SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 14-188599- -00000-0000

Fecha: 2014-08-27 17:02:08 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 6

T=F=5

Industria y Comercio
SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: 6-ALQUINILO PIRIDINAS COMO MIMÉTICOS SMAC

SOLICITANTE: BOEHRINGER INGELHEIM INTERNATIONAL GMBH

DIRECCIÓN: Binger Strasse 173, 55216 Ingelheim Am Rhein

APODERADO: CARLOS R. OLARTE

BOGOTÁ 26 de agosto de 2014

P2014/000111

OLARTEMOURE

OLARTE MOURE & ASOCIADOS LTDA.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 14-188599- -00000-0000

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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 8

PETITORIO - FORMULARIO Ú
PATENTE P
ENTRADA EN FASE NACIONAL **P2014/000111**

SOLICITUD DE:

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: BOEHRINGER INGELHEIM INTERNATIONAL GMBH
Dirección: Binger Strasse 173, 55216 Ingelheim am Rhein (DE).
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/EP2013/053689 Fecha Febrero 25, 2013

Publicación Internacional No. WO2013/127729 Fecha Septiembre 06, 2013

(6) **Título (54** **6-ALQUINILO PIRIDINAS COMO MIMÉTICOS SMAC**

Clasificación Internacional (51) C07D 213/75, C07D 217/22, C07D 401/04, C07D 401/06, C07D 401/14, C07D 405/14, C07D 407/06, C07D 407/12, C07D 409/04, C07D 409/06, C07D 409/14, C07D 413/04, C07D 413/14, C07D 417/04, C07D 417/06

Prioridad

SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
EP	Febrero 27, 2012	12157199.6

(9) **Comprobante de pago No.** 14- **Fecha**

(10) **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [x] Declaraciones. Declaración bajo la Regla 4.17 (ii) del PCT.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] 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/EP2013/053689

Ulrich REISER
Corporate Patents
Binger Strasse 173
Ingelheim Am Rhein
55216
Alemania

Gerd BADER
Corporate Patents
Binger Strasse 173
Ingelheim Am Rhein
55216
Alemania

Walter SPEVAK
Corporate Patents
Binger Strasse 173
Ingelheim Am Rhein
55216
Alemania

Andreas STEFFEN
Corporate Patents
Binger Strasse 173
Ingelheim Am Rhein
55216
Alemania

Alastair L.PARKES
EVOTEC Evotec OAI AG
Evotec Neurosciences GmbH
Manfred Eigen Campus Essener Bogen 7
Hamburg 22419
Alemania

4

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 14 - 0091753

Bogotá D.C., Agosto 27 de 2014 - 16:18:06

RECIBIDO DE : OLARTE MOURE & ASOCIADOS NI 830.122.870

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
RECIBO DE CA	999999999	86032	11/08/2014		520.000.00

*** Conceptos Pagados ***

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

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

Responsable: _____
-*****-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 14-188599- -00000-0000
Fecha: 2014-08-27 17:02:08 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 5
16

5

Industria y Comercio
SUPERINTENDENCIA

PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA
RELACIÓN DE ANEXOS

Dependencia: 2020	Fecha: 14 8 27 (AAAA MM DD)	Recorrido:
Tipo de Radicación: Entrada: ☐ Salida: ☐ Traslado: ☐ Convenio: ☐		
Radicador:		Planilla:

ID	No. Radicación	Consecutivo	Item
1	14-188699	0	
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Item	Unidad de Conservación
1	Bolsa
2	Caja
3	Libro
4	Sobre
5	Tomo
6	Otro
Item	*Soporte Documental*
7	CD X
8	Disquete
9	DVD
10	Folleto
11	Foto
12	Periódico
13	Plano
14	Publicación Periódica
15	USB
16	Otro

Observaciones:
El adjunto contiene 7 archivos en formato PDF, los cuales son procesados y subidos al sistema
Olvidar

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 14-188599- -00000-0000
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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 6 6

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 ☐

OLARTEMOURE

OLARTE MOURE & ASOCIADOS LTDA.

Industria y Comercio
SUPERINTENDENCIA

Espacio reservado para el adhesivo de radicación.

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2014/000111**

SOLICITUD DE:

1

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

[X] Capítulo I. [ ] Capítulo II.

2

SOLICITANTE (71)

Nombre: **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**
Dirección: Binger Strasse 173, 55216 Ingelheim am Rhein (DE).
Nacionalidad o Domicilio: Alemania
Lugar de Constitución: Alemania

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

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

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA
Dirección: VER PAGINA ADJUNTA
Nacionalidad o Domicilio: VER PAGINA ADJUNTA

5

PCT (86)

Solicitud Internacional No. PCT/EP2013/053689 Fecha Febrero 25, 2013

Publicación Internacional No. WO2013/127729 Fecha Septiembre 06, 2013

6

Título (54 **6-ALQUINILO PIRIDINAS COMO MIMÉTICOS SMAC**

Clasificación Internacional (51) C07D 213/75, C07D 217/22, C07D 401/04, C07D 401/06, C07D 401/14, C07D 405/14, C07D 407/06, C07D 407/12, C07D 409/04, C07D 409/06, C07D 409/14, C07D 413/04, C07D 413/14, C07D 417/04, C07D 417/06

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
EP	Febrero 27, 2012	12157199.6

9

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

10 ANEXOS

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- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso.
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- [ ] 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.
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- [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/EP2013/053689

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Binger Strasse 173
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Alemania

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Ingelheim Am Rhein
55216
Alemania

Alastair L.PARKES
EVOTEC Evotec OAI AG
Evotec Neurosciences GmbH
Manfred Eigen Campus Essener Bogen 7
Hamburg 22419
Alemania

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 ENTREGO UNA MINUTA QUE ARCHIVO EN SU LEGAJO RESPECTIVO BAJO EL NUMERO DE ORDEN CORRESPONDIENTE Y CUYO TENOR LITERAL ES COMO SIGUE: ==

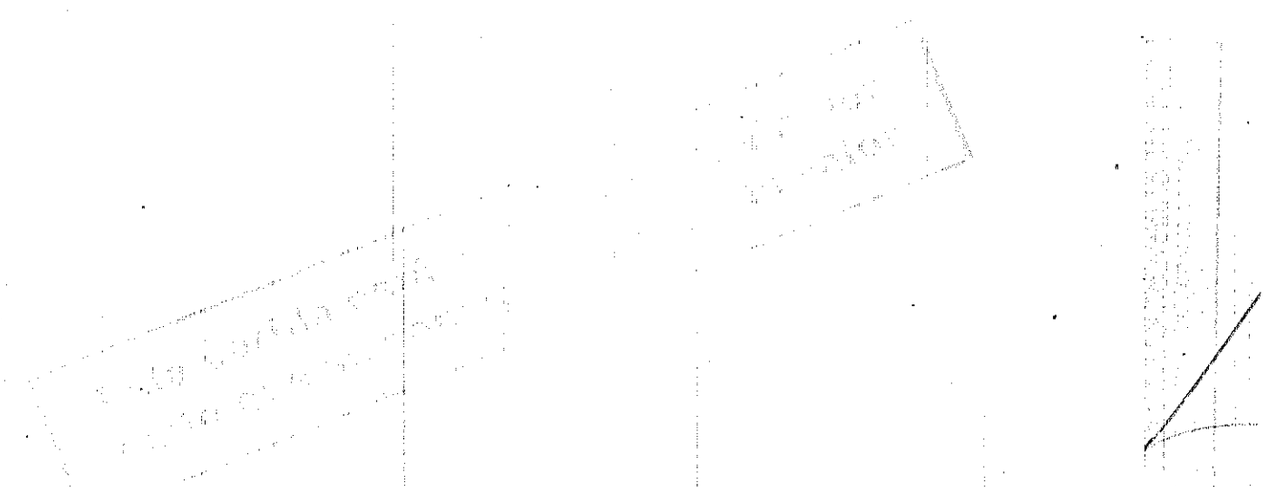
M I N U T A: ===

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:

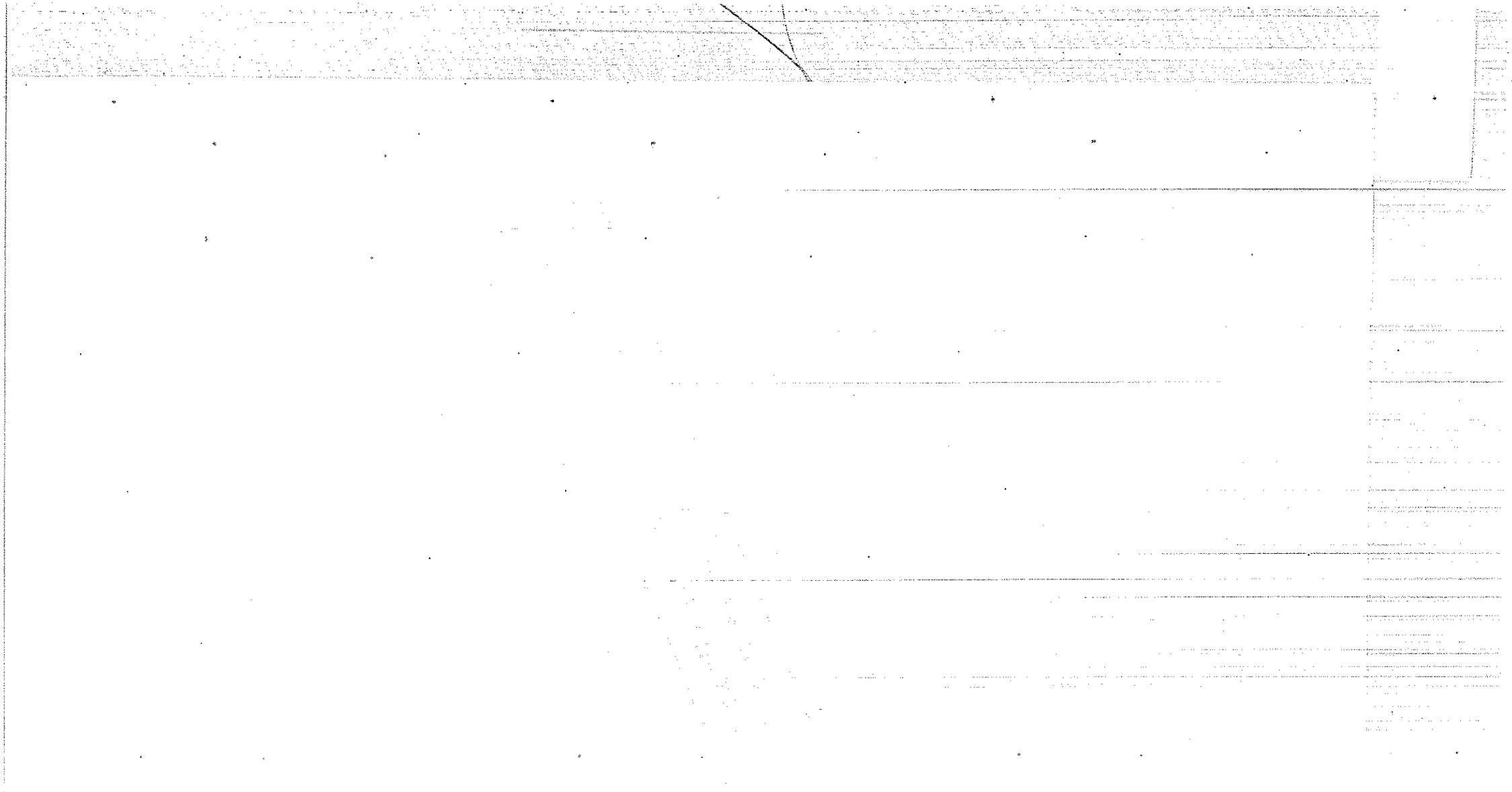
- Dr. Michael Kompter, nacido el 11 de mayo de 1955, con domicilio en 55216 Ingelheim am Rhein, Binger Straße 173.
- Dr. Christian Hauke, nacido el 31 de agosto de 1947, con domicilio en 55216 Ingelheim am Rhein, Binger Straße 173.

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

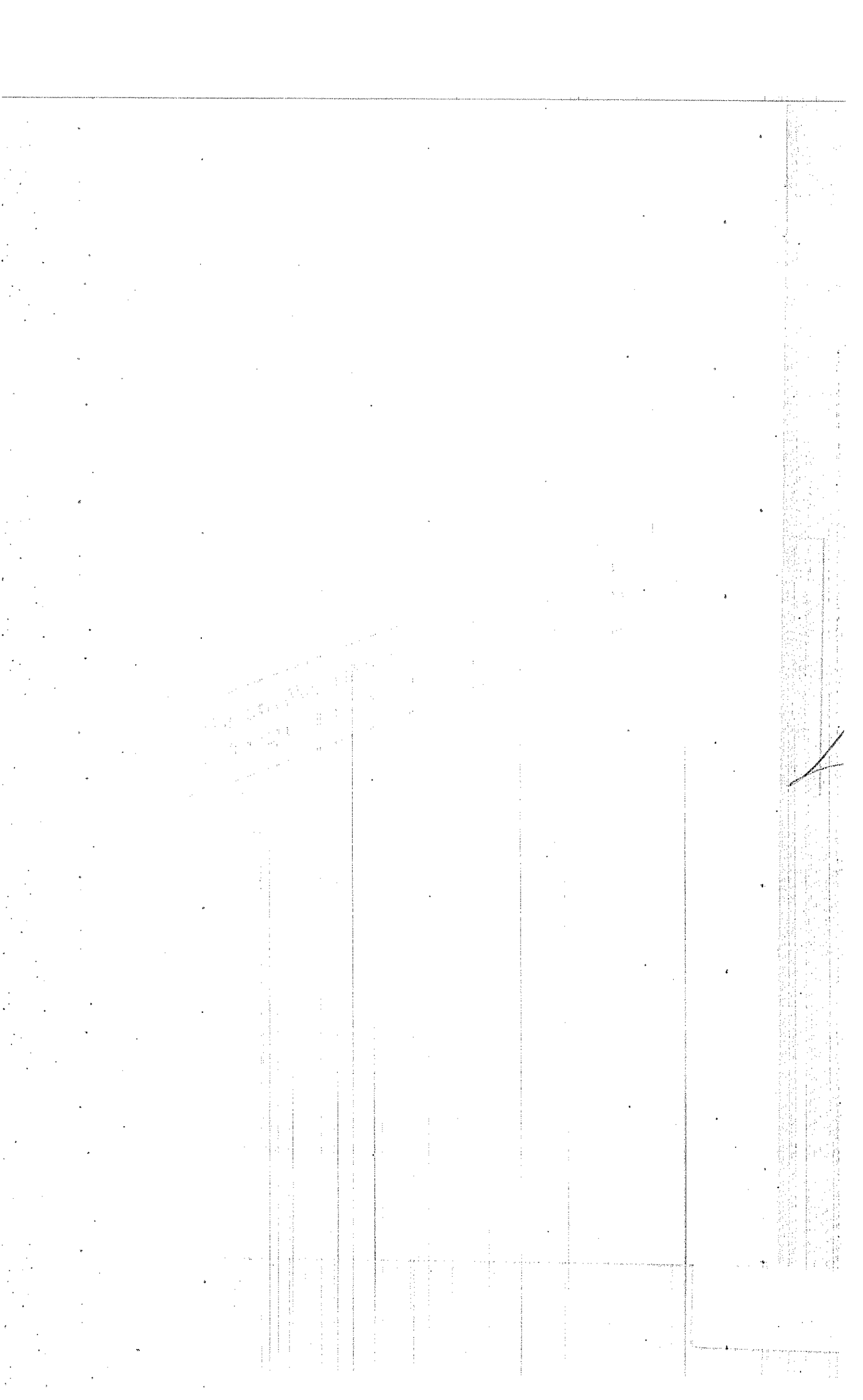
(firmado ilegible)

Notario Público

Mary Ann Montesinos Medina
Traductora Pública Juramentada
Registro N° 105

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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..

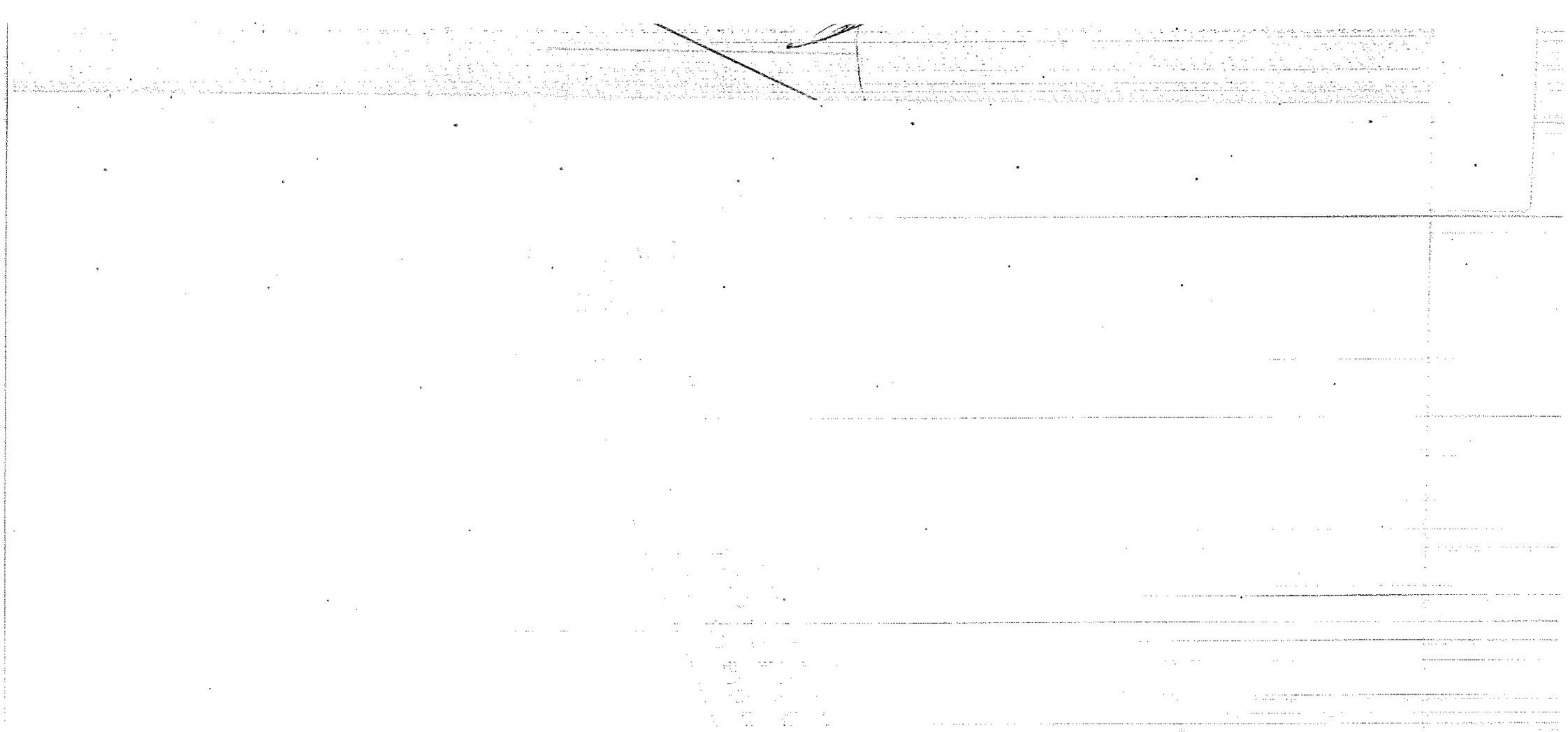
MINISTERIO DE RELACIONES EXTERIORES
DIRECCIÓN GENERAL DE POLÍTICA CONSULAR
Legalización N°
Se legaliza la firma que antecede del Sr.(a)

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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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.

Los apoderados podrán ejercer el presente poder actuando en forma individual e indistinta, y gozarán de las siguientes facultades, tales como 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 procesal, revocar los poderes otorgados, recibir notificaciones en nombre de la compañía y los demás actos que exprese la ley.

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

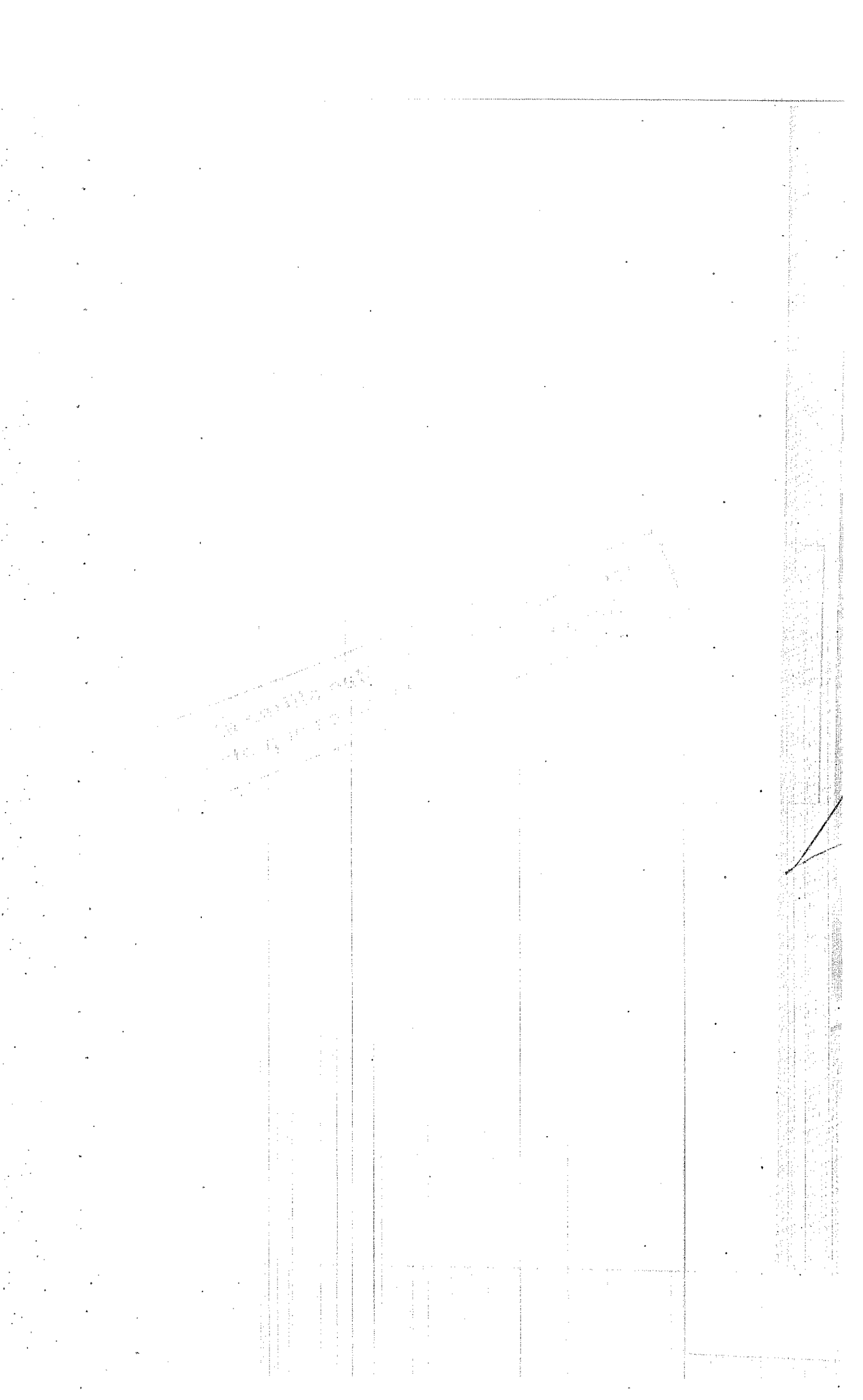
ppa.

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.

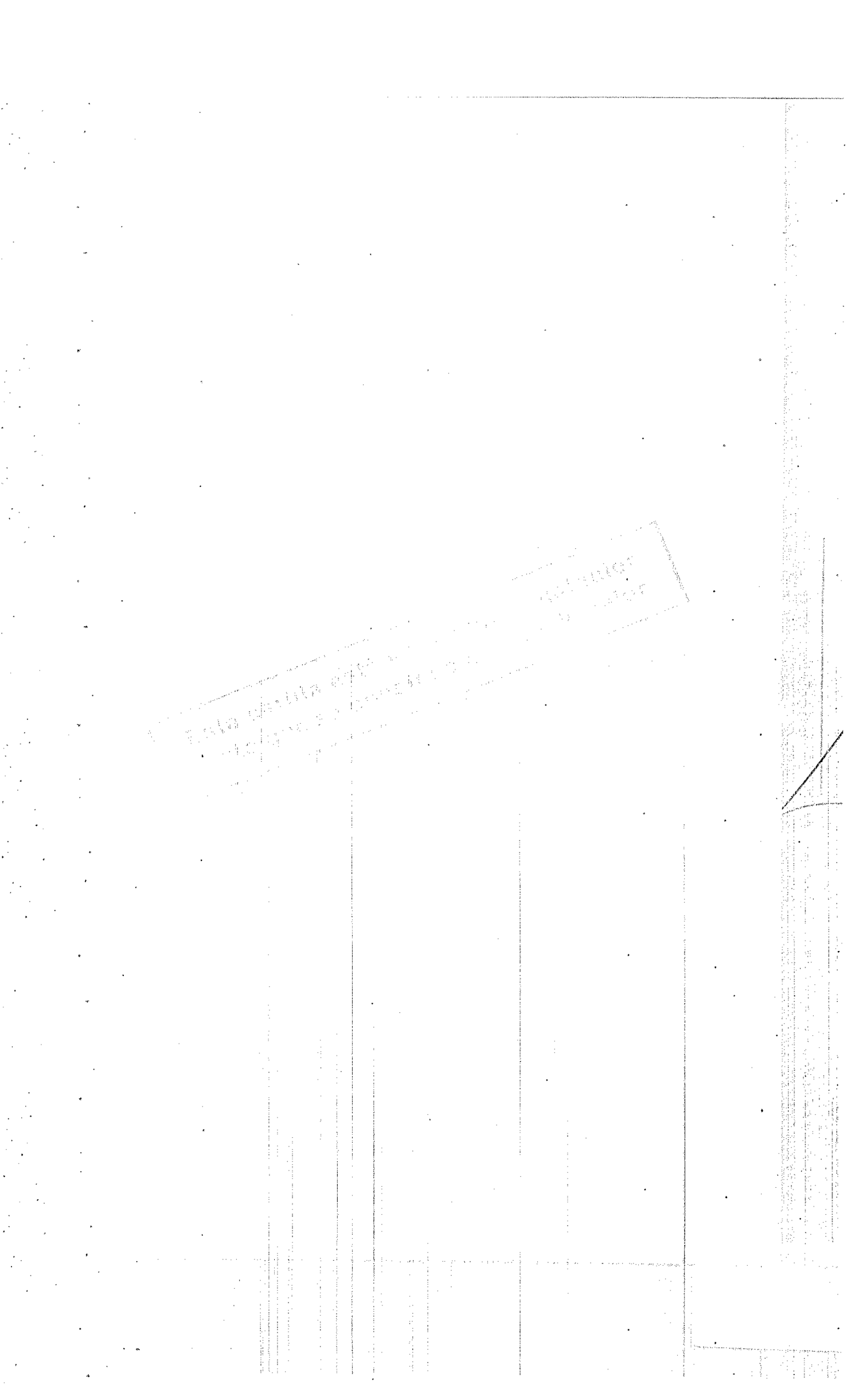
It is herewith certified that **Boehringer Ingelheim International GmbH** is a corporation duly organized and existing under the laws of the Federal Republic of Germany having its principal place of business at Binger Strasse 173, 55216 Ingelheim am Rhein, Germany.

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
DIRECCIÓN GENERAL DE POLÍTICA CONSULAR
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Alfredo Arecco - Sablich
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Maribel del Rosario Llaya Jaylar
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LIMA, 23 JUL 2010

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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

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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.

El suscrito Cónsul General no asume responsabilidad alguna por el contenido de este documento.

Pago Impuesto de Timbre US$10.00
Y derechos consulares US$15.00

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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MINISTERIO DE
RELACIONES
EXTERIORES

2 6 4 8 7 5

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

2010 AUG 0 A 1:51

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BOGOTA D.C.

NO ASUME
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DEL TEXTO

PCT

Print Out (Original in Electronic Form)

VIII-2-1	**Declaration: Entitlement to apply for and be granted a patent** Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	In relation to this international application BOEHRINGER INGELHEIM INTERNATIONAL GMBH is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(ii)		BOEHRINGER INGELHEIM RCV GMBH & CO KG is entitled as employer of the inventor, REISER, Ulrich
VIII-2-1(ii)		BOEHRINGER INGELHEIM RCV GMBH & CO KG is entitled as employer of the inventor, BADER, Gerd
VIII-2-1(ii)		BOEHRINGER INGELHEIM RCV GMBH & CO KG is entitled as employer of the inventor, SPEVAK, Walter
VIII-2-1(ii)		BOEHRINGER INGELHEIM RCV GMBH & CO KG is entitled as employer of the inventor, STEFFEN, Andreas
VIII-2-1(ii)		Evotec Ltd. is entitled as employer of the inventor, PARKES, Alastair L.
VIII-2-1(iii)		an agreement between BOEHRINGER INGELHEIM INTERNATIONAL GMBH and BOEHRINGER INGELHEIM RCV GMBH & CO KG, dated 01 January 2006 (01.01.2006)
VIII-2-1(iii)		an agreement between BOEHRINGER INGELHEIM INTERNATIONAL GMBH and EVOTEC Ltd, dated 23 August 2004 (23.08.2004)

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

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C07D 217/22 (2006.01) *C07D 409/06* (2006.01)
C07D 401/04 (2006.01) *C07D 409/14* (2006.01)
C07D 401/06 (2006.01) *C07D 413/04* (2006.01)
C07D 401/14 (2006.01) *C07D 413/14* (2006.01)
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(71) Applicant: **BOEHRINGER INGELHEIM INTERNATIONAL GMBH** [DE/DE]; Binger Strasse 173, 55216 Ingelheim Am Rhein (DE).

(72) Inventors: **REISER, Ulrich**; BOEHRINGER INGELHEIM GMBH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **BADER, Gerd**; BOEHRINGER INGELHEIM GMBH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **SPEVAK, Walter**; BOEHRINGER INGELHEIM GMBH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **STEFFEN, Andreas**; BOEHRINGER INGELHEIM GMBH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **PARKES, Alastair L.**; EVOTEC Evotec OAI AG, Evotec Neurosciences GmbH, Manfred Eigen Campus, Essener Bogen 7, 22419 Hamburg (DE).

(74) Agents: **SIMON, Elke** et al.; Boehringer Ingelheim Gmbh, Corporate Patents, Binger Strasse 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, BN, 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, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, 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.

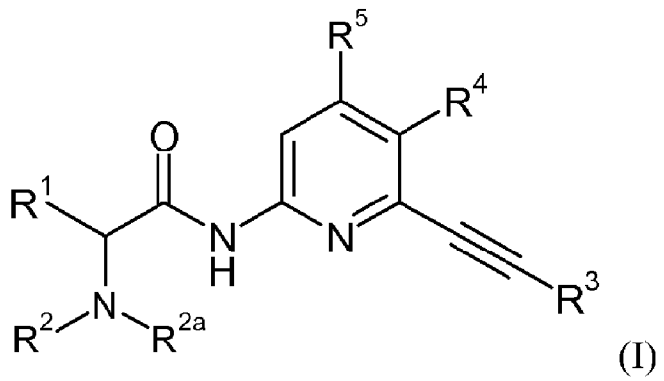
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, 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))*

[Continued on next page]

(54) Title: 6 - ALKYNYL PYRIDINES AS SMAC MIMETICS



(I)

(57) Abstract: This invention relates to 6-alkynyl-pyridines of general formula (I) their use as SMAC mimetics, pharmaceutical compositions containing them, and their use as a medicaments for the treatment and/or prevention of diseases characterized by excessive or abnormal cell proliferation and associated conditions such as cancer. The groups R^1 to R^5 have the meanings given in the claims and in the specification.

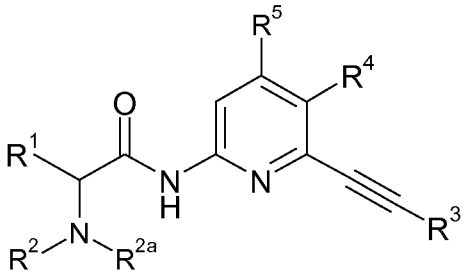
WO 2013/127729 A1

Published:

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

6 - ALKYNYL PYRIDINES AS SMAC MIMETICS

This invention relates to compounds of the general formula (I)



(I)

wherein the groups **R**^{1} to **R**^{5} have the meanings given in the claims and in the specification. The compounds of the invention are suitable for the treatment of diseases characterized by excessive or abnormal cell proliferation, pharmaceutical preparations containing such compounds and their uses as a medicament. The compounds of the invention modulate IAP activity.

Background of the invention

Apoptosis, a form of programmed cell death, typically occurs in the normal development and maintenance of healthy tissues in multicellular organisms. It is a complex process, which results in the removal of damaged, diseased or developmentally redundant cells, without signs of inflammation or necrosis. Apoptosis thus occurs as a normal part of development, the maintenance of normal cellular homeostasis, or as a consequence of stimuli such as chemotherapy and radiation.

The intrinsic apoptotic pathway is known to be deregulated in cancer and lymphoproliferative syndromes, as well as autoimmune disorders such as multiple sclerosis and rheumatoid arthritis. Additionally, alterations in a host apoptotic response have been described in the development or maintenance of viral and bacterial infections. Cancer cells gain the ability to overcome or circumvent apoptosis and continue with inappropriate proliferation despite strong pro-apoptotic signals such as hypoxia, endogenous cytokines, radiation treatments and chemotherapy. In autoimmune disease, pathogenic effector cells

can become resistant to normal apoptotic cues. Resistance can be caused by numerous mechanisms, including alterations in the apoptotic machinery due to increased activity of anti-apoptotic pathways or expression of anti-apoptotic genes. Thus, approaches that reduce the threshold of apoptotic induction in cancer cells by overcoming resistance mechanisms may be of significant clinical utility.

Caspases serve as key effector molecules in apoptosis signaling. Caspases (cysteine containing aspartate specific proteases) are strong proteases and once activated, digest vital cell proteins from within the cell. Since caspases are highly active proteases, tight control of this family of proteins is necessary to prevent premature cell death. In general, caspases are synthesized as largely inactive zymogens that require proteolytic processing for activation. This proteolytic processing is only one of the ways in which caspases are regulated. The second mechanism of regulation is through a family of proteins that bind and inhibit caspases.

One family of molecules that inhibit caspases are the Inhibitors of Apoptosis (IAP) (Deveraux et al., J Clin Immunol (1999), 19: 388-398). IAPs were originally discovered in baculovirus by their ability to substitute for P35 protein function, an anti-apoptotic gene (Crook et al. (1993) J Virology 67, 2168-2174). Human IAPs are characterized by the presence of one to three homologous structural domains known as baculovirus IAP repeat (BIR) domains. Some IAP family members also contain a RING zinc finger domain at the C-terminus, with the capability to ubiquitylate target proteins via their E3 ligase function. The human IAPs, XIAP, HIAP1 (also referred to as cIAP2), and HIAP2 (cIAP1) each have three BIR domains, and a carboxy terminal RING zinc finger. Another IAP, NAIP, has three BIR domains (BIR1 , BIR2 and BIR3), but no RING domain, whereas Livin, TsIAP and MLIAP have a single BIR domain and a RING domain. The X chromosome-linked inhibitor of apoptosis (XIAP) is an example of an IAP, which can inhibit the initiator caspase Caspase-9, and the effector caspases, Caspase-3 and Caspase-7, by direct binding. XIAP can also induce the degradation of caspases through the ubiquitylation-mediated proteasome pathway via the E3 ligase activity of a RING zinc finger domain. Inhibition of Caspase-9 is mediated by the BIR3 domains of XIAP, whereas effector caspases are inhibited by binding to the linker-BIR2 domain. The BIR domains also mediate the

interactions of IAPs with tumor necrosis factor-receptor associated factor (TRAFs)-I and -2, and with TAB1, adaptor proteins affecting survival signaling through NFkB activation. IAP proteins can thus function as direct brakes on the apoptosis cascade by inhibiting active caspases or by redirecting cellular signaling to a pro-survival mode. Survivin is another member of the IAP family of antiapoptotic proteins. It is shown to be conserved in function across evolution as homologues of the protein are found both in vertebrates and invertebrates.

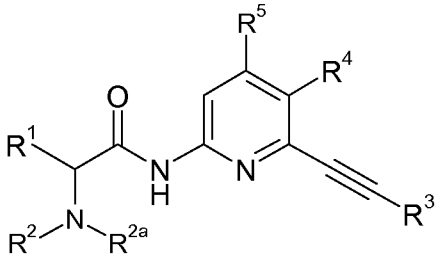
Cancer cells and cells involved in autoimmune disease may avoid apoptosis by the sustained over-expression of one or more members of the IAP family of proteins. For example, IAP overexpression has been demonstrated to be prognostic of poor clinical outcome in multiple cancers, and decreased IAP expression through RNAi strategies sensitizes tumor cells to a wide variety of apoptotic insults including chemotherapy, radiotherapy and death receptor ligands. For XIAP, this is shown in cancers as diverse as leukemia and ovarian cancer. Over expression of cIAP1 and cIAP2 resulting from the frequent chromosome amplification of the 11q21-q23 region, which encompasses both genes, has been observed in a variety of malignancies, including medulloblastomas, renal cell carcinomas, glioblastomas, and gastric carcinomas.

The interaction between the baculoviral IAP repeat-3 (BIR3) domain of X-linked inhibitor of apoptosis (XIAP) and caspase-9 is of therapeutic interest because this interaction is inhibited by the NH2-terminal seven-amino-acid residues of the so-called "second mitochondrial-derived activator of caspase" (in short and hereinafter Smac), a naturally occurring antagonist of IAPs. Small-molecule Smac mimetics have been generated anticipating efficacy in cancer by reconstituting apoptotic signaling.

Thus, there is the need to provide SMAC mimetics useful for the prevention and/or treatment of diseases characterized by excessive or abnormal cell proliferation, such as cancer.

Detailed description of the invention

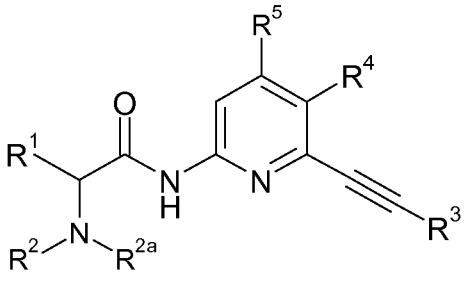
The present invention relates to compounds of formula (**I**)



(**I**)

wherein $\mathbf{R^1}$ to $\mathbf{R^5}$ are as defined in the description and in the claims. The compounds according to formula (I) act as Smac mimetics. Thus, the compounds of the invention may be used for example for the treatment of diseases which are characterized by an increased apoptosis threshold due to overexpression of IAP protein. Preferably, the compounds of the invention can be used in the treatment of cancer.

The present invention therefore relates to compounds of general formula (**I**)



(I)

wherein

$\mathbf{R^1}$ is -H or -C_{1-5}alkyl;

$\mathbf{R^2}$, $\mathbf{R^{2a}}$ are independently selected from -H or -C_{1-5}alkyl optionally substituted with one or more -F;

$\mathbf{R^3}$ is selected from -C_{6-10}aryl, 5-14 membered heteroaryl, each of which groups can be optionally and independently substituted with one or more, independently selected, $\mathbf{R^6}$; or $\mathbf{R^3}$ is selected from -C_{1-6}alkyl, -C_{4-7}cycloalkyl, -C_{4-}

$_{7}$cycloalkenyl, or 5-14 membered aromatic ring system, each of which groups can be optionally and independently substituted with one or more, independently selected, **R**^{6a};

R^{6} is selected from -CN, halogen, -C$_{1-3}$alkyl, -O-C$_{1-3}$alkyl, -C(O)-**R**^{12}, 5-6 membered heteroaryl, which 5-6 membered heteroaryl group can be optionally subsituted with -C$_{1-3}$alkyl; or **R**^{6} is phenyl, which phenyl can be optionally substituted with -O-C$_{1-3}$alkyl

R^{6a} is selected from =O, -CN, halogen, -C$_{1-3}$alkyl, -O-C$_{1-3}$alkyl, -C(O)-**R**^{12}, 5-6 membered heteroaryl, which 5-6 membered heteroaryl group can be optionally subsituted with -C$_{1-3}$alkyl; or **R**^{6a} is phenyl, which phenyl can be optionally substituted with -O-C$_{1-3}$alkyl;

R^{12} is selected from -NH$_2$, -NH-C$_{1-3}$alkyl, 5-7 membered heterocyclyl, or -O-C$_{1-3}$alkyl, which -C$_{1-3}$alkyl groups can be optionally subsituted with a 5-7 membered heterocyclyl;

R^{4} is selected from -H, -C$_{6-10}$aryl, 5-14 membered heteroaryl, each of which groups is optionally and independently substituted with one or more, independently selected, **R**^{7} or **R**^{4} is selected from C$_{1-6}$alkyl, 5-14 membered aromatic ring system, -C$_{5-7}$cycloalkyl, each of which group is optionally and independently substituted with one or more, independently selected, **R**^{7a},

or **R**^{4} is selected from -N(**R**^{8},**R**^{9}) wherein

R^{8}, **R**^{9} are independently selected from H, -C$_{1-3}$alkyl, -C(O)-**R**^{10} -S(O)$_2$-**R**^{11}

R^{10}, **R**^{11} are independently selected from 5-7 membered heterocyclyl, -C$_{5-7}$cycloalkyl, -C$_{6-10}$aryl, 5-10 membered heteroaryl;

R^{7} is selected from -CN, halogen, -CF$_3$, -NO$_2$, -C$_{1-3}$alkyl, -S-C$_{1-3}$alkyl, -NH-C$_{1-3}$alkyl, -N(C$_{1-3}$alkyl)$_2$, -NHC(O)-C$_{1-3}$alkyl, -C(O)-**R**^{13}, -O-C$_{1-3}$alkyl, 5-14 membered heteroaryl, -O-phenyl, -CH$_2$-phenyl, phenyl, which phenyl group can be optionally substituted with halogen, or 5-6 membered heterocyclyl, which 5-6 membered heterocyclyl can be optionally substituted with -C$_{1-3}$alkyl;

R^{7a} is selected from =O, -CN, halogen, -CF$_3$, -NO$_2$, -C$_{1-3}$alkyl, -S-C$_{1-3}$alkyl, -NH-C$_{1-3}$alkyl, -N(C$_{1-3}$alkyl)$_2$, -NHC(O)-C$_{1-3}$alkyl, -C(O)-**R**^{13}, -O-C$_{1-3}$alkyl,

5-14 membered heteroaryl, -O-phenyl, -CH_2-phenyl, phenyl, which phenyl group can be optionally substituted with halogen, or 5-6 membered heterocyclyl, which 5-6 membered heterocyclyl can be optionally substituted with -C_{1-3}alkyl; wherein

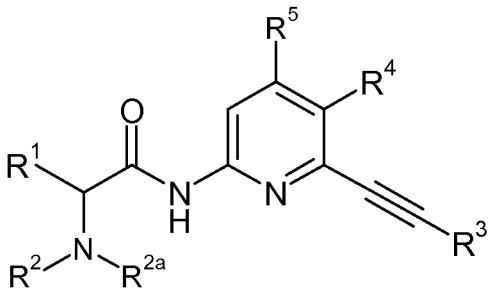
$\mathbf{R^{13}}$ is selected from -OH, -NH_2, -NH-C_{1-3}alkyl, -C_{1-3}alkyl;

$\mathbf{R^5}$ is selected from -H, halogen, -C_{1-3}alkyl, -O-C_{1-3}alkyl, which -C_{1-3}alkyl groups can be optionally subsituted with one or more halogen;

or $\mathbf{R^4}$ and $\mathbf{R^5}$ taken together form a -C_{6-10}aryl or 5-14 membered heteroaryl,

and wherein the compounds of formula (I) may optionally be present in the form of salts.

In a preferred embodiment the invention relates to compounds of formula (**I**),



(I)

wherein

$\mathbf{R^1}$ is -H or -C_{1-5}alkyl;

$\mathbf{R^2}$, $\mathbf{R^{2a}}$ are independently selected from -H or -C_{1-5}alkyl optionally substituted with one or more -F;

$\mathbf{R^3}$ is selected from -C_{6-10}aryl, 5-14 membered heteroaryl, each of which groups can be optionally and independently substituted with one or more, independently selected, $\mathbf{R^6}$; or $\mathbf{R^3}$ is selected from -C_{1-6}alkyl, -C_{4-7}cycloalkyl, -C_{4-7}cycloalkenyl, or 5-14 membered aromatic ring system, each of which groups can be optionally and independently substituted with one or more, independently selected, $\mathbf{R^{6a}}$;

$\mathbf{R^6}$ is selected from -CN, halogen, -C_{1-3}alkyl, -O-C_{1-3}alkyl, -C(O)-$\mathbf{R^{12}}$, 5-6 membered heteroaryl, which 5-6 membered heteroaryl group can be optionally substituted with -C_{1-3}alkyl; or $\mathbf{R^6}$ is phenyl, which phenyl can be optionally substituted with -O-C_{1-3}alkyl

$\mathbf{R^{6a}}$ is selected from =O, -CN, halogen, -C_{1-3}alkyl, -O-C_{1-3}alkyl, -C(O)-$\mathbf{R^{12}}$, 5-6 membered heteroaryl, which 5-6 membered heteroaryl group can be optionally subsituted with -C_{1-3}alkyl; or $\mathbf{R^{6a}}$ is phenyl, which phenyl can be optionally substituted with -O-C_{1-3}alkyl;

$\mathbf{R^{12}}$ is selected from -NH_2, -NH-C_{1-3}alkyl, 5-7 membered non aromatic heterocyclyl, or -O-C_{1-3}alkyl, which -C_{1-3}alkyl groups can be optionally subsituted with a 5-7 membered non aromatic heterocyclyl;

$\mathbf{R^4}$ is selected from -H, -C_{6-10}aryl, 5-14 membered heteroaryl, each of which groups is optionally and independently substituted with one or more, independently selected, $\mathbf{R^7}$, or $\mathbf{R^4}$ is selected from C_{1-6}alkyl, 5-14 membered aromatic ring system, -C_{5-7}cycloalkyl, each of which group is optionally and independently substituted with one or more, independently selected, $\mathbf{R^{7a}}$,

or $\mathbf{R^4}$ is selected from -N($\mathbf{R^8}$,$\mathbf{R^9}$) wherein

$\mathbf{R^8}$, $\mathbf{R^9}$ are independently selected from H, -C_{1-3}alkyl, -C(O)-$\mathbf{R^{10}}$ -$S(O)_2$-$\mathbf{R^{11}}$

$\mathbf{R^{10}}$, $\mathbf{R^{11}}$ are independently selected from 5-7 membered non aromatic heterocyclyl, -C_{5-7}cycloalkyl, -C_{6-10}aryl, 5-10 membered heteroaryl;

$\mathbf{R^7}$ is selected from -CN, halogen, -CF_3, -NO_2, -C_{1-3}alkyl, -S-C_{1-3}alkyl, -NH-C_{1-3}alkyl, -N(C_{1-3}alkyl)$_2$, -NHC(O)-C_{1-3}alkyl, -C(O)-$\mathbf{R^{13}}$, -O-C_{1-3}alkyl, 5-14 membered heteroaryl, -O-phenyl, -CH_2-phenyl, phenyl, each of which phenyl group can be optionally substituted with halogen, or 5-6 membered non aromatic heterocyclyl, which 5-6 membered non aromatic heterocyclyl can be optionally substituted with -C_{1-3}alkyl;

$\mathbf{R^{7a}}$ is selected from =O, -CN, halogen, -CF_3, -NO_2, -C_{1-3}alkyl, -S-C_{1-3}alkyl, -NH-C_{1-3}alkyl, -N(C_{1-3}alkyl)$_2$, -NHC(O)-C_{1-3}alkyl, -C(O)-$\mathbf{R^{13}}$, -O-C_{1-3}alkyl, 5-14 membered heteroaryl, -O-phenyl, -CH_2-phenyl, phenyl, each of which phenyl group can be optionally substituted with halogen, or 5-6 membered

non aromatic heterocyclyl, which 5-6 membered non aromatic heterocyclyl can be optionally substituted with -C_{1-3}alkyl; wherein

$\mathbf{R^{13}}$ is selected from -OH, -NH_2, -NH-C_{1-3}alkyl, -C_{1-3}alkyl;

$\mathbf{R^5}$ is selected from -H, halogen, -C_{1-3}alkyl, -O-C_{1-3}alkyl, which -C_{1-3}alkyl groups can be optionally subsituted with one or more halogen;

or $\mathbf{R^4}$ and $\mathbf{R^5}$ taken together form a -C_{6-10}aryl or 5-14 membered heteroaryl,

and wherein the compounds of formula (I) may optionally be present in the form of salts.

In a preferred embodiment the invention relates to compounds of formula (**I**), wherein $\mathbf{R^1}$ is selected from -CH_3, -CH_2-CH_3.

In a preferred embodiment the invention relates to compounds of formula (**I**), wherein $\mathbf{R^2}$ and $\mathbf{R^{2a}}$ are independently selected from -H, -CH_3, -CH_2-CH_3. -CH-$(CH_3)_2$, -$(CH_2)_2$-CH_3.

In a preferred embodiment the invention relates to compounds of formula (**I**), wherein $\mathbf{R^5}$ is selected from -H, -Cl, -F, -CF_3, -OCH_3, -CH_3.

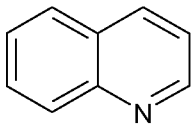
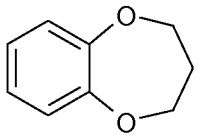
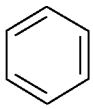
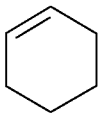
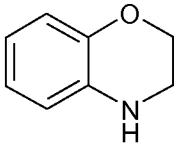
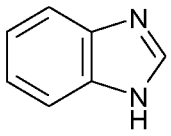
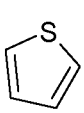
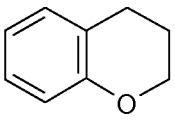
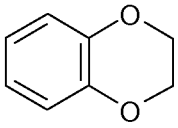
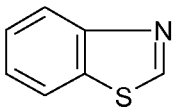
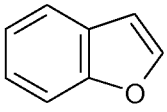
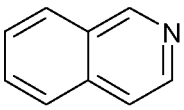
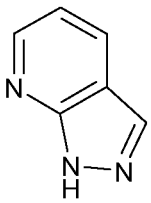
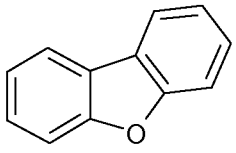
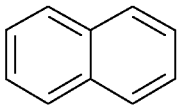
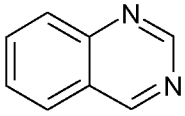
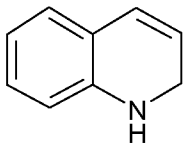
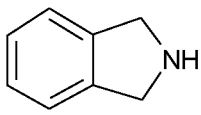
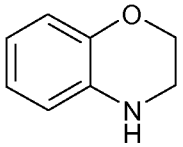
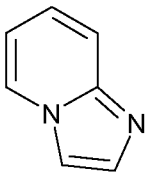
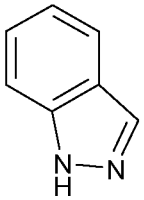
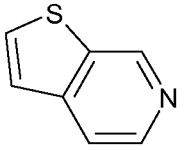
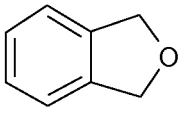
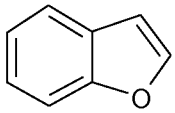
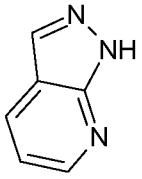
In a preferred embodiment the invention relates to compounds of formula (**I**), wherein $\mathbf{R^3}$ is selected from -C_{6-10}aryl, 5-14 membered heteroaryl, -CH_2-phenyl, -C_{5-7}cycloalkenyl, 5-14 membered aromatic ring system, each of which groups can be optionally and independently substituted with one or more, independently selected, $\mathbf{R^6}$ or $\mathbf{R^{6a}}$ as defined in the claims and the description.

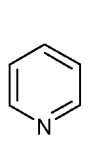
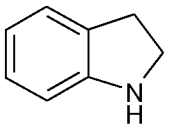
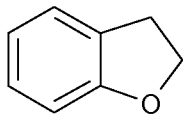
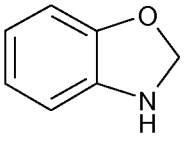
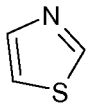
In a preferred embodiment the invention relates to compounds of formula (**I**), wherein $\mathbf{R^3}$ is selected from -C_{6-10}aryl, 5-14 membered heteroaryl, each of which groups can be optionally and independently substituted with one or more, independently selected, $\mathbf{R^6}$, or $\mathbf{R^3}$ is selected from-C_{5-7}cycloalkenyl, 5-14 membered aromatic ring system, each of which groups can be optionally and independently substituted with one or more, independently selected $\mathbf{R^{6a}}$, or $\mathbf{R^3}$ is -CH_2-phenyl, which phenyl can be optionally substituted with -O-C_{1-3}alkyl, and wherein $\mathbf{R^6}$ and $\mathbf{R^{6a}}$ are as defined in the claims and the description.

In a preferred embodiment the invention relates to compounds of formula (**I**), wherein $\mathbf{R^3}$ is selected from -C_{6-10}aryl, 5-14 membered heteroaryl, 5-14 membered aromatic ring

system, which groups can be optionally and independently substituted with one or more, independently selected, **R**^{6} or **R**^{6a} as defined in the claims and the description.

In a preferred embodiment the invention relates to compounds of formula (**I**), wherein **R**^{3} is selected from -C_{6-10}aryl, 5-14 membered heteroaryl, each of which groups can be optionally and independently substituted with one or more, independently selected, **R**^{6}, or **R**^{3} is selected from 5-14 membered aromatic ring system, which groups can be optionally and independently substituted with one or more, independently selected, **R**^{6a}, wherein **R**^{6} and **R**^{6a} are as defined in the claims and the description.

In a preferred embodiment the invention relates to compounds of formula (**I**), wherein **R**^{3} is selected from –CH_2-phenyl,  ;  ;  ;   ;  ;  ;  ;  ;  ;  ;  ;   ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;

 ;  ;  ;  ;  each of which group is optionally substituted as defined in the claims and the description.

In a preferred embodiment the invention relates to compounds of formula (**I**), wherein $\mathbf{R^4}$ is selected from -H, -C_{1-6}alkyl, -C_{6-10}aryl, 5-14 membered heteroaryl, 5-14 membered aromatic ring system, -C_{5-7}cycloalkyl, each of which group is optionally and independently substituted with one or more, independently selected, $\mathbf{R^7}$ or $\mathbf{R^{7a}}$ as defined in claim 1, or $\mathbf{R^4}$ is selected from -N($\mathbf{R^8}$,$\mathbf{R^9}$), wherein $\mathbf{R^8}$ and $\mathbf{R^9}$ are as defined in the claims and the description.

In a preferred embodiment the invention relates to compounds of formula (**I**), wherein $\mathbf{R^4}$ is selected from -H, -C_{6-10}aryl, 5-14 membered heteroaryl, each of which group is optionally and independently substituted with one or more, independently selected, $\mathbf{R^7}$, or $\mathbf{R^4}$ is selected from -C_{1-6}alkyl, 5-14 membered aromatic ring system and -C_{5-7}cycloalkyl, each of which group is optionally and independently substituted with one or more, independently selected, $\mathbf{R^{7a}}$, or $\mathbf{R^4}$ is selected from -N($\mathbf{R^8}$,$\mathbf{R^9}$), wherein $\mathbf{R^7}$, $\mathbf{R^{7a}}$, $\mathbf{R^8}$ and $\mathbf{R^9}$ are as defined in the claims and in the description.

In a preferred embodiment the invention relates to compounds of formula (**I**), wherein $\mathbf{R^4}$ is selected from -C_{6-10}aryl, 5-14 membered heteroaryl, 5-14 membered aromatic ring system, -C_{5-7}cycloalkyl, each of which group is optionally and independently substituted with one or more, independently selected, $\mathbf{R^7}$ or $\mathbf{R^{7a}}$ as defined in the description and the claims, or $\mathbf{R^4}$ is selected from -N($\mathbf{R^8}$,$\mathbf{R^9}$), wherein $\mathbf{R^8}$ and $\mathbf{R^9}$ are as defined in the claims and the description.

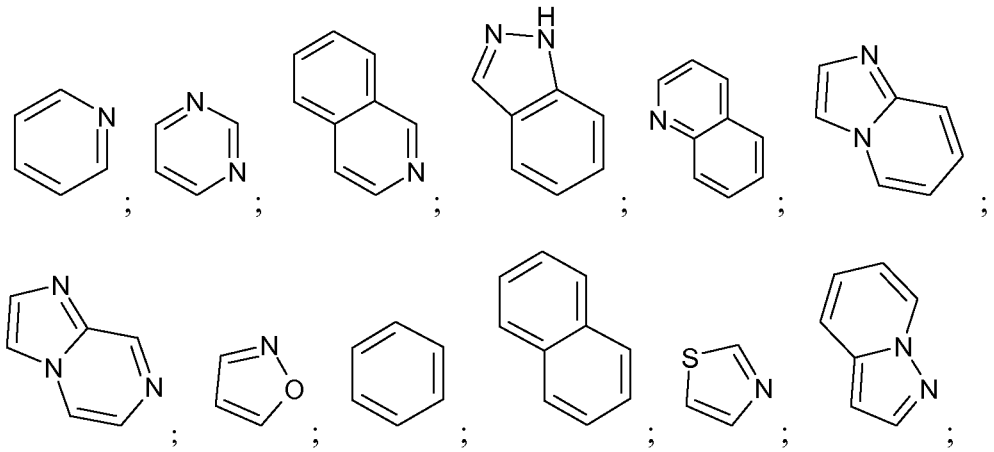
In a preferred embodiment the invention relates to compounds of formula (**I**), wherein $\mathbf{R^4}$ is selected from -C_{6-10}aryl, 5-14 membered heteroaryl, each of which group is optionally and independently substituted with one or more, independently selected, $\mathbf{R^7}$, or $\mathbf{R^4}$ is selected from 5-14 membered aromatic ring system, -C_{5-7}cycloalkyl, each of which group is optionally and independently substituted with one or more, independently selected, $\mathbf{R^{7a}}$

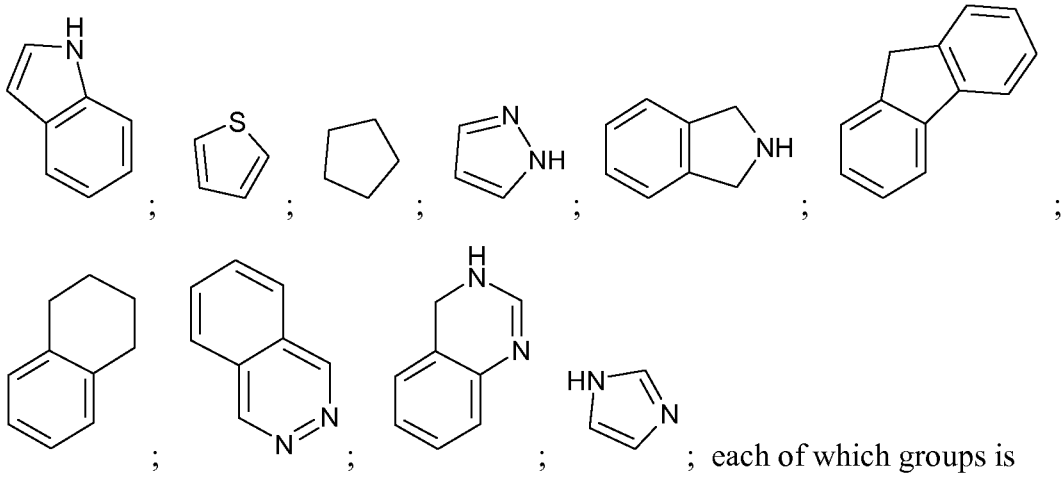
or $\mathbf{R^4}$ is selected from -N($\mathbf{R^8}$,$\mathbf{R^9}$), wherein $\mathbf{R^7}$, $\mathbf{R^{7a}}$, $\mathbf{R^8}$ and $\mathbf{R^9}$ are as defined in the claims and in the description.

In a preferred embodiment the invention relates to compounds of formula (**I**), wherein $\mathbf{R^4}$ is selected from -C_{6-10}aryl, 5-14 membered heteroaryl, 5-14 membered aromatic ring system, each of which group is optionally and independently substituted with one or more, independently selected, $\mathbf{R^7}$ or $\mathbf{R^{7a}}$ as defined in the claims and the description.

In a preferred embodiment the invention relates to compounds of formula (**I**), wherein $\mathbf{R^4}$ is selected from -C_{6-10}aryl, 5-14 membered heteroaryl, each of which group is optionally and independently substituted with one or more, independently selected, $\mathbf{R^7}$, or $\mathbf{R^4}$ is 5-14 membered aromatic ring system, each of which group is optionally and independently substituted with one or more, independently selected, $\mathbf{R^{7a}}$,wherein $\mathbf{R^7}$ and $\mathbf{R^{7a}}$ are as defined in the claims and in the description.

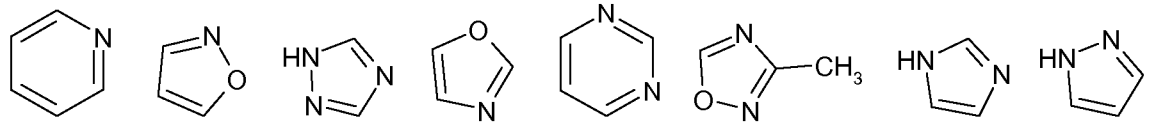
In a preferred embodiment the invention relates to compounds of formula (**I**), wherein $\mathbf{R^4}$ is selected from –H, -C_{1-3}alkyl, -CH_2-phenyl, -N(CH_3)-SO_2-phenyl, -N(CH_3)CO-$\mathbf{R^{10}}$; -NH-CO-$\mathbf{R^{10}}$, wherein $\mathbf{R^{10}}$ is independently selected from morpholin, cyclopentyl, phenyl, or $\mathbf{R^4}$ is selected from



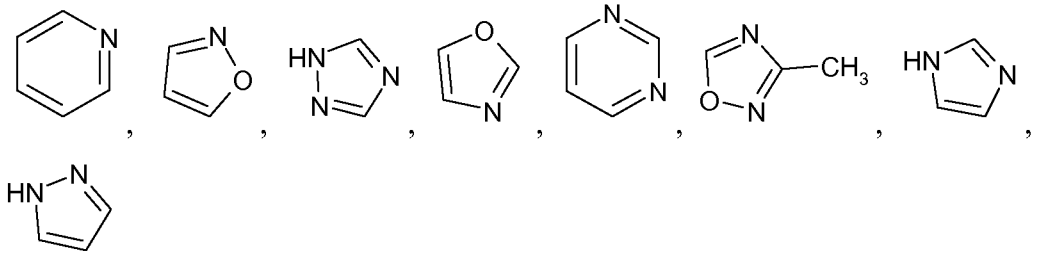


; each of which groups is optionally substituted as defined in the claims and the description.

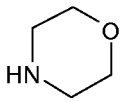
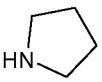
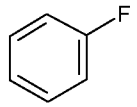
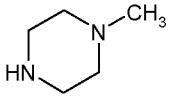
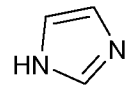
In a preferred embodiment the invention relates to compounds of formula (**I**), wherein $\mathbf{R^6}$ is selected from -F, -Cl, -CN $-CH_3$, $-O-CH_3$, $-C(O)NHCH_3$, $-C(O)NH_2$, $C(O)OCH_3$, -C(O)-morpholinyl, $-C(O)-O-CH_2$-tetrahydropyran, phenyl,

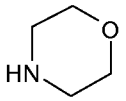
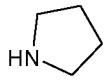
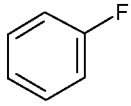
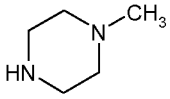
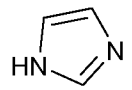


In a preferred embodiment the invention relates to compounds of formula (**I**), wherein $\mathbf{R^{6a}}$ is selected from =O, -F, -Cl, -CN $-CH_3$, $-O-CH_3$, $-C(O)NHCH_3$, $-C(O)NH_2$, $C(O)OCH_3$, -C(O)-morpholinyl, $-C(O)-O-CH_2$-tetrahydropyran, phenyl,



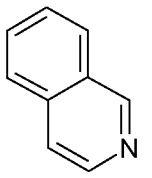
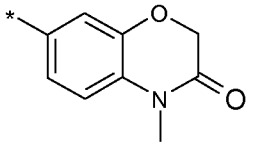
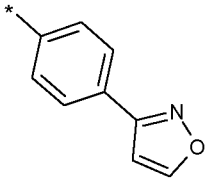
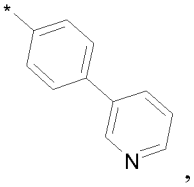
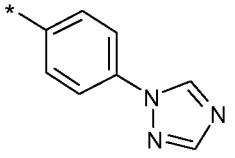
In a preferred embodiment the invention relates to compounds of formula (**I**), wherein $\mathbf{R^7}$ is selected from -CN, -F, -Cl, $-CF_3$, $-NO_2$, $-CH_3$, $-CH_2CH_3$, $-CH_2(CH_3)_2$, $-S-CH_3$, $-NH_2$, $-NH-CH_3$, $-N(CH_3)_2$, -C(O)OH, $-C(O)OCH_3$, $-C(O)NH_2$, $-C(O)NH-CH_3$, $-NHC(O)CH_3$, -O-

CH_3, -O-CH_2CH_3, pyridyl, phenyl, -O-Phenyl, -CH_2-phenyl,  ,  ,  ,  ,  .

In a preferred embodiment the invention relates to compounds of formula (**I**), wherein $\mathbf{R^{7a}}$ is selected from =O, -CN, -F, -Cl, -CF_3, -NO_2, -CH_3, -CH_2CH_3, -$CH_2(CH_3)_2$, -S-CH_3, -NH_2, -NH-CH_3, -$N(CH_3)_2$, -C(O)OH, -$C(O)OCH_3$, -$C(O)NH_2$, -C(O)NH-CH_3, -NHC(O)CH_3, -O-CH_3, -O-CH_2CH_3, pyridyl, phenyl, -O-Phenyl, -CH_2-phenyl,  ,  ,  ,  ,  .

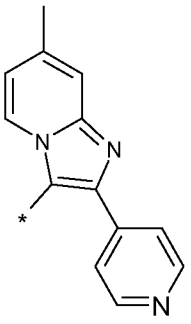
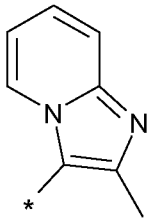
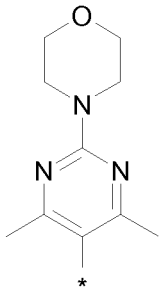
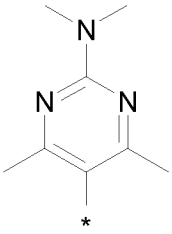
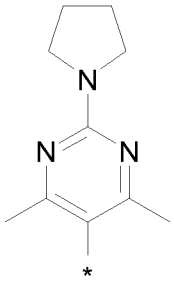
In a preferred embodiment the invention relates to compounds of formula (**I**), wherein $\mathbf{R^4}$ and $\mathbf{R^5}$ taken together form a phenyl.

In a preferred embodiment the invention relates to compounds of formula (**I**), wherein $\mathbf{R^3}$ is selected from

 ,  ,  ,  , 

and .

In a preferred embodiment the invention relates to compounds of formula (**I**), wherein $\mathbf{R^4}$ is selected from


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In another aspect the invention relates to compounds of general formula **(I)** or of anyone of the embodiments as disclosed above for use in the treatment of cancer.

In another aspect the invention relates to compounds of general formula **(I)** or of anyone of the embodiments as disclosed above – or the pharmaceutically acceptable salts thereof – as medicaments.

In another aspect the invention relates to compounds of general formula **(I)** or of anyone of the embodiments as disclosed above – or the pharmaceutically acceptable salts thereof – for use in the treatment and/or prevention of cancer, infections, inflammations and autoimmune diseases.

In another aspect the invention relates to compounds of general formula **(I)** or of anyone of the embodiments as disclosed above – or the pharmaceutically acceptable salts thereof – for use in the treatment and/or prevention of cancer, preferably of carcinomas of the breast, prostate, brain or ovary, non-small-cell bronchial carcinomas (NSCLC), melanomas and chronic lymphatic leukaemias (CLL).

In another aspect the invention relates to compounds of general formula **(I)** or of anyone of the embodiments as disclosed above – or the pharmaceutically acceptable salts thereof – for use in the treatment and/or prevention of carcinomas of the breast, prostate, brain or ovary, non-small-cell bronchial carcinomas (NSCLC), melanomas and chronic lymphatic leukaemias (CLL).

In another aspect the invention relates to a method for the treatment and/or prevention of cancer comprising administering a therapeutically effective amount of a compound of general formula **(I)** or of anyone of the embodiments as disclosed above – or one of the pharmaceutically acceptable salts thereof – to a human being.

In another aspect the invention relates to a method for the treatment and/or prevention of carcinoma of the breast, prostate, brain or ovary, non-small-cell bronchial carcinomas (NSCLC), melanomas and chronic lymphatic leukemias (CLL) comprising administering a therapeutically effective amount of a compound of general formula **(I)** or of anyone of the embodiments as disclosed above – or one of the pharmaceutically acceptable salts thereof – to a human being.

In another aspect the invention relates to a pharmaceutical preparation containing as active substance one or more compounds of general formula **(I)** or of anyone of the embodiments as disclosed above – or the pharmaceutically acceptable salts thereof – optionally in combination with conventional excipients and/or carriers.

In another aspect the invention relates to a pharmaceutical preparation comprising a compound of general formula **(I)** or of anyone of the embodiments as disclosed above – or one of the pharmaceutically acceptable salts thereof – and at least one other cytostatic or cytotoxic active substance, different from formula **(I)**.

Definitions

Terms that are not specifically defined here have the meanings that are apparent to the skilled man in the light of the overall disclosure and the context as a whole.

As used herein, the following definitions apply, unless stated otherwise:

In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, -C_{1-5}alkyl means an alkyl group or radical having 1 to 5 carbon atoms. In general, for groups comprising two or more subgroups, the first named sub-group is the radical attachment point, for example the substitutent -C_{1-5}alkyl-C_{3-10}cylcoalkyl, means a C_{3-10}cylcoalkyl group which is bound to a C_{1-5}alkyl, the

latter of which is bound to the core structure or to the group to which the substitutent is attached.

The indication of the number of members in groups that contain one or more heteroatom(s) (heteroalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocycylalkyl) relates to the total atomic number of all the ring members or chain members or the total of all the ring and chain members.

The person skilled in the art will appreciate that substituent groups containing a nitrogen atom can also be indicated as **amine** or **amino**. Similarly, groups containing oxygen atom can also be indicated with **-oxy**, like for example **alkoxy**. Groups containing –C(O)- can also be indicated as **carboxy**; groups containing -NC(O)- can also be indicated as **amide**; groups containing –NC(O)N- can also be indicated as **urea**; groups containing $-NS(O)_2-$ can also be indicated as **sulfonamide**.

Alkyl denotes monovalent, saturated hydrocarbon chains, which may be present in both linear and branched form. If an **alkyl** is substituted, the substitution may take place independently of one another, by mono- or polysubstitution in each case, on all the hydrogen-carrying carbon atoms.

The term "**C_{1-5}-alkyl**" includes for example methyl (Me; $-CH_3$), ethyl (Et; $-CH_2CH_3$), 1-propyl (*n*-propyl; *n*-Pr; $-CH_2CH_2CH_3$), 2-propyl (*i*-Pr; *iso*-propyl; $-CH(CH_3)_2$), 1-butyl (*n*-butyl; *n*-Bu; $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (*iso*-butyl; *i*-Bu; $-CH_2CH(CH_3)_2$), 2-butyl (*sec*-butyl; *sec*-Bu; $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (*tert*-butyl; *t*-Bu; $-C(CH_3)_3$), 1-pentyl (*n*-pentyl; $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 3-methyl-1-butyl (*iso*-pentyl; $-CH_2CH_2CH(CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 2,2-dimethyl-1-propyl (*neo*-pentyl; $-CH_2C(CH_3)_3$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$).

By the terms propyl, butyl, pentyl, etc. without any further definition are meant saturated hydrocarbon groups with the corresponding number of carbon atoms, wherein all isomeric forms are included.

The above definition for **alkyl** also applies if **alkyl** is a part of another group such as for example C_{x-y}-**alkyl**amino or C_{x-y}-**alkyl**oxy or C_{x-y}-**alk**oxy, wherein C_{x-y}-**alkyl**oxy and C_{x-y}-**alk**oxy indicate the same group.

The term **alkylene** can also be derived from **alkyl**. **Alkylene** is bivalent, unlike **alkyl,** and requires two binding partners. Formally, the second valency is produced by removing a hydrogen atom in an **alkyl**. Corresponding groups are for example $-CH_3$ and $-CH_2$, $-CH_2CH_3$ and $-CH_2CH_2$ or $>CHCH_3$ etc.

The term "**C_{1-4}-alkylene**" includes for example $-(CH_2)-$, $-(CH_2-CH_2)-$, $-(CH(CH_3))-$, $-(CH_2-CH_2-CH_2)-$, $-(C(CH_3)_2)-$, $-(CH(CH_2CH_3))-$, $-(CH(CH_3)-CH_2)-$, $-(CH_2-CH(CH_3))-$, $-(CH_2-CH_2-CH_2-CH_2)-$, $-(CH_2-CH_2-CH(CH_3))-$, $-(CH(CH_3)-CH_2-CH_2)-$, $-(CH_2-CH(CH_3)-CH_2)-$, $-(CH_2-C(CH_3)_2)-$, $-(C(CH_3)_2-CH_2)-$, $-(CH(CH_3)-CH(CH_3))-$, $-(CH_2-CH(CH_2CH_3))-$, $-(CH(CH_2CH_3)-CH_2)-$, $-(CH(CH_2CH_2CH_3))-$, $-(CHCH(CH_3)_2)-$ and $-C(CH_3)(CH_2CH_3)-$.

Other examples of **alkylene** are methylene, ethylene, propylene, 1-methylethylene, butylene, 1-methylpropylene, 1.1-dimethylethylene, 1,2-dimethylethylene, pentylene, 1,1-dimethylpropylene, 2,2-dimethylpropylene, 1,2-dimethylpropylene, 1,3-dimethylpropylene, etc.

By the generic terms propylene, butylene, pentylene, hexylene etc. without any further definition are meant all the conceivable isomeric forms with the corresponding number of carbon atoms, i.e. propylene includes 1-methylethylene and butylene includes 1-methylpropylene, 2-methylpropylene, 1,1-dimethylethylene and 1,2-dimethylethylene.

The above definition for **alkylene** also applies if **alkylene** is part of another group such as for example in HO-C_{x-y}-**alkylen**amino or H_2N-C_{x-y}-**alkylen**oxy.

Unlike **alkyl, alkenyl** consists of at least two carbon atoms, wherein at least two adjacent carbon atoms are joined together by a C-C double bond. If in an **alkyl** as hereinbefore defined having at least two carbon atoms, two hydrogen atoms on adjacent carbon atoms are formally removed and the free valencies are saturated to form a second bond, the corresponding **alkenyl** is formed.

Examples of **alkenyl** are vinyl (ethenyl), prop-1-enyl, allyl (prop-2-enyl), isopropenyl, but-1-enyl, but-2-enyl, but-3-enyl, 2-methyl-prop-2-enyl, 2-methyl-prop-1-enyl,

1-methyl-prop-2-enyl, 1-methyl-prop-1-enyl, 1-methylidenepropyl, pent-1-enyl, pent-2-enyl, pent-3-enyl, pent-4-enyl, 3-methyl-but-3-enyl, 3-methyl-but-2-enyl, 3-methyl-but-1-enyl, hex-1-enyl, hex-2-enyl, hex-3-enyl, hex-4-enyl, hex-5-enyl, 2,3-dimethyl-but-3-enyl, 2,3-dimethyl-but-2-enyl, 2-methylidene-3-methylbutyl, 2,3-dimethyl-but-1-enyl, hexa-1,3-dienyl, hexa-1,4-dienyl, penta-1,4-dienyl, penta-1,3-dienyl, buta-1,3-dienyl, 2,3-dimethylbuta-1,3-diene etc.

By the generic terms propenyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, heptadienyl, octadienyl, nonadienyl, decadienyl etc. without any further definition are meant all the conceivable isomeric forms with the corresponding number of carbon atoms, i.e. propenyl includes prop-1-enyl and prop-2-enyl, butenyl includes but-1-enyl, but-2-enyl, but-3-enyl, 1-methyl-prop-1-enyl, 1-methyl-prop-2-enyl etc.

Alkenyl may optionally be present in the *cis* or *trans* or *E* or *Z* orientation with regard to the double bond(s).

The above definition for **alkenyl** also applies when **alkenyl** is part of another group such as for example in C_{x-y}-**alkenyl**amino or C_{x-y}-**alkenyl**oxy.

Unlike **alkylene, alkenylene** consists of at least two carbon atoms, wherein at least two adjacent carbon atoms are joined together by a C-C double bond. If in an **alkylene** as hereinbefore defined having at least two carbon atoms, two hydrogen atoms at adjacent carbon atoms are formally removed and the free valencies are saturated to form a second bond, the corresponding **alkenylene** is formed.

Examples of **alkenylene** are ethenylene, propenylene, 1-methylethenylene, butenylene, 1-methylpropenylene, 1,1-dimethylethenylene, 1,2-dimethylethenylene, pentenylene, 1,1-dimethylpropenylene, 2,2-dimethylpropenylene, 1,2-dimethylpropenylene, 1,3-dimethylpropenylene, hexenylene etc.

By the generic terms propenylene, butenylene, pentenylene, hexenylene etc. without any further definition are meant all the conceivable isomeric forms with the corresponding number of carbon atoms, i.e. propenylene includes 1-methylethenylene and butenylene includes 1-methylpropenylene, 2-methylpropenylene, 1,1-dimethylethenylene and 1,2-dimethylethenylene.

Alkenylene may optionally be present in the *cis* or *trans* or *E* or *Z* orientation with regard to the double bond(s).

The above definition for **alkenylene** also applies when **alkenylene** is a part of another group as in for example HO-C_{x-y}-**alkenylen**amino or H_2N-C_{x-y}-**alkenylen**oxy.

Unlike **alkyl, alkynyl** consists of at least two carbon atoms, wherein at least two adjacent carbon atoms are joined together by a C-C triple bond. If in an **alkyl** as hereinbefore defined having at least two carbon atoms, two hydrogen atoms in each case at adjacent carbon atoms are formally removed and the free valencies are saturated to form two further bonds, the corresponding **alkynyl** is formed.

Examples of **alkynyl** are ethynyl, prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl, but-3-ynyl, 1-methyl-prop-2-ynyl, pent-1-ynyl, pent-2-ynyl, pent-3-ynyl, pent-4-ynyl, 3-methyl-but-1-ynyl.

By the generic terms propynyl, butynyl, pentynyl, etc. without any further definition are meant all the conceivable isomeric forms with the corresponding number of carbon atoms, i.e. propynyl includes prop-1-ynyl and prop-2-ynyl, butynyl includes but-1-ynyl, but-2-ynyl, but-3-ynyl, 1-methyl-prop-1-ynyl, 1-methyl-prop-2-ynyl.

If a hydrocarbon chain carries both at least one double bond and also at least one triple bond, by definition it belongs to the **alkynyl** subgroup.

The above definition for **alkynyl** also applies if **alkynyl** is part of another group, as in C_{x-y}-**alkynyl**amino or C_{x-y}-**alkynyl**oxy, for example.

Unlike **alkylene, alkynylene** consists of at least two carbon atoms, wherein at least two adjacent carbon atoms are joined together by a C-C triple bond. If in an **alkylene** as hereinbefore defined having at least two carbon atoms, two hydrogen atoms in each case at adjacent carbon atoms are formally removed and the free valencies are saturated to form two further bonds, the corresponding **alkynylene** is formed.

Examples of **alkynylene** are ethynylene, propynylene, 1-methylethynylene, butynylene, 1-methylpropynylene, 1,1-dimethylethynylene, 1,2-dimethylethynylene, pentynylene,

1,1-dimethylpropynylene, 2,2-dimethylpropynylene, 1,2-dimethylpropynylene, 1,3-dimethylpropynylene, hexynylene etc.

By the generic terms propynylene, butynylene, pentynylene, ect. without any further definition are meant all the conceivable isomeric forms with the corresponding number of carbon atoms, i.e. propynylene includes 1-methylethynylene and butynylene includes 1-methylpropynylene, 2-methylpropynylene, 1,1-dimethylethynylene and 1,2-dimethylethynylene.

The above definition for **alkynylene** also applies if **alkynylene** is part of another group, as in HO-C_{x-y}-**alkynylene**amino or H_2N-C_{x-y}-**alkynylene**oxy, for example.

By **heteroatoms** are meant oxygen, nitrogen and sulphur atoms.

Haloalkyl (haloalkenyl, haloalkynyl) is derived from the previously defined **alkyl (alkenyl, alkynyl)** by replacing one or more hydrogen atoms of the hydrocarbon chain independently of one another by halogen atoms, which may be identical or different. If a **haloalkyl (haloalkenyl, haloalkynyl)** is to be further substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon atoms.

Examples of **haloalkyl (haloalkenyl, haloalkynyl)** are $-CF_3$, $-CHF_2$, $-CH_2F$, $-CF_2CF_3$, $-CHFCF_3$, $-CH_2CF_3$, $-CF_2CH_3$, $-CHFCH_3$, $-CF_2CF_2CF_3$, $-CF_2CH_2CH_3$, $-CF{=}CF_2$, $-CCl{=}CH_2$, $-CBr{=}CH_2$, $-CI{=}CH_2$, $-C{\equiv}C-CF_3$, $-CHFCH_2CH_3$, $-CHFCH_2CF_3$ etc.

From the previously defined **haloalkyl (haloalkenyl, haloalkynyl)** are also derived the terms **haloalkylene (haloalkenylene, haloalkynylene)**. **Haloalkylene (haloalkenyl, haloalkynyl)**, unlike **haloalkyl**, is bivalent and requires two binding partners. Formally, the second valency is formed by removing a hydrogen atom from a **haloalkyl**.

Corresponding groups are for example $-CH_2F$ and $-CHF-$, $-CHFCH_2F$ and $-CHFCHF-$ or $>CFCH_2F$ etc.

The above definitions also apply if the corresponding halogen groups are part of another group.

Halogen relates to fluorine, chlorine, bromine and/or iodine atoms.

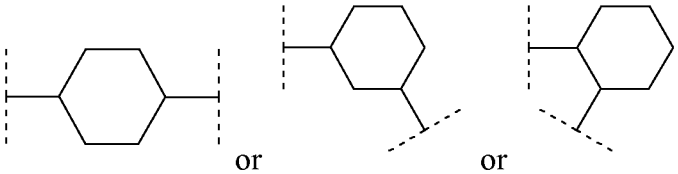
Cycloalkyl is made up of the subgroups **monocyclic hydrocarbon rings**, **bicyclic hydrocarbon rings** and **spiro-hydrocarbon rings**. The systems are saturated. In bicyclic hydrocarbon rings two rings are joined together so that they have at least two carbon atoms together. In spiro-hydrocarbon rings a carbon atom (spiroatom) belongs to two rings together. If a **cycloalkyl** is to be substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon atoms. **Cycloalkyl** itself may be linked as a substituent to the molecule via every suitable position of the ring system.

Examples of **cycloalkyl** are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.0]hexyl, bicyclo[3.2.0]heptyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo[4.3.0]nonyl (octahydroindenyl), bicyclo[4.4.0]decyl (decahydronaphthalene), bicyclo[2.2.1]heptyl (norbornyl), bicyclo[4.1.0]heptyl (norcaranyl), bicyclo-[3.1.1]heptyl (pinanyl), spiro[2.5]octyl, spiro[3.3]heptyl etc.

The above definition for **cycloalkyl** also applies if **cycloalkyl** is part of another group as in C_{x-y}-**cycloalkyl**amino or C_{x-y}-**cycloalkyl**oxy, for example.

If the free valency of a **cycloalkyl** is saturated, then an **alicyclic group** is obtained.

The term **cycloalkylene** can thus be derived from the previously defined **cycloalkyl**. **Cycloalkylene**, unlike **cycloalkyl**, is bivalent and requires two binding partners. Formally, the second valency is obtained by removing a hydrogen atom from a **cycloalkyl**. Corresponding groups are for example



cyclohexyl and or or (cyclohexylene).

The above definition for **cycloalkylene** also applies if **cycloalkylene** is part of another group as in HO-C_{x-y}-**cycloalkylene**amino or H_2N-C_{x-y}-**cycloalkylene**oxy, for example.

Cycloalkenyl is also made up of the subgroups **monocyclic hydrocarbon rings**, **bicyclic hydrocarbon rings** and **spiro-hydrocarbon rings**. However, the systems are unsaturated, i.e. there is at least one C-C double bond but no aromatic system. If in a **cycloalkyl** as hereinbefore defined two hydrogen atoms at adjacent cyclic carbon atoms are formally

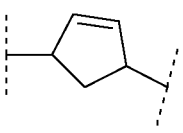
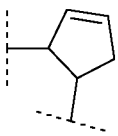
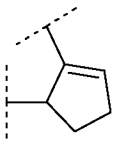
removed and the free valencies are saturated to form a second bond, the corresponding **cycloalkenyl** is obtained. If a **cycloalkenyl** is to be substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon atoms. **Cycloalkenyl** itself may be linked as a substituent to the molecule via every suitable position of the ring system.

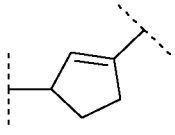
Examples of **cycloalkenyl** are cycloprop-1-enyl, cycloprop-2-enyl, cyclobut-1-enyl, cyclobut-2-enyl, cyclopent-1-enyl, cyclopent-2-enyl, cyclopent-3-enyl, cyclohex-1-enyl, cyclohex-2-enyl, cyclohex-3-enyl, cyclohept-1-enyl, cyclohept-2-enyl, cyclohept-3-enyl, cyclohept-4-enyl, cyclobuta-1,3-dienyl, cyclopenta-1,4-dienyl, cyclopenta-1,3-dienyl, cyclopenta-2,4-dienyl, cyclohexa-1,3-dienyl, cyclohexa-1,5-dienyl, cyclohexa-2,4-dienyl, cyclohexa-1,4-dienyl, cyclohexa-2,5-dienyl, bicyclo[2.2.1]hepta-2,5-dienyl (norborna-2,5-dienyl), bicyclo[2.2.1]hept-2-enyl (norbornenyl), spiro[4.5]dec-2-ene etc.

The above definition for **cycloalkenyl** also applies when **cycloalkenyl** is part of another group as in C_{x-y}-**cycloalkenyl**amino or C_{x-y}-**cycloalkenyl**oxy, for example.

If the free valency of a **cycloalkenyl** is saturated, then an **unsaturated alicyclic group** is obtained.

The term **cycloalkenylene** can thus be derived from the previously defined **cycloalkenyl**. **Cycloalkenylene**, unlike **cycloalkenyl**, is bivalent and requires two binding partners. Formally the second valency is obtained by removing a hydrogen atom from a **cycloalkenyl**. Corresponding groups are for example

cyclopentenyl and  or  or  or



(cyclopentenylene) etc.

The above definition for **cycloalkenylene** also applies when **cycloalkenylene** is part of another group as in HO-C_{x-y}-**cycloalkenylene**amino or H_2N-C_{x-y}-**cycloalkenylene**oxy, for example.

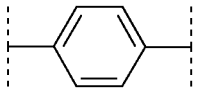
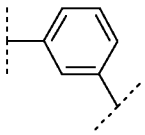
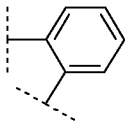
Aryl denotes a mono-, bi- or tricyclic group with at least one aromatic carbocycle. Preferably it denotes a a monocyclic group with six carbon atoms (phenyl) or a bicyclic group with nine or ten carbon atoms (two six-membered rings or one six-membered ring with a five-membered ring), wherein the second ring may also be aromatic or, however, may also be saturated or partially saturated. If an **aryl** is to be substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon atoms. **Aryl** itself may be linked as a substituent to the molecule via every suitable position of the ring system.

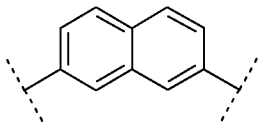
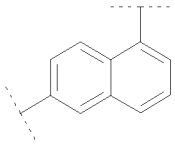
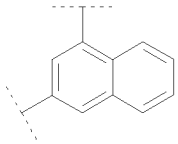
Examples of **aryl** are phenyl, naphthyl, indanyl (2,3-dihydroindenyl), indenyl, anthracenyl, phenanthrenyl, tetrahydronaphthyl (1,2,3,4-tetrahydronaphthyl, tetralinyl), dihydronaphthyl (1,2- dihydronaphthyl), fluorenyl etc.

The above definition of **aryl** also applies when **aryl** is part of another group as in **aryl**amino or **aryl**oxy, for example.

If the free valency of an **aryl** is saturated, then an **aromatic group** is obtained.

The term **arylene** can also be derived from the previously defined **aryl**. **Arylene**, unlike **aryl**, is bivalent and requires two binding partners. Formally, the second valency is formed by removing a hydrogen atom from an **aryl**. Corresponding groups are e.g.

phenyl and  or  or  (*o*, *m*, *p*-phenylene),

naphthyl and  or  or  etc.

The above definition for **arylene** also applies when **arylene** is part of another group as in HO-**arylene**amino or H_2N-**arylene**oxy for example.

Heterocyclyl denotes ring systems, which are derived from the previously defined **cycloalkyl**, **cycloalkenyl** and **aryl** by replacing one or more of the groups -CH_2- independently of one another in the hydrocarbon rings by the groups -O-, -S- or -NH- or by replacing one or more of the groups =CH- by the group =N-, wherein a total of not more

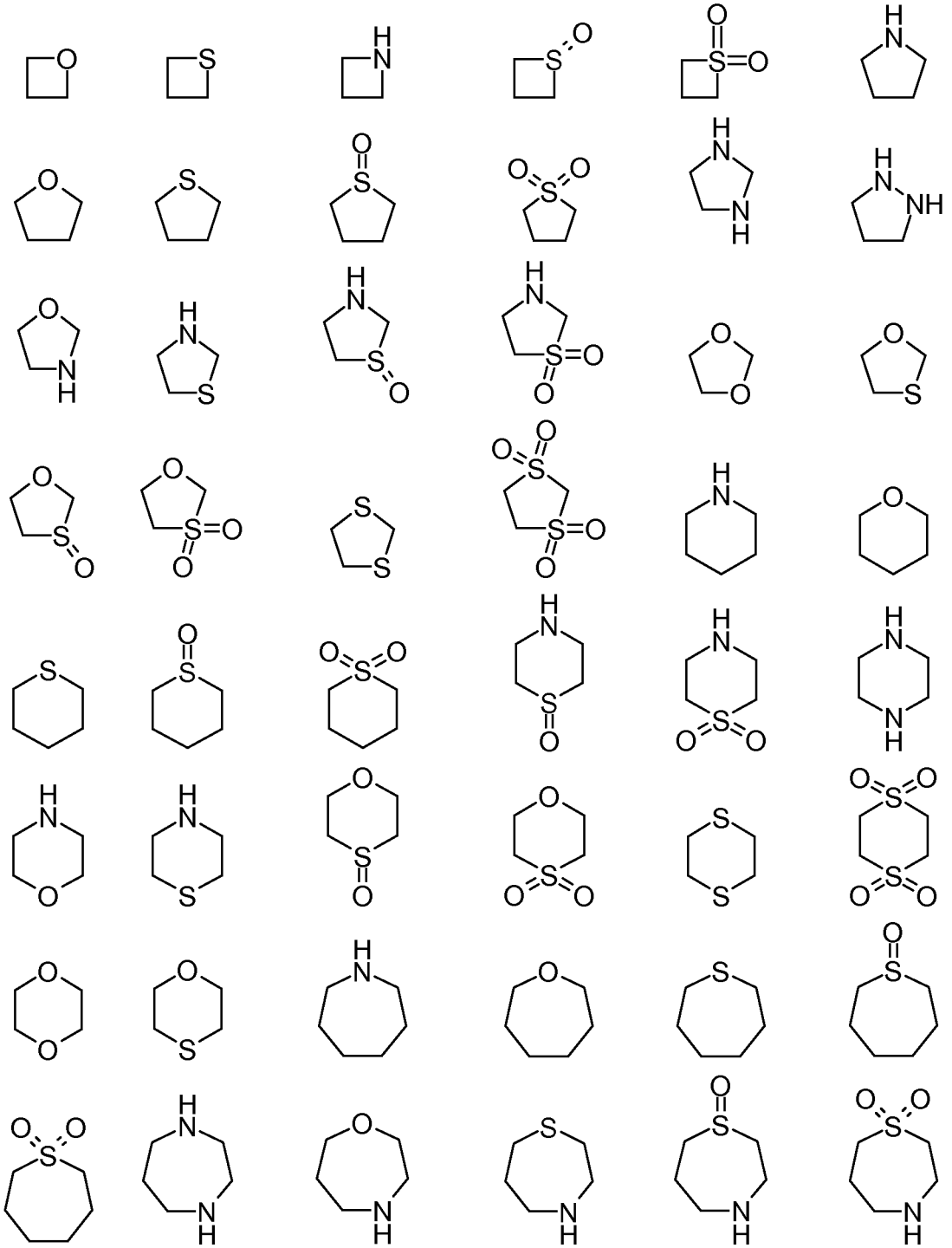
than five heteroatoms may be present, at least one carbon atom may be present between two oxygen atoms and between two sulphur atoms or between one oxygen and one sulphur atom and the ring as a whole must have chemical stability. Heteroatoms may optionally be present in all the possible oxidation stages (sulphur → sulphoxide -SO, sulphone -SO_2-; nitrogen → N-oxide). Preferred heterocylyl are non aromatic heterocyclyl.

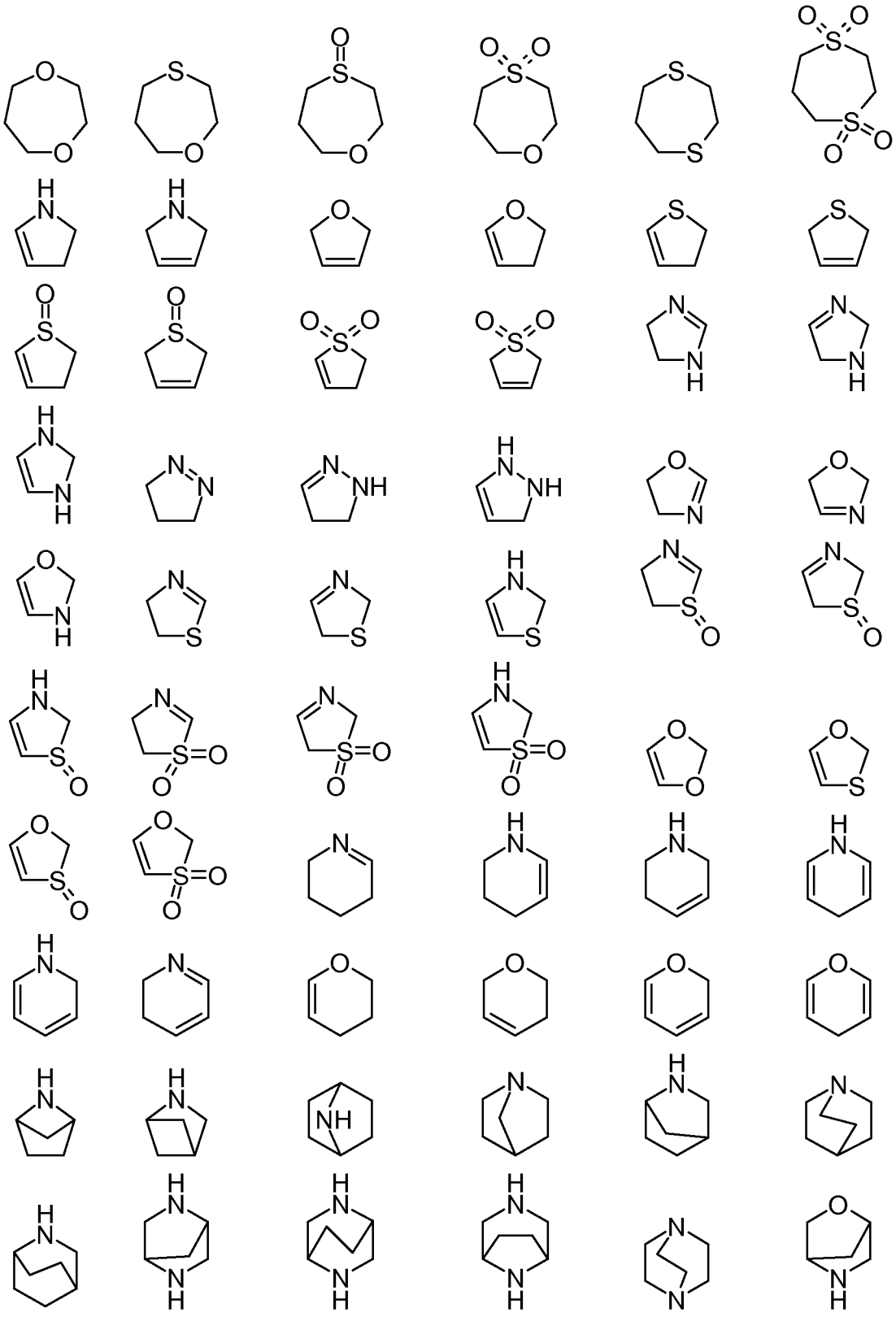
A direct result of the derivation from **cycloalkyl**, **cycloalkenyl** and **aryl** is that **heterocyclyl** is made up of the subgroups **monocyclic heterorings**, **bicyclic heterorings**, **tricyclic heterorings** and **spiro-heterorings**, which may be present in saturated or unsaturated form. By unsaturated is meant that there is at least one double bond in the ring system in question, but no heteroaromatic system is formed. In bicyclic heterorings two rings are linked together so that they have at least two (hetero)atoms in common. In spiro-heterorings a carbon atom (spiroatom) belongs to two rings together. If a **heterocyclyl** is substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon and/or nitrogen atoms. **Heterocyclyl** itself may be linked as a substituent to the molecule via every suitable position of the ring system. When the heterocyclyl has a nitrogen atom, the preferred position to bind the heterocyclyl substituent to the molecule is the nitrogen atom.

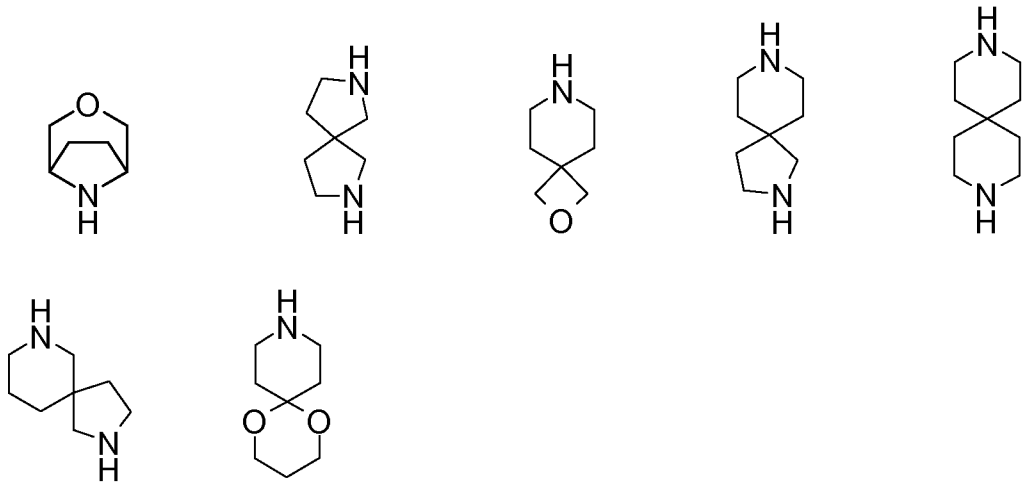
Examples of **heterocyclyl** are tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, thiazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidinyl, piperazinyl, oxiranyl, aziridinyl, azetidinyl, 1,4-dioxanyl, azepanyl, diazepanyl, morpholinyl, thiomorpholinyl, homomorpholinyl, homopiperidinyl, homopiperazinyl, homothiomorpholinyl, thiomorpholinyl-*S*-oxide, thiomorpholinyl-*S,S*-dioxide, 1,3-dioxolanyl, tetrahydropyranyl, tetrahydrothiopyranyl, [1.4]-oxazepanyl, tetrahydrothienyl, homothiomorpholinyl-*S,S*-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl, dihydropyrazinyl, dihydropyridyl, dihydro-pyrimidinyl, dihydrofuryl, dihydropyranyl, tetrahydrothienyl-*S*-oxide, tetrahydrothienyl-*S,S*-dioxide, homothiomorpholinyl-*S*-oxide, 2,3-dihydroazet, 2*H*-pyrrolyl, 4*H*-pyranyl, 1,4-dihydropyridinyl, 8-azabicyclo[3.2.1]octyl, 8-azabicyclo[5.1.0]octyl, 2-oxa-5-azabicyclo[2.2.1]heptyl, 8-oxa-3-aza-bicyclo[3.2.1]octyl, 3,8-diaza-bicyclo[3.2.1]octyl, 2,5-diaza-bicyclo-[2.2.1]heptyl, 1-aza-bicyclo[2.2.2]octyl, 3,8-diaza-bicyclo[3.2.1]octyl, 3,9-diaza-bicyclo[4.2.1]nonyl, 2,6-diaza-bicyclo[3.2.2]-nonyl, 1,4-dioxa-spiro[4.5]decyl, 1-oxa-3.8-diaza-spiro[4.5]decyl, 2,6-diaza-spiro[3.3]-

heptyl, 2,7-diaza-spiro[4.4]nonyl, 2,6-diaza-spiro[3.4]octyl, 3,9-diaza-spiro[5.5]undecyl, 2.8-diaza-spiro[4.5]decyl etc.

Further examples are the structures illustrated below, which may be attached via each hydrogen-carrying atom (exchanged for hydrogen):



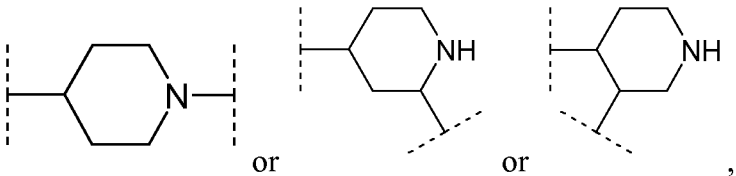


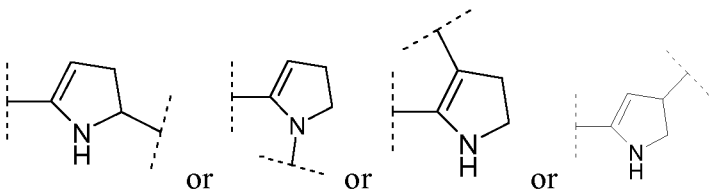


The above definition of **heterocyclyl** also applies if **heterocyclyl** is part of another group as in **heterocyclyl**amino or **heterocyclyl**oxy for example.

If the free valency of a **heteroyclyl** is saturated, then a **heterocyclic group** is obtained.

The term **heterocyclylene** is also derived from the previously defined **heterocyclyl**. **Heterocyclylene**, unlike **heterocyclyl**, is bivalent and requires two binding partners. Formally, the second valency is obtained by removing a hydrogen atom from a **heterocyclyl**. Corresponding groups are for example

piperidinyl and  ,

2,3-dihydro-1*H*-pyrrolyl and  etc.

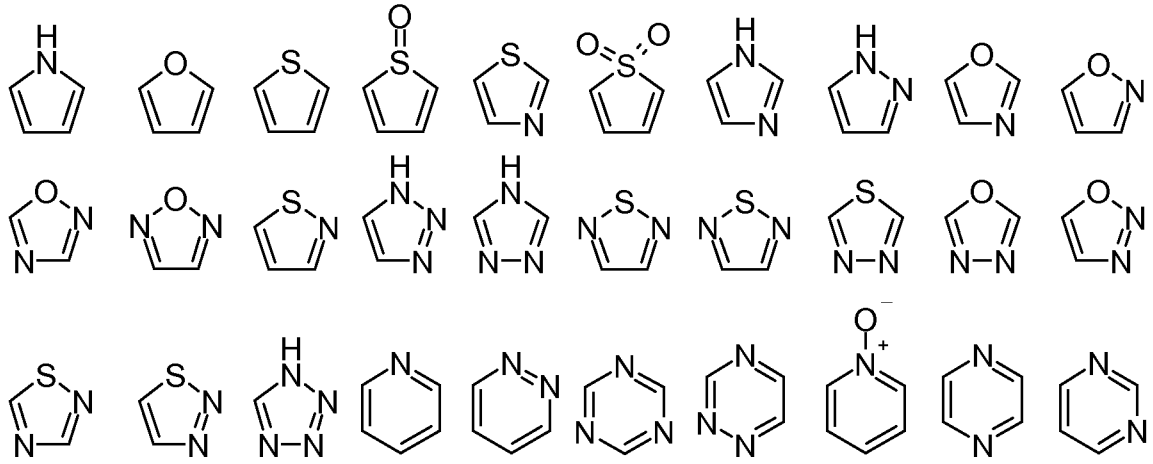
The above definition of **heterocyclylene** also applies if **heterocyclylene** is part of another group as in HO-**heterocyclylene**amino or H_2N-**heterocyclylene**oxy for example.

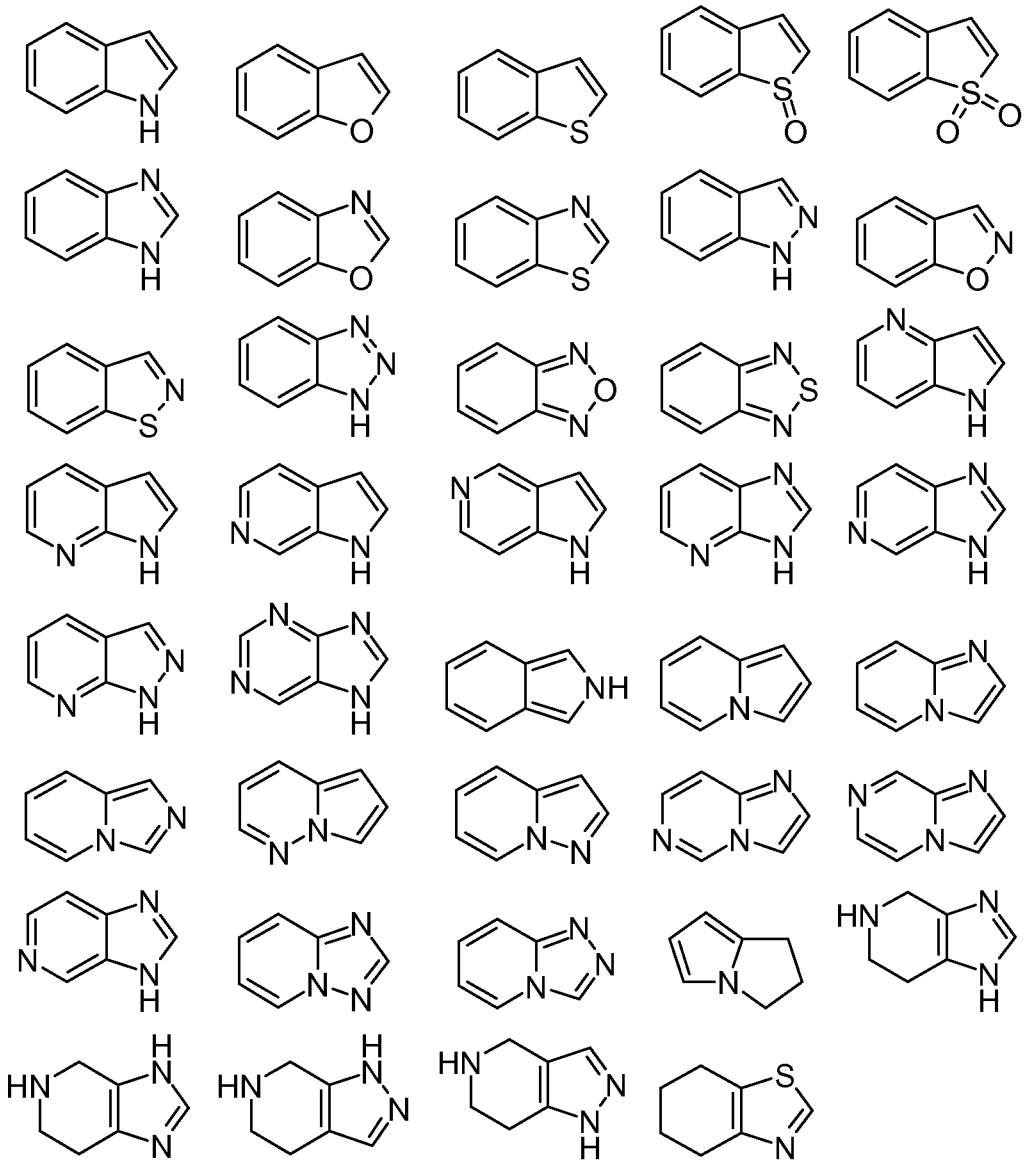
Heteroaryl denotes monocyclic heteroaromatic rings or polycyclic rings with at least one heteroaromatic ring, which compared with the corresponding **aryl** or **cycloalkyl (cycloalkenyl)** contain, instead of one or more carbon atoms, one or more identical or different heteroatoms, selected independently of one another from among nitrogen, sulphur

and oxygen, wherein the resulting group must be chemically stable. The prerequisite for the presence of **heteroaryl** is a heteroatom and a heteroaromatic system. If a **heteroaryl** is to be substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon and/or nitrogen atoms. **Heteroaryl** itself may be linked as a substituent to the molecule via every suitable position of the ring system, both carbon and nitrogen.

Examples of **heteroaryl** are furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, triazinyl, pyridyl-*N*-oxide, pyrrolyl-*N*-oxide, pyrimidinyl-*N*-oxide, pyridazinyl-*N*-oxide, pyrazinyl-*N*-oxide, imidazolyl-*N*-oxide, isoxazolyl-*N*-oxide, oxazolyl-*N*-oxide, thiazolyl-*N*-oxide, oxadiazolyl-*N*-oxide, thiadiazolyl-*N*-oxide, triazolyl-*N*-oxide, tetrazolyl-*N*-oxide, indolyl, isoindolyl, benzofuryl, benzothienyl, benzoxazolyl, benzothiazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, indazolyl, isoquinolinyl, quinolinyl, quinoxalinyl, cinnolinyl, phthalazinyl, quinazolinyl, benzotriazinyl, indolizinyl, oxazolopyridyl, imidazopyridyl, naphthyridinyl, benzoxazolyl, pyridopyridyl, purinyl, pteridinyl, benzothiazolyl, imidazopyridyl, imidazothiazolyl, quinolinyl-*N*-oxide, indolyl-*N*-oxide, isoquinolyl-*N*-oxide, quinazolinyl-*N*-oxide, quinoxalinyl-*N*-oxide, phthalazinyl-*N*-oxide, indolizinyl-*N*-oxide, indazolyl-*N*-oxide, benzothiazolyl-*N*-oxide, benzimidazolyl-*N*-oxide etc.

Further examples are the structures illustrated below, which may be attached via each hydrogen-carrying atom (exchanged for hydrogen):

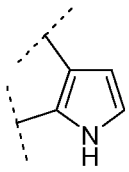
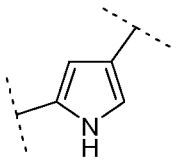
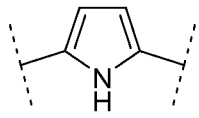
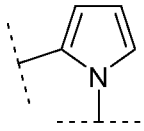




The above definition of **heteroaryl** also applies when **heteroaryl** is part of another group as in **heteroaryl**amino or **heteroaryl**oxy, for example.

If the free valency of a **heteroaryl** is saturated, a **heteroaromatic group** is obtained.

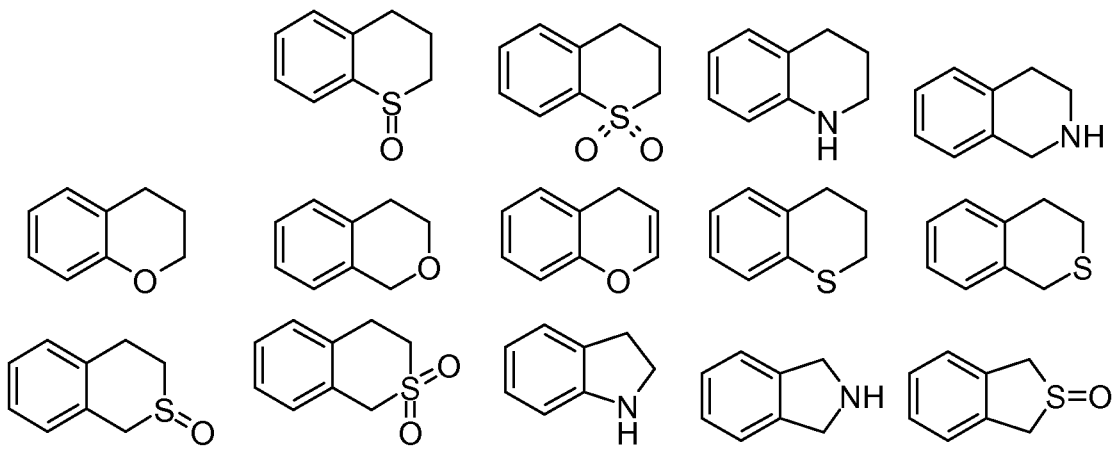
The term **heteroarylene** can therefore be derived from the previously defined **heteroaryl**. **Heteroarylene**, unlike **heteroaryl**, is bivalent and requires two binding partners. Formally, the second valency is obtained by removing a hydrogen atom from a **heteroaryl**. Corresponding groups are for example

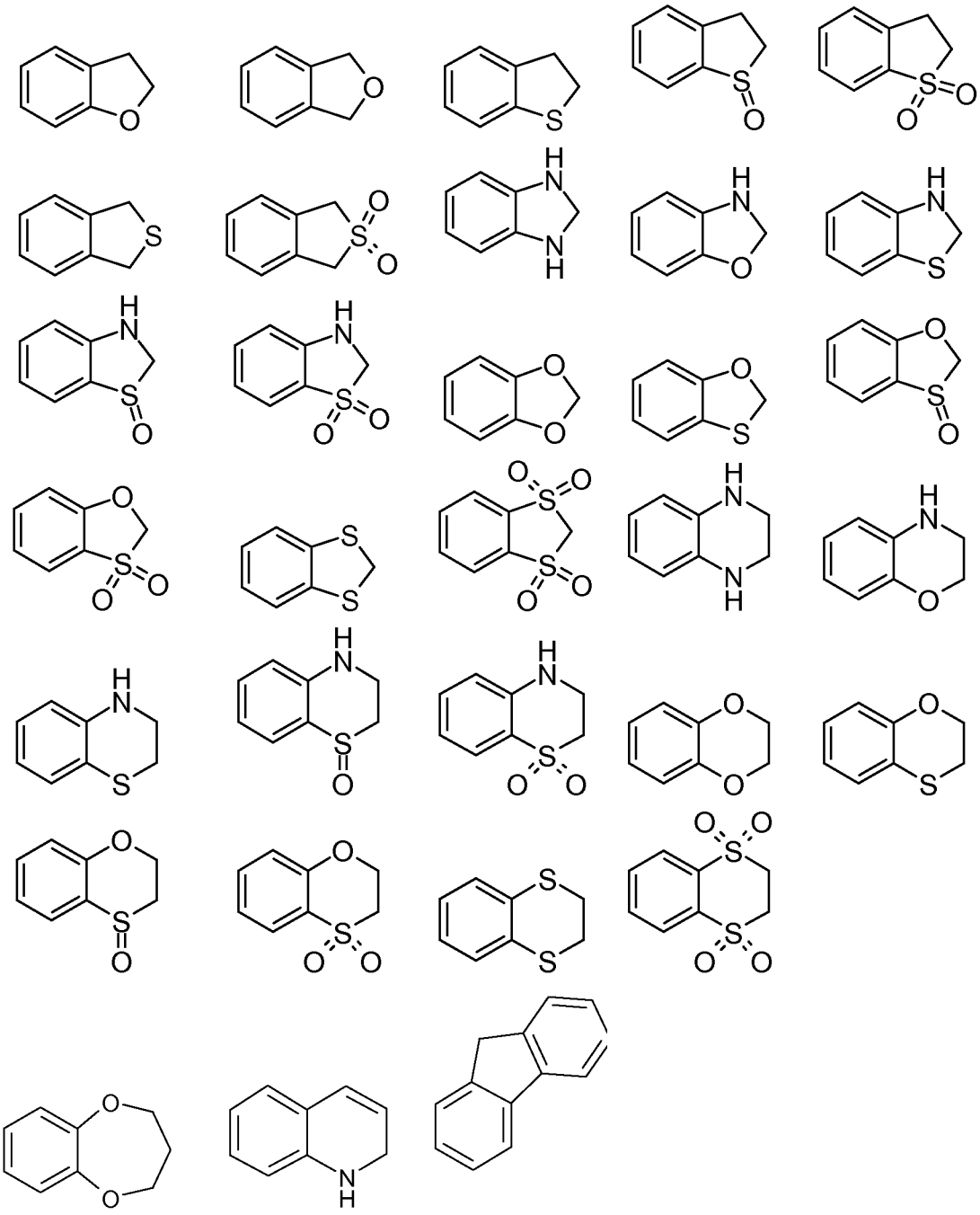
pyrrolyl and  or  or  or  etc.

The above definition of **heteroarylene** also applies when **heteroarylene** is part of another group as in HO-**heteroarylene**amino or H_2N-**heteroarylene**oxy, for example.

The bivalent groups mentioned above (alkylene, alkenylene, alkynylene etc.) may also be part of composite groups (e.g. H_2N-C_{1-4}alkylene- or HO-C_{1-4}alkylene-). In this case one of the valencies is saturated by the attached group (here: $-NH_2$, -OH), so that a composite group of this kind written in this way is only a monovalent substituent over all.

Aromatic ring system means a mono- or multi-ring structure, preferably a multi-ring structure, comprising between one, preferably two, to four cyclic groups, wherein at least one of these cyclic groups is an aromatic or heteroaromatic ring. Multi-ring structure comprises two to four cyclic groups, which are fused together, wherein at least one of the cyclic groups is aromatic (or heteroaromatic). Preferred multi-ring structures are 9-14 membered multi-ring structures. The cyclic groups described herein can be fused together in order to obtain a multi-ring structure, i.e., an aromatic ring system. For example, multi-ring structure comprises an aryl fused with a heterocycle but also a heteroaryl fused to a cycloalkyl. Non-limitative examples of aromatic systems are





By **substituted** is meant that a hydrogen atom which is bound directly to the atom under consideration, is replaced by another atom or another group of atoms (**substituent**). Depending on the starting conditions (number of hydrogen atoms) mono- or polysubstitution may take place on one atom. Substitution with a particular substituent is only possible if the permitted valencies of the substituent and of the atom that is to be

substituted correspond to one another and the substitution leads to a stable compound (i.e. to a compound which is not converted spontaneously, e.g. by rearrangement, cyclisation or elimination).

Bivalent substituents such as =S, =NR, =NOR, =NNRR, =NN(R)C(O)NRR, $=N_2$ or the like, may only be substituted at carbon atoms, wherein the bivalent substituent =O may also be a substituent at sulphur. Generally, substitution may be carried out by a bivalent substituent only at ring systems and requires replacement by two geminal hydrogen atoms, i.e. hydrogen atoms that are bound to the same carbon atom that is saturated prior to the substitution. Substitution by a bivalent substituent is therefore only possible at the group -CH_2- or sulphur atoms of a ring system.

Stereochemistry/Solvates/Hydrates: Unless stated otherwise a structural formula given in the description or in the claims or a chemical name refers to the corresponding compound itself, but also encompasses the tautomers, stereoisomers, optical and geometric isomers (e.g. enantiomers, diastereomers, *E*/*Z* isomers, etc.), racemates, mixtures of separate enantiomers in any desired combinations, mixtures of diastereomers, mixtures of the forms mentioned hereinbefore (if such forms exist) as well as salts, particularly pharmaceutically acceptable salts thereof. The compounds and salts according to the invention may be present in solvated form (e.g. with pharmaceutically acceptable solvents such as e.g. water, ethanol etc.) or in unsolvated form. Generally, for the purposes of the present invention the solvated forms, e.g. hydrates, are to be regarded as of equal value to the unsolvated forms.

Salts: The term "**pharmaceutically acceptable**" is used herein to denote compounds, materials, compositions and/or formulations which are suitable, according to generally recognised medical opinion, for use in conjunction with human and/or animal tissue and do not have or give rise to any excessive toxicity, irritation or immune response or lead to other problems or complications, i.e. correspond overall to an acceptable risk/benefit ratio.

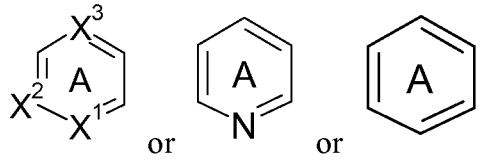
The term "**pharmaceutically acceptable salts**" relates to derivatives of the chemical compounds disclosed in which the parent compound is modified by the addition of acid or base. Examples of pharmaceutically acceptable salts include (without being restricted thereto) salts of mineral or organic acids in relation to basic functional groups such as for example amines, alkali metal or organic salts of acid functional groups such as for example

carboxylic acids, etc. These salts include in particular acetate, ascorbate, benzenesulphonate, benzoate, besylate, bicarbonate, bitartrate, bromide/hydrobromide, Ca-edetate/edetate, camsylate, carbonate, chloride/hydrochloride, citrate, edisylate, ethane disulphonate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolate, glycollylarsnilate, hexylresorcinate, hydrabamine, hydroxymaleate, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, malate, maleate, mandelate, methanesulphonate, mesylate, methylbromide, methylnitrate, methylsulphate, mucate, napsylate, nitrate, oxalate, pamoate, pantothenate, phenyl acetate, phosphate/diphosphate, polygalacturonate, propionate, salicylate, stearate, subacetate, succinate, sulphamide, sulphate, tannate, tartrate, teoclate, toluenesulphonate, triethiodide, ammonium, benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumin and procaine. Other pharmaceutically acceptable salts may be formed with cations of metals such as aluminium, calcium, lithium, magnesium, potassium, sodium, zinc, etc. (cf. also Pharmaceutical salts, Birge, S.M. et al., J. Pharm. Sci., (1977), 66, 1-19).

The pharmaceutically acceptable salts of the present invention may be prepared starting from the parent compound, which carries a basic or acidic functionality, by conventional chemical methods. Generally, such salts may be synthesised by reacting the free acid or base form of these compounds with a sufficient amount of the corresponding base or acid in water or an organic solvent such as for example ether, ethyl acetate, ethanol, isopropanol, acetonitrile (or mixtures thereof).

Salts of acids other than those mentioned above, which are useful for example for purifying or isolating the compounds from the reaction mixtures (e.g. trifluoroacetates), are also to be regarded as part of the invention.

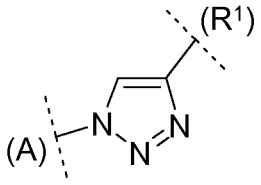
In a representation such as for example



or or

the letter A has the function of a ring designation in order to make it easier, for example, to indicate the attachment of the ring in question to other rings.

For bivalent groups in which it is crucial to determine which adjacent groups they bind and with which valency, the corresponding binding partners are indicated in brackets, where necessary for clarification purposes, as in the following representations:



or (R^2)-C(O)NH- or (R^2)-NHC(O)-;

Groups or substituents are frequently selected from among a number of alternative groups/ substituents with a corresponding group designation (e.g. $\mathbf{R^a}$, $\mathbf{R^b}$ etc). If such a group is used repeatedly to define a compound according to the invention in different molecular parts, it must always be borne in mind that the various uses are to be regarded as totally independent of one another.

By a **therapeutically effective amount** for the purposes of this invention is meant a quantity of substance that is capable of obviating symptoms of illness or of preventing or alleviating these symptoms, or which prolong the survival of a treated patient.

List of abbreviations

ACN	acetonitrile
Bu	butyl
conc.	concentrated
d	day(s)
DCM	dichloromethane
DIPEA	diisopropylethyl amine
DMA	*N,N*-dimethylacetamide
DMAP	*N,N*-dimethylpyridin-4-amine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulphoxide
Et	ethyl
h	hour(s)
HATU	*N*-[(dimethylamino)-(1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl)-methylene]-*N*-methylmethan-aminium hexafluorophosphate *N*-oxide
HPLC	high performance liquid chromatography

*i*Pr	isopropyl
M	molar
m.p.	melting point
Me	methyl
min	minute(s)
mL	millilitre
MS	mass spectrometry
N	normal
NMP	*N*-methylpyrrolindinone
NMR	nuclear resonance spectroscopy
NP	normal phase
ppm	part per million
prep	preparative
R_f	retention factor
RP	reversed phase
RT	room temperature
tert	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
tR	retention time

Other features and avantages of the present invention will become appearent from the following more detailed examples which exemplarily illustrate the principles of the invention without restricting its scope.

General

Unless stated otherwise, all the reactions are carried out in commercially obtainable apparatuses using methods that are commonly used in chemical laboratories. Starting materials that are sensitive to air and/or moisture are stored under protective gas and corresponding reactions and manipulations therewith are carried out under protective gas (nitrogen or argon).

The compounds according to the invention are named in accordance with IUPAC guidelines using the software Lexichem (OpenEye Scientific Software Inc., release 2.0.0).

If a compound is to be represented both by a structural formula and by its nomenclature, in the event of a conflict the structural formula is decisive.

Chromatography

Thin layer chromatography is carried out on ready-made TLC plates of silica gel 60 on glass (with fluorescence indicator F-254) made by Merck.

For **preparative medium pressure chromatography (NP chromatography)** silica gel made by Millipore (Granula Silica Si-60A 35-70 µm, NP phase) is used.

Automated normal phase chromatography is also carried out on a CombiFlash Companion XL apparatus in combination with a CombiFlash Foxy 200 fraction collector made by Isco. For this, commercially obtainable RediSepRf (120 g silica gel) one-way columns are used. Furthermore, automated normal phase chromatography can also be carried out on an Isolera Flash Purification apparatus made by Biotage. For this, commercially obtainable one-way SNAP-Cartridges (e.g. 50 g silica gel) are used.

The **preparative high pressure chromatography (RP HPLC)** is carried out with columns made by Waters (Sunfire C18, 5 µm, 30 x 100 mm Part. No. 186002572; X-Bridge C18, 5 µm, 30 x 100 mm Part. No. 186002982).

The compounds are eluted using either different gradients of H_2O/acetonitrile or H_2O/MeOH, where 0.1 % HCOOH is added to the water, or with different gradients utilizing a basic aqueous buffer solution (1L water contains 5 mL of an ammonium hydrogencarbonate solution (158 g per 1 L H_2O) and 2 mL ammonia (7 mol/l solution in MeOH)) instead of the water-HCOOH-mixture.

The **analytical HPLC (reaction monitoring)** of intermediate compounds is carried out with columns made by Agilent and Waters. The analytical equipment is also provided with a mass detector in each case.

HPLC mass spectroscopy/UV spectrometry

The retention times/MS-ESI$^+$ for characterising the example compounds according to the invention are produced using an HPLC-MS apparatus (high performance liquid chromatography with mass detector) made by Agilent. Compounds that elute at the injection peak are given the retention time tR = 0.

Analytical HPLC Methods

***Method_1**

HPLC:	Agilent 1100 Series	
MS:	Agilent LC/MSD SL	
Column:	Waters, Xbridge C18, 2.5 µm, 2.1x20 mm, Part.No. 186003201	
Solvent	A: 20mM NH_4HCO_3/ NH_3	
	B: ACN HPLC grade	
Detection:	MS: Positive and negative	
	Mass range: 120 - 800 m/z	
Injection:	5 µL	
Flow:	1.00 mL/min	
Column temperature:	60 °C	
Gradient:	0.00 min	10 % B
	0.00 – 1.50 min	10 % -> 95 % B
	1.50 – 2.00 min	95 % B
	2.00 – 2.10 min	95 % -> 10 % B

***Method_2**

HPLC:	Agilent 1100/1200 Series	
MS:	Agilent 1100 LC/MSD SL	
Column:	Waters Sunfire, 5.0 µm, 2.1 x 50 mm	
Eluant:	A: H_2O + 0.2 % HCOOH; B: ACN	
Detection:	ESI	
Mass range:	100 – 1200 m/z	
Flow:	1.20 ml/min	
Column temp.: 35°C		
Gradient:	0.01 min:	5 % B
	0.01 – 1.50 min:	5 % → 95 % B
	1.50 – 2.00 min:	100 % B

***Method_3**

HPLC:	Agilent 1100 Series	
MS:	Agilent LC/MSD SL	
Column:	Waters X-Bridge C18, 2.1 x 50mm, 5.0 µm	
Eluant:	A: 5 mM NH_4HCO_3/19 mM NH_3 in H_2O; B: ACN (HPLC grade)	
Detection:	MS: Positive and negative mode	
Mass range:	105 – 1200 m/z	
Flow:	1.20 ml/min	
Column temp.:35°C		
Gradient:	0.01 min:	5 % B
	0.01 – 1.25 min:	5 % → 95 % B
	1.25 – 2.00 min:	95 % B
	2.00 – 2.01 min:	95 % → 5 % B

***Method_4**

HPLC:	Agilent 1100 Series	
MS:	Agilent LC/MSD SL	
Column:	Waters X-Bridge C18, 2.1 x 50mm, 3.5µm	
Eluant:	A: 5 mM NH_4HCO_3/20 mM NH_3 in H_2O; B: ACN (HPLC grade)	
Detection:	MS: Positive and negative mode	
Mass range:	105 – 1200 m/z	
Flow:	1.20 ml/min	
Column temp.:	35°C	
Gradient:	0.01 min:	5 % B
	0.01 – 1.25 min:	5 % → 95 % B
	1.25 – 2.00 min:	95 % B
	2.00 – 2.01 min:	95 % → 5 % B

***Method_5**

HPLC:	Agilent 1100 Series	
MS:	Agilent LC/MSD SL	
Column:	WatersXBridge C18 2.1x50mm, 5,0 µm	
Eluant:	A: 5 mM NH_4HCO_3/19 mM NH_3 in H_2O; B: ACN (HPLC grade)	
Detection:	MS: Positive and negative mode	
Mass range:	105 – 1200 m/z	
Flow:	1.20 ml/min	
Column temp.:	35°C	
Gradient:	0.01 min:	5 % B
	0.01 – 1.25 min:	5 % → 95 % B
	1.25 – 2.00 min:	95 % B
	2.00 – 2.01 min:	95 % → 5 % B

***Method_6**

HPLC:	Agilent 1100 Series	
MS:	Agilent LC/MSD SL	
Column:	Waters Sunfire,2.1x50mm, 5.0 µm	
Eluant:	A: H_2O + 0.2 % HCOOH; B: ACN (HPLC grade) + 0.2 % HCOOH	
Detection:	MS: Positive and negative mode	
Mass range:	105 – 1200 m/z	
Flow:	1.20 ml/min	
Column temp.:	35°C	
Gradient:	0.01 min:	5 % B
	0.01 – 1.50 min:	5 % →95 % B
	1.50 – 2.00 min:	95 % B
	2.00 – 2.01 min:	95 % → 5 % B

Preparation of the compounds according to the invention

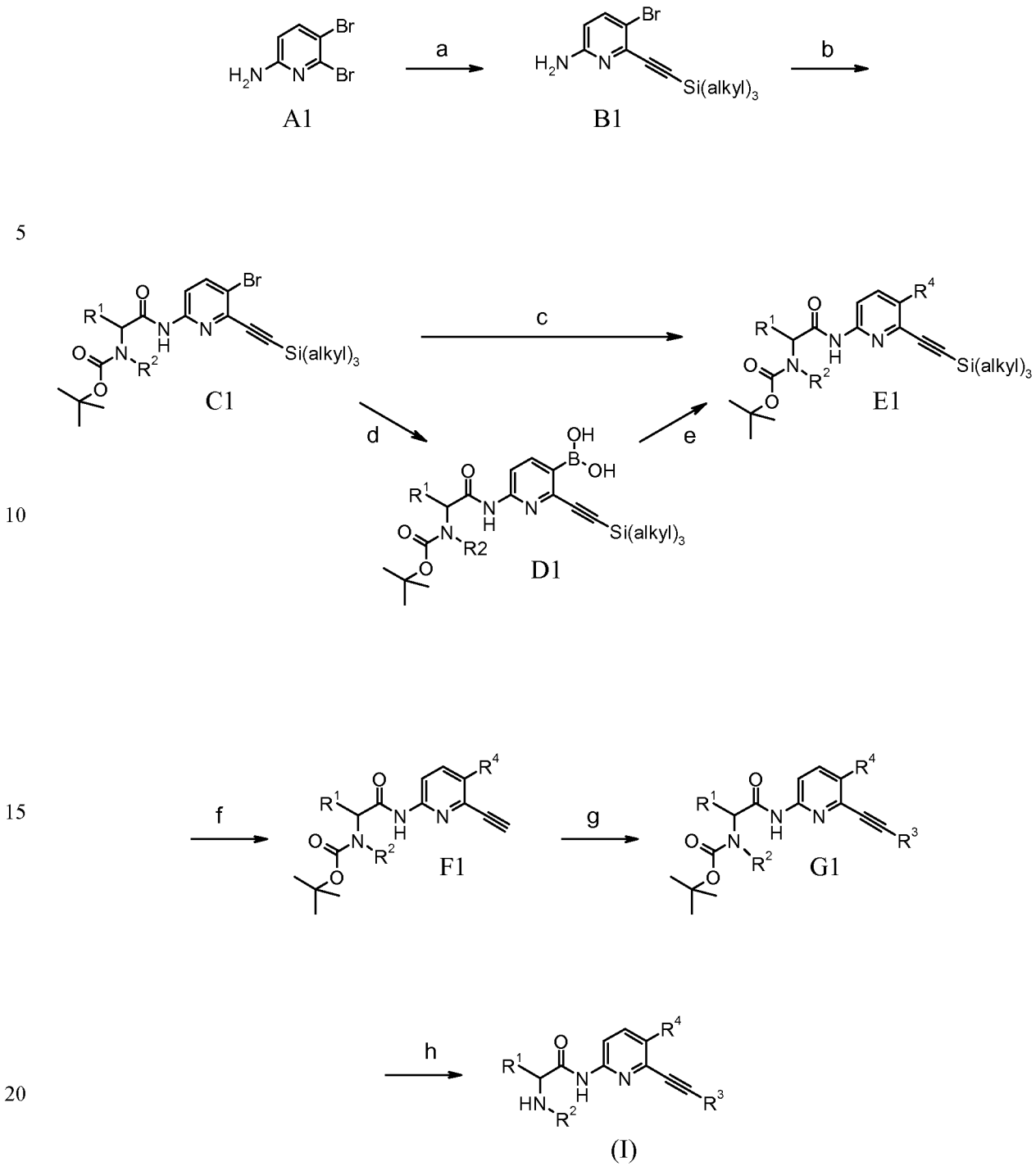
The compounds according to the invention are prepared by methods of synthesis described hereinafter, in which the substituents of the general formulae have the meanings given hereinbefore. These methods are intended as an illustration of the invention, without restricting its subject matter and the scope of the compounds claimed to these examples. Where the preparation of starting compounds is not described, they are commercially obtainable or may be prepared analogously to known compounds or methods described herein. Substances described in literature are prepared according to the published methods.

Unless otherwise specified, the substituents $\mathbf{R^1}$ through $\mathbf{R^5}$ of the following reaction schemes are as defined in the specification and claims.

The compounds of formula (**I**) may be prepared according to the following schemes (1-5).

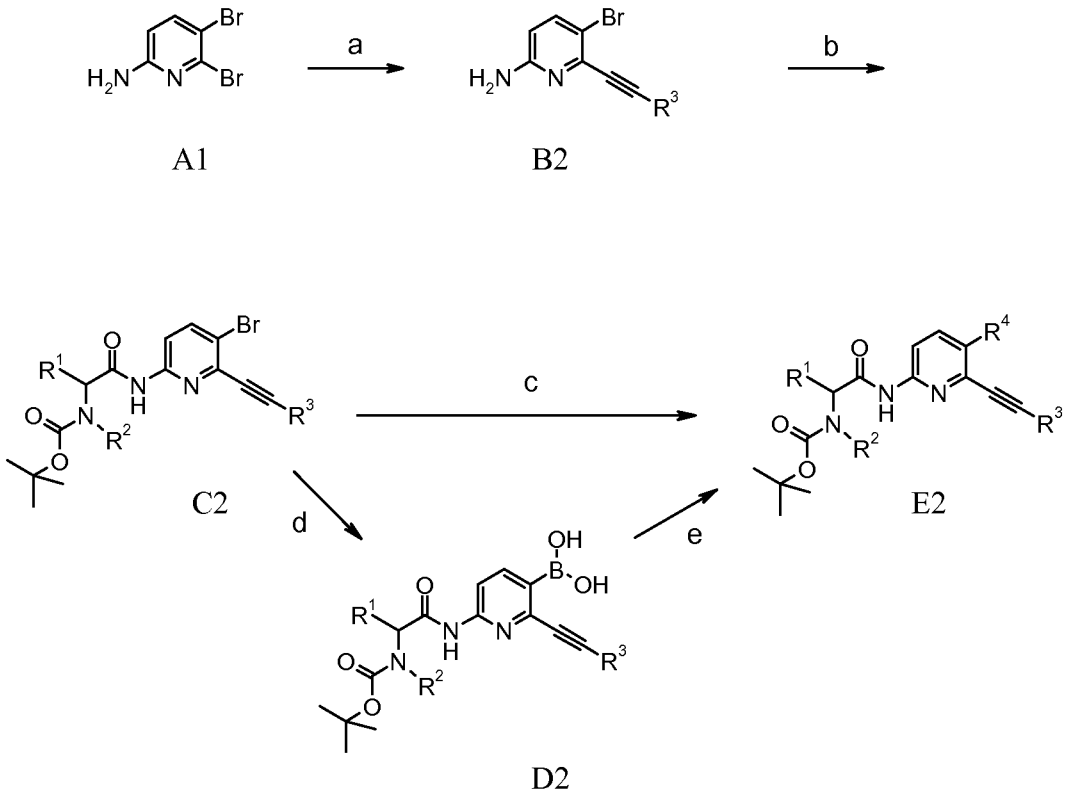
One method for the preparation of compounds of formula (**I**) starts from building block **A**1 as depicted in Scheme 1. In step (a) A1 is reacted with a trialkylsilylacetylene to obtain B1 which is converted into C1 via amidation. C1 compounds can be converted into the

boronic acids D1 which allows the transformation to E1 e.g. via Suzuki coupling. Alternatively, intermediates C1 can be converted into E1 compounds via step (c), e.g via coupling reactions with suitable boronic acids, organozinc reagents or other methods known in the art. With step (f) F1 compounds can be obtained via desilylation reaction. F1 can be converted into G1 in step (g) e.g. via Sonogashira coupling. Finally, compounds of the formula (I) are optained via deprotection reaction. The products are isolated by conventional means and preferably purified by chromatography.



Scheme 1

Another method for the preparation of compounds of formula (I) is depicted in Scheme 2. In step (a) a suitable alkyne is coupled to A1. In step (b) compounds of the type B2 are converted to the corresponding amides C2. As described for Scheme 1, compounds C2 can be converted to E2 via step (c) or via boronic acids B2 in step (d) + (e). In step (f) compounds E2 are deprotected to compounds (I). The products are isolated by conventional means and preferably purified by chromatography.

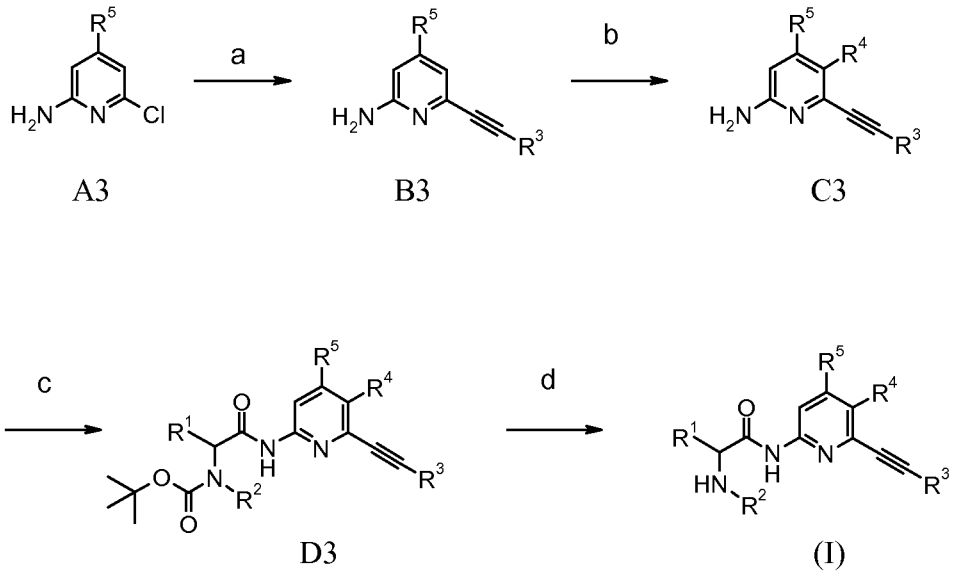


Scheme 2

Another alternative method for the preparation of compounds of formula (I) is depicted in Scheme 3. In step (a) a suitable alkyne is coupled to A3. In step (b) R4 moieties are

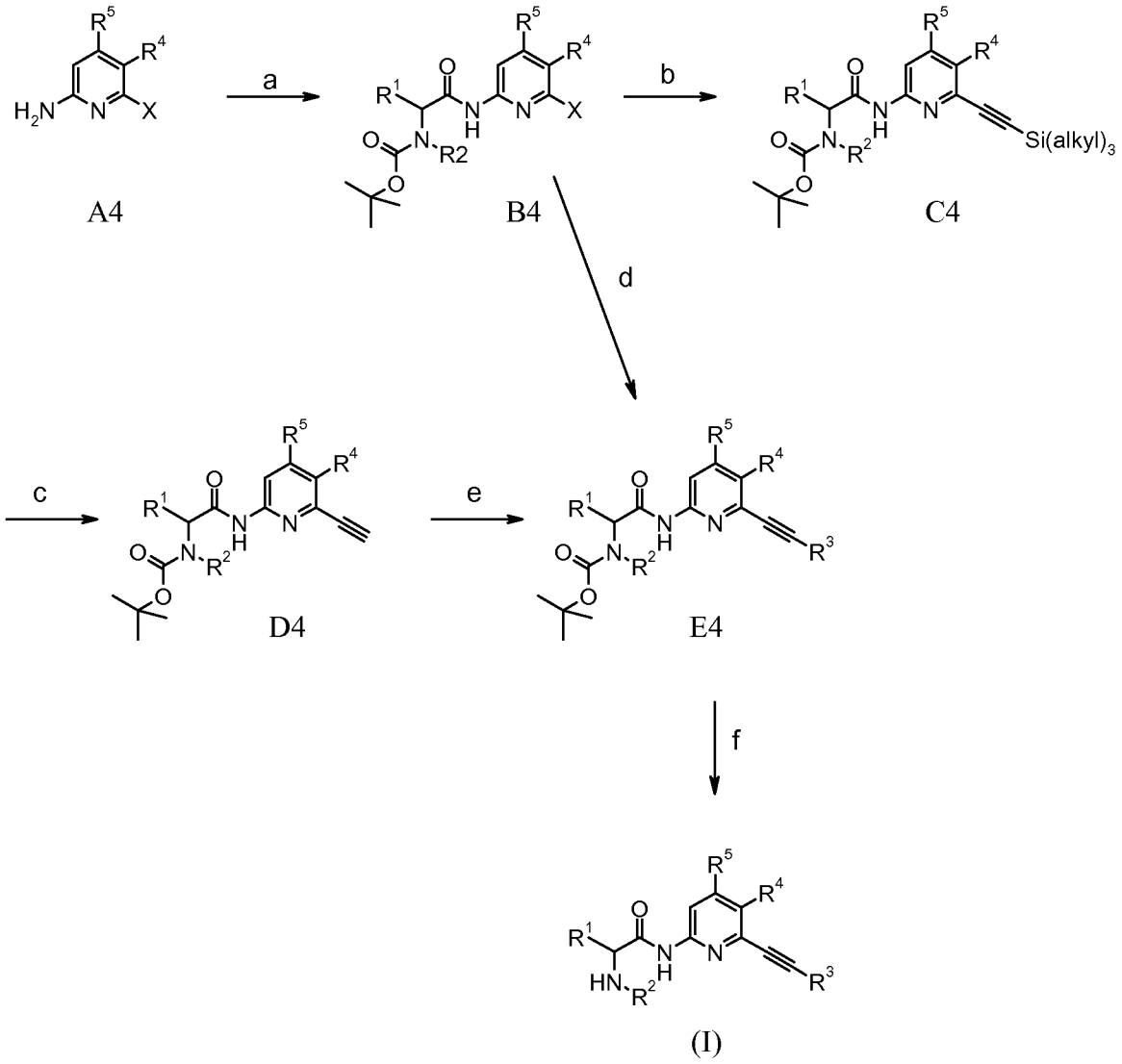
introduced, e.g. by halogenation reaction and optionally subsequently further modified. In step (c) compounds of the type C3 are converted to corresponding amides D3. In step (d) D3 compounds are deprotected to compounds of the formula (I). The products are isolated by conventional means and preferably purified by chromatography.

R4 or R5 moieties might be further modified during the reaction sequence.



Scheme 3

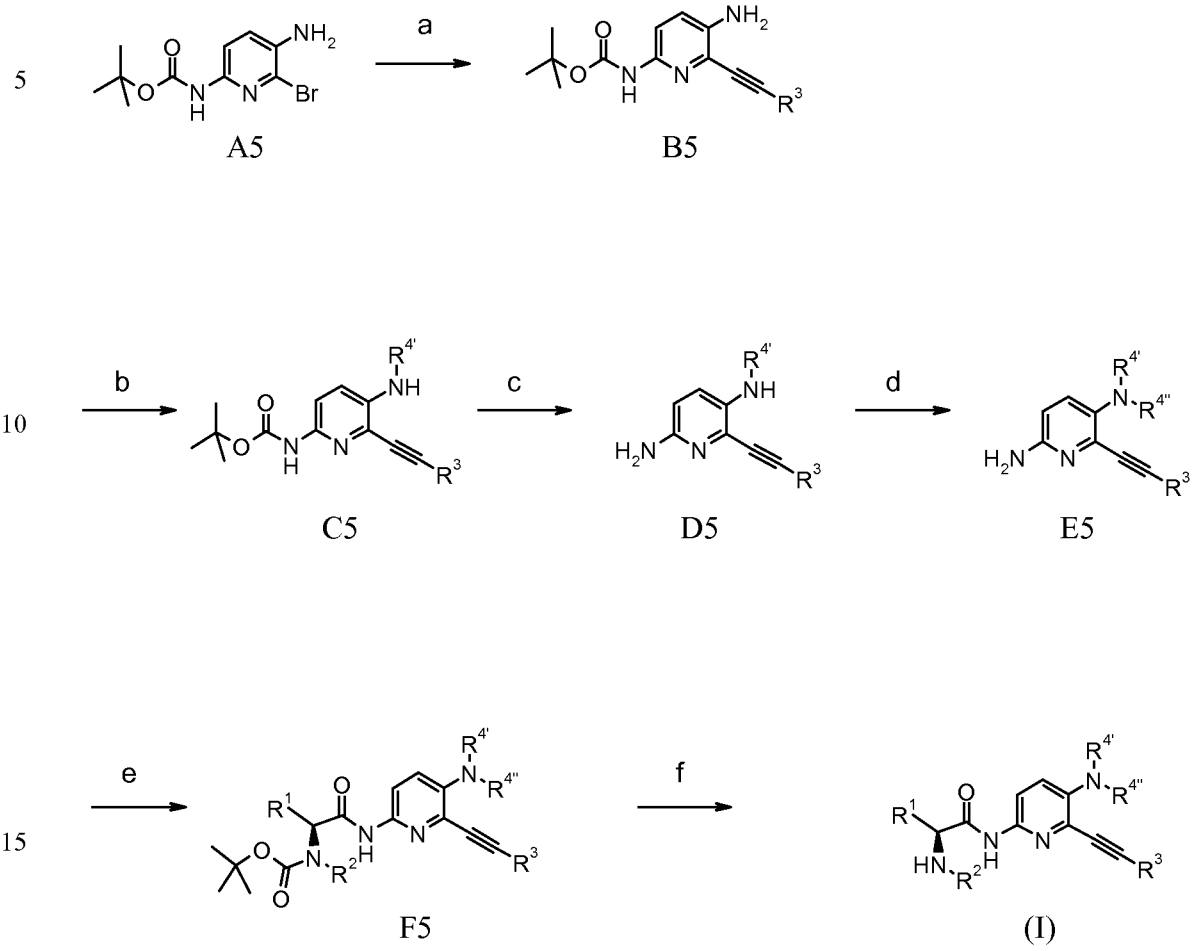
Another method for the preparation of compounds of formula (I) is depicted in Scheme 4. Building blocks of type A4 are converted in step (a) into the corresponding amides B4, to which suitable alkynes can be coupled in step (d) to obtain compounds of type E4. Alternatively, trialkylsilylacetylenes can be coupled to compounds B4, which can be desilylated to D4 in step (c) and the alkyne group further converted to obtain compounds E4 (step (e), e.g. via Sonogashira coupling). Finally, compounds of the formula (I) are obtained via deprotection reaction. The products are isolated by conventional means and preferably purified by chromatography.



Scheme 4

Another method for the preparation of compounds of formula (I) is depicted in Scheme 5. In step (a) a suitable alkyne is coupled to building blocks of type A5 to result in compounds B5. The NH_2-moiety in B5 can be further transformed to NH-$R^{4'}$ groups in C5, e.g. via acylation, alkylation or sulfonamidation. After deprotection in step (c) the NH-$R^{4'}$-group might optionally be further modified to $NR^{4'}R^{4''}$ e.g. via alkylation reactions, before the conversion to compounds of type F5 in an amidation reaction. Finally, compounds of

the formula (I) are optained via deprotection reaction. The products are isolated by conventional means and preferably purified by chromatography.

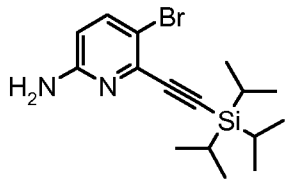


Scheme 5

As exemplified in the experimental part, initial products of formula (I) can optionally be further modified to obtain additional compounds of formula (I).

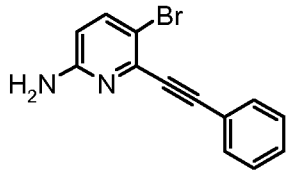
Preparation of compounds B

B1a) 5-bromo-6-[2-tri(propan-2-yl)silylethynyl]pyridin-2-amine



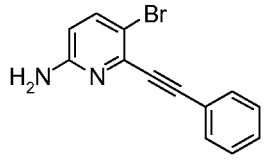
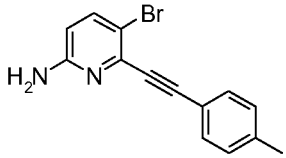
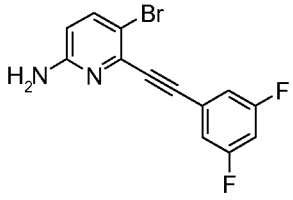
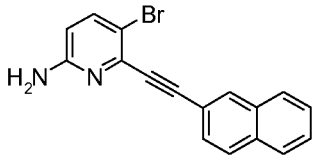
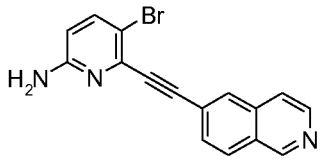
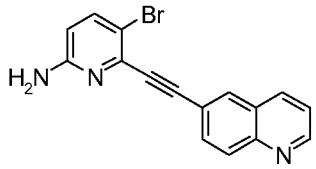
A mixture of 5,6-dibromopyridin-2-amine (60 g, 233 mmol), ethynyl-tri(propan-2-yl)silane (64 ml, 285 mmol), copper(I) iodide (1.5 g, 7.88 mmol), Dichlorobis(triphenylphosphine)-palladium(II) (4.0 g, 5.48 mmol) and triethylamine (80 ml, 577 mmol) is stirred under argon atmosphere in ACN (200 ml) with THF (100 ml) for 2 h at 50°C. The mixture is concentrated in vacuo and the product purified by NP chromatography. Yield: 76 g (92%). HPLC-MS: M+H=353/355; tR=1.79 min (*Method_1).

B2a) 5-bromo-6-(2-phenylethynyl)pyridin-2-amine

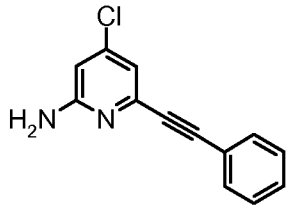


A mixture of 5,6-dibromopyridin-2-amine (80 g, 318 mmol), ethynylbenzene (78 ml, 698 mmol), copper(I) iodide (1.51 g, 7.94 mmol), Dichlorobis(triphenylphosphine)-palladium(II) (5.79 g, 7.94 mmol) and triethylamine (110 ml, 794 mmol) is stirred under argon atmosphere in ACN (500 ml) with THF (250 ml) for 21 h at 50°C. The mixture is diluted with water and extracted with DCM. The combined organic layers are dried over $MgSO_4$, concentrated in vacuo and the product purified by NP chromatography. Yield: 82 g (94%). HPLC-MS: M+H=273/275; tR=1.34 min (*Method_1).

The following compounds are prepared analogously:

#	Molecular Structure	Chemical Name
B2a		5-bromo-6-(2-phenyl-ethynyl)pyridin-2-amine
B2b		5-bromo-6-[2-(4-methyl-phenyl)ethynyl]pyridin-2-amine
B2c		5-bromo-6-[2-(3,5-difluorophenyl)ethynyl]-pyridin-2-amine
B2d		5-bromo-6-(2-naphthalen-2-ylethynyl)pyridin-2-amine
B2e		5-bromo-6-(2-isoquinolin-6-ylethynyl)pyridin-2-amine
B2f		5-bromo-6-(2-quinolin-6-yl-ethynyl)pyridin-2-amine

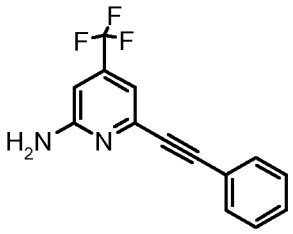
B3a) 4-chloro-6-(2-phenylethynyl)pyridin-2-amine



A mixture of 4,6-dichloropyridin-2-amine (2.0 g, 12.3 mmol), ethynylbenzene (2.51 g, 24.5 mmol), copper(I) iodide (234 mg, 1.23 mmol), Dichlorobis(triphenylphosphine)-

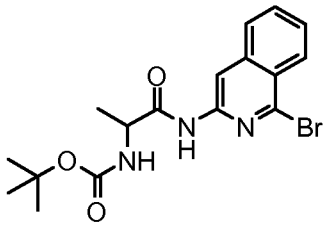
palladium(II) (1.0 g, 1.23 mmol) and triethylamine (4.3 ml, 31 mmol) is stirred under argon atmosphere in ACN (20 ml) with THF (10 ml) for 6 h at 90°C. The mixture is diluted with water and extracted with EtOAc. The combined organic layers are dried over $MgSO_4$, concentrated in vacuo and the product purified by NP chromatography. Yield: 1.2 g (43%). HPLC-MS: M+H=229; tR=1.96 min (*Method_2).

B3b) 6-(2-phenylethynyl)-4-(trifluoromethyl)pyridin-2-amine



A mixture of 6-chloro-4-(trifluoromethyl)pyridin-2-amine (1.0 g, 5.09 mmol) ethynylbenzene (779 mg, 7.63 mmol), 1,1′-Bis(diphenylphosphino)ferrocene]dichloro-palladium(II) (372 mg, 0.51 mmol), copper(I) iodide (96 mg, 0.51 mmol), triethylamine (1.8 ml, 12.7 mmol), ACN (10 ml) and THF (5 ml) is stirred for 6 h at 90°C. The mixture is concentrated in vacuo, water is added (100 ml) and the mixture extracted with EtOAc. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The product is purified by NP chromatography. Yield: 680 mg (51%). HPLC-MS: M+H=263.

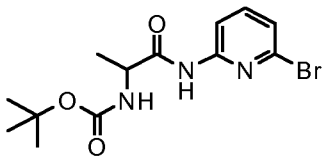
B4a) tert-butyl-N-[1-[(1-bromoisoquinolin-3-yl)amino]-1-oxopropan-2-yl]carbamate



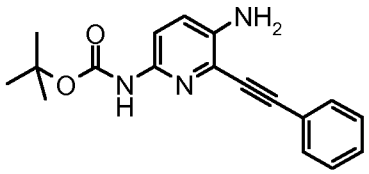
HATU (7.5 g, 19.7 mmol) is added to a mixture of 1-bromoisoquinolin-3-amine (2.0 g, 9.0 mmol), 2-[(2-methylpropan-2-yl)oxycarbonylamino]propanoic acid (1.7 g, 9.0 mmol) and DIPEA (3.4 ml, 200 mmol) in DMA (10 ml). After stirring for 3 days at RT the

mixture is concentrated in vacuo and the product purified by RP HPLC. Yield: 3.3 g (94%). HPLC-MS: M-H=392/394; tR=1.97 min (*Method_1).

The following compound is prepared analogously:

#	Molecular Structure	Chemical Name
B4b		tert-butyl N-[1-[(6-bromo-pyridin-2-yl)amino]-1-oxo-propan-2-yl]carbamate

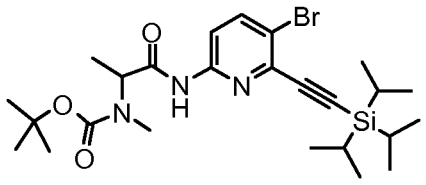
B5a) tert-butyl-N-[5-amino-6-(2-phenylethynyl)pyridin-2-yl]carbamate



Tert-butyl-N-(5-amino-6-bromopyridin-2-yl)carbamate A5 (617 mg, 1.82 mmol), ethynylbenzene (420 µl, 3.82 mmol), copper(I) iodide (35 mg, 0.18 mmol), 1,1′-Bis-(diphenylphosphino)ferrocene]dichloropalladium(II) (66.4 mg, 0.09 mmol) and triethylamine (631 µl, 4.55 mmol) are stirred under argon atmosphere in a mixture of ACN (10 ml) and THF (5 ml) for 2 h at RT. The mixture is warmed to 45°C and stirred for 70 h. The mixture is concentrated in vacuo and the product purified by RP HPLC. Yield: 320 mg (57%). HPLC-MS: M+H=310; tR=2.05 min (*Method_2).

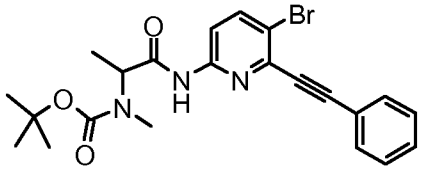
Preparation of compounds C

C1a) tert-butyl-N-[1-[[5-bromo-6-[2-tri(propan-2-yl)silylethynyl]pyridin-2-yl]-amino]-1-oxopropan-2-yl]-N-methylcarbamate



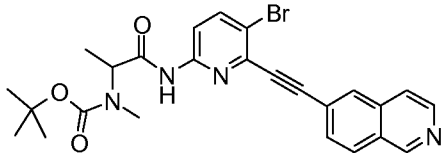
A mixture of 2-[methyl-[(2-methylpropan-2-yl)oxycarbonyl]amino]propanoic acid (55 g, 271 mmol) and N,N'-dicyclohexylcarbodiimide (35 g, 170 mmol) in DCM (200 ml) is stirred with ice bath cooling for 30 minutes. A solution of 5-bromo-6-[2-tri(propan-2-yl)-silylethynyl]pyridin-2-amine B1a (40 g, 113 mmol) in DCM (100 ml) is added. After stirring for 14 days at RT the reaction mixture is diluted with DCM and extracted with water. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The product is purified by NP chromatography. Yield: 51 g (95%). HPLC-MS: M+H= 538/540; tR=1.97 min (*Method_1).

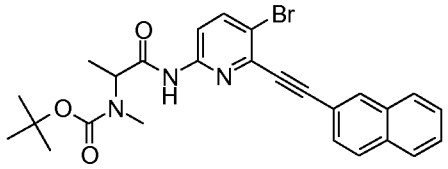
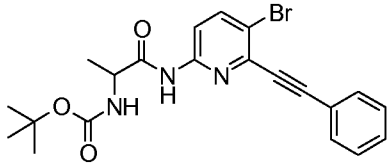
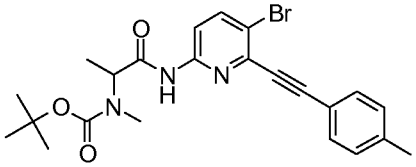
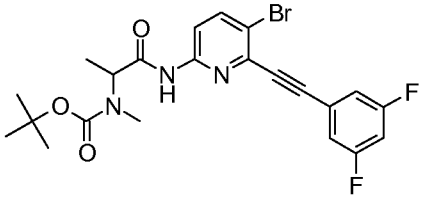
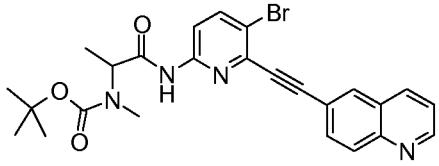
C2a) tert-butyl-N-[1-[[5-bromo-6-(2-phenylethynyl)pyridin-2-yl]amino]-1-oxo-propan-2-yl]-N-methylcarbamate



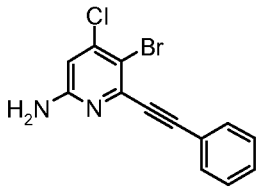
A mixture of 2-[methyl-[(2-methylpropan-2-yl)oxycarbonyl]amino]propanoic acid (36 g, 177 mmol) and N,N'-dicyclohexylcarbodiimide (22.5 g, 109 mmol) in DCM (150 ml) is stirred with ice bath cooling for 30 minutes. A solution of 5-bromo-6-(2-phenylethynyl)-pyridin-2-amine B2a (20 g, 73.2 mmol) in DCM (100 ml) is added. After stirring for 7 days at RT the reaction mixture is diluted with DCM and extracted with water. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The product is purified by NP chromatography. Yield: 25 g (74%). HPLC-MS: M+H= 458/460; tR=2.33 min (*Method_1).

The following compounds are prepared analogously:

#	Molecular Structure	Chemical Name
C2b		tert-butyl N-[1-[[5-bromo-6-(2-naphthalen-2-ylethynyl)-pyridin-2-yl]amino]-1-oxo-propan-2-yl]-N-methyl-carbamate

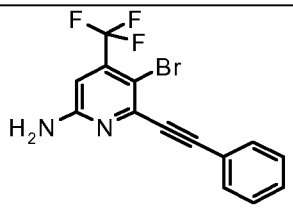
C2c		tert-butyl N-[1-[[5-bromo-6-(2-phenylethynyl)pyridin-2-yl]-amino]-1-oxopropan-2-yl]-carbamate
C2d		tert-butyl N-[1-[[5-bromo-6-(2-phenylethynyl)pyridin-2-yl]-amino]-1-oxopropan-2-yl]-N-methylcarbamate
C2e		tert-butyl N-[1-[[5-bromo-6-[2-(4-methylphenyl)ethynyl]-pyridin-2-yl]amino]-1-oxo-propan-2-yl]-N-methyl-carbamate
C2f		tert-butyl N-[1-[[5-bromo-6-[2-(3,5-difluorophenyl)ethynyl]-pyridin-2-yl]amino]-1-oxo-propan-2-yl]-N-methyl-carbamate
C2g		tert-butyl N-[1-[[5-bromo-6-(2-quinolin-6-ylethynyl)pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate

C3a) 5-bromo-4-chloro-6-(2-phenylethynyl)pyridin-2-amine

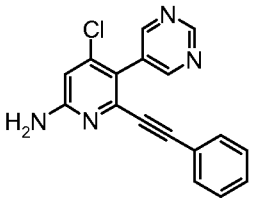


A mixture of 4-chloro-6-(2-phenylethynyl)pyridin-2-amine B3a (1.0 g, 4.37 mmol), NBS (778 mg, 4.37 mmol) and ACN (20 ml) is stirred for 3h at RT in the dark. The mixture is concentrated in vacuo and the product purified NP chromatography. Yield: 1.0 g (74%). HPLC-MS: M+H=307/309.

The following compound is prepared analogously:

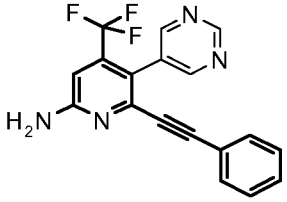
#	Molecular Structure	Chemical Name
C3b		5-bromo-6-(2-phenylethynyl)-4-(trifluoromethyl)pyridin-2-amine

C3c) 4-chloro-6-(2-phenylethynyl)-5-pyrimidin-5-ylpyridin-2-amine

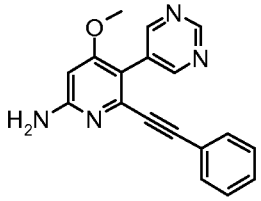


A mixture of 5-bromo-4-chloro-6-(2-phenylethynyl)pyridin-2-amine C3a (1.0 g, 3.25 mmol), pyrimidin-5-ylboronic acid (604 mg, 4.88 mmol), Tetrakis(triphenylphosphine)palladium(0) (375 mg, 0.33 mmol), sodium carbonate (aqueous solution, 2 mol/l, 4.88 ml, 9.75 mmol) and ACN (15 ml) is stirred in a sealed tube at 120°C until C3a is almost completely consumed. The mixture is then concentrated in vacuo and the product purified by NP chromatography. Yield: 420 mg (42%). HPLC-MS: M+H=307.

The following compounds are prepared analogously:

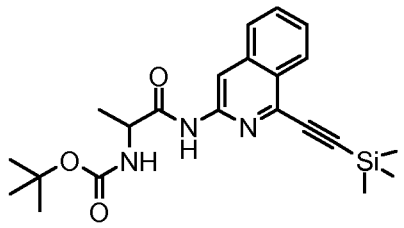
#	Molecular Structure	Chemical Name
C3d		6-(2-phenylethynyl)-5-pyrimidin-5-yl-4-(trifluoromethyl)pyridin-2-amine

C3e) 4-methoxy-6-(2-phenylethynyl)-5-pyrimidin-5-ylpyridin-2-amine



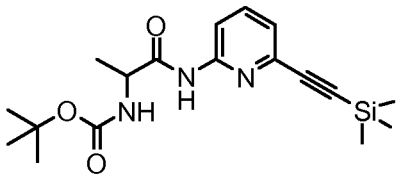
A mixture of 4-chloro-6-(2-phenylethynyl)-5-pyrimidin-5-ylpyridin-2-amine C3c (400 mg, 1.3 mmol), sodium methoxide (a solution of 2,61 mmol in 0.29 ml MeOH) and MeOH (2 ml) is stirred for 20 minutes at 100°C and 10 minutes at 110°C. The mixture is diluted with water and extracted with DCM. The combined organic layers are dried over Na_2SO_4, concentrated in vacuo and the product purified by NP chromatography. Yield: 228 mg (58%). HPLC-MS: M+H=303.

C4a) tert-butyl-N-[1-oxo-1-[[1-(2-trimethylsilylethynyl)isoquinolin-3-yl]amino]-propan-2-yl]carbamate

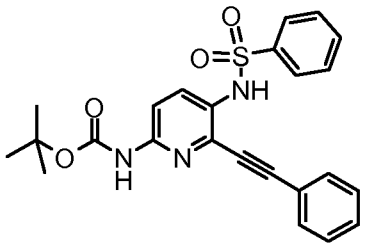


A mixture of tert-butyl-N-[1-[(1-bromoisoquinolin-3-yl)amino]-1-oxopropan-2-yl]-carbamate B4a (500 mg, 1.27 mmol), ethynyl(trimethyl)silane (137 mg, 1.4 mmol), copper(I) iodide (23 mg, 0.12 mmol), Dichlorobis(triphenylphosphine)palladium(II) (90 mg, 0.13 mmol) and DIPEA (700 µl, 4.12 mmol) is stirred under argon atmosphere in NMP (4 ml) for 1 h at 80°C. The mixture is concentrated in vacuo and the product purified by RP HPLC. Yield: 319 mg (61%). HPLC-MS: M+H=412; tR=2.11 min (*Method_4).

The following compound is prepared analogously:

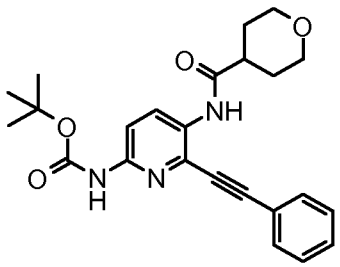
#	Molecular Structure	Chemical Name
C4b		tert-butyl-N-[1-oxo-1-[[6-(2-trimethylsilylethynyl)pyridin-2-yl]amino]propan-2-yl]-carbamate

C5a) tert-butyl-N-[5-(benzenesulfonamido)-6-(2-phenylethynyl)pyridin-2-yl]-carbamate



Benzenesulfonyl chloride (20 µl, 0.4 mmol) diluted with 400 µl DCM is added to a mixture of tert-butyl-N-[5-amino-6-(2-phenylethynyl)pyridin-2-yl]carbamate B5a (40 mg, 0.13 mmol), pyridine (32 µl, 0.4 mmol) and 400 µl DCM at RT and stirred for 1h. The mixture is concentrated in vacuo and the product purified by RP HPLC. Yield: 37 mg (64%). HPLC-MS: M+H=450; tR=2.16 min (*Method_2).

C5b) tert-butyl-N-[5-(oxane-4-carbonylamino)-6-(2-phenylethynyl)pyridin-2-yl]-carbamate

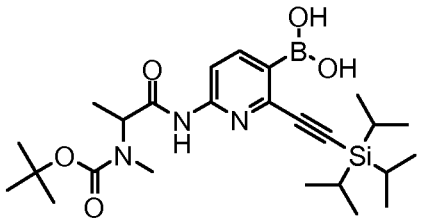


A mixture of oxane-4-carboxylic acid (45 mg, 0.34 mmol), HATU (162 mg, 0.43 mmol) and DIPEA (43 µl, 0.25 mmol) in DMF (1 ml) is stirred at RT for 30 minutes. Tert-butyl-

N-[5-amino-6-(2-phenylethynyl)pyridin-2-yl]carbamate B5a (60 mg, 0.19 mmol) is added and stirring continued for 17 h. The mixture is concentrated in vacuo and the product purified by RP HPLC. Yield: 40 mg (49%). HPLC-MS: M+H=422; tR=1.73 min (*Method_5).

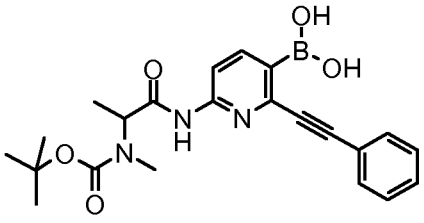
Preparation of compounds D

D1a) [6-[2-[methyl-[(2-methylpropan-2-yl)oxycarbonyl]amino]propanoylamino]-2-[2-tri(propan-2-yl)silylethynyl]pyridin-3-yl]boronic acid



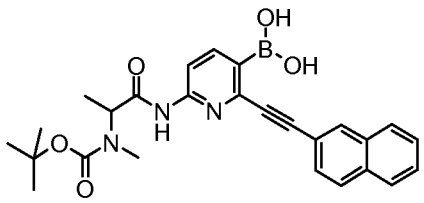
A mixture of tert-butyl-N-[1-[[5-bromo-6-[2-tri(propan-2-yl)silylethynyl]pyridin-2-yl]-amino]-1-oxopropan-2-yl]-N-methylcarbamate C1a (51 g, 90 mmol), bis(neopentyl glycolato)diboron (40.5 g, 179 mmol), KOAc (26.4 g, 269 mmol), 1,1'-Bis(diphenyl-phosphino)ferrocene]dichloropalladium(II) (3.3 g, 4.5 mmol) and dioxane (400 ml) is stirred under argon atmosphere for 17 h at 50°C. The mixture is diluted with DCM and extracted with a saturated aqueous solution of $NaHCO_3$. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The product is purified by NP chromatography. Yield: 21.9 g (48%). HPLC-MS: M+H=504; tR=2.17 min (*Method_4).

D2a) [6-[2-[methyl-[(2-methylpropan-2-yl)oxycarbonyl]amino]propanoylamino]-2-(2-phenylethynyl)pyridin-3-yl]boronic acid

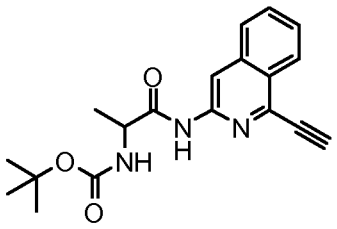


A mixture of tert-butyl-N-[1-[[5-bromo-6-(2-phenylethynyl)pyridin-2-yl]amino]-1-oxo-propan-2-yl]-N-methylcarbamate C2a (2.5 g, 5.45 mmol), bis(neopentyl glycolato)diboron (2.46 g, 10.9 mmol), KOAc (1.61 g, 16.4 mmol), 1,1′-Bis(diphenylphosphino)ferrocene]-dichloropalladium(II) (399 mg, 0.55 mmol) and DMSO (20 ml) is stirred under argon atmosphere for 39 h at 65°C. The mixture is diluted with water and extracted with DCM. The combined organic layers are dried over $MgSO_4$, concentrated in vacuo and the product purified by RP HPLC. Yield: 1.73 g (75%). HPLC-MS: M+H=424; tR=1.59 min (*Method_5).

The following compound is prepared analogously:

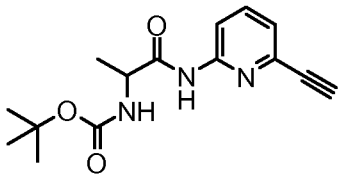
#	Molecular Structure	Chemical Name
D2b		[6-[2-[methyl-[(2-methylpropan-2-yl)-oxycarbonyl]amino]-propanoylamino]-2-(2-naphthalen-2-ylethynyl)-pyridin-3-yl]boronic acid

D4a) tert-butyl-N-[1-[(1-ethynylisoquinolin-3-yl)amino]-1-oxopropan-2-yl]-carbamate

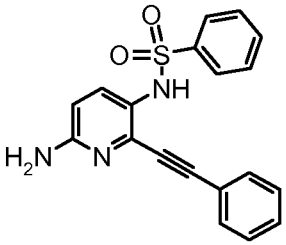


A mixture of tert-butyl-N-[1-oxo-1-[[1-(2-trimethylsilylethynyl)isoquinolin-3-yl]amino]-propan-2-yl]carbamate C4a (319 mg, 0.78 mmol), aqueous 1 N KOH solution (3 ml) and MeOH (10 ml) is stirred at RT for 2 h. The mixture is diluted with water and extracted with EtOAc. The combined organic layers are dried over Na_2SO_4 and concentrated in vacuo and the product purified by RP HPLC. Yield: 225 mg (86%). HPLC-MS: M+H=340; tR=1.84 min (*Method_1).

The following compound is prepared analogously:

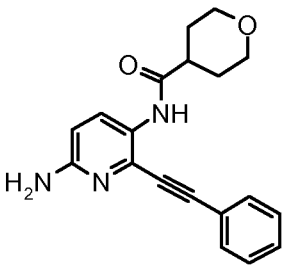
#	Molecular Structure	Chemical Name
D4b		tert-butyl-N-[1-[(6-ethynyl-pyridin-2-yl)amino]-1-oxo-propan-2-yl]carbamate

D5a) N-[6-amino-2-(2-phenylethynyl)pyridin-3-yl]benzenesulfonamide



A mixture of tert-butyl-N-[5-(benzenesulfonamido)-6-(2-phenylethynyl)pyridin-2-yl]-carbamate C5a (37 mg, 0.08 mmol) and DCM:TFA (9:1, 4 ml) is stirred at RT for 2 h. The mixture is diluted with DCM and extracted with a saturated aqueous solution of $NaHCO_3$. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The crude D5a (27 mg) is used in the next step without further purification.

D5b) N-[6-amino-2-(2-phenylethynyl)pyridin-3-yl]oxane-4-carboxamide

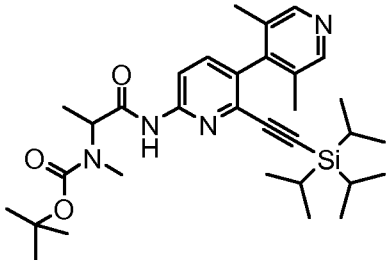


A mixture of tert-butyl-N-[5-(oxane-4-carbonylamino)-6-(2-phenylethynyl)pyridin-2-yl]-carbamate C5b (29 mg, 0.07 mmol) and DCM:TFA (9:1, 3 ml) is stirred at RT for 2 h. The mixture is diluted with DCM and extracted with a saturated aqueous solution of $NaHCO_3$.

The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The crude product (28 mg) is used in the next step without further purification.

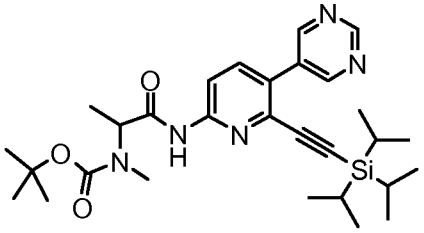
Preparation of compounds E

E1a) tert-butyl-N-[1-[[5-(3,5-dimethylpyridin-4-yl)-6-[2-tri(propan-2-yl)silyl-ethynyl]pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate



A mixture of tert-butyl-N-[1-[[5-bromo-6-[2-tri(propan-2-yl)silylethynyl]pyridin-2-yl]-amino]-1-oxopropan-2-yl]-N-methylcarbamate C1a (300 mg, 0.56 mmol), 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (169 mg, 0.72 mmol), Na_2CO_3 (118 mg, 1.11 mmol), 1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (40.8 mg, 0.06 mmol), dioxane (2 ml) and water (0.4 ml) is stirred under argon atmosphere for 17 h at 90°C. The mixture is concentrated in vacuo and the product purified by RP HPLC. Yield: 26 mg (51%). HPLC-MS: M+H=565; tR=2.32 min (*Method_4).

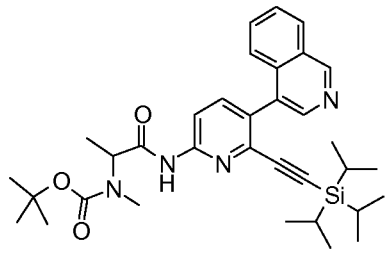
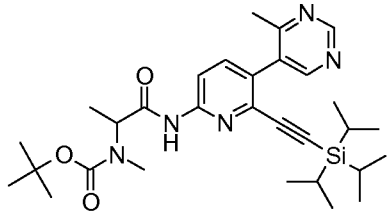
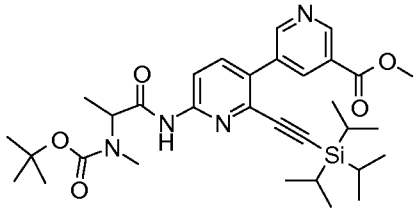
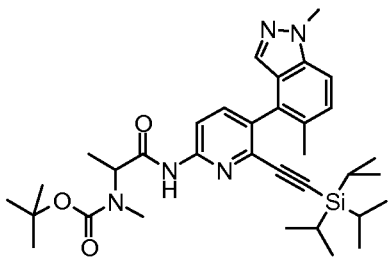
E1b) tert-butyl-N-methyl-N-[1-oxo-1-[[5-pyrimidin-5-yl-6-[2-tri(propan-2-yl)silyl-ethynyl]pyridin-2-yl]amino]propan-2-yl]carbamate

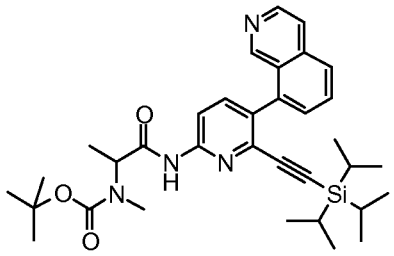
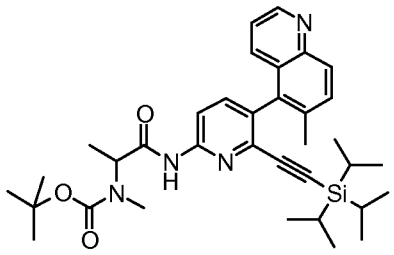


A mixture of tert-butyl-N-[1-[[5-bromo-6-[2-tri(propan-2-yl)silylethynyl]pyridin-2-yl]-amino]-1-oxopropan-2-yl]-N-methylcarbamate C1a (3.5 g, 6.5 mmol), pyrimidin-5-

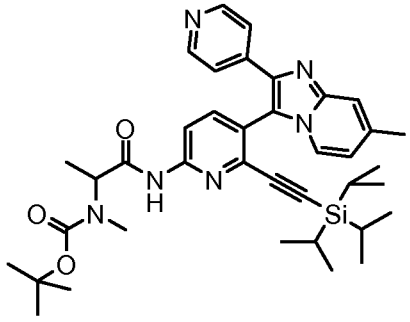
ylboronic acid (1.0 g, 7.8 mmol), Na_2CO_3 (1.4 g, 13.2 mmol), Dichlorobis(triphenylphosphine)palladium(II) (450 mg, 0.64 mmol), dioxane (20 ml), MeOH (5 ml) and water (3.5 ml) is stirred under argon atmosphere for 17 h at 80°C. The mixture is diluted with water and extracted with DCM. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The product is purified by RP HPLC. Yield: 2.33 g (67%). HPLC-MS: M+H=538; tR=2.26 min (*Method_4).

The following compounds are prepared analogously:

#	Molecular Structure	Chemical Name
E1c		tert-butyl N-[1-[[5-isoquinolin-4-yl-6-[2-tri(propan-2-yl)silylethynyl]-pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate
E1d		tert-butyl N-methyl-N-[1-[[5-(4-methylpyrimidin-5-yl)-6-[2-tri-(propan-2-yl)silylethynyl]pyridin-2-yl]amino]-1-oxopropan-2-yl]-carbamate
E1e		methyl 5-[6-[2-[methyl-[(2-methylpropan-2-yl)oxycarbonyl]-amino]propanoylamino]-2-[2-tri-(propan-2-yl)silylethynyl]pyridin-3-yl]pyridine-3-carboxylate
E1f		tert-butyl N-[1-[[5-(1,5-dimethyl-indazol-4-yl)-6-[2-tri(propan-2-yl)-silylethynyl]pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate

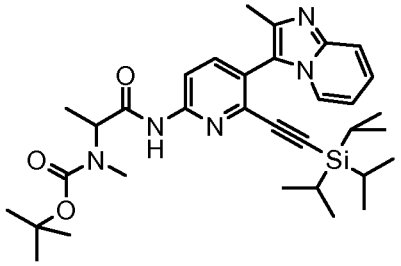
#	Molecular Structure	Chemical Name
E1g		tert-butyl N-[1-[[5-isoquinolin-8-yl-6-[2-tri(propan-2-yl)silylethynyl]-pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate
E1i		tert-butyl N-methyl-N-[1-[[5-(6-methylquinolin-5-yl)-6-[2-tri(propan-2-yl)silylethynyl]pyridin-2-yl]amino]-1-oxopropan-2-yl]-carbamate

E1j) tert-butyl-N-methyl-N-[1-[[5-(7-methyl-2-pyridin-4-ylimidazo[1,2-a]pyridin-3-yl)-6-[2-tri(propan-2-yl)silylethynyl]pyridin-2-yl]amino]-1-oxopropan-2-yl]-carbamate



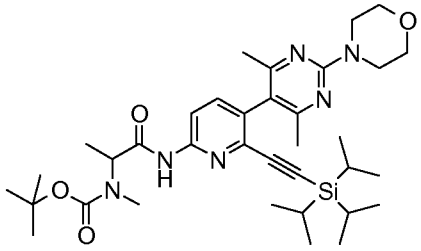
A mixture of [6-[2-[methyl-[(2-methylpropan-2-yl)oxycarbonyl]amino]propanoylamino]-2-[2-tri(propan-2-yl)silylethynyl]pyridin-3-yl]boronic acid D1a (1.5 g, 3.0 mmol), 3-iodo-7-methyl-2-pyridin-4-ylimidazo[1,2-a]pyridine Za (1.3 g, 3.9 mmol), Na_2CO_3 (0.95 g, 8.9 mmol), Dichlorobis(triphenylphosphine)palladium(II) (209 mg, 0.3 mmol), dioxane (30 ml) and water (5 ml) is stirred under argon atmosphere for 17 h at 70°C. The mixture is diluted with water and extracted with DCM. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The product is purified by RP HPLC. Yield: 965 mg (49%). HPLC-MS: M+H=667; tR=2.04 min (*Method_3).

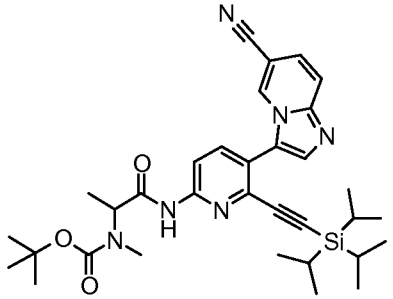
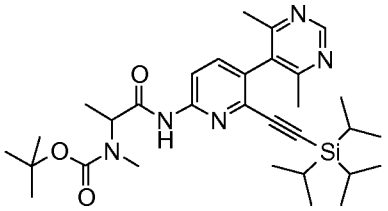
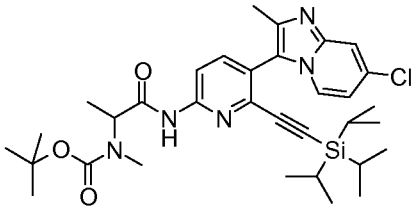
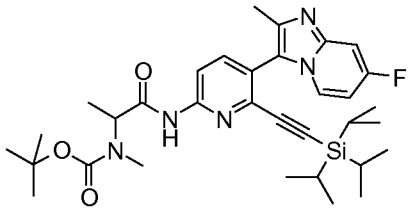
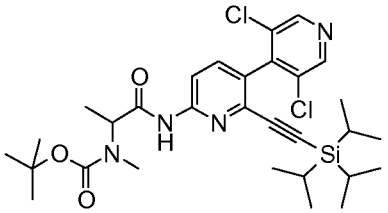
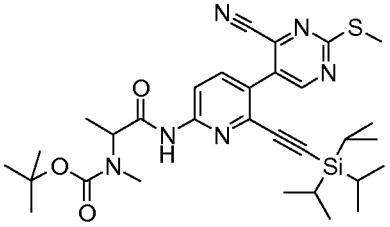
E1k) tert-butyl-N-methyl-N-[1-[[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-[2-tri-(propan-2-yl)silylethynyl]pyridin-2-yl]amino]-1-oxopropan-2-yl]carbamate

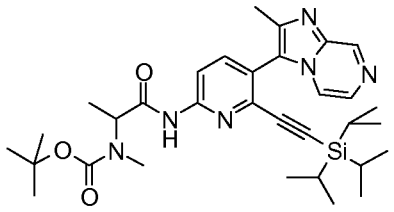
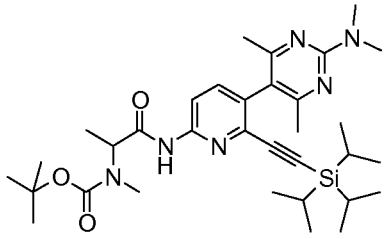
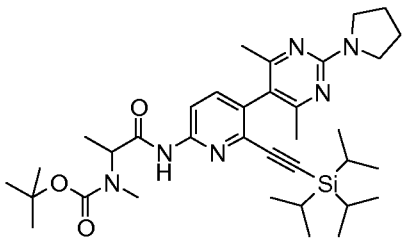


A mixture of [6-[2-[methyl-[(2-methylpropan-2-yl)oxycarbonyl]amino]propanoylamino]-2-[2-tri(propan-2-yl)silylethynyl]pyridin-3-yl]boronic acid D1a (1.5 g, 3.0 mmol), 3-bromo-2-methylimidazo[1,2-a]pyridine (842 mg, 3.9 mmol), Na_2CO_3 (0.95 g, 8.9 mmol), Dichlorobis(triphenylphosphine)palladium(II) (209 mg, 0.3 mmol), dioxane (30 ml) and water (5 ml) is stirred under argon atmosphere for 2 h at 60°C. The mixture is diluted with water and extracted with DCM. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The product is purified by RP HPLC. Yield: 0.6 g (34%). HPLC-MS: M+H=590; tR=2.05 min (*Method_3).

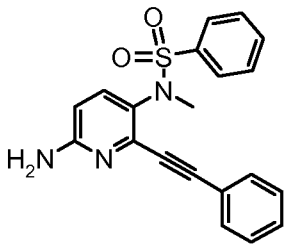
The following compounds are prepared analogously. For compounds E1l, E1o, E1s and E1u the building blocks Zb-Ze are utilized.

#	Molecular Structure	Chemical Name
E1l		tert-butyl N-[1-[[5-(4,6-dimethyl-2-morpholin-4-ylpyrimidin-5-yl)-6-[2-tri(propan-2-yl)silylethynyl]pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate

#	Molecular Structure	Chemical Name
E1m		tert-butyl N-[1-[[5-(6-cyanoimidazo[1,2-a]pyridin-3-yl)-6-[2-tri(propan-2-yl)silylethynyl]-pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate
E1n		tert-butyl N-[1-[[5-(4,6-dimethylpyrimidin-5-yl)-6-[2-tri(propan-2-yl)silylethynyl]pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate
E1o		tert-butyl N-[1-[[5-(7-chloro-2-methylimidazo[1,2-a]pyridin-3-yl)-6-[2-tri(propan-2-yl)silylethynyl]-pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate
E1p		tert-butyl N-[1-[[5-(7-fluoro-2-methyl-imidazo[1,2-a]pyridin-3-yl)-6-[2-tri(propan-2-yl)silylethynyl]pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate
E1q		tert-butyl N-[1-[[5-(3,5-dichloropyridin-4-yl)-6-[2-tri(propan-2-yl)silylethynyl]pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methyl-carbamate
E1r		tert-butyl N-[1-[[5-(4-cyano-2-methylsulfanylpyrimidin-5-yl)-6-[2-tri(propan-2-yl)silylethynyl]pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate

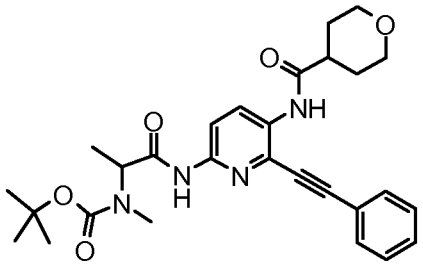
#	Molecular Structure	Chemical Name
E1s		tert-butyl N-methyl-N-[1-[[5-(2-methylimidazo[1,2-a]pyrazin-3-yl)-6-[2-tri(propan-2-yl)silylethynyl]-pyridin-2-yl]amino]-1-oxopropan-2-yl]carbamate
E1t		tert-butyl N-[1-[[5-[2-(dimethyl-amino)-4,6-dimethylpyrimidin-5-yl]-6-[2-tri(propan-2-yl)silylethynyl]-pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate
E1u		tert-butyl N-[1-[[5-(4,6-dimethyl-2-pyrrolidin-1-ylpyrimidin-5-yl)-6-[2-tri(propan-2-yl)silylethynyl]pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate

E5a) N-[6-amino-2-(2-phenylethynyl)pyridin-3-yl]-N-methylbenzenesulfonamide



At RT NaH (60% dispersion in mineral oil, 4.6 mg, 0.12 mmol) is added to N-[6-amino-2-(2-phenylethynyl)pyridin-3-yl]benzenesulfonamide D5a (27mg, approx. 0.07 mmol) in THF (0.6 ml). After stirring for 10 minutes dimethylsulfate (8 µl, 0.08 mmol) is added to the mixture and stirring continued for 1 h. The mixture is concentrated in vacuo and the product purified by RP HPLC. Yield: 16 mg (57%). HPLC-MS: M+H=364; tR=1.85 min (*Method_2).

E5b) tert-butyl-N-methyl-N-[1-[[5-(oxane-4-carbonylamino)-6-(2-phenylethynyl)-pyridin-2-yl]amino]-1-oxopropan-2-yl]carbamate

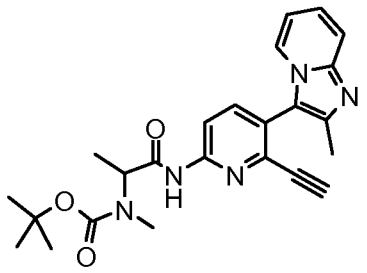


A mixture of 2-[methyl-[(2-methylpropan-2-yl)oxycarbonyl]amino]propanoic acid (34 mg, 0.17 mmol) and N,N'-dicyclohexylcarbodiimide (17 mg, 0.08 mmol) in DCM (1 ml) is stirred at RT for 20 minutes. This mixture is added to N-[6-amino-2-(2-phenylethynyl)-pyridin-3-yl]oxane-4-carboxamide D5b (28 mg, 0.09 mmol) and DIPEA (17 µl; 0.10 mmol) in DCM (1 ml). After stirring for 6 days at 40°C the reaction mixture is diluted with DCM and extracted with water. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The crude product (70 mg) is used in the next step without further purification.

Preparation of compounds F1

All triisopropyl-alkyne containing compounds (e.g. E1a-E1u) are desilylated analogously as exemplified for F1a:

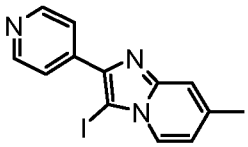
F1a tert-butyl-N-[1-[[6-ethynyl-5-(2-methylimidazo[1,2-a]pyridin-3-yl)pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate



A mixture of tert-butyl-N-methyl-N-[1-[[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-[2-tri-(propan-2-yl)silylethynyl]pyridin-2-yl]amino]-1-oxopropan-2-yl]carbamate E1k (16.7 g, 28.3 mmol), THF (200 ml) and tetrabutylammonium fluoride (1 mol/l solution in THF, 34 ml, 34 mmol) is stirred at RT for 15 minutes. The mixture is diluted with DCM and extracted with a saturated aqueous solution of $NaHCO_3$. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The mixture is concentrated in vacuo and the product purified by NP chromatography. Yield: 10.6 g (86%). HPLC-MS: M+H=434; tR=1.20 min (*Method_1).

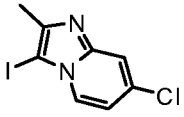
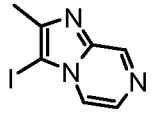
Additional building blocks Z are synthesized as follows:

Za) 3-iodo-7-methyl-2-pyridin-4-ylimidazo[1,2-a]pyridine

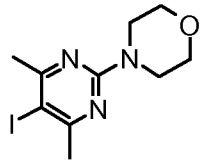


A mixture of 7-methyl-2-pyridin-4-ylimidazo[1,2-a]pyridine (6.52 g, 31.1 mmol), N-iodosuccinimide (7.0 g, 31.1 mmol) and ACN (180 ml) is stirred at RT for 17 h. The precipitate is collected, washed with ACN and dried. Yield: 4.4 g (42%). HPLC-MS: M+H=336; tR=1.55 min (*Method_3).

The following building blocks are prepared analogously:

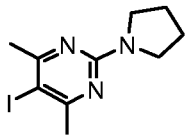
#	Molecular Structure	Chemical Name
Zb		7-chloro-3-iodo-2-methyl-imidazo[1,2-a]pyridine
Zc		3-iodo-2-methylimidazo[1,2-a]pyrazine

Zd) 4-(5-iodo-4,6-dimethylpyrimidin-2-yl)morpholine



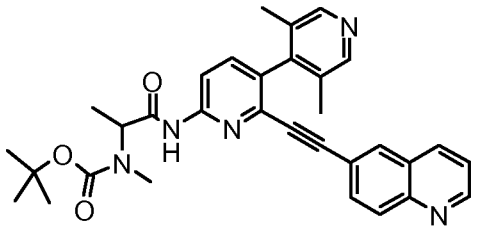
A mixture of 4-(4,6-dimethylpyrimidin-2-yl)morpholine (20.6 g, 107 mmol), N-iodosuccinimide (28.8 g, 128 mmol) and ACN (400 ml) is stirred at RT for 24 h. DCM and an aqueous solution containing 3% sodium thiosulfate is added and the mixture extracted with DCM. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. This material is used without further purification. Yield: 33.7 g (89%).

The following building block is prepared analogously:

#	Molecular Structure	Chemical Name
Ze		5-iodo-4,6-dimethyl-2-pyrrolidin-1-ylpyrimidine

Preparation of examples (I): The following section comprises the respective last step towards the examples combined with the corresponding subsequent deprotection step where required:

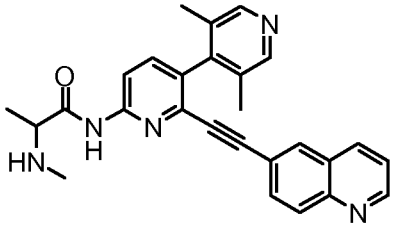
G1a tert-butyl-N-[1-[[5-(3,5-dimethylpyridin-4-yl)-6-(2-quinolin-6-ylethynyl)-pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate



A mixture of tert-butyl-N-[1-[[5-(3,5-dimethylpyridin-4-yl)-6-ethynylpyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate (E1a desilylated according to the general method exemplified for F1a) (50 mg, 0.12 mmol), 6-iodoquinoline (89 mg, 0.35 mmol), copper(I)

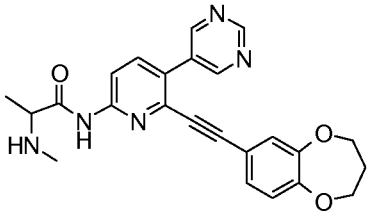
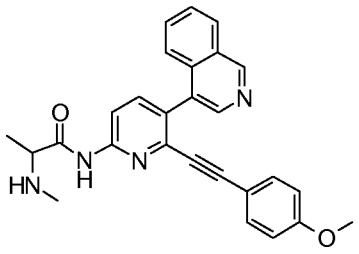
iodide (2.2 mg, 0.01 mmol), Dichlorobis(triphenylphosphine)palladium(II) (8.1 mg, 0.01 mmol) and triethylamine (64 µl, 0.47 mmol) is stirred under argon atmosphere in NMP (0.5 ml) for 1 h at 50°C. The mixture is concentrated in vacuo and the product purified by RP HPLC. Yield: 28 mg (45%). HPLC-MS: M+H=536; tR=1.79 min (*Method_3).

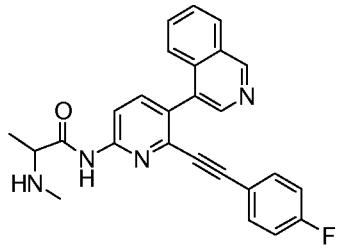
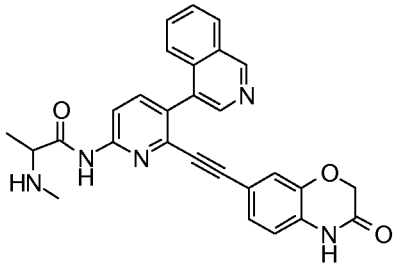
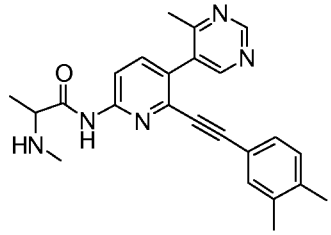
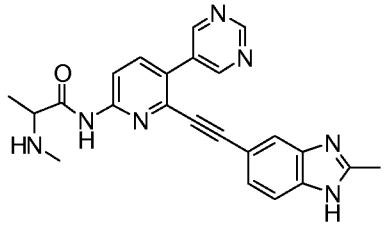
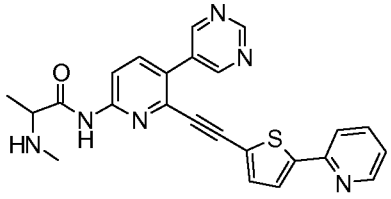
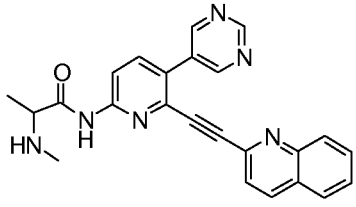
Example 1 N-[5-(3,5-dimethylpyridin-4-yl)-6-(2-quinolin-6-ylethynyl)pyridin-2-yl]-2-(methylamino)propanamide

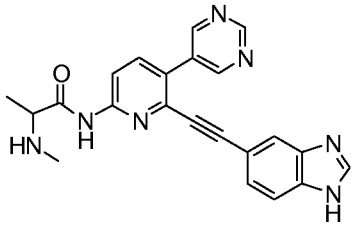
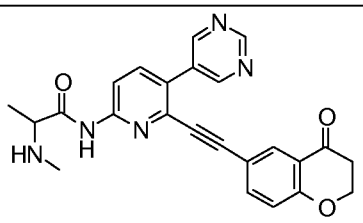
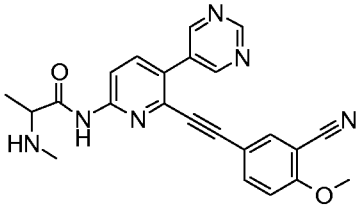
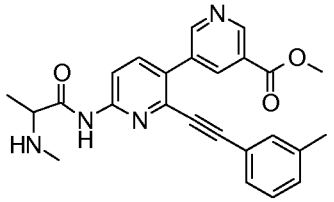
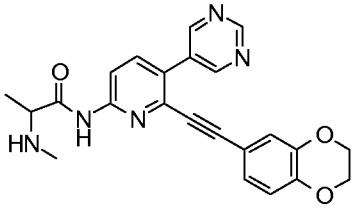
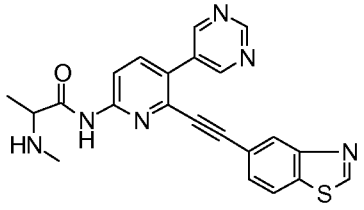
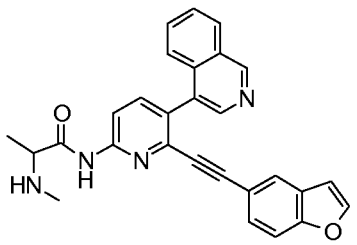


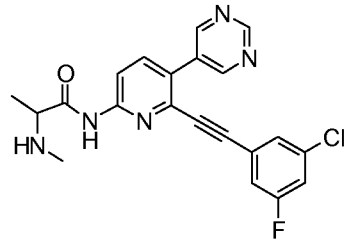
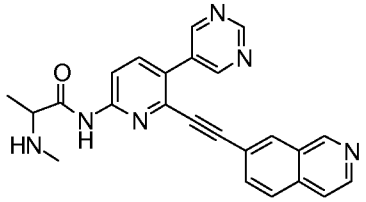
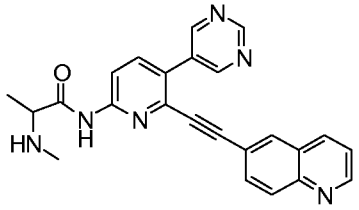
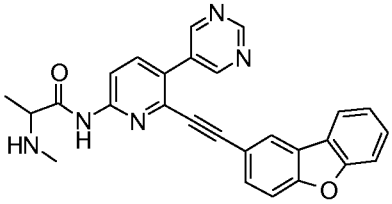
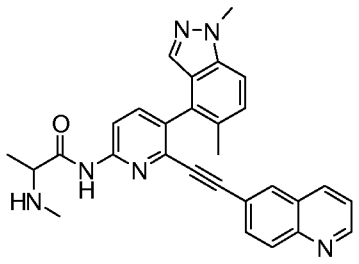
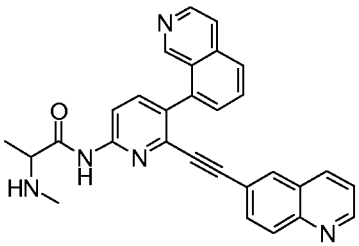
A mixture of tert-butyl-N-[1-[[5-(3,5-dimethylpyridin-4-yl)-6-(2-quinolin-6-ylethynyl)-pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate G1a (28 mg, 0.05 mmol) and DCM:TFA (8:2, 10 ml) is stirred at RT for 15 minutes. The mixture is diluted with toluene (10 ml) and concentrated in vacuo. The product is purified by RP HPLC. Yield: 16 mg (70%). HPLC-MS: M+H=436; tR=1.09 min (*Method_1).

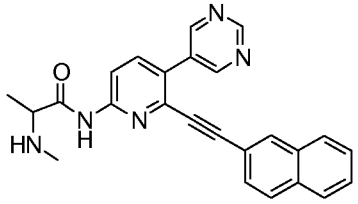
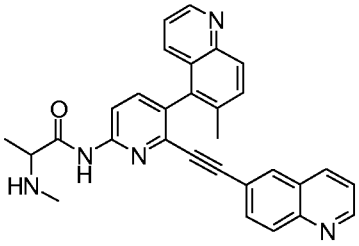
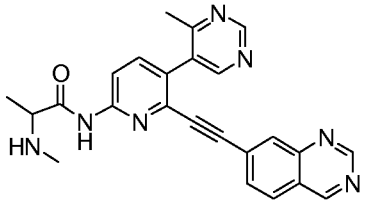
The following examples are prepared analogously:

#	Molecular Structure	Chemical Name	HPLC-MS
2		N-[6-[2-(3,4-dihydro-2H-1,5-benzodioxepin-7-yl)ethynyl]-5-pyrimidin-5-ylpyridin-2-yl]-2-(methylamino)propanamide	M+H=430; tR=1.23
3		N-[5-isoquinolin-4-yl-6-[2-(4-methoxyphenyl)ethynyl]-pyridin-2-yl]-2-(methyl-amino)propanamide	M+H=437; tR=1.92

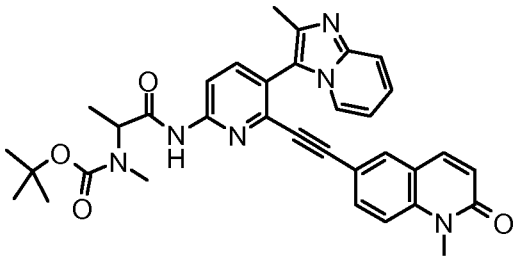
#	Molecular Structure	Chemical Name	HPLC-MS
4		N-[6-[2-(4-fluorophenyl)-ethynyl]-5-isoquinolin-4-ylpyridin-2-yl]-2-(methyl-amino)propanamide	M+H=425; tR=1.95
5		N-[5-isoquinolin-4-yl-6-[2-(3-oxo-4H-1,4-benzoxazin-7-yl)-ethynyl]pyridin-2-yl]-2-(methylamino)propanamide	M+H=478; tR=1.64
6		N-[6-[2-(3,4-dimethylphenyl)-ethynyl]-5-(4-methylpyrimidin-5-yl)pyridin-2-yl]-2-(methylamino)propan-amide	M+H=400; tR=1.40
7		2-(methylamino)-N-[6-[2-(2-methyl-1H-benzimidazol-5-yl)ethynyl]-5-pyrimidin-5-ylpyridin-2-yl]propanamide	M+H=412; tR=0.97
8		2-(methylamino)-N-[6-[2-(5-pyridin-2-ylthiophen-2-yl)-ethynyl]-5-pyrimidin-5-ylpyridin-2-yl]propanamide	M+H=441; tR=1.27
9		2-(methylamino)-N-[5-pyrimidin-5-yl-6-(2-quinolin-2-ylethynyl)pyridin-2-yl]-propanamide	M+H=409; tR=1.24

#	Molecular Structure	Chemical Name	HPLC-MS
10		N-[6-[2-(1H-benzimidazol-5-yl)ethynyl]-5-pyrimidin-5-ylpyridin-2-yl]-2-(methyl-amino)propanamide	M+H=398; tR=0.94
11		2-(methylamino)-N-[6-[2-(4-oxo-2,3-dihydrochromen-6-yl)ethynyl]-5-pyrimidin-5-ylpyridin-2-yl]propanamide	M+H=428; tR=1.21
12		N-[6-[2-(3-cyano-4-methoxyphenyl)ethynyl]-5-pyrimidin-5-ylpyridin-2-yl]-2-(methylamino)propanamide	M+H=413; tR=1.23
13		methyl 5-[6-[[2-(methyl-amino)propanoyl]amino]-2-[2-(3-methylphenyl)ethynyl]-pyridin-3-yl]pyridine-3-carboxylate	M+H=429; tR=1.98
14		N-[6-[2-(2,3-dihydro-1,4-benzodioxin-6-yl)ethynyl]-5-pyrimidin-5-ylpyridin-2-yl]-2-(methylamino)propanamide	M+H=416; tR=1.19
15		N-[6-[2-(1,3-benzothiazol-5-yl)ethynyl]-5-pyrimidin-5-ylpyridin-2-yl]-2-(methyl-amino)propanamide	M+H=415; tR=1.13
16		N-[6-[2-(1-benzofuran-5-yl)-ethynyl]-5-isoquinolin-4-ylpyridin-2-yl]-2-(methyl-amino)propanamide	M+H=447; tR=1.94

#	Molecular Structure	Chemical Name	HPLC-MS
17		N-[6-[2-(3-chloro-5-fluorophenyl)ethynyl]-5-pyrimidin-5-ylpyridin-2-yl]-2-(methylamino)propanamide	M+H=410; tR=1.36
18		N-[6-(2-isoquinolin-7-yl-ethynyl)-5-pyrimidin-5-ylpyridin-2-yl]-2-(methyl-amino)propanamide	M+H=409; tR=1.11
19		2-(methylamino)-N-[5-pyrimidin-5-yl-6-(2-quinolin-6-ylethynyl)pyridin-2-yl]-propanamide	M+H=409; tR=1.11
20		N-[6-(2-dibenzofuran-2-yl-ethynyl)-5-pyrimidin-5-ylpyridin-2-yl]-2-(methyl-amino)propanamide	M+H=448; tR=1.46
21		N-[5-(1,5-dimethylindazol-4-yl)-6-(2-quinolin-6-ylethynyl)-pyridin-2-yl]-2-(methyl-amino)propanamide	M+H=475; tR=1.00
22		N-[5-isoquinolin-8-yl-6-(2-quinolin-6-ylethynyl)pyridin-2-yl]-2-(methylamino)propan-amide	M+H=458; tR=1.11

#	Molecular Structure	Chemical Name	HPLC-MS
23		2-(methylamino)-N-[6-(2-naphthalen-2-ylethynyl)-5-pyrimidin-5-ylpyridin-2-yl]-propanamide	M+H=408; tR=1.83
24		2-(methylamino)-N-[5-(6-methylquinolin-5-yl)-6-(2-quinolin-6-ylethynyl)pyridin-2-yl]propanamide	M+H=472; tR=1.16
25		2-(methylamino)-N-[5-(4-methylpyrimidin-5-yl)-6-(2-quinazolin-7-ylethynyl)-pyridin-2-yl]propanamide	M+H=424; tR=1.13

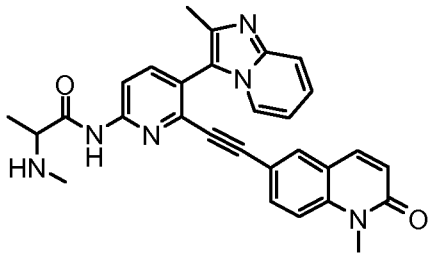
G1b tert-butyl-N-methyl-N-[1-[[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-[2-(1-methyl-2-oxoquinolin-6-yl)ethynyl]pyridin-2-yl]amino]-1-oxopropan-2-yl]-carbamate



A mixture of tert-butyl-N-[1-[[6-ethynyl-5-(2-methylimidazo[1,2-a]pyridin-3-yl)pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate F1a (60 mg, 0.14 mmol), 6-bromo-1-methylquinolin-2-one (82 mg, 0.35 mmol), copper(I) iodide (2.6 mg, 0.01 mmol), Dichlorobis(triphenylphosphine)palladium(II) (8.1 mg, 0.01 mmol) and DIPEA (94 µl, 0.55 mmol) is stirred under argon atmosphere in NMP (0.5 ml) for 2 h at 50°C. The

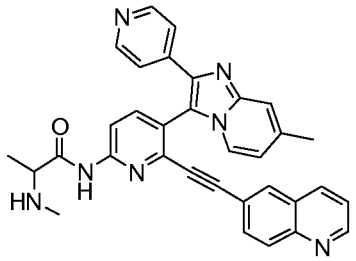
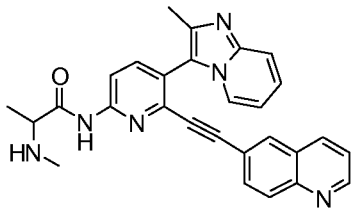
mixture is concentrated in vacuo and the product purified by RP HPLC. Yield: 17 mg (21%). HPLC-MS: M+H=591; tR=1.79 min (*Method_4).

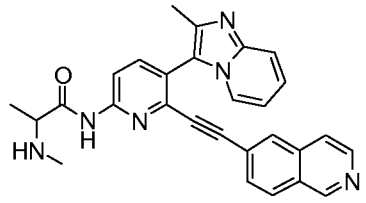
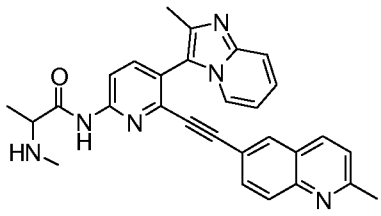
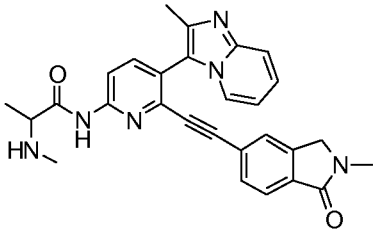
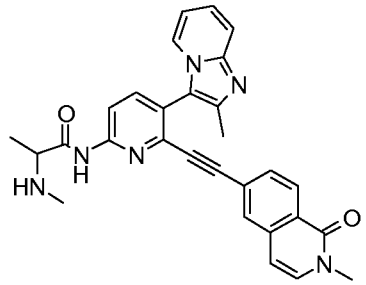
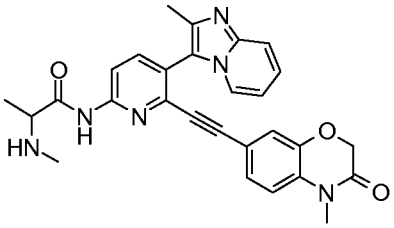
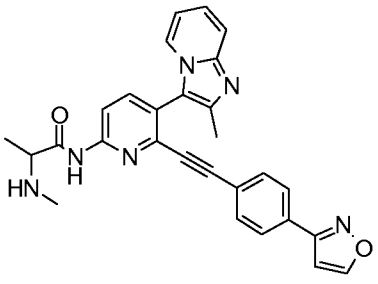
Example 26 2-(methylamino)-N-[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-[2-(1-methyl-2-oxoquinolin-6-yl)ethynyl]pyridin-2-yl]propanamide

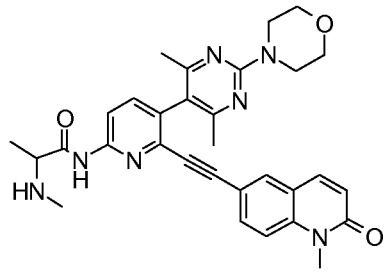
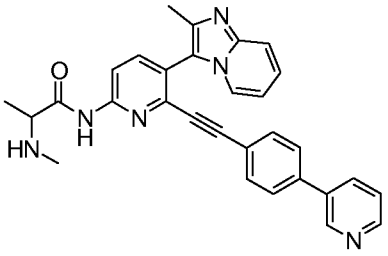
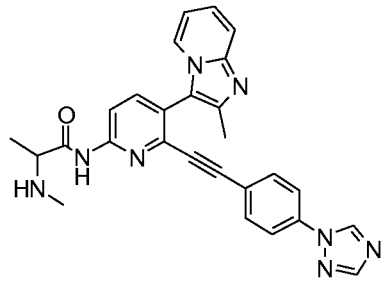
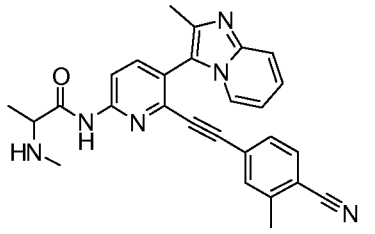
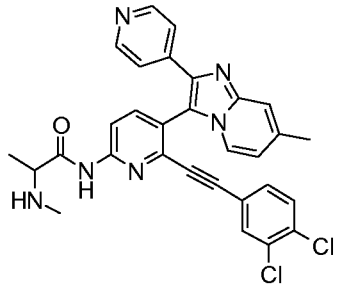


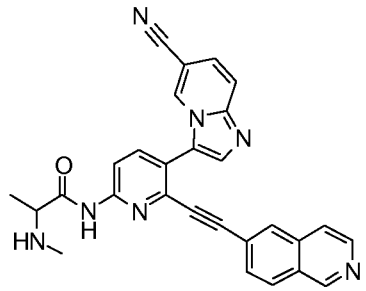
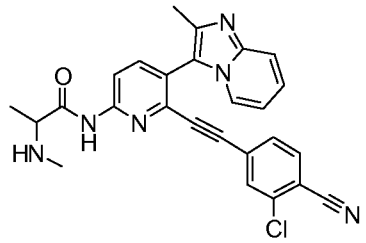
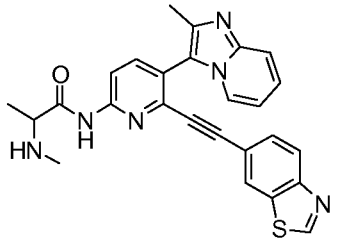
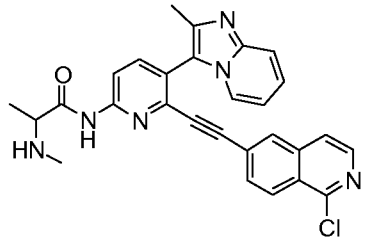
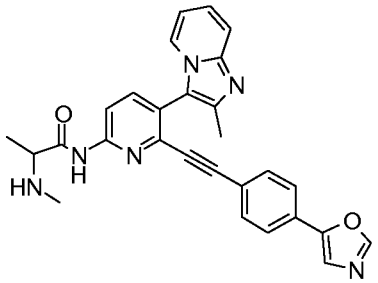
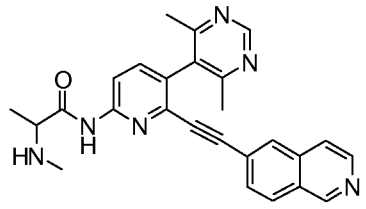
A mixture of tert-butyl-N-methyl-N-[1-[[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-[2-(1-methyl-2-oxoquinolin-6-yl)ethynyl]pyridin-2-yl]amino]-1-oxopropan-2-yl]carbamate G1b (17 mg, 0.03 mmol) and DCM:TFA (9:1, 2 ml) is stirred at RT for 2 h. The mixture is diluted with DCM and a saturated aqueous solution of $NaHCO_3$ is added. The mixture is extracted with DCM. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The product is purified by RP HPLC. Yield: 14 mg (99%). HPLC-MS: M+H=491; tR=0.97 min (*Method_1).

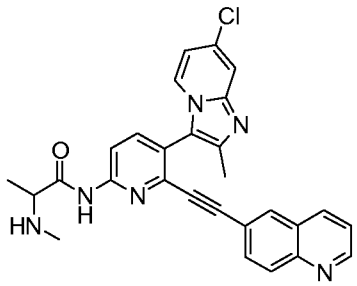
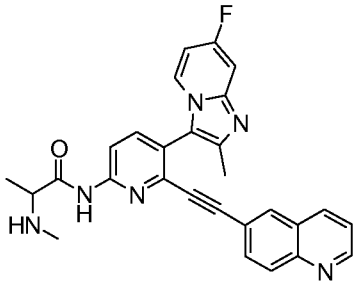
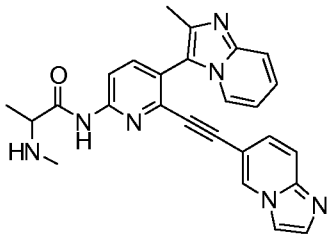
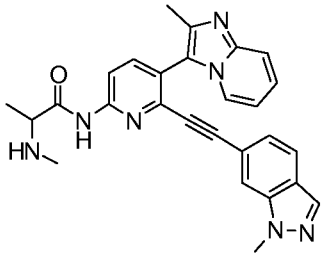
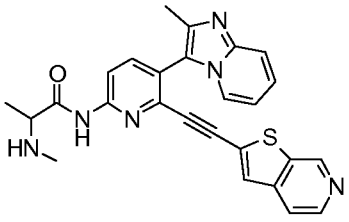
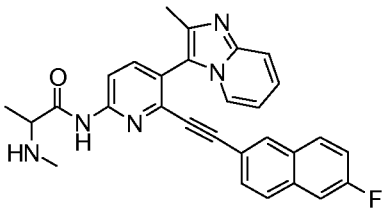
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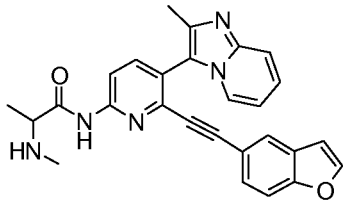
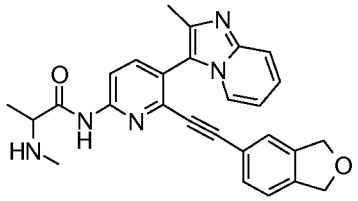
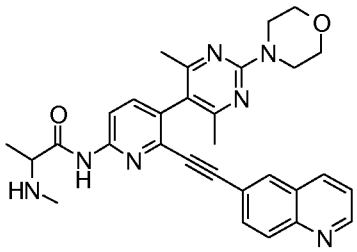
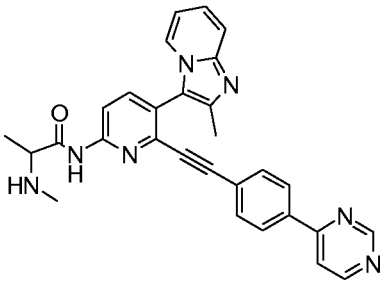
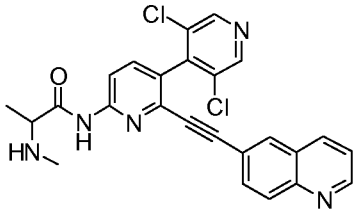
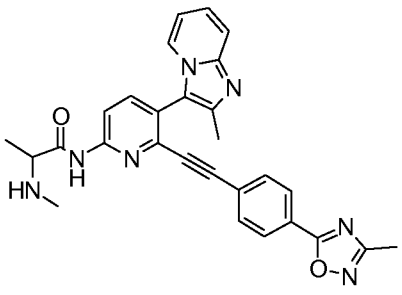
#	Molecular Structure	Chemical Name	HPLC-MS
27		2-(methylamino)-N-[5-(7-methyl-2-pyridin-4-ylimidazo[1,2-a]pyridin-3-yl)-6-(2-quinolin-6-ylethynyl)pyridin-2-yl]propanamide	M+H=538; tR=1.23
28		2-(methylamino)-N-[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-(2-quinolin-6-ylethynyl)-pyridin-2-yl]propanamide	M+H=461; tR=1.20

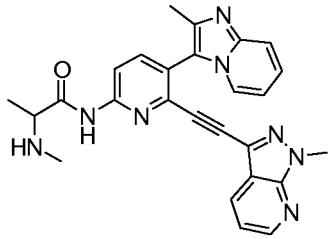
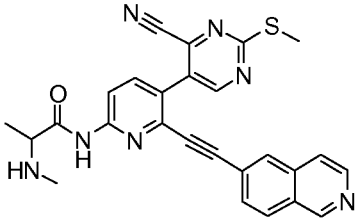
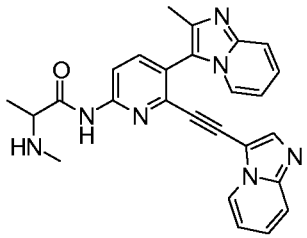
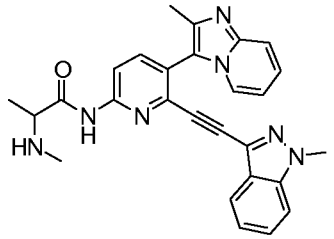
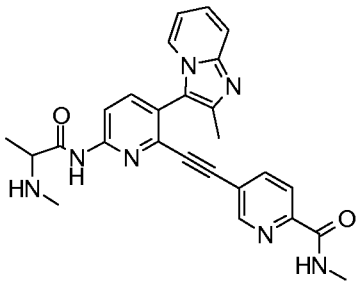
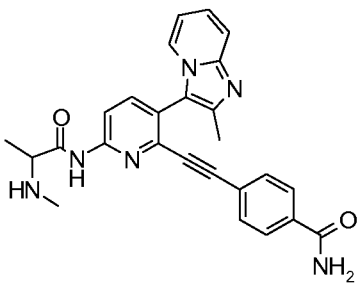
29		N-[6-(2-isoquinolin-6-yl-ethynyl)-5-(2-methyl-imidazo[1,2-a]pyridin-3-yl)-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=461; tR=t0
30		2-(methylamino)-N-[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-[2-(2-methylquinolin-6-yl)ethynyl]pyridin-2-yl]propan-amide	M+H=475; tR=1.06
31		2-(methylamino)-N-[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-[2-(2-methyl-1-oxo-3H-isoindol-5-yl)ethynyl]pyridin-2-yl]propanamide	M+H=479; tR=0.93
32		2-(methylamino)-N-[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-[2-(2-methyl-1-oxoisoquinolin-6-yl)ethynyl]-pyridin-2-yl]propanamide	M+H=491; tR=1.01
33		2-(methylamino)-N-[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-[2-(4-methyl-3-oxo-1,4-benzoxazin-7-yl)ethynyl]-pyridin-2-yl]propanamide	M+H=495; tR=1.03
34		2-(methylamino)-N-[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-[2-[4-(1,2-oxazol-3-yl)-phenyl]ethynyl]pyridin-2-yl]-propanamide	M+H=477; tR=1.14

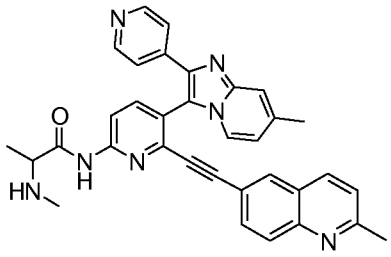
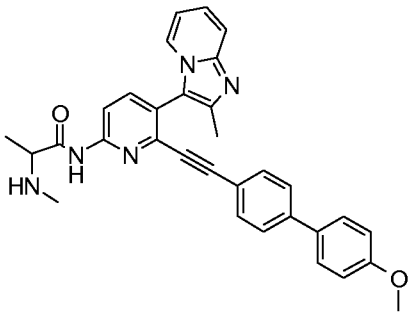
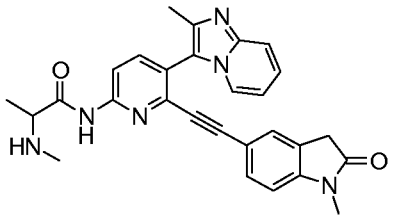
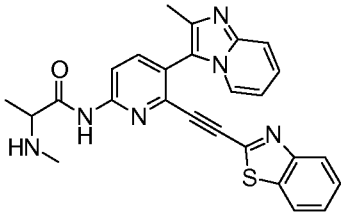
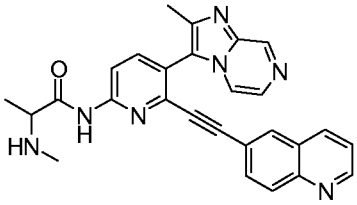
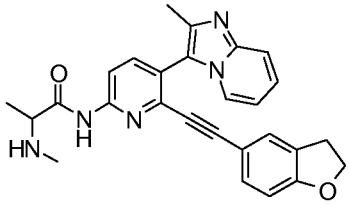
35		N-[5-(4,6-dimethyl-2-morpholin-4-ylpyrimidin-5-yl)-6-[2-(1-methyl-2-oxoquinolin-6-yl)ethynyl]pyridin-2-yl]-2-(methylamino)propanamide	M+H=552; tR=1.17
36		2-(methylamino)-N-[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-[2-(4-pyridin-3-ylphenyl)-ethynyl]pyridin-2-yl]propan-amide	M+H=487; tR=1.10
37		2-(methylamino)-N-[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-[2-[4-(1,2,4-triazol-1-yl)-phenyl]ethynyl]pyridin-2-yl]-propanamide	M+H=477; tR=1.00
38		N-[6-[2-(4-cyano-3-methyl-phenyl)ethynyl]-5-(2-methyl-imidazo[1,2-a]pyridin-3-yl)-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=449; tR=1.57
39		N-[6-[2-(3,4-dichlorophenyl)-ethynyl]-5-(7-methyl-2-pyridin-4-ylimidazo[1,2-a]pyridin-3-yl)-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=555; tR=1.83

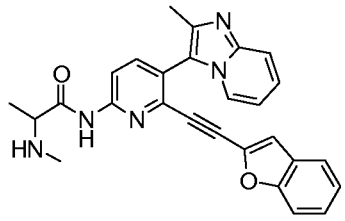
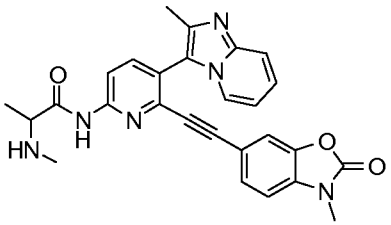
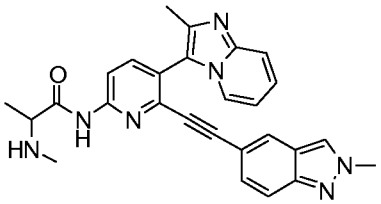
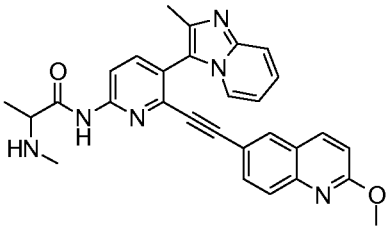
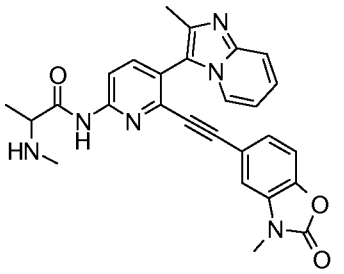
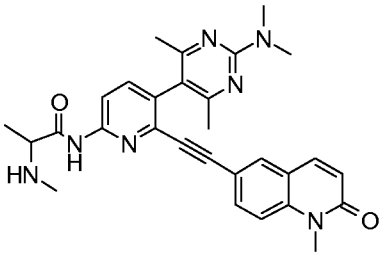
40		N-[5-(6-cyanoimidazo[1,2-a]-pyridin-3-yl)-6-(2-isoquinolin-6-ylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=472; tR=1.24
41		N-[6-[2-(3-chloro-4-cyanophenyl)ethynyl]-5-(2-methylimidazo[1,2-a]pyridin-3-yl)pyridin-2-yl]-2-(methyl-amino)propanamide	M+H=469/ 471; tR=1.32
42		N-[6-[2-(1,3-benzothiazol-6-yl)-ethynyl]-5-(2-methyl-imidazo[1,2-a]pyridin-3-yl)-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=467; tR=1.04
43		N-[6-[2-(1-chloroisoquinolin-6-yl)ethynyl]-5-(2-methyl-imidazo[1,2-a]pyridin-3-yl)-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=495; tR=1.18
44		2-(methylamino)-N-[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-[2-[4-(1,3-oxazol-5-yl)-phenyl]ethynyl]pyridin-2-yl]-propanamide	M+H=477; tR=1.09
45		N-[5-(4,6-dimethylpyrimidin-5-yl)-6-(2-isoquinolin-6-yl-ethynyl)pyridin-2-yl]-2-(methyl-amino)propanamide	M+H=437; tR=1.16

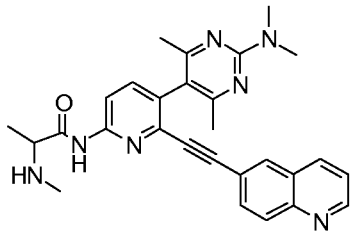
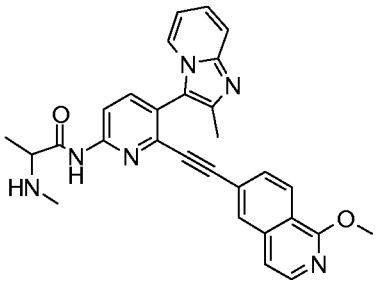
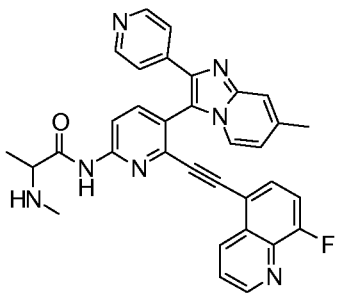
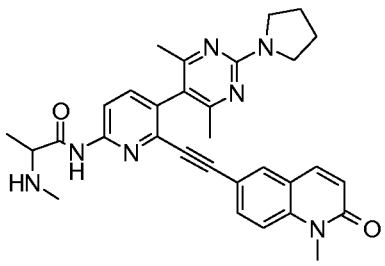
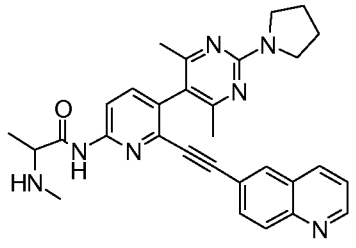
46		N-[5-(7-chloro-2-methyl-imidazo[1,2-a]pyridin-3-yl)-6-(2-quinolin-6-ylethynyl)pyridin-2-yl]-2-(methylamino)propan-amide	M+H=495; tR=1.11
47		N-[5-(7-fluoro-2-methyl-imidazo[1,2-a]pyridin-3-yl)-6-(2-quinolin-6-ylethynyl)pyridin-2-yl]-2-(methylamino)propan-amide	M+H=479; tR=1.04
48		N-[6-(2-imidazo[1,2-a]pyridin-6-ylethynyl)-5-(2-methyl-imidazo[1,2-a]pyridin-3-yl)-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=450; tR=0.92
49		2-(methylamino)-N-[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-[2-(1-methylindazol-6-yl)-ethynyl]pyridin-2-yl]propan-amide	M+H=464; tR=1.05
50		2-(methylamino)-N-[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-(2-thieno[2,3-c]pyridin-2-ylethynyl)pyridin-2-yl]propan-amide	M+H=467; tR=1.00
51		N-[6-[2-(6-fluoronaphthalen-2-yl)ethynyl]-5-(2-methyl-imidazo[1,2-a]pyridin-3-yl)-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=478; tR=1.24

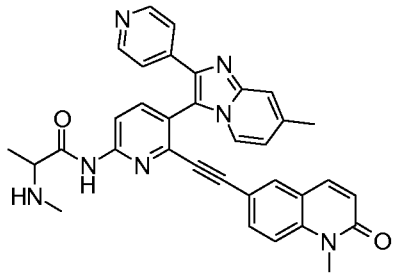
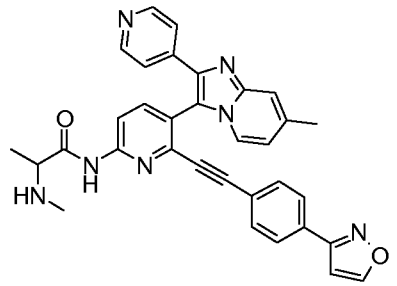
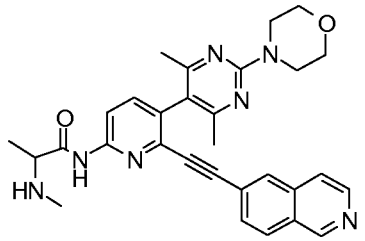
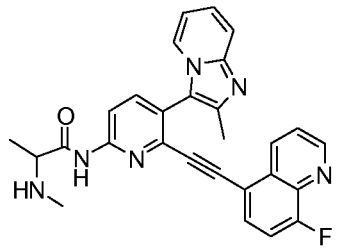
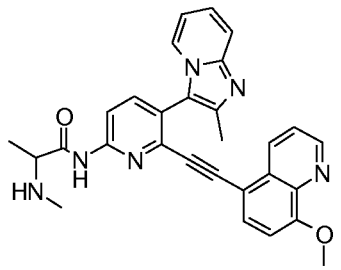
52		N-[6-[2-(1-benzofuran-5-yl)-ethynyl]-5-(2-methyl-imidazo[1,2-a]pyridin-3-yl)-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=450; tR=1.13
53		N-[6-[2-(1,3-dihydro-2-benzofuran-5-yl)ethynyl]-5-(2-methylimidazo[1,2-a]pyridin-3-yl)pyridin-2-yl]-2-(methyl-amino)propanamide	M+H=452; tR=1.02
54		N-[5-(4,6-dimethyl-2-morpholin-4-ylpyrimidin-5-yl)-6-(2-quinolin-6-ylethynyl)-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=522; tR=1.23
55		2-(methylamino)-N-[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-[2-(4-pyrimidin-4-ylphenyl)ethynyl]pyridin-2-yl]-propanamide	M+H=488; tR=1.06
56		N-[5-(3,5-dichloropyridin-4-yl)-6-(2-quinolin-6-ylethynyl)-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=476; tR=1.23
57		2-(methylamino)-N-[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-[2-[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]ethynyl]-pyridin-2-yl]propanamide	M+H=492; tR=1.16

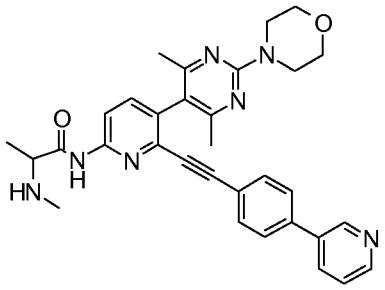
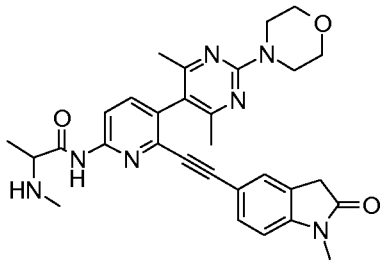
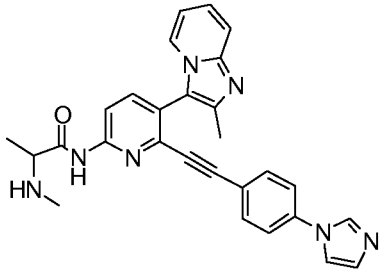
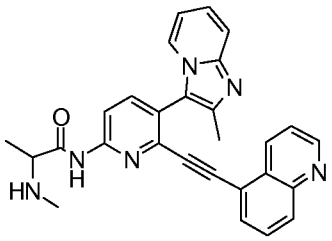
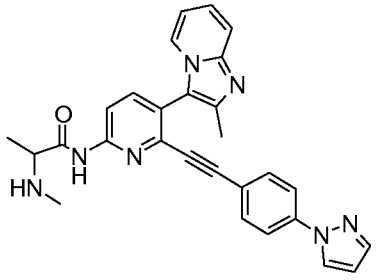
58		2-(methylamino)-N-[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-[2-(1-methylpyrazolo[3,4-b]pyridin-3-yl)ethynyl]pyridin-2-yl]propanamide	M+H=465; tR=1.01
59		N-[5-(4-cyano-2-methylsulfanylpyrimidin-5-yl)-6-(2-isoquinolin-6-ylethynyl)-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=480; tR=1.44
60		N-[6-(2-imidazo[1,2-a]pyridin-3-ylethynyl)-5-(2-methyl-imidazo[1,2-a]pyridin-3-yl)-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=450; tR=0.96
61		2-(methylamino)-N-[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-[2-(1-methylindazol-3-yl)-ethynyl]pyridin-2-yl]propan-amide	M+H=464; tR=1.09
62		N-methyl-5-[2-[6-[[2-(methyl-amino)propanoyl]amino]-3-(2-methylimidazo[1,2-a]pyridin-3-yl)pyridin-2-yl]ethynyl]pyridine-2-carboxamide	M+H=468; tR=0.95
63		4-[2-[6-[[2-(methylamino)-propanoyl]amino]-3-(2-methyl-imidazo[1,2-a]pyridin-3-yl)-pyridin-2-yl]ethynyl]benzamide	M+H=453; tR=0.90

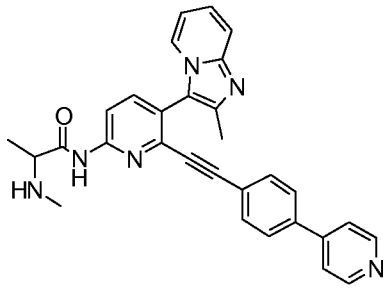
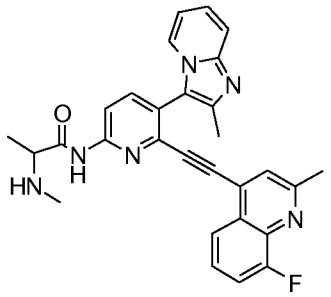
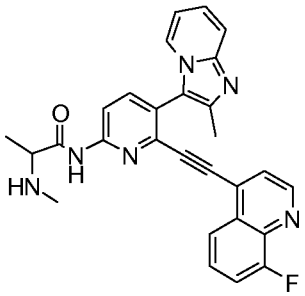
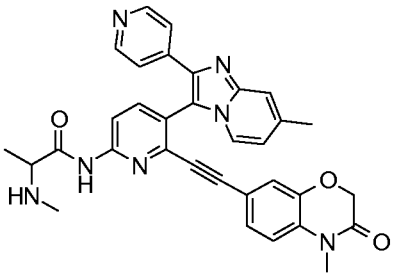
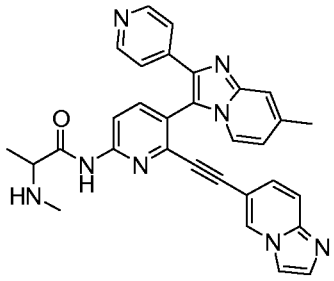
64		2-(methylamino)-N-[5-(7-methyl-2-pyridin-4-ylimidazo[1,2-a]pyridin-3-yl)-6-[2-(2-methylquinolin-6-yl)-ethynyl]pyridin-2-yl]propan-amide	M+H=552; tR=1.13
65		N-[6-[2-[4-(4-methoxyphenyl)-phenyl]ethynyl]-5-(2-methyl-imidazo[1,2-a]pyridin-3-yl)-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=516; tR=1.33
66		2-(methylamino)-N-[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-[2-(1-methyl-2-oxo-3H-indol-5-yl)ethynyl]pyridin-2-yl]-propanamide	M+H=479; tR=1.00
67		N-[6-[2-(1,3-benzothiazol-2-yl)-ethynyl]-5-(2-methyl-imidazo[1,2-a]pyridin-3-yl)-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=467; tR=1.14
68		2-(methylamino)-N-[5-(2-methylimidazo[1,2-a]pyrazin-3-yl)-6-(2-quinolin-6-ylethynyl)-pyridin-2-yl]propanamide	M+H=462; tR=1.27
69		N-[6-[2-(2,3-dihydro-1-benzofuran-5-yl)ethynyl]-5-(2-methylimidazo[1,2-a]pyridin-3-yl)pyridin-2-yl]-2-(methyl-amino)propanamide	M+H=452; tR=1.08

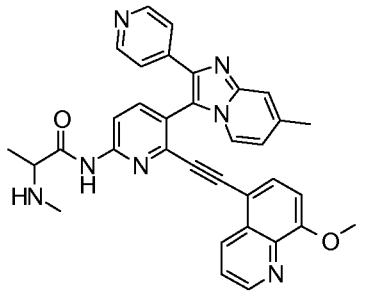
70		N-[6-[2-(1-benzofuran-2-yl)-ethynyl]-5-(2-methyl-imidazo[1,2-a]pyridin-3-yl)-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=450; tR=1.19
71		2-(methylamino)-N-[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-[2-(3-methyl-2-oxo-1,3-benzoxazol-6-yl)ethynyl]-pyridin-2-yl]propanamide	M+H=481; tR=0.97
72		2-(methylamino)-N-[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-[2-(2-methylindazol-5-yl)-ethynyl]pyridin-2-yl]propan-amide	M+H=464; tR=0.96
73		N-[6-[2-(2-methoxyquinolin-6-yl)ethynyl]-5-(2-methyl-imidazo[1,2-a]pyridin-3-yl)-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=491; tR=1.22
74		2-(methylamino)-N-[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-[2-(3-methyl-2-oxo-1,3-benzoxazol-5-yl)ethynyl]-pyridin-2-yl]propanamide	M+H=481; tR=1.03
75		N-[5-[2-(dimethylamino)-4,6-dimethylpyrimidin-5-yl]-6-[2-(1-methyl-2-oxoquinolin-6-yl)-ethynyl]pyridin-2-yl]-2-(methyl-amino)propanamide	M+H=510; tR=1.22

76		N-[5-[2-(dimethylamino)-4,6-dimethylpyrimidin-5-yl]-6-(2-quinolin-6-ylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=480; tR=1.28
77		N-[6-[2-(1-methoxyisoquinolin-6-yl)ethynyl]-5-(2-methyl-imidazo[1,2-a]pyridin-3-yl)-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=491; tR=1.21
78		N-[6-[2-(8-fluoroquinolin-5-yl)-ethynyl]-5-(7-methyl-2-pyridin-4-ylimidazo[1,2-a]pyridin-3-yl)-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=556; tR=1.09
79		N-[5-(4,6-dimethyl-2-pyrrolidin-1-ylpyrimidin-5-yl)-6-[2-(1-methyl-2-oxoquinolin-6-yl)-ethynyl]pyridin-2-yl]-2-(methyl-amino)propanamide	M+H=536; tR=1.24
80		N-[5-(4,6-dimethyl-2-pyrrolidin-1-ylpyrimidin-5-yl)-6-(2-quinolin-6-ylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=506; tR=1.31

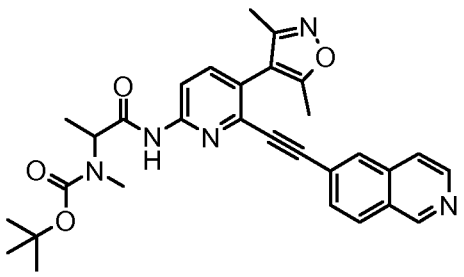
81		2-(methylamino)-N-[6-[2-(1-methyl-2-oxoquinolin-6-yl)-ethynyl]-5-(7-methyl-2-pyridin-4-ylimidazo[1,2-a]pyridin-3-yl)-pyridin-2-yl]propanamide	M+H=568; tR=1.04
82		2-(methylamino)-N-[5-(7-methyl-2-pyridin-4-ylimidazo[1,2-a]pyridin-3-yl)-6-[2-[4-(1,2-oxazol-3-yl)phenyl]-ethynyl]pyridin-2-yl]propan-amide	M+H=554; tR=1.17
83		N-[5-(4,6-dimethyl-2-morpholin-4-ylpyrimidin-5-yl)-6-(2-isoquinolin-6-ylethynyl)-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=522; tR=1.23
84		N-[6-[2-(8-fluoroquinolin-5-yl)-ethynyl]-5-(2-methyl-imidazo[1,2-a]pyridin-3-yl)-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=479; tR=1.05
85		N-[6-[2-(8-methoxyquinolin-5-yl)ethynyl]-5-(2-methyl-imidazo[1,2-a]pyridin-3-yl)-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=491; tR=1.00

86		N-[5-(4,6-dimethyl-2-morpholin-4-ylpyrimidin-5-yl)-6-[2-(4-pyridin-3-ylphenyl)-ethynyl]pyridin-2-yl]-2-(methyl-amino)propanamide	M+H=548; tR=1.28
87		N-[5-(4,6-dimethyl-2-morpholin-4-ylpyrimidin-5-yl)-6-[2-(1-methyl-2-oxo-3H-indol-5-yl)ethynyl]pyridin-2-yl]-2-(methylamino)propanamide	M+H=540; tR=1.16
88		N-[6-[2-(4-imidazol-1-ylphenyl)ethynyl]-5-(2-methyl-imidazo[1,2-a]pyridin-3-yl)-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=476; tR=1.00
89		2-(methylamino)-N-[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-(2-quinolin-5-ylethynyl)-pyridin-2-yl]propanamide	M+H=461; tR=1.04
90		2-(methylamino)-N-[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-[2-(4-pyrazol-1-ylphenyl)-ethynyl]pyridin-2-yl]propan-amide	M+H=476; tR=1.12

91		2-(methylamino)-N-[5-(2-methylimidazo[1,2-a]pyridin-3-yl)-6-[2-(4-pyridin-4-ylphenyl)-ethynyl]pyridin-2-yl]propan-amide	M+H=487; tR=1.09
92		N-[6-[2-(8-fluoro-2-methylquinolin-4-yl)ethynyl]-5-(2-methylimidazo[1,2-a]pyridin-3-yl)pyridin-2-yl]-2-(methyl-amino)propanamide	M+H=493; tR=1.11
93		N-[6-[2-(8-fluoroquinolin-4-yl)-ethynyl]-5-(2-methyl-imidazo[1,2-a]pyridin-3-yl)-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=479; tR=1.06
94		2-(methylamino)-N-[6-[2-(4-methyl-3-oxo-1,4-benzoxazin-7-yl)ethynyl]-5-(7-methyl-2-pyridin-4-ylimidazo[1,2-a]-pyridin-3-yl)pyridin-2-yl]-propanamide	M+H=572; tR=1.08
95		N-[6-(2-imidazo[1,2-a]pyridin-6-ylethynyl)-5-(7-methyl-2-pyridin-4-ylimidazo[1,2-a]-pyridin-3-yl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=527; tR=0.98

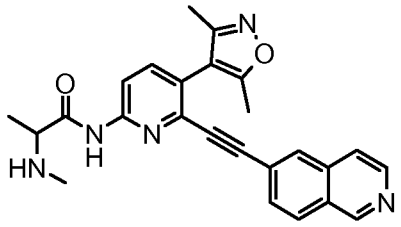
96		N-[6-[2-(8-methoxyquinolin-5-yl)ethynyl]-5-(7-methyl-2-pyridin-4-ylimidazo[1,2-a]-pyridin-3-yl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=568; tR=1.04

E2a) tert-butyl-N-[1-[[5-(3,5-dimethyl-1,2-oxazol-4-yl)-6-(2-isoquinolin-6-ylethynyl)-pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate



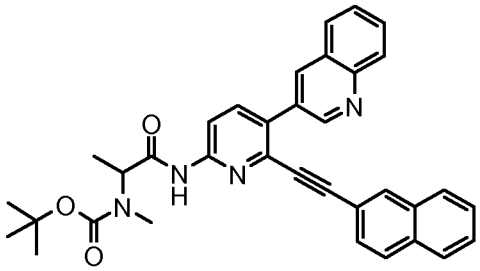
A mixture of tert-butyl-N-[1-[[5-bromo-6-(2-isoquinolin-6-ylethynyl)pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate C2b (300 mg, 0.59 mmol), (3,5-dimethyl-1,2-oxazol-4-yl)boronic acid (166 mg, 1.18 mmol), CsF (358 mg, 2.36 mmol) tris-(dibenzylideneacetone)dipalladium(0) (41 mg, 0.06 mmol), tri-tert-butylphosphonium tetrafluoroborate (34 mg, 0.12 mmol) and dioxane (4.5 ml) is stirred under argon atmosphere at 50°C for 2h. The mixture is diluted with DCM and extracted with a saturated aqueous solution of $NaHCO_3$. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The product is purified by RP HPLC. Yield: 191 mg (62%). HPLC-MS: M+H=526; tR=1.89 min (*Method_2).

Example 97 N-[5-(3,5-dimethyl-1,2-oxazol-4-yl)-6-(2-isoquinolin-6-ylethynyl)-pyridin-2-yl]-2-(methylamino)propanamide



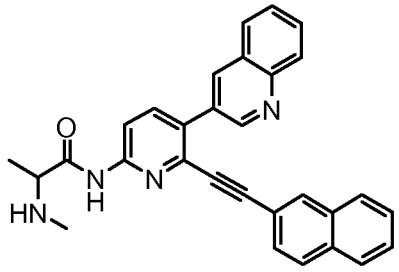
A mixture of tert-butyl-N-[1-[[5-(3,5-dimethyl-1,2-oxazol-4-yl)-6-(2-isoquinolin-6-yl-ethynyl)pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate E2a (191 mg, 0.36 mmol) and DCM:TFA (9:1, 10 ml) is stirred at RT for 2 h. The mixture is diluted with DCM and extracted with a saturated aqueous solution of $NaHCO_3$. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The product is purified by RP HPLC. Yield: 101 mg (65%). HPLC-MS: M+H=426; tR=1.30 min (*Method_1).

E2b) tert-butyl-N-methyl-N-[1-[[6-(2-naphthalen-2-ylethynyl)-5-quinolin-3-yl-pyridin-2-yl]amino]-1-oxopropan-2-yl]carbamate



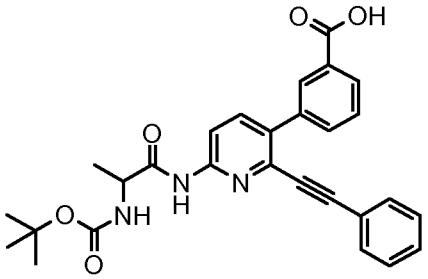
A mixture of tert-butyl-N-[1-[[5-bromo-6-(2-naphthalen-2-ylethynyl)pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate C2c (150 mg, 0.30 mmol), quinolin-3-ylboronic acid (61 mg, 0.35 mmol), Dichlorobis(triphenylphosphine)palladium(II) (40 mg, 0.06 mmol), Na_2CO_3 (63 mg, 0.59 mmol), dioxane (1 ml), MeOH (0.2 ml) and water (0.1 ml) is stirred under argon atmosphere for 2 h at 85°C. The mixture is diluted with DCM and extracted with a saturated aqueous solution of $NaHCO_3$. The combined organic layers are dried over $MgSO_4$, concentrated in vacuo and the product purified by RP HPLC. Yield: 91 mg (55%).

Example 98 2-(methylamino)-N-[6-(2-naphthalen-2-ylethynyl)-5-quinolin-3-yl-pyridin-2-yl]propanamide



A mixture of tert-butyl-N-methyl-N-[1-[[6-(2-naphthalen-2-ylethynyl)-5-quinolin-3-yl-pyridin-2-yl]amino]-1-oxopropan-2-yl]carbamate E2b (91 mg, 0.16 mmol) and DCM:TFA (9:1, 5 ml) is stirred at RT for 1 h. The mixture is diluted with toluene (10 ml) and concentrated in vacuo. The product is purified by RP HPLC. Yield: 74 mg (99%). HPLC-MS: M+H=457; tR=1.58 min (*Method_1).

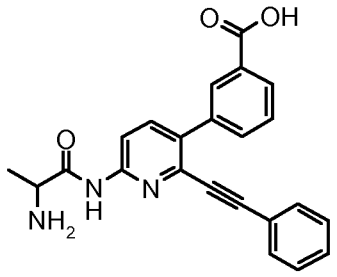
E2c) 3-[6-[2-[(2-methylpropan-2-yl)oxycarbonylamino]propanoylamino]-2-(2-phenylethynyl)pyridin-3-yl]benzoic acid



A mixture of tert-butyl-N-[1-[[5-bromo-6-(2-phenylethynyl)pyridin-2-yl]amino]-1-oxo-propan-2-yl]carbamate C2d (40 mg, 0.09 mmol), 3-boronobenzoic acid (18 mg, 0.11 mmol), Dichlorobis(triphenylphosphine)palladium(II) (6.3 mg, 0.01 mmol), Na_2CO_3 (19 mg, 0.18 mmol), dioxane (0.9 ml), MeOH (0.2 ml) and water (0.1 ml) is stirred under argon atmosphere for 4 h at 70°C. The reaction mixture is concentrated in vacuo and the

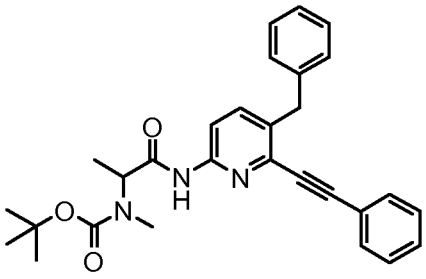
product purified by RP HPLC. Yield: 16 mg (37%). HPLC-MS: M+H=486; tR=1.49 min (*Method_5).

Example 99 3-[6-(2-aminopropanoylamino)-2-(2-phenylethynyl)pyridin-3-yl]-benzoic acid



A mixture of 3-[6-[2-[(2-methylpropan-2-yl)oxycarbonylamino]propanoylamino]-2-(2-phenylethynyl)pyridin-3-yl]benzoic acid E2c (16 mg, 0.03 mmol) and DCM:TFA (9:1, 1.7 ml) is stirred at RT for 90 minutes. The mixture is diluted with toluene (10 ml) and concentrated in vacuo. The product is purified by RP HPLC. Yield: 3 mg (24%). HPLC-MS: M+H=386; tR=1.03 min (*Method_1).

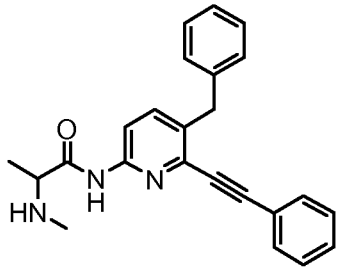
E2d) tert-butyl-N-[1-[[5-benzyl-6-(2-phenylethynyl)pyridin-2-yl]amino]-1-oxo-propan-2-yl]-N-methylcarbamate



A mixture of tert-butyl-N-[1-[[5-bromo-6-(2-phenylethynyl)pyridin-2-yl]amino]-1-oxo-propan-2-yl]-N-methylcarbamate C2a (50 mg, 0.11 mmol), 9-benzyl-9-borabicyclo[3.3.1]-nonane (283 µl, 0.14 mmol) Cs_2CO_3 (71 mg, 0.22 mmol), 1,1′-Bis(diphenylphosphino)-ferrocene]dichloropalladium(II) (8.0 mg, 0.01 mmol) and dioxane (0.6 ml) is stirred under

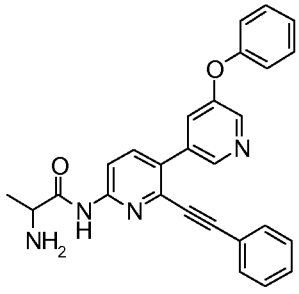
argon atmosphere for 45 minutes at 70°C. The mixture is concentrated in vacuo and the product purified by RP HPLC. Yield: 26 mg (51%). HPLC-MS: M+H=470; tR=1.97 min (*Method_4).

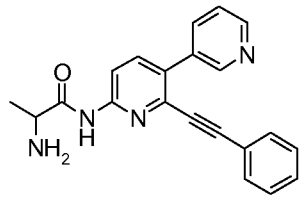
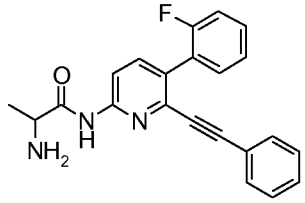
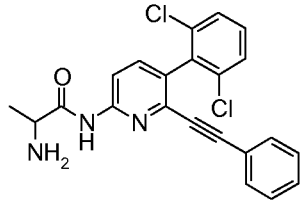
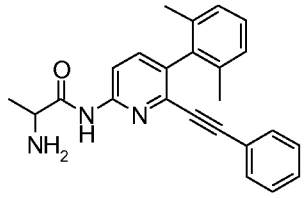
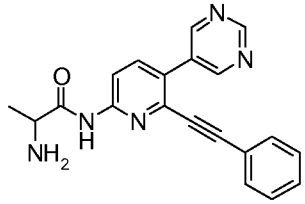
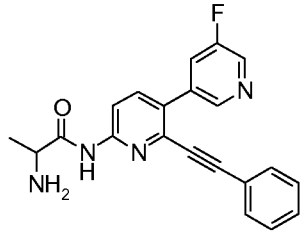
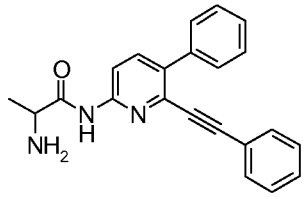
Example 119 N-[5-benzyl-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)-propan-amide

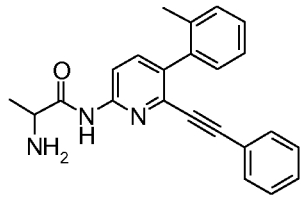
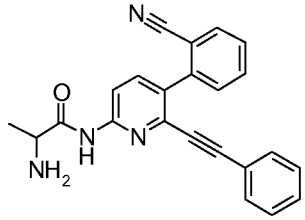
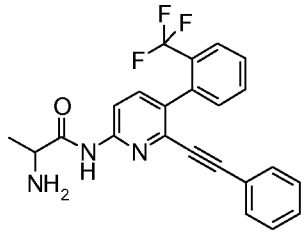
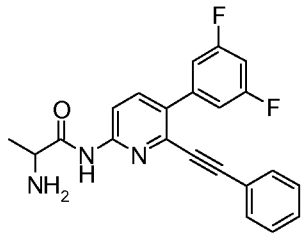
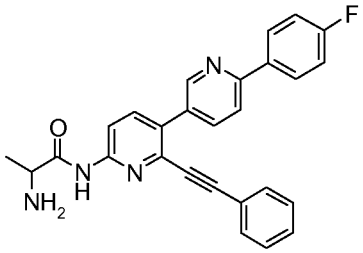
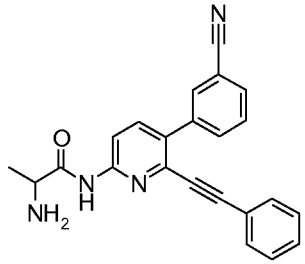


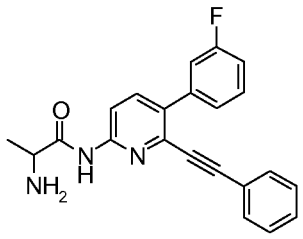
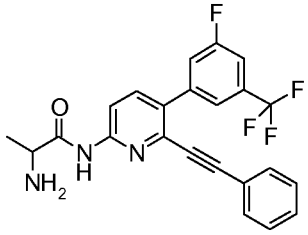
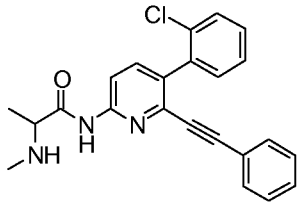
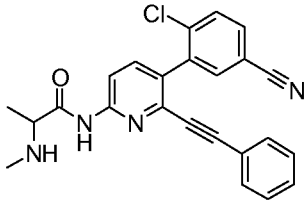
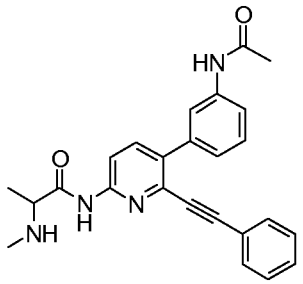
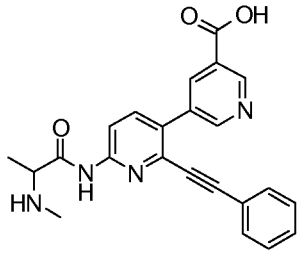
A mixture of tert-butyl-N-[1-[[5-benzyl-6-(2-phenylethynyl)pyridin-2-yl]amino]-1-oxo-propan-2-yl]-N-methylcarbamate E2d (26 mg, 0.6 mmol) and DCM:TFA (9:1, 2 ml) is stirred at RT for 90 minutes. The mixture is diluted with DCM and extracted with a saturated aqueous solution of $NaHCO_3$. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The product is purified by RP HPLC. Yield: 4 mg (20%). HPLC-MS: M+H=370; tR=2.16 min (*Method_1).

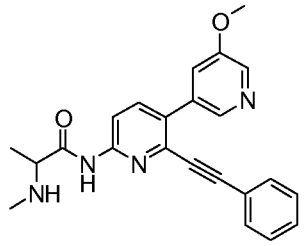
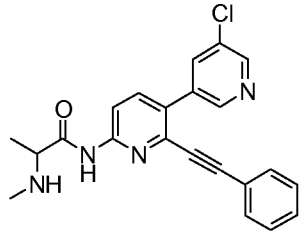
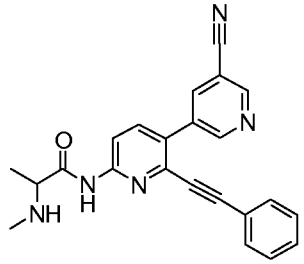
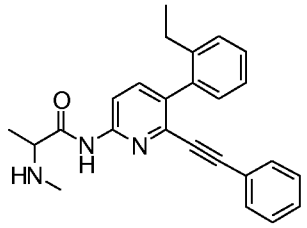
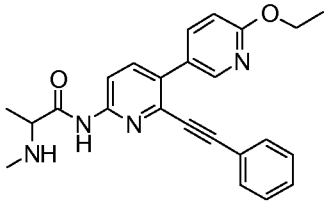
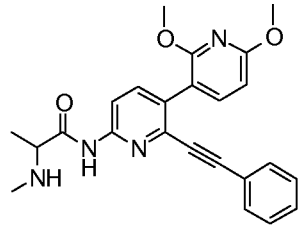
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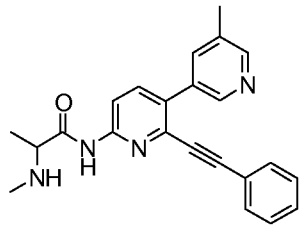
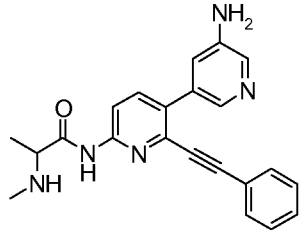
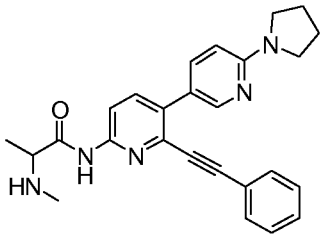
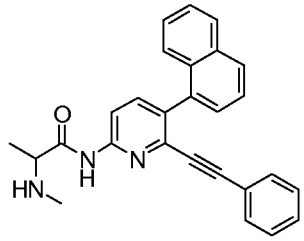
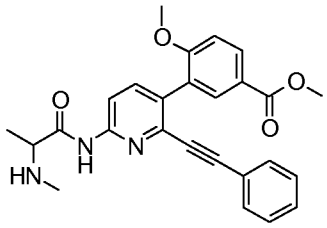
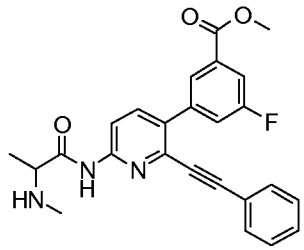
#	Molecular Structure	Chemical Name	HPLC-MS
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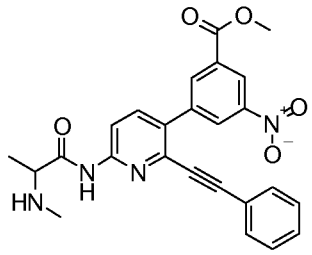
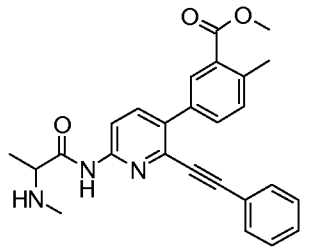
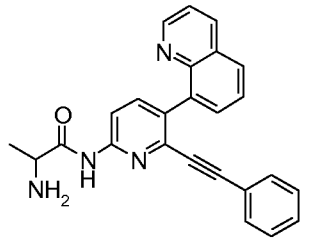
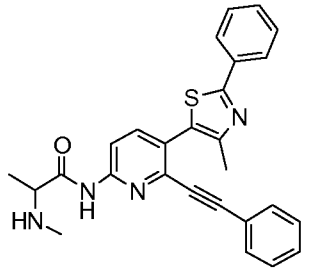
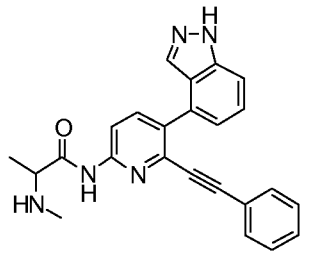
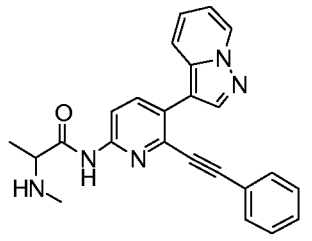
101		2-amino-N-[6-(2-phenylethynyl)-5-pyridin-3-ylpyridin-2-yl]-propanamide	M+H=343; tR=1.61
102		2-amino-N-[5-(2-fluorophenyl)-6-(2-phenylethynyl)pyridin-2-yl]-propanamide	M+H=360; tR=1.97
103		2-amino-N-[5-(2,6-dichlorophenyl)-6-(2-phenyl-ethynyl)pyridin-2-yl]propanamide	M+H=410/ 412/414
104		2-amino-N-[5-(2,6-dimethyl-phenyl)-6-(2-phenylethynyl)-pyridin-2-yl]propanamide	M+H=370; tR=2.21
105		2-amino-N-[6-(2-phenylethynyl)-5-pyrimidin-5-ylpyridin-2-yl]-propanamide	M+H=344; tR=1.49
106		2-amino-N-[5-(5-fluoropyridin-3-yl)-6-(2-phenylethynyl)pyridin-2-yl]propanamide	M+H=361; tR=1.75
107		2-amino-N-[5-phenyl-6-(2-phenylethynyl)pyridin-2-yl]-propanamide	M+H=342; tR=1.98

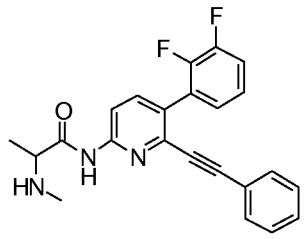
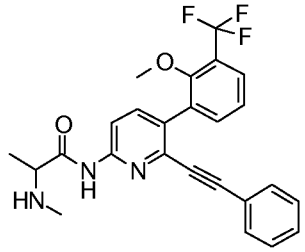
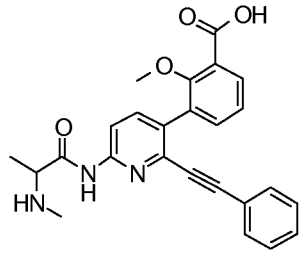
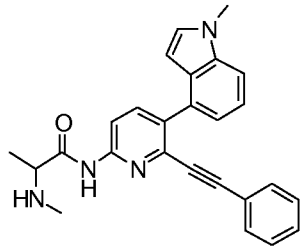
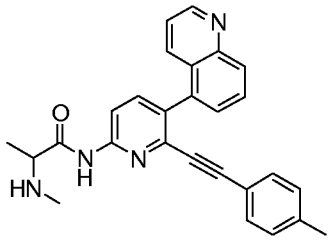
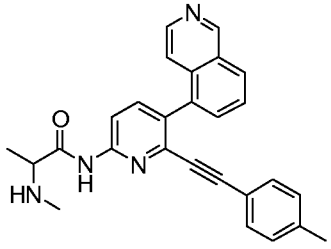
108		2-amino-N-[5-(2-methylphenyl)-6-(2-phenylethynyl)pyridin-2-yl]-propanamide	M+H=356; tR=2.04
109		2-amino-N-[5-(2-cyanophenyl)-6-(2-phenylethynyl)pyridin-2-yl]-propanamide	M+H=367; tR=1.84
110		2-amino-N-[6-(2-phenylethynyl)-5-[2-(trifluoromethyl)phenyl]-pyridin-2-yl]propanamide	M+H=410; tR=2.06
111		2-amino-N-[5-(3,5-difluorophenyl)-6-(2-phenyl-ethynyl)pyridin-2-yl]propanamide	M+H=378; tR=1.99
112		2-amino-N-[5-[6-(4-fluorophenyl)pyridin-3-yl]-6-(2-phenylethynyl)pyridin-2-yl]-propanamide	M+H=437; tR=2.11
113		2-amino-N-[5-(3-cyanophenyl)-6-(2-phenylethynyl)pyridin-2-yl]-propanamide	M+H=367; tR=1.86

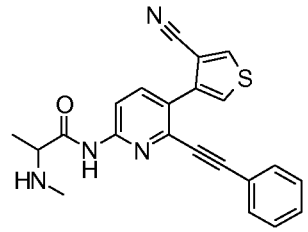
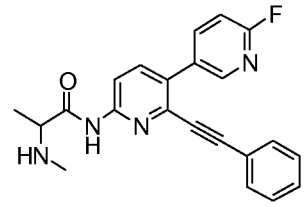
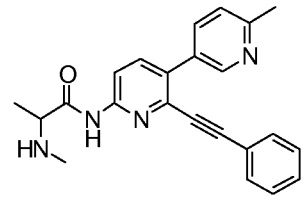
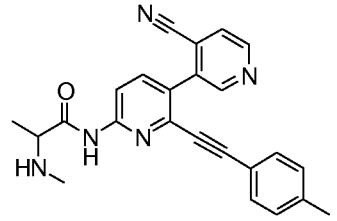
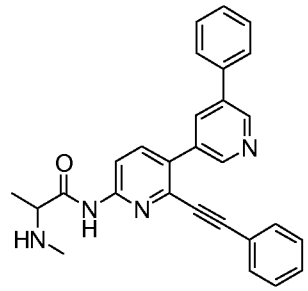
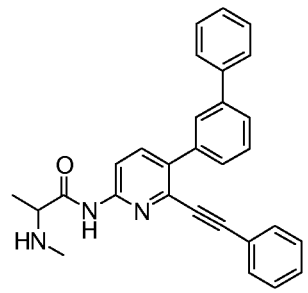
114		2-amino-N-[5-(3-fluorophenyl)-6-(2-phenylethynyl)pyridin-2-yl]-propanamide	M+H=360; tR=2.01
115		2-amino-N-[5-[3-fluoro-5-(trifluoromethyl)phenyl]-6-(2-phenylethynyl)pyridin-2-yl]-propanamide	M+H=428; tR=2.32
116		N-[5-(2-chlorophenyl)-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=390/ 392; tR=2.10
117		N-[5-(2-chloro-5-cyanophenyl)-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=415; tR=2.00
118		N-[5-(3-acetamidophenyl)-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=413; tR=1.72
120		5-[6-[[2-(methylamino)-propanoyl]amino]-2-(2-phenyl-ethynyl)pyridin-3-yl]pyridine-3-carboxylic acid	M+H=401; tR=1.04

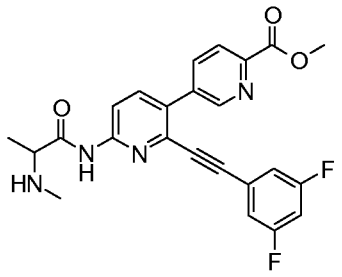
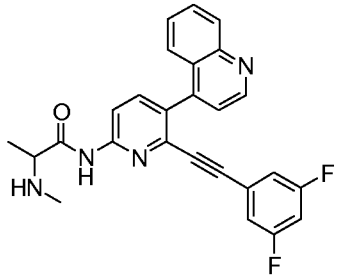
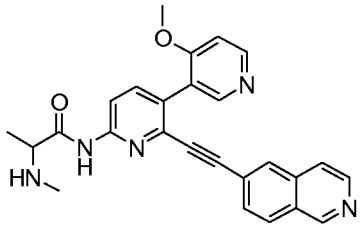
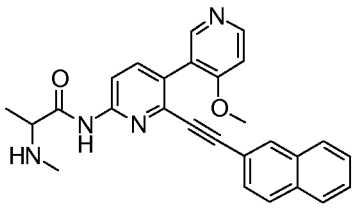
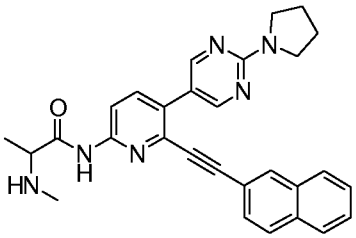
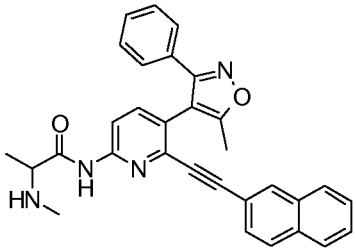
121		N-[5-(5-methoxypyridin-3-yl)-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=387; tR=1.77
122		N-[5-(5-chloropyridin-3-yl)-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=391; tR=1.94
123		N-[5-(5-cyanopyridin-3-yl)-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=382; tR=1.75
124		N-[5-(2-ethylphenyl)-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=384; tR=2.25
125		N-[5-(6-ethoxypyridin-3-yl)-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=401; tR=2.05
126		N-[5-(2,6-dimethoxypyridin-3-yl)-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=417; tR=2.08

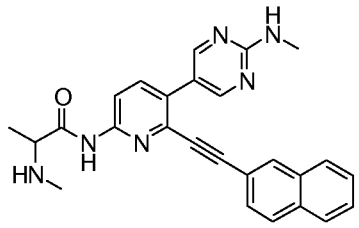
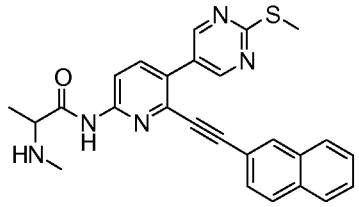
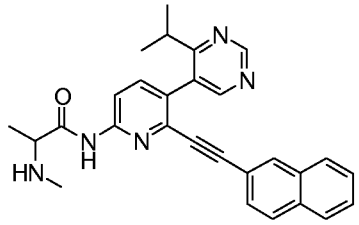
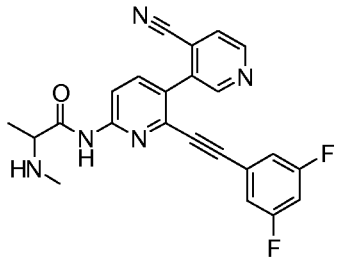
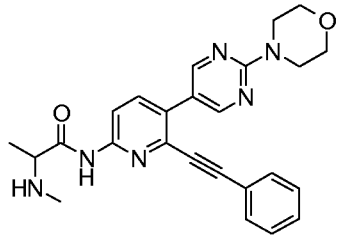
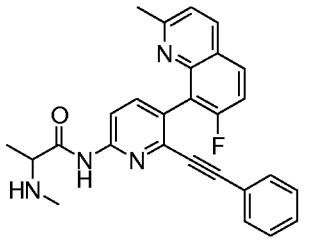
127		2-(methylamino)-N-[5-(5-methylpyridin-3-yl)-6-(2-phenyl-ethynyl)pyridin-2-yl]propanamide	M+H=371; tR=1.78
128		N-[5-(5-aminopyridin-3-yl)-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=372; tR=1.47
129		2-(methylamino)-N-[6-(2-phenyl-ethynyl)-5-(6-pyrrolidin-1-ylpyridin-3-yl)pyridin-2-yl]-propanamide	M+H=426; tR=2.02
130		2-(methylamino)-N-[5-naphthalen-1-yl-6-(2-phenyl-ethynyl)pyridin-2-yl]propanamide	M+H=406; tR=2.17
131		methyl 4-methoxy-3-[6-[[2-(methylamino)propanoyl]amino]-2-(2-phenylethynyl)pyridin-3-yl]-benzoate	M+H=444; tR=1.95
132		methyl 3-fluoro-5-[6-[[2-(methyl-amino)propanoyl]amino]-2-(2-phenylethynyl)pyridin-3-yl]-benzoate	M+H=432; tR=2.11

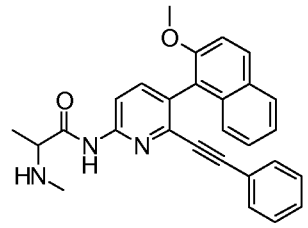
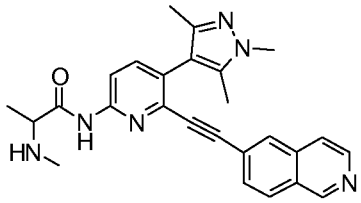
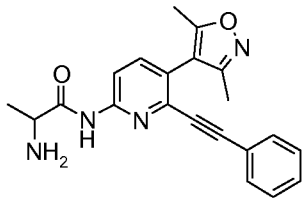
133		methyl 3-[6-[[2-(methylamino)-propanoyl]amino]-2-(2-phenyl-ethynyl)pyridin-3-yl]-5-nitrobenzoate	M+H=459; tR=2.06
134		methyl 2-methyl-5-[6-[[2-(methylamino)propanoyl]amino]-2-(2-phenylethynyl)pyridin-3-yl]-benzoate	M+H=428; tR=2.10
135		2-amino-N-[6-(2-phenylethynyl)-5-quinolin-8-ylpyridin-2-yl]-propanamide	M+H=393; tR=1.80
136		2-(methylamino)-N-[5-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-6-(2-phenylethynyl)pyridin-2-yl]-propanamide	M+H=453; tR=2.30
137		N-[5-(1H-indazol-4-yl)-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=396; tR=1.76
138		2-(methylamino)-N-[6-(2-phenyl-ethynyl)-5-pyrazolo[1,5-a]-pyridin-3-ylpyridin-2-yl]propan-amide	M+H=396; tR=1.85

139		N-[5-(2,3-difluorophenyl)-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=392; tR=2.13
140		N-[5-[2-methoxy-3-(trifluoromethyl)phenyl]-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=454; tR=2.22
141		2-methoxy-3-[6-[[2-(methyl-amino)propanoyl]amino]-2-(2-phenylethynyl)pyridin-3-yl]-benzoic acid	M+H=430; tR=1.16
142		2-(methylamino)-N-[5-(1-methylindol-4-yl)-6-(2-phenyl-ethynyl)pyridin-2-yl]propanamide	M+H=409; tR=2.07
143		2-(methylamino)-N-[6-[2-(4-methylphenyl)ethynyl]-5-quinolin-5-ylpyridin-2-yl]propan-amide	M+H=421; tR=1.92
144		N-[5-isoquinolin-5-yl-6-[2-(4-methylphenyl)ethynyl]pyridin-2-yl]-2-(methylamino)propanamide	M+H=421; tR=1.92

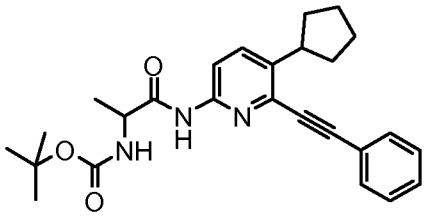
145		N-[5-(4-cyanothiophen-3-yl)-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=387; tR=1.87
146		N-[5-(6-fluoropyridin-3-yl)-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=375; tR=1.85
147		2-(methylamino)-N-[5-(6-methylpyridin-3-yl)-6-(2-phenylethynyl)pyridin-2-yl]propanamide	M+H=371; tR=1.77
148		N-[5-(4-cyanopyridin-3-yl)-6-[2-(4-methylphenyl)ethynyl]pyridin-2-yl]-2-(methylamino)propanamide	M+H=396; tR=1.79
149		2-(methylamino)-N-[6-(2-phenylethynyl)-5-(5-phenylpyridin-3-yl)pyridin-2-yl]propanamide	M+H=433; tR=2.12
150		2-(methylamino)-N-[6-(2-phenylethynyl)-5-(3-phenylphenyl)-pyridin-2-yl]propanamide	M+H=432; tR=2.41

151		methyl 5-[2-[2-(3,5-difluorophenyl)ethynyl]-6-[[2-(methylamino)propanoyl]amino]-pyridin-3-yl]pyridine-2-carboxylate	M+H=451; tR=1.82
152		N-[6-[2-(3,5-difluorophenyl)-ethynyl]-5-quinolin-4-ylpyridin-2-yl]-2-(methylamino)propanamide	M+H=443; tR=1.95
153		N-[6-(2-isoquinolin-6-ylethynyl)-5-(4-methoxypyridin-3-yl)-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=438; tR=1.17
154		N-[5-(4-methoxypyridin-3-yl)-6-(2-naphthalen-2-ylethynyl)-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=437; tR=1.48
155		2-(methylamino)-N-[6-(2-naphthalen-2-ylethynyl)-5-(2-pyrrolidin-1-ylpyrimidin-5-yl)-pyridin-2-yl]propanamide	M+H=477; tR=1.60
156		2-(methylamino)-N-[5-(5-methyl-3-phenyl-1,2-oxazol-4-yl)-6-(2-naphthalen-2-ylethynyl)pyridin-2-yl]propanamide	M+H=487; tR=1.62

157		2-(methylamino)-N-[5-[2-(methylamino)pyrimidin-5-yl]-6-(2-naphthalen-2-ylethynyl)-pyridin-2-yl]propanamide	M+H=437; tR=1.39
158		2-(methylamino)-N-[5-(2-methylsulfanylpyrimidin-5-yl)-6-(2-naphthalen-2-ylethynyl)-pyridin-2-yl]propanamide	M+H=454; tR=1.62
159		2-(methylamino)-N-[6-(2-naphthalen-2-ylethynyl)-5-(4-propan-2-ylpyrimidin-5-yl)-pyridin-2-yl]propanamide	M+H=450; tR=1.55
160		N-[5-(4-cyanopyridin-3-yl)-6-[2-(3,5-difluorophenyl)ethynyl]-pyridin-2-yl]-2-(methylamino)-propanamide	M+H=418; tR=1.68
161		2-(methylamino)-N-[5-(2-morpholin-4-ylpyrimidin-5-yl)-6-(2-phenylethynyl)pyridin-2-yl]-propanamide	M+H=443; tR=1.63
162		N-[5-(7-fluoro-2-methylquinolin-8-yl)-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propan-amide	M+H=439; tR=1.73

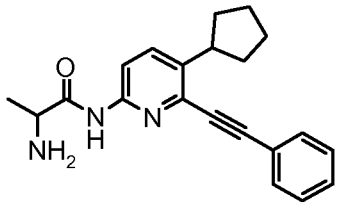
163		N-[5-(2-methoxynaphthalen-1-yl)-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=436; tR=2.02
164		N-[6-(2-isoquinolin-6-ylethynyl)-5-(1,3,5-trimethylpyrazol-4-yl)-pyridin-2-yl]-2-(methylamino)-propanamide	M-H=437; tR=1.21
165		2-amino-N-[5-(3,5-dimethyl-1,2-oxazol-4-yl)-6-(2-phenylethynyl)-pyridin-2-yl]propanamide	M+H=361; tR=1.27

E2e) tert-butyl-N-[1-[[5-cyclopentyl-6-(2-phenylethynyl)pyridin-2-yl]amino]-1-oxo-propan-2-yl]carbamate



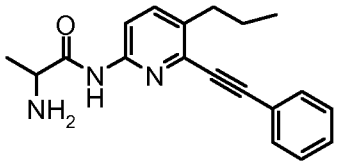
A mixture of tert-butyl-N-[1-[[5-bromo-6-(2-phenylethynyl)pyridin-2-yl]amino]-1-oxo-propan-2-yl]carbamate C2d (60 mg, 0.14 mmol), bromo(cyclopentyl)zinc (0.5 M solution in THF, 1.6 ml, 0.81 mmol), Palladium(II) acetate (1.5 mg, 0.01 mmol), 2-Dicyclohexyl-phosphino-2′,4′,6′-triisopropylbiphenyl (6.4 mg, 0.01 mmol) in toluene (0.25 ml) is stirred at RT for 6 days. The reaction mixture is concentrated in vacuo and the product purified by RP HPLC. Yield: 18 mg (31%). HPLC-MS: M+H=434; tR=1.97 min (*Method_5).

Example 166 2-amino-N-[5-cyclopentyl-6-(2-phenylethynyl)pyridin-2-yl]-propan-amide



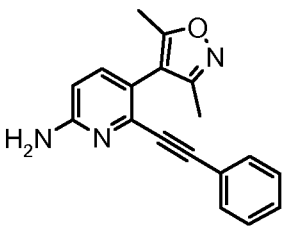
A mixture of tert-butyl-N-[1-[[5-cyclopentyl-6-(2-phenylethynyl)pyridin-2-yl]amino]-1-oxopropan-2-yl]carbamate E2e (18 mg, 0.04 mmol) and DCM:TFA (9:1, 2 ml) is stirred at RT for 90 minutes. The mixture is diluted with DCM and extracted with a saturated aqueous solution of $NaHCO_3$. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The product is purified by RP HPLC. Yield: 13 mg (94%). HPLC-MS: M+H=334; tR=2.09 min (*Method_1).

The following compound is prepared analogously:

#	Molecular Structure	Chemical Name	HPLC-MS
167		2-amino-N-[6-(2-phenylethynyl)-5-propylpyridin-2-yl]propanamide	M+H=308; tR=1.95

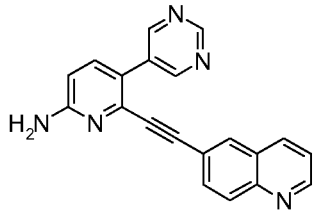
In a variant of the route depicted in scheme 2, the following examples 168-172 are prepared:

G2a) 5-(3,5-dimethyl-1,2-oxazol-4-yl)-6-(2-phenylethynyl)pyridin-2-amine

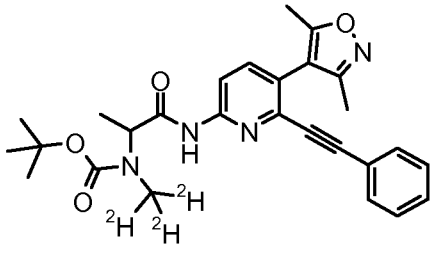


A mixture of 5-bromo-6-(2-phenylethynyl)pyridin-2-amine B2a (20 g, 73 mmol), (3,5-dimethyl-1,2-oxazol-4-yl)boronic acid (24 g, 170 mmol), CsF (44 g, 289 mmol) tris-(dibenzylideneacetone)dipalladium(0) (10.28 g, 11.2 mmol), tri-tert-butylphosphonium tetrafluoroborate (8.6 g, 296 mmol) and THF (200 ml) is stirred under argon atmosphere at 50°C for 1h. The mixture is filtrated and the precipitate washed with THF. The combined organic layers are concentrated in vacuo, diluted with DCM and extracted with a saturated aqueous solution of $NaHCO_3$. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The product is purified by NP chromatography. Yield: 12.2 g (58%). HPLC-MS: M+H=290; tR=1.54 min (*Method_6).

The following compound is prepared analogously:

#	Molecular Structure	Chemical Name
G2b		5-pyrimidin-5-yl-6-(2-quinolin-6-ylethynyl)pyridin-2-amine

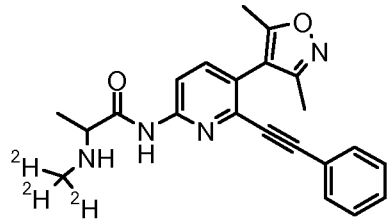
E2f) tert-butyl-N-[1-[[5-(3,5-dimethyl-1,2-oxazol-4-yl)-6-(2-phenylethynyl)pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-(trideuteriomethyl)carbamate



A mixture of 2-[(2-methylpropan-2-yl)oxycarbonyl-(trideuteriomethyl)amino]propanoic acid (1.4 g, 6.79 mmol) and N,N'-dicyclohexylcarbodiimide (0.71 g, 3.46 mmol) in DCM (20 ml) is stirred at RT for 30 minutes. This mixture is added to 5-(3,5-dimethyl-1,2-oxazol-4-yl)-6-(2-phenylethynyl)pyridin-2-amine G2a (1.0 g, 3.46 mmol) and DIPEA

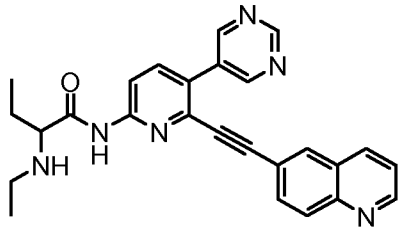
(700 µl; 4.12 mmol) in DCM (10 ml). After stirring for 7 days at RT the reaction mixture is filtrated, concentrated in vacuo, and the product purified by RP HPLC. The product (1.29 g, 78%) is used directly in the following step.

Example 168 N-[5-(3,5-dimethyl-1,2-oxazol-4-yl)-6-(2-phenylethynyl)pyridin-2-yl]-2-(trideuteriomethylamino)propanamide



A mixture of tert-butyl-N-[1-[[5-(3,5-dimethyl-1,2-oxazol-4-yl)-6-(2-phenylethynyl)-pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-(trideuteriomethyl)carbamate E2f (1.29 g, 2.70 mmol) and DCM:TFA (9:1, 20 ml) is stirred at RT for 2 h. The mixture is diluted with DCM and extracted with a saturated aqueous solution of $NaHCO_3$. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The product is purified by RP HPLC. Yield: 0.75 g (73%). HPLC-MS: M+H=378; tR=1.44 min (*Method_1).

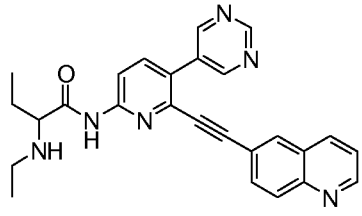
Example 169 2-(ethylamino)-N-[5-pyrimidin-5-yl-6-(2-quinolin-6-ylethynyl)pyridin-2-yl]butanamide



5-pyrimidin-5-yl-6-(2-quinolin-6-ylethynyl)pyridin-2-amine G2b (600 mg, 1.86 mmol) is mixed with NMP (10 ml) and DIPEA (1.42 ml, 8.35 mmol). 2-Bromobutanoyl bromide (985 µl, 8.17 mmol) is added dropwise. The mixture stirred for 1 h at RT. The mixture is diluted with DCM and extracted with a saturated aqueous solution of $NaHCO_3$. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The crude

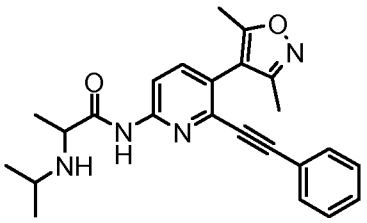
intermediate is mixed with a THF solution of methylamine (2 mol/l, 5 ml, 10 mmol) and stirred at RT for 16 h. The mixture is diluted with DCM and extracted with a saturated aqueous solution of $NaHCO_3$. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The product is purified by RP HPLC. Yield: 250 mg (32%). HPLC-MS: M+H=423; tR=1.25 min (*Method_1).

The following example is prepared analogously:

#	Molecular Structure	Chemical Name	HPLC-MS
170		2-(ethylamino)-N-[5-pyrimidin-5-yl-6-(2-quinolin-6-ylethynyl)pyridin-2-yl]-butanamide	M+H=437; tR=1.29

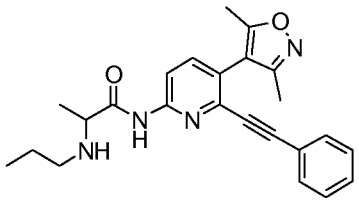
Examples 171-172 are obtained by further modifying example 166:

Example 171 N-[5-(3,5-dimethyl-1,2-oxazol-4-yl)-6-(2-phenylethynyl)pyridin-2-yl]-2-(propan-2-ylamino)propanamide

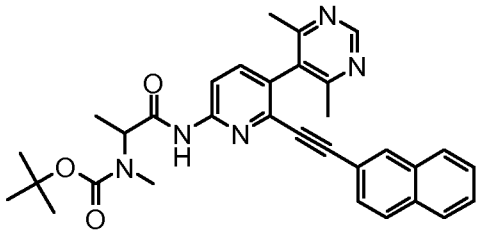


A mixture of 2-amino-N-[5-(3,5-dimethyl-1,2-oxazol-4-yl)-6-(2-phenylethynyl)pyridin-2-yl]propanamide (example 165, 20 mg, 0.06 mmol), propan-2-one (16.2 ml, 0.28 mmol), acetic acid (4 µl, 0.07 mmol), MeOH (0.5 ml) and sodium cyanoborohydride (5.5 mg, 0.08 mmol) is stirred at 50°C for 30 minutes. The reaction mixture is concentrated in vacuo and the product purified by RP HPLC. Yield: 11 mg (48%). HPLC-MS: M+H=403; tR=1.52 min (*Method_1).

The following example is prepared analogously:

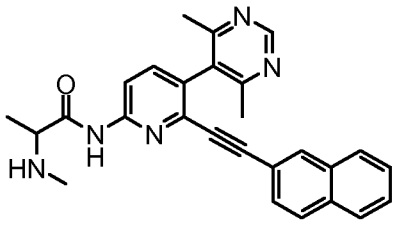
#	Molecular Structure	Chemical Name	HPLC-MS
172		N-[5-(3,5-dimethyl-1,2-oxazol-4-yl)-6-(2-phenylethynyl)-pyridin-2-yl]-2-(propylamino)-propanamide	M+H=403; tR=1.38

E2g) tert-butyl-N-[1-[[5-(4,6-dimethylpyrimidin-5-yl)-6-(2-naphthalen-2-ylethynyl)-pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate



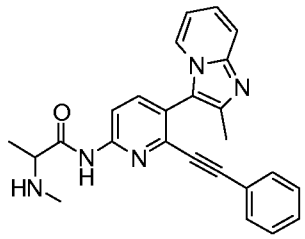
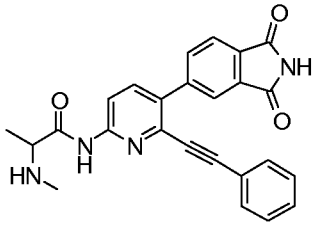
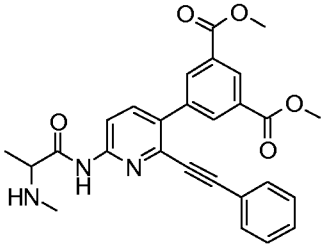
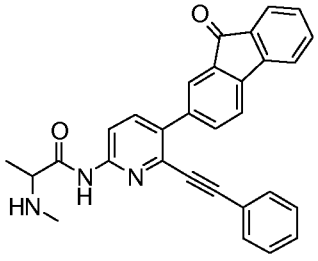
A mixture of [6-[2-[methyl-[(2-methylpropan-2-yl)oxycarbonyl]amino]propanoylamino]-2-(2-naphthalen-2-ylethynyl)pyridin-3-yl]boronic acid D2b (50 mg, 0.11 mmol), 5-bromo-4,6-dimethylpyrimidine (26 mg, 0.14 mmol), Dichlorobis(triphenylphosphine)-palladium(II) (8 mg, 0.01 mmol), Na_2CO_3 (34 mg, 0.32 mmol), dioxane (0.9 ml), MeOH (0.3 ml) and water (0.1 ml) is stirred under argon atmosphere for 2 h at 80°C. The mixture is concentrated in vacuo and the product purified by RP HPLC. Yield: 12 mg (21%). HPLC-MS: M+H=536; tR=2.22 min (*Method_6).

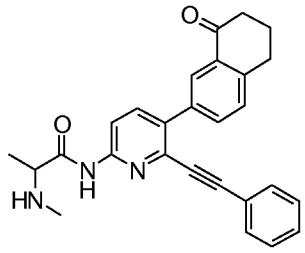
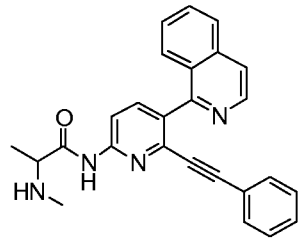
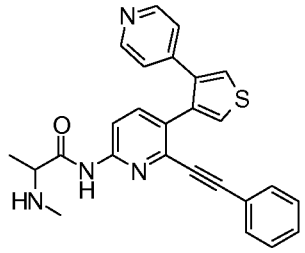
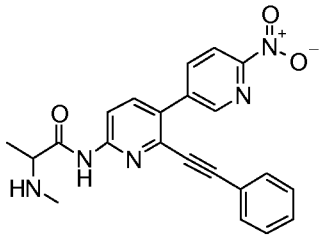
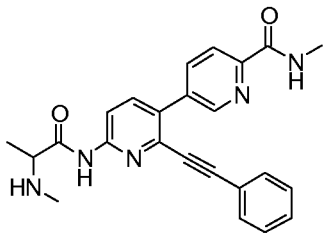
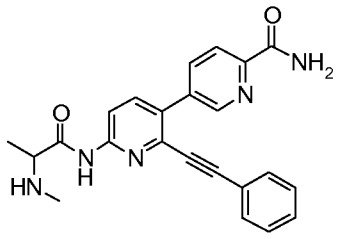
Example 173 N-[5-(4,6-dimethylpyrimidin-5-yl)-6-(2-naphthalen-2-ylethynyl)-pyridin-2-yl]-2-(methylamino)propanamide

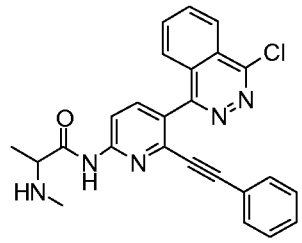
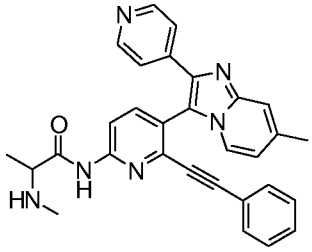
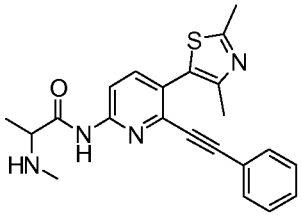
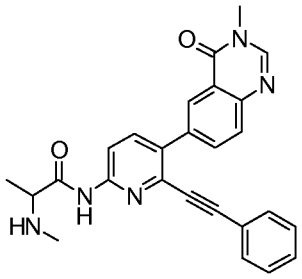
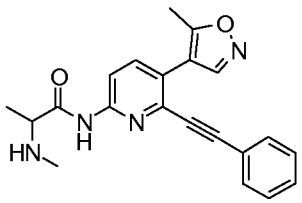
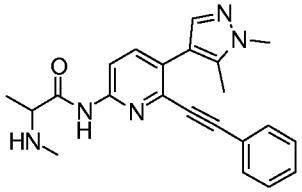


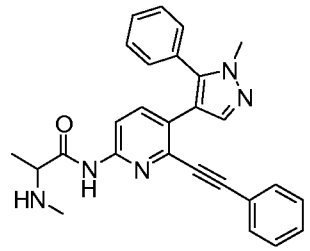
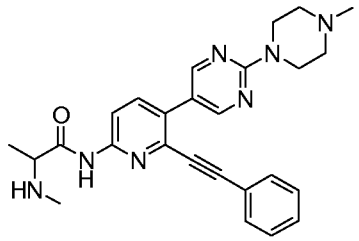
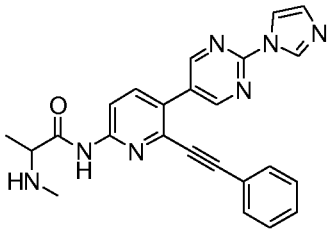
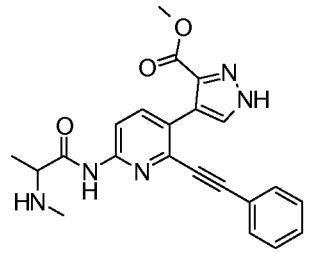
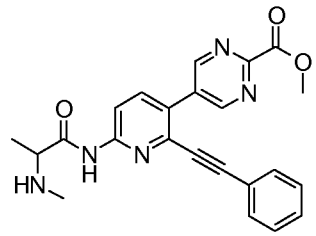
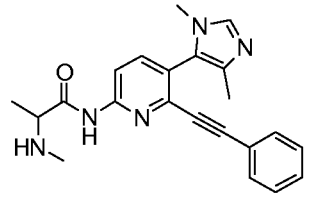
A mixture of tert-butyl-N-[1-[[5-(4,6-dimethylpyrimidin-5-yl)-6-(2-naphthalen-2-yl-ethynyl)pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate E2g (12 mg, 0.02 mmol) and DCM:TFA (9:1, 5 ml) is stirred at RT for 60 minutes. The mixture is diluted with toluene (10 ml) and concentrated in vacuo. The product is purified by RP HPLC. Yield: 6 mg (61%). HPLC-MS: M+H=436; tR=1.38 min (*Method_1).

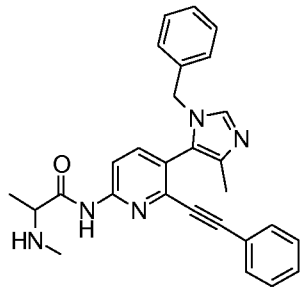
The following examples are prepared analogously:

#	Molecular Structure	Chemical Name	HPLC-MS
174		2-(methylamino)-N-[5-(2-methyl-imidazo[1,2-a]pyridin-3-yl)-6-(2-phenylethynyl)pyridin-2-yl]-propanamide	M+H=410; tR=1.27
175		N-[5-(1,3-dioxoisoindol-5-yl)-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=425; tR=1.66
176		dimethyl 5-[6-[[2-(methylamino)-propanoyl]amino]-2-(2-phenyl-ethynyl)pyridin-3-yl]benzene-1,3-dicarboxylate	M+H=472; tR=1.87
177		2-(methylamino)-N-[5-(9-oxofluoren-2-yl)-6-(2-phenyl-ethynyl)pyridin-2-yl]propanamide	M+H=458; tR=2.04

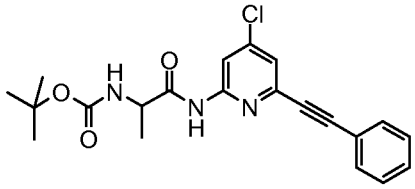
178		2-(methylamino)-N-[5-(8-oxo-6,7-dihydro-5H-naphthalen-2-yl)-6-(2-phenylethynyl)pyridin-2-yl]-propanamide	M+H=424; tR=1.83
179		N-[5-isoquinolin-1-yl-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=407; tR=2.48
180		2-(methylamino)-N-[6-(2-phenyl-ethynyl)-5-(4-pyridin-4-ylthiophen-3-yl)pyridin-2-yl]-propanamide	M+H=439; tR=1.91
181		2-(methylamino)-N-[5-(6-nitropyridin-3-yl)-6-(2-phenyl-ethynyl)pyridin-2-yl]propanamide	M+H=402; tR=1.83
182		N-methyl-5-[6-[[2-(methyl-amino)propanoyl]amino]-2-(2-phenylethynyl)pyridin-3-yl]-pyridine-2-carboxamide	M+H=414; tR=1.67
183		5-[6-[[2-(methylamino)-propanoyl]amino]-2-(2-phenyl-ethynyl)pyridin-3-yl]pyridine-2-carboxamide	M+H=400; tR=1.56

184		N-[5-(4-chlorophthalazin-1-yl)-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=442/444; tR=1.89
185		2-(methylamino)-N-[5-(7-methyl-2-pyridin-4-ylimidazo[1,2-a]-pyridin-3-yl)-6-(2-phenylethynyl)pyridin-2-yl]propanamide	M+H=487; tR=1.32
186		N-[5-(2,4-dimethyl-1,3-thiazol-5-yl)-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=391; tR=1.38
187		2-(methylamino)-N-[5-(3-methyl-4-oxoquinazolin-6-yl)-6-(2-phenylethynyl)pyridin-2-yl]-propanamide	M+H=438; tR=1.65
188		2-(methylamino)-N-[5-(5-methyl-1,2-oxazol-4-yl)-6-(2-phenylethynyl)pyridin-2-yl]propanamide	M+h=361; tr=1.37
189		N-[5-(1,5-dimethylpyrazol-4-yl)-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=374; tR=1.25

190		2-(methylamino)-N-[5-(1-methyl-5-phenylpyrazol-4-yl)-6-(2-phenylethynyl)pyridin-2-yl]-propanamide	M+H=436; tR=1.92
191		2-(methylamino)-N-[5-[2-(4-methylpiperazin-1-yl)pyrimidin-5-yl]-6-(2-phenylethynyl)pyridin-2-yl]propanamide	M+H=456; tR=1.45
192		N-[5-(2-imidazol-1-ylpyrimidin-5-yl)-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propan-amide	M+H=424; tR=1.36
193		methyl 4-[6-[[2-(methylamino)-propanoyl]amino]-2-(2-phenyl-ethynyl)pyridin-3-yl]-1H-pyrazole-3-carboxylate	M+H=404; tR=1.15
194		methyl 5-[6-[[2-(methylamino)-propanoyl]amino]-2-(2-phenyl-ethynyl)pyridin-3-yl]pyrimidine-2-carboxylate	M+H=416; tR=1.27
195		N-[5-(3,5-dimethylimidazol-4-yl)-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=374; tR=1.19

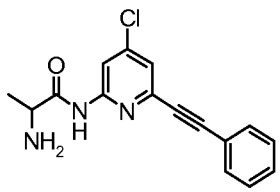
196		N-[5-(3-benzyl-5-methylimidazol-4-yl)-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propanamide	M+H=450; tR=1.34

D3a) tert-butylN-[1-[[4-chloro-6-(2-phenylethynyl)pyridin-2-yl]amino]-1-oxopropan-2-yl]carbamate



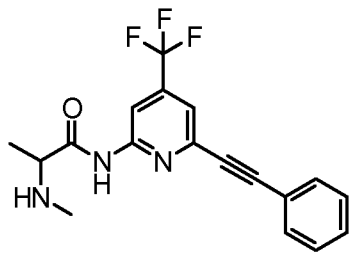
A mixture of 2-[(2-methylpropan-2-yl)oxycarbonylamino]propanoic acid (1.17 g, 6.19 mmol), 4-chloro-6-(2-phenylethynyl)pyridin-2-amine B3a (1.09 g, 4.76 mmol), triethylamine (3.63 ml, 25.7 mmol) HATU (2.89 g, 7.61 mmol) and NMP (3.75 ml) is stirred at 40°C for 60 h. 2-[(2-methylpropan-2-yl)oxycarbonylamino]propanoic acid (0.72 g, 3.81 mmol) and HATU (1.45 g, 3.81 mmol) is added to the mixture and stirring continued for 48 h at 60°C. At RT water is added and the mixture extracted with DCM. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The product is purified by RP HPLC. Yield: 712 mg (37%). HPLC-MS: M+H=400; tR=2.27 min (*Method_2).

Example 197 2-amino-N-[4-chloro-6-(2-phenylethynyl)pyridin-2-yl]propanamide



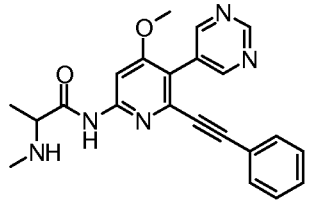
A mixture of tert-butylN-[1-[[4-chloro-6-(2-phenylethynyl)pyridin-2-yl]amino]-1-oxo-propan-2-yl]carbamate D3a (20 mg, 0.05 mmol) and DCM:TFA (9:1, 1.8 ml) is stirred at RT for 90 minutes. The mixture is diluted with DCM and extracted with a saturated aqueous solution of $NaHCO_3$. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The product is purified by RP HPLC. Yield: 14 mg (93%). HPLC-MS: M+H=300; tR=1.92 min (*Method_1).

Example 198 2-(methylamino)-N-[6-(2-phenylethynyl)-4-(trifluoromethyl)pyridin-2-yl]propanamide

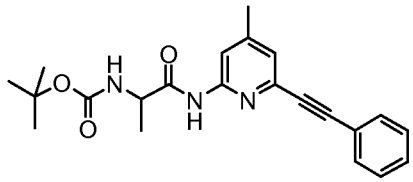


A mixture of 2-[methyl-[(2-methylpropan-2-yl)oxycarbonyl]amino]propanoic acid (620 mg, 3.05 mmol) and N,N'-dicyclohexylcarbodiimide (315 mg, 1.53 mmol) in DCM (4 ml) is stirred at RT for 30 minutes. This mixture is added to 6-(2-phenylethynyl)-4-(trifluoromethyl)pyridin-2-amine B3b (100 mg, 0.38 mmol) and DIPEA (73 µl; 0.42 mmol) in NMP (5 ml). After stirring for 6 days at 50°C the reaction mixture is concentrated in vacuo and the boc-protected product purified by NP chromatography. The boc-protected product is treated with DCM:TFA (9:1, 4 ml) for 1.5 h at RT. This mixture is diluted with DCM and extracted with a saturated aqueous solution of $NaHCO_3$. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The product is purified by RP HPLC. Yield: 10.2 mg (8%). HPLC-MS: M+H=348; tR=1.46 (*Method_1).

The following example is prepared analogously starting from compound C3e:

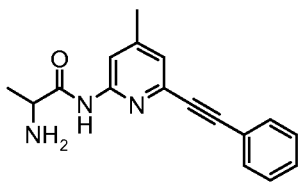
#	Molecular Structure	Chemical Name	HPLC-MS
199		N-[4-methoxy-6-(2-phenyl-ethynyl)-5-pyrimidin-5-ylpyridin-2-yl]-2-(methyl-amino)propanamide	M+H=388; tR=1.10

D3b) tert-butyl-N-[1-[[4-methyl-6-(2-phenylethynyl)pyridin-2-yl]amino]-1-oxopropan-2-yl]carbamate



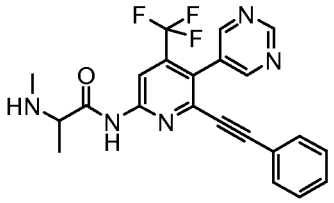
A mixture of tert-butylN-[1-[[4-chloro-6-(2-phenylethynyl)pyridin-2-yl]amino]-1-oxo-propan-2-yl]carbamate D3a (40 mg, 0.10 mmol), 2,4,6-trihydroxy-1,3,5,2,4,6-trioxatriborinane (36 µl, 0 .26 mmol), Tetrakis(triphenylphosphine)palladium(0) (16.6 mg, 0.01 mmol), potassium carbonate (41.5 mg, 0.30 mmol), 1,2-dimethoxyethane (600 µl) and water (100 µl) is stirred for 2 day at 80°C. The mixture is concentrated in vacuo and the product purified by RP HPLC. Yield: 2 mg (5%). HPLC-MS: M+H=380; tR=2,18 min (*Method_2).

Example 200 2-amino-N-[4-methyl-6-(2-phenylethynyl)pyridin-2-yl]propanamide



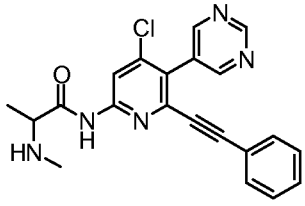
A mixture of tert-butyl-N-[1-[[4-methyl-6-(2-phenylethynyl)pyridin-2-yl]amino]-1-oxopropan-2-yl]carbamate D3b (2 mg, 5 µmol) and DCM:TFA (9:1, 400 µl) is stirred at RT for 4 hours. The mixture is diluted with DCM and extracted with a saturated aqueous solution of $NaHCO_3$. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. Yield: 1.5 mg (quant.). HPLC-MS: M+H=280; tR=1.77 min (*Method_1).

Example 201 2-(methylamino)-N-[6-(2-phenylethynyl)-5-pyrimidin-5-yl-4-(trifluoromethyl)pyridin-2-yl]propanamide

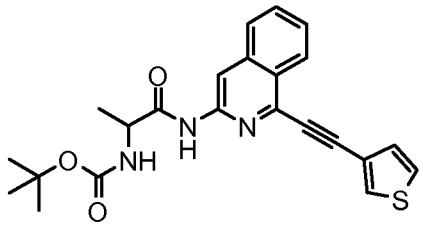


Under stirring at 0°C 2-bromopropanoyl bromide (44 µl, 0.42 mmol) is added dropwise to a mixture of 6-(2-phenylethynyl)-5-pyrimidin-5-yl-4-(trifluoromethyl)pyridin-2-amine C3d (95 mg, 0.28 mmol), triethylamine (59 µl, 0.42 mmol), DMAP (0.3 mg, 3 µmol) and dioxane (1.4 ml). The mixture is warmed to RT and stirred for 1 h. Methylamine (solution in THF 2 mol/l, 1.4 ml, 2.8 mmol) is added and stirring continued for 6 h. The mixture is concentrated in vacuo and the product purified by RP HPLC. Yield: 45 mg (38%). HPLC-MS: M+H=426; tR=1.27 min (*Method_1).

The following example is prepared analogously:

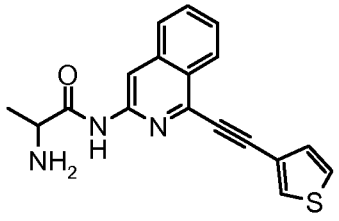
#	Molecular Structure	Chemical Name	HPLC-MS
202		N-[4-chloro-6-(2-phenylethynyl)-5-pyrimidin-5-ylpyridin-2-yl]-2-(methylamino)propanamide	M+H=392; tR=1.19

E4a) tert-butyl-N-[1-oxo-1-[[1-(2-thiophen-3-ylethynyl)isoquinolin-3-yl]amino]-propan-2-yl]carbamate



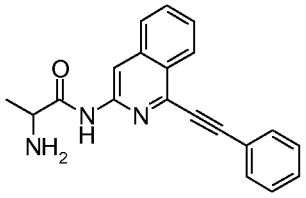
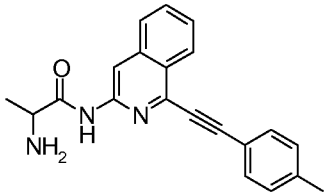
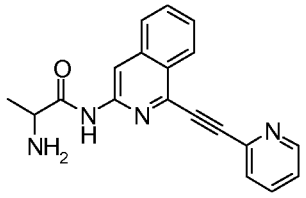
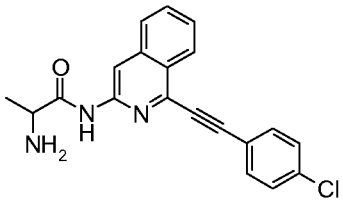
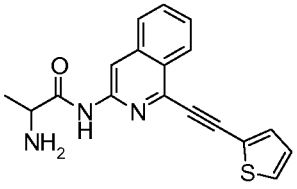
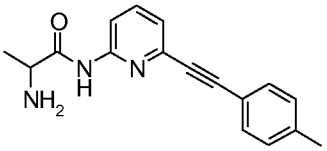
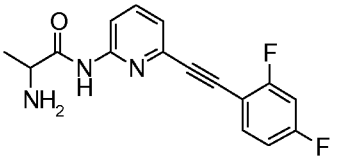
A mixture of tert-butyl-N-[1-[(1-bromoisoquinolin-3-yl)amino]-1-oxopropan-2-yl]-carbamate B4a (150 mg, 0.38 mmol), 3-ethynylthiophene (45 mg, 0.42 mmol), copper(I) iodide (7 mg, 0.04 mmol), Dichlorobis(triphenylphosphine)palladium(II) (27 mg, 0.04 mmol) and DIPEA (200 µl, 1.2 mmol) is stirred under argon atmosphere in NMP (1 ml) for 1 h at 80°C. The mixture is concentrated in vacuo and the product purified by RP HPLC. Yield: 102 mg (64%). HPLC-MS: M+H=422; tR=1.99 min (*Method_4).

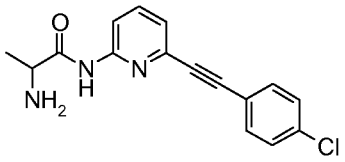
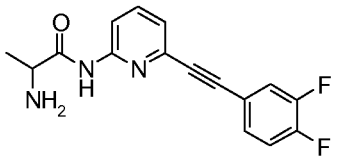
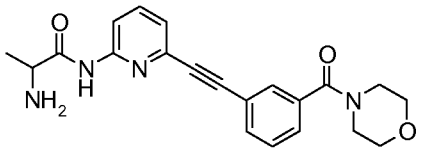
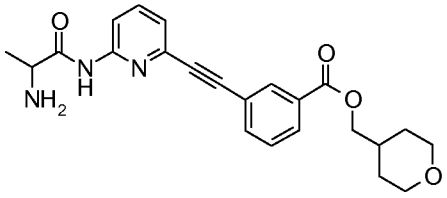
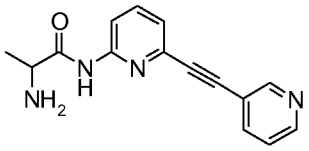
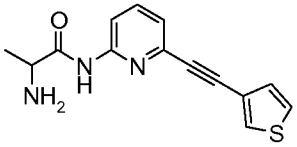
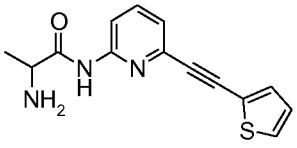
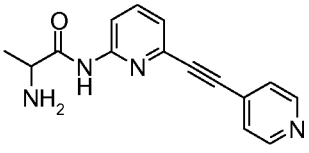
Example 203 2-amino-N-[1-(2-thiophen-3-ylethynyl)isoquinolin-3-yl]propanamide

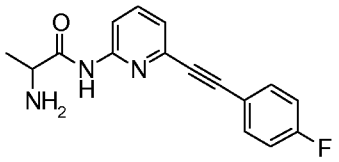
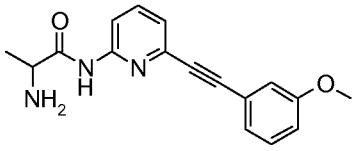
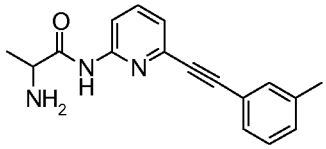
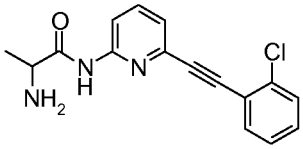
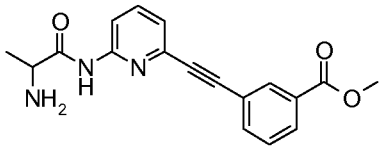
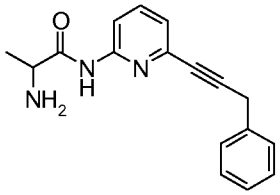
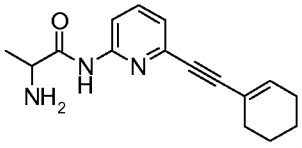


A mixture of tert-butyl-N-[1-oxo-1-[[1-(2-thiophen-3-ylethynyl)isoquinolin-3-yl]amino]-propan-2-yl]carbamate E4a (102 mg, 0.24 mmol) and DCM:TFA (9:1, 2 ml) is stirred at RT for 1 h. The mixture is diluted with toluene (10 ml) and concentrated in vacuo. The product is purified by RP HPLC. Yield: 65 mg (84%). HPLC-MS: M+H=322; tR=1.84 min (*Method_1).

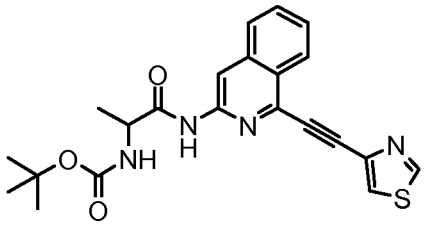
The following examples are prepared analogously:

#	Molecular Structure	Chemical Name	HPLC-MS
204		2-amino-N-[1-(2-phenyl-ethynyl)isoquinolin-3-yl]-propanamide	M+H=316; tR=1.92
205		2-amino-N-[1-[2-(4-methyl-phenyl)ethynyl]isoquinolin-3-yl]propanamide	M+H=330; tR=2.05
206		2-amino-N-[1-(2-pyridin-2-ylethynyl)isoquinolin-3-yl]-propanamide	M+H=317; tR=1.54
207		2-amino-N-[1-[2-(4-chlorophenyl)ethynyl]-isoquinolin-3-yl]propan-amide	M+H=350/352; tR=2.05
208		2-amino-N-[1-(2-thiophen-2-ylethynyl)isoquinolin-3-yl]-propanamide	M+H=322; tR=1.87
209		2-amino-N-[6-[2-(4-methylphenyl)ethynyl]pyridin-2-yl]propanamide	M+H=280; tR=1.79
210		2-amino-N-[6-[2-(2,4-difluorophenyl)ethynyl]pyridin-2-yl]propanamide	M+H=302; tR=1.71

#	Molecular Structure	Chemical Name	HPLC-MS
211		2-amino-N-[6-[2-(4-chlorophenyl)ethynyl]pyridin-2-yl]propanamide	M+H=300; tR=1.82
212		2-amino-N-[6-[2-(3,4-difluorophenyl)ethynyl]pyridin-2-yl]propanamide	M+H=302; tR=1.72
213		2-amino-N-[6-[2-[3-(morpholine-4-carbonyl)-phenyl]ethynyl]pyridin-2-yl]propanamide	M+H=379; tR=1.41
214		oxan-4-ylmethyl 3-[2-[6-[[2-aminopropanoyl]-amino]pyridin-2-yl]ethynyl]benzoate	M+H=408; tR=1.78
215		2-amino-N-[6-(2-pyridin-3-ylethynyl)pyridin-2-yl]propanamide	M+H=267; tR=1.33
216		2-amino-N-[6-(2-thiophen-3-ylethynyl)pyridin-2-yl]propanamide	M+H=272; tR=1.62
217		2-amino-N-[6-(2-thiophen-2-ylethynyl)pyridin-2-yl]propanamide	M+H=272; tR=1.75
218		2-amino-N-[6-(2-pyridin-4-ylethynyl)pyridin-2-yl]propanamide	M+H=267; tR=1.30

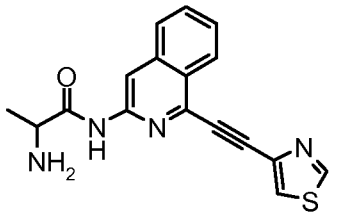
#	Molecular Structure	Chemical Name	HPLC-MS
219		2-amino-N-[6-[2-(4-fluorophenyl)ethynyl]pyridin-2-yl]propanamide	M+H=284; tR=1.68
220		2-amino-N-[6-[2-(3-methoxyphenyl)ethynyl]pyridin-2-yl]propanamide	M+H=296; tR=1.69
221		2-amino-N-[6-[2-(3-methylphenyl)ethynyl]pyridin-2-yl]propanamide	M+H=280; tR=1.82
222		2-amino-N-[6-[2-(2-chlorophenyl)ethynyl]pyridin-2-yl]propanamide	M+H=300; tR=1.82
223		methyl 3-[2-[6-[[2-aminopropanoyl]amino]pyridin-2-yl]ethynyl]benzoate	M+H=324; tR=1.68
224		2-amino-N-[6-(3-phenylprop-1-ynyl)pyridin-2-yl]propanamide	M+H=280; tR=1.64
225		2-amino-N-[6-[2-(cyclohexen-1-yl)ethynyl]pyridin-2-yl]propanamide	M+H=270; tR=1.78

E4b) tert-butyl-N-[1-oxo-1-[[1-[2-(1,3-thiazol-4-yl)ethynyl]isoquinolin-3-yl]amino]-propan-2-yl]carbamate



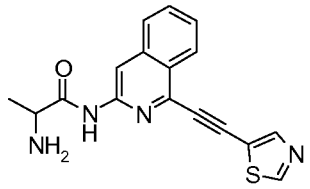
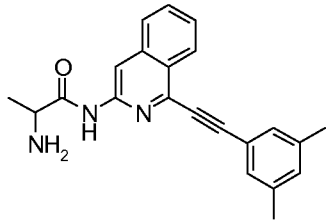
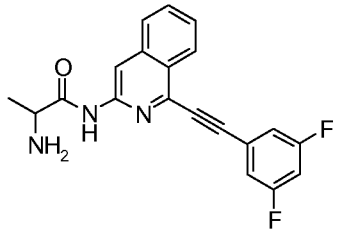
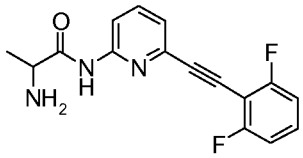
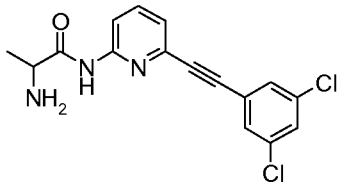
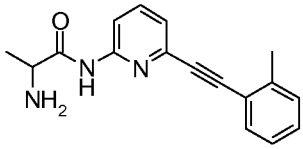
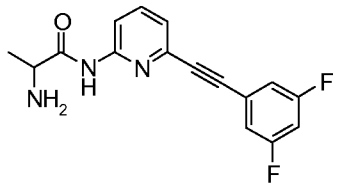
A mixture of tert-butyl-N-[1-[(1-ethynylisoquinolin-3-yl)amino]-1-oxopropan-2-yl]-carbamate D4a (50 mg, 0.15 mmol), 4-bromo-1,3-thiazole (24 mg, 0.15 mmol), copper(I) iodide (3 mg, 0.02 mmol), Dichlorobis(triphenylphosphine)palladium(II) (10 mg, 0.01 mmol) and DIPEA (75 µl, 0.44 mmol) is stirred under argon atmosphere in NMP (1 ml) for 2 h at 80°C. The mixture is concentrated in vacuo and the product purified by RP HPLC. Yield: 12 mg (19%). HPLC-MS: M+H=423; tR=1.84 min (*Method_4).

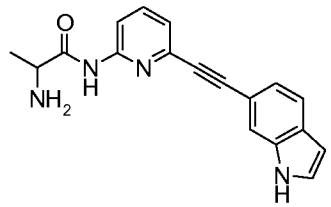
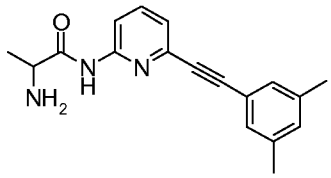
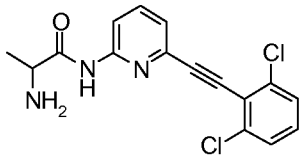
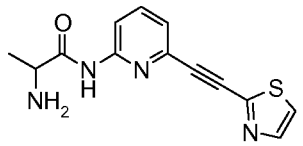
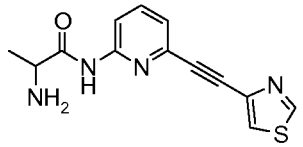
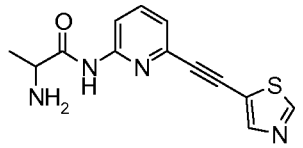
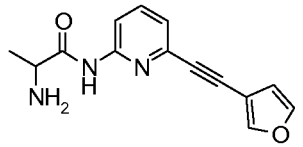
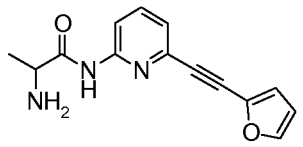
Example 226 2-amino-N-[1-[2-(1,3-thiazol-4-yl)ethynyl]isoquinolin-3-yl]propan-amide

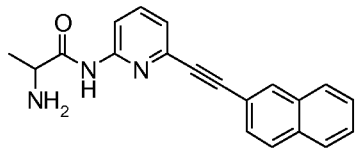


A mixture of tert-butyl-N-[1-oxo-1-[[1-[2-(1,3-thiazol-4-yl)ethynyl]isoquinolin-3-yl]-amino]propan-2-yl]carbamate E4b (12 mg, 0.03 mmol) and DCM:TFA (9:1, 3 ml) is stirred at RT for 1 h. The mixture is diluted with DCM and extracted with a saturated aqueous solution of $NaHCO_3$. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The product is purified by RP HPLC. Yield: 2 mg (22%). HPLC-MS: M+H=323; tR=1.65 min (*Method_1).

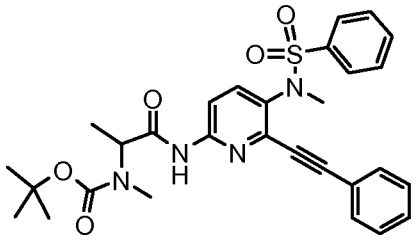
The following examples are prepared analogously:

#	Molecular Structure	Chemical Name	HPLC-MS
227		2-amino-N-[1-[2-(1,3-thiazol-5-yl)ethynyl]isoquinolin-3-yl]-propanamide	M+H=323; tR=1.59
228		2-amino-N-[1-[2-(3,5-dimethyl-phenyl)ethynyl]isoquinolin-3-yl]propanamide	M+H=344; tR=2.18
229		2-amino-N-[1-[2-(3,5-difluorophenyl)ethynyl]-isoquinolin-3-yl]propanamide	M+H=352; tR=2.01
230		2-amino-N-[6-[2-(2,6-difluorophenyl)ethynyl]pyridin-2-yl]propanamide	M+H=302; tR=1.50
231		2-amino-N-[6-[2-(3,5-dichlorophenyl)ethynyl]pyridin-2-yl]propanamide	M+H=334; tR=1.85
232		2-amino-N-[6-[2-(2-methylphenyl)ethynyl]pyridin-2-yl]propanamide	M+H=280; tR=1.86
233		2-amino-N-[6-[2-(3,5-difluorophenyl)ethynyl]pyridin-2-yl]propanamide	M+H=302; tR=1.80

#	Molecular Structure	Chemical Name	HPLC-MS
234		2-amino-N-[6-[2-(1H-indol-6-yl)ethynyl]pyridin-2-yl]propanamide	M+H=305; tR=0.25
235		2-amino-N-[6-[2-(3,5-dimethylphenyl)ethynyl]pyridin-2-yl]propanamide	M+H=294; tR=2.02
236		2-amino-N-[6-[2-(2,6-dichlorophenyl)ethynyl]pyridin-2-yl]propanamide	M+H=334; tR=1.90
237		2-amino-N-[6-[2-(1,3-thiazol-2-yl)ethynyl]pyridin-2-yl]propanamide	M+H=273; tR=1.29
238		2-amino-N-[6-[2-(1,3-thiazol-4-yl)ethynyl]pyridin-2-yl]propanamide	M+H=273; tR=1.22
239		2-amino-N-[6-[2-(1,3-thiazol-5-yl)ethynyl]pyridin-2-yl]propanamide	M+H=273; tR=1.28
240		2-amino-N-[6-[2-(furan-3-yl)ethynyl]pyridin-2-yl]propanamide	M+H=256; tR=1.46
241		2-amino-N-[6-[2-(furan-2-yl)ethynyl]pyridin-2-yl]propanamide	M+H=256; tR=1.50

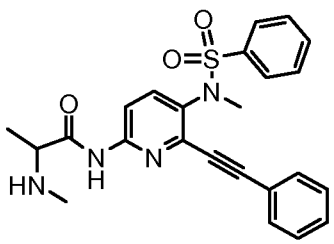
#	Molecular Structure	Chemical Name	HPLC-MS
242		2-amino-N-[6-(2-naphthalen-2-ylethynyl)pyridin-2-yl]propanamide	M+H=316; tR=1.93

F5a) tert-butyl-N-[1-[[5-[benzenesulfonyl(methyl)amino]-6-(2-phenylethynyl)-pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate



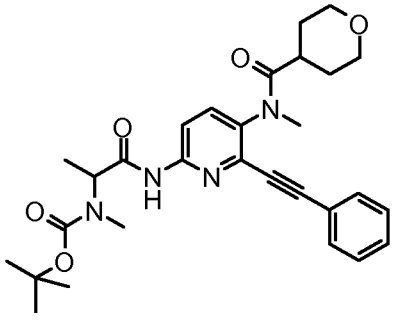
A mixture of 2-[methyl-[(2-methylpropan-2-yl)oxycarbonyl]amino]propanoic acid (54 mg, 0.26 mmol) and N,N'-dicyclohexylcarbodiimide (27 mg, 0.13 mmol) in DCM (1.5 ml) is stirred at RT for 20 minutes. This mixture is added to N-[6-amino-2-(2-phenylethynyl)-pyridin-3-yl]-N-methylbenzenesulfonamide E5a (16 mg, 0.04 mmol) and DIPEA (9 µl; 0.05 mmol) in DCM (0.5 ml). After stirring for 4 days at 40°C the reaction mixture is diluted with DCM and extracted with water. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The crude product (22 mg) is used in the next step without further purification.

Example 243 N-[5-[benzenesulfonyl(methyl)amino]-6-(2-phenylethynyl)pyridin-2-yl]-2-(methylamino)propanamide



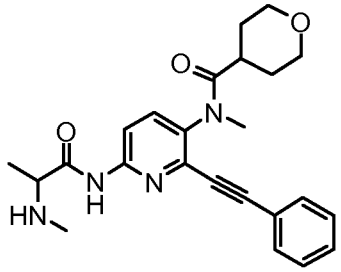
A mixture of tert-butyl-N-[1-[[5-[benzenesulfonyl(methyl)amino]-6-(2-phenylethynyl)-pyridin-2-yl]amino]-1-oxopropan-2-yl]-N-methylcarbamate F5a (25 mg) and DCM:TFA (9:1, 3 ml) is stirred at RT for 2 h. The mixture is diluted with DCM and extracted with a saturated aqueous solution of $NaHCO_3$. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The product is purified by RP HPLC. Yield: 7 mg. HPLC-MS: M+H=449; tR=1.49 min (*Method_1).

F5b) tert-butyl-N-methyl-N-[1-[[5-[methyl(oxane-4-carbonyl)amino]-6-(2-phenylethynyl)pyridin-2-yl]amino]-1-oxopropan-2-yl]carbamate



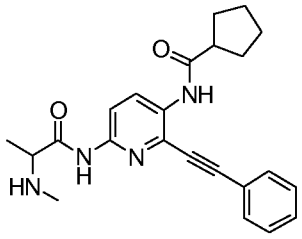
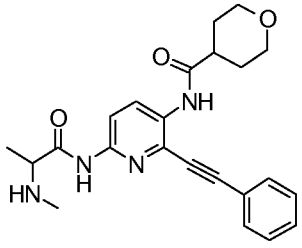
At RT NaH (60% dispersion in mineral oil, 2.3 mg, 0.0.06 mmol) is added to tert-butyl-N-methyl-N-[1-[[5-(oxane-4-carbonylamino)-6-(2-phenylethynyl)pyridin-2-yl]amino]-1-oxopropan-2-yl]carbamate E5b (35mg, 0.04 mmol) in THF (1 ml). After stirring for 10 minutes dimethylsulfate (4 µl, 0.06 mmol) is added to the mixture and stirring continued for 20 minutes. The mixture is concentrated in vacuo and the product purified by RP HPLC. Yield: 5 mg (23%). HPLC-MS: M+H=521; tR=2.06 min (*Method_2).

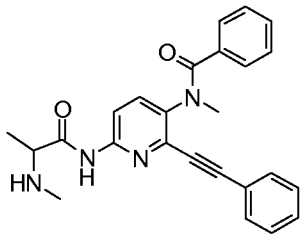
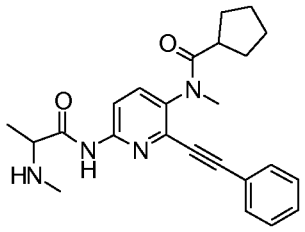
Example 244 N-methyl-N-[6-[2-(methylamino)propanoylamino]-2-(2-phenylethynyl)pyridin-3-yl]oxane-4-carboxamide



A mixture of tert-butyl-N-methyl-N-[1-[[5-[methyl(oxane-4-carbonyl)amino]-6-(2-phenylethynyl)pyridin-2-yl]amino]-1-oxopropan-2-yl]carbamate F5b (5 mg) and DCM:TFA (9:1, 1 ml) is stirred at RT for 100 minutes. The mixture is diluted with DCM and extracted with a saturated aqueous solution of $NaHCO_3$. The combined organic layers are dried over $MgSO_4$ and concentrated in vacuo. The product is purified by RP HPLC. Yield: 7 mg. HPLC-MS: M+H=421; tR=1.33 min (*Method_1).

The following examples are prepared analogously. For examples 214-215 the alkylation step (transmoration D5→E5) is skipped.

#	Molecular Structure	Chemical Name	HPLC-MS
245		N-[6-[[2-(methylamino)-propanoyl]amino]-2-(2-phenylethynyl)pyridin-3-yl]-cyclopentanecarboxamide	M+H=391; tR=1.41
246		N-[6-[[2-(methylamino)-propanoyl]amino]-2-(2-phenylethynyl)pyridin-3-yl]-oxane-4-carboxamide	M+H=407; tR=1.25

247		N-methyl-N-[6-[[2-(methyl-amino)propanoyl]amino]-2-(2-phenylethynyl)pyridin-3-yl]-benzamide	M+H=413; tR=1.36
248		N-methyl-N-[6-[[2-(methyl-amino)propanoyl]amino]-2-(2-phenylethynyl)pyridin-3-yl]-cyclopentanecarboxamide	M+H=405; tR=1.44

Biological Methods

XIAP BIR3 and cIAP1 BIR3 binding assays (DELFIA)

BIR3 domains of human XIAP (covering amino acids 241 to 356; XIAP BIR3) and cIAP1 (covering amino acids 256 to 363; cIAP1 BIR3) were expressed and purified from Ecoli as GST-fusion proteins. Peptide AVPIAQKSE-Lys(Biotin), representing the N-terminus of mature human SMAC (SMAC peptide), was used as interaction partner in the protein-peptide interaction assay.

BIR3 domains (10 nM) were incubated with SMAC peptide (10 nM) in Assay Buffer (50 mM Tris, 120 mM NaCl, 0.1% BSA, 1 mM DTT, 0.05% TritonX100) for one hour at room temperature in the presence of inhibitiory compounds. The assay mixture was transferred to a strepatvidin coated plate and incubated for one hour at room temperature to allow binding of the biotinylated peptide and associated BIR3 domains to the plate. After several washing steps Eu labeled anti-GST antibody (e.g. Perkin Elmer DELFIA Eu-N1-antiGST AD0250) was added to detect BIR3 domain-SMAC peptide interactions according to Perkin Elmer´s instructions. Briefly, the antibody was added (dilution 1:5000 in Perkin Elmer DELFIA Assay Buffer 2013-01) and incubated for one hour. After 3 washing steps using Delfia Washing Buffer (Perkin Elmer DELFIA Wash 2013-05),

Enhancement Solution (Perkin Elmer Enhancement Asolution 2013-02) was added and incubation continued for 10 minutes. Time resolved Europium fluoresecence was measured in a Wallac Victor using Standard assay settings.

IC_{50} values for inhibitory compounds were calculated from assay results obtained by incubating BIR3 domains with SMAC peptide in the presence of serially diluted compounds (e.g. 1:5). DELFIA assay results were plotted against compound concentrations and Software GraphPad Prizm was used to calculate half maximal inhibitory concentrations (IC_{50} values).

The IC_{50} values representing the biological activity of the examples are listed in the tables below. All IC_{50} values are reported in nM and represent the activity of the (S)-isomers in case the compounds contain a chiral center adjacent to R1 according to formula (I):

example #	IC_{50} XIAP BIR3
1	287
2	259
3	1152
4	643
5	509
6	214
7	460
8	351
9	1010
10	787
11	1214
12	1433
13	96
14	417
15	711
16	554
17	122
18	745
19	867
20	4281

example #	IC_{50} XIAP BIR3
21	540
22	1300
23	265
24	698
25	653
26	579
27	79
28	200
29	145
30	417
31	228
32	228
33	277
34	279
35	1477
36	112
37	166
38	142
39	87
40	445
41	123
42	94
43	310
44	136
45	431
46	145
47	180
48	212
49	107
50	95
51	453
52	145
53	116
54	863
55	310
56	2876
57	n.a.
58	224

example #	IC_{50} XIAP BIR3
59	918
60	184
61	187
62	620
63	70
64	152
65	1188
66	252
67	270
68	165
69	110
70	66
71	300
72	145
73	378
74	175
75	1674
76	1066
77	196
78	47
79	2399
80	1308
81	253
82	61
83	446
84	130
85	259
86	770
87	1453
88	207
89	92
90	166
91	267
92	172
93	198
94	107
95	97
96	83

example #	IC_{50} XIAP BIR3
97	644
98	526
99	521
100	461
101	128
102	1984
103	3043
104	2023
105	220
106	243
107	1012
108	1605
109	650
110	3192
111	1550
112	1070
113	228
114	1628
115	2036
116	1768
117	406
118	287
119	327
120	185
121	97
122	148
123	121
124	2839
125	580
126	1007
127	128
128	101
129	436
130	3204
131	305
132	326
133	142
134	581

example #	IC_{50} XIAP BIR3
135	490
136	1042
137	155
138	55
139	1411
140	1992
141	558
142	503
143	388
144	400
145	317
146	257
147	125
148	416
149	195
150	2450
151	326
152	431
153	1243
154	569
155	284
156	3178
157	276
158	772
159	767
160	474
161	102
162	1822
163	4449
164	335
165	67
166	898
167	874
168	151
169	1149
170	1370
171	1031
172	502

example #	IC_{50} XIAP BIR3
173	324
174	51
175	103
176	50
177	337
178	214
179	3802
180	260
181	222
182	135
183	146
184	138
185	16
186	151
187	49
188	128
189	87
190	276
191	102
192	76
193	141
194	102
195	269
196	609
197	3182
198	10483
199	268
200	1788
201	10804
202	483
203	760
204	703
205	2303
206	3615
207	4236
208	467
209	1458
210	2613

example #	IC_{50} XIAP BIR3
211	2008
212	3064
213	9955
214	7381
215	9697
216	2135
217	895
218	6537
219	359
220	2156
221	222
222	1417
223	2457
224	3559
225	7036
226	1199
227	1893
228	1919
229	2423
230	2407
231	4860
232	1247
233	2907
234	2731
235	2193
236	1974
237	5925
238	7187
239	4576
240	3017
241	3199
242	4235
243	160
244	1475
245	1287
246	1520
247	745
248	794

example #	IC_{50} cIAP1 BIR3
13	12
26	1
27	1
28	1
29	1
30	1
31	1
33	1
34	1
35	1
36	1
37	1
39	1
41	1
42	1
44	1
45	2
46	1
47	1
48	1
49	1
50	1
52	1
53	1
54	1
58	5
60	2
61	5
63	1
64	1
66	1
69	2
70	1
71	1
72	1
74	1

example #	IC_{50} cIAP1 BIR3
75	1
77	1
78	2
79	1
80	1
81	1
82	1
87	1
88	1
89	2
90	1
92	1
93	1
94	1
95	1
96	1
100	324
108	175
113	67
118	92
121	31
122	23
123	25
125	131
126	166
127	21
129	98
130	172
132	97
138	12
145	94
147	32
149	80
161	22
165	1
168	3
174	1
175	16

example #	IC_{50} cIAP1 BIR3
176	23
177	92
182	36
184	17
185	1
186	16
187	9
189	30
191	22
192	22
194	23
195	4
198	4926
203	251
204	430
206	880
208	255
213	2123
215	985
217	206
223	2622
226	332
228	1472
229	589
232	672
234	1234
240	1339

On the basis of their biological properties the compounds of general formula **(1)** according to the invention, their tautomers, racemates, enantiomers, diastereomers, mixtures thereof and the salts of all the above-mentioned forms are suitable for treating diseases characterised by excessive or abnormal cell proliferation.

Such diseases include for example: viral infections (e.g. HIV and Kaposi's sarcoma); inflammatory and autoimmune diseases (e.g. colitis, arthritis, Alzheimer's disease,

glomerulonephritis and wound healing); bacterial, fungal and/or parasitic infections; leukaemias, lymphomas and solid tumours (e.g. carcinomas and sarcomas), skin diseases (e.g. psoriasis); diseases based on hyperplasia which are characterised by an increase in the number of cells (e.g. fibroblasts, hepatocytes, bones and bone marrow cells, cartilage or smooth muscle cells or epithelial cells (e.g. endometrial hyperplasia)); bone diseases and cardiovascular diseases (e.g. restenosis and hypertrophy). They are also suitable for protecting proliferating cells (e.g. hair, intestinal, blood and progenitor cells) from DNA damage caused by radiation, UV treatment and/or cytostatic treatment.

For example, the following cancers may be treated with compounds according to the invention, without being restricted thereto: brain tumours such as for example acoustic neurinoma, astrocytomas such as pilocytic astrocytomas, fibrillary astrocytoma, protoplasmic astrocytoma, gemistocytary astrocytoma, anaplastic astrocytoma and glioblastoma, brain lymphomas, brain metastases, hypophyseal tumour such as prolactinoma, HGH (human growth hormone) producing tumour and ACTH producing tumour (adrenocorticotropic hormone), craniopharyngiomas, medulloblastomas, meningeomas and oligodendrogliomas; nerve tumours (neoplasms) such as for example tumours of the vegetative nervous system such as neuroblastoma sympathicum, ganglioneuroma, paraganglioma (pheochromocytoma, chromaffinoma) and glomus-caroticum tumour, tumours on the peripheral nervous system such as amputation neuroma, neurofibroma, neurinoma (neurilemmoma, Schwannoma) and malignant Schwannoma, as well as tumours of the central nervous system such as brain and bone marrow tumours; intestinal cancer such as for example carcinoma of the rectum, colon carcinoma, colorectal carcinoma, anal carcinoma, carcinoma of the large bowel, tumours of the small intestine and duodenum; eyelid tumours such as basalioma or basal cell carcinoma; pancreatic cancer or carcinoma of the pancreas; bladder cancer or carcinoma of the bladder; lung cancer (bronchial carcinoma) such as for example small-cell bronchial carcinomas (oat cell carcinomas) and non-small cell bronchial carcinomas (NSCLC) such as plate epithelial carcinomas, adenocarcinomas and large-cell bronchial carcinomas; breast cancer such as for example mammary carcinoma such as infiltrating ductal carcinoma, colloid carcinoma, lobular invasive carcinoma, tubular carcinoma, adenocystic carcinoma and papillary

carcinoma; non-Hodgkin's lymphomas (NHL) such as for example Burkitt's lymphoma, low-malignancy non-Hodgkin's lymphomas (NHL) and mucosis fungoides; uterine cancer or endometrial carcinoma or corpus carcinoma; CUP syndrome (Cancer of Unknown Primary); ovarian cancer or ovarian carcinoma such as mucinous, endometrial or serous cancer; gall bladder cancer; bile duct cancer such as for example Klatskin tumour; testicular cancer such as for example seminomas and non-seminomas; lymphoma (lymphosarcoma) such as for example malignant lymphoma, Hodgkin's disease, non-Hodgkin's lymphomas (NHL) such as chronic lymphatic leukaemia, leukaemic reticuloendotheliosis, immunocytoma, plasmocytoma (multiple myeloma), immunoblastoma, Burkitt's lymphoma, T-zone mycosis fungoides, large-cell anaplastic lymphoblastoma and lymphoblastoma; laryngeal cancer such as for example tumours of the vocal cords, supraglottal, glottal and subglottal laryngeal tumours; bone cancer such as for example osteochondroma, chondroma, chondroblastoma, chondromyxoid fibroma, osteoma, osteoid osteoma, osteoblastoma, eosinophilic granuloma, giant cell tumour, chondrosarcoma, osteosarcoma, Ewing's sarcoma, reticulo-sarcoma, plasmocytoma, fibrous dysplasia, juvenile bone cysts and aneurysmatic bone cysts; head and neck tumours such as for example tumours of the lips, tongue, floor of the mouth, oral cavity, gums, palate, salivary glands, throat, nasal cavity, paranasal sinuses, larynx and middle ear; liver cancer such as for example liver cell carcinoma or hepatocellular carcinoma (HCC); leukaemias, such as for example acute leukaemias such as acute lymphatic/lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML); chronic leukaemias such as chronic lymphatic leukaemia (CLL), chronic myeloid leukaemia (CML); stomach cancer or gastric carcinoma such as for example papillary, tubular and mucinous adenocarcinoma, signet ring cell carcinoma, adenosquamous carcinoma, small-cell carcinoma and undifferentiated carcinoma; melanomas such as for example superficially spreading, nodular, lentigo-maligna and acral-lentiginous melanoma; renal cancer such as for example kidney cell carcinoma or hypernephroma or Grawitz's tumour; oesophageal cancer or carcinoma of the oesophagus; penile cancer; prostate cancer; throat cancer or carcinomas of the pharynx such as for example nasopharynx carcinomas, oropharynx carcinomas and hypopharynx carcinomas; retinoblastoma such as for example vaginal cancer or vaginal carcinoma; plate epithelial carcinomas, adenocarcinomas, in situ carcinomas, malignant melanomas and

sarcomas; thyroid carcinomas such as for example papillary, follicular and medullary thyroid carcinoma, as well as anaplastic carcinomas; spinalioma, epidormoid carcinoma and plate epithelial carcinoma of the skin; thymomas, cancer of the urethra and cancer of the vulva.

Preferred cancers, which may be treated with compounds according to the invention, are lung, liver, colon, brain, breast, ovary, prostate cancer, pancreas, kidney, stomach, head, neck, lymphoma and leukemia.

The new compounds may be used for the prevention, short-term or long-term treatment of the above-mentioned diseases, optionally also in combination with radiotherapy or other "state-of-the-art" compounds, such as e.g. cytostatic or cytotoxic substances, cell proliferation inhibitors, anti-angiogenic substances, steroids or antibodies.

The compounds of general formula (1) may be used on their own or in combination with other active substances according to the invention, optionally also in combination with other pharmacologically active substances.

Chemotherapeutic agents which may be administered in combination with the compounds according to the invention, include, without being restricted thereto, hormones, hormone analogues and antihormones (e.g. tamoxifen, toremifene, raloxifene, fulvestrant, megestrol acetate, flutamide, nilutamide, bicalutamide, aminoglutethimide, cyproterone acetate, finasteride, buserelin acetate, fludrocortisone, fluoxymesterone, medroxyprogesterone, octreotide), aromatase inhibitors (e.g. anastrozole, letrozole, liarozole, vorozole, exemestane, atamestane), LHRH agonists and antagonists (e.g. goserelin acetate, luprolide), inhibitors of growth factors (growth factors such as for example "platelet derived growth factor" and "hepatocyte growth factor", inhibitors are for example "growth factor" antibodies, "growth factor receptor" antibodies and tyrosine kinase inhibitors, such as for example cetuximab, gefitinib, imatinib, lapatinib and trastuzumab); antimetabolites (e.g. antifolates such as methotrexate, raltitrexed, pyrimidine analogues such as 5-fluorouracil, capecitabin and gemcitabin, purine and adenosine analogues such as mercaptopurine, thioguanine, cladribine and pentostatin, cytarabine, fludarabine); antitumour antibiotics (e.g. anthracyclins such as doxorubicin, daunorubicin, epirubicin

and idarubicin, mitomycin-C, bleomycin, dactinomycin, plicamycin, streptozocin); platinum derivatives (e.g. cisplatin, oxaliplatin, carboplatin); alkylation agents (e.g. estramustin, meclorethamine, melphalan, chlorambucil, busulphan, dacarbazin, cyclophosphamide, ifosfamide, temozolomide, nitrosoureas such as for example carmustin and lomustin, thiotepa); antimitotic agents (e.g. Vinca alkaloids such as for example vinblastine, vindesin, vinorelbin and vincristine; and taxanes such as paclitaxel, docetaxel); topoisomerase inhibitors (e.g. epipodophyllotoxins such as for example etoposide and etopophos, teniposide, amsacrin, topotecan, irinotecan, mitoxantron) and various chemotherapeutic agents such as amifostin, anagrelid, clodronat, filgrastin, interferon alpha, leucovorin, rituximab, procarbazine, levamisole, mesna, mitotane, pamidronate and porfimer.

Other possible combination partners are 2-chlorodesoxyadenosine, 2-fluorodesoxycytidine, 2-methoxyoestradiol, 2C4, 3-alethine, 131-I-TM-601, 3CPA, 7-ethyl-10-hydroxycamptothecin, 16-aza-epothilone B, A 105972, A 204197, aldesleukin, alitretinoin, altretamine, alvocidib, amonafide, anthrapyrazole, AG-2037, AP-5280, apaziquone, apomine, aranose, arglabin, arzoxifene, atamestane, atrasentan, auristatin PE, AVLB, AZ10992, ABX-EGF, ARRY-300, ARRY-142886/AZD-6244, ARRY-704/AZD-8330, AS-703026, azacytidine, azaepothilone B, azonafide, BAY-43-9006, BBR-3464, BBR-3576, bevacizumab, biricodar dicitrate, BCX-1777, bleocin, BLP-25, BMS-184476, BMS-247550, BMS-188797, BMS-275291, BNP-1350, BNP-7787, BIBW 2992, BIBF 1120, bleomycinic acid, bleomycin A, bleomycin B, bryostatin-1, bortezomib, brostallicin, busulphan, CA-4 prodrug, CA-4, CapCell, calcitriol, canertinib, canfosfamide, capecitabine, carboxyphthalatoplatin, CCI-779, CEP-701, CEP-751, CBT-1 cefixime, ceflatonin, ceftriaxone, celecoxib, celmoleukin, cemadotin, CH4987655/RO-4987655, chlorotrianisene, cilengitide, ciclosporin, CDA-II, CDC-394, CKD-602, clofarabin, colchicin, combretastatin A4, CHS-828, CLL-Thera, CMT-3 cryptophycin 52, CTP-37, CP-461, CV-247, cyanomorpholinodoxorubicin, cytarabine, D 24851, decitabine, deoxorubicin, deoxyrubicin, deoxycoformycin, depsipeptide, desoxyepothilone B, dexamethasone, dexrazoxanet, diethylstilbestrol, diflomotecan, didox, DMDC, dolastatin 10, doranidazole, E7010, E-6201, edatrexat, edotreotide, efaproxiral,

eflornithine, EKB-569, EKB-509, elsamitrucin, epothilone B, epratuzumab, ER-86526, erlotinib, ET-18-OCH3, ethynylcytidine, ethynyloestradiol, exatecan, exatecan mesylate, exemestane, exisulind, fenretinide, floxuridine, folic acid, FOLFOX, FOLFIRI, formestane, galarubicin, gallium maltolate, gefinitib, gemtuzumab, gimatecan, glufosfamide, GCS-IOO, G17DT immunogen, GMK, GPX-100, GSK-5126766, GSK-1120212, GW2016, granisetron, hexamethylmelamine, histamine, homoharringtonine, hyaluronic acid, hydroxyurea, hydroxyprogesterone caproate, ibandronate, ibritumomab, idatrexate, idenestrol, IDN-5109, IMC-1C11, immunol, indisulam, interferon alpha-2a, interferon alfa-2b, interleukin-2, ionafarnib, iproplatin, irofulven, isohomohalichondrin-B, isoflavone, isotretinoin, ixabepilone, JRX-2, JSF-154, J-107088, conjugated oestrogens, kahalid F, ketoconazole, KW-2170, lobaplatin, leflunomide, lenograstim, leuprolide, leuporelin, lexidronam, LGD-1550, linezolid, lutetium texaphyrin, lometrexol, losoxantrone, LU 223651, lurtotecan, mafosfamide, marimastat, mechloroethamine, methyltestosteron, methylprednisolone, MEN-10755, MDX-H210, MDX-447, MGV, midostaurin, minodronic acid, mitomycin, mivobulin, MK-2206, MLN518, motexafin gadolinium, MS-209, MS-275, MX6, neridronate, neovastat, nimesulide, nitroglycerin, nolatrexed, norelin, N-acetylcysteine, 06-benzylguanine, omeprazole, oncophage, ormiplatin, ortataxel, oxantrazole, oestrogen, patupilone, pegfilgrastim, PCK-3145, pegfilgrastim, PBI-1402, PEG-paclitaxel, PEP-005, P-04, PKC412, P54, PI-88, pelitinib, pemetrexed, pentrix, perifosine, perillylalcohol, PG-TXL, PG2, PLX-4032/RO-5185426, PT-100, picoplatin, pivaloyloxymethylbutyrate, pixantrone, phenoxodiol O, PKI166, plevitrexed, plicamycin, polyprenic acid, porfiromycin, prednisone, prednisolone, quinamed, quinupristin, RAF-265, ramosetron, ranpirnase, RDEA-119/BAY 869766, rebeccamycin analogues, revimid, RG-7167, rhizoxin, rhu-MAb, risedronate, rituximab, rofecoxib, Ro-31-7453, RO-5126766, RPR 109881A, rubidazon, rubitecan, R-flurbiprofen, S-9788, sabarubicin, SAHA, sargramostim, satraplatin, SB 408075, SU5416, SU6668, SDX-101, semustin, seocalcitol, SM-11355, SN-38, SN-4071, SR-27897, SR-31747, SRL-172, sorafenib, spiroplatin, squalamine, suberanilohydroxamic acid, sutent, T 900607, T 138067, TAS-103, tacedinaline, talaporfin, tariquitar, taxotere, taxoprexin, tazarotene, tegafur, temozolamide, tesmilifene, testosterone, testosterone propionate, tesmilifene, tetraplatin, tetrodotoxin,

tezacitabine, thalidomide, theralux, therarubicin, thymectacin, tiazofurin, tipifarnib, tirapazamine, tocladesine, tomudex, toremofin, trabectedin, TransMID-107, transretinic acid, traszutumab, tretinoin, triacetyluridine, triapine, trimetrexate, TLK-286TXD 258, urocidin, valrubicin, vatalanib, vincristine, vinflunine, virulizin, WX-UK1, vectibix, xeloda, XELOX, XL-281, XL-518/R-7420, YM-511, YM-598, ZD-4190, ZD-6474, ZD-4054, ZD-0473, ZD-6126, ZD-9331, ZDI839, zoledronat and zosuquidar.

Suitable preparations include for example tablets, capsules, suppositories, solutions - particularly solutions for injection (s.c., i.v., i.m.) and infusion - elixirs, emulsions or dispersible powders. The content of the pharmaceutically active compound(s) should be in the range from 0.1 to 90 wt.-%, preferably 0.5 to 50 wt.-% of the composition as a whole, i.e. in amounts which are sufficient to achieve the dosage range specified below. The doses specified may, if necessary, be given several times a day.

Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number of layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, e.g. a flavouring such as vanillin or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl

cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

Solutions for injection and infusion are prepared in the usual way, e.g. with the addition of isotonic agents, preservatives such as p-hydroxybenzoates, or stabilisers such as alkali metal salts of ethylenediamine tetraacetic acid, optionally using emulsifiers and/or dispersants, whilst if water is used as the diluent, for example, organic solvents may optionally be used as solvating agents or dissolving aids, and transferred into injection vials or ampoules or infusion bottles.

Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

Excipients which may be used include, for example, water, pharmaceutically acceptable organic solvents such as paraffins (e.g. petroleum fractions), vegetable oils (e.g. groundnut or sesame oil), mono- or polyfunctional alcohols (e.g. ethanol or glycerol), carriers such as e.g. natural mineral powders (e.g. kaolins, clays, talc, chalk), synthetic mineral powders (e.g. highly dispersed silicic acid and silicates), sugars (e.g. cane sugar, lactose and glucose) emulsifiers (e.g. lignin, spent sulphite liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

The preparations are administered by the usual methods, preferably by oral or transdermal route, most preferably by oral route. For oral administration the tablets may, of course contain, apart from the abovementioned carriers, additives such as sodium citrate, calcium carbonate and dicalcium phosphate together with various additives such as starch, preferably potato starch, gelatine and the like. Moreover, lubricants such as magnesium

stearate, sodium lauryl sulphate and talc may be used at the same time for the tabletting process. In the case of aqueous suspensions the active substances may be combined with various flavour enhancers or colourings in addition to the excipients mentioned above.

For parenteral use, solutions of the active substances with suitable liquid carriers may be used.

However, it may sometimes be necessary to depart from the amounts specified, depending on the body weight, the route of administration, the individual response to the drug, the nature of its formulation and the time or interval over which the drug is administered. Thus, in some cases it may be sufficient to use less than the minimum dose given above, whereas in other cases the upper limit may have to be exceeded. When administering large amounts it may be advisable to divide them up into a number of smaller doses spread over the day.

The formulation examples which follow illustrate the present invention without restricting its scope:

Examples of pharmaceutical formulations

A)	Tablets	per tablet
	active substance according to formula **(I)**	100 mg
	lactose	140 mg
	corn starch	240 mg
	polyvinylpyrrolidone	15 mg
	magnesium stearate	5 mg
		500 mg

The finely ground active substance, lactose and some of the corn starch are mixed together. The mixture is screened, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet-granulated and dried. The granules, the remaining corn starch and the magnesium stearate are screened and mixed together. The mixture is compressed to produce tablets of suitable shape and size.

B) Tablets per tablet

active substance according to formula **(I)**	80 mg
lactose	55 mg
corn starch	190 mg
microcrystalline cellulose	35 mg
polyvinylpyrrolidone	15 mg
sodium-carboxymethyl starch	23 mg
magnesium stearate	2 mg
	400 mg

The finely ground active substance, some of the corn starch, lactose, microcrystalline cellulose and polyvinylpyrrolidone are mixed together, the mixture is screened and worked with the remaining corn starch and water to form a granulate which is dried and screened. The sodiumcarboxymethyl starch and the magnesium stearate are added and mixed in and the mixture is compressed to form tablets of a suitable size.

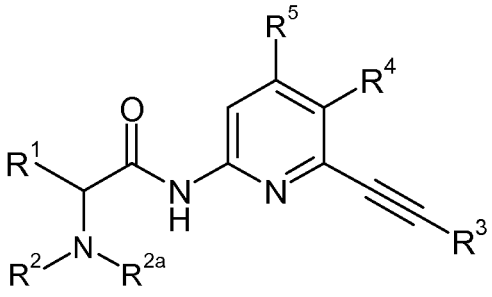
C) Ampoule solution

active substance according to formula **(I)**	50 mg
sodium chloride	50 mg
water for inj.	5 mL

The active substance is dissolved in water at its own pH or optionally at pH 5.5 to 6.5 and sodium chloride is added to make it isotonic. The solution obtained is filtered free from pyrogens and the filtrate is transferred under aseptic conditions into ampoules which are then sterilised and sealed by fusion. The ampoules contain 5 mg, 25 mg and 50 mg of active substance.

Claims

1. A compound according to Formula **(I)**



(I)

wherein

R^1 is -H or -C_{1-5}alkyl;

R^2, **R^{2a}** are independently selected from -H or -C_{1-5}alkyl optionally substituted with one or more -F;

R^3 is selected from -C_{6-10}aryl, 5-14 membered heteroaryl, each of which groups can be optionally and independently substituted with one or more, independently selected, **R^6**; or **R^3** is selected from -C_{1-6}alkyl, -C_{4-7}cycloalkyl, -C_{4-7}cycloalkenyl, or 5-14 membered aromatic ring system, each of which groups can be optionally and independently substituted with one or more, independently selected, **R^{6a}**;

R^6 is selected from -CN, halogen, -C_{1-3}alkyl, -O-C_{1-3}alkyl, -C(O)-**R^{12}**, 5-6 membered heteroaryl, which 5-6 membered heteroaryl group can be optionally substituted with -C_{1-3}alkyl; or **R^6** is phenyl, which phenyl can be optionally substituted with -O-C_{1-3}alkyl

R^{6a} is selected from =O, -CN, halogen, -C_{1-3}alkyl, -O-C_{1-3}alkyl, -C(O)-**R^{12}**, 5-6 membered heteroaryl, which 5-6 membered heteroaryl group can be optionally subsituted with -C_{1-3}alkyl; or **R^{6a}** is phenyl, which phenyl can be optionally substituted with -O-C_{1-3}alkyl;

R^{12} is selected from -NH_2, -NH-C_{1-3}alkyl, 5-7 membered non aromatic heterocyclyl, or -O-C_{1-3}alkyl, which -C_{1-3}alkyl groups can be optionally subsituted with a 5-7 membered non aromatic heterocyclyl;

$\mathbf{R^4}$ is selected from -H, -C_{6-10}aryl, 5-14 membered heteroaryl, each of which groups is optionally and independently substituted with one or more, independently selected, $\mathbf{R^7}$, or $\mathbf{R^4}$ is selected from C_{1-6}alkyl, 5-14 membered aromatic ring system, -C_{5-7}cycloalkyl, each of which group is optionally and independently substituted with one or more, independently selected, $\mathbf{R^{7a}}$,

or $\mathbf{R^4}$ is selected from -N($\mathbf{R^8}$,$\mathbf{R^9}$) wherein

$\mathbf{R^8}$, $\mathbf{R^9}$ are independently selected from H, -C_{1-3}alkyl, -C(O)-$\mathbf{R^{10}}$ -$S(O)_2$-$\mathbf{R^{11}}$

$\mathbf{R^{10}}$, $\mathbf{R^{11}}$ are independently selected from 5-7 membered non aromatic heterocyclyl, -C_{5-7}cycloalkyl, -C_{6-10}aryl, 5-10 membered heteroaryl;

$\mathbf{R^7}$ is selected from -CN, halogen, -CF_3, -NO_2, -C_{1-3}alkyl, -S-C_{1-3}alkyl, -NH-C_{1-3}alkyl, -N(C_{1-3}alkyl)$_2$, -NHC(O)-C_{1-3}alkyl, -C(O)-$\mathbf{R^{13}}$, -O-C_{1-3}alkyl, 5-14 membered heteroaryl, -O-phenyl, -CH_2-phenyl, phenyl, each of which phenyl group can be optionally substituted with halogen, or 5-6 membered non aromatic heterocyclyl, which 5-6 membered non aromatic heterocyclyl can be optionally substituted with -C_{1-3}alkyl;

$\mathbf{R^{7a}}$ is selected from =O, -CN, halogen, -CF_3, -NO_2, -C_{1-3}alkyl, -S-C_{1-3}alkyl, -NH-C_{1-3}alkyl, -N(C_{1-3}alkyl)$_2$, -NHC(O)-C_{1-3}alkyl, -C(O)-$\mathbf{R^{13}}$, -O-C_{1-3}alkyl, 5-14 membered heteroaryl, -O-phenyl, -CH_2-phenyl, phenyl, each of which phenyl group can be optionally substituted with halogen, or 5-6 membered non aromatic heterocyclyl, which 5-6 membered non aromatic heterocyclyl can be optionally substituted with -C_{1-3}alkyl; wherein

$\mathbf{R^{13}}$ is selected from -OH, -NH_2, -NH-C_{1-3}alkyl, -C_{1-3}alkyl;

$\mathbf{R^5}$ is selected from -H, halogen, -C_{1-3}alkyl, -O-C_{1-3}alkyl, which -C_{1-3}alkyl groups can be optionally subsituted with one or more halogen;

or $\mathbf{R^4}$ and $\mathbf{R^5}$ taken together form a -C_{6-10}aryl or 5-14 membered heteroaryl,

and wherein the compounds of formula (I) may optionally be present in the form of salts.

2. The compound according to claim 1, wherein $\mathbf{R^1}$ is selected from -CH_3, -CH_2-CH_3.

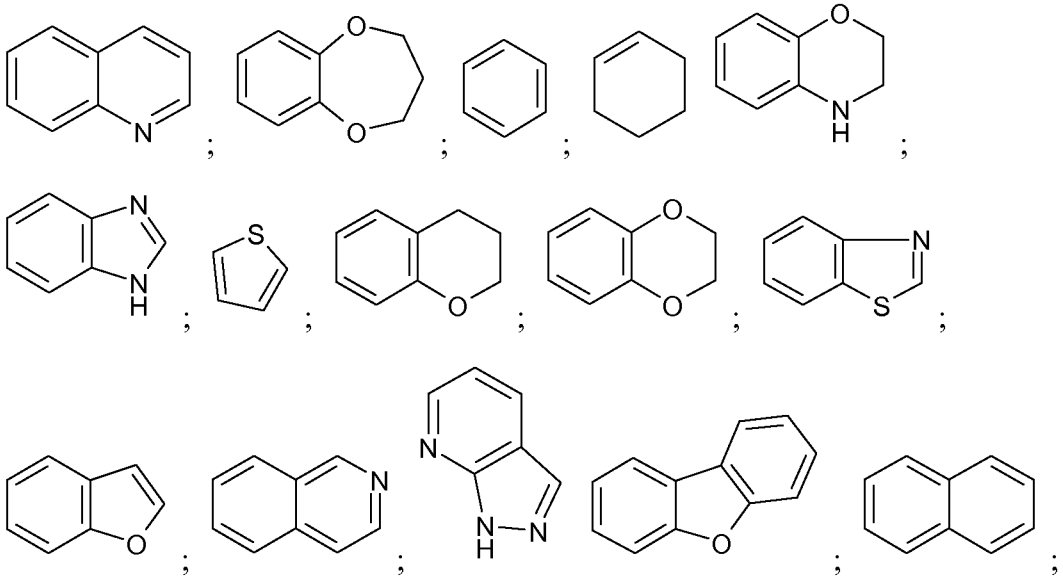
3. The compound of claim 1 or 2, wherein $\mathbf{R^2}$ and $\mathbf{R^{2a}}$ are independently selected from -H, $-CH_3$, $-CH_2-CH_3$. $-CH-(CH_3)_2$, $-(CH_2)_2-CH_3$.

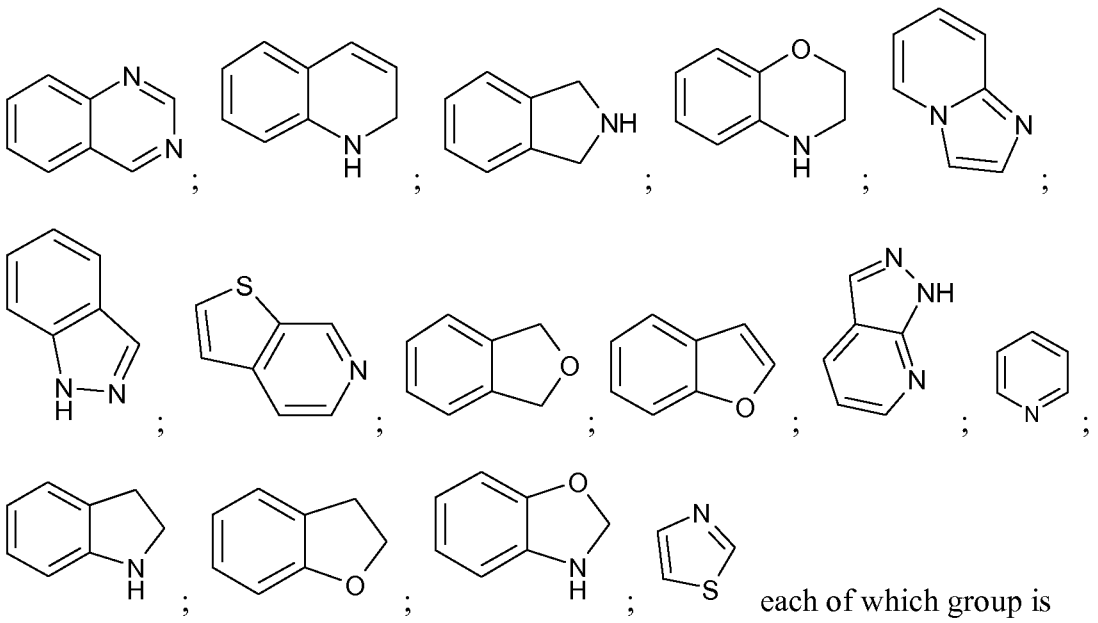
4. The compound of anyone of claims 1 to 3, wherein $\mathbf{R^5}$ is selected from -H, -Cl, -F, $-CF_3$, $-OCH_3$, $-CH_3$.

5. The compund of anyone of claims 1 to 4, wherein $\mathbf{R^3}$ is selected from $-C_{6-10}$aryl, 5-14 membered heteroaryl, each of which groups can be optionally and independently substituted with one or more, independently selected, $\mathbf{R^6}$, or $\mathbf{R^3}$ is selected from-C_{5-7}cycloalkenyl, 5-14 membered aromatic ring system, each of which groups can be optionally and independently substituted with one or more, independently selected $\mathbf{R^{6a}}$, or $\mathbf{R^3}$ is $-CH_2$-phenyl, which phenyl can be optionally substituted with -O-C_{1-3}alkyl, and wherein $\mathbf{R^6}$ and $\mathbf{R^{6a}}$ are as defined in claim 1.

6. The compund of anyone of claims 1 to 5, wherein $\mathbf{R^3}$ is selected from $-C_{6-10}$aryl, 5-14 membered heteroaryl, each of which groups can be optionally and independently substituted with one or more, independently selected, $\mathbf{R^6}$, or $\mathbf{R^3}$ is selected from 5-14 membered aromatic ring system, which groups can be optionally and independently substituted with one or more, independently selected, $\mathbf{R^{6a}}$, wherein $\mathbf{R^6}$ and $\mathbf{R^{6a}}$ are as defined in claim 1.

7. The compound of anyone of claims 1 to 5, wherein $\mathbf{R^3}$ is selected from $-CH_2$-phenyl,





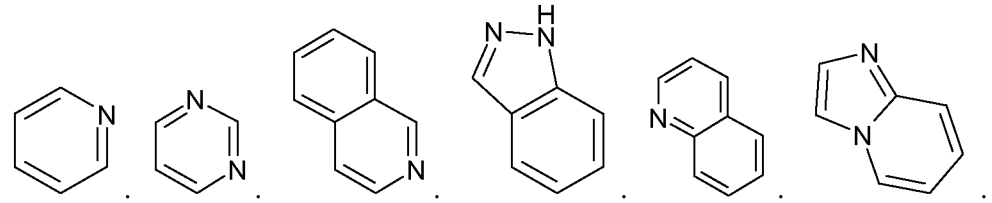
each of which group is optionally substituted as defined in claim 1.

8. The compound of anyone of claims 1 to 7, wherein $\mathbf{R^4}$ is selected from -H, -C_{6-10}aryl, 5-14 membered heteroaryl, each of which group is optionally and independently substituted with one or more, independently selected, $\mathbf{R^7}$,
or $\mathbf{R^4}$ is selected from -C_{1-6}alkyl, 5-14 membered aromatic ring system and -C_{5-7}cycloalkyl, each of which group is optionally and independently substituted with one or more, independently selected, $\mathbf{R^{7a}}$,
or $\mathbf{R^4}$ is selected from -N($\mathbf{R^8}$,$\mathbf{R^9}$), wherein $\mathbf{R^7}$, $\mathbf{R^{7a}}$, $\mathbf{R^8}$ and $\mathbf{R^9}$ are as defined in claim 1.

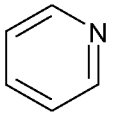
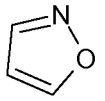
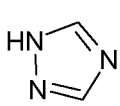
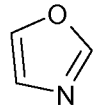
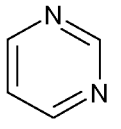
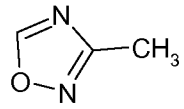
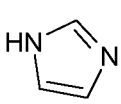
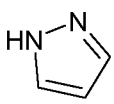
9. The compound of anyone of claims 1 to 8, wherein $\mathbf{R^4}$ is selected from -C_{6-10}aryl, 5-14 membered heteroaryl, each of which group is optionally and independently substituted with one or more, independently selected, $\mathbf{R^7}$,
or $\mathbf{R^4}$ is selected from 5-14 membered aromatic ring system, -C_{5-7}cycloalkyl, each of which group is optionally and independently substituted with one or more, independently selected, $\mathbf{R^{7a}}$, or $\mathbf{R^4}$ is selected from -N($\mathbf{R^8}$,$\mathbf{R^9}$), wherein $\mathbf{R^7}$, $\mathbf{R^{7a}}$, $\mathbf{R^8}$ and $\mathbf{R^9}$ are as defined in claim 1.

10. The compound of anyone of claims 1 to 9, wherein $\mathbf{R^4}$ is selected from -C_{6-10}aryl, 5-14 membered heteroaryl, each of which group is optionally and independently substituted with one or more, independently selected, $\mathbf{R^7}$,
or $\mathbf{R^4}$ is 5-14 membered aromatic ring system, each of which group is optionally and independently substituted with one or more, independently selected, $\mathbf{R^{7a}}$,wherein $\mathbf{R^7}$ and $\mathbf{R^{7a}}$ are as defined in claim 1.

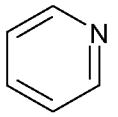
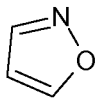
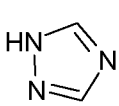
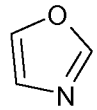
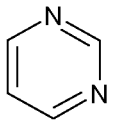
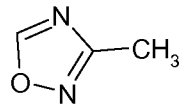
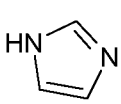
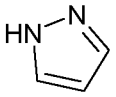
11. The compound of anyone of claims 1 to 9, wherein $\mathbf{R^4}$ is selected from –H, -C_{1-3}alkyl, -CH_2-phenyl, -N(CH_3)-SO_2-phenyl, -N(CH_3)CO-$\mathbf{R^{10}}$; -NH-CO-$\mathbf{R^{10}}$, wherein $\mathbf{R^{10}}$ is independently selected from morpholin, cyclopentyl, phenyl, or $\mathbf{R^4}$ is selected from


; each of which groups is optionally substituted as defined in claim 1.

12. The compound of anyone of claims 1 to 11, wherein $\mathbf{R^6}$ is selected from -F, -Cl, -CN -CH_3, -O-CH_3, -C(O)NHCH$_3$, -C(O)NH$_2$, C(O)OCH$_3$, -C(O)-morpholinyl, -C(O)-O-CH_2-tetrahydropyran, phenyl,

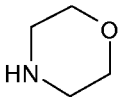
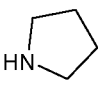
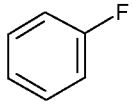
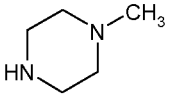
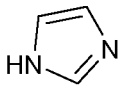









or $\mathbf{R^{6a}}$ is selected from =O, -F, -Cl, -CN -CH_3, -O-CH_3, -C(O)NHCH$_3$, -C(O)NH$_2$, C(O)OCH$_3$, -C(O)-morpholinyl, -C(O)-O-CH_2-tetrahydropyran, phenyl,

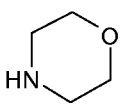
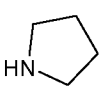
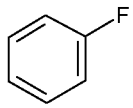
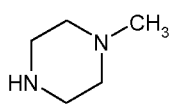
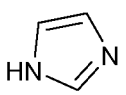









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13. The compound of anyone of claims 1 to 12, wherein $\mathbf{R^7}$ is selected from -CN, -F, -Cl, -CF_3, -NO_2, -CH_3, -CH_2CH_3, -$CH_2(CH_3)_2$, -S-CH_3, -NH_2, -NH-CH_3, -N(CH_3)$_2$, -C(O)OH, -C(O)OCH$_3$, -C(O)NH$_2$, -C(O)NH-CH_3, -NHC(O)CH_3, -O-CH_3, -O-CH_2CH_3, pyridyl, phenyl, -O-Phenyl, -CH_2-phenyl,

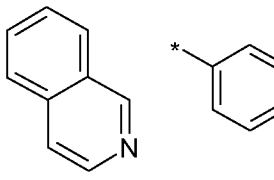
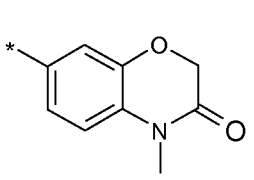
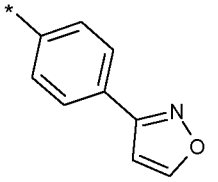
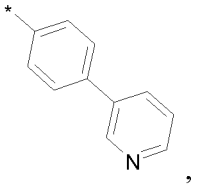
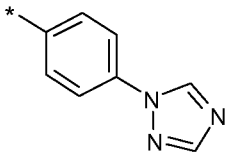
or $\mathbf{R^{7a}}$ is selected from =O, -CN, -F, -Cl, -CF_3, -NO_2, -CH_3, -CH_2CH_3, -$CH_2(CH_3)_2$, -S-CH_3, -NH_2, -NH-CH_3, -N(CH_3)$_2$, -C(O)OH, -C(O)OCH$_3$, -C(O)NH$_2$, -C(O)NH-CH_3, -NHC(O)CH_3, -O-CH_3, -O-CH_2CH_3, pyridyl, phenyl, -O-Phenyl, -CH_2-phenyl,

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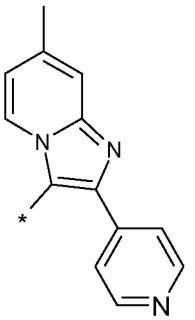
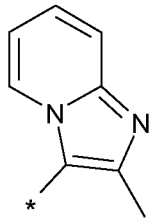
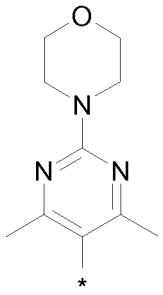
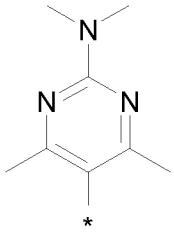
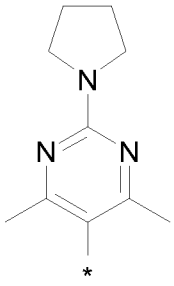
14. The compound of anyone of claims 1 to 3 and 5 to 7, wherein $\mathbf{R^4}$ and $\mathbf{R^5}$ taken together form a phenyl.

15. The compounds of anyone of claims 1 to 14, wherein $\mathbf{R^3}$ is selected from

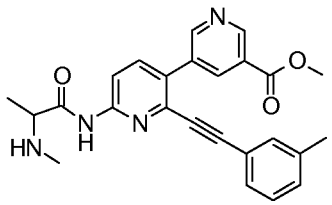
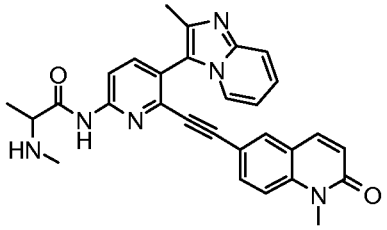
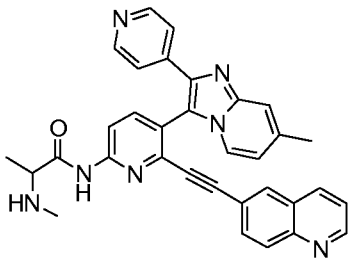
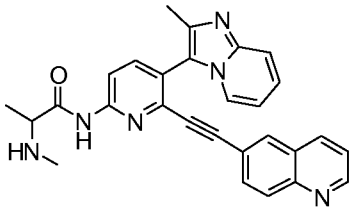






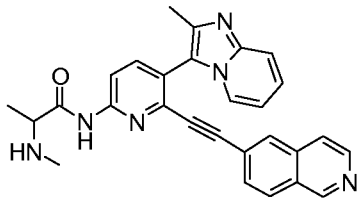
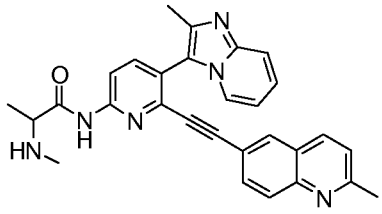
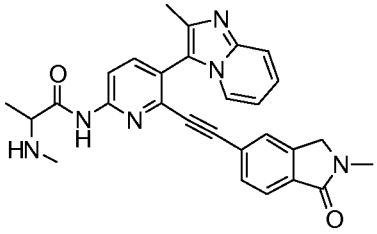
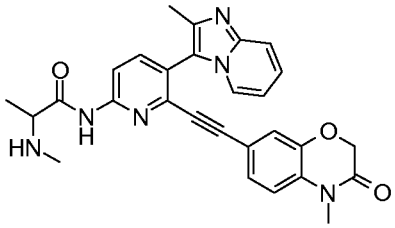
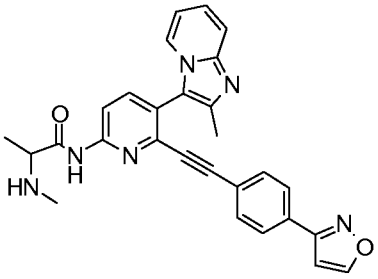
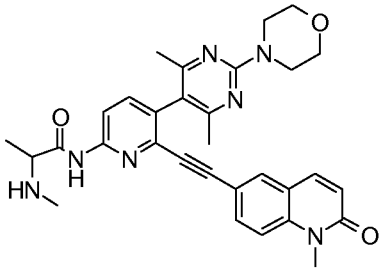
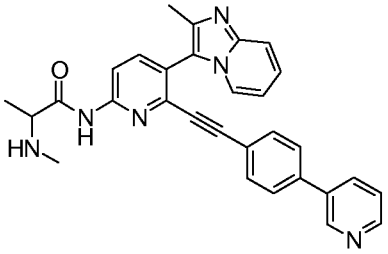
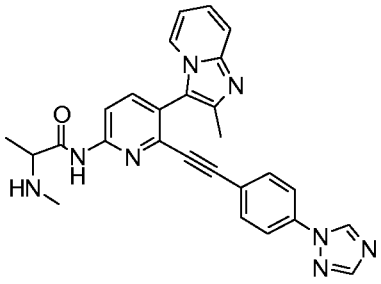
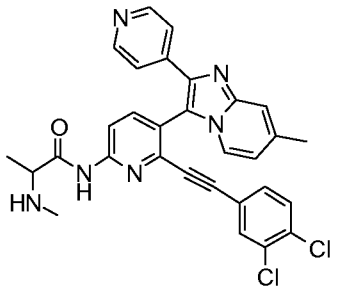
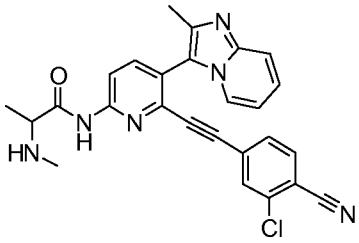
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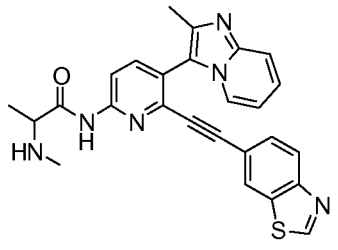
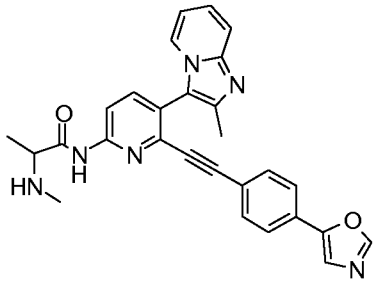
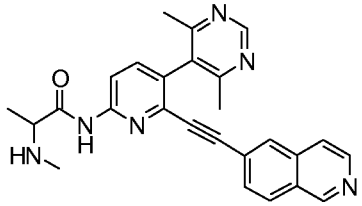
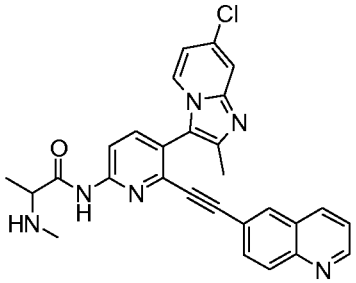
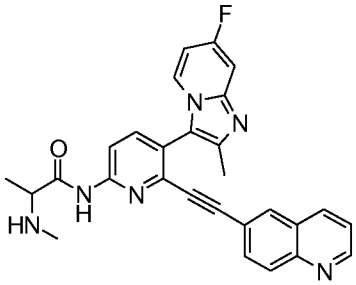
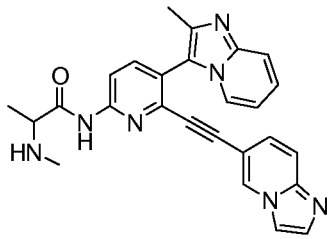
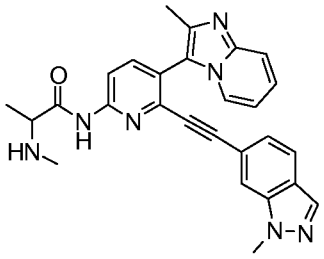
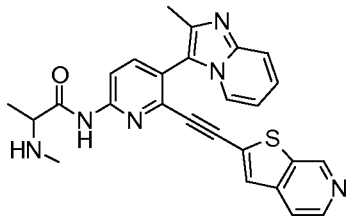
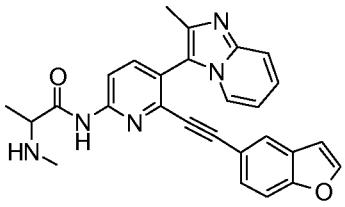
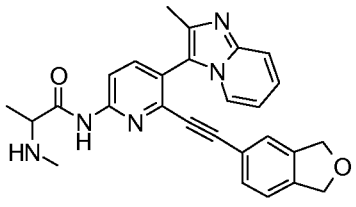
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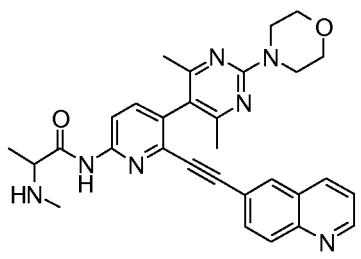
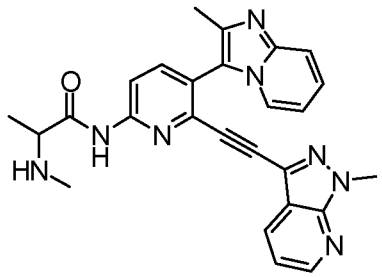
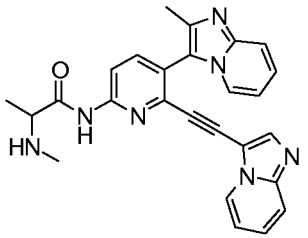
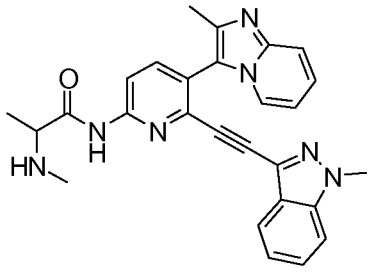
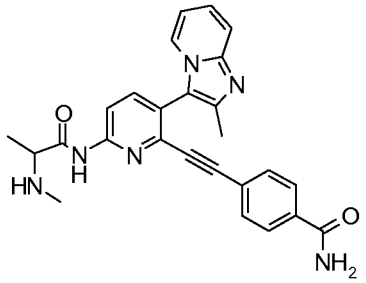
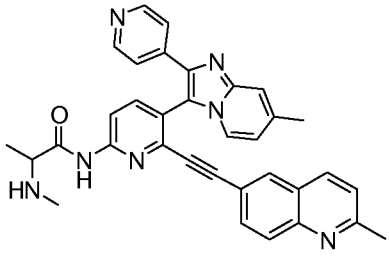
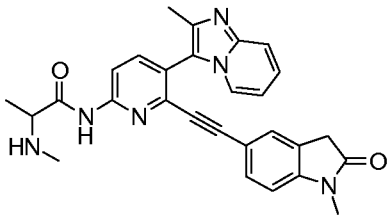
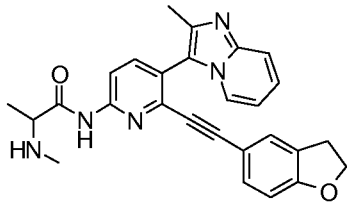
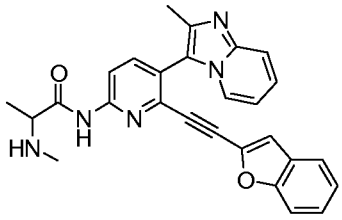
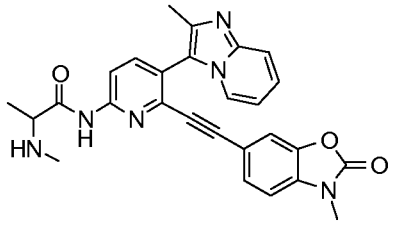

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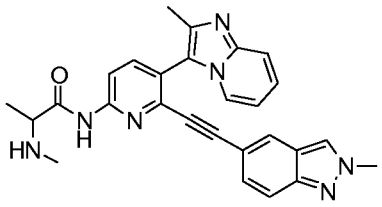
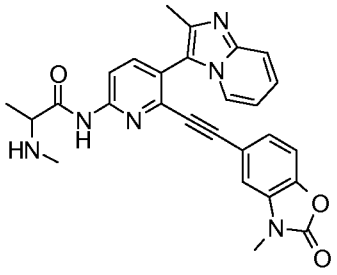
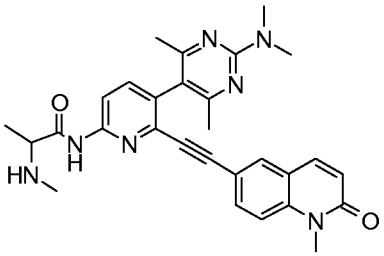
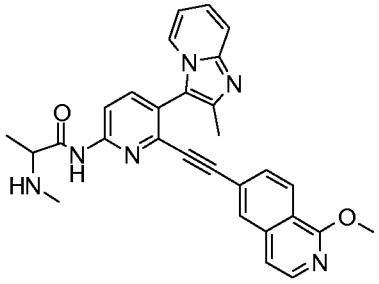
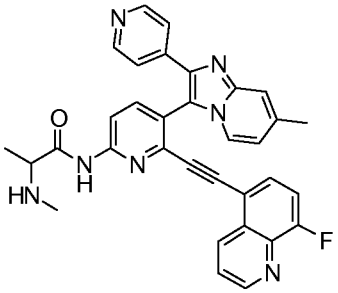
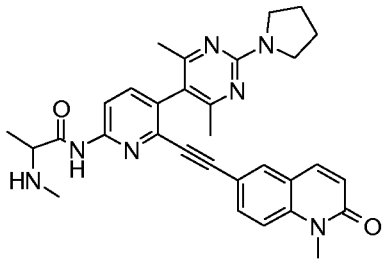
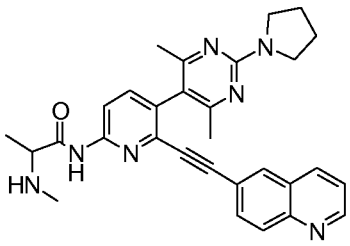
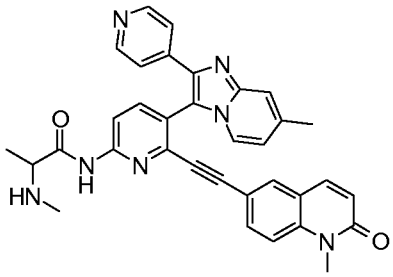
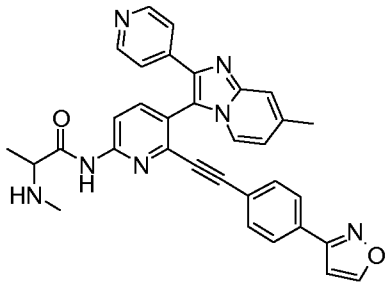
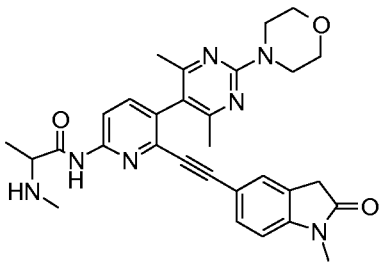
17. The compound of claim 1, selected from

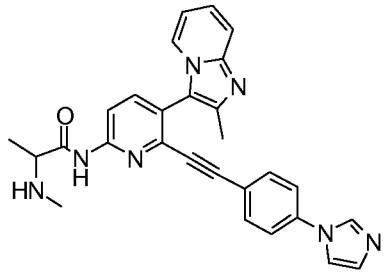
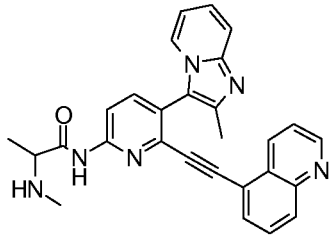
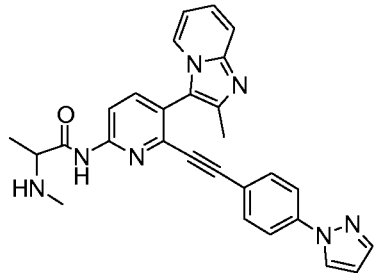
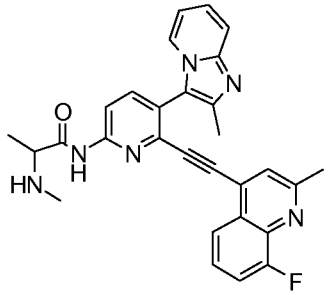
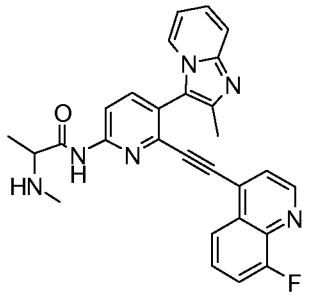
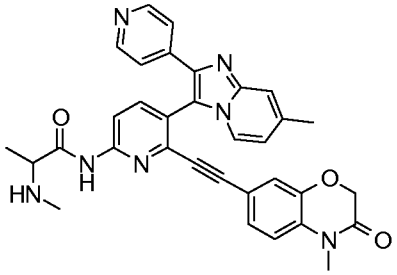
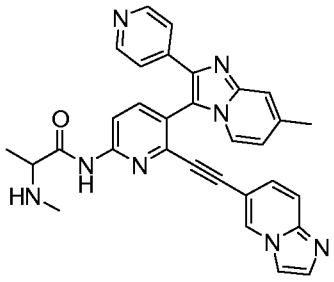
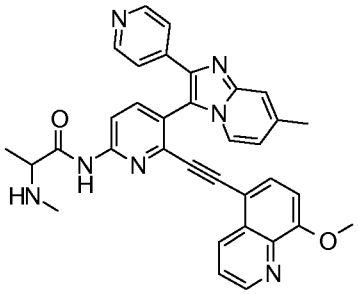
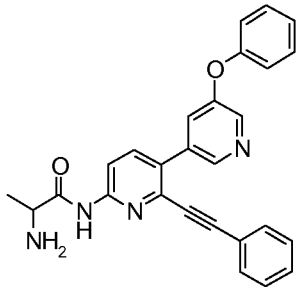
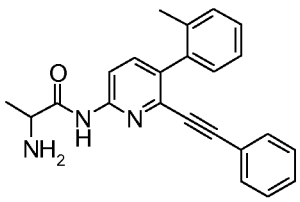
#	Molecular Structure	#	Molecular Structure
13		26	
27		28	

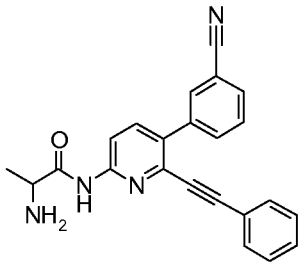
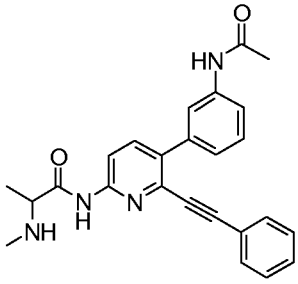
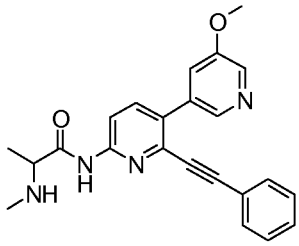
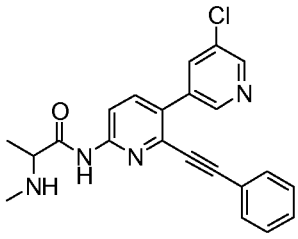
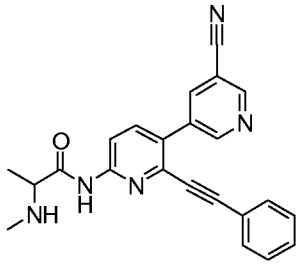
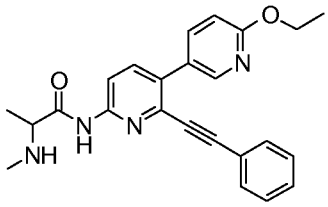
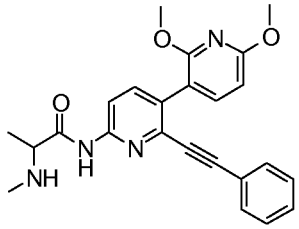
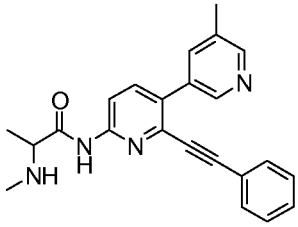
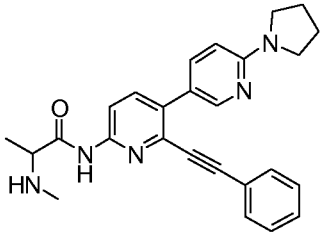
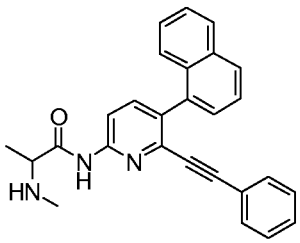
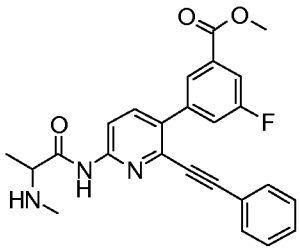
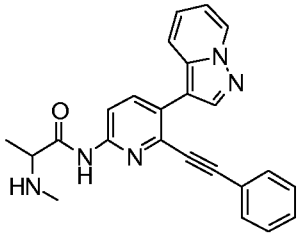
#	Molecular Structure	#	Molecular Structure
29		30	
31		33	
34		35	
36		37	
39		41	

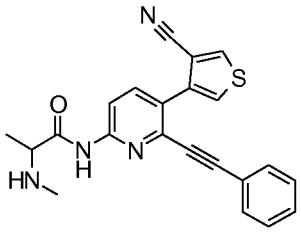
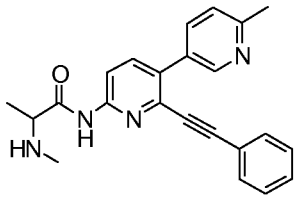
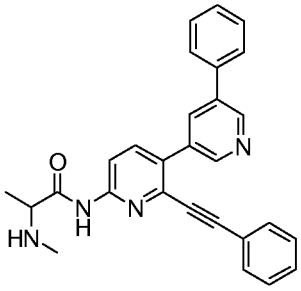
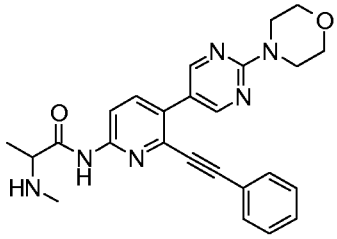
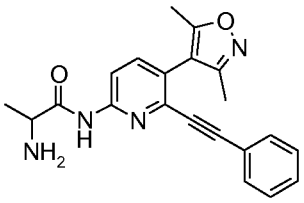
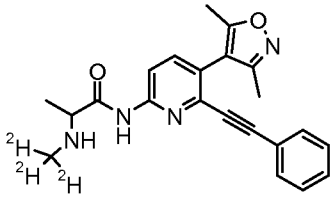
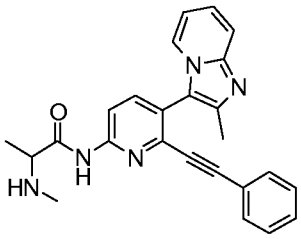
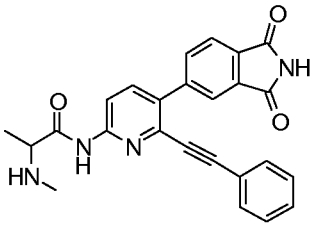
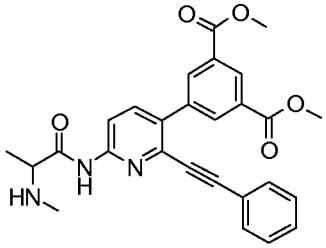
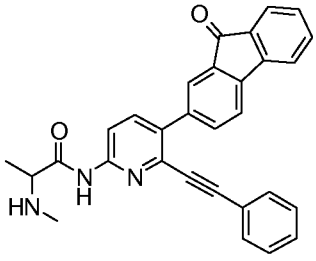
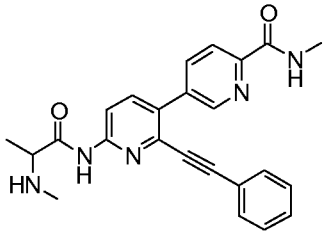
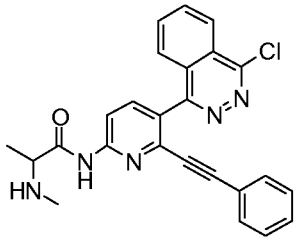
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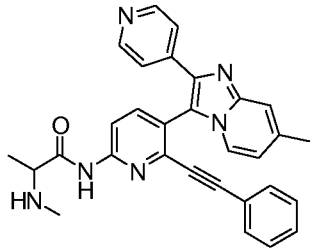
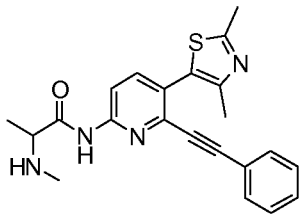
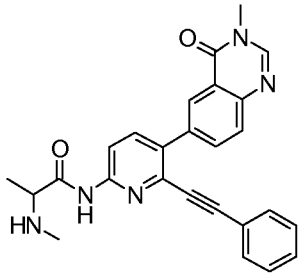
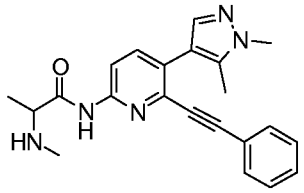
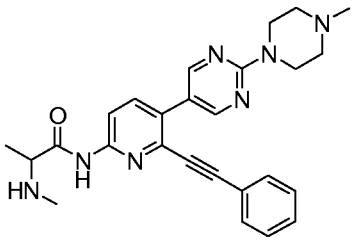
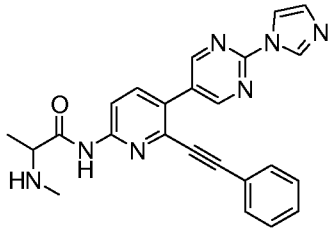
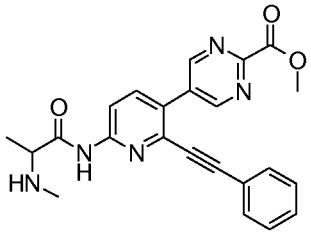
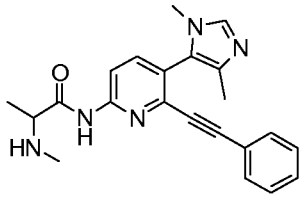
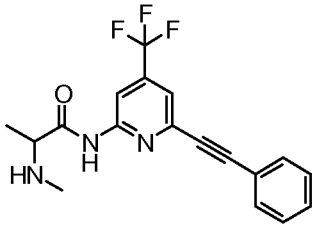
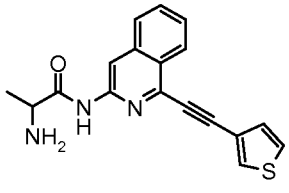
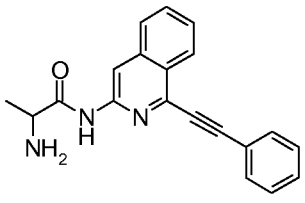
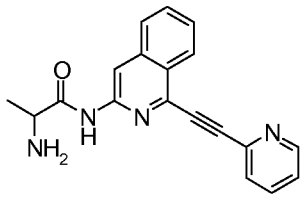
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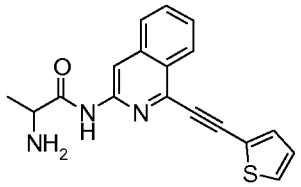
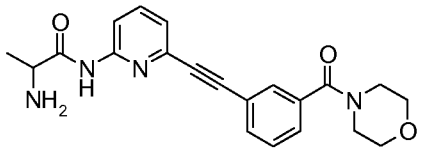
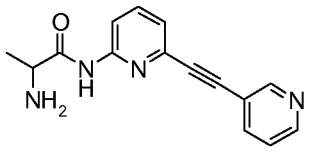
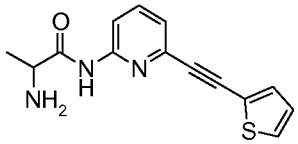
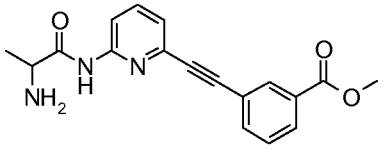
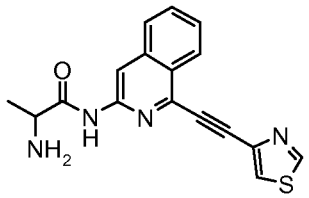
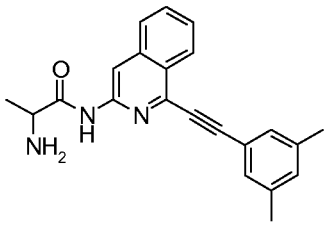
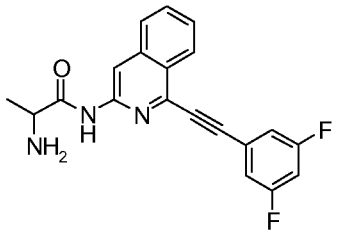
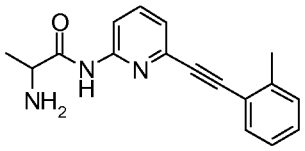
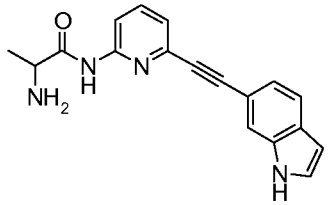
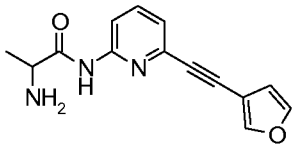
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240			

18. A compound according to anyone of claims 1 to 17, for use in the treatment of cancer.

19. A compound according to anyone of claims 1 to 18 for use in the treatment and /or prevention of carcinoma of the breast, prostate, brain or ovary, non-small-cell bronchial carcinomas (NSCLC), melanomas and chronic lymphatic leukemias (CLL).

20. A pharmaceutical composition comprising a compound according to anyone of claims 1 to 18.

21. A pharmaceutical composition comprising a compound according to anyone of claims 1 to 18 for use in the treatment and/or prevention of cancer.

22. A pharmaceutical composition comprising a compound according to anyone of claims 1 to 18 for use in the treatment and /or prevention of carcinoma of the breast, prostate, brain or ovary, non-small-cell bronchial carcinomas (NSCLC), melanomas and chronic lymphatic leukemias (CLL).

23. A method for the treatment and/or prevention of cancer comprising administering a therapeutically effective amount of a compound according to anyone of claims 1 to 18 – or one of the pharmaceutically acceptable salts thereof – to a human being.

24. A method for the treatment and/or prevention of carcinoma of the breast, prostate, brain or ovary, non-small-cell bronchial carcinomas (NSCLC), melanomas and chronic lymphatic leukemias (CLL) comprising administering a therapeutically effective amount of a compound according to anyone of claims 1 to 18 – or one of the pharmaceutically acceptable salts thereof – to a human being.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/053689

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/75 C07D217/22 C07D401/04 C07D401/06 C07D401/14
C07D405/14 C07D407/06 C07D407/12 C07D409/04 C07D409/06
C07D409/14 C07D413/04 C07D413/14 C07D417/04 C07D417/06

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 practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/073306 A1 (NOVARTIS AG [CH]; CHEN ZHUOLIANG [US]; WANG RUN-MING DAVID [US]; CHEN) 19 June 2008 (2008-06-19) 3rd paragraph on page 2 claim 1	1-24
A	WO 2006/133147 A2 (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; CHEN ZHUOLIANG [US]; PALE) 14 December 2006 (2006-12-14) claim 1 page 2, line 8 - line 14	1-24
A	WO 2007/101347 A1 (AEGERA THERAPEUTICS INC [CA]; JAQUITH JAMES [CA]) 13 September 2007 (2007-09-13) claim 1 page 5, line 12 - line 18	1-24

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 March 2013	26/03/2013

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

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

INTERNATIONAL SEARCH REPORT

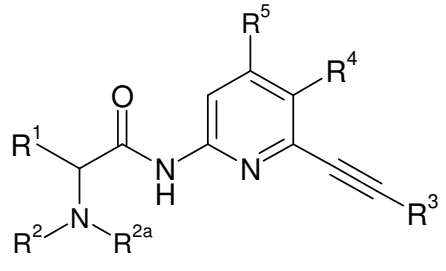
Information on patent family members

International application No
PCT/EP2013/053689

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008073306 A1	19-06-2008	AT 542798 T	15-02-2012
		AU 2007332862 A1	19-06-2008
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		WO 2008073306 A1	19-06-2008
WO 2006133147 A2	14-12-2006	AU 2006255084 A1	14-12-2006
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		WO 2006133147 A2	14-12-2006
WO 2007101347 A1	13-09-2007	NONE	

6-ALQUINILO PIRIDINAS COMO MIMÉTICOS SMAC

Esta invención se refiere a los compuestos de la fórmula general (I)



(I)

donde los grupos **R[1]** a **R[5]** tienen los significados en las reivindicaciones y en la memoria descriptiva. Los compuestos de la invención son adecuados para el tratamiento de las enfermedades caracterizadas por la proliferación celular excesiva o anormal, preparaciones farmacéuticos que contienen tales compuestos y sus usos como medicamento. Los compuestos de la invención modulan la actividad de IAP.

ANTECEDENTES DE LA INVENCIÓN

La apoptosis, una forma de muerte celular programada normalmente ocurre en el desarrollo y mantenimiento normal de los tejidos sanos en los organismos multicelulares. Es un proceso complejo, que produce la eliminación de células dañadas, enfermas o de desarrollo redundante, sin signos de inflamación o necrosis. En consecuencia la apoptosis se produce como una parte normal del desarrollo, el mantenimiento de la homeostasis celular normal, o como una consecuencia de estímulos tales como quimioterapia y radiación.

Se sabe que la vía apoptótica intrínseca está desregulada en cáncer y síndromes mieloproliferativos, así como en los trastornos autoinmunes tales como esclerosis múltiple y artritis reumatoide. En forma adicional, se han descripto alteraciones en una respuesta apoptótica del huésped en el desarrollo o mantenimiento de las infecciones virales o bacterianas. Las células cancerosas adquieren la capacidad de superar o evitar la apoptosis y continuar con la proliferación inapropiada a pesar de las señales pro-apoptóticas fuertes tales como hipoxia, citoquinas endógenas, tratamientos de radiación y quimioterapia. En las enfermedades autoinmunes, las células efectoras patogénicas pueden ser resistentes a las señales apoptóticas normales. La resistencia puede ser causada por numerosos mecanismos, que incluyen las alteraciones en la maquinaria apoptótica y debido al aumento de actividad de las vías anti-apoptóticas o la expresión de los genes f anti-apoptóticos. En

consecuencia, los métodos que reducen el umbral de la inducción apoptóticas en las células cancerosas mediante la superación de los mecanismos de resistencia pueden ser de utilidad clínica significativa.

Las caspasas sirven como moléculas efectoras en la señalización de la apoptosis. Las caspasas (proteasas específicas de aspartato que contienen cisteína) son proteasas fuertes y una vez activadas, digieren proteínas de las células vitales desde el interior de la célula. Debido a que las caspasas son proteasas muy activas, el control estricto de esta familia de proteínas es necesario para evitar la muerte celular programada. En general, las caspasas se sintetizan como zimógenos mayormente inactivos que requieren el procesamiento proteolítico para la activación. Este procesamiento proteolítico es una de las maneras en que se regulan las caspasas. El segundo mecanismo de regulación es a través de una familia de proteínas que se unen e inhiben a las caspasas.

Una familia de moléculas que inhiben las caspasas son los inhibidores de la apoptosis (IAP) (Deveraux et al., J Clin Immunol (1999), 19: 388-398). Los IAP se descubrieron en forma original en el baculovirus por sus capacidad para sustituir la función de la proteína P35, un gen anti-apoptótico (Crook et al. (1993) J Virology 67, 2168-2174). Los IAP humanos se caracterizan por la presencia de uno a tres dominios estructurales homólogos conocidos como dominios repetidos de IAP de baculovirus (BIR). Algunos miembros de la familia IAP también contienen un dominio de dedos de zinc RING en el extremo C-terminal, con la capacidad de ubiquitilar las proteínas blanco por medio de su función de E3 ligasa. Los IAP, XIAP, HIAP1 humano (también denominados como cIAP2), y HIAP2 (cIAP1) tienen cada uno tres dominios BIR y un dedo de zinc RING carboxi terminal. Otro IAP, NAIP, tiene tres dominios BIR (BIR1, BIR2 y BIR3), pero ningún dominio RING, mientras que Livin, TsIAP y MLIAP tienen un dominio BIR único y un dominio RING. El inhibidor de la apoptosis ligado al cromosoma X de apoptosis (XIAP) es un ejemplo de un IAP, que puede inhibir el iniciador de caspasa Caspasa-9, y las caspasas efectoras, Caspasa-3 y Caspasa-7, por la unión directa. XIAP también puede inducir la degradación de las caspasas a través de la vía de proteasoma mediada por ubiquitilación por medio de la actividad de E3 ligasa de un dominio de dedos de zinc RING. La inhibición de la Caspasa 9 está mediada por los dominios de BIR3 de XIAP, mientras que las caspasas efectoras son inhibidas por la unión al dominio del ligador BIR2. Los dominios BIR también median las interacciones de las IAP con el factor asociado con factor-receptor de necrosis tumoral (TRAF)-I y -2, y con TAB1, proteínas adaptadoras que afectan la señalización

de la supervivencia a través de la activación de NFkB. Las proteínas IAP en consecuencia pueden funcionar como frenos directos sobre la cascada de la apoptosis mediante la inhibición de las caspasas activas o por la redirección de la señalización celular a un modo de pro-supervivencia. La survivina es otro elemento de la familia IAP de la familia de proteínas antiapoptóticas. Se demuestra que la función se conserva a través de la evolución ya que se hallan homólogos de la proteína en vertebrados e invertebrados.

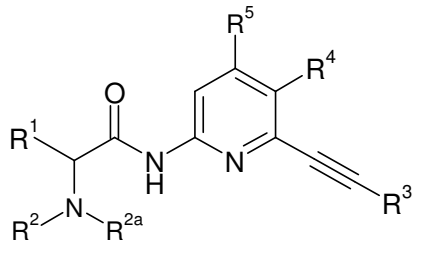
Las células cancerosas y las células involucradas en las enfermedades autoinmunes pueden evitar la apoptosis mediante la sobreexpresión sostenida de uno o más miembros de la familia IAP de las proteínas. Por ejemplo, la sobreexpresión IAP se ha demostrado que es pronóstico de peor evolución clínica en múltiples cánceres y la disminución de la expresión de IAP a través de estrategias de ARNi sensibiliza las células tumorales en una amplia variedad de lesiones apoptóticas que incluyen quimioterapia, radioterapia y ligandos del receptor de muerte. Para XIAP, esto se muestra en cánceres tan diversos como leucemia y cáncer ovárico. Se ha observado la sobre expresión de cIAP1 y cIAP2 resultante de la frecuente amplificación del cromosoma de la región 11q21-q23, que abarca ambos genes en una variedad de neoplasias, que incluyen meduloblastomas, carcinomas de células renales, glioblastomas, y carcinomas gástricos.

La interacción entre el dominio de la repetición 3 IAP baculoviral (BIR3) del inhibidor ligado a X de apoptosis (XIAP) y caspasa 9 es de interés terapéutico porque esta interacción es inhibida por los residuos de siete aminoácidos NH2-terminales del llamado “segundo activador derivado mitocondrial de caspasa” (en breve y de aquí en adelante Smac), un antagonista natural de los IAP. Se han generado miméticos Smac de molécula pequeña que anticipan la eficacia en el cáncer por la reconstitución de la señalización apoptótica.

En consecuencia, existe la necesidad de proporcionar miméticos SMAC útiles para la prevención y/o tratamiento de enfermedades caracterizadas por proliferación proliferación celular excesiva o anormal, tal como cáncer.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

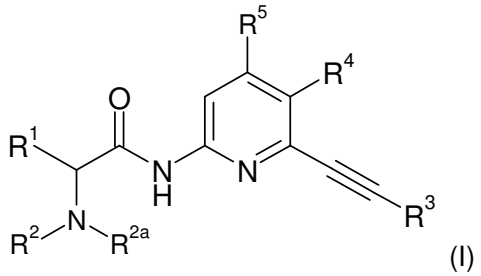
La presente invención se refiere a los compuestos de fórmula (**I**)



(**I**)

donde **R1** a **R5** son como se definen en la descripción y en las reivindicaciones. Los compuestos de acuerdo con la fórmula (I) actúan como miméticos Smac. En consecuencia, los compuestos de la invención se pueden usar por ejemplo para el tratamiento de las enfermedades que se caracterizan por un aumento del umbral de la apoptosis debido a la sobreexpresión de la proteína IAP. Con preferencia, los compuestos de la invención se pueden usar en el tratamiento del cáncer.

La presente invención en consecuencia se refiere a los compuestos de fórmula general (**I**)



(I)

donde

R1 es -H o -alquilo C_{1-5};

R2, **R2a** se seleccionan de modo independiente de -H o -alquilo C_{1-5} opcionalmente sustituido con uno o más -F;

R3 se selecciona de -arilo C_{6-10}, heteroarilo de 5-14 miembros, cada uno de estos grupos se puede sustituir en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R6**; o **R3** se selecciona de alquilo C_{1-6}, cicloalquilo -C_{4-7}, cicloalquenilo -C_{4-7}, o sistema anular aromático de 5-14 miembros, cada uno de estos grupos se puede sustituir en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R6a**;

R6 se selecciona de -CN, halógeno, alquilo -C1-3, -Oalquilo -C_{1-3}, -C(O)-**R12**, heteroarilo de 5-6 miembros, tal grupo heteroarilo de 5-6 miembros puede estar opcionalmente sustituido con alquilo -C_{1-3}; o **R6** es fenilo, tal fenilo puede estar opcionalmente sustituido con -Oalquilo -C_{1-3}

R6a se selecciona de =O, -CN, halógeno, alquilo -C_{1-3}, -Oalquilo -C_{1-3}, -C(O)-**R12**, heteroarilo de 5-6 miembros, tal grupo heteroarilo de 5-6 miembros

puede estar opcionalmente sustituido con alquilo -C_{1-3}; o **R^{6a}** es fenilo, tal fenilo puede estar opcionalmente sustituido con -Oalquilo -C_{1-3};

R^{12} se selecciona de -NH_2, -NHalquilo -C_{1-3}, heterociclilo de $_{5-7}$ miembros, o -Oalquilo -C_{1-3}, tales grupo alquilo -C_{1-3} pueden estar opcionalmente sustituido con un heterociclilo de $_{5-7}$ miembros;

R^4 se selecciona de -H, -arilo C_{6-10}, heteroarilo de 5-14 miembros, cada uno de tales grupos está sustituido en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^7** o **R^4** se selecciona de alquilo C_{1-6}, sistema anular aromático de 5-14 miembros, cicloalquilo -C_{5-7}, cada grupo está sustituido en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^{7a}**,

o **R^4** se selecciona de -N(**R^8**,**R^9**) donde

R^8, **R^9** se seleccionan de modo independiente de H, alquilo -C_{1-3}, -C(O)-**R^{10}** -$S(O)_2$-**R^{11}**

R^{10}, **R^{11}** se seleccionan de modo independiente de heterociclilo de $_{5-7}$ miembros, cicloalquilo -C_{5-7}, -arilo C_{6-10}, heteroarilo de 5-10 miembros;

R^7 se selecciona de -CN, halógeno, -CF_3, -NO_2, alquilo -C_{1-3}, -Salquilo -C_{1-3}, -NHalquilo -C_{1-3}, -N(C_{1-3}alquil)$_2$, -NHC(O)alquilo -C_{1-3}, -C(O)-**R^{13}**, -Oalquilo -C_{1-3}, heteroarilo de 5-14 miembros, -O-fenilo, -CH_2-fenilo, fenilo, tal grupo fenilo puede estar opcionalmente sustituido con halógeno, o heterociclilo de 5-6 miembros, tal heterociclilo de 5-6 miembros puede estar opcionalmente sustituido con alquilo -C_{1-3};

R^{7a} se selecciona de =O, -CN, halógeno, -CF_3, -NO_2, alquilo -C_{1-3}, -Salquilo -C_{1-3}, -NHalquilo -C_{1-3}, -N(alquilo C_{1-3})$_2$, -NHC(O)alquilo -C_{1-3}, -C(O)-**R^{13}**, -Oalquilo -C_{1-3}, heteroarilo de 5-14 miembros, -O-fenilo, -CH_2-fenilo, fenilo, tal grupo fenilo puede estar opcionalmente sustituido con halógeno, o heterociclilo de 5-6 miembros, tal heterociclilo de 5-6 miembros puede estar opcionalmente sustituido con alquilo -C_{1-3}; donde

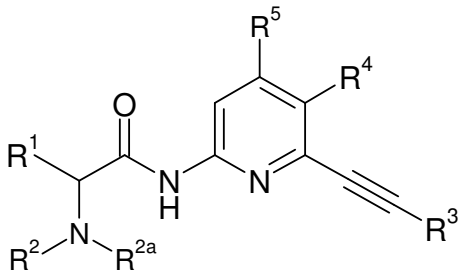
R^{13} se selecciona de -OH, -NH_2, -NHalquilo -C_{1-3}, alquilo -C_{1-3};

R^5 se selecciona de -H, halógeno, alquilo -C_{1-3}, -Oalquilo -C_{1-3}, tales grupo alquilo -C_{1-3} puede estar opcionalmente sustituido con uno o más halógeno;

o **R^4** y **R^5** tomados entre sí forman un -arilo C_{6-10} o heteroarilo de 5-14 miembros,

y donde los compuestos de fórmula (I) opcionalmente puede estar presentes en la forma de sales.

En una forma de realización preferida la invención se refiere a los compuestos de fórmula (**I**),



(I)

donde

R^1 es -H o -alquilo C_{1-5};

R^2, **R^{2a}** se seleccionan de modo independiente de -H o -alquilo C_{1-5} opcionalmente sustituido con uno o más -F;

R^3 se selecciona de -arilo C_{6-10}, heteroarilo de 5-14 miembros, cada uno de estos grupos se puede sustituir en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^6**; o **R^3** se selecciona de alquilo C_{1-6}, cicloalquilo -C_{4-7}, cicloalquenilo -C_{4-7}, o sistema anular aromático de 5-14 miembros, cada uno de estos grupos se puede sustituir en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^{6a}**;

R^6 se selecciona de -CN, halógeno, alquilo -C_{1-3}, -Oalquilo -C_{1-3}, -C(O)-**R^{12}**, heteroarilo de 5-6 miembros, tal grupo heteroarilo de 5-6 miembros puede estar opcionalmente sustituido con alquilo -C_{1-3}; o **R^6** es fenilo, tal fenilo puede estar opcionalmente sustituido con -Oalquilo -C_{1-3}

R^{6a} se selecciona de =O, -CN, halógeno, alquilo -C_{1-3}, -Oalquilo -C_{1-3}, -C(O)-**R^{12}**, heteroarilo de 5-6 miembros, tal grupo heteroarilo de 5-6 miembros puede estar opcionalmente sustituido con alquilo -C_{1-3}; o **R^{6a}** es fenilo, tal fenilo puede estar opcionalmente sustituido con -Oalquilo -C_{1-3};

R^{12} se selecciona de -NH_2, -NHalquilo -C_{1-3}, heterociclilo no aromático de $_{5-7}$ miembros, o -Oalquilo -C_{1-3}, tales grupo alquilo -C_{1-3} puede estar opcionalmente sustituido con a heterociclilo no aromático de $_{5-7}$ miembros;

R^4 se selecciona de -H, -arilo C_{6-10}, heteroarilo de 5-14 miembros, cada uno de tales grupos está sustituido en forma opcional e independiente con

uno o más, seleccionados de modo independiente, **R[7]**, o **R[4]** se selecciona de alquilo C_{1-6}, sistema anular aromático de 5-14 miembros, cicloalquilo -C_{5-7}, cada grupo está sustituido en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R[7a]**,

o **R[4]** se selecciona de -N(**R[8]**,**R[9]**) donde

R[8], **R[9]** se seleccionan de modo independiente de H, alquilo -C_{1-3}, -C(O)-**R[10]** -$S(O)_2$-**R[11]**

R[10], **R[11]** se seleccionan de modo independiente de heterociclilo no aromático de 5-7 miembros, cicloalquilo -C_{5-7}, -arilo C_{6-10}, heteroarilo de 5-10 miembros;

R[7] se selecciona de -CN, halógeno, -CF_3, -NO_2, alquilo -C_{1-3}, -Salquilo -C_{1-3}, -NHalquilo -C_{1-3}, -N(C_{1-3}alquil)$_2$, -NHC(O)alquilo -C_{1-3}, -C(O)-**R[13]**, -Oalquilo -C_{1-3}, heteroarilo de 5-14 miembros, -O-fenilo, -CH_2-fenilo, fenilo, cada uno del grupo fenilo puede estar opcionalmente sustituido con halógeno, o heterociclilo no aromático de 5-6 miembros, tal heterociclilo no aromático de 5-6 miembros puede estar opcionalmente sustituido con alquilo -C_{1-3};

R[7a] se selecciona de =O, -CN, halógeno, -CF_3, -NO_2, alquilo -C_{1-3}, -Salquilo -C_{1-3}, -NHalquilo -C_{1-3}, -N(alquilo C_{1-3})$_2$, -NHC(O)alquilo -C_{1-3}, -C(O)-**R[13]**, -Oalquilo -C_{1-3}, heteroarilo de 5-14 miembros, -O-fenilo, -CH_2-fenilo, fenilo, cada uno del grupo fenilo puede estar opcionalmente sustituido con halógeno, o heterociclilo no aromático de 5-6 miembros, tal heterociclilo no aromático de 5-6 miembros puede estar opcionalmente sustituido con alquilo -C_{1-3}; donde

R[13] se selecciona de -OH, -NH_2, -NHalquilo -C_{1-3}, alquilo -C_{1-3};

R[5] se selecciona de -H, halógeno, alquilo -C_{1-3}, -Oalquilo -C_{1-3}, tales grupo alquilo -C_{1-3} puede estar opcionalmente sustituido con uno o más halógeno;

o **R[4]** y **R[5]** tomados entre sí forman un -arilo C_{6-10} o heteroarilo de 5-14 miembros,

y donde los compuestos de fórmula (I) opcionalmente puede estar presentes en la forma de sales.

En una forma de realización preferida la invención se refiere a los compuestos

de fórmula (**I**), donde **R^1** se selecciona de -CH_3, -CH_2-CH_3.

En una forma de realización preferida la invención se refiere a los compuestos de fórmula (**I**), donde **R^2** y **R^{2a}** se seleccionan de modo independiente de -H, -CH_3, -CH_2-CH_3. -CH-$(CH_3)_2$, -$(CH_2)_2$-CH_3.

en una forma de realización preferida la invención se refiere a los compuestos de fórmula (**I**), donde **R^5** se selecciona de -H, -Cl, -F, -CF_3, -OCH_3, -CH_3.

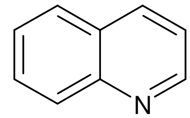
En una forma de realización preferida la invención se refiere a los compuestos de fórmula (**I**), donde **R^3** se selecciona de -arilo C_{6-10}, heteroarilo de 5-14 miembros, -CH_2-fenilo, -cicloalquenilo C_{5-7}, sistema anular aromático de 5-14 miembros, cada uno de estos grupos se puede sustituir en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^6** o **R^{6a}** como se define en las reivindicaciones y la descripción.

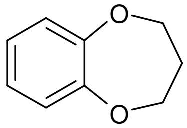
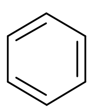
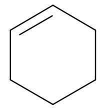
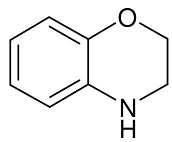
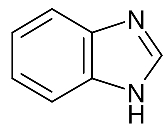
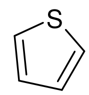
En una forma de realización preferida la invención se refiere a los compuestos de fórmula (**I**), donde **R^3** se selecciona de -arilo C_{6-10}, heteroarilo de 5-14 miembros, cada uno de estos grupos se puede sustituir en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^6**, o **R^3** se selecciona de-cicloalquenilo C_{5-7}, sistema anular aromático de 5-14 miembros, cada uno de estos grupos se puede sustituir en forma opcional e independiente con uno o más, seleccionados de modo independiente **R^{6a}**, o **R^3** es -CH_2-fenilo, tal fenilo puede estar opcionalmente sustituido con -Oalquilo -C_{1-3}, y donde **R^6** y **R^{6a}** son como se definen en las reivindicaciones y la descripción.

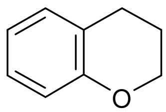
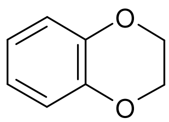
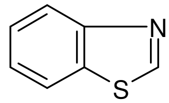
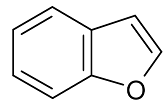
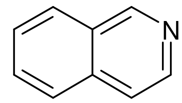
En una forma de realización preferida la invención se refiere a los compuestos de fórmula (**I**), donde **R^3** se selecciona de -arilo C_{6-10}, heteroarilo de 5-14 miembros, sistema anular aromático de 5-14 miembros, tales grupos pueden estar sustituidos en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^6** o **R^{6a}** como se define en las reivindicaciones y la descripción.

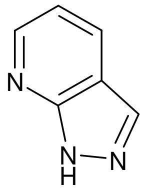
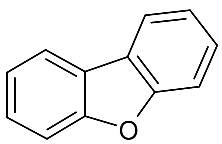
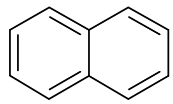
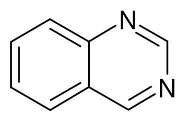
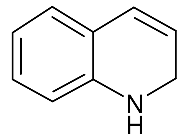
En una forma de realización preferida la invención se refiere a los compuestos de fórmula (**I**), donde **R^3** se selecciona de arilo C_{6-10}, heteroarilo de 5-14 miembros, cada uno de estos grupos se puede sustituir en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^6**, o **R^3** se selecciona de sistema anular aromático de 5-14 miembros, tales grupos pueden estar sustituidos en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^{6a}**, donde **R^6** y **R^{6a}** son como se definen en las reivindicaciones y la descripción.

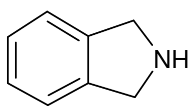
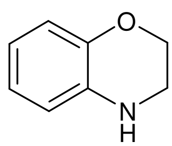
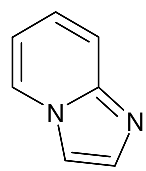
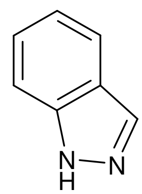
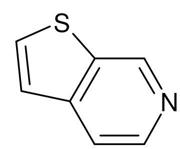
En una forma de realización preferida la invención se refiere a los compuestos

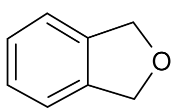
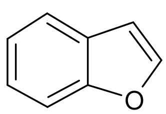
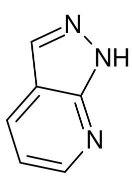
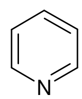
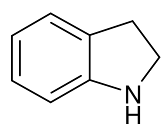
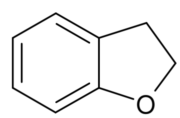
de fórmula (**I**), donde $\mathbf{R^3}$ se selecciona de $–CH_2$-fenilo,  ;

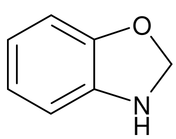
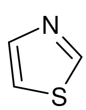
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 ;  cada grupo está opcionalmente sustituido como se define en las reivindicaciones y la descripción.

En una forma de realización preferida la invención se refiere a los compuestos de fórmula (**I**), donde $\mathbf{R^4}$ se selecciona de -H, alquilo C_{1-6}, -arilo C_{6-10}, heteroarilo de 5-14 miembros, sistema anular aromático de 5-14 miembros, cicloalquilo $-C_{5-7}$, cada grupo está sustituido en forma opcional e independiente con uno o más, seleccionados de modo independiente, $\mathbf{R^7}$ o $\mathbf{R^{7a}}$ como se define en la reivindicación 1, o $\mathbf{R^4}$ se selecciona de -N($\mathbf{R^8}$,$\mathbf{R^9}$), donde $\mathbf{R^8}$ y $\mathbf{R^9}$ son como se definen en las reivindicaciones y la descripción.

En una forma de realización preferida la invención se refiere a los compuestos de fórmula (**I**), donde **R^4** se selecciona de -H, -arilo C_{6-10}, heteroarilo de 5-14 miembros, cada grupo está sustituido en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^7**,

o **R^4** se selecciona de alquilo C_{1-6}, sistema anular aromático de 5-14 miembros y cicloalquilo -C_{5-7}, cada grupo está sustituido en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^{7a}**, o **R^4** se selecciona de -N(**R^8**,**R^9**), donde **R^7**, **R^{7a}**, **R^8** y **R^9** son como se definen en las reivindicaciones y en la descripción.

En una forma de realización preferida la invención se refiere a los compuestos de fórmula (**I**), donde **R^4** se selecciona de -arilo C_{6-10}, heteroarilo de 5-14 miembros, sistema anular aromático de 5-14 miembros, cicloalquilo -C_{5-7}, cada grupo está sustituido en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^7** o **R^{7a}** como se define en la descripción y las reivindicaciones, o **R^4** se selecciona de -N(**R^8**,**R^9**), donde **R^8** y **R^9** son como se definen en las reivindicaciones y la descripción.

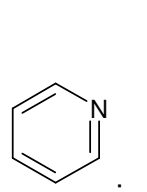
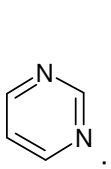
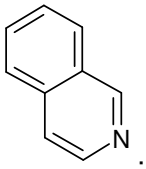
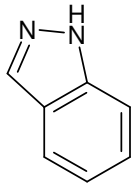
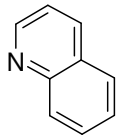
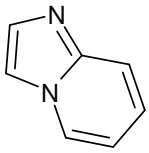
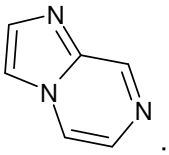
En una forma de realización preferida la invención se refiere a los compuestos de fórmula (**I**), donde **R^4** se selecciona de -arilo C_{6-10}, heteroarilo de 5-14 miembros, cada grupo está sustituido en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^7**, o **R^4** se selecciona de sistema anular aromático de 5-14 miembros, cicloalquilo -C_{5-7}, cada grupo está sustituido en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^{7a}** o **R^4** se selecciona de -N(**R^8**,**R^9**), donde **R^7**, **R^{7a}**, **R^8** y **R^9** son como se definen en las reivindicaciones y en la descripción.

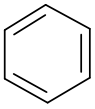
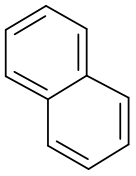
En una forma de realización preferida la invención se refiere a los compuestos de fórmula (**I**), donde **R^4** se selecciona de -arilo C_{6-10}, heteroarilo de 5-14 miembros, sistema anular aromático de 5-14 miembros, cada grupo está sustituido en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^7** o **R^{7a}** como se define en las reivindicaciones y la descripción.

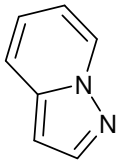
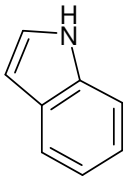
En una forma de realización preferida la invención se refiere a los compuestos de fórmula (**I**), donde **R^4** se selecciona de -arilo C_{6-10}, heteroarilo de 5-14 miembros, cada grupo está sustituido en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^7**, o **R^4** es el sistema anular aromático de 5-14 miembros, cada grupo está sustituido en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^{7a}**,donde **R^7** y **R^{7a}** son como se definen

en las reivindicaciones y en la descripción.

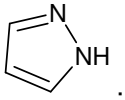
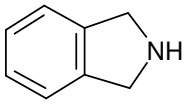
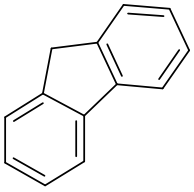
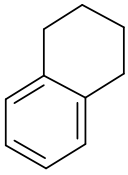
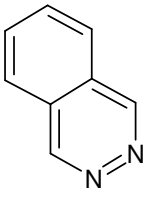
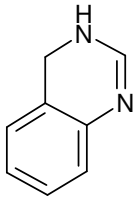
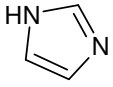
En una forma de realización preferida la invención se refiere a los compuestos de fórmula (**I**), donde **R^4** se selecciona de –H, alquilo -C_{1-3}, -CH_2-fenilo, -N(CH_3)-SO_2-fenilo, -N(CH_3)CO-**R^{10}**; -NH-CO-**R^{10}**, donde **R^{10}** se selecciona de modo independiente de morfolina, ciclopentilo, fenilo, o **R^4** se selecciona de


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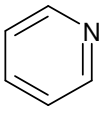
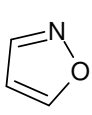
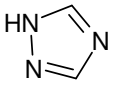
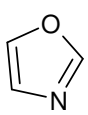
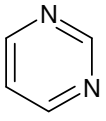
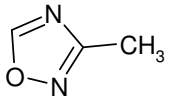
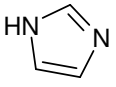
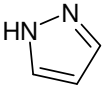
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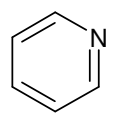
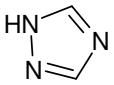
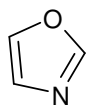
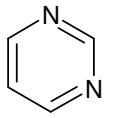
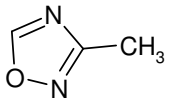
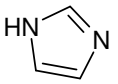
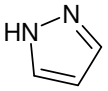
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; cada uno de tales grupos está opcionalmente sustituido como se define en las reivindicaciones y la descripción.

En una forma de realización preferida la invención se refiere a los compuestos de fórmula (**I**), donde **R^6** se selecciona de -F, -Cl, -CN -CH_3, -O-CH_3, -C(O)NHCH_3, -C(O)NH_2, C(O)OCH_3, -C(O)-morfolinilo, -C(O)-O-CH_2-tetrahidropirano, fenilo,

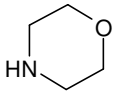
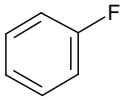
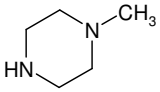
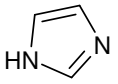

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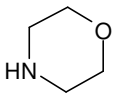
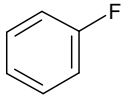
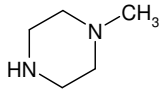
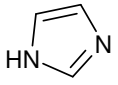
En una forma de realización preferida la invención se refiere a los compuestos de fórmula (**I**), donde **R^{6a}** se selecciona de =O, -F, -Cl, -CN -CH_3, -O-CH_3,

-C(O)NHCH$_3$, -C(O)NH$_2$, C(O)OCH$_3$, -C(O)-morfolinilo, -C(O)-O-CH$_2$-tetrahidropirano, fenilo,

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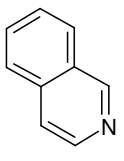
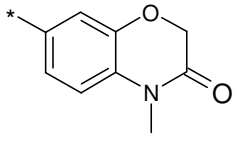
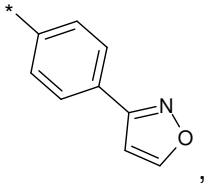
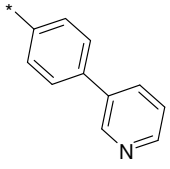
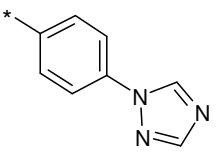
En una forma de realización preferida la invención se refiere a los compuestos de fórmula (**I**), donde **R^7** se selecciona de -CN, -F, -Cl, -CF$_3$, -NO$_2$, -CH$_3$, -CH$_2$CH$_3$, -CH$_2$(CH$_3$)$_2$, -S-CH$_3$, -NH$_2$, -NH-CH$_3$, -N(CH$_3$)$_2$, -C(O)OH, -C(O)OCH$_3$, -C(O)NH$_2$, -C(O)NH-CH$_3$, -NHC(O)CH$_3$, -O-CH$_3$, -O-CH$_2$CH$_3$, piridilo, fenilo, -O-Fenilo, -CH$_2$-fenilo,

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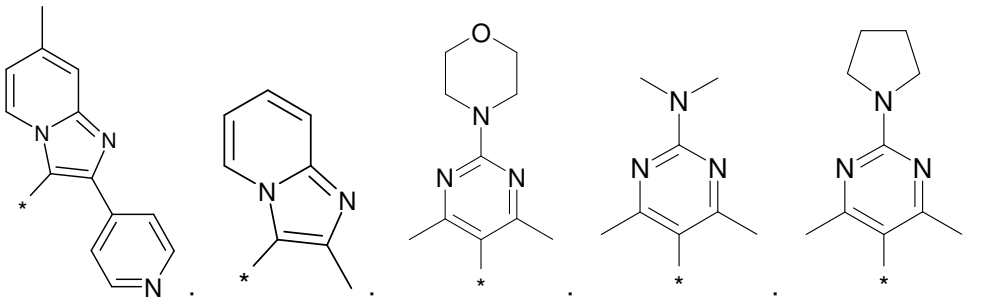
En una forma de realización preferida la invención se refiere a los compuestos de fórmula (**I**), donde **R^{7a}** se selecciona de =O, -CN, -F, -Cl, -CF$_3$, -NO$_2$, -CH$_3$, -CH$_2$CH$_3$, -CH$_2$(CH$_3$)$_2$, -S-CH$_3$, -NH$_2$, -NH-CH$_3$, -N(CH$_3$)$_2$, -C(O)OH, -C(O)OCH$_3$, -C(O)NH$_2$, -C(O)NH-CH$_3$, -NHC(O)CH$_3$, -O-CH$_3$, -O-CH$_2$CH$_3$, piridilo, fenilo, -O-Fenilo, -CH$_2$-fenilo,  ,  ,  ,  ,  .

En una forma de realización preferida la invención se refiere a los compuestos de fórmula (**I**), donde **R^4** y **R^5** tomados entre sí forman un fenilo.

En una forma de realización preferida la invención se refiere a los compuestos de fórmula (**I**), donde **R^3** se selecciona de

 ,  ,  ,  , y  .

En una forma de realización preferida la invención se refiere a los compuestos de fórmula (**I**), donde **R^4** se selecciona de



En otro aspecto la invención se refiere a los compuestos de fórmula general **(I)** o de alguna de las formas de realización que se describieron anteriormente para usar en el tratamiento de cáncer.

En otro aspecto la invención se refiere a los compuestos de fórmula general **(I)** o de alguna de las formas de realización que se describieron anteriormente – o sus sales farmacéuticamente aceptables – como medicamentos.

En otro aspecto la invención se refiere a los compuestos de fórmula general **(I)** o de alguna de las formas de realización que se describieron anteriormente – o sus sales farmacéuticamente aceptables – para usar en el tratamiento y/o prevención de cáncer, infecciones, inflamaciones y enfermedades autoinmunes.

En otro aspecto la invención se refiere a los compuestos de fórmula general **(I)** o de alguna de las formas de realización que se describieron anteriormente – o sus sales farmacéuticamente aceptables – para usar en el tratamiento y/o prevención de cáncer, con preferencia de carcinomas de mama, próstata, cerebro u ovario, carcinomas bronquiales de células no pequeñas (NSCLC), melanomas y leucemias linfáticas crónicas (CLL).

En otro aspecto la invención se refiere a los compuestos de fórmula general **(I)** o de alguna de las formas de realización que se describieron anteriormente – o sus sales farmacéuticamente aceptables – para usar en el tratamiento y/o prevención de carcinomas de mama, próstata, cerebro o ovario, carcinomas bronquiales de células no pequeñas (NSCLC), melanomas y leucemias linfáticas crónicas (CLL).

En otro aspecto la invención se refiere a un método para el tratamiento y/o prevención de cáncer que comprende la administración de una cantidad terapéuticamente efectiva de un compuesto de fórmula general **(I)** o de alguna de las formas de realización que se describieron anteriormente – o una de sus sales farmacéuticamente aceptables – a un ser humano.

En otro aspecto, la invención se refiere a un método para el tratamiento y/o

prevención de carcinoma de mama, próstata, cerebro u ovario, carcinomas bronquiales de células no pequeñas (NSCLC), melanomas y leucemias linfáticas crónicas (CLL), que comprende la administración de una cantidad terapéuticamente efectiva de un compuesto de fórmula general **(I)** o de alguna de las formas de realización que se describieron anteriormente – o una de sus sales farmacéuticamente aceptables – a un ser humano.

En otro aspecto la invención se refiere a una preparación farmacéutica que contiene como sustancia activa uno o más compuestos de fórmula general **(I)** o de alguna de las formas de realización que se describieron anteriormente – o sus sales farmacéuticamente aceptables – opcionalmente en combinación con excipientes y/o portadores convencionales.

En otro aspecto la invención se refiere a a preparación farmacéutica que comprende un compuesto de fórmula general **(I)** o de alguna de las formas de realización que se describieron anteriormente – o una de sus sales farmacéuticamente aceptables – y al menos una sustancia activa citostática o citotóxica diferente de la fórmula **(I)**.

Definiciones

Los términos que no se definen específicamente en la presente tienen los significados que son evidentes para los expertos a la luz de la descripción total y el contexto en su conjunto.

Como se usa en la presenten, se aplican las siguientes definiciones, a menos que se indique de otro modo:

En los grupos, radicales, o restos definidos a continuación, el número de átomos de carbono a menudo se especifica antes del grupo, por ejemplo -alquilo C_{1-5} significa un grupo o radical alquilo que tiene 1 a 5 átomos de carbono. En general, en los grupos que comprenden dos o más subgrupos, el primer subgrupo nombrado es el punto de unión del radical, por ejemplo el sustituyente -alquilo C_{1-5}-cicloalquilo C_{3-10}, significa un grupo cicloalquilo C_{3-10} que se une a un alquilo C_{1-5}, el último de los cuales se une a la estructura central o al grupo al que se une el sustituyente.

La indicación del número de los elementos de los grupos que contienen uno o más heteroátomos) (heteroalquilo, heteroarilo, heteroarilalquilo, heterociclilo, heterociclialquil) se refiere al número atómico total de todos los miembros anulares o miembros de la cadena el total de los miembros anulares y de cadena.

Los expertos en la técnica apreciarán que los grupos sustituyentes que

contienen un átomo de nitrógeno también se pueden indicar como **amina** o **amino**. De modo similar, los grupos que contienen el átomo de oxígeno también se pueden indicar con **-oxi**, como por ejemplo **alcoxi**. Los grupos que contienen –C(O)- también se pueden indicar como **carboxi**; los grupos que contienen -NC(O)- también se pueden indicar como **amida**; los grupos que contienen –NC(O)N- también se pueden indicar como **urea**; los grupos que contienen $–NS(O)_2-$ también se pueden indicar como **sulfonamida.**

Alquilo indica cadenas hidrocarbonatos saturados monovalentes, que pueden estar presentes en forma lineal y ramificada. Si un **alquilo** está sustituido, la sustitución puede ocurrir de modo independiente entre sí, por mono- o polisustitución en cada caso, en todo los átomos de carbono portadores de hidrógeno.

El término "**alquilo C_{1-5}**" incluye por ejemplo metilo (Me; $-CH_3$), etilo (Et; $-CH_2CH_3$), 1-propilo (*n*-propilo; *n*-Pr; $-CH_2CH_2CH_3$), 2-propilo (*i*-Pr; *iso*-propilo; $-CH(CH_3)_2$), 1-butilo (*n*-butilo; *n*-Bu; $-CH_2CH_2CH_2CH_3$), 2-metil-1-propilo (*iso*-butilo; *i*-Bu; $-CH_2CH(CH_3)_2$), 2-butilo (*sec*-butilo; *sec*-Bu; $-CH(CH_3)CH_2CH_3$), 2-metil-2-propilo (*ter*-butilo; *t*-Bu; $-C(CH_3)_3$), 1-pentilo (*n*-pentilo; $-CH_2CH_2CH_2CH_2CH_3$), 2-pentilo ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentilo ($-CH(CH_2CH_3)_2$), 3-metil-1-butilo (*iso*-pentilo; $-CH_2CH_2CH(CH_3)_2$), 2-metil-2-butilo ($-C(CH_3)_2CH_2CH_3$), 3-metil-2-butil ($-CH(CH_3)CH(CH_3)_2$), 2,2-dimetil-1-propilo (*neo*-pentilo; $-CH_2C(CH_3)_3$), 2-metil-1-butilo ($-CH_2CH(CH_3)CH_2CH_3$).

Por los términos propilo, butilo, pentilo, etc, sin ninguna definición adicional se entienden grupos hidrocarbonados saturados con el correspondiente número de átomos de carbono, donde se incluyen todas las formas isoméricas.

La definición anterior para **alquilo** también se aplica si **alquilo** es una parte de otro grupo tal como por ejemplo alquil Cx-yamino o alquil Cx-yoxi o alcoxi Cx-y, donde alquil Cx-yoxi y alcoxi Cx-y indican el mismo grupo.

El término **alquileno** también puede derivar de **alquilo**. A**lquileno** es bivalente, a diferencia de **alquilo,** y requiere dos compañeros de unión. Formalmente, la segunda valencia se produce por la eliminación de un átomo de hidrógeno en un **alquilo**. Los correspondientes grupos son por ejemplo $-CH_3$ y $-CH_2$, $-CH_2CH_3$ y $-CH_2CH_2$ o $>CHCH_3$ etc.

El término "**alquileno C_{1-4}**" incluye por ejemplo $-(CH_2)-$, $-(CH_2-CH_2)-$, $-(CH(CH_3))-$, $-(CH_2-CH_2-CH_2)-$, $-(C(CH_3)_2)-$, $-(CH(CH_2CH_3))-$, $-(CH(CH_3)-CH_2)-$, $-(CH_2-CH(CH_3))-$, $-(CH_2-CH_2-CH_2-CH_2)-$, $-(CH_2-CH_2-CH(CH_3))-$, $-(CH(CH_3)-CH_2-CH_2)-$, $-(CH_2-CH(CH_3)-CH_2)-$, $-(CH_2-C(CH_3)_2)-$, $-(C\ (CH_3)_2-CH_2)-$, $-(CH(CH_3)-CH(CH_3))-$, $-(CH_2-$

$CH(CH_2CH_3))$-, -$(CH(CH_2CH_3)$-$CH_2)$-, -$(CH(CH_2CH_2CH_3))$-, -$(CHCH(CH_3)_2)$- y -$C(CH_3)(CH_2CH_3)$-.

Otros ejemplos de **alquileno son** metileno, etileno, propileno, 1-metiletileno, butileno, 1-metilpropileno, 1,1-dimetiletileno, 1,2-dimetiletileno, pentileno, 1,1-dimetilpropileno, 2,2-dimetilpropileno, 1,2-dimetilpropileno, 1,3-dimetilpropileno, etc.

Por los términos genéricos propileno, butileno, pentileno, hexileno etc. sin ninguna otra definición se entiende todas las formas isoméricas concebibles con el correspondiente número de átomos de carbono, es decir, propileno incluye 1-metiletileno y butileno incluye 1-metilpropileno, 2-metilpropileno, 1,1-dimetiletileno y 1,2-dimetiletileno.

La definición anterior para **alquileno** también se aplica si el **alquileno** es parte de otro grupo tal como por ejemplo en HO-alquilen Cx-y amino o H_2N-alquilen Cx-y oxi.

A diferencia de **alquilo, alquenilo** consiste en al menos dos átomos de carbono, donde al menos dos átomos de carbono adyacentes se unen entre sí mediante un enlace C-C. Si un **alquilo** como se definió anteriormente en la presente que tiene al menos dos átomos de carbono, dos átomos de hidrógeno en átomos adyacentes de carbono se eliminan formalmente y las valencias libres se saturan para formar un segundo enlace, se forma el correspondiente **alquenilo**.

Los ejemplos de **alquenilo son** vinilo (etenilo), prop-1-enilo, alilo (prop-2-enilo), isopropenilo, but-1-enilo, but-2-enilo, but-3-enilo, 2-metil-prop-2-enilo, 2-metil-prop-1-enilo, 1-metil-prop-2-enilo, 1-metil-prop-1-enilo, 1-metilidenepropilo, pent-1-enilo, pent-2-enilo, pent-3-enilo, pent-4-enilo, 3-metil-but-3-enilo, 3-metil-but-2-enilo, 3-metil-but-1-enilo, hex-1-enilo, hex-2-enilo, hex-3-enilo, hex-4-enilo, hex-5-enilo, 2,3-dimetil-but-3-enilo, 2,3-dimetil-but-2-enilo, 2-metilidene-3-metilbutilo, 2,3-dimetil-but-1-enilo, hexa-1,3-dienilo, hexa-1,4-dienilo, penta-1,4-dienilo, penta-1,3-dienilo, buta-1,3-dienilo, 2,3-dimetilbuta-1,3-dieno etc.

Por los términos genéricos propenilo, butenilo, pentenilo, hexenilo, butadienilo, pentadienilo, hexadienilo, heptadienilo, octadienilo, nonadienilo, decadienilo etc. sin ninguna otra definición se entienden todas las formas isoméricas concebibles con el correspondiente número de átomos de carbono, es decir, propenilo incluye prop-1-enilo y prop-2-enilo, butenilo incluye but-1-enilo, but-2-enilo, but-3-enilo, 1-metil-prop-1-enilo, 1-metil-prop-2-enilo etc.

Alquenilo opcionalmente puede estar presente en la orientación *cis* o *trans* o *E* o *Z* con respecto a los enlaces dobles.

La definición anterior para **alquenilo** también se aplica cuando el **alquenilo** es

parte de otro grupo tal como por ejemplo en **alquenil** C_{x-y}-amino o **alquenil** C_{x-y}-oxi.

A diferencia de **alquileno,** **alquenileno** consiste en al menos dos átomos de carbono, donde al menos dos átomos adyacentes de carbono se unen entre sí mediante un enlace doble C-C. Si un **alquileno** como se definió anteriormente en la presente que tiene al menos dos átomos de carbono, dos átomos de hidrógeno en átomos adyacentes de carbono se eliminan formalmente y las valencias libres se saturar para formar un segundo enlace, se forme el correspondiente **alquenileno**.

Los ejemplos de **alquenileno** son etenileno, propenileno, 1-metiletenileno, butenileno, 1-metilpropenileno, 1,1-dimetiletenileno, 1,2-dimetiletenileno, pentenileno, 1,1-dimetilpropenileno, 2,2-dimetilpropenileno, 1,2-dimetilpropenileno, 1,3-dimetilpropenileno, hexenileno etc.

Por los términos genéricos propenileno, butenileno, pentenileno, hexenileno etc. sin ninguna otra definición se entienden todas las formas isoméricas concebibles con el correspondiente número de átomos de carbono, es decir, propenileno incluye 1-metiletenileno y butenileno incluye 1-metilpropenileno, 2-metilpropenileno, 1,1-dimetiletenileno y 1,2-dimetiletenileno.

Alquenileno opcionalmente puede estar presente en la orientación *cis* o *trans* o *E* o *Z* con respecto a los enlaces dobles.

La definición anterior para **alquenileno** también se aplica cuando **alquenileno** es una parte de otro grupo como en por ejemplo HO-alquenilen Cx-y-amino o H_2N-alquenilen Cx-y-oxi.

a diferencia de **alquilo,** **alquinilo** consiste en al menos dos átomos de carbono, donde al menos dos átomos adyacentes de carbono se unen entre sí mediante un enlace triple C-C. Si en un **alquilo** como se definió anteriormente en la presente que tiene al menos dos átomos de carbono, dos átomos de hidrógeno en cada caso, los átomos adyacentes de carbono se eliminan formalmente y las valencias libres se saturan para formar dos enlaces adicionales, se forma el correspondiente **alquinilo**.

Los ejemplos de **alquinilo** son etinilo, prop-1-inilo, prop-2-inilo, but-1-inilo, but-2-inilo, but-3-inilo, 1-metil-prop-2-inilo, pent-1-inilo, pent-2-inilo, pent-3-inilo, pent-4-inilo, 3-metil-but-1-inilo.

Por los términos genéricos propinilo, butinilo, pentinilo, etc. sin ninguna otra definición se entienden todas las formas isoméricas concebibles con el correspondiente número de átomos de carbono, es decir, propinilo incluye prop-1-inilo y prop-2-inilo, butinilo incluye but-1-inilo, but-2-inilo, but-3-inilo, 1-metil-prop-1-inilo, 1-

metil-prop-2-inilo.

Si una cadena hidrocarbonada porta al menos un enlace doble y también al menos un enlace triple, por definition pertenece al subgrupo **alquinilo**.

La definición anterior para **alquinilo** también se aplica si **alquinilo** es parte de otro grupo, como en alquinil Cx-y-amino o alquinil Cx-y-oxi, por ejemplo.

A diferencia de **alquileno, alquinileno** consiste en al menos dos átomos de carbono, donde al menos dos átomos adyacentes de carbono se unen entre sí mediante un enlace triple C-C. Si un **alquileno** como se definió anteriormente en la presente que tiene al menos dos átomos de carbono, dos átomos de hidrógeno en caso en átomos adyacentes de carbono se eliminan formalmente y las valencias libres están saturadas para formar dos enlaces adicionales, se forma el correspondiente **alquinileno.**

Los ejemplos de **alquinileno** son etinileno, propinileno, 1-metiletinileno, butinileno, 1-metilpropinileno, 1,1-dimetiletinileno, 1,2-dimetiletinileno, pentinileno, 1,1-dimetilpropinileno, 2,2-dimetilpropinileno, 1,2-dimetilpropinileno, 1,3-dimetilpropinileno, hexinileno etc.

Por los términos genéricos propinileno, butinileno, pentinileno, ect. sin ninguna otra definición se entienden todas las formas isoméricas concebibles con el correspondiente número de átomos de carbono, es decir, propinileno incluye 1-metil-etinileno y butinileno incluye 1-metilpropinileno, 2-metilpropinileno, 1,1-dimetiletinileno y 1,2-dimetiletinileno.

La definición anterior para **alquinileno** también se aplica si el **alquinileno** es parte de otro grupo, como por ejemplo, en HO-alquinilen Cx-y-amino o H_2N-alquinilen Cx-y-oxi.

Por **heteroátomos** se entienden átomos de oxígeno, nitrógeno y azufre.

Haloalquilo (haloalquenilo, haloalquinilo) se deriva del **alquilo** previamente definido **(alquenilo, alquinilo)** por el reemplazo de uno o más átomos de hidrógeno de la cadena hidrocarbonada de modo independiente entre sí por átomos de halógeno, que pueden ser idénticos o diferentes. Si un **haloalquilo (haloalquenilo, haloalquinilo)** también se debe sustituir, las sustituciones pueden ocurrir de modo independiente entre sí, en la forma de mono- o polisustituciones en cada caso, en todos los átomos de carbono portadores de hidrógeno.

Los ejemplos de **haloalquilo (haloalquenilo, haloalquinilo)** son $-CF_3$, $-CHF_2$, $-CH_2F$, $-CF_2CF_3$, $-CHFCF_3$, $-CH_2CF_3$, $-CF_2CH_3$, $-CHFCH_3$, $-CF_2CF_2CF_3$, $-CF_2CH_2CH_3$, $-CF=CF_2$, $-CCl=CH_2$, $-CBr=CH_2$, $-CI=CH_2$, $-C\equiv C-CF_3$, $-CHFCH_2CH_3$, $-CHFCH_2CF_3$ etc.

A partir del previamente definido **haloalquilo (haloalquenilo, haloalquinilo)** también derivan los términos **haloalquileno (haloalquenileno, haloalquinileno)**. **Haloalquileno (haloalquenilo, haloalquinilo)**, a diferencia de **haloalquilo,** es bivalente y requiere dos compañeros de unión. Formalmente, la segunda valencia se forma mediante la eliminación de un átomo de hidrógeno de un **haloalquilo**.

Los grupos correspondientes son por ejemplo $-CH_2F$ y -CHF-, $-CHFCH_2F$ y -CHFCHF- o $>CFCH_2F$ etc.

Las definiciones anteriores también se aplican si los correspondientes grupos halógeno son parte de otro grupo.

Halógeno se refiere a átomos de flúor, cloro, bromo y/o yodo.

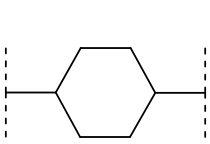
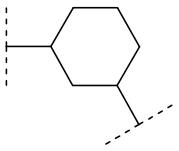
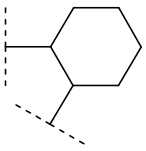
Cicloalquilo está compuesto de los subgrupos **anillos hidrocarbonados monocíclicos**, **anillos hidrocarbonados bicíclicos** y **anillos hidrocarbonados espiro**. Los sistemas están saturados. En los anillos hidrocarbonados bicíclicos dos anillos se unen entre sí de modo que tienen al menos dos átomos de carbono juntos. En los anillos hidrocarbonados espiro un átomo de carbono (espiroátomo) pertenece a dos anillos juntos. Si un **cicloalquilo** se debe sustituir, las sustituciones pueden ocurrir de modo independiente entre sí, en la forma de mono- o polisustituciones en cada caso, en todos los átomos de carbono portadores de hidrógeno. El c**icloalquilo** mismo se puede unir como un sustituyente a la molécula por medio de toda posición adecuada del sistema anular.

Los ejemplos de **cicloalquilo** son ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, biciclo[2.2.0]hexilo, biciclo[3.2.0]heptilo, biciclo[3.2.1]octilo, biciclo[2.2.2]octilo, biciclo[4.3.0]nonil (octahidroindenilo), biciclo[4.4.0]decil (decahidronaftaleno), biciclo[2.2.1]heptil (norbornililo), biciclo[4.1.0]heptil (norcaranilo), biciclo-[3.1.1]heptilo (pinanilo), spiro[2.5]octilo, spiro[3.3]heptilo, etc.

La definición anterior para **cicloalquilo** también se aplica si **cicloalquilo** es parte de otro grupo como en **cicloalquil** C_{x-y}-amino o **cicloalquil** C_{x-y}-oxi, por ejemplo.

Si la valencia libre de un **cicloalquilo** está saturada, entonces se forma un grupo **alicíclico**.

El término **cicloalquileno** en consecuencia puede derivar del **cicloalquilo** definido previamente. **Cicloalquileno**, a diferencia de **cicloalquilo,** es bivalente y requiere dos compañeros de unión. Formalmente, la segunda valencia se obtiene por la eliminación de un átomo de hidrógeno de un **cicloalquilo**. Los grupos correspondientes son por ejemplo

ciclohexilo y  o  o  (ciclohexileno).

La definición anterior para **cicloalquileno** también se aplica si **cicloalquileno** es parte de otro grupo como en HO-**cicloalquilen** C_{x-y} amino o H_2N- **cicloalquilen** C_{x-y}-oxi, por ejemplo.

Cicloalquenilo también está compuesto de los subgrupos de **anillos hidrocarbonados monocíclicos**, **anillos hidrocarbonados bicíclicos** y **anillos hidrocarbonados espiro**. Sin embargo, los sistemas son insaturados, es decir, existe al menos un enlace doble C-C pero no sistema aromático. Si en un **cicloalquilo** como se definió anteriormente en la presente se eliminan formalmente dos átomos de hidrógeno de átomos de carbono cíclicos adyacentes y las valencias libres se saturan para formar un segundo enlace, se obtiene el correspondiente **cicloalquenilo**. Si un **cicloalquenilo** se va a sustituir, las sustituciones pueden ocurrir de modo independiente entre sí, en la forma de mono o polisustituciones en cada caso, en todos los átomos de carbono portadores de hidrógeno. El **cicloalquenilo** mismo se puede ligar como un sustituyente a la molécula por medio de cada posición adecuada del sistema anular.

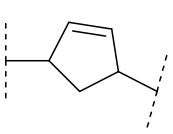
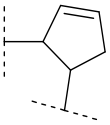
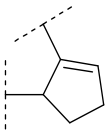
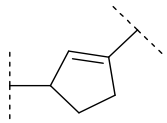
Los ejemplos de **cicloalquenilo** son cicloprop-1-enilo, cicloprop-2-enilo, ciclobut-1-enilo, ciclobut-2-enilo, ciclopent-1-enilo, ciclopent-2-enilo, ciclopent-3-enilo, ciclohex-1-enilo, ciclohex-2-enilo, ciclohex-3-enilo, ciclohept-1-enilo, ciclohept-2-enilo, ciclohept-3-enilo, ciclohept-4-enilo, ciclobuta-1,3-dienilo, ciclopenta-1,4-dienilo, ciclopenta-1,3-dienilo, ciclopenta-2,4-dienilo, ciclohexa-1,3-dienilo, ciclohexa-1,5-dienilo, ciclohexa-2,4-dienilo, ciclohexa-1,4-dienilo, ciclohexa-2,5-dienilo, biciclo[2.2.1]-hepta-2,5-dienilo (norborna-2,5-dienilo), biciclo[2.2.1]hept-2-enilo (norbornenilo), spiro[4.5]dec-2-eno, etc.

La definición anterior para **cicloalquenilo** también se aplica cuando **cicloalquenilo** es parte de otro grupo como en cicloalquenil Cx-y-amino o cicloalquenil Cx-y-oxi, por ejemplo.

Si la valencia libre de un **cicloalquenilo** está saturada, entonces se obtiene un **grupo alicíclico insaturado**.

El término **cicloalquenileno** en consecuencia puede derivar del previamente definido **cicloalquenilo**. **Cicloalquenileno,** a diferencia de **cicloalquenilo,** es bivalente y requiere dos compañeros de unión. Formalmente la segunda valencia se

obtiene por la eliminación de un átomo de hidrógeno de un **cicloalquenilo**. Los grupos correspondientes son por ejemplo

ciclopentenilo  y  o  o  o (ciclopentenileno) etc.

La definición anterior para **cicloalquenileno** también se aplica cuando **cicloalquenileno** es parte de otro grupo como en HO-cicloalquenilen Cx-y-amino o H_2N-cicloalquenilen Cx-y-oxi, por ejemplo.

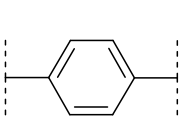
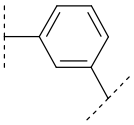
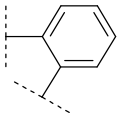
Arilo indica un grupo mono-, bi- o tricíclico con al menos un carbociclo aromático. Con preferencia indica un grupo monocíclico con seis átomos de carbono (fenilo) o un grupo bicíclico con nueve o diez átomos de carbono (dos anillos de seis miembros o un anillo de seis miembros con un anillo de cinco miembros), donde el segundo anillo también puede ser aromático o, sin embargo, también puede ser saturado o parcialmente saturado. Si un **arilo** debe ser sustituido, las sustituciones pueden ocurrir de modo independiente entre sí, en la forma de mono o polisustituciones en cada caso, en todos los átomos de carbono portadores de hidrógeno. **Arilo** mismo se puede ligar como un sustituyente en la molécula por medio de cada posición adecuada del sistema anular.

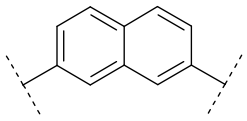
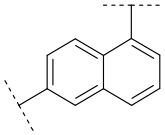
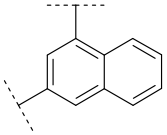
Los ejemplos de **arilo** son fenilo, naftilo, indanilo (2,3-dihidroindenilo), indenilo, antracenilo, fenantrenilo, tetrahidronaftilo (1,2,3,4-tetrahidronaftilo, tetralinilo), dihidronaftilo (1,2- dihidronaftilo), fluorenilo etc.

La definición anterior de **arilo** también se aplica cuando **arilo** es parte de otro grupo como por ejemplo, en **aril**amino o **aril**oxi.

Si la valencia libre de un **arilo** está saturada, entonces se obtiene un **grupo aromático**.

El término **arileno** también se puede derivar del **arilo** previamente definido. **Arileno,** a diferencia de **arilo,** es bivalente y requiere dos compañeros de unión. Formalmente, la segunda valencia se forma por la eliminación de un átomo de hidrógeno de un **arilo**. Los grupos correspondientes son por ejemplo

fenilo y  o  o  (*o*, *m*, *p*-fenileno),

naftilo y  o  o  etc.

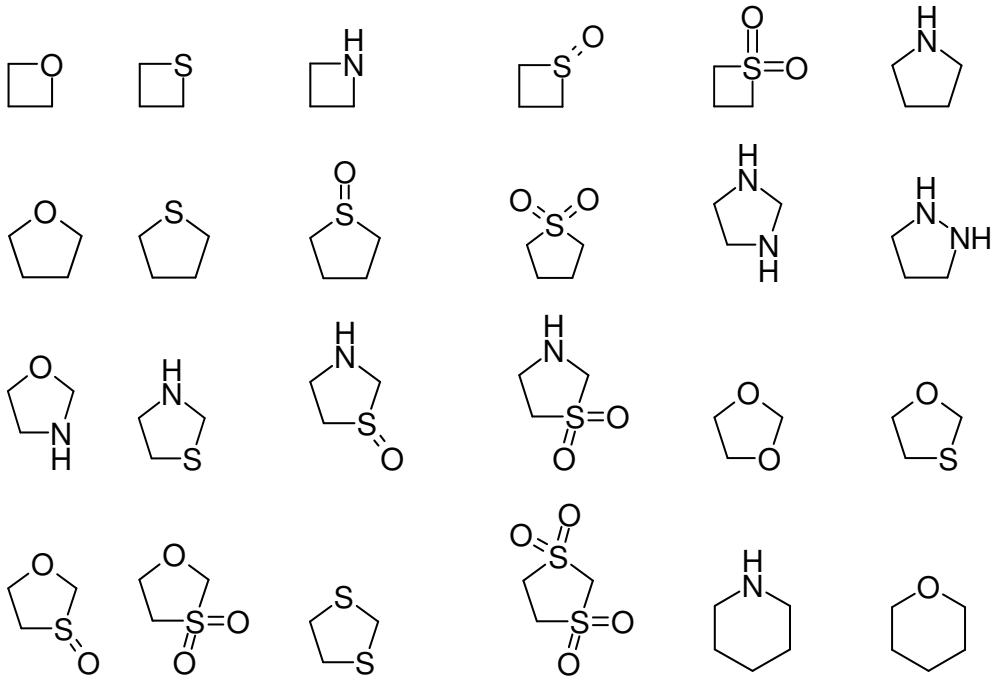
La definición anterior para **arileno** también se aplica cuando el **arileno** es parte de otro grupo como por ejemplo, en HO-**arilen**amino o H_2N-**arilen**oxi.

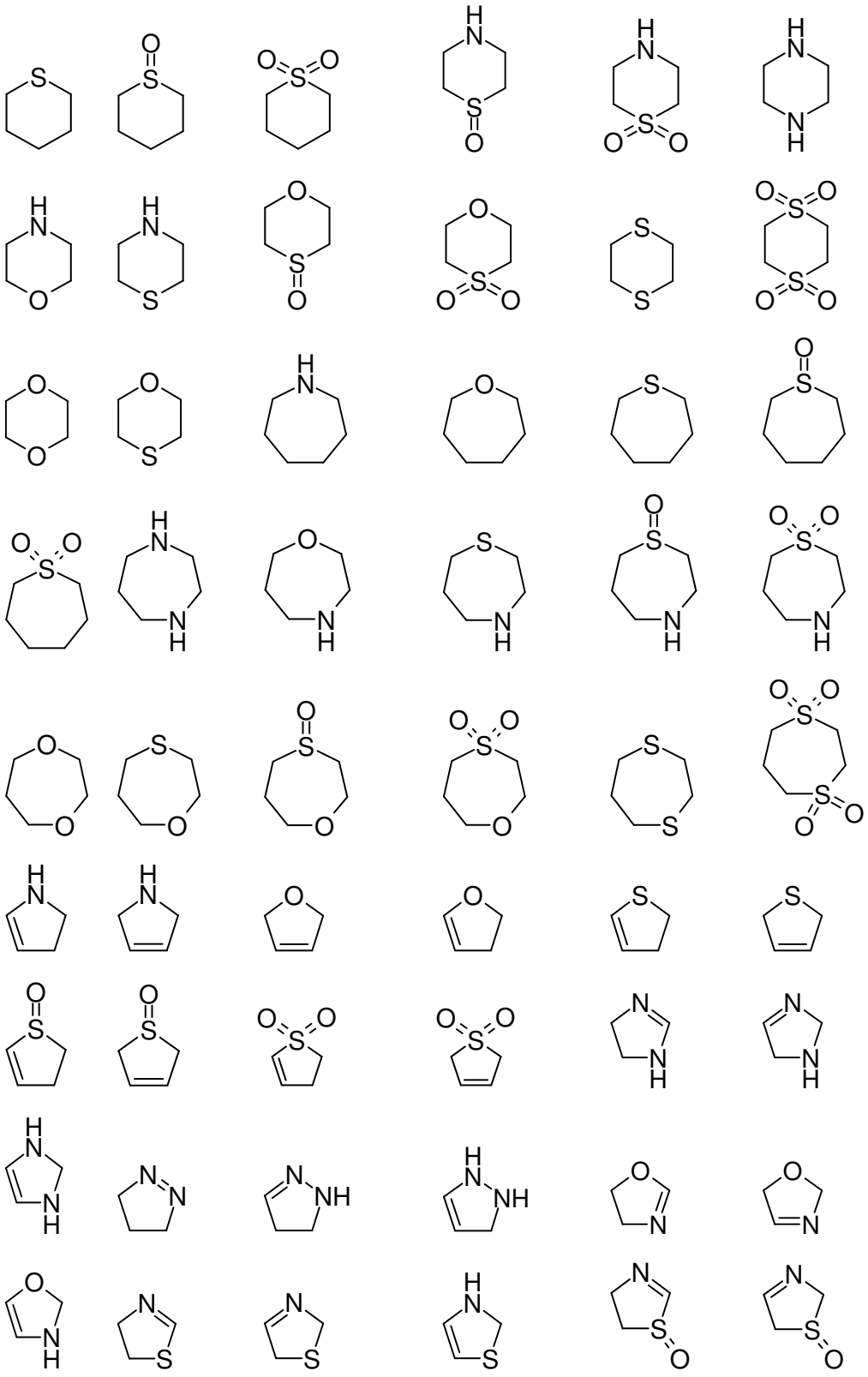
Heterociclilo indica los sistemas anulares, que derivan de **cicloalquilo, cicloalquenilo** y **arilo** previamente definidos por el reemplazo de uno o más de los grupos -CH_2- de modo independiente entre sí en los anillos hidrocarbonados por los grupos -O-, -S- o -NH- o por el reemplazo de uno o más de los grupos =CH- por el grupo =N-, donde un total de no más de cinco heteroátomos puede estar presente, al menos un átomo de carbono puede estar presente entre dos átomos de oxígeno y entre dos átomos de azufre o entre un átomo de oxígeno y uno de azufre y el anillo en conjunto debe tener estabilidad química. Los heteroátomos opcionalmente pueden estar presente en todas las etapas de oxidación posibles (azufre → sulfóxido -SO, sulfona -SO_2-; nitrógeno → N-óxido). El heterociclilo preferido es heterociclilo no aromático.

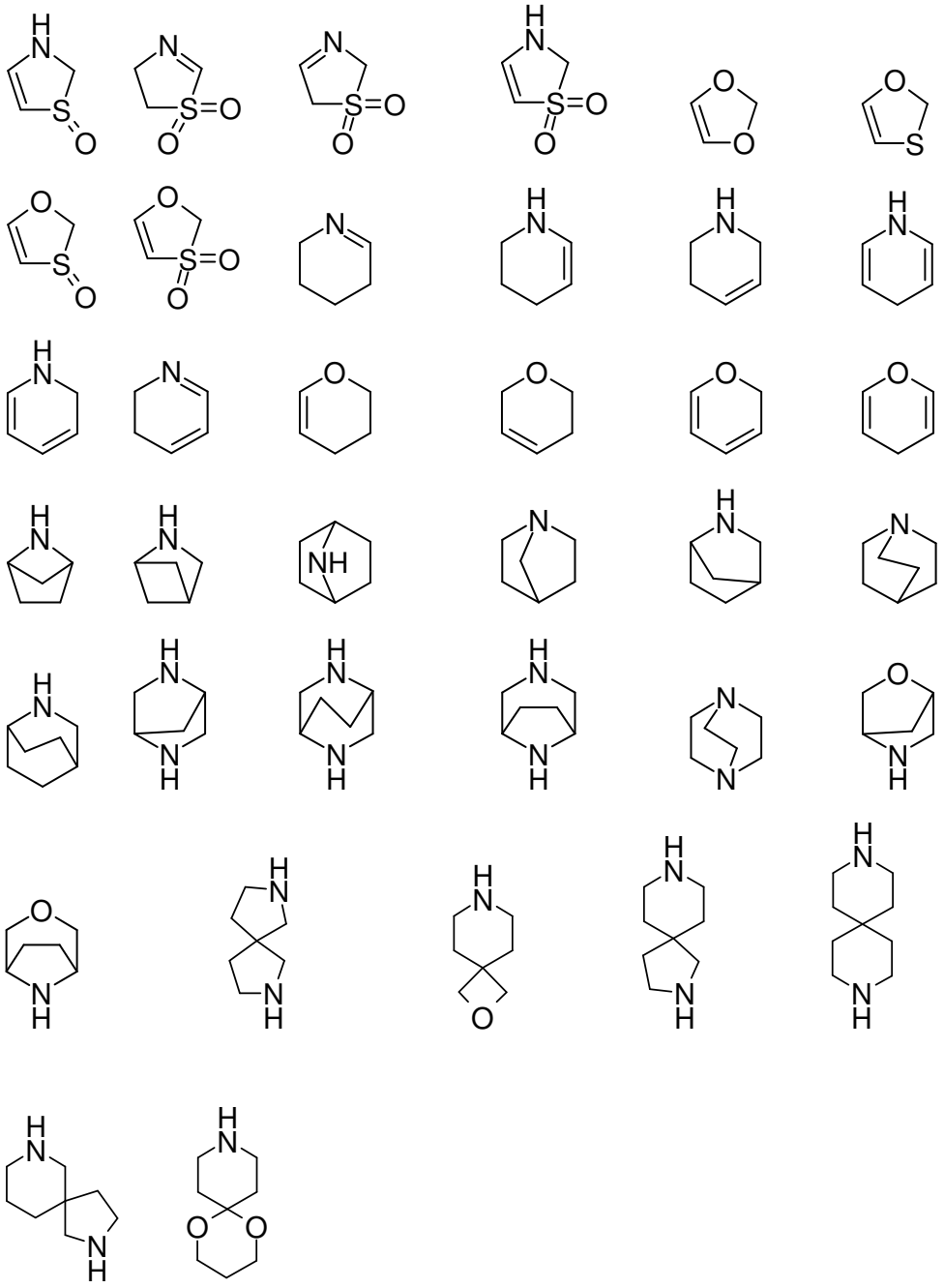
Un resultado directo de la derivación de **cicloalquilo, cicloalquenilo** y **arilo** es que el **heterociclilo** se compone de los subgrupos **heteroanillos monocíclicos**, **heteroanillos bicíclicos**, **heteroanillos tricíclicos** y **heteroanillos espiro**, que pueden estar presentes en forma saturada o insaturada. Por insaturado se entiende que existe al menos un enlace doble en el sistema anular en cuestión, pero no se forma el sistema heteroaromático. En los heteroanillos bicíclicos dos anillos se unen entre sí de modo que tienen al menos dos (hetero)átomos en común, En los heteroanillos espiro un átomo de carbono (espiroátomo) pertenece a dos anillos juntos. Si un **heterociclilo** está sustituido, las sustituciones pueden ocurrir de modo independiente entre sí, en la forma de mono o polisustituciones en cada caso, en todos los átomos carbono portadores de hidrógeno y/o nitrógeno. El **heterociclilo** mismo se puede ligar como un sustituyente en la molécula por medio de toda posición adecuada del sistema anular. Cuando el heterociclilo tiene un átomo de nitrógeno, la posición preferida para unir el sustituyente heterociclilo a la molécula es el átomo de nitrógeno.

Los ejemplos de **heterociclilo** son tetrahidrofurilo, pirrolidinilo, pirrolinilo, imidazolidinilo, thiazolidinilo, imidazolinilo, pirazolidinilo, pirazolinilo, piperidinilo, piperazinilo, oxiranilo, aziridinilo, azetidinilo, 1,4-dioxanilo, azepanilo, diazepanilo, morfolinilo, tiomorfolinilo, homomorfolinilo, homopiperidinilo, homopiperazinilo, homotiomorfolinilo, tiomorfolinail-*S*-oxide, tiomorfolinail-*S,S*-dioxide, 1,3-dioxolanilo, tetrahidropiranoilo, tetrahidrotiopiranilo, [1.4]-oxazepanilo, tetrahidrotienilo, homotiomorfolinail-*S,S*-dióxido, oxazolidinonilo, dihidropirazolilo, dihidropirrolilo, dihidropirazinilo, dihidropiridilo, dihidro-pirimidinilo, dihidrofurilo, dihidropiranilo, tetrahidrotienil-*S*-óxido, tetrahidrotienil-*S,S*-dióxido, homotiomorfolinail-*S*-óxido, 2,3-dihidroazet, 2*H*-pirrolilo, 4*H*-piranilo, 1,4-dihidropiridinilo, 8-azabiciclo[3.2.1]octilo, 8-azabiciclo[5.1.0]octilo, 2-oxa-5-azabiciclo[2.2.1]heptilo, 8-oxa-3-aza-biciclo[3.2.1]octilo, 3,8-diaza-biciclo[3.2.1]octilo, 2,5-diaza-biciclo-[2.2.1]heptilo, 1-aza-biciclo[2.2.2]octilo, 3,8-diaza-biciclo[3.2.1]octilo, 3,9-diaza-biciclo[4.2.1]nonilo, 2,6-diaza-biciclo[3.2.2]-nonilo, 1,4-dioxa-spiro[4.5]decilo, 1-oxa-3.8-diaza-spiro[4.5]decilo, 2,6-diaza-spiro[3.3]-heptilo, 2,7-diaza-spiro[4.4]nonilo, 2,6-diaza-spiro[3.4]octilo, 3,9-diaza-spiro[5.5]-undecilo, 2.8-diaza-spiro[4.5]decil, etc.

Otros ejemplos son las estructuras ilustradas a continuación, que se pueden unir por medio de cada átomo portador de hidrógeno (intercambiado por hidrógeno):





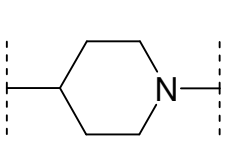
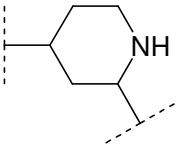
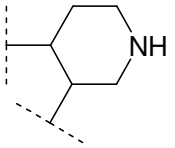


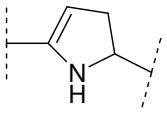
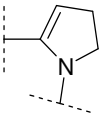
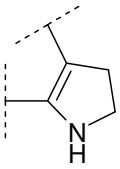
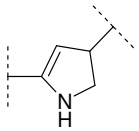
La definición anterior de **heterociclilo** también se aplica si **heterociclilo** es parte de otro grupo como por ejemplo en **heterociclil**amino o **heterociclil**oxi.

Si la valencia libre de un **heterocicliclo** está saturada, entonces se obtiene un **grupo heterocíclico**.

El término **heterociclilene** también deriva del **heterociclilo** previamente definido. **Heterociclileno,** a diferencia de **heterociclilo,** es bivalente y requiere dos

compañeros de unión. Formalmente, la segunda valencia se obtiene por la eliminación de un átomo de hidrógeno de un **heterociclilo**. Los grupos correspondientes son, por ejemplo

piperidinilo y  o  o  ,

2,3-dihidro-1*H*-pirrolilo y  o  o  o  etc.

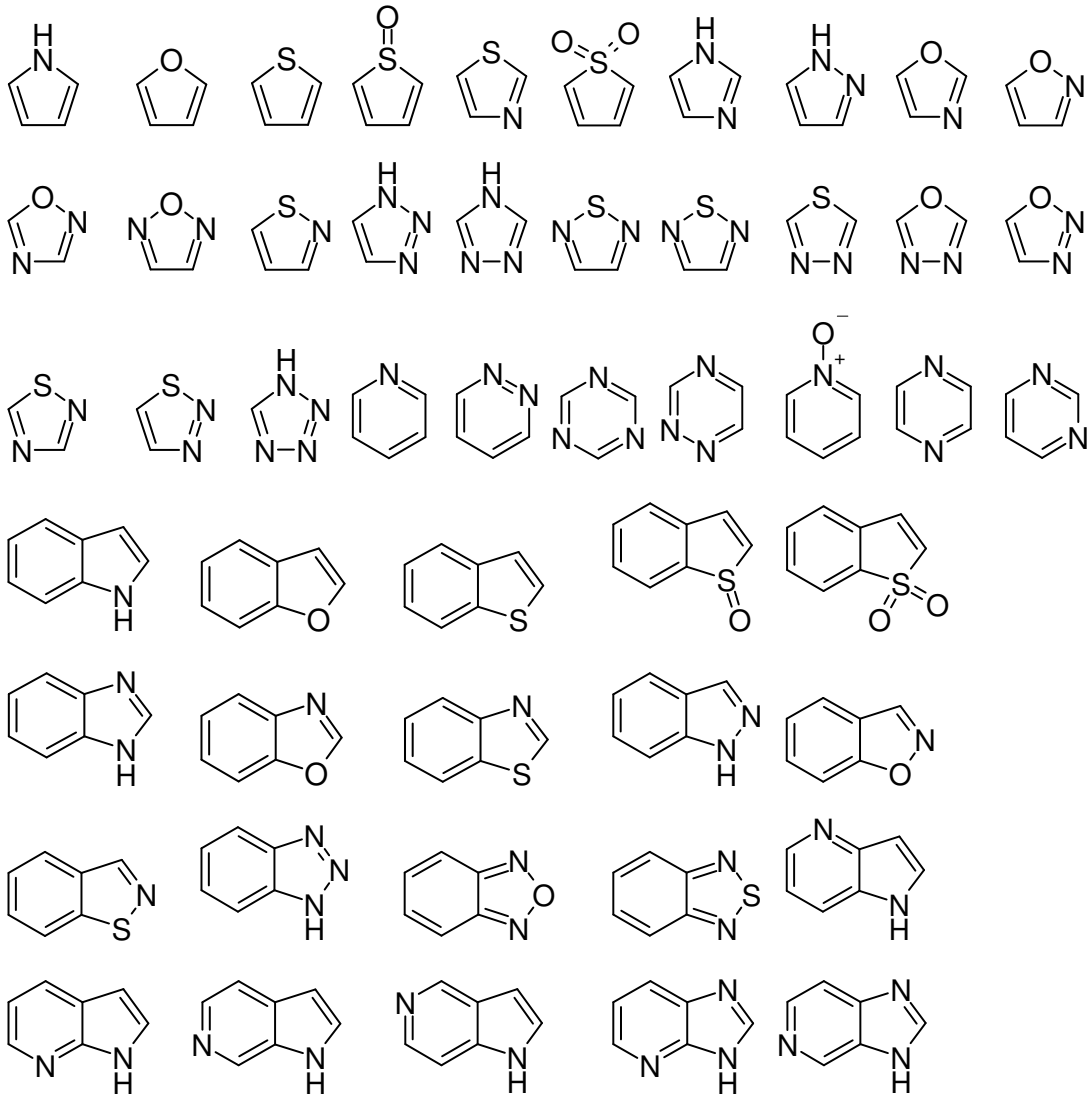
La definición anterior def **heterociclileno** también se aplica si **heterociclileno** es parte de otro grupo como por ejemplo, en HO-**heterociclilen**amino o H_2N-**heterociclilen**oxi por ejemplo.

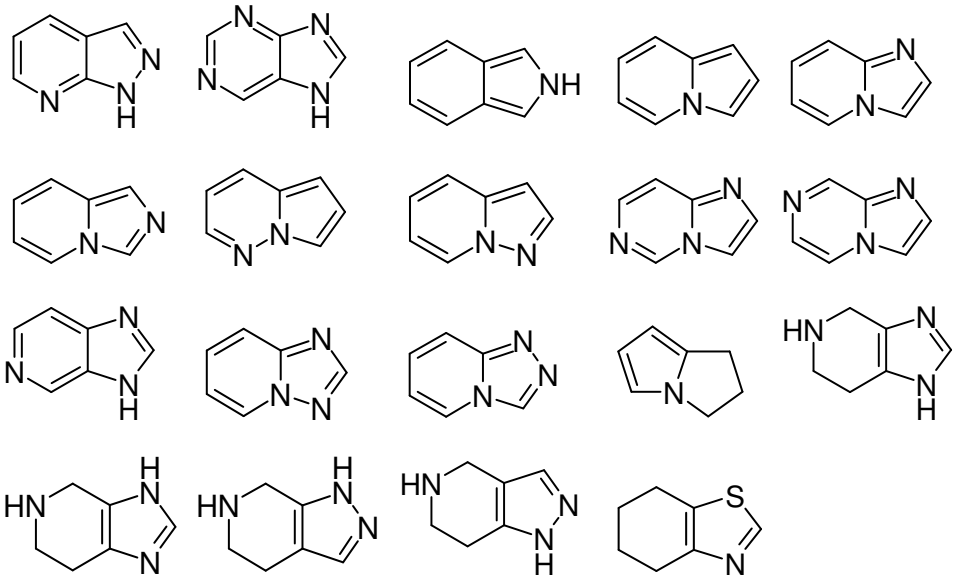
Heteroarilo indica denotes anillos heteroaromáticos monocíclicos o anillos policíclicos con al menos un anillo heteroaromático, que en comparación con el correspondiente **arilo** o **cicloalquilo (cicloalquenilo)** contiene, en vez de uno o más átomos de carbono, uno o más heteroátomos idénticos o diferentes, seleccionados de modo independiente entre sí entre nitrógeno, azufre y oxígeno, donde el grupo resultante debe ser químicamente estable. El prerrequisito para la presencia de **heteroarilo** es un heteroátomo y un sistema heteroaromático. Si un **heteroarilo** se debe sustituir, las sustituciones pueden ocurrir de modo independiente entre sí, en la forma de mono- o polisustituciones en cada caso, en todos los átomos portadores de hidrógeno y/o nitrógeno. El **heteroarilo** mismo se puede ligar como un sustituyente a la molécula por medio de toda posición adecuada del sistema anular, tanto carbono como nitrógeno.

Los ejemplos de **heteroarilo** son furilo, tienilo, pirrolilo, oxazolilo, tiazolilo, isoxazolilo, isotiazolilo, pirazolilo, imidazolilo, triazolilo, tetrazolilo, oxadiazolilo, tiadiazolilo, piridilo, pirimidilo, piridazinilo, pirazinilo, triazinilo, piridil-*N*-óxido, pirrolil-*N*-óxido, pirimidinil-*N*-óxido, piridazinil-*N*-óxido, pirazinil-*N*-óxido, imidazolil-*N*-óxido, isoxazolil-*N*-óxido, oxazolil-*N*-óxido, tiazolil-*N*-óxido, oxadiazolil-*N*-óxido, tiadiazolil-*N*-

óxido, triazolil-*N*-óxido, tetrazolil-*N*-óxido, indolilo, isoindolilo, benzofurilo, benzotienilo, benzoxazolilo, benzotiazolilo, benzisoxazolilo, benzisotiazolilo, bencimidazolilo, indazolilo, isoquinolinilo, quinolinilo, quinoxalinilo, cinnolinilo, ftalazinilo, quinazolinilo, benzotriazinilo, indolizinilo, oxazolopiridilo, imidazopiridilo, naftiridinilo, benzoxazolilo, piridopiridilo, purinilo, pteridinilo, benzotiazolilo, imidazopiridilo, imidazotiazolilo, quinolinil-*N*-óxido, indolil-*N*-óxido, isoquinolil-*N*-óxido, quinazolinil-*N*-óxido, quinoxalinil-*N*-óxido, ftalazinil-*N*-óxido, indolizinil-*N*-óxido, indazolil-*N*-óxido, benzotiazolil-*N*-óxido, bencimidazolil-*N*-óxido etc.

Otros ejemplos son las estructuras ilustradas a continuación, que se pueden unir por medio de cada átomo portador de hidrógeno (intercambiado por hidrógeno):

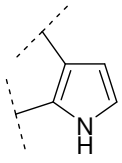
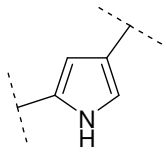
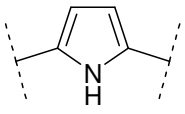
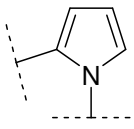




La definición anterior de **heteroarilo** también se aplica cuando **heteroarilo** es parte de otro grupo como por ejemplo **heteroaril**amino o **heteroaril**oxi.

Si la valencia libre de un **heteroarilo** está saturada, se obtiene un **grupo heteroaromático.**

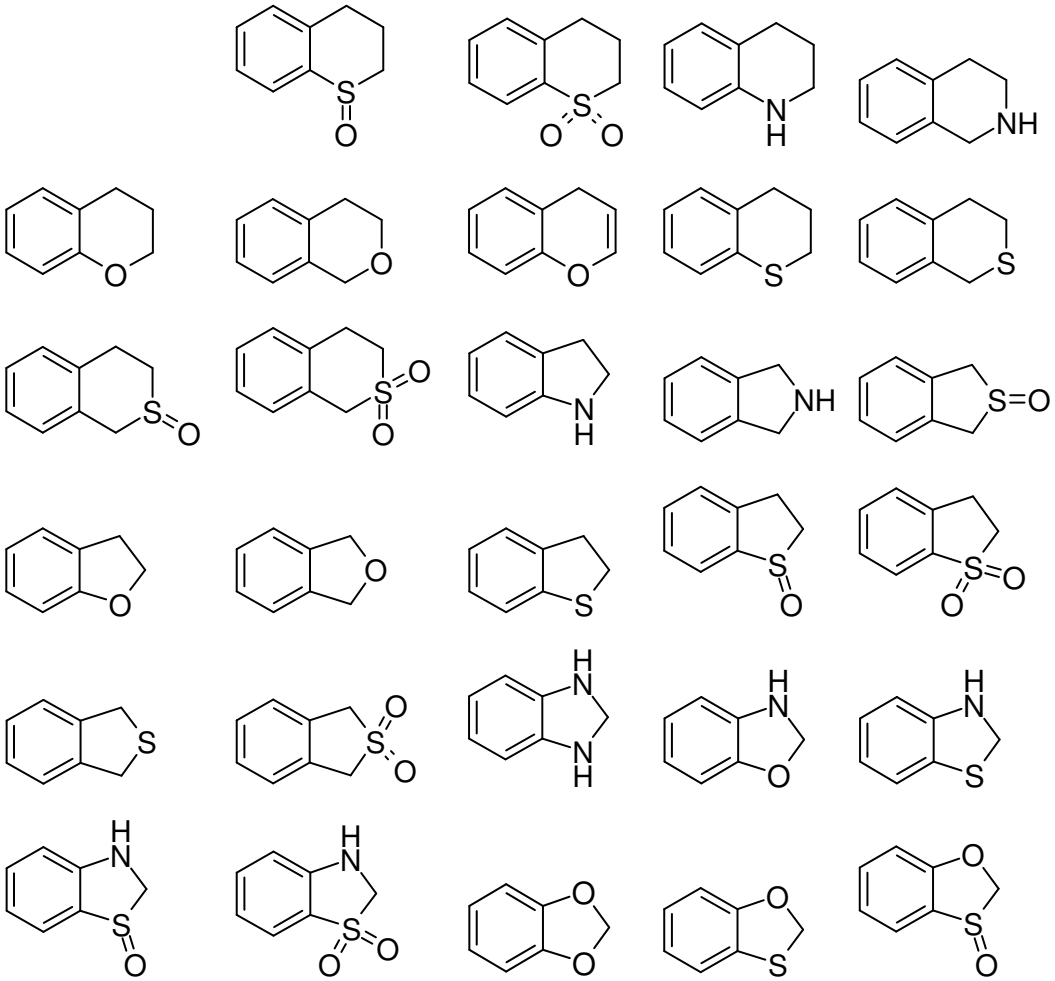
El término **heteroarileno** en consecuencia se puede derivar del **heteroarilo** previamente definido. **Heteroarileno,** a diferencia de **heteroarilo,** es bivalente y requiere dos compañeros de unión. Formalmente, la segunda valencia se obtiene por la eliminación de un átomo de hidrógeno de un **heteroarilo**. Los grupos correspondientes son por ejemplo

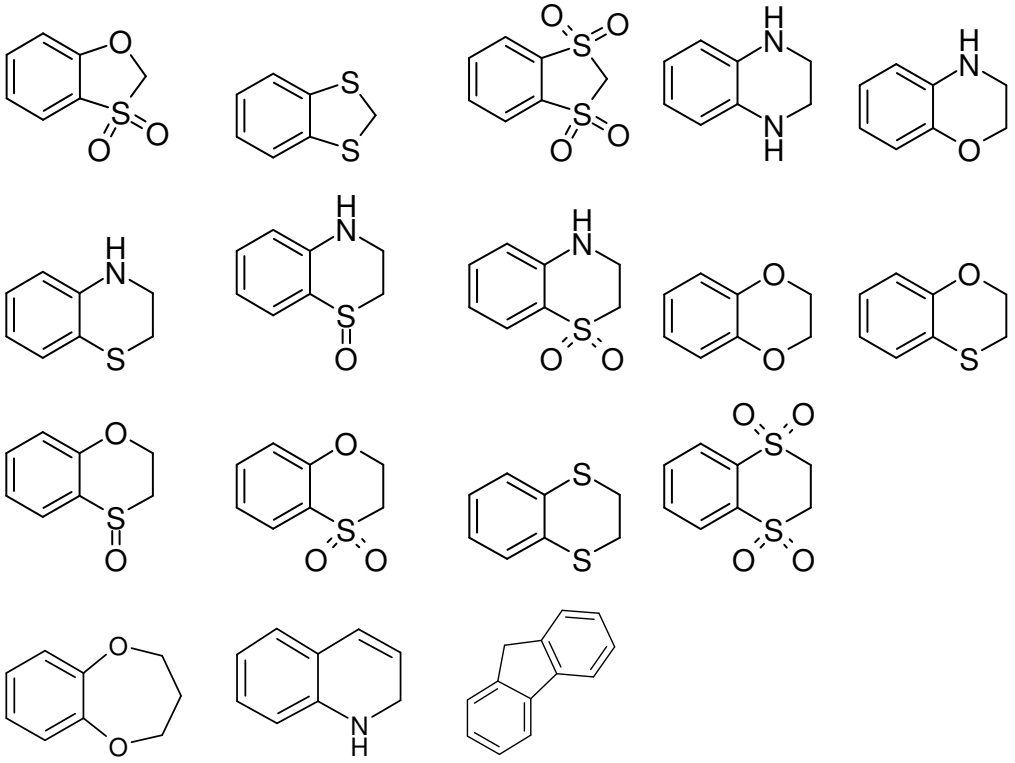
pirrolilo y  o  o  o  etc.

La definición anterior de **heteroarileno** también se aplica cuando el **heteroarileno** es parte de otro grupo como por ejemplo en HO-**heteroarilen**amino o H_2N-**heteroarilen**oxi.

Los grupos bivalentes mencionados anteriormente (alquileno, alquenileno, alquinileno etc.) también puede ser parte de grupos compuestos (por ejemplo H_2N-C_{1-4}alquileno- o HO-alquilen C_{1-4}-). En este caso una de las valencias está saturada por el grupo unido (en la presente: -NH_2, -OH), de modo que un grupo compuesto de esta clase escrito de este modo solo es sobre todo un sustituyente monovalente.

Sistema anular aromático significa una estructura mono- o multi-anular, con preferencia una estructura multi-anular, que comprende entre uno, con preferencia dos, a cuatro grupos cíclicos, donde al menos uno de estos grupos cíclicos es un anillo aromático o heteroaromático. La estructura multianular comprende dos a cuatro grupos cíclicos, que se fusionan entre sí, donde al menos uno de los grupos cíclicos es aromático (o heteroaromático). Las estructuras multianulares preferidas son estructuras multianulares de 9-14 miembros. Los grupos cíclicos descriptos en la presente se pueden fusionar entre sí para obtener una estructura multianular, es decir, un sistema anular aromático. Por ejemplo, la estructura multianular comprende un arilo fusionado con un heterociclo sino también un heteroarilo fusionado a un cicloalquilo. Los ejemplos no limitantes de sistemas aromáticos son





Por **sustituido** se entiende de un átomo de hidrógeno que se une directamente al átomo en consideración, es reemplazado por otro átomo u otro grupo de átomos (**sustituyente**). De acuerdo con las condiciones iniciales (número de átomos de hidrógeno), la mono- o polisustitución puede ocurrir en un átomo. La sustitución con un sustituyente particular solo es posible si las valencias permitidas del sustituyente y del átomo que se va a sustituir corresponde al otro y la sustitución lleva a un compuesto estable (es decir, a un compuesto que no se convierte espontáneamente, por ejemplo, por reordenamiento, ciclación o eliminación).

Los sustituyentes bivalentes tales como =S, =NR, =NOR, =NNRR, =NN(R)C(O)NRR, $=N_2$ o similares, solo pueden estar sustituidos en los átomos de carbono, donde el sustituyente bivalente =O también puede ser un sustituyente en el azufre. En general, la sustitución se puede llevar a cabo con un sustituyente bivalente solo en los sistemas anulares y requiere el reemplazo con dos átomos de hidrógeno geminales, es decir, átomos de hidrógeno que se unen al mismo átomo de carbono que está saturada antes de la sustitución. La sustitución con un sustituyente bivalente en consecuencia solo es posible en el grupo $-CH_{2-}$ o los átomos de azufre de un sistema anular.

Estereoquímica/Solvatos/Hidratos: A menos que se indique de otro modo

una fórmula estructural dada en la descripción o en las reivindicaciones o un nombre químico se refiere al correspondiente compuesto mismo, pero también abarca los tautómeros, estereoisómeros, isómeros ópticos y geométricos (por ejemplo enantiómeros, diastereómeros, isómeros *E*/*Z*, etc.), racematos, mezclas de enantiómeros separados en cualquiera de las combinaciones deseadas, mezclas de diastereómeros, mezclas de las formas mencionadas anteriormente presente (si existen tales formas) así como sales, en particular sus sales farmacéuticamente aceptables. Los compuestos y sales de acuerdo con la invención pueden estar presentes en la forma solvatada (por ejemplo, con solventes farmacéuticamente aceptables tales como, por ejemplo, agua, etanol etc.) o en forma no solvatada. En general, para los fines de la presente invención las formas solvatadas, por ejemplo, hidratos, se deben considerar de igual valor para las formas no solvatadas.

Sales: El término "**farmacéuticamente aceptable**" se usa en la presente para indicar compuestos, materiales, composiciones y/o formulaciones que son adecuados, de acuerdo con la opinión médica generalmente reconocida, para usar en conjunto con el tejido humano y/o animal y no tienen o dan origen a ninguna toxicidad excesiva, irritación o respuesta inmune o llevan a otros problemas o complicaciones, es decir, corresponden en general a una relación de riesgo/beneficio aceptable.

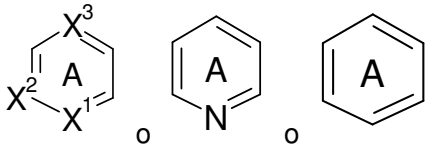
El término "**sales farmacéuticamente aceptables**" se refiere a derivados de los compuestos químicos descriptos en que el compuesto original es modificado por la adición de ácido o base. Los ejemplos de sales farmacéuticamente aceptables incluyen (sin restringirse a ellas) sales de ácidos minerales u orgánicos en relación con grupos funcionales básicos como por ejemplo, aminas, sales metal alcalino u orgánicas de grupos funcionales ácidos tales como por ejemplo ácidos carboxílicos, etc. Estas sales incluyen en particular acetato, ascorbato, bencensulfonato, benzoato, besilato, bicarbonato, bitartrato, bromuro/bromhidrato, Ca-edetato/edetato, camsilato, carbonato, cloruro/clorhidrato, citrato, edisilato, etandisulfonato, estolato, esilato, fumarato, gluceptato, gluconato, glutamato, glicolato, glicolilarsnilato, hexilresorcinato, hidrabamina, hidroximaleato, hidroxinaftoato, yoduro, isotionato, lactato, lactobionato, malato, maleato, mandelato, metansulfonato, mesilato, metilbromuro, metilnitrato, metilsulfato, mucato, napsilato, nitrato, oxalato, pamoato, pantotenato, fenilacetato, fosfato/difosfato, poligalacturonato, propionato, salicilato, estearato, subacetato, succinato, sulfamida, sulfato, tannato, tartrato, teoclato, toluensulfonato, trietiyoduro, amonio, benzatina, cloroprocaína, colina, dietanolamina, etilendiamina, meglumina y procaína. Otras sales farmacéuticamente aceptables se pueden formar con cationes

de metales tales como aluminio, calcio, litio, magnesio, potasio, sodio, zinc, etc. (cf. También Pharmaceutical sales, Birge, S.M. et al., J. Farm. Sci., (1977), 66, 1-19).

Las sales farmacéuticamente aceptables de la presente invención se pueden preparar a partir del compuesto original, que porta un grupo funcional básico o ácido, por métodos químicos convencionales. En general, tales sales se pueden sintetizar por la reacción de la forma de ácido o base libre de estos compuestos con una cantidad suficiente de la correspondiente base o ácido en agua o un solvente orgánico tal como por ejemplo, éter, acetato de etilo, etanol, isopropanol, acetonitrilo (o sus mezclas).

Las sales de ácidos diferentes de los mencionados anteriormente, que son útiles por ejemplo, para purificar o aislar los compuestos de las mezclas de reacción por ejemplo trifluoroacetatos), también se consideran como parte de la invención.

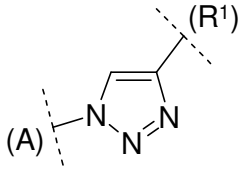
En una representación tal como por ejemplo



o o

la letra A tiene la función de una denominación del anillo a fin de hacerla más fácil, por ejemplo, para indicar la unión del anillo en cuestión a otros anillos.

Para los grupos bivalentes en que es crítico determinar cuáles grupos adyacentes unen y con qué valencia, los correspondientes compañeros de unión se indican entre paréntesis, cuando sea necesario para los fines de clarificación, como en las siguientes representaciones:



o (R^2)-C(O)NH- o (R^2)-NHC(O)-;

Los grupos o sustituyentes se seleccionan con frecuencia entre un número alternativo de grupos/ sustituyentes con un correspondiente denominación del grupo (por ejemplo **R^a**, **R^b** etc). Si se usa tal grupo en forma repetida para definir un compuesto de acuerdo con la invención en diferentes partes moleculares, siempre se debe tener en cuenta que los diferentes usos se consideran como totalmente independiente entre sí.

Por una **cantidad terapéuticamente efectiva** para los fines de esta invención se entiende una cantidad de sustancia que es capaz de obviar síntomas de enfermedad o de prevenir o aliviar estos síntomas o que prolongan la supervivencia de

un paciente tratado.

Lista de abreviaturas

ACN	acetonitrilo
Bu	butilo
conc.	concentrado
d	día
DCM	diclorometano
DIPEA	diisopropiletil amina
DMA	*N,N*-dimetilacetamida
DMAP	*N,N*-dimetilpiridin-4-amina
DMF	*N,N*-dimetilformamida
DMSO	dimetilsulfóxido
Et	etilo
h	hora(s)
HATU	hexafluorofosfato *N*-óxido de *N*-[(dimetilamino)-(1*H*-1,2,3-triazolo[4,5-*b*]-piridin-1-il)-metilen]-*N*-metilmetan-aminio
HPLC	Cromatografía líquida de alto rendimiento
*i*Pr	isopropilo
M	molar
m.p.	punto de fusión
Me	metilo
min	minutos
mL	mililitro
MS	espectrometría de masa
N	Normal
NMP	*N*-metilpirrolindinona
RMN	espectroscopia de resonancia nuclear
NP	fase normal
ppm	parte por millones
prep	preparativa
R_f	factor de retención
RP	fase inversa
RT	temperatura ambiente
tert	terciario
TFA	ácido trifluoroacético
THF	tetrahidrofurano
TLC	cromatografía de capa fina
tR	tiempo de retención

Otros rasgos y ventajas de la presente invención serán evidentes a partir de los siguientes ejemplos más detallados que ilustran a modo de ejemplo los principios sin restringir el alcance.

General

A menos que se indica de otro modo, todas las reacciones se llevan cabo en aparatos comercialmente obtenibles usando métodos que se usan comúnmente en los laboratorios químicos. Los materiales de partida que son sensibles al aire y/o humedad se almacenar bajo gas protector y las correspondientes reacciones y manipulaciones con eso se llevan a cabo bajo gas protector (nitrógeno o argón).

Los compuestos de acuerdo con la invención se nombran de acuerdo con las pautas IUPAC usando el programa de computación Lexichem (OpenEye Scientific Software Inc., versión 2.0.0). Si un compuesto se debe representar tanto con una fórmula estructura y con su nomenclatura, en el caso de un conflicto la fórmula estructural es decisiva.

Cromatografía

La cromatografía en capa fina se lleva a cabo en placas de TLC listas para usar de gel de sílice 60 en vidrio (con indicador de fluorescencia F-254) fabricado por Merck.

Para la **cromatografía de presión media preparativa (cromatografía NP)** se usa gel de sílice fabricado por Millipore (Granula Silica Si-60A $3_{5\text{-}7}0$ µm, fase NP).

La cromatografía en fase normal automatizada también se lleva a cabo en un aparato de CombiFlash Companion XL en combinación con un colector de fracciones CombiFlash Foxi 200 fabricado por Isco. Para esto, se usan columnas de una vía obtenibles en el comercio RediSepRf (120 g gel de sílice). Además, la cromatografía en fase normal automatizada también se puede llevar cabo en un aparato de purificación flash Isolera fabricado por Biotage. Para esto, se usan cartuchos SNAP de una vía obtenibles en el comercio (por ejemplo 50 g de gel de sílice).

La **cromatografía de presión alta preparativa (RP HPLC)** se lleva a cabo con columnas fabricadas por Waters (Sunfire C18, 5 µm, 30 x 100 mm Part. No. 186002572; X-Bridge C18, 5 µm, 30 x 100 mm Part. No. 186002982).

Los compuestos se eluyen usando diferentes gradientes de H_2O/acetonitrilo o H_2O/MeOH, donde 0.1% de HCOOH se añade al agua, o con diferentes gradientes que utilizan una solución de buffer acuoso básico (1L de agua contiene 5 mL de una solución de hidrógenocarbonato de amonio (158 g por 1 L de H_2O) y 2 mL de

amoníaco (solución 7 mol/l en MeOH)) en vez de la mezcla de agua -HCOOH.

La **HPLC analítica (reacción de control)** de compuestos intermediarios se lleva a cabo con las columnas fabricadas por Agilent y Waters. En cada caso el equipo analítico también está provisto de un detector de masa.

Espectroscopia de masa de HPLC/espectrometría UV

Los tiempos de retención/MS-ESI$^+$ para caracterizar los ejemplos de compuestos de acuerdo con la invención se producen usando un aparato HPLC-MS (cromatografía líquida de alto rendimiento con detector de masa) fabricado por Agilent. Los compuestos que eluyen en el pico de inyección se dan en el tiempo de retención tR = 0.

Métodos analíticos HPLC

***Método_1**

HPLC:	Agilent 1100 Series	
MS:	Agilent LC/MSD SL	
Columna:	Waters, Xbridge C18, 2.5 µm, 2.1x20 mm,	
	Part.No. 186003201	
Solvente	A: 20mM NH_4HCO_3/ NH_3	
	B: ACN grado HPLC	
Detección:	MS: Positivo y negativo	
	Rango de masa:	120 - 800 m/z
Inyección:	5 µL	
Flujo:	1.00 mL/min	
Temperatura de columna:	60 °C	
Gradiente:	0.00 min	10 % B
	0.00 – 1.50 min	10 % -> 95 % B
	1.50 – 2.00 min	95 % B
	2.00 – 2.10 min	95 % -> 10 % B

***Método_2**

HPLC:	Agilent 1100/1200 Series
MS:	Agilent 1100 LC/MSD SL
Columna:	Waters Sunfire, 5.0 µm, 2.1 x 50 mm
Eluyente:	A: H_2O + 0.2 % HCOOH; B: ACN
Detección:	ESI

Rango de masa: 100 – 1200 m/z

Flujo: 1.20 ml/min

Temperatura de columna: 35°C

Gradiente:	0.01 min:	5 % B
	0.01 – 1.50 min:	5 % → 95 % B
	1.50 – 2.00 min:	100 % B

***Método_3**

HPLC: Agilent 1100 Series

MS: Agilent LC/MSD SL

Columna: Waters X-Bridge C18, 2.1 x 50mm, 5.0 µm

Eluyente: A: 5 mM NH_4HCO_3/19 mM NH_3 in H_2O; B: ACN (grado HPLC)

Detección: MS: Modo positivo y negativo

Rango de masa: 105 – 1200 m/z

Flujo: 1.20 ml/min

Temperatura de columna: 35°C

Gradiente:

0.01 min:	5 % B
0.01 – 1.25 min:	5 % → 95 % B
1.25 – 2.00 min:	95 % B
2.00 – 2.01 min:	95 % → 5 % B

***Método_4**

HPLC: Agilent 1100 Series

MS: Agilent LC/MSD SL

Columna: Waters X-Bridge C18, 2.1 x 50mm, 3.5µm

Eluyente: A: 5 mM NH_4HCO_3/20 mM NH_3 in H_2O; B: ACN (grado HPLC)

Detección: MS: Modo positivo y negativo

Rango de masa: 105 – 1200 m/z

Flujo: 1.20 ml/min

Temperatura de columna: 35°C

Gradiente:

0.01 min:	5 % B
0.01 – 1.25 min:	5 % → 95 % B
1.25 – 2.00 min:	95 % B
2.00 – 2.01 min:	95 % → 5 % B

***Método_5**

HPLC: Agilent 1100 Series

MS: Agilent LC/MSD SL

Columna: WatersXBridge C18 2.1x50mm, 5,0 µm

Eluyente: A: 5 mM NH_4HCO_3/19 mM NH_3 in H_2O; B: ACN (grado HPLC)

Detección: MS: Modo positivo y negativo

Rango de masa: 105 – 1200 m/z

Flujo: 1.20 ml/min
Temperatura de columna: 35°C
Gradiente: 0.01 min: 5 % B
0.01 – 1.25 min: 5 % → 95 % B
1.25 – 2.00 min: 95 % B
2.00 – 2.01 min: 95 % → 5 % B

***Método_6**
HPLC: Agilent 1100 Series
MS: Agilent LC/MSD SL
Columna: Waters Sunfire,2.1x50mm, 5.0 µm
Eluyente: A: H_2O + 0.2 % HCOOH; B: ACN (grado HPLC) + 0.2 % HCOOH
Detección: MS: Modo positivo y negativo
Rango de masa: 105 – 1200 m/z
Flujo: 1.20 ml/min
Temperatura de columna: 35°C
Gradiente: 0.01 min: 5 % B
0.01 – 1.50 min: 5 % →95 % B
1.50 – 2.00 min: 95 % B
2.00 – 2.01 min: 95 % → 5 % B

Preparación de los compuestos de acuerdo con la invención

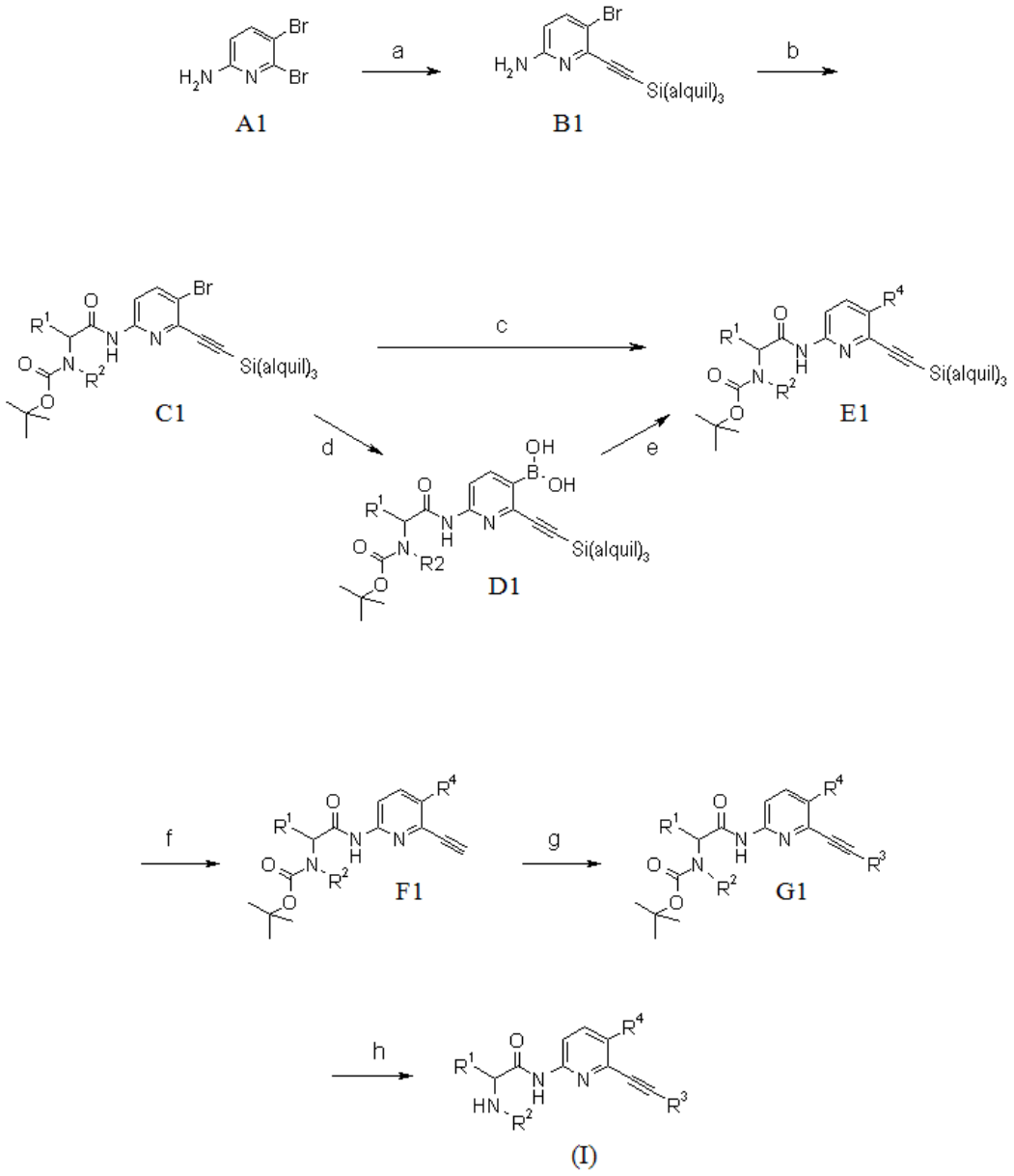
Los compuestos de acuerdo con la invención se preparan por los métodos de síntesis descriptos anteriormente en la presente, en que los sustituyentes de las fórmulas generales tienen los significados dados anteriormente en la presente. Estos métodos se consideran como una ilustración de la invención, sin restringir su tema y el alcance de los compuestos reivindicados para estos ejemplos. Cuando no se describe la preparación de los compuestos de partida, ellos se pueden obtener en el comercio o se pueden preparar de modo análogo a los compuestos conocidos o métodos descriptos en la presente. Las sustancias descriptas en la bibliografía se preparan de acuerdo con los métodos publicados.

A menos que se especifique de otro modo, los sustituyentes $\mathbf{R^1}$ a $\mathbf{R^5}$ de los siguientes esquemas de reacción son como se definen en la memoria descriptiva y reivindicaciones.

Los compuestos de fórmula (**I**) se pueden preparar de acuerdo con los

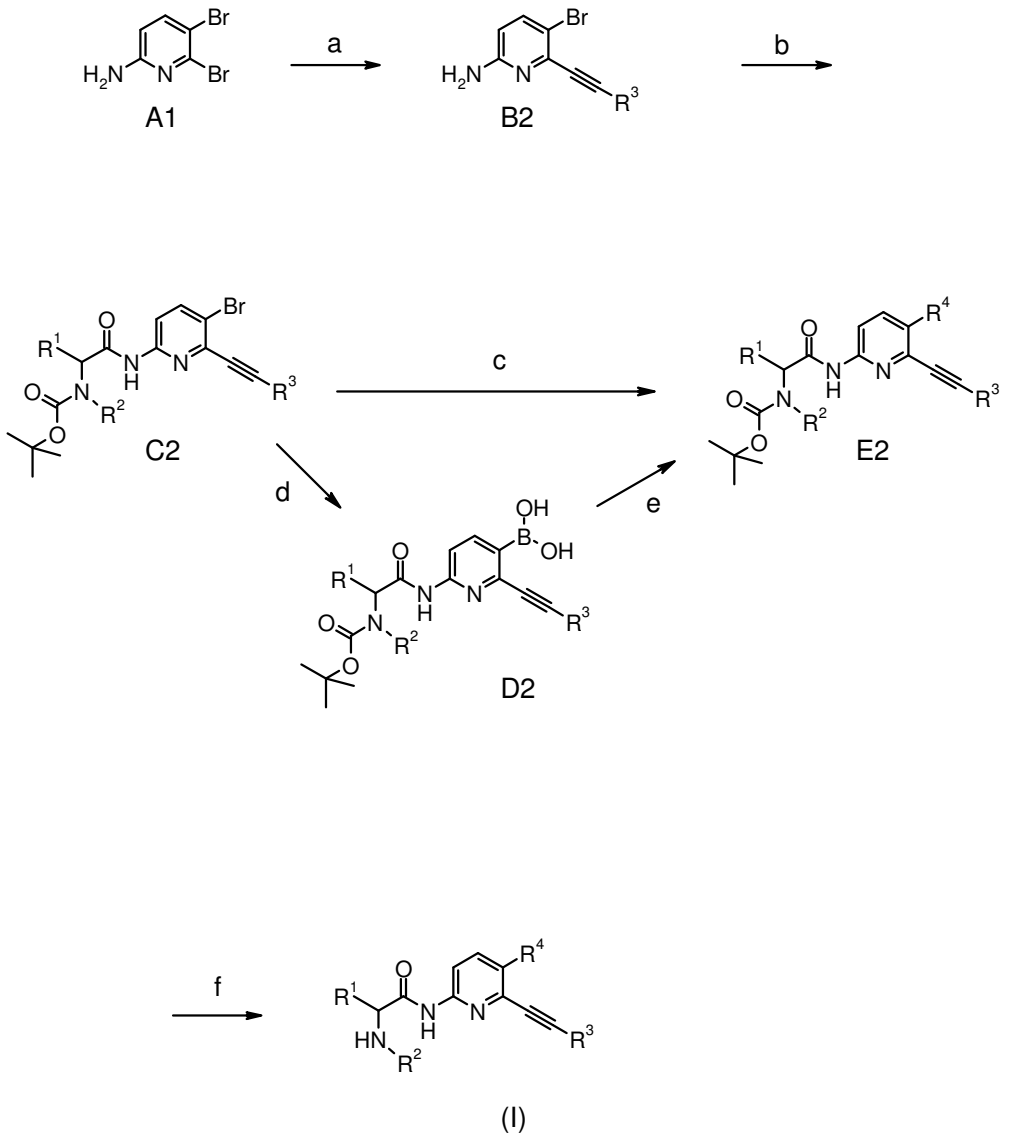
siguientes esquemas ($_{1-5}$).

Un método para la preparación de compuestos de fórmula (**I)** comienza a partir del bloque de construcción **A**1 como se ilustra en el Esquema 1. En la etapa (a) A1 se hace reaccionar con un trialquilsililacetileno para obtener B1 que se convierte en C1 por medio de la amidación. Los compuestos C1 se pueden convertir en los ácidos borónicos D1 que permite la transformación a E1 por ejemplo por medio del acoplamiento de Suzuki. Alternativamente, los intermediarios C1 se pueden convertir en E1 compuestos por medio de la etapa (c), por ejemplo, por medio de las reacciones de acoplamiento con ácidos borónicos adecuados, reactivos de organozinc u otros métodos conocidos en la técnica. En la etapa (f) los compuestos F1 se pueden obtener por medio de la reacción de desililación. F1 se puede convertir en G1 en la etapa (g) por ejemplo por medio del acoplamiento Sonogashira. Finalmente, los compuestos de la fórmula (I) se obtienen por medio de la reacción de desprotección. Los productos se aíslan por medios convencionales y con preferencia se purifican por cromatografía.



Esquema 1

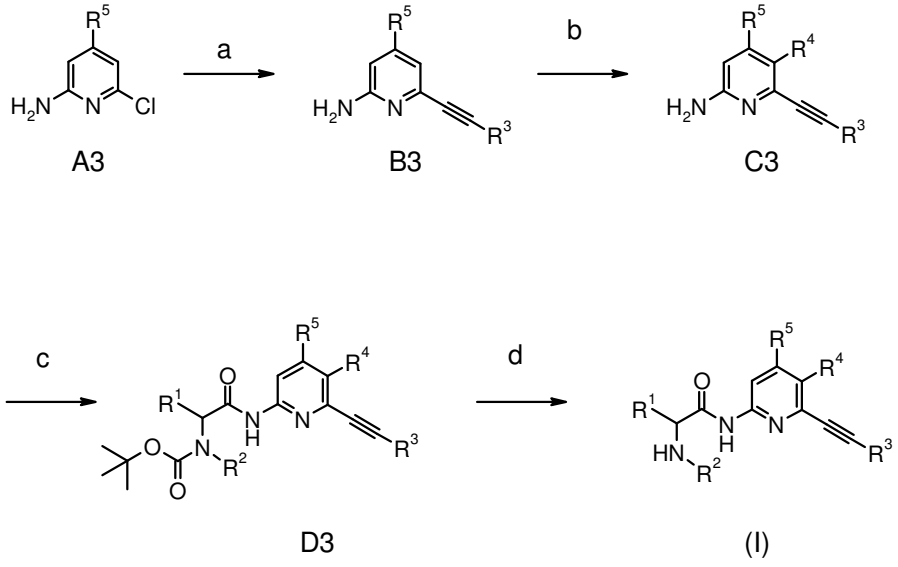
Otro métodos para la preparación de los compuestos de fórmula (I) se ilustra en el Esquema 2. En la etapa (a) un alquino adecuado se acopla a A1. En la etapa (b) los compuestos del tipo B2 se convierten en las correspondientes amidas C2. Como se describe en el Esquema 1, los compuestos C2 se pueden convertir en E2 por medio de la etapa (c) o por medio de ácidos borónicos B2 en la etapa (d) + (e). En la etapa (f) los compuestos E2 se desprotegen en los compuestos (I). Los productos se aíslan por medios convencionales y con preferencia se purifican por cromatografía.



Esquema 2

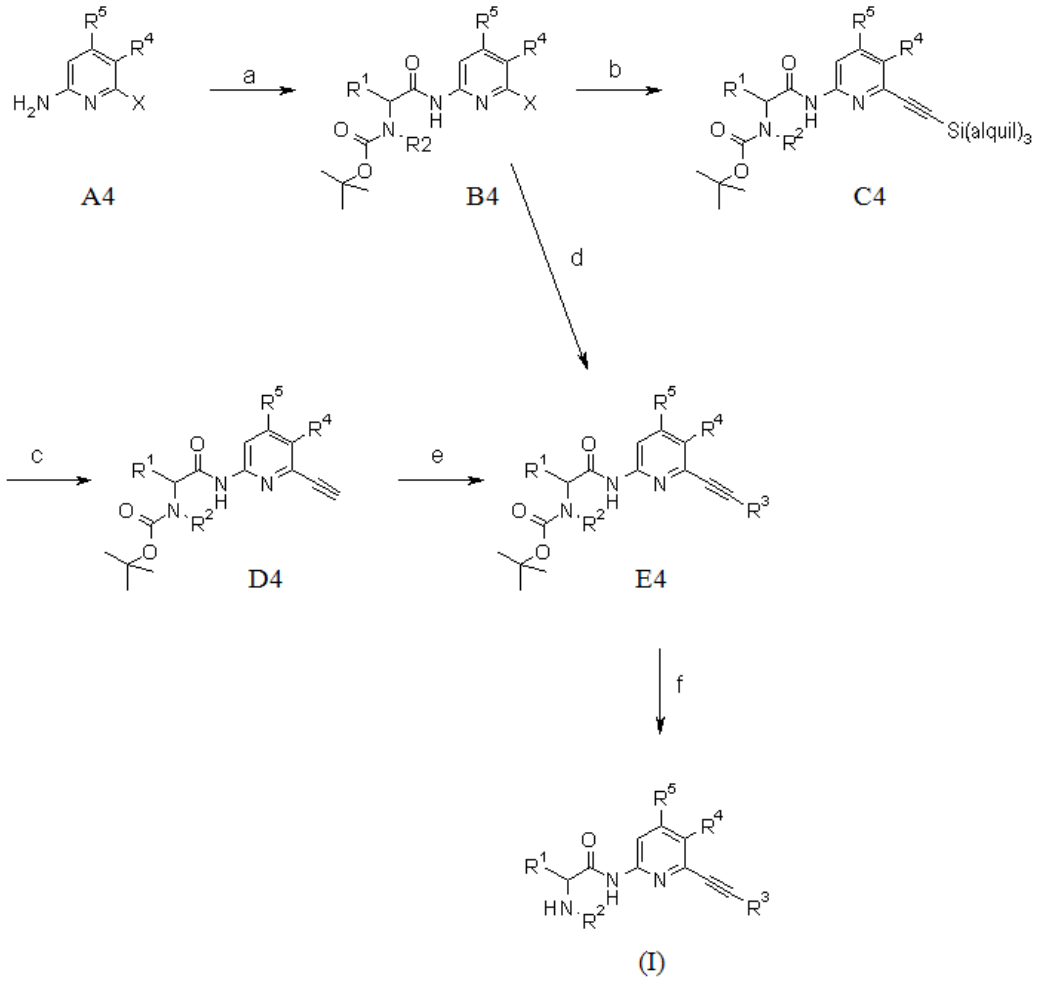
Otro método alternativo para la preparación de compuestos de fórmula (I) se ilustra en el Esquema 3. En la etapa (a) un alquino adecuado se acopla con A3. En la etapa (b) los restos R4 se introducen por ejemplo por la reacción de halogenación y opcionalmente también se modifican posteriormente. En la etapa (c) los compuestos de tipo C3 se convierten en las amidas correspondientes D3. En la etapa (d) los compuestos D3 se desprotegen a los compuestos de la fórmula (I). Los productos se aíslan por medios convencionales y con preferencia se purifican por medio de cromatografía.

Los restos R4 o R5 se podrían modificar adicionalmente durante la secuencia de reacción.



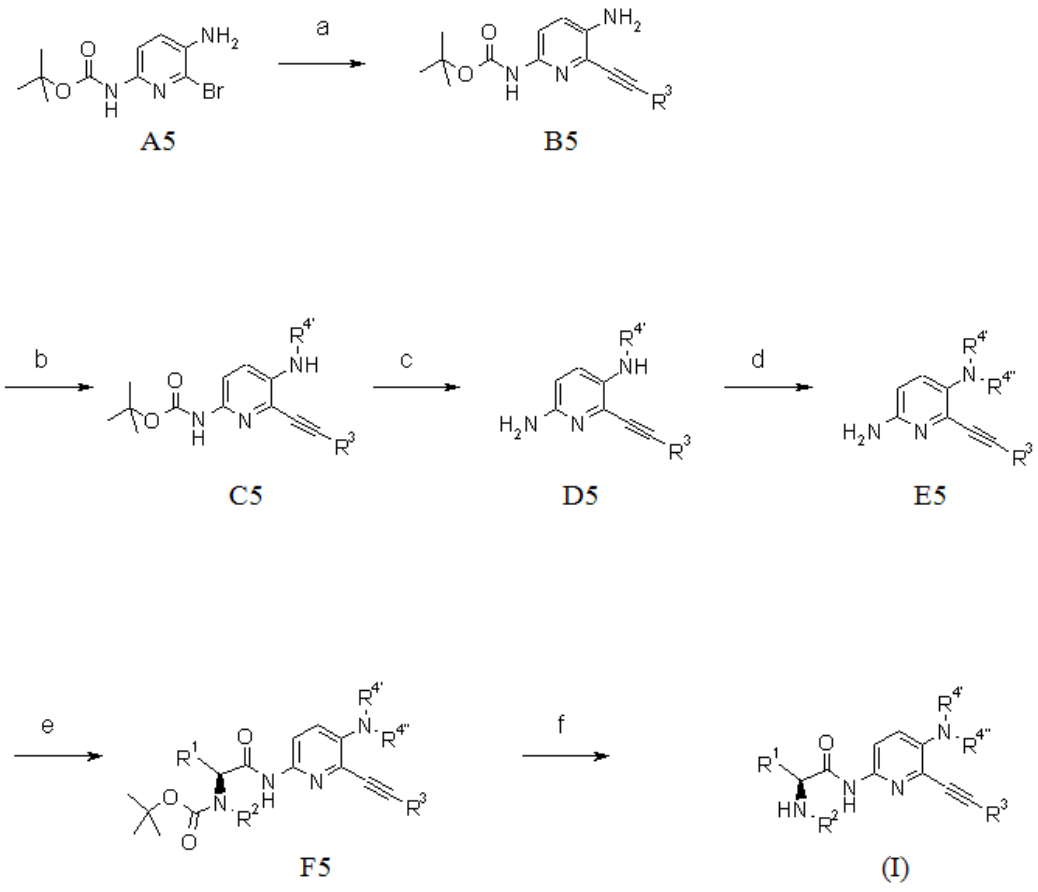
Esquema 3

Otro método para la preparación de compuestos de fórmula (I) se ilustra en el Esquema 4. Los Bloques de construcción del tipo A4 se convierten en la etapa (a) en las correspondientes amidas B4, al que se pueden acoplar alquinos adecuados en la etapa (d) para obtener compuestos de tipo E4. Alternativamente, los trialquilsililacetilenos se pueden acoplar con los compuestos B4, que se puede desililar a D4 en la etapa (c) y el grupo alquino también se convierte para obtener los compuestos E4 (etapa (e), por ejemplo por medio del acoplamiento Sonogashira). Finalmente, los compuestos de la fórmula (I) se obtienen por medio de la reacción de desprotección. Los productos se aíslan por medios convencionales y con preferencia se purifican por cromatografía.



Esquema 4

Otro método para la preparación de los compuestos de fórmula (I) se ilustra en el Esquema 5. En la etapa (a) un alquino adecuado se acopla a los bloques de construcción de tipo A5 para producir los compuestos B5. el resto NH_2-en B5 también se puede transformar en los grupos NH-$R^{4'}$ en C5, por ejemplo por medio de acilación, alquilación o sulfonamidación. Después de la desprotección en la etapa (c) el grupo NH-R^4 opcionalmente también se puede modificar a $NR^{4'}R^{4''}$ por ejemplo por medio de las reacciones de alquilación, antes de la conversión en los compuestos de tipo F5 en una reacción de amidación. Finalmente, los compuestos de la fórmula (I) se obtienen por medio de la reacción de desprotección. Los productos se aíslan por medios convencionales y con preferencia se purifican por cromatografía.

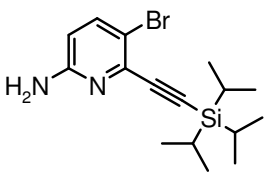


Esquema 5

Como se ejemplifica en la parte experimental, los productos iniciales de fórmula (I) opcionalmente también se pueden modificar para obtener compuestos de fórmula (I) adicionales.

Preparación de compuestos B

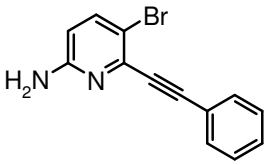
B1a) 5-bromo-6-[2-tri(propan-2-il)sililetinil]piridin-2-amina



Una mezcla de 5,6-dibromopiridin-2–amina (60 g, 233 mmol), etinil-tri(propan-

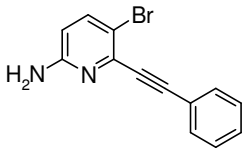
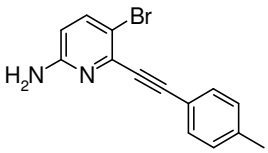
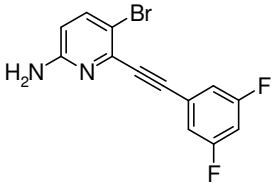
2-il)silano (64 ml, 285 mmol), yoduro de cobre(I) (1,5 g, 7,88 mmol), Diclorobis(trifenil-fosfino)paladio(II) (4,0 g, 5,48 mmol) y trietilamina (80 ml, 577 mmol) se agita bajo atmósfera de argón en ACN (200 ml) con THF (100 ml) durante 2 horas a 50°C. La mezcla se concentra in vacuo y el producto se purifica por cromatografía NP. Rendimiento: 76 g (92%). HPLC-MS: M+H=353/355; tR=1,79 min (*Método_1).

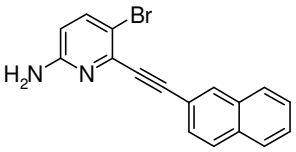
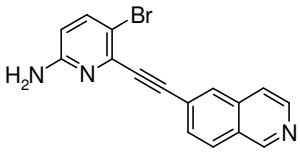
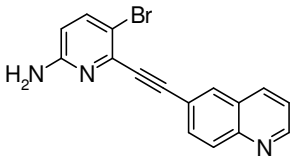
B2a) 5-bromo-6-(2-feniletinil)piridin-2–amina



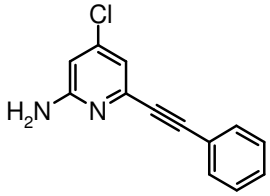
Una mezcla de 5,6-dibromopiridin-2–amina (80 g, 318 mmol), etinilbenceno (78 ml, 698 mmol), yoduro de cobre(I) (1,51 g, 7,94 mmol), Diclorobis(trifenilfosfino)-paladio(II) (5,79 g, 7,94 mmol) y trietilamina (110 ml, 794 mmol) se agita bajo atmósfera de argón en ACN (500 ml) con THF (250 ml) durante 21 horas a 50°C. La mezcla se diluye con agua y se extrae con DCM. Las fases orgánicas combinadas se secan en $MgSO_4$, se concentran al vacío y el producto se purifica por cromatografía NP. Rendimiento: 82 g (94%). HPLC-MS: M+H=273/275; tR=1,34 min (*Método_1).

Los siguientes compuestos se preparan de modo análogo:

#	**Estructura molecular**	**Nombre químico**
B2a		5-bromo-6-(2-feniletinil)piridin-2–amina
B2b		5-bromo-6-[2-(4-metilfenil)etinil]piridin-2–amina
B2c		5-bromo-6-[2-(3,5-difluorofenil)etinil]piridin-2–amina

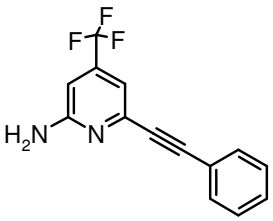
B2d		5-bromo-6-(2-naftalen-2-iletinil)piridin-2–amina
B2e		5-bromo-6-(2-isoquinolin-6-iletinil)piridin-2–amina
B2f		5-bromo-6-(2-quinolin-6-iletinil)piridin-2–amina

B3a) 4-cloro-6-(2-feniletinil)piridin-2–amina



Una mezcla de 4,6-dicloropiridin-2–amina (2,0 g, 12,3 mmol), etinilbenceno (2,51 g, 24,5 mmol), yoduro de cobre(I) (234 mg, 1,23 mmol), Diclorobis(trifenilfosfino)-paladio(II) (1,0 g, 1,23 mmol) y trietilamina (4,3 ml, 31 mmol) se agita bajo atmósfera de argón en ACN (20 ml) con THF (10 ml) durante 6 horas a 90°C. La mezcla se diluye con agua y se extrae con EtOAc. Las fases orgánicas combinadas se secan en $MgSO_4$, se concentran al vacío y el producto se purifica por cromatografía NP. Rendimiento: 1,2 g (43%). HPLC-MS: M+H=229; tR=1,96 min (*Método_2).G

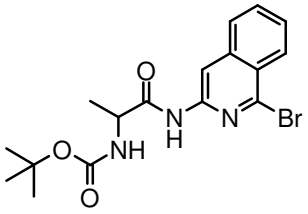
B3b) 6-(2-feniletinil)-4-(trifluorometil)piridin-2–amina



Una mezcla de 6-cloro-4-(trifluorometil)piridin-2–amina (1,0 g, 5,09 mmol) etinilbenceno (779 mg, 7,63 mmol), 1,1′-Bis(difenilfosfino)ferroceno]dicloropaladio(II)

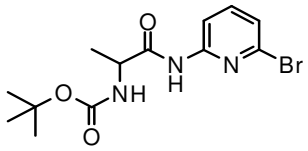
(372 mg, 0,51 mmol), yoduro de cobre(I) (96 mg, 0,51 mmol), trietilamina (1,8 ml, 12,7 mmol), ACN (10 ml) y THF (5 ml) se agita durante 6 horas a 90°C. La mezcla se concentra en vacuo, se añade agua (100 ml) y la mezcla se extrae con EtOAc. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. El producto se purifica por cromatografía NP. Rendimiento: 680 mg (51%). HPLC-MS: M+H=263.

B4a) N-[1-[(1-bromoisoquinolin-3-il)amino]-1-oxopropan-2-il]carbamato de ter-butilo

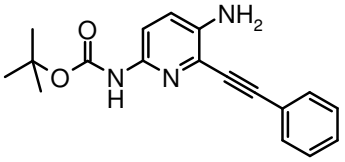


Se añade HATU (7,5 g, 19,7 mmol) a una mezcla de 1-bromoisoquinolin-3–amina (2,0 g, 9,0 mmol), ácido 2-[(2-metilpropan-2-il)oxicarbonilamino]propanoico (1,7 g, 9,0 mmol) y DIPEA (3,4 ml, 200 mmol) en DMA (10 ml). Después de agitar durante 3 días a RT la mezcla se concentra al vacío y el producto se purifica por RP HPLC. Rendimiento: 3,3 g (94%). HPLC-MS: M-H=392/394; tR=1,97 min (*Método_1).

El siguiente compuesto se prepara de modo análogo:

#	Estructura molecular	Nombre químico
B4b		N-[1-[(6-bromopiridin-2-il)amino]-1-oxopropan-2-il]carbamato de ter-butilo

B5a) N-[5-amino-6-(2-feniletinil)piridin-2-il]carbamato de ter-butilo

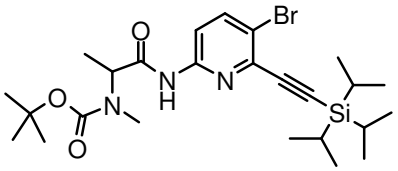


N-(5-amino-6-bromopiridin-2-il)carbamato de ter–butilo A5 (617 mg, 1,82 mmol), etinilbenceno (420 µl, 3,82 mmol), yoduro de cobre(I) (35 mg, 0,18 mmol), 1,1′-Bis(difenilfosfino)ferroceno]dicloropaladio(II) (66,4 mg, 0,09 mmol) y trietilamina (631 µl, 4,55 mmol) se agitan bajo atmósfera de argón en una mezcla de ACN (10 ml)

y THF (5 ml) durante 2 horas a RT. La mezcla se calienta a 45ºC y se agita durante 70 h. La mezcla se concentra al vacío y el producto se purifica por RP HPLC. Rendimiento: 320 mg (57%). HPLC-MS: M+H=310; tR=2,05 min (*Método_2).

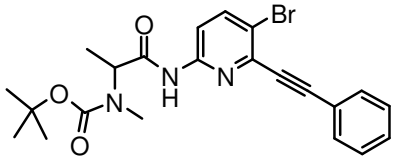
Preparación de compuestos C

C1a) N-[1-[[5-bromo-6-[2-tri(propan-2-il)sililetinil]piridin-2-il]amino]-1-oxo-propan-2-il]-N-metilcarbamato de ter–butilo



Una mezcla de ácido 2-[metil-[(2-metilpropan-2-il)oxicarbonil]amino]propanoico (55 g, 271 mmol) y N,N'-diciclohexilcarbodiimida (35 g, 170 mmol) en DCM (200 ml) se agita con enfriamiento en baño de hielo durante 30 minutos. Se añade una solución de 5-bromo-6-[2-tri(propan-2-il)sililetinil]piridin-2–amina B1a (40 g, 113 mmol) en DCM (100 ml). Después de agitar durante 14 días a RT la mezcla de reacción se diluye con DCM y se extrae con agua. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. El producto se purifica por cromatografía NP. Rendimiento: 51 g (95%). HPLC-MS: M+H= 538/540; tR=1,97 min (*Método_1).

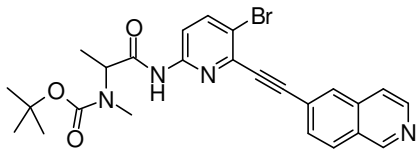
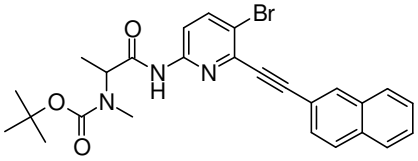
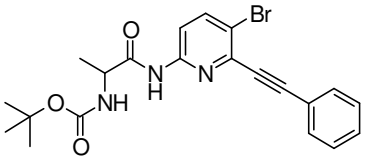
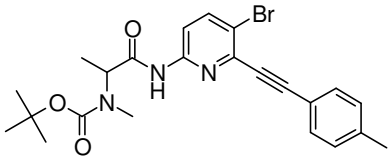
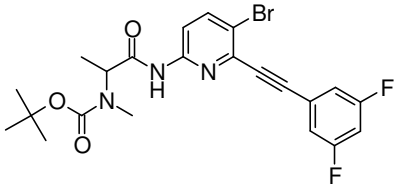
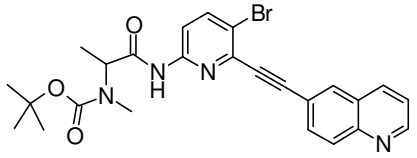
C2a) N-[1-[[5-bromo-6-(2-feniletinil)piridin-2-il]amino]-1-oxopropan-2-il]-N-metil-carbamato de ter–butilo



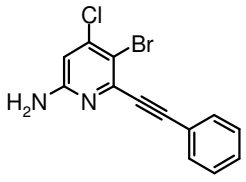
Una mezcla de ácido 2-[metil-[(2-metilpropan-2-il)¬oxicarbonil]¬amino]¬propanoico (36 g, 177 mmol) y N,N'-diciclohexilcarbodiimide (22,5 g, 109 mmol) en DCM (150 ml) se agita con enfriamiento en baño de hielo durante 30 minutos. Se añade una solución de 5-bromo-6-(2-feniletinil)piridin-2–amina B2a (20 g, 73,2 mmol) en DCM (100 ml). Después de agitar durante 7 días a RT la mezcla de reacción se diluye con DCM y se extrae con agua. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. El producto se purifica por cromatografía NP. Rendimiento: 25 g (74%). HPLC-MS: M+H= 458/460; tR=2,33 min

(*Método_1).

Los siguientes compuestos se preparan de modo análogo:

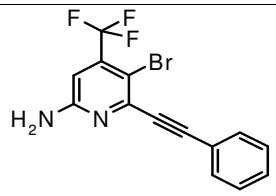
#	Estructura molecular	Nombre químico
C2b		N-[1-[[5-bromo-6-(2-naftalen-2-il-etinil)piridin-2-il]amino]-1-oxo-propan-2-il]-N-metilcarbamato de ter–butilo
C2c		N-[1-[[5-bromo-6-(2-feniletinil)-piridin-2-il]amino]-1-oxopropan-2-il]carbamato de ter–butilo
C2d		N-[1-[[5-bromo-6-(2-feniletinil)-piridin-2-il]amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo
C2e		N-[1-[[5-bromo-6-[2-(4-metilfenil)-etinil]piridin-2-il]amino]-1-oxo-propan-2-il]-N-metilcarbamato de ter–butilo
C2f		N-[1-[[5-bromo-6-[2-(3,5-difluorofenil)etinil]piridin-2-il]amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo
C2g		N-[1-[[5-bromo-6-(2-quinolin-6-il-etinil)piridin-2-il]amino]-1-oxo-propan-2-il]-N-metilcarbamato de ter–butilo

C3a) 5-bromo-4-cloro-6-(2-feniletinil)piridin-2–amina

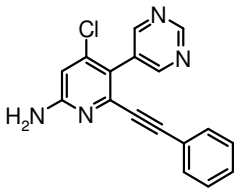


Una mezcla de 4-cloro-6-(2-feniletinil)piridin-2–amina B3a (1,0 g, 4,37 mmol), NBS (778 mg, 4,37 mmol) y ACN (20 ml) se agita durante 3 horas a RT en la oscuridad. La mezcla se concentra al vacío y el producto se purifica por cromatografía NP. Rendimiento: 1,0 g (74%). HPLC-MS: M+H=307/309.

El siguiente compuesto se prepara de modo análogo:

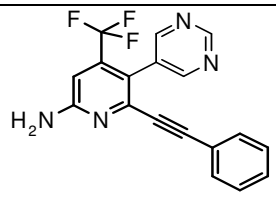
#	Estructura molecular	Nombre químico
C3b		5-bromo-6-(2-feniletinil)-4-(trifluorometil)piridin-2–amina

C3c) 4-cloro-6-(2-feniletinil)-5-pirimidin-5-ilpiridin-2–amina

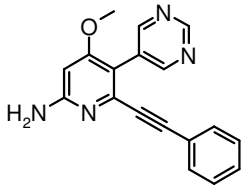


Una mezcla de 5-bromo-4-cloro-6-(2-feniletinil)piridin-2–amina C3a (1,0 g, 3,25 mmol), ácido pirimidin-5-ilborónico (604 mg, 4,88 mmol), Tetrakis(trifenilfosfino)-paladio(0) (375 mg, 0,33 mmol), carbonato de sodio (solución acuosa, 2 mol/l, 4,88 ml, 9,75 mmol) y ACN (15 ml) se agita en un tubo sellado a 120°C hasta que C3a casi se consumió por completo. La mezcla luego se concentran al vacío y el producto se purifica por cromatografía NP. Rendimiento: 420 mg (42%). HPLC-MS: M+H=307.

Los siguientes compuestos se preparan de modo análogo:

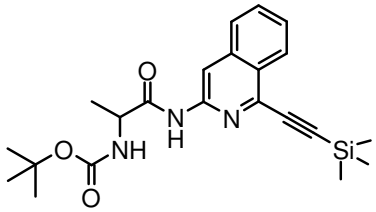
#	Estructura molecular	Nombre químico
C3d		6-(2-feniletinil)-5-pirimidin-5-il-4-(trifluorometil)piridin-2–amina

C3e) 4-methoxi-6-(2-feniletinil)-5-pirimidin-5-ilpiridin-2–amina



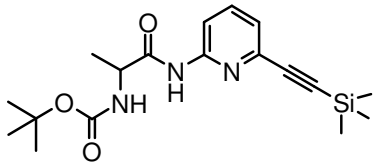
Una mezcla de 4-cloro-6-(2-feniletinil)-5-pirimidin-5-ilpiridin-2–amina C3c (400 mg, 1,3 mmol), metóxido de sodio (una solución de 2,61 mmol en 0,29 ml MeOH) y MeOH (2 ml) se agita durante 20 minutos a 100°C y 10 minutos a 110°C. La mezcla se diluye con agua y se extrae con DCM. Las fases orgánicas combinadas se secan en Na_2SO_4, se concentran al vacío y el producto se purifica por cromatografía NP. Rendimiento: 228 mg (58%). HPLC-MS: M+H=303.

C4a) N-[1-oxo-1-[[1-(2-trimetilsililetinil)isoquinolin-3-il]amino]propan-2-il]-carbamato de ter–butilo

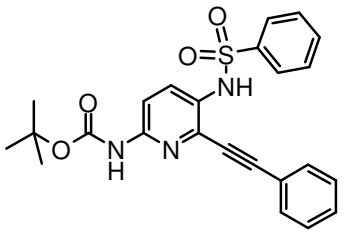


Una mezcla de N-[1-[(1-bromoisoquinolin-3-il)amino]-1-oxopropan-2-il]-carbamato de ter–butilo B4a (500 mg, 1,27 mmol), etinil(trimetil)silano (137 mg, 1,4 mmol), yoduro de cobre(I) (23 mg, 0,12 mmol), Diclorobis(trifenilfosfino)paladio(II) (90 mg, 0,13 mmol) y DIPEA (700 µl, 4,12 mmol) se agita bajo atmósfera de argón en NMP (4 ml) durante 1 hora a 80°C. La mezcla se concentra al vacío y el producto se purifica por RP HPLC. Rendimiento: 319 mg (61%). HPLC-MS: M+H=412; tR=2,11 min (*Método_4).

El siguiente compuesto se prepara de modo análogo:

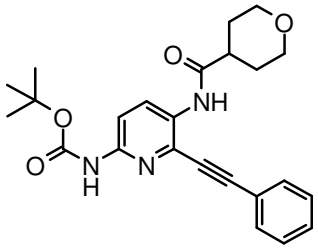
#	Estructura molecular	Nombre químico
C4b		N-[1-oxo-1-[[6-(2-trimetilsililetinil)piridin-2-il]amino]propan-2-il]carbamato de ter–butilo

C5a) N-[5-(bencensulfonamido)-6-(2-feniletinil)piridin-2-il]carbamato de ter–butilo



Cloruro de bencensulfonilo (20 µl, 0,4 mmol) diluido con 400 µl DCM se añade a una mezcla de N-[5-amino-6-(2-feniletinil)piridin-2-il]carbamato de ter–butilo B5a (40 mg, 0,13 mmol), piridina (32 µl, 0,4 mmol) y 400 µl DCM a RT y se agita durante 1h. La mezcla se concentra al vacío y el producto se purifica por RP HPLC. Rendimiento: 37 mg (64%). HPLC-MS: M+H=450; tR=2,16 min (*Método_2).

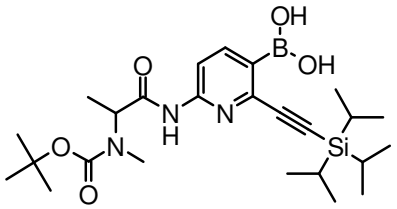
C5b) N-[5-(oxano-4-carbonilamino)-6-(2-feniletinil)piridin-2-il]carbamato de ter–butilo



Una mezcla de ácido oxano-4-carboxílico (45 mg, 0,34 mmol), HATU (162 mg, 0,43 mmol) y DIPEA (43 µl, 0,25 mmol) en DMF (1 ml) se agita a RT durante 30 minutos. Se añade N-[5-amino-6-(2-feniletinil)piridin-2-il]carbamato de ter–butilo B5a (60 mg, 0,19 mmol) y se continúa agitando durante 17 h. La mezcla se concentra al vacío y el producto se purifica por RP HPLC. Rendimiento: 40 mg (49%). HPLC-MS: M+H=422; tR=1,73 min (*Método_5).

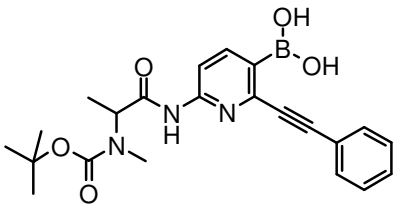
Preparación de los compuestos D

D1a) ácido [6-[2-[metil-[(2-metilpropan-2-il)oxicarbonil]amino]propanoilamino]-2-[2-tri(propan-2-il)sililetinil]piridin-3-il]borónico



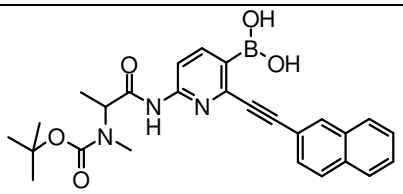
Una mezcla de N-[1-[[5-bromo-6-[2-tri(propan-2-il)sililetinil]piridin-2-il]amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo C1a (51 g, 90 mmol), bis(neopentil glicolato)diboro (40,5 g, 179 mmol), KOAc (26,4 g, 269 mmol), 1,1′-Bis(difenilfosfino)-ferroceno]dicloropaladio(II) (3,3 g, 4,5 mmol) y dioxano (400 ml) se agita bajo atmósfera de argón durante 17 horas a 50°C. La mezcla se diluye con DCM y se extrae con una solución acuosa saturada de $NaHCO_3$. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. El producto se purifica por cromatografía NP. Rendimiento: 21,9 g (48%). HPLC-MS: M+H=504; tR=2,17 min (*Método_4).

D2a) ácido [6-[2-[metil-[(2-metilpropan-2-il)oxicarbonil]amino]propanoilamino]-2-(2-feniletinil)piridin-3-il]borónico

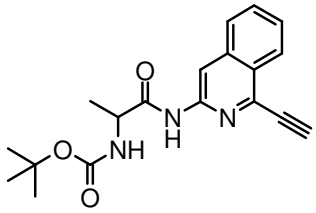


Una mezcla de N-[1-[[5-bromo-6-(2-feniletinil)piridin-2-il]amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo C2a (2,5 g, 5,45 mmol), bis(neopentil glicolato)diboro (2,46 g, 10,9 mmol), KOAc (1,61 g, 16,4 mmol), 1,1′-Bis(difenilfosfino)ferroceno]dicloro-paladio(II) (399 mg, 0,55 mmol) y DMSO (20 ml) se agita bajo atmósfera de argón durante 39 horas a 65°C. La mezcla se diluye con agua y se extrae con DCM. Las fases orgánicas combinadas se secan en $MgSO_4$, se concentran al vacío y el producto se purifica por RP HPLC. Rendimiento: 1,73 g (75%). HPLC-MS: M+H=424; tR=1,59 min (*Método_5).

El siguiente compuesto se prepara de modo análogo:

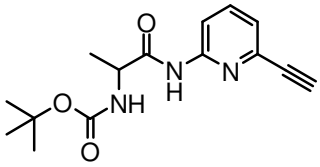
#	Estructura molecular	Nombre químico
D2b		Ácido [6-[2-[metil-[(2-metilpropan-2-il)-oxicarbonil]amino]propanoilamino]-2-(2-naftalen-2-iletinil)piridin-3-il]borónico

D4a) N-[1-[(1-etinilisoquinolin-3-il)amino]-1-oxopropan-2-il]carbamato de ter–butilo

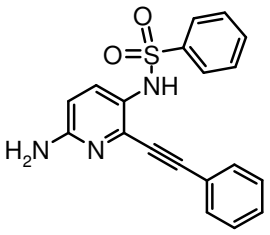


Una mezcla de N-[1-oxo-1-[[1-(2-trimetilsililetinil)isoquinolin-3-il]amino]propan-2-il]carbamato de ter–butilo C4a (319 mg, 0,78 mmol), solución acuosa de KOH 1 N (3 ml) y MeOH (10 ml) se agita a RT durante 2 h. La mezcla se diluye con agua y se extrae con EtOAc. Las fases orgánicas combinadas se secan en Na_2SO_4 y se concentran al vacío y el producto se purifica por RP HPLC. Rendimiento: 225 mg (86%). HPLC-MS: M+H=340; tR=1,84 min (*Método_1).

El siguiente compuesto se prepara de modo análogo:

#	Estructura molecular	Nombre químico
D4b		N-[1-[(6-etinilpiridin-2-il)amino]-1-oxopropan-2-il]carbamato de ter–butilo

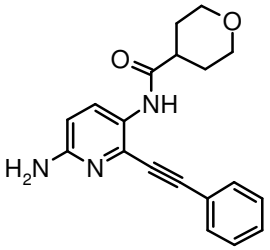
D5a) N-[6-amino-2-(2-feniletinil)piridin-3-il]bencensulfonamida



Una mezcla de N-[5-(bencensulfonamido)-6-(2-feniletinil)piridin-2-il]carbamato de ter–butilo C5a (37 mg, 0,08 mmol) y DCM:TFA (9:1, 4 ml) se agita a RT durante 2 horas. La mezcla se diluye con DCM y se extrae con una solución acuosa saturada of $NaHCO_3$.

Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. El producto bruto D5a (27 mg) se usa en la próxima etapa sin purificación adicional.

D5b) N-[6-amino-2-(2-feniletinil)piridin-3-il]oxane-4-carboxamida

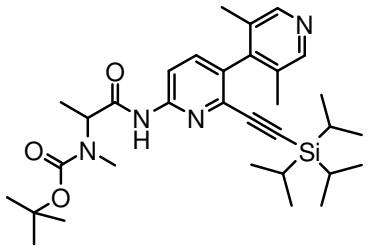


Una mezcla de N-[5-(oxano-4-carbonilamino)-6-(2-feniletinil)piridin-2-il]-carbamato de ter–butilo C5b (29 mg, 0,07 mmol) y DCM:TFA (9:1, 3 ml) se agita a RT durante 2 h. La mezcla se diluye con DCM y se extrae con una solución acuosa saturada de $NaHCO_3$.

Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. E l producto bruto (28 mg) se usa en la próxima etapa sin purificación adicional.

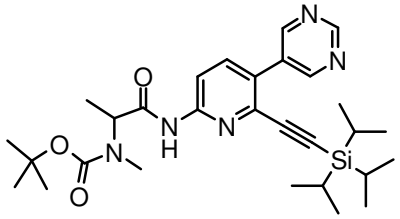
Preparación de los compuestos E

E1a) N-[1-[[5-(3,5-dimetilpiridin-4-il)-6-[2-tri(propan-2-il)sililetinil]piridin-2-il]-amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo



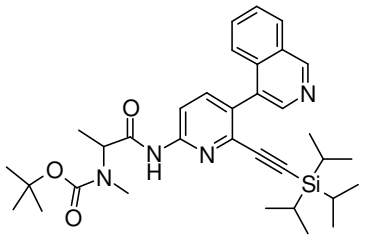
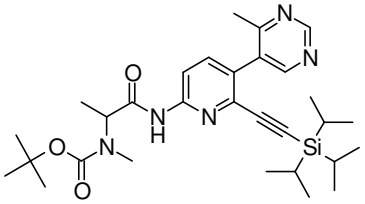
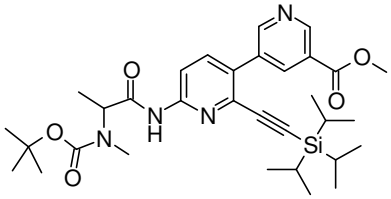
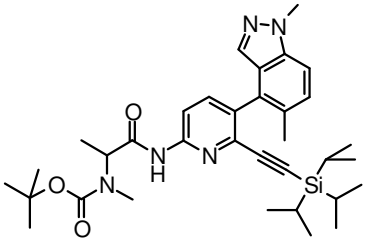
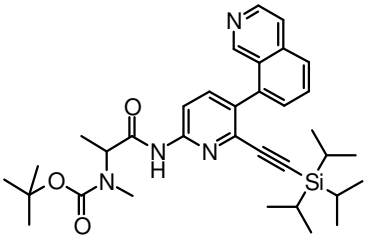
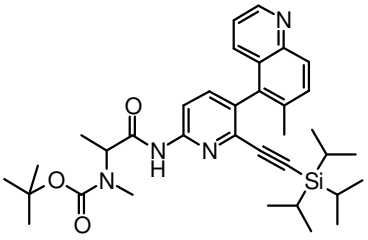
Una mezcla de N-[1-[[5-bromo-6-[2-tri(propan-2-il)sililetinil]piridin-2-il]amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo C1a (300 mg, 0,56 mmol), 3,5-dimetil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridina (169 mg, 0,72 mmol), Na_2CO_3 (118 mg, 1,11 mmol), 1,1′-Bis(difenilfosfino)ferroceno]dicloropaladio(II) (40,8 mg, 0,06 mmol), dioxano (2 ml) y agua (0,4 ml) se agita bajo atmósfera de argón durante 17 horas a 90°C. La mezcla se concentra al vacío y el producto se purifica por RP HPLC. Rendimiento: 26 mg (51%). HPLC-MS: M+H=565; tR=2,32 min (*Método_4).

E1b) N-metil-N-[1-oxo-1-[[5-pirimidin-5-il-6-[2-tri(propan-2-il)sililetinil]piridin-2-il]amino]propan-2-il]carbamato de ter–butilo

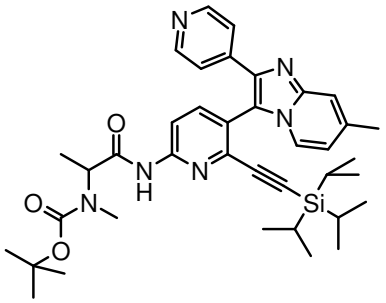


Una mezcla de N-[1-[[5-bromo-6-[2-tri(propan-2-il)sililetinil]piridin-2-il]amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo C1a (3,5 g, 6,5 mmol), ácido pirimidin-5-ilborónico (1,0 g, 7,8 mmol), Na_2CO_3 (1,4 g, 13,2 mmol), Diclorobis(trifenilfosfino)-paladio(II) (450 mg, 0,64 mmol), dioxano (20 ml), MeOH (5 ml) y agua (3,5 ml) se agita bajo atmósfera de argón durante 17 horas a 80°C. La mezcla se diluye con agua y se extrae con DCM. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. El producto se purifica por RP HPLC. Rendimiento: 2,33 g (67%). HPLC-MS: M+H=538; tR=2,26 min (*Método_4).

Los siguientes compuestos se preparan de modo análogo:

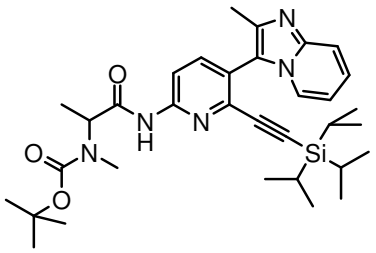
#	Estructura molecular	Nombre químico
E1c		N-[1-[[5-isoquinolin-4-il-6-[2-tri(propan-2-il)sililetinil]piridin-2-il]-amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo
E1d		N-metil-N-[1-[[5-(4-metilpirimidin-5-il)-6-[2-tri(propan-2-il)sililetinil]piridin-2-il]amino]-1-oxopropan-2-il]-carbamato de ter–butilo
E1e		5-[6-[2-[metil-[(2-metilpropan-2-il)oxi-carbonil]amino]propanoilamino]-2-[2-tri(propan-2-il)sililetinil]piridin-3-il]-piridina-3-carboxilato de metilo
E1f		N-[1-[[5-(1,5-dimetilindazol-4-il)-6-[2-tri(propan-2-il)sililetinil]piridin-2-il]-amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo
E1g		N-[1-[[5-isoquinolin-8-il-6-[2-tri(propan-2-il)sililetinil]piridin-2-il]-amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo
E1i		N-metil-N-[1-[[5-(6-metilquinolin-5-il)-6-[2-tri(propan-2-il)sililetinil]piridin-2-il]amino]-1-oxopropan-2-il]carbamato de ter–butilo

E1j) N-metil-N-[1-[[5-(7-metil-2-piridin-4-ilimidazo[1,2-a]piridin-3-il)-6-[2-tri(propan-2-il)sililetinil]piridin-2-il]amino]-1-oxopropan-2-il]carbamato de ter–butilo



Una mezcla de ácido [6-[2-[metil-[(2-metilpropan-2-il)oxicarbonil]amino]-propanoilamino]-2-[2-tri(propan-2-il)sililetinil]piridin-3-il]borónico D1a (1,5 g, 3,0 mmol), 3–yodo-7-metil-2-piridin-4-ilimidazo[1,2-a]piridina Za (1,3 g, 3,9 mmol), Na_2CO_3 (0,95 g, 8,9 mmol), Diclorobis(trifenilfosfino)paladio(II) (209 mg, 0,3 mmol), dioxano (30 ml) y agua (5 ml) se agita bajo atmósfera de argón durante 17 horas a 70°C. La mezcla se diluye con agua y se extrae con DCM. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. El producto se purifica por RP HPLC. Rendimiento: 965 mg (49%). HPLC-MS: M+H=667; tR=2,04 min (*Método_3).

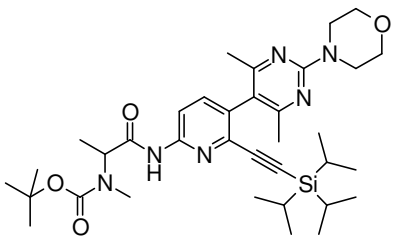
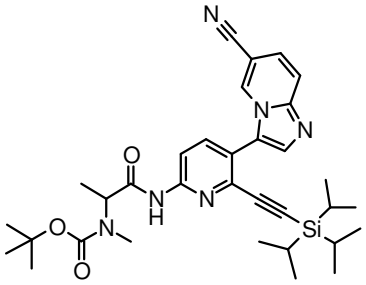
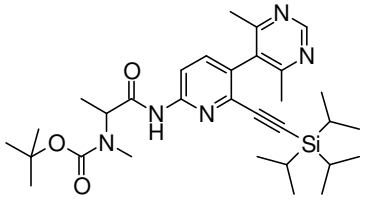
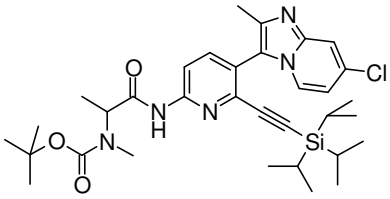
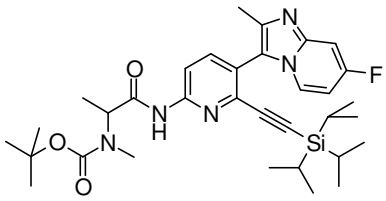
E1k) N-metil-N-[1-[[5-(2-metilimidazo[1,2-a]piridin-3-il)-6-[2-tri(propan-2-il)silil-etinil]piridin-2-il]amino]-1-oxopropan-2-il]carbamato de ter–butilo

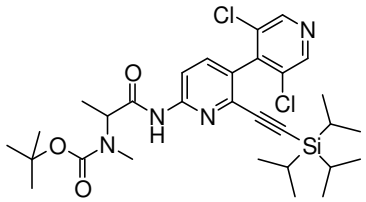
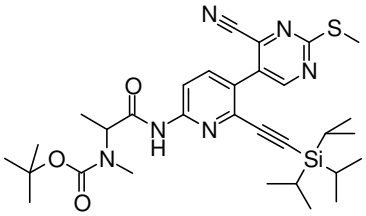
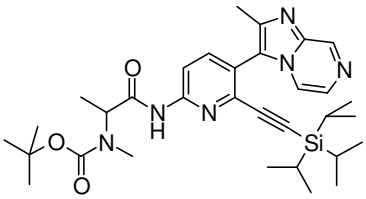
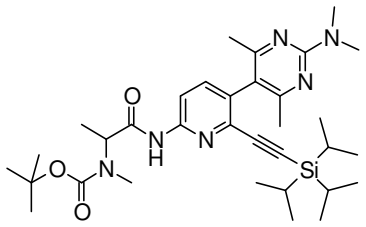
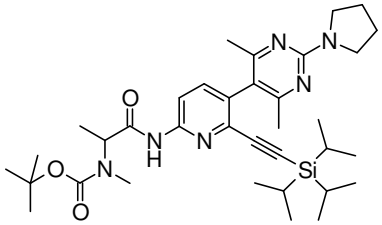


Una mezcla de [6-[2-[metil-[(2-metilpropan-2-il)oxicarbonil]amino]-propanoilamino]-2-[2-tri(propan-2-il)sililetinil]piridin-3-il]borónico D1a (1,5 g, 3,0 mmol), 3-bromo-2-metilimidazo[1,2-a]piridina (842 mg, 3,9 mmol), Na_2CO_3 (0,95 g, 8,9 mmol), Diclorobis(trifenilfosfino)paladio(II) (209 mg, 0,3 mmol), dioxano (30 ml) y agua (5 ml) se agita bajo atmósfera de argón durante 2 horas a 60°C. La mezcla se diluye con agua y se extrae con DCM. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. El producto se purifica por RP HPLC. Rendimiento: 0,6 g (34%).

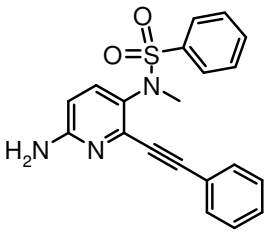
HPLC-MS: M+H=590; tR=2,05 min (*Método_3).

Los siguientes compuestos se preparan de modo análogo. Para los compuestos E1l, E1o, E1s y E1u se utilizan los bloques de construcción Zb-Ze.

#	**Estructura molecular**	**Nombre químico**
E1l		N-[1-[[5-(4,6-dimetil-2-morfolina-4-ilpirimidin-5-il)-6-[2-tri(propan-2-il)silil-etinil]piridin-2-il]amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo
E1m		N-[1-[[5-(6-cianoimidazo[1,2-a]piridin-3-il)-6-[2-tri(propan-2-il)sililetinil]-piridin-2-il]amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo
E1n		N-[1-[[5-(4,6-dimetilpirimidin-5-il)-6-[2-tri(propan-2-il)sililetinil]piridin-2-il]-amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo
E1o		N-[1-[[5-(7-cloro-2-metilimidazo[1,2-a]-piridin-3-il)-6-[2-tri(propan-2-il)silil-etinil]piridin-2-il]amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo
E1p		N-[1-[[5-(7-fluoro-2-metilimidazo[1,2-a]piridin-3-il)-6-[2-tri(propan-2-il)silil-etinil]piridin-2-il]amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo

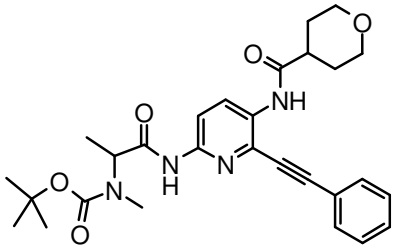
#	Estructura molecular	Nombre químico
E1q		N-[1-[[5-(3,5-dicloropiridin-4-il)-6-[2-tri(propan-2-il)sililetinil]piridin-2-il]-amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo
E1r		N-[1-[[5-(4-ciano-2-metilsulfanilpirimidin-5-il)-6-[2-tri(propan-2-il)sililetinil]piridin-2-il]-amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo
E1s		N–metil-N-[1-[[5-(2-metilimidazo[1,2-a]pirazin-3-il)-6-[2-tri(propan-2-il)silil-etinil]piridin-2-il]amino]-1-oxopropan-2-il]carbamato de ter–butilo
E1t		N–[1-[[5-[2-(dimetilamino)-4,6-dimetilpirimidin-5-il]-6-[2-tri(propan-2-il)sililetinil]piridin-2-il]amino]-1-oxo-propan-2-il]-N-metilcarbamato de ter–butilo
E1u		N–[1-[[5-(4,6-dimetil-2-pirrolidin-1-ilpirimidin-5-il)-6-[2-tri(propan-2-il)silil-etinil]piridin-2-il]amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo

E5a) N-[6-amino-2-(2-feniletinil)piridin-3-il]-N-metilbencensulfonamida



A RT NaH (60% de dispersión en aceite mineral, 4,6 mg, 0,12 mmol) se añade a N-[6-amino-2-(2-feniletinil)piridin-3-il]bencensulfonamida D5a (27 mg, aprox 0,07 mmol) en THF (0,6 ml). Después de agitar durante 10 minutos se añade dimetilsulfato (8 µl, 0,08 mmol) a la mezcla y se continúa agitando durante 1 h. La mezcla se concentra al vacío y el producto se purifica por RP HPLC. Rendimiento: 16 mg (57%). HPLC-MS: M+H=364; tR=1,85 min (*Método_2).

E5b) N–-metil-N-[1-[[5-(oxane-4-carbonilamino)-6-(2-feniletinil)piridin-2-il]-amino]-1-oxopropan-2-il]carbamato de ter–butilo

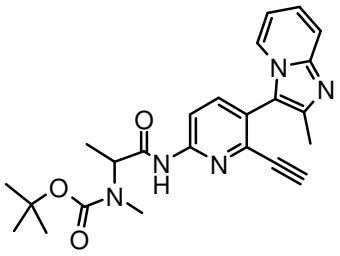


Una mezcla de ácido 2-[metil-[(2-metilpropan-2-il)¬oxicarbonil]¬amino]¬propanoico (34 mg, 0,17 mmol) y N,N'-diciclohexilcarbodiimida (17 mg, 0,08 mmol) en DCM (1 ml) se agita a RT durante 20 minutos. Esta mezcla se añade a N-[6-amino-2-(2-feniletinil)piridin-3-il]oxane-4-carboxamida D5b (28 mg, 0,09 mmol) y DIPEA (17 µl; 0,10 mmol) en DCM (1 ml). Después de agitar durante 6 días a 40℃ la mezcla de reacción se diluye con DCM y se extrae con agua. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. El producto bruto (70 mg) se usa en la próxima etapa sin purificación adicional.

Preparación de los compuestos F1

Todos los compuestos que contienen triisopropil-alquino (por ejemplo E1a-E1u) se desililan de modo análogo al que se ejemplifica para:

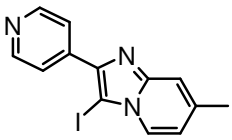
F1a N–-[1-[[6-etinil-5-(2-metilimidazo[1,2-a]piridin-3-il)piridin-2-il]amino]-1-oxo-propan-2-il]-N-metilcarbamato de ter–butilo



Una mezcla de N–-metil-N-[1-[[5-(2-metilimidazo[1,2-a]piridin-3-il)-6-[2-tri-(propan-2-il)sililetinil]piridin-2-il]amino]-1-oxopropan-2-il]carbamato de ter–butilo E1k (16,7 g, 28,3 mmol), THF (200 ml) y fluoruro de tetrabutilamonio (1 mol/l solución en THF, 34 ml, 34 mmol) se agita a RT durante 15 minutos. La mezcla se diluye con DCM y se extrae con una solución acuosa saturada de $NaHCO_3$. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. La mezcla se concentra al vacío y el producto se purifica por cromatografía NP. Rendimiento: 10,6 g (86%). HPLC-MS: M+H=434; tR=1,20 min (*Método_1).

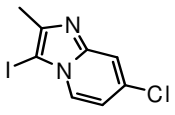
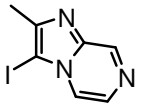
Los bloques de construcción Z adicionales se sintetizan de la siguiente manera:

Za) 3–yodo-7-metil-2-piridin-4-ilimidazo[1,2-a]piridina

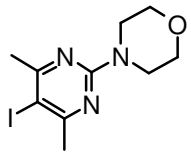


Una mezcla de 7-metil-2-piridin-4-ilimidazo[1,2-a]piridina (6,52 g, 31,1 mmol), N–yodosuccinimida (7,0 g, 31,1 mmol) y ACN (180 ml) se agita a RT durante 17 h. El precipitado se recolecta, se lava con ACN y se seca. Rendimiento: 4,4 g (42%). HPLC-MS: M+H=336; tR=1,55 min (*Método_3).

Los siguientes bloques de construcción se preparan de modo análogo:

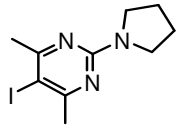
#	Estructura molecular	Nombre químico
Zb		7-cloro-3–yodo-2-metilimidazo[1,2-a]piridina
Zc		3–yodo-2-metilimidazo[1,2-a]pirazina

Zd) 4-(5–yodo-4,6-dimetilpirimidin-2-il)morfolina



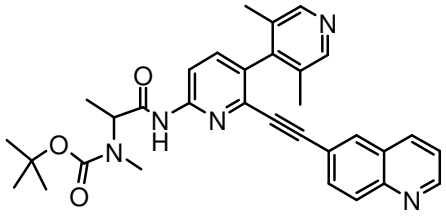
Una mezcla de 4-(4,6-dimetilpirimidin-2-il)morfolina (20,6 g, 107 mmol), N–yodosuccinimida (28,8 g, 128 mmol) y ACN (400 ml) se agita a RT durante 24 h. DCM y se añade una solución acuosa que contiene 3% tiosulfato de sodio y la mezcla se extrae con DCM. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. Este material se usa sin purificación adicional. Rendimiento: 33,7 g (89%).

El siguiente bloque de construcción se prepara de modo análogo:

#	**Estructura molecular**	**Nombre químico**
Ze		5–yodo-4,6-dimetil-2-pirrolidin-1-ilpirimidina

Preparación de los ejemplos (I): La siguiente sección comprende la última etapa respectiva hacia los ejemplos combinados con la correspondiente etapa de desprotección posterior, cuando sea requerido:

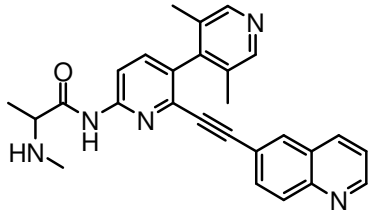
G1a N–-[1-[[5-(3,5-dimetilpiridin-4-il)-6-(2-quinolin-6-iletinil)piridin-2-il]amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo



Una mezcla de N–-[1-[[5-(3,5-dimetilpiridin-4-il)-6-etinilpiridin-2-il]amino]-1-oxo-propan-2-il]-N-metilcarbamato de ter–butilo (E1a desililado de acuerdo con el método general ejemplificado para F1a) (50 mg, 0,12 mmol), 6–yodoquinolina (89 mg, 0,35 mmol), yoduro de cobre(I) (2,2 mg, 0,01 mmol), Diclorobis(trifenilfosfino)paladio(II) (8,1

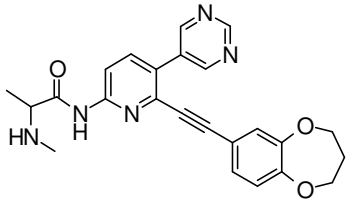
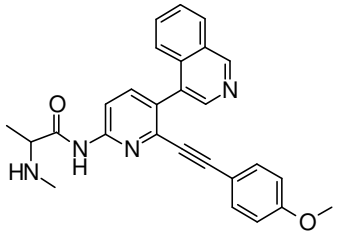
mg, 0,01 mmol) y trietilamina (64 µl, 0,47 mmol) se agita bajo atmósfera de argón en NMP (0,5 ml) durante 1 hora a 50°C. La mezcla se concentra al vacío y el producto se purifica por RP HPLC. Rendimiento: 28 mg (45%). HPLC-MS: M+H=536; tR=1,79 min (*Método_3).

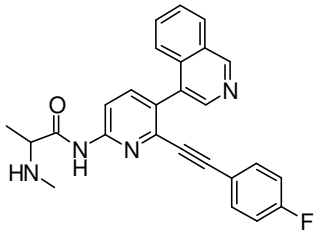
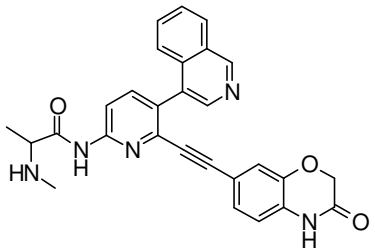
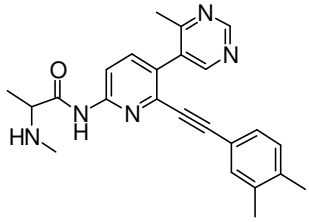
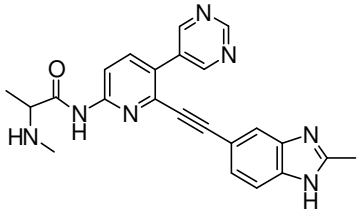
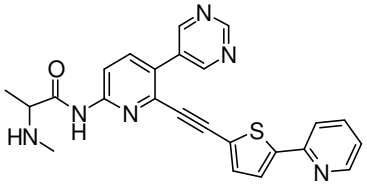
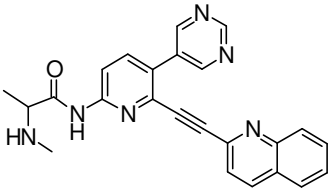
Ejemplo 1 N-[5-(3,5-dimetilpiridin-4-il)-6-(2-quinolin-6-iletinil)piridin-2-il]-2-(metilamino)propanamida

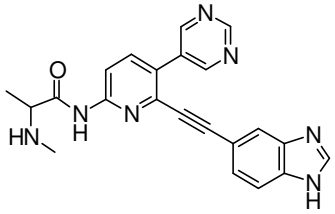
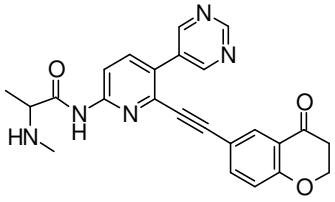
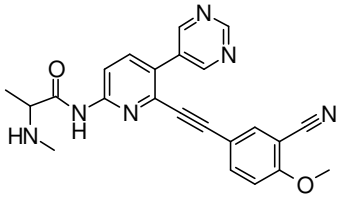
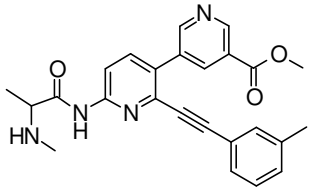
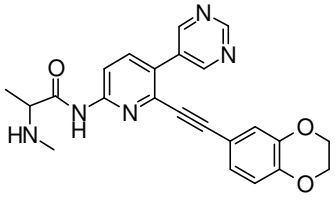
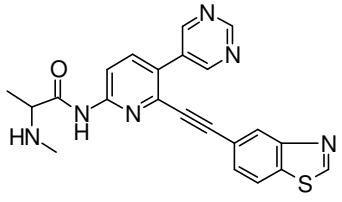


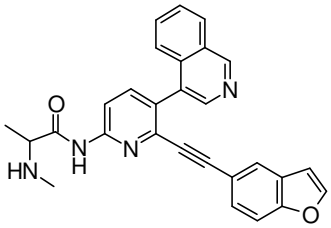
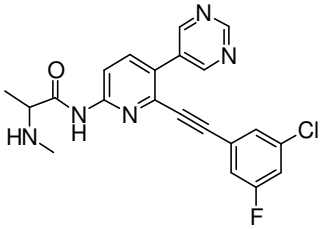
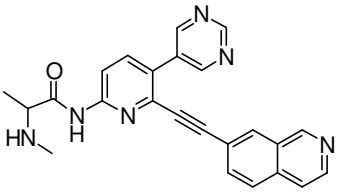
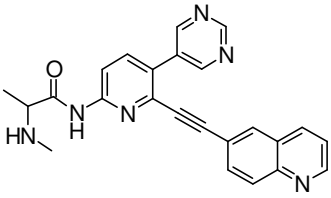
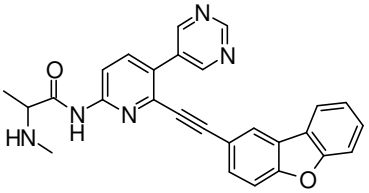
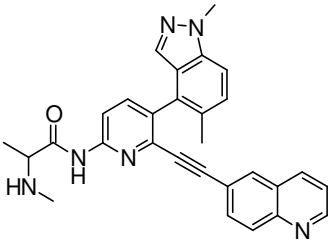
Una mezcla de N–-[1-[[5-(3,5-dimetilpiridin-4-il)-6-(2-quinolin-6-iletinil)piridin-2-il]amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo G1a (28 mg, 0,05 mmol) y DCM:TFA (8:2, 10 ml) se agita a RT durante 15 minutos. La mezcla se diluye con tolueno (10 ml) y se concentran al vacío. El producto se purifica por RP HPLC. Rendimiento: 16 mg (70%). HPLC-MS: M+H=436; tR=1,09 min (*Método_1).

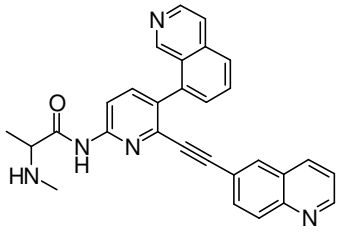
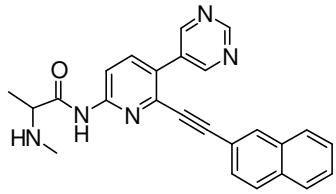
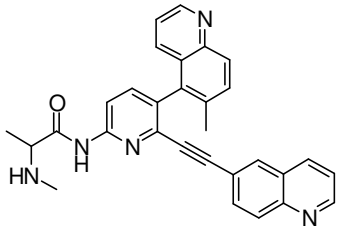
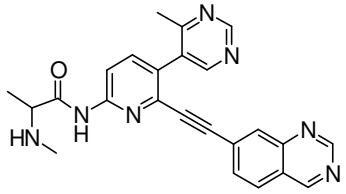
Los siguientes ejemplos se preparan de modo análogo:

#	Estructura molecular	Nombre químico	HPLC-MS
2		N-[6-[2-(3,4-dihidro-2H-1,5-benzodioxepin-7-il)etinil]-5-pirimidin-5-ilpiridin-2-il]-2-(metilamino)propanamida	M+H=430; tR=1,23
3		N-[5-isoquinolin-4-il-6-[2-(4-metoxifenil)etinil]piridin-2-il]-2-(metilamino)propanamida	M+H=437; tR=1,92

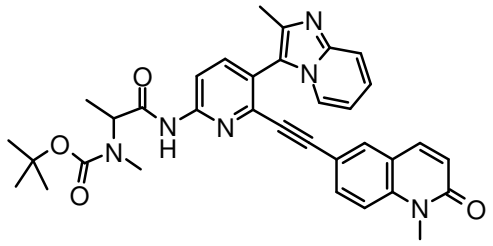
#	Estructura molecular	Nombre químico	HPLC-MS
4		N-[6-[2-(4-fluorofenil)etinil]-5-isoquinolin-4-ilpiridin-2-il]-2-(metilamino)propanamida	M+H=425; tR=1,95
5		N-[5-isoquinolin-4-il-6-[2-(3-oxo-4H-1,4-benzoxazin-7-il)-etinil]piridin-2-il]-2-(metil-amino)propanamida	M+H=478; tR=1,64
6		N-[6-[2-(3,4-dimetilfenil)etinil]-5-(4-metilpirimidin-5-il)piridin-2-il]-2-(metilamino)propan-amida	M+H=400; tR=1,40
7		2-(metilamino)-N-[6-[2-(2-metil-1H-bencimidazol-5-il)-etinil]-5-pirimidin-5-ilpiridin-2-il]propanamida	M+H=412; tR=0,97
8		2-(metilamino)-N-[6-[2-(5-piridin-2-iltiofen-2-il)etinil]-5-pirimidin-5-ilpiridin-2-il]propan-amida	M+H=441; tR=1,27
9		2-(metilamino)-N-[5-pirimidin-5-il-6-(2-quinolin-2-iletinil)-piridin-2-il]propanamida	M+H=409; tR=1,24

#	Estructura molecular	Nombre químico	HPLC-MS
10		N-[6-[2-(1H-bencimidazol-5-il)-etinil]-5-pirimidin-5-ilpiridin-2-il]-2-(metilamino)propanamida	M+H=398; tR=0,94
11		2-(metilamino)-N-[6-[2-(4-oxo-2,3-dihidrochromen-6-il)etinil]-5-pirimidin-5-ilpiridin-2-il]-propanamida	M+H=428; tR=1,21
12		N-[6-[2-(3-ciano-4-metoxifenil)etinil]-5-pirimidin-5-ilpiridin-2-il]-2-(metilamino)-propanamida	M+H=413; tR=1,23
13		5-[6-[[2-(metilamino)-propanoil]amino]-2-[2-(3-metil-fenil)etinil]piridin-3-il]piridina-3-carboxilato de metilo	M+H=429; tR=1,98
14		N-[6-[2-(2,3-dihidro-1,4-benzodioxin-6-il)etinil]-5-pirimidin-5-ilpiridin-2-il]-2-(metilamino)propanamida	M+H=416; tR=1,19
15		N-[6-[2-(1,3-benzotiazol-5-il)-etinil]-5-pirimidin-5-ilpiridin-2-il]-2-(metilamino)propanamida	M+H=415; tR=1,13

#	Estructura molecular	Nombre químico	HPLC-MS
16		N-[6-[2-(1-benzofuran-5-il)-etinil]-5-isoquinolin-4-ilpiridin-2-il]-2-(metilamino)propan-amida	M+H=447; tR=1,94
17		N-[6-[2-(3-cloro-5-fluorofenil)-etinil]-5-pirimidin-5-ilpiridin-2-il]-2-(metilamino)propanamida	M+H=410; tR=1,36
18		N-[6-(2-isoquinolin-7-iletinil)-5-pirimidin-5-ilpiridin-2-il]-2-(metilamino)propanamida	M+H=409; tR=1,11
19		2-(metilamino)-N-[5-pirimidin-5-il-6-(2-quinolin-6-iletinil)-piridin-2-il]propanamida	M+H=409; tR=1,11
20		N-[6-(2-dibenzofuran-2-iletinil)-5-pirimidin-5-ilpiridin-2-il]-2-(metilamino)propanamida	M+H=448; tR=1,46
21		N-[5-(1,5-dimetilindazol-4-il)-6-(2-quinolin-6-iletinil)piridin-2-il]-2-(metilamino)propanamida	M+H=475; tR=1,00

#	Estructura molecular	Nombre químico	HPLC-MS
22		N-[5-isoquinolin-8-il-6-(2-quinolin-6-iletinil)piridin-2-il]-2-(metilamino)propanamida	M+H=458; tR=1,11
23		2-(metilamino)-N-[6-(2-naftalen-2-iletinil)-5-pirimidin-5-ilpiridin-2-il]propanamida	M+H=408; tR=1,83
24		2-(metilamino)-N-[5-(6-metilquinolin-5-il)-6-(2-quinolin-6-iletinil)piridin-2-il]-propanamida	M+H=472; tR=1,16
25		2-(metilamino)-N-[5-(4-metilpirimidin-5-il)-6-(2-quinazolin-7-iletinil)piridin-2-il]-propanamida	M+H=424; tR=1,13

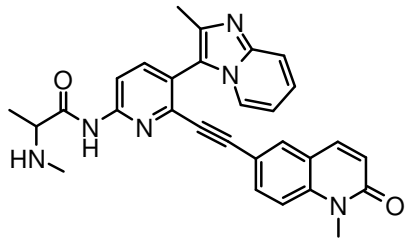
G1b N–metil-N-[1-[[5-(2-metilimidazo[1,2-a]piridin-3-il)-6-[2-(1-metil-2-oxoquinolin-6-il)etinil]piridin-2-il]amino]-1-oxopropan-2-il]carbamato de ter–butilo



Una mezcla de N–[1-[[6-etinil-5-(2-metilimidazo[1,2-a]piridin-3-il)piridin-2-il]-amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo F1a (60 mg, 0,14 mmol), 6-bromo-1-metilquinolin-2-one (82 mg, 0,35 mmol), yoduro de cobre(I) (2,6 mg, 0,01 mmol), Diclorobis(trifenilfosfino)paladio(II) (8,1 mg, 0,01 mmol) y DIPEA (94 µl, 0,55

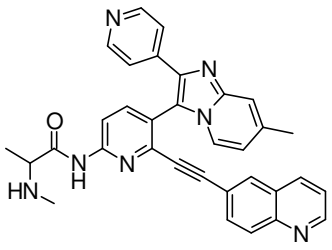
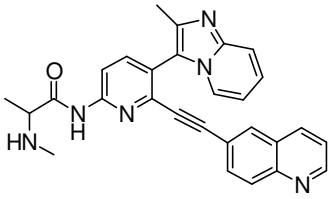
mmol) se agita bajo atmósfera de argón en NMP (0,5 ml) durante 2 horas a 50°C. La mezcla se concentra al vacío y el producto se purifica por RP HPLC. Rendimiento: 17 mg (21%). HPLC-MS: M+H=591; tR=1,79 min (*Método_4).

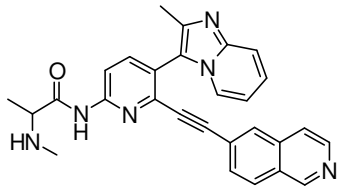
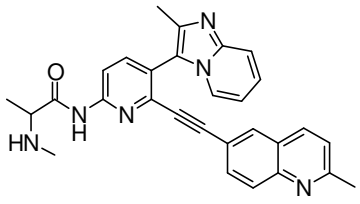
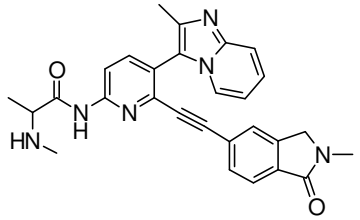
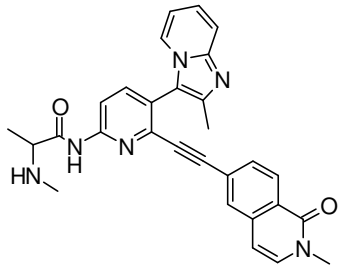
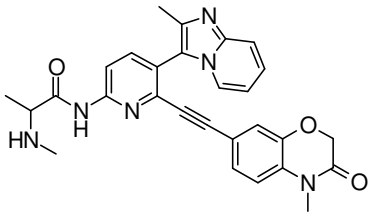
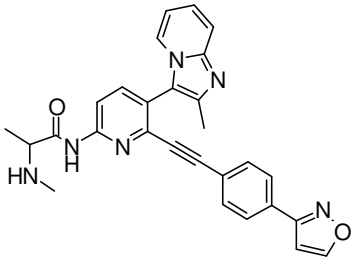
Ejemplo 26 2-(metilamino)-N-[5-(2-metilimidazo[1,2-a]piridin-3-il)-6-[2-(1-metil-2-oxoquinolin-6-il)etinil]piridin-2-il]propanamida

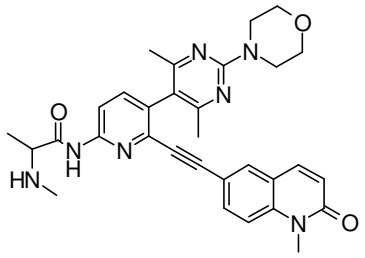
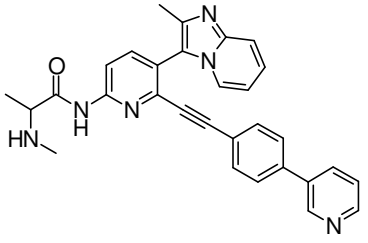
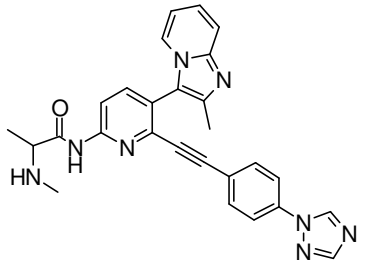
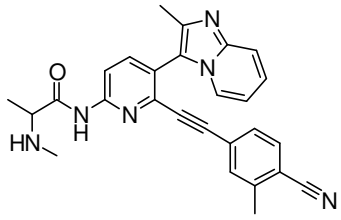
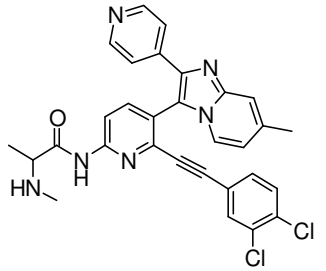


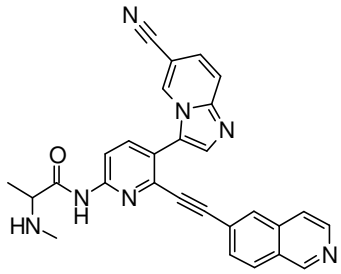
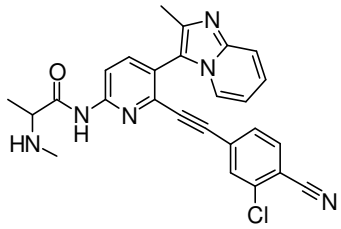
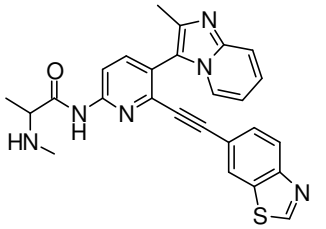
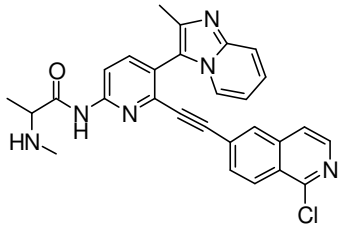
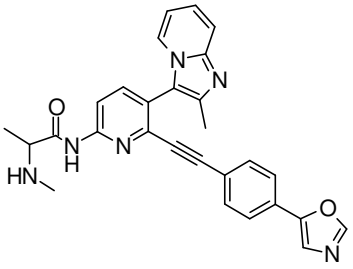
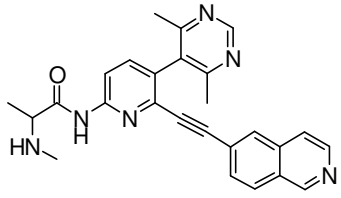
Una mezcla de N–-metil-N-[1-[[5-(2-metilimidazo[1,2-a]piridin-3-il)-6-[2-(1-metil-2-oxoquinolin-6-il)etinil]piridin-2-il]amino]-1-oxopropan-2-il]carbamato de ter–butilo G1b (17 mg, 0,03 mmol) y DCM:TFA (9:1, 2 ml) se agita a RT durante 2 h. La mezcla se diluye con DCM y se añade una solución acuosa saturada de $NaHCO_3$. La mezcla se extrae con DCM. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. El producto se purifica por RP HPLC. Rendimiento: 14 mg (99%). HPLC-MS: M+H=491; tR=0,97 min (*Método_1).

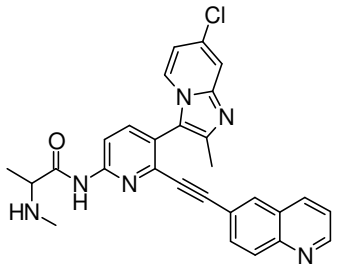
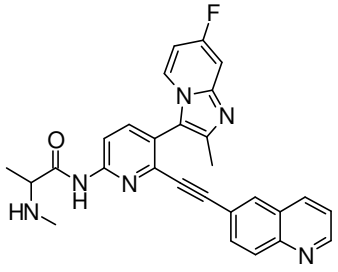
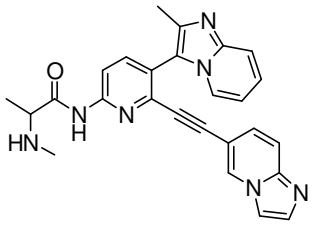
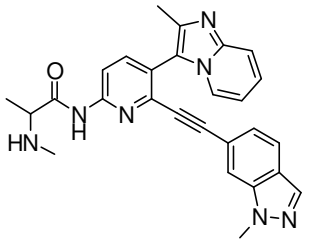
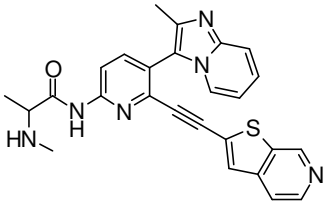
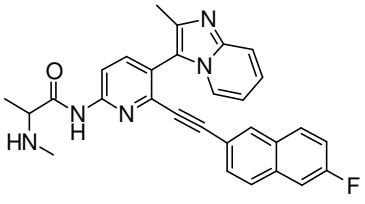
Los siguientes ejemplos se preparan de modo análogo.

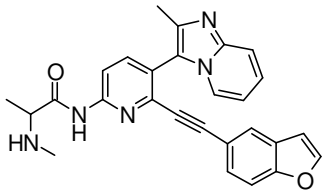
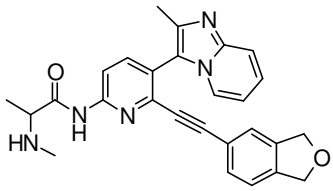
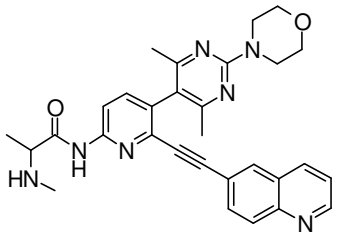
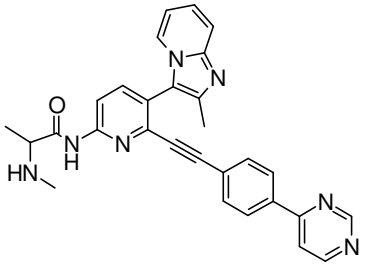
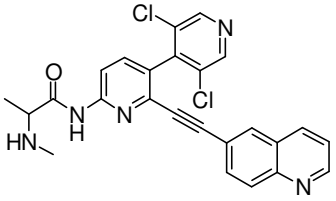
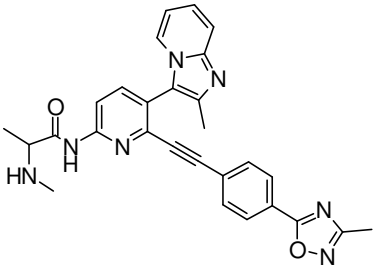
#	Estructura molecular	Nombre químico	HPLC-MS
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28		2-(metilamino)-N-[5-(2-metil-imidazo[1,2-a]piridin-3-il)-6-(2-quinolin-6-iletinil)piridin-2-il]-propanamida	M+H=461; tR=1,20

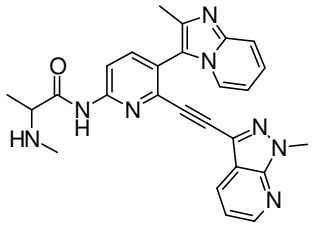
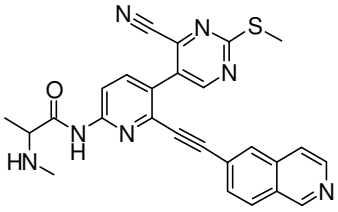
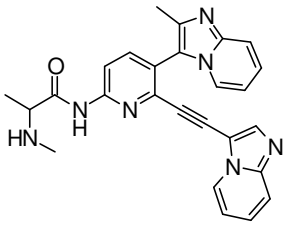
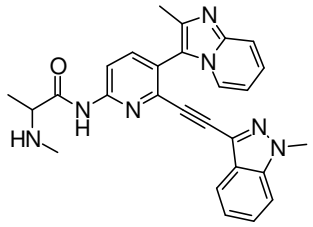
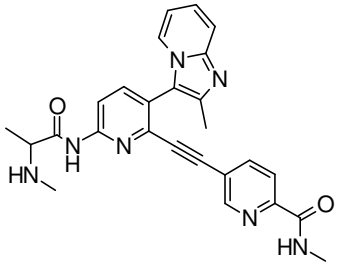
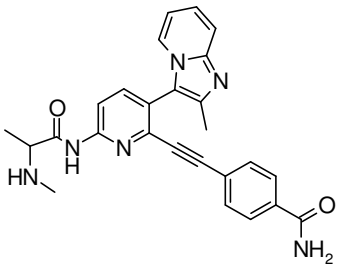
29		N-[6-(2-isoquinolin-6-iletinil)-5-(2-metilimidazo[1,2-a]piridin-3-il)piridin-2-il]-2-(metilamino)-propanamida	M+H=461; tR=t0
30		2-(metilamino)-N-[5-(2-metil-imidazo[1,2-a]piridin-3-il)-6-[2-(2-metilquinolin-6-il)etinil]piridin-2-il]propanamida	M+H=475; tR=1,06
31		2-(metilamino)-N-[5-(2-metil-imidazo[1,2-a]piridin-3-il)-6-[2-(2-metil-1-oxo-3H-isoindol-5-il)-etinil]piridin-2-il]propanamida	M+H=479; tR=0,93
32		2-(metilamino)-N-[5-(2-metil-imidazo[1,2-a]piridin-3-il)-6-[2-(2-metil-1-oxoisoquinolin-6-il)-etinil]piridin-2-il]propanamida	M+H=491; tR=1,01
33		2-(metilamino)-N-[5-(2-metil-imidazo[1,2-a]piridin-3-il)-6-[2-(4-metil-3-oxo-1,4-benzoxazin-7-il)etinil]piridin-2-il]propanamida	M+H=495; tR=1,03
34		2-(metilamino)-N-[5-(2-metil-imidazo[1,2-a]piridin-3-il)-6-[2-[4-(1,2-oxazol-3-il)fenil]etinil]-piridin-2-il]propanamida	M+H=477; tR=1,14

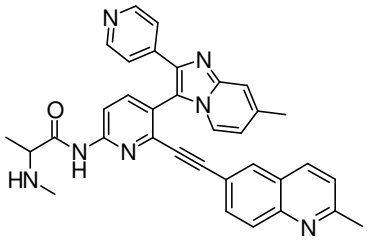
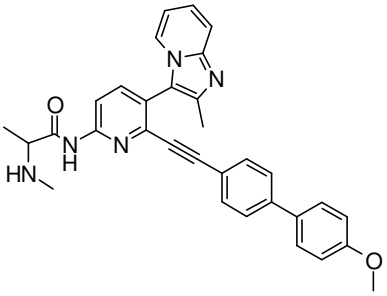
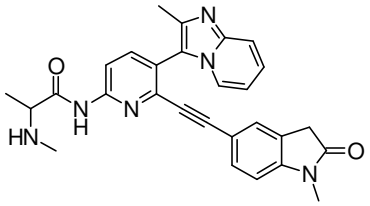
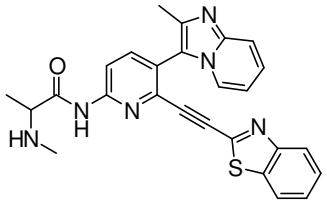
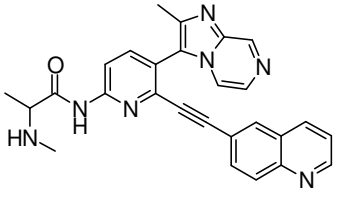
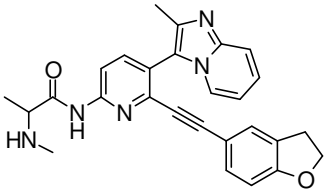
35		N-[5-(4,6-dimetil-2-morfolina-4-ilpirimidin-5-il)-6-[2-(1-metil-2-oxoquinolin-6-il)etinil]piridin-2-il]-2-(metilamino)propanamida	M+H=552; tR=1,17
36		2-(metilamino)-N-[5-(2-metil-imidazo[1,2-a]piridin-3-il)-6-[2-(4-piridin-3-ilfenil)etinil]piridin-2-il]propanamida	M+H=487; tR=1,10
37		2-(metilamino)-N-[5-(2-metil-imidazo[1,2-a]piridin-3-il)-6-[2-[4-(1,2,4-triazol-1-il)fenil]etinil]-piridin-2-il]propanamida	M+H=477; tR=1,00
38		N-[6-[2-(4-ciano-3-metilfenil)-etinil]-5-(2-metilimidazo[1,2-a]-piridin-3-il)piridin-2-il]-2-(metil-amino)propanamida	M+H=449; tR=1,57
39		N-[6-[2-(3,4-diclorofenil)etinil]-5-(7-metil-2-piridin-4-ilimidazo[1,2-a]piridin-3-il)piridin-2-il]-2-(metil-amino)propanamida	M+H=555; tR=1,83

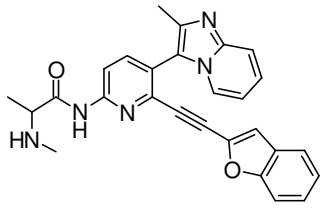
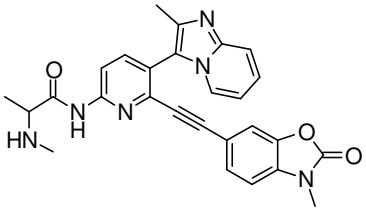
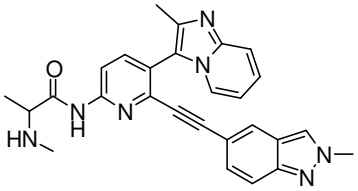
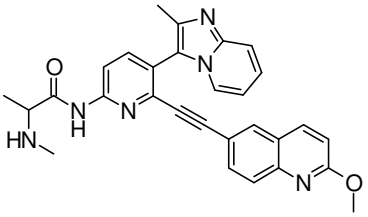
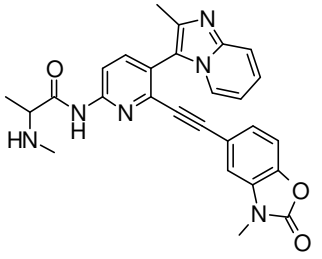
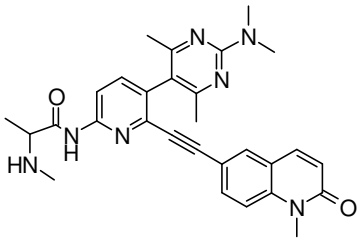
40		N-[5-(6-cianoimidazo[1,2-a]-piridin-3-il)-6-(2-isoquinolin-6-il-etinil)piridin-2-il]-2-(metilamino)-propanamida	M+H=472; tR=1,24
41		N-[6-[2-(3-cloro-4-cianofenil)-etinil]-5-(2-metilimidazo[1,2-a]-piridin-3-il)piridin-2-il]-2-(metil-amino)propanamida	M+H=469/471; tR=1,32
42		N-[6-[2-(1,3-benzotiazol-6-il)-etinil]-5-(2-metilimidazo[1,2-a]-piridin-3-il)piridin-2-il]-2-(metil-amino)propanamida	M+H=467; tR=1,04
43		N-[6-[2-(1-cloroisoquinolin-6-il)-etinil]-5-(2-metilimidazo[1,2-a]-piridin-3-il)piridin-2-il]-2-(metil-amino)propanamida	M+H=495; tR=1,18
44		2-(metilamino)-N-[5-(2-metil-imidazo[1,2-a]piridin-3-il)-6-[2-[4-(1,3-oxazol-5-il)fenil]etinil]-piridin-2-il]propanamida	M+H=477; tR=1,09
45		N-[5-(4,6-dimetilpirimidin-5-il)-6-(2-isoquinolin-6-iletinil)piridin-2-il]-2-(metilamino)propanamida	M+H=437; tR=1,16

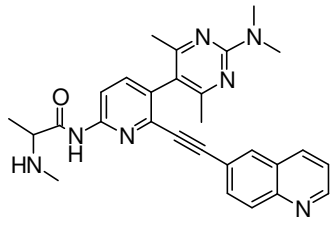
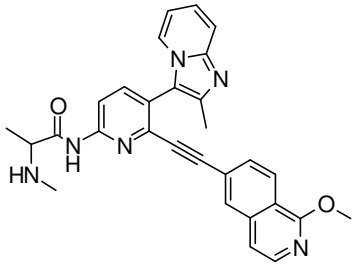
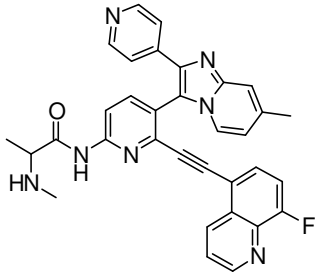
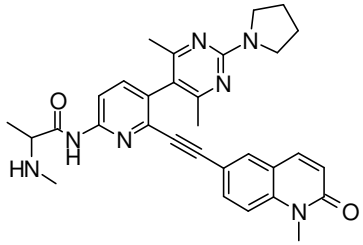
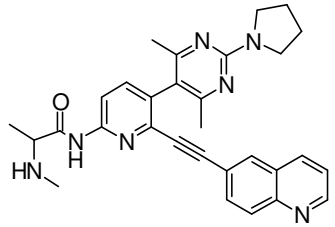
46		N-[5-(7-cloro-2-metilimidazo[1,2-a]piridin-3-il)-6-(2-quinolin-6-il-etinil)piridin-2-il]-2-(metilamino)-propanamida	M+H=495; tR=1,11
47		N-[5-(7-fluoro-2-metil-imidazo[1,2-a]piridin-3-il)-6-(2-quinolin-6-iletinil)piridin-2-il]-2-(metilamino)propanamida	M+H=479; tR=1,04
48		N-[6-(2-imidazo[1,2-a]piridin-6-il-etinil)-5-(2-metilimidazo[1,2-a]-piridin-3-il)piridin-2-il]-2-(metil-amino)propanamida	M+H=450; tR=0,92
49		2-(metilamino)-N-[5-(2-metil-imidazo[1,2-a]piridin-3-il)-6-[2-(1-metilindazol-6-il)etinil]piridin-2-il]propanamida	M+H=464; tR=1,05
50		2-(metilamino)-N-[5-(2-metil-imidazo[1,2-a]piridin-3-il)-6-(2-tieno[2,3-c]piridin-2-iletinil)-piridin-2-il]propanamida	M+H=467; tR=1,00
51		N-[6-[2-(6-fluoronaftalen-2-il)-etinil]-5-(2-metilimidazo[1,2-a]-piridin-3-il)piridin-2-il]-2-(metil-amino)propanamida	M+H=478; tR=1,24

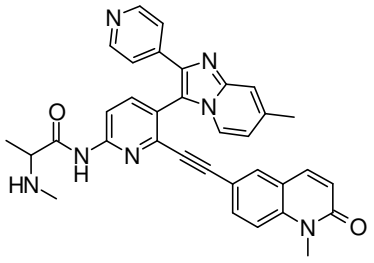
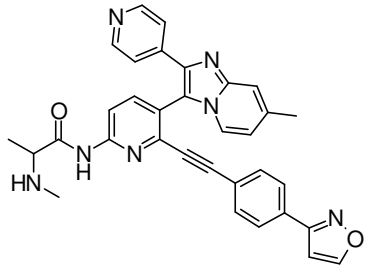
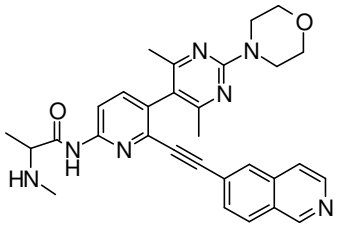
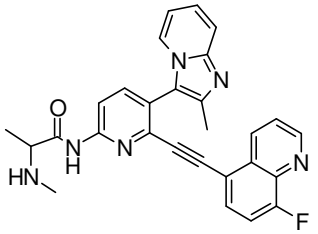
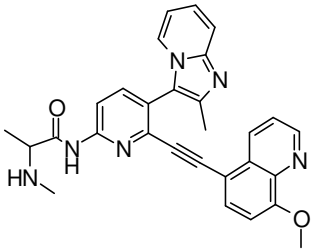
52		N-[6-[2-(1-benzofuran-5-il)etinil]-5-(2-metilimidazo[1,2-a]piridin-3-il)piridin-2-il]-2-(metilamino)-propanamida	M+H=450; tR=1,13
53		N-[6-[2-(1,3-dihidro-2-benzofuran-5-il)etinil]-5-(2-metil-imidazo[1,2-a]piridin-3-il)piridin-2-il]-2-(metilamino)propanamida	M+H=452; tR=1,02
54		N-[5-(4,6-dimetil-2-morfolina-4-ilpirimidin-5-il)-6-(2-quinolin-6-il-etinil)piridin-2-il]-2-(metilamino)-propanamida	M+H=522; tR=1,23
55		2-(metilamino)-N-[5-(2-metil-imidazo[1,2-a]piridin-3-il)-6-[2-(4-pirimidin-4-ilfenil)etinil]piridin-2-il]propanamida	M+H=488; tR=1,06
56		N-[5-(3,5-dicloropiridin-4-il)-6-(2-quinolin-6-iletinil)piridin-2-il]-2-(metilamino)propanamida	M+H=476; tR=1,23
57		2-(metilamino)-N-[5-(2-metil-imidazo[1,2-a]piridin-3-il)-6-[2-[4-(3-metil-1,2,4-oxadiazol-5-il)-fenil]etinil]piridin-2-il]propan-amida	M+H=492; tR=1,16

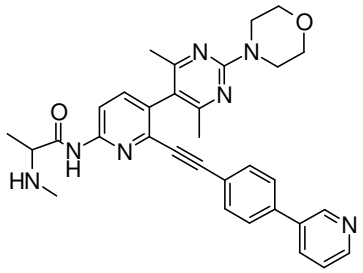
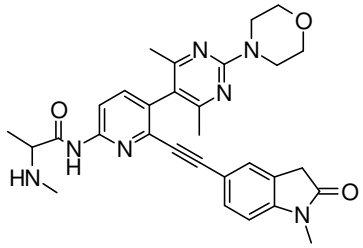
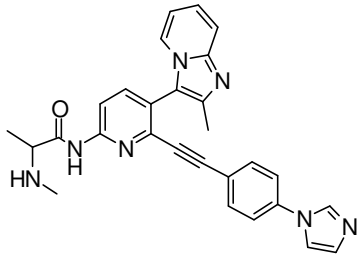
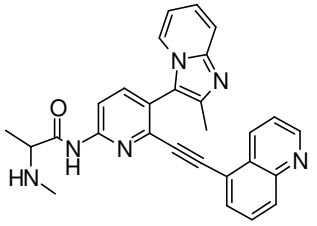
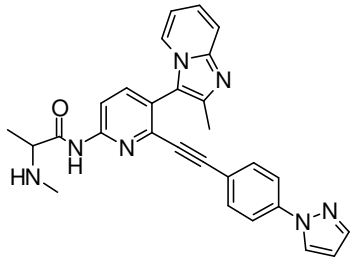
58		2-(metilamino)-N-[5-(2-metil-imidazo[1,2-a]piridin-3-il)-6-[2-(1-metilpirazolo[3,4-b]piridin-3-il)etinil]piridin-2-il]propanamida	M+H=465; tR=1,01
59		N-[5-(4-ciano-2-metilsulfanilpirimidin-5-il)-6-(2-isoquinolin-6-iletinil)piridin-2-il]-2-(metilamino)propanamida	M+H=480; tR=1,44
60		N-[6-(2-imidazo[1,2-a]piridin-3-il-etinil)-5-(2-metilimidazo[1,2-a]-piridin-3-il)piridin-2-il]-2-(metil-amino)propanamida	M+H=450; tR=0,96
61		2-(metilamino)-N-[5-(2-metil-imidazo[1,2-a]piridin-3-il)-6-[2-(1-metilindazol-3-il)etinil]piridin-2-il]propanamida	M+H=464; tR=1,09
62		N-metil-5-[2-[6-[[2-(metilamino)-propanoil]amino]-3-(2-metil-imidazo[1,2-a]piridin-3-il)piridin-2-il]etinil]piridina-2-carboxamida	M+H=468; tR=0,95
63		4-[2-[6-[[2-(metilamino)-propanoil]amino]-3-(2-metil-imidazo[1,2-a]piridin-3-il)piridin-2-il]etinil]benzamida	M+H=453; tR=0,90

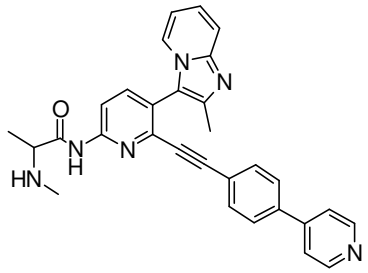
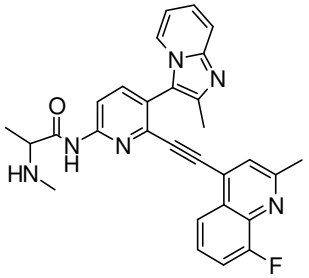
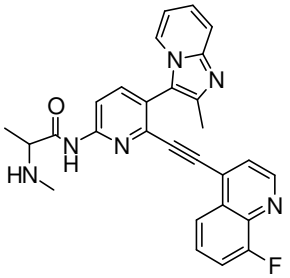
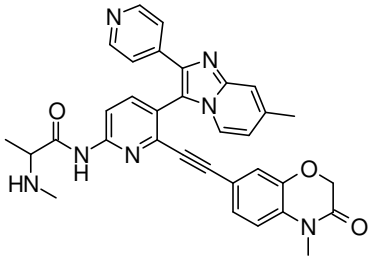
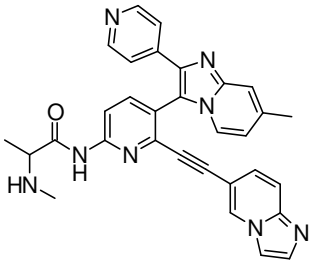
64		2-(metilamino)-N-[5-(7-metil-2-piridin-4-ilimidazo[1,2-a]piridin-3-il)-6-[2-(2-metilquinolin-6-il)-etinil]piridin-2-il]propanamida	M+H=552; tR=1,13
65		N-[6-[2-[4-(4-metoxifenil)fenil]-etinil]-5-(2-metilimidazo[1,2-a]-piridin-3-il)piridin-2-il]-2-(metil-amino)propanamida	M+H=516; tR=1,33
66		2-(metilamino)-N-[5-(2-metil-imidazo[1,2-a]piridin-3-il)-6-[2-(1-metil-2-oxo-3H-indol-5-il)-etinil]piridin-2-il]propanamida	M+H=479; tR=1,00
67		N-[6-[2-(1,3-benzotiazol-2-il)-etinil]-5-(2-metilimidazo[1,2-a]-piridin-3-il)piridin-2-il]-2-(metil-amino)propanamida	M+H=467; tR=1,14
68		2-(metilamino)-N-[5-(2-metil-imidazo[1,2-a]pirazin-3-il)-6-(2-quinolin-6-iletinil)piridin-2-il]-propanamida	M+H=462; tR=1,27
69		N-[6-[2-(2,3-dihidro-1-benzofuran-5-il)etinil]-5-(2-metil-imidazo[1,2-a]piridin-3-il)piridin-2-il]-2-(metilamino)propanamida	M+H=452; tR=1,08

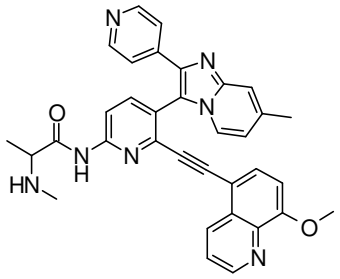
70		N-[6-[2-(1-benzofuran-2-il)etinil]-5-(2-metilimidazo[1,2-a]piridin-3-il)piridin-2-il]-2-(metilamino)-propanamida	M+H=450; tR=1,19
71		2-(metilamino)-N-[5-(2-metil-imidazo[1,2-a]piridin-3-il)-6-[2-(3-metil-2-oxo-1,3-benzoxazol-6-il)etinil]piridin-2-il]propanamida	M+H=481; tR=0,97
72		2-(metilamino)-N-[5-(2-metil-imidazo[1,2-a]piridin-3-il)-6-[2-(2-metilindazol-5-il)etinil]piridin-2-il]propanamida	M+H=464; tR=0,96
73		N-[6-[2-(2-metoxiquinolin-6-il)-etinil]-5-(2-metilimidazo[1,2-a]-piridin-3-il)piridin-2-il]-2-(metil-amino)propanamida	M+H=491; tR=1,22
74		2-(metilamino)-N-[5-(2-metil-imidazo[1,2-a]piridin-3-il)-6-[2-(3-metil-2-oxo-1,3-benzoxazol-5-il)etinil]piridin-2-il]propanamida	M+H=481; tR=1,03
75		N-[5-[2-(dimetilamino)-4,6-dimetilpirimidin-5-il]-6-[2-(1-metil-2-oxoquinolin-6-il)etinil]-piridin-2-il]-2-(metilamino)-propanamida	M+H=510; tR=1,22

76		N-[5-[2-(dimetilamino)-4,6-dimetilpirimidin-5-il]-6-(2-quinolin-6-iletinil)piridin-2-il]-2-(metilamino)propanamida	M+H=480; tR=1,28
77		N-[6-[2-(1-metoxiisoquinolin-6-il)etinil]-5-(2-metilimidazo[1,2-a]-piridin-3-il)piridin-2-il]-2-(metil-amino)propanamida	M+H=491; tR=1,21
78		N-[6-[2-(8-fluoroquinolin-5-il)-etinil]-5-(7-metil-2-piridin-4-ilimidazo[1,2-a]piridin-3-il)piridin-2-il]-2-(metilamino)propanamida	M+H=556; tR=1,09
79		N-[5-(4,6-dimetil-2-pirrolidin-1-ilpirimidin-5-il)-6-[2-(1-metil-2-oxoquinolin-6-il)etinil]piridin-2-il]-2-(metilamino)propanamida	M+H=536; tR=1,24
80		N-[5-(4,6-dimetil-2-pirrolidin-1-ilpirimidin-5-il)-6-(2-quinolin-6-il-etinil)piridin-2-il]-2-(metilamino)-propanamida	M+H=506; tR=1,31

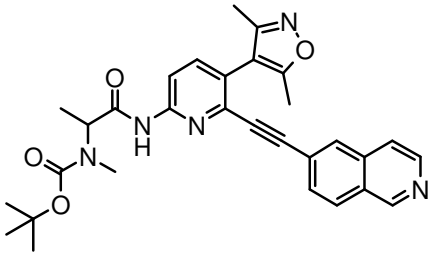
81		2-(metilamino)-N-[6-[2-(1-metil-2-oxoquinolin-6-il)etinil]-5-(7-metil-2-piridin-4-ilimidazo[1,2-a]-piridin-3-il)piridin-2-il]propan-amida	M+H=568; tR=1,04
82		2-(metilamino)-N-[5-(7-metil-2-piridin-4-ilimidazo[1,2-a]piridin-3-il)-6-[2-[4-(1,2-oxazol-3-il)-fenil]etinil]piridin-2-il]propan-amida	M+H=554; tR=1,17
83		N-[5-(4,6-dimetil-2-morfolina-4-ilpirimidin-5-il)-6-(2-isoquinolin-6-iletinil)piridin-2-il]-2-(metil-amino)propanamida	M+H=522; tR=1,23
84		N-[6-[2-(8-fluoroquinolin-5-il)-etinil]-5-(2-metilimidazo[1,2-a]-piridin-3-il)piridin-2-il]-2-(metil-amino)propanamida	M+H=479; tR=1,05
85		N-[6-[2-(8-metoxiquinolin-5-il)-etinil]-5-(2-metilimidazo[1,2-a]-piridin-3-il)piridin-2-il]-2-(metil-amino)propanamida	M+H=491; tR=1,00

86		N-[5-(4,6-dimetil-2-morfolina-4-ilpirimidin-5-il)-6-[2-(4-piridin-3-ilfenil)etinil]piridin-2-il]-2-(metil-amino)propanamida	M+H=548; tR=1,28
87		N-[5-(4,6-dimetil-2-morfolina-4-ilpirimidin-5-il)-6-[2-(1-metil-2-oxo-3H-indol-5-il)etinil]piridin-2-il]-2-(metilamino)propanamida	M+H=540; tR=1,16
88		N-[6-[2-(4-imidazol-1-ilfenil)-etinil]-5-(2-metilimidazo[1,2-a]-piridin-3-il)piridin-2-il]-2-(metil-amino)propanamida	M+H=476; tR=1,00
89		2-(metilamino)-N-[5-(2-metil-imidazo[1,2-a]piridin-3-il)-6-(2-quinolin-5-iletinil)piridin-2-il]-propanamida	M+H=461; tR=1,04
90		2-(metilamino)-N-[5-(2-metil-imidazo[1,2-a]piridin-3-il)-6-[2-(4-pirazol-1-ilfenil)etinil]piridin-2-il]propanamida	M+H=476; tR=1,12

91		2-(metilamino)-N-[5-(2-metil-imidazo[1,2-a]piridin-3-il)-6-[2-(4-piridin-4-ilfenil)etinil]piridin-2-il]propanamida	M+H=487; tR=1,09
92		N-[6-[2-(8-fluoro-2-metilquinolin-4-il)etinil]-5-(2-metilimidazo[1,2-a]piridin-3-il)piridin-2-il]-2-(metil-amino)propanamida	M+H=493; tR=1,11
93		N-[6-[2-(8-fluoroquinolin-4-il)-etinil]-5-(2-metilimidazo[1,2-a]-piridin-3-il)piridin-2-il]-2-(metil-amino)propanamida	M+H=479; tR=1,06
94		2-(metilamino)-N-[6-[2-(4-metil-3-oxo-1,4-benzoxazin-7-il)etinil]-5-(7-metil-2-piridin-4-ilimidazo[1,2-a]piridin-3-il)piridin-2-il]propanamida	M+H=572; tR=1,08
95		N-[6-(2-imidazo[1,2-a]piridin-6-il-etinil)-5-(7-metil-2-piridin-4-ilimidazo[1,2-a]piridin-3-il)piridin-2-il]-2-(metilamino)propanamida	M+H=527; tR=0,98

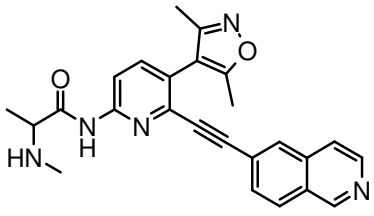
96		N-[6-[2-(8-metoxiquinolin-5-il)-etinil]-5-(7-metil-2-piridin-4-ilimidazo[1,2-a]piridin-3-il)piridin-2-il]-2-(metilamino)propanamida	M+H=568; tR=1,04

E2a) N–-[1-[[5-(3,5-dimetil-1,2-oxazol-4-il)-6-(2-isoquinolin-6-iletinil)piridin-2-il]-amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo



Una mezcla de N–[1-[[5-bromo-6-(2-isoquinolin-6-iletinil)piridin-2-il]amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo C2b (300 mg, 0,59 mmol), ácido (3,5-dimetil-1,2-oxazol-4-il)borónico (166 mg, 1,18 mmol), CsF (358 mg, 2,36 mmol) tris-(dibencilidenacetona)dipaladio(0) (41 mg, 0,06 mmol), tetrafluoroborato de tri-ter–butilfosfonio (34 mg, 0,12 mmol) y dioxano (4,5 ml) se agita bajo atmósfera de argón a 50°C durante 2 horas. La mezcla se diluye con DCM y se extrae con una solución acuosa saturada de $NaHCO_3$. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. El producto se purifica por RP HPLC. Rendimiento: 191 mg (62%). HPLC-MS: M+H=526; tR=1,89 min (*Método_2).

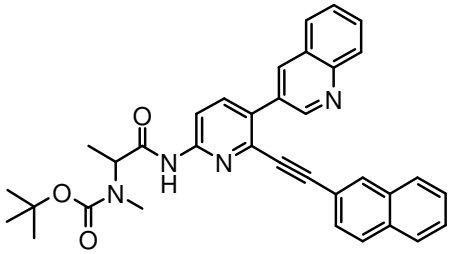
Ejemplo 97 N-[5-(3,5-dimetil-1,2-oxazol-4-il)-6-(2-isoquinolin-6-iletinil)piridin-2-il]-2-(metilamino)propanamida



Una mezcla de N–[1-[[5-(3,5-dimetil-1,2-oxazol-4-il)-6-(2-isoquinolin-6-iletinil)-piridin-2-il]amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo E2a (191 mg, 0,36

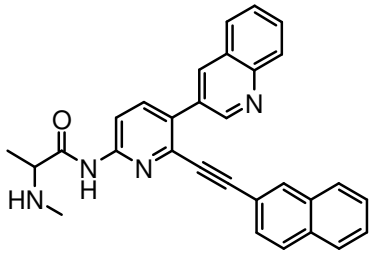
mmol) y DCM:TFA (9:1, 10 ml) se agita a RT durante 2 h. La mezcla se diluye con DCM y se extrae con una solución acuosa saturada de $NaHCO_3$. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. El producto se purifica por RP HPLC. Rendimiento: 101 mg (65%). HPLC-MS: M+H=426; tR=1,30 min (*Método_1).

E2b) N–metil-N-[1-[[6-(2-naftalen-2-iletinil)-5-quinolin-3-ilpiridin-2-il]amino]-1-oxopropan-2-il]carbamato de ter–butilo



Una mezcla de N–[1-[[5-bromo-6-(2-naftalen-2-iletinil)piridin-2-il]amino]-1-oxo-propan-2-il]-N-metilcarbamato de ter–butilo C2c (150 mg, 0,30 mmol), ácido quinolin-3-ilborónico (61 mg, 0,35 mmol), Diclorobis(trifenilfosfino)paladio(II) (40 mg, 0,06 mmol), Na_2CO_3 (63 mg, 0,59 mmol), dioxano (1 ml), MeOH (0,2 ml) y agua (0,1 ml) se agita bajo atmósfera de argón durante 2 horas a 85ºC. La mezcla se diluye con DCM y se extrae con una solución acuosa saturada de $NaHCO_3$. Las fases orgánicas combinadas se secan en $MgSO_4$, se concentran al vacío y el producto se purifica por RP HPLC. Rendimiento: 91 mg (55%).

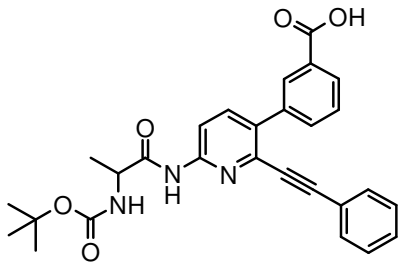
Ejemplo 98 2-(metilamino)-N-[6-(2-naftalen-2-iletinil)-5-quinolin-3-ilpiridin-2-il]-propanamida



Una mezcla de N–metil-N-[1-[[6-(2-naftalen-2-iletinil)-5-quinolin-3-ilpiridin-2-il]-amino]-1-oxopropan-2-il]carbamato de ter–butilo E2b (91 mg, 0,16 mmol) y DCM:TFA (9:1, 5 ml) se agita a RT durante 1 h. La mezcla se diluye con tolueno (10 ml) y se

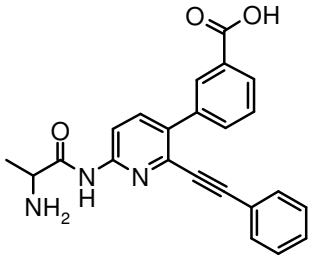
concentran al vacío. El producto se purifica por RP HPLC. Rendimiento: 74 mg (99%). HPLC-MS: M+H=457; tR=1,58 min (*Método_1).

E2c) ácido 3-[6-[2-[(2-metilpropan-2-il)oxicarbonilamino]propanoilamino]-2-(2-feniletinil)piridin-3-il]benzoico



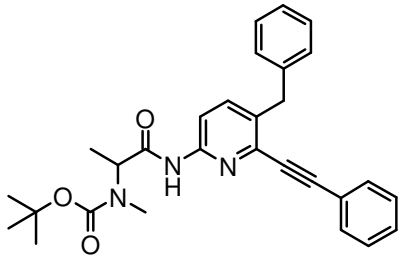
Una mezcla de N–[1-[[5-bromo-6-(2-feniletinil)piridin-2-il]amino]-1-oxopropan-2-il]carbamato de ter–butilo C2d (40 mg, 0,09 mmol), ácido 3-boronobenzoico (18 mg, 0,11 mmol), Diclorobis(trifenilfosfino)paladio(II) (6,3 mg, 0,01 mmol), Na_2CO_3 (19 mg, 0,18 mmol), dioxano (0,9 ml), MeOH (0,2 ml) y agua (0,1 ml) se agita bajo atmósfera de argón durante 4 horas a 70°C. La mezcla de reacción se concentra al vacío y el producto se purifica por RP HPLC. Rendimiento: 16 mg (37%). HPLC-MS: M+H=486; tR=1,49 min (*Método_5).

Ejemplo 99 ácido 3-[6-(2-aminopropanoilamino)-2-(2-feniletinil)piridin-3-il]-benzoico



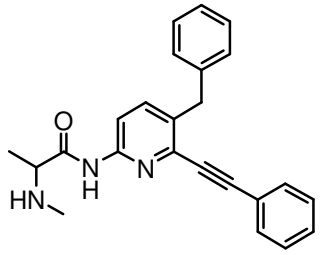
Una mezcla de ácido 3-[6-[2-[(2-metilpropan-2-il)oxicarbonilamino]-propanoilamino]-2-(2-feniletinil)piridin-3-il]benzoico E2c (16 mg, 0,03 mmol) y DCM:TFA (9:1, 1,7 ml) se agita a RT durante 90 minutos. La mezcla se diluye con tolueno (10 ml) y se concentran al vacío. El producto se purifica por RP HPLC. Rendimiento: 3 mg (24%). HPLC-MS: M+H=386; tR=1,03 min (*Método_1).

E2d) N–[1-[[5-benzil-6-(2-feniletinil)piridin-2-il]amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo



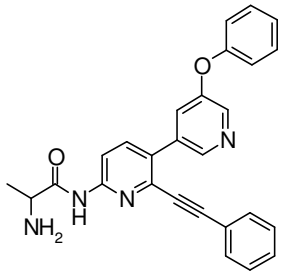
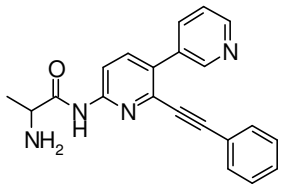
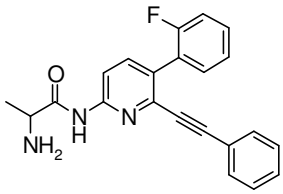
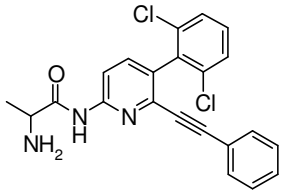
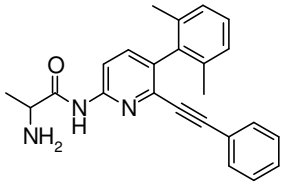
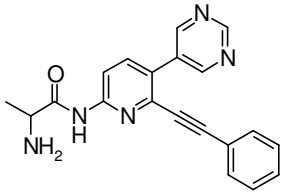
Una mezcla de N–[1-[[5-bromo-6-(2-feniletinil)piridin-2-il]amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo C2a (50 mg, 0,11 mmol), 9-bencil-9-bora-biciclo[3,3,1]nonano (283 µl, 0,14 mmol) Cs_2CO_3 (71 mg, 0,22 mmol), 1,1′-Bis(difenil-fosfino)ferroceno]dicloropaladio(II) (8,0 mg, 0,01 mmol) y dioxano (0,6 ml) se agita bajo atmósfera de argón durante 45 minutos a 70°C. La mezcla se concentra al vacío y el producto se purifica por RP HPLC. Rendimiento: 26 mg (51%). HPLC-MS: M+H=470; tR=1,97 min (*Método_4).

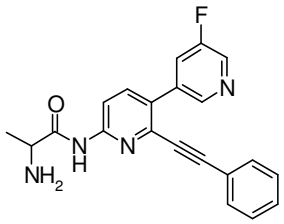
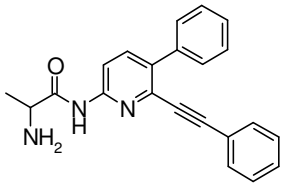
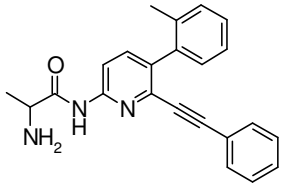
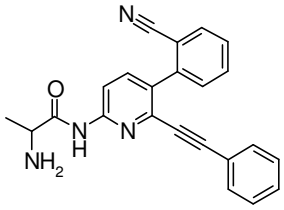
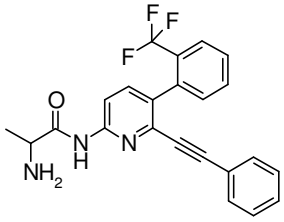
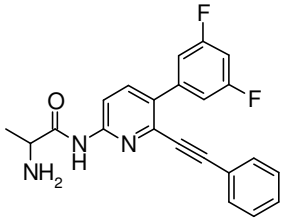
Ejemplo 119 N-[5-benzil-6-(2-feniletinil)piridin-2-il]-2-(metilamino)propan-amida

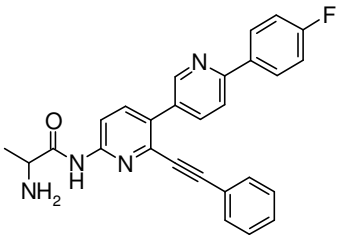
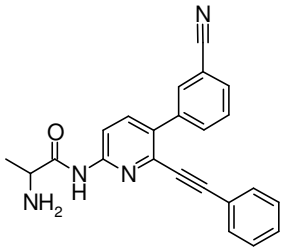
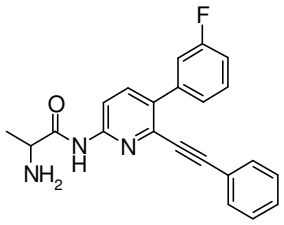
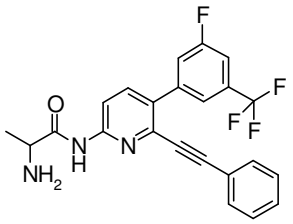
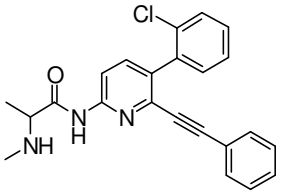
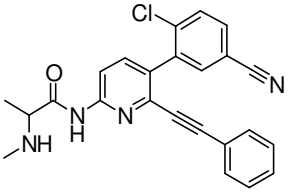


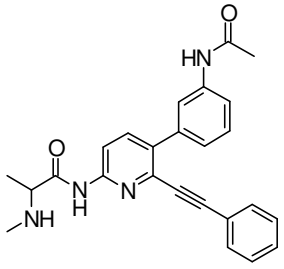
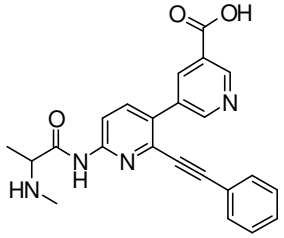
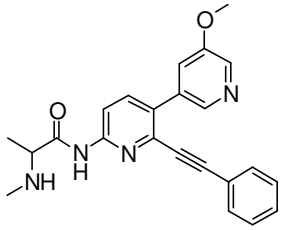
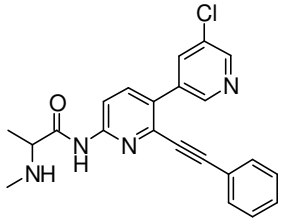
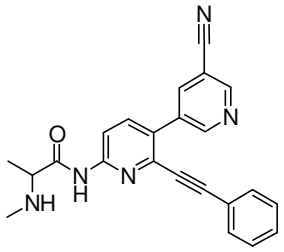
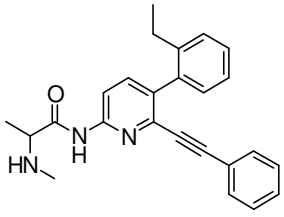
Una mezcla de N–[1-[[5-benzil-6-(2-feniletinil)piridin-2-il]amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo E2d (26 mg, 0,6 mmol) y DCM:TFA (9:1, 2 ml) se agita a RT durante 90 minutos. La mezcla se diluye con DCM y se extrae con una solución acuosa saturada de $NaHCO_3$. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. El producto se purifica por RP HPLC. Rendimiento: 4 mg (20%). HPLC-MS: M+H=370; tR=2,16 min (*Método_1).

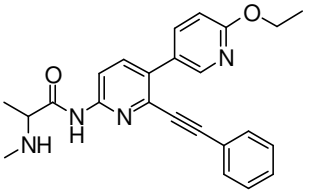
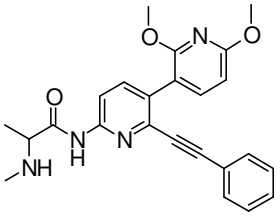
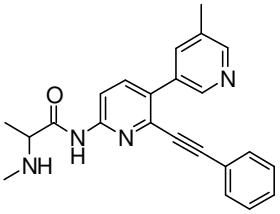
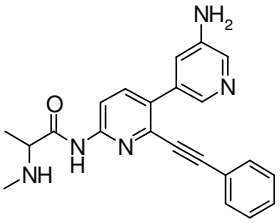
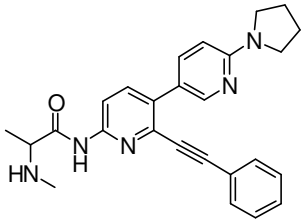
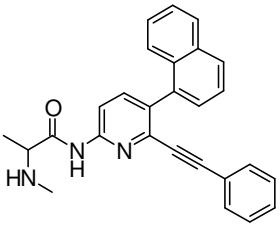
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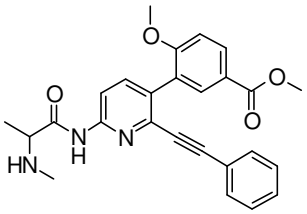
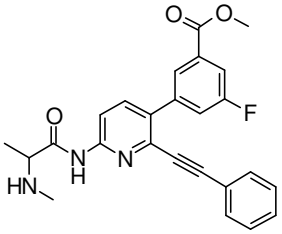
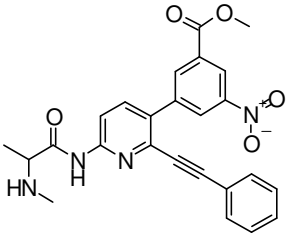
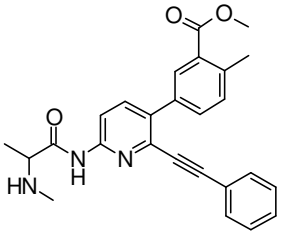
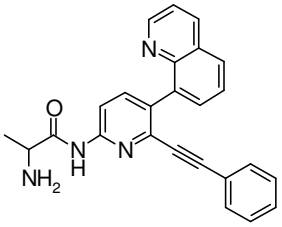
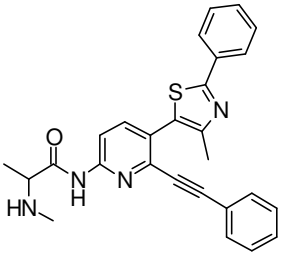
#	Estructura molecular	Nombre químico	HPLC-MS
100		2-amino-N-[5-(5-fenoxipiridin-3-il)-6-(2-feniletinil)piridin-2-il]propan-amida	M+H=435; tR=1,99
101		2-amino-N-[6-(2-feniletinil)-5-piridin-3-ilpiridin-2-il]propanamida	M+H=343; tR=1,61
102		2-amino-N-[5-(2-fluorofenil)-6-(2-feniletinil)piridin-2-il]propanamida	M+H=360; tR=1,97
103		2-amino-N-[5-(2,6-diclorofenil)-6-(2-feniletinil)piridin-2-il]propan-amida	M+H=410/412/414
104		2-amino-N-[5-(2,6-dimetilfenil)-6-(2-feniletinil)piridin-2-il]propan-amida	M+H=370; tR=2,21
105		2-amino-N-[6-(2-feniletinil)-5-pirimidin-5-ilpiridin-2-il]propan-amida	M+H=344; tR=1,49

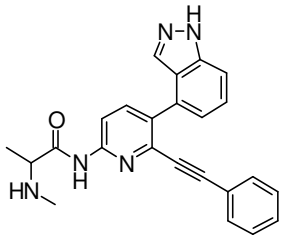
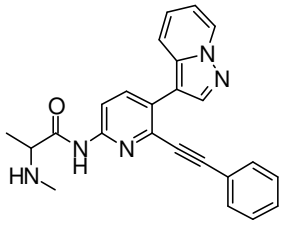
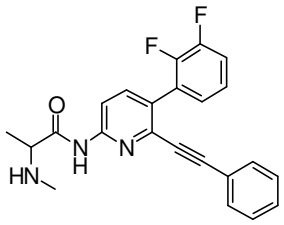
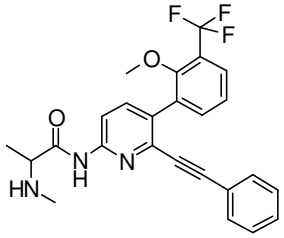
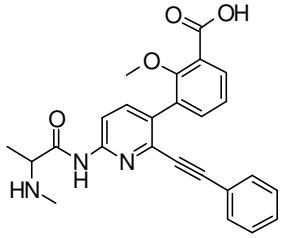
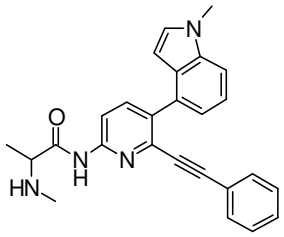
106		2-amino-N-[5-(5-fluoropiridin-3-il)-6-(2-feniletinil)piridin-2-il]propan-amida	M+H=361; tR=1,75
107		2-amino-N-[5-fenilo-6-(2-fenil-etinil)piridin-2-il]propanamida	M+H=342; tR=1,98
108		2-amino-N-[5-(2-metilfenil)-6-(2-feniletinil)piridin-2-il]propanamida	M+H=356; tR=2,04
109		2-amino-N-[5-(2-cianofenil)-6-(2-feniletinil)piridin-2-il]propanamida	M+H=367; tR=1,84
110		2-amino-N-[6-(2-feniletinil)-5-[2-(trifluorometil)fenil]piridin-2-il]-propanamida	M+H=410; tR=2,06
111		2-amino-N-[5-(3,5-difluorofenil)-6-(2-feniletinil)piridin-2-il]propan-amida	M+H=378; tR=1,99

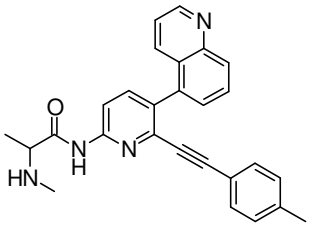
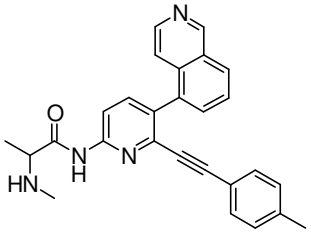
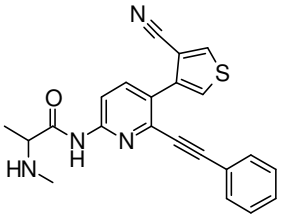
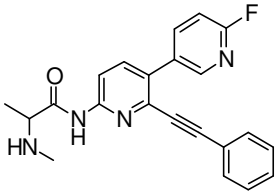
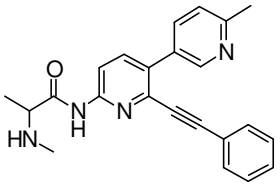
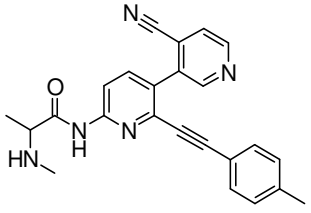
112		2-amino-N-[5-[6-(4-fluorofenil)-piridin-3-il]-6-(2-feniletinil)piridin-2-il]propanamida	M+H=437; tR=2,11
113		2-amino-N-[5-(3-cianofenil)-6-(2-feniletinil)piridin-2-il]propanamida	M+H=367; tR=1,86
114		2-amino-N-[5-(3-fluorofenil)-6-(2-feniletinil)piridin-2-il]propanamida	M+H=360; tR=2,01
115		2-amino-N-[5-[3-fluoro-5-(trifluorometil)fenil]-6-(2-fenil-etinil)piridin-2-il]propanamida	M+H=428; tR=2,32
116		N-[5-(2-clorofenil)-6-(2-feniletinil)-piridin-2-il]-2-(metilamino)propan-amida	M+H=390/392; tR=2,10
117		N-[5-(2-cloro-5-cianofenil)-6-(2-feniletinil)piridin-2-il]-2-(metil-amino)propanamida	M+H=415; tR=2,00

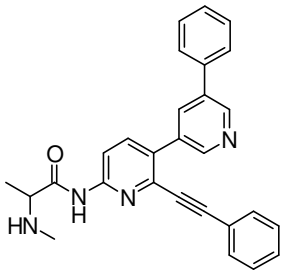
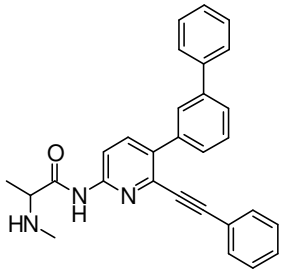
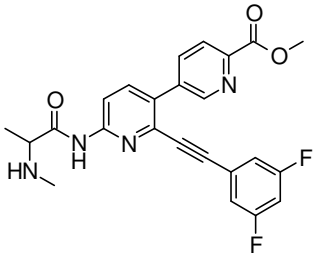
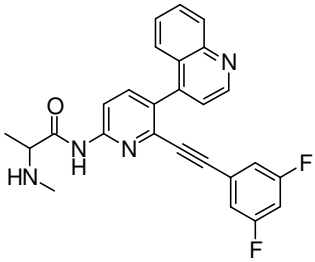
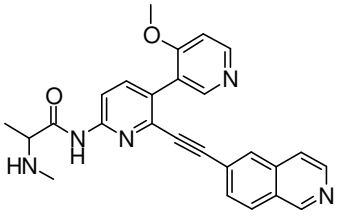
118		N-[5-(3-acetamidofenil)-6-(2-fenil-etinil)piridin-2-il]-2-(metilamino)-propanamida	M+H=413; tR=1,72
120		Ácido 5-[6-[[2-(metilamino)-propanoil]amino]-2-(2-feniletinil)-piridin-3-il]piridina-3-carboxílico	M+H=401; tR=1,04
121		N-[5-(5-metoxipiridin-3-il)-6-(2-feniletinil)piridin-2-il]-2-(metil-amino)propanamida	M+H=387; tR=1,77
122		N-[5-(5-cloropiridin-3-il)-6-(2-fenil-etinil)piridin-2-il]-2-(metilamino)-propanamida	M+H=391; tR=1,94
123		N-[5-(5-cianopiridin-3-il)-6-(2-fenil-etinil)piridin-2-il]-2-(metilamino)-propanamida	M+H=382; tR=1,75
124		N-[5-(2-etilfenil)-6-(2-feniletinil)-piridin-2-il]-2-(metilamino)propan-amida	M+H=384; tR=2,25

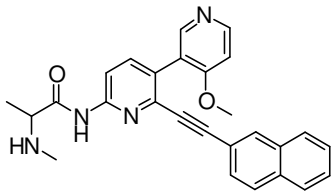
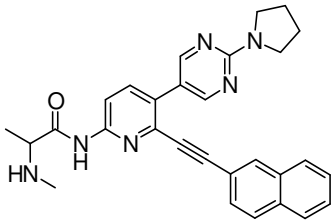
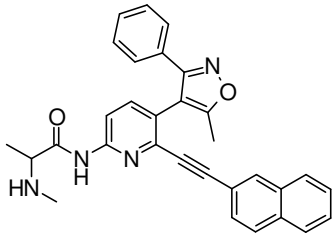
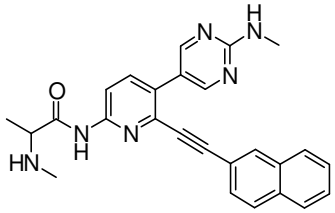
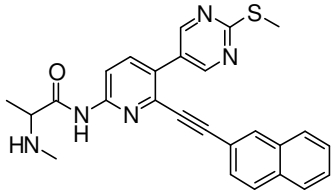
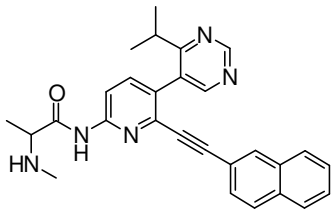
125		N-[5-(6-etoxipiridin-3-il)-6-(2-fenil-etinil)piridin-2-il]-2-(metilamino)-propanamida	M+H=401; tR=2,05
126		N-[5-(2,6-dimetoxipiridin-3-il)-6-(2-feniletinil)piridin-2-il]-2-(metil-amino)propanamida	M+H=417; tR=2,08
127		2-(metilamino)-N-[5-(5-metilpiridin-3-il)-6-(2-feniletinil)-piridin-2-il]propanamida	M+H=371; tR=1,78
128		N-[5-(5-aminopiridin-3-il)-6-(2-feniletinil)piridin-2-il]-2-(metil-amino)propanamida	M+H=372; tR=1,47
129		2-(metilamino)-N-[6-(2-feniletinil)-5-(6-pirrolidin-1-ilpiridin-3-il)-piridin-2-il]propanamida	M+H=426; tR=2,02
130		2-(metilamino)-N-[5-naftalen-1-il-6-(2-feniletinil)piridin-2-il]propan-amida	M+H=406; tR=2,17

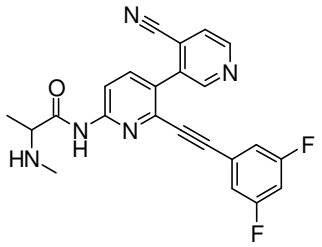
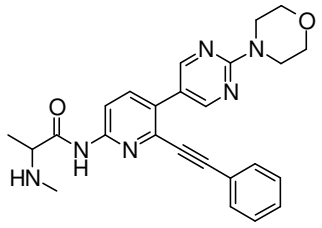
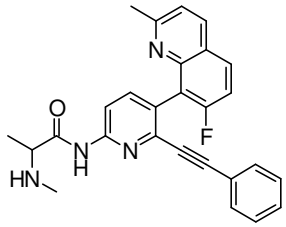
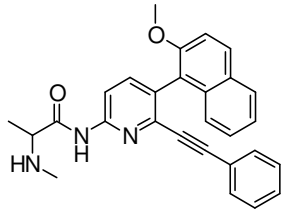
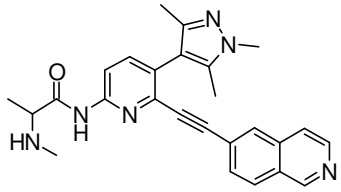
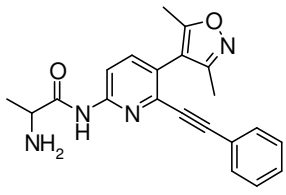
131		4-metoxi-3-[6-[[2-(metilamino)-propanoil]amino]-2-(2-feniletinil)-piridin-3-il]benzoato de metilo	M+H=444; tR=1,95
132		3-fluoro-5-[6-[[2-(metilamino)-propanoil]amino]-2-(2-feniletinil)-piridin-3-il]benzoato de metilo	M+H=432; tR=2,11
133		3-[6-[[2-(metilamino)propanoil]-amino]-2-(2-feniletinil)piridin-3-il]-5-nitrobenzoato de metilo	M+H=459; tR=2,06
134		2-metil-5-[6-[[2-(metilamino)-propanoil]amino]-2-(2-feniletinil)-piridin-3-il]benzoato de metilo	M+H=428; tR=2,10
135		2-amino-N-[6-(2-feniletinil)-5-quinolin-8-ilpiridin-2-il]propan-amida	M+H=393; tR=1,80
136		2-(metilamino)-N-[5-(4-metil-2-fenilo-1,3-tiazol-5-il)-6-(2-fenil-etinil)piridin-2-il]propanamida	M+H=453; tR=2,30

137		N-[5-(1H-indazol-4-il)-6-(2-fenil-etinil)piridin-2-il]-2-(metilamino)-propanamida	M+H=396; tR=1,76
138		2-(metilamino)-N-[6-(2-feniletinil)-5-pirazolo[1,5-a]piridin-3-ilpiridin-2-il]propanamida	M+H=396; tR=1,85
139		N-[5-(2,3-difluorofenil)-6-(2-fenil-etinil)piridin-2-il]-2-(metilamino)-propanamida	M+H=392; tR=2,13
140		N-[5-[2-metoxi-3-(trifluorometil)-fenil]-6-(2-feniletinil)piridin-2-il]-2-(metilamino)propanamida	M+H=454; tR=2,22
141		Ácido 2-metoxi-3-[6-[[2-(metil-amino)propanoil]amino]-2-(2-fenil-etinil)piridin-3-il]benzoico	M+H=430; tR=1,16
142		2-(metilamino)-N-[5-(1-metilindol-4-il)-6-(2-feniletinil)piridin-2-il]-propanamida	M+H=409; tR=2,07

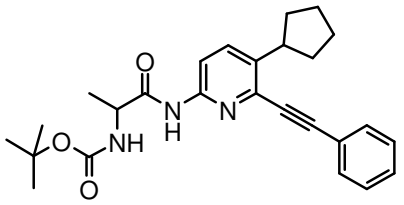
143		2-(metilamino)-N-[6-[2-(4-metil-fenil)etinil]-5-quinolin-5-ilpiridin-2-il]propanamida	M+H=421; tR=1,92
144		N-[5-isoquinolin-5-il-6-[2-(4-metil-fenil)etinil]piridin-2-il]-2-(metil-amino)propanamida	M+H=421; tR=1,92
145		N-[5-(4-cianotiofen-3-il)-6-(2-fenil-etinil)piridin-2-il]-2-(metilamino)-propanamida	M+H=387; tR=1,87
146		N-[5-(6-fluoropiridin-3-il)-6-(2-feniletinil)piridin-2-il]-2-(metil-amino)propanamida	M+H=375; tR=1,85
147		2-(metilamino)-N-[5-(6-metilpiridin-3-il)-6-(2-feniletinil)-piridin-2-il]propanamida	M+H=371; tR=1,77
148		N-[5-(4-cianopiridin-3-il)-6-[2-(4-metilfenil)etinil]piridin-2-il]-2-(metilamino)propanamida	M+H=396; tR=1,79

149		2-(metilamino)-N-[6-(2-feniletinil)-5-(5-fenilpiridin-3-il)piridin-2-il]-propanamida	M+H=433; tR=2,12
150		2-(metilamino)-N-[6-(2-feniletinil)-5-(3-fenilfenil)piridin-2-il]propan-amida	M+H=432; tR=2,41
151		5-[2-[2-(3,5-difluorofenil)etinil]-6-[[2-(metilamino)propanoil]amino]-piridin-3-il]piridina-2-carboxilato de metilo	M+H=451; tR=1,82
152		N-[6-[2-(3,5-difluorofenil)etinil]-5-quinolin-4-ilpiridin-2-il]-2-(metil-amino)propanamida	M+H=443; tR=1,95
153		N-[6-(2-isoquinolin-6-iletinil)-5-(4-metoxipiridin-3-il)piridin-2-il]-2-(metilamino)propanamida	M+H=438; tR=1,17

154		N-[5-(4-metoxipiridin-3-il)-6-(2-naftalen-2-iletinil)piridin-2-il]-2-(metilamino)propanamida	M+H=437; tR=1,48
155		2-(metilamino)-N-[6-(2-naftalen-2-iletinil)-5-(2-pirrolidin-1-ilpirimidin-5-il)piridin-2-il]propanamida	M+H=477; tR=1,60
156		2-(metilamino)-N-[5-(5-metil-3-fenilo-1,2-oxazol-4-il)-6-(2-naftalen-2-iletinil)piridin-2-il]-propanamida	M+H=487; tR=1,62
157		2-(metilamino)-N-[5-[2-(metil-amino)pirimidin-5-il]-6-(2-naftalen-2-iletinil)piridin-2-il]propanamida	M+H=437; tR=1,39
158		2-(metilamino)-N-[5-(2-metilsulfanilpirimidin-5-il)-6-(2-naftalen-2-iletinil)piridin-2-il]-propanamida	M+H=454; tR=1,62
159		2-(metilamino)-N-[6-(2-naftalen-2-iletinil)-5-(4-propan-2-ilpirimidin-5-il)piridin-2-il]propanamida	M+H=450; tR=1,55

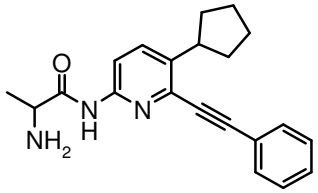
160		N-[5-(4-cianopiridin-3-il)-6-[2-(3,5-difluorofenil)etinil]piridin-2-il]-2-(metilamino)propanamida	M+H=418; tR=1,68
161		2-(metilamino)-N-[5-(2-morfolina-4-ilpirimidin-5-il)-6-(2-feniletinil)-piridin-2-il]propanamida	M+H=443; tR=1,63
162		N-[5-(7-fluoro-2-metilquinolin-8-il)-6-(2-feniletinil)piridin-2-il]-2-(metil-amino)propanamida	M+H=439; tR=1,73
163		N-[5-(2-metoxinaftalen-1-il)-6-(2-feniletinil)piridin-2-il]-2-(metil-amino)propanamida	M+H=436; tR=2,02
164		N-[6-(2-isoquinolin-6-iletinil)-5-(1,3,5-trimetilpirazol-4-il)piridin-2-il]-2-(metilamino)propanamida	M-H=437; tR=1,21
165		2-amino-N-[5-(3,5-dimetil-1,2-oxazol-4-il)-6-(2-feniletinil)piridin-2-il]propanamida	M+H=361; tR=1,27

E2e) N–[1-[[5-ciclopentil-6-(2-feniletinil)piridin-2-il]amino]-1-oxopropan-2-il]-carbamato de ter–butilo



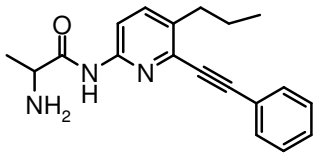
Una mezcla de N–[1-[[5-bromo-6-(2-feniletinil)piridin-2-il]amino]-1-oxopropan-2-il]carbamato de ter–butilo C2d (60 mg, 0,14 mmol), bromo(ciclopentil)zinc (solución 0,5 M en THF, 1,6 ml, 0,81 mmol), acetato de paladio(II) (1,5 mg, 0,01 mmol), 2-Diciclohexilfosfino-2′,4′,6′-triisopropilbifenilo (6,4 mg, 0,01 mmol) en tolueno (0,25 ml) se agita a RT durante 6 días. La mezcla de reacción se concentra al vacío y el producto se purifica por RP HPLC. Rendimiento: 18 mg (31%). HPLC-MS: M+H=434; tR=1,97 min (*Método_5).

Ejemplo 166 2-amino-N-[5-ciclopentil-6-(2-feniletinil)piridin-2-il]propan-amida



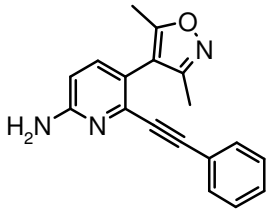
Una mezcla de N–[1-[[5-ciclopentil-6-(2-feniletinil)piridin-2-il]amino]-1-oxo-propan-2-il]carbamato de ter–butilo E2e (18 mg, 0,04 mmol) y DCM:TFA (9:1, 2 ml) se agita a RT durante 90 minutos. La mezcla se diluye con DCM y se extrae con una solución acuosa saturada de $NaHCO_3$. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. El producto se purifica por RP HPLC. Rendimiento: 13 mg (94%). HPLC-MS: M+H=334; tR=2,09 min (*Método_1).

El siguiente compuesto se prepara de modo análogo:

#	Estructura molecular	Nombre químico	HPLC-MS
167		2-amino-N-[6-(2-feniletinil)-5-propilpiridin-2-il]propanamida	M+H=308; tR=1,95

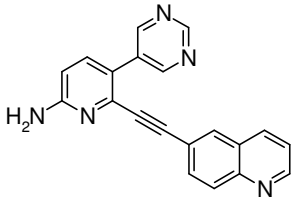
En una variante de la vía ilustrada en el esquema 2, se preparar los siguientes ejemplos 168-172:

G2a) 5-(3,5-dimetil-1,2-oxazol-4-il)-6-(2-feniletinil)piridin-2–amina

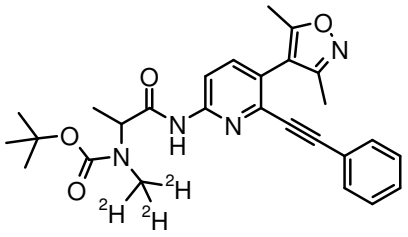


Una mezcla de 5-bromo-6-(2-feniletinil)piridin-2–amina B2a (20 g, 73 mmol), ácido (3,5-dimetil-1,2-oxazol-4-il)borónico (24 g, 170 mmol), CsF (44 g, 289 mmol) tris-(dibencilidenacetona)dipaladio(0) (10,28 g, 11,2 mmol), tetrafluoroborato de tri-ter–butilfosfonio (8,6 g, 296 mmol) y THF (200 ml) se agita bajo atmósfera de argón a 50°C durante 1 hora. La mezcla se filtra y el precipitado se lava con THF. Las fases orgánicas combinadas se concentran al vacío, se diluyen con DCM y se extraen con una solución acuosa saturada de $NaHCO_3$. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. El producto se purifica por cromatografía NP. Rendimiento: 12,2 g (58%). HPLC-MS: M+H=290; tR=1,54 min (*Método_6).

El siguiente compuesto se prepara de modo análogo:

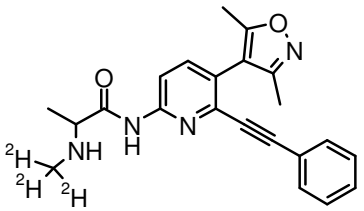
#	**Estructura molecular**	**Nombre químico**
G2b		5-pirimidin-5-il-6-(2-quinolin-6-iletinil)piridin-2–amina

E2f) N–[1-[[5-(3,5-dimetil-1,2-oxazol-4-il)-6-(2-feniletinil)piridin-2-il]amino]-1-oxopropan-2-il]-N-(trideuteriometil)carbamato de ter–butilo



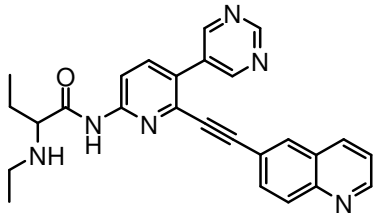
Una mezcla de ácido 2-[(2-metilpropan-2-il)oxicarbonil-(trideuteriometil)amino]-propanoico (1,4 g, 6,79 mmol) y N,N'-diciclohexilcarbodiimida (0,71 g, 3,46 mmol) en DCM (20 ml) se agita a RT durante 30 minutos. Esta mezcla se añade a 5-(3,5-dimetil-1,2-oxazol-4-il)-6-(2-feniletinil)piridin-2–amina G2a (1,0 g, 3,46 mmol) y DIPEA (700 µl; 4,12 mmol) en DCM (10 ml). Después de agitar durante 7 días a RT la mezcla de reacción se filtra, se concentran al vacío, y el producto se purifica por RP HPLC. El producto (1,29 g, 78%) se usa directamente en la siguiente etapa.

Ejemplo 168 N-[5-(3,5-dimetil-1,2-oxazol-4-il)-6-(2-feniletinil)piridin-2-il]-2-(trideuteriometilamino)propanamida



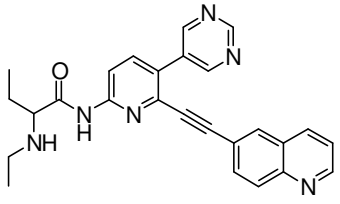
Una mezcla de N–[1-[[5-(3,5-dimetil-1,2-oxazol-4-il)-6-(2-feniletinil)piridin-2-il]-amino]-1-oxopropan-2-il]-N-(trideuteriometil)carbamato de ter–butilo E2f (1,29 g, 2,70 mmol) y DCM:TFA (9:1, 20 ml) se agita a RT durante 2 h. La mezcla se diluye con DCM y se extrae con una solución acuosa saturada de $NaHCO_3$. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. El producto se purifica por RP HPLC. Rendimiento: 0,75 g (73%). HPLC-MS: M+H=378; tR=1,44 min (*Método_1).

Ejemplo 169 2-(etilamino)-N-[5-pirimidin-5-il-6-(2-quinolin-6-iletinil)piridin-2-il]-butanamida



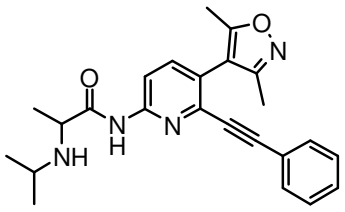
Se mezcla 5-pirimidin-5-il-6-(2-quinolin-6-iletinil)piridin-2–amina G2b (600 mg, 1,86 mmol) con NMP (10 ml) y DIPEA (1,42 ml, 8,35 mmol). Se añade bromuro de 2-Bromobutanoílo (985 µl, 8,17 mmol) gota a gota. La mezcla se agita durante 1 h a RT. La mezcla se diluye con DCM y se extrae con una solución acuosa saturada de $NaHCO_3$. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. El intermediario bruto se mezcla con una solución THF de metilamina (2 mol/l, 5 ml, 10 mmol) y se agita RT durante 16 h. La mezcla se diluye con DCM y se extrae con una solución acuosa saturada de $NaHCO_3$. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. El producto se purifica por RP HPLC. Rendimiento: 250 mg (32%). HPLC-MS: M+H=423; tR=1,25 min (*Método_1).

El siguiente ejemplo se prepara de modo análogo:

#	**Estructura molecular**	**Nombre químico**	**HPLC-MS**
170		2-(etilamino)-N-[5-pirimidin-5-il-6-(2-quinolin-6-iletinil)piridin-2-il]butanamida	M+H=437; tR=1,29

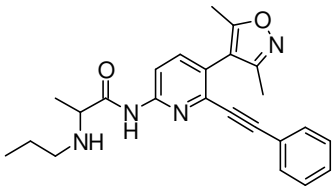
Los Ejemplos 171-172 se obtienen por la modificación adicional del ejemplo 166:

Ejemplo 171 N-[5-(3,5-dimetil-1,2-oxazol-4-il)-6-(2-feniletinil)piridin-2-il]-2-(propan-2-ilamino)propanamida

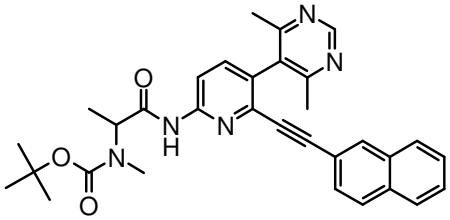


Una mezcla de 2-amino-N-[5-(3,5-dimetil-1,2-oxazol-4-il)-6-(2-feniletinil)piridin-2-il]propanamida (ejemplo 165, 20 mg, 0,06 mmol), propan-2-ona (16,2 ml, 0,28 mmol), ácido acético (4 µl, 0,07 mmol), MeOH (0,5 ml) y cianoborohidruro de sodio (5,5 mg, 0,08 mmol) se agita a 50°C durante 30 minutos. La mezcla de reacción se concentra al vacío y el producto se purifica por RP HPLC. Rendimiento: 11 mg (48%). HPLC-MS: M+H=403; tR=1,52 min (*Método_1).

El siguiente ejemplo se prepara de modo análogo:

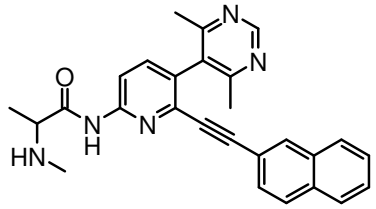
#	Estructura molecular	Nombre químico	HPLC-MS
172		N-[5-(3,5-dimetil-1,2-oxazol-4-il)-6-(2-feniletinil)piridin-2-il]-2-(propilamino)propanamida	M+H=403; tR=1,38

E2g) N–[1-[[5-(4,6-dimetilpirimidin-5-il)-6-(2-naftalen-2-iletinil)piridin-2-il]amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo



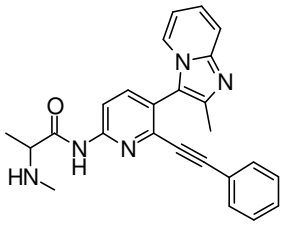
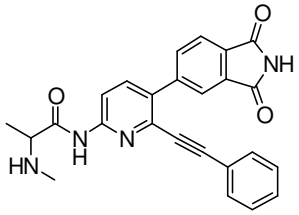
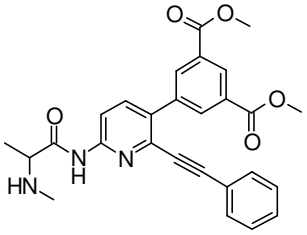
Una mezcla de ácido [6-[2-[metil-[(2-metilpropan-2-il)oxicarbonil]amino]-propanoilamino]-2-(2-naftalen-2-iletinil)piridin-3-il]borónico D2b (50 mg, 0,11 mmol), 5-bromo-4,6-dimetilpirimidina (26 mg, 0,14 mmol), Diclorobis(trifenilfosfino)paladio(II) (8 mg, 0,01 mmol), Na_2CO_3 (34 mg, 0,32 mmol), dioxano (0,9 ml), MeOH (0,3 ml) y agua (0,1 ml) se agita bajo atmósfera de argón durante 2 horas a 80°C. La mezcla se concentra al vacío y el producto se purifica por RP HPLC. Rendimiento: 12 mg (21%). HPLC-MS: M+H=536; tR=2,22 min (*Método_6).

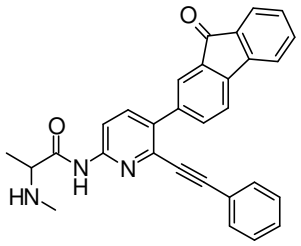
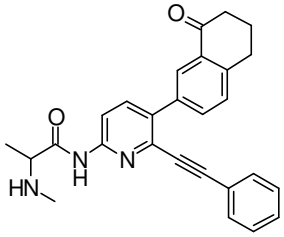
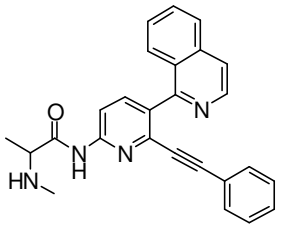
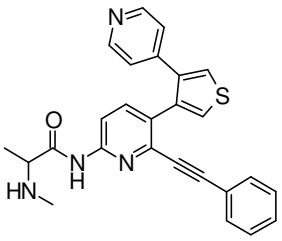
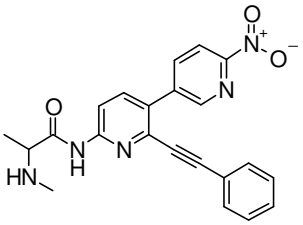
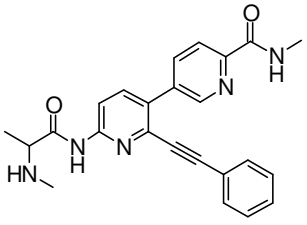
Ejemplo 173 N-[5-(4,6-dimetilpirimidin-5-il)-6-(2-naftalen-2-iletinil)piridin-2-il]-2-(metilamino)propanamida

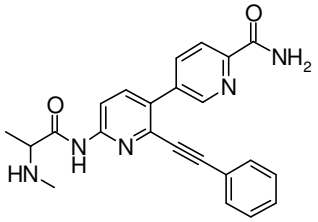
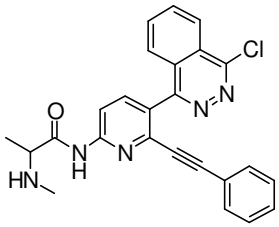
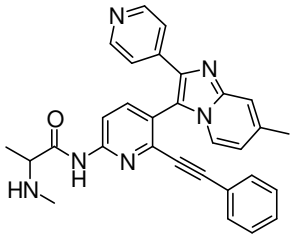
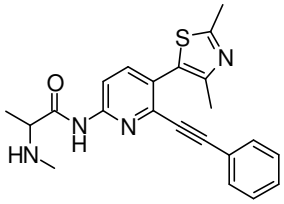
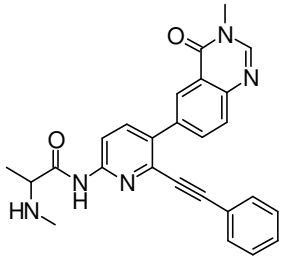
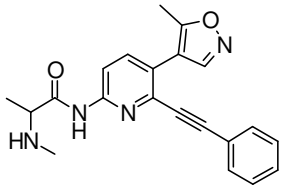


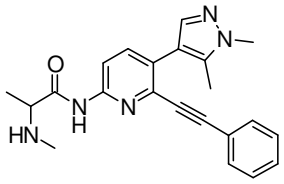
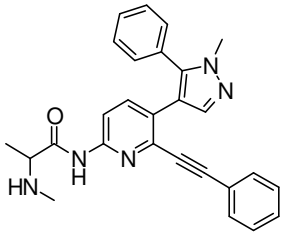
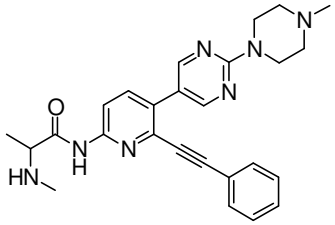
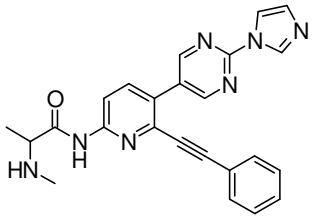
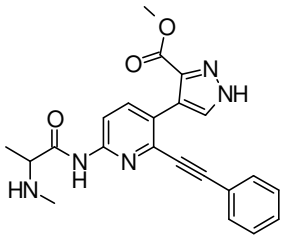
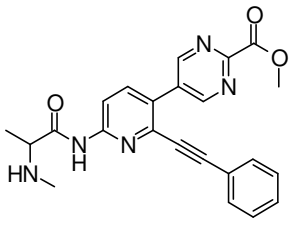
Una mezcla de N–[1-[[5-(4,6-dimetilpirimidin-5-il)-6-(2-naftalen-2-iletinil)piridin-2-il]amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo E2g (12 mg, 0,02 mmol) y DCM:TFA (9:1, 5 ml) se agita a RT durante 60 minutos. La mezcla se diluye con tolueno (10 ml) y se concentran al vacío. El producto se purifica por RP HPLC. Rendimiento: 6 mg (61%). HPLC-MS: M+H=436; tR=1,38 min (*Método_1).

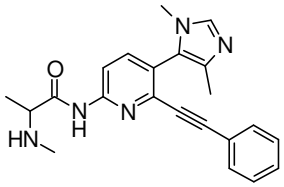
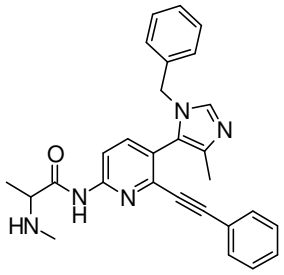
Los siguientes ejemplos se preparan de modo análogo:

#	**Estructura molecular**	**Nombre químico**	**HPLC-MS**
174		2-(metilamino)-N-[5-(2-metil-imidazo[1,2-a]piridin-3-il)-6-(2-feniletinil)piridin-2-il]propanamida	M+H=410; tR=1,27
175		N-[5-(1,3-dioxoisoindol-5-il)-6-(2-feniletinil)piridin-2-il]-2-(metil-amino)propanamida	M+H=425; tR=1,66
176		5-[6-[[2-(metilamino)propanoil]-amino]-2-(2-feniletinil)piridin-3-il]-benceno-1,3-dicarboxilato de dimetilo	M+H=472; tR=1,87

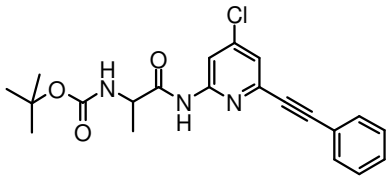
177		2-(metilamino)-N-[5-(9-oxofluoren-2-il)-6-(2-feniletinil)-piridin-2-il]propanamida	M+H=458; tR=2,04
178		2-(metilamino)-N-[5-(8-oxo-6,7-dihidro-5H-naftalen-2-il)-6-(2-fenil-etinil)piridin-2-il]propanamida	M+H=424; tR=1,83
179		N-[5-isoquinolin-1-il-6-(2-fenil-etinil)piridin-2-il]-2-(metilamino)-propanamida	M+H=407; tR=2,48
180		2-(metilamino)-N-[6-(2-feniletinil)-5-(4-piridin-4-iltiofen-3-il)piridin-2-il]propanamida	M+H=439; tR=1,91
181		2-(metilamino)-N-[5-(6-nitropiridin-3-il)-6-(2-feniletinil)piridin-2-il]-propanamida	M+H=402; tR=1,83
182		N-metil-5-[6-[[2-(metilamino)-propanoil]amino]-2-(2-feniletinil)-piridin-3-il]piridina-2-carboxamida	M+H=414; tR=1,67

183		5-[6-[[2-(metilamino)propanoil]-amino]-2-(2-feniletinil)piridin-3-il]-piridina-2-carboxamida	M+H=400; tR=1,56
184		N-[5-(4-cloroftalazin-1-il)-6-(2-feniletinil)piridin-2-il]-2-(metil-amino)propanamida	M+H=442/444; tR=1,89
185		2-(metilamino)-N-[5-(7-metil-2-piridin-4-ilimidazo[1,2-a]piridin-3-il)-6-(2-feniletinil)piridin-2-il]-propanamida	M+H=487; tR=1,32
186		N-[5-(2,4-dimetil-1,3-tiazol-5-il)-6-(2-feniletinil)piridin-2-il]-2-(metil-amino)propanamida	M+H=391; tR=1,38
187		2-(metilamino)-N-[5-(3-metil-4-oxoquinazolin-6-il)-6-(2-feniletinil)-piridin-2-il]propanamida	M+H=438; tR=1,65
188		2-(metilamino)-N-[5-(5-metil-1,2-oxazol-4-il)-6-(2-feniletinil)piridin-2-il]propanamida	M+h=361; tr=1,37

189		N-[5-(1,5-dimetilpirazol-4-il)-6-(2-feniletinil)piridin-2-il]-2-(metil-amino)propanamida	M+H=374; tR=1,25
190		2-(metilamino)-N-[5-(1-metil-5-fenilpirazol-4-il)-6-(2-feniletinil)-piridin-2-il]propanamida	M+H=436; tR=1,92
191		2-(metilamino)-N-[5-[2-(4-metilpiperazin-1-il)pirimidin-5-il]-6-(2-feniletinil)piridin-2-il]propan-amida	M+H=456; tR=1,45
192		N-[5-(2-imidazol-1-ilpirimidin-5-il)-6-(2-feniletinil)piridin-2-il]-2-(metil-amino)propanamida	M+H=424; tR=1,36
193		4-[6-[[2-(metilamino)propanoil]-amino]-2-(2-feniletinil)piridin-3-il]-1H-pirazol-3-carboxilato de metilo	M+H=404; tR=1,15
194		5-[6-[[2-(metilamino)propanoil]-amino]-2-(2-feniletinil)piridin-3-il]-pirimidin-2-carboxilato de metilo	M+H=416; tR=1,27

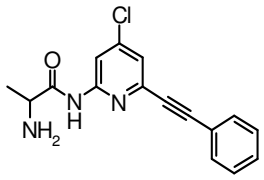
195		N-[5-(3,5-dimetilimidazol-4-il)-6-(2-feniletinil)piridin-2-il]-2-(metil-amino)propanamida	M+H=374; tR=1,19
196		N-[5-(3-benzil-5-metilimidazol-4-il)-6-(2-feniletinil)piridin-2-il]-2-(metilamino)propanamida	M+H=450; tR=1,34

D3a) N-[1-[[4-cloro-6-(2-feniletinil)piridin-2-il]amino]-1-oxopropan-2-il]-carbamato de ter–butilo



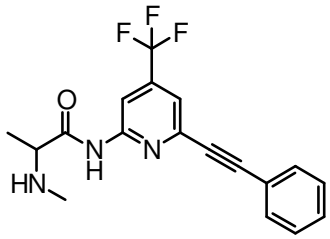
Una mezcla de ácido 2-[(2-metilpropan-2-il)oxicarbonilamino]propanoico (1,17 g, 6,19 mmol), 4-cloro-6-(2-feniletinil)piridin-2–amina B3a (1,09 g, 4,76 mmol), trietilamina (3,63 ml, 25,7 mmol) HATU (2,89 g, 7,61 mmol) y NMP (3,75 ml) se agita a 40°C durante 60 h. Se añade ácido 2-[(2-metilpropan-2-il)oxicarbonilamino]propanoico (0,72 g, 3,81 mmol) y HATU (1,45 g, 3,81 mmol) a la mezcla y se continúa agitando durante 48 horas a 60°C. A RT se añade agua y la mezcla se extrae con DCM. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. El producto se purifica por RP HPLC. Rendimiento: 712 mg (37%). HPLC-MS: M+H=400; tR=2,27 min (*Método_2).

Ejemplo 197 2-amino-N-[4-cloro-6-(2-feniletinil)piridin-2-il]propanamida



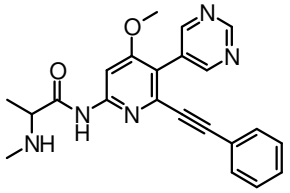
Una mezcla de ter–butilN-[1-[[4-cloro-6-(2-feniletinil)piridin-2-il]amino]-1-oxo-propan-2-il]carbamato de ter–butilo D3a (20 mg, 0,05 mmol) y DCM:TFA (9:1, 1,8 ml) se agita a RT durante 90 minutos. La mezcla se diluye con DCM y se extrae con una solución acuosa saturada de $NaHCO_3$. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. El producto se purifica por RP HPLC. Rendimiento: 14 mg (93%). HPLC-MS: M+H=300; tR=1,92 min (*Método_1).

Ejemplo 198 2-(metilamino)-N-[6-(2-feniletinil)-4-(trifluorometil)piridin-2-il]-propanamida

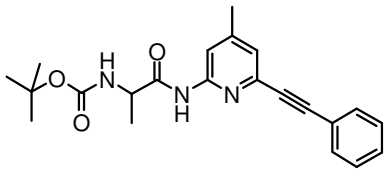


Una mezcla de ácido 2-[metil-[(2-metilpropan-2-il)¬oxicarbonil]¬amino]¬propanoico (620 mg, 3,05 mmol) y N,N'-diciclohexilcarbodiimida (315 mg, 1,53 mmol) en DCM (4 ml) se agita a RT durante 30 minutos. Esta mezcla se añade a 6-(2-feniletinil)-4-(trifluorometil)piridin-2–amina B3b (100 mg, 0,38 mmol) y DIPEA (73 µl; 0,42 mmol) en NMP (5 ml). Después de agitar durante 6 días a 50℃ la mezcla de reacción se concentra al vacío y el producto protegido con boc se purifica por cromatografía NP. El producto protegido con boc se trata con DCM:TFA (9:1, 4 ml) durante 1,5 h a RT. Esta mezcla se diluye con DCM y se extrae con una solución acuosa saturada de $NaHCO_3$. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. El producto se purifica por RP HPLC. Rendimiento: 10,2 mg (8%). HPLC-MS: M+H=348; tR=1,46 (*Método_1).

El siguiente ejemplo se prepara de modo análogo a partir del compuesto C3e:

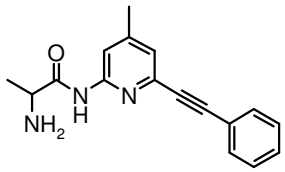
#	Estructura molecular	Nombre químico	HPLC-MS
199		N-[4-metoxi-6-(2-feniletinil)-5-pirimidin-5-ilpiridin-2-il]-2-(metilamino)propanamida	M+H=388; tR=1,10

D3b) N–[1-[[4-metil-6-(2-feniletinil)piridin-2-il]amino]-1-oxopropan-2-il]-carbamato de ter–butilo



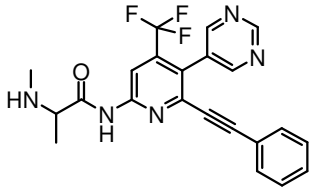
Una mezcla de ter–butilN-[1-[[4-cloro-6-(2-feniletinil)piridin-2-il]amino]-1-oxo-propan-2-il]carbamato de ter–butilo D3a (40 mg, 0,10 mmol), 2,4,6-trihidroxi-1,3,5,2,4,6-trioxatriborinano (36 µl, 0,26 mmol), Tetrakis(trifenilfosfino)paladio(0) (16,6 mg, 0,01 mmol), carbonato de potasio (41,5 mg, 0,30 mmol), 1,2-dimetoxietano (600 µl) y agua (100 µl) se agita durante 2 días a 80°C. La mezcla se concentra al vacío y el producto se purifica por RP HPLC. Rendimiento: 2 mg (5%). HPLC-MS: M+H=380; tR=2,18 min (*Método_2).

Ejemplo 200 2-amino-N-[4-metil-6-(2-feniletinil)piridin-2-il]propanamida



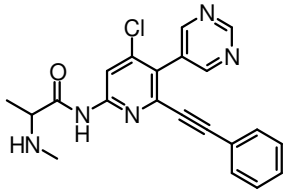
Una mezcla de N–[1-[[4-metil-6-(2-feniletinil)piridin-2-il]amino]-1-oxopropan-2-il]carbamato de ter–butilo D3b (2 mg, 5 µmol) y DCM:TFA (9:1, 400 µl) se agita a RT durante 4 horas. La mezcla se diluye con DCM y se extrae con una solución acuosa saturada de $NaHCO_3$. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. Rendimiento: 1,5 mg (cuantitativo). HPLC-MS: M+H=280; tR=1,77 min (*Método_1).

Ejemplo 201 2-(metilamino)-N-[6-(2-feniletinil)-5-pirimidin-5-il-4-(trifluoro-metil)piridin-2-il]propanamida

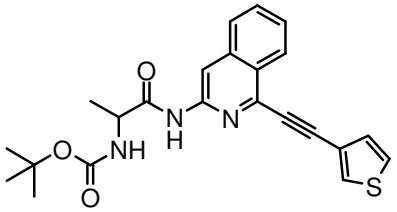


Con agitación a 0°C se añade bromuro de 2-bromopropanoílo (44 µl, 0,42 mmol) gota a gota a una mezcla de 6-(2-feniletinil)-5-pirimidin-5-il-4-(trifluoro-metil)piridin-2–amina C3d (95 mg, 0,28 mmol), trietilamina (59 µl, 0,42 mmol), DMAP (0,3 mg, 3 µmol) y dioxano (1,4 ml). La mezcla se calienta a RT y se agita durante 1 h. Se añade metilamina (solución en THF 2 mol/l, 1,4 ml, 2,8 mmol) y se continúa agitando durante 6 horas. La mezcla se concentra al vacío y el producto se purifica por RP HPLC. Rendimiento: 45 mg (38%). HPLC-MS: M+H=426; tR=1,27 min (*Método_1).

El siguiente ejemplo se prepara de modo análogo:

#	Estructura molecular	Nombre químico	HPLC-MS
202		N-[4-cloro-6-(2-feniletinil)-5-pirimidin-5-ilpiridin-2-il]-2-(metilamino)propanamida	M+H=392; tR=1,19

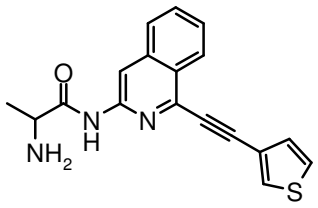
E4a) N–[1-oxo-1-[[1-(2-tiofen-3-iletinil)isoquinolin-3-il]amino]propan-2-il]-carbamato de ter–butilo



Una mezcla de N–[1-[(1-bromoisoquinolin-3-il)amino]-1-oxopropan-2-il]-

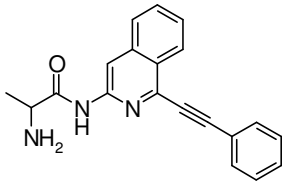
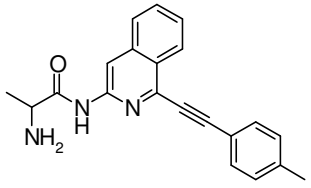
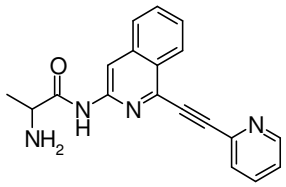
carbamato de ter–butilo B4a (150 mg, 0,38 mmol), 3-etiniltiofeno (45 mg, 0,42 mmol), yoduro de cobre(I) (7 mg, 0,04 mmol), Diclorobis(trifenilfosfino)paladio(II) (27 mg, 0,04 mmol) y DIPEA (200 µl, 1,2 mmol) se agita bajo atmósfera de argón en NMP (1 ml) durante 1 hora a 80°C. La mezcla se concentra al vacío y el producto se purifica por RP HPLC. Rendimiento: 102 mg (64%). HPLC-MS: M+H=422; tR=1,99 min (*Método_4).

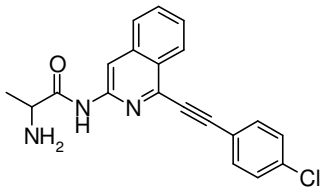
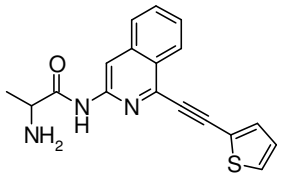
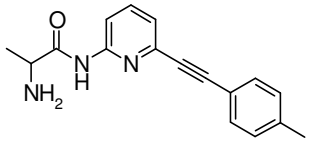
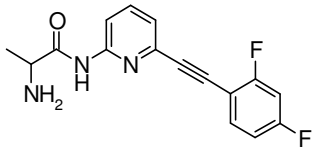
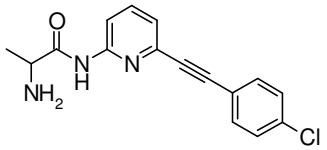
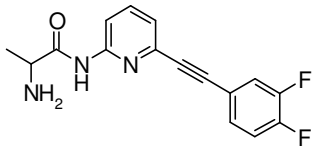
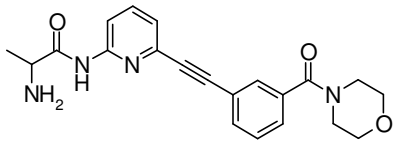
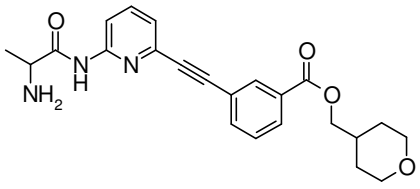
Ejemplo 203 2-amino-N-[1-(2-tiofen-3-iletinil)isoquinolin-3-il]propanamida

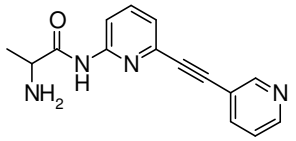
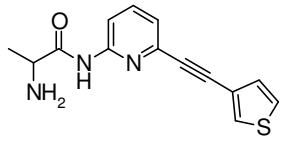
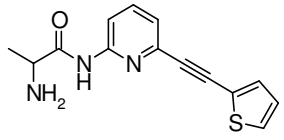
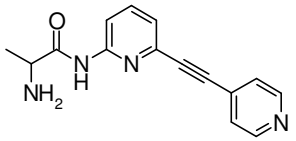
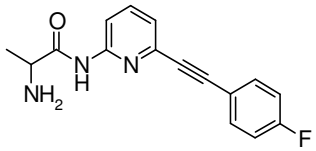
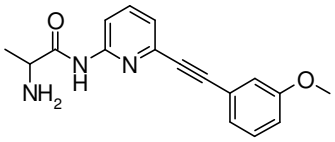
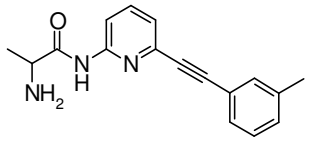
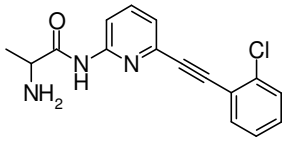


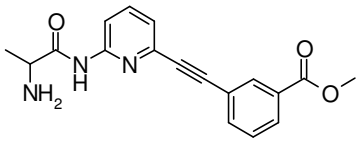
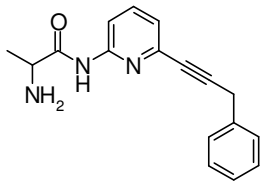
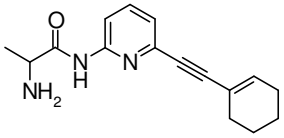
Una mezcla de N–[1-oxo-1-[[1-(2-tiofen-3-iletinil)isoquinolin-3-il]amino]propan-2-il]carbamato de ter–butilo E4a (102 mg, 0,24 mmol) y DCM:TFA (9:1, 2 ml) se agita a RT durante 1 h. La mezcla se diluye con tolueno (10 ml) y se concentran al vacío. El producto se purifica por RP HPLC. Rendimiento: 65 mg (84%). HPLC-MS: M+H=322; tR=1,84 min (*Método_1).

Los siguientes ejemplos se preparan de modo análogo:

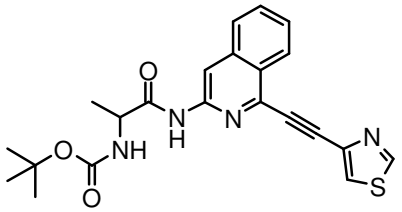
#	Estructura molecular	Nombre químico	HPLC-MS
204		2-amino-N-[1-(2-feniletinil)-isoquinolin-3-il]propanamida	M+H=316; tR=1,92
205		2-amino-N-[1-[2-(4-metil-fenil)etinil]isoquinolin-3-il]-propanamida	M+H=330; tR=2,05
206		2-amino-N-[1-(2-piridin-2-il-etinil)isoquinolin-3-il]propan-amida	M+H=317; tR=1,54

#	Estructura molecular	Nombre químico	HPLC-MS
207		2-amino-N-[1-[2-(4-clorofenil)etinil]isoquinolin-3-il]propanamida	M+H=350/352; tR=2,05
208		2-amino-N-[1-(2-tiofen-2-il-etinil)isoquinolin-3-il]propan-amida	M+H=322; tR=1,87
209		2-amino-N-[6-[2-(4-metilfenil)etinil]piridin-2-il]propanamida	M+H=280; tR=1,79
210		2-amino-N-[6-[2-(2,4-difluorofenil)etinil]piridin-2-il]propanamida	M+H=302; tR=1,71
211		2-amino-N-[6-[2-(4-clorofenil)etinil]piridin-2-il]propanamida	M+H=300; tR=1,82
212		2-amino-N-[6-[2-(3,4-difluorofenil)etinil]piridin-2-il]propanamida	M+H=302; tR=1,72
213		2-amino-N-[6-[2-[3-(morfolina-4-carbonil)-fenil]etinil]piridin-2-il]propanamida	M+H=379; tR=1,41
214		3-[2-[6-[[2-aminopropanoil]-amino]piridin-2-il]etinil]benzoato de oxan-4-ilmetilo	M+H=408; tR=1,78

#	Estructura molecular	Nombre químico	HPLC-MS
215		2-amino-N-[6-(2-piridin-3-iletinil)piridin-2-il]propanamida	M+H=267; tR=1,33
216		2-amino-N-[6-(2-tiofen-3-iletinil)piridin-2-il]propanamida	M+H=272; tR=1,62
217		2-amino-N-[6-(2-tiofen-2-iletinil)piridin-2-il]propanamida	M+H=272; tR=1,75
218		2-amino-N-[6-(2-piridin-4-iletinil)piridin-2-il]propanamida	M+H=267; tR=1,30
219		2-amino-N-[6-[2-(4-fluorofenil)etinil]piridin-2-il]propanamida	M+H=284; tR=1,68
220		2-amino-N-[6-[2-(3-metoxifenil)etinil]piridin-2-il]propanamida	M+H=296; tR=1,69
221		2-amino-N-[6-[2-(3-metilfenil)etinil]piridin-2-il]propanamida	M+H=280; tR=1,82
222		2-amino-N-[6-[2-(2-clorofenil)etinil]piridin-2-il]propanamida	M+H=300; tR=1,82

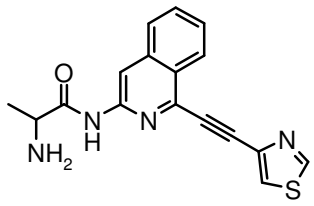
#	Estructura molecular	Nombre químico	HPLC-MS
223		3-[2-[6-[[2-aminopropanoil]amino]piridin-2-il]etinil]benzoato de metilo	M+H=324; tR=1,68
224		2-amino-N-[6-(3-fenilprop-1-inil)piridin-2-il]propanamida	M+H=280; tR=1,64
225		2-amino-N-[6-[2-(ciclohexen-1-il)etinil]piridin-2-il]propanamida	M+H=270; tR=1,78

E4b) N–[1-oxo-1-[[1-[2-(1,3-tiazol-4-il)etinil]isoquinolin-3-il]amino]propan-2-il]-carbamato de ter–butilo



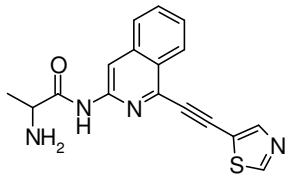
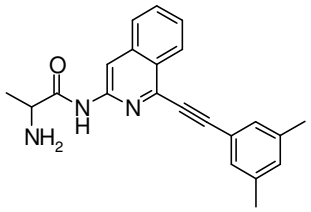
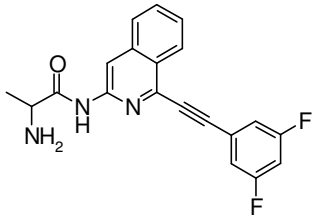
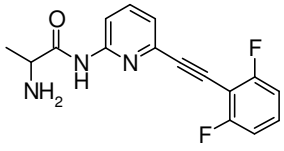
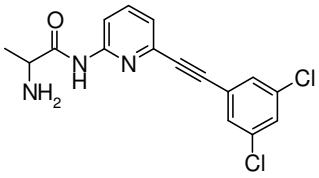
Una mezcla de N–[1-[(1-etinilisoquinolin-3-il)amino]-1-oxopropan-2-il]carbamato de ter–butilo D4a (50 mg, 0,15 mmol), 4-bromo-1,3-tiazol (24 mg, 0,15 mmol), yoduro de cobre(I) (3 mg, 0,02 mmol), Diclorobis(trifenilfosfino)paladio(II) (10 mg, 0,01 mmol) y DIPEA (75 µl, 0,44 mmol) se agita bajo atmósfera de argón en NMP (1 ml) durante 2 horas a 80ºC. La mezcla se concentra al vacío y el producto se purifica por RP HPLC. Rendimiento: 12 mg (19%). HPLC-MS: M+H=423; tR=1,84 min (*Método_4).

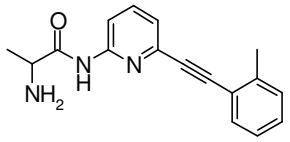
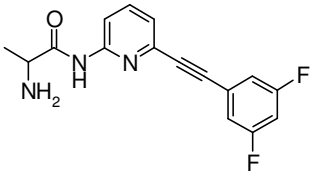
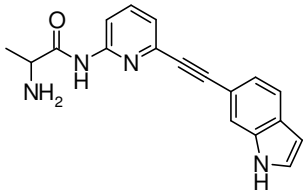
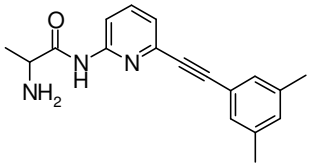
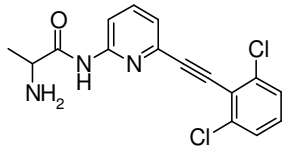
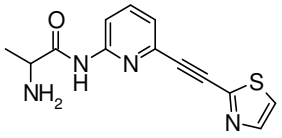
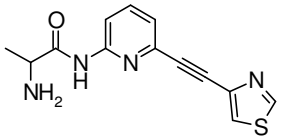
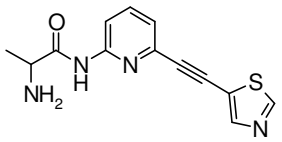
Ejemplo 226 2-amino-N-[1-[2-(1,3-tiazol-4-il)etinil]isoquinolin-3-il]propanamida

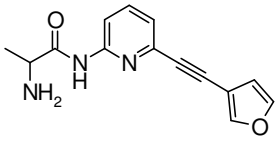
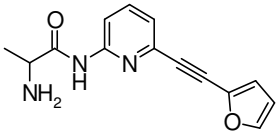
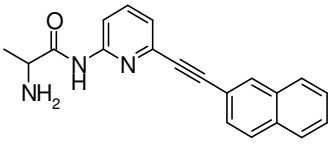


Una mezcla de N–[1-oxo-1-[[1-[2-(1,3-tiazol-4-il)etinil]isoquinolin-3-il]amino]-propan-2-il]carbamato de ter–butilo E4b (12 mg, 0,03 mmol) y DCM:TFA (9:1, 3 ml) se agita a RT durante 1 h. La mezcla se diluye con DCM y se extrae con una solución acuosa saturada de $NaHCO_3$. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. El producto se purifica por RP HPLC. Rendimiento: 2 mg (22%). HPLC-MS: M+H=323; tR=1,65 min (*Método_1).

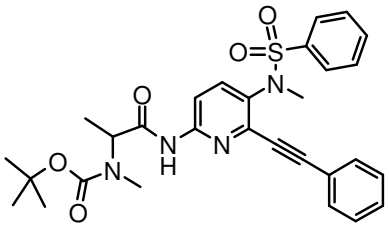
Los siguientes ejemplos se preparan de modo análogo:

#	Estructura molecular	Nombre químico	HPLC-MS
227		2-amino-N-[1-[2-(1,3-tiazol-5-il)-etinil]isoquinolin-3-il]propan-amida	M+H=323; tR=1,59
228		2-amino-N-[1-[2-(3,5-dimetil-fenil)etinil]isoquinolin-3-il]-propanamida	M+H=344; tR=2,18
229		2-amino-N-[1-[2-(3,5-difluorofenil)etinil]isoquinolin-3-il]propanamida	M+H=352; tR=2,01
230		2-amino-N-[6-[2-(2,6-difluorofenil)etinil]piridin-2-il]propanamida	M+H=302; tR=1,50
231		2-amino-N-[6-[2-(3,5-diclorofenil)etinil]piridin-2-il]propanamida	M+H=334; tR=1,85

#	Estructura molecular	Nombre químico	HPLC-MS
232		2-amino-N-[6-[2-(2-metilfenil)etinil]piridin-2-il]propanamida	M+H=280; tR=1,86
233		2-amino-N-[6-[2-(3,5-difluorofenil)etinil]piridin-2-il]propanamida	M+H=302; tR=1,80
234		2-amino-N-[6-[2-(1H-indol-6-il)etinil]piridin-2-il]propanamida	M+H=305; tR=0,25
235		2-amino-N-[6-[2-(3,5-dimetilfenil)etinil]piridin-2-il]propanamida	M+H=294; tR=2,02
236		2-amino-N-[6-[2-(2,6-diclorofenil)etinil]piridin-2-il]propanamida	M+H=334; tR=1,90
237		2-amino-N-[6-[2-(1,3-tiazol-2-il)etinil]piridin-2-il]propanamida	M+H=273; tR=1,29
238		2-amino-N-[6-[2-(1,3-tiazol-4-il)etinil]piridin-2-il]propanamida	M+H=273; tR=1,22
239		2-amino-N-[6-[2-(1,3-tiazol-5-il)etinil]piridin-2-il]propanamida	M+H=273; tR=1,28

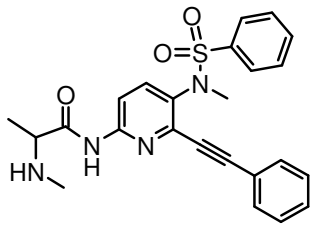
#	Estructura molecular	Nombre químico	HPLC-MS
240		2-amino-N-[6-[2-(furan-3-il)etinil]piridin-2-il]propanamida	M+H=256; tR=1,46
241		2-amino-N-[6-[2-(furan-2-il)etinil]piridin-2-il]propanamida	M+H=256; tR=1,50
242		2-amino-N-[6-(2-naftalen-2-iletinil)piridin-2-il]propanamida	M+H=316; tR=1,93

F5a) N–[1-[[5-[bencensulfonil(metil)amino]-6-(2-feniletinil)piridin-2-il]amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo



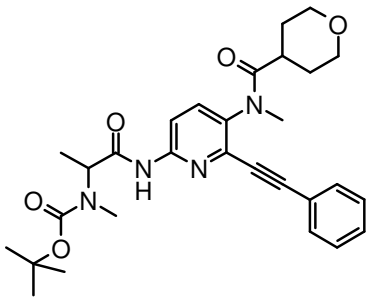
Una mezcla de ácido 2-[metil-[(2-metilpropan-2-il)¬oxicarbonil]¬amino]¬propanoico (54 mg, 0,26 mmol) y N,N'-diciclohexilcarbodiimide (27 mg, 0,13 mmol) en DCM (1,5 ml) se agita a RT durante 20 minutos. Esta mezcla se añade a N-[6-amino-2-(2-feniletinil)piridin-3-il]-N-metilbencensulfonamida E5a (16 mg, 0,04 mmol) y DIPEA (9 µl; 0,05 mmol) en DCM (0,5 ml). Después de agitar durante 4 días a 40°C la mezcla de reacción se diluye con DCM y se extrae con agua. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. El producto bruto (22 mg) se usa en la próxima etapa sin purificación adicional.

Ejemplo 243 N-[5-[bencensulfonil(metil)amino]-6-(2-feniletinil)piridin-2-il]-2-(metilamino)propanamida



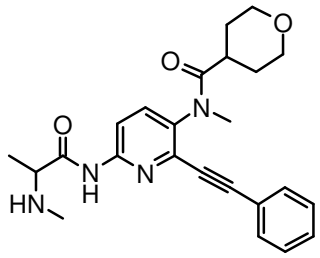
Una mezcla de N–[1-[[5-[bencensulfonil(metil)amino]-6-(2-feniletinil)piridin-2-il]-amino]-1-oxopropan-2-il]-N-metilcarbamato de ter–butilo F5a (25 mg) y DCM:TFA (9:1, 3 ml) se agita a RT durante 2 h. La mezcla se diluye con DCM y se extrae con una solución acuosa saturada de $NaHCO_3$. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. El producto se purifica por RP HPLC. Rendimiento: 7 mg. HPLC-MS: M+H=449; tR=1,49 min (*Método_1).

F5b) N–metil-N-[1-[[5-[metilo(oxane-4-carbonil)amino]-6-(2-feniletinil)piridin-2-il]amino]-1-oxopropan-2-il]carbamato de ter–butilo



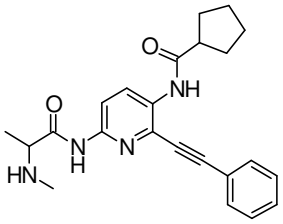
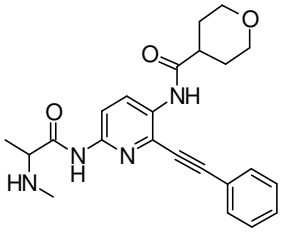
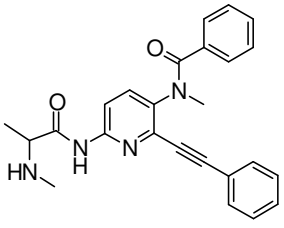
A RT NaH (60% dispersión en aceite mineral, 2,3 mg, 0,0,06 mmol) se añade a N–metil-N-[1-[[5-(oxane-4-carbonilamino)-6-(2-feniletinil)piridin-2-il]amino]-1-oxo-propan-2-il]carbamato de ter–butilo E5b (35mg, 0,04 mmol) en THF (1 ml). Después de agitar durante 10 minutos dimetilsulfato (4 µl, 0,06 mmol) se añade a la mezcla y se continúa agitando durante 20 minutos. La mezcla se concentra al vacío y el producto se purifica por RP HPLC. Rendimiento: 5 mg (23%). HPLC-MS: M+H=521; tR=2,06 min (*Método_2).

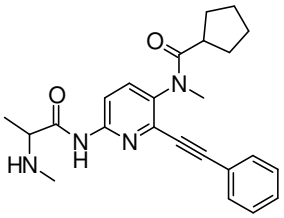
Ejemplo 244 N-metil-N-[6-[2-(metilamino)propanoilamino]-2-(2-feniletinil)piridin-3-il]oxane-4-carboxamida



Una mezcla de N–metil-N-[1-[[5-[metilo(oxane-4-carbonil)amino]-6-(2-fenil-etinil)piridin-2-il]amino]-1-oxopropan-2-il]carbamato de ter–butilo F5b (5 mg) y DCM:TFA (9:1, 1 ml) se agita a RT durante 100 minutos. La mezcla se diluye con DCM y se extrae con una solución acuosa saturada de $NaHCO_3$. Las fases orgánicas combinadas se secan en $MgSO_4$ y se concentran al vacío. El producto se purifica por RP HPLC. Rendimiento: 7 mg. HPLC-MS: M+H=421; tR=1,33 min (*Método_1).

Los siguientes ejemplos se preparan de modo análogo. Para los ejemplos 214-215 se saltea la etapa de alquilación (transformación D5→E5).

#	**Estructura molecular**	**Nombre químico**	**HPLC-MS**
245		N-[6-[[2-(metilamino)-propanoil]amino]-2-(2-fenil-etinil)piridin-3-il]-ciclopentanocarboxamida	M+H=391; tR=1,41
246		N-[6-[[2-(metilamino)-propanoil]amino]-2-(2-fenil-etinil)piridin-3-il]oxano-4-carboxamida	M+H=407; tR=1,25
247		N-metil-N-[6-[[2-(metilamino)-propanoil]amino]-2-(2-fenil-etinil)piridin-3-il]benzamida	M+H=413; tR=1,36

248		N-metil-N-[6-[[2-(metilamino)-propanoil]amino]-2-(2-fenil-etinil)piridin-3-il]-ciclopentanecarboxamida	M+H=405; tR=1,44

Métodos biológicos

Ensayos de unión XIAP BIR3 y cIAP1 BIR3 (DELFIA)

Los dominios de BIR3 de XIAP humano (que abarca los aminoácidos 241 a 356; XIAP BIR3) y cIAP1 (que abarca los aminoácidos 256 a 363; cIAP1 BIR3) se expresaron y purificaron a partir de Ecoli como proteínas de fusión GST. El péptido AVPIAQKSE-Lys(Biotina), que representa el extremo N-terminal de SMAC humana madura (péptido SMAC), se usó como compañero de interacción en el ensayo de interacción proteína-péptido.

Los dominios BIR3 (10 nM) se incubaron con el péptido SMAC (10 nM) en buffer de ensayo (50 mM de Tris, 120 mM de NaCl, 0,1% de BSA, 1 mM de DTT, 0,05% de TritonX100) durante una hora a temperatura ambiente en presencia de compuestos inhibidores. La mezcla de ensayo se transfirió a la placa recubierta con estreptavidina y se incubó durante una hora a temperatura ambiente para permitir la unión del péptido biotinilado y los dominios de BIR3 asociados a la placa. Después de varias etapas de lavado se añadió el anticuerpo anti-GST marcado con Eu (por ejemplo Perkin Elmer DELFIA Eu-N1-antiGST AD0250) para detectar las interacciones del dominio BIR3-péptido SMAC de acuerdo con las instrucciones de Perkin Elmer. En breves palabras, se añadió el anticuerpo (dilución 1:5000 en buffer de ensayo DELFIA Perkin Elmer 2013-01) y se incubó durante una hora. Después de 3 etapas de lavado usando un buffer de lavado Delfia (Perkin Elmer DELFIA Wash 2013-05), se añadió solución de potenciación (Perkin Elmer Enhancement Asolution 2013-02) y la incubación continuó durante 10 minutos. Se midió la fluorescencia de europio resuelta por tiempo en un Wallac Victor usando los ajustes de ensayo estándares.

Se calcularon los valores de IC_{50} para los compuestos inhibidores a partir de los resultados del ensayo obtenidos por la incubación de los dominios BIR3 con el péptido SMAC en presencia de compuestos diluidos seriados (por ejemplo 1:5). Los resultados del ensayo DELFIA se graficaron contra las concentraciones del compuesto y se usó el programa de computación GrafPad Prizm para calcular la mitad de las concentraciones inhibitorias máximas (valores de IC_{50}).

Los valores de IC_{50} que representan la actividad biológica de los ejemplos se listan en las siguientes tablas. Todos los valores de IC_{50} se informan en nM y representan la actividad de los isómeros (S) en el caso de los compuestos que contienen un centro quiral adyacente para R1 de acuerdo con la fórmula (I):

ejemplo #	IC_{50} XIAP BIR3
1	287
2	259
3	1152
4	643
5	509
6	214
7	460
8	351
9	1010
10	787
11	1214
12	1433
13	96
14	417
15	711
16	554
17	122
18	745
19	867
20	4281
21	540
22	1300
23	265
24	698
25	653
26	579
27	79
28	200
29	145
30	417
31	228
32	228
33	277
34	279
35	1477
36	112
37	166
38	142
39	87
40	445
41	123
42	94
43	310
44	136

ejemplo #	IC_{50} XIAP BIR3
45	431
46	145
47	180
48	212
49	107
50	95
51	453
52	145
53	116
54	863
55	310
56	2876
57	n.a.
58	224
59	918
60	184
61	187
62	620
63	70
64	152
65	1188
66	252
67	270
68	165
69	110
70	66
71	300
72	145
73	378
74	175
75	1674
76	1066
77	196
78	47
79	2399
80	1308
81	253
82	61
83	446
84	130
85	259
86	770
87	1453
88	207
89	92
90	166
91	267
92	172
93	198
94	107

ejemplo #	IC_{50} XIAP BIR3
95	97
96	83
97	644
98	526
99	521
100	461
101	128
102	1984
103	3043
104	2023
105	220
106	243
107	1012
108	1605
109	650
110	3192
111	1550
112	1070
113	228
114	1628
115	2036
116	1768
117	406
118	287
119	327
120	185
121	97
122	148
123	121
124	2839
125	580
126	1007
127	128
128	101
129	436
130	3204
131	305
132	326
133	142
134	581
135	490
136	1042
137	155
138	55
139	1411
140	1992
141	558
142	503
143	388
144	400

ejemplo #	IC_{50} XIAP BIR3
145	317
146	257
147	125
148	416
149	195
150	2450
151	326
152	431
153	1243
154	569
155	284
156	3178
157	276
158	772
159	767
160	474
161	102
162	1822
163	4449
164	335
165	67
166	898
167	874
168	151
169	1149
170	1370
171	1031
172	502
173	324
174	51
175	103
176	50
177	337
178	214
179	3802
180	260
181	222
182	135
183	146
184	138
185	16
186	151
187	49
188	128
189	87
190	276
191	102
192	76
193	141
194	102

ejemplo #	IC_{50} XIAP BIR3
195	269
196	609
197	3182
198	10483
199	268
200	1788
201	10804
202	483
203	760
204	703
205	2303
206	3615
207	4236
208	467
209	1458
210	2613
211	2008
212	3064
213	9955
214	7381
215	9697
216	2135
217	895
218	6537
219	359
220	2156
221	222
222	1417
223	2457
224	3559
225	7036
226	1199
227	1893
228	1919
229	2423
230	2407
231	4860
232	1247
233	2907
234	2731
235	2193
236	1974
237	5925
238	7187
239	4576
240	3017
241	3199
242	4235
243	160
244	1475

ejemplo #	IC_{50} XIAP BIR3
245	1287
246	1520
247	745
248	794

ejemplo #	IC_{50} cIAP1 BIR3
13	12
26	1
27	1
28	1
29	1
30	1
31	1
33	1
34	1
35	1
36	1
37	1
39	1
41	1
42	1
44	1
45	2
46	1
47	1
48	1
49	1
50	1
52	1
53	1
54	1
58	5
60	2
61	5
63	1
64	1
66	1
69	2
70	1
71	1
72	1
74	1
75	1
77	1
78	2
79	1
80	1
81	1
82	1

ejemplo #	IC_{50} cIAP1 BIR3
87	1
88	1
89	2
90	1
92	1
93	1
94	1
95	1
96	1
100	324
108	175
113	67
118	92
121	31
122	23
123	25
125	131
126	166
127	21
129	98
130	172
132	97
138	12
145	94
147	32
149	80
161	22
165	1
168	3
174	1
175	16
176	23
177	92
182	36
184	17
185	1
186	16
187	9
189	30
191	22
192	22
194	23
195	4
198	4926
203	251
204	430
206	880
208	255
213	2123
215	985

ejemplo #	IC_{50} cIAP1 BIR3
217	206
223	2622
226	332
228	1472
229	589
232	672
234	1234
240	1339

Sobre la base de sus propiedades biológicas los compuestos de fórmula general **(1)** de acuerdo con la invención, sus tautómeros, racematos, enantiómeros, diastereómeros, sus mezclas y las sales de todas las formas mencionadas anteriormente son adecuados para tratar las enfermedades caracterizadas por la proliferación celular excesiva o anormal.

Tales enfermedades incluyen por ejemplo: infecciones virales (por ejemplo, VIH y sarcoma de Kaposi); enfermedades inflamatorias y autoinmunes (por ejemplo colitis, artritis, enfermedad de Alzheimer, glomerulonefritis y cura de heridas); infecciones bacterianas, fúngicas y/o parasitarias; leucemias, linfomas y tumores sólidos (por ejemplo carcinomas y sarcomas), enfermedades cutáneas (por ejemplo psoriasis); enfermedades basadas en hiperplasia que se caracterizan por un aumento en el número de células (por ejemplo fibroblastos, hepatocitos, huesos y células de la médula ósea, células de cartílago o músculo liso o células epiteliales (por ejemplo, hiperplasia endometrial)); enfermedades óseas y enfermedades cardiovasculares (por ejemplo, restenosis e hipertrofia). También son adecuadas para proteger las células proliferantes (por ejemplo, células capilares, intestinales, sanguíneas y progenitoras) del daño de ADN causado por la radiación, tratamiento UV y/o tratamiento citostático.

Por ejemplo, los siguientes cánceres se pueden tratar con los compuestos de acuerdo con la invención, sin estar restringidos a estos: tumores cerebrales tales como por ejemplo, neuroma acústico, astrocitomas tales como, astrocitomas pilocíticos, astrocitoma fibrilar, astrocitoma protoplásmico, astrocitoma gemistocítico, astrocitoma anaplásico y glioblastoma, linfomas cerebrales, metástasis cerebrales, tumor hipofisario tal como prolactinoma, tumor que produce HGH (hormona de crecimiento humano) y tumor que produce ACTH (hormona adrenocorticotrófica), craniofaringiomas, meduloblastomas, meningeomas y oligodendrogliomas; tumores nerviosos (neoplasmas) tales como por ejemplo, tumores del sistema neuronal vegetativo tales como neuroblastoma simpático, ganglioneuroma, paraganglioma (feocromocitoma, cromafinoma) y tumor de glomus-caroticum, tumores del sistema

nervioso periférico tales como neuroma de amputación, neurofibroma, neurinoma (neurilemoma, Schwannoma) y Schwannoma maligno, así como tumores del sistema nervioso central tales como tumores de cerebro y médula ósea; cáncer intestinal tal como por ejemplo carcinoma del recto, carcinoma del colon, carcinoma colorrectal, carcinoma anal, carcinoma del intestino grueso, tumores del intestino delgado y duodeno; tumores del párpado tales como basalioma o carcinoma de células basales; cáncer pancreático o carcinoma del páncreas; cáncer de vejiga o carcinoma de la vejiga; cáncer de pulmón (carcinoma bronquial) tales como por ejemplo carcinoma bronquial de células pequeñas (carcinomas microcíticos) y carcinoma bronquial de células no pequeñas (NSCLC) tales como carcinomas epiteliales en placa, adenocarcinomas y carcinomas bronquiales de células grandes; cáncer de mama tal como por ejemplo carcinoma mamario, tal como carcinoma ductal infiltrante, carcinoma coloide, carcinoma invasivo lobular, carcinoma tubular, carcinoma adenoquístico y carcinoma papilar; linfomas no Hodgkin (NHL) tales como por ejemplo linfoma de Burkitt, linfomas no Hodgkin de malignidad baja (NHL) y mucosis fungoides; cáncer uterino o carcinoma endometrial o carcinoma del corpus; síndrome CUP (Cáncer primario desconocido); cáncer de ovario o carcinoma ovárico tal como cáncer mucinoso, endometrial o seroso; cáncer de vesícula; cáncer de conducto biliar tales como por ejemplo, tumor de Klatskin; tumor testicular tal como por ejemplo seminomas y no seminomas; linfoma (linfosarcoma) tales como por ejemplo linfoma maligno, enfermedad de Hodgkin, linfoma no Hodgkin (NHL) tales como leucemia linfática crónica, reticuloendoteliosis leucémica, inmunocitoma, plasmocitoma (mieloma múltiple), inmunoblastoma, linfoma de Burkitt, micosis fungoides de la zona T, linfoblastoma anaplásico de células grandes y linfoblastoma; cáncer de laringe tal como por ejemplo tumores de las cuerdas vocales, tumores laríngeos supraglóticos, glótico y subglóticos; cáncer de hueso tal como por ejemplo osteocondroma, condroma, condroblastoma, fibroma condromixoide, osteoma, osteoma osteoide, osteoblastoma, granuloma eosinofílico, tumor de las células gigantes, condrosarcoma, osteosarcoma, sarcoma de Ewing, reticulo-sarcoma, plasmocitoma, displasia fibrosa, quistes óseos juveniles y quistes óseos aneurismáticos; tumores de cabeza y cuello tales como por ejemplo tumores de labios, lengua, piso de la boca, cavidad oral, encías, paladar, glándulas salivales, garganta, cavidad nasal, senos paranasales, laringe y oído medio; cáncer hepático tal como por ejemplo carcinoma de células hepáticas o carcinoma hepatocelular (HCC); leucemias, tales como por ejemplo, leucemias agudas tales como leucemia linfática aguda/linfoblástica (ALL), leucemia

mieloide aguda (AML); leucemias crónicas tales como leucemia linfática crónica (CLL), leucemia mieloide crónica (CML); cáncer de estómago o carcinoma gástrico tal como por ejemplo, adenocarcinoma papilar, tubular y mucinoso, carcinoma de células en anillo de sello, carcinoma adenoescamoso, carcinoma de células pequeñas y carcinoma no diferenciado; melanomas tales como por ejemplo melanomas extensivo superficial, nodular, lentiginoso maligno y acral-lentiginoso; cáncer renal tal como por ejemplo, carcinoma de células renales o hipernefroma o tumor de Grawitz; cáncer esofágico o carcinoma del esófago; cáncer de pene; cáncer de próstata; cáncer de garganta o carcinomas de la faringe tales como por ejemplo carcinomas de nasofaringe, carcinomas de orofaringe y carcinomas de hipofaringe; retinoblastoma tal como por ejemplo cáncer vaginal o carcinoma vaginal; carcinomas epiteliales de placa, adenocarcinomas, carcinomas in situ, melanomas y sarcomas malignos; carcinomas tiroideos como por ejemplo, carcinoma papilar, folicular y medular, así como carcinomas anaplásicos; espinalioma, carcinoma epidermoide y carcinoma epitelial de placa, carcinoma de la piel; timomas, cáncer de la uretra y cáncer de la vulva.

Los cánceres preferidos, que se pueden tratar con compuestos de acuerdo con la invención, son cáncer de pulmón, hígado, colon, cerebro, mama, ovario, próstata, páncreas, riñón, estómago, cabeza, cuello, linfoma y leucemia.

Los nuevos compuestos se pueden usar para la prevención, tratamiento a corto plazo o largo plazo de las enfermedades mencionadas anteriormente, opcionalmente también en combinación con radioterapia u otros compuestos de "última generación", tales como por ejemplo, sustancias citostáticas o citotóxicas, inhibidores de la proliferación celular, sustancias anti-angiogénicas, esteroides o anticuerpos.

Los compuestos de fórmula general (1) se pueden usar por sí mismos o en combinación con otras sustancias activas de acuerdo con la invención, opcionalmente también en combinación con otras sustancias farmacológicamente activas.

Los agentes quimioterapéuticos que se pueden administrar en combinación con los compuestos de acuerdo con la invención, incluyen, sin restricciones, hormonas, análogos de hormona y antihormonas (por ejemplo tamoxifeno, torremifeno, raloxifeno, fulvestrant, acetato de megestrol, flutamida, nilutamida, bicalutamida, aminoglutetimida, acetato de ciproterona, finasterida, acetato de buserelina, fludrocortisona, fluoximesterona, medroxiprogesterona, octreotide), inhibidores de aromatasa (por ejemplo anastrozol, letrozol, liarozol, vorozol, exemestano, atamestano), agonistas y antagonistas de LHRH (por ejemplo, acetato de goserelina, luprolida), inhibidores de los factores de crecimiento (factores de

crecimiento tales como por ejemplo "factor de crecimiento derivado de plaquetas" y " factor de crecimiento de hepatocitos", los inhibidores son por ejemplo anticuerpos del "factor de crecimiento", "receptor del factor de crecimiento" e inhibidores de la tirosina quinasa, tales como por ejemplo cetuximab, gefitinib, imatinib, lapatinib y trastuzumab); antimetabolitos (por ejemplo antifolatos tales como metotrexato, raltitrexed, análogos de pirimidina tales como 5-fluorouracilo, capecitabina y gemcitabina, análogos de purina y adenosina tales como mercaptopurina, tioguanine, cladribina y pentostatina, citarabina, fludarabina); antibióticos antitumorales (por ejemplo, antraciclinas tales como doxorrubicina, daunorrubicina, epirrubicina e idarrubicina, mitomicina-C, bleomicina, dactinomicina, plicamicina, estreptozocina); derivados de platino (por ejemplo cisplatino, oxaliplatino, carboplatino); agentes de alquilación (por ejemplo estramustina, mecloretamina, melfalan, clorambucilo, busulfano, dacarbazina, ciclofosfamida, ifosfamida, temozolomida, nitrosoureas tales como por ejemplo carmustina y lomustina, tiotepa); agentes antimicóticos (por ejemplo, alcaloides de la vinca tales como por ejemplo vinblastina, vindesina, vinorelbina y vincristina; y taxanos tales como paclitaxel, docetaxel); inhibidores de topoisomerasa (por ejemplo epipodofilotoxinas tales como por ejemplo etopósido y etopofos, tenipósido, amsacrin, topotecano, irinotecano, mitoxantrona) y varios agentes quimioterapéuticos tales como amifostina, anagrelid, clodronat, filgrastina, interferón alfa, leucovorina, rituximab, procarbazina, levamisol, mesna, mitotano, pamidronato y porfímero.

Otros compañeros de combinación posibles son 2-clorodesoxiadenosina, 2-fluorodesoxicitidina, 2-metoxioestradiol, 2C4, 3-aletina, 131-I-TM-601, 3CPA, 7-etilo-10-hidroxicamptotecina, 16-aza-epotilón B, A 105972, A 204197, aldesleukina, alitretinoína, altretamina, alvocidib, amonafide, antrapirazol, AG-2037, AP-5280, apaziquona, apomina, aranosa, arglabin, arzoxifeno, atamestano, atrasentan, auristatina PE, AVLB, AZ10992, ABX-EGF, ARRY-300, ARRY-142886/AZD-6244, ARRY-704/AZD-8330, AS-703026, azacitidina, azaepotilón B, azonafide, BAY-43-9006, BBR-3464, BBR-3576, bevacizumab, biricodar dicitrato, BCX-1777, bleocina, BLP-25, BMS-184476, BMS-247550, BMS-188797, BMS-275291, BNP-1350, BNP-7787, BIBW 2992, BIBF 1120, ácido bleomicinaico, bleomicina A, bleomicina B, briostatina-1, bortezomib, brostallicina, busulfano, profármaco CA-4, CA-4, CapCell, calcitriol, canertinib, canfosfamida, capecitabina, carboxiftalatoplatino, CCI-779, CEP-701, CEP-751, CBT-1 cefixime, ceflatonina, ceftriaxona, celecoxib, celmoleuquina, cemadotina, CH4987655/RO-4987655, clorotrianiseno, cilengitida, ciclosporina, CDA-

II, CDC-394, CKD-602, clofarabina, colchicina, combretastatina A4, CHS-828, CLL-Thera, CMT-3 criptoficina 52, CTP-37, CP-461, CV-247, cianomorfolinaodoxorrubicina, citarabina, D 24851, decitabina, deoxorrubicina, deoxirrubicina, deoxicoformicina, depsipéptido, desoxiepotilón B, dexametasona, dexrazoxanet, dietilstilbestrol, diflomotecano, didox, DMDC, dolastatina 10, doranidazol, E7010, E-6201, edatrexat, edotreotide, efaproxiral, eflornitina, EKB-569, EKB-509, elsamitrucina, epotilón B, epratuzumab, ER-86526, erlotinib, ET-18-OCH3, etinilcitidina, etiniloestradiol, exatecano, mesilato de exatecano, exemestano, exisulind, fenretinida, floxuridina, ácido fólico, FOLFOX, FOLFIRI, formestano, galarrubicina, maltolato de galio, gefinitib, gemtuzumab, gimatecano, glufosfamida, GCS-IOO, inmunógeno G17DT, GMK, GPX-100, GSK-5126766, GSK-1120212, GW2016, granisetron, hexametilmelamina, histamina, homoharringtonina, ácido hialurónico, hidroxiurea, caproato de hidroxiprogesterona, ibandronato, ibritumomab, idatrexato, idenestrol, IDN-5109, IMC-1C11, immunol, indisulam, interferón alfa-2a, interferón alfa-2b, interleuquina-2, ionafarnib, iproplatino, irofulven, isohomohalicondrina-B, isoflavona, isotretinoína, ixabepilon, JRX-2, JSF-154, J-107088, estrógenos conjugados, kahalid F, ketoconazol, KW-2170, lobaplatino, leflunomida, lenograstim, leuprolida, leuporelina, lexidronam, LGD-1550, linezolida, texafirina lutecio, lometrexol, losoxantrona, LU 223651, lurtotecano, mafosfamida, marimastat, mecloroetamina, metiltestosterona, metilprednisolona, MEN-10755, MDX-H210, MDX-447, MGV, midostaurina, ácido minodrónico, mitomicina, mivobulina, MK-2206, MLN518, motexafin gadolinio, MS-209, MS-275, MX6, neridronato, neovastat, nimesulida, nitroglicerina, nolatrexed, norelina, N-acetilcisteina, 06-benzilguanina, omeprazol, oncofage, ormiplatino, ortataxel, oxantrazol, estrógeno, patupilona, pegfilgrastim, PCK-3145, pegfilgrastim, PBI-1402, PEG-paclitaxel, PEP-005, P-04, PKC412, P54, PI-88, pelitinib, pemetrexed, pentrix, perifosina, alcohol perílico, PG-TXL, PG2, PLX-4032/RO-5185426, PT-100, picoplatino, pivaloiloximetilbutirato, pixantrona, fenoxodiol O, PKI166, plevitrexed, plicamicina, ácido poliprénico, porfiromicina, prednisona, prednisolona, quinamed, quinupristina, RAF-265, ramosetrona, ranpirnasa, RDEA-119/BAY 869766, análogos de rebeccamicina, revimid, RG-7167, rizoxina, rhu-MAb, risedronato, rituximab, rofecoxib, Ro-31-7453, RO-5126766, RPR 109881A, rubidazon, rubitecano, R-flurbiprofeno, S-9788, sabarrubicina, SAHA, sargramostim, satraplatino, SB 408075, SU5416, SU6668, SDX-101, semustina, seocalcitol, SM-11355, SN-38, SN-4071, SR-27897, SR-31747, SRL-172, sorafenib, spiroplatin, squalamina, ácido suberanilhidroxámicos, sutent, T 900607, T 138067, TAS-103, tacedinalina,

talaporfina, tariquitar, taxotero, taxoprexina, tazaroteno, tegafur, temozolamida, tesmilifeno, testosterona, propionato de testosterona, tesmilifeno, tetraplatino, tetrodotoxina, tezacitabina, talidomida, teralux, terarrubicina, timectacina, tiazofurina, tipifarnib, tirapazamina, tocladesina, tomudex, toremofina, trabectedina, TransMID-107, ácido transretínico, traszutumab, tretinoína, triacetiluridina, triapina, trimetrexato, TLK-286TXD 258, urocidina, valrrubicina, vatalanib, vincristina, vinflunina, virulizina, WX-UK1, vectibix, xeloda, XELOX, XL-281, XL-518/R-7420, YM-511, YM-598, ZD-4190, ZD-6474, ZD-4054, ZD-0473, ZD-6126, ZD-9331, ZDI839, zoldronat y zosuquidar.

Las preparaciones adecuadas incluyen por ejemplo, comprimidos, cápsulas, supositorios, soluciones - particularmente soluciones para inyección (s.c., i.v., i.m.) e infusión - elixires, emulsiones o polvos dispersables. El contenido del compuesto farmacéuticamente activo debe estar en el rango de 0,1 a 90% en peso, con preferencia 0,5 a 50% en peso de la composición total, es decir, en cantidades que son suficientes para obtener el rango de dosis especificado a continuación. Las dosis especificadas se pueden dar, si es necesario, varias veces por día.

Los comprimidos adecuados se pueden obtener, por ejemplo, por la mezcla de sustancias activas con excipientes conocidos, por ejemplo, diluyentes inertes tales como carbonato de calcio, fosfato de calcio o lactosa, desintegrantes tales como almidón de maíz o ácido algínico, aglutinantes tales como almidón o gelatina, lubricantes tales como estearato de magnesio o talco y/o agentes para retardar la liberación, tales como carboximetil celulosa, acetato ftalato de celulosa, o acetato de polivinilo. Los comprimidos también pueden comprender varias capas.

Los comprimidos recubiertos se pueden preparar por consiguiente por el recubrimiento de los núcleos producidos en forma análoga para los comprimidos como sustancias normalmente usadas para las coberturas de comprimidos, por ejemplo collidona o goma laca, goma arábiga, talco, dióxido de titanio o azúcar. Para obtener la liberación retardada o evitar las incompatibilidades, el núcleo también puede consistir en numerosas capas. De modo similar la cobertura del comprimido puede consistir en numerosas capas para obtener la liberación retardada, posiblemente usando los excipientes mencionados anteriormente para los comprimidos.

Los jarabes o elixires que contienen las sustancias o combinaciones de estos de acuerdo con la invención pueden contener adicionalmente un edulcorante tales como sacarina, ciclamato, glicerol o azúcar y un potenciador del sabor, por ejemplo, un saborizante tales como vanillina o extracto de naranja. También pueden contener adyuvantes o espesantes de la suspensión tales como carboximetil celulosa sódica,

agentes humectantes tales como, por ejemplo, productos de condensación de los alcoholes grasos con óxido de etileno o conservantes tales como p-hidroxibenzoatos.

Las soluciones para inyección o infusión se preparan de la manera usual, por ejemplo con la adición de agentes isotónicos, conservantes tales como p-hidroxibenzoatos, o estabilizantes tales como sales de metal alcalino, ácido etilendiaminotetraacético, opcionalmente usando emulsionantes y/o dispersantes, mientras que si se usa agua como diluyente, por ejemplo, opcionalmente se pueden usar solventes orgánicos como agentes de solvatación o auxiliares de disolución, y se transfieren a viales de o ampollas de inyección o frascos de infusión.

Las cápsulas que contienen una o más sustancias activas o combinaciones de sustancias activas por ejemplo, se pueden preparar mediante la mezcla de las sustancias activas con portadores inertes tales como lactosa o sorbitol y el envasado en las cápsulas de gelatina.

Los supositorios adecuados se pueden fabricar por ejemplo, mediante la mezcla con portadores provistos para este fin, tales como grasas neutras o polietilenglicol o sus derivados.

Los excipientes que se pueden usar incluyen, por ejemplo, agua, solventes orgánicos farmacéuticamente aceptables tales como parafinas (por ejemplo, fracciones de petróleo), aceites vegetales (por ejemplo, aceite de maní o sésamo), alcoholes mono- o polifuncionales (por ejemplo, etanol o glicerol), portadores tales como por ejemplo, polvos minerales naturales (por ejemplo, caolines, arcillas, talco, tiza), polvos minerales sintéticos (por ejemplo, ácido silícico altamente disperso y silicatos), azúcares (por ejemplo, caña de azúcar, lactosa y glucosa), emulsionantes (por ejemplo, lignina, licores de sulfito residual, metilcelulosa, almidón y polivinilpirrolidona) y lubricantes (por ejemplo, estearato de magnesio, talco, ácido esteárico y lauril sulfato de sodio).

Las preparaciones se administran por los métodos usuales, con preferencia por vía oral o transdérmica, con máxima preferencia por vía oral. Para la administración oral los comprimidos, obviamente pueden contener, además de los portadores mencionados anteriormente, aditivos tales como citrato de sodio, carbonato de calcio y fosfato dicálcico junto con diversos aditivos tales como almidón, con preferencia, almidón de papa, gelatina y similares. Además, los lubricantes tales como estearato de magnesio, lauril sulfato de sodio y talco se pueden usar al mismo tiempo para el proceso de formación de comprimidos. En el caso de suspensiones acuosas, las sustancias activas se pueden combinar con varios potenciadores del sabor o

colorantes además de los excipientes mencionados anteriormente.

Para uso parenteral, se pueden usar las soluciones con portadores de líquidos adecuados.

Sin embargo, algunas veces puede ser necesario apartarse de las cantidades especificadas, de acuerdo con el peso corporal, la vía de administración, la respuesta individual al fármaco, la naturaleza de su formulación y el tiempo o intervalo durante el cual se administra el fármaco. En consecuencia, en algunos casos puede ser suficiente usar menos de la dosis mínima dada anteriormente, mientras que en otros casos el límite superior se puede haber excedido. Cuando se administran grandes cantidades puede ser recomendable dividirlos en varias dosis más pequeñas repartidas durante el día.

Los ejemplos de formulación siguientes ilustran la presente invención sin restringir su alcance:

Los ejemplos de formulaciones farmacéuticas

A)	Comprimidos	por comprimido
	Sustancia activa de acuerdo con la fórmula **(I)**	100 mg
	lactosa	140 mg
	almidón de maíz	240 mg
	polivinilpirrolidona	15 mg
	estearato de magnesio	5 mg
		500 mg

La sustancia activa finamente dividida, lactosa y algo de almidón de maíz se mezclan entre sí. La mezcla se tamiza, luego se humedece con una solución de polivinilpirrolidona en agua, se amasa y granula en húmedo y se seca. Los gránulos, el almidón de maíz restante y el estearato de magnesio se tamizan y mezclan entre sí. La mezcla se comprime para producir comprimidos de forma y tamaño adecuados.

B)	Comprimidos	por comprimido
	sustancia activa de acuerdo con la fórmula **(I)**	80 mg
	lactosa	55 mg
	almidón de maíz	190 mg

celulosa microcristalina	35 mg
polivinilpirrolidona	15 mg
carboximetil almidón sódico	23 mg
estearato de magnesio	2 mg
	400 mg

La sustancia activa finamente dividida, algo de almidón de maíz, lactosa, celulosa microcristalina y polivinilpirrolidona se mezclan entre sí, la mezcla se tamiza y trabaja con el restante almidón de maíz y agua para formar un granulado que se seca y tamiza. Se añaden carboximetil almidón sódico y estearato de magnesio y se mezclan y la mezcla se comprime para producir comprimidos de un tamaño adecuado.

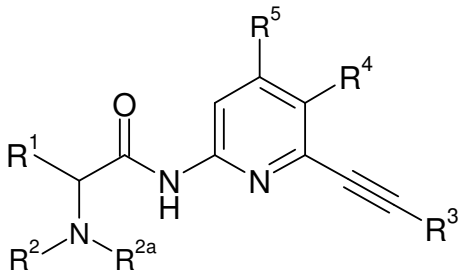
C) Solución de ampolla

Sustancia activa de acuerdo con la fórmula **(I)**	50 mg
Cloruro de sodio	50 mg
agua para inyección	5 mL

La sustancia activa se disuelve en agua a su propio pH u opcionalmente a pH 5,5 a 6,5 y se añade cloruro de sodio para hacerla isotónica. La solución obtenida se filtra libre de pirógenos y el filtrado se transfiere en condiciones asépticas en ampollas que luego se esterilizan y sellan por fusión. Las ampollas contienen 5 mg, 25 mg y 50 mg de sustancia activa.

REIVINDICACIONES

1. Un compuesto de acuerdo con la Fórmula **(I)**



(I)

donde

R^1 es -H o -alquilo C_{1-5};

R^2, **R^{2a}** se seleccionan de modo independiente de -H o -alquilo C_{1-5} opcionalmente sustituido con uno o más -F;

R^3 se selecciona de -arilo C_{6-10}, heteroarilo de 5-14 miembros, cada uno de estos grupos se puede sustituir en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^6**; o **R^3** se selecciona de alquilo C_{1-6}, cicloalquilo -C_{4-7}, cicloalquenilo -C_{4-7}, o sistema anular aromático de 5-14 miembros, cada uno de estos grupos se puede sustituir en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^{6a}**;

R^6 se selecciona de -CN, halógeno, alquilo -C_{1-3}, -Oalquilo -C_{1-3}, -C(O)-**R^{12}**, heteroarilo de 5-6 miembros, tal grupo heteroarilo de 5-6 miembros puede estar opcionalmente sustituido con alquilo -C_{1-3}; o **R^6** es fenilo, tal fenilo puede estar opcionalmente sustituido con -Oalquilo -C_{1-3}

R^{6a} se selecciona de =O, -CN, halógeno, alquilo -C_{1-3}, -Oalquilo -C_{1-3}, -C(O)-**R^{12}**, heteroarilo de 5-6 miembros, tal grupo heteroarilo de 5-6 miembros puede estar opcionalmente sustituido con alquilo -C_{1-3}; o **R^{6a}** es fenilo, tal fenilo puede estar opcionalmente sustituido con -Oalquilo -C_{1-3};

R^{12} se selecciona de -NH_2, -NHalquilo -C_{1-3}, heterociclilo no aromático de 5-7 miembros, o -Oalquilo -C_{1-3}, tales grupos alquilo -C_{1-3} pueden estar opcionalmente sustituido con un heterociclilo no aromático de $_{5-7}$ miembros;

R^4 se selecciona de -H, -arilo C_{6-10}, heteroarilo de 5-14 miembros, cada uno de tales grupos está sustituido en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^7**, o **R^4** se selecciona de alquilo C_{1-6}, sistema anular aromático de 5-14 miembros, cicloalquilo -C_{5-7}, cada grupo está sustituido en forma opcional e independiente con uno o más, seleccionados de

modo independiente, **R^{7a}**,

o **R^{4}** se selecciona de -N(**R^{8}**,**R^{9}**) donde

R^{8}, **R^{9}** se seleccionan de modo independiente de H, alquilo -C_{1-3}, -C(O)-**R^{10}** -$S(O)_2$-**R^{11}**

R^{10}, **R^{11}** se seleccionan de modo independiente de heterociclilo no aromático de 5-7 miembros, cicloalquilo -C_{5-7}, -arilo C_{6-10}, heteroarilo de 5-10 miembros;

R^{7} se selecciona de -CN, halógeno, -CF_3, -NO_2, alquilo -C_{1-3}, -Salquilo -C_{1-3}, -NHalquilo -C_{1-3}, -N(alquilo C_{1-3})$_2$, -NHC(O)alquilo -C_{1-3}, -C(O)-**R^{13}**, -Oalquilo -C_{1-3}, heteroarilo de 5-14 miembros, -O-fenilo, -CH_2-fenilo, fenilo, cada uno del grupo fenilo puede estar opcionalmente sustituido con halógeno, o heterociclilo no aromático de 5-6 miembros, tal heterociclilo no aromático de 5-6 miembros puede estar opcionalmente sustituido con alquilo -C_{1-3};

R^{7a} se selecciona de =O, -CN, halógeno, -CF_3, -NO_2, alquilo -C_{1-3}, -Salquilo -C_{1-3}, -NHalquilo -C_{1-3}, -N(alquilo C_{1-3})$_2$, -NHC(O)alquilo -C_{1-3}, -C(O)-**R^{13}**, -Oalquilo -C_{1-3}, heteroarilo de 5-14 miembros, -O-fenilo, -CH_2-fenilo, fenilo, cada uno del grupo fenilo puede estar opcionalmente sustituido con halógeno, o heterociclilo no aromático de 5-6 miembros, tal heterociclilo no aromático de 5-6 miembros puede estar opcionalmente sustituido con alquilo -C_{1-3}; donde

R^{13} se selecciona de -OH, -NH_2, -NHalquilo -C_{1-3}, alquilo -C_{1-3};

R^{5} se selecciona de -H, halógeno, alquilo -C_{1-3}, -Oalquilo -C_{1-3}, tales grupos alquilo -C_{1-3} pueden estar opcionalmente sustituido con uno o más halógeno;

o **R^{4}** y **R^{5}** tomados entre sí forman un -arilo C_{6-10} o heteroarilo de 5-14 miembros,

y donde los compuestos de fórmula (I) opcionalmente pueden estar presentes en la forma de sales.

2. El compuesto de acuerdo con la reivindicación 1, donde **R^{1}** se selecciona de -CH_3, -CH_2-CH_3.

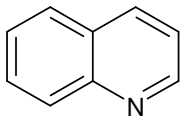
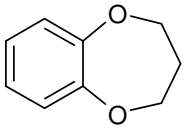
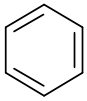
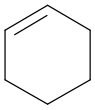
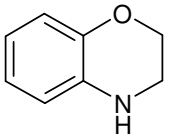
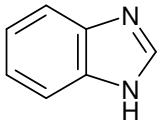
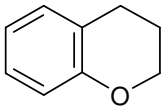
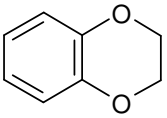
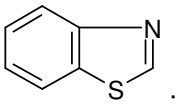
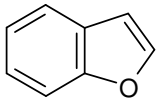
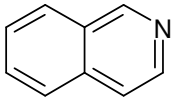
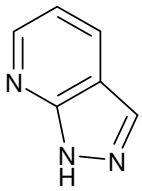
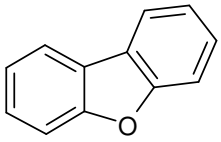
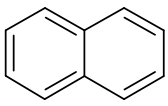
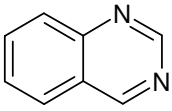
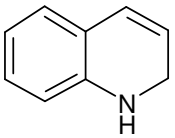
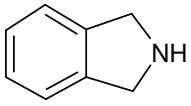
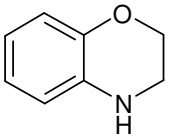
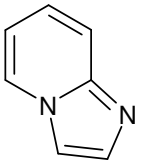
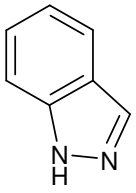
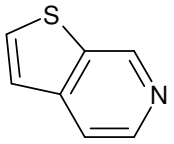
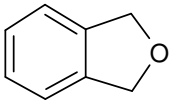
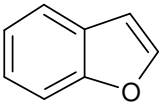
3. El compuesto de acuerdo con la reivindicación 1 o 2, donde **R^{2}** y **R^{2a}** se seleccionan de modo independiente de -H, -CH_3, -CH_2-CH_3. -CH-(CH_3)$_2$, -(CH_2)$_2$-CH_3.

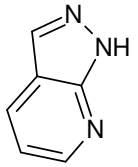
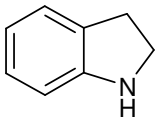
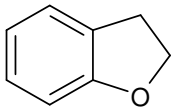
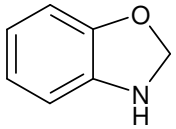
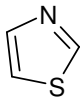
4. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 3, donde **R^{5}** se selecciona de -H, -Cl, -F, -CF_3, -OCH_3, -CH_3.

5. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 4, donde **R^{3}** se selecciona de -arilo C_{6-10}, heteroarilo de 5-14 miembros, cada uno de estos

grupos se puede sustituir en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R6**, o **R3** se selecciona de cicloalquenilo -C_{5-7}, sistema anular aromático de 5-14 miembros, cada uno de estos grupos se puede sustituir en forma opcional e independiente con uno o más, seleccionados de modo independiente **R6a**, o **R3** es -CH_2-fenilo, tal fenilo puede estar opcionalmente sustituido con -Oalquilo -C_{1-3}, y donde **R6** y **R6a** son como se definen en la reivindicación 1.

6. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 5, donde **R3** se selecciona de -arilo C_{6-10}, heteroarilo de 5-14 miembros, cada uno de estos grupos se puede sustituir en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R6**, o **R3** se selecciona de sistema anular aromático de 5-14 miembros, tales grupos pueden estar sustituidos en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R6a**, donde **R6** y **R6a** son como se definen en la reivindicación 1.

7. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 5, donde **R3** se selecciona de –CH_2-fenilo,  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;


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cada grupo está opcionalmente sustituido como se define en la reivindicación 1.

8. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 7, donde **R^4** se selecciona de -H, -arilo C_{6-10}, heteroarilo de 5-14 miembros, cada grupo está sustituido en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^7**,

o **R^4** se selecciona de alquilo C_{1-6}, sistema anular aromático de 5-14 miembros y cicloalquilo -C_{5-7}, cada grupo está sustituido en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^{7a}**,

o **R^4** se selecciona de -N(**R^8**,**R^9**), donde **R^7**, **R^{7a}**, **R^8** y **R^9** son como se definen en la reivindicación 1.

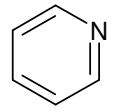
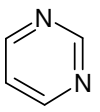
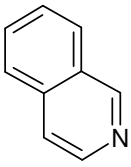
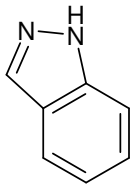
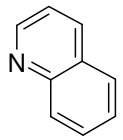
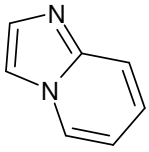
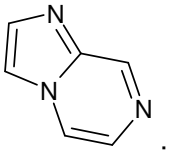
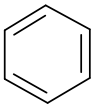
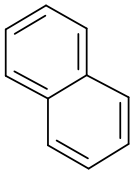
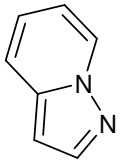
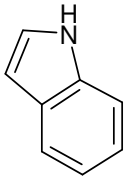
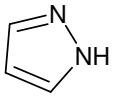
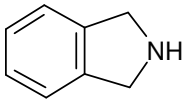
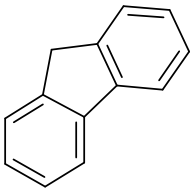
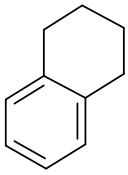
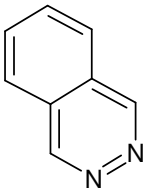
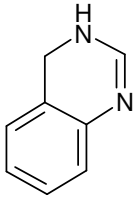
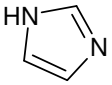
9. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 8, donde **R^4** se selecciona de -arilo C_{6-10}, heteroarilo de 5-14 miembros, cada grupo está sustituido en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^7**,

o **R^4** se selecciona de sistema anular aromático de 5-14 miembros, cicloalquilo -C_{5-7}, cada grupo está sustituido en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^{7a}**, o **R^4** se selecciona de -N(**R^8**,**R^9**), donde **R^7**, **R^{7a}**, **R^8** y **R^9** son como se definen en la reivindicación 1.

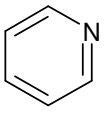
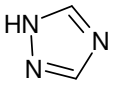
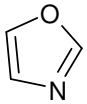
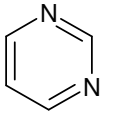
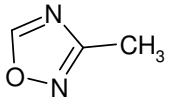
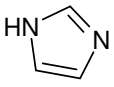
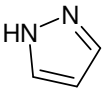
10. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 9, donde **R^4** se selecciona de -arilo C_{6-10}, heteroarilo de 5-14 miembros, cada grupo está sustituido en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^7**,

o **R^4** es el sistema anular aromático de 5-14 miembros, cada grupo está sustituido en forma opcional e independiente con uno o más, seleccionados de modo independiente, **R^{7a}**,donde **R^7** y **R^{7a}** son como se definen en la reivindicación 1.

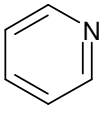
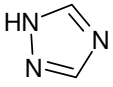
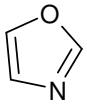
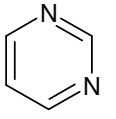
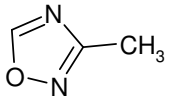
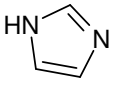
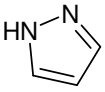
11. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 9, donde **R^4** se selecciona de –H, alquilo -C_{1-3}, -CH_2-fenilo, -N(CH_3)-SO_2-fenilo, -N(CH_3)CO-**R^{10}**; -NH-CO-**R^{10}**, donde **R^{10}** se selecciona de modo independiente de morfolina, ciclopentilo, fenilo, o **R^4** se selecciona de

 ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ; cada uno de tales grupos está opcionalmente sustituido como se define en la reivindicación 1.

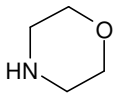
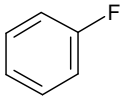
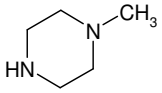
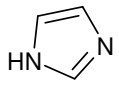
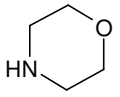
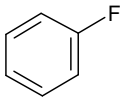
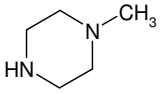
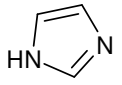
12. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 11, donde **R^6** se selecciona de -F, -Cl, -CN -CH_3, -O-CH_3, -C(O)NHCH$_3$, -C(O)NH$_2$, C(O)OCH$_3$, -C(O)-morfolinilo, -C(O)-O-CH_2-tetrahidropirano, fenilo,

 ,  ,  ,  ,  ,  ,  , 

o **R^{6a}** se selecciona de =O, -F, -Cl, -CN -CH_3, -O-CH_3, -C(O)NHCH$_3$, -C(O)NH$_2$, C(O)OCH$_3$, -C(O)-morfolinilo, -C(O)-O-CH_2-tetrahidropirano, fenilo,

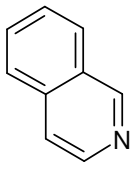
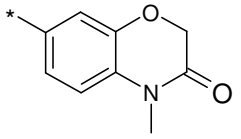
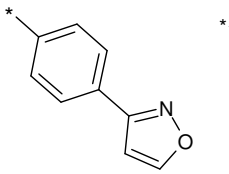
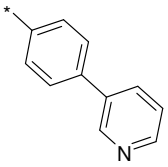
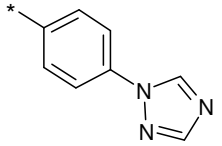
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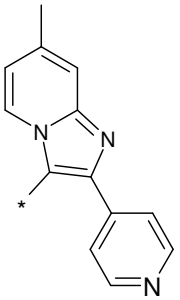
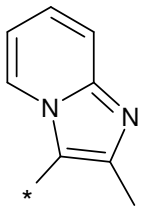
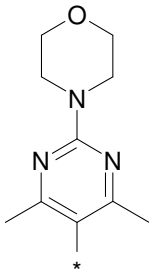
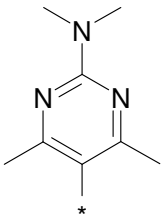
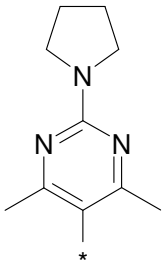
13. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 12, donde **R^{7}** se selecciona de -CN, -F, -Cl, -CF_3, -NO_2, -CH_3, -CH_2CH_3, -$CH_2(CH_3)_2$, -S-CH_3, -NH_2, -NH-CH_3, -$N(CH_3)_2$, -C(O)OH, -$C(O)OCH_3$, -$C(O)NH_2$, -C(O)NH-CH_3, -$NHC(O)CH_3$, -O-CH_3, -O-CH_2CH_3, piridilo, fenilo, -O-Fenilo, -CH_2-fenilo,  ,  ,  ,  ,  o **R^{7a}** se selecciona de =O, -CN, -F, -Cl, -CF_3, -NO_2, -CH_3, -CH_2CH_3, -$CH_2(CH_3)_2$, -S-CH_3, -NH_2, -NH-CH_3, -$N(CH_3)_2$, -C(O)OH, -$C(O)OCH_3$, -$C(O)NH_2$, -C(O)NH-CH_3, -$NHC(O)CH_3$, -O-CH_3, -O-CH_2CH_3, piridilo, fenilo, -O-Fenilo, -CH_2-fenilo,  ,  ,  ,  ,  .

14. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 3 y 5 a 7, donde **R^{4}** y **R^{5}** tomados entre sí forman un fenilo.

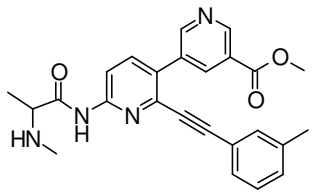
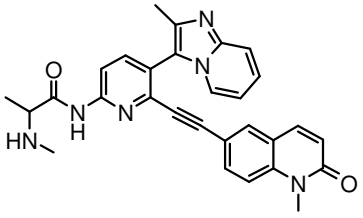
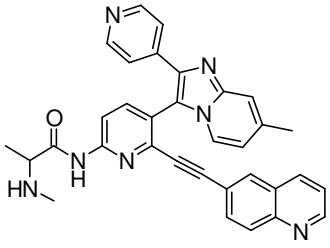
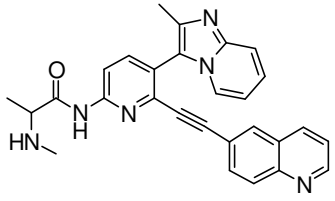
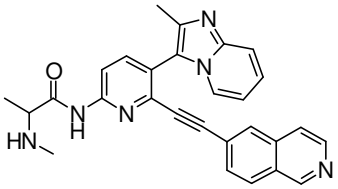
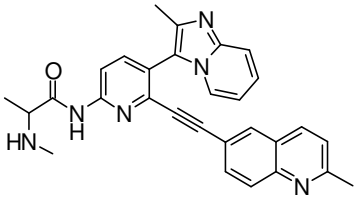
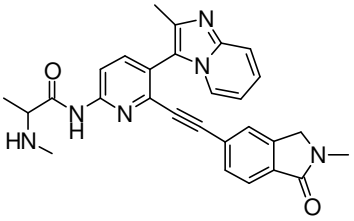
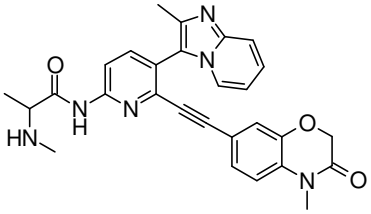
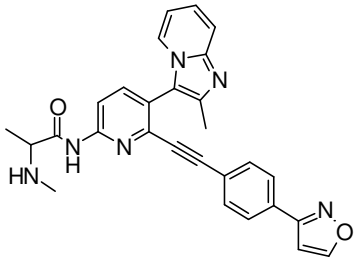
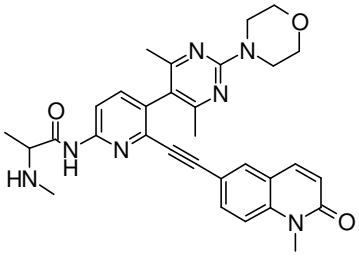
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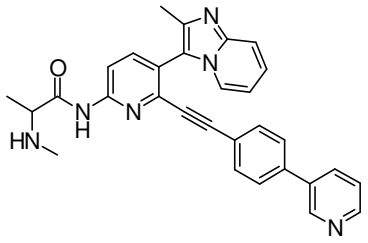
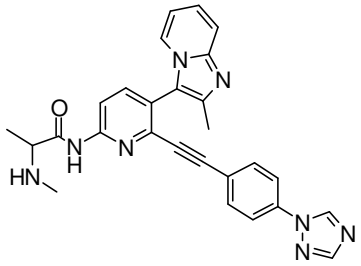
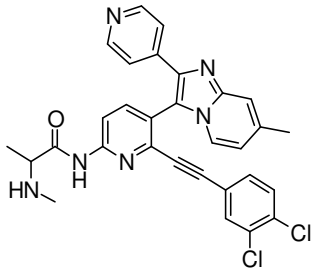
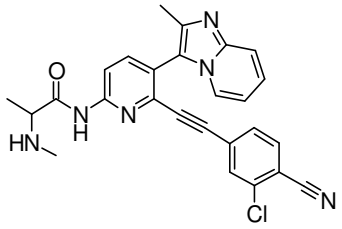
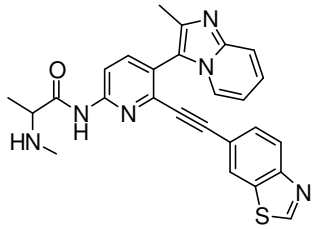
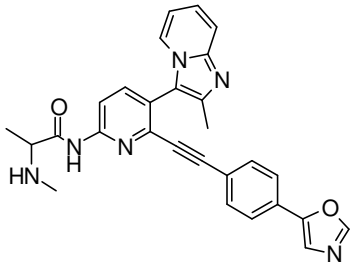
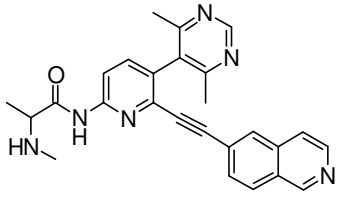
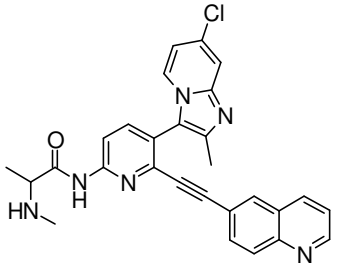
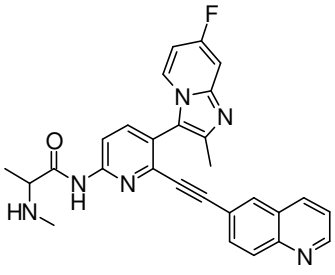
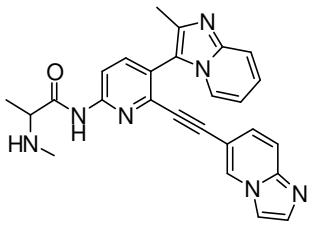
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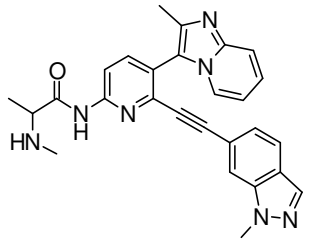
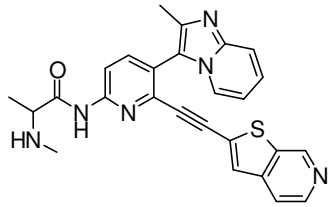
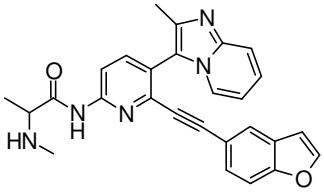
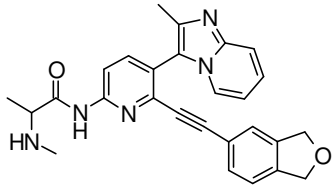
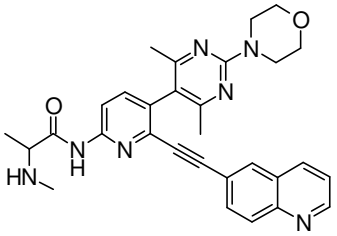
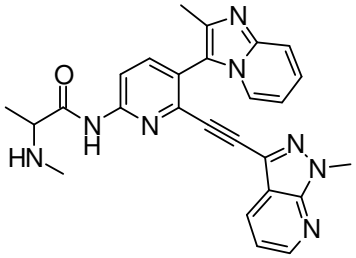
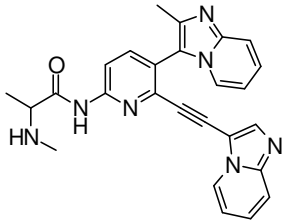
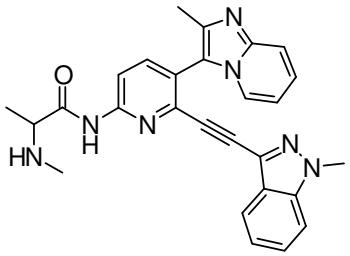
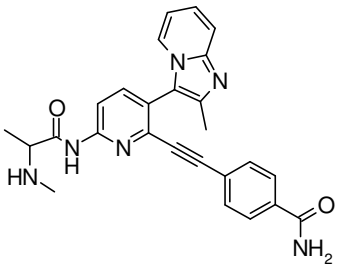
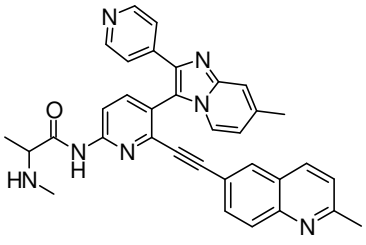
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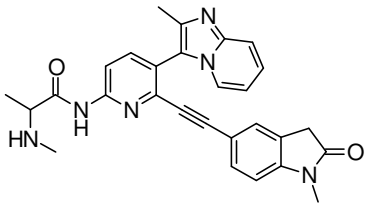
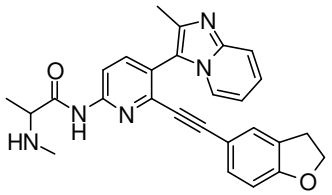
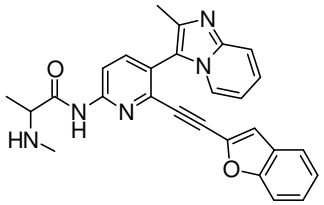
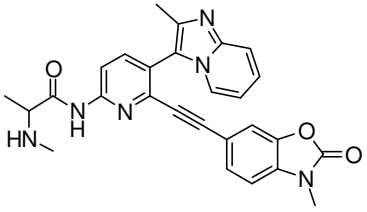
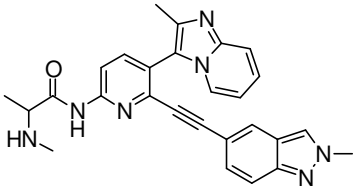
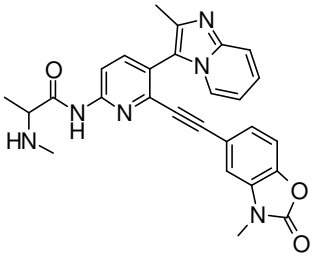
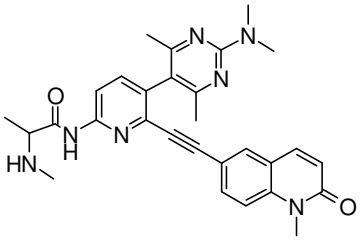
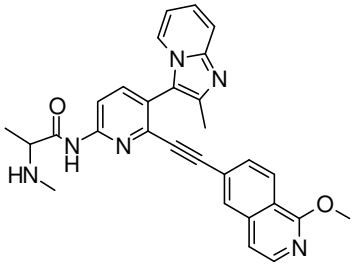
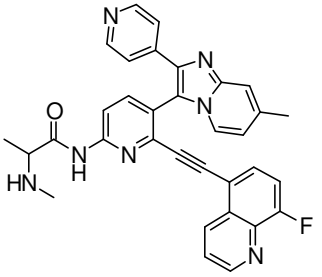
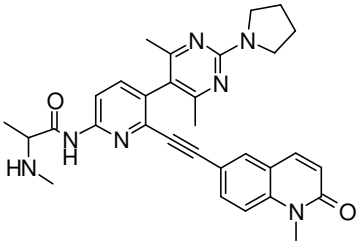
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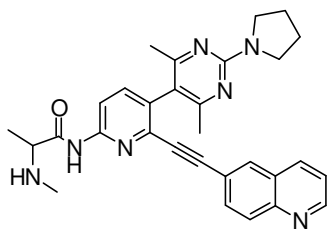
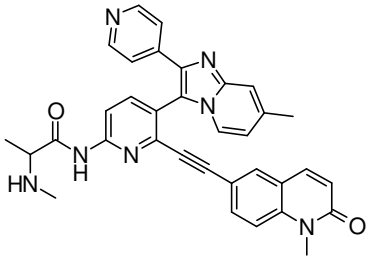
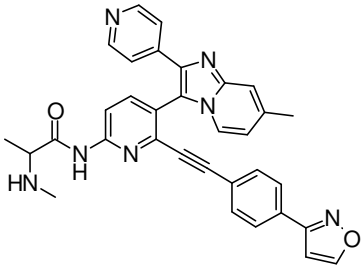
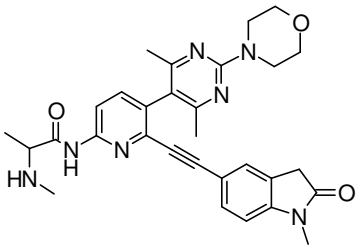
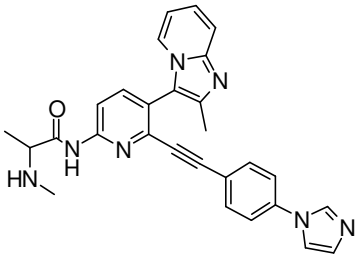
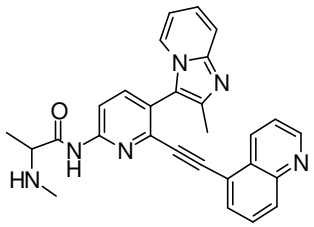
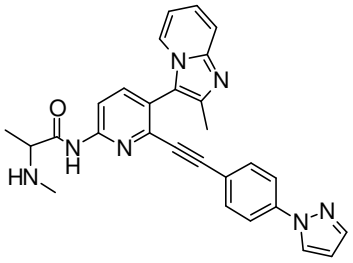
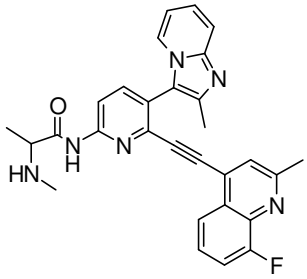
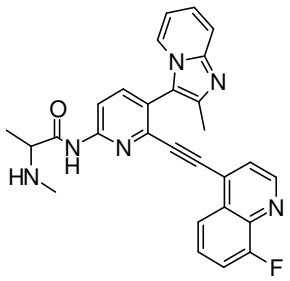
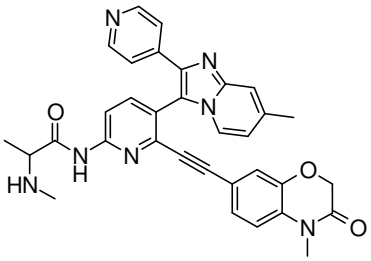
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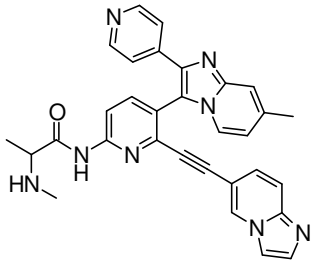
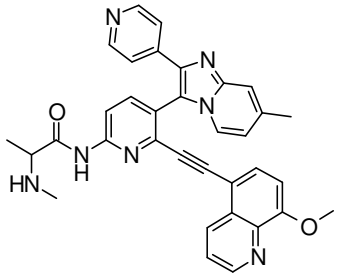
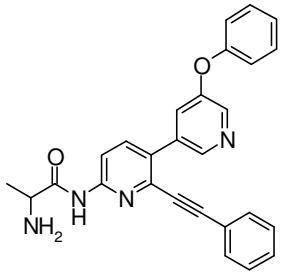
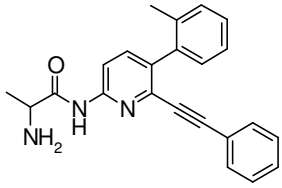
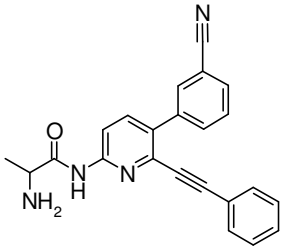
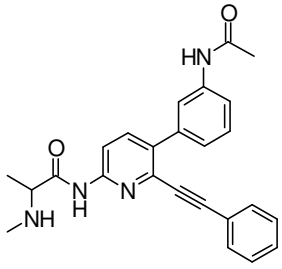
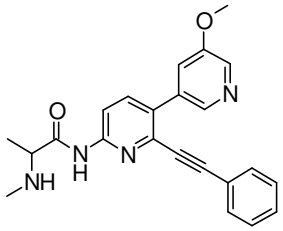
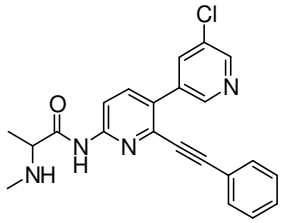
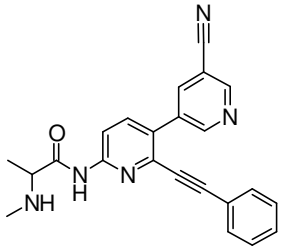
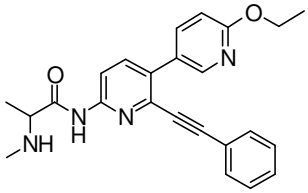
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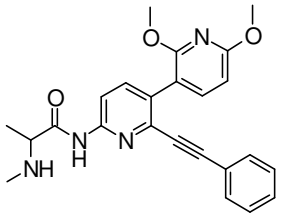
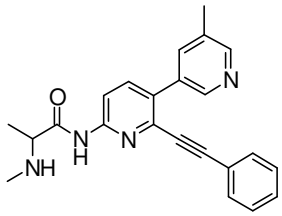
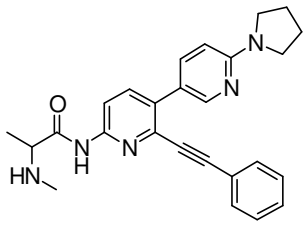
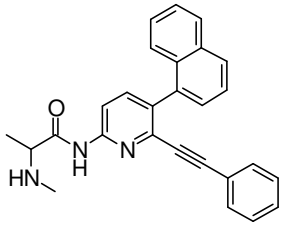
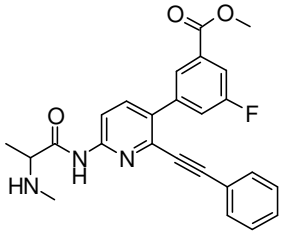
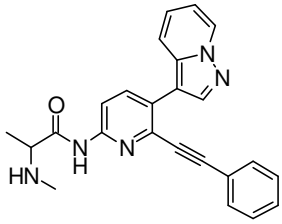
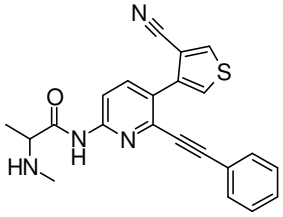
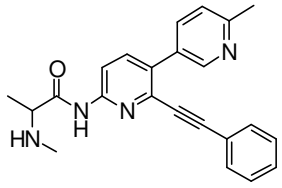
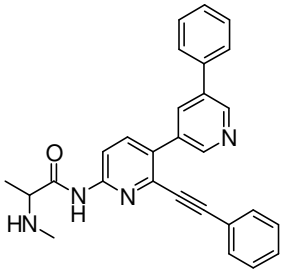
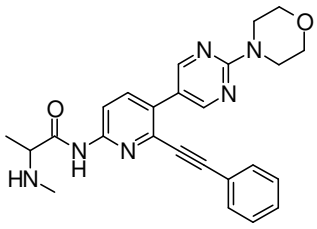
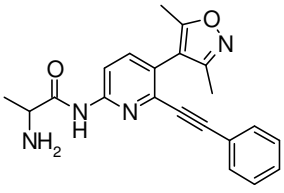
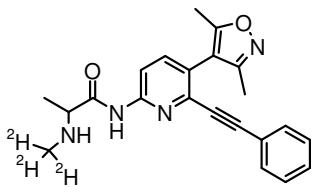
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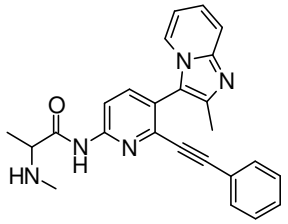
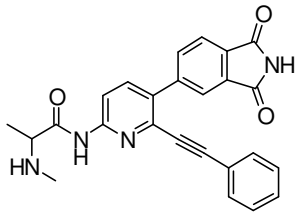
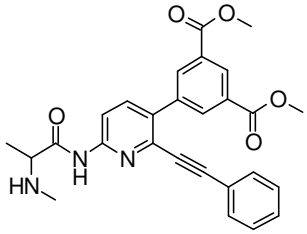
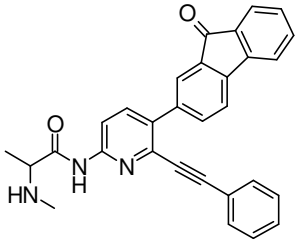
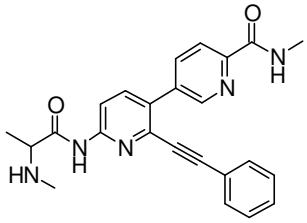
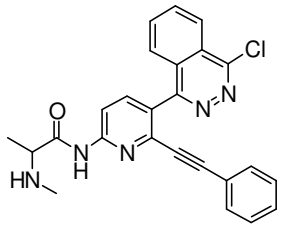
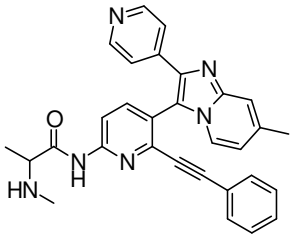
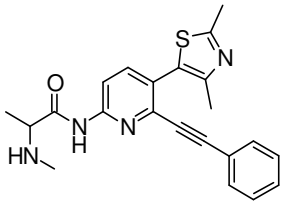
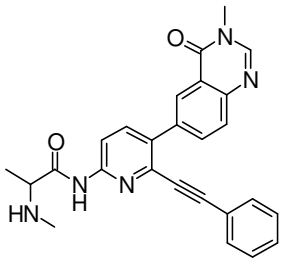
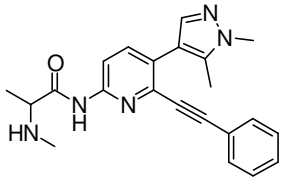
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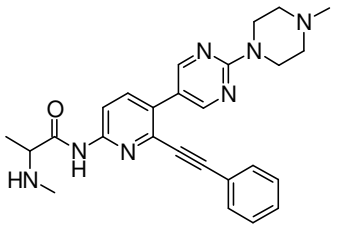
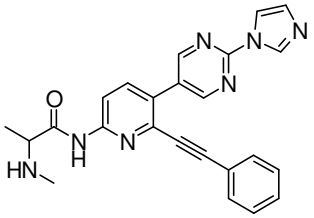
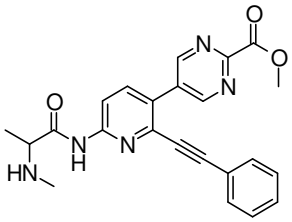
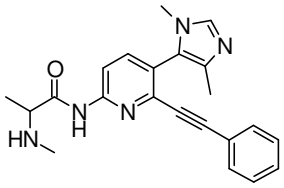
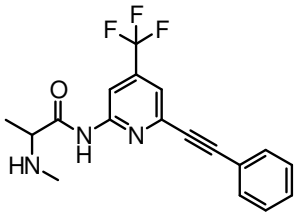
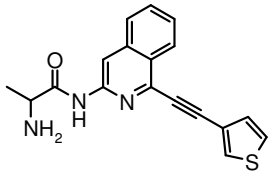
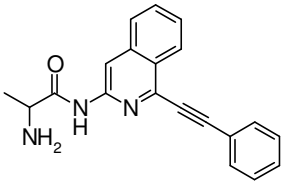
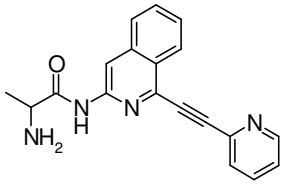
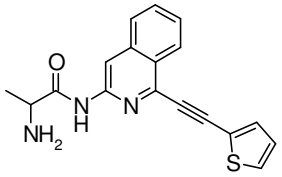
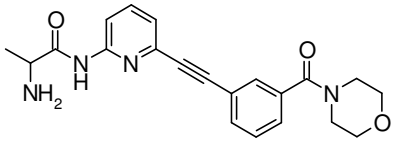
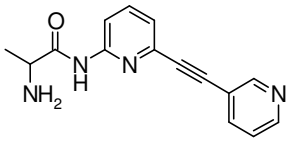
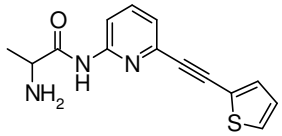
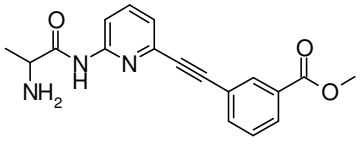
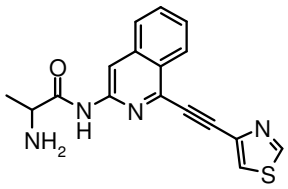
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78		79	

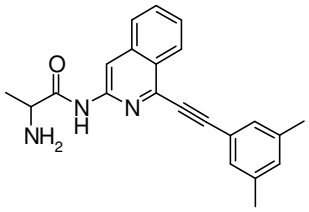
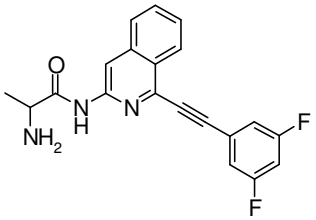
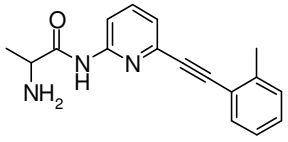
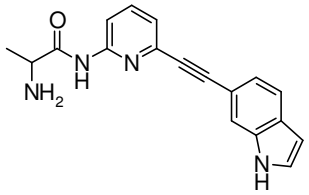
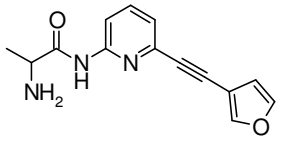
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#	Estructura molecular	#	Estructura molecular
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100		108	
113		118	
121		122	
123		125	

#	Estructura molecular	#	Estructura molecular
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132		138	
145		147	
149		161	
165		168	

#	Estructura molecular	#	Estructura molecular
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182		184	
185		186	
187		189	

#	Estructura molecular	#	Estructura molecular
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194		195	
198		203	
204		206	
208		213	
215		217	
223		226	

#	Estructura molecular	#	Estructura molecular
228		229	
232		234	
240			

18. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 17, para usar en el tratamiento del cáncer.

19. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 18 para usar en el tratamiento y /o prevención de carcinoma de la mama, próstata, cerebro u ovario, carcinomas bronquiales de células no pequeñas (NSCLC), melanomas y leucemias linfáticas crónicas (CLL).

20. Una composición farmacéutica que comprende un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 18.

21. Una composición farmacéutica que comprende un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 18 para usar en el tratamiento y/o prevención del cáncer.

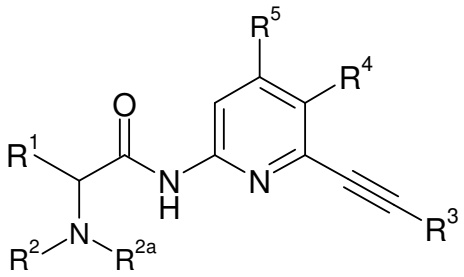
22. Una composición farmacéutica que comprende un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 18 para usar en el tratamiento y /o prevención del carcinoma de mamas, próstata, cerebro u ovario, carcinomas bronquiales de células no pequeñas (NSCLC), melanomas y leucemias linfáticas crónicas (CLL).

23. Un método para el tratamiento y/o prevención del cáncer que comprende la administración de una cantidad terapéuticamente efectiva de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 18 – o una de sus sales farmacéuticamente aceptables – a un ser humano.

24. Un método para el tratamiento y/o prevención del carcinoma de mama, próstata, cerebro u ovario, carcinomas bronquiales de células no pequeñas (NSCLC), melanomas y leucemias linfáticas crónicas (CLL) que comprende la administración de una cantidad terapéuticamente efectiva de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 18 – o una de sus sales farmacéuticamente aceptables – a un ser humano.

RESUMEN

Esta invención se refiere a 5-alquinilo-piridina de fórmula general (I)



(I)

su uso como miméticos SMAC, composiciones farmacéuticas que los contienen y su uso como medicamentos para el tratamiento y/o prevención de enfermedades caracterizadas por proliferación de células excesiva o anormal y afecciones asociadas tales como cáncer.

Los grupos **R**^{1} a **R**^{5} tienen los significados dados en las reivindicaciones y en la memoria descriptiva.

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.
P12-0349/WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2013/053689	25/02/2013	27/02/2012
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 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established by this Authority to read as follows:

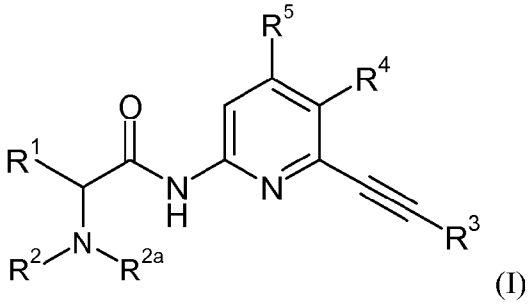
   6-ALKYNYL PYRIDINES AS SMAC MIMETICS

5. With regard to the **abstract,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established, according to Rule 38.2, 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

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

This invention relates to 6-alkynyl-pyridines of general formula (I)



(I)

their use as SMAC mimetics, pharmaceutical compositions containing them, and their use as a medicaments for the treatment and/or prevention of diseases characterized by excessive or abnormal cell proliferation and associated conditions such as cancer.

The groups R^1 to R^5 have the meanings given in the claims and in the specification.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/053689

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/75 C07D217/22 C07D401/04 C07D401/06 C07D401/14
C07D405/14 C07D407/06 C07D407/12 C07D409/04 C07D409/06
C07D409/14 C07D413/04 C07D413/14 C07D417/04 C07D417/06

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 practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/073306 A1 (NOVARTIS AG [CH]; CHEN ZHUOLIANG [US]; WANG RUN-MING DAVID [US]; CHEN) 19 June 2008 (2008-06-19) 3rd paragraph on page 2 claim 1 -----	1-24
A	WO 2006/133147 A2 (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; CHEN ZHUOLIANG [US]; PALE) 14 December 2006 (2006-12-14) claim 1 page 2, line 8 - line 14 -----	1-24
A	WO 2007/101347 A1 (AEGERA THERAPEUTICS INC [CA]; JAQUITH JAMES [CA]) 13 September 2007 (2007-09-13) claim 1 page 5, line 12 - line 18 -----	1-24

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 March 2013	26/03/2013

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2013/053689

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		US 2009069294 A1	12-03-2009
		US 2011281845 A1	17-11-2011
		WO 2006133147 A2	14-12-2006
WO 2007101347 A1	13-09-2007	NONE	