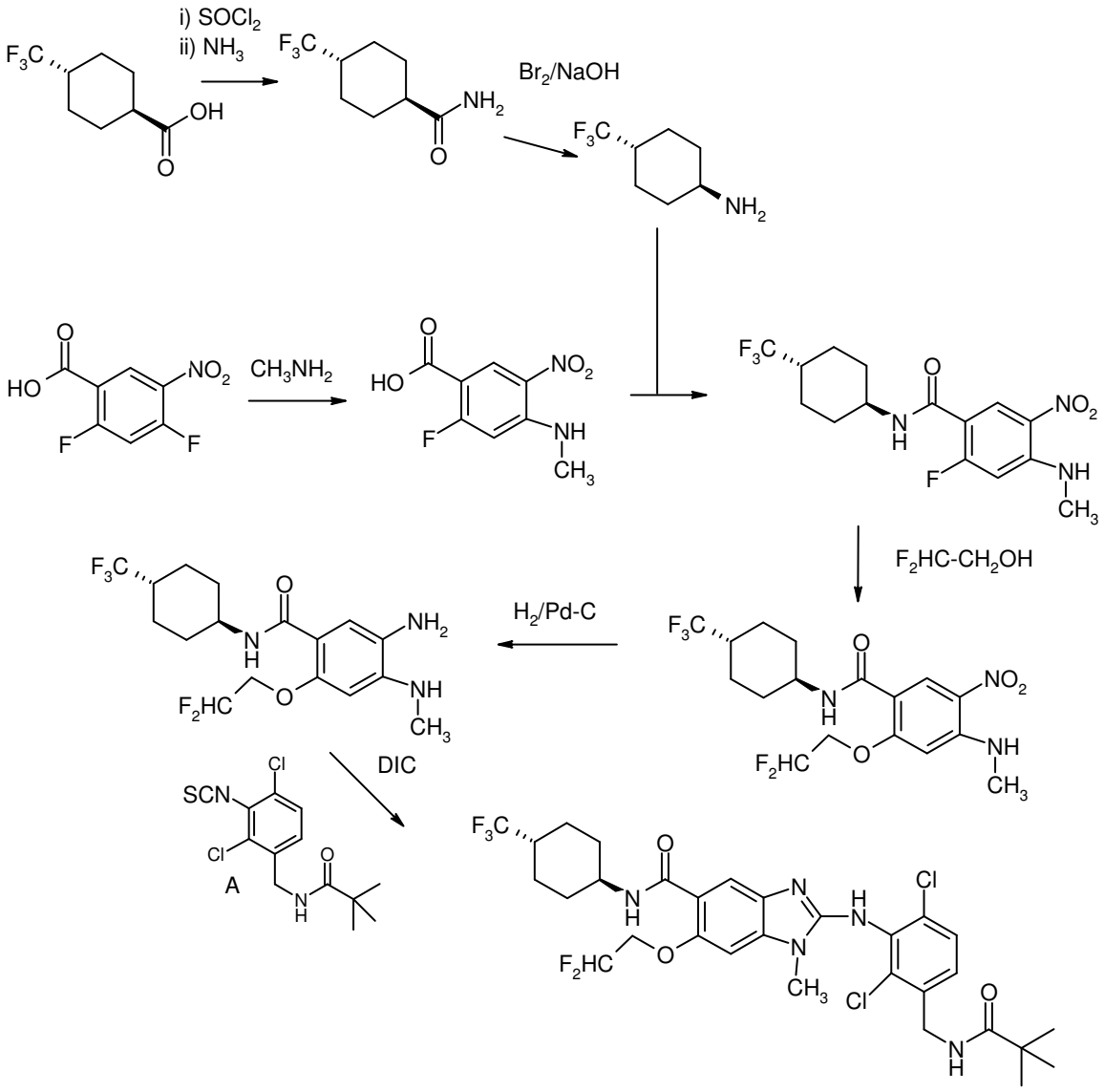
(b) N-(2,4-Dicloro-3-isotiocianato-bencil)-1-trifluorometil-ciclopropano-carboxamida

El compuesto del título se prepara a partir de N-(2,4-dicloro-3-amino-bencil)-1-trifluorometil-ciclopropano-carboxamida (150 mg, 0,45 mmol) y 1,1'-tiocarbonildi-2-piridona (89 mg, 0,38 mmol) análogamente a la etapa Af.

Rendimiento: 92 mg (crudo).

Ejemplo 1

Amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoro-etoxi)-1-metil-1H-bencimidazol-5-carboxílico



(a) Amida del ácido *trans*-4-trifluorometil-ciclohexil-carboxílico

Una mezcla de ácido *trans*-4-trifluorometil-ciclohexano-carboxílico (10,4 g, 53,1 mmol), $SOCl_2$ (10 mL, 137 mmol), DCM (100 mL) y DMF (200 µl) se calienta a reflujo durante 1,5 h y se concentra. El cloruro de ácido crudo se diluye con 100 mL de THF y se añade lentamente NH_3 concentrado (350 mL). Se agita durante 5 min y se concentra la mezcla y se seca a 40°.

Rendimiento: 9,7 g.

(b) *trans*-4-Trifluorometil-ciclohexil-amina

Se agita bromo (2,85 mL, 55 mmol) durante 10 min en solución acuosa de NaOH 1 N (200 mL), después se añade la amida del ácido *trans*-4-trifluorometil-ciclohexil-carboxílico y se agita durante 45 min a temperatura ambiente y durante 3 h a reflujo. Después de enfriar a

temperatura ambiente se extrae la mezcla con Et_2O, se seca la fase orgánica con $MgSO_4$, se filtra, se trata con HCl 2 N en Et_2O y se concentra para dar el compuesto del subtítulo como sal HCl.

Rendimiento: 8,5 g MS *m/z*: 168 [M+H]+.

(c) Ácido 2-fluoro-4-metilamino-5-nitro-benzoico

Se añade metilamina (13,5 mL, 40 % en agua) a una mezcla enfriada con hielo de ácido 2,4-difluoro-5-nitro-benzoico (10,0 g, 49 mmol) en agua (100 mL) y se agita durante 30 min a temperatura ambiente. Se acidifica la mezcla con solución acuosa de HCl 6 N y el precipitado se filtra, se lava con agua y se seca a 60 °C. Se recristalizó el material crudo en MeOH. El producto final estaba ligeramente contaminado por su regioisómero ácido 4-fluoro-2-metilamino-5-nitro-benzoico.

(d) Amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-fluoro-4-metilamino-5-nitro-benzoico

Una mezcla de ácido 2-fluoro-4-metilamino-5-nitro-benzoico crudo (4,88 g que contienen trazas de regioisómero), DIPEA (11,7 mL, 68,3 mmol), TBTU (8,05 g, 25,1 mmol) y THF (100 mL) se agita durante 15 min, después se añade *trans*-4-trifluorometil-ciclohexil-amina (4,64 g, sal de HCl) y se agita durante la noche. Se concentra la mezcla, se añade $NaHCO_3$ acuoso y el precipitado resultante se filtra, se lava y se seca.

Rendimiento: 8,14 g. R_f = 0,3 (gel de sílice, DCM:EtOH 98:2). HPLC R_t = 1,44 min (método B). MS m/z: 364 [M+H]+.

(e) Amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-(2,2-difluoro-etoxi)-4-metilamino-5-nitro-benzoico

Una mezcla de 2,2-difluoroetanol (2,12 mL, 33,6 mmol), KOtBu (3,84 g, 32,4 mmol) y THF (100 mL) se agita durante 15 min, después se añade amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-fluoro-4-metilamino-5-nitro-benzoico (8,14 g, 22,4 mmol) y se agita durante 1,5 h. Se añade agua a la mezcla y se separa por destilación el THF. Se filtra el precipitado resultante, se lava con agua y se seca.

Rendimiento: 8,60 g. R_f = 0,35 (gel de sílice, PE:Et_2O 1:1). HPLC R_t = 1,47 min (método B). MS m/z: 426 [M+H]+.

(f) Amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-(2,2-difluoro-etoxi)-4-metilamino-5-amino-benzoico

Una mezcla de amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-(2,2-difluoro-etoxi)-4-metilamino-5-nitro-benzoico (6,38 g, 15,0 mmol), Pd/C (0,50 g) y MeOH (100 mL) se

agita a 344,8 KPa de atmósfera de H_2 durante 4 h. Se filtra la mezcla, se lava el catalizador con THF y se concentra el filtrado reunido. Se purifica la mezcla cruda por cromatografía rápida (gel de sílice; DCM/EtOH 97/3).

Rendimiento: 5,38 g (91 %). R_f = 0,3 (DCM/EtOH 95:5). HPLC R_t = 1,25 min (método B). MS m/z: 396 [M+H]+.

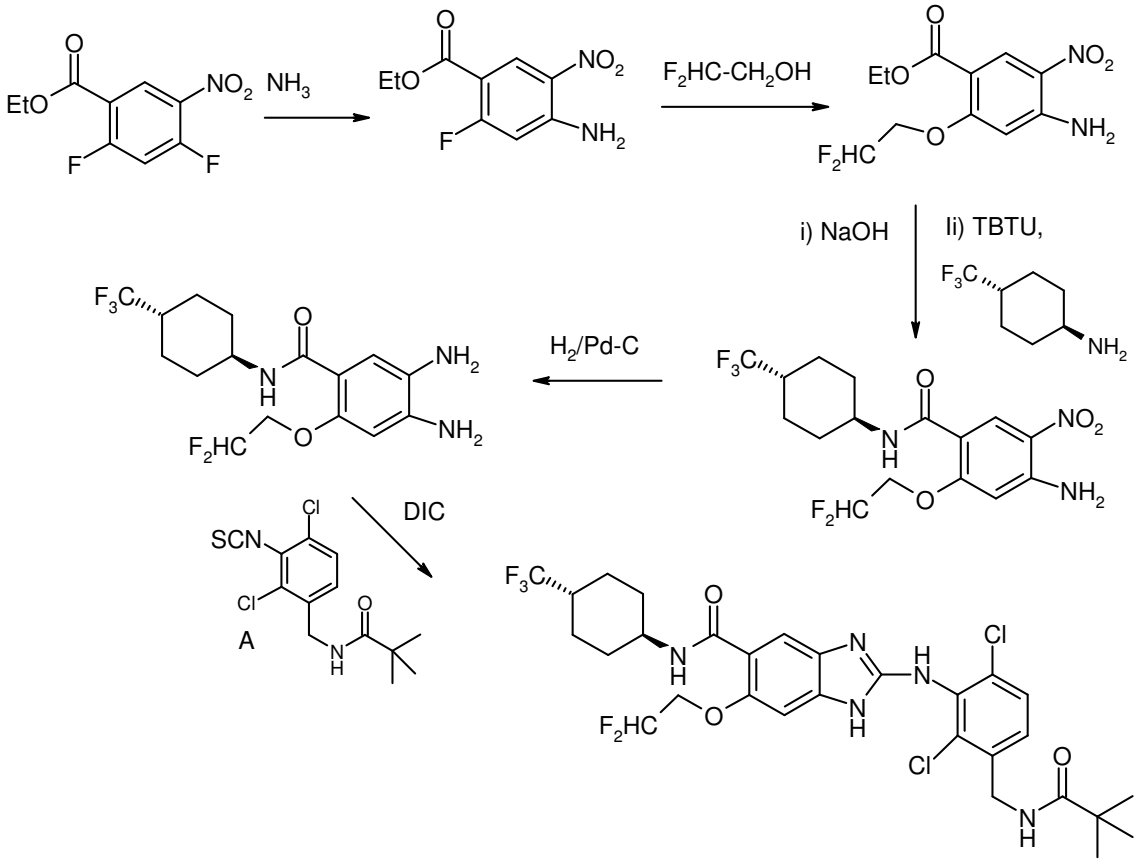
(g) Amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoro-etoxi)-1-metil-1H-bencimidazol-5-carboxílico

Una mezcla de amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-(2,2-difluoro-etoxi)-4-metilamino-5-amino-benzoico (200 mg, 0,506 mmol), *N*-(2,4-dicloro-3-isotiocianato-bencil)-2,2-dimetil-propionamida (160 mg, 0,505 mmol) y DMF (2,0 mL) se agita durante 3 h, después se añade DIC (102 µl, 0,658 mmol) y se agita a 80 °C durante 2 h. Se concentra la mezcla cruda y se purifica por cromatografía rápida (gel de sílice; DCM/EtOH 98:2 -> 97:3.

Rendimiento: 0,320 g (93 %). Rf = 0,35 (DCM/EtOH 95:5). HPLC R_t = 1,42 min (método B). MS m/z: 678 [M+H]+.

Ejemplo 2

Amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoro-etoxi)-1H-bencimidazol-5-carboxílico



(a) 2-Fluoro-4-amino-5-nitro-benzoato de etilo

Una mezcla de 2,4-difluoro-5-nitro-benzoato de etilo (5,0 g, 21 mmol), 5,2 mL de NH_3 conc. y THF (25 mL) se agita durante 30 min en un baño de hielo y durante la noche a temperatura ambiente. Se concentra la mezcla y se diluye con agua. Se filtra el precipitado, se lava con agua y se seca a 55 °C para dar el compuesto del subtítulo crudo.

Rendimiento: 4,58 g. R_f = 0,57 (gel de sílice, PE/EtOAc 3:2). MS m/z: 227 $[M-H]^-$.

(b) 2-(2,2-Difluoro-etoxi)-4-amino-5-nitro-benzoato de etilo

Una mezcla de 2,2-difluoroetanol (0,062 mL, 0,97 mmol), KOtBu (0,108 g, 0,964 mmol) y THF (5 mL) se agita durante 15 min, después se añade 2-fluoro-4-amino-5-nitro-benzoato de etilo (0,200 g) y se agita durante 15 h. Se añade agua a la mezcla y se extrae con EtOAc. Se lava la fase orgánica con agua y salmuera, se seca con Na_2SO_4 y se concentra.

Rendimiento: 0,24 g. R_f = 0,7 (gel de sílice, DCM/EtOH 95:5). HPLC R_t = 1,34 min (método B). MS m/z: 291 $[M+H]^+$.

(c) Ácido 2-(2,2-difluoro-etoxi)-4-amino-5-nitro-benzoico

Una mezcla de 2-(2,2-difluoro-etoxi)-4-amino-5-nitro-benzoato de etilo (0,24 g, 0,827 mmol), solución acuosa de NaOH 4 N (0,845 mL) y MeOH (10 mL) se agita durante 1,5 h a 70 °C. Se concentra la mezcla y se diluye el residuo con agua y se acidifica con solución acuosa de HCl 4 N. Se separa el precipitado por filtración, se lava con agua y se seca a 50 °C.

Rendimiento: 0,17 g (78 %). R_f = 0,4 (gel de sílice, DCM/EtOH 9:1). HPLC R_t = 1,14 min (método B). MS m/z: 263 $[M+H]^+$.

(d) Amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-(2,2-difluoro-etoxi)-4-amino-5-nitro-benzoico

El compuesto del subtítulo se prepara a partir de ácido 2-(2,2-difluoro-etoxi)-4-amino-5-nitro-benzoico y *trans*-4-trifluorometil-ciclohexil-amina con TBTU y DIPEA análogamente al ejemplo 1d.

Rendimiento: 100 %. R_f = 0,7 (gel de sílice, DCM:EtOH 9:1). HPLC R_t = 1,43 min (método B). MS m/z: 412 $[M+H]^+$.

(e) Amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-(2,2-difluoro-etoxi)-4,5-diamino-benzoico

El compuesto del subtítulo se prepara a partir de la amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-(2,2-difluoro-etoxi)-4-amino-5-nitro-benzoico con Pd/C y H_2 análogamente al ejemplo 1f.

Rendimiento: cuantitativo. R_f = 0,4 (DCM/EtOH 9:1). HPLC R_t = 1,19 min (método B). MS m/z: 382 $[M+H]^+$.

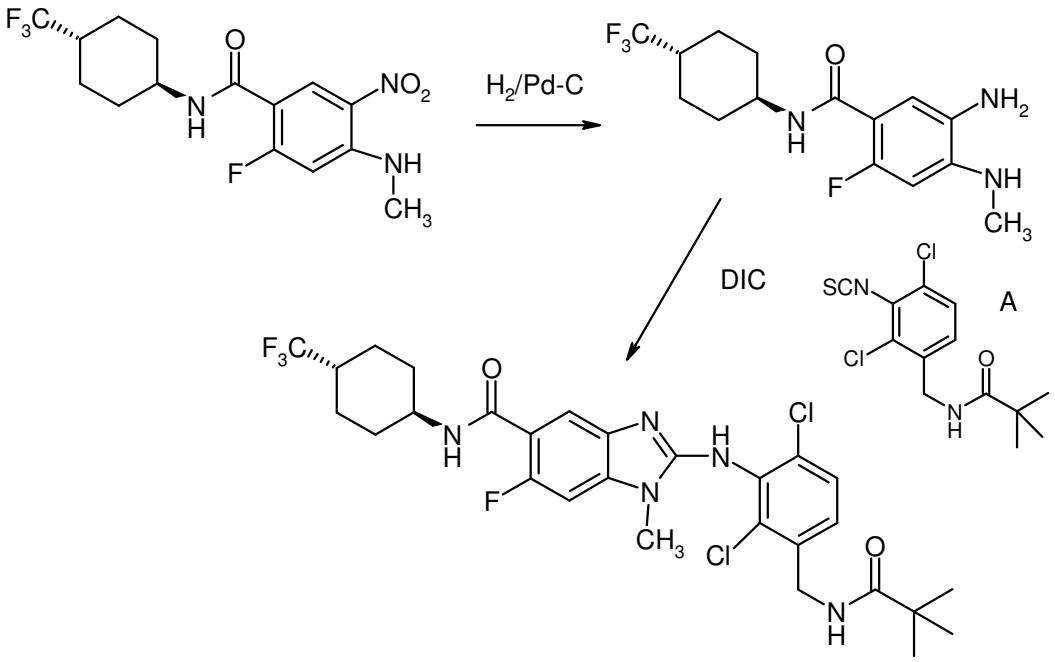
(f) Amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoro-etoxi)-1H-bencimidazol-5-carboxílico

El compuesto del título se prepara a partir de la amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-(2,2-difluoro-etoxi)-4,5-diamino-benzoico y *N*-(2,4-dicloro-3-isotiocianato-bencil)-2,2-dimetil-propionamida con DIC análogamente al ejemplo 1g.

Rendimiento: 43 %. R_f = 0,2 (DCM/EtOH 95:5). HPLC R_t = 1,34 min (método B). MS m/z: 664 $[M+H]^+$

Ejemplo 3

Amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-fluoro-1-metil-1H-bencimidazol-5-carboxílico



(a) Amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-fluoro-4-metilamino-5-amino-benzoico

El compuesto del subtítulo se prepara a partir de la amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-fluoro-4-metilamino-5-nitro-benzoico con Pd/C y H_2 análogamente al ejemplo 1f.

Rendimiento: 98 %. R_f = 0,25 (DCM/EtOH 95:5). HPLC R_t = 1,32 min (método B). MS m/z: 334 $[M+H]^+$.

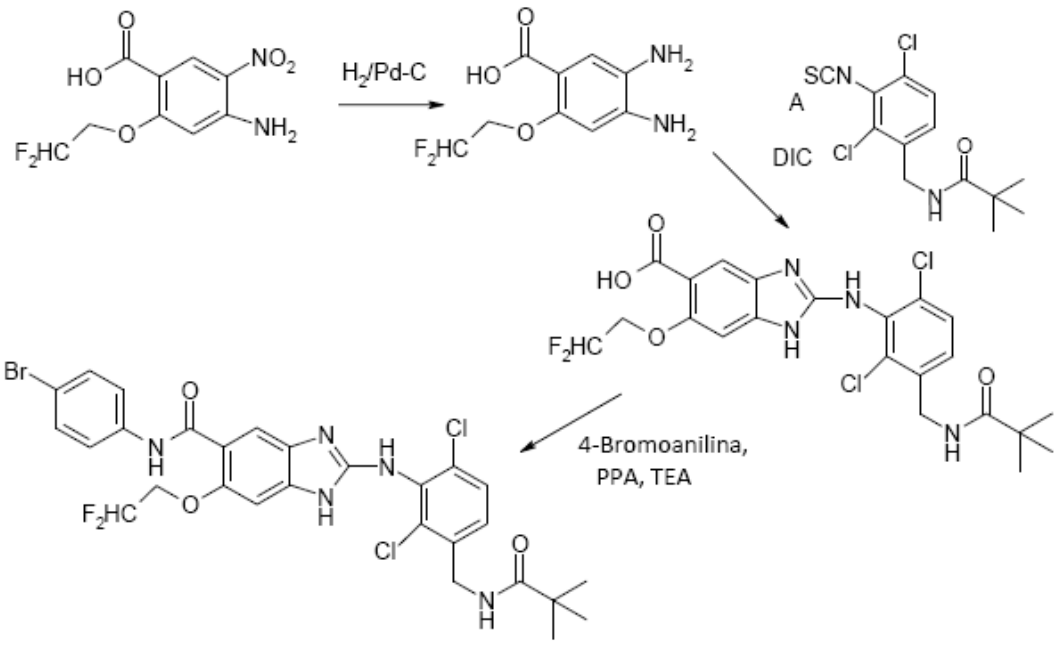
(b) Amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-fluoro-1-metil-1H-bencimidazol-5-carboxílico

El compuesto del título se prepara a partir de la amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-fluoro-4-metilamino-5-amino-benzoico y *N*-(2,4-dicloro-3-isotiocianato-bencil)-2,2-dimetil-propionamida con DIC análogamente al ejemplo 1g.

Rendimiento: 60 %. R_f = 0,4 (DCM/EtOH 95:5). HPLC R_t = 1,36 min (método B). MS m/z: 616 $[M+H]^+$

Ejemplo 4

Amida del ácido *N*-(4-bromo-fenil)-2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoro-etoxi)-1H-bencimidazol-5-carboxílico



(a) Ácido 2-(2,2-difluoro-etoxi)-4,5-diamino-benzoico

El compuesto del subtítulo se prepara a partir de ácido 2-(2,2-difluoro-etoxi)-4-amino-5-nitro-benzoico (ejemplo 2c) con Pd/C y H_2 análogamente al ejemplo 1f.

Rendimiento: 99 %. R_f = 0,3 (DCM/EtOH 9:1).

(b) Ácido 2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoro-etoxi)-1H-bencimidazol-5-carboxílico

Una mezcla de ácido 2-(2,2-difluoro-etoxi)-4,5-diamino-benzoico (732 mg, 3,15 mmol), *N*-(2,4-dicloro-3-isotiocianato-bencil)-2,2-dimetil-propionamida (1,00 g, 3,15 mmol) y

MeCN (15 mL) se agita durante 48 h, después se añade BSTFA (1,03 mL, 3,15 mmol) y se agita a reflujo durante 10 min. Después se añade DIC (0,494 mL, 3,15 mmol) y se agita durante otras 4 h. Se enfría la mezcla a temperatura ambiente, se diluye con HOAc y se concentra. Se agita el residuo con NaOH 1 N, se filtra y se acidifica el filtrado con HCl 4 N, se extrae con EtOAc y se purifica por cromatografía [DCM -> DCM + 10 % EtOH/HOAc (95:5)] para dar el compuesto del subtítulo.

Rendimiento: 0,720 g (44 %). R_f = 0,13 (DCM/EtOH 95:5 + unas gotas de HOAc). MS m/z: 515 $[M+H]^+$.

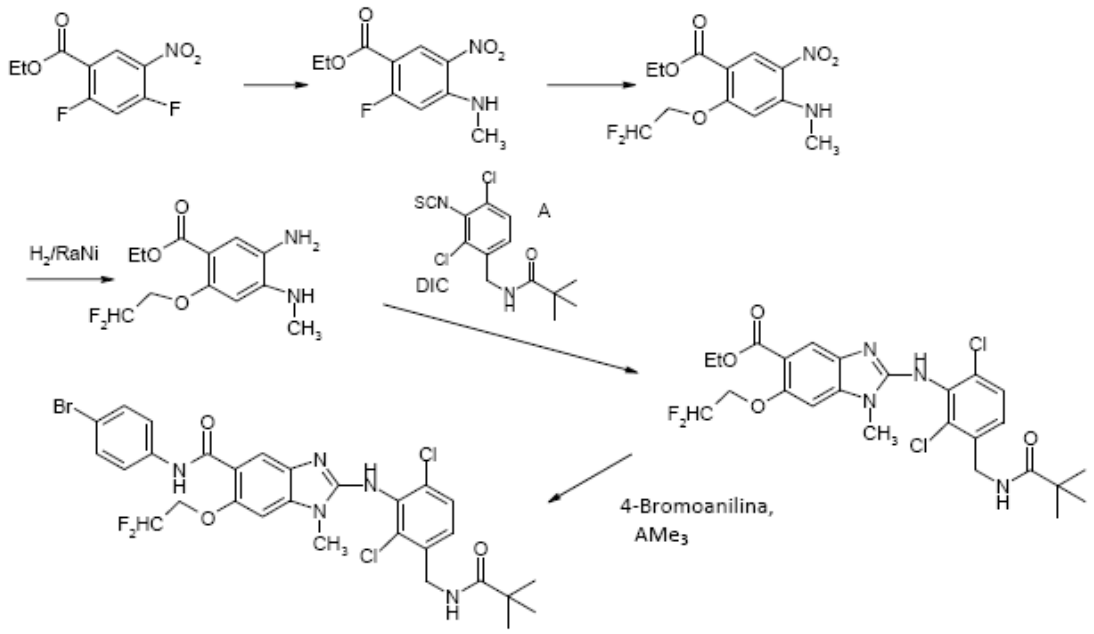
(c) Amida del ácido *N*-(4-bromo-fenil)-2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoro-etoxi)-1H-bencimidazol-5-carboxílico

Se añade PPA (0,223 mL, al 50 % en EtOAc, ~0,38 mmol) lentamente a una mezcla de ácido 2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoro-etoxi)-1H-bencimidazol-5-carboxílico (0,150 g, 0,291 mmol), 4-bromoanilina (50 mg, 0,291 mmol), TEA (0,101 mL, 0,728 mmol) y THF (10 mL). Se mantiene la mezcla a reflujo durante 3 días, se concentra y se purifica mediante HPLC preparativa (columna: Zorbax stable bond C18, 5 µm, 30 x 100 mm, gradiente: agua +0,15 % de HCOOH/MeOH 95:5 ->10:90) para dar el compuesto del título.

Rendimiento: 0,043 g (22 %). HPLC R_t = 1,67 min (método B). MS m/z: 668 $[M+H]^+$.

Ejemplo 5

Amida del ácido *N*-(4-bromo-fenil)-2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoro-etoxi)-1-metil-1H-bencimidazol-5-carboxílico



(a) 2-Fluoro-4-(metilamino)-5-nitrobenzoato de etilo

Una solución 2 M de $MeNH_2$ en THF (21,6 mL; 43,3 mmol) se añade gota a gota a una solución de 2,4-difluoro-5-nitrobenzoato de etilo (5,0 g; 21,6 mmol) en THF (70 mL) a -5 °C. Se deja la mezcla durante la noche a temperatura y después se añade una porción adicional de $MeNH_2$ 2 M en THF (10,0 mL; 2 M; 21,6 mmol) a 0 °C. Después de 3 h a temperatura ambiente, se añade agua y se concentra la mezcla. El precipitado resultante se separa por filtración y se seca para dar el compuesto del subtítulo. Rendimiento: 5,0 g (96 %).

(b) 2-(2,2-Difluoroetoxi)-4-(metilamino)-5-nitrobenzoato de etilo

Se añade una solución de 2,2-difluoroetanol (1,7 g; 20,6 mmol) en THF (50 mL) a una solución de 2-fluoro-4-(metilamino)-5-nitrobenzoato de etilo (5,0 g; 20,6 mmol) en DMF (100 mL). Se añade hidruro de sodio (0,824 g; 60 %; 20,6 mmol) en porciones y se agita la mezcla durante la noche a temperatura ambiente. Se añade una solución de TFA (30 mL; 0,45 M acuoso) y se concentra la mezcla. Se separa por filtración el precipitado resultante, se lava con agua, se seca y se recristaliza en EtOH/agua para dar el compuesto del subtítulo. Rendimiento: 4,8 g (76 %).

(c) 5-Amino-2-(2,2-difluoroetoxi)-4-(metilamino)benzoato de etilo

Una mezcla de 2-(2,2-difluoroetoxi)-4-(metilamino)-5-nitrobenzoato de etilo (2,0 g; 6,57 mmol), Ra-Ni (1,0 g) y THF (100 mL) se agita en atmósfera de H_2 (8 atm) durante la noche a temperatura ambiente. Se añade Na_2SO_4 y se agita la mezcla durante otros 30 min

en atmósfera de H_2. Se filtra la mezcla a través de celita y se concentra y el compuesto del subtítulo se utiliza en la siguiente etapa sin purificación adicional.

(d) Éster etílico del ácido 2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoro-etoxi)-1-metil-1H-bencimidazol-5-carboxílico

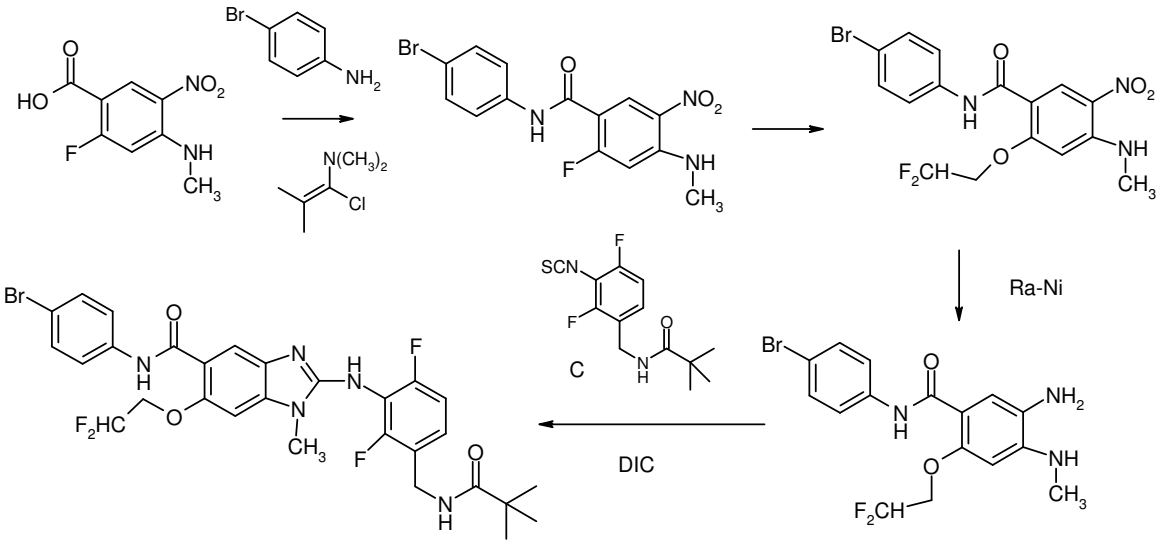
Una mezcla de 5-amino-2-(2,2-difluoroetoxi)-4-(metilamino)benzoato de etilo (0,942 g; 3,44 mmol), *N*-(2,4-dicloro-3-isotiocianato-bencil)-2,2-dimetil-propionamida (1,09 g, 3,44 mmol) y DMF (5 mL) se agita durante la noche a temperatura ambiente. Después se añade DIC (0,695 mL, 4,44 mmol) y se calienta la mezcla durante 6 h a 80 °C. Se concentra la mezcla, se diluye con EtOAc, se lava con agua y la fase orgánica resultante se seca con Na_2SO_4. Después de concentración y purificación mediante cromatografía en columna (gel de sílice, DCM -> DCM/EtOH 97:3) se obtiene el compuesto del subtítulo.
Rendimiento: 1,35 g (71 %). R_f = 0,42 (DCM/EtOH 95:5). MS m/z: 557 $[M+H]^+$.

(e) Amida del ácido *N*-(4-bromo-fenil)-2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoro-etoxi)-1-metil-1H-bencimidazol-5-carboxílico

Se añade Me_3Al en heptano (1,08 mL; 1 M; 1,08 mmol) a una solución de 4-bromoanilina (0,139 g; 0,807 mmol) en 1,4-dioxano (5 mL) y se agita la mezcla durante 30 min a temperatura ambiente. Después se añade lentamente éster etílico del ácido 2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoro-etoxi)-1-metil-1H-bencimidazol-5-carboxílico en 5 mL de 1,4-dioxano y se agita la mezcla durante 10 h a 60 °C, se enfría y se añade MeOH cuidadosamente. Se acidifica la mezcla cruda con HOAc, se concentra y se purifica mediante cromatografía (gel de sílice, DCM -> DCM/EtOH 95:5).
Rendimiento: 85 mg (46 %). HPLC R_t = 2,80 min (método G). MS m/z: 682 $[M+H]^+$.

Ejemplo 6

Amida del ácido *N*-(4-bromo-fenil)-2-{2,6-difluoro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoro-etoxi)-1-metil-1H-bencimidazol-5-carboxílico



(a) *N*-(4-Bromofenil)-2-fluoro-4-metilamino-5-nitro-benzamida

Una mezcla de ácido 2-fluoro-4-metilamino-5-nitro-benzoico (0,500 g, 2,34 mmol), (1-cloro-2-metil-propenil)-dimetilamina (0,371 mL, 2,80 mmol) y DCM (50 mL) se agita durante 30 min, después se añaden 4-bromoanilina (0,402 mg, 2,34 mmol) y DIPEA (0,549 mL, 3,15 mmol) y se agita durante 2 h. Se concentra la mezcla, se añade agua y el precipitado se filtra, se lava con agua y se seca para dar el compuesto del subtítulo.

Rendimiento: 0,820 g (95 %). HPLC R_t = 1,47 min (método B). MS m/z: 368 $[M+H]^+$.

(b) *N*-(4-Bromofenil)-2-(2,2-difluoro-etoxi)-4-metilamino-5-nitro-benzamida

El compuesto del subtítulo se prepara a partir de *N*-(4-bromofenil)-2-fluoro-4-metilamino-5-nitro-benzamida, 2,2-difluoroetanol y KOtBu análogamente al ejemplo 1e.

Rendimiento: 0,94 g (98 %). HPLC R_t = 1,54 min (método B). MS m/z: 430 $[M+H]^+$.

(c) *N*-(4-Bromofenil)-2-(2,2-difluoro-etoxi)-4-metilamino-5-amino-benzamida

El compuesto del subtítulo se prepara a partir de *N*-(4-bromofenil)-2-(2,2-difluoro-etoxi)-4-metilamino-5-nitro-benzamida, Ra-Ni y H_2 análogamente al ejemplo 5c.

Rendimiento: 0,86 g (98 %). R_f = 0,40 (DCM/EtOH 95:5). MS m/z: 400 $[M+H]^+$.

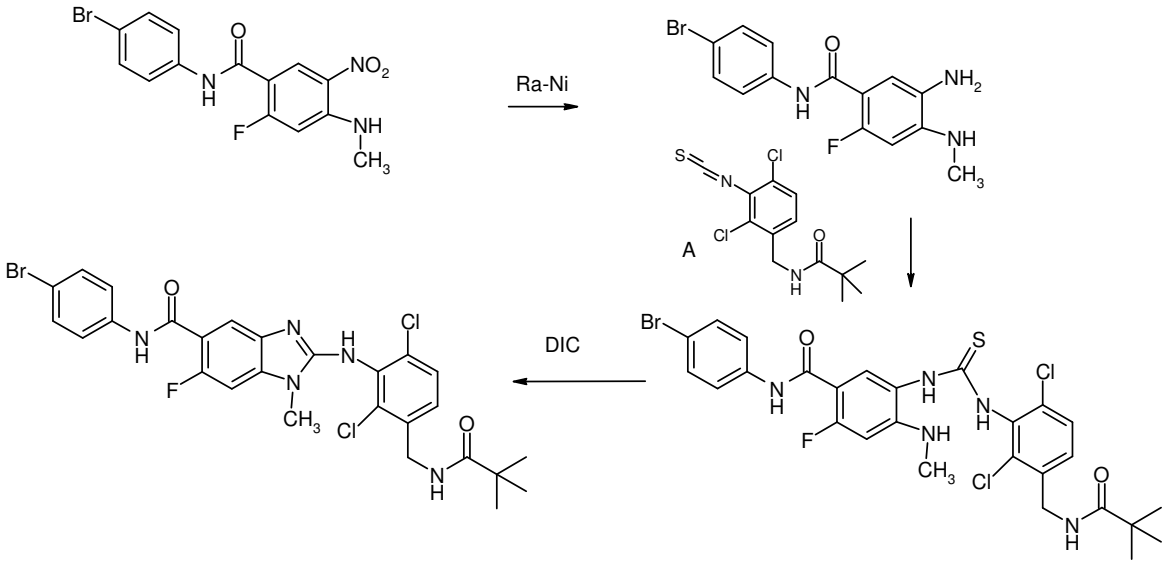
(d) Amida del ácido *N*-(4-bromo-fenil)-2-{2,6-difluoro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoro-etoxi)-1-metil-1H-bencimidazol-5-carboxílico

El compuesto del título se prepara a partir de *N*-(4-bromofenil)-2-(2,2-difluoro-etoxi)-4-metilamino-5-amino-benzamida y *N*-(2,4-difluoro-3-isotiocianato-bencil)-2,2-dimetil-propionamida con DIC análogamente al ejemplo 1g.

Rendimiento: 0,12 g (52 %). R_f = 0,35 (DCM/EtOH 95:5). HPLC R_t = 1,52 min (método B). MS m/z: 650 $[M+H]^+$.

Ejemplo 7

Amida del ácido *N*-(4-bromo-fenil)-2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-fluoro-1-metil-1H-bencimidazol-5-carboxílico



(a) *N*-(4-Bromofenil)-2-fluoro-4-metilamino-5-amino-benzamida

El compuesto del subtítulo se prepara a partir de *N*-(4-bromofenil)-2-fluoro-4-metilamino-5-nitro-benzamida, Ra-Ni y H_2 análogamente al ejemplo 5c.

Rendimiento: cuantitativo. HPLC R_t = 1,34 min (método B). MS m/z: 339 $[M+H]^+$.

(b) *N*-(4-Bromofenil)-5-(3-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenil}-tioureido)-2-fluoro-4-metilamino-benzamida

Una mezcla de *N*-(4-bromofenil)-2-fluoro-4-metilamino-5-amino-benzamida (220 mg, 0,543 mmol), *N*-(2,4-dicloro-3-isotiocianato-bencil)-2,2-dimetil-propionamida (0,172 mg, 0,543 mmol) y DMF (5 mL) se agita durante 3 días, se diluye con agua, y se extrae con EtOAc. Se lava la fase orgánica con agua, se seca con Na_2SO_4 y se concentra para dar el producto crudo.

HPLC R_t = 1,48 min (método B). MS m/z: 656 $[M+H]^+$.

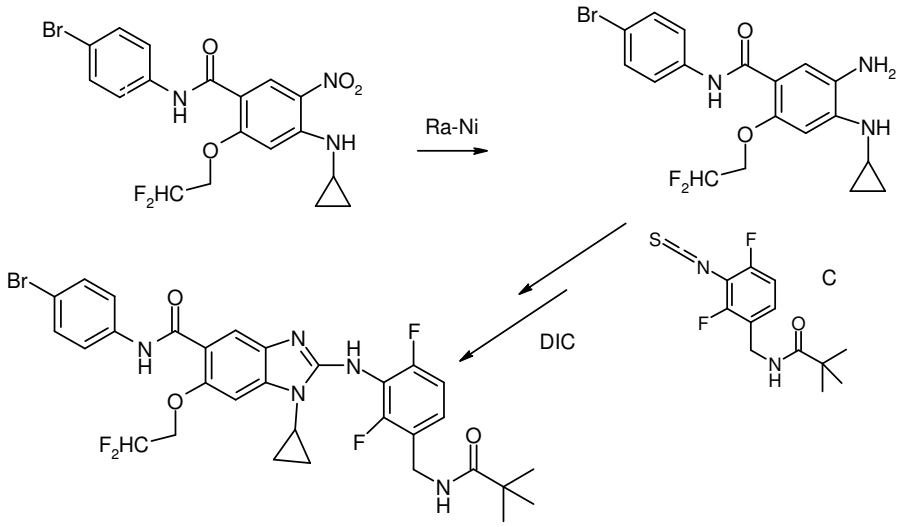
(c) Amida del ácido *N*-(4-bromo-fenil)-2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-fluoro-1-metil-1H-bencimidazol-5-carboxílico

Una mezcla de *N*-(4-bromofenil)-5-(3-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenil}-tioureido)-2-fluoro-4-metilamino-benzamida cruda (400 mg), DIC (111 µl, 0,700 mmol) y DMF (5 mL) se agita a 80 °C durante 8 h. Se concentra la mezcla cruda y se purifica por cromatografía rápida (gel de sílice; DCM -> DCM/EtOH 97:3) para dar el compuesto del título.

Rendimiento: 0,230 g (68 %). R_f = 0,34 (DCM/EtOH 95:5). MS m/z: 620 $[M+H]^+$.

Ejemplo 11

Amida del ácido *N*-(4-bromo-fenil)-2-{2,6-difluoro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoroetoxi-1-ciclopropil-1H-bencimidazol-5-carboxílico



(a) *N*-(4-Bromofenil)-2-(2,2-difluoroetoxi)-4-ciclopropilamino-5-amino-benzamida

El compuesto del subtítulo se prepara a partir de *N*-(4-bromofenil)-2-(2,2-difluoroetoxi)-4-ciclopropilamino-5-nitro-benzamida (preparada a partir de ácido 2,4-difluoro-5-nitrobenzoico, ciclopropilamina, 4-bromoanilina y 2,2-difluoroetanol análogamente a los ejemplos 1c, 6a, 1e) y Ra-Ni/H_2 análogamente al ejemplo 5c.

HPLC R_t = 1,4 min (método B). MS m/z: 427 $[M+H]^+$.

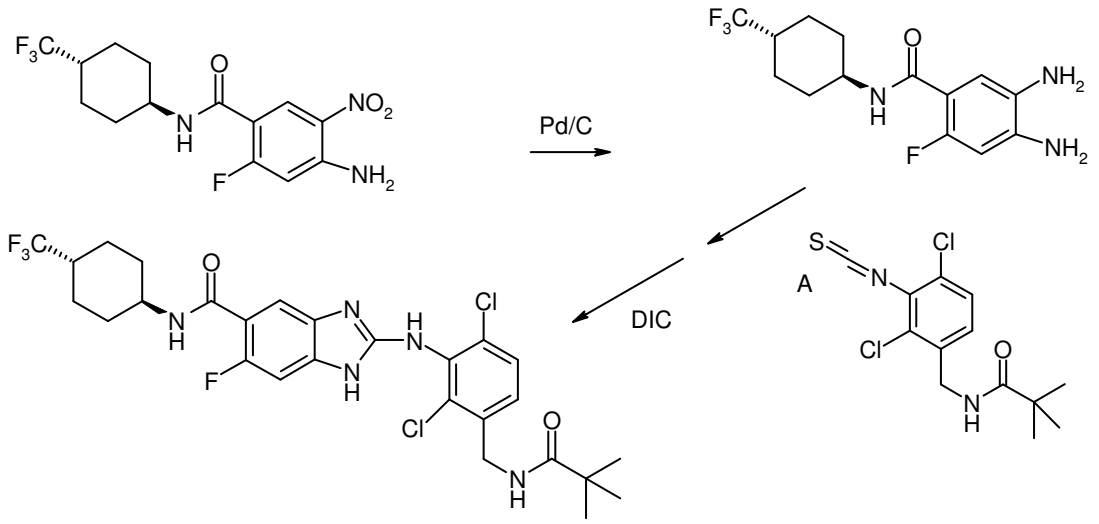
(b) Amida del ácido *N*-(4-bromo-fenil)-2-{2,6-difluoro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoroetoxi-1-ciclopropil-1H-bencimidazol-5-carboxílico

El compuesto del título se prepara a partir de *N*-(4-bromofenil)-2-(2,2-difluoroetoxi)-4-ciclopropilamino-5-amino-benzamida y *N*-(2,4-difluoro-3-isotiocianato-bencil)-2,2-dimetil-propionamida con DIC análogamente a los ejemplos 7b/7c.

R_f = 0,36 (DCM/EtOH 95:5). MS m/z: 676 $[M+H]^+$.

Ejemplo 12

Amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-fluoro-1H-bencimidazol-5-carboxílico



(a) Amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-fluoro-4,5-diamino-benzoico

El compuesto del subtítulo se prepara a partir de la amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-fluoro-4-amino-5-nitro-benzoico (preparada a partir de ácido 2-fluoro-4-amino-5-nitro-benzoico, *trans*-4-trifluorometil-ciclohexilamina análogamente al ejemplo 2d) con Pd/C y H_2 análogamente al ejemplo 1f.

HPLC R_t = 1,58 min (método B). MS m/z: 320 $[M+H]^+$.

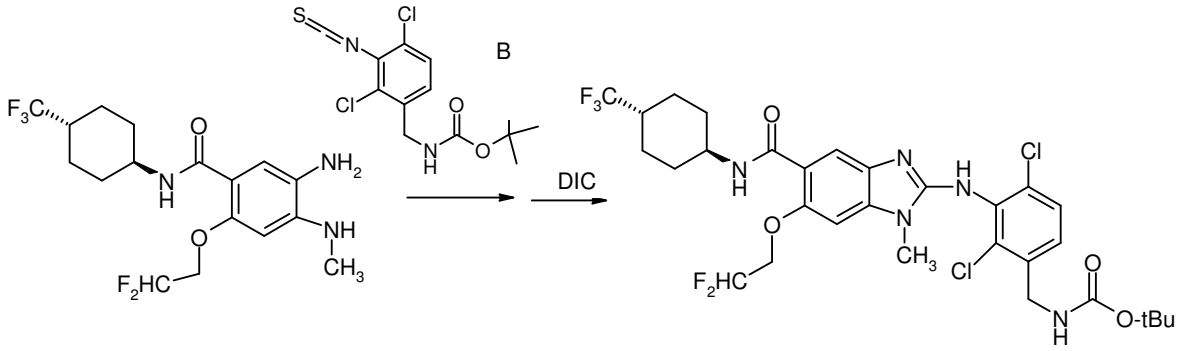
(b) Amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-fluoro-1H-bencimidazol-5-carboxílico

El compuesto del título se prepara a partir de la amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-fluoro-4,5-diamino-benzoico y *N*-(2,4-dicloro-3-isotiocianato-bencil)-2,2-dimetil-propionamida con DIC análogamente a los ejemplos 7b/7c.

HPLC R_t = 2,52 min (método G). MS m/z: 602 $[M+H]^+$.

Ejemplo 13

Amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-{2,6-dicloro-3-[(*terc*-butoxi-carbonilamino)-metil]-fenilamino}-6-(2,2-difluoroetoxi)-1-metil-1H-bencimidazol-5-carboxílico

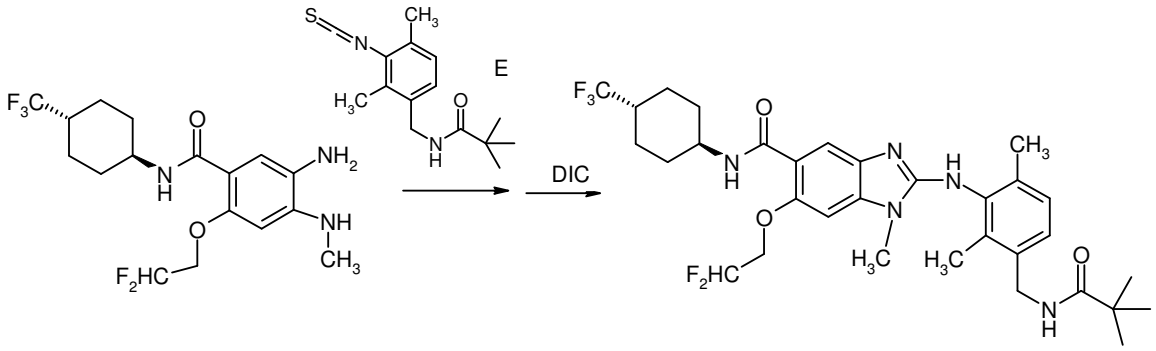


El compuesto del título se prepara a partir de la amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-(2,2-difluoro-etoxi)-4-metilamino-5-amino-benzoico y el éster *terc*-butílico del ácido (2,4-dicloro-3-isotiocianato-bencil)-carbámico con DIC análogamente a los ejemplos 7b/7c.

R_f = 0,25 (DCM/EtOH 95:5). MS m/z: 694 $[M+H]^+$.

Ejemplo 14

Amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-{2,6-dimetil-3-[(2,2-dimetil-propionil-amino)-metil]-fenilamino}-6-(2,2-difluoroetoxi)-1-metil-1H-bencimidazol-5-carboxílico

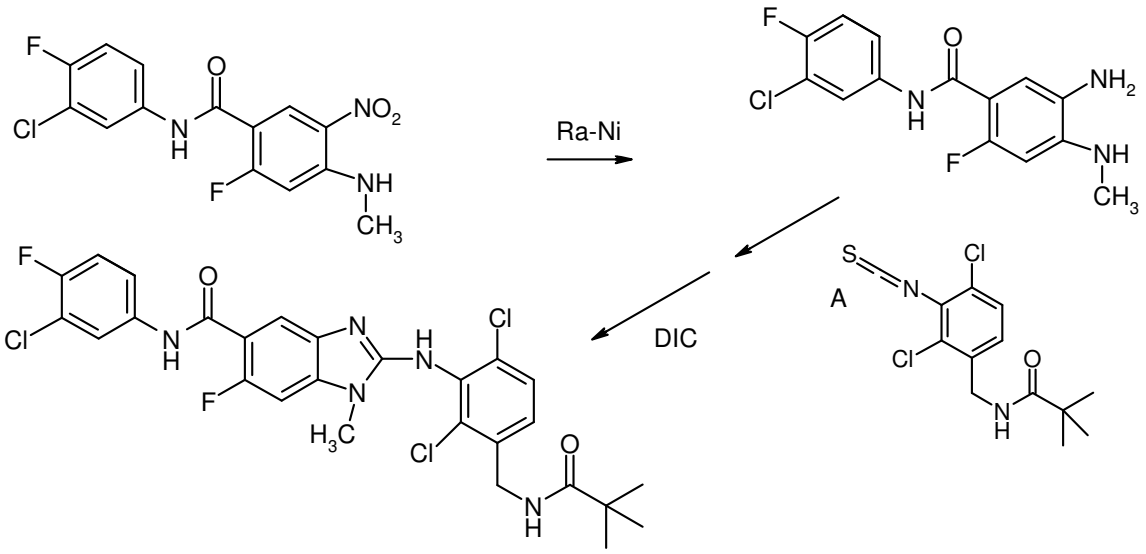


El compuesto del título se prepara a partir de la amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-(2,2-difluoro-etoxi)-4-metilamino-5-amino-benzoico y *N*-(2,4-dimetil-3-isotiocianato-bencil)-2,2-dimetil-propionamida con DIC análogamente a los ejemplos 7b/7c.

R_f = 0,15 (DCM/EtOH 95:5). MS m/z: 638 $[M+H]^+$.

Ejemplo 17

Amida del ácido *N*-(4-fluoro-3-cloro-fenil)-2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-fluoro-1-metil-1H-bencimidazol-5-carboxílico



(a) Amida del ácido *N*-(4-fluoro-3-cloro-fenil)-2-fluoro-4-metilamino-5-amino-benzoico

El compuesto del subtítulo se prepara a partir de la amida del ácido *N*-(4-fluoro-3-cloro-fenil)-2-fluoro-4-metilamino-5-nitro-benzoico (preparada a partir de ácido 2-fluoro-4-metilamino-5-nitro-benzoico, 4-fluoro-3-cloro-anilina análogamente a la etapa 6a) con Ra-Ni y H_2 análogamente al ejemplo 5c.

MS m/z: 312 $[M+H]^+$.

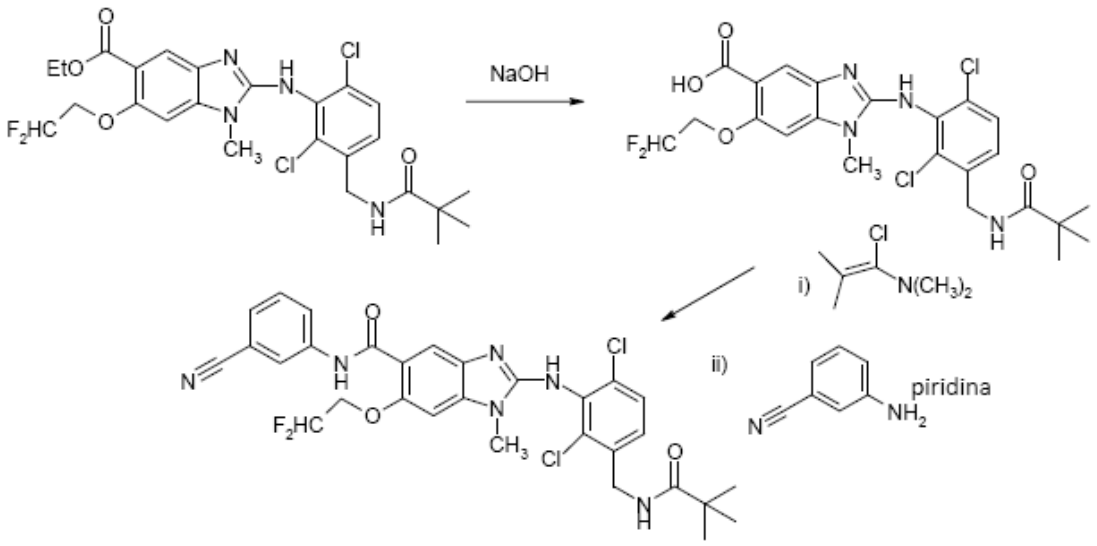
(b) Amida del ácido *N*-(4-fluoro-3-cloro-fenil)-2-{2,6-dicloro-3-[(2,2-dimetil-propionil-amino)-metil]-fenilamino}-6-fluoro-1-metil-1H-bencimidazol-5-carboxílico

El compuesto del título se prepara a partir de la amida del ácido *N*-(4-fluoro-3-cloro-fenil)-2-fluoro-4-metilamino-5-amino-benzoico y *N*-(2,4-dicloro-3-isotiocianato-bencil)-2,2-dimetil-propionamida con DIC análogamente a los ejemplos 7b/7c.

HPLC R_t = 2,52 min (método G). MS m/z: 594 $[M+H]^+$.

Ejemplo 28

Amida del ácido *N*-(3-ciano-fenil)-2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoro-etoxi)-1-metil-1H-bencimidazol-5-carboxílico



(a) Ácido 2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoro-etoxi)-1-metil-1H-bencimidazol-5-carboxílico

Una mezcla de éster etílico del ácido 2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoro-etoxi)-1-metil-1H-bencimidazol-5-carboxílico (1,170 g; 2,10 mmol), solución acuosa 4 N de NaOH (2,10 mL, 8,4 mmol) y EtOH (30 mL), se agita durante 4 días. Después, se concentra la mezcla, se diluye con agua y se acidifica con solución acuosa 4 N de HCl. Se filtra el precipitado, se lava con agua y se seca para dar 0,60 g del producto. Se extrae el filtrado con EtOAc, la fase orgánica se seca con Na_2SO_4, y se concentra para dar 0,23 g adicionales del compuesto del subtítulo.

Rendimiento: 0,83 g (75 %). HPLC R_t = 1,16 min (método C). MS m/z: 529 $[M+H]^+$.

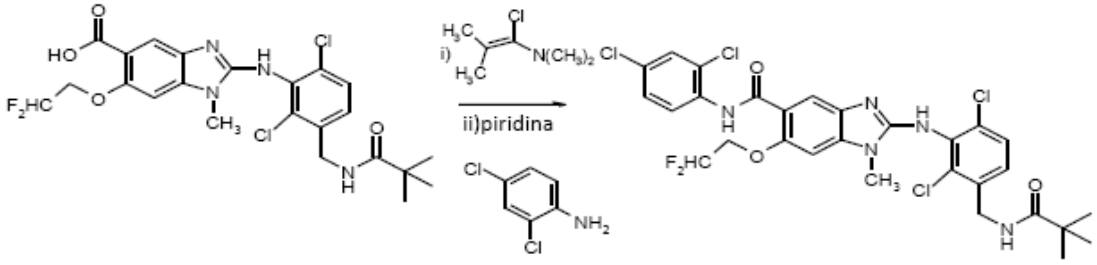
(b) Amida del ácido *N*-(3-ciano-fenil)-2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoro-etoxi)-1-metil-1H-bencimidazol-5-carboxílico

Se añade (1-cloro-2-metil-propenil)-dimetilamina (20 µl) a una mezcla de ácido 2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoro-etoxi)-1-metil-1H-bencimidazol-5-carboxílico (53 mg, 0,10 mmol) en 2,0 mL de acetonitrilo y se agita durante 10 min a temperatura ambiente. Se añade (1-cloro-2-metil-propenil)-dimetilamina adicional (20 µl) y se agita la mezcla durante 20 min adicionales a temperatura ambiente. Se añade la solución de cloruro de ácido crudo a una mezcla de 3-aminobenzonitrilo (12 mg, 0,10 mmol), piridina (24 µL, 0,30 mmol) y acetonitrilo (1,0 mL) y se agita durante 15 min a temperatura ambiente y durante 5 h adicionales a 55 °C. Se separa el disolvente a vacío y se disuelve el residuo en 2 mL de una solución de DMF/agua 19:1 y se purifica mediante HPLC preparativa para dar el compuesto del título.

Rendimiento: 26 mg (42 %). HPLC R_t = 1,65 min (método A). MS m/z: 629 $[M+H]^+$.

Ejemplo 60

Amida del ácido *N*-(2,4-dicloro-fenil)-2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoro-etoxi)-1-metil-1H-bencimidazol-5-carboxílico

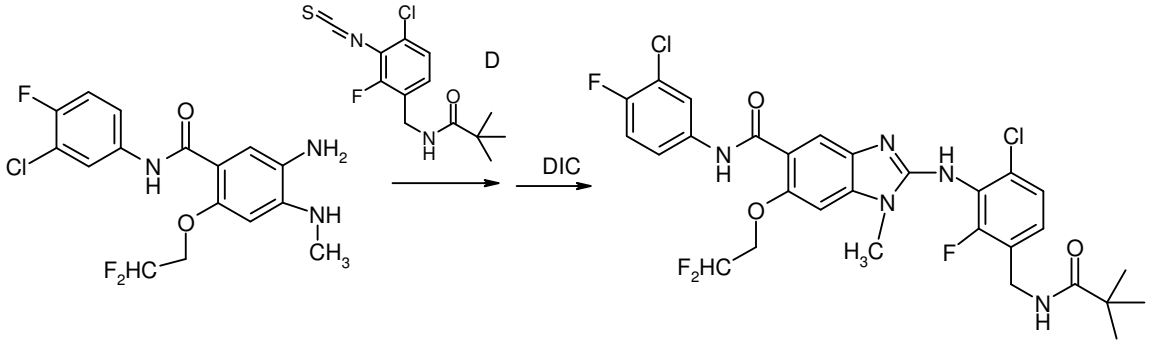


Se añade (1-cloro-2-metil-propenil)-dimetilamina (20 µl) a una mezcla de ácido 2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoro-etoxi)-1-metil-1H-bencimidazol-5-carboxílico (53 mg, 0,10 mmol) en 1,0 mL de acetonitrilo y se agita durante 15 min a temperatura ambiente. Se añade la solución de cloruro de ácido crudo a una mezcla de 2,4-dicloroanilina (16 mg, 0,10 mmol), piridina (24 µL, 0,30 mmol) y acetonitrilo (1,0 mL) y se agita durante el fin de semana a 60 °C. Se separa el disolvente a vacío y se disuelve el residuo en 2 mL de una solución de DMF/agua 9:1 y se purifica mediante HPLC preparativa.

Rendimiento: 53 mg (79 %). HPLC R_t = 2,83 min (método D). MS m/z: 672 $[M+H]^+$.

Ejemplo 75

Amida del ácido *N*-(3-cloro-4-fluoro-fenil)-2-{6-cloro-2-fluoro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoroetoxi)-1-metil-1H-bencimidazol-5-carboxílico



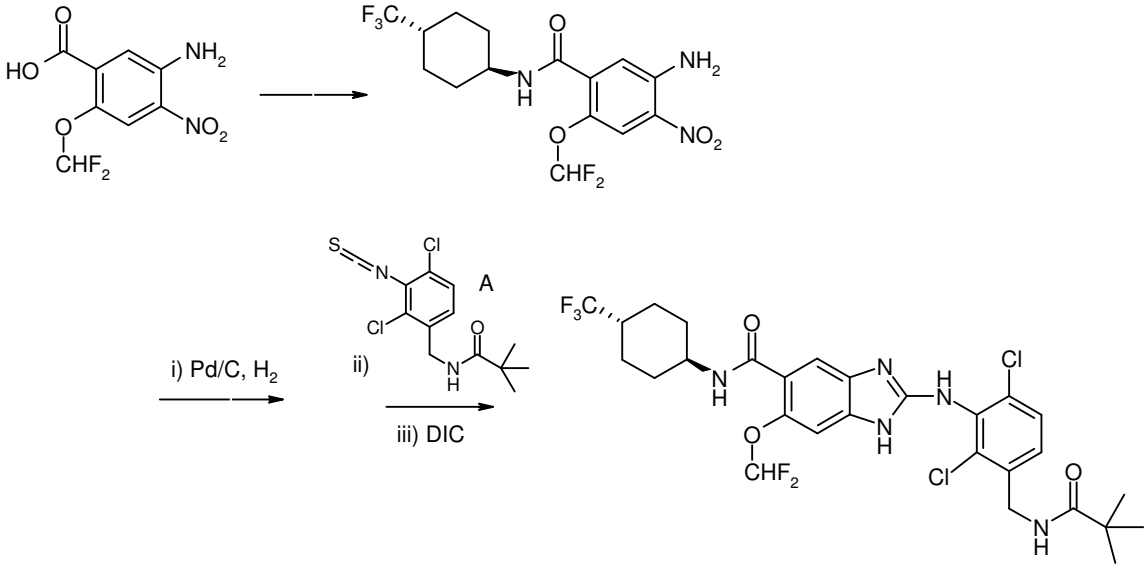
Una mezcla de *N*-(3-cloro-4-fluorofenil)-2-(2,2-difluoroetoxi)-4-metilamino-5-amino-benzamida (60 mg, 0,161 mmol, preparada a partir de 3-cloro-4-fluoro-anilina, 2,2-difluoroetanol y ácido 2-fluoro-4-metilamino-5-nitro-benzoico según la secuencia 1d-1f), *N*-(4-cloro-2-fluoro-3-isotiocianato-bencil)-2,2-dimetil-propionamida (0,48 mg, 0,161 mmol) y DMF (2 mL) se agita durante 3 h. Después se añade DIC (25 µl, 0,16 mmol) y se agita a 80 °C durante la noche. Se concentra la mezcla cruda y se purifica por cromatografía rápida (gel

de sílice; DCM -> DCM/EtOH 98:2).

Rendimiento: 80 mg (78 %). R_f = 0,45 (DCM/EtOH 95:5). HPLC R_t = 1,48 min (método B). MS m/z: 640 $[M+H]^+$.

Ejemplo 78

Amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-{2,6-dicloro-3-[(2,2-dimetil-propionil-amino)-metil]-fenilamino}-6-(difluorometoxi)-1H-bencimidazol-5-carboxílico



a) Amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-(difluorometoxi)-5-amino-4-nitro-benzoico

Se añade (1-cloro-2-metil-propenil)-dimetilamina (102 µl) a una mezcla de ácido 2-(difluoro-metoxi)-5-amino-4-nitro-benzoico (175 mg, 0,705 mmol, preparada análogamente al documento WO2010/034797), 5 mL de THF y 10 mL de DCM y se agita durante 5 h. Después se añaden *trans*-4-trifluorometil-ciclohexilamina (158 mg, 0,776 mmol) y piridina (139 µL, 1,77 mmol) y se agita durante la noche. Se separa el disolvente a vacío, se añade solución semisaturada acuosa de $NaHCO_3$ y se extrae con DCM. Se secan las capas orgánicas con Na_2SO_4, se filtran, se concentran y se purifican mediante HPLC preparativa (Método F).

Rendimiento: 70 mg (25 %). HPLC R_t = 2,06 min (método E). MS m/z: 398 $[M+H]^+$.

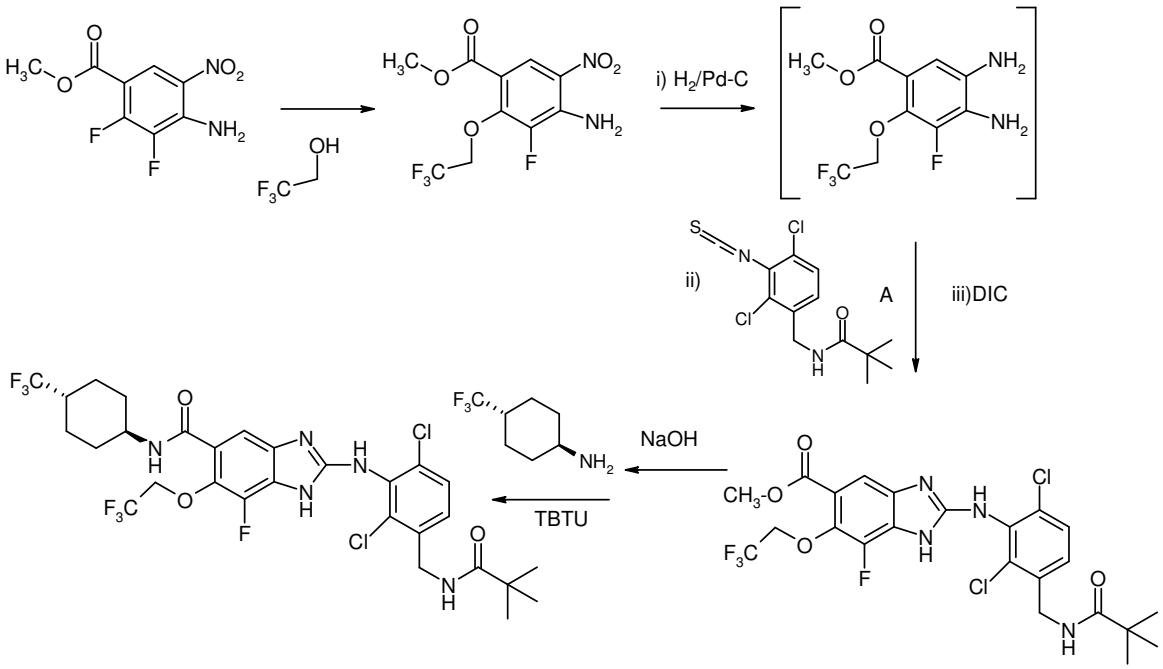
b) Amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(difluorometoxi)-1H-bencimidazol-5-carboxílico

Una mezcla de la amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-(difluorometoxi)-5-amino-4-nitro-benzoico (70 mg, 0,176 mmol), Pd/C (15 mg) y 10 mL THF,

se agita en atmósfera de H_2 (3 bares) durante 2 h. Se filtra la mezcla cruda a un matraz cargado con *N*-(2,4-dicloro-3-isotiocianato-bencil)-2,2-dimetil-propionamida (59 mg, 0,185 mmol) y se lava la torta del filtro con 40 mL de THF. Se agita la mezcla durante 4 h a temperatura ambiente y durante la noche a 60 °C. Después se concentra la mezcla de reacción a ~10 mL y se agita durante 8 h adicionales a 60 °C. Después se concentra a vacío, se diluye con MeCN (2,0 mL) y se añade DIC (29 µl, 0,186 mmol) y se agita durante 4 días. Después se concentra la mezcla, se diluye con DMF y THF y se purifica mediante HPLC.
Rendimiento: 34 mg (30 %). HPLC R_t = 2,00 min (método E). MS m/z: 650 $[M+H]^+$.

Ejemplo 79

Amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-{2,6-dicloro-3-[(2,2-dimetil-propionil-amino)-metil]-fenilamino}-6-(2,2,2-trifluoroetoxi)-7-fluoro-1H-bencimidazol-5-carboxílico



(a) Éster metílico del ácido 2-(2,2,3-trifluoro-etoxi)-3-fluoro-4-amino-5-nitro-benzoico

Una mezcla de 2,2,2-triifluoroetanol (0,377 mL, 5,2 mmol), KOtBu (0,580 g, 0,5,2 mmol) y THF (20 mL), se agita durante 15 min a 0 °C, después se añade 2,3-difluoro-4-amino-5-nitro-benzoato de metilo (1,00 g) en THF (20 mL) y se agita durante 15 h a temperatura ambiente. Se añade agua a la mezcla y se concentra la mezcla. Se filtra el precipitado resultante, se lava con agua y se seca a 50 °C.
Rendimiento:1,15 g (86 %). HPLC R_t = 1,95 min (método E). MS m/z: 313 $[M+H]^+$.

(b) Éster metílico del ácido 2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2,2-trifluoroetoxi)-7-fluoro-1H-bencimidazol-5-carboxílico

El compuesto del subtítulo se prepara a partir del éster metílico del ácido 2-(2,2,3-trifluoro-etoxi)-3-fluoro-4-amino-5-nitro-benzoico análogamente al 78b utilizando i) Pd/C y H_2; ii) *N*-(2,4-dicloro-3-isotiocianato-bencil)-2,2-dimetil-propionamida y iii) DIC.
Rendimiento: 90 mg (45 %). HPLC R_t = 2,01 min (método E). MS m/z: 565 $[M+H]^+$.

(c) Ácido 2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2,2-trifluoroetoxi)-7-fluoro-1H-bencimidazol-5-carboxílico

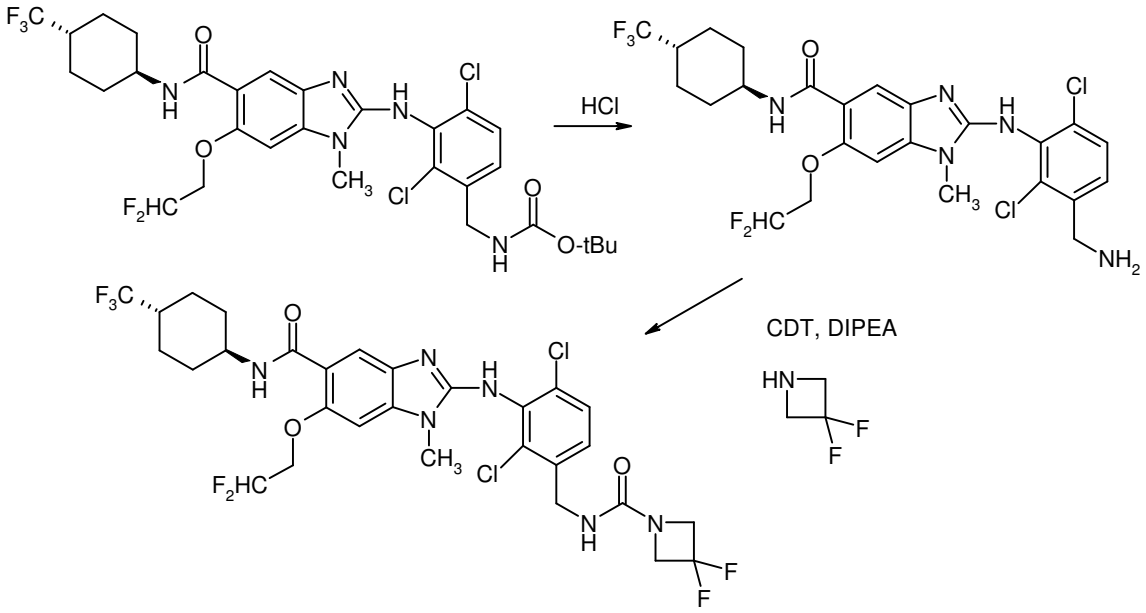
El compuesto del subtítulo se prepara a partir del éster metílico del ácido 2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2,2-trifluoroetoxi)-7-fluoro-1H-bencimidazol-5-carboxílico y NaOH análogamente al ejemplo 28a.
Rendimiento: 60 mg (62 %). HPLC R_t = 1,81 min (método E). MS m/z: 551 $[M+H]^+$.

(d) Amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2,2-trifluoroetoxi)-7-fluoro-1H-bencimidazol-5-carboxílico

Una mezcla de ácido 2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2,2,2-trifluoroetoxi)-7-fluoro-1H-bencimidazol-5-carboxílico (60 mg, 0,109 mmol), TBTU (36,7 mg, 0,114 mmol), DIPEA (66 µl, 0,38 mmol) y DMF (1 mL), se agita durante 30 min, después se añade *trans*-4-trifluorometil-ciclohexilamina (24 mg, sal HCl) y se agita durante 1 h. Se diluye la mezcla con EtOAc, se lava con solución acuosa saturada de $NaHCO_3$, se seca con Na_2SO_4 y se concentra para dar el compuesto del título.
Rendimiento: 76 mg (100 %). HPLC R_t = 2,24 min (método E). MS m/z: 700 $[M+H]^+$.

Ejemplo 80

Amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-{2,6-dicloro-3-[(3,3-difluoro-azetidin-1-carbonilamino)-metil]-fenilamino}-6-(2,2-difluoroetoxi)-1-metil-1H-bencimidazol-5-carboxílico



(a) Amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-(2,6-dicloro-3-aminometil-fenilamino)-6-(2,2-difluoroetoxi)-1-metil-1H-bencimidazol-5-carboxílico

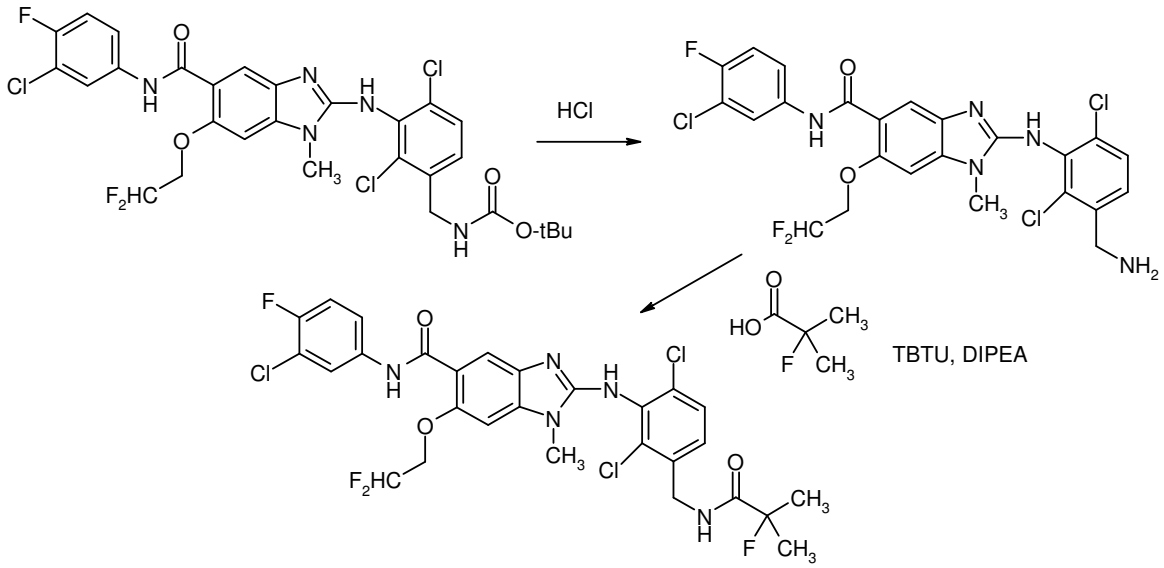
Una mezcla de amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-{2,6-dicloro-3-[(*terc*-butoxi-carbonilamino)-metil]-fenilamino}-6-(2,2-difluoroetoxi)-1-metil-1H-bencimidazol-5-carboxílico (350 mg, 0,504 mmol), solución acuosa 6 M de HCl (15 mL) y THF (15 mL), se agita durante la noche, se concentra la mezcla y se usa directamente en la siguiente etapa. Rendimiento: 320 mg (cuantitativo). HPLC R_t = 1,23 min (método B). MS m/z: 594 $[M+H]^+$.

(b) Amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-{2,6-dicloro-3-[(3,3-difluoro-azetidin-1-carbonilamino)-metil]-fenilamino}-6-(2,2-difluoroetoxi)-1-metil-1H-bencimidazol-5-carboxílico

Se añade CDT (45 mg, 90 %) a una mezcla enfriada con hielo de amida del ácido *N*-(*trans*-4-trifluorometil-ciclohex-1-il)-2-(2,6-dicloro-3-aminometil-fenilamino)-6-(2,2-difluoro-etoxi)-1-metil-1H-bencimidazol-5-carboxílico cruda (140 mg), DIPEA (0,12 mL, 0,68 mmol) y THF (5,0 mL) y se agita durante 30 min. Después se añade 3,3-difluoroazetidina x HCl (30 mg, 0,22 mmol) y se calienta la mezcla a 60 °C durante 4 días (cada día se añaden otros 30 mg de la azetidina). Se concentra la mezcla de reacción y se purifica mediante cromatografía (gel de sílice, DCM->DCM/EtOH 95:5).
Rendimiento: 60 mg (38 %). R_f (TLC): 0,26 (DCM/EtOH 95:5). MS m/z: 713 $[M+H]^+$.

Ejemplo 84

Amida del ácido *N*-(3-cloro-4-fluoro-fenil)-2-{2,6-dicloro-3-[(2-fluoro-2-metil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoroetoxi)-1-metil-1H-bencimidazol-5-carboxílico



(a) Amida del ácido *N*-(3-cloro-4-fluoro-fenil)-2-(2,6-dicloro-3-aminometil-fenilamino)-6-(2,2-difluoroetoxi)-1-metil-1H-bencimidazol-5-carboxílico

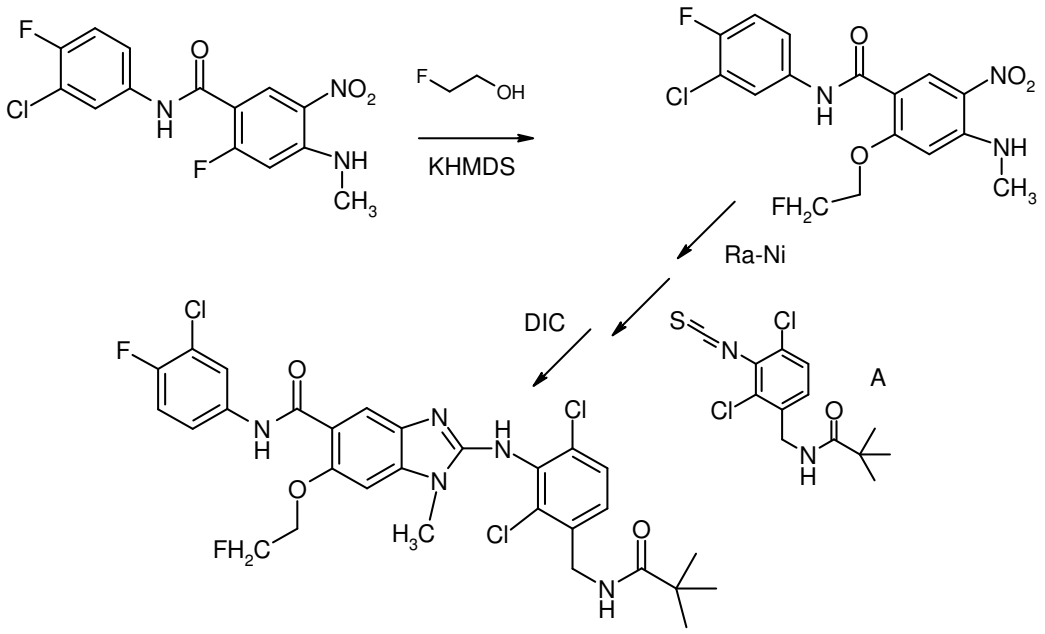
Una mezcla de amida del ácido *N*-(3-cloro-4-fluoro-fenil)-2-{2,6-dicloro-3-[(*terc*-butoxi-carbonilamino)-metil]-fenilamino}-6-(2,2-difluoroetoxi)-1-metil-1H-bencimidazol-5-carboxílico (4,0 g, 5,9 mmol, preparada análogamente al ejemplo 75 a partir de *N*-(3-cloro-4-fluorofenil)-2-(2,2-difluoroetoxi)-4-metilamino-5-amino-benzamida con bloque estructural B), HCl 4 M en dioxano (50 mL) y dioxano (200 mL), se agita durante 2 h. Se separa el precipitado por filtración, se lava con agua y se diluye con 10 mL de NH_3 acuoso concentrado. Se extrae la mezcla con EtOAc, la fase orgánica se seca con Na_2SO_4 y se concentra.
Rendimiento: 2,62 g (77 %). MS m/z: 572 $[M+H]^+$.

(b) Amida del ácido *N*-(3-cloro-4-fluoro-fenil)-2-{2,6-dicloro-3-[(2-fluoro-2-metil-propionilamino)-metil]-fenilamino}-6-(2,2-difluoroetoxi)-1-metil-1H-bencimidazol-5-carboxílico

Se añade TBTU (1,0 mL de una solución 0,11 M en DMF) a una mezcla de amida del ácido *N*-(3-cloro-4-fluoro-fenil)-2-(2,6-dicloro-3-aminometil-fenilamino)-6-(2,2-difluoroetoxi)-1-metil-1H-bencimidazol-5-carboxílico (1,0 mL de una solución 0,10 M en DMF), DIPEA (52 µl, 0,3 mmol) y ácido 2-fluoro-2-metilpropiónico (1,0 mL de una solución 0,13 M en DMF) y se agita durante 3 días y se purifica la mezcla por HPLC preparativa.
Rendimiento: 38 mg (57 %). HPLC R_t = 1,69 min (método I). MS m/z: 661 $[M+H]^+$.

Ejemplo 177

Amida del ácido *N*-(3-cloro-4-fluoro-fenil)-2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2-fluoroetoxi)-1-metil-1H-bencimidazol-5-carboxílico



a) *N*-(3-Cloro-4-fluorofenil)-2-(2-fluoroetoxi)-4-metilamino-5-nitro-benzamida

Se añade KHMDS (0,320 g, 1,60 mmol) a una mezcla enfriada en hielo de amida del ácido *N*-(4-fluoro-3-cloro-fenil)-2-fluoro-4-metilamino-5-nitro-benzoico (500 mg, 1,46 mmol), 2-fluoroetanol (0,129 ml, 2,19 mmol) y 30 ml de THF. Después de 30 min se aumenta la temperatura a 60 °C durante 4,5 h, después se agita a temperatura ambiente durante la noche. Se añade 2-fluoroetanol adicional (0,129 ml, 2,19 mmol) y KHMDS (0,160 g, 0,80 mmol) y se agita durante 4,5 h a 60 °C. Después se diluye la mezcla con dicha solución acuosa saturada de $NaHCO_3$ y se separa el precipitado por filtración, se lava con agua y se seca.

Rendimiento: 360 mg (64 %). HPLC R_t = 2,28 min (método E). MS m/z: 386 $[M+H]^+$.

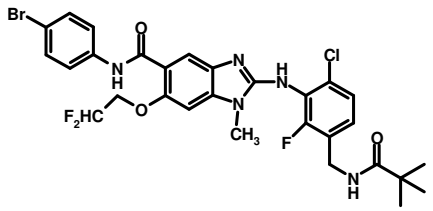
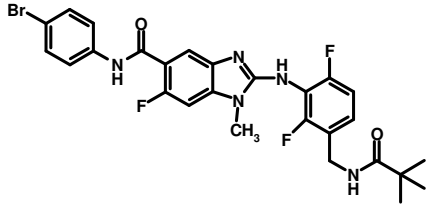
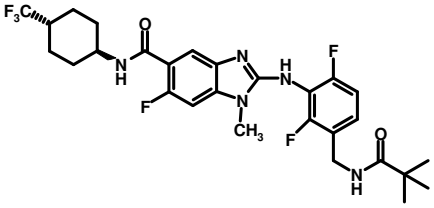
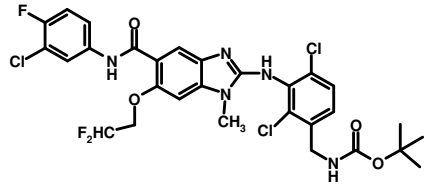
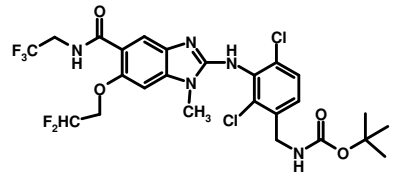
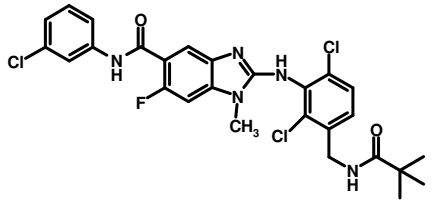
b) Amida del ácido *N*-(3-cloro-4-fluoro-fenil)-2-{2,6-dicloro-3-[(2,2-dimetil-propionilamino)-metil]-fenilamino}-6-(2-fluoroetoxi)-1-metil-1H-bencimidazol-5-carboxílico

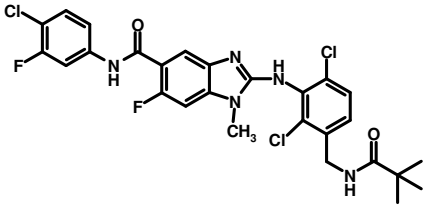
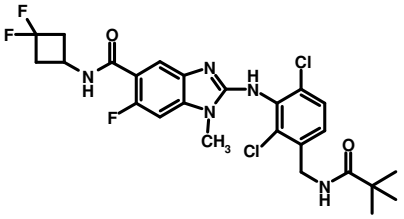
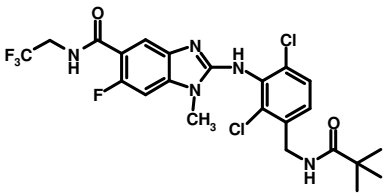
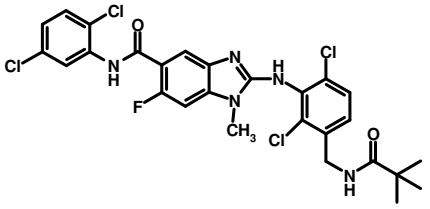
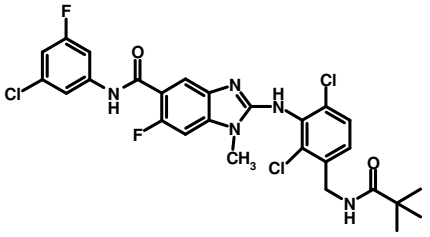
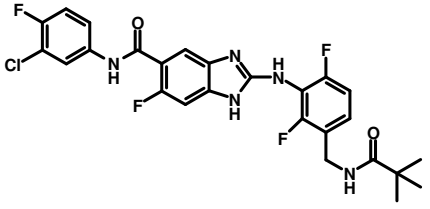
Una mezcla de *N*-(3-cloro-4-fluorofenil)-2-(2-fluoroetoxi)-4-metilamino-5-nitro-benzamida (67,9 mg, 0,176 mmol), Pd/C (15 mg) y 10 mL THF, se agita en atmósfera de H_2 (3 bares) durante 8 h. Se filtra la mezcla cruda a un matraz cargado con *N*-(2,4-dicloro-3-isotiocianato-bencil)-2,2-dimetil-propionamida (59 mg, 0,185 mmol) y se concentra hasta ~5 mL. Se agita la mezcla durante 2 h a temperatura ambiente y se concentra a vacío. Se diluye la mezcla con MeCN (2,0 mL), se añade DIC (29 µl, 0,186 mmol) y se agita durante la noche a temperatura ambiente y 2 h a 60 °C. Se enfría la mezcla a temperatura ambiente y se separa el precipitado resultante por filtración, se lava con MeCN, se redisuelve en dioxano/MeCN y unas gotas de HCOOH y se liofilizó.

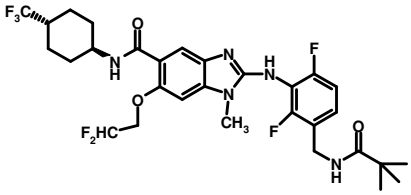
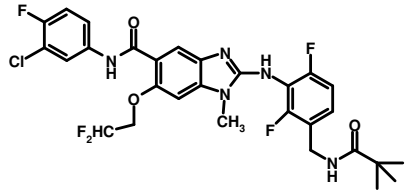
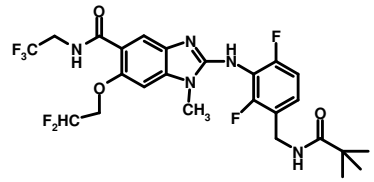
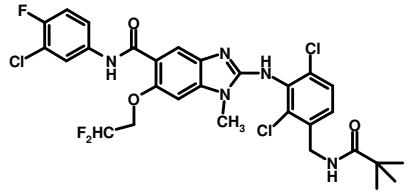
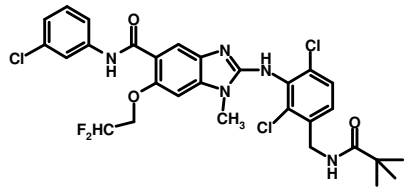
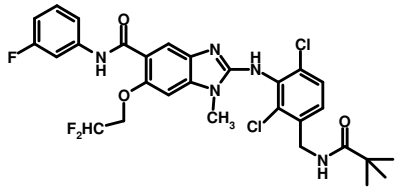
Rendimiento: 29 mg (26 %). HPLC R_t = 2,09 min (método E). MS m/z: 638 $[M+H]^+$.

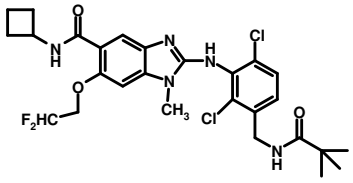
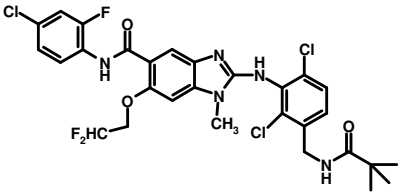
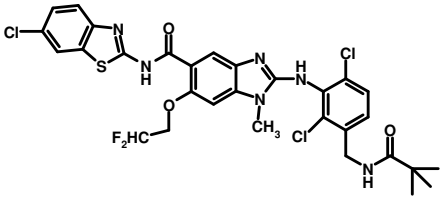
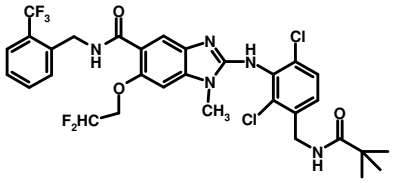
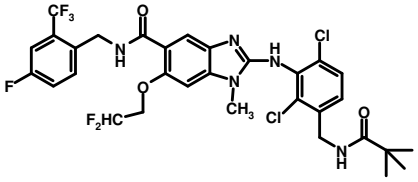
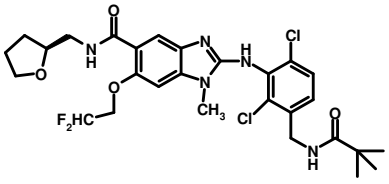
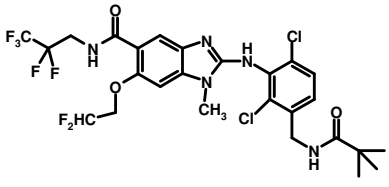
Los siguientes ejemplos de la Tabla 1 se preparan análogamente a los métodos descritos anteriormente.

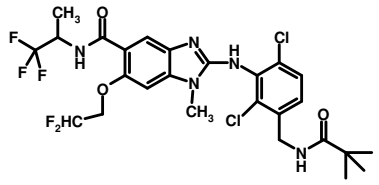
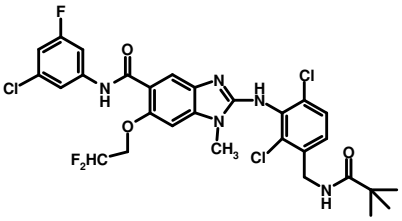
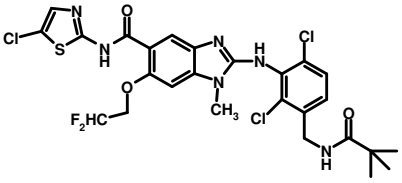
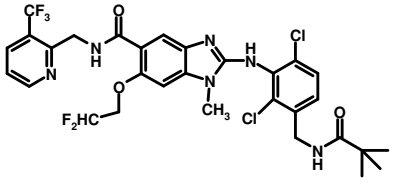
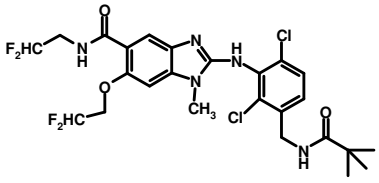
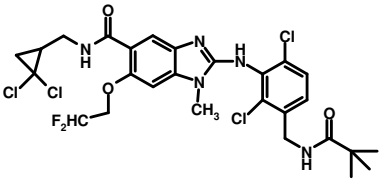
Tabla 1

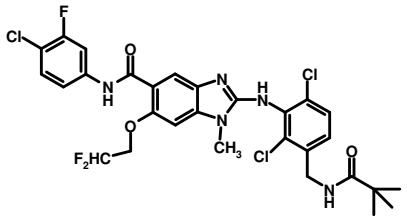
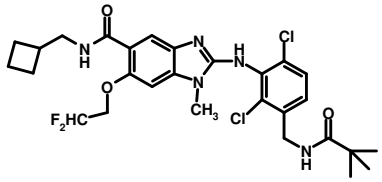
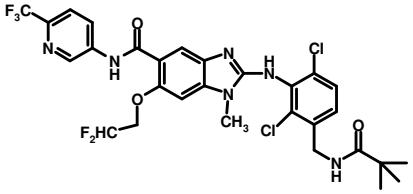
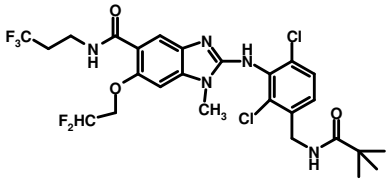
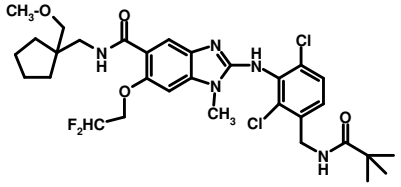
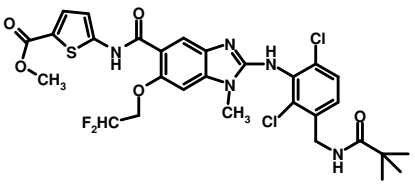
Ej.	Estructura	Fórmula/Peso molecular	MS* *m/z* $[M+H]^+$	R_f (TLC, gel de sílice) o R_t [min] (método HPLC)	Preparado de forma análoga al ejemplo
8		$C_{29}H_{28}BrCl$ $F_3N_5O_3$ 666,916	666	R_t = 1,44 (método B)	**6**
9		$C_{27}H_{25}Br$ $F_3N_5O_2$ 588,419	589	R_t = 1,39 (método B)	**7**
10		$C_{28}H_{31}$ $F_6N_5O_2$ 583,569	584	R_f = 0,25 (DCM/EtOH 95:5)	**3**
15		$C_{29}H_{37}Cl_3$ $F_3N_5O_4$ 672,909	672	R_t = 2,21 (método E)	**13**
16		$C_{25}H_{26}Cl_2$ $F_5N_5O_4$ 626,403	626	R_f = 0,36 (PE/EtOAc 1:1)	**13**
18		$C_{27}H_{25}Cl_3$ FN_5O_2 576,876	576	R_f = 0,35 (DCM/EtOH 95:5)	**17**

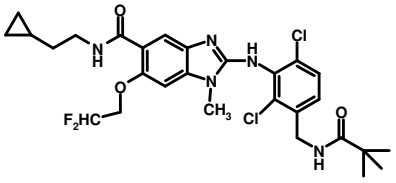
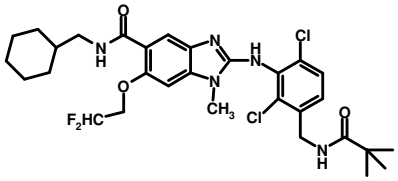
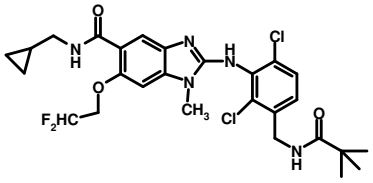
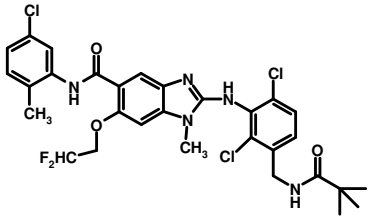
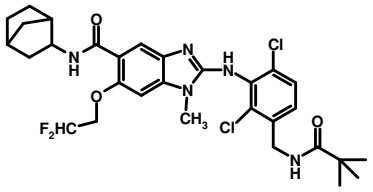
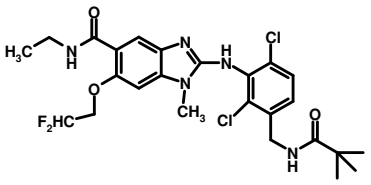
Ej.	Estructura	Fórmula/Peso molecular	MS* *m/z* $[M+H]^+$	R_f (TLC, gel de sílice) o R_t [min] (método HPLC)	Preparado de forma análoga al ejemplo
19		$C_{27}H_{24}Cl_3F_2N_5O_2$ 594,867	594	R_f = 0,27 (DCM/EtOH 95:5)	**17**
20		$C_{25}H_{26}Cl_2F_3N_5O_2$ 556,407	556	R_f = 0,22 (DCM/EtOH 95:5)	**17**
21		$C_{23}H_{23}Cl_2F_4N_5O_2$ 548,360	548	R_f = 0,24 (DCM/EtOH 95:5)	**17**
22		$C_{27}H_{24}Cl_4FN_5O_2$ 611,321	610	R_f = 0,35 (DCM/EtOH 95:5)	**17**
23		$C_{27}H_{24}Cl_3F_2N_5O_2$ 594,867	594	R_f = 0,29 (DCM/EtOH 95:5)	**17**
24		$C_{26}H_{22}Cl_3F_2N_5O_2$ 547,932	548	R_f = 0,19 (DCM/EtOH 95:5)	**17**

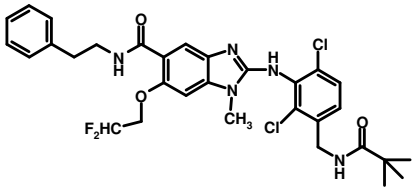
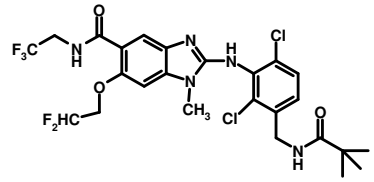
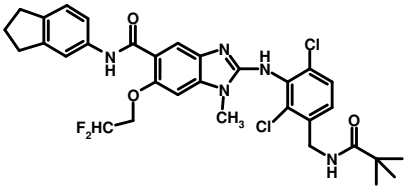
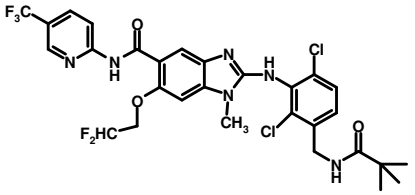
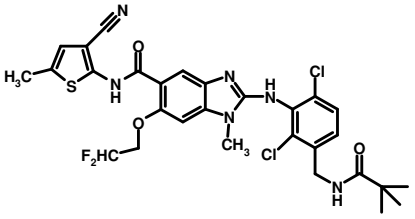
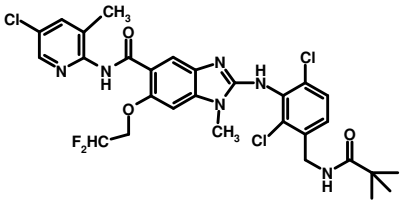
Ej.	Estructura	Fórmula/Peso molecular	MS* *m/z* $[M+H]^+$	R_f (TLC, gel de sílice) o R_t [min] (método HPLC)	Preparado de forma análoga al ejemplo
25		$C_{30}H_{34}$ $F_7N_5O_3$ 645,612	646	R_f = 0,22 (DCM/EtOH 95:5)	**1**
26		$C_{29}H_{27}Cl$ $F_5N_5O_3$ 624,001	624	R_f = 0,27 (DCM/EtOH 95:5)	**11**
27		$C_{25}H_{26}$ $F_7N_5O_3$ 577,495	578	R_f = 0,19 (DCM/EtOH 95:5)	**11**
29		$C_{29}H_{27}Cl_3$ $F_3N_5O_3$ 656,917	656	R_t = 1,78 (método A)	**28**
30		$C_{29}H_{28}Cl_3$ $F_2N_5O_3$ 638,927	638	R_t = 1,76 (método A)	**28**
31		$C_{29}H_{28}Cl_2$ $F_3N_5O_3$ 622,472	622	R_t = 1,69 (método A)	**28**

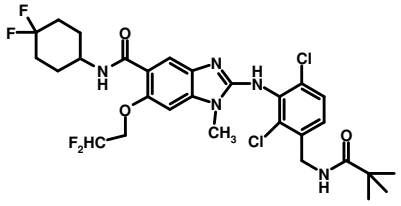
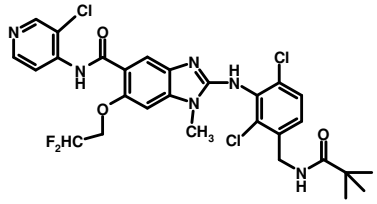
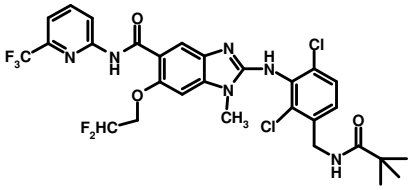
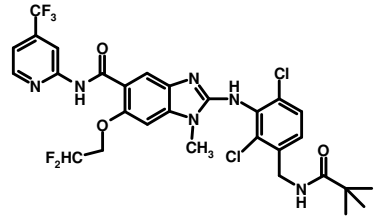
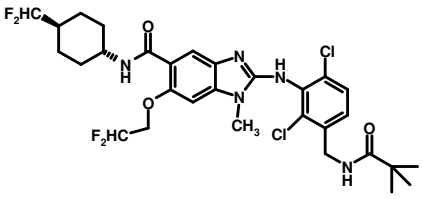
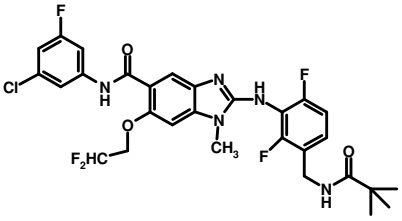
Ej.	Estructura	Fórmula/Peso molecular	MS* *m/z* $[M+H]^+$	R_f (TLC, gel de sílice) o R_t [min] (método HPLC)	Preparado de forma análoga al ejemplo
32		$C_{27}H_{31}Cl_2F_2N_5O_3$ 582,476	582	R_t = 1,51 (método A)	**28**
33		$C_{29}H_{27}Cl_3F_3N_5O_3$ 656,917	656	R_t = 1,82 (método A)	**28**
34		$C_{30}H_{27}Cl_3F_3N_6O_3S$ 696,003	695	R_t = 1,93 (método A)	**28**
35		$C_{31}H_{30}Cl_2F_5N_5O_3$ 686,506	686	R_t = 1,70 (método A)	**28**
36		$C_{31}H_{29}Cl_2F_6N_5O_3$ 704,496	704	R_t = 1,72 (método A)	**28**
37		$C_{28}H_{33}Cl_2F_2N_5O_4$ 612,502	612	R_t = 1,42 (método A)	**28**
38		$C_{26}H_{26}Cl_2F_7N_5O_3$ 660,415	660	R_t = 1,65 (método A)	**28**

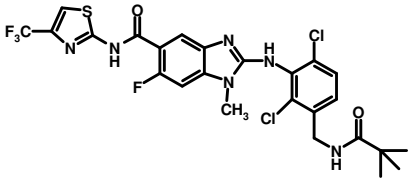
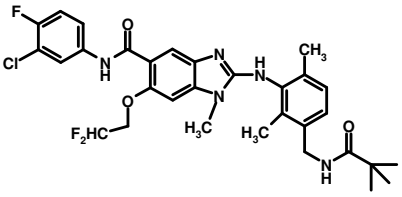
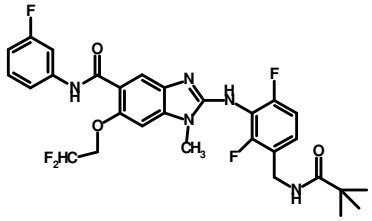
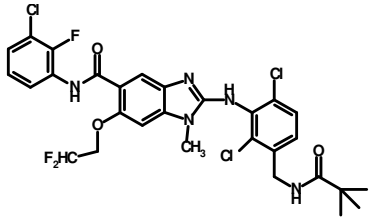
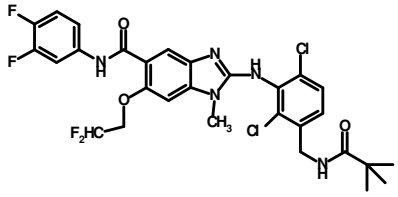
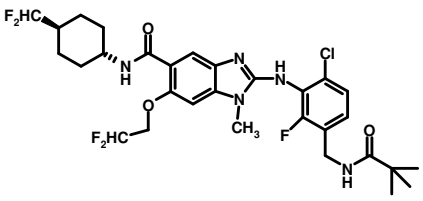
Ej.	Estructura	Fórmula/Peso molecular	MS* *m/z* $[M+H]^+$	R_f (TLC, gel de sílice) o R_t [min] (método HPLC)	Preparado de forma análoga al ejemplo
39		$C_{26}H_{28}Cl_2F_5N_5O_3$ 624,435	624	R_t = 1,60 (método A)	**28**
40		$C_{29}H_{27}Cl_3F_3N_5O_3$ 656,917	656	R_t = 1,83 (método A)	**28**
41		$C_{26}H_{25}Cl_3F_2N_6O_3S$ 645,943	645	R_t = 1,79 (método A)	**28**
42		$C_{30}H_{29}Cl_2F_5N_6O_3$ 687,494	687	R_t = 1,62 (método A)	**28**
43		$C_{25}H_{27}Cl_2F_4N_5O_3$ 592,418	592	R_t = 1,44 (método A)	**28**
44		$C_{27}H_{29}Cl_4F_2N_5O_3$ 651,366	650	R_t = 1,62 (método A)	**28**

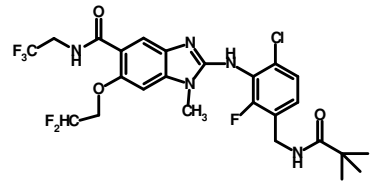
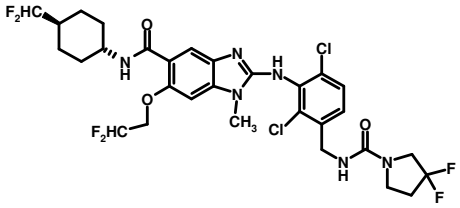
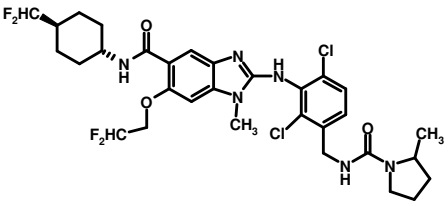
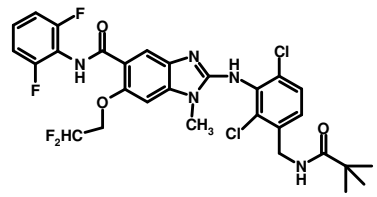
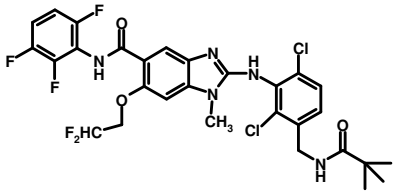
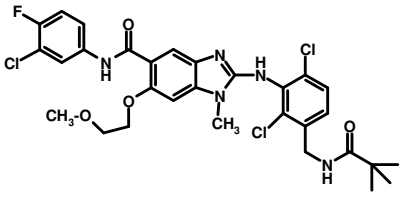
Ej.	Estructura	Fórmula/Peso molecular	MS* *m/z* $[M+H]^+$	R_f (TLC, gel de sílice) o R_t [min] (método HPLC)	Preparado de forma análoga al ejemplo
45		$C_{29}H_{27}Cl_3F_3N_5O_3$ 656,917	656	R_t = 1,81 (método A)	**28**
46		$C_{28}H_{33}Cl_2F_2N_5O_3$ 596,503	596	R_t = 1,58 (método A)	**28**
47		$C_{29}H_{27}Cl_2F_5N_6O_3$ 673,467	673	R_t = 1,74 (método A)	**28**
48		$C_{26}H_{28}Cl_2F_5N_5O_3$ 624,435	624	R_t = 1,54 (método A)	**28**
49		$C_{31}H_{39}Cl_2F_2N_5O_4$ 654,582	654	R_t = 1,66 (método A)	**28**
50		$C_{29}H_{29}Cl_2F_2N_5O_5S$ 668,546	668	R_t = 1,70 (método A)	**28**

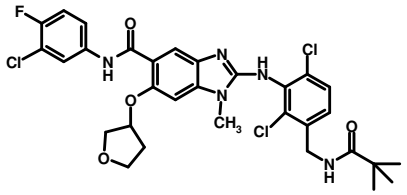
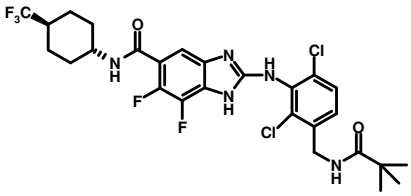
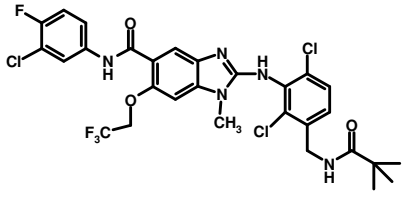
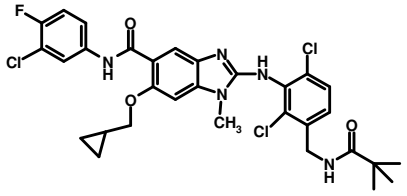
Ej.	Estructura	Fórmula/Peso molecular	MS* *m/z* $[M+H]^+$	R_f (TLC, gel de sílice) o R_t [min] (método HPLC)	Preparado de forma análoga al ejemplo
51		$C_{28}H_{33}Cl_2F_2N_5O_3$ 596,503	596	R_t = 1,56 (método A)	**28**
52		$C_{30}H_{37}Cl_2F_2N_5O_3$ 624,556	624	R_t = 1,69 (método A)	**28**
53		$C_{27}H_{31}Cl_2F_2N_5O_3$ 582,476	582	R_t = 1,50 (método A)	**28**
54		$C_{30}H_{30}Cl_3F_2N_5O_3$ 652,954	652	R_t = 1,77 (método A)	**28**
55		$C_{30}H_{35}Cl_2F_2N_5O_3$ 622,541	622	R_t = 1,65 (método A)	**28**
56		$C_{25}H_{29}Cl_2F_2N_5O_3$ 556,438	556	R_t = 1,36 (método A)	**28**

Ej.	Estructura	Fórmula/Peso molecular	MS* *m/z* $[M+H]^+$	R_f (TLC, gel de sílice) o R_t [min] (método HPLC)	Preparado de forma análoga al ejemplo
57		$C_{31}H_{33}Cl_2F_2N_5O_3$ 632,536	632	R_t = 1,62 (método A)	**28**
58		$C_{25}H_{26}Cl_2F_5N_5O_3$ 610,408	610	R_t = 1,54 (método A)	**28**
59		$C_{32}H_{33}Cl_2F_2N_5O_3$ 644,647	644	R_t = 1,77 (método A)	**28**
61		$C_{29}H_{27}Cl_2F_5N_6O_3$ 673,461	673	R_t = 2,74 (método D)	**60**
62		$C_{29}H_{28}Cl_2F_2N_6O_3S$ 649,539	649	R_t = 2,73 (método D)	**60**
63		$C_{29}H_{29}Cl_3F_5N_6O_3$ 653,934	653	R_t = 2,63 (método D)	**60**

Ej.	Estructura	Fórmula/Peso molecular	MS* *m/z* $[M+H]^+$	R_f (TLC, gel de sílice) o R_t [min] (método HPLC)	Preparado de forma análoga al ejemplo
64		$C_{29}H_{33}Cl_2F_4N_5O_3$ 646,503	646	R_t = 2,61 (método D)	**60**
65		$C_{29}H_{27}Cl_3F_2N_6O_3$ 639,908	639	R_t = 2,65 (método D)	**60**
66		$C_{29}H_{27}Cl_2F_5N_6O_3$ 673,461	673	R_t = 2,70 (método D)	**60**
67		$C_{29}H_{27}Cl_2F_5N_6O_3$ 673,461	673	R_t = 2,72 (método D)	**60**
68		$C_{30}H_{35}Cl_2F_4N_5O_3$ 660,530	660	R_t = 2,64 (método D)	**60**
69		$C_{29}H_{27}ClF_5N_5O_3$ 624,001	624	R_f = 0,26 (DCM/EtOH 95:5)	**11**

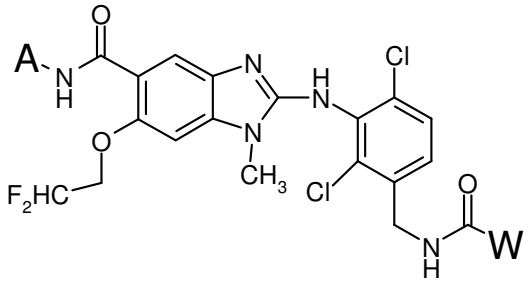
Ej.	Estructura	Fórmula/Peso molecular	MS* *m/z* $[M+H]^+$	R_f (TLC, gel de sílice) o R_t [min] (método HPLC)	Preparado de forma análoga al ejemplo
70		$C_{25}H_{22}Cl_2F_4N_6O_2S$ 617,446	617	R_f = 0,26 (DCM/EtOH 95:5)	**17**
71		$C_{31}H_{33}ClF_3N_5O_3$ 616,074	616	R_f = 0,19 (DCM/EtOH 95:5)	**14**
72		$C_{29}H_{28}F_5N_5O_3$ 589,557	590	R_f = 0,27 (DCM/EtOH 95:5)	**6**
73		$C_{29}H_{27}Cl_3F_3N_5O_3$ 656,910	656	R_f = 0,28 (DCM/EtOH 95:5)	**7**
74		$C_{29}H_{27}Cl_2F_4N_5O_3$ 640,456	640	R_t = 1,45 (método B)	**7**
76		$C_{30}H_{34}ClF_6N_5O_3$ 662,066	662	R_t = 1,42 (método B)	**75**

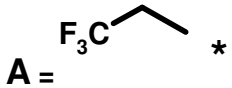
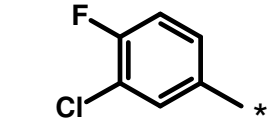
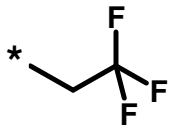
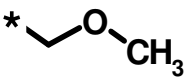
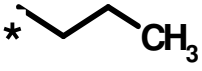
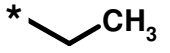
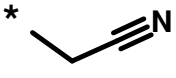
Ej.	Estructura	Fórmula/Peso molecular	MS* *m/z* $[M+H]^+$	R_f (TLC, gel de sílice) o R_t [min] (método HPLC)	Preparado de forma análoga al ejemplo
77		$C_{25}H_{26}ClF_6N_5O_3$ 593,949	594	R_t = 1,31 (método B)	**75**
81		$C_{30}H_{31}Cl_2F_7N_6O_3$ 727,500	727	R_f = 0,28 (DCM/EtOH 95:5)	**80**
82		$C_{30}H_{31}Cl_2F_7N_6O_3$ 705,546	705	R_f = 0,23 (DCM/EtOH 95:5)	**80**
83		$C_{29}H_{27}Cl_2F_4N_5O_3$ 640,456	640	R_f = 0,28 (DCM/EtOH 95:5)	**7**
85		$C_{29}H_{26}Cl_2F_5N_5O_3$ 658,446	658	R_f = 0,25 (DCM/EtOH 95:5)	**7**
178		$C_{30}H_{31}Cl_3FN_5O_4$ 650,955	650	R_t = 2,08 (método E)	**177**

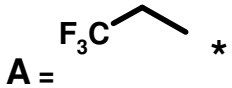
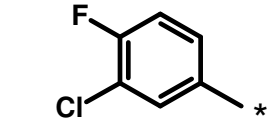
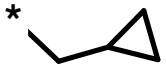
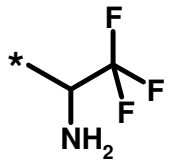
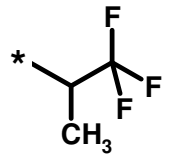
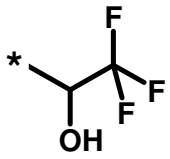
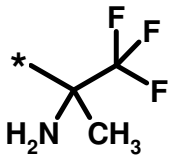
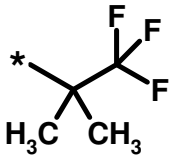
Ej.	Estructura	Fórmula/Peso molecular	MS* *m/z* $[M+H]^+$	R_f (TLC, gel de sílice) o R_t [min] (método HPLC)	Preparado de forma análoga al ejemplo
179		$C_{31}H_{31}Cl_3FN_5O_4$ 662,966	662	R_t = 2,01 (método E)	**177**
180		$C_{27}H_{28}Cl_2F_5N_5O_2$ 620,441	620	R_t = 2,10 (método E)	**79**
181		$C_{29}H_{26}Cl_3F_4N_5O_3$ 674,900	674	R_t = 2,18 (método E)	**177**
182		$C_{31}H_{31}Cl_3FN_5O_3$ 646,966	646	Rt = 2,23 (método E)	**177**

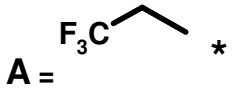
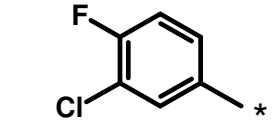
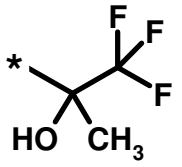
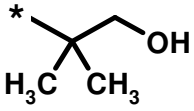
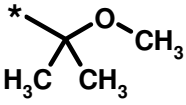
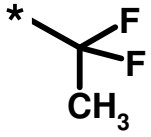
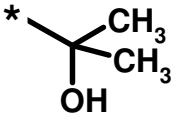
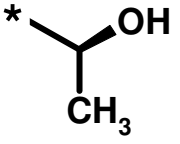
Los siguientes ejemplos de la Tabla 2 se preparan análogamente al ejemplo 84 (A y W son como se definen en la tabla).

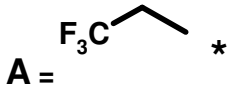
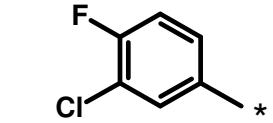
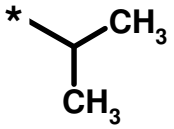
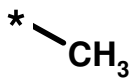
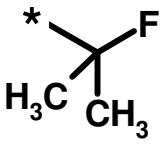
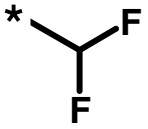
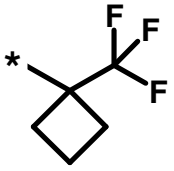
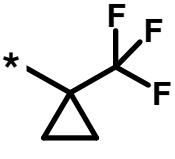
Tabla 2

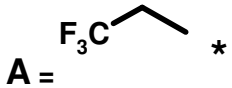
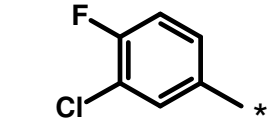
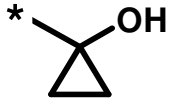
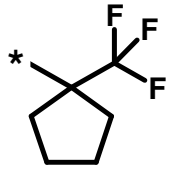
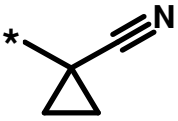
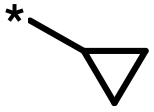
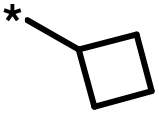


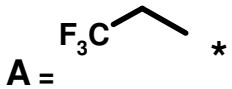
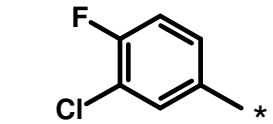
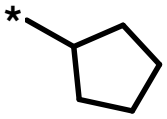
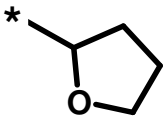
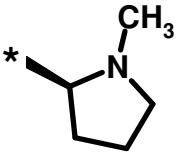
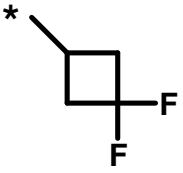
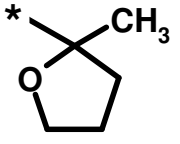
Ej.	A = 	Ej.	A = 	W =
128	$C_{23}H_{19}Cl_2F_8N_5O_3$ MW: 636,325 MS* *m/z* $[M+H]^+$ = 636 R_t = 1,5 (método I)	**131**	$C_{27}H_{20}Cl_3F_6N_5O_3$ MW: 682,834 MS* *m/z* $[M+H]^+$ = 682 R_t = 1,70 (método I)	
101	$C_{23}H_{22}Cl_2F_5N_5O_4$ MW: 598,354 MS* *m/z* $[M+H]^+$ = 598 Rt = 1,40 (método I)	**163**	$C_{27}H_{23}Cl_3F_3N_5O_4$ MW: 644,863 MS* *m/z* $[M+H]^+$ = 644 Rt = 1,61 (método I)	
104	$C_{22}H_{20}Cl_2F_5N_5O_4$ MW: 584,33 MS* *m/z* $[M+H]^+$ = 584 Rt = 1,34 (método I)	**139**	$C_{26}H_{21}Cl_3F_3N_5O_4$ MW: 630,836 MS* *m/z* $[M+H]^+$ = 630 Rt = 1,54 (método I)	
106	$C_{24}H_{24}Cl_2F_5N_5O_3$ MW: 596,382 MS* *m/z* $[M+H]^+$ = 596 Rt = 0,47 (método H)	**132**	$C_{28}H_{25}Cl_3F_3N_5O_3$ MW: 642,89 MS* *m/z* $[M+H]^+$ = 642 Rt = 1,67 (método I)	
111	$C_{23}H_{22}Cl_2F_5N_5O_3$ MW: 582,355 MS* *m/z* $[M+H]^+$ = 582 Rt = 1,42 (método I)	**146**	$C_{27}H_{23}Cl_3F_3N_5O_3$ MW: 628,864 MS* *m/z* $[M+H]^+$ = 528 Rt = 1,63 (método I)	
112	$C_{23}H_{19}Cl_2F_5N_6O_3$ MW: 593,338 MS* *m/z* $[M+H]^+$ = 593 Rt = 1,41 (método I)	**154**	$C_{27}H_{20}Cl_3F_3N_6O_3$ MW: 639,847 MS* *m/z* $[M+H]^+$ = 639 Rt = 0,52 (método H)	

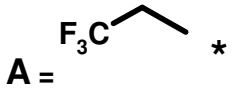
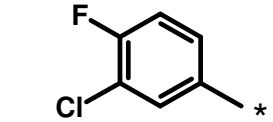
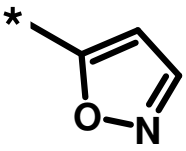
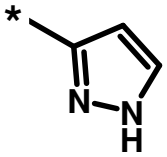
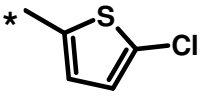
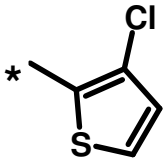
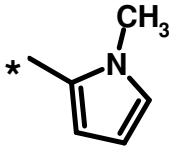
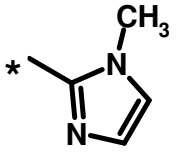
Ej.	A = 	Ej.	A = 	W =
88	$C_{25}H_{24}Cl_2F_5N_5O_3$ MW: 608,393 MS* *m/z* $[M+H]^+$ = 608 Rt = 1,48 (método I)	**144**	$C_{29}H_{25}Cl_3F_3N_5O_3$ MW: 654,902 MS* *m/z* $[M+H]^+$ = 654 Rt = 1,68 (método I)	
87	$C_{23}H_{20}Cl_2F_8N_6O_3$ MW: 651,34 MS* *m/z* $[M+H]^+$ = 651 Rt = 0,46 (método H)	**164**	$C_{27}H_{21}Cl_3F_6N_6O_3$ MW: 697,849 MS* *m/z* $[M+H]^+$ = 697 Rt = 0,54 (método H)	
89	$C_{24}H_{21}Cl_2F_8N_5O_3$ MW: 650,352 MS* *m/z* $[M+H]^+$ = 650 Rt = 0,50 (método H)	**141**	$C_{28}H_{22}Cl_3F_6N_5O_3$ MW: 696,861 MS* *m/z* $[M+H]^+$ = 696 Rt = 0,58 (método H)	
96	$C_{23}H_{19}Cl_2F_8N_5O_4$ MW: 652,324 MS* *m/z* $[M+H]^+$ = 652 Rt = 1,47 (método I)	**161**	$C_{27}H_{20}Cl_3F_6N_5O_4$ MW: 698,833 MS* *m/z* $[M+H]^+$ = 698 Rt = 1,66 (método I)	
98	$C_{24}H_{22}Cl_2F_8N_6O_3$ MW: 665,367 MS* *m/z* $[M+H]^+$ = 665 Rt = 0,48 (método H)	**152**	$C_{28}H_{23}Cl_3F_6N_6O_3$ MW: 711,876 MS* *m/z* $[M+H]^+$ = 711 Rt = 0,56 (método H)	
116	$C_{25}H_{23}Cl_2F_8N_5O_3$ MW: 664,379 MS* *m/z* $[M+H]^+$ = 664 Rt = 0,52 (método H)	**176**	$C_{29}H_{24}Cl_3F_6N_5O_3$ MW: 710,88 MS* *m/z* $[M+H]^+$ = 710 Rt = 1,78 (método I)	

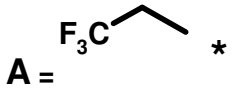
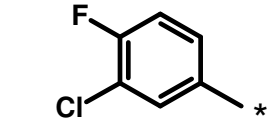
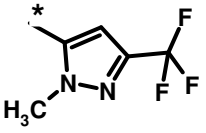
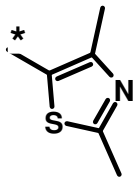
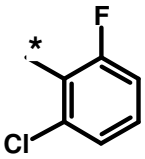
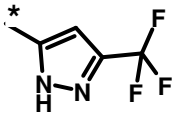
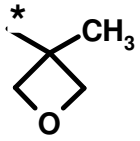
Ej.	A = 	Ej.	A = 	W =
123	$C_{24}H_{21}Cl_2F_8N_5O_4$ MW: 666,351 MS* *m/z* $[M+H]^+$ = 666 Rt = 1,49 (método I)	**149**	$C_{28}H_{22}Cl_3F_6N_5O_4$ MW: 712,86 MS* *m/z* $[M+H]^+$ = 712 Rt = 0,56 (método H)	
126	$C_{25}H_{26}Cl_2F_5N_5O_4$ MW: 626,407 MS* *m/z* $[M+H]^+$ = 626 Rt = 1,41 (método I)	**155**	$C_{29}H_{27}Cl_3F_3N_5O_4$ MW: 672,916 MS* *m/z* $[M+H]^+$ = 672 Rt = 0,53 (método H)	
130	$C_{25}H_{26}Cl_2F_5N_5O_4$ MW: 626,407 MS* *m/z* $[M+H]^+$ = 626 Rt = 1,48 (método I)	**135**	$C_{29}H_{27}Cl_3F_3N_5O_4$ MW: 672,916 MS* *m/z* $[M+H]^+$ = 672 Rt = 1,68 (método I)	
95	$C_{23}H_{20}Cl_2F_7N_5O_3$ MW: 618,335 MS* *m/z* $[M+H]^+$ = 618 Rt = 0,48 (método H)	**162**	$C_{27}H_{21}Cl_3F_3N_5O_3$ MW: 664,844 MS* *m/z* $[M+H]^+$ = 664 Rt = 1,70 (método I)	
108	$C_{24}H_{24}Cl_2F_5N_5O_4$ MW: 612,381 MS* *m/z* $[M+H]^+$ = 612 Rt = 0,44 (método H)	**175**	$C_{28}H_{25}Cl_3F_3N_5O_4$ MW: 658,89 MS* *m/z* $[M+H]^+$ = 658 Rt = 1,60 (método I)	
109	$C_{23}H_{22}Cl_2F_5N_5O_4$ MW: 598,354 MS* *m/z* $[M+H]^+$ = 598 Rt = 1,36 (método I)	**147**	$C_{27}H_{23}Cl_3F_3N_5O_4$ MW: 644,863 MS* *m/z* $[M+H]^+$ = 644 Rt = 0,51 (método H)	

Ej.	A = 	Ej.	A = 	W =
110	$C_{24}H_{24}Cl_2F_5N_5O_3$ MW: 596,382 MS* *m/z* $[M+H]^+$ = 596 Rt = 1,47 (método I)	**151**	$C_{28}H_{25}Cl_3F_3N_5O_3$ MW: 642,89 MS* *m/z* $[M+H]^+$ = 642 Rt = 0,55 (método H)	
115	$C_{22}H_{20}Cl_2F_5N_5O_3$ MW: 568,328 MS* *m/z* $[M+H]^+$ = 568 Rt = 1,37 (método I)	**173**	$C_{26}H_{21}Cl_3F_3N_5O_3$ MW: 614,837 MS* *m/z* $[M+H]^+$ = 614 Rt = 1,58 (método I)	
118	$C_{24}H_{23}Cl_2F_6N_5O_3$ MW: 614,372 MS* *m/z* $[M+H]^+$ = 614 Rt = 0,49 (método H)			
124	$C_{22}H_{18}Cl_2F_7N_5O_3$ MW: 604,308 MS* *m/z* $[M+H]^+$ = 604 Rt = 1,45 (método I)	**159**	$C_{26}H_{19}Cl_3F_5N_5O_3$ MW: 650,817 MS* *m/z* $[M+H]^+$ = 650 Rt = 0,55 (método H)	
86	$C_{26}H_{23}Cl_2F_8N_5O_3$ MW: 676,39 MS* *m/z* $[M+H]^+$ = 676 Rt = 0,53 (método H)	**157**	$C_{30}H_{24}Cl_3F_6N_5O_3$ MW: 722,899 MS* *m/z* $[M+H]^+$ = 722 Rt = 1,78 (método I)	
99	$C_{25}H_{21}Cl_2F_8N_5O_3$ MW: 662,363 MS* *m/z* $[M+H]^+$ = 662 Rt = 0,52 (método H)	**174**	$C_{29}H_{22}Cl_3F_6N_5O_3$ MW: 708,872 MS* *m/z* $[M+H]^+$ = 708 Rt = 1,76 (método I)	

Ej.	A = 	Ej.	A = 	W =
103	$C_{25}H_{24}Cl_2F_5N_5O_3$ MW: 608,393 MS* *m/z* $[M+H]^+$ = 608 Rt = 1,50 (método I)	**133**	$C_{29}H_{25}Cl_3F_3N_5O_3$ MW: 654,902 MS* *m/z* $[M+H]^+$ = 654 Rt = 0,57 (método H)	
93	$C_{24}H_{22}Cl_2F_5N_5O_4$ MW: 610,365 MS* *m/z* $[M+H]^+$ = 610 Rt = 0,43 (método H)	**171**	$C_{28}H_{23}Cl_3F_3N_5O_4$ MW: 656,874 MS* *m/z* $[M+H]^+$ = 656 Rt = 1,60 (método I)	
97	$C_{27}H_{25}Cl_2F_8N_5O_3$ MW: 690,417 MS* *m/z* $[M+H]^+$ = 690 Rt = 0,55 (método H)	**165**	$C_{31}H_{26}Cl_3F_6N_5O_3$ MW: 736,925 MS* *m/z* $[M+H]^+$ = 736 Rt = 1,84 (método I)	
113	$C_{25}H_{21}Cl_2F_5N_6O_3$ MW: 619,378 MS* *m/z* $[M+H]^+$ = 619 Rt = 0,47 (método H)	**145**	$C_{29}H_{22}Cl_3F_3N_6O_3$ MW: 665,885 MS* *m/z* $[M+H]^+$ = 665 Rt = 0,56 (método H)	
100	$C_{24}H_{22}Cl_2F_5N_5O_3$ MW: 594,366 MS* *m/z* $[M+H]^+$ = 594 Rt = 1,45 (método I)	**148**	$C_{28}H_{23}Cl_3F_3N_5O_3$ MW: 640,875 MS* *m/z* $[M+H]^+$ = 640 Rt = 0,55 (método H)	
91	$C_{25}H_{24}Cl_2F_5N_5O_3$ MW: 608,393 MS* *m/z* $[M+H]^+$ = 608 Rt = 1,49 (método I)	**172**	$C_{29}H_{25}Cl_3F_3N_5O_3$ MW: 654,902 MS* *m/z* $[M+H]^+$ = 654 Rt = 0,56 (método H)	

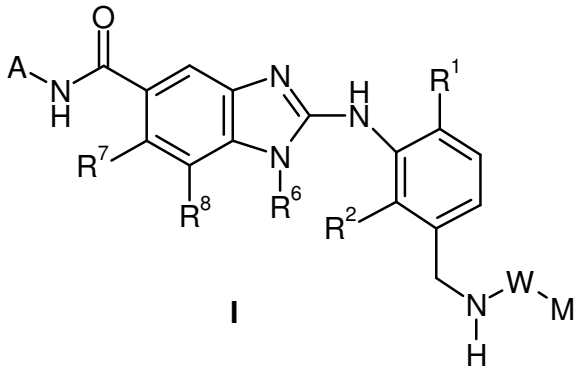
Ej.	A = 	Ej.	A = 	W =
120	$C_{26}H_{26}Cl_2F_5N_5O_3$ MW: 622,419 MS* *m/z* $[M+H]^+$ = 622 Rt = 1,54 (método I)	**160**	$C_{30}H_{27}Cl_3F_3N_5O_3$ MW: 668,928 MS* *m/z* $[M+H]^+$ = 668 Rt = 1,74 (método I)	
90	$C_{25}H_{24}Cl_2F_5N_5O_4$ MW: 624,392 MS* *m/z* $[M+H]^+$ = 624 Rt = 0,46 (método H)	**137**	$C_{29}H_{25}Cl_3F_3N_5O_4$ MW: 670,9 MS* *m/z* $[M+H]^+$ = 670 Rt = 0,54 (método H)	
94	$C_{26}H_{27}Cl_2F_5N_6O_3$ MW: 637,434 MS* *m/z* $[M+H]^+$ = 637 Rt = 0,49 (método H)	**169**	$C_{30}H_{28}Cl_3F_3N_6O_3$ MW: 683,943 MS* *m/z* $[M+H]^+$ = 683 Rt = 0,57 (método H)	
102	$C_{25}H_{22}Cl_2F_7N_5O_3$ MW: 644,373 MS* *m/z* $[M+H]^+$ = 644 Rt = 0,49 (método H)	**167**	$C_{29}H_{23}Cl_3F_5N_5O_3$ MW: 690,882 MS* *m/z* $[M+H]^+$ = 690 Rt = 0,57 (método H)	
119	$C_{24}H_{20}Cl_2F_7N_5O_3$ MW: 630,346 MS* *m/z* $[M+H]^+$ = 630 Rt = 0,48 (método H)	**153**	$C_{28}H_{21}Cl_3F_5N_5O_3$ MW: 676,855 MS* *m/z* $[M+H]^+$ = 676 Rt = 1,69 (método I)	
122	$C_{26}H_{26}Cl_2F_5N_5O_4$ MW: 638,418 MS* *m/z* $[M+H]^+$ = 638 Rt = 1,48 (método I)	**170**	$C_{30}H_{27}Cl_3F_3N_5O_4$ MW: 684,927 MS* *m/z* $[M+H]^+$ = 684 Rt = 0,56 (método H)	

Ej.	A = 	Ej.	A = 	W =
107	$C_{24}H_{19}Cl_2F_5N_6O_4$ MW: 621,348 MS* *m/z* $[M+H]^+$ = 621 Rt = 1,44 (método I)	**166**	$C_{28}H_{20}Cl_3F_3N_6O_4$ MW: 667,857 MS* *m/z* $[M+H]^+$ = 667 Rt = 0,54 (método H)	
127	$C_{24}H_{20}Cl_2F_5N_7O_3$ MW: 620,364 MS* *m/z* $[M+H]^+$ = 620 Rt = 0,44 (método H)	**134**	$C_{28}H_{21}Cl_3F_3N_7O_3$ MW: 666,873 MS* *m/z* $[M+H]^+$ = 666 Rt = 0,54 (método H)	
92	$C_{25}H_{19}Cl_3F_5N_5O_3S$ MW: 670,872 MS* *m/z* $[M+H]^+$ = 670 Rt = 0,54 (método H)	**140**	$C_{29}H_{20}Cl_4F_3N_5O_3S$ MW: 717,381 MS* *m/z* $[M+H]^+$ = 717 Rt = 1,82 (método I)	
117	$C_{25}H_{19}Cl_3F_5N_5O_3S$ MW: 670,872 MS* *m/z* $[M+H]^+$ = 670 Rt = 0,53 (método H)	**168**	$C_{29}H_{20}Cl_4F_3N_5O_3S$ MW: 717,381 MS* *m/z* $[M+H]^+$ = 717 Rt = 1,76 (método I)	
114	$C_{26}H_{23}Cl_2F_5N_6O_3$ MW: 633,403 MS* *m/z* $[M+H]^+$ = 633 Rt = 1,53 (método I)	**142**	$C_{30}H_{24}Cl_3F_3N_6O_3$ MW: 679,912 MS* *m/z* $[M+H]^+$ = 679 Rt = 0,54 (método H)	
121	$C_{25}H_{22}Cl_2F_5N_7O_3$ MW: 634,391 MS* *m/z* $[M+H]^+$ = 634 Rt = 1,35 (método I)	**156**	$C_{29}H_{23}Cl_3F_3N_7O_3$ MW: 680,9 MS* *m/z* $[M+H]^+$ = 680 Rt = 0,55 (método H)	

Ej.	A = 	Ej.	A = 	W =
125	$C_{26}H_{21}Cl_2F_8N_7O_3$ MW: 702,388 MS* *m/z* $[M+H]^+$ = 702 Rt = 0,54 (método H)	**143**	$C_{30}H_{22}Cl_3F_6N_7O_3$ MW: 748,897 MS* *m/z* $[M+H]^+$ = 748 Rt = 1,81 (método I)	
129	$C_{26}H_{23}Cl_2F_5N_6O_3S$ MW: 665,469 MS* *m/z* $[M+H]^+$ = 665 Rt = 0,47 (método H)	**138**	$C_{30}H_{24}Cl_3F_3N_6O_3S$ MW: 711,978 MS* *m/z* $[M+H]^+$ = 711 Rt = 1,64 (método I)	
105	$C_{27}H_{20}Cl_3F_6N_5O_3$ MW: 682,834 MS* *m/z* $[M+H]^+$ = 682 Rt = 0,47 (método H)	**158**	$C_{31}H_{21}Cl_4F_4N_5O_3$ MW: 729,343 MS* *m/z* $[M+H]^+$ = 729 Rt = 1,74 (método I)	
		136	$C_{29}H_{20}Cl_3F_6N_7O_3$ MW: 734,87 MS* *m/z* $[M+H]^+$ = 734 Rt = 1,74 (método I)	
		150	$C_{29}H_{25}Cl_3F_3N_5O_4$ MW: 670,9 MS* *m/z* $[M+H]^+$ = 670 Rt = 1,60 (método I)	

REIVINDICACIONES

1. Un compuesto de la fórmula I



I

en la que

R^1 y **R^2** representan independientemente halo, -alquilo C_{1-3}, y este último grupo alquilo está opcionalmente sustituido con uno o más átomos de flúor;

W representa -C(O)-, -C(O)O-, y estos grupos están unidos al nitrógeno del resto –NH- por medio del átomo de carbono;

M representa

-alquilo C_{1-6}, -cicloalquilo C_{3-7}, y ambos grupos están opcionalmente sustituidos con uno o más grupos seleccionados de -F, -OH, -CN, $-NH_2$, -NH(alquilo C_{1-2}), -N(alquil $C_{1-2})_2$, -O-alquilo C_{1-3}, -alquilo C_{1-5}, -cicloalquilo C_{3-4}, en cuyos tres últimos grupos los grupos alquilo o cicloalquilo están opcionalmente sustituidos con uno o más átomos de flúor;

o

oxetanilo-, tetrahidrofuranilo-, tetrahidropiranilo-, azetidinilo-, pirrolidinilo-, piperidinilo-, y todos estos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de fluoro, -CN, -alquilo C_{1-3} , y este último grupo alquilo está opcionalmente sustituido con uno o más átomos de flúor;

o

fenilo-, piridilo-, tienilo-, pirrolilo-, pirazolilo-, imidazolilo-, tiazolilo-, oxazolilo-, o isoxazolilo-, y todos estos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de halo, -CN o -alquilo C_{1-3}, y este último grupo alquilo está opcionalmente sustituido además con uno o más átomos de flúor;

R^8 representa –H, halógeno, -alquilo C_{1-3}, y este último grupo alquilo está opcionalmente sustituido con uno o más átomos de flúor;

R^6 representa –H, -alquilo C_{1-5}, -cicloalquil C_{3-5}-alquilo C_{0-2}, en cuyos tres últimos grupos los fragmentos alquilo o cicloalquilo están opcionalmente sustituidos con uno o más átomos de flúor;

R^7 representa halo, alquil C_{1-5}-O-, cicloalquil C_{3-7}-alquil C_{0-2}-O-, (heterocicloalquil de 4-7-miembros)-alquil C_{0-2}-O-, en cuyos tres últimos grupos los fragmentos alquilo, cicloalquilo o heterocicloalquilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F y -O-alquilo C_{1-3} y este último grupo alquilo está opcionalmente sustituido además con uno o más átomos de flúor;

A representa alquilo C_{1-8}-, fenilo-, indanilo-, naftilo-, 1,2,3,4-tetrahidronaftilo-, piridilo-, tienilo-, benzotienilo-, pirrolilo-, indolil-pirazolilo-, indazolilo-, tiazolilo-, benzotiazolilo-, oxazolilo-, benzoxazolilo-, isoxazolilo-, bencisoxazolilo-, fenil-alquilo C_{1-3}-, tienil-alquilo C_{1-3}-, piridil-alquilo C_{1-3}-, cicloalquil C_{3-7}-alquilo C_{0-3}-, oxetanil-alquilo C_{0-3}-, tetrahidrofuranil-alquilo C_{0-3}, tetrahidropiranil-alquilo C_{0-3}, en cuyos grupos los fragmentos alquilo-, cicloalquilo- y heterocicloalquilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de **R^{9a}** y los fragmentos arilo y heteroarilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de **R^{9b}**;

cada R^{9a} representa independientemente -F, -Cl, -alquilo C_{1-3} que está opcionalmente sustituido con uno o más sustituyentes seleccionados de -F, -O-alquilo C_{1-3} ;

cada R^{9b} representa independientemente -halo, -CN; -alquilo C_{1-3} que está opcionalmente sustituido con uno o más átomos de flúor;

o una sal de los mismos.

2. Un compuesto según la reivindicación 1, en el que:

R^8 representa –H o fluoro.

3. Un compuesto según la reivindicación 1 o 2, en el que:

R^6 representa -H, $-CH_3$, ciclopropilo.

4. Un compuesto según una cualquiera de las reivindicaciones precedentes, en el que

R^1 y **R^2** representan independientemente cloro, fluoro, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$.

5. Un compuesto según una cualquiera de las reivindicaciones precedentes, en el que

R^7 representa fluoro, $-OCHF_2$, $-OCF_3$, $-OCH_2CH_2F$, $-OCH_2CHF_2$, $-OCH_2CF_3$, -O-tetrahidrofuran-3-ilo, $-O-CH_2$-ciclopropilo.

6. Un compuesto según una cualquiera de las reivindicaciones precedentes, en el que

A representa alquilo C_{1-4} -, cicloalquil C_{3-7}-alquilo C_{0-2}-, tetrahidrofuranil-metilo-, fenil-alquilo C_{1-2} -, piridil-metilo-, fenilo-, indanilo-, piridilo-, tienilo-, tiazolilo-, benzotiazolilo-, en cuyos grupos los fragmentos alquilo-, cicloalquilo- y heterocicloalquilo- están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, y los fragmentos arilo y heteroarilo están opcionalmente sustituidos con -F, -Cl, -Br, -CN, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$.

7. Un compuesto según una cualquiera de las reivindicaciones precedentes, en el que

M representa

-alquilo C_{1-4}, -cicloalquilo C_{3-5}, y ambos grupos están opcionalmente sustituidos con uno o más grupos seleccionados de -F, -OH, -CN, $-NH_2$, $-OCH_3$, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, ciclopropilo;

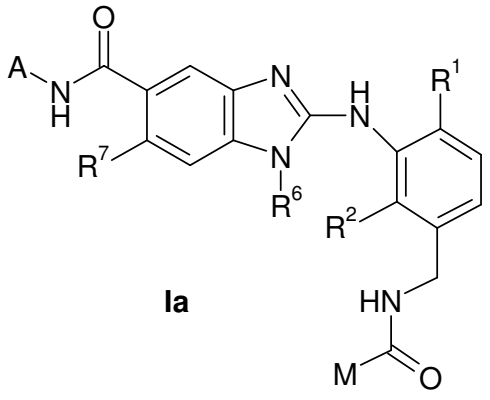
o

oxetanilo-, tetrahidrofuranilo-, azetidinilo- o pirrolidinilo-, y todos estos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$;

o

fenilo-, indanilo-, tienilo-, pirrolilo-, pirazolilo-, imidazolilo-, tiazolilo-, o isoxazolilo-, y todos estos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, -Cl, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$.

8. Un compuesto según una cualquiera de las reivindicaciones precedentes, esto es un compuesto de la fórmula **Ia**



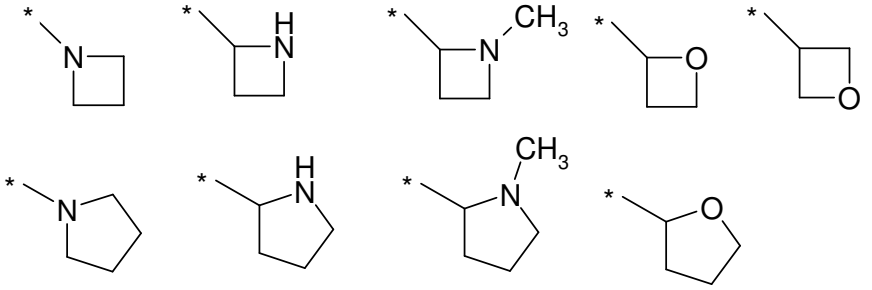
Ia

en la que

M representa

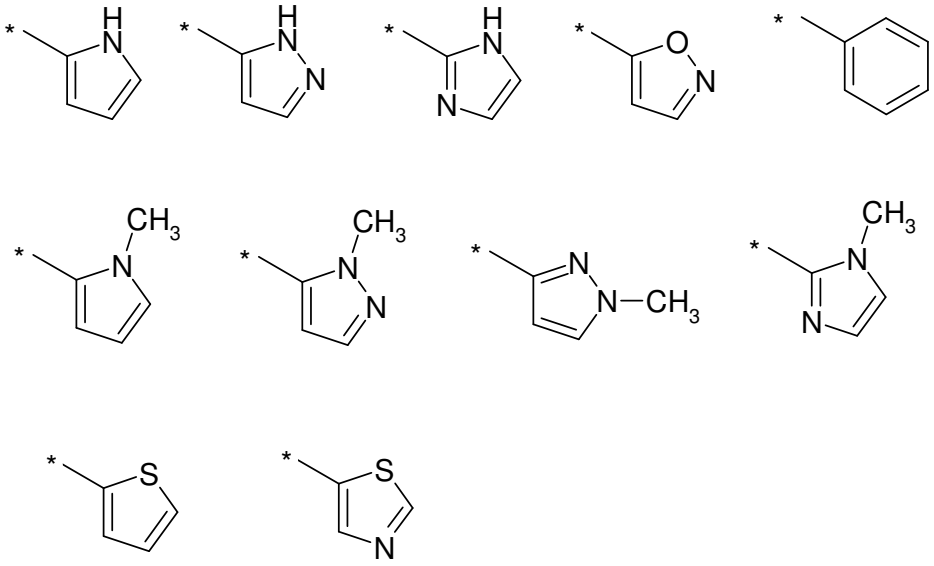
metilo, etilo, propilo, *i*-propilo, *n*-butilo, *s*-butilo, *t*-butilo, ciclopropilo, -CH_2-ciclopropilo, ciclobutilo, ciclopentilo, y todos estos grupos están opcionalmente sustituidos con uno o más grupos seleccionados de -F, -OH, -CN, -NH_2, -OCH_3, -CH_3, -CF_3;

o se selecciona de los siguientes grupos



y estos nueve últimos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, -CH_3, -CF_3;

o se selecciona de los siguientes grupos



y estos once últimos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, -Cl, -CH_3, -CF_3;

y

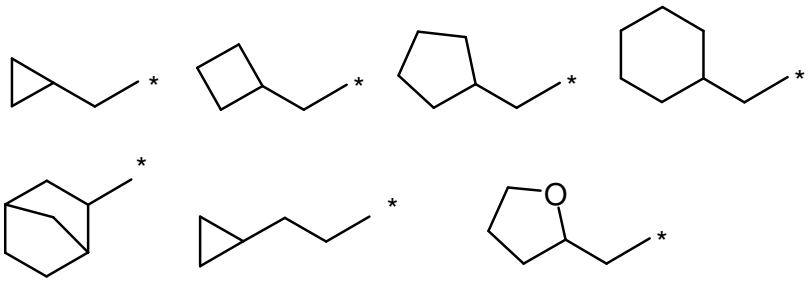
A, R^1, R^2, R^6, R^7 tienen el mismo significado que se ha definido en cualquiera de las reivindicaciones precedentes.

9. Un compuesto de acuerdo con la reivindicación 8, en el que:

A representa metilo, etilo, propilo, *i*-propilo, *n*-butilo, *s*-butilo, *t*-butilo, y estos siete últimos grupos están opcionalmente sustituidos con uno o más átomos de flúor,

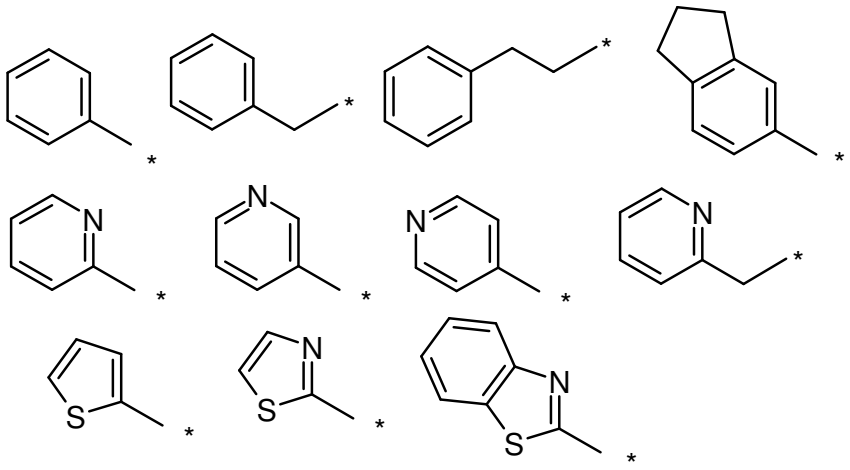
o ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, y estos cuatro últimos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, $-CH_3$, $-CHF_2$, $-CF_3$;

o se selecciona de los siguientes grupos:



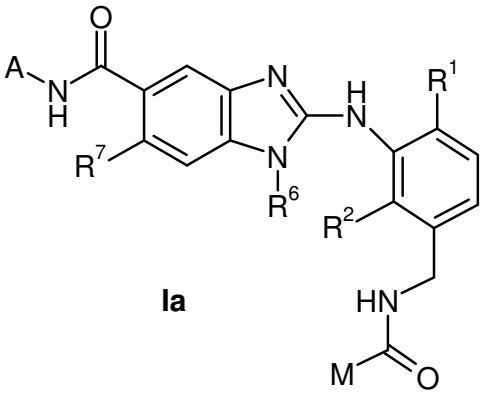
y estos siete últimos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, $-CH_3$, $-CHF_2$, $-CF_3$;

o se selecciona de los siguientes grupos:

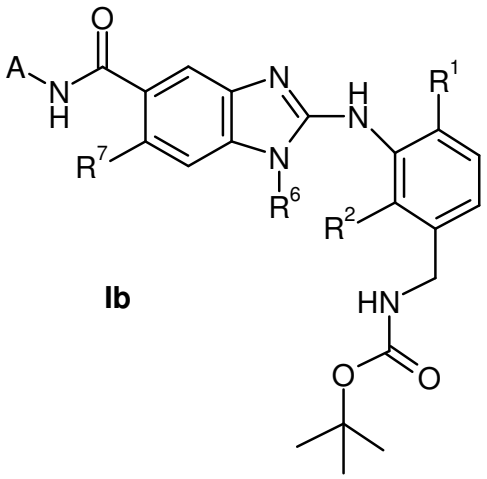


en cuyos once últimos grupos los fragmentos arilo y heteroarilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, -Cl, -Br, -CN, $-CH_3$, $-CF_3$.

10. Un compuesto según una cualquiera de las reivindicaciones precedentes, esto es un compuesto de la fórmula **Ia** o **Ib**



Ia



Ib

en la que

R^1 y R^2 representan independientemente –cloro, fluoro, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$;

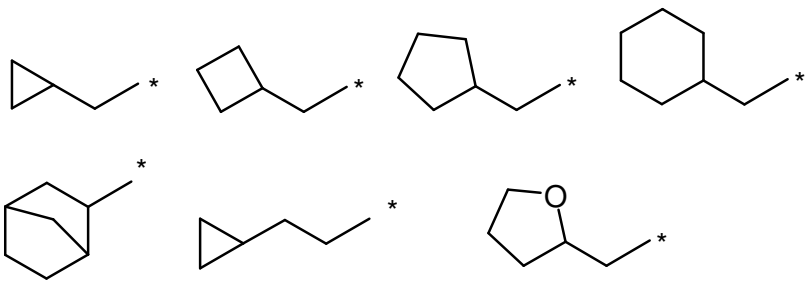
R^6 representa -H, $-CH_3$, ciclopropilo;

R^7 representa fluoro, $-OCHF_2$, $-OCF_3$, $-OCH_2CH_2F$, $-OCH_2CHF_2$, $-OCH_2CF_3$, tetrahidrofuran-3-il-O-, -O-CH_2-ciclopropilo;

A representa metilo, etilo, propilo, *i*-propilo, *n*-butilo, *s*-butilo, *t*-butilo, y estos siete últimos grupos están opcionalmente sustituidos con uno o más átomos de flúor,

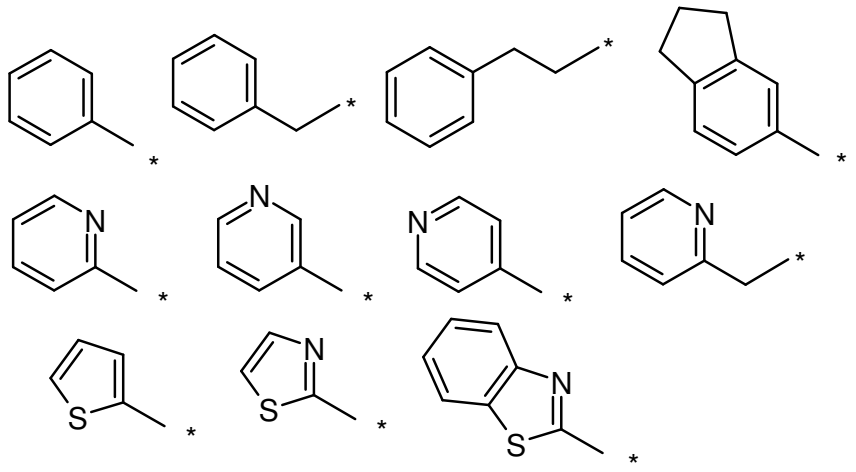
o ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, y estos cuatro últimos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, $-CH_3$, $-CHF_2$, $-CF_3$;

o se selecciona de los siguientes grupos:



y estos siete últimos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, $-CH_3$, $-CHF_2$, $-CF_3$;

o se selecciona de los siguientes grupos:

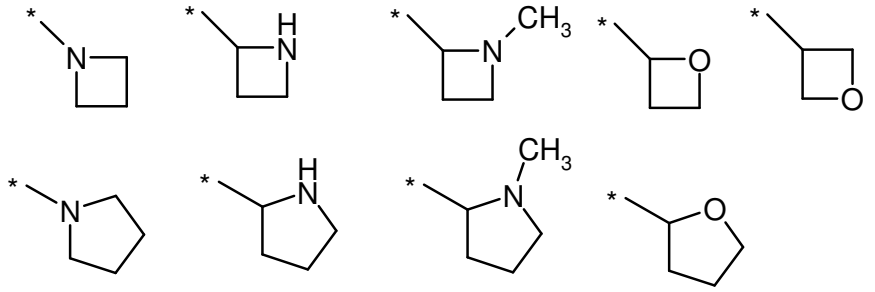


en cuyos once últimos grupos los fragmentos arilo y heteroarilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, -Cl, -Br, -CN, $-CH_3$, $-CF_3$;

M representa

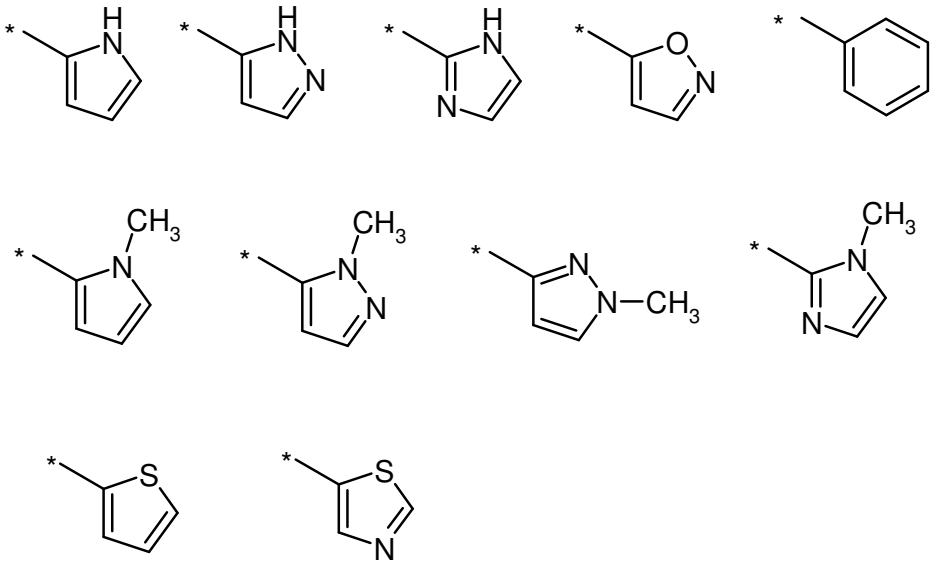
metilo, etilo, propilo, *i*-propilo, *n*-butilo, *s*-butilo, *t*-butilo, ciclopropilo, $-CH_2$-ciclopropilo, ciclobutilo, ciclopentilo, y todos estos grupos están opcionalmente sustituidos con uno o más grupos seleccionados de -F, -OH, -CN, $-NH_2$, $-OCH_3$, $-CH_3$, $-CF_3$;

o se selecciona de los siguientes grupos



y estos nueve últimos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, $-CH_3$, $-CF_3$;

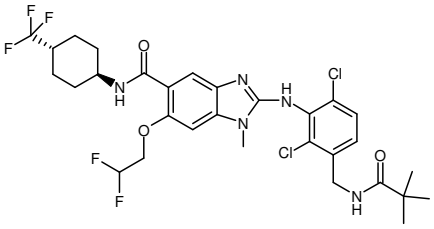
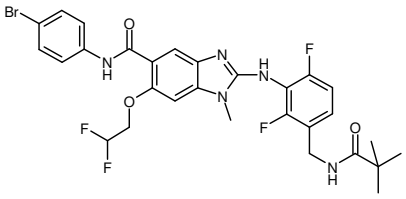
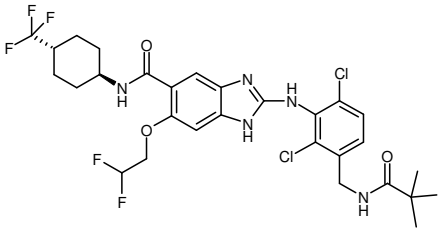
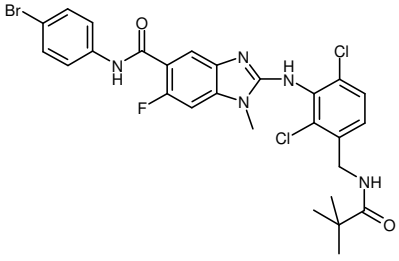
o se selecciona de los siguientes grupos

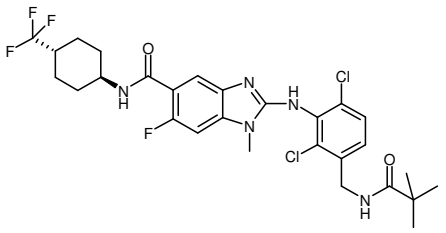
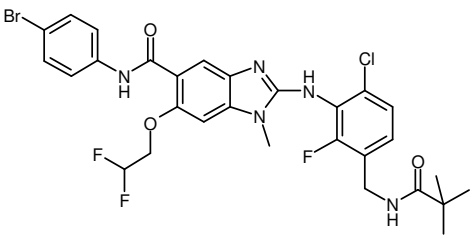
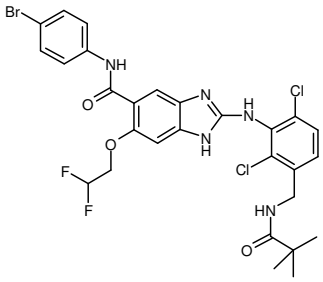
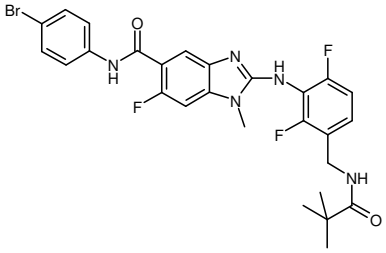
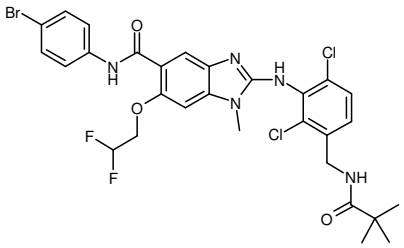
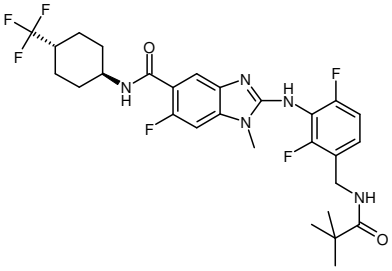
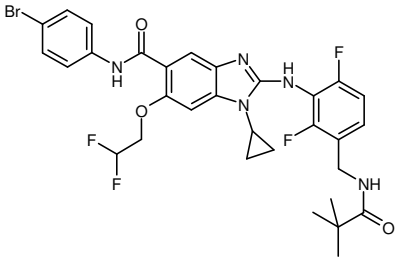
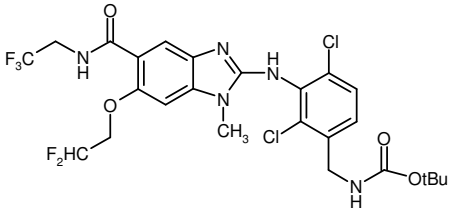
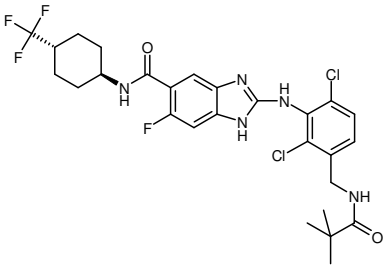
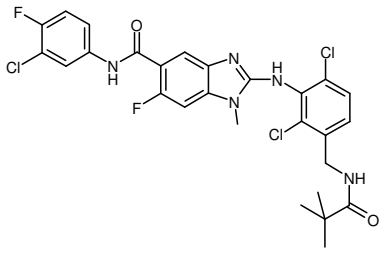


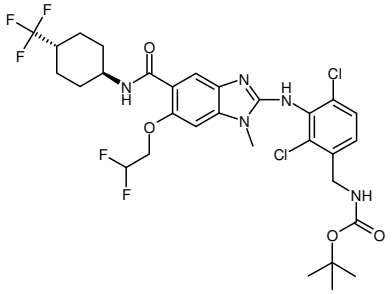
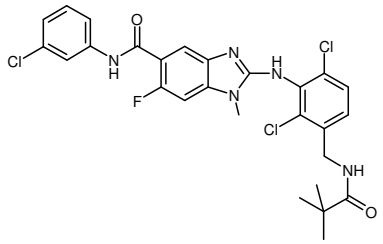
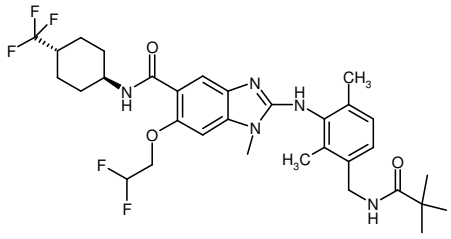
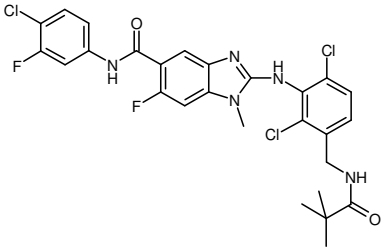
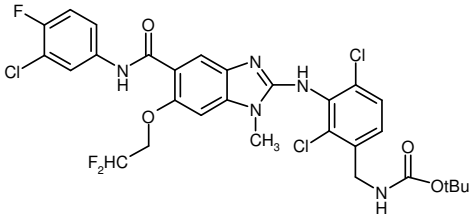
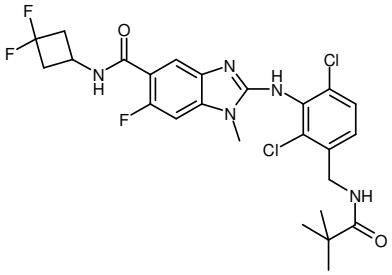
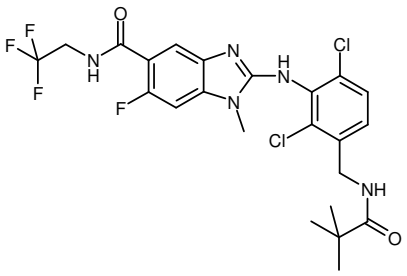
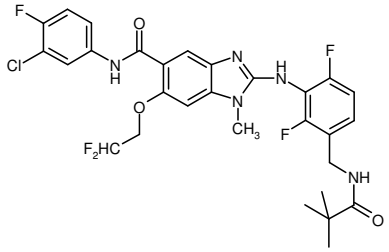
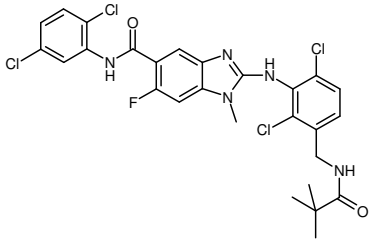
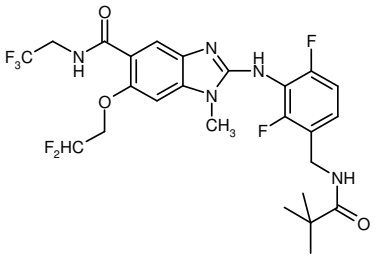
y estos once últimos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, -Cl, $-CH_3$, $-CF_3$;

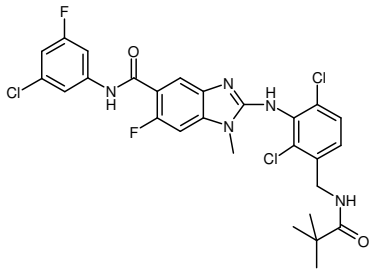
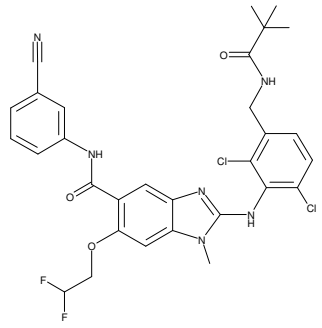
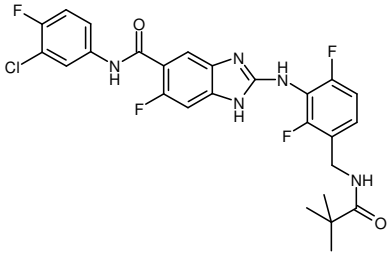
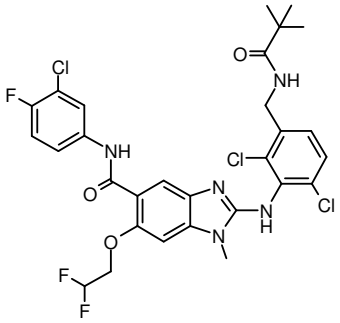
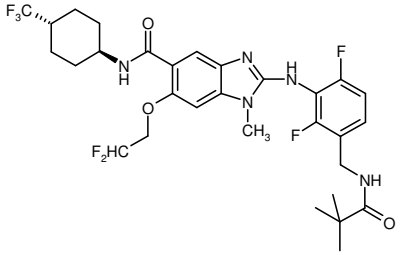
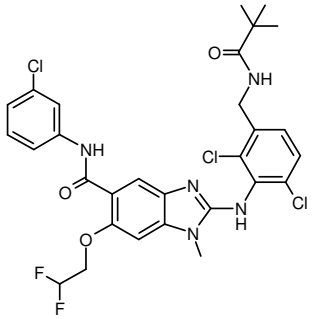
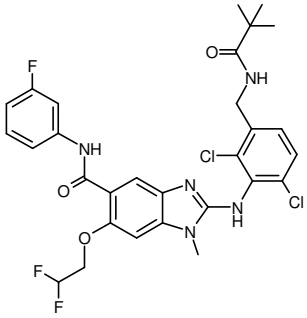
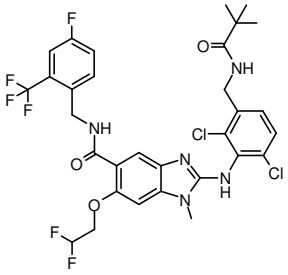
o una sal de los mismos.

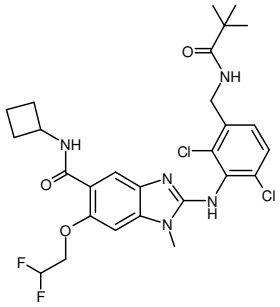
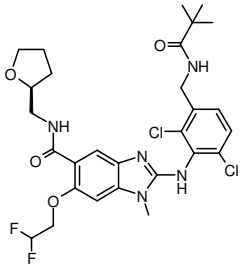
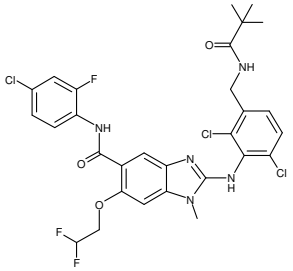
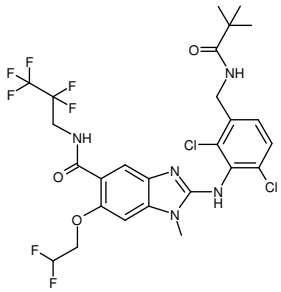
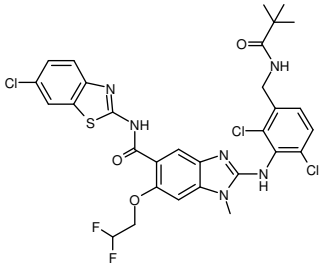
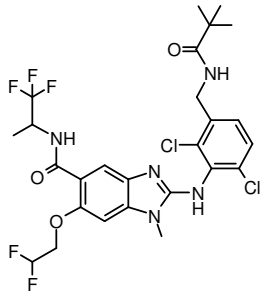
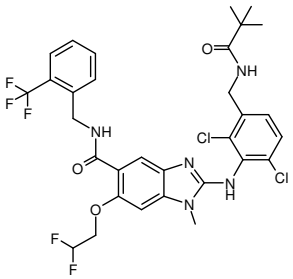
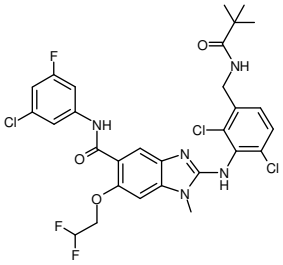
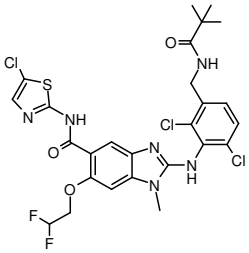
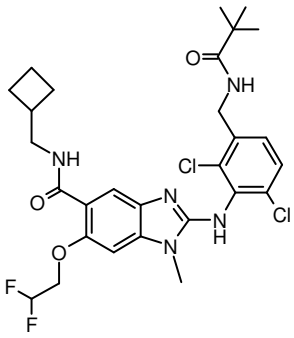
11. Un compuesto según una cualquiera de las reivindicaciones precedentes seleccionado del grupo que comprende

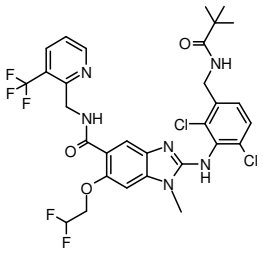
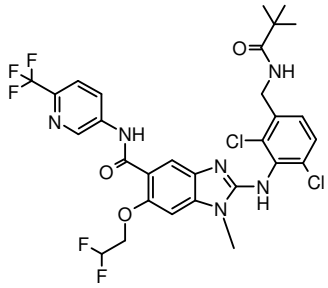
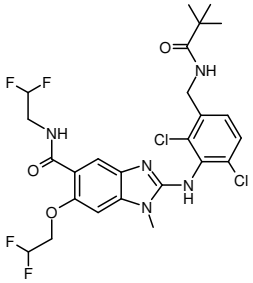
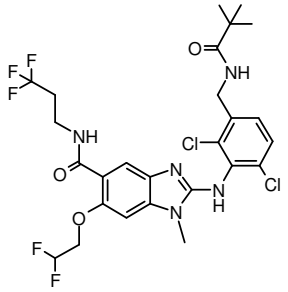
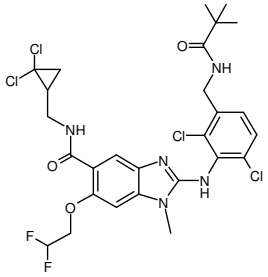
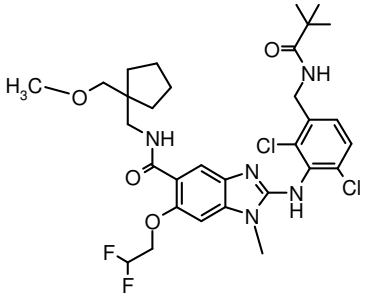
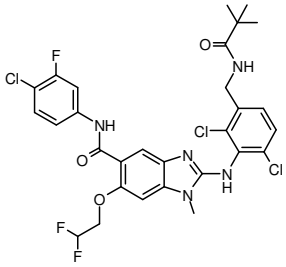
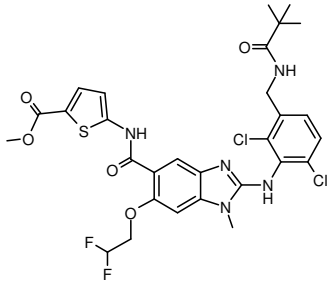
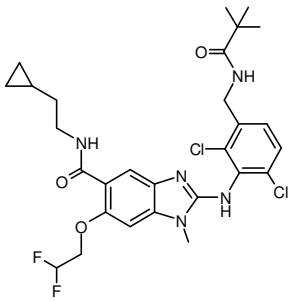
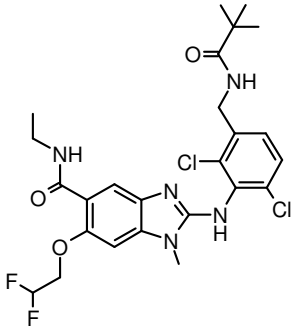
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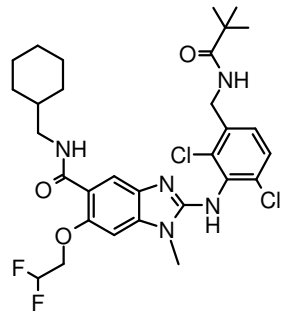
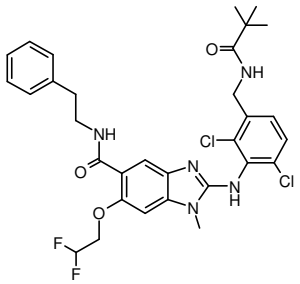
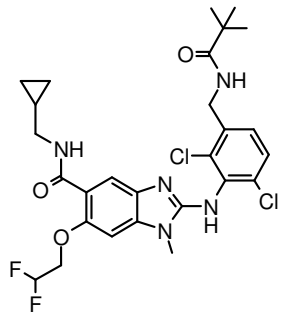
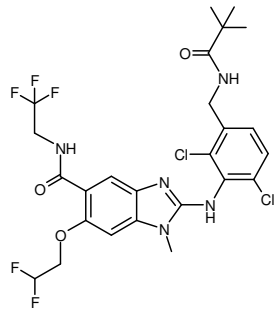
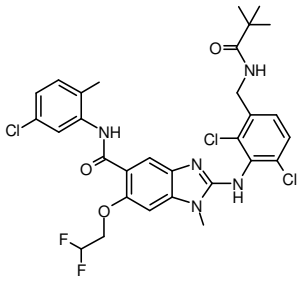
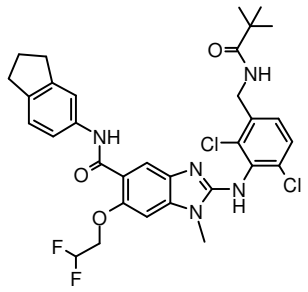
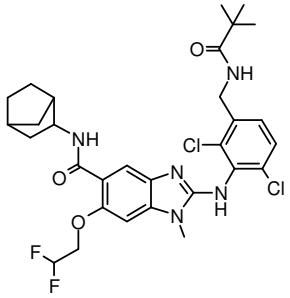
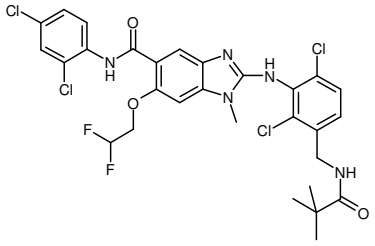
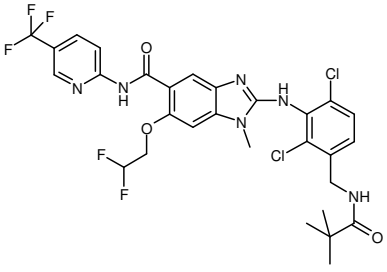
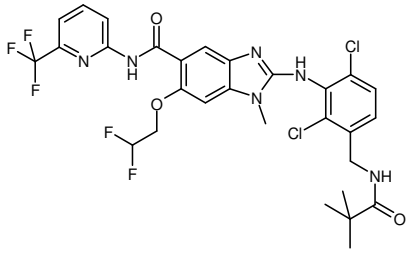
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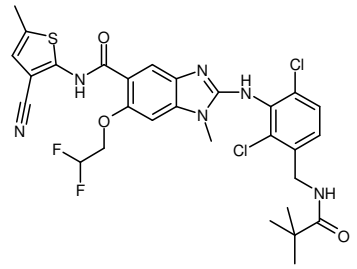
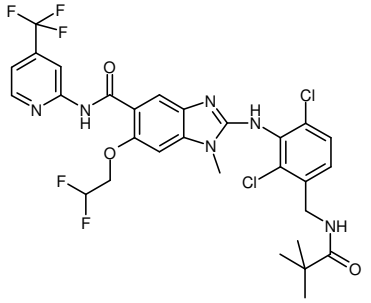
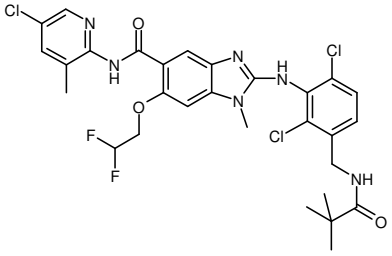
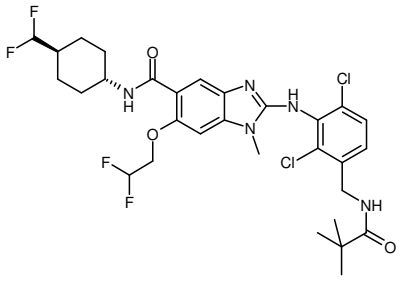
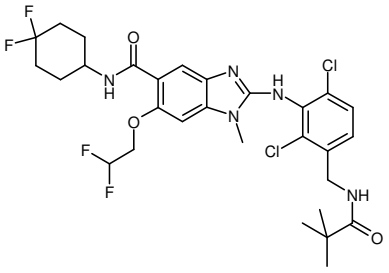
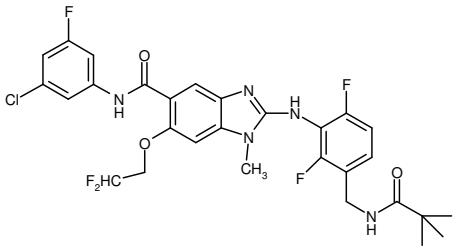
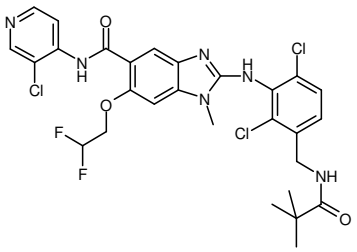
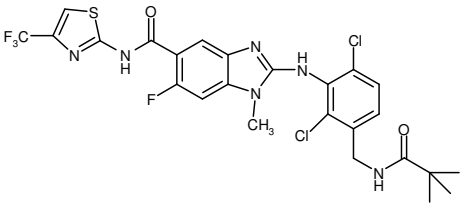
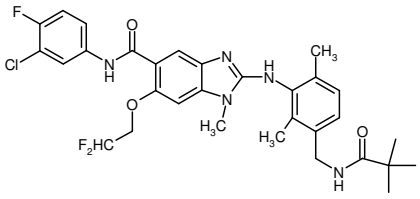
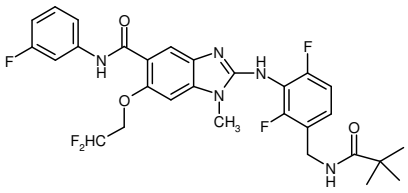
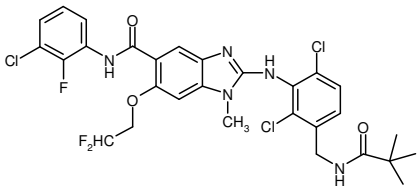
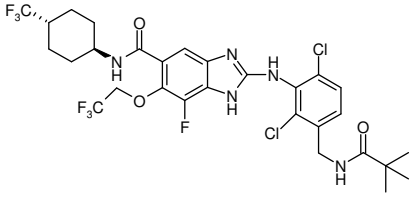
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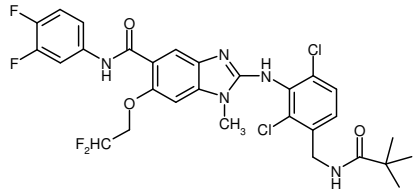
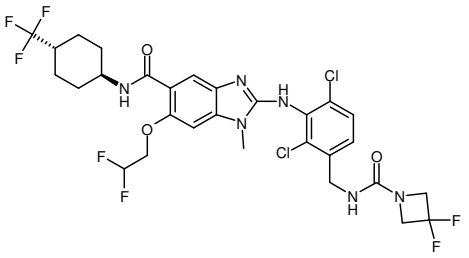
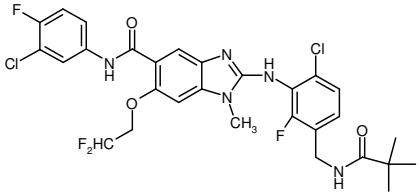
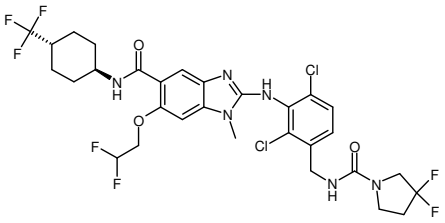
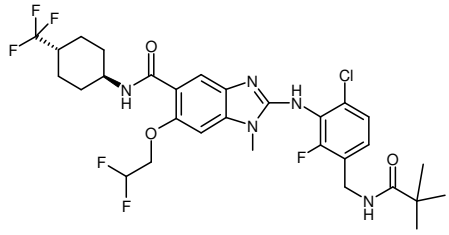
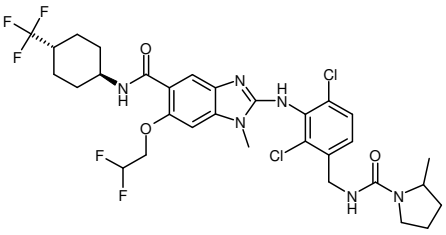
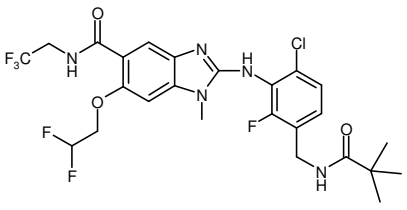
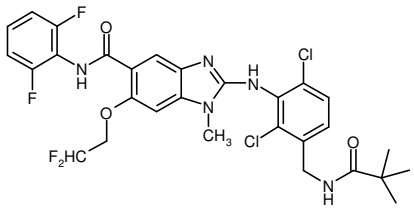
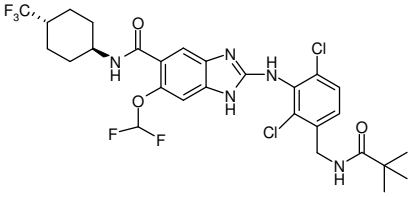
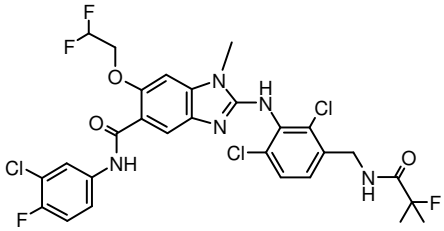
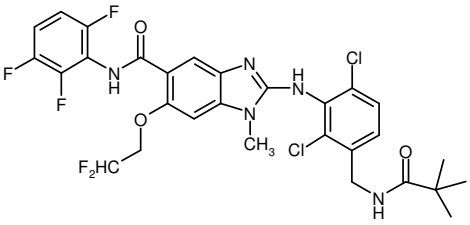
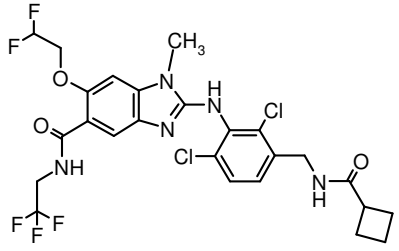
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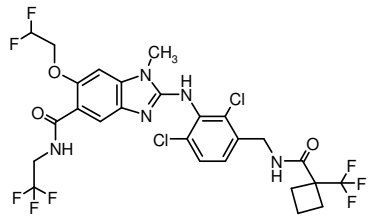
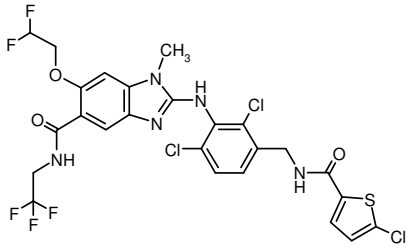
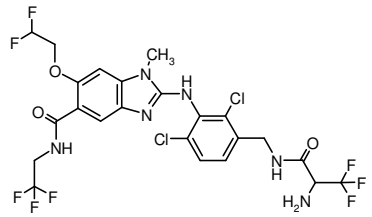
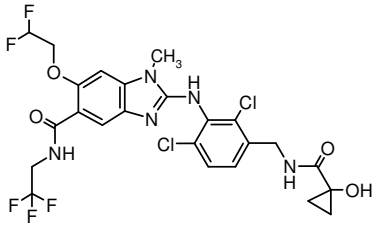
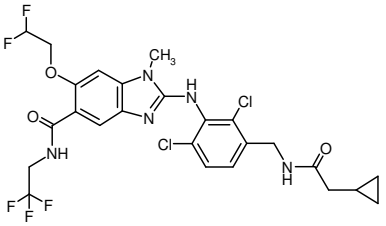
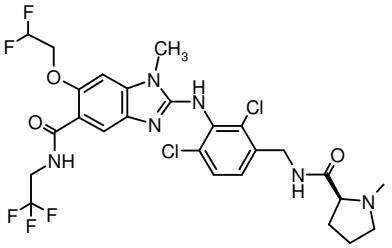
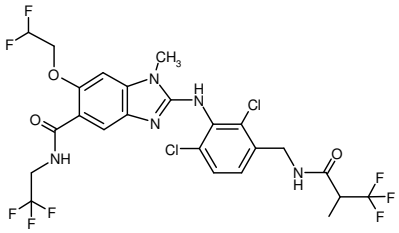
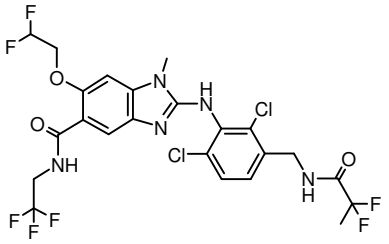
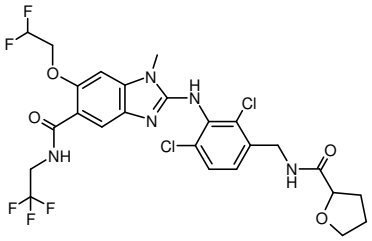
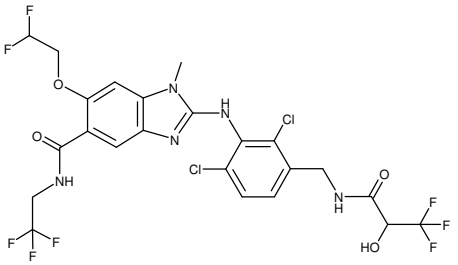
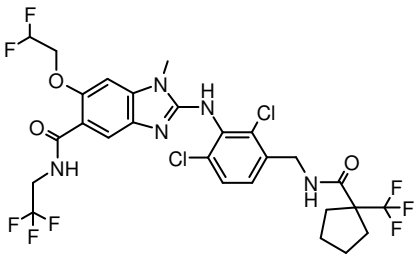
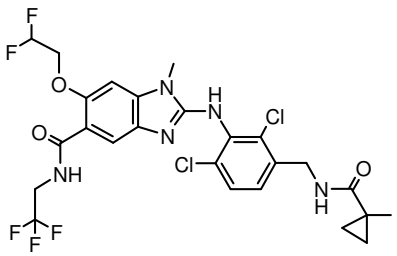
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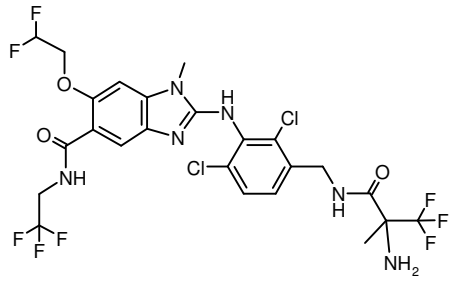
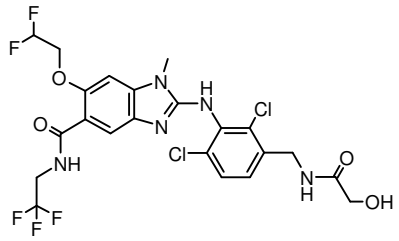
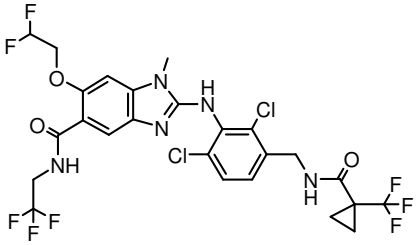
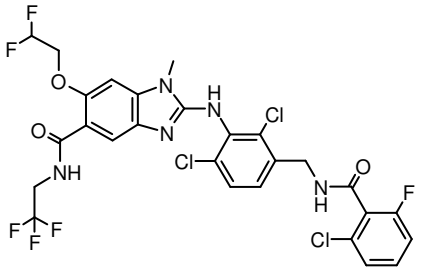
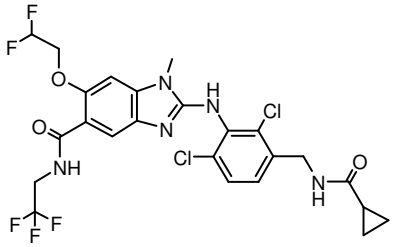
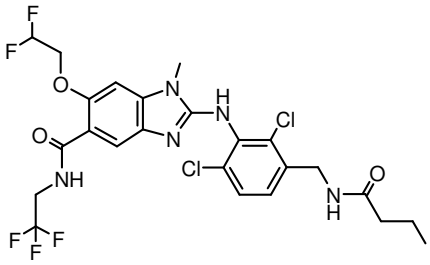
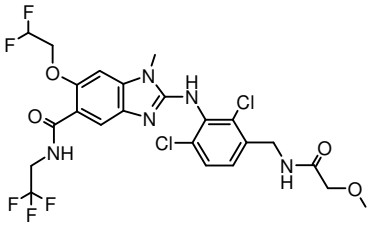
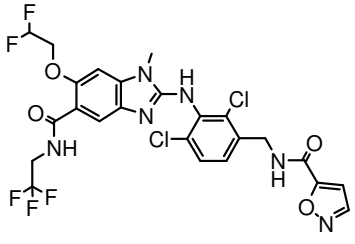
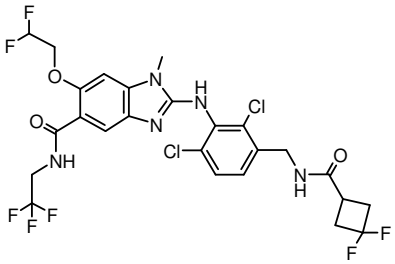
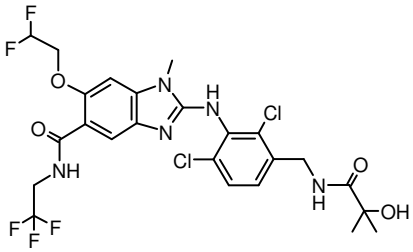
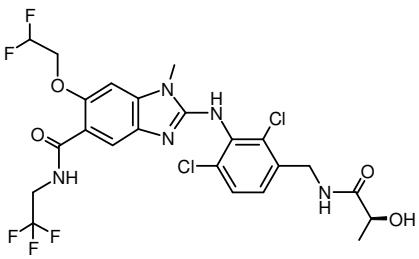
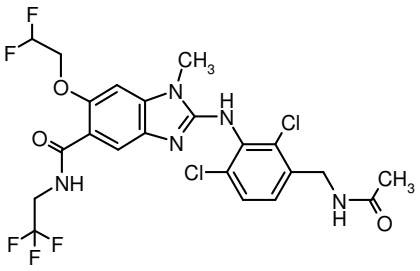
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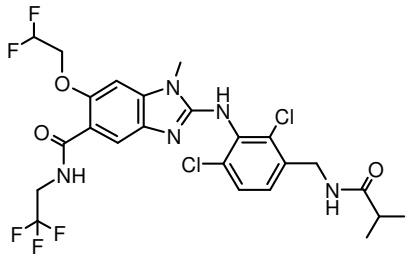
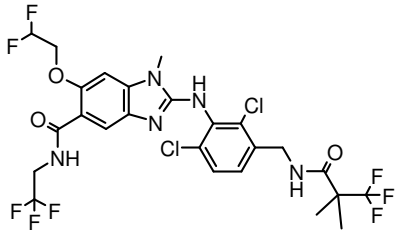
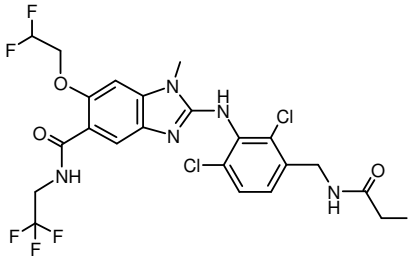
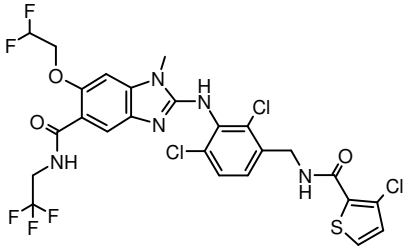
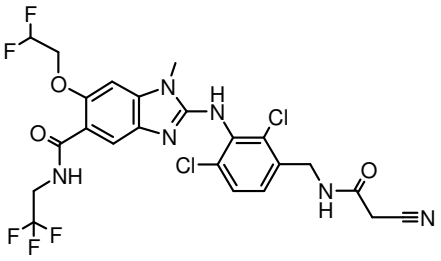
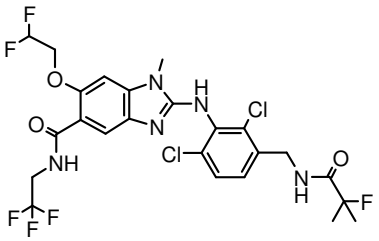
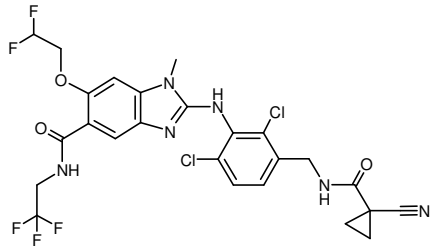
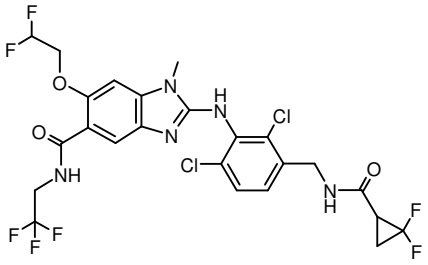
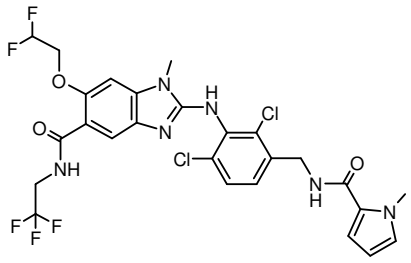
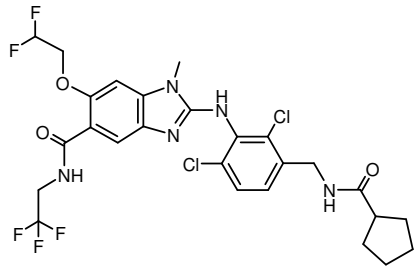
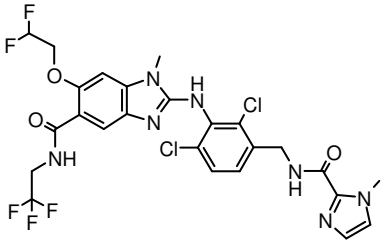
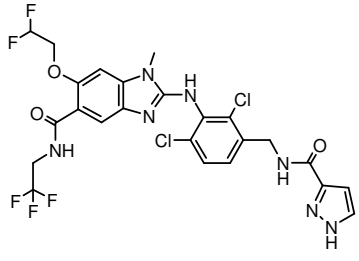
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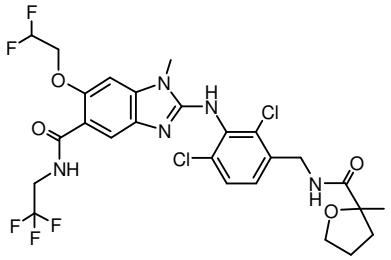
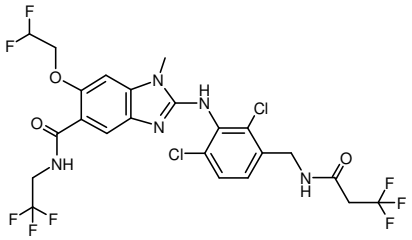
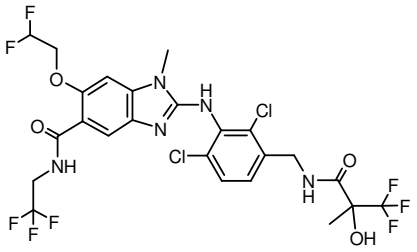
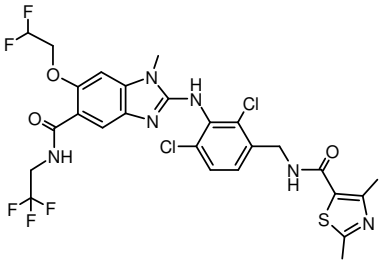
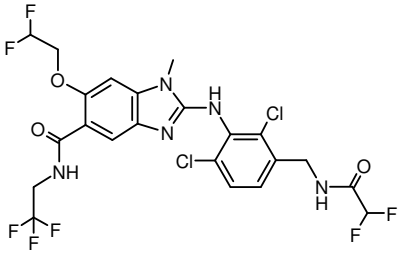
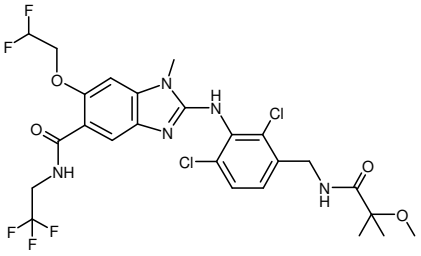
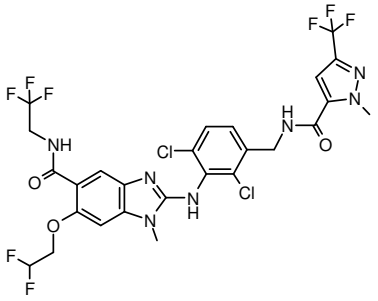
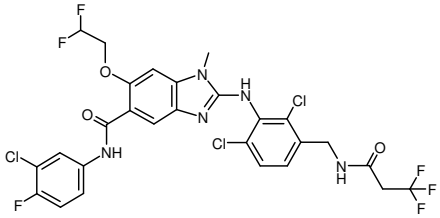
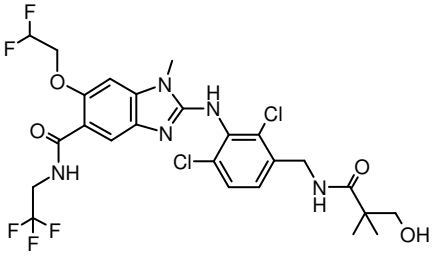
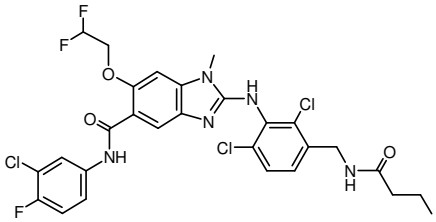
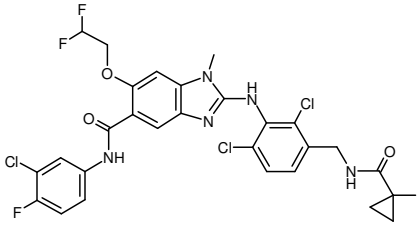
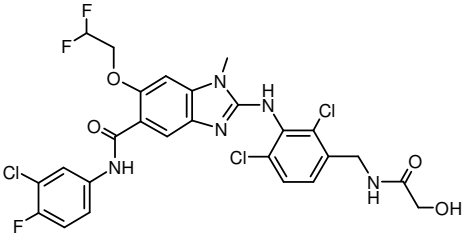
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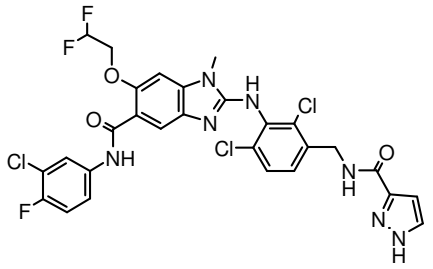
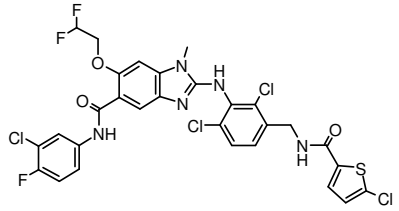
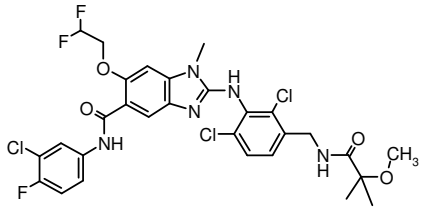
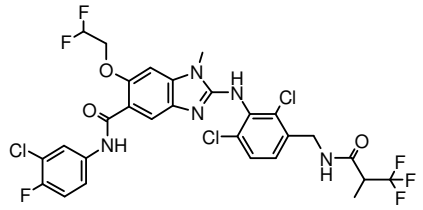
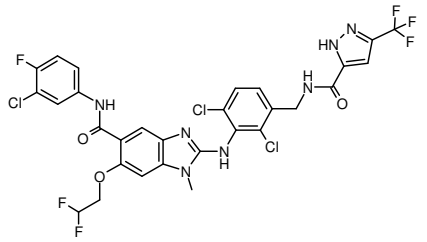
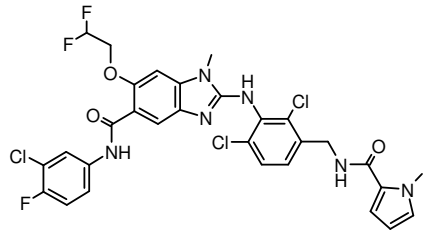
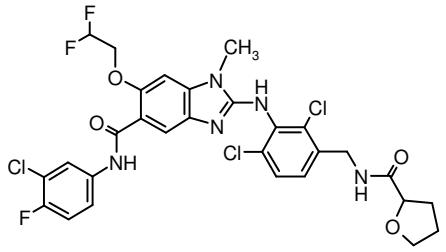
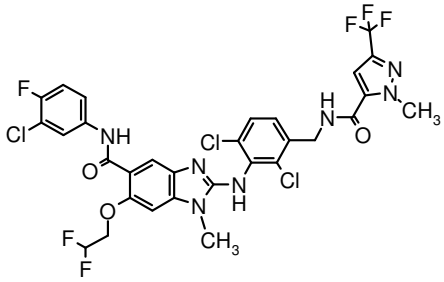
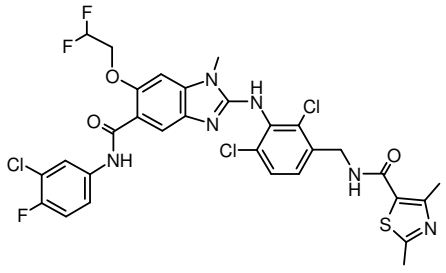
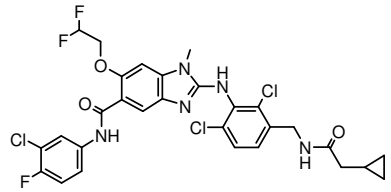
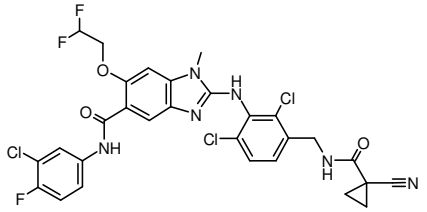
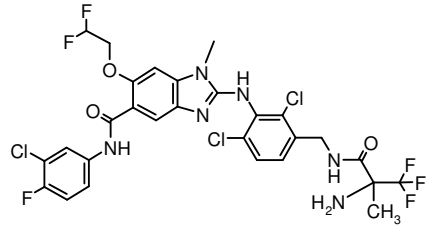
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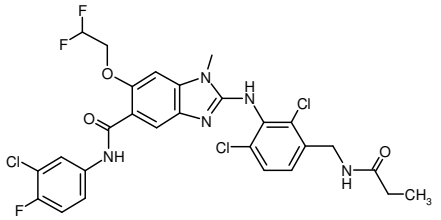
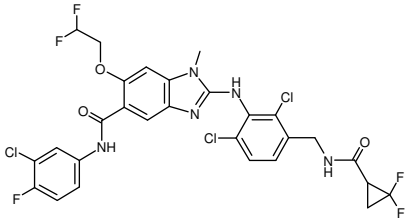
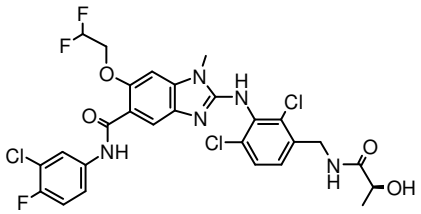
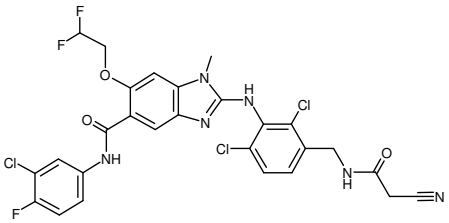
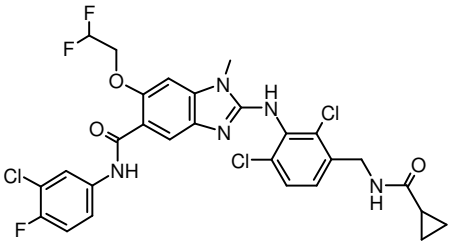
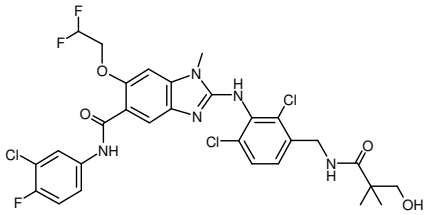
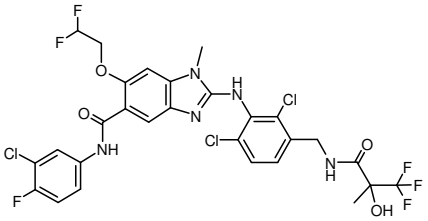
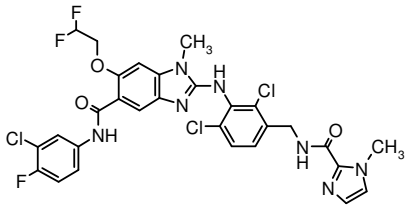
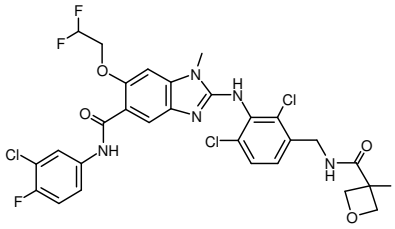
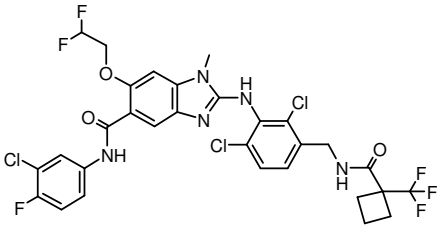
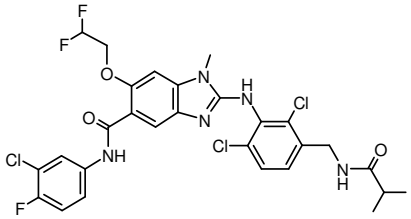
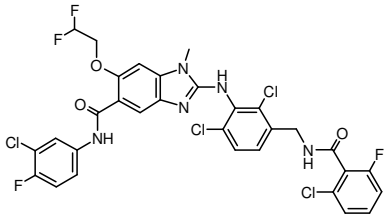
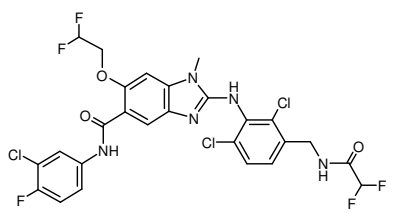
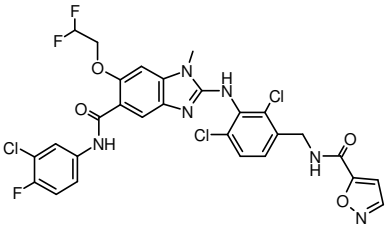
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97		**103**	

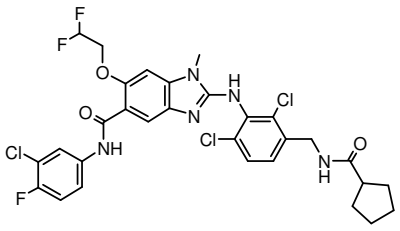
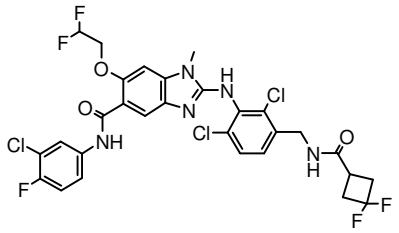
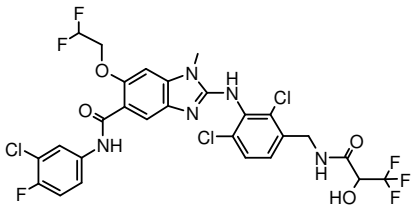
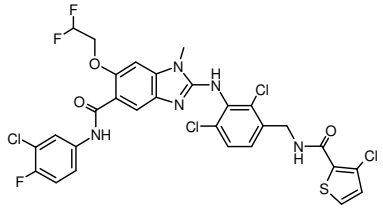
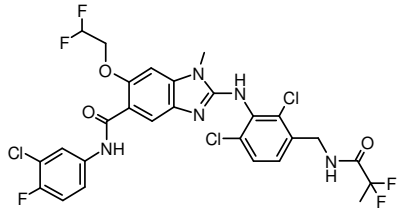
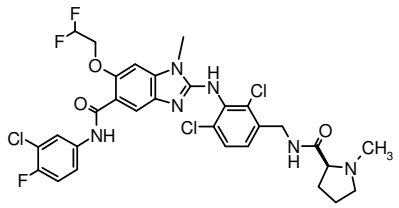
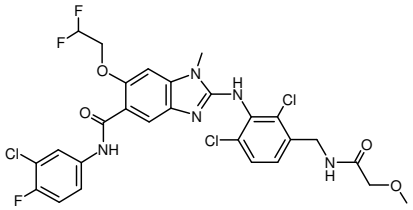
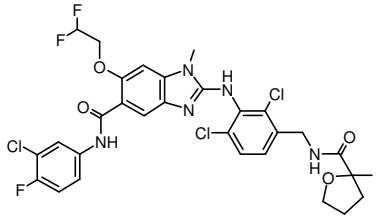
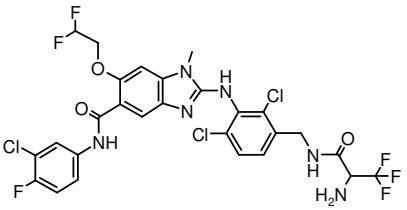
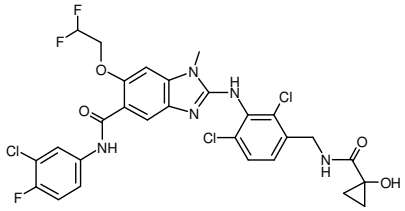
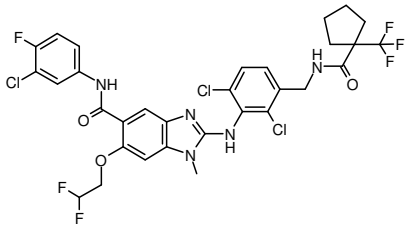
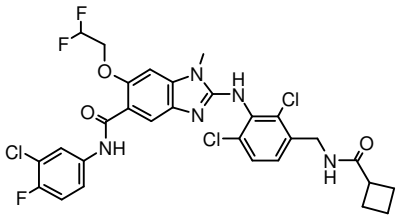
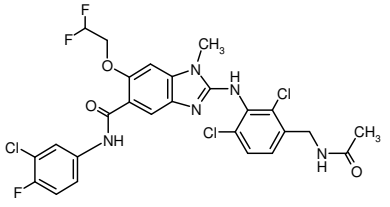
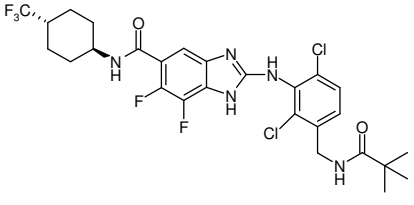
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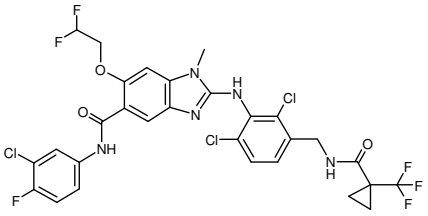
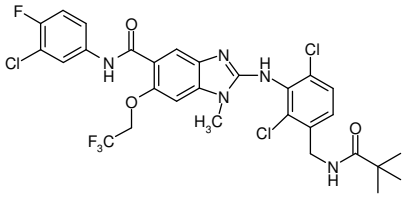
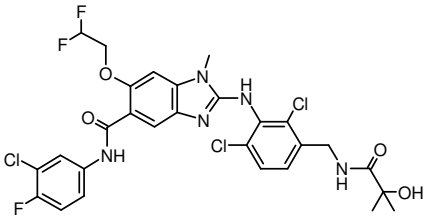
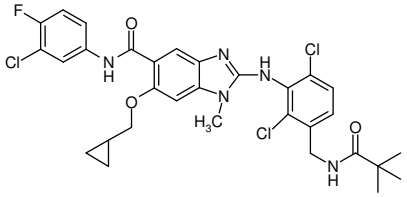
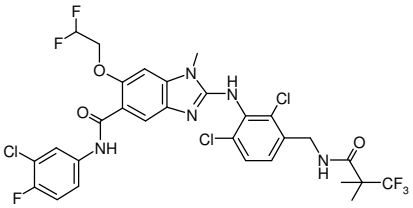
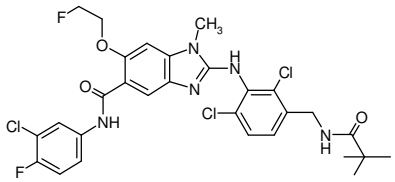
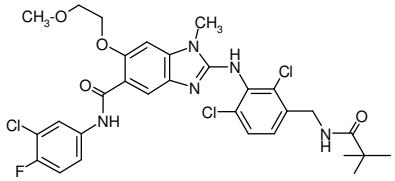
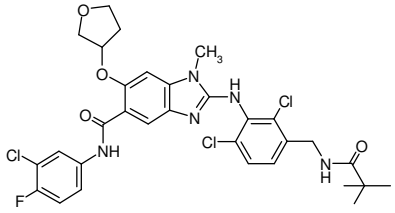
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	Estructura		Estructura
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	Estructura		Estructura
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138		**144**	
145		**152**	

	Estructura		Estructura
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150		157	
151		158	
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	Estructura		Estructura
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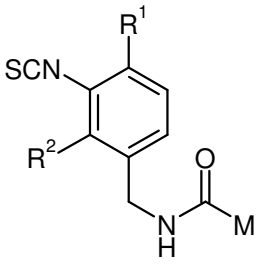
	Estructura		Estructura
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176			
177			
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179			

12. Un compuesto según cualquiera de las reivindicaciones precedentes, para uso como un medicamento.

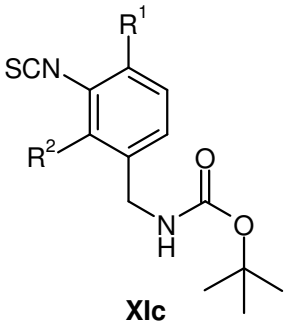
13. Una composición farmacéutica que comprende al menos un compuesto según cualquiera de las reivindicaciones 1 a 11, o una de sus sales farmacéuticamente aceptables, en mezcla con un adyuvante, diluyente y/o vehículo farmacéuticamente aceptable.

14. Un compuesto según una cualquiera de las reivindicaciones 1 a 11, o una de sus sales farmacéuticamente aceptables, para uso en el tratamiento y/o prevención de las enfermedades inflamatorias y/o afecciones asociadas, en particular el dolor.

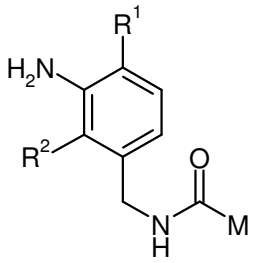
15. Un intermedio de la fórmula **XIb, XIc, XVIIb, XVIIc, XIX o XX**



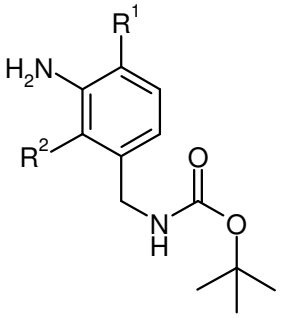
XIb



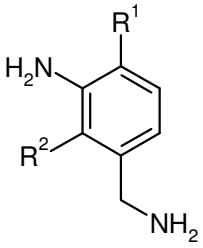
XIc



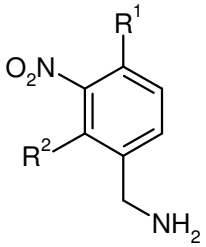
XVIIb



XVIIc



XIX



XX

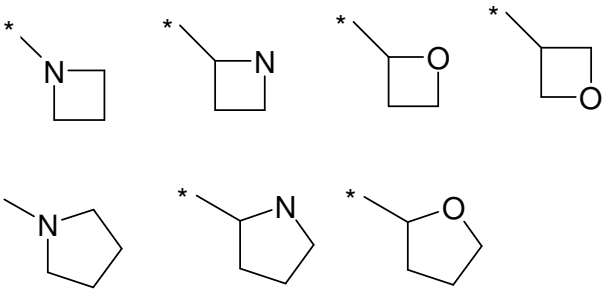
en las que

R^1 y R^2 representan independientemente –cloro, fluoro o $–CH_3$;

M representa

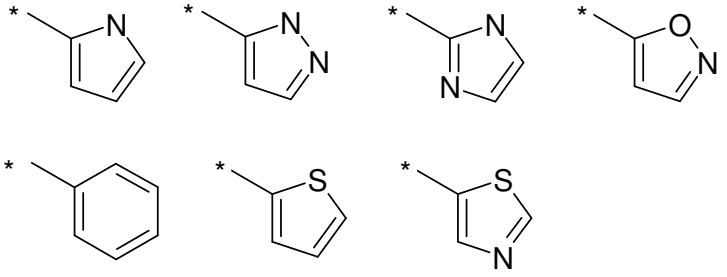
metilo, etilo, propilo, *i*-propilo, *n*-butilo, *s*-butilo, *t*-butilo, ciclopropilo, $-CH_2$-ciclopropilo, ciclobutilo, ciclopentilo, y todos estos grupos están opcionalmente sustituidos con uno o más grupos seleccionados de -F, -OH, -CN, $-NH_2$, $-OCH_3$, $-CH_3$, $-CF_3$;

o se selecciona de los siguientes grupos



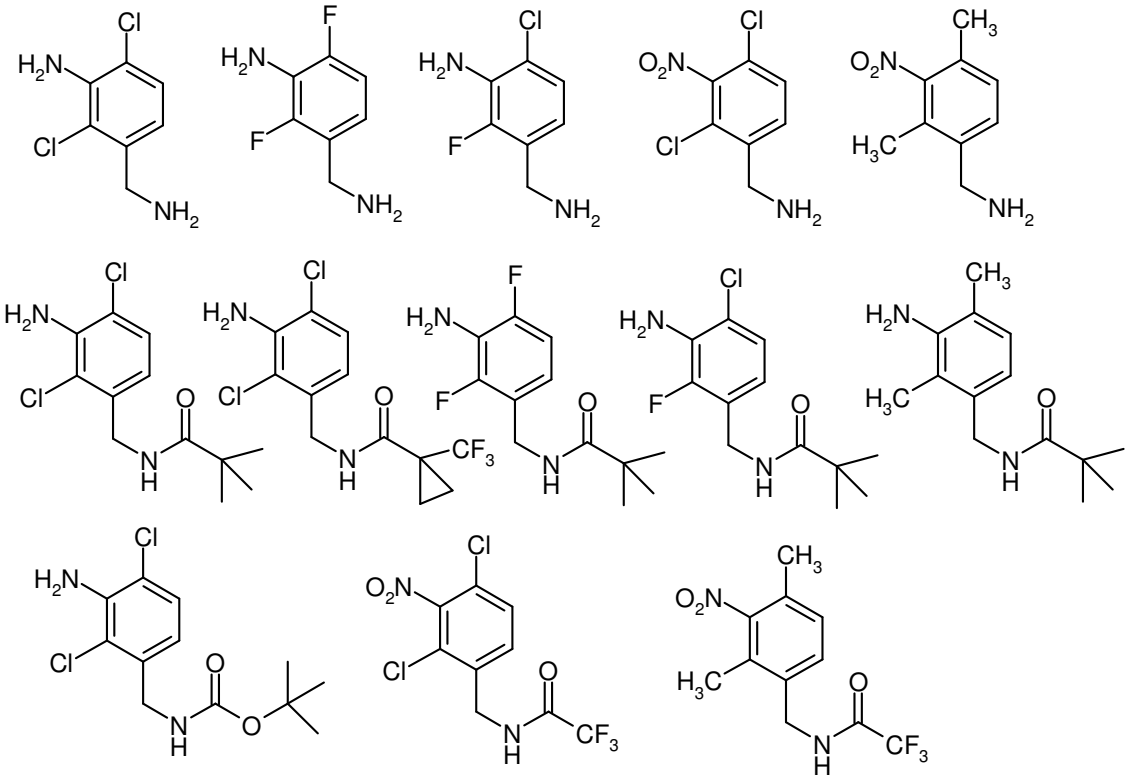
y todos estos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, $-CH_3$, o $-CF_3$;

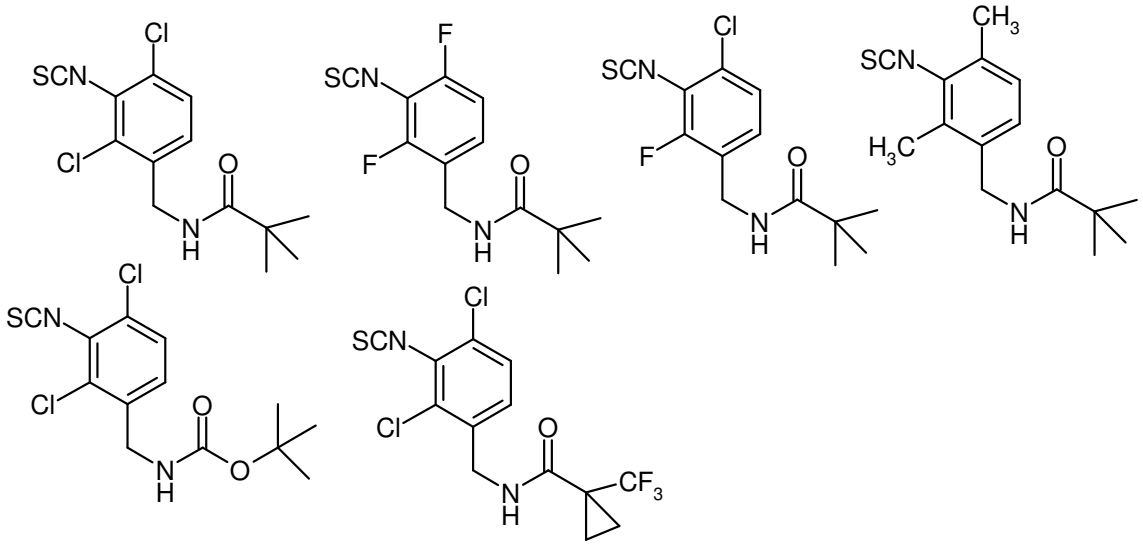
o se selecciona de los siguientes grupos



y todos estos grupos están opcionalmente sustituidos con uno o más sustituyentes seleccionados de -F, -Cl, $-CH_3$, o $-CF_3$.

16. Un intermedio según la reivindicación 15, seleccionado del grupo de compuestos que comprende



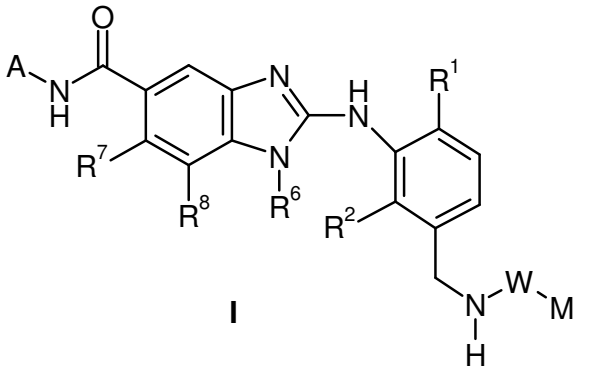


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RESUMEN

NUEVOS COMPUESTOS

Esta invención se refiere a compuestos de la fórmula I,



I

,

a su uso como inhibidores de la prostaglandina E_2 sintasa-1 microsómica (mPGES-1), a composiciones farmacéuticas que los contienen, y a su uso como medicamentos para el tratamiento y/o prevención de enfermedades inflamatorias y condiciones asociadas.

A, M, W, R^1, R^2, R^6, R^7, R^8 tienen los significados dados en la descripción.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2011/064258	19.08.2011	20.08.2010

International Patent Classification (IPC) or both national classification and IPC
INV. C07D235/30 A61K31/4184 A61P11/00 A61P29/00

Applicant
BOEHRINGER INGELHEIM INTERNATIONAL GMBH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office

D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Date of completion of this opinion

see form PCT/ISA/210

Authorized Officer

Herz, Claus

Telephone No. +49 89 2399-8275

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ 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)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-16
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations

see separate sheet

Due to the invariable presence of a carboxamide group at position 6 of the benzimidazole core and a carbonylaminomethyl group at the aniline moiety the compounds claimed are considered to be novel vis-à-vis the state of the art as represented by the documents cited in the International Search Report (ISER).

With regard to the presence of inventive step reference is made to the documents classified "Y" in the ISER wherein similar compounds possessing anti-inflammatory activity have been disclosed. Substituents therein are the same as or similar to those given in the present application.

Taking into account these facts the man skilled in the art would have to expect the anti-inflammatory activity without affecting their fundamental capabilities when modifying the substituents of the groups of compounds disclosed in the state of the art. Thus representing only predictable effects the compounds claimed are considered to be obvious.

Consequently, at present, Claims 1 to 16 are lacking inventive step under Article 33 (3) PCT.

Accordingly it is to be demonstrated wherein the inventive step lies in the compounds claimed, e.g. by showing a significant improvement in the property relevant to the solution of the stated problem. If it is chosen to give evidence using comparative tests, these must be carried out in respect of the closest state of the art.

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.
P01-2633/WO1		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2011/064258	19/08/2011	20/08/2010
Applicant		
BOEHRINGER INGELHEIM INTERNATIONAL 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 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **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(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/064258

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D235/30 A61K31/4184 A61P11/00 A61P29/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN 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.
Y	WO 2005/070906 A (NOVARTIS PHARMA GMBH) 4 August 2005 (2005-08-04) claims 1-13	1-16
Y	WO 2010/034796 A1 (BOEHRINGER INGELHEIM INT [DE]; PFAU ROLAND [DE]; ARNDT KIRSTEN [DE]; D) 1 April 2010 (2010-04-01) claims 1-18	1-16
A	WO 2007/095124 A (TRANSTECH PHARMA, INC.) 23 August 2007 (2007-08-23) * Examples *claims 1-40; tables 1-11	1-16

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search	Date of mailing of the international search report
27 September 2011	10/10/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Herz, Claus

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