SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 13-285797- -00000-0000
Fecha: 2013-12-05 14:44:06 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 598 599

-Top Ranked Chambers Latin America 2012
-Firma Colombiana del año 2011
-Firma Colombiana del año 2010

Industria y Comercio
SUPERINTENDENCIA

DELEGATURA DE NUEVAS CREACIONES

SOLICITUD
FASE NACIONAL -PCT

21. EXPEDIENTE No. _____

54. TITULO: PIRROLOTRIAZINAS SUSTITUIDAS CON HIDROXIMETILARILO Y SUS USOS

51. CLASIFICACION INTERNACIONAL:
C07D 487/04 (2006.01) A61K 31/53 (2006.01)
A61P 27/00 (2006.01)

71. SOLICITANTE: 1. BAYER INTELLECTUAL PROPERTY GMBH
2. BAYER PHARMA AKTIENGESELLSCHAFT

DOMICILIO: 1. Alfred Nobel Strasse 10, Monheim ALEMANIA
2. Müllerstr. 178, Berlin ALEMANIA

74. APODERADO: ERNESTO CAVELIER FRANCO

22. BOGOTÁ D.C., DICIEMBRE 5 DE 2013

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 13-285797- -00000-0000

Fecha: 2013-12-05 14:44:06 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: ~~598~~ 599

DIRECCIÓN DE NUEVAS CREACIONES
SOLICITUD FASE NACIONAL –PCT

1	TIPO DE SOLICITUD	[X] Patente de invención [X] Capítulo I	[ ] Patente de Modelo de Utilidad [ ] Capitulo II

2 DATOS SOLICITUD INTERNACIONAL PCT (86)

Solicitud Internacional No.	PCT/EP2012/062366	Fecha	26/06/2012
Publicación Internacional No.	WO 2013/004551 A1	Fecha	10/01/2013

3 TÍTULO DE LA INVENCIÓN (200 caracteres o espacios máximos)

PIRROLOTRIAZINAS SUSTITUIDAS CON HIDROXIMETILARILO Y SUS USOS

4 CLASIFICACIÓN INTERNACIONAL (CIP)

C07D 487/04 (2006.01) *A61K 31/53* (2006.01) *A61P 27/00* (2006.01)

5 SOLICITANTE (S) Esta persona también es inventor. Para datos adicionales utilizar hoja de información complementaria

APELLIDOS O RAZÓN SOCIAL	NOMBRE	IDENTIFICACIÓN	TIPO
1. BAYER INTELLECTUAL PROPERTY GMBH			
2. BAYER PHARMA AKTIENGESELLSCHAFT			

6 DATOS DEL SOLICITANTE

1. DIRECCIÓN	Alfred Nobel Strasse 10, Monheim	No. TELÉFONO	
CIUDAD	Monheim	CORREO ELECTRÓNICO	
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DEPARTAMENTO/ESTADO		NACIONALIDAD O LUGAR DE CONSTITUCIÓN	ALEMANIA

7 INVENTOR (ES) Para datos adicionales utilizar hoja de información complementaria

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7. BÖTTGER	Michael	ALEMANIA
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9. LANG	Dieter	ALEMANIA
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8 DATOS INVENTOR (ES)

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3. ALEMANIA		3. Wuppertal	3. Krummacherstraße 127, 42115
4. ALEMANIA		4. Wuppertal	4. Am Eigenbach 16, 42113
5. ALEMANIA		5. München	5. Baubergerstr.5, 80992
6. ALEMANIA		6. Velbert	6. Im Wiesengrund 40, 42553
7. ALEMANIA		7. Wuppertal	7. Hainstr. 115, 42109
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9. ALEMANIA		9. Velbert	9. Wimmersberger Str.60, 42553
10. ALEMANIA		10. Wuppertal	10. Wildsteig 22 a, 42113
11. ALEMANIA		11. Haan	11. Rietmacherweg 1, 42781
12. ALEMANIA		12. Wuppertal	12. Straßburger Str. 15, 42107
13. ESTADOS UNIDOS DE AMERICA		13. New Jersey	13. 609 Sun Valley Way, Florham Park

OTRO(S) SOLICITANTE(S) Y/O (OTRO(S)) INVENTOR(ES)

☐ Los demás solicitantes y/o (demás) inventores se indican en una hoja a continuación.

9 ☐ **REPRESENTANTE LEGAL** ☒ **APODERADO**

APELLIDOS	NOMBRES	IDENTIFICACIÓN
CAVELIER FRANCO	ERNESTO	C.C 19.081.620 T.P 11519

DIRECCIÓN: **CARRERA 7 Nº 71 – 52, TORRE A, PISO 5**
No. TELÉFONO: **3257300**
CIUDAD: **BOGOTÁ**
CORREO ELECTRÓNICO: **ernesto.cavelier@phrlegal.com**
PAÍS: **COLOMBIA**
No. RADICACIÓN DE PROTOCOLO DE PODER GENERAL: **PODER PROT. 13 102341**

10 DECLARACIONES DE PRIORIDAD ☒ SI ☐ NO

(33) PAÍS DE ORIGEN	CÓDIGO PAÍS	(31) NÚMERO	(32) FECHA (AAAA/MM/DD)
1. ESTADOS UNIDOS DE AMERICA		61/503,840	01/07/2011
2. COMUNIDAD EUROPEA		12161547.0	27/03/2012

11 DECLARACIÓN SOBRE USO DE RECURSOS GENÉTICOS O BIOLÓGICOS

Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de recursos genéticos o biológicos de los que cualquiera de los países miembros de la Comunidad Andina es país de origen.

☐ SI ☒ NO

12 DECLARACIÓN SOBRE USO DE CONOCIMIENTOS TRADICIONALES

Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de conocimientos tradicionales de comunidades indígenas, afroamericanas o locales de países miembros de la Comunidad Andina.

☐ SI ☒ NO

13 REDUCCIÓN DE TASAS

Declaro que carezco de medios económicos para presentar la solicitud de patente.

☐ SI ☒ NO

Micro, pequeñas y medianas empresas ☐
Universidades públicas o privadas ☐
Entidades sin ánimo de lucro ☐

Debe aportar los documentos que se indican en el numeral 17 de anexos

14 AUTORIZACIÓN DE NOTIFICACIÓN EN LÍNEA ☒ SI ☐ NO

Manifiesto que he leído y entendido perfectamente los términos y condiciones de uso de medios electrónicos para las notificaciones en línea a través de Internet de los actos administrativos proferidos por la Superintendencia de Industria y Comercio que deben ser notificados personalmente y, en consecuencia, autorizo el servicio de notificación a través de internet.

15 COMPROBANTE DE PAGO O PAGO ELECTRÓNICO | **Nº** | **Fecha**

16 FIRMA DEL SOLICITANTE, DEL APODERADO O DEL REPRESENTANTE LEGAL
Junto a cada firma, indicar el nombre del firmante y su calidad (si tal calidad no es obvia al leer el petitorio)

Ernesto Cavelier

ERNESTO CAVELIER FRANCO

3

17	ANEXOS

Documentación Técnica
Solicitud Internacional en castellano

1. ☒ Descripción N° de folios:
2. ☒ Reivindicaciones N° Reivindicaciones:
3. ☒ Dibujos y/o figuras N° folios:
4. ☒ Resumen.
5. ☐ Certificado de depósito de material biológico si fuera el caso.
6. ☐ Listado de secuencias de nucleótidos y/o aminoácidos en forma digital si fuera el caso.
7. ☒ Arte final 12 x 12.
8. ☐ Anexo formato digital.

Documentación Jurídica

9. ☐ Poderes, si fuera el caso, **PODER PROT. 13 102341**
10. ☐ Documento que legalmente pruebe la cesión del inventor al solicitante o a su causante.
11. ☐ Copia del contrato de acceso de recursos genéticos o productos derivados, *certificado o número de registro, si fuera el caso.*
12. ☐ Copia de la licencia o autorización de Conocimientos Tradicionales, certificado o número de registro, si fuera el caso.
13. **Reducción de tasas**

Micro, pequeñas o medinas empresas

☐ Copia simple de la declaración de renta del año inmediatamente anterior, o en su defecto prueba documental idónea.

☐ Documento de constancia de cumplimiento con lo establecido en la ley 905 de 2004.

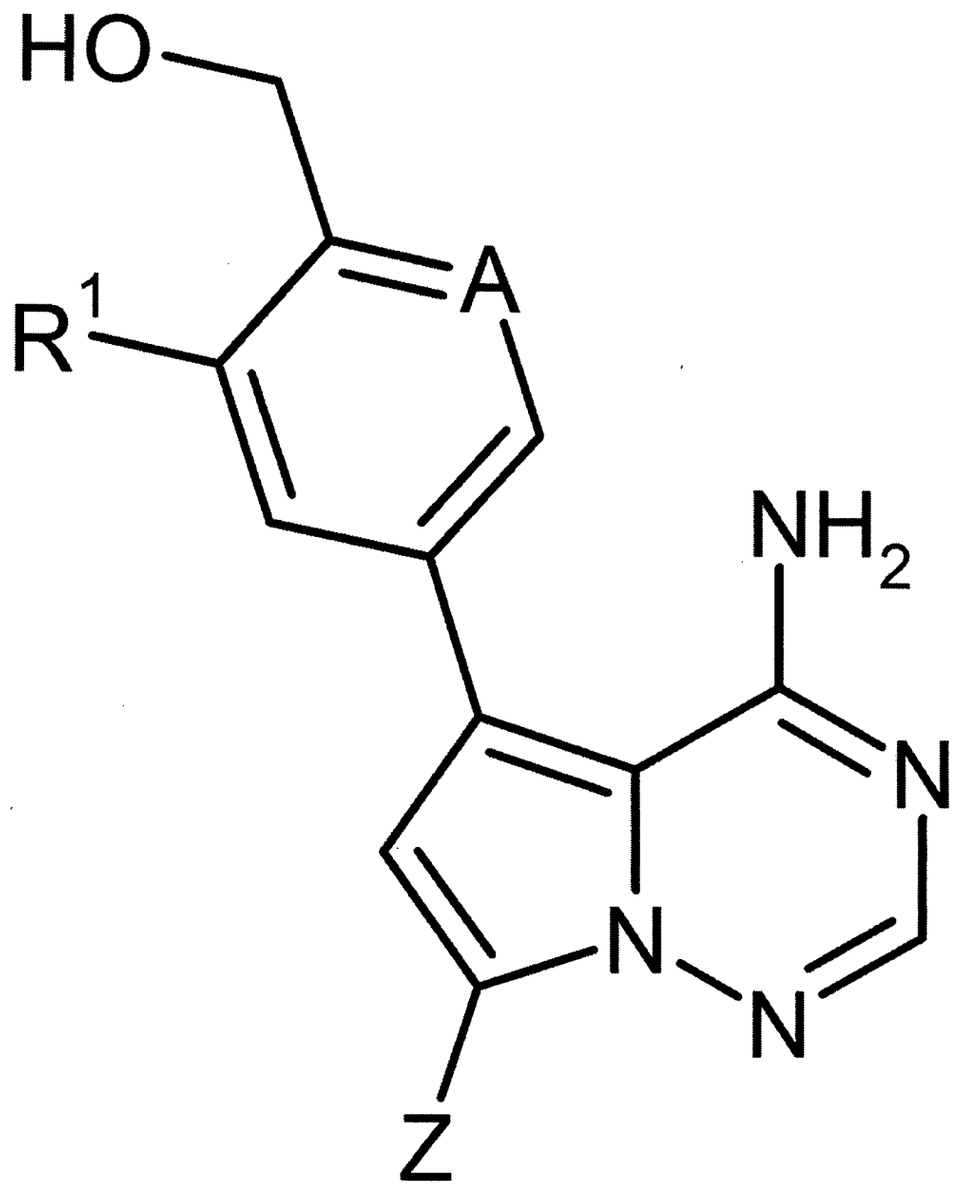
Universidades públicas o privadas

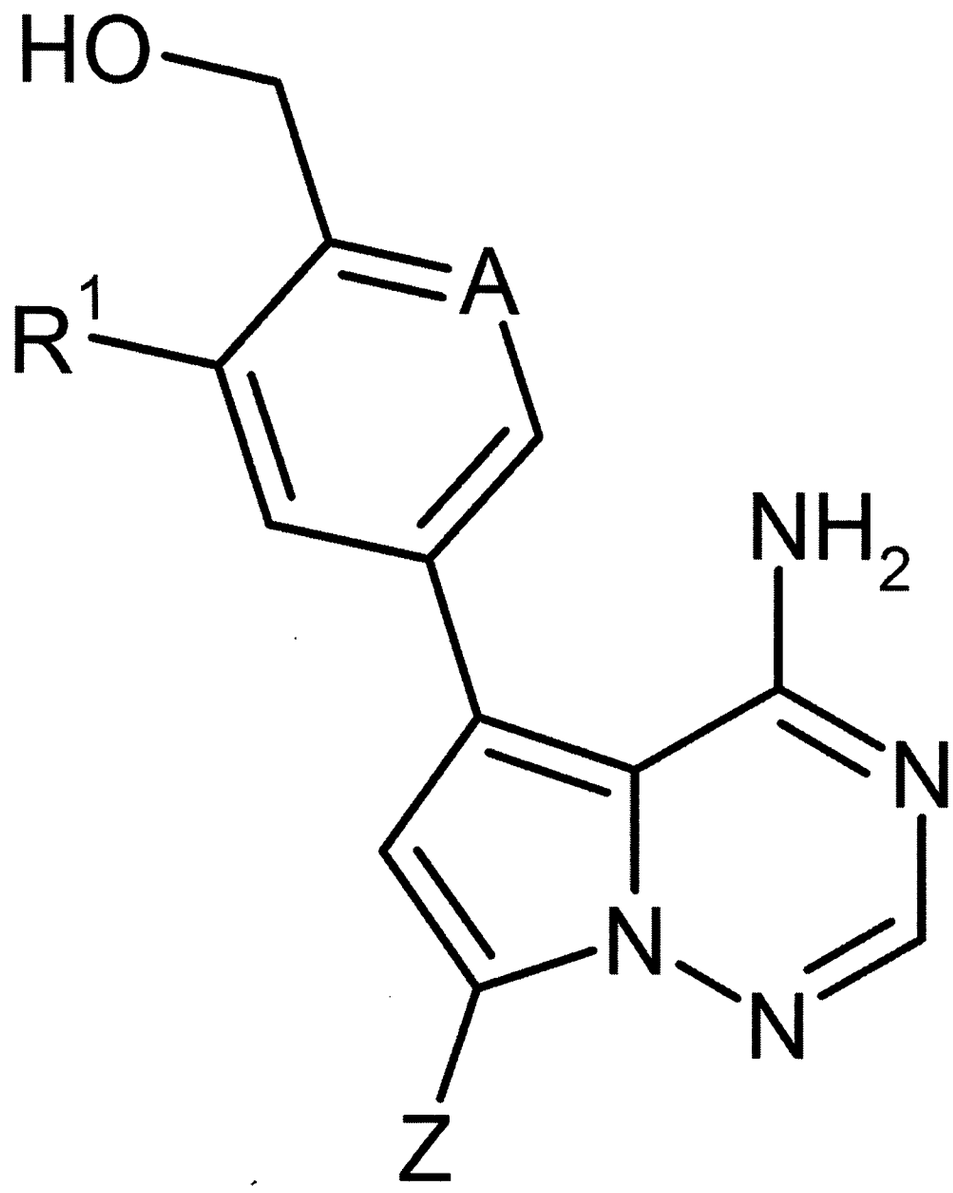
☐ Copia acto de reconocimiento institucional emitido por el Ministerio de Educación

Entidades sin ánimo de lucro

☐ Copia de registro vigente en Cámara de comercio.
☐ Hoja de información complementaria.
☐ Otros, especificar

14. ☒ Comprobante de pago de la tasa de presentación de la solicitud.
15. ☐ Comprobante de pago por reivindicación de prioridad.
16. ☒ Comprobante de pago de la tasa por concepto de excedente de palabras en la publicación.
17. ☒ Comprobante de pago por reivindicación adicional a 10.


HO
R1
A
NH2
N
N
N
Z


HO
R1
A
NH2
N
N
N
Z

Pirrolotriazinas sustituidas con hidroximetilarilo y sus usos

La presente invención se refiere a pirrolo[2,1-f][1,2,4]triazin-4-aminas sustituidas con 5-[(hidroximetil)arilo] novedosas, a procedimientos para la preparación de tales compuestos, a composiciones farmacéuticas que contienen tales compuestos, y al uso de tales compuestos o composiciones para tratar trastornos relacionados con la angiogénesis, en particular trastornos oculares relacionados con la angiogénesis.

El término angiogénesis, también denominada neovascularización, significa el procedimiento de formación de nuevos vasos sanguíneos. Este está involucrado en el desarrollo normal, así como en numerosos estados patológicos que incluyen, por ejemplo, cáncer, artritis reumatoide, cicatrización de heridas luego de una lesión en un tejido, aterosclerosis, psoriasis, y enfermedades de los ojos.

Varios trastornos oculares que son responsables de la mayoría de las morbididades visuales y cegueras en los países desarrollados están caracterizados por, son causados por y/o dan lugar a neovascularización coroidea, retiniana o del iris o edema retiniano [Campochiaro (2004), *Exp. Opin. Biol. Ther.* 4: 1395-1402].

Por ejemplo, la retinopatía asociada con diabetes es una causa que lleva a la ceguera en la diabetes de tipo 1, y también es común en la diabetes de tipo 2. Otro trastorno ocular que involucra la neovascularización es la degeneración macular relacionada con la edad (DME). La DME es la causa más común de pérdida de la visión en Occidente en sujetos de 50 años o más, y su prevalencia aumenta con la edad. La DME se clasifica como húmeda (neovascular) o seca (no neovascular). La forma húmeda de la enfermedad es responsable de la pérdida de la visión más severa.

Varias otras retinopatías menos comunes, pero sin embargo debilitantes, incluyen membrana neovascular coroidea (MNVC), edema macular cistoideo (EMC, también denominado edema macular o hinchazón macular), membrana epi-retiniana (MER, carnosidad macular), y agujero macular. En la MNVC, los vasos

sanguíneos anormales que surgen del coroide crecen a través de las capas retinianas. Los nuevos vasos frágiles se rompen fácilmente, lo que causa que se junten sangre y fluido dentro de las capas de la retina. En el EMC, que puede producirse como un resultado de una enfermedad, lesión o cirugía, se reúne fluido dentro de las capas de la mácula, lo que causa una visión central borrosa, distorsionada. La MER (carnosidad macular) es una membrana similar a un celofán que se forma sobre la mácula, que afecta la visión central tornándola borrosa y distorsionada.

También están relacionados trastornos como cambios hipertróficos y atróficos del epitelio del pigmento retiniano (EPR), desprendimiento de retina, oclusión de la vena coroidea, oclusión de la vena retiniana, angiogénesis en la córnea luego de, por ejemplo, queratitis, transplante de córnea o queratoplastía, angiogénesis en la córnea causada por hipoxia (*por ej.*, como un resultado del uso extensivo de lentes de contacto), pterigión en la conjuntiva, edema subretiniano, y edema intrarretiniano.

Se ha descubierto que el factor de crecimiento endotelial vascular (FCEV) es un modulador importante de la angiogénesis y se ha implicado en la patología de un número de afecciones que incluyen DME y retinopatía diabética. Además, se ha demostrado para DME que la inyección intravítrea de un inhibidor anti-FCEV como pegaptanib, ranibizumab o aflibercept reduce la angiogénesis coroidea y fuga vascular [Gragoudas (2004), *N. Engl. J. Med.* 351: 2805-2816; Rosenfeld (2006), *N. Engl. J. Med.* 355: 1419-1431; Dixon (2009), *Expert Opin. Investig. Drugs* 18: 1573-1580].

El estándar de cuidado corriente para DME es lucentis (ranibizumab), una terapia anti-FCEV. Sin embargo, únicamente 1/3 de todos los pacientes con DME tratados con lucentis muestran una mejora en la visión [Rosenfeld (2006), *N. Engl. J. Med.* 355: 1419-1431]. Por lo tanto, nuevas opciones terapéuticas anti-angiogénicas con un modo de acción independiente de FCEV tienen el potencial de mejorar el

estándar de cuidado corriente en enfermedades oculares como retinopatía diabética y DME.

El ALK1 (receptor de activina tipo quinasa-1) es un receptor de la Ser/Thr quinasa de la familia de receptores de TGFβ preferentemente expresado en las células endoteliales e involucrado en la angiogénesis. Los miembros de esta familia median su actividad biológica por la unión de ligandos a un complejo del receptor heterotetramérico de receptores de serina/treonina quinasa de tipo I y tipo II TβRI y TβRII y receptores de tipo III accesorios. TGFβ así como los ligandos de alta afinidad BMP9 y BMP10 pueden activar el ALK1 en complejos receptores con BMPRII o ActRII y endoglina del receptor de tipo III [Scharpfenecker (2007), *J. Cell Sci.* 120: 964-972]. La unión de BMP9 al ALK1 en células endoteliales microvasculares activa la vía Smad1/5/8 [David (2007), *Blood* 109 (5): 1953-1961]. Se ha postulado que BMP9 inhibe la migración y el crecimiento de las células endoteliales. Sin embargo, la mayoría de los estudios concluyen en que la activación del receptor ALK1 promueve la migración, proliferación de células endoteliales, y la formación de tubo [Goumans (2002), *EMBO Journal* 21 (7): 1743-1753; Wu (2006), *Microvasc. Res.* 71: 12-19].

BMP9 y BMP10 activan los complejos del receptor ALK1. En las células endoteliales, TGFβ también puede activar el ALK1 mientras que en la mayoría de los tipos de células, TGFβ se señaliza a través de ALK5. La activación de ALK5 deriva en la fosforilación de Smad2/3, mientras que la activación de ALK1 da lugar a la fosforilación de Smad1/5. Cada vía de señalización de Smad finalmente da lugar a la regulación de grupos específicos de genes diana: la señalización de Smad2/3 induce la expresión de PAI-1 y la represión de Id-1, mientras que la señalización de Smad1/5 induce la expresión de Smad6, Smad7 e Id-1 y reduce la expresión de PAI-1 [Deng (2006), *J. Cell Biol.* 134: 1563-1571; Ota (2002), *J. Cell Physiol.* 193: 299-318].

La endoglina del receptor de tipo III cumple un rol en el ajuste fino de las vías de ALK1 y ALK5, en especial en las células endoteliales, por la regulación de las

interacciones del ligando-receptor [ten Dijke (2008), *Angiogenesis* 11: 79-89]. La endoglina facilita la interacción TGFβ/ALK1, pero reduce la interacción TGFβ/ALK5 [David (2007), *Blood* 109: 1953-1961].

Las mutaciones en la endoglina y en el ALK1 están vinculadas al trastorno dominante autosómico denominado telangiectasia hemorrágica hereditaria (HHT1 y HHT2, respectivamente) con características de perturbaciones angiogénicas como malformaciones venoso-arteriales y telangiectasias [Fernandez-Lopez (2006), *Clin. Med. & Res.* 4: 66-78]. Los ratones RIP1-Tag2 con sólo una copia funcional del gen ALK1 ($ALK1^{+/-}$) muestran una progresión retardada del tumor y una densidad menor de los microvasos en comparación con los ratones $ALK1^{wt}$. Se realizaron observaciones similares con el constructo RAP-041 del receptor ALK1-Fc soluble, que inhibió la angiogénesis tumoral *in vivo* y limitó el crecimiento tumoral [Cunha (2010), *J. Exp. Med.* 207: 85-100].

El descubrimiento de los inhibidores potentes y selectivos de ALK1 es, por lo tanto, altamente deseable para elucidar en forma adicional el rol del ALK1 en la fisiología y patología de los vasos sanguíneos, y para derivar opciones terapéuticas potenciales para enfermedades asociadas con la angiogénesis y la remodelación vascular.

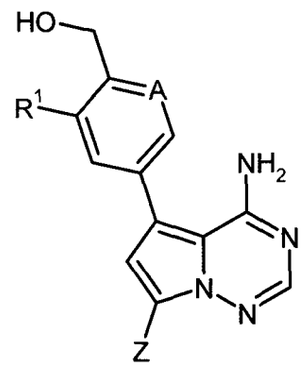
En el documento WO 2007/147647-A1, ciertos derivados de pirazolo[1,5-a]pirimidina sustituidos con 3-arilo se describieron como los primeros inhibidores de la ALK1 quinasa de moléculas pequeñas publicados hasta ese momento. Se afirmaba que tales compuestos eran útiles para el tratamiento de enfermedades del crecimiento vascular desregulado, en particular de tumores sólidos y sus metástasis y, también, de enfermedades de los ojos dependientes de la angiogénesis, tales como degeneración macular relacionada con la edad.

Varios derivados de pirrolo[2,1-f][1,2,4]triazin-4-amina con perfiles de inhibición distintivos contra un rango de proteína quinasas se han desvelado, *inter alia*, en los documentos WO 00/71129-A1, WO 2005/121147-A1, WO 2007/056170-A2, WO 2007/061882-A2, WO 2007/064883-A2, WO 2007/064931-A2,

WO 2007/079164-A2, WO 2008/089105-A2, WO 2009/136966-A1, y WO 2010/126960-A1. Generalmente, se afirmó que estos compuestos eran útiles para el tratamiento de trastornos proliferativos y/o relacionados con la angiogénesis, tales como cáncer. Sin embargo, ninguna de estas publicaciones se refiere a ALK1 como una quinasa diana potencial.

Sorprendentemente, ahora se ha descubierto que los derivados de pirrolo[2,1-f]-[1,2,4]triazin-4-amina, que tienen un sustituyente de hidroximetilarilo en la posición 5, exhiben una inhibición potente y selectiva de la ALK1 quinasa que torna a estos compuestos particularmente útiles para el tratamiento de trastornos oculares relacionados con la angiogénesis.

Por lo tanto, en un aspecto, la presente invención se refiere a pirrolo-[2,1 f][1,2,4]triazin-4-aminas sustituidas con 5-[(hidroximetil)arilo] de la fórmula general (I)



(I),

en la que

A es N o C-R^2, en la que

R^2 representa hidrógeno, fluoro o cloro,

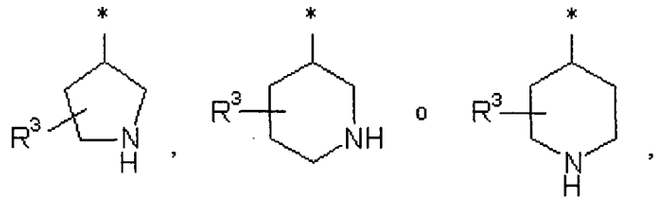
R^1 representa hidrógeno, fluoro, cloro, metilo, etilo o metoxi,

y

Z representa alquilo (C_1-C_4) o cicloalquilo (C_3-C_6), en el que cada uno puede estar sustituido con hidroxi,

o

Z representa un grupo heterocíclico de la fórmula



en la que * indica el punto de unión al resto de pirrolotriazina,

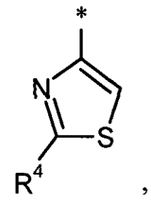
y

R^3 representa hidrógeno o hidroxi,

con la condición de que cuando R^3 sea hidroxi, este hidroxi no esté unido a un átomo de carbono del anillo situado adyacente al átomo de nitrógeno del anillo,

o

Z representa un grupo tiazol de la fórmula



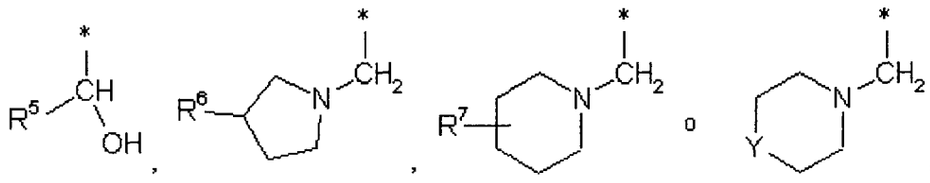
en la que * indica el punto de unión al resto de pirrolotriazina,

y

R^4 representa hidrógeno, metilo, etilo, amino o aminometilo,

o

Z representa un grupo de la fórmula



en la que * indica el punto de unión al resto de pirrolotriazina,

R^5 representa cicloalquilo (C_3-C_6), oxetanilo, tetrahidrofuranilo o tetrahidropiranilo,

R^6 representa hidrógeno o hidroxi,

R^7 representa hidrógeno o hidroxi,

con la condición de que cuando R^7 sea hidroxi, este hidroxi no esté unido a un átomo de carbono del anillo situado adyacente al átomo de nitrógeno del anillo,

e

Y es O, NH o NCH_3.

Los compuestos de acuerdo con la presente invención también pueden estar presentes en la forma de sus sales, solvatos y/o solvatos de las sales.

Los compuestos de acuerdo con la invención son los compuestos de la formula (I) y sus sales, solvatos y solvatos de las sales, los compuestos incluidos en la fórmula (I) de las fórmulas mencionadas a continuación y sus sales, solvatos y solvatos de las sales, y los compuestos incluidos en la fórmula (I) y mencionados a continuación como realizaciones representativas y sus sales, solvatos y solvatos de las sales, en los que los compuestos incluidos en la fórmula (I) y mencionados a continuación no sean ya sales, solvatos y solvatos de las sales.

Sales, por los propósitos de la presente invención, son preferentemente sales farmacéuticamente aceptables de los compuestos de acuerdo con la invención (por ejemplo, véase S. M. Berge *et al.*, "Pharmaceutical Salts", *J. Pharm. Sci.* **1977**, 66, 1-19). También se incluyen las sales que no son en sí mismas adecuadas para usos farmacéuticos pero que pueden utilizarse, por ejemplo, para el aislamiento o purificación de los compuestos de acuerdo con la invención.

Sales farmacéuticamente aceptables incluyen sales con adición de ácido de ácidos minerales, ácidos carboxílicos, ácidos sulfónicos, por ejemplo sales de ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido fosfórico, ácido metansulfónico, ácido etansulfónico, ácido bencensulfónico, ácido toluensulfónico, ácido naftalendisulfónico, ácido acético, ácido propionico, ácido láctico, ácido tartárico, ácido málico, ácido cítrico, ácido fumárico, ácido maleico y ácido benzoico.

Solvatos en el contexto de la invención se designan como aquellas formas de los compuestos de acuerdo con la invención que forman un complejo en el estado sólido o líquido por coordinación estoiquiométrica con moléculas de disolventes.

Los hidratos son una forma específica de solvatos, en los que la coordinación se lleva a cabo con agua. Los hidratos son solvatos preferentes en el contexto de la presente invención.

Los compuestos de la presente invenciónpueden, sea por la naturaleza de los centros asimétricos o por la rotación restringida, estar presentes en la forma de isómeros (enantiómeros, diastereómeros). Cualquier isómero puede estar presente en el que el centro asimétrico esté en la configuración (*R*)-, (*S*), o (*R,S*).

Asimismo, se apreciará que cuando dos o más centros asimétricos están presentes en los compuestos de la invención, también serán posibles varios diastereómeros y enantiómeros de las estructuras ejemplificadas, y que los diastereómeros puros y enantiómeros puros representan realizaciones preferentes. Se pretende que los estereoisómeros puros, diastereómeros puros, enantiómeros puros, y sus mezclas, estén dentro del ámbito de la invención.

Isómeros geométricos por la naturaleza de los sustituyentes alrededor de un enlace doble o un anillo pueden estar presentes en formas *cis* (= *Z*-) o *trans* (= *E*-), y ambas formas isoméricas están dentro del ámbito de la invención.

Todos los isómeros, independientemente de si están separados, son puros, parcialmente puros, o están en mezcla racémica, de los compuestos de la presente invención están abarcados dentro del ámbito de esta invención. La purificación de dichos isómeros y la separación de dichas mezclas isoméricas pueden lograrse por técnicas estándar conocidas en la técnica. Por ejemplo, las mezclas diastereoméricas pueden separarse en isómeros individuales por procedimientos cromatográficos o cristalización, y los racematos pueden separarse en los enantiómeros respectivos ya sea por procedimientos cromatográficos sobre fases quirales o por resolución.

Además, se incluyen de acuerdo con la presente invención todas las formas tautoméricas posibles de los compuestos descritos con anterioridad.

A menos que se indique lo contrario, las siguientes definiciones aplican para los sustituyentes y residuos utilizados a lo largo de la presente memoria descriptiva y reivindicaciones:

Alquilo (C_1-C_4) representa un radical hidrocarbonado saturado de cadena recta o ramificada que tiene 1 a 4 átomos de carbono. Los ejemplos incluyen metilo, etilo, *n*-propilo, isopropilo, *n*-butilo, isobutilo, *sec*-butilo, *terc*-butilo.

Cicloalquilo (C_3-C_6) representa un radical hidrocarbonado saturado monocíclico que tiene 3 a 6 átomos de carbono del anillo. Los ejemplos incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo.

A lo largo de este documento, con propósitos de simplicidad, se da preferencia al uso de términos singulares sobre términos plurales, pero, en general, con la intención de incluir los términos plurales a menos que se indique lo contrario. Por ejemplo, con la expresión "Un procedimiento para tratar una enfermedad en un paciente, que comprende administrar a un paciente una cantidad efectiva de un compuesto de la fórmula (I)" se pretende incluir el tratamiento simultáneo de más de una enfermedad así como la administración de más de un compuesto de la fórmula (I).

En una realización preferente, la presente invención se refiere a compuestos de la fórmula general (I), en la que

A es C-R^2, en la que

R^2 representa hidrógeno o fluoro,

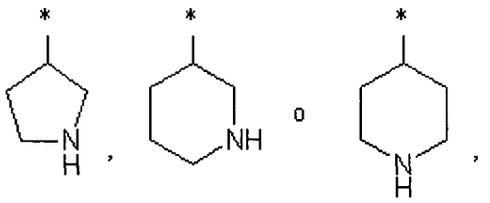
R^1 representa hidrógeno, fluoro, cloro, metilo, etilo o metoxi,

y

Z representa *n*-propilo, *n*-butilo o ciclohexilo, en el que cada uno puede estar sustituido con hidroxi,

o

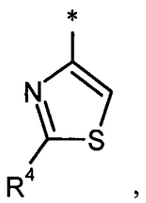
Z representa un grupo heterocíclico de la fórmula



en la que * indica el punto de unión al resto de pirrolotriazina,

o

Z representa un grupo tiazol de la fórmula



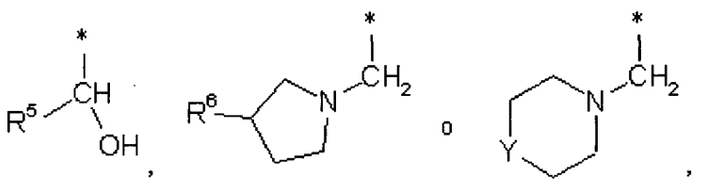
en la que * indica el punto de unión al resto de pirrolotriazina,

y

R^4 representa metilo, etilo, amino o aminometilo,

o

Z representa un grupo de la fórmula



en la que * indica el punto de unión al resto de pirrolotriazina,

R^5 representa ciclopropilo o tetrahidropiran-4-ilo,

R^6 representa hidroxi,

e

Y es O.

En una realización particularmente preferente, la presente invención se refiere a compuestos de la fórmula general (I), en la que

A es C-R^2, en la que

R^2 representa hidrógeno o fluoro,

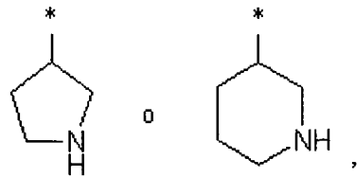
R^1 representa hidrógeno, fluoro, metilo, etilo o metoxi,

y

Z representa 4-hidroxibutilo o 4-hidroxiciclohexilo,

o

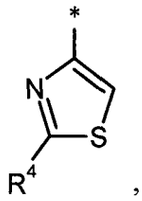
Z representa un grupo heterocíclico de la fórmula



en la que * indica el punto de unión al resto de pirrolotriazina,

o

Z representa un grupo tiazol de la fórmula



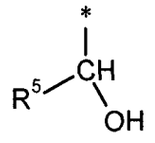
en la que * indica el punto de unión al resto de pirrolotriazina,

y

R^4 representa metilo, etilo, amino o aminometilo,

o

Z representa un grupo de la fórmula



en la que * indica el punto de unión al resto de pirrolotriazina,

y

R^5 representa ciclopropilo.

En una realización distinta, la presente invención se refiere a compuestos de la fórmula general (I), en la que

A es C-R^2, en la que

R^2 representa hidrógeno o fluoro.

En otra realización distinta, la presente invención se refiere a compuestos de la fórmula general (I), en la que

A es C-R^2, en la que

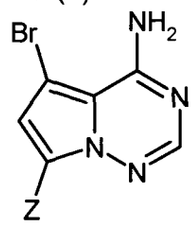
R^2 representa fluoro,

y

R^1 representa fluoro.

Las definiciones de residuos indicadas específicamente en las combinaciones respectivas o combinaciones preferentes de residuos también se reemplazan de acuerdo con lo deseado por las definiciones de residuos de otras combinaciones, independientemente de las combinaciones particulares indicadas para los residuos. En particular, se prefieren combinaciones de dos o más de los intervalos preferentes mencionados con anterioridad.

En otra realización, la presente invención se refiere a un procedimiento para preparar los compuestos de la fórmula general (I), caracterizado porque una bromopirrolotriazina de la fórmula (II)

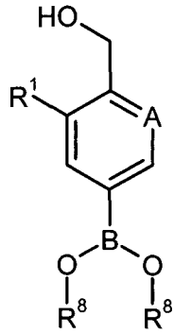


(II),

en la que Z tiene el significado descrito con anterioridad,

está

[A] acoplada con un ácido arilborónico o éster de la fórmula (III)

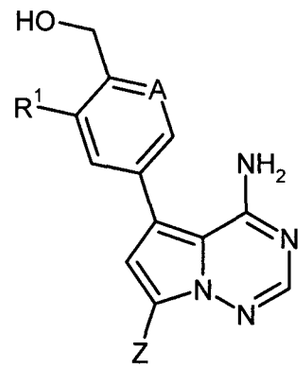


(III),

en la que A y R^1 tienen los significados descritos con anterioridad,

y

R^8 representa hidrógeno o alquilo (C_1-C_4), o ambos residuos R^8 están unidos para formar un puente -$(CH_2)_2$-, -$C(CH_3)_2$-$C(CH_3)_2$-, -$(CH_2)_3$- o -CH_2-$C(CH_3)_2$-CH_2-, en presencia de un catalizador de paladio adecuado y una base para dar el compuesto diana de la fórmula (I)

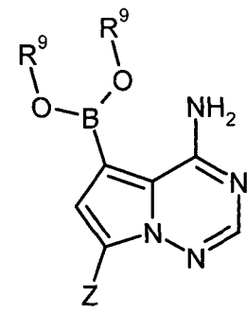


(I),

en la que A, Z y R^1 tienen los significados descritos con anterioridad,

o

[B] convertida en primer lugar en el ácido borónico correspondiente o derivado de éster de la fórmula (IV)

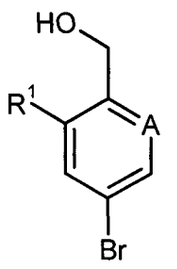


(IV),

en la que Z tiene el significado descrito con anterioridad,

y

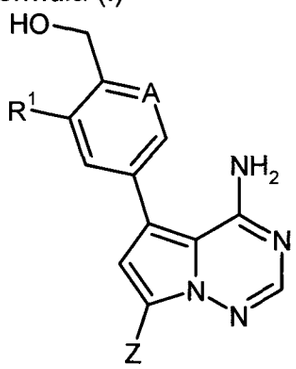
R^9 representa hidrógeno o alquilo (C_1-C_4), o ambos residuos R^9 están unidos para formar un puente -$(CH_2)_2$-, -$C(CH_3)_2$-$C(CH_3)_2$-, -$(CH_2)_3$- o -CH_2-$C(CH_3)_2$-CH_2-, que luego se acopla con un bromuro de arilo de la fórmula (V)



(V),

en la que A y R^1 tienen los significados descritos con anterioridad,

en presencia de un catalizador de paladio adecuado y una base para también dar el compuesto diana de la fórmula (I)



(I),

en la que A, Z y R^1 tienen los significados descritos con anterioridad,

opcionalmente seguido, donde sea adecuado, por (*i*) la separación de los compuestos de la fórmula (I) en sus respectivos enantiómeros y/o diastereómeros, preferentemente usando procedimientos cromatográficos, y/o (*ii*) la conversión de los compuestos de la fórmula (I) en sus respectivos hidratos, solvatos, sales y/o hidratos o solvatos de las sales por el tratamiento con los disolventes y/o ácidos correspondientes.

Como se esboza con anterioridad, se pueden sintetizar compuestos de la fórmula (I) por una reacción de acoplamiento ("acoplamiento de Suzuki") entre la bromopirrolotriazina (II) y un boronato de arilo o ácido borónico (III). Este acoplamiento generalmente se lleva a cabo a una temperatura elevada usando un catalizador de paladio, una base y un disolvente inerte. Una perspectiva general de los catalizadores y condiciones de reacción se puede hallar en la bibliografía [véase, por ejemplo, S. Kotha *et al.*, *Tetrahedron* **2002**, *58*, 9633-9695; T. E. Barder *et al.*, *J. Am. Chem. Soc.* **2005**, *127*, 4685-4696]. El catalizador preferente

en esta reacción es tetrakis(trifenilfosfina)paladio (0). La base preferente es carbonato de sodio empleado como una solución acuosa. La reacción se lleva a cabo en disolventes orgánicos que son inertes bajo las condiciones de reacción, tales como 1,4-dioxano, acetonitrilo, *N,N*-dimetilformamida (DMF) o dimetilsulfóxido (DMSO), o en agua o en mezclas de estos disolventes. Preferentemente, la reacción se lleva a cabo en una mezcla de 1,4-dioxano y agua o acetonitrilo y agua. La reacción generalmente se lleva a cabo a temperaturas entre +100 °C y +250 °C, preferentemente a +120 °C y +150 °C. El calentamiento preferentemente se efectúa mediante un dispositivo de microondas de modo único. Las reacciones normalmente se operan bajo una atmósfera de gas inerte, preferentemente bajo argón.

Una reactividad inversa de los pares de reacción para el acoplamiento de Suzuki puede a menudo ser favorable. Con este propósito, la bromopirrolotriazina (II) en primer lugar se convierte al boronato correspondiente (IV) y luego se acopla en forma cruzada con un bromuro de arilo (V) de acuerdo con uno de los procedimientos descritos con anterioridad. La conversión de (II) a (IV) se logra por una reacción de borilación mediada con metal. El procedimiento preferente es la "borilación de Miyaura" catalizada con paladio [véase, por ejemplo, J. Takagi *et al.*, *J. Am. Chem. Soc.* **2002**, *124*, 8001-8006; T. Ishiyama *et al.*, *J. Org. Chem.* **1995**, *60*, 7508-7510; A. L. S. Thompson *et al.*, *Synthesis* **2005**, 547-550]. Los procedimientos, reactivos y disolventes para la reacción de acoplamiento cruzado (IV) + (V) → (I) se seleccionan de los mencionados en la sección previa.

Los ácidos arilborónicos (III) [R^8 = H] y boronatos de arilo (III) [R^8 = alquilo, o ambos R^8 están unidos para formar un éster borónico cíclico, *por ej.*, un éster de pinacolato] se encuentran comercialmente disponibles, o se pueden preparar en forma conveniente a partir de los haluros de arilo o triflatos de arilo correspondientes usando una reacción de borilación mediada con metal (por referencias, véase la sección previa). La borilación y el acoplamiento de Suzuki subsiguiente se pueden llevar a cabo en dos etapas separadas que incluyen

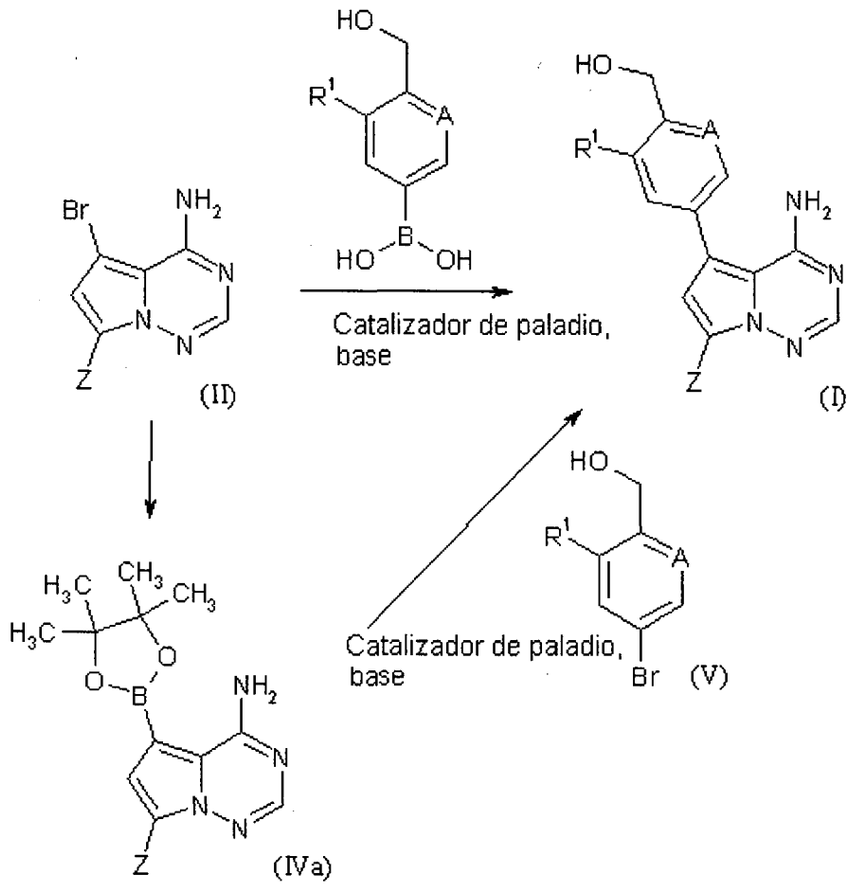
aislamiento y purificación del intermedio (III). Alternativamente, la borilación y el acoplamiento cruzado se pueden llevar a cabo como un procedimiento único usando (III) directamente sin aislamiento ni purificación.

En casos en los que un resto de amina primaria o secundaria forme parte del grupo Z en los compuestos diana de la fórmula (I), puede, a menudo, ser beneficioso en las reacciones de borilación y acoplamiento descritas con anterioridad utilizar un derivado protegido de esta amina como la pirrolotriazina de inicio (II) en lugar del compuesto de amina libre. Con este propósito, se pueden emplear grupos de protección de amino temporarios convencionales, tales como grupos acilo (*por ej.*, acetilo o trifluoroacetilo) o grupos de protección del tipo carbamato (*por ej.*, un grupo Boc, Cbz o Fmoc). Preferentemente, se utiliza un trifluoroacetilo o un grupo Boc. Similarmente, la función de hidroxi en los componentes de acoplamiento (III) y (V), respectivamente, se puede bloquear temporalmente durante el procedimiento, preferentemente como un derivado de éter de sililo tal como un éter de trimetilsililo o *terc*-butildimetilsililo.

Después, estos grupos de protección se pueden escindir en forma concomitante durante el tratamiento acuoso de las mezclas de reacción de acoplamiento, o se puede eliminar en una etapa de reacción separada subsiguiente usando procedimientos estándar conocidos en la técnica. La preparación de los intermedios protegidos descritos con anterioridad a partir de las aminas libres o alcoholes de la fórmula (II), (III) y (V) correspondientes, respectivamente, o a partir de otros compuestos precursores (véase la sección a continuación) también se logra fácilmente siguiendo procedimientos generales descritos en la bibliografía [véase, por ejemplo, T. W. Greene and P. Wuts, *Protective Groups in Organic Synthesis*, Wiley, New York, 1999].

La preparación de los compuestos de la invención se puede ilustrar por medio del siguiente esquema de síntesis:

Esquema 1



Las metodologías sintéticas que se pueden utilizar para preparar las bromopirrolotriazinas de la fórmula (II) se pueden estructurar de acuerdo con el quimiotipo del grupo Z presente en (II). Se presentan a continuación ejemplos que ilustran numerosas tales vías (véanse los esquemas de síntesis 2-6). Se proporcionan procedimientos más detallados en la Sección Experimental en la que se describen intermedios específicos y compuestos representativos de la invención.

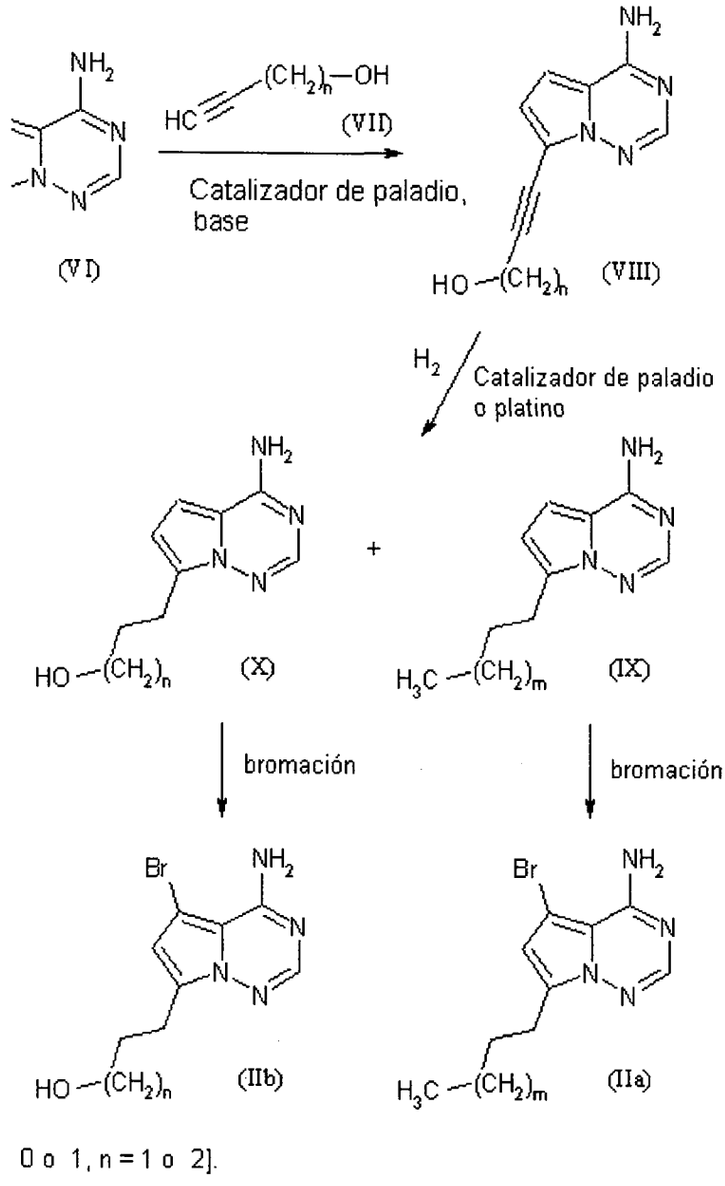
Por ejemplo, se pueden obtener compuestos de la fórmula (II) que contienen un residuo alquilo o hidroxialquilo como el grupo Z por el empleo de una reacción de acoplamiento entre la bromopirrolotriazina (VI) y un alquino terminal de la fórmula (VII) como la etapa clave (esquema 2). Este tipo de reacción ("reacción de Sonogashira") normalmente se lleva a cabo en presencia de un sistema catalizador de

paladio-carbono y una base. Se han descrito en la bibliografía varios ejemplos de esta reacción [véase, por ejemplo, R. Chinchilla and C. Nájera, *Chem. Rev.* **2007**, *107*, 874-922]. En la presente invención, la fuente de cobre preferente es yoduro de cobre (I), tetrakis(trifenilfosfina)paladio (0) se utiliza como un catalizador de paladio, y pirrolidina actúa como base y como disolvente. La reacción de acoplamiento ventajosamente se lleva a cabo bajo irradiación concurrente de microondas.

Después, el alquino resultante (VIII) se somete a una hidrogenación catalítica por el empleo de un catalizador de paladio o platino habitual. Preferentemente, se utiliza óxido de platino (IV) como el catalizador, y la reacción se lleva a cabo en ácido acético como el disolvente. En algunos casos, se obtiene una mezcla de productos (IX) y (X) por este procedimiento que, en cualquier caso, se puede separar fácilmente a través de procedimientos cromatográficos. Una reacción de bromación subsiguiente, preferentemente usando 1,3-dibromo-5,5-dimetil-hidantoína como la fuente de bromo, en un disolvente inerte tal como THF o DMF da las pirrolotriazinas (IIa) y (IIb) diana, respectivamente.

La preparación del compuesto de inicio 7-bromopirrolo[2,1-f][1,2,4]triazin-4-amina (VI) se ha descrito previamente [véase el documento WO 2007/056170-A2 (Intermedio B)].

Esquema 2



0 o 1, n = 1 o 2].

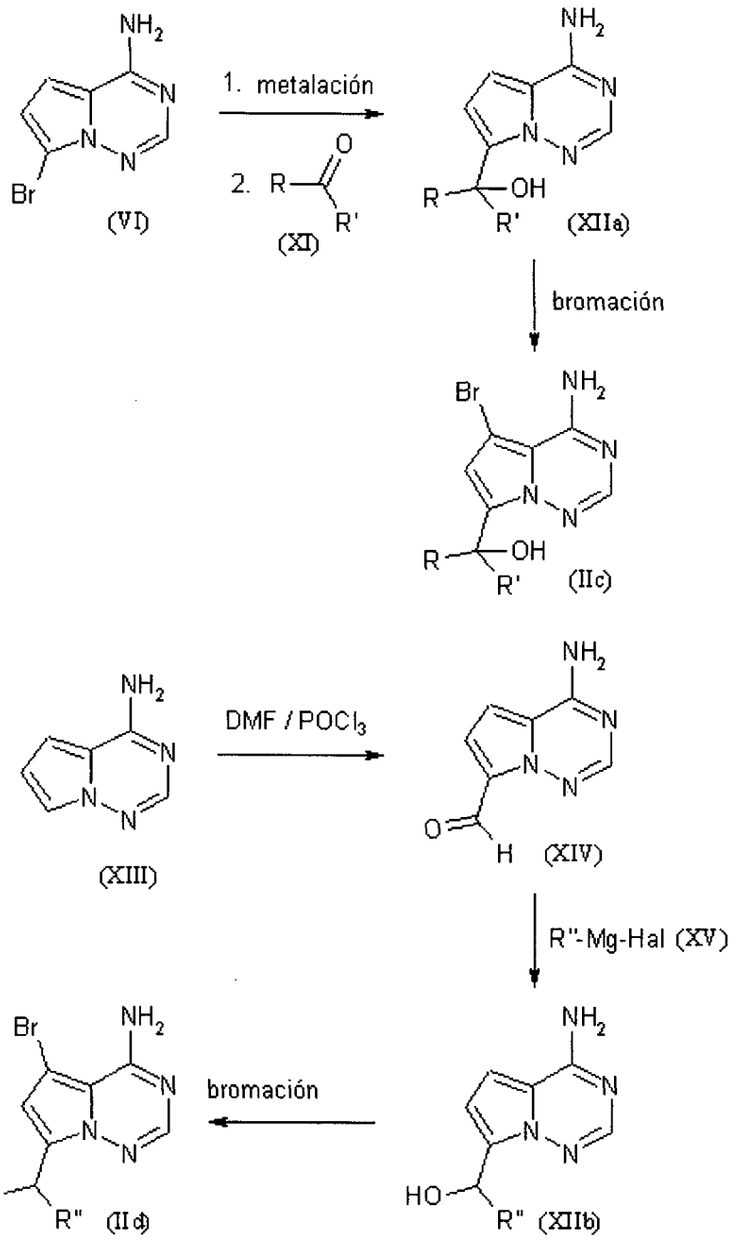
Se pueden preparar precursores de bromopirrolotriazina de tipo (IIc) (esquema 3) por la metalación del compuesto (VI) con un metal tal como magnesio o litio o por un intercambio de halógeno-metal usando un reactivo de organo-magnesio u organo-litio. El metal preferente es magnesio que se introduce en (VI) por el tratamiento con bromuro de isopropilmagnesio en un disolvente tal como THF o éter de dietilo. Después, las especies organo-metálicas intermedias se hacen reaccionar con una cicloalcanona o heterocicloalcanona (XI) [R, R' están unidos

para formar un anillo cicloalquilo o heterocicloalquilo] para dar el alcohol terciario (XIIa).

Una vía complementaria que lleva a alcoholes secundarios de la fórmula (XIIb) utiliza una reacción de formulación de Vilsmeier a través de la que aminopirrolotriazina (XIII) se transforma en el aldehído (XIV) (esquema 3). La introducción de cadena lateral se logra por la adición subsiguiente de un reactivo de Grignard adecuado (XV) [R'' = alquilo o cicloalquilo] en un disolvente tal como THF o dietil éter. Finalmente, la bromación de compuestos (XIIa) y (XIIb), preferentemente usando 1,3-dibromo-5,5-dimetilhidantoína, en un disolvente inerte tal como THF o DMF proporciona las pirrolotriazinas (IIc) y (IId) diana, respectivamente.

La preparación del compuesto de inicio pirrolo[2,1-f][1,2,4]triazin-4-amina (XIII) se ha descrito previamente [véase el documento WO 2007/056170-A2 (Intermedio A)].

Esquema 3

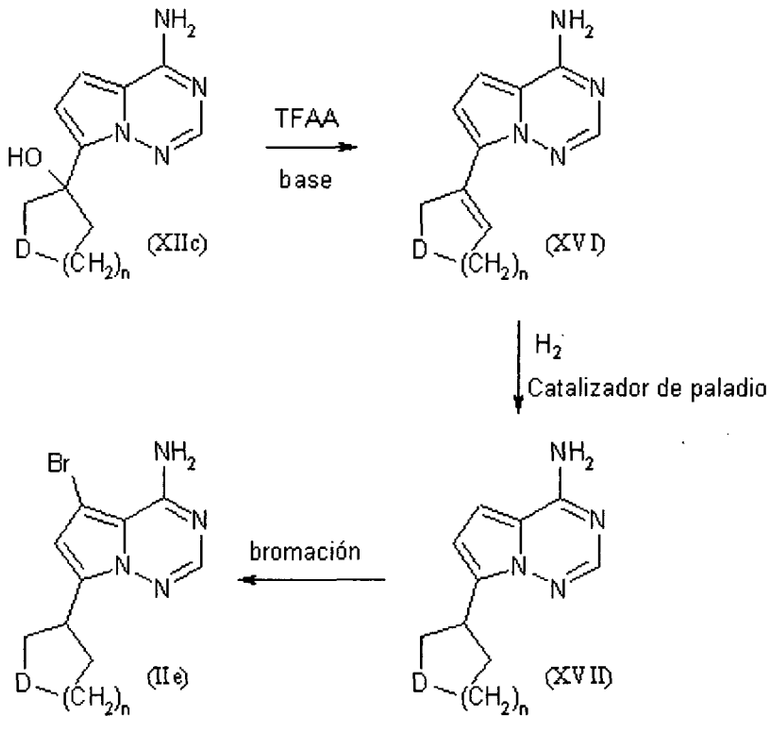


Se pueden preparar pirrolotriazinas de la fórmula (II) en la que Z representa un grupo aza-heterociclilo unido a cicloalquilo o carbono no sustituido por la deshidratación de un alcohol terciario de la fórmula (XIIc) al carbo o heterociclo no saturado de la fórmula (XVI), por el empleo de agentes habituales tales como anhídrido del ácido trifluoroacético, anhídrido del ácido trifluorometanosulfónico, óxido de fósforo (V), ácido sulfúrico u otros ácidos fuertes (esquema 4). La hidrogenación catalítica subsiguiente usando un catalizador convencional tal como

paladio sobre carbono da el análogo saturado de la fórmula (XVII). La etapa de hidrogenación preferentemente se lleva a cabo en un disolvente como metanol, etanol o THF que contiene una pequeña cantidad de ácido trifluoroacético acuoso. Finalmente, la bromación con 1,3-dibromo-5,5-dimetilhidantoína, como se describe con anterioridad, proporciona la pirrolotriazina diana (IIe).

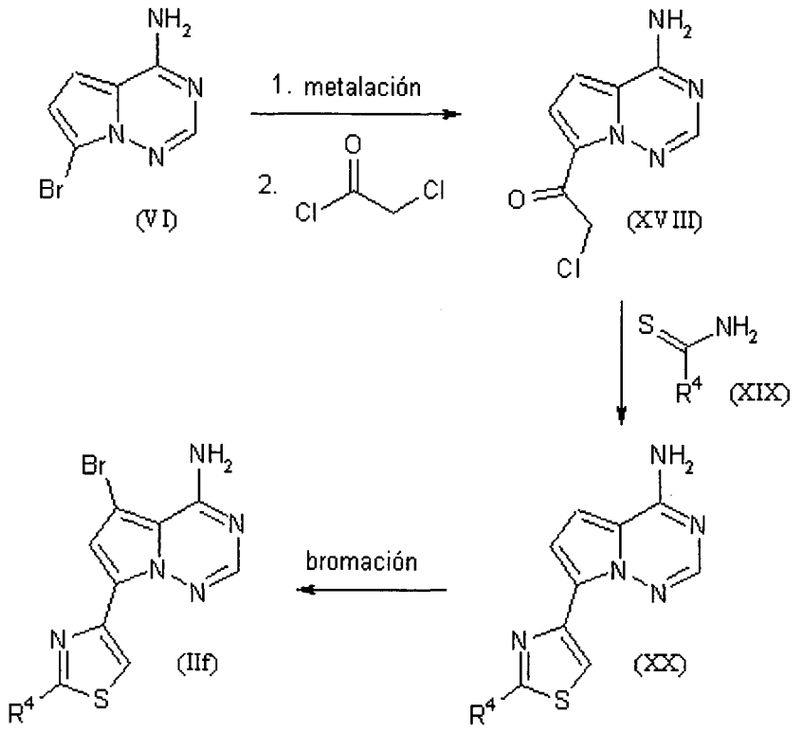
Los precursores de alcohol (XIIc) en sí mismos son fácilmente accesibles por la vía sintética representada en el esquema 3 [*cf.* preparación del compuesto (XIIa)].

Esquema 4



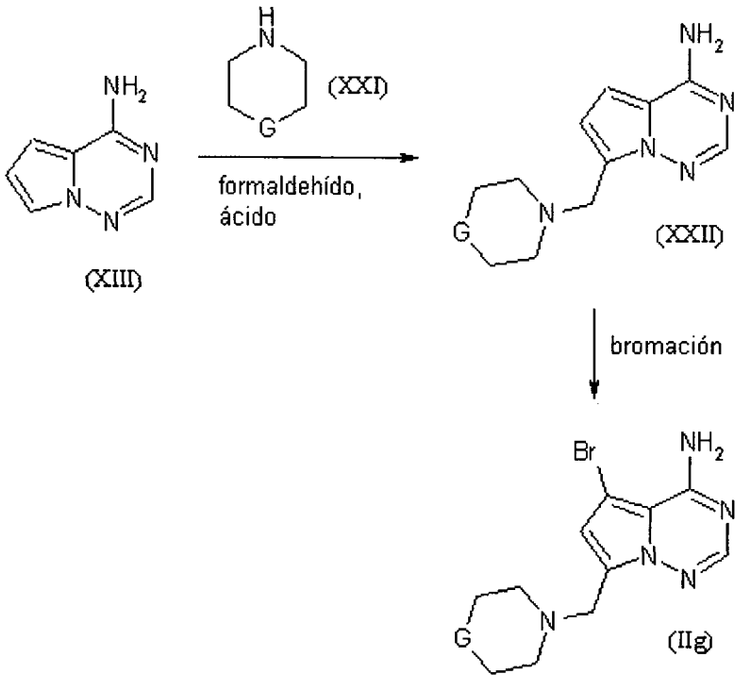
Se pueden preparar pirrolotriazinas de la fórmula (II) en la que Z representa un grupo 1,3-tiazol-4-ilo por la metalación del compuesto (VI), como se describe con anterioridad, seguido por reacción con cloruro de cloroacetilo para dar el intermedio (XVIII), y después por condensación con una tioamida o tiourea (XIX) [como R^4 como lo definido con anterioridad] para dar el compuesto precursor (XX) (esquema 5). La bromación con 1,3-dibromo-5,5-dimetilhidantoína, como se describe con anterioridad, finalmente proporciona la pirrolotriazina diana (IIf).

Esquema 5



Se pueden obtener pirrolotriazinas de la fórmula (II) en la que Z representa un grupo aminometilo *N*-cíclico por la reacción de pirrolotriazina (XIII) con formaldehído y una amina cíclica de tipo (XXI) en un disolvente acídico, tal como ácido acético, o en una mezcla de un ácido un disolvente orgánico (esquema 6). La bromación del producto resultante (XXII) con 1,3-dibromo-5,5-dimetilhidantoína, como se describe con anterioridad, luego proporciona la pirrolotriazina diana (IIg).

Esquema 6



[G = por ej., CH_2, CH(OH), O o N-Boc].

Los compuestos de las fórmulas (V), (VII), (XI), (XV), (XIX) y (XXI) se encuentran comercialmente disponibles, son conocidos de la bibliografía, o se pueden preparar a partir de materiales de inicio fácilmente disponibles por la adaptación de procedimientos estándar descritos en la bibliografía.

Los compuestos de la presente invención tienen propiedades farmacológicas valiosas y se pueden utilizar para la prevención y tratamiento de enfermedades en seres humanos y animales.

Los compuestos de la presente invención son inhibidores potentes y selectivos de la ALK1 quinasa. Por lo tanto, se pueden utilizar para el tratamiento y/o prevención de trastornos relacionados con la angiogénesis, en particular enfermedades oculares relacionadas con la angiogénesis.

Para la presente invención, el término "tratamiento" o "tratando" incluye inhibir, retrasar, aliviar, mitigar, detener, reducir o causar la regresión de una enfermedad, trastorno, afección o estado, su desarrollo y/o progresión, y/o sus síntomas. El término "prevención" o "previniendo" incluye reducir el riesgo de sufrir, contraer o

experimentar una enfermedad, trastorno, afección o estado, su desarrollo y/o progresión, y/o sus síntomas. El término prevención incluye profilaxis. El tratamiento o prevención de una enfermedad, trastorno, afección o estado puede ser parcial o completo.

Los trastornos oculares relacionados con la angiogénesis que se pueden tratar y/o prevenir con los compuestos de la presente invención incluyen, pero sin limitación, degeneración macular relacionada con la edad (DME), retinopatía diabética, en particular edema macular diabético (EMD), otras retinopatías tales como neovascularización coroidea (NVC), membrana neovascular coroidea (MNVC), edema macular cistoideo (EMC), membrana epi-retiniana (MER) y agujero macular, cambios hipertróficos del epitelio del pigmento retiniano (EPR), cambios atróficos del epitelio del pigmento retiniano, desprendimiento de retina, oclusión de la vena coroidea, oclusión de la vena retiniana, angiogénesis en la córnea luego de, por ejemplo, queratitis, transplante de córnea o queratoplastía, angiogénesis en la córnea causada por hipoxia (*por ej.*, inducida por el uso extensivo de lentes de contacto), pterigión en la conjuntiva, edema subretiniano, y edema intrarretiniano.

En el contexto de la presente invención, el término degeneración macular relacionada con la edad (DME) abarca las manifestaciones tanto húmedas (o exudativas, neovasculares) como secas (o no exudativas, no neovasculares) de la DME.

Los compuestos de la presente invención se pueden además utilizar para el tratamiento y/o prevención de enfermedades inflamatorias asociadas con angiogénesis, tales como artritis reumatoide, psoriasis, dermatitis de contacto, asma, hipertensión pulmonar, esclerosis múltiples, y enfermedades inflamatorias de los intestinos tales como enfermedad de Crohn. También se pueden tratar y/o prevenir enfermedades fibróticas, tales como fibrosis y cirrosis, con los compuestos de la presente invención.

Gracias a su perfil de actividad, los compuestos de la presente invención son particularmente adecuados para el tratamiento y/o prevención de enfermedades oculares, tales como degeneración macular relacionada con la edad (DME), neovascularización coroidea (NVC), retinopatía diabética, y edema macular diabético (EMD).

Los trastornos mencionados con anterioridad se han caracterizado en forma adecuada en seres humanos, pero también existen como una etiología similar en otros animales, que incluyen mamíferos, y se pueden tratar en tales animales con los compuestos de la presente invención.

Por lo tanto, la presente invención además se refiere al uso de los compuestos de acuerdo con la invención para el tratamiento y/o prevención de trastornos, en especial de los trastornos mencionados con anterioridad.

La presente invención además se refiere al uso de los compuestos de acuerdo con la invención para preparar una composición farmacéutica para el tratamiento y/o prevención de trastornos, en especial de los trastornos mencionados con anterioridad.

La presente invención además se refiere al uso de los compuestos de acuerdo con la invención en un procedimiento para el tratamiento y/o prevención de trastornos, en especial de los trastornos mencionados con anterioridad.

La presente invención además se refiere a un procedimiento para el tratamiento y/o la prevención de trastornos, en especial de los trastornos mencionados con anterioridad, usando una cantidad efectiva de al menos uno de los compuestos de acuerdo con la invención.

Se pueden administrar compuestos de la presente invención como el único agente farmacéutico o en combinación con uno o más agentes terapéuticos en los que la combinación no causa efectos adversos inaceptables. Esta terapia combinada incluye la administración de una formulación de dosis farmacéutica única que contiene un compuesto de la fórmula (I), como el definido con anterioridad, y uno o más agentes terapéuticos adicionales, así como la administración de un

compuesto de la fórmula (I) y cada agente terapéutico adicional en su propia formulación de dosis farmacéutica separada. Por ejemplo, un compuesto de la fórmula (I) y un agente terapéutico se pueden administrar al paciente en forma conjunta en una composición de dosis oral única tal como un comprimido o cápsula, o cada agente se puede administrar en formulaciones de dosis separadas.

En el caso en que se utilizan formulaciones de dosis separadas, el compuesto de la fórmula (I) y uno o más agentes terapéuticos adicionales se pueden administrar esencialmente en el mismo momento (*es decir*, concurrentemente) o en momentos escalonadamente separados (*es decir*, secuencialmente).

En particular, los compuestos de la presente invención se pueden utilizar en combinación fija o separada con inhibidores de la angiogénesis mediada por FCEV, tales como, por ejemplo, ACTB-1003, aflibercept, apatinib, axitinib, bevacizumab, bevasiranib, BMS-690514, brivanib, cediranib, CT-322, dovitinib, E7080, foretinib, KH-902, linifanib, MGCD-265, motesanib, OTS-102, pazopanib, pegaptanib, ranibizumab, regorafenib, ruboxistaurina, sorafenib, SU-14813, sunitinib, telatinib, TG-100801, tivozanib, TSU-68, vandetanib, vargatef, vatalanib y XL-184, o con inhibidores de otras vías de señalización, tales como, por ejemplo, ACU-4429, disulfiram, E-10030, fenretinida, mecamilamina, PF-04523655, sirolimus, sonepcizumab, tandospirona y volociximab.

Así, en una realización adicional, la presente invención se refiere a composiciones farmacéuticas que comprenden al menos uno de los compuestos de acuerdo con la invención y uno o más agentes terapéuticos adicionales para el tratamiento y/o prevención de trastornos, en especial de los trastornos mencionados con anterioridad.

Los compuestos de la presente invención también se pueden utilizar, como tales o en composiciones, en investigación y diagnósticos, o como estándares de referencia analítica y similares.

En otro aspecto, la presente invención se refiere a composiciones farmacéuticas que comprenden al menos uno de los compuestos de acuerdo con la invención junto con uno o más excipientes inertes, no tóxicos, farmacéuticamente aceptables, y a sus usos para los propósitos mencionados con anterioridad.

Los compuestos de acuerdo con la invención pueden actuar sistémica y/o localmente. Con este propósito, se pueden administrar de una forma adecuada tal como, por ejemplo, por vía oral, parenteral, pulmonar, nasal, lingual, sublingual, bucal, rectal, dérmica, transdérmica, conjuntiva, subconjuntiva, intravítrea, ótica o tópica.

Los compuestos de acuerdo con la invención se pueden administrar en formas de aplicación adecuadas para estas vías de administración.

Son adecuadas para administración oral formas de aplicación que funcionan de acuerdo con la técnica previa y que administran los compuestos de acuerdo con la invención rápidamente y/o en forma modificada, y que contienen los compuestos de acuerdo con la invención en forma cristalina, amorfa y/o disuelta, tal como, por ejemplo, comprimidos (comprimidos revestidos o no revestidos, por ejemplo que tienen revestimientos entéricos o revestimientos que son insolubles o se disuelven con un retraso y controlan la liberación del compuesto de acuerdo con la invención), comprimidos que se desintegran rápidamente en la boca, o películas/obleas, películas/liofilisatos, cápsulas (*por ej.*, cápsulas de gelatina dura o blanda), comprimidos con revestimientos de azúcar, gránulos, pelets, polvos, emulsiones, suspensiones, aerosoles o soluciones.

La administración parenteral se puede llevar a cabo con la omisión de una etapa de absorción (*por ej.*, intravenosa, intraarterial, intracardíaca, intraespinal o intralumbar) o con la inclusión de una absorción (*por ej.*, intramuscular, subcutánea, intracutánea, percutánea o intraperitoneal). Las formas de aplicación adecuadas para administración parenteral son, *inter al.*, preparaciones para inyección e infusión en la forma de soluciones, suspensiones, emulsiones, liofilisatos o polvos estériles.

Las formas adecuadas para otras vías de administración incluyen, por ejemplo, formas farmacéuticas para inhalación (*por ej.*, inhaladores de polvo, nebulizadores), gotas nasales, soluciones o pulverizadores, comprimidos o cápsulas para administración lingual, sublingual o bucal (*por ej.*, pastillas, pastillas para chupar), supositorios, preparaciones para los oídos y los ojos (*por ej.*, gotas, ungüentos), cápsulas vaginales, suspensiones acuosas (lociones, mezclas para agitar), suspensiones lipofílicas, ungüentos, cremas, leche, pastas, espumas, polvos secantes, y sistemas terapéuticos transdérmicos (*por ej.*, parches).

Los compuestos de acuerdo con la invención se pueden convertir a las formas de aplicación mencionadas de una manera conocida *per se* por la mezcla con excipientes inertes, no tóxicos, farmacéuticamente aceptables. Estos excipientes incluyen, *inter al.*, vehículos (*por ej.*, celulosa microcristalina, lactosa, manitol), disolventes (*por ej.*, polietilenglicoles líquidos), emulsificantes (*por ej.*, dodecil sulfato de sodio), tensioactivos (*por ej.*, oleato de polioxisorbitán), dispersantes (*por ej.*, polivinilpirrolidona), polímeros sintéticos y naturales (*por ej.*, albúmina), estabilizadores (*por ej.*, antioxidantes tales como, por ejemplo, ácido ascórbico), colorantes (*por ej.*, pigmentos inorgánicos tales como, por ejemplo, óxidos de hierro), y agentes enmascarantes del sabor y/u olor.

Generalmente, ha resultado ser ventajoso administrar cantidades de administración parenteral de aproximadamente 0,001 a 1 mg/kg, preferentemente, de aproximadamente 0,01 a 0,5 mg/kg, del peso corporal para lograr resultados efectivos. En la administración oral, un intervalo de dosis representativo es de aproximadamente 0,01 a 100 mg/kg, preferentemente, de aproximadamente 0,01 a 20 mg/kg, y, más preferentemente, de aproximadamente 0,1 a 10 mg/kg de peso corporal.

No obstante, los niveles de dosificación y el curso de tiempo de administración reales de los componentes activos en las composiciones farmacéuticas de la invención pueden variar de modo de obtener una cantidad del componente activo que sea efectiva para lograr la respuesta terapéutica deseada para un paciente,

composición y modo de administración particulares, sin ser tóxica para el paciente. Por lo tanto, puede ser necesario, en el caso en que sea adecuado, desviarse de las cantidades declaradas, en particular como una función de la edad, género, peso corporal, dieta y estado de salud general del paciente, vía de administración, respuesta individual al componente activo, naturaleza de la preparación, y tiempo o intervalo sobre el que se lleva a cabo la administración. Así, puede ser satisfactorio, en algunos casos, utilizar menos que la cantidad mínima mencionada con anterioridad mientras que, en otros casos, debe excederse el límite superior declarado. En el caso de una administración de mayores cantidades, puede ser aconsejable dividir estas cantidades en múltiples dosis individuales a lo largo del día.

Para el tratamiento y/o la prevención de enfermedades oculares, como las descritas con anterioridad, la vía de administración preferente de los compuestos de la invención es en forma tópica al ojo o por un sistema de administración ocular de fármacos. Las inyecciones intraoculares son otra manera de administrar los compuestos de la presente invención que es adecuada para tales propósitos.

La administración a áreas dentro del ojo puede lograrse por inyección, a través del empleo de una cánula u otro dispositivo invasivo diseñado para introducir cantidades medidas con precisión de una formulación deseada a un compartimiento o tejido particular dentro del ojo (*por ej.*, cámara posterior o retina). Una inyección intraocular puede aplicarse al vítreo (intravítrea), bajo la conjuntiva (subconjutiva), detrás del ojo (retrobulbar), dentro de la esclera, o bajo la Cápsula de Tenon (sub-Tenon), y puede hacerse en forma de liberación prolongada. También se contemplan otras vías de administración y sitios y formas de inyección intraocular que están dentro del ámbito de la invención.

Los compuestos de acuerdo con la invención se pueden formular de una manera conocida por aquellos con experiencia en la técnica de modo que proporcionen una administración adecuada al fondo del ojo, que puede ser a través de una dosificación regular, tal como con gotas oculares, o usando un sistema de

administración para proporcionar una liberación controlada, tal como una liberación lenta, de los compuestos de acuerdo con la invención.

Las formulaciones oculares preferentes para los compuestos de la presente invención incluyen soluciones acuosas, suspensiones o geles de estos compuestos en la forma de gotas de líquido, jabones líquidos, pulverizadores, ungüentos o geles, mezclados con excipientes adecuados para la elaboración y uso de tales formas de aplicación. Alternativamente, los compuestos de la presente invención se pueden aplicar al ojo vía liposomas u otros sistemas de administración ocular que son bien conocidos en la técnica.

Los niveles de dosificación adecuados se pueden determinar por cualquier procedimiento adecuado conocido por aquellos con experiencia en la técnica para tratar enfermedades de los ojos. Preferentemente, el principio activo se administra en una frecuencia de 1 a 4 veces por día para administración tópica, o con menor frecuencia si se utiliza un sistema de administración de fármacos. Típicamente, una formulación ocular pretendida para aplicación tópica contiene el principio activo en un intervalo de concentración de aproximadamente 0,001 % a 10 %.

Las siguientes realizaciones representativas ilustran la invención. La invención no se restringe a los ejemplos.

Los porcentajes presentes en los siguientes ensayos y ejemplos se expresan, a menos que se indique lo contrario, en peso; las partes están en peso. Cada una de las proporciones de disolvente, las proporciones de dilución y las concentraciones informadas para soluciones líquidas/líquidas se basan en volumen.

A. Ejemplos

Abreviaturas y Acrónimos:

Ac	acetilo
aq.	acuosa (solución)
Boc	*terc*-butoxicarbonilo
br.	ancho (señal de ^{1}H RMN)
Cbz	benciloxicarbonilo
Celite®	marca registrada de la marca de tierra diatomácea de Celite Corp.
conc.	concentrado
DCI	ionización química directa (MS)
DCM	diclorometano
DMF	*N,N*-dimetilformamida
DMSO	dimetilsulfóxido
e.e.	exceso enantiomérico
EI	ionización por impacto de electrones (MS)
ent	enantiómero, enantioméricamente puro
eq.	equivalente(s)
ESI	ionización por electropulverización (MS)
Et	etilo
EtOAc	acetato de etilo
Fmoc	(9*H*-fluoren-9-ilmetoxi)carbonilo
GC/MS	espectroscopía de masas acoplada a cromatografía de gases
h	hora(s)
Hal	halógeno
RMN ^{1}H	espectroscopía de resonancia magnética nuclear de protones
HPLC	cromatografía líquida de alto rendimiento

LC/MS	espectroscopía de masas acoplada a cromatografía líquida
Me	metilo
MeOH	metanol
min	minuto(s)
MS	espectroscopía de masas
del t.	de teoría (rendimiento químico)
$PdCl_2$(dppf)	[1,1'-bis(difenilfosfino)ferrocene]dicloropaladio (II)
Ph	fenilo
rac	racémico, racemato
R_f	factor de retención TLC
RT	temperatura ambiente
R_t	tiempo de retención (HPLC)
satd.	saturado
TBAF	fluoruro de tetrabutilamonio
tBu	*terc*-butilo
terc	terciario
TFA	ácido trifluoroacético
TFAA	anhídrido del ácido trifluoroacético
THF	tetrahidrofurano
TLC	cromatografía en capa fina

Procedimientos de purificación por HPLC preparativa:

Procedimiento 1:

Dispositivo: HPLC Gilson Abimed, sistema de bomba binaria; columna: ReproSil C18, 250 mm x 30 mm; eluyente A: agua / amoníaco 1 %, eluyente B: acetonitrilo; gradiente: 0-3 min. B 10 %, 5,01-31 min. B 95 %, 31 min. 95 % B; caudal de flujo: 50 ml/min.; detección UV: 210 nm.

Procedimiento 2:

Dispositivo: HPLC Gilson Abimed, sistema de bomba binaria; columna: Kromasil-100A C18, 5 µm, 250 mm x 30 mm; eluyente A: agua / TFA 0,05-0,5 %, eluyente

B: acetonitrilo; gradiente: 0-5 min. 5 % B, 5,01-10 min. B 10 %, 10,01-20 min. B 40 %, 20,01-27 min. B 50 %, 27,01-40 min. B 60 %, 40,01-45 min. B 90 %, 45,01-60 min. B 100 %; caudal de flujo: 15-60 ml/min; detección UV: 210 nm.

Procedimiento 3:

Dispositivo: HPLC Gilson Abimed, sistema de bomba binaria; columna: Grom-Sil-120 ODS-4HE, 250 mm x 30 mm; eluyente A: agua, eluyente B: acetonitrilo; gradiente: 0-3 min. B 10 %, 3,01-35 min. B 98 %, 35,01-40 min. B 98 %; caudal de flujo: 50 ml/min; detección UV: 210 nm.

Procedimiento 4:

Dispositivo: HPLC Gilson Abimed, sistema de bomba binaria; columna: Grom-Sil-120 ODS-4HE, 250 mm x 30 mm; eluyente A: agua / amoníaco 0,5 %, eluyente B: acetonitrilo; gradiente: 0-3 min. B 10 %, 3,01-35 min. B 98 %, 35,01-40 min. B 98 %; caudal de flujo: 50 ml/min; detección UV: 210 nm.

Procedimiento 5:

Dispositivo: HPLC Gilson Abimed, sistema de bomba binaria; columna: Chromatorex C18 10 µm, 250 mm x 30 mm; eluyente A: agua, eluyente B: acetonitrilo; gradiente: 0-3 min. B 10 %, 5,01-31 min. B 90 %, 31 min. 90 % B; caudal de flujo: 50 ml/min; detección UV: 210 nm.

Procedimiento 6:

Dispositivo: HPLC Gilson Abimed, sistema de bomba binaria; columna: Chromatorex C18 10 µm, 250 mm x 30 mm; eluyente A: agua / 0.5 % TFA, eluyente B: acetonitrilo; gradiente: 0-3 min. B 10 %, 5,01-31 min. B 90 %, 31 min. 90 % B; caudal de flujo: 50 ml/min; detección UV: 210 nm.

Procedimiento 7:

Dispositivo: HPLC Gilson Abimed, sistema de bomba binaria; columna: ReproSil C18 10 µm, 250 mm x 40 mm; eluyente A: agua, eluyente B: acetonitrilo; gradiente: 0-3 min. B 10 %, 5,01-31 min. B 95 %, 31 min. 95 % B; caudal de flujo: 50 ml/min; detección UV: 210 nm.

Procedimiento 8:

Dispositivo: HPLC Gilson Abimed, sistema de bomba binaria; columna: ReproSil C18 10 µm, 250 mm x 30 mm; eluyente A: agua, eluyente B: acetonitrilo; gradiente: 0-3 min. B 10 %, 5,01-31 min. B 95 %, 31 min. 95 % B; caudal de flujo: 50 ml/min; detección UV: 210 nm.

Procedimiento 9:

Dispositivo: HPLC Gilson Abimed, sistema de bomba binaria; columna: Waters Sunfire C18 5 µm, 250 mm x 20 mm; eluyente A: agua, eluyente B: acetonitrilo; gradiente: 0 min. B 20 %, 15 min. B 60 %, 15,01-19 min. B 20 %; caudal de flujo: 25 ml/min; detección UV: 210 nm.

Procedimientos analíticos HPLC, LC/MS y GC/MS:

Procedimiento 1 (HPLC):

Instrumento: Agilent 1100 con detección DAD; columna: Agilent Zorbax Eclipse XDB-C8 4,6, 150 mm x 5 mm; eluyente A: TFA 0,01 % en agua, eluyente B: TFA 0,01 % en acetonitrilo; gradiente: 0-1 min. B 10 %, 4-5 min. B 90 %, 5,5 min. B 10 %; caudal de flujo: 2,0 ml/min; temperatura: 30 °C; detección UV: 210 nm.

Procedimiento 2 (HPLC):

Instrumento: HP 1100 con detección DAD; columna: Kromasil 100 RP-18, 60 mm x 2,1 mm, 3,5 µm; eluyente A: ácido perclórico 5 ml (70 %) / agua en L, eluyente B: acetonitrilo; gradiente: 0 min. B 2 %, 0,5 min. B 2 %, 4,5 min. B 90 %, 6,5 min. B 90 %, 6,7 min. B 2 %, 7,5 min. B 2 %; caudal de flujo: 0,75 ml/min; temperatura: 30 °C; detección UV: 210 nm.

Procedimiento 3 (HPLC):

Instrumento: HP 1100 con detección DAD; columna: Kromasil 100 RP-18, 60 mm x 2,1 mm, 3,5 µm; eluyente A: ácido perclórico 5 ml (70 %) / agua en L, eluyente B: acetonitrilo; gradiente: 0 min. B 2 %, 0,5 min. B 2 %, 4,5 min. B 90 %, 9 min. B 90 %, 9,2 min. B 2 % , 10 min. B 2 %; caudal de flujo: 0,75 ml/min; temperatura: 30 °C; detección UV: 210 nm.

Procedimiento 4 (LC/MS):

Instrumento: Micromass Platform LCZ con HPLC Agilent 1100 Series; columna: Thermo Hypersil GOLD 3µ, 20 mm x 4 mm; eluyente A: 1 L de agua + 0,5 ml de ácido fórmico 50 %, eluyente B: 1 L de acetonitrilo + 0,5 ml de ácido fórmico 50 %; gradiente: 0,0 min. A 100 % → 0,2 min. A 100 % → 2,9 min. A 30 % → 3,1 min. A 10 % → 5,5 min. A 10 %; temperatura: 50 °C; caudal de flujo: 0,8 ml/min; detección UV: 210 nm.

Procedimiento 5 (LC/MS):

Instrumento: Micromass ZQ con HPLC Waters Alliance 2795 / HP 1100; columna: Phenomenex Synergi 2,5µ MAX-RP 100A Mercury, 20 mm x 4 mm; eluyente A: 1 L de agua + 0,5 ml de ácido fórmico 50 %, eluyente B: 1 L de acetonitrilo + 0,5 ml de ácido fórmico 50 %; gradiente: 0,0 min. A 90 % → 2,5 min. A 30 % → 3,0 min. A 5 % → 4,0 min. A 5 %; caudal de flujo: 2 ml/min; temperatura: 50 °C; detección UV: 210 nm.

Procedimiento 6 (LC/MS):

Instrumento: Micromass Quattro Premier con Waters UPLC Acquity; columna: Thermo Hypersil GOLD 1,9µ, 50 mm x 1 mm; eluyente A: 1 L de agua + 0,5 ml de ácido fórmico 50 %, eluyente B: 1 L de acetonitrilo + 0,5 ml de ácido fórmico 50 %; gradiente: 0,0 min. A 90 % → 0,1 min. A 90 % → 1,5 min. A 10 % → 2,2 min. A 10 %; temperatura: 50 °C; caudal de flujo: 0,33 ml/min; detección UV: 210 nm.

Procedimiento 7 (LC/MS):

Instrumento: Micromass ZQ con HPLC Waters Alliance 2795; columna: Phenomenex Synergi 2,5µ MAX-RP 100A Mercury, 20 mm x 4 mm; eluyente A: 1 L de agua + 0,5 ml de ácido fórmico 50 %, eluyente B: 1 L de acetonitrilo + 0,5 ml de ácido fórmico 50 %; gradiente: 0,0 min. A 90 % → 0,1 min. A 90 % → 3,0 min. A 5 % → 4,0 min. A 5 % → 4,01 min. A 90 %; caudal de flujo: 2 ml/min; temperatura: 50 °C; detección UV: 210 nm.

Procedimiento 8 (GC/MS):

Instrumento: Micromass GCT, GC6890; columna: Restek RTX-35, 15 m x 200 µm x 0,33 µm; flujo constante con helio: 0,88 ml/min; horno: 70 °C; entrada: 250 °C; gradiente: 70 °C, 30 °C/min. → 310 °C (mantener durante 3 min).

Procedimiento 9 (HPLC):

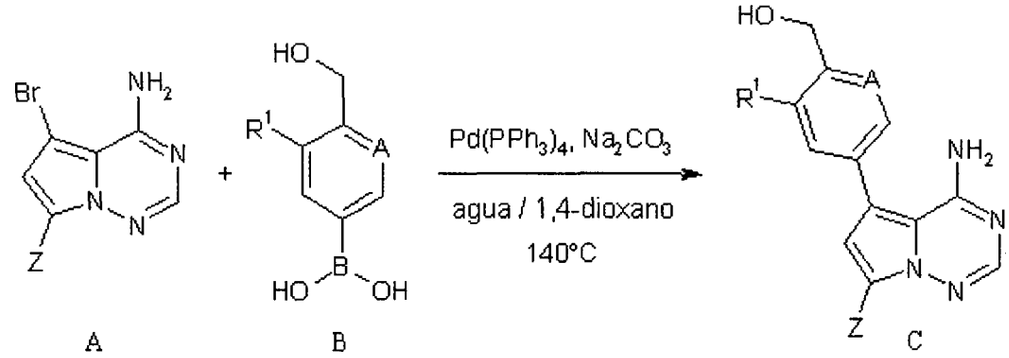
Instrumento: Agilent 1100 con detección DAD; columna: Merck Chromolith Speed ROD, 150 mm x 5 mm; eluyente A: ácido fórmico 0,01 % en agua, eluyente B: acetonitrilo; gradiente: 0 min. B 5 %, 2,5 min. B 95 %, 3 min. B 95 %; caudal de flujo: 5,0 ml/min; temperatura: 40 °C; detección UV: 210 nm.

Procedimiento 10 (LC/MS):

Instrumento: Sistema UPLC de Waters Acquity SQD; columna: Waters Acquity UPLC HSS T3 1,8µ, 50 mm x 1 mm; eluyente A: 1 L de agua + 0,25 ml de ácido fórmico 99 %, eluyente B: 1 L de acetonitrilo + 0,25 ml de ácido fórmico 99 %; gradiente: 0,0 min. A 90 % → 1,2 min. A 5 % → 2,0 min. A 5 %; temperatura: 50 °C; caudal de flujo: 0,40 ml/min; detección UV: 208-400 nm.

Procedimiento de síntesis general 1:

Acoplamiento de Suzuki de derivados de 5-bromopirrolo[2,1-f][1,2,4]triazina con ácidos o ésteres arilborónicos:

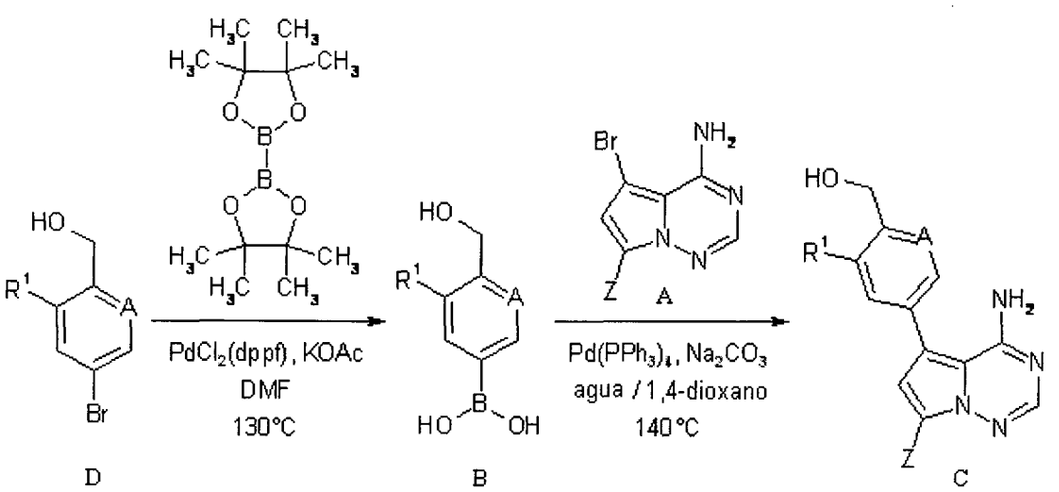


Una 5-bromopirrolo[2,1-f][1,2,4]triazina A (aproximadamente 0,5 mmol), ácido arilborónico B (1,2 equivalentes) o un éster borónico correspondiente, *por ej.*, un boronato de dimetilo o boronato de pinacolato, y tetrakis(trifenilfosfina)paladio (0) (0,1 equivalentes) se disuelven en una mezcla de 1,4-dioxano (aproximadamente 4,0 ml) y solución acuosa de carbonato de sodio 2 M (1,5 ml) en un vial reactor de

microondas. Al recipiente de reacción se le coloca una tapa engastada, y la mezcla se calienta a 140 °C durante 1 h en un dispositivo de microondas de modo único. Tras el enfriamiento, la mezcla de reacción se filtra sobre un lecho de Celite que se enjuaga con 1,4-dioxano para eluir todo el material orgánico. El filtrado combinado se evapora a sequedad bajo presión reducida, y el residuo se purifica por HPLC preparativa para dar el compuesto C diana.

Procedimiento de síntesis general 2:

Borilación de bromuros de arilo y acoplamiento de Suzuki subsiguiente con derivados de 5-bromopirrolo[2,1-f][1,2,4]triazina sin aislamiento del ácido o éster arilborónico intermedio:



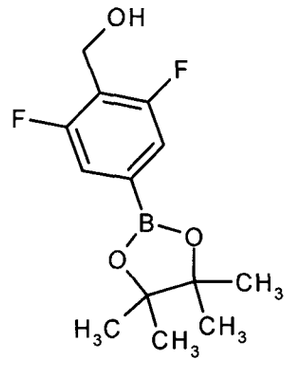
Se disuelve bromuro de arilo D (aproximadamente 0,5 mmol) en DMF (3 ml) en un recipiente reactor de microondas, se burbujea argón a través de la solución durante 5 min., y se añaden complejo de [1,1'-bis(difenilfosfino)ferroceno]dicloropaladio(II)-diclorometano (0,1 equivalentes), acetato de potasio (3 equivalentes) y bis(pinacolato)diboro (1,2 equivalentes). Al recipiente se le coloca una tapa engastada, y la mezcla se calienta a 130 °C durante 60 min. en un dispositivo de microondas de modo único. Después, la suspensión se filtra, el filtrado se transfiere a otro vial de procedimiento de microondas, y se añaden tetrakis(trifenilfosfina)paladio (0) (0,1 equivalentes),

solución acuosa de carbonato de sodio 2 M (4 equivalentes) y la 5-bromopirrolo-[2,1-f][1,2,4]triazina A (1 equivalente). Al vial se le coloca una tapa engastada, y la mezcla se calienta a 140 °C durante 1 h en un dispositivo de microondas de modo único. La mezcla de reacción bruta así obtenida se inyecta directamente sobre una columna de HPLC preparativa para la separación y purificación del compuesto C diana.

Materiales de Inicio e Intermedios:

Intermedio 1A

[2,6-Difluoro-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil]metanol

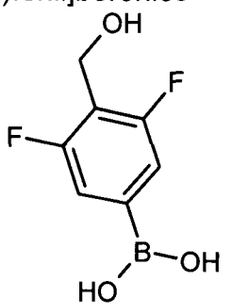


Se disolvió (4-bromo-2,6-difluorofenil)metanol (1,03 g, 4,62 mmol) en 1,4-dioxano seco (10 ml). Se burbujeó argón a través de la solución, después se añadieron complejo de [1,1'-bis(difenilfosfino)ferroceno]dicloropaladio-diclorometano (302 mg, 0,37 mmol, 0,08 eq.), acetato de potasio anhidro (907 mg, 9,24 mmol, 2 eq.) y bis(pinacolato)diboro (1,23 g, 4,85 mmol, 1,05 eq.), y la mezcla se calentó a 130 °C durante 1 h en un dispositivo de microondas de modo único. Tras el enfriamiento, la mezcla se filtró, y el disolvente se eliminó bajo presión reducida. Se añadió ciclohexano (200 ml) al residuo, y la mezcla se agitó vigorosamente durante 30 min. Después, el material no disuelto se eliminó por filtración, el ciclohexano se destiló, y el residuo se purificó por cromatografía flash sobre gel de sílice (gradiente de diclorometano/acetonitrilo). Las fracciones que contenían el producto se combinaron y evaporaron. El compuesto del título cristalizó espontáneamente como un sólido parduzco: 790 mg (63 % del t.).

GC-MS (procedimiento 8): R_t = 5,36 min; MS (EI): *m/z* (%) = 270,3 (15) $[M]^+$.

Intermedio 2A

Ácido [3,5-difluoro-4-(hidroximetil)fenil]borónico

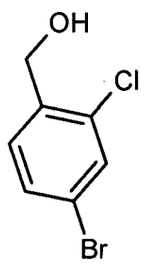


Se disolvió ácido [4-({[*terc*-butil(dimetil)silil]oxi}metil)-3,5-difluorofenil]borónico (19,3 g, 63,9 mmol; material bruto, preparado por el procedimiento de Hattori, *Bioorg. Med. Chem.* **2006**, *14*, 3258-3262) en 400 ml de ácido acético acuoso (66 %) y se agitó a 40 °C durante 5 h. Después, la solución se evaporó bajo presión reducida, y el residuo se purificó por cromatografía flash sobre gel de sílice (elución de gradiente de metanol en diclorometano 0 % a 2 %) para dar 3,46 g (25 % del t., Pureza de LC-MS 87 %) del compuesto del título.

LC-MS (procedimiento 7): R_t = 0,50 min; MS (ESIpos): *m/z* (%) = 171,2 (100) $[M-OH]^+$, MS (ESIneg): *m/z* (%) = 187,3 (100) $[M-H]^-$.

Intermedio 3A

(4-Bromo-2-clorofenil)metanol

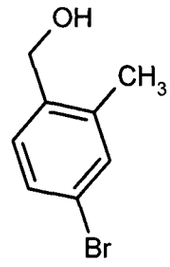


El compuesto del título se preparó de acuerdo con el procedimiento descrito en el documento WO 2004/074270-A2 [Ejemplo A(147), etapa 1].

RMN ^{1}H (400 MHz, $CDCl_3$): δ (ppm) = 2,00 (br, 1H), 4,74 (s, 2H), 7,38 (d, 1H), 7,43 (dd, 1H), 7,53 (d, 1H).

Intermedio 4A

(4-Bromo-2-metilfenil)metanol

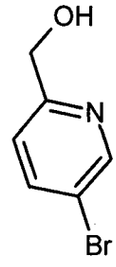


El compuesto del título se preparó de acuerdo con el procedimiento descrito en EP 1 544 208-A1 (Ejemplo de Referencia 14).

RMN ^{1}H (400 MHz, $CDCl_3$): δ (ppm) = 1,62 (t, 3H), 2,32 (s, 3H), 4,64 (d, 2H), 7,23 (d, 1H), 7,32 (s, 1H), 7,33 (d, 1H).

Intermedio 5A

(5-Bromopiridin-2-il)metanol

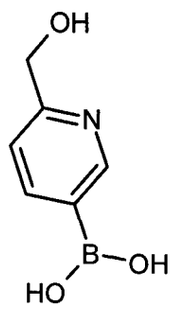


Se disolvió 5-bromopiridin-2-carboxilato de metilo (2,00 g, 9,27 mmol) en etanol (20,0 ml). Se añadió borohidruro de sodio (1,05 g, 27,8 mmol) a 0 °C, y la mezcla se agitó a temperatura ambiente durante 18 h. Después, la mezcla se concentró bajo presión reducida, se inactivó con ácido clorhídrico 1N, se neutralizó con carbonato de potasio sólido y se extrajo con diclorometano. La capa orgánica se secó sobre sulfato de magnesio y se evaporó para dar 1,57 g (90 % del t.) del compuesto del título.

LC-MS (procedimiento 6): R_t = 0,56 min; MS (ESIpos): *m/z* (%) = 188,0 (100) $[M+H]^+$.

Intermedio 6A

Ácido [6-(hidroximetil)piridin-3-il]borónico

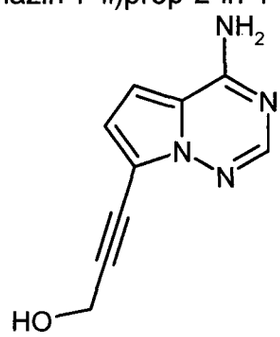


A una solución del Intermedio 5A (1,50 g, 7,98 mmol) y bis(pinacolato)diboro (2,23 g, 8,28 mmol) en DMF desgasificado (120 ml) se añadió bajo una atmósfera de argón cloruro de 1,1'-bis(difenilfosfino)ferroceno-paladio (II) (292 mg, 0,40 mmol) y acetato de potasio (2,35 g, 23,9 mmol). La mezcla se calentó a 80°C durante 18 h y después se enfrió a temperatura ambiente. La suspensión se filtró, y el residuo se lavó con dioxano. Los filtrados combinados se concentraron bajo presión reducida, y el residuo aceitoso se tomó en 50 ml de acetato de etilo y 50 ml de ciclohexano y se dejó reposar a temperatura ambiente hasta el día siguiente. El precipitado resultante se recolectó por filtración y se descartó. El filtrado se evaporó, y el residuo se disolvió nuevamente en 100 ml de acetato de etilo y se extrajo dos veces con 50 ml de agua. La capa acuosa se concentró para dar 690 mg (56 % del t.) del compuesto del título que se utilizó sin purificación adicional.

LC-MS (procedimiento 6): R_t = 0,18 min; MS (ESIpos): *m/z* (%) = 154,0 (100) $[M+H]^+$.

Intermedio 7A

3-(4-Aminopirrolo[2,1-f][1,2,4]triazin-7-il)prop-2-in-1-ol



El material de inicio 7-bromopirrolo[2,1-f][1,2,4]triazin-4-amina se sintetizó de acuerdo con el procedimiento descrito en el documento WO 2007/056170-A2 (Intermedio B).

Se cargaron 7-bromopirrolo[2,1-f][1,2,4]triazin-4-amina (1,0 g, 4,69 mmol), yoduro de cobre (I) (89 mg, 0,47 mmol, 0,1 eq.) y tetrakis(trifenilfosfina)paladio (0) (542 mg, 0,47 mmol, 0,1 eq.) en un vial reactor de microondas y se evacuaron durante 1 h. Después, el recipiente se ventiló con argón, se añadieron pirrolidina (15 ml) y 2-propin-1-ol (2,63 g, 47 mmol, 10 eq.), y al recipiente se le colocó una tapa engastada y se calentó a 85 °C durante 120 min. en un dispositivo de microondas de modo único. Tras el enfriamiento, la mezcla de reacción se vertió en 120 ml de solución concentrada acuosa de cloruro de amonio que se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se secaron sobre sulfato de sodio anhidro y se evaporaron, y el residuo se purificó por cromatografía flash (columna de sílice de Biotage, acetato de etilo). El producto resultante (222 mg) surgió puro por LC-MS (procedimiento 6) y se utilizó para transformaciones adicionales.

HPLC (procedimiento 2): R_t = 2,59 min;

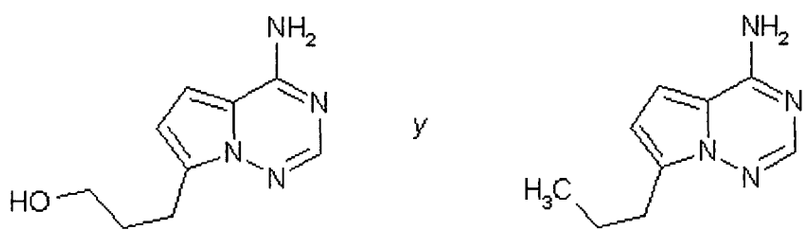
LC-MS (procedimiento 6): R_t = 0,28 min; MS (ESIpos): *m/z* (%) = 189,2 (100) $[M+H]^+$.

Intermedio 8A e Intermedio 9A

3-(4-Aminopirrolo[2,1-f][1,2,4]triazin-7-il)propan-1-ol

y

7-Propilpirrolo[2,1-f][1,2,4]triazin-4-amina



El Intermedio 7A (444 mg, 2,36 mmol) se disolvió en ácido acético (18 ml) bajo una atmósfera de argón. Se añadió óxido de platino (IV) (40 mg, 0,18 mmol, 0,08 eq.), y la mezcla se agitó vigorosamente durante 3 h a temperatura ambiente bajo una atmósfera de hidrógeno a presión de ambiente. Luego, el catalizador se eliminó por filtración, el disolvente se destiló, y el residuo se sometió a cromatografía flash (columna de sílice de Biotage, gradiente de ciclohexano/acetato de etilo). Los Intermedios 8A (185 mg, 41 % del t.) y 9A (170 mg, 41 % del t.) se obtuvieron en dos fracciones cromatográficas diferentes:

Intermedio 8A:

HPLC (procedimiento 2): R_t = 2,68 min;

LC-MS (procedimiento 4): R_t = 0,83 min; MS (ESIpos): *m/z* (%) = 193,1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 191,1 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,80 (m, 2H), 2,86 (t, *J* = 7,7 Hz, 2H), 3,45 (m, 2H), 4,49 (t, *J* = 5,1 Hz, 1H), 6,41 (d, *J* = 4,2 Hz, 1H), 6,69 (d, *J* = 4,2 Hz, 1H), 7,50 (br, s, 2H), 7,78 (s, 1H).

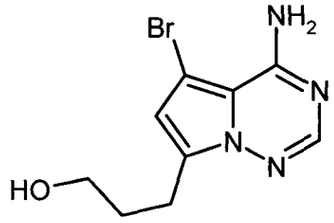
Intermedio 9A:

HPLC (procedimiento 1): R_t = 3,22 min;

LC-MS (procedimiento 4): R_t = 1,23 min; MS (ESIpos): *m/z* (%) = 177,1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 175,2 (30) $[M-H]^-$.

Intermedio 10A

3-(4-Amino-5-bromopirrolo[2,1-f][1,2,4]triazin-7-il)propan-1-ol



El Intermedio 8A (105 mg, 0,55 mmol) se disolvió en THF (8,75 ml) y se enfrió a -20 °C. Se añadió 1,3-dibromo-5,5-dimetilhidantoína (78,1 mg, 0,5 eq.), y la mezcla se agitó a -20 °C durante 1 h. Después, la reacción se inactivó con 0,5 ml de solución concentrada acuosa de ditionita de sodio, se calentó a temperatura

ambiente y se particionó entre acetato de etilo y agua. La fase orgánica se secó sobre sulfato de sodio anhidro, y el disolvente se destiló. Rendimiento: 145 mg (98 % del t.).

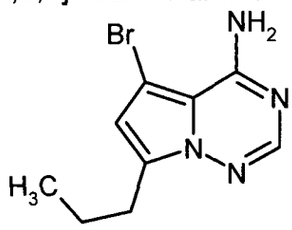
HPLC (procedimiento 1): R_t = 2,96 min; HPLC (procedimiento 2): R_t = 2,95 min;

LC-MS (procedimiento 5): R_t = 1,03 min; MS (ESIpos): *m/z* (%) = 271,0 (100) y 273,0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 269,0 (99) y 271,0 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,75 (m, 2H), 2,83 (t, *J* = 8,1 Hz, 2H), 3,43 (m, 2H), 4,50 (t, *J* = 5,4 Hz, 1H), 6,62 (s, 1H), 7,81 (s, 1H).

Intermedio 11A

5-Bromo-7-Propilpirrolo[2,1-f][1,2,4]triazin-4-amina



El Intermedio 9A (110 mg, 0,62 mmol) se disolvió en THF (4,44 ml) y se enfrió a -20 °C. Se añadió 1,3-dibromo-5,5-dimetilhidantoína (89 mg, 0,5 eq.), y la mezcla se agitó a -20 °C durante 1 h. Después, la reacción se inactivó con 0,5 ml de solución concentrada acuosa de ditionita de sodio, se calentó a temperatura ambiente y se particionó entre acetato de etilo y agua. La fase orgánica se secó sobre sulfato de sodio anhidro, y el disolvente se destiló. Rendimiento: 154 mg (85 % puro, 82 % del t.).

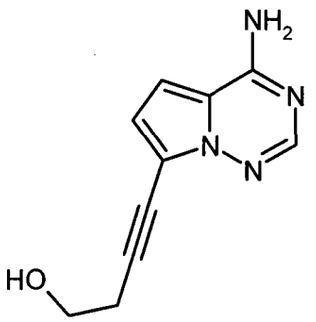
HPLC (procedimiento 1): R_t = 3,78 min;

LC-MS (procedimiento 7): R_t = 1,55 min; MS (ESIpos): *m/z* (%) = 255,0 (99) y 257,2 (100) $[M+H]^+$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 0,91 (t, *J* = 7,3 Hz, 3H), 1,65 (m, 2H), 2,79 (t, *J* = 7,6 Hz, 2H), 3,31 (s, 2H), 6,63 (s, 1H), 7,95 (s, 1H).

Intermedio 12A

4-(4-Aminopirrolo[2,1-f][1,2,4]triazin-7-il)but-3-in-1-ol



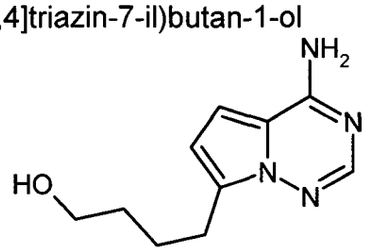
Se cargaron 7-bromopirrolo[2,1-f][1,2,4]triazin-4-amina (1,0 g, 4,69 mmol), yoduro de cobre (I) (89 mg, 0,47 mmol, 0,1 eq.) y tetrakis(trifenilfosfina)paladio (0) (542 mg, 0,47 mmol, 0,1 eq.) en un vial reactor de microondas y se evacuaron durante 1 h. Después, el recipiente se ventiló con argón, se añadieron pirrolidina (15 ml) y 3-butin-1-ol (3,36 g, 47 mmol, 10 eq.), y al recipiente se le colocó una tapa engastada y se calentó a 85 °C durante 120 min. en un dispositivo de microondas de modo único. Tras el enfriamiento, la mezcla de reacción se vertió en 120 ml de solución concentrada acuosa de cloruro de amonio y se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se secaron sobre sulfato de sodio anhidro y se evaporaron, y el residuo se purificó por cromatografía flash (columna de sílice de Biotage, acetato de etilo). El producto resultante (735 mg) eran lo suficientemente puro (66 % por HPLC) para transformaciones adicionales.

HPLC (procedimiento 2): R_t = 2,77 min;

LC-MS (procedimiento 4): R_t = 0,96 min; MS (ESIpos): *m/z* (%) = 203,1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 201,1 (100) $[M-H]^-$.

Intermedio 13A

4-(4-Aminopirrolo[2,1-f][1,2,4]triazin-7-il)butan-1-ol



El intermedio 12A (607 mg, 3,00 mmol) se disolvió en ácido acético (64 ml), y se añadió óxido de platino (IV) (50 mg, 0,22 mmol, 0,07 eq.). La mezcla se agitó bajo una atmósfera de hidrógeno a presión ambiente durante 15 horas. Luego, el

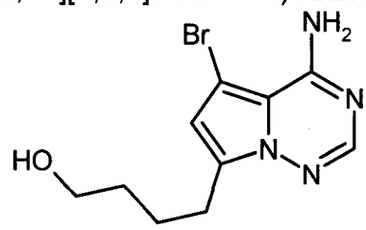
catalizador se eliminó por filtración, el filtrado se evaporó a presión reducida, y el residuo se purificó por cromatografía flash (columna de sílice de Biotage, acetato de etilo). Rendimiento: 350 mg (57 % del t.).

HPLC (procedimiento 2): R_t = 2,92 min;

LC-MS (procedimiento 4): R_t = 0,94 min; MS (ESIpos): *m/z* (%) = 207,1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 205,3 (100) $[M-H]^-$.

Intermedio 14A

4-(4-Amino-5-bromopirrolo[2,1-f][1,2,4]triazin-7-il)butan-1-ol



El Intermedio 13A (330 mg, 1,60 mmol) se disolvió en THF (26 ml) a -20 °C, y se añadió 1,3-dibromo-5,5-dimetilhidantoína (229 mg, 0,80 mmol). La mezcla se agitó a -20 °C durante 1 h. Después, la reacción se inactivó con solución concentrada acuosa de sulfito de sodio (0,5 ml). Se añadió acetato de etilo, se separó la capa acuosa, y la capa orgánica se secó sobre sulfato de sodio y se evaporó. El producto bruto se purificó subsiguientemente por HPLC preparativa (procedimiento 2) para dar 175 mg (84 % del t.) del compuesto del título.

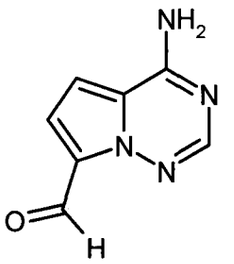
HPLC (procedimiento 1): R_t = 3,13 min;

LC-MS (procedimiento 5): R_t = 1,23 min; MS (ESIpos): *m/z* (%) = 285,0 (98) y 287,0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 283,0 (100) y 285,0 (98) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,39-1,48 (m, 2H), 1,60-1,69 (m, 2H), 3,31 (t, *J* = 7,3 Hz, 2H), 3,40 (m, 2H), 4,46 (br, s, 1H), 6,61 (s, 1H), 7,82 (s, 1H).

Intermedio 15A

4-Aminopirrolo[2,1-f][1,2,4]triazin-7-carbaldehído

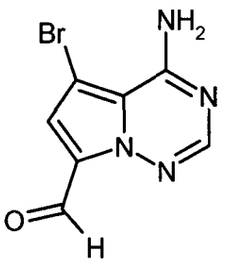


El material de inicio pirrolo[2,1-f][1,2,4]triazin-4-amina se sintetizó de acuerdo con el procedimiento descrito en el documento WO 2007/056170-A2 (Intermedio A).

Se disolvió pirrolo[2,1-f][1,2,4]triazin-4-amina (20,5 g, 152 mmol) en 150 ml de DMF. Bajo enfriamiento con hielo, se añadió cloruro de fosforilo (31,3 ml, 336 mmol) gota a gota a una velocidad tal que la temperatura interna no se elevara a más de 30 °C. Después, la mezcla se calentó durante 2 días a 50 °C. Tras el enfriamiento, se añadió otra porción de cloruro de fosforilo (14,2 ml, 152 mmol), y la agitación continuó durante otras 24 h a 50 °C. Tras el enfriamiento, la partida de reacción se vertió lentamente en una mezcla de 2,0 L de solución saturada acuosa de bicarbonato de sodio y 2,0 L de acetato de etilo. Se añadió bicarbonato de sodio sólido hasta que se detuviera la evolución del gas. Las capas se separaron, la capa acuosa se extrajo con 0,5 L de acetato de etilo, y las fases orgánicas combinadas se secaron sobre sulfato de sodio y concentraron. El residuo se suspendió en 100 ml de éter de diisopropilo, se agitó a temperatura ambiente durante 10 min. y después se filtró. El residuo seco se agitó en ácido clorhídrico 6 N (500 ml) durante 1 h a 50 °C y después se vertió en una mezcla de hielo/agua (1000 ml). La mezcla se neutralizó cuidadosamente con bicarbonato de sodio sólido, se agitó durante 30 min. a temperatura ambiente y después se filtró nuevamente. El residuo se lavó con agua y ligroína para dar 20,6 g (83 % del t.) de cristales blancos que se utilizaron en la próxima etapa sin purificación adicional.

Intermedio 16A

4-Amino-5-bromopirrolo[2,1-f][1,2,4]triazin-7-carbaldehído

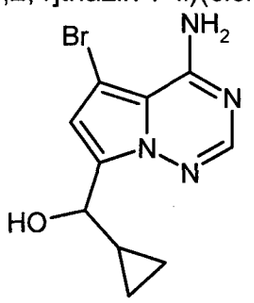


El Intermedio 15A (20,6 g, 127 mmol) se disolvió en 525 ml de DMF. A 0 °C, se añadió 1,3-dibromo-5,5-dimetilhidantoína (21,8 g, 76,2 mmol), y la mezcla se agitó durante 1 h bajo enfriamiento con hielo y durante 2 h adicionales a temperatura ambiente. La suspensión resultante se filtró, y el residuo se lavó con DMF y éter de dietilo. El filtrado se descartó, y los pocos cristales solubles restantes se secaron para dar 20,0 g (65 % del t., 80 % de pureza de HPLC) del compuesto del título. Este material se utilizó sin purificación adicional.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 7,42 (s, 1H), 8,12 (s, 1H), 10,22 (s, 1H).

Intermedio 17A

(4-Amino-5-bromopirrolo[2,1-f][1,2,4]triazin-7-il)(ciclopropil)metanol



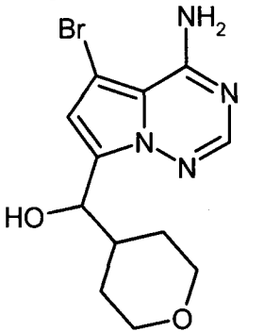
El Intermedio 16A (500 mg, 1,66 mmol) se suspendió en THF seco (30 ml). A 0 °C, se añadió una solución 0,5 M de bromuro de ciclopropil magnesio en éter de dietilo (10 ml, 5,0 mmol). La mezcla se agitó a temperatura ambiente durante 1 h. Después, se añadió otra porción de la solución de Grignard (6,6 ml, 3,3 mmol). Tras la agitación adicional durante 30 min. a temperatura ambiente, la reacción se inactivó con solución saturada acuosa de cloruro de amonio y se extrajo con acetato de etilo (2 x 20 ml). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de magnesio y se concentraron. El residuo se purificó por HPLC preparativa (procedimiento 4). Rendimiento: 0,14 g (29 % del t.).

LC-MS (procedimiento 6): R_t = 0,75 min; MS (ESIpos): *m/z* (%) = 283,0 (100) $[M+H]^+$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 0,35 (m, 3H), 0,45 (m, 1H), 1,28 (m, 1H), 4,62 (t, 1H), 5,26 (d, 1H), 6,75 (s, 1H), 7,84 (s, 1H).

Intermedio 18A

(4-Amino-5-bromopirrolo[2,1-f][1,2,4]triazin-7-il)(tetrahidro-2*H*-piran-4-il)metanol

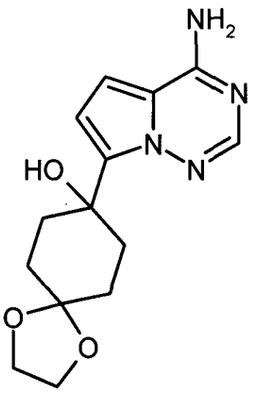


En un matraz de 3 cuellos de 50 ml equipado con un condensador, un termómetro y un embudo de goteo, que se purgó con argón, se preparó un reactivo de Grignard a partir de virutas de magnesio (484 mg, 19,9 mmol) y 4-clorotetrahidropirano (2,4 g, 19,9 mmol) en THF seco (14 ml). A esta solución se añadió a 0 °C una suspensión del Intermedio 16A (1,2 g, 3,98 mmol) en THF (20 ml), y la mezcla de reacción se dejó agitar durante 1 h a temperatura ambiente. Después, esta se inactivó con una solución saturada acuosa de cloruro de amonio y se extrajo con acetato de etilo (2 x 50 ml). La capa orgánica se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró. El residuo se purificó por HPLC preparativa (procedimiento 3). Rendimiento: 0,5 g (38 % del t.).

LC-MS (procedimiento 6): R_t = 0,66 min; MS (ESIpos): *m/z* (%) = 327,0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 325,1 (100) $[M-H]^-$.

Intermedio 19A

8-(4-Aminopirrolo[2,1-f][1,2,4]triazin-7-il)-1,4-dioxaspiro[4.5]decan-8-ol



El material de inicio 7-bromopirrolo[2,1-f][1,2,4]triazin-4-amina se sintetizó de acuerdo con el procedimiento descrito en el documento WO 2007/056170-A2 (Intermedio B).

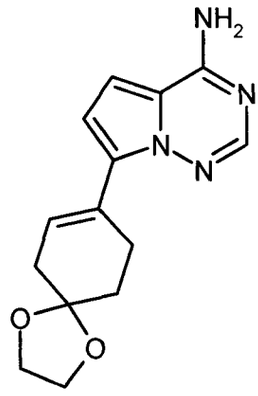
Se disolvió 7-bromopirrolo[2,1-f][1,2,4]triazin-4-amina (9,20 g, 35,41 mmol) en THF (105 ml) bajo argón a temperatura ambiente, se añadió clorotrimetilsilano (9,08 ml, 7,77 g, 70,82 mmol, 2 eq.), y la mezcla se agitó a temperatura ambiente durante 3 h. Después, esta se enfrió a 0 °C, y se añadió cloruro de 2-propil magnesio (74 ml de una solución 2,0 M en THF, 149 mmol, 4.2 eq.). La mezcla se agitó durante 3 h adicionales mientras se calentaba a temperatura ambiente. Después, se añadió 1,4-dioxaspiro[4.5]decan-8-ona (8,38 g, 53,12 mmol, 1,5 eq.), y la agitación continuó durante otras 16 h. La reacción se inactivó con una mezcla 1:1 de solución concentrada acuosa de cloruro de amonio y hielo hasta que el valor del pH alcanzara 6-7. La mezcla se extrajo con dos porciones de acetato de etilo, y los extractos orgánicos combinados se secaron sobre carbonato de sodio anhidro y se concentró a sequedad. El compuesto del título se cristalizó a partir de éter de dietilo. Rendimiento: 6,05 g (58 % del t.).

HPLC (procedimiento 1): R_t = 2,89 min;

LC-MS (procedimiento 6): R_t = 0,38 min; MS (ESIpos): *m/z* (%) = 291,2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 289,4 (100) $[M-H]^-$.

Intermedio 20A

7-(1,4-Dioxaspiro[4.5]dec-7-en-8-il)pirrolo[2,1-f][1,2,4]triazin-4-amina



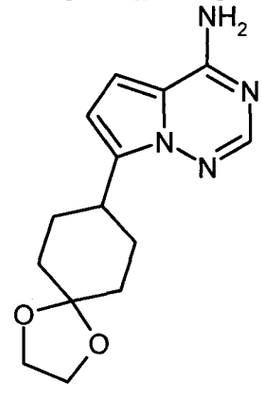
El Intermedio 19A (2,81 g, 60 % de pureza, 5,82 mmol) se disolvió en piridina (18 ml) a 0 °C. Se añadió anhídrido trifluoroacético (2,46 ml, 3,66 g, 17,45 mmol, 3 eq.) lentamente, y la mezcla de reacción se agitó a temperatura ambiente durante 16 h. El disolvente se destiló, y el residuo se particionó entre agua y acetato de etilo. El extracto orgánico se secó sobre sulfato de sodio y se evaporó. El residuo se trituró con éter de dietilo a 0 °C para dar 2,95 g (92 % puro por HPLC, 99 % del t.) del compuesto del título.

HPLC (procedimiento 1): R_t = 4,55 min;

LC-MS (procedimiento 5): R_t = 2,28 min; MS (ESIpos): *m/z* (%) = 369,1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 367,1 (100) $[M-H]^-$.

Intermedio 21A

7-(1,4-Dioxaspiro[4.5]dec-8-il)pirrolo[2,1-f][1,2,4]triazin-4-amina



El Intermedio 20A (2,95 g, 10,8 mmol) se disolvió en metanol (1,07 L) bajo argón. Se añadió paladio sobre carbón (10 %, 400 mg), y la mezcla se agitó vigorosamente durante 24 horas bajo una atmósfera de hidrógeno a presión ambiente y temperatura ambiente. El catalizador se eliminó por filtración, y el

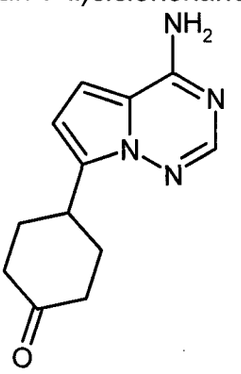
disolvente se destiló a presión reducida para dar 2,11 g (71 % del t.) del compuesto del título.

HPLC (procedimiento 1): R_t = 3,14 min;

LC-MS (procedimiento 6): R_t = 0,68 min; MS (ESIpos): *m/z* (%) = 275,3 (100) $[M+H]^+$.

Intermedio 22A

4-(4-Aminopirrolo[2,1-f][1,2,4]triazin-7-il)ciclohexanona



El Intermedio 21A (2,11 g, 7,69 mmol) se disolvió en una mezcla de ácido clorhídrico 1 M (23 ml) y metanol (6,80 ml) a 0 °C y se agitó bajo enfriamiento con hielo durante 3 h. Después, el valor del pH se ajustó a 6-7 por la adición de una solución concentrada acuosa de bicarbonato de sodio. La mezcla se extrajo con tres porciones de diclorometano, y los extractos orgánicos combinados se secaron sobre sulfato de sodio anhidro, se filtraron y se evaporaron. El residuo (923 mg, 52 % del t.) se utilizó sin purificación adicional en la próxima etapa sintética.

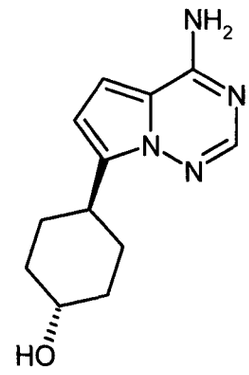
HPLC (procedimiento 2): R_t = 3,06 min;

LC-MS (procedimiento 4): R_t = 1,02 min; MS (ESIpos): *m/z* (%) = 231,1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 229,2 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,86 (ddd, 2H), 2,25-2,36 (m, 4H), 2,59 (ddd, 2H), 3,59 (m, 1H), 6,45 (d, 1H), 6,82 (d, 1H), 7,60 (br, s, 1H), 7,82 (s, 1H).

Intermedio 23A

trans-4-(4-Aminopirrolo[2,1-f][1,2,4]triazin-7-il)ciclohexanol



El Intermedio 22A (452 mg, 1,96 mmol) se disolvió en THF (15 ml), y la solución se enfrió a 0 °C. Se añadió una solución de hidruro de litio y aluminio (1 M en THF, 2,94 ml, 2,94 mmol) gota a gota. Subsiguientemente, la solución se agitó a 0 °C durante 10 min. y después se inactivó por la adición de una solución concentrada acuosa de cloruro de amonio. La mezcla se extrajo con 3 porciones de diclorometano, y los extractos orgánicos combinados se secaron sobre sulfato de sodio anhidro, se filtraron y se evaporaron. El residuo (360 mg, 77 % de pureza, 61 % del t.) se utilizó en la próxima etapa sintética sin purificación adicional.

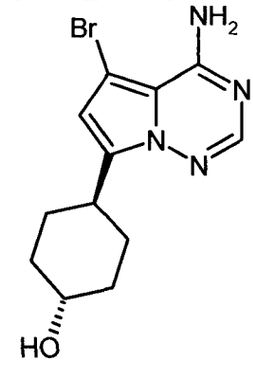
HPLC (procedimiento 1): R_t = 2.62 min;

LC-MS (procedimiento 6): R_t = 0,29 min; MS (ESIpos): *m/z* (%) = 233,2 (100) $[M+H]^+$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,30 (m, 2H), 1,42 (m, 2H), 1,91 (m, 2H), 1,99 (m, 2H), 2,97 (tt, 1H), 3,45 (m, 1H), 4,60 (d, 1H), 6,39 (d, 1H), 6,79 (d, 1H), 7,53 (br, s, 2H), 7,80 (s, 1H).

Intermedio 24A

trans-4-(4-Amino-5-bromopirrolo[2,1-f][1,2,4]triazin-7-il)ciclohexanol



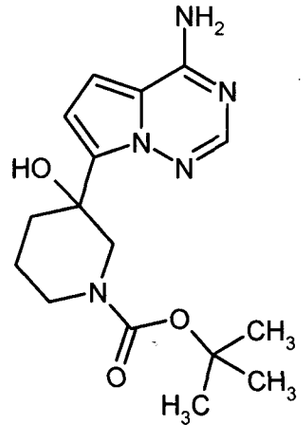
El Intermedio 23A (360 mg, 85 % de pureza, 1,19 mmol) se disolvió en THF (8 ml) a -20 °C, y se añadió 1,3-dibromo-5,5-dimetilhidantoína (188 mg, 0,66 mmol, 0,55 eq.). La mezcla se agitó a -20 °C durante 1 h, después se añadieron 0,5 ml de solución concentrada acuosa de ditionita de sodio, y la mezcla se extrajo con acetato de etilo. El extracto orgánico se secó sobre sulfato de sodio anhidro, se filtró y se evaporó. El producto bruto (463 mg, 66 % de pureza, 83 % del t.) se utilizó en la próxima etapa sintética sin purificación adicional.

HPLC (procedimiento 1): R_t = 3,22 min;

LC-MS (procedimiento 7): R_t = 1,03 min; MS (ESIpos): *m/z* (%) = 311,2 y 313,0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 309,2 (50) y 311,2 (40) $[M-H]^-$.

Intermedio 25A

3-(4-Aminopirrolo[2,1-f][1,2,4]triazin-7-il)-3-hidroxipiperidin-1-carboxilato de *terc*-butilo



El material de inicio 7-bromopirrolo[2,1-f][1,2,4]triazin-4-amina se sintetizó de acuerdo con el procedimiento descrito en el documento WO 2007/056170-A2 (Intermedio B).

Se disolvió 7-bromopirrolo[2,1-f][1,2,4]triazin-4-amina (17,29 g, 81 mmol) en THF (214 ml) bajo argón a temperatura ambiente, se añadió clorotrimetilsilano (20,60 ml, 17,63 g, 162 mmol, 2 eq.), y la mezcla se agitó a temperatura ambiente durante 3 h. Después, esta se enfrió a 0 °C, y se añadió cloruro de 2-propil magnesio (170 ml de una solución 2,0 M en THF, 340 mmol, 4.2 eq.). La mezcla se agitó durante 3 h adicionales mientras se calentaba a temperatura ambiente.

Después, se añadió 3-oxopiperidin-1-carboxilato de *terc*-butilo (25,00 g, 121 mmol, 1,5 eq.), y la agitación continuó durante otras 16 h. La reacción se inactivó con una mezcla 1:1 de solución concentrada acuosa de cloruro de amonio y hielo hasta que el valor del pH alcanzara 6-7. La mezcla se extrajo con dos porciones de acetato de etilo, y los extractos orgánicos combinados se secaron sobre carbonato de sodio anhidro y se concentraron a sequedad. El compuesto del título cristalizó tras la trituración del residuo con éter de dietilo (50 ml). Los cristales se lavaron con éter de dietilo y se secaron para dar 17,20 g (64 % del t.).

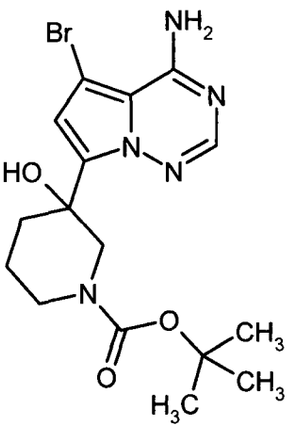
HPLC (procedimiento 2): R_t = 3,53 min;

LC-MS (procedimiento 5): R_t = 1,36 min; MS (ESIpos): *m/z* (%) = 334,1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 332,0 (100) $[M-H]^-$,

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,19-1,43 (m, 9H), 1,72-1,88 (m, 2H), 2,38-2,46 (m, 1H), 3,02-3,20 (m, 1H), 3,44-3,96 (m, 4H), 6,58 (d, 1H), 6,81 (d, 1H), 7,82 (s, 1H).

Intermedio 26A

3-(4-amino-5-bromopirrolo[2,1-f][1,2,4]triazin-7-il)-3-hidroxipiperidin-1-carboxilato de *rac-terc*-butilo



El Intermedio 25A (120 mg, 0,36 mmol) se disolvió en THF (6,0 ml) a -20 °C, y se añadió 1,3-dibromo-5,5-dimetilhidantoína (51 mg, 0,18 mmol, 0,5 eq.). La mezcla se agitó a -20 °C durante 2 h y después se inactivó con una solución concentrada acuosa de sulfito de sodio (0,5 ml). Se añadió acetato de etilo, se separó la capa

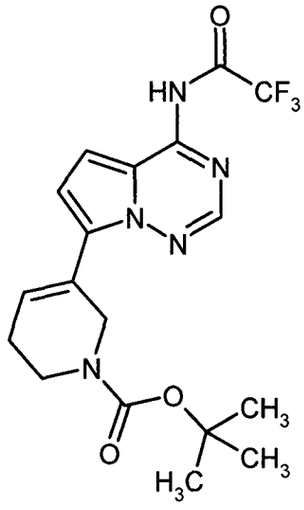
acuosa, y el extracto orgánico se secó sobre sulfato de sodio y se evaporó. El compuesto del título (148 mg, 95 % del t.) se obtuvo como un sólido amarillo claro.

HPLC (procedimiento 1): R_t = 4,03 min;

LC-MS (procedimiento 5): R_t = 1,99 min; MS (ESIpos): *m/z* (%) = 412,0 (90) y 414,0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 410,0 (100) y 412,0 (85) $[M-H]^-$.

Intermedio 27A

5-{4-[(trifluoroacetil)amino]pirrolo[2,1-f][1,2,4]triazin-7-il}-3,6-dihidropiridin-1(2*H*)-carboxilato de *terc*-butilo



El Intermedio 25A (8,32 g, 24,95 mmol) se disolvió en piridina (116 ml) a 0 °C. Se añadió anhídrido trifluoroacético (8,81 ml, 13,10 g, 62,36 mmol, 2,5 eq.) lentamente, y la mezcla de reacción se agitó a temperatura ambiente durante 16 h. Después, se enfrió nuevamente a 0 °C, y se añadieron 150 ml de éter de dietilo. La mezcla se agitó a 0 °C mientras precipitaba lentamente el compuesto del título. Finalmente, el producto se filtró y lavó con éter de dietilo. El filtrado se evaporó *in vacuo*, y el residuo se trituró con éter de dietilo a 0 °C para dar un segundo cultivo del compuesto del título después de un lavado con éter de dietilo. Los dos cultivos se combinaron para dar 7,80 g (92 % puro por HPLC, 76 % del t.) del compuesto del título como cristales amarillos.

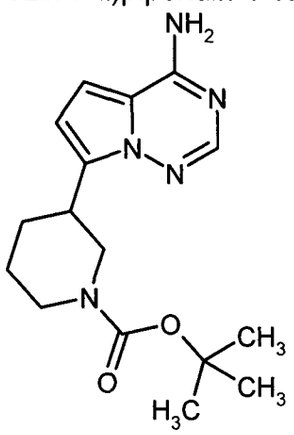
HPLC (procedimiento 1): R_t = 3,91 min;

LC-MS (procedimiento 7): R_t = 2,45 min; MS (ESIpos): *m/z* (%) = 412,2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 410,2 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,48 (s, 9H), 1,92 (m, 2H), 3,58 (m, 2H), 6,90 (d, 1H), 7,30 (d, 1H), 8,03-8,10 (m, 1H), 8,42 (s, 1H).

Intermedio 28A

3-(4-Aminopirrolo[2,1-f][1,2,4]triazin-7-il)piperidin-1-carboxilato de *rac-terc*-butilo



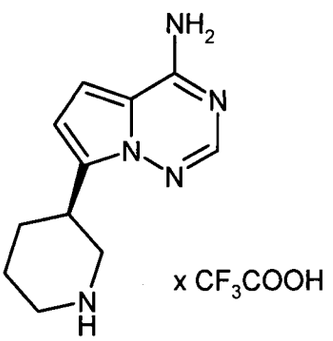
El Intermedio 27A (7,80 g, 92 % de pureza, 17,54 mmol) se disolvió en metanol (400 ml). Se añadieron ácido trifluoroacético (6,76 ml, 10,0 g, 88 mmol, 5 eq.), agua (3,16 ml, 175 mmol, 10 eq.) y paladio 10 % sobre carbón (30 mg), y la mezcla se hidrogenó durante 24 h a temperatura ambiente y presión ambiente. Luego, el catalizador se eliminó por filtración, y el disolvente se evaporó *in vacuo*. El producto bruto (8,79 g, 75 % puro, rendimiento cuantitativo) se utilizó en la próxima etapa sintética sin purificación adicional.

HPLC (procedimiento 1): R_t = 3.64 min;

LC-MS (procedimiento 7): R_t = 1,26 min; MS (ESIpos): *m/z* (%) = 318,3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 316,4 (100) $[M-H]^-$.

Intermedio 29A

Trifluoroacetato de 7-[(3*R*)-piperidin-3-il]pirrolo[2,1-f][1,2,4]triazin-4-amina



El material de inicio (*R*)-3-(4-amino-5-bromopirrolo[2,1-f][1,2,4]triazin-7-il)piperidin-1-carboxilato de bencilo se ha descrito en el documento WO 2007/056170-A2 (Intermedio DDD).

1,50 g (3,49 mmol) de este material se hidrogenaron durante 16 h a temperatura ambiente y presión ambiente en presencia de paladio 10 % sobre carbón (30 mg) en una mezcla de metanol (50 ml) y ácido trifluoroacético (2,70 ml). Subsiguientemente, el catalizador se eliminó por filtración, y todos los volátiles se evaporaron *in vacuo* para dar 1,10 g (95 % del t.) del compuesto del título.

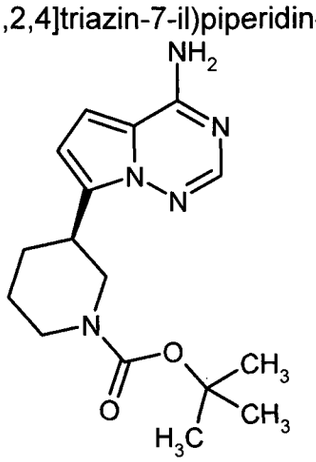
HPLC (procedimiento 2): R_t = 2,17 min;

LC-MS (procedimiento 6): R_t = 0,17 min; MS (ESIpos): *m/z* (%) = 218 (100) $[M+H]^+$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,75 (m, 2H), 1,92 (m, 1H), 2,05 (m, 1H), 2,93 (m, 1H), 3,06 (m, 1H), 3,31 (d, 1H), 3,50 (d, 1H), 3,57 (m, 1H), 6,78 (d, 1H), 7,20 (m, 1H), 8,10 (s, 1H), 8,63 (m, 1H), 8,82 (m, 1H), 9,02 (br, s, 1H).

Intermedio 30A

(3*R*)-3-(4-Aminopirrolo[2,1-f][1,2,4]triazin-7-il)piperidin-1-carboxilato de *terc*-butilo



El Intermedio 29A (1,10 g, 5,06 mmol) se suspendió en diclorometano (6,60 ml), se añadió trietilamina (1,55 ml, 1,13 g, 11,14 mmol, 2,20 eq.), y la mezcla se agitó durante 30 min. hasta que el material de inicio se disolviera completamente. Después, se añadió dicarbonato de di-*terc*-butilo (1,22 g, 5,57 mmol, 1,1 eq.), y la mezcla de reacción se agitó durante 16 h. Subsiguientemente, se añadió ácido cítrico acuoso 5 %, las fases se separaron, y la capa orgánica se secó sobre sulfato de sodio y se evaporó. El residuo se purificó por HPLC preparativa (procedimiento 2). Rendimiento: 595 mg (37 % del t.).

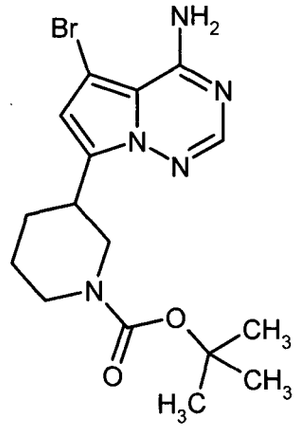
HPLC (procedimiento 2): R_t = 4,01 min;

LC-MS (procedimiento 5): R_t = 1,54 min; MS (ESIpos): *m/z* (%) = 318,1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 316,1 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,38 (s, 9H), 1,45 (m, 2H), 1,72 (m, 2H), 2,02 (m, 2H), 2,90 (m, 1H), 3,17 (m, 1H), 3,85 (m, 1H), 4,08 (m, 1H), 6,47 (d, 1H), 6,80 (d, 1H), 7,58 (br, s, 1H), 7,81 (s, 1H).

Intermedio 31A

3-(4-amino-5-bromopirrolo[2,1-f][1,2,4]triazin-7-il)piperidin-1-carboxilato de *rac*-*terc*-butilo



El Intermedio 28A (8,28 g, 75 % de pureza, 14,39 mmol) se disolvió en THF (222 ml) a -20 °C, y se añadió 1,3-dibromo-5,5-dimetilhidantoína (2,06 g, 7,19 mmol, 0,5 eq.). La mezcla se agitó a -20 °C durante 2 h y después se inactivó con solución concentrada acuosa de sulfito de sodio (0,5 ml). Se añadió acetato de etilo, se separó la capa acuosa, y el extracto orgánico se secó sobre sulfato de sodio y se

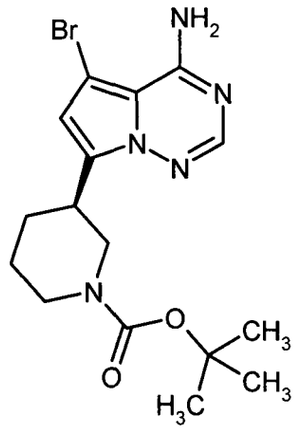
evaporó. El compuesto del título (6,30 g, 86 % del t.) se obtuvo como un sólido amarillo claro.

LC-MS (procedimiento 5): R_t = 2,27 min; MS (ESIpos): *m/z* (%) = 396,0 (80) y 397,9 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 394,0 (90) y 396,0 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,35 (s, 9H), 1,40-1,44 (m, 2H), 1,71 (m, 1H), 1,98 (m, 1H), 2,95 (m, 1H), 3,20 (m, 1H), 3,75 (m, 1H), 4,00 (m, 1H), 6,67 (s, 1H), 7,86 (s, 1H).

Intermedio 32A

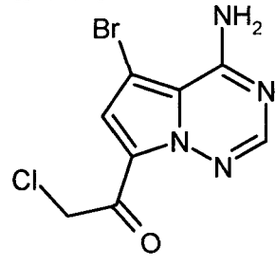
(3*R*)-3-(4-amino-5-bromopirrolo[2,1-f][1,2,4]triazin-7-il)piperidin-1-carboxilato de *terc*-butilo



El compuesto del título se preparó de la misma forma que la mezcla racémica (Intermedio 31A), comenzando a partir del Intermedio 30A. Los datos analíticos son idénticos a los mostrados para el Intermedio 31A.

Intermedio 33A

1-(4-Amino-5-bromopirrolo[2,1-f][1,2,4]triazin-7-il)-2-cloroetanona



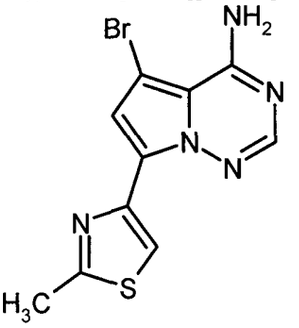
El compuesto se preparó de acuerdo con el procedimiento descrito en el documento WO 2007/056170-A2 (Intermedio N, etapa 1).

HPLC (procedimiento 1): R_t = 4,27 min;

LC-MS (procedimiento 5): R_t = 1,70 min; MS (ESIpos): *m/z* (%) = 289,0 (75) y 290,9 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 287,0 (75) y 288,9 (100) $[M-H]^-$.

Intermedio 34A

5-Bromo-7-(2-metil-1,3-tiazol-4-il)pirrolo[2,1-f][1,2,4]triazin-4-amina



El Intermedio 33A (100 mg, 0,35 mmol) y tioacetamida (30 mg, 0,40 mmol, 1,15 eq.) se disolvieron en 1,4-dioxano (3,0 ml) en un vial de reacción de microondas. Al vial se le colocó una tapa engastada, y la mezcla se calentó a 130 °C durante 60 min. en un dispositivo de microondas de modo único. Tras el enfriamiento, el disolvente se destiló, y el residuo se trituró con acetonitrilo y se filtró. El filtrado se descartó. El compuesto del título se aisló como un sólido cristalino. Rendimiento: 99 mg (92 % del t.).

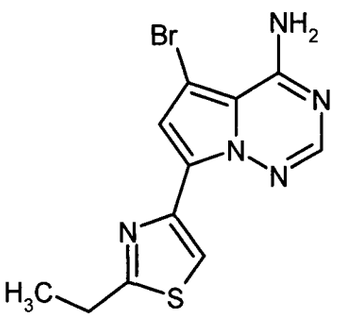
HPLC (procedimiento 1): R_t = 4,00 min;

LC-MS (procedimiento 6): R_t = 1,05 min; MS (ESIpos): *m/z* (%) = 310,0 (90) y 312 (100) $[M+H]^+$,

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 2,71 (s, 3H), 7,20 (s, 1H), 8,02 (s, 1H), 8,28 (s, 1H).

Intermedio 35A

5-Bromo-7-(2-etil-1,3-tiazol-4-il)pirrolo[2,1-f][1,2,4]triazin-4-amina



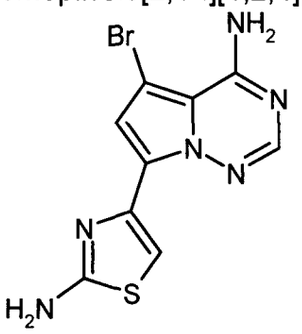
El Intermedio 33A (100 mg, 0,35 mmol) y tiopropionamida (32 mg, 0,36 mmol, 1,05 eq.) se calentaron a reflujo en etanol (3,0 ml) durante un período de 4,5 h. Tras el enfriamiento, la mezcla se particionó entre acetato de etilo y solución acuosa de bicarbonato de sodio. La capa orgánica se secó sobre sulfato de sodio anhidro, y el disolvente se destiló. El producto se secó al vacío para dar 91 mg (0,28 mmol, 81 % del t.) del compuesto del título como un sólido blancuzco.

HPLC (procedimiento 1): R_t = 4,30 min;

LC-MS (procedimiento 7): R_t = 1,84 min; MS (ESIpos): *m/z* (%) = 324,2 (100) y 325,8 (98) $[M+H]^+$.

Intermedio 36A

7-(2-Amino-1,3-tiazol-4-il)-5-bromopirrolo[2,1-f][1,2,4]triazin-4-amina



El Intermedio 33A (100 mg, 0,35 mmol) y tiourea (32 mg, 0,41 mmol, 1,2 eq.) se suspendieron en 1,4-dioxano (3 ml) en un vial de reacción de microondas al que después se colocó una tapa engastada. La mezcla se calentó a 120 °C durante 60 min. en un dispositivo de microondas de modo único. Tras el enfriamiento, se añadió agua, y el precipitado resultante se recolectó por filtración y se lavó con dioxano. El sólido blancuzco se secó al vacío para dar 98 mg (91 % del t.) del compuesto del título.

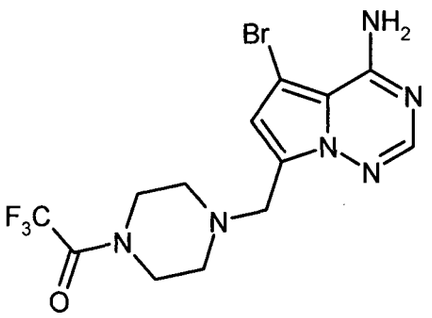
HPLC (procedimiento 1): R_t = 3,19 min;

LC-MS (procedimiento 5): R_t = 1,25 min; MS (ESIpos): *m/z* (%) = 310,9 (95) y 312,9 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 309,0 (100) y 310,9 (70) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 7,17 (s, 1H), 7,52 (s, 1H), 8,07 (s, 1H).

Intermedio 37A

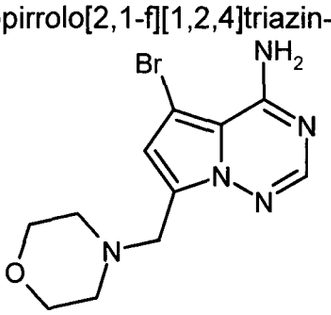
1-{4-[(4-Amino-5-bromopirrolo[2,1-f][1,2,4]triazin-7-il)metil]piperazin-1-il}-2,2,2-trifluoroetanona



El compuesto se preparó de acuerdo con el procedimiento descrito en el documento WO 2007/056170-A2 (Ejemplo 416, etapa 6).

Intermedio 38A

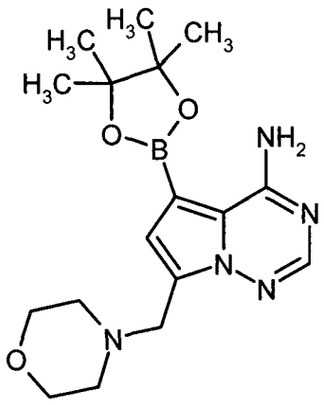
5-Bromo-7-(morfolin-4-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-amina



El compuesto se preparó de acuerdo con el procedimiento descrito en el documento WO 2007/064931-A2 (Intermedio C).

Intermedio 39A

7-(Morfolin-4-ilmetil)-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)pirrolo[2,1-f]-[1,2,4]triazin-4-amina

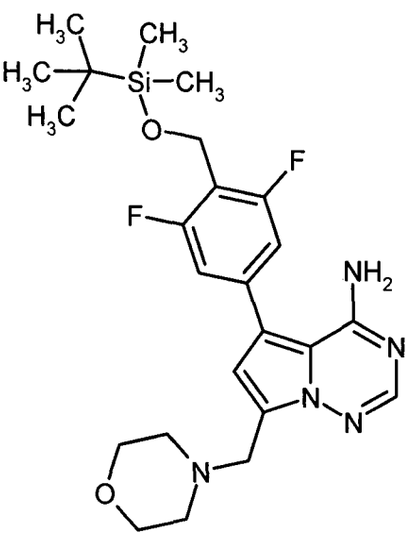


A una solución del Intermedio 38A (5,59 g, 17,9 mmol) y bis(pinacolato)diboro (10,0 g, 39,4 mmol) en DMF desgasificado (120 ml) se añadió bajo una atmósfera de argón cloruro de 1,1'-bis(difenilfosfino)ferroceno-paladio (II) (786 mg, 1,07 mmol) y acetato de potasio (7,03 g, 71,6 mmol). La mezcla se calentó a 80°C durante 5 h y después se enfrió a temperatura ambiente. Se añadió éter de metil *terc*-butilo (100 ml), y la suspensión se filtró. El filtrado se evaporó a sequedad bajo presión reducida, y el residuo se purificó por cromatografía flash sobre gel de sílice (elución de gradiente de metanol 2 % a 5 % en diclorometano) para dar 1,30 g (20 % del t.) del compuesto del título que contenía cierta cantidad del derivado de ácido borónico. Este producto se utilizó sin purificación adicional.

LC-MS (procedimiento 6): R_t = 0,73 min; MS (ESIpos): *m/z* (%) = 360,3 (30) $[M+H]^+$.

Intermedio 40A

5-[4-({[*terc*-butil(dimetil)silil]oxi}metil)-3,5-difluorofenil]-7-(morfolin-4-ilmetil)pirrolo-[2,1-f][1,2,4]triazin-4-amina

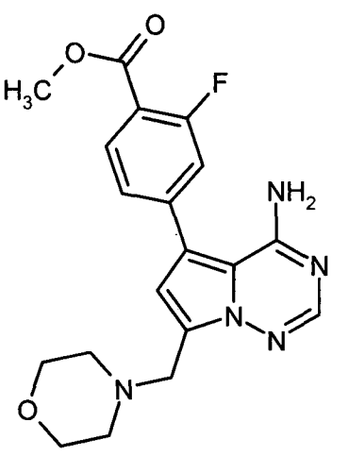


El compuesto del título se obtuvo por el procedimiento de síntesis general 1 a partir del Intermedio 38A (200 mg, 0,64 mmol) y ácido [4-({[terc-butil(dimetil)silil]oxi}metil)-3,5-difluorofenil]borónico (314 mg, 0,77 mmol, 74 % de pureza; preparado por el procedimiento de Hattori, *Bioorg. Med. Chem.* **2006**, *14*, 3258-3262). La purificación del producto bruto se llevó a cabo por HPLC preparativa (procedimiento 3). Rendimiento: 110 mg (32 % del t., Pureza de LC-MS 92 %).

LC-MS (procedimiento 6): R_t = 1,18 min; MS (ESIpos): *m/z* (%) = 490,1 (30) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 488,3 (100) $[M-H]^-$.

Intermedio 41A

4-[4-amino-7-(morfolin-4-ilmetil)pirrolo[2,1-f][1,2,4]triazin-5-il]-2-fluorobenzoato de metilo

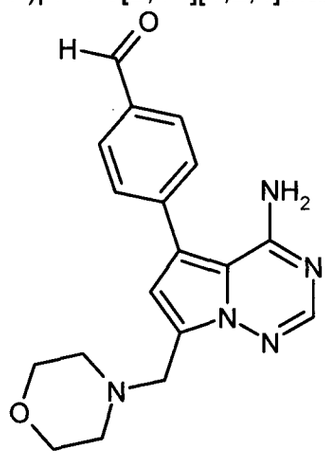


El compuesto del título se obtuvo por el procedimiento de síntesis general 1 a partir del Intermedio 38A (200 mg, 0,64 mmol) y ácido [3-fluoro-4-(metoxicarbonil)fenil]borónico (139 mg, 0,71 mmol). La purificación del producto bruto se llevó a cabo por HPLC preparativa (procedimiento 3). Rendimiento: 80 mg (32 % del t.).

LC-MS (procedimiento 6): R_t = 0,66 min; MS (ESIpos): *m/z* (%) = 38,1 (80) $[M+H]^+$.

Intermedio 42A

4-[4-Amino-7-(morfolin-4-ilmetil)pirrolo[2,1-f][1,2,4]triazin-5-il]benzaldehído

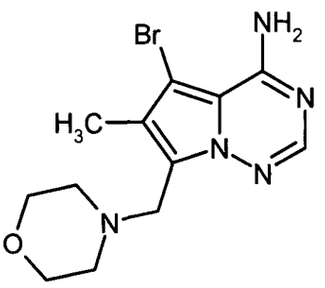


A una solución del Intermedio 38A (300 mg, 0,96 mmol) en DMF desgasificado (9,0 ml) se añadió ácido (4-formilfenil)borónico (216 mg, 1,44 mmol), tetrakis(trifenilfosfina)paladio (0) (111 mg, 0,1 mmol) y solución acuosa de carbonato de sodio 2 M (2,4 ml). La mezcla se calentó a 90 °C bajo argón durante 17 h, después se enfrió a temperatura ambiente y se purificó directamente por HPLC preparativa (procedimiento 3). Rendimiento: 150 mg (46 % del t.).

LC-MS (procedimiento 6): R_t = 0,44 min; MS (ESIpos): *m/z* (%) = 338,2 (30) $[M+H]^+$.

Intermedio 43A

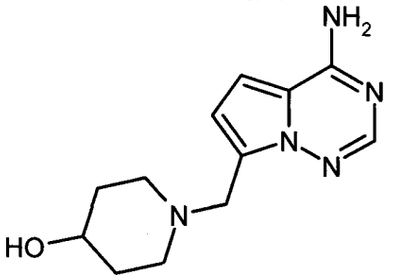
5-Bromo-6-metil-7-(morfolin-4-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-amina



El compuesto se preparó de acuerdo con el procedimiento descrito en el documento WO 2007/056170-A2 (Intermedio O).

Intermedio 44A

1-[(4-Aminopirrolo[2,1-f][1,2,4]triazin-7-il)metil]piperidin-4-ol



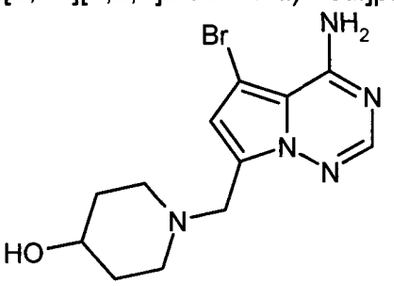
Se disolvieron 4-hidroxipiperidina (3,62 g, 35,8 mmol) y solución de formalina 37 % (2,9 g, 35,8 mmol) en ácido acético (150 ml) y se agitó a temperatura ambiente durante 1 h. A esta solución se añadió una solución de pirrolo[2,1-f][1,2,4]triazin-4-amina (2,0 g, 14,9 mmol; preparada de acuerdo con el procedimiento descrito en el documento WO 2007/056170-A2, Intermedio A) en ácido acético (150 ml), y la mezcla se agitó a 60 °C durante 2 h. Después, el disolvente se evaporó, y el residuo se tomó en 200 ml de una solución de bicarbonato de sodio medio concentrada acuosa y se extrajo con 200 ml de diclorometano. La capa orgánica se lavó con agua (2 x 50 ml) y se descartó. Las capas acuosas combinadas se evaporaron a sequedad, y el residuo se trató con una mezcla 10:1 de diclorometano y metanol (2 x 100 ml). Los extractos orgánicos se evaporaron, y el residuo se purificó por HPLC preparativa (procedimiento 4) para dar 1,16 g (15 % del t.) del compuesto del título.

LC-MS (procedimiento 7): R_t = 0,18 min; MS (ESIpos): *m/z* (%) = 248,3 (30) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 246,5 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,35 (br. m, 2H), 1,67 (br. m, 2H), 2,07 (t, 2H), 2,70 (br. m, 2H), 3,38 (br. m, 1H), 3,75 (s, 2H), 4,51 (br. 1H), 6,52 (d, 1H), 6,84 (d, 1H), 7,62 (br. 2H), 7,82 (s, 1H).

Intermedio 45A

1-[(4-Amino-5-bromopirrolo[2,1-f][1,2,4]triazin-7-il)metil]piperidin-4-ol



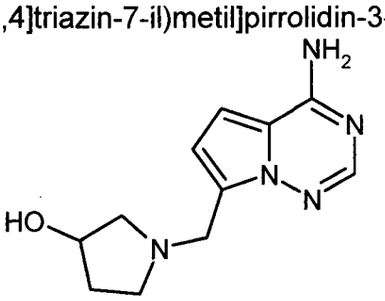
El Intermedio 44A (1,10 g, 4,45 mmol) se disolvió en DMF (16,5 ml) y se enfrió a -20 °C. Se añadió 1,3-dibromo-5,5-dimetilhidantoína (636 mg, 2,22 mmol) cada 10 min. en aproximadamente porciones de 100 mg. Subsiguientemente, la mezcla se agitó a temperatura ambiente durante una hora adicional y después se purificó directamente por HPLC preparativa (procedimiento 4). Rendimiento: 0,61 g (42 % del t.).

LC-MS (procedimiento 4): R_t = 0,75 min; MS (ESIpos): *m/z* (%) = 326,0 (30) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 324,0 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,35 (br, m, 2H), 1,67 (br, m, 2H), 2,08 (t, 2H), 2,68 (br, m, 2H), 3,39 (br, m, 1H), 3,74 (s, 2H), 4,51 (br, 1H), 6,69 (s, 1H), 7,86 (s, 1H).

Intermedio 46A

1-[(4-Aminopirrolo[2,1-f][1,2,4]triazin-7-il)metil]pirrolidin-3-ol



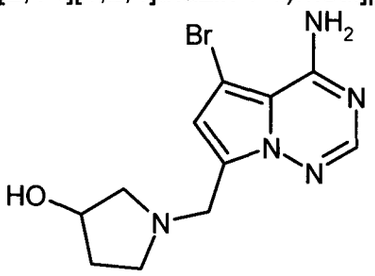
Se disolvieron 3-pirrolidinol (1,56 g, 17,9 mmol) y una solución de formalina 37 % (1,45 g, 17,9 mmol) en ácido acético (75 ml) y se agitó a temperatura ambiente durante 10 min. A esta solución se añadió una solución de pirrolo[2,1-f][1,2,4]triazin-4-amina (2,0 g, 14,9 mmol) en ácido acético (75 ml), y la mezcla se agitó a 60 °C durante 4 h. Tras la evaporación, el residuo se tomó en 200 ml de una solución acuosa de carbonato de potasio 1 N y se extrajo con acetato de etilo (3 x 200 ml). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de magnesio y se concentraron bajo presión reducida. El residuo se purificó por HPLC preparativa (procedimiento 4) para dar 390 mg (11 % del t.) del compuesto del título.

LC-MS (procedimiento 4): R_t = 0,22 min; MS (ESIpos): *m/z* (%) = 234,2 (20) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 223,0 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,50 (br, m, 1H), 1,94 (m, 1H), 2,34 (dd, 1H), 2,44 (dd, 1H), 2,60 (dd, 1H), 2,71 (dd, 1H), 3,84 (dd, 2H), 4,15 (br, 1H), 4,65 (d, 1H), 6,52 (d, 1H), 6,83 (d, 1H), 7,61 (br, 2H), 7,82 (s, 1H).

Intermedio 47A

1-[(4-Amino-5-bromopirrolo[2,1-f][1,2,4]triazin-7-il)metil]pirrolidin-3-ol



El Intermedio 46A (0,9 g, 3,86 mmol) se disolvió en DMF (14,2 ml) y se enfrió a -20 °C. Se añadió 1,3-dibromo-5,5-dimetilhidantoína (606 mg, 2,12 mmol) cada 10 min. en aproximadamente porciones de 100 mg, y la agitación continuó a temperatura ambiente durante 1 h. La mezcla se particionó entre solución acuosa de bicarbonato de potasio 10 % (50 ml) y acetato de etilo (100 ml). La capa acuosa se extrajo con otra porción de acetato de etilo (100 ml) y después con diclorometano (100 ml). Las capas orgánicas combinadas se secaron sobre sulfato

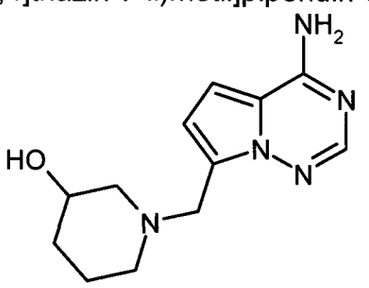
de magnesio y se evaporaron, y el residuo se purificó por HPLC preparativa (procedimiento 4). Rendimiento: 0,44 g (37 % del t.).

LC-MS (procedimiento 6): R_t = 0,21 min; MS (ESIpos): *m/z* (%) = 314,0 (100) $[M+H]^+$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,50 (br, m, 1H), 1,95 (m, 1H), 2,34 (dd, 1H), 2,45 (m, 1H), 2,60 (m, 1H), 2,70 (dd, 1H), 3,84 (dd, 2H), 4,15 (br, 1H), 4,65 (d, 1H), 6,71 (s, 1H), 7,86 (s, 1H).

Intermedio 48A

1-[(4-Aminopirrolo[2,1-f][1,2,4]triazin-7-il)metil]piperidin-3-ol



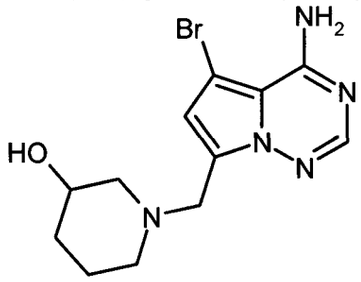
El compuesto del título se preparó en analogía al Intermedio 46A con 3-hidroxipiperidina (1,80 g, 17,9 mmol) como material de inicio. Tras la concentración de la mezcla de reacción, el residuo se tomó en una solución saturada acuosa de carbonato de potasio y se extrajo con 300 ml de diclorometano. La capa orgánica se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró bajo presión reducida. El residuo se purificó por HPLC preparativa (procedimiento 4) para dar 650 mg (18 % del t.) del compuesto del título.

LC-MS (procedimiento 6): R_t = 0,16 min; MS (ESIpos): *m/z* (%) = 248,2 (60) $[M+H]^+$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 0,99 (m, 1H), 1,37 (br, m, 1H), 1,57 (br, m, 1H), 1,74 (m, 2H), 1,88 (t, 1H), 2,68 (br, m, 1H), 2,83 (br, dd, 1H), 3,41 (br, m, 1H), 3,78 (dd, 2H), 4,54 (d, 1H), 6,52 (d, 1H), 6,84 (d, 1H), 7,61 (br, 2H), 7,82 (s, 1H).

Intermedio 49A

1-[(4-Amino-5-bromopirrolo[2,1-f][1,2,4]triazin-7-il)metil]piperidin-3-ol



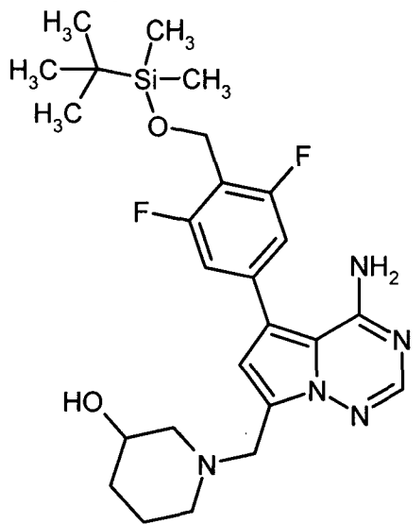
En analogía a la preparación del Intermedio 47A, el compuesto del título se preparó a partir del Intermedio 48A (690 mg, 2,79 mmol) para dar 348 mg (93 % de pureza por LC-MS, 36 % del t.) del producto tras la purificación por HPLC preparativa (procedimiento 4).

LC-MS (procedimiento 4): R_t = 0,85 min; MS (ESIpos): *m/z* (%) = 226,0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 223,9 (70) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 0,99 (m, 1H), 1,37 (m, 1H), 1,57 (br, m, 1H), 1,74 (m, 2H), 1,89 (m, 1H), 2,66 (br, m, 1H), 2,81 (br, m, 1H), 3,41 (br, m, 1H), 3,77 (dd, 2H), 4,54 (d, 1H), 6,70 (s, 1H), 7,86 (s, 1H).

Intermedio 50A

1-({4-Amino-5-[4-({[*terc*-butil(dimetil)silil]oxi}metil)-3,5-difluorofenil]pirrolo[2,1-f]-[1,2,4]triazin-7-il}metil)piperidin-3-ol



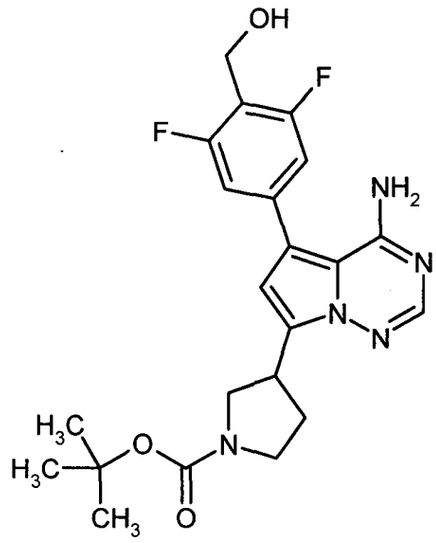
El compuesto del título se obtuvo por el procedimiento de síntesis general 1 a partir del Intermedio 49A (200 mg, 0,61 mmol) y ácido [4-({[terc-butil(dimetil)silil]oxi}metil)-3,5-difluorofenil]borónico (222 mg, 0,74 mmol; preparado por el procedimiento de Hattori, *Bioorg. Med. Chem.* **2006**, *14*, 3258-3262). La purificación del producto bruto se llevó a cabo por HPLC preparativa (procedimiento 3). Rendimiento: 153 mg (50 % del t.).

LC-MS (procedimiento 7): R_t = 1,55 min; MS (ESIpos): *m/z* (%) = 504,1 (100) $[M+H]^+$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 0,11 (s, 6H), 0,86 (s, 9H), 1,01 (m, 1H), 1,40 (br, m, 1H), 1,59 (br, m, 1H), 1,77 (m, 2H), 1,94 (m, 1H), 2,72 (br, m, 1H), 2,87 (br, m, 1H), 3,43 (m, 1H), 3,82 (dd, 2H), 4,55 (d, 1H), 4,74 (s, 2H), 6,75 (s, 1H), 7,18 (dd, 2H), 7,95 (s, 1H).

Intermedio 51A

3-{4-amino-5-[3,5-difluoro-4-(hidroximetil)fenil]pirrolo[2,1-f][1,2,4]triazin-7-il}-pirrolidin-1-carboxilato de *rac-terc*-butilo



La preparación del material de inicio 3-(4-amino-5-bromopirrolo[2,1-f][1,2,4]triazin-7-il)pirrolidino-1-carboxilato de *terc*-butilo se ha descrito en el documento WO 2007/056170-A2 (Intermedio I).

Este compuesto (60 mg, 0,16 mmol) se acopló de acuerdo con el procedimiento de síntesis general 1 con el Intermedio 2A (47 mg, 0,17 mmol, 1,1 eq.). El

producto bruto se purificó por HPLC preparativa (procedimiento 2) para dar 67 mg (84 % del t.) del compuesto del título.

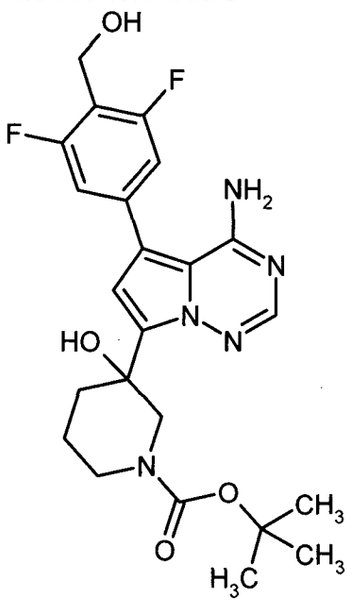
HPLC (procedimiento 2): R_t = 4,08 min;

LC-MS (procedimiento 7): R_t = 1,66 min; MS (ESIpos): *m/z* (%) = 446,2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 444,3 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,39 (s, 9H), 2,10 (m, 1H), 2,33 (m, 1H), 3,37 (m, 2H), 3,46 (m, 1H), 3,70-3,89 (m, 2H), 4,51 (s, 2H), 6,80 (s, 1H), 7,15 (m, 2H), 8,03 (s, 1H).

Intermedio 52A

3-{4-amino-5-[3,5-difluoro-4-(hidroximetil)fenil]pirrolo[2,1-f][1,2,4]triazin-7-il}-3-hidroxipiperidin-1-carboxilato de *rac-terc*-butilo



El Intermedio 26A (148 mg, 0,35 mmol) y (4-bromo-2,6-difluorofenil)metanol (75 mg, 0,34 mmol) se acoplaron de acuerdo con el procedimiento de síntesis general 2. La purificación del producto bruto se llevó a cabo usando HPLC preparativa (procedimiento 2). Rendimiento: 46 mg (28 % de th.).

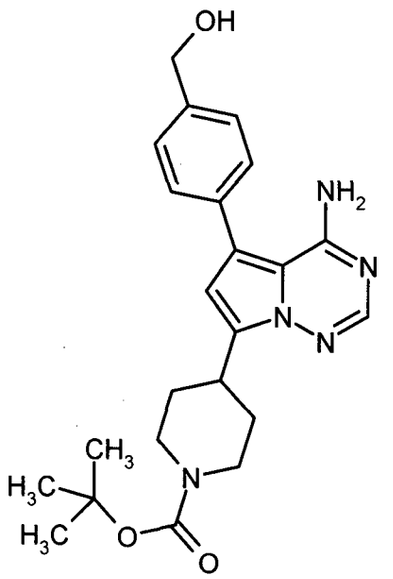
HPLC (procedimiento 3): R_t = 3,90 min;

LC-MS (procedimiento 7): R_t = 1,56 min; MS (ESIpos): *m/z* (%) = 476,2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 474,2 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,22-1,58 (m, 10H), 1,80 (m, 2H), 3,19 (m, 1H), 3,48 (m, 1H), 3,62 (m, 1H), 3,74 (m, 1H), 4,00 (m, 1H), 4,52 (m, 2H), 5,39 (t, 1H), 6,78 (s, 1H), 7,10 (m, 2H), 7,94 (s, 1H).

Intermedio 53A

4-{4-amino-5-[4-(hidroximetil)fenil]pirrolo[2,1-f][1,2,4]triazin-7-il}piperidin-1-carboxilato de *terc*-butilo



El material de inicio 4-(4-amino-5-bromopirrolo[2,1-f][1,2,4]triazin-7-il)piperidin-1-carboxilato de *terc*-butilo se preparó de acuerdo con el procedimiento descrito en el documento WO 2007/056170-A2 (Ejemplo 1, etapa 3).

Este compuesto (400 mg, 1,01 mmol) después se hizo reaccionar con ácido 4-(hidroximetil)fenilborónico (184 mg, 1,21 mmol, 1,2 eq.) de acuerdo con el procedimiento de síntesis general 1. El producto bruto se purificó por HPLC preparativa (procedimiento 2) para dar 326 mg (76 % del t.) del compuesto del título.

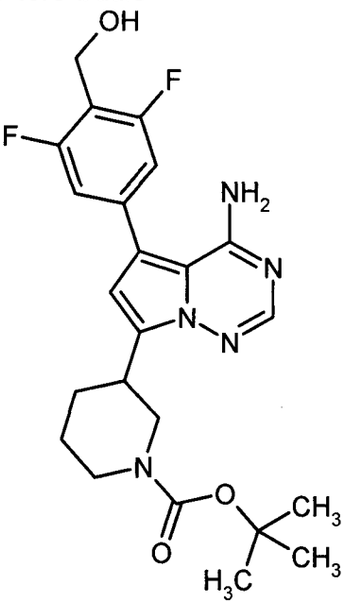
HPLC (procedimiento 2): R_t = 4,07 min;

LC-MS (procedimiento 6): R_t = 1,06 min; MS (ESIpos): *m/z* (%) = 424,3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 422,3 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,52-1,65 (m, 2H), 1,92-2,00 (m, 2H), 2,89 (br, s, 2H), 3,10 (m, 1H), 3,28-3,37 (m, 2H), 4,06 (d, 2H), 4,60 (s, 2H), 6,68 (s, 1H), 7,47 (s, 5H), 8,02 (s, 1H).

Intermedio 54A

3-{4-amino-5-[3,5-difluoro-4-(hidroximetil)fenil]pirrolo[2,1-f][1,2,4]triazin-7-il}-piperidin-1-carboxilato de *rac-terc*-butilo



El Intermedio 31A (200 mg, 0,39 mmol) y el Intermedio 2A (138 mg, 0,51 mmol, 1,3 eq.) se hicieron reaccionar de acuerdo con el procedimiento de síntesis general 1 para dar 130 mg (72 % del t.) del compuesto del título tras la purificación por HPLC preparativa (procedimiento 2).

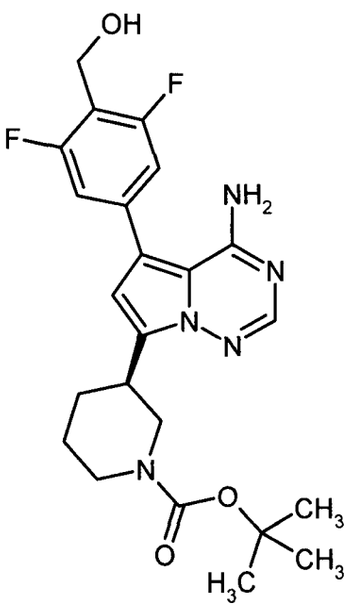
HPLC (procedimiento 3): R_t = 4,23 min;

LC-MS (procedimiento 6): R_t = 1,17 min; MS (ESIpos): *m/z* (%) = 460,1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 458,1 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,39 (s, 9H), 1,48 (m, 2H), 1,74 (m, 2H), 2,93 (m, 1H), 3,22 (m, 1H), 3,85 (m, 1H), 4,11 (m, 1H), 4,53 (s, 2H), 6,78 (s, 1H), 7,12 (m, 2H), 8,02 (s, 1H).

Intermedio 55A

(3*R*)-3-{4-amino-5-[3,5-difluoro-4-(hidroximetil)fenil]pirrolo[2,1-f][1,2,4]triazin-7-il}piperidin-1-carboxilato de *terc*-butilo



El isómero *R* enantioméricamente puro se sintetizó por el acoplamiento del Intermedio 32A (115 mg, 0,28 mmol) con (4-bromo-2,6-difluorofenil)metanol (76 mg, 0,33 mmol, 1,2 eq.) de acuerdo con el procedimiento de síntesis general 2. Rendimiento: 48 mg (38 % del t.).

Alternativamente, el compuesto del título se obtuvo por la separación del compuesto racémico del Intermedio 54A (40 mg) usando HPLC quiral preparativa [columna: fase quiral en gel de sílice basada en el selector poli(N-metacriloil-L-leucina-*terc*-butilamida), 250 mm x 20 mm; eluyente: acetato de etilo/isohexano 4:1; caudal de flujo: 20 ml/min; detección UV: 260 nm]. Rendimiento: 20 mg (isómero *R*).

HPLC quiral analítica [columna: fase quiral en gel de sílice basada en el selector poli(N-metacriloil-L-leucina-*terc*-butilamida), 250 mm x 4 mm; eluyente: acetato de etilo/isohexano 4:1; caudal de flujo: 1 ml/min; detección UV: 260 nm]: R_t = 5,68 min; e.e. >99.5.

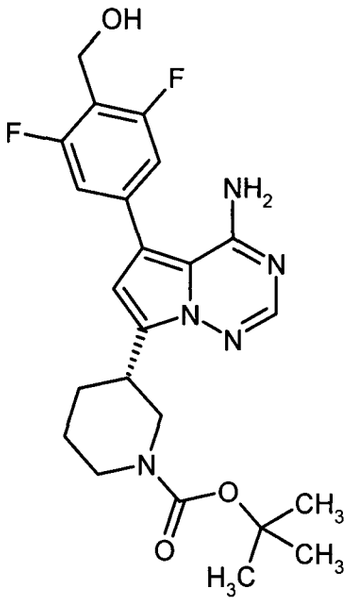
HPLC (procedimiento 3): R_t = 4,23 min;

LC-MS (procedimiento 6): R_t = 1,17 min; MS (ESIpos): *m/z* (%) = 460,1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 458,1 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,39 (s, 9H), 1,48 (m, 2H), 1,74 (m, 2H), 2,93 (m, 1H), 3,22 (m, 1H), 3,85 (m, 1H), 4,11 (m, 1H), 4,53 (s, 2H), 6,78 (s, 1H), 7,12 (m, 2H), 8,02 (s, 1H).

Intermedio 56A

(3*S*)-3-{4-amino-5-[3,5-difluoro-4-(hidroximetil)fenil]pirrolo[2,1-f][1,2,4]triazin-7-il}piperidin-1-carboxilato de *terc*-butilo



El isómero *S* enantioméricamente puro se obtuvo por la separación del compuesto racémico del Intermedio 54A (40 mg) usando HPLC quiral preparativa como se describe para el Intermedio 55A. Rendimiento: 19 mg (isómero *S*).

HPLC quiral analítica [columna: fase quiral en gel de sílice basada en el selector poli(N-metacriloil-L-leucina-*terc*-butilamida), 250 mm x 4 mm; eluyente: acetato de etilo/isohexano 4:1; caudal de flujo: 1 ml/min; detección UV: 260 nm]: R_t = 7,87 min; e.e. >99,5.

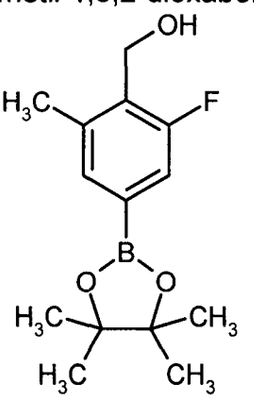
HPLC (procedimiento 3): R_t = 4,23 min;

LC-MS (procedimiento 6): R_t = 1,17 min; MS (ESIpos): *m/z* (%) = 460,1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 458,1 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,39 (s, 9H), 1,48 (m, 2H), 1,74 (m, 2H), 2,93 (m, 1H), 3,22 (m, 1H), 3,85 (m, 1H), 4,11 (m, 1H), 4,53 (s, 2H), 6,78 (s, 1H), 7,12 (m, 2H), 8,02 (s, 1H).

Intermedio 57A

[2-Fluoro-6-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil]metanol

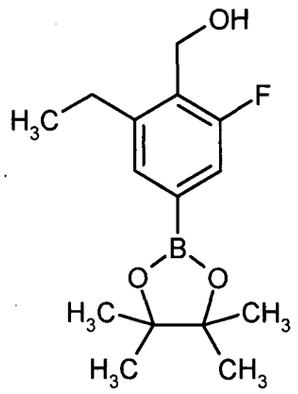


Se disolvió (4-bromo-2-fluoro-6-metilfenil)metanol (2,0 g, 9,13 mmol) en 1,4-dioxano (20,0 ml) en un vial reactor de microondas, y la solución se lavó con chorro con argón. Después, se añadieron bis(pinacolato)diboro (2,43 g, 9,59 mmol), cloruro de 1,1'-bis(difenilfosfino)ferroceno-paladio (II) (298 mg, 0,37 mmol) y acetato de potasio (1,34 g, 13,7 mmol). Al recipiente de reacción se le colocó una tapa engastada, y la mezcla se calentó a 130 °C durante 1 h en un dispositivo de microondas de modo único. Tras el enfriamiento, la mezcla de reacción se filtró y el filtrado se evaporó. El residuo se trató con ciclohexano (100 ml) y se agitó durante 10 min. La solución se filtró nuevamente, el filtrado se evaporó, y el residuo se purificó por cromatografía (cartucho de sílice de 25M de Biotage, caudal de flujo diclorometano a 15 ml/min.). Las fracciones que contenían el compuesto del título se combinaron y se evaporaron, y el compuesto del título cristalizó espontáneamente como un sólido amarillo (2,18 g, 90 % del t.).

RMN ^{1}H (400 MHz, DMSO-d_6): δ (ppm) = 1,30 (s, 12H), 2,39 (s, 3H), 4,51 (m, 2H), 5,01 (t, 1H), 7,14 (d, 1H), 7,31 (s, 1H).

Intermedio 58A

[2-Etil-6-fluoro-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil]metanol

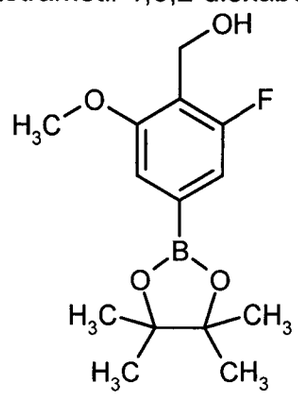


El compuesto del título se sintetizó y purificó en analogía al Intermedio 57A usando (4-bromo-2-etil-6-fluorofenil)metanol (2,00 g, 8,58 mmol), bis(pinacolato)diboro (2,29 g, 9,01 mmol), cloruro de 1,1'-bis(difenilfosfino)ferroceno-paladio (II) (280 mg, 0,34 mmol) y acetato de potasio (1,26 g, 12,87 mmol) en 1,4-dioxano (20 ml). Rendimiento: 2,16 g (90 % del t.) como cristales amarillos.

RMN ^{1}H (400 MHz, DMSO-d_6): δ (ppm) = 1,17 (t, 3H), 1,30 (s, 12H), 2,76 (q, 2H), 4,50 (m, 2H), 5,03 (t, 1H), 7,14 (d, 1H), 7,32 (s, 1H).

Intermedio 59A

[2-Fluoro-6-metoxi-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil]metanol

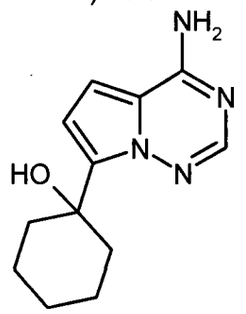


El compuesto del título se sintetizó y purificó en analogía al Intermedio 57A usando (4-bromo-2-metoxi-6-fluorofenil)metanol (2,00 g, 8,51 mmol), bis(pinacolato)diboro (2,27 g, 8,90 mmol), cloruro de 1,1'-bis(difenilfosfino)ferroceno-paladio (II) (278 mg, 0,34 mmol) y acetato de potasio (1,25 g, 12,76 mmol) en 1,4-dioxano (20 ml). Rendimiento: 1,81 g (75 % del t.) como cristales amarillos.

RMN ^{1}H (400 MHz, DMSO-d_6): δ (ppm) = 1,30 (s, 12H), 3,83 (s, 3H), 4,47 (m, 2H), 4,86 (t, 1H), 6,97 (d, 1H), 7,02 (s, 1H).

Intermedio 60A

1-(4-Aminopirrolo[2,1-f][1,2,4]triazin-7-il)ciclohexanol



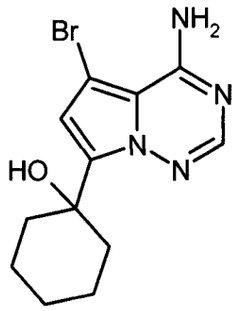
Se disolvió 7-bromopirrolo[2,1-f][1,2,4]triazin-4-amina (1,20 g, 5,63 mmol) en THF (25 ml) bajo argón a temperatura ambiente. Se añadió clorotrimetilsilano (1,43 ml, 11,27 mmol), y la mezcla se agitó a temperatura ambiente durante 3 h. Después, esta se enfrió a 0 °C, se añadió cloruro de 2-propil magnesio (11,8 ml de una solución 2,0 M en THF, 23,7 mmol), y la agitación se mantuvo durante otras 3 h mientras que la mezcla de reacción se dejó calentar a temperatura ambiente. Después, se añadió ciclohexanona (0,88 ml, 8,45 mmol), y la agitación continuó durante 16 h. La reacción se inactivó con una mezcla (1:1) de solución concentrada acuosa de cloruro de amonio y hielo hasta que el pH alcanzara 6-7. La mezcla se extrajo con dos porciones de acetato de etilo, y los extractos orgánicos combinados se secaron sobre carbonato de sodio anhidro y se concentraron a sequedad. El producto así obtenido se utilizó sin purificación adicional (pureza ~68 % por HPLC). Rendimiento: 1,87 g (97 % del t.).

LC-MS (procedimiento 5): R_t = 1,10 min; MS (ESIpos): *m/z* (%) = 233 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 231 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, DMSO-d_6): δ (ppm) = 1,28-1,33 (m, 1H), 1,42-1,50 (m, 2H), 1,58-1,63 (m, 1H), 1,67-1,78 (m, 4H), 2,13-2,23 (m, 2H), 6,69 (d, 1H), 7,20 (d, 1H), 8,02 (s, 1H), 8,58 (br, s, 1H), 9,00 (br, s, 1H).

Intermedio 61A

1-(4-Amino-5-bromopirrolo[2,1-f][1,2,4]triazin-7-il)ciclohexanol



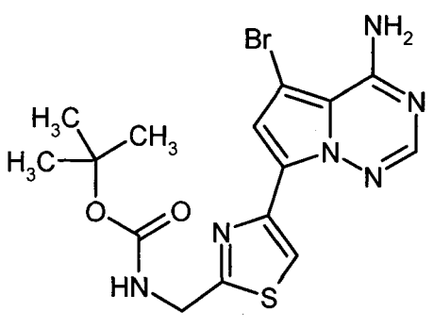
El Intermedio 60A (80 mg, 0,34 mmol) se disolvió en THF (5,0 ml), y la mezcla se enfrió a -20 °C. Se añadió 1,3-dibromo-5,5-dimetilhidantoína (49 mg, 0,17 mmol) de una vez, y la agitación continuó durante 1 h. La reacción se inactivó con una solución concentrada acuosa de ditionito de sodio (0,5 ml), y la mezcla se extrajo con acetato de etilo. El extracto orgánico se lavó con salmuera, se secó sobre sulfato de sodio, y el disolvente se destiló para dar 98 mg (91 % del t.) del compuesto del título.

LC-MS (procedimiento 4): R_t = 1,90 min; MS (ESIpos): *m/z* (%) = 311 (95) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 309 (90) $[M-H]^-$.

RMN ^{1}H (400 MHz, DMSO-d_6): δ (ppm) = 1,20-1,33 (m, 1H), 1,42-1,52 (m, 2H), 1,58-1,78 (m, 5H), 2,15-2,23 (m, 2H), 5,01 (br, s, 2H), 6,63 (s, 1H), 7,82 (s, 1H).

Intermedio 62A

{[4-(4-amino-5-bromopirrolo[2,1-f][1,2,4]triazin-7-il)-1,3-tiazol-2-il]metil}carbamato de *terc*-butilo



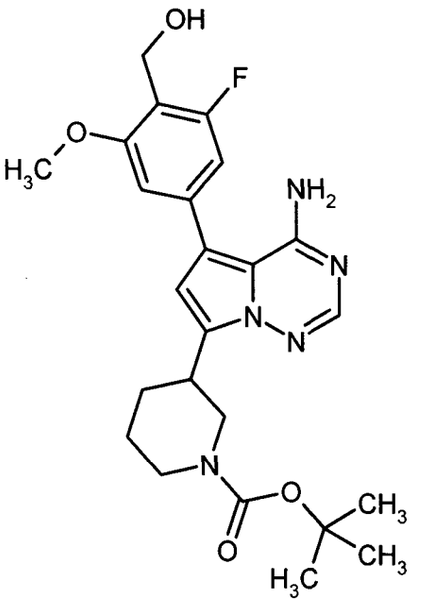
El Intermedio 33A (109 mg, 0,38 mmol) y (2-amino-2-tioxoetil)carbamato de *terc*-butilo (79 mg, 0,41 mmol) se disolvieron en etanol (6,5 ml). La mezcla se calentó a reflujo durante 20 h. Después, la mezcla se filtró, y el filtrado se evaporó. El

residuo se trituró con acetonitrilo para dar 67 mg (42 % del t.) del compuesto del título como un sólido cristalino parduzco-gris.

LC-MS (procedimiento 7): R_t = 1,81 min; MS (ESIpos): *m/z* (%) = 425 (80) y 427 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 423 (50) y 425 (100) $[M-H]^-$.

Intermedio 63A

3-{4-amino-5-[3-fluoro-4-(hidroximetil)-5-metoxifenil]pirrolo[2,1-f][1,2,4]triazin-7-il}piperidin-1-carboxilato de *terc*-butilo



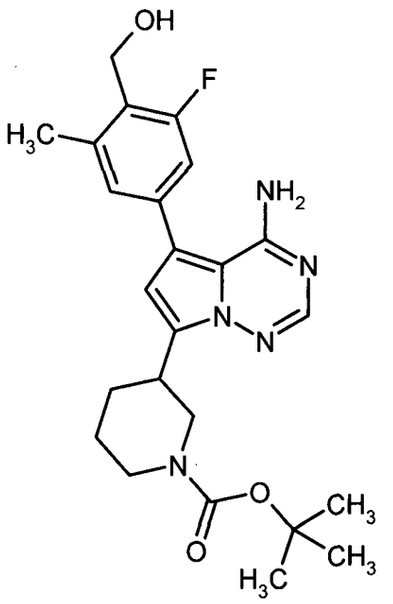
El Intermedio 31A (120 mg, 0,30 mmol) y el Intermedio 59A (104 mg, 0,36 mmol) se disolvieron en acetonitrilo (2,0 ml) en un vial reactor de microondas y se lavaron con chorro con argón. Se añadieron tetrakis(trifenilfosfina)paladio (0) (35 mg, 0,03 mmol) y una solución ac. de carbonato de sodio 2,0 M (0,5 ml), y la mezcla se calentó a 150 °C durante 1 h en un dispositivo de microondas de modo único. Tras el enfriamiento, la mezcla se filtró, y el filtrado se evaporó. El residuo se purificó por cromatografía flash (cartucho de sílice de 25M de Biotage, diclorometano + metanol 2-5 %, caudal de flujo 10 ml/min.) para dar 51 mg (36 % del t.) del compuesto del título.

LC-MS (procedimiento 6): R_t = 1,16 min; MS (ESIpos): *m/z* (%) = 472 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 470 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, DMSO-d_6): δ (ppm) = 1,31-2,10 (m, 13H), 2,88-2,91 (m, 2H), 3,19-3,27 (m, 2H), 3,87 (s, 1H), 4,12 (m, 1H), 4,50 (m, 1H), 4,82 (t, 1H), 6,68 (s, 1H), 6,83 (d, 1H), 6,90 (s, 1H), 7,92 (s, 1H).

Intermedio 64A

3-{4-amino-5-[3-fluoro-4-(hidroximetil)-5-metilfenil]pirrolo[2,1-f][1,2,4]triazin-7-il}piperidin-1-carboxilato de *terc*-butilo



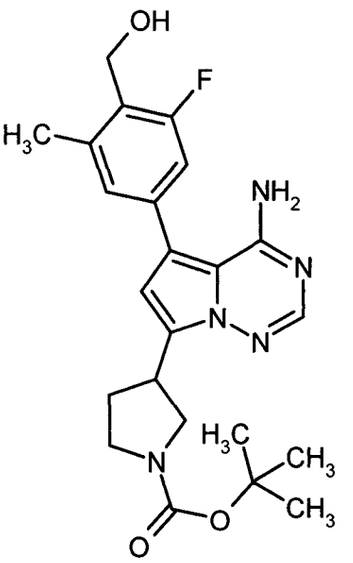
El Intermedio 31A (120 mg, 0,30 mmol) y el Intermedio 57A (97 mg, 0,36 mmol) se disolvieron en acetonitrilo (2,0 ml) en un vial reactor de microondas y se lavaron con chorro con argón. Se añadieron tetrakis(trifenilfosfina)paladio (0) (35 mg, 0,03 mmol) y una solución aq. de carbonato de sodio 2,0 M (0.5 ml), y la mezcla se calentó a 150 °C durante 1 h en un dispositivo de microondas de modo único. Tras el enfriamiento, la mezcla se filtró, y el filtrado se evaporó. El residuo se purificó por cromatografía flash (cartucho de sílice de 25M de Biotage, diclorometano + metanol 2-5 %, caudal de flujo 10 ml/min.) para dar 110 mg (71 % del t.) del compuesto del título.

LC-MS (procedimiento 4): R_t = 2,03 min; MS (ESIpos): *m/z* (%) = 456 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 454 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, DMSO-d_6): δ (ppm) = 1,31-2,11 (m, 13H), 2,42 (s, 3H), 2,88-2,91 (m, 2H), 3,17-3,30 (m, 2H), 3,80 (m, 1H), 4,54 (m, 1H), 4,82 (t, 1H), 6,64 (s, 1H), 7,04 (d, 1H), 7,12 (s, 1H), 7,93 (s, 1H).

Intermedio 65A

3-{4-amino-5-[3-fluoro-4-(hidroximetil)-5-metilfenil]pirrolo[2,1-f][1,2,4]triazin-7-il}pirrolidin-1-carboxilato de *terc*-butilo



El material de inicio 3-(4-amino-5-bromopirrolo[2,1-f][1,2,4]triazin-7-il)pirrolidin-1-carboxilato de *terc*-butilo se sintetizó de acuerdo con el procedimiento descrito en el documento WO 2007/056170-A2 (Intermedio I).

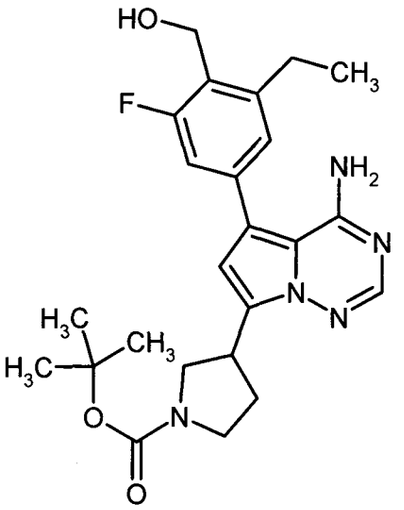
Se disolvió 3-(4-amino-5-bromopirrolo[2,1-f][1,2,4]triazin-7-il)pirrolidin-1-carboxilato de *terc*-butilo (120 mg, 0,31 mmol) en acetonitrilo (2,2 ml) en un vial reactor de microondas y se lavaron con chorro con argón. Se añadieron el Intermedio 57A (100 mg, 0,38 mmol), tetrakis(trifenilfosfina)paladio (0) (36 mg, 0,03 mmol) y una solución aq. de carbonato de sodio 2,0 M (0.5 ml), y la mezcla se calentó a 150 °C durante 1 h en un dispositivo de microondas de modo único. Tras el enfriamiento, la mezcla se filtró, y el filtrado se evaporó. El residuo se purificó por cromatografía flash (cartucho de sílice de 25M de Biotage, diclorometano + metanol 2-5 %, caudal de flujo 10 ml/min) para dar 91 mg (54 % del t.) del compuesto del título.

LC-MS (procedimiento 5): R_t = 2,00 min; MS (ESIpos): *m/z* (%) = 442 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 440 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, DMSO-d_6): δ (ppm) = 1,41 (m, 9H), 2,00-2,48 (m, 2H), 3,29-3,53 (m, 3H), 3,71-3,90 (m, 2H), 4,55 (m, 2H), 4,99 (t, 1H), 6,63 (s, 1H), 7,06 (d, 1H), 7,12 (s, 1H), 7,92 (s, 1H).

Intermedio 66A

3-{4-amino-5-[3-etil-5-fluoro-4-(hidroximetil)fenil]pirrolo[2,1-f][1,2,4]triazin-7-il}pirrolidin-1-carboxilato de *rac-terc*-butilo



El material de inicio 3-(4-amino-5-bromopirrolo[2,1-f][1,2,4]triazin-7-il)pirrolidin-1-carboxilato de *terc*-butilo se sintetizó de acuerdo con el procedimiento descrito en el documento WO 2007/056170-A2 (Intermedio I).

Se disolvieron 3-(4-amino-5-bromopirrolo[2,1-f][1,2,4]triazin-7-il)pirrolidin-1-carboxilato de *terc*-butilo (111 mg, 0,29 mmol), el Intermedio 58A (98 mg, 0,35 mmol) y tetrakis(trifenilfosfina)paladio (0) (17 mg, 0,015 mmol) en una mezcla de acetonitrilo (2,3 ml) y solución acuosa de carbonato de sodio 2 M (0,53 ml) en un vial reactor de microondas. Tras la desgasificación durante 5 min. usando argón, al recipiente de reacción se le colocó una tapa engastada, y la mezcla se calentó a 150 °C durante 1 h en un dispositivo de microondas de modo único. Tras el enfriamiento a temperatura ambiente, se añadió una solución saturada acuosa de bicarbonato de sodio, y la mezcla se extrajo con acetato de etilo. Las capas orgánicas combinadas se secaron sobre sulfato de sodio, se filtraron y se

concentraron. El residuo se purificó por HPLC preparativa (procedimiento 5). Rendimiento: 83 mg (63 % del t.).

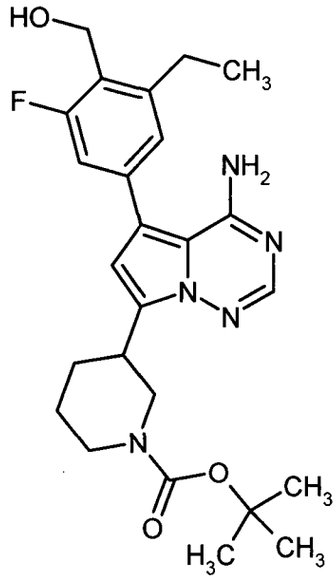
HPLC (procedimiento 9): R_t = 1,61 min;

LC-MS (procedimiento 10): R_t = 1,02 min; MS (ESIpos): *m/z* (%) = 456,4 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 454,4 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,22 (t, 3H), 1,41 (s, 9H), 2,1 (m, 1H), 2,80 (q, 2H), 3,30-3,43 (m, 2H), 3,44-3,51 (m, 1H), 3,78 (m, 1H), 4,55 (d, 2H), 5,00 (t, 1H), 6,68 (s, 1H), 7,09 (d, 1H), 7,15 (s, 1H), 7,95 (s, 1H).

Intermedio 67A

3-{4-amino-5-[3-etil-5-fluoro-4-(hidroximetil)fenil]pirrolo[2,1-f][1,2,4]triazin-7-il}piperidin-1-carboxilato de *rac-terc*-butilo



El Intermedio 31A (148 mg, 0,29 mmol), el Intermedio 58A (98 mg, 0,35 mmol) y tetrakis(trifenilfosfina)paladio (0) (17 mg, 0,015 mmol) se disolvieron en una mezcla de acetonitrilo (2,3 ml) y solución acuosa de carbonato de sodio 2 M (0,67 ml) en un vial reactor de microondas. Tras la desgasificación durante 5 min. usando argón, al recipiente de reacción se le colocó una tapa engastada, y la mezcla se calentó a 150 °C durante 1 h en un dispositivo de microondas de modo único. Tras el enfriamiento a temperatura ambiente, se añadió una solución saturada acuosa de bicarbonato de sodio, y la mezcla se extrajo con acetato de

etilo. Las capas orgánicas combinadas se secaron sobre sulfato de sodio, se filtraron y se concentraron. El residuo se purificó por HPLC preparativa (procedimiento 5). Rendimiento: 105 mg (76 % del t.).

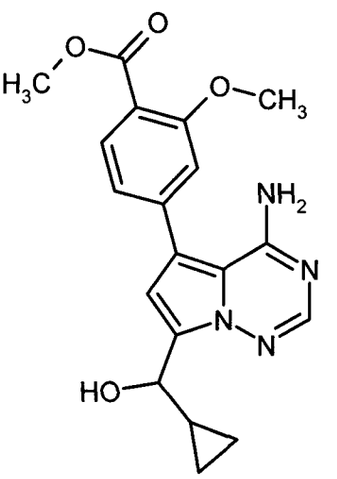
HPLC (procedimiento 9): R_t = 1,71 min;

LC-MS (procedimiento 10): R_t = 1,08 min; MS (ESIpos): *m/z* (%) = 470,4 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 468,4 (75) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,22 (t, 3H), 1,38 (s, 9H), 1,50 (m, 1H), 1,65-1,90 (m, 2H), 2,06 (m, 1H), 2,80 (q, 2H), 2,98 (m, 1H), 3,20-3,43 (m, 2H), 3,8 (m, 1H), 4,08 (m, 1H), 4,55 (d, 2H), 5,02 (t, 1H), 6,65 (s, 1H), 7,07 (d, 1H), 7,13 (s, 1H), 7,93 (s, 1H).

Intermedio 68A

4-{4-amino-7-[ciclopropil(hidroxi)metil]pirrolo[2,1-f][1,2,4]triazin-5-il}-2-metoxi-benzoato de *rac*-metilo



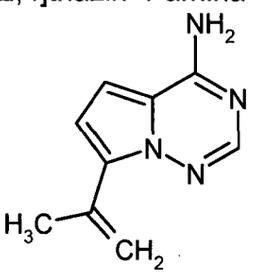
El Intermedio 17A (250 mg, 0,88 mmol), ácido [3-metoxi-4-(metoxicarbonil)fenil]borónico (223 mg, 1,06 mmol) y tetrakis(trifenilfosfina)paladio (0) (102 mg, 0,088 mmol) se disolvieron en una mezcla de 1,4-dioxano (5,5 ml) y solución acuosa de carbonato de sodio 2 M (1,32 ml) bajo argón y se calentaron a reflujo durante 16 h. Después, se añadió otra porción de tetrakis-(trifenilfosfina)paladio (0) (102 mg, 0,088 mmol), y el calentamiento continuó durante otras 24 h. Tras el enfriamiento a temperatura ambiente, la mezcla de

reacción se filtró, el filtrado se concentró, y el residuo se purificó por HPLC preparativa (procedimiento 7). Rendimiento: 130 mg (80 % de pureza, 32 % del t.). LC-MS (procedimiento 10): R_t = 0,80 min; MS (ESIpos): *m/z* (%) = 369,3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 367,3 (75) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 0,41 (m, 3H), 0,49 (m, 1H), 1,37 (m, 1H), 3,81 (s, 3H), 4,68 (d, 1H), 6,92 (s, 1H), 7,13 (dd, 1H), 7,22 (d, 1H), 7,77 (d, 1H), 8,05 (s, 1H).

Intermedio 69A

7-(Prop-1-en-2-il)pirrolo[2,1-f][1,2,4]triazin-4-amina



El material de inicio 7-bromopirrolo[2,1-f][1,2,4]triazin-4-amina se sintetizó de acuerdo con el procedimiento descrito en el documento WO 2007/056170-A2 (Intermedio B).

Bajo una atmósfera de argón, se disolvieron 7-bromopirrolo[2,1-f][1,2,4]triazin-4-amina (426 mg, 2 mmol) y 4,4,5,5-tetrametil-2-(prop-1-en-2-il)-1,3,2-dioxaborolano (420 mg, 2,5 mmol) en una mezcla de 1,2-dimetoxietano (10 ml) y solución acuosa de carbonato de sodio (2 M, 4 ml). La mezcla de reacción se desgasificó, y se añadió cloruro de 1,1'-bis(difenilfosfino)ferrocenopaladio (II) (73 mg, 0,1 mmol). Tras la agitación a 90 °C hasta el día siguiente, la mezcla de reacción se diluyó con acetato de etilo (40 ml), se añadió agua (10 ml), y las capas se separaron. La capa acuosa se extrajo con acetato de etilo (2 x 40 ml), y las capas orgánicas combinadas se secaron sobre sulfato de sodio, se filtraron y se concentraron. El residuo se purificó por cromatografía flash (puriFlash, Interchim, ciclohexano/acetato de etilo 1:1 a gradiente de acetato de etilo 100 %) para dar el

producto del título como un sólido ligeramente amarillo. Rendimiento: 304 mg (81 % del t.).

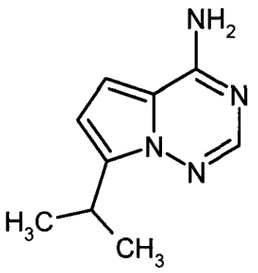
HPLC (procedimiento 10): R_t = 0,83 min;

LC-MS (procedimiento 10): R_t = 0,57 min; MS (ESIpos): *m/z* (%) = 175,1 (100) $[M+H]^+$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 2,15 (s, 3H), 5,22 (m, 1H), 6,30 (m, 1H), 6,73 (d, 1H), 6,91 (d, 1H), 7,69 (m, 1H), 7,91 (s, 1H).

Intermedio 70A

7-Isopropilpirrolo[2,1-f][1,2,4]triazin-4-amina



El Intermedio 69A (149 mg, 0,86 mmol) se disolvió en una mezcla de etanol y acetato de etilo (1:1, 40 ml) bajo argón. Se añadió paladio sobre carbón (10 %, 9,1 mg), y la mezcla se agitó vigorosamente durante 16 h bajo una atmósfera de hidrógeno a presión ambiente y temperatura ambiente. Después, el catalizador se eliminó por filtración, y el disolvente se destiló a presión reducida para dar 131 mg (80 % del t.) del compuesto del título como un sólido incoloro. Este producto se utilizó en la próxima etapa sintética sin purificación adicional.

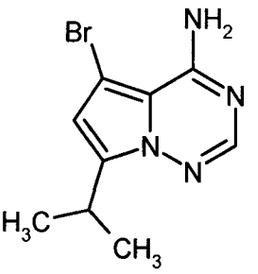
HPLC (procedimiento 10): R_t = 0,81 min;

LC-MS (procedimiento 10): R_t = 0,56 min; MS (ESIpos): *m/z* (%) = 177,0 (100) $[M+H]^+$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,27 (d, 6H), 3,36 (m, 1H), 6,41 (d, 1H), 6,80 (d, 1H), 7,48-7,59 (m, 2H), 7,80 (s, 1H).

Intermedio 71A

5-Bromo-7-isopropilpirrolo[2,1-f][1,2,4]triazin-4-amina



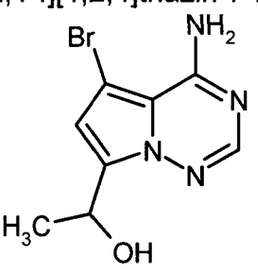
El Intermedio 70A (125 mg, 0,71 mmol) se disolvió en THF seco (21 ml) y se enfrió a -78 °C. Se añadió 1,3-dibromo-5,5-dimetilhidantoína (81 mg, 0,28 mmol) en dos porciones iguales. La mezcla de reacción se agitó a -78 °C durante 1 h y después se dejó calentar a temperatura ambiente hasta el día siguiente. Tras la adición de agua (20 ml) y la agitación adicional durante 20 min., el sólido precipitado se recolectó por filtración y se secó *in vacuo*. El producto bruto así obtenido (209 mg, >100 % del t.) se utilizó en la próxima etapa sintética sin purificación adicional.

HPLC (procedimiento 9): R_t = 1,35 min.

LC-MS (procedimiento 10): R_t = 0,91 min; MS (ESIpos): *m/z* (%) = 257,0 (100) $[M+H]^+$.

Intermedio 72A

rac-1-(4-Amino-5-bromopirrolo[2,1-f][1,2,4]triazin-7-il)etanol



El Intermedio 16A (500 mg, 1,66 mmol) se suspendió en THF (10 ml) y se enfrió a 0 °C. Se añadió una solución de bromuro de metil magnesio (3 N en éter de dietilo, 1,7 ml), y la mezcla de reacción se agitó durante 30 min. Después, se añadió una solución saturada acuosa de cloruro de amonio, y la mezcla se extrajo con acetato de etilo (2 x 20 ml). Las capas orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron para dar 235 mg (46 % del t.) del producto del título que se utilizó en la próxima etapa sintética sin purificación adicional.

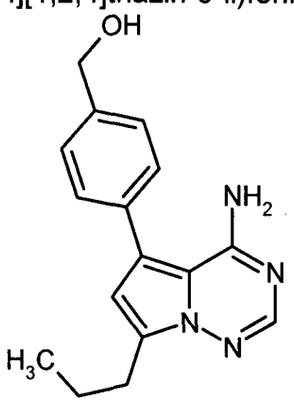
LC-MS (procedimiento 5): R_t = 0,73 min; MS (ESIpos): *m/z* (%) = 259,1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 257,1 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,41 (d, 3H), 5,16 (m, 1H), 5,30 (m, 1H), 6,70 (s, 1H), 7,85 (s, 1H).

Ejemplos de Preparación:

Ejemplo 1

[4-(4-Amino-7-Propilpirrolo[2,1-f][1,2,4]triazin-5-il)fenil]metanol



El compuesto del título se obtuvo por el procedimiento de síntesis general 1 a partir del Intermedio 11A (100 mg, 0,39 mmol) y ácido 4-(hidroximetil)fenilborónico (60 mg, 0,39 mmol). La purificación del producto bruto se llevó a cabo por HPLC preparativa (procedimiento 2). Rendimiento: 33 mg (30 % del t.).

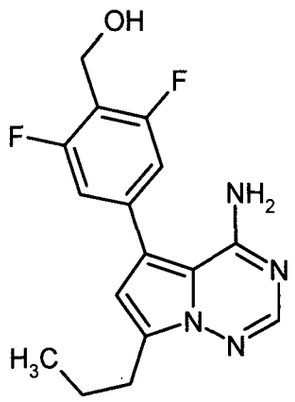
HPLC (procedimiento 1): R_t = 3,47 min; HPLC (procedimiento 2): R_t = 3,78 min;

LC-MS (procedimiento 4): R_t = 0,91 min; MS (ESIpos): *m/z* (%) = 283,2 (100) $[M+H]^+$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 0,97 (t, *J* = 7,4 Hz, 3H), 1,71 (m, 2H), 3,31 (s, 2H), 4,52 (s, 2H), 6,54 (s, 1H), 7,42 (s, 4H), 7,89 (s, 1H).

Ejemplo 2

[4-(4-Amino-7-propilpirrolo[2,1-f][1,2,4]triazin-5-il)-2,6-difluorofenil]metanol



El compuesto del título se obtuvo por el procedimiento de síntesis general 2 a partir del Intermedio 11A (118 mg, 0,46 mmol) y (4-bromo-2,6-difluorofenil)metanol (108 mg, 0,49 mmol). La purificación del producto bruto se llevó a cabo por HPLC preparativa (procedimiento 2). Rendimiento: 59 mg (40 % del t.).

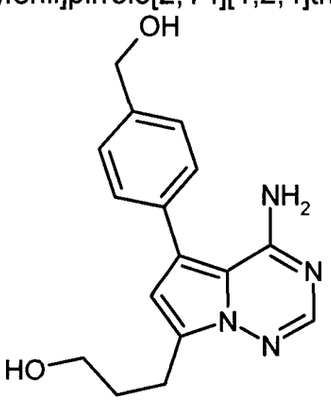
HPLC (procedimiento 2): R_t = 3,94 min;

LC-MS (procedimiento 7): R_t = 1,47 min; MS (ESIpos): *m/z* (%) = 319,3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 317,3 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 0,95 (t, 3H), 1,71 (m, 2H), 4,52 (m, 2H), 5,26 (t, 1H), 6,64 (s, 1H), 7,10 (m, 2H), 7,91 (s, 1H).

Ejemplo 3

3-{4-Amino-5-[4-(hidroximetil)fenil]pirrolo[2,1-f][1,2,4]triazin-7-il}propan-1-ol



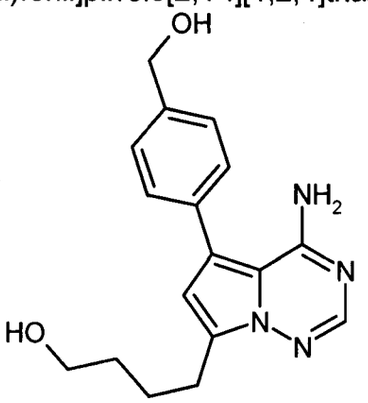
El compuesto del título se obtuvo a partir del Intermedio 10A (100 mg, 0,37 mmol) y ácido 4-(hidroximetil)fenilborónico (67 mg, 0,44 mmol, 1,2 eq.) de acuerdo con el procedimiento de síntesis general 1. El producto bruto se purificó por HPLC preparativa (procedimiento 2) para dar 73 mg (66 % del t.) del compuesto del título como un sólido incoloro.

HPLC (procedimiento 1): R_t = 2,91 min; HPLC (procedimiento 2): R_t = 3,14 min; LC-MS (procedimiento 6): R_t = 0,60 min; MS (ESIpos): *m/z* (%) = 299,3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 297,4 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,84 (m, 2H), 2,95 (t, *J* = 7,6 Hz, 2H), 3,50 (m, 2H), 4,58 (s, 2H), 6,67 (s, 1H), 7,41 (s, 4H), 8,03 (s, 1H).

Ejemplo 4

4-{4-Amino-5-[4-(hidroximetil)fenil]pirrolo[2,1-f][1,2,4]triazin-7-il}butan-1-ol



El compuesto del título se obtuvo por el procedimiento de síntesis general 1 a partir del Intermedio 14A (75 mg, 0,26 mmol) y ácido 4-(hidroximetil)fenilborónico (48 mg, 0,32 mmol). La purificación del producto bruto se llevó a cabo por HPLC preparativa (procedimiento 2). Rendimiento: 66 mg (80 % del t.).

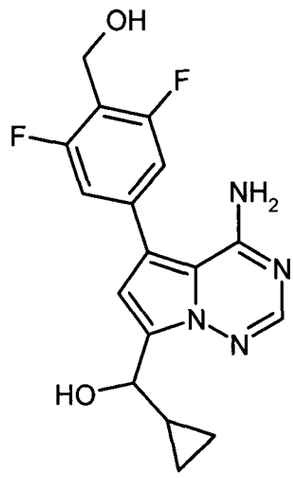
HPLC (procedimiento 2): R_t = 3,28 min;

LC-MS (procedimiento 6): R_t = 0,68 min; MS (ESIpos): *m/z* (%) = 313,3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 311,2 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,48-1,51 (m, 2H), 1,67-1,70 (m, 2H), 2,91 (t, *J* = 7,6 Hz, 2H), 3,42 (t, *J* = 6,4 Hz, 2H), 4,58 (s, 2H), 6,67 (s, 1H), 7,42 (s, 4H), 8,03 (s, 1H).

Ejemplo 5

{4-Amino-5-[3,5-difluoro-4-(hidroximetil)fenil]pirrolo[2,1-f][1,2,4]triazin-7-il}-(ciclopropil)metanol



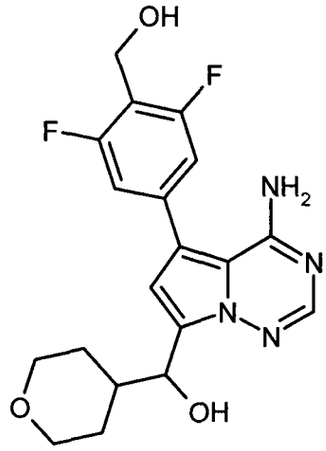
El compuesto del título se obtuvo a partir del Intermedio 17A (125 mg, 0,44 mmol) y el Intermedio 2A (114 mg, 0,53 mmol) por el procedimiento de síntesis general 1. El producto bruto se purificó por HPLC preparativa (procedimiento 3). Rendimiento: 73 mg (48 % del t.).

LC-MS (procedimiento 7): R_t = 1,09 min; MS (ESIpos): *m/z* (%) = 347,3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 345,3 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 0,39 (m, 3H), 0,48 (m, 1H), 1,35 (m, 1H), 4,54 (d, 2H), 4,67 (m, 1H), 5,26 (m, 2H), 6,80 (s, 1H), 7,14 (m, 2H), 7,92 (s, 1H).

Ejemplo 6

{4-Amino-5-[3,5-difluoro-4-(hidroximetil)fenil]pirrolo[2,1-f][1,2,4]triazin-7-il}(tetrahidro-2*H*-piran-4-il)metanol



El compuesto del título se obtuvo a partir del Intermedio 18A (200 mg, 0,61 mmol) y el Intermedio 2A (158 mg, 0,73 mmol) por el procedimiento de síntesis general 1.

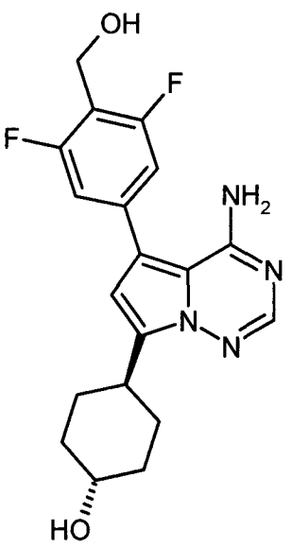
El producto bruto se purificó por HPLC preparativa (procedimiento 3). Rendimiento: 125 mg (52 % del t.).

LC-MS (procedimiento 5): R_t = 1,29 min; MS (ESIpos): *m/z* (%) = 391,1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 389,0 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,24 (br, d, 1H), 1,36 (m, 2H), 1,68 (br, d, 1H), 2,03 (m, 1H), 2,60 (t, 2H), 3,82 (m, 2H), 4,54 (s, 2H), 4,95 (br, d, 1H), 5,28 (br, 1H), 5,33 (br, 1H), 6,73 (s, 1H), 7,14 (m, 2H), 7,93 (s, 1H).

Ejemplo 7

trans-4-{4-Amino-5-[3,5-difluoro-4-(hidroximetil)fenil]pirrolo[2,1-f][1,2,4]triazin-7-il}-ciclohexanol



El compuesto del título se obtuvo por el procedimiento de síntesis general 1 a partir del Intermedio 24A (323 mg, 85 % de pureza, 0,88 mmol) y el Intermedio 1A (286 mg, 1,06 mmol, 1,2 eq.). La purificación del producto bruto se llevó a cabo en primer lugar por cromatografía flash (cartucho empacado de sílice de Biotage, eluyente diclorometano/metanol 95:5). Se llevó a cabo una purificación adicional por HPLC preparativa (procedimiento 2). Rendimiento: 72 mg (21 % del t.).

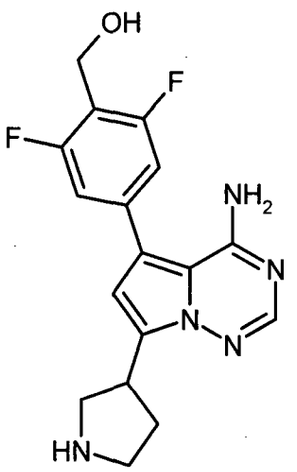
HPLC (procedimiento 2): R_t = 3,37 min;

LC-MS (procedimiento 7): R_t = 1,01 min; MS (ESIpos): *m/z* (%) = 375,3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 373,3 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,32 (m, 2H), 1,50 (m, 2H), 1,98 (m, 2H), 2,04 (m, 2H), 3,04 (tt, 1H), 3,47 (m, 1H), 4,51 (m, 2H), 4,61 (d, 1H), 5,26 (t, 1H), 6,60 (s, 1H), 7,12 (m, 2H), 7,91 (s, 1H).

Ejemplo 8

rac-{4-[4-Amino-7-(pirrolidin-3-il)pirrolo[2,1-f][1,2,4]triazin-5-il]-2,6-difluorofenil}-metanol



El Intermedio 51A (67 mg, 0,15 mmol) se disolvió en una solución 30 % de ácido trifluoroacético en diclorometano (6 ml) a 0 °C. La mezcla de reacción se agitó a esta temperatura durante 20 min., después, todos los volátiles se eliminaron bajo presión reducida. El residuo se purificó por HPLC preparativa (procedimiento 2). El producto así obtenido se disolvió en acetato de etilo y se lavó con una solución saturada acuosa de carbonato de sodio. La capa orgánica se secó sobre sulfato de sodio anhidro, y el disolvente se destiló para dar 21 mg (41 % del t.) del compuesto del título.

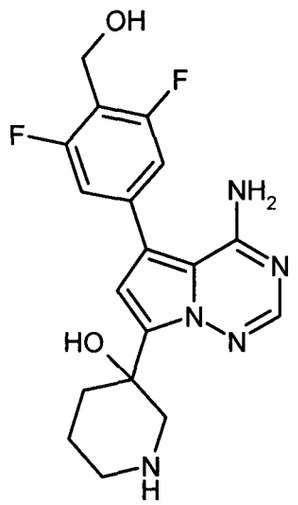
HPLC (procedimiento 2): R_t = 2,96 min;

LC-MS (procedimiento 6): R_t = 0,34 min; MS (ESIpos): *m/z* (%) = 346,1 (20) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 344,2 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,94 (m, 1H), 2,22 (m, 1H), 2,94 (m, 1H), 3,00-3,16 (m, 2H), 3,40 (m, 2H), 3,72 (m, 1H), 4,51 (s, 2H), 5,22 (br, s, 1H), 6,71 (s, 1H), 7,11 (m, 2H), 7,92 (s, 1H).

Ejemplo 9

rac-3-{4-Amino-5-[3,5-difluoro-4-(hidroximetil)fenil]pirrolo[2,1-f][1,2,4]triazin-7-il}-piperidin-3-ol



El Intermedio 52A (46 mg, 0,10 mmol) se disolvió en una solución 30 % de ácido trifluoroacético en diclorometano (1,5 ml) a 0 °C. La mezcla de reacción se agitó a esta temperatura durante 30 min., después, todos los volátiles se eliminaron bajo presión reducida. El residuo se purificó por HPLC preparativa (procedimiento 2). El producto así obtenido se disolvió en acetato de etilo y se lavó con una solución saturada acuosa de carbonato de sodio. La capa orgánica se secó sobre sulfato de sodio anhidro, y el disolvente se destiló para dar 20 mg (55 % del t.) del compuesto del título.

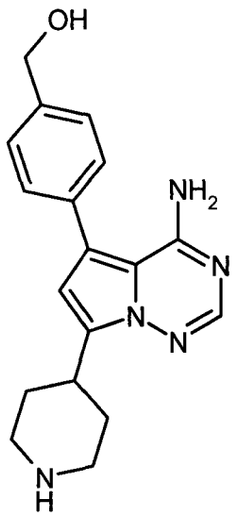
HPLC (procedimiento 2): R_t = 2,94 min;

LC-MS (procedimiento 4): R_t = 1,01 min; MS (ESIpos): *m/z* (%) = 358,1 (100) $[M-H_2O+H]^+$, MS (ESIneg): *m/z* (%) = 374,1 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,48 (m, 1H), 1,89 (m, 2H), 2,40-2,69 (m, 2H), 2,92 (d, 1H), 3,02 (d, 1H), 3,40 (m, 1H), 4,52 (m, 2H), 5,26 (t, 1H), 5,45 (s, 1H), 6,72 (s, 1H), 7,13 (m, 2H), 7,94 (s, 1H).

Ejemplo 10

{4-[4-Amino-7-(piperidin-4-il)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil}metanol



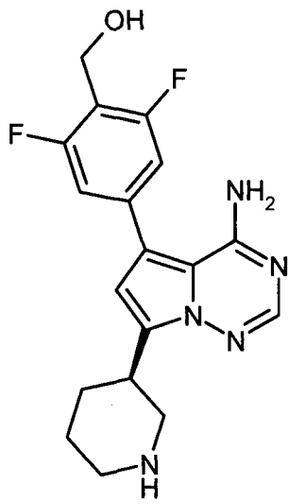
El Intermedio 53A (324 mg, 0,77 mmol) se disolvió en diclorometano (15 ml). Se añadió ácido trifluoroacético (1,5 ml), y la mezcla se agitó a temperatura ambiente durante 16 h. Se añadió otra porción de ácido trifluoroacético (1,5 ml), y la agitación continuó hasta que HPLC (procedimiento 1) indicara la conversión completa del material de inicio. Después, todos los volátiles se eliminaron bajo presión reducida, y el residuo se purificó por HPLC preparativa (procedimiento 1) para dar 226 mg (91 % del t.) del compuesto del título.

HPLC (procedimiento 1): R_t = 3,37 min; HPLC (procedimiento 2): R_t = 2,90 min; LC-MS (procedimiento 4): R_t = 0,90 min; MS (ESIpos): *m/z* (%) = 324,1 (75) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 322,2 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,79-1,95 (m, 2H), 2,16-2,23 (m, 2H), 3,05-3,19 (m, 2H), 3,37-3,52 (m, 3H), 4,56 (s, 2H), 5,49 (s, 2H), 6,66 (s, 1H), 7,43 (s, 4H), 8,03 (s, 1H), 8,39-8,50 (m, 1H), 8,65-8,69 (m, 1H).

Ejemplo 11

(4-{4-Amino-7-[(3*R*)-piperidin-3-il]pirrolo[2,1-f][1,2,4]triazin-5-il}-2,6-difluorofenil)-metanol



El Intermedio 55A (35 mg, 0,08 mmol) se disolvió en una solución 30 % de ácido trifluoroacético en diclorometano (1,5 ml) a 0 °C. La mezcla de reacción se agitó a esta temperatura durante 30 min., después, todos los volátiles se eliminaron bajo presión reducida. El residuo se purificó por HPLC preparativa (procedimiento 2). El producto así obtenido se disolvió en acetato de etilo y se lavó con una solución saturada acuosa de carbonato de sodio. La capa orgánica se secó sobre sulfato de sodio anhidro, y el disolvente se destiló para dar 18 mg (66 % del t.) del compuesto del título.

HPLC (procedimiento 2): R_t = 3,10 min;

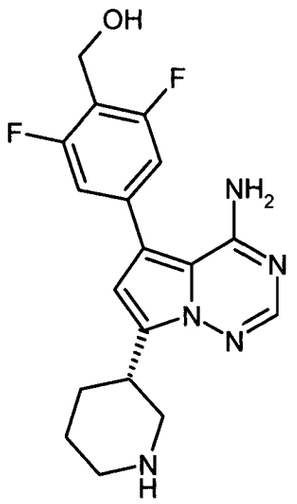
LC-MS (procedimiento 6): R_t = 0,55 min; MS (ESIpos): *m/z* (%) = 360,2 (20) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 358,3 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,67 (m, 2H), 1,83 (m, 1H), 2,75 (m, 1H), 2,86 (m, 1H), 3,20 (d, 1H), 3,41 (m, 2H), 4,53 (m, 2H), 5,29 (t, 1H), 6,70 (s, 1H), 7,11 (m, 1H), 7,94 (s, 1H).

$[\alpha]_{589}^{20}$ = +16,8° (c = metanol, 0,515).

Ejemplo 12

(4-{4-Amino-7-[(3*S*)-piperidin-3-il]pirrolo[2,1-f][1,2,4]triazin-5-il}-2,6-difluorofenil)-metanol

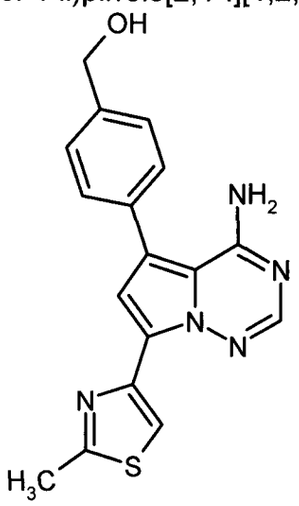


El compuesto del título se obtuvo a partir del Intermedio 56A (19 mg, 0,04 mmol) por el mismo procedimiento que se describe para la conversión del Intermedio 55A al Ejemplo 11. Rendimiento: 12 mg (81 % del t.).

Los datos de HPLC, LC-MS y RMN ^{1}H son idénticos a los mostrados para el Ejemplo 11.

Ejemplo 13

{4-[4-Amino-7-(2-metil-1,3-tiazol-4-il)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil}metanol



El Intermedio 33A (60 mg, 0,21 mmol) y tioacetamida (15 mg, 0,20 mmol, 0,95 eq.) se disolvieron en 1,4-dioxano (2 ml) y se calentaron a reflujo durante 4,5 h. Tras el enfriamiento, se añadieron ácido 4-(hidroximetil)fenilborónico (38 mg, 0,25 mmol, 1,2 eq.), tetrakis(trifenilfosfina)paladio (0) (59 mg, 0,07 mmol, 0,25 eq.) y solución acuosa de carbonato de sodio 2 M (0,4 ml). La mezcla se agitó cuidadosamente a

100 °C durante 16 h. Después, se añadió otra porción de tetrakis(trifenilfosfina)-paladio (0) (24 mg, 0,1 eq.), y la agitación a 100 °C continuó durante otras 4 h. Después, la mezcla de reacción se filtró, el filtrado se evaporó a presión reducida, y el residuo se purificó por HPLC preparativa (procedimiento 2) para dar 28 mg (40 % del t.) del compuesto del título como cristales blancuzcos.

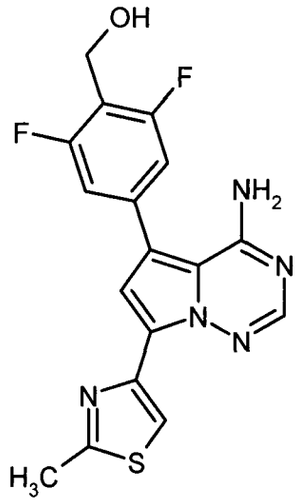
HPLC (procedimiento 1): R_t = 3,85 min; HPLC (procedimiento 2): R_t = 3,60 min;

LC-MS (procedimiento 6): R_t = 0,94 min; MS (ESIpos): *m/z* (%) = 338,2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 336,1 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 2,73 (s, 3H), 4,58 (s, 2H), 7,17 (s, 1H), 7,45 (d, *J* = 8,3 Hz, 2H), 7,50 (d, *J* = 8,3 Hz, 2H), 8,09 (s, 1H), 8,33 (s, 1H).

Ejemplo 14

{4-[4-Amino-7-(2-metil-1,3-tiazol-4-il)pirrolo[2,1-f][1,2,4]triazin-5-il]-2,6-difluorofenil}-metanol



El compuesto del título se obtuvo por el procedimiento de síntesis general 1 a partir del Intermedio 34A (75 mg, 0,24 mmol) y el Intermedio 1A (78 mg, 0,29 mmol, 1,2 eq.). La purificación del producto bruto se llevó a cabo por HPLC preparativa (procedimiento 2). Rendimiento: 27 mg (30 % del t.).

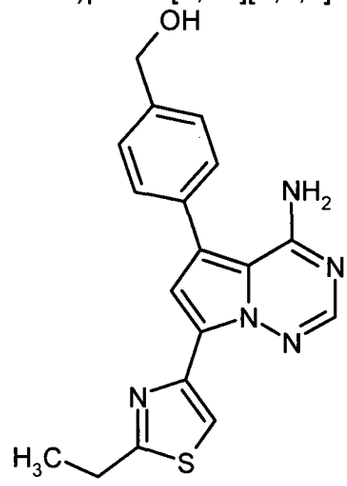
HPLC (procedimiento 1): R_t = 3,79 min;

LC-MS (procedimiento 6): R_t = 1,03 min; MS (ESIpos): *m/z* (%) = 374,0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 372,2 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 2,72 (s, 3H), 4,53 (s, 2H), 7,18-7,27 (m, 2H), 8,11 (s, 1H), 8,33 (s, 1H).

Ejemplo 15

{4-[4-Amino-7-(2-etil-1,3-tiazol-4-il)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil}metanol



El Intermedio 35A (91 mg, 0,28 mmol) se hizo reaccionar con ácido 4-(hidroximetil)fenilborónico (51 mg, 0,34 mmol, 1,2 eq.) de acuerdo con el procedimiento de síntesis general 1. El producto bruto se purificó por HPLC preparativa (procedimiento 2) para dar 68 mg (69 % del t.) del compuesto del título como cristales incoloros.

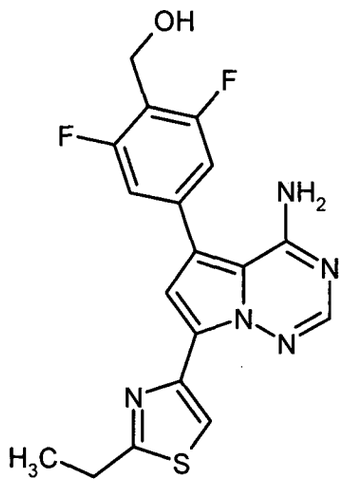
HPLC (procedimiento 1): R_t = 3,73 min;

LC-MS (procedimiento 6): R_t = 1,05 min; MS (ESIpos): *m/z* (%) = 352,2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 350,3 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,36 (t, *J* = 7,6 Hz, 3H), 3,06 (q, *J* = 7,6 Hz, 2H), 4,58 (s, 2H), 7,19 (s, 1H), 7,46 (d, *J* = 8,0 Hz, 2H), 7,52 (d, *J* = 8,0 Hz, 2H), 8,12 (s, 1H), 8,36 (s, 1H).

Ejemplo 16

{4-[4-Amino-7-(2-etil-1,3-tiazol-4-il)pirrolo[2,1-f][1,2,4]triazin-5-il]-2,6-difluorofenil}-metanol



El compuesto del título se obtuvo por el procedimiento de síntesis general 1 a partir del Intermedio 35A (34 mg, 0,11 mmol) y el Intermedio 1A (34 mg, 0,13 mmol, 1,2 eq.). La purificación del producto bruto se llevó a cabo por HPLC preparativa (procedimiento 2). Rendimiento: 16 mg (40 % del t.).

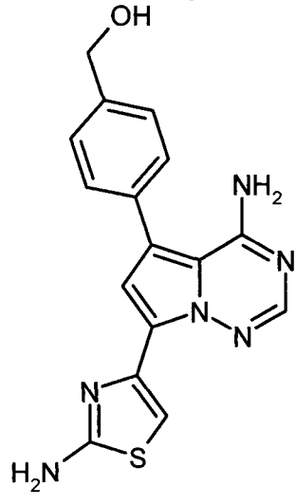
HPLC (procedimiento 1): R_t = 4,04 min;

LC-MS (procedimiento 6): R_t = 1,15 min; MS (ESIpos): *m/z* (%) = 388,0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 386,1 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,38 (t, 3H), 3,06 (q, 2H), 4,55 (s, 2H), 7,20-7,31 (m, 3H), 8,16 (s, 1H), 8,38 (s, 1H).

Ejemplo 17

{4-[4-Amino-7-(2-amino-1,3-tiazol-4-il)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil}metanol



El compuesto del título se obtuvo por el procedimiento de síntesis general 1 a partir del Intermedio 36A (55 mg, 0,18 mmol) y ácido 4-(hidroximetil)fenilborónico

(32 mg, 0,21 mmol). La purificación del producto bruto se llevó a cabo por HPLC preparativa (procedimiento 2). Rendimiento: 29 mg (49 % del t.).

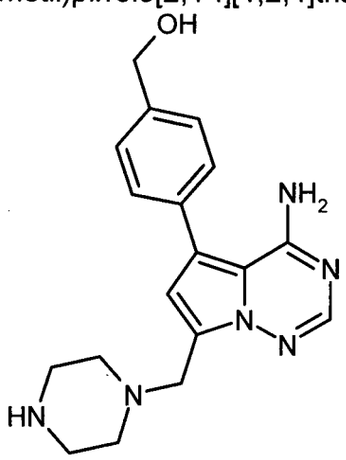
HPLC (procedimiento 1): R_t = 3,03 min;

LC-MS (procedimiento 5): R_t = 1,21 min; MS (ESIpos): *m/z* (%) = 339,1 (30) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 337,1 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 4,58 (m, 2H), 5,75 (m, 1H), 6,93 (s, 1H), 7,05 (m, 2H), 7,43 (m, 4H), 7,55 (s, 1H), 8,08 (s, 1H).

Ejemplo 18

{4-[4-Amino-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil}metanol



El Intermedio 37A (200 mg, 0,49 mmol), ácido 4-(hidroximetil)fenilborónico (90 mg, 0,59 mmol, 1,2 eq.) y tetrakis(trifenilfosfina)paladio (0) (57 mg, 0,05 mmol, 0,1 eq.) se disolvieron en una mezcla de 1,4-dioxano (4,0 ml) y solución acuosa de carbonato de sodio 2 M (1,0 ml) en un vial reactor de microondas. Al recipiente de reacción se le colocó una tapa engastada, y la mezcla se calentó a 140 °C durante 1 h en un dispositivo de microondas de modo único. Tras el enfriamiento, la mezcla se filtró sobre un lecho de Celite que se enjuagó con 1,4-dioxano para eluir todo el material orgánico. El filtrado combinado se evaporó a sequedad bajo presión reducida, y el residuo se purificó por HPLC preparativa (procedimiento 1) para dar 75 mg (45 % del t.) del compuesto del título.

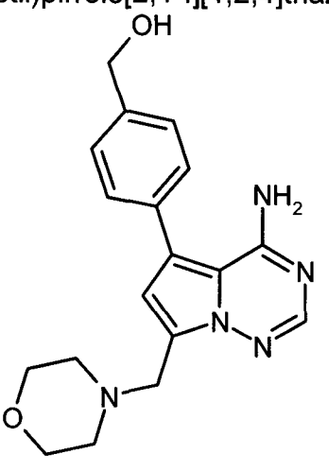
HPLC (procedimiento 1): R_t = 2,85 min;

LC-MS (procedimiento 4): R_t = 0,93 min; MS (ESIpos): *m/z* (%) = 339,1 (30) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 337,2 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 2,38 (br, s, 4H), 2,63 (m, 4H), 3,80 (s, 2H), 4,55 (s, 2H), 5,26 (br, s, 1H), 6,60 (s, 1H), 7,39 (s, 4H), 7,90 (s, 1H).

Ejemplo 19

{4-[4-Amino-7-(morfolin-4-ilmetil)pirrolo[2,1-f][1,2,4]triazin-5-il]fenil}metanol



El compuesto del título se obtuvo a partir del Intermedio 38A (200 mg, 0,64 mmol) y ácido 4-(hidroximetil)fenilborónico (116 mg, 0,77 mmol, 1,2 eq.) de acuerdo con el procedimiento de síntesis general 1. El producto bruto se purificó por HPLC preparativa (procedimiento 2). El material así obtenido se disolvió en unos pocos mililitros de una mezcla de acetonitrilo y agua, se añadió una solución acuosa de carbonato de sodio 2 M, y la mezcla se agitó durante 10 min. Durante este tiempo, el compuesto del título precipitó. Los cristales se aislaron por filtración y se secaron *in vacuo* para dar 95 mg (49 % del t.) de un sólido incoloro.

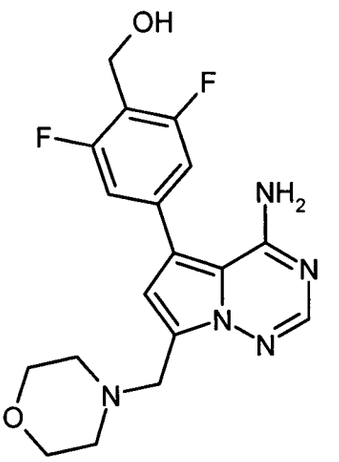
HPLC (procedimiento 1): R_t = 3,21 min;

LC-MS (procedimiento 4): R_t = 0,93 min; MS (ESIpos): *m/z* (%) = 340 (1) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 338,2 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 2,47 (m, 4H), 3,31 (s, 4H), 3,53 (t, 2H), 3,82 (s, 1H), 4,56 (d, 2H), 5,22 (t, 1H), 6,63 (s, 1H), 7,42 (s, 4H), 7,90 (s, 1H).

Ejemplo 20

{4-[4-Amino-7-(morfolin-4-ilmetil)pirrolo[2,1-f][1,2,4]triazin-5-il]-2,6-difluorofenil}-metanol



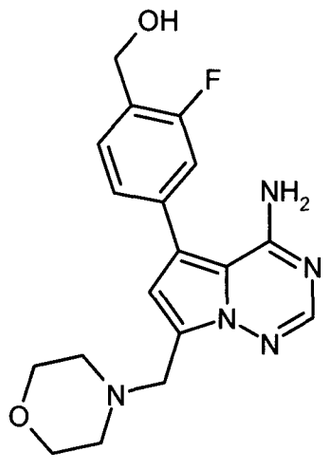
A una solución del Intermedio 40A (110 mg, 0,22 mmol) en THF (2,2 ml) se añadieron 0,45 ml (0,45 mmol) de una solución de fluoruro de tetrabutilamonio 1 M (TBAF) en THF, y la mezcla se agitó a temperatura ambiente durante 1 h. Después, la mezcla de reacción se evaporó bajo presión reducida, y el residuo se suspendió en 3 ml de metanol y se agitó a temperatura ambiente durante 5 min. El precipitado resultante se filtró, se lavó con una pequeña cantidad de metanol y se secó *in vacuo* para dar 68 mg (81 % del t.) del compuesto del título.

LC-MS (procedimiento 4): R_t = 1,03 min; MS (ESIpos): *m/z* (%) = 376,0 (80) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 374,1 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 2,45 (br, m, 4H), 3,56 (t, 4H), 3,82 (s, 2H), 4,54 (d, 2H), 5,27 (t, 1H), 6,75 (s, 1H), 7,16 (m, 2H), 7,95 (s, 1H).

Ejemplo 21

{4-[4-Amino-7-(morfolin-4-ilmetil)pirrolo[2,1-f][1,2,4]triazin-5-il]-2-fluorofenil}metanol



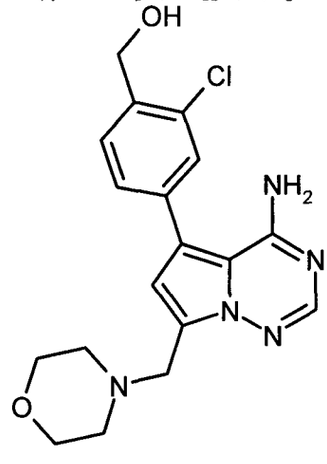
A una suspensión del Intermedio 41A (65,0 mg, 0,17 mmol) en THF (2,0 ml) se añadieron 0,2 ml (0,2 mmol) de una solución de hidruro de litio y aluminio 1 M en THF, y la mezcla se agitó a temperatura ambiente durante 1 h. La solución resultante se inactivó con agua y después se purificó directamente por HPLC preparativa (procedimiento 3) para dar 35 mg (58 % del t.) del compuesto del título.

LC-MS (procedimiento 6): R_t = 0,98 min; MS (ESIpos): *m/z* (%) = 358,1 (20) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 356,2 (100) $[M-H]^-$.

RMN ^1H (400 MHz, d_6-DMSO): δ (ppm) = 2,46 (br, m, 4H), 3,56 (t, 4H), 3,83 (s, 2H), 4,60 (d, 2H), 5,32 (t, 1H), 6,70 (s, 1H), 7,27 (dd, 2H), 7,55 (t, 1H), 7,94 (s, 1H).

Ejemplo 22

{4-[4-Amino-7-(morfolin-4-ilmetil)pirrolo[2,1-f][1,2,4]triazin-5-il]-2-clorofenil}metanol



El Intermedio 39A (200 mg, 0,56 mmol), el Intermedio 3A (112 mg, 0,51 mmol) y tetrakis(trifenilfosfina)paladio (0) (58 mg, 0,05 mmol) se disolvieron en una mezcla

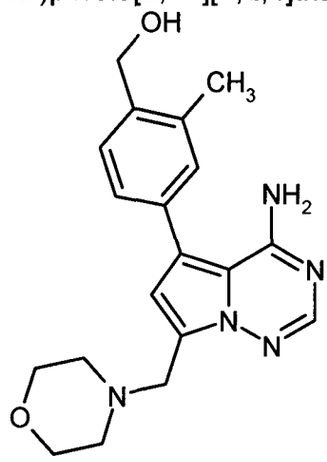
de 1,4-dioxano (4,0 ml) y solución acuosa de carbonato de sodio 2 M (1,0 ml) en un vial reactor de microondas. Al recipiente de reacción se le colocó una tapa engastada, y la mezcla se calentó a 140 °C durante 1 h en un dispositivo de microondas de modo único. Tras el enfriamiento, la mezcla se filtró, y el filtrado se purificó por HPLC preparativa (procedimiento 3) para dar 48 mg (23 % del t.) del compuesto del título.

LC-MS (procedimiento 6): R_t = 0,53 min; MS (ESIpos): *m/z* (%) = 374,1 (80) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 372,2 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 2,46 (br, m, 4H), 3,56 (t, 4H), 3,83 (s, 2H), 4,61 (d, 2H), 5,45 (t, 1H), 6,70 (s, 1H), 7,44 (dd, 1H), 7,49 (d, 1H), 7,63 (t, 1H), 7,94 (s, 1H).

Ejemplo 23

{4-[4-Amino-7-(morfolin-4-ilmetil)pirrolo[2,1-f][1,2,4]triazin-5-il]-2-metilfenil}metanol



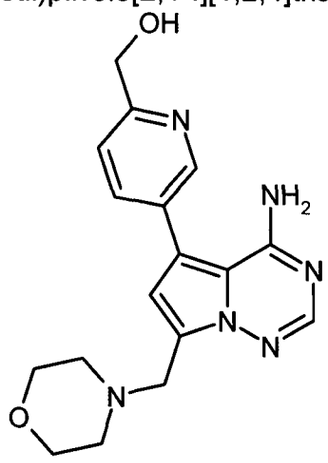
En analogía a la preparación del Ejemplo 28, el Intermedio 39A (200 mg, 0,56 mmol) se hizo reaccionar con Intermedio 4A (102 mg, 0,51 mmol) para dar 9 mg (5 % del t.) del compuesto del título.

LC-MS (procedimiento 4): R_t = 1,00 min; MS (ESIpos): *m/z* (%) = 354,3 (10) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 372,2 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 2,30 (s, 3H), 2,45 (br, m, 4H), 3,56 (t, 4H), 3,83 (s, 2H), 4,54 (d, 2H), 5,13 (t, 1H), 6,63 (s, 1H), 7,26 (s, 1H), 7,26 (d, 1H), 7,45 (d, 1H), 7,91 (s, 1H).

Ejemplo 24

{5-[4-Amino-7-(morfolin-4-ilmetil)pirrolo[2,1-f][1,2,4]triazin-5-il]piridin-2-il}metanol



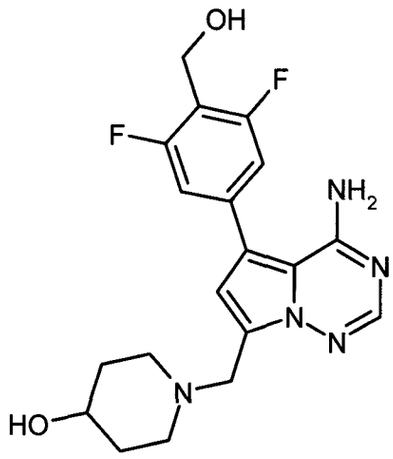
El compuesto del título se obtuvo a partir del Intermedio 38A (200 mg, 0,64 mmol) y el Intermedio 6A (147 mg, 0,96 mmol) por el procedimiento de síntesis general 1. El producto bruto se purificó por HPLC preparativa (procedimiento 4). Las impurezas restantes se eliminaron por la suspensión del producto en acetonitrilo (2 ml) y la recolección del sólido restante por filtración. Rendimiento: 27 mg (12 % del t.).

LC-MS (procedimiento 4): R_t = 0,78 min; MS (ESIpos): *m/z* (%) = 341 (10) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 339,3 (100) $[M-H]^-$.

RMN ^1H (400 MHz, d_6-DMSO): δ (ppm) = 2,46 (br, m, 4H), 3,56 (t, 4H), 3,84 (s, 2H), 4,62 (d, 2H), 5,46 (t, 1H), 6,73 (s, 1H), 7,54 (d, 1H), 7,86 (dd, 1H), 7,95 (d, 1H), 8,56 (s, 1H).

Ejemplo 25

1-({4-Amino-5-[3,5-difluoro-4-(hidroximetil)fenil]pirrolo[2,1-f][1,2,4]triazin-7-il}metil)-piperidin-4-ol



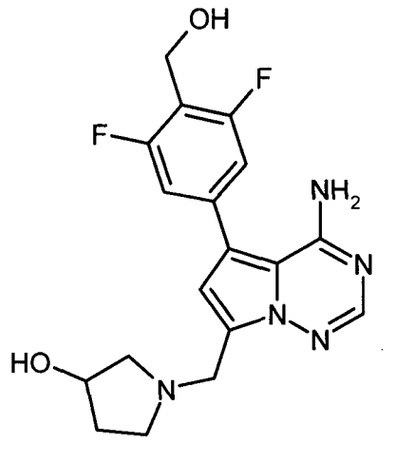
El compuesto del título se obtuvo a partir del Intermedio 45A (200 mg, 0,61 mmol) y el Intermedio 2A (159 mg, 0,74 mmol) por el procedimiento de síntesis general 1. El producto bruto se purificó por HPLC preparativa (procedimiento 3). Rendimiento: 103 mg (43 % del t.).

LC-MS (procedimiento 4): R_t = 0,98 min; MS (ESIpos): *m/z* (%) = 390,1 (60) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 388,2 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,36 (br, m, 2H), 1,68 (br, m, 2H), 2,12 (br, m, 2H), 2,75 (br, m, 2H), 3,41 (br, m, 1H), 3,79 (s, 2H), 4,51 (d, 1H), 4,54 (d, 2H), 5,27 (t, 1H), 6,72 (s, 1H), 7,15 (m, 2H), 7,94 (s, 1H).

Ejemplo 26

1-({4-Amino-5-[3,5-difluoro-4-(hidroximetil)fenil]pirrolo[2,1-f][1,2,4]triazin-7-il}metil)-pirrolidin-3-ol



El compuesto del título se obtuvo a partir del Intermedio 47A (110 mg, 0,35 mmol) y el Intermedio 2A (91,3 mg, 0,42 mmol) por el procedimiento de síntesis general

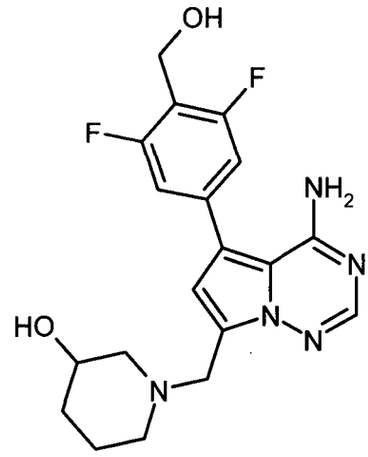
1. El producto bruto se purificó por HPLC preparativa (procedimiento 3). Rendimiento: 69 mg (52 % del t.).

LC-MS (procedimiento 4): R_t = 0,25 min; MS (ESIpos): *m/z* (%) = 376,1 (20) $[M+H]^+$.

RMN ^1H (400 MHz, d_6-DMSO): δ (ppm) = 1,54 (m, 1H), 1,98 (m, 1H), 2,43 (br, d, 1H), 2,69 (m, 1H), 2,79 (dd, 1H), 3,93 (dd, 2H), 4,18 (br, 1H), 4,53 (d, 2H), 4,69 (d, 1H), 5,27 (t, 1H), 6,75 (s, 1H), 7,16 (m, 2H), 7,95 (s, 1H).

Ejemplo 27

1-({4-Amino-5-[3,5-difluoro-4-(hidroximetil)fenil]pirrolo[2,1-f][1,2,4]triazin-7-il}metil)-piperidin-3-ol



A una solución del Intermedio 50A (150 mg, 0,30 mmol) en THF (3,0 ml) se añadieron 0,60 ml (0,60 mmol) de una solución de fluoruro de tetrabutilamonio 1M (TBAF) en THF, y la mezcla se agitó a temperatura ambiente durante 1 h. Después, la mezcla de reacción se concentró, y el residuo se purificó por HPLC preparativa (procedimiento 3) para dar 65 mg (56 % del t.) del compuesto del título.

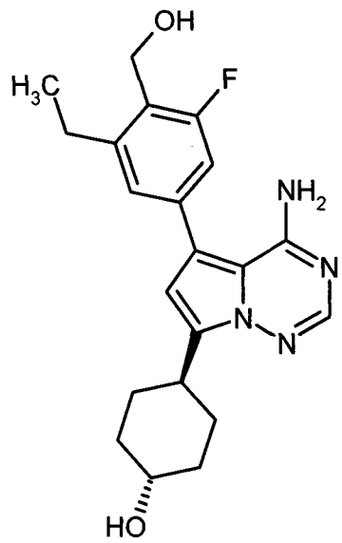
LC-MS (procedimiento 7): R_t = 0,33 min; MS (ESIpos): *m/z* (%) = 390,3 (100) $[M+H]^+$.

RMN ^1H (400 MHz, d_6-DMSO): δ (ppm) = 1,02 (br, m, 1H), 1,40 (br, m, 1H), 1,60 (br, m, 1H), 1,77 (br, m, 2H), 1,95 (br, m, 1H), 2,73 (br, m, 1H), 2,88 (br, m, 1H),

3,43 (br, m, 1H), 3,83 (br, m, 2H), 4,54 (br, d, 3H), 5,27 (t, 1H), 6,74 (s, 1H), 7,15 (m, 2H), 7,95 (s, 1H).

Ejemplo 28

trans-4-{4-Amino-5-[3-etil-5-fluoro-4-(hidroximetil)fenil]pirrolo[2,1-f][1,2,4]triazin-7-il}ciclohexanol



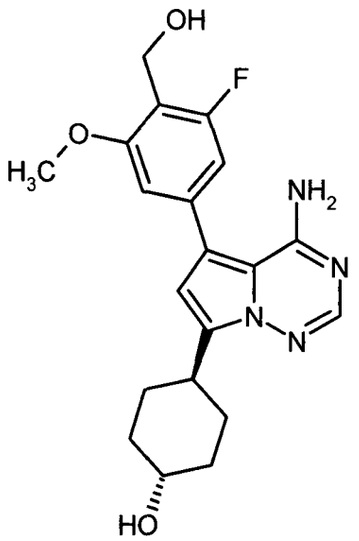
El Intermedio 24A (120 mg, 0,39 mmol) y el Intermedio 58A (130 mg, 0,46 mmol) se disolvieron en acetonitrilo (3,0 ml) en un vial reactor de microondas y se lavaron con chorro con argón. Se añadieron tetrakis(trifenilfosfina)paladio (0) (22 mg, 0,02 mmol) y una solución ac. de carbonato de sodio 2,0 M (0,7 ml), y la mezcla se calentó a 150 °C durante 1 h en un dispositivo de microondas de modo único. Tras el enfriamiento, la mezcla se filtró, y el filtrado se evaporó. El residuo se purificó por HPLC preparativa (procedimiento 2) para dar 36 mg (23 % del t.) del compuesto del título.

LC-MS (procedimiento 6): R_t = 0,82 min; MS (ESIpos): *m/z* (%) = 385 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 383 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, DMSO-d_6): δ (ppm) = 1,24 (t, 3H), 1,28-1,38 (m, 2H), 1,46-1,54 (m, 2H), 1,94-1,97 (m, 2H), 2,01-2,05 (m, 2H), 2,82 (q, 2H), 3,03 (m, 1H), 3,47 (m, 1H), 4,53 (m, 2H), 4,61 (d, 1H), 5,02 (t, 1H), 6,58 (s, 1H), 7,08 (d, 1H), 7,15 (s, 1H), 7,90 (s, 1H).

Ejemplo 29

trans-4-{4-Amino-5-[3-fluoro-4-(hidroximetil)-5-metoxifenil]pirrolo[2,1-f][1,2,4]triazin-7-il}ciclohexanol



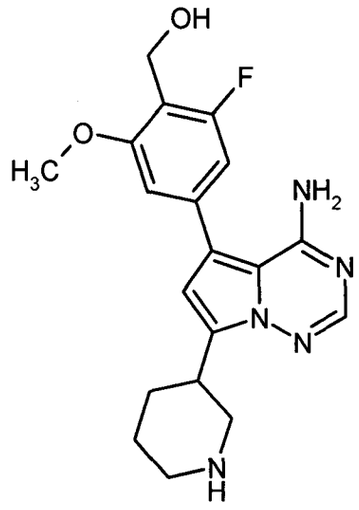
El Intermedio 24A (120 mg, 0,39 mmol) y el Intermedio 59A (163 mg, 80 % de pureza, 0,46 mmol) se disolvieron en acetonitrilo (2,0 ml) en un vial reactor de microondas y se lavaron con chorro con argón. Se añadieron tetrakis-(trifenilfosfina)paladio (0) (45 mg, 0,04 mmol) y una solución aq. de carbonato de sodio 2,0 M (0,5 ml), y la mezcla se calentó a 150 °C durante 1 h en un dispositivo de microondas de modo único. Tras el enfriamiento, la mezcla se filtró, y el filtrado se evaporó. El residuo se purificó por HPLC preparativa (procedimiento 2) para dar 6 mg (4 % del t.) del compuesto del título.

LC-MS (procedimiento 5): R_t = 1,36 min; MS (ESIpos): *m/z* (%) = 387 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 385 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, DMSO-d_6): δ (ppm) = 1,24-1,33 (m, 2H), 1,42-1,53 (m, 2H), 1,90-1,93 (m, 2H), 2,00-2,04 (m, 2H), 3,04 (m, 1H), 3,46 (m, 1H), 3,82 (s, 3H), 4,48 (m, 2H), 4,60 (d, 1H), 4,83 (t, 1H), 6,60 (s, 1H), 6,85 (d, 1H), 6,90 (s, 1H), 7,91 (s, 1H).

Ejemplo 30

{4-[4-Amino-7-(piperidin-3-il)pirrolo[2,1-f][1,2,4]triazin-5-il]-2-fluoro-6-metoxifenil}-metanol



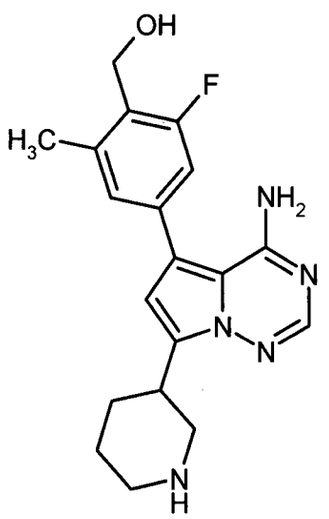
El Intermedio 63A (50 mg, 0,11 mmol) se disolvió en una solución 30 % de ácido trifluoroacético en diclorometano (5,0 ml) a 0 °C. La mezcla de reacción se agitó a esta temperatura durante 30 min., después, todos los volátiles se eliminaron por destilación bajo presión reducida. El residuo se purificó por HPLC preparativa (procedimiento 2). El producto así obtenido se disolvió en acetato de etilo y se lavó con una solución saturada acuosa de carbonato de sodio. La capa orgánica se secó sobre sulfato de sodio anhidro, y el disolvente se destiló para dar 30 mg (76 % del t.) del compuesto del título.

LC-MS (procedimiento 6): R_t = 0,59 min; MS (ESIpos): *m/z* (%) = 372 (10) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 370 (100) $[M-H]^-$.

RMN ^1H (400 MHz, DMSO-d_6): δ (ppm) = 1,50-2,08 (m, 4H), 2,94 (m, 2H), 3,17-3,30 (m, 3H), 3,85 (s, 3H), 4,51 (m, 2H), 4,82 (t, 1H), 6,60 (s, 1H), 6,84 (d, 1H), 6,89 (s, 1H), 7,90 (s, 1H).

Ejemplo 31

{4-[4-Amino-7-(piperidin-3-il)pirrolo[2,1-f][1,2,4]triazin-5-il]-2-fluoro-6-metilfenil}-metanol



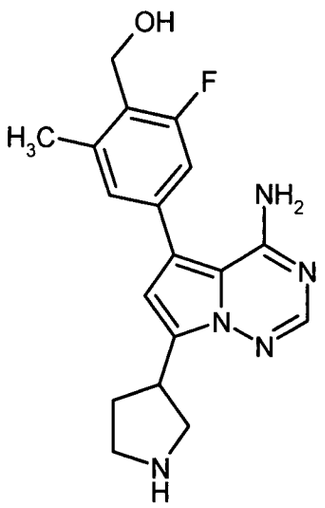
El Intermedio 64A (110 mg, 0,21 mmol) se disolvió en una solución 30 % de ácido trifluoroacético en diclorometano (5,0 ml) a 0 °C. La mezcla de reacción se agitó a esta temperatura durante 30 min., después, todos los volátiles se eliminaron por destilación bajo presión reducida. El residuo se purificó por HPLC preparativa (procedimiento 2). El producto así obtenido se disolvió en acetato de etilo y se lavó con una solución saturada acuosa de carbonato de sodio. La capa orgánica se secó sobre sulfato de sodio anhidro, y el disolvente se destiló para dar 59 mg (78 % del t.) del compuesto del título.

LC-MS (procedimiento 4): R_t = 1,10 min; MS (ESIpos): *m/z* (%) = 356 (40) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 354 (100) $[M-H]^-$.

RMN ^{1H} (400 MHz, DMSO-d_6): δ (ppm) = 1,44-2,08 (m, 4H), 2,42 (s, 3H), 2,94 (m, 2H), 3,17-3,27 (m, 3H), 4,53 (m, 2H), 4,98 (t, 1H), 6,54 (s, 1H), 7,06 (d, 1H), 7,11 (s, 1H), 7,90 (s, 1H).

Ejemplo 32

{4-[4-Amino-7-(pirrolidin-3-il)pirrolo[2,1-f][1,2,4]triazin-5-il]-2-fluoro-6-metilfenil}-metanol



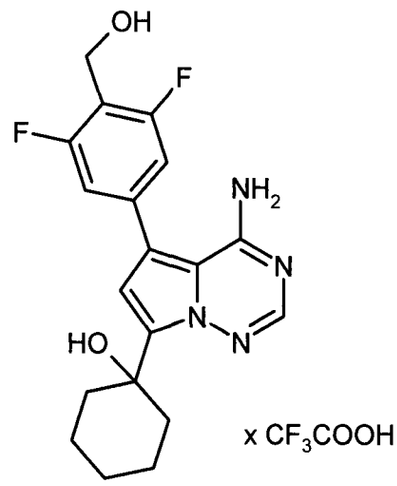
El Intermedio 65A (90 mg, 0,17 mmol) se disolvió en una solución 30 % de ácido trifluoroacético en diclorometano (5,0 ml) a 0 °C. La mezcla de reacción se agitó a esta temperatura durante 30 min., después, todos los volátiles se eliminaron por destilación bajo presión reducida. El residuo se purificó por HPLC preparativa (procedimiento 2). El producto así obtenido se disolvió en acetato de etilo y se lavó con una solución saturada acuosa de carbonato de sodio. La capa orgánica se secó sobre sulfato de sodio anhidro, y el disolvente se destiló para dar 27 mg (47 % del t.) del compuesto del título.

LC-MS (procedimiento 4): R_t = 1,03 min; MS (ESIpos): *m/z* (%) = 342 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 340 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, DMSO-d_6): δ (ppm) = 1,80-2,21 (m, 2H), 2,43 (s, 3H), 2,78-2,81 (m, 1H), 2,85-3,02 (m, 2H), 3,22-3,27 (m, 1H), 3,63 (m, 1H), 4,55 (br, s, 2H), 4,98 (t, 1H), 6,63 (s, 1H), 7,06 (d, 1H), 7,11 (s, 1H), 7,90 (s, 1H).

Ejemplo 33

Trifluoroacetato de 1-{4-amino-5-[3,5-difluoro-4-(hidroximetil)fenil]pirrolo[2,1-f][1,2,4]triazin-7-il}ciclohexanol



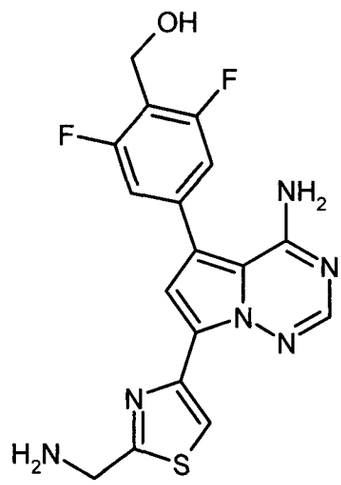
El Intermedio 61A (95 mg, 0,31 mmol) y el Intermedio 1A (87 mg, 0,32 mmol) se disolvieron en DMF (2,0 ml) en un recipiente reactor de microondas y se lavaron con chorro con argón. Se añadieron tetrakis(trifenilfosfina)paladio (0) (35 mg, 0,03 mmol) y una solución aq. de carbonato de sodio 2,0 M (0,5 ml), y la mezcla se calentó a 150 °C durante 1 h en un dispositivo de microondas de modo único. Tras el enfriamiento, la mezcla se filtró, y el filtrado se purificó directamente por HPLC preparativa (procedimiento 2) para dar 6 mg (4 % del t.) del compuesto del título.

LC-MS (procedimiento 6): R_t = 1,05 min; MS (ESIpos): *m/z* (%) = 375 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 373 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, DMSO-d_6): δ (ppm) = 1,20-1,33 (m, 1H), 1,42-1,51 (m, 2H), 1,60-1,82 (m, 5H), 2,17-2,28 (m, 2H), 4,51 (s, 2H), 6,76 (s, 1H), 7,17 (m, 2H), 8,02 (s, 1H).

Ejemplo 34

(4-{4-Amino-7-[2-(aminometil)-1,3-tiazol-4-il]pirrolo[2,1-f][1,2,4]triazin-5-il}-2,6-difluorofenil)metanol



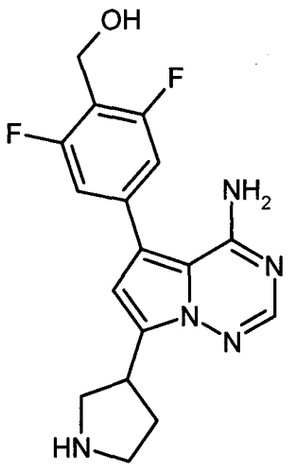
El Intermedio 62A (67 mg, 0,16 mmol), el Intermedio 1A (51 mg, 0,19 mmol), tetrakis(trifenilfosfina)paladio (0) (18 mg, 0,02 mmol) y una solución aq. de carbonato de sodio 2,0 M (0,94 ml) se disolvieron en 1,4-dioxano (2,50 ml) en un vial reactor de microondas. Al vial se le colocó una tapa engastada, y la mezcla se calentó a 140 °C durante 3 h en un dispositivo de microondas de modo único. Después, la mezcla de reacción se filtró, y el filtrado se diluyó con acetonitrilo y se trató con éter de dietilo. El precipitado resultante se recolectó y purificó por HPLC preparativa (procedimiento 2). El producto así obtenido (15 mg) se trató subsiguientemente con una solución 20 % de ácido trifluoroacético en diclorometano (2 ml) durante 20 min. Los volátiles se eliminaron por destilación, y el residuo se trató con una solución concentrada acuosa de carbonato de sodio y se extrajo con acetato de etilo. El extracto orgánico se secó sobre sulfato de sodio anhidro, y el disolvente se destiló para dar el compuesto del título (10 mg, 13 % del t.) como un sólido incoloro.

LC-MS (procedimiento 4): R_t = 1,12 min; MS (ESIpos): *m/z* (%) = 389 (25) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 387 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 4,24 (s, 2H), 4,53 (m, 2H), 5,30 (t, 1H), 7,18-7,23 (m, 3H), 8,11 (s, 1H), 8,40 (s, 1H).

Ejemplo 35

ent-{4-[4-Amino-7-(pirrolidin-3-il)pirrolo[2,1-f][1,2,4]triazin-5-il]-2,6-difluorofenil}-metanol (*enantiómero 1*)



El compuesto del título se obtuvo por la separación del Ejemplo racémico 8 (54 mg) usando HPLC quiral preparativa [columna: Daicel Chiralpak AD-H, 250 mm x 20 mm; eluyente: isohexano/etanol 35:65; caudal de flujo: 20 ml/min; detección UV: 220 nm]. Rendimiento: 12,5 mg.

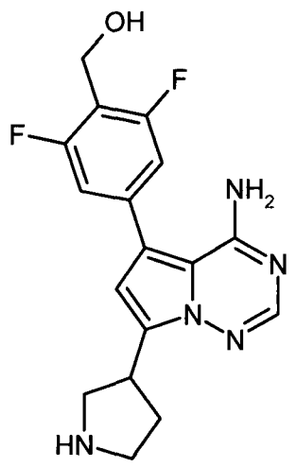
HPLC quiral analítica [columna: Daicel Chiralpak AD-H, 5 µm, 250 mm x 4,6 mm; eluyente: isohexano/etanol 50:50 + dietilamina 0,2 %; caudal de flujo: 1,0 ml/min; temperatura: 40 °C; detección UV: 220 nm]: R_t = 9.452 min, e.e. >99 %.

HPLC (procedimiento 9): R_t = 0,70 min;

LC-MS (procedimiento 10): R_t = 0,42 min; MS (ESIpos): *m/z* (%) = 346,1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 344,0 (100) $[M-H]^-$.

Ejemplo 36

ent-{4-[4-Amino-7-(pirrolidin-3-il)pirrolo[2,1-f][1,2,4]triazin-5-il]-2,6-difluorofenil}-metanol (*enantiómero 2*)



El compuesto del título se obtuvo por la separación del Ejemplo racémico 8 (54 mg) usando HPLC quiral preparativa [columna: Daicel Chiralpak AD-H, 250 mm x 20 mm; eluyente: isohexano/etanol 35:65; caudal de flujo: 20 ml/min; detección UV: 220 nm]. Rendimiento: 14 mg.

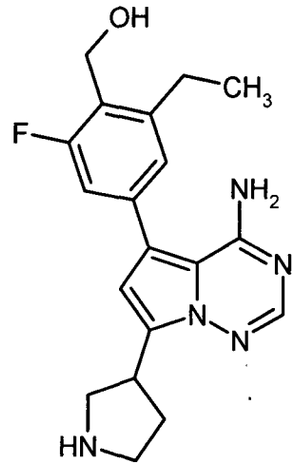
HPLC quiral analítica [columna: Daicel Chiralpak AD-H, 5 µm, 250 mm x 4.6 mm; eluyente: isohexano/etanol 50:50 + dietilamina 0,2 %; caudal de flujo: 1,0 ml/min; temperatura: 40 °C; detección UV: 220 nm]: R_t = 13,695 min, e.e. >99 %.

HPLC (procedimiento 9): R_t = 0,71 min;

LC-MS (procedimiento 10): R_t = 0,42 min; MS (ESIpos): *m/z* (%) = 346,1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 344,0 (100) $[M-H]^-$.

Ejemplo 37

rac-{4-[4-Amino-7-(pirrolidin-3-il)pirrolo[2,1-f][1,2,4]triazin-5-il]-2-etil-6-fluorofenil}-metanol



El Intermedio 66A (72 mg, 0,158 mmol) se disolvió en diclorometano (3,8 ml) a 0 °C y se añadió ácido trifluoroacético (1,0 ml). La mezcla de reacción se agitó a 0 °C durante 40 min, después, todos los volátiles se eliminaron bajo presión reducida. El residuo se purificó por HPLC preparativa (procedimiento 6). Las fracciones combinadas que contenían producto se ajustaron a pH básico usando una solución saturada acuosa de carbonato de sodio y se concentraron a sequedad. El residuo resultante se suspendió en acetato de etilo (50 ml) y se filtró. La capa orgánica se lavó con salmuera (5 ml), se secó sobre sulfato de sodio

anhidro, y el disolvente se destiló para dar 31 mg (56 % del t.) del compuesto del título.

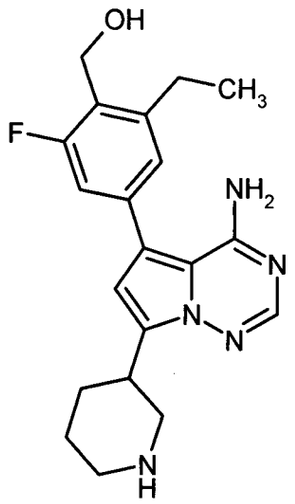
HPLC (procedimiento 9): R_t = 0,81 min;

LC-MS (procedimiento 10): R_t = 0,55 min; MS (ESIpos): *m/z* (%) = 356,3 (50) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 354,2 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,23 (t, 3H), 1,84-2,24 (m, 1H), 2,81 (q, 2H), 2,80-2,99 (m, 1H), 3,00-3,72 (m, 1H), 4,56 (d, 2H), 5,00 (t, 1H), 6,68 (s, 1H), 7,09 (d, 1H), 7,14 (m, 2H), 7,92 (s, 1H).

Ejemplo 38

rac-{4-[4-Amino-7-(piperidin-3-il)pirrolo[2,1-f][1,2,4]triazin-5-il]-2-etil-6-fluorofenil}-metanol



El Intermedio 67A (108 mg, 0,230 mmol) se disolvió en diclorometano (5,2 ml) a 0 °C y se añadió ácido trifluoroacético (1,4 ml). La mezcla de reacción se agitó a 0 °C durante 40 min., después, todos los volátiles se eliminaron bajo presión reducida. El residuo se purificó por HPLC preparativa (procedimiento 6). Las fracciones combinadas que contenían producto se ajustaron a pH básico usando una solución saturada acuosa de carbonato de sodio y se concentraron a sequedad. El residuo resultante se suspendió en acetato de etilo (50 ml) y se filtró. La capa orgánica se lavó con salmuera (5 ml), se secó sobre sulfato de sodio anhidro, y el disolvente se destiló para dar 83 mg (85 % del t.) del compuesto del título.

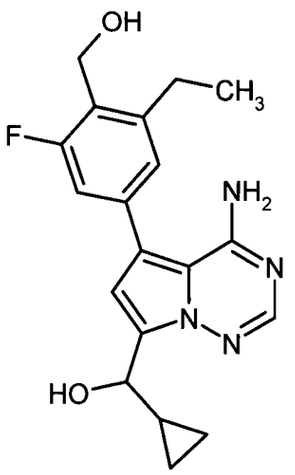
HPLC (procedimiento 9): R_t = 0,81 min;

LC-MS (procedimiento 10): R_t = 0,58 min; MS (ESIpos): *m/z* (%) = 370,3 (50) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 368,3 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,22 (t, 3H), 1,51-1,72 (m, 2H), 2,00-2,10 (m, 1H), 2,51-2,65 (m, 2H), 2,81 (q, 2H), 2,95-3,03 (m, 1H), 3,20-3,27 (m, 1H), 4,56 (d, 2H), 5,00 (t, 1H), 6,60 (s, 1H), 7,07 (d, 1H), 7,14 (m, 2H), 7,91 (s, 1H).

Ejemplo 39

rac-{4-Amino-5-[3-etil-5-fluoro-4-(hidroximetil)fenil]pirrolo[2,1-f][1,2,4]triazin-7-il}-(ciclopropil)metanol



El Intermedio 17A (83 mg, 0,29 mmol), el Intermedio 58A (98 mg, 0,35 mmol) y tetrakis(trifenilfosfina)paladio (0) (17 mg, 0,015 mmol) se disolvieron en una mezcla de acetonitrilo (2,3 ml) y solución acuosa de carbonato de sodio 2 M (0,53 ml) en un vial reactor de microondas. Tras la desgasificación durante 5 min. usando argón, al recipiente de reacción se le colocó una tapa engastada, y la mezcla se calentó a 150 °C durante 1 h en un dispositivo de microondas de modo único. Tras el enfriamiento a temperatura ambiente, se añadió una solución saturada acuosa de bicarbonato de sodio, y la mezcla se extrajo tres veces con acetato de etilo. Las capas orgánicas combinadas se secaron sobre sulfato de sodio, se filtraron y se concentraron. El residuo se purificó por HPLC preparativa (procedimiento 5) para dar el compuesto del título. Rendimiento: 63 mg (61 % del t.).

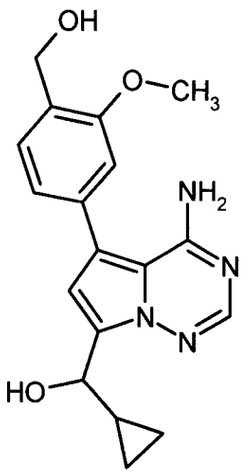
HPLC (procedimiento 9): R_t = 1,13 min;

LC-MS (procedimiento 10): R_t = 0,78 min; MS (ESIpos): *m/z* (%) = 357,3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 355,3 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 0,39 (m, 3H), 0,48 (m, 1H), 1,23 (t, 3H), 1,35 (m, 1H), 2,81 (q, 2H), 4,56 (d, 2H), 4,68 (m, 1H), 5,01 (m, 1H), 5,21 (m, 1H), 6,76 (s, 1H), 7,09 (d, 1H), 7,14 (s, 1H), 7,90 (s, 1H).

Ejemplo 40

rac-{4-Amino-5-[4-(hidroximetil)-3-metoxifenil]pirrolo[2,1-f][1,2,4]triazin-7-il}-(ciclopropil)metanol

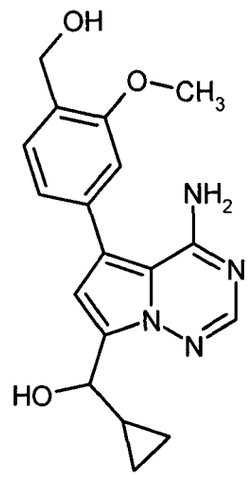


El Intermedio 68A (130 mg, 0,353 mmol) se disolvió en tetrahidrofurano (6,9 ml) y se enfrió a 0 °C. Se añadió una solución de hidruro de litio y aluminio (1 M en dietiléter, 0,78 ml) gota a gota, y la mezcla de reacción se dejó calentar a temperatura ambiente hasta el día siguiente. Después, la mezcla de reacción se inactivó con agua y se filtró. El filtrado se concentró, y el residuo se purificó por HPLC preparativa (procedimiento 8) para dar el compuesto del título. Rendimiento: 63 mg (51 % del t.).

LC-MS (procedimiento 10): R_t = 0,62 min; MS (ESIpos): *m/z* (%) = 341,2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 339,1 (100) $[M-H]^-$.

Ejemplo 41

ent-4-Amino-5-[4-(hidroximetil)-3-metoxifenil]pirrolo[2,1-f][1,2,4]triazin-7-il}-(ciclopropil)metanol (*enantiómero 1*)



El compuesto del título se obtuvo por la separación del Ejemplo racémico 40 (63 mg) usando HPLC quiral preparativa [columna: Daicel Chiralpak IC, 5 µm, 250 mm x 20 mm; eluyente: éter de *terc*-butil metilo/metanol 85:15; caudal de flujo: 15 ml/min; temperatura: 40 °C; detección UV: 220 nm]. Rendimiento: 17 mg.

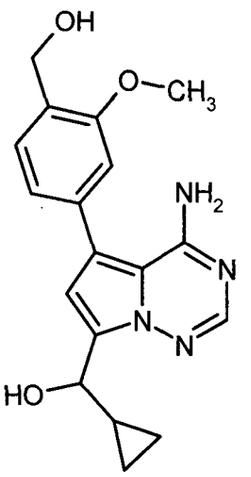
HPLC quiral analítica [columna: Daicel Chiralpak IC, 5 µm, 250 mm x 4,6 mm; eluyente: éter de *terc*-butil metilo/metanol 85:15; caudal de flujo: 1,0 ml/min; temperatura: 40 °C; detección UV: 220 nm]: R_t = 4.76 min, e.e. >99 %.

LC-MS (procedimiento 10): R_t = 0,67 min; MS (ESIpos): *m/z* (%) = 341,2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 339,1 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 0,40 (m, 3H), 0,48 (m, 1H), 1,36 (m, 1H), 3,83 (s, 3H), 4,54 (d, 2H), 4,68 (m, 1H), 5,07 (t, 1H), 5,25 (d, 1H), 6,74 (s, 1H), 7,00 (s, 1H), 7,03 (d, 1H), 7,47 (d, 1H), 7,89 (s, 1H).

Ejemplo 42

ent-4-Amino-5-[4-(hidroximetil)-3-metoxifenil]pirrolo[2,1-f][1,2,4]triazin-7-il}-(ciclopropil)metanol (*enantiómero 2*)



El compuesto del título se obtuvo por la separación del Ejemplo racémico 40 (63 mg) usando HPLC quiral preparativa [columna: Daicel Chiralpak IC, 5 µm, 250 mm x 20 mm; eluyente: éter de *terc*-butil metilo/metanol 85:15; caudal de flujo: 15 ml/min; temperatura: 40 °C; detección UV: 220 nm]. Rendimiento: 25 mg.

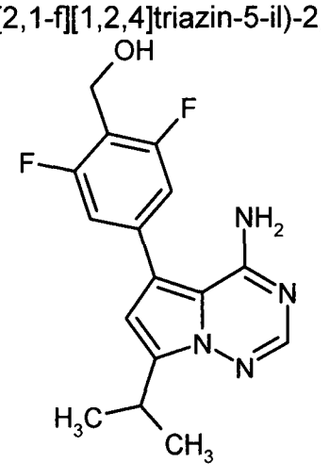
HPLC quiral analítica [columna: Daicel Chiralpak IC, 5 µm, 250 mm x 4,6 mm; eluyente: éter de *terc*-butil metilo/metanol 85:15; caudal de flujo: 1,0 ml/min; temperatura: 40 °C; detección UV: 220 nm]: R_t = 6,37 min, e.e. >99 %.

LC-MS (procedimiento 10): R_t = 0,67 min; MS (ESIpos): *m/z* (%) = 341,2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 339,1 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 0,40 (m, 3H), 0,48 (m, 1H), 1,36 (m, 1H), 3,83 (s, 3H), 4,54 (d, 2H), 4,68 (m, 1H), 5,07 (t, 1H), 5,25 (d, 1H), 6,74 (s, 1H), 7,00 (s, 1H), 7,03 (d, 1H), 7,47 (d, 1H), 7,89 (s, 1H).

Ejemplo 43

[4-(4-Amino-7-isopropilpirrolo[2,1-f][1,2,4]triazin-5-il)-2,6-difluorofenil]metanol



El Intermedio 71A (181 mg, 0,709 mmol), el Intermedio 1A (239 mg, 0,887 mmol) y tetrakis(trifenilfosfina)paladio (0) (41 mg, 0,035 mmol) se disolvieron en una mezcla de *N,N*-dimetilformamida (12,5 ml) y solución acuosa de carbonato de sodio 2 M (1,42 ml) en un vial reactor de microondas. Al recipiente de reacción se le colocó una tapa engastada, y la mezcla se calentó a 130 °C durante 2 h en un dispositivo de microondas de modo único. Tras el enfriamiento a temperatura ambiente, la mezcla de reacción se filtró a través de Celite y se concentró. El residuo resultante se disolvió en acetato de etilo (100 ml) y se lavó con agua y con salmuera (10 ml c/u). La capa orgánica se secó sobre sulfato de sodio, se filtró y se concentró. El residuo se purificó por cromatografía flash (puriFlash, Interchim, ciclohexano/acetato de etilo 1:1 a gradiente de acetato de etilo 100 %) seguido por HPLC preparativa (procedimiento 6). Las fracciones que contenían producto se combinaron y ajustaron a pH básico usando una solución saturada acuosa de carbonato de sodio. El disolvente de acetonitrilo se eliminó, y el producto precipitado se recolectó por filtración. Rendimiento: 69 mg (31 % del t.).

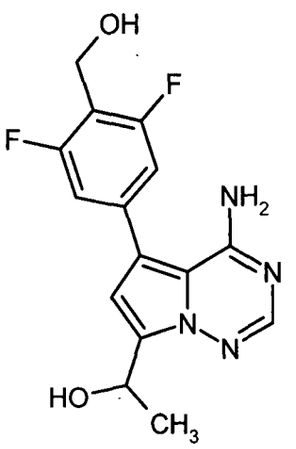
HPLC (procedimiento 9): R_t = 1,35 min;

LC-MS (procedimiento 10): R_t = 0,90 min; MS (ESIpos): *m/z* (%) = 319,0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 317,0 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,30 (d, 6H), 3,42 (m, 1H), 4,54 (s, 2H), 5,26 (s, 1H), 6,65 (s, 1H), 7,14 (m, 2H), 7,94 (s, 1H).

Ejemplo 44

rac-1-{4-Amino-5-[3,5-difluoro-4-(hidroximetil)fenil]pirrolo[2,1-f][1,2,4]triazin-7-il}-etanol



El Intermedio 72A (230 mg, 0,743 mmol), el Intermedio 2A (192 mg, 0,89 mmol) y tetrakis(trifenilfosfina)paladio (0) (86 mg, 0,074 mmol) se disolvieron en una mezcla de 1,4-dioxano (4,6 ml) y solución acuosa de carbonato de sodio 2 M (1,16 ml) en un vial reactor de microondas. Al recipiente de reacción se le colocó una tapa engastada, y la mezcla se calentó a 140 °C durante 1 h en un dispositivo de microondas de modo único. Tras el enfriamiento a temperatura ambiente, la mezcla de reacción se purificó por HPLC preparativa (procedimiento 8) para dar 48 mg de material que se purificó en forma adicional por HPLC preparativa (procedimiento 9). Rendimiento: 11 mg (4,6 % del t.).

LC-MS (procedimiento 5): R_t = 0,89 min; MS (ESIpos): *m/z* (%) = 321,3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 319,3 (100) $[M-H]^-$.

RMN ^{1}H (400 MHz, d_6-DMSO): δ (ppm) = 1,47 (d, 3H), 4,54 (m, 2H), 5,16-5,39 (m, 2H), 6,74 (s, 1H), 6,88 (m, 1H), 7,14 (m, 2H), 7,94 (s, 1H).

B. Evaluación de la Actividad Biológica

Abreviaturas y Acrónimos:

ATCC	Recolección de Cultivos de Tipo Americana
ATP	trifosfato de adenosina
Bq	Bequerel
BrdU	5-bromo-2-desoxiuridina
BSA	albúmina de suero bovino
CHO	ovario de hámster chino
cpm	recuentos por minuto

Ct	umbral del ciclo
DMEM/F12	medio de Eagle modificado por Dulbecco / medio F12 de Ham (1:1)
DMSO	sulfóxido de dimetilo
ADN	ácido desoxirribonucleico
DTT	dithiothreitol
EDTA	etilendiamina-ácido tetraacético
ENGS MV	medio de cultivo celular endotelial microvascular
FAM	carboxifluoresceína éster de succinimidilo
FCS	suero fetal bovino
hBMP9	factor 9 morfogenético óseo humano
HEPES	ácido 4-(2-hidroxietil)piperazin-1-etansulfónico
HMVEC	células endoteliales microvasculares humanas
HPMC	hidroxipropil metil celulosa
HTRF	fluorescencia homogénea resuelta en el tiempo
HUVEC	células endoteliales vasculares humanas
[I]	concentración del inhibidor
IC_{50}	concentración con un efecto inhibitorio del 50 %
LDH	lactato deshidrogenasa
ARNm	ácido ribonucleico mensajero
NADH	dinucleótido de nicotinamida adenina
Nonidet P40	4-etilfenoxi-poli(etilenglicol)éter (*n = 11*)
PBS	solución salina tamponada con fosfato
PE	polietileno
PEG	polietilenglicol
PK	piruvato quinasa
p.o.	*per os*
PCRq	reacción en cadena de la polimerasa cuantitativa
ARN	ácido ribonucleico

tampón RTL	tampón de lisis RNeasy
Núm. de ID SEQ	número de identidad de secuencia
SFM	medio libre de suero
TAMRA	carboxitetrametilrodamina
Tris	2-amino-2-hidroximetilpropan-1,3-diol
Triton X-100	4-*terc*-octilfenoxi-poli(etilenglicol)éter (*n = 10*)

La demostración de la actividad de los compuestos de la presente invención se puede lograr a través de valoraciones *in vitro, ex vivo*, e *in vivo* que son bien conocidas en la técnica. Por ejemplo, para demostrar la actividad de los compuestos de la presente invención, se pueden utilizar las siguientes valoraciones.

B-1a. Inhibición de enzimas *in vitro* usando centelleo de radiomarcado incorporado (valoración flashplate)

Principio del ensayo:

Se mezclan compuestos de ensayo diluidos en DMSO con un sustrato / co-sustrato adecuado (en la presente: α-caseína biotinilada y ^{33}P-ATP) en un tampón de valoración correspondiente. La adición de la enzima de interés (en la presente: ALK1 quinasa) inicia la reacción de la enzima. La incorporación catalizada por enzima del radiomarcado en el sustrato se mide por centelleo. El radiomarcado incorporado se separa del radiomarcado libre vía una unión específica del sustrato biotinilado a placas de microtitulación revestidas con estreptavidina (flashplates) y etapas de lavado concomitantes. La intensidad de la señal de centelleo (recuentos por minuto, cpm) es proporcional a la actividad de la enzima. La inhibición de enzimas da lugar a una reducción en la intensidad de la señal. Los valores de IC_{50} de los compuestos de ensayo se determinan por trazados de cpm-versus-[I].

Tampón de reacción:

El tampón de reacción contiene Tris 50 mM pH 8,0 (Sigma), $MnCl_2$ 1 mM (Sigma), Nonidet P40 0,01 % (Fluka), inhibidores de proteasa Complete EDTA-free 0,5 x

(Roche; que contienen una mezcla de varios inhibidores de proteasa para la inhibición de serina y cisteína (pero no metalo-) proteasas; 1 comprimido contiene inhibidores de proteasa suficientes para un extracto de células de 50 ml; la concentración utilizada en esta valoración corresponde a 1 comprimido en 100 ml).

Otros tampones:

1.) Solución quelante: PBS de Dulbecco (PAA, Pasching, Austria), EDTA 25 mM (Sigma), ATP 25 µM (Roche), Triton X-100 0,05 % (Sigma);

2.) Tampón de saturación: PBS de Dulbecco (PAA, Pasching, Austria), ATP 100 µM (Roche), Triton X-100 0,2 % (Sigma);

3.) Tampón de lavado: PBS de Dulbecco (PAA, Pasching, Austria).

Solución de enzimas:

Se diluye solución patrón (35,7 ng/µl) de ALK1 (Invitrogen, Paisley, Reino Unido) a 4 ng/µl; la concentración final en la reacción es de 1 ng/µl.

Solución de sustrato:

Se biotinila α-caseína desfosforilada (Sigma) de acuerdo con el protocolo del fabricante (Pierce, Bonn, Alemania) lo que da lugar a una solución patrón de 61,6 µM. En resumen, se añade un reactivo de Sulfo-NHS-Biotina de EZ-Link® (sulfosuccinimidil-6-(biotinamido)hexanoato; Pierce, Bonn, Alemania) en una molaridad igual a α-caseína y se incuba sobre hielo durante 2 h. Después, el reactivo de biotina se elimina por diálisis (2 x 2 h y hasta el día siguiente).

Una solución 100 mM de ATP (Roche) fría (no marcada) se diluye a 1:100 antes de cada ensayo. Para la mezcla del sustrato, se diluye α-caseína a 2,22 µM dando lugar a una concentración final de α-caseína 1 µM en la reacción. Además, se añade ATP frío para dar una solución 1,11 µM que da lugar a una concentración final de 500 nM en la reacción.

Solución de ATP radiactivo:

La solución patrón (9,25 MBq/25 µl de ^{33}P-ATP; Perkin Elmer, Rodgau, Alemania) se diluye a 651,2 Bq/µl. Esto corresponde a una concentración final de 162,8 Bq/µl.

Solución de compuestos:

Se disuelven compuestos en DMSO 100 % (solución patrón 10 mM) y se diluyen a 2 mM. Se llevan a cabo diluciones adicionales por etapas a 1:3,16 en DMSO.

Protocolo por etapas:

Un volumen de 9 µl de solución de sustrato se proporciona en cada pocillo de una placa de microtitulación de 384 pocillos (Greiner Bio-One, Solingen, Alemania). Se añaden 1 µl de solución de compuesto y 5 µl de la solución de ATP radiactivo. La reacción de enzimas comienza con la adición de 5 µl de solución de enzimas. La mezcla se incuba durante 60 minutos a temperatura ambiente y después se detiene por la adición de 10 µl de solución quelante. Las *flashplates* de microtitulación de 384 pocillos (Perkin Elmer, Rodgau, Alemania) se saturan con 50 µl de tampón de saturación por pocillo durante al menos 60 minutos. Subsiguientemente, se descarta un volumen de 20 µl que se reemplaza con 20 µl de la mezcla de reacción de ALK1 detenida. La unión de sustrato biotinilado a la *flashplate* se permite durante la incubación hasta el día siguiente a temperatura ambiente. El sustrato unido se separa de los componentes no unidos a través de etapas de lavado repetidas (3 x 50 µl de tampón de lavado por pocillo). Finalmente, se añaden 50 µl de tampón de lavado, y la señal de centelleo (cpm) se mide en un contador adecuado (Perkin Elmer, Rodgau, Alemania).

Los valores de IC_{50} para los compuestos individuales de la presente invención se enumeran en la Tabla 1 a continuación:

Tabla 1

Núm. de Ejemplo	IC_{50} de ALK1 [nM]
1	2,0
2	2,8
3	4,0
4	1,0
5	1,3

Núm. de Ejemplo	IC_{50} de ALK1 [nM]
6	40
7	2,0
8	4,4
9	5,7
10	8,0
11	1,9
12	5,9
13	4,0
14	5,3
15	60
16	2,6
17	2,0
18	80
19	19
20	30
21	25
22	17
23	30
24	140
25	65
26	30
27	70
28	170
29	1,0
30	2,0
31	4,0
32	4,0

Núm. de Ejemplo	IC_{50} de ALK1 [nM]
33	15
34	4,1
40	3,2
41	3,5
42	1,2
43	1,9
44	3,8

B-1b. Valoración de ALK1 quinasa (protocolo ProQinase)

La actividad de la ALK1 (Invitrogen, Carlsbad, CA, EE.UU.) quinasa se midió en una valoración radiométrica de ProQinase GmbH (Freiburg, Alemania) usando γ-^{33}P-ATP y caseína (Sigma, St. Louis, MO, EE.UU.) como sustrato en FlashPlates™ PerkinElmer de 96 pocillos (Boston, MA, EE.UU.). Los compuestos se ensayaron en 10 concentraciones en el intervalo de 1×10^{-4} M a 3×10^{-9} M en un volumen total de 50 µl con una concentración final de DMSO de 1 % c/u. Los componentes de valoración se mezclaron en el siguiente orden:

- 20 µl de tampón de valoración (HEPES-NaOH 70 mM, pH 7,5, $MgCl_2$ 3 mM, $MnCl_2$ 3 mM, ortovanadato de sodio 2 µM, DTT 1,2 mM);
- 5 µl de γ-^{33}P-ATP (1,0 µM en agua, aproximadamente 6×10^5 cpm por pocillo);
- 5 µl de solución de compuesto de ensayo (en DMSO 10 %);
- Solución (mezcla 1:1) de 10 µl de sustrato (200 µg/ml, 1,0 µg/50 µl de concentración final) / enzima (4 µg/ml, 20 ng/50 µl = 5,5 nM de concentración final).

Las mezclas de reacción se incubaron a 30 °C durante 60 minutos y se detuvieron por la adición de 50 µl de ácido fosfórico 2 % (v/v). Las placas se aspiraron y lavaron dos veces con 200 µl de cloruro de sodio 0,9 % (p/v). La incorporación de $^{33}P_i$ se determinó con un contador de centelleos de microplacas (Microbeta,

Wallac). Todas las valoraciones se llevaron a cabo usando un Sistema Central de BeckmanCoulter/SAGIAN™.

Los valores medios obtenidos a partir de la unión de sustrato no específico de ATP marcado se ajustaron como un nivel basal, mientras que se consideró que los valores medios medidos en ausencia de cualquier inhibidor reflejaban la actividad total de la ALK1 quinasa. La actividad basal (ba) se sutrajo del valor de la actividad total (fa) así como de los valores obtenidos a partir del compuesto de ensayo que contenía muestras (actividad del compuesto de ensayo, tca). La actividad residual en el último se calculó como sigue:

actividad residual (%) = 100 x [(tca-ba)/(fa-ba)]

Las actividades residuales para cada concentración y los valores de IC_{50} del compuesto se calcularon usando Quattro Workflow V3.1.0 (Quattro Research GmbH, Munich, Alemania). El modelo de ajuste para las determinaciones de la IC_{50} fue "Respuesta sigmoidal (pendiente variable)" con parámetros "superiores" fijos al 100 % e "inferiores" al 0 %. El procedimiento de ajuste utilizado fue un ajuste por cuadrados mínimos.

Los valores de IC_{50} representativos a partir de esta valoración se enumeran en la Tabla 2 a continuación:

Tabla2

Núm. de Ejemplo	**IC_{50} de ALK1 [nM]**
7	6,7
11	3,0
28	124
35	6,9
36	21
37	< 3
38	4,0

Núm. de Ejemplo	IC_{50} de ALK1 [nM]
39	5,7

B-2a. Inducción del gen diana Smad7: valoración de células HMVEC y análisis de expresión TaqMan

La activación de los receptores de ALK1 por BMP9 induce la vía de señalización Smad1/5 y potencia la expresión de genes diana Smad6, Smad7 e Id-1. Se determinó que la inducción de Smad7-ARNm en células endoteliales estimuladas por BMP9 monitoree la potencia celular de los inhibidores de la ALK1 quinasa.

Se sembraron células endoteliales microvasculares humanas (HMVECadult, Cell Systems, St. Katharinen) en medio MV ENGS completo con todos los suplementos (LifeLine Cell Technology) en placas con 96 pocillos con 10.000 células por pocillo. Tras 4 h de incubación a 37 °C y con CO_2 7,5 % en una incubadora humidificada, el medio se reemplazó con medio mínimo (ENGS MV sin suplementos que contuvieran FCS 0,02 %). Tras 16 h, se añadieron compuestos de prueba o medio (controles) a los cultivos, seguido 30 min. después por la adición de hBMP9 (R&D Systems). El medio se eliminó 1 a 4 h después, las placas se lavaron cuidadosamente con solución salina tamponada con fosfato, y las células se lisaron con 150 µl por pocillo de tampón RLT helado (Qiagen).

Se aisló ARN celular total con el protocolo del reactivo Trizol® de acuerdo con las especificaciones del fabricante (Invitrogen, EE.UU.) y se trató con ADNsa I para eliminar la contaminación de ADN genómico.

Para la cuantificación relativa de la distribución del ARNm de hSmad7, el ARN total de cada muestra en primer lugar se transcribió en forma inversa usando el Sistema de Transcripción Inversa ImProm-II (Promega, EE.UU.) de acuerdo con el protocolo del fabricante. El volumen final se ajustó a 200 µl con agua.

Para la cuantificación relativa del ARNm seleccionado, se utilizó el Sistema de Detección de Secuencia ABI 7900HT de Applied Bioscience de acuerdo con las especificaciones y los protocolos del fabricante. Las reacciones de PCR se ajustaron para cuantificar hSmad7- y el gen constitutivo L32-ARNm. Los

cebadores directos e inversos y las sondas para hSmad7 y L32 se diseñaron usando el software ABI Primer Express™ de Applied Bioscience y se sintetizaron por Eurogentec (Bélgica). La secuencia del cebador directo de hSmad7 fue: Cebador 1 (SEC. ID Nº 1). La secuencia del cebador inverso de hSmad7 fue: Cebador 2 (SEC. ID Nº 2). La sonda 1 (SEC. ID Nº 3), marcada con FAM como el tinte reportero y TAMRA como el inactivador, se utilizó como una sonda para hSmad7. La secuencia del cebador directo de L32 fue: Cebador 3 (SEC. ID Nº 4). La secuencia del cebador inverso de L32 fue: Cebador 4 (SEC ID Nº 5). La sonda 2 (SEC. ID Nº 6), marcada con FAM como el tinte reportero y TAMRA como el inactivador, se utilizó como una sonda para L32.

Listado de SEC. ID:

		5' a 3'
SEC. ID Nº 1	cebador 1 de hSmad7 (cebador directo)	CCCTCCTTACTCCAGATACCC
SEC. ID Nº 2	cebador 2 de hSmad7 (cebador inverso)	GGAGGAAGGCACAGCATCT
SEC. ID Nº 3	sonda 1 de hSmad7	TTTTCTCAAACCAACTGCAGACTGTCC
SEC. ID Nº 4	cebador 3 de L32 (cebador directo)	AAGTTCATCCGGCACCAGTC
SEC. ID Nº 5	cebador 4 de L32 (cebador inverso)	TGGCCCTTGAATCTTCTACGA
SEC. ID Nº 6	sonda 2 de L32	CCCAGAGGCATTGACAACAGGG

Los siguientes reactivos se prepararon en un total de 20 µl adicionados por pocillo: 1 x qPCR-MasterMix (Eurogentec, Bélgica) y cebadores directos e inversos de hSmad7 cada uno a 200 nM, sonda 1 de hSmad7 200 nM marcada con FAM/TAMRA (SEC. ID Nº 3), y 5 µl de plantilla de ADNc. En consecuencia, se

preparó una segunda mezcla en un total de 20 µl usando la zona 2 de L32 marcada con FAM/TAMRA (SEC. ID Nº 6) y cebadores directos e inversos de L32 adicionados por pocillo en muestras paralelas.

Los parámetros de ciclación térmica fueron de 2 min. a 50 °C, seguido por 10 min. a 95 °C, seguido por 40 ciclos de fusión a 95 °C durante 15 seg. y anillado/extensión a 60 °C durante 1 min.

Cálculo de la expresión relativa:

Los valores Ct (umbral del ciclo) se calcularon a partir del punto de giro de las curvas de cantidad del producto de PCR por el procedimiento ΔΔCt (delta-delta Ct):

$\Delta Ct = Ct_{hSmad7} - Ct_{L32}$; expresión relativa = $2^{(15-\Delta Ct)}$.

Los valores IC_{50} de los compuestos de ensayo se calcularon sobre la base de las expresiones relativas de Smad7 en diferentes concentraciones de compuesto. Los valores representativos se enumeran en la Tabla 3 a continuación:

Tabla 3

Núm. de Ejemplo	**IC_{50} de hSmad7 [nM]**
1	100
2	125
3	180
5	150
7	130
8	60
11	90
17	120
20	4400
21	6000

Núm. de Ejemplo	IC_{50} de hSmad7 [nM]
22	800

B-2b. Inducción del gen diana Smad7: valoración de células HUVEC y análisis de expresión TaqMan

La potencia *in vitro* de los inhibidores de ALK1 se ensayó en una valoración basada en células. La proteína morfogenética ósea 9 (BMP9) induce la expresión de ARNm de Smad7 en las células endoteliales vasculares humanas (HUVEC) vía la activación de ALK1.

Se sembraron HUVEC de pasaje 2 1,5 x 10^4 (Lonza, Basilea, Suiza) por pocillo en una placa de 96 pocillos en medio de EBM-2 que contenía aditivos de EGM-2 y factores de crecimiento (Lonza, CC-3156 y CC-4176). Tras 4 h, el medio se cambió a EBM-2 con suero fetal bovino 0,2 % (FCS) y las células se privaron de suero durante 20 h en una incubadora humidificada a 37 °C, CO_2 5 %. Se añadieron compuestos de ensayo en 11 concentraciones diferentes entre 0 y 10 000 nM una hora antes de la estimulación de las células durante 3 h con proteína BMP9 recombinante humana a 1 ng/ml (disuelta en ácido clorhídrico 4 mM, BSA 0,1 % a 10 µg/ml; R&D Systems, Minneapolis, MN, EE.UU., 3209BP). El medio se eliminó, y las células se lisaron en 100 µl de tampón RLT (Qiagen, Hilden, Alemania). Se aisló ARN usando el Kit RNeasy 96 de Qiagen (Núm. de orden 74182) de acuerdo con las instrucciones del fabricante que se eluyó a partir de las columnas con 65 µl de agua libre de ARNsa. La transcripción inversa para RT-PCR cuantitativa se llevó a cabo con el Kit Omniscript (Qiagen, 205113) en placas de fondo redondo de 96 pocillos libres de ARNsa. Por pocillo, se añadieron 6,8 µl de una mezcla maestra de reacción que contenía 2 µl de tampón RT 10x, 2 µl de dNTPs (5 mM c/u), 1,6 µl de cebador aleatorio N6 (125 µM), 0,25 µl de Rnase Out (40 U/µl) y 1 µl de Transcriptasa Inversa de Omniscript. Tras la adición de 13,2 µl de la mezcla de ARN/agua, los contenidos de las placas se mezclaron,

se incubaron durante 1 h a 37 °C y el volumen total se ajustó a 100 µl en cada pocillo por la adición de 80 µl de agua libre de ARNsa.

La cuantificación del ARNm de Smad7 humano se llevó a cabo en un TaqMan usando Eurogentec qPCR Mastermix Plus (RT-QP2X-03-075+; Colonia, Alemania) y el empleo de L32 humana como un ARNm de referencia constitutiva. Por reacción de PCRc, se añadieron 2,8 µl de mezcla cebadora, 10 µl de mezcla maestra, 2,2 µl de agua y 5 µl de ADNc. Los parámetros de ciclación térmica fueron de 2 min. a 50 °C, seguido por 10 min. a 95 °C, seguido por 40 ciclos de fusión a 95 °C durante 15 seg. y anillado/extensión a 60 °C durante 1 min.

Los niveles de ARNm de Smad7 inducidos por 1 ng/ml de BMP9 sin la adición de ningún inhibidor se ajustaron a una inducción del 100 %, y el porcentaje de inhibición se calculó para cada compuesto de prueba con este valor. Para cada compuesto de ensayo, cada valor se determinó por cuadruplicado. Los valores de IC_{50} se determinaron usando Microsoft Excel. El procedimiento de ajuste utilizado fue un ajuste por ML no limitado ponderado.

Los valores de IC_{50} representativos de esta valoración se enumeran en la Tabla 4 a continuación:

Tabla 4

Núm. de Ejemplo	**IC_{50} de hSmad7 [nM]**
1	94
2	160
3	120
5	290
7	140
11	180
17	290
20	5900

Núm. de Ejemplo	IC_{50} de hSmad7 [nM]
21	790
22	3100
30	51
37	330
39	500
40	62
41	77
42	6,6
43	27

B-3. Eficacia sistémica en el modelo de neovascularización coroidea inducida por láser (NVC)

El objetivo de este estudio fue determinar si una administración sistémica diaria (i.p.) de un compuesto de ensayo daba lugar a una reducción de la fuga vascular y/o neovascularización coroidea en un modelo de ratas de neovascularización coroidea inducida por láser.

Con este propósito, se seleccionaron 16 ratas pardas sin signos visibles de defectos oculares y se dividieron aleatoriamente en dos grupos de ocho animales cada uno. El día 0, los animales se anestesiaron por una inyección intraperitoneal (15 mg/kg de xilacina y 80 mg/kg de ketamina). Tras la instilación de una gota de tropicamida 0,5 % para dilatar las pupilas, se indujo la neovascularización coroidea por la ejecución de seis quemaduras coroideas con un tamaño de 75 µm alrededor del disco óptico del ojo derecho usando fotocoagulación con láser de argón de 532 nm a 150 mW durante 100 ms. El compuesto de ensayo y el vehículo de control (etanol 10 %, PEG 400 90 %) se administraron una vez al día por inyecciones intraperitoneales (i.p.) con una dosificación del compuesto de ensayo a 50 mg/kg los días 0 y 1, continuando después con 20 mg/kg desde el día 2 hasta el día 23.

El peso corporal de todos los animales se registró antes del comienzo y una vez al día durante el estudio.

Se llevó a cabo una angiografía el día 21 usando el Angiógrafo Retiniano de Heidelberg (HRA). Tras la anestesia y la dilatación pupilar, se inyectó subcutáneamente tinte de fluoresceína de sodio 10 %, y se registraron imágenes 10 min. después de la inyección del tinte. La fuga vascular de la fluoresceína sobre los angiogramas se evaluó por dos examinadores en una forma enmascarada y se calificó con 0 (sin fugas) a 3 (intensamente manchada).

Tras la eutanasia el día 23, los ojos se cosecharon y fijaron en solución de paraformaldehído al 4 % durante 1 hora a temperatura ambiente. Tras el lavado, la retina se peló cuidadosamente, y la esclera-coroide se laminó en plano y se incubó tras el bloqueo con un anticuerpo de FITC-isolectina B4. Las preparaciones laminadas en plano se examinaron bajo un microscopio de fluorescencia (Apotom) con una longitud de onda de excitación de 488 nm. El volumen de la neovascularización coroidea se calificó por el análisis morfométrico de imágenes usando el software 4.6 de Axiovision.

Para el Ejemplo 11 como un representante de los compuestos de la presente invención, los siguientes resultados se obtuvieron en este modelo:

	fuga vascular [calificación de angiografía]	**volumen de lesión de neovascularización coroidea** [μm^3 x 100 000]
Ejemplo 11	0,68 ± 0,35	3,48 ± 0,40
Vehículo de control	1,7 ± 0,32	5,83 ± 0,55

B-4. Eficacia tópica en el modelo de neovascularización coroidea (NVC) inducida por láser

El objetivo de este estudio fue determinar si una administración tópica dos veces al día (gotas oculares) de un compuesto de ensayo daba lugar a una reducción de

la fuga vascular y/o neovascularización coroidea en un modelo de ratas de neovascularización coroidea inducida por láser.

Con este propósito, se seleccionaron 65 ratas de Noruega marrones sin signos visibles de defectos oculares y se asignaron aleatoriamente a seis grupos diferentes (por los números n, véase la tabla a continuación). El día 0, los animales se anestesiaron por una inyección intraperitoneal (15 mg/kg de xilacina y 80 mg/kg de ketamina). Tras la instilación de una gota de tropicamida 0,5 % para dilatar las pupilas, se indujo la neovascularización coroidea por la quemadura de seis agujeros en la retina (rotura de la membrana de Bruch) de un ojo por animal usando un láser de argón (tamaño de la lesión: 50 µm; intensidad del láser: 150 mW; duración del estímulo: 100 ms). Los compuestos de ensayo y los vehículos de control se administraron tópicamente dos veces al día por la instilación de las respectivas gotas oculares al ojo afectado. Los compuestos de ensayo se dosificaron como sigue: se aplicaron 10 µl de una formulación de gotas oculares que contenía 20 mg/ml del compuesto de ensayo respectivo suspendido en parafina líquida 100 % o en un vehículo acuoso (HPMC 15 cP 3,5 %, polisorbato 80 0,5 %, NaCl 0,9 % en agua) al ojo afectado dos veces al día con un intervalo de 10 a 14 horas durante el período de observación completo de 23 días. Los animales de control recibieron el vehículo respectivo (parafina líquida 100 % o vehículo acuoso) tópicamente dos veces al día. El peso corporal de todos los animales se registró antes del comienzo y una vez al día durante el estudio.

Se llevó a cabo una angiografía el día 21 usando una cámara de fondo de fluorescencia (Kowe). En la presente, tras la anestesia y la dilatación pupilar, se inyectó subcutáneamente tinte de fluoresceína de sodio 10 %, y se registraron imágenes 2 y 10 min. después de la inyección del tinte. La fuga vascular de la fluoresceína sobre los angiogramas se evaluó por tres examinadores diferentes que se cegaron por la distribución de los grupos (compuesto de prueba versus vehículo), y se calificó con 0 (sin fugas) a 3 (intensamente manchada).

El día 23, los animales se sacrificaron, y los ojos se cosecharon y fijaron en solución de paraformaldehído al 4 % durante 1 hora a temperatura ambiente. Tras el lavado, la retina se peló cuidadosamente, se lavó, bloqueó y manchó con un anticuerpo de FITC-isolectina B4 con el fin de visualizar la vasculatura. Después, las esclera-coroides se laminaron en plano y se examinaron bajo un microscopio de fluorescencia (Keyence Biozero) con una longitud de onda de excitación de 488 nm. El área (en μm^2) de la neovascularización coroidea se midió usando el software de ImageTool.

Para los Ejemplos 7 y 11 como compuestos representativos de la presente invención, los siguientes resultados se obtuvieron en este modelo:

	fuga vascular [calificación de HRA]	**tamaño de lesión de neovascularización coroidea** [μm^2 x 10 000]
Ejemplo 7 (vehículo acuoso; n = 9)	1,49 ± 0,24	6,14 ± 1,60
Ejemplo 7 (vehículo de parafina; n = 8)	1,52 ± 0,21	6,21 ± 0,99
Ejemplo 11 (vehículo acuoso; n = 7)	1,66 ± 0,29	5,50 ± 1,38
Ejemplo 11 (vehículo de parafina; n = 12)	1,41 ± 0,29	6,45 ± 1,63
vehículo acuoso de control (n = 12)	1,87 ± 0,27	7,84 ± 1,09
vehículo de parafina de control (n = 17)	1,97 ± 0,19	7,00 ± 1,00

Aunque la invención se ha divulgado con referencia a realizaciones específicas, es aparente que aquellos con experiencia en la técnica pueden concebir otras realizaciones y variaciones de la invención sin desviarse del espíritu y ámbito verdaderos de la invención. Se pretende que las reivindicaciones se interpreten con la inclusión de todas las tales realizaciones y variaciones equivalentes.

C. Ejemplos referentes a Composiciones Farmacéuticas

Composiciones farmacéuticas de acuerdo con la presente invención se pueden ilustrar como sigue:

Solución i.v. estéril:

Una solución de 5 mg/ml del compuesto deseado de la invención se puede preparar usando agua inyectable, estéril, y, de ser necesario, por el ajuste del pH. La solución se diluye para administración a 1-2 mg/ml con dextrosa 5 % estéril y se administra como una infusión i.v. durante aproximadamente 60 minutos.

Polvo liofilizado para administración i.v.:

Una preparación estéril se puede preparar con (*i*) 100–1000 mg del compuesto deseado de la invención como un polvo liofilizado, (*ii*) 32–327 mg/ml de citrato de sodio, y (*iii*) 300–3000 mg de Dextran 40. La formulación se reconstituye con solución salina inyectable, estéril o dextrosa 5 % a una concentración de 10 a 20 mg/ml, que se diluye en forma adicional con solución salina o dextrosa 5 % de 0,2 a 0,4 mg/ml, y se administra como un bolo i.v. o por infusión i.v. durante 15–60 minutos.

Suspensión intramuscular:

La siguiente solución o suspensión se puede preparar para inyección intramuscular:

50 mg/ml del compuesto no soluble en agua deseado de la invención; 5 mg/ml de carboximetilcelulosa de sodio; 4 mg/ml de Tween 80; 9 mg/ml de cloruro de sodio; 9 mg/ml de alcohol bencílico.

Cápsulas de cubierta dura:

Se prepara un gran número de cápsulas unitarias por el llenado de cápsulas de gelatina dura de dos piezas estándar con 100 mg del compuesto pulverizado deseado de la invención, 150 mg de lactosa, 50 mg de celulosa y 6 mg de estearato de magnesio cada pieza.

Cápsulas de gelatina blanda:

Una mezcla del compuesto deseado de la invención en un aceite digerible, tal como aceite de soja, aceite de semillas de algodón o aceite de oliva, se prepara e inyecta por medio de una bomba de desplazamiento positivo en gelatina molida para formar cápsulas de gelatina blanda que contienen 100 mg del componente activo. Las cápsulas se lavan y secan. El compuesto deseado de la invención se puede disolver en una mezcla de polietilen glicol, glicerina y sorbitol para preparar una mezcla medicinal miscible en agua.

Comprimidos:

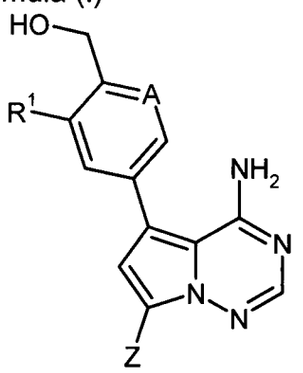
Se prepara un gran número de comprimidos por procedimientos convencionales, de manera tal que la unidad de dosificación sea de 100 mg del compuesto deseado de la invención, 0,2 mg de dióxido de silicio coloidal, 5 mg de estearato de magnesio, 275 mg de celulosa microcristalina, 11 mg de almidón, y 98,8 mg de lactosa. Se pueden aplicar revestimientos acuosos y no acuosos adecuados para aumentar la palatabilidad, mejorar la elegancia y estabilidad, o retrasar la absorción.

Solución o suspensión para aplicación tópica al ojo (gotas oculares):

Una formulación estéril se puede preparar con 100 mg del compuesto deseado de la invención como un polvo liofilizado reconstituido en 5 ml de solución salina estéril. Como un conservante, se pueden utilizar cloruro de benzalconio, timerosal, nitrato fenilmercúrico, o similares en un intervalo de aproximadamente 0,001 % a 1 % en peso.

REIVINDICACIONES

1. Un compuesto de la fórmula (I)



(I),

en la que

A es N o C-R^2, en la que

R^2 representa hidrógeno, fluoro o cloro,

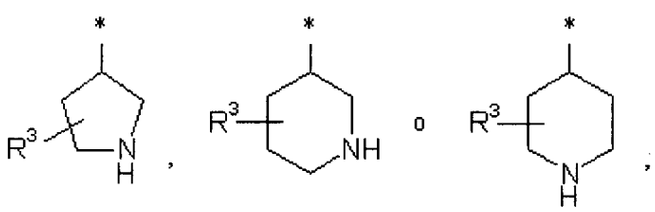
R^1 representa hidrógeno, fluoro, cloro, metilo, etilo o metoxi,

y

Z representa alquilo (C_1-C_4) o cicloalquilo (C_3-C_6), cada uno de los cuales puede estar sustituido con hidroxi,

o

Z representa un grupo heterocíclico de la fórmula



en la que * indica el punto de unión al resto de pirrolotriazina,

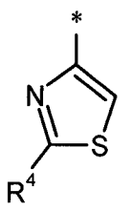
y

R^3 representa hidrógeno o hidroxi,

con la condición de que cuando R^3 sea hidroxi, este hidroxi no esté unido a un átomo de carbono del anillo situado adyacente al átomo de nitrógeno del anillo,

o

Z representa un grupo tiazol de la fórmula



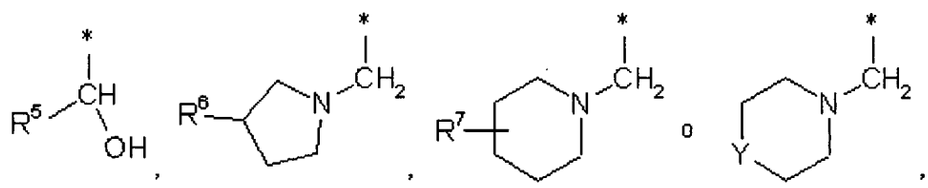
en la que * indica el punto de unión al resto de pirrolotriazina,

y

R^4 representa hidrógeno, metilo, etilo, amino o aminometilo,

o

Z representa un grupo de la fórmula



en la que * indica el punto de unión al resto de pirrolotriazina,

R^5 representa cicloalquilo (C_3-C_6), oxetanilo, tetrahidrofuranilo o tetrahidropiranilo,

R^6 representa hidrógeno o hidroxi,

R^7 representa hidrógeno o hidroxi,

con la condición de que cuando R^7 sea hidroxi, este hidroxi no esté unido a un átomo de carbono del anillo situado adyacente al átomo de nitrógeno del anillo,

e

Y es O, NH o NCH_3,

o una sal, un hidrato y/o un solvato del mismo farmacéuticamente aceptables.

2. El compuesto de la fórmula (I) de acuerdo con la Reivindicación 1, en la que

A es C-R^2, en la que

R^2 representa hidrógeno o fluoro,

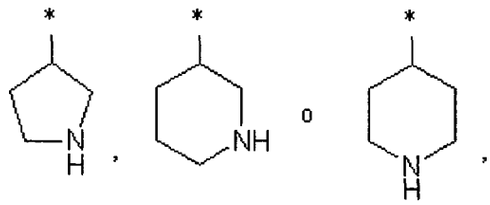
R^1 representa hidrógeno, fluoro, cloro, metilo, etilo o metoxi,

y

Z representa *n*-propilo, *n*-butilo o ciclohexilo, cada uno de los cuales puede estar sustituido con hidroxi,

o

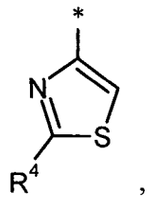
Z representa un grupo heterocíclico de la fórmula



en la que * indica el punto de unión al resto de pirrolotriazina,

o

Z representa un grupo tiazol de la fórmula



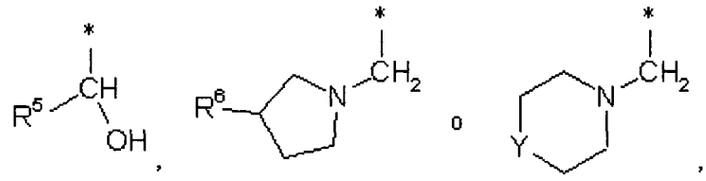
en la que * indica el punto de unión al resto de pirrolotriazina,

y

R^4 representa metilo, etilo, amino o aminometilo,

o

Z representa un grupo de la fórmula



en la que * indica el punto de unión al resto de pirrolotriazina,

R^5 representa ciclopropilo o tetrahidropiran-4-ilo,

R^6 representa hidroxi,

e

Y es O,

o una sal, un hidrato y/o un solvato del mismo farmacéuticamente aceptables.

3. El compuesto de la fórmula (I) de acuerdo con la Reivindicación 1 o 2, en la que

A es C-R^2, en la que

R^2 representa hidrógeno o fluoro,

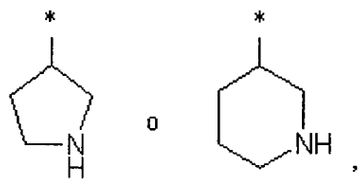
R^1 representa hidrógeno, fluoro, metilo, etilo o metoxi,

y

Z representa 4-hidroxibutilo o 4-hidroxiciclohexilo,

o

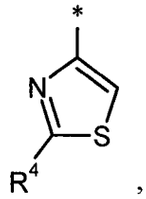
Z representa un grupo heterocíclico de la fórmula



en la que * indica el punto de unión al resto de pirrolotriazina,

o

Z representa un grupo tiazol de la fórmula



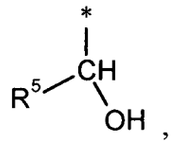
en la que * indica el punto de unión al resto de pirrolotriazina,

y

R^4 representa metilo, etilo, amino o aminometilo,

o

Z representa un grupo de la fórmula



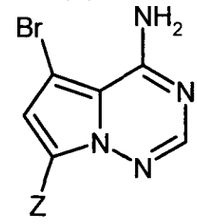
en la que * indica el punto de unión al resto de pirrolotriazina,

y

R^5 representa ciclopropilo,

o una sal aceptable, un hidrato y/o un solvato del mismo, farmacéuticamente aceptables.

4. Un procedimiento para preparar un compuesto de la fórmula (I) como se define en las Reivindicaciones 1 a 3, caracterizado porque una bromopirrolotriazina de la fórmula (II)

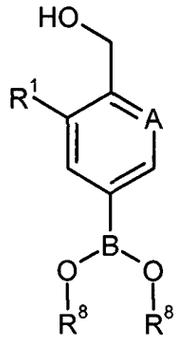


(II),

en la que Z tiene el significado indicado en la Reivindicación 1 a 3,

está

[A] acoplada con un ácido arilborónico o éster de la fórmula (III)



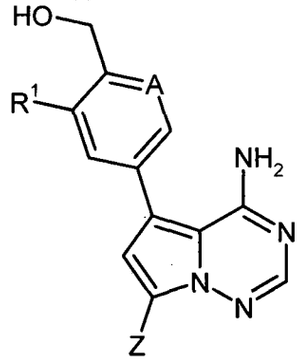
(III),

en la que A y R^1 tienen los significados indicados en la Reivindicación 1 a 3,

y

R^8 representa hidrógeno o alquilo (C_1-C_4), o ambos residuos R^8 están unidos para formar un puente -$(CH_2)_2$-, -$C(CH_3)_2$-$C(CH_3)_2$-, -$(CH_2)_3$- o -CH_2-$C(CH_3)_2$-CH_2-,

en presencia de un catalizador de paladio adecuado y una base para dar el compuesto diana de la fórmula (I)

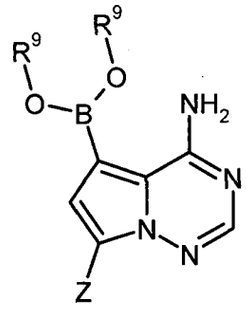


(I),

en la que A, Z y R^1 tienen los significados indicados en la Reivindicación 1 a 3,

o

[B] convertida en primer lugar en el ácido borónico correspondiente o derivado de éster de la fórmula (IV)

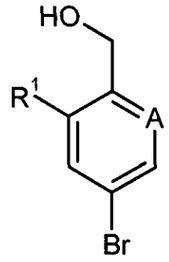


(IV),

en la que Z tiene el significado indicado en la Reivindicación 1 a 3,

y

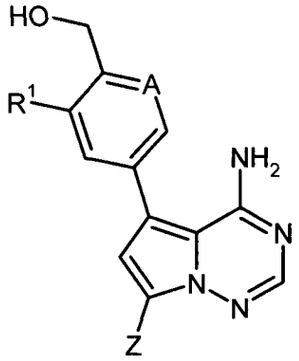
R^9 representa hidrógeno o alquilo (C_1-C_4), o ambos residuos R^9 están unidos para formar un puente -$(CH_2)_2$-, -$C(CH_3)_2$-$C(CH_3)_2$-, -$(CH_2)_3$- o -CH_2-$C(CH_3)_2$-CH_2-, que luego se acopla con un bromuro de arilo de la fórmula (V)



(V),

en la que A y R^1 tienen los significados indicados en la Reivindicación 1 a 3,

en presencia de un catalizador de paladio adecuado y una base para también dar el compuesto diana de la fórmula (I)



(I),

en la que A, Z y R^1 tienen los significados indicados en la Reivindicación 1 a 3,

opcionalmente seguido, donde sea adecuado, por (*i*) la separación de los compuestos de la fórmula (I) en sus respectivos enantiómeros y/o diastereómeros, y/o (*ii*) la conversión de los compuestos de la fórmula (I) en sus respectivos hidratos, solvatos, sales y/o hidratos o solvatos de las sales por medio del tratamiento con los disolventes y/o ácidos correspondientes.

5. Compuesto como se define en cualquiera de las Reivindicaciones 1 a 3 para el tratamiento o la prevención de enfermedades.

6. Uso de un compuesto como se define en cualquiera de las Reivindicaciones 1 a 3 para la elaboración de una composición farmacéutica para el tratamiento o la prevención de degeneración macular relacionada con la edad (DME), neovascularización coroidea (NVC), retinopatía diabética y edema macular diabético (EMD).

7. Una composición farmacéutica que comprende un compuesto como se define en cualquiera de las Reivindicaciones 1 a 3, o una sal, un hidrato y/o un solvato del mismo farmacéuticamente aceptables, y uno o más excipientes farmacéuticamente aceptables.

8. La composición farmacéutica de la Reivindicación 7 que además comprende uno o más agentes terapéuticos adicionales.

9. La composición farmacéutica como se define en la Reivindicación 7 u 8 para el tratamiento o la prevención de degeneración macular relacionada con la edad (DME), neovascularización coroidea (NVC), retinopatía diabética y edema macular diabético (EMD).

10. Un procedimiento para tratar o prevenir la degeneración macular relacionada con la edad (DME), neovascularización coroidea (NVC), retinopatía diabética y edema macular diabético (EMD) en un mamífero, que comprende administrar a un mamífero que lo necesita una cantidad terapéuticamente efectiva de uno o más compuestos como se definen en cualquiera de las Reivindicaciones 1 a 3, o de una composición farmacéutica como se define en cualquiera de las Reivindicaciones 7 a 9.

Pirrolotriazinas sustituidas con hidroximetilarilo y sus usos

Resumen

La presente invención se refiere a pirrolo[2,1-f][1,2,4]triazin-4-aminas sustituidas con 5-[(hidroximetil)arilo] novedosas, a procedimientos para la preparación de tales compuestos, a composiciones farmacéuticas que contienen tales compuestos, y al uso de tales compuestos o composiciones para tratar trastornos relacionados con la angiogénesis, en particular trastornos oculares relacionados con la angiogénesis.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 January 2013 (10.01.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/004551 A1

(51) International Patent Classification:
C07D 487/04 (2006.01) *A61P 27/00* (2006.01)
A61K 31/53 (2006.01)

(21) International Application Number:
PCT/EP2012/062366

(22) International Filing Date:
26 June 2012 (26.06.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/503,840 1 July 2011 (01.07.2011) US
12161547.0 27 March 2012 (27.03.2012) EP

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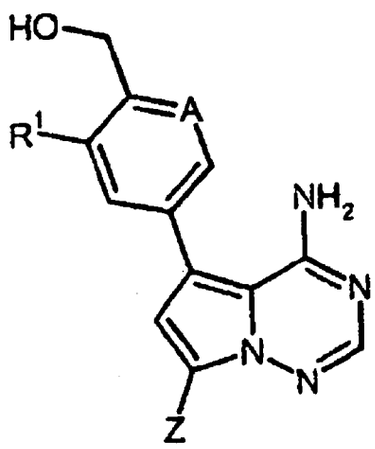
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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD,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

[Continued on next page]

(54) Title: HYDROXYMETHYLARYL-SUBSTITUTED PYRROLOTRIAZINES AS ALK1 INHIBITORS

(57) Abstract: This invention relates to novel 5-[(hydroxymethyl)aryl] -substituted pyrrolo[2, 1-f] [1, 2, 4] triazin-4-amines of formula (I), to processes for the preparation of such compounds, to pharmaceutical compositions containing such compounds, and to the use of such compounds or compositions for treating angiogenesis-related disorders, in particular angiogenesis-related ocular disorders.



(I),

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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))*

Published:

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

HYDROXYMETHYLARYL-SUBSTITUTED PYRROLOTRIAZINES AS ALK1 INHIBITORS

This invention relates to novel 5-[(hydroxymethyl)aryl]-substituted pyrrolo[2,1-f][1,2,4]triazin-4-amines, to processes for the preparation of such compounds, to pharmaceutical compositions containing such compounds, and to the use of such compounds or compositions for treating angiogenesis-related disorders, in particular angiogenesis-related ocular disorders.

The term angiogenesis, also called neovascularisation, signifies the process of forming new blood vessels. It is involved in normal development as well as in numerous pathological states including, for example, cancer, rheumatoid arthritis, wound healing following injury to a tissue, atherosclerosis, psoriasis, and diseases of the eye.

Various ocular disorders which are responsible for the majority of visual morbidities and blindness in the developed countries are characterized by, caused by and/or result in choroidal, retinal or iris neovascularisation or retinal edema [Campochiaro (2004), *Exp. Opin. Biol. Ther.* 4: 1395-1402].

For example, retinopathy associated with diabetes is a leading cause of blindness in type 1 diabetes, and is also common in type 2 diabetes. Another ocular disorder involving neovascularisation is age-related macular degeneration (AMD). AMD is the most common cause of vision loss in the western world in those 50 or older, and its prevalence increases with age. AMD is classified as either wet (neovascular) or dry (non-neovascular). The wet form of the disease is responsible for the most severe loss of vision.

Several other less common, but nonetheless debilitating retinopathies include choroidal neovascular membrane (CNVM), cystoid macular edema (CME, also referred to as macular edema or macular swelling), epi-retinal membrane (ERM, macular pucker), and macular hole. In CNVM, abnormal blood vessels stemming from the choroid grow up through the retinal layers. The fragile new vessels break easily, causing blood and fluid to pool within the layers of the retina. In CME, which can occur as a result of disease, injury or surgery, fluid collects within the layers of the macula, causing blurred, distorted central vision. ERM (macular pucker) is a cellophane-like membrane that forms over the macula, affecting the central vision by causing blur and distortion.

Also related are disorders like hypertrophic and atrophic changes of the retinal pigment epithelium (RPE), retinal detachment, choroidal vein occlusion, retinal vein occlusion, corneal angiogenesis following, for example, keratitis, cornea transplantation or keratoplasty, corneal angiogenesis due to hypoxia (*e.g.*, as a result of extensive contact lens wearing), pterygium conjunctivae, subretinal edema, and intraretinal edema.

Vascular endothelial growth factor (VEGF) has been found to be an important modulator of angiogenesis and has been implicated in the pathology of a number of conditions including AMD and diabetic retinopathy. Furthermore, for AMD it was shown that intravitreal injection of an anti-VEGF inhibitor like pegaptanib, ranibizumab or aflibercept reduces choroidal angiogenesis and vascular leakage [Gragoudas (2004), *N. Engl. J. Med.* 351: 2805-2816; Rosenfeld (2006), *N. Engl. J. Med.* 355: 1419-1431; Dixon (2009), *Expert Opin. Investig. Drugs* 18: 1573-1580].

The current standard of care for AMD is lucentis (ranibizumab), an anti-VEGF therapy. However, only 1/3 of all AMD patients treated with lucentis show improvement in vision [Rosenfeld (2006), *N. Engl. J. Med.* 355: 1419-1431]. Therefore new anti-angiogenic therapeutic options with a VEGF-independent mode of action have the potential to improve the current standard of care in ocular diseases like diabetic retinopathy and AMD.

ALK1 (activin receptor-like kinase-1) is a Ser/Thr kinase receptor of the TGFβ receptor family preferentially expressed in endothelial cells and involved in angiogenesis. Members of this family mediate their biological activity by ligand binding to a heterotetrameric receptor complex of type I and type II serine/threonine kinase receptors TβRI and TβRII and accessory type III receptors. TGFβ as well as the high-affinity ligands BMP9 and BMP10 can activate ALK1 in receptor complexes with BMPRII or ActRII and type III receptor endoglin [Scharpfenecker (2007), *J. Cell Sci.* 120: 964-972]. Binding of BMP9 to ALK1 in microvascular endothelial cells activates the Smad1/5/8 pathway [David (2007), *Blood* 109 (5): 1953-1961]. It was postulated that BMP9 inhibits endothelial cell migration and growth. Most studies, however, find that ALK1 receptor activation promotes endothelial cell migration, proliferation, and tube formation [Goumans (2002), *EMBO Journal* 21 (7): 1743-1753; Wu (2006), *Microvasc. Res.* 71: 12-19].

BMP9 and BMP10 activate ALK1 receptor complexes. In endothelial cells, TGFβ can also activate ALK1 while in most cell types TGFβ signals through ALK5. ALK5 activation leads to phosphorylation of Smad2/3 while ALK1 activation results in phosphorylation of Smad1/5. Each Smad signalling pathway finally results in regulation of specific sets of target genes: Smad2/3 signalling induces expression of PAI-1 and repression of Id-1, while Smad1/5 signalling induces Smad6, Smad7 and Id-1 expression and reduces PAI-1 expression [Deng (2006), *J. Cell Biol.* 134: 1563-1571; Ota (2002), *J. Cell Physiol.* 193: 299-318].

Type III receptor endoglin plays a role in fine-tuning of ALK1 and ALK5 pathways especially in endothelial cells, regulating ligand receptor interactions [ten Dijke (2008), *Angiogenesis* 11: 79-89]. Endoglin facilitates TGFβ/ALK1-interaction but reduces TGFβ/ALK5-interaction [David (2007), *Blood* 109: 1953-1961].

Mutations in endoglin and in ALK1 are linked to the autosomal dominant disorder called hereditary hemorrhagic telangiectasia (HHT1 and HHT2, respectively) with characteristics of angiogenic disturbances like arterial venous malformations and telangiectases [Fernandez-Lopez (2006), *Clin. Med. & Res.* 4: 66-78]. RIP1-Tag2 mice with only one functional copy of the ALK1 gene ($ALK1^{+/-}$) show retarded tumor progression and lower microvessel density compared to $ALK1^{wt}$ mice. Similar observations were made with the soluble ALK1-Fc receptor construct RAP-041, that inhibited tumor angiogenesis *in vivo* and limited tumor growth [Cunha (2010), *J. Exp. Med.* 207: 85-100].

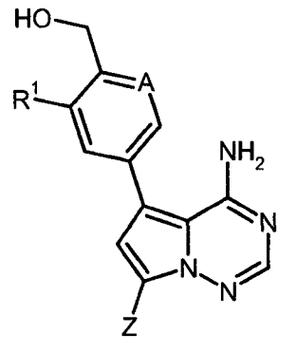
The discovery of potent and selective ALK1 inhibitors is therefore highly desirable to further elucidate the role of ALK1 in blood vessel physiology and pathology, and to derive potential therapeutic options for diseases associated with angiogenesis and vascular remodelling.

In WO 2007/147647-A1, certain 3-aryl-substituted pyrazolo[1,5-a]pyrimidine derivatives were described to be the first small molecule ALK1 kinase inhibitors published until then. These compounds were said to be useful for the treatment of diseases of dysregulated vascular growth, in particular of solid tumors and metastases thereof and also of angiogenesis-dependent diseases of the eye such as age-related macular degeneration.

Various pyrrolo[2,1-f][1,2,4]triazin-4-amine derivatives with distinctive inhibition profiles against a range of protein kinases have been disclosed in, *inter alia*, WO 00/71129-A1, WO 2005/121147-A1, WO 2007/056170-A2, WO 2007/061882-A2, WO 2007/064883-A2, WO 2007/064931-A2, WO 2007/079164-A2, WO 2008/089105-A2, WO 2009/136966-A1, and WO 2010/126960-A1. Generally, these compounds were stated to be useful for the treatment of proliferative and/or angiogenesis-related disorders such as cancer. None of these publications, however, refer to ALK1 as a potential target kinase.

Surprisingly, it has now been found that pyrrolo[2,1-f][1,2,4]triazin-4-amine derivatives having a hydroxymethylaryl substituent in 5-position exhibit potent and selective inhibition of ALK1 kinase which renders these compounds particularly useful for the treatment of angiogenesis-related ocular disorders.

Thus, in one aspect, the present invention relates to 5-[(hydroxymethyl)aryl]-substituted pyrrolo-[2,1-f][1,2,4]triazin-4-amines of the general formula (I)



(I),

wherein

A is N or C-R^2, wherein

R^2 represents hydrogen, fluoro or chloro,

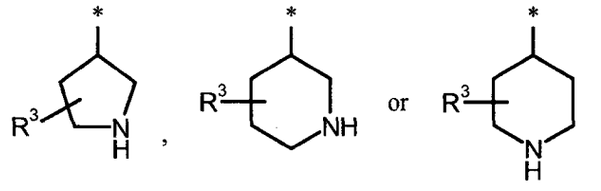
R^1 represents hydrogen, fluoro, chloro, methyl, ethyl or methoxy,

and

Z represents (C_1-C_4)-alkyl or (C_3-C_6)-cycloalkyl each of which may be substituted with hydroxy,

or

Z represents a heterocyclic group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

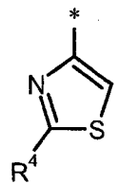
and

R^3 represents hydrogen or hydroxy,

with the proviso that when R^3 is hydroxy, this hydroxy is not attached to a ring carbon atom located adjacent to the ring nitrogen atom,

or

Z represents a thiazole group of the formula



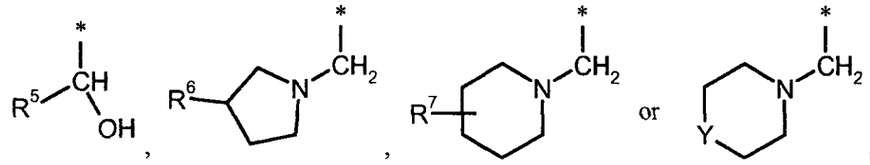
wherein * indicates the point of attachment to the pyrrolotriazine moiety,

and

R^4 represents hydrogen, methyl, ethyl, amino or aminomethyl,

or

Z represents a group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

R^5 represents (C_3-C_6)-cycloalkyl, oxetanyl, tetrahydrofuranyl or tetrahydropyranyl,

R^6 represents hydrogen or hydroxy,

R^7 represents hydrogen or hydroxy,

with the proviso that when R^7 is hydroxy, this hydroxy is not attached to a ring carbon atom located adjacent to the ring nitrogen atom,

and

Y is O, NH or NCH_3.

The compounds according to this invention can also be present in the form of their salts, solvates and/or solvates of the salts.

Compounds according to the invention are the compounds of the formula (I) and their salts, solvates and solvates of the salts, the compounds included in the formula (I) of the formulae

mentioned in the following and their salts, solvates and solvates of the salts, and the compounds included in the formula (I) and mentioned in the following as embodiment examples and their salts, solvates and solvates of the salts, where the compounds included in the formula (I) and mentioned in the following are not already salts, solvates and solvates of the salts.

Salts for the purposes of the present invention are preferably pharmaceutically acceptable salts of the compounds according to the invention (for example, see S. M. Berge *et al.*, "Pharmaceutical Salts", *J. Pharm. Sci.* **1977**, 66, 1-19). Salts which are not themselves suitable for pharmaceutical uses but can be used, for example, for isolation or purification of the compounds according to the invention are also included.

Pharmaceutically acceptable salts include acid addition salts of mineral acids, carboxylic acids and sulfonic acids, for example salts of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, naphthalenedisulfonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.

Solvates in the context of the invention are designated as those forms of the compounds according to the invention which form a complex in the solid or liquid state by stoichiometric coordination with solvent molecules. Hydrates are a specific form of solvates, in which the coordination takes place with water. Hydrates are preferred solvates in the context of the present invention.

The compounds of this invention may, either by nature of asymmetric centers or by restricted rotation, be present in the form of isomers (enantiomers, diastereomers). Any isomer may be present in which the asymmetric center is in the (*R*)-, (*S*)-, or (*R,S*)-configuration.

It will also be appreciated that when two or more asymmetric centers are present in the compounds of the invention, several diastereomers and enantiomers of the exemplified structures will often be possible, and that pure diastereomers and pure enantiomers represent preferred embodiments. It is intended that pure stereoisomers, pure diastereomers, pure enantiomers, and mixtures thereof, are within the scope of the invention.

Geometric isomers by nature of substituents about a double bond or a ring may be present in *cis* (= *Z*-) or *trans* (= *E*-) form, and both isomeric forms are encompassed within the scope of this invention.

All isomers, whether separated, pure, partially pure, or in racemic mixture, of the compounds of this invention are encompassed within the scope of this invention. The purification of said isomers and the separation of said isomeric mixtures may be accomplished by standard techniques known

in the art. For example, diastereomeric mixtures can be separated into the individual isomers by chromatographic processes or crystallization, and racemates can be separated into the respective enantiomers either by chromatographic processes on chiral phases or by resolution.

In addition, all possible tautomeric forms of the compounds described above are included according to the present invention.

Unless otherwise stated, the following definitions apply for the substituents and residues used throughout this specification and claims:

$(C_1\text{-}C_4)$-alkyl represents a straight-chain or branched saturated hydrocarbon radical having 1 to 4 carbon atoms. Examples include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl.

$(C_3\text{-}C_6)$-cycloalkyl represents a monocyclic saturated hydrocarbon radical having 3 to 6 ring carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

Throughout this document, for the sake of simplicity, the use of singular language is given preference over plural language, but is generally meant to include the plural language if not otherwise stated. *E.g.*, the expression "A method of treating a disease in a patient, comprising administering to a patient an effective amount of a compound of formula (I)" is meant to include the simultaneous treatment of more than one disease as well as the administration of more than one compound of formula (I).

In a preferred embodiment, the present invention relates to compounds of general formula (I), wherein

A is C-R^2, wherein

R^2 represents hydrogen or fluoro,

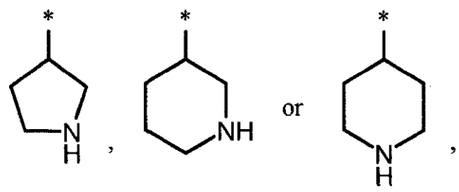
R^1 represents hydrogen, fluoro, chloro, methyl, ethyl or methoxy,

and

Z represents *n*-propyl, *n*-butyl or cyclohexyl each of which may be substituted with hydroxy,

or

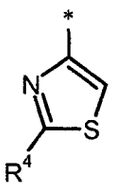
Z represents a heterocyclic group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

or

Z represents a thiazole group of the formula



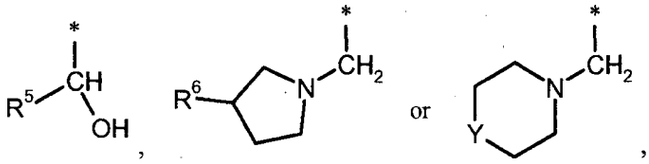
wherein * indicates the point of attachment to the pyrrolotriazine moiety,

and

R^4 represents methyl, ethyl, amino or aminomethyl,

or

Z represents a group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

R^5 represents cyclopropyl or tetrahydropyran-4-yl,

R^6 represents hydroxy,

and

Y is O.

In a particularly preferred embodiment, the present invention relates to compounds of general formula (I), wherein

A is C-R^2, wherein

R^2 represents hydrogen or fluoro,

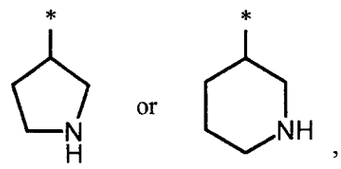
R^1 represents hydrogen, fluoro, methyl, ethyl or methoxy,

and

Z represents 4-hydroxybutyl or 4-hydroxycyclohexyl,

or

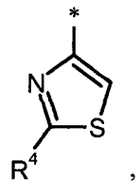
Z represents a heterocyclic group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

or

Z represents a thiazole group of the formula



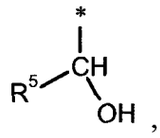
wherein * indicates the point of attachment to the pyrrolotriazine moiety,

and

R^4 represents methyl, ethyl, amino or aminomethyl,

or

Z represents a group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

and

R^5 represents cyclopropyl.

In a distinct embodiment, the present invention relates to compounds of general formula (I), wherein

A is C-R^2, wherein

R^2 represents hydrogen or fluoro.

In a further distinct embodiment, the present invention relates to compounds of general formula (I), wherein

A is C-R^2, wherein

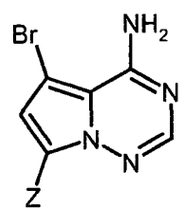
R^2 represents fluoro,

and

R^1 represents fluoro.

The definitions of residues indicated specifically in the respective combinations or preferred combinations of residues are also replaced as desired by definitions of residues of other combinations, irrespective of the particular combinations indicated for the residues. Combinations of two or more of the abovementioned preferred ranges are particularly preferred.

In another embodiment, the present invention relates to a process for preparing the compounds of general formula (I), characterized in that a bromopyrrolotriazine of formula (II)

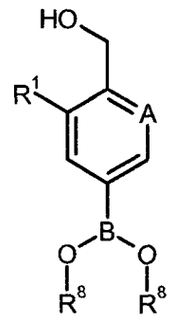


(II),

wherein Z has the meaning described above,

is either

[A] coupled with an arylboronic acid or ester of formula (III)



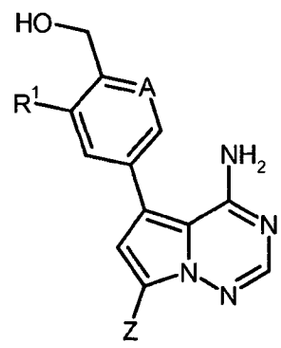
(III),

wherein A and R^1 have the meanings described above,

and

R^8 represents hydrogen or $(C_1\text{-}C_4)$-alkyl, or both R^8 residues are linked together to form a $-(CH_2)_2-$, $-C(CH_3)_2\text{-}C(CH_3)_2-$, $-(CH_2)_3-$ or $-CH_2\text{-}C(CH_3)_2\text{-}CH_2-$ bridge,

in the presence of a suitable palladium catalyst and a base to yield the target compound of formula (I)

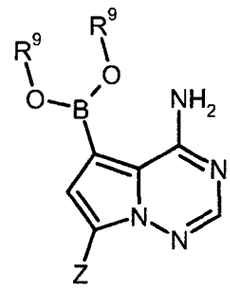


(I),

wherein A, Z and R^1 have the meanings described above,

or

[B] first converted into the corresponding boronic acid or ester derivative of formula (IV)



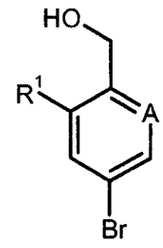
(IV),

wherein Z has the meaning described above,

and

R^9 represents hydrogen or (C_1-C_4)-alkyl, or both R^9 residues are linked together to form a $-(CH_2)_2-$, $-C(CH_3)_2-C(CH_3)_2-$, $-(CH_2)_3-$ or $-CH_2-C(CH_3)_2-CH_2-$ bridge,

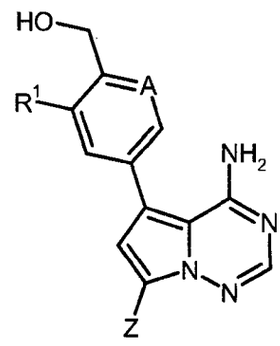
which is then coupled with an aryl bromide of formula (V)



(V),

wherein A and R^1 have the meanings described above,

in the presence of a suitable palladium catalyst and a base to also give the target compound of formula (I)



(I),

wherein A, Z and R^1 have the meanings described above,

optionally followed, where appropriate, by (*i*) separating the compounds of formula (I) into their respective enantiomers and/or diastereomers, preferably using chromatographic methods, and/or (*ii*) converting the compounds of formula (I) into their respective hydrates, solvates, salts and/or hydrates or solvates of the salts by treatment with the corresponding solvents and/or acids.

As outlined above, compounds of formula (I) can be synthesized by a coupling reaction ("Suzuki coupling") between the bromopyrrolotriazine (II) and an aryl boronate or boronic acid (III). This coupling is generally carried out at elevated temperature using a palladium catalyst, a base and an inert solvent. An overview of catalysts and reaction conditions can be found in the literature [see, for instance, S. Kotha *et al.*, *Tetrahedron* **2002**, *58*, 9633-9695; T. E. Barder *et al.*, *J. Am. Chem. Soc.* **2005**, *127*, 4685-4696]. The preferred catalyst in this reaction is tetrakis(triphenylphosphine)-palladium(0). The preferred base is sodium carbonate employed as an aqueous solution. The reaction is carried out in organic solvents that are inert under the reaction conditions, such as 1,4-dioxane, acetonitrile, *N,N*-dimethylformamide (DMF) or dimethylsulfoxide (DMSO), or in water or in mixtures of these solvents. Preferably, the reaction is carried out in a mixture of 1,4-dioxane and water or acetonitrile and water. The reaction is generally performed at temperatures between +100°C and +250°C, preferably at +120°C to +150°C. Heating is preferably effected by a single-mode microwave device. The reactions are usually run under an inert gas atmosphere, preferably under argon.

An inverse reactivity of the reaction partners for the Suzuki coupling may sometimes be favorable. For this purpose, the bromopyrrolotriazine (II) is first converted into the corresponding boronate (IV) and then cross-coupled with an aryl bromide (V) according to one of the methods described above. The conversion of (II) to (IV) is achieved by a metal-mediated borylation reaction. The preferred method is the palladium-catalyzed "Miyaura borylation" [see, for instance, J. Takagi *et al.*, *J. Am. Chem. Soc.* **2002**, *124*, 8001-8006; T. Ishiyama *et al.*, *J. Org. Chem.* **1995**, *60*, 7508-7510; A. L. S. Thompson *et al.*, *Synthesis* **2005**, 547-550]. Procedures, reagents and solvents for the cross-coupling reaction (IV) + (V) → (I) are chosen from those mentioned in the previous section.

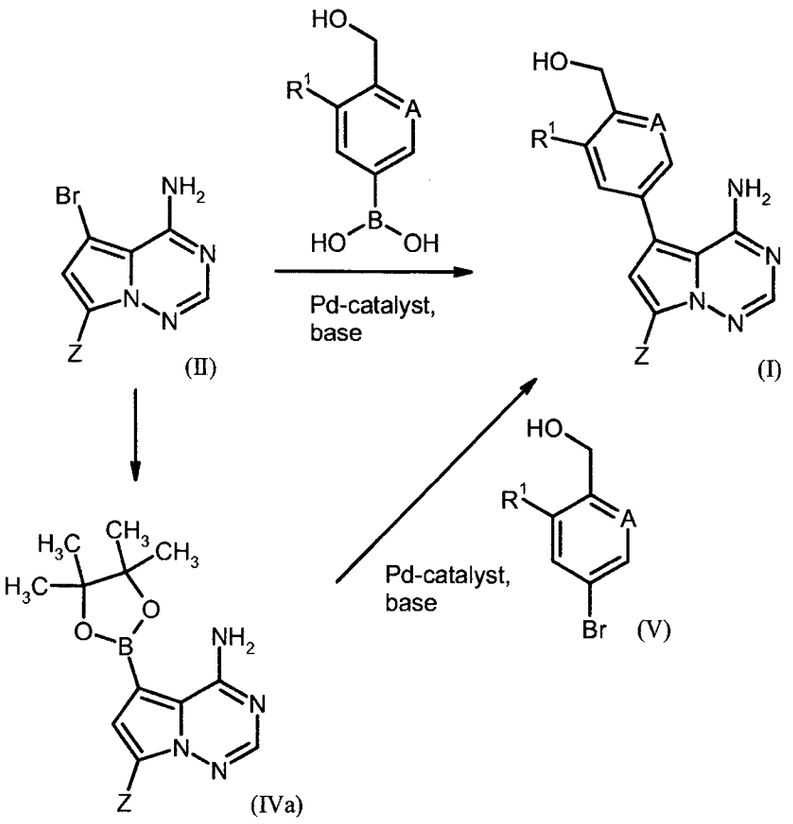
Arylboronic acids (III) [R^8 = H] and aryl boronates (III) [R^8 = alkyl, or both R^8 are linked together to form a cyclic boronic ester, *e.g.*, a pinacolato ester] are either commercially available, or they can be conveniently prepared from the corresponding aryl halides or aryl triflates using a metal-mediated borylation reaction (for references, see previous section). Borylation and subsequent Suzuki coupling may be carried out in two separate steps including isolation and purification of intermediate (III). Alternatively, borylation and cross-coupling may be carried out as a one-pot procedure using (III) directly without isolation and purification.

In cases where a primary or secondary amine moiety forms part of the Z group in the target compounds of formula (I), it may often be beneficial in the borylation and coupling reactions described above to use a protected derivative of this amine as the starting pyrrolotriazine (II) instead of the free amine compound. For this purpose, conventional temporary amino-protecting groups, such as acyl groups (*e.g.*, acetyl or trifluoroacetyl) or carbamate-type protecting groups (*e.g.*, a Boc-, Cbz- or Fmoc-group), may be employed. Preferably, a trifluoroacetyl or a Boc group is used. Similarly, the hydroxy function in the coupling components (III) and (V), respectively, may temporarily be blocked during the process, preferably as a silyl ether derivative such as a trimethylsilyl or *tert*-butyldimethylsilyl ether.

These protecting groups may then be cleaved off concomitantly during the aqueous work-up of the coupling reaction mixtures, or they are removed in a subsequent, separate reaction step using standard methods known in the art. The preparation of the protected intermediates described above from the corresponding free amines or alcohols of formula (II), (III) and (V), respectively, or from other precursor compounds (see section below) is also readily accomplished following general procedures described in the literature [see, for example, T. W. Greene and P. Wuts, *Protective Groups in Organic Synthesis*, Wiley, New York, 1999].

The preparation of the compounds of the invention may be illustrated by means of the following synthesis scheme:

Scheme 1



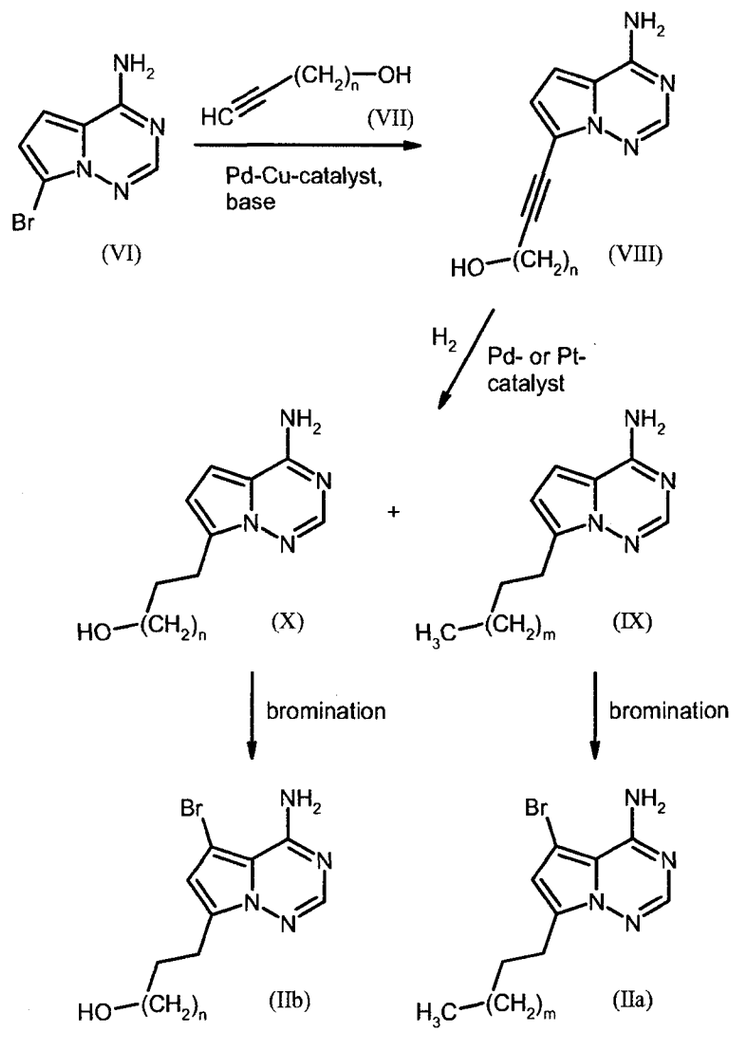
The synthetic methodologies that may be used to prepare the bromopyrrolotriazines of formula (II) can be structured according to the chemotype of the Z group present in (II). Examples illustrating these various routes are given below (see synthesis schemes 2-6). More detailed procedures are provided in the Experimental Section describing specific intermediate and example compounds of the invention.

For example, compounds of formula (II) containing an alkyl or hydroxyalkyl residue as the Z group can be obtained by employing a coupling reaction between the bromopyrrolotriazine (VI) and a terminal alkyne of formula (VII) as the key step (scheme 2). This type of reaction ("Sonogashira reaction") is usually performed in the presence of a palladium-copper catalyst system and a base. Several examples of this reaction have been described in the literature [see, for instance, R. Chinchilla and C. Nájera, *Chem. Rev.* **2007**, *107*, 874-922]. In the present invention, the preferred copper source is copper(I) iodide, tetrakis(triphenylphosphine)palladium(0) is used as palladium catalyst, and pyrrolidine serves both as base and solvent. The coupling reaction is advantageously carried out under concurrent microwave irradiation.

The resulting alkyne (VIII) is then subjected to catalytic hydrogenation employing a customary palladium or platinum catalyst. Preferably, platinum(IV) oxide is used as the catalyst, and the reaction is run in acetic acid as the solvent. In some cases, a mixture of products (IX) and (X) is obtained by this procedure which, in any event, can be separated easily by chromatographic methods. A subsequent bromination reaction, preferably using 1,3-dibromo-5,5-dimethylhydantoin as the bromine source, in an inert solvent such as THF or DMF yields the target pyrrolotriazines (IIa) and (IIb), respectively.

The preparation of the starting compound 7-bromopyrrolo[2,1-f][1,2,4]triazin-4-amine (VI) has been described previously [see WO 2007/056170-A2 (Intermediate B)].

Scheme 2



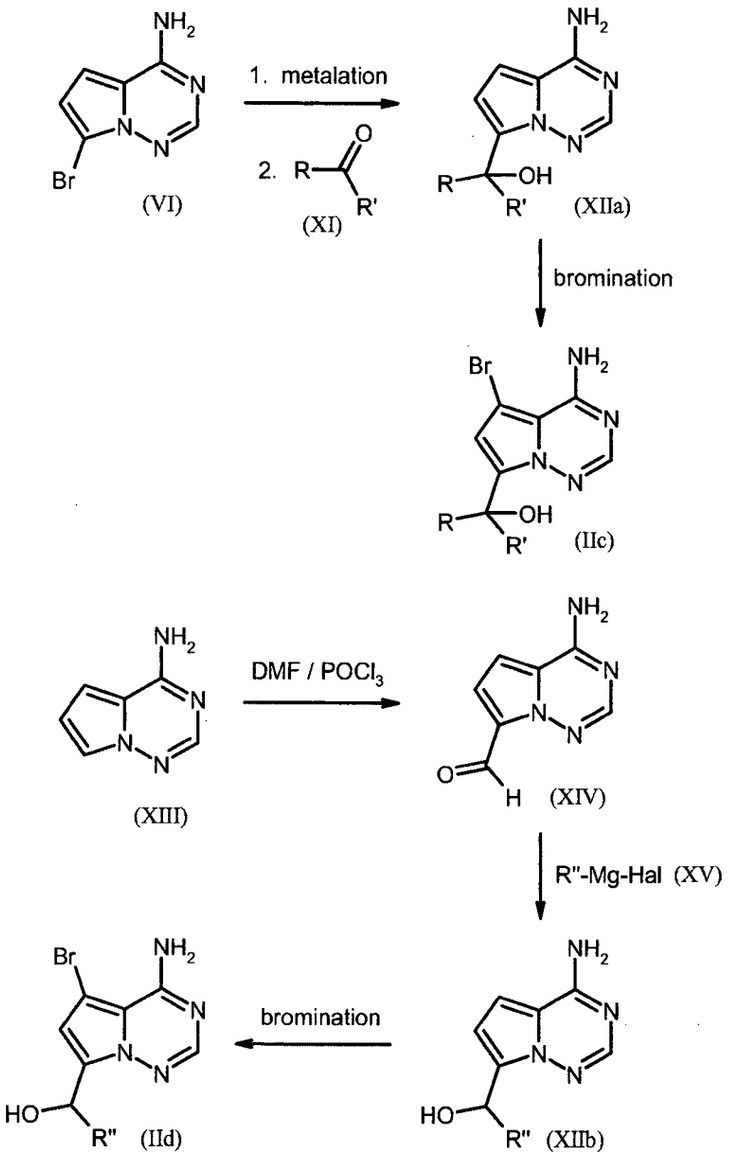
[m = 0 or 1, n = 1 or 2].

Bromopyrrolotriazine precursors of type (IIc) (scheme 3) can be prepared by metalation of compound (VI) with a metal such as magnesium or lithium or by halogen-metal exchange using an organo-magnesium or organo-lithium reagent. The preferred metal is magnesium which is introduced into (VI) by treatment with isopropylmagnesium bromide in a solvent such as THF or diethyl ether. The intermediate organo-metal species is then reacted with a cycloalkanone or heterocycloalkanone (XI) [R, R' are linked together to form a cycloalkyl or heterocycloalkyl ring] to give the tertiary alcohol (XIIa).

A complementary route leading to secondary alcohols of formula (XIIb) utilizes a Vilsmeier formylation reaction whereby aminopyrrolotriazine (XIII) is transformed into the aldehyde (XIV) (scheme 3). Side chain introduction is accomplished by subsequent addition of an appropriate Grignard reagent (XV) [R" = alkyl or cycloalkyl] in a solvent such as THF or diethyl ether. Finally, bromination of compounds (XIIa) and (XIIb), preferably using 1,3-dibromo-5,5-dimethylhydantoin, in an inert solvent such as THF or DMF provides the target pyrrolotriazines (IIc) and (IId), respectively.

The preparation of the starting compound pyrrolo[2,1-f][1,2,4]triazin-4-amine (XIII) has been described previously [see WO 2007/056170-A2 (Intermediate A)].

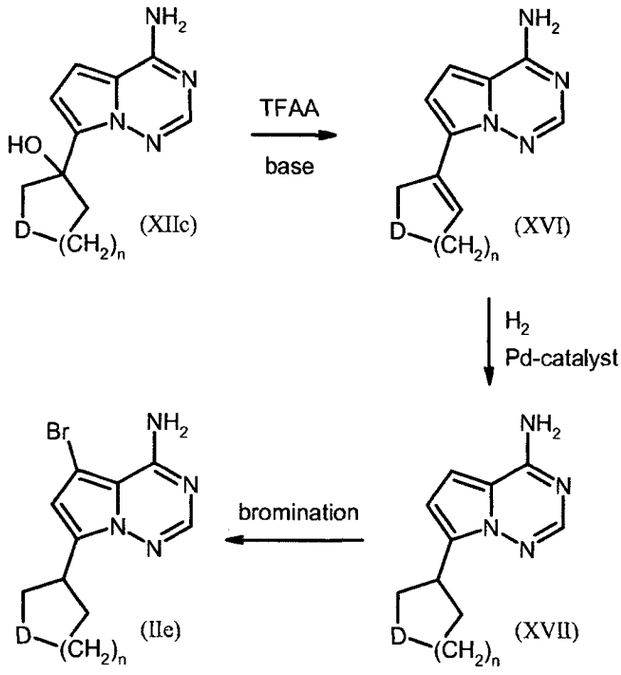
Scheme 3



Pyrrolotriazines of formula (II) wherein Z is representing an unsubstituted cycloalkyl or carbon-bonded aza-heterocyclyl group can be prepared by dehydration of a tertiary alcohol of formula (XIIc) to the unsaturated carbo- or heterocycle of formula (XVI), employing customary agents such as trifluoroacetic acid anhydride, trifluoromethanesulfonic acid anhydride, phosphorus(V) oxide, sulfuric acid or other strong acids (scheme 4). Subsequent catalytic hydrogenation using a conventional catalyst such as palladium on charcoal yields the saturated analog of formula (XVII). The hydrogenation step is preferably carried out in a solvent like methanol, ethanol or THF which contains a small amount of aqueous trifluoroacetic acid. Finally, bromination with 1,3-dibromo-5,5-dimethylhydantoin, as described above, provides the target pyrrolotriazine (IIe).

The alcohol precursors (XIIc) themselves are readily accessible by the synthetic route depicted in scheme 3 [*cf.* preparation of compound (XIIa)].

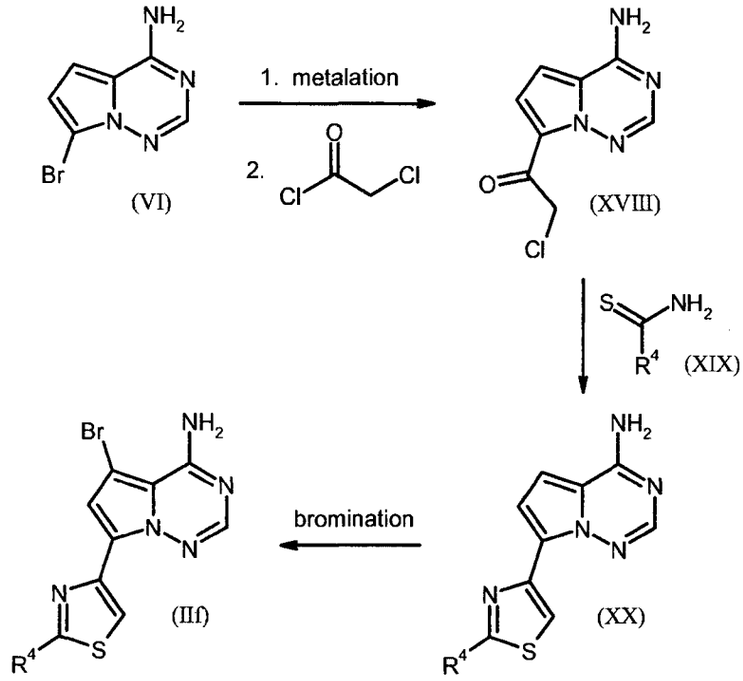
Scheme 4



[D = *e.g.* CH_2 or N-Boc; n = 1 or 2].

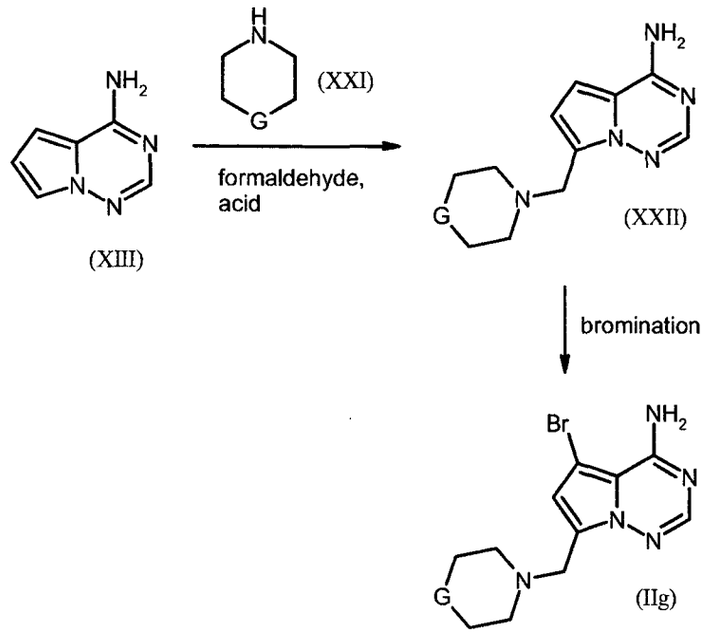
Pyrrolotriazines of formula (II) wherein Z is representing a 1,3-thiazol-4-yl group can be prepared by metalation of compound (VI), as described above, followed by reaction with chloroacetyl chloride to give the intermediate (XVIII), and then condensation with a thioamide or thiourea (XIX) [with R^4 as defined above] to yield the precursor compound (XX) (scheme 5). Bromination with 1,3-dibromo-5,5-dimethylhydantoin, as described above, finally provides the target pyrrolotriazine (IIf).

Scheme 5



Pyrrolotriazines of formula (II) wherein Z is representing an *N*-cyclic aminomethyl group can be obtained by reacting pyrrolotriazine (XIII) with formaldehyde and a cyclic amine of type (XXI) in an acidic solvent, such as acetic acid, or in a mixture of an acid with an organic solvent (scheme 6). Bromination of the resulting product (XXII) with 1,3-dibromo-5,5-dimethylhydantoin, as described above, then provides the target pyrrolotriazine (IIg).

Scheme 6



[G = *e.g.* CH_2, CH(OH), O or N-Boc].

The compounds of the formulae (V), (VII), (XI), (XV), (XIX) and (XXI) are either commercially available, known from the literature, or can be prepared from readily available starting materials by adaptation of standard methods described in the literature.

The compounds of the present invention have valuable pharmacological properties and can be used for the prevention and treatment of diseases in humans and animals.

The compounds of the present invention are potent and selective inhibitors of ALK1 kinase. They can therefore be used for the treatment and/or prevention of angiogenesis-related disorders, in particular angiogenesis-related ocular disorders.

For the present invention, the term "treatment" or "treating" includes inhibiting, delaying, relieving, mitigating, arresting, reducing or causing the regression of a disease, disorder, condition or state, the development and/or progression thereof, and/or the symptoms thereof. The term "prevention" or "preventing" includes reducing the risk of having, contracting or experiencing a disease, disorder, condition or state, the development and/or progression thereof, and/or the symptoms thereof. The term prevention includes prophylaxis. Treatment or prevention of a disease, disorder, condition or state may be partial or complete.

Angiogenesis-related ocular disorders that may be treated and/or prevented with the compounds of the present invention include, but are not limited to, age-related macular degeneration (AMD),

diabetic retinopathy, in particular diabetic macula edema (DME), other retinopathies such as choroidal neovascularisation (CNV), choroidal neovascular membrane (CNVM), cystoid macular edema (CME), epi-retinal membrane (ERM) and macular hole, hypertrophic changes of the retinal pigment epithelium (RPE), atrophic changes of the retinal pigment epithelium, retinal detachment, choroidal vein occlusion, retinal vein occlusion, corneal angiogenesis following, for example, keratitis, cornea transplantation or keratoplasty, corneal angiogenesis due to hypoxia (*e.g.*, induced by extensive contact lens wearing), pterygium conjunctivae, subretinal edema, and intraretinal edema.

In the context of the present invention, the term age-related macular degeneration (AMD) encompasses both wet (or exudative, neovascular) and dry (or non-exudative, non-neovascular) manifestations of AMD.

The compounds of the present invention can additionally be used for the treatment and/or prevention of inflammatory diseases associated with angiogenesis, such as rheumatoid arthritis, psoriasis, contact dermatitis, asthma, pulmonary hypertension, multiple sclerosis, and inflammatory diseases of the bowel such as Crohn's disease. Fibrotic diseases, such as fibrosis and cirrhosis, may also be treated and/or prevented with the compounds of the present invention.

By virtue of their activity profile, the compounds of the present invention are particularly suitable for the treatment and/or prevention of ocular disorders, such as age-related macular degeneration (AMD), choroidal neovascularisation (CNV), diabetic retinopathy, and diabetic macula edema (DME).

The disorders mentioned above have been well characterized in humans, but also exist with a similar etiology in other animals, including mammals, and can be treated in these with the compounds of the present invention.

Thus, the present invention further relates to the use of the compounds according to the invention for the treatment and/or prevention of disorders, especially of the aforementioned disorders.

The present invention further relates to the use of the compounds according to the invention for preparing a pharmaceutical composition for the treatment and/or prevention of disorders, especially of the aforementioned disorders.

The present invention further relates to the use of the compounds according to the invention in a method for the treatment and/or prevention of disorders, especially of the aforementioned disorders.

The present invention further relates to a method for the treatment and/or prevention of disorders, especially of the aforementioned disorders, by using an effective amount of at least one of the compounds according to the invention.

Compounds of the present invention may be administered as the sole pharmaceutical agent or in combination with one or more additional therapeutic agents where the combination causes no unacceptable adverse effects. This combination therapy includes administration of a single pharmaceutical dosage formulation which contains a compound of formula (I), as defined above, and one or more additional therapeutic agents, as well as administration of a compound of formula (I) and each additional therapeutic agent in its own separate pharmaceutical dosage formulation. For example, a compound of formula (I) and a therapeutic agent may be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent may be administered in separate dosage formulations.

Where separate dosage formulations are used, the compound of formula (I) and one or more additional therapeutic agents may be administered at essentially the same time (*i.e.*, concurrently) or at separately staggered times (*i.e.*, sequentially).

In particular, the compounds of the present invention may be used in fixed or separate combination with inhibitors of VEGF-mediated angiogenesis, such as, for example, ACTB-1003, aflibercept, apatinib, axitinib, bevacizumab, bevasiranib, BMS-690514, brivanib, cediranib, CT-322, dovitinib, E7080, foretinib, KH-902, linifanib, MGCD-265, motesanib, OTS-102, pazopanib, pegaptanib, ranibizumab, regorafenib, ruboxystaurin, sorafenib, SU-14813, sunitinib, telatinib, TG-100801, tivozanib, TSU-68, vandetanib, vargatef, vatalanib and XL-184, or with inhibitors of other signaling pathways, such as, for example, ACU-4429, disulfiram, E-10030, fenretinide, mecamylamine, PF-04523655, sirolimus, sonepcizumab, tandospirone and volociximab.

Thus, in a further embodiment, the present invention relates to pharmaceutical compositions comprising at least one of the compounds according to the invention and one or more additional therapeutic agents for the treatment and/or prevention of disorders, especially of the aforementioned disorders.

The compounds of the present invention may also be utilized, as such or in compositions, in research and diagnostics, or as analytical reference standards and the like.

In another aspect, the present invention relates to pharmaceutical compositions comprising at least one of the compounds according to the invention together with one or more inert, non-toxic, pharmaceutically suitable excipients, and to the use thereof for the aforementioned purposes.

The compounds according to the invention can act systemically and/or locally. For this purpose, they can be administered in a suitable way such as, for example, by the oral, parenteral, pulmonary, nasal, lingual, sublingual, buccal, rectal, dermal, transdermal, conjunctival, subconjunctival, intravitreal, otic or topical routes.

The compounds according to the invention can be administered in application forms suitable for these administration routes.

Suitable for oral administration are application forms which function according to the prior art and deliver the compounds according to the invention rapidly and/or in modified fashion, and which contain the compounds according to the invention in crystalline, amorphous and/or dissolved form, such as, for example, tablets (uncoated or coated tablets, for example having enteric coatings or coatings which are insoluble or dissolve with a delay and control the release of the compound according to the invention), tablets which disintegrate rapidly in the mouth, or films/wafers, films/lyophilisates, capsules (*e.g.*, hard or soft gelatin capsules), sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, aerosols or solutions.

Parenteral administration can take place with avoidance of an absorption step (*e.g.*, intravenous, intraarterial, intracardiac, intraspinal or intralumbar) or with inclusion of an absorption (*e.g.*, intramuscular, subcutaneous, intracutaneous, percutaneous or intraperitoneal). Application forms suitable for parenteral administration are, *inter al.*, preparations for injection and infusion in the form of solutions, suspensions, emulsions, lyophilisates or sterile powders.

Forms suitable for other administration routes include, for example, pharmaceutical forms for inhalation (*e.g.*, powder inhalers, nebulizers), nasal drops, solutions or sprays, tablets or capsules for lingual, sublingual or buccal administration (*e.g.*, troches, lozenges), suppositories, ear and eye preparations (*e.g.*, drops, ointments), vaginal capsules, aqueous suspensions (lotions, shaking mixtures), lipophilic suspensions, ointments, creams, milk, pastes, foams, dusting powders, and transdermal therapeutic systems (*e.g.*, patches).

The compounds according to the invention can be converted into the recited application forms in a manner known *per se* by mixing with inert, non-toxic, pharmaceutically suitable excipients. These excipients include, *inter al.*, carriers (*e.g.*, microcrystalline cellulose, lactose, mannitol), solvents (*e.g.*, liquid polyethylene glycols), emulsifiers (*e.g.*, sodium dodecyl sulfate), surfactants (*e.g.*, polyoxysorbitan oleate), dispersants (*e.g.*, polyvinylpyrrolidone), synthetic and natural polymers (*e.g.*, albumin), stabilizers (*e.g.*, antioxidants such as, for example, ascorbic acid), colorants (*e.g.*, inorganic pigments such as, for example, iron oxides), and taste and/or odour masking agents.

It has generally proved advantageous to administer on parenteral administration amounts of about 0.001 to 1 mg/kg, preferably about 0.01 to 0.5 mg/kg, of body weight to achieve effective results. On oral administration, an exemplary dose range is about 0.01 to 100 mg/kg, preferably about 0.01 to 20 mg/kg, and more preferably about 0.1 to 10 mg/kg of body weight.

Nevertheless, actual dosage levels and time course of administration of the active ingredients in the pharmaceutical compositions of the invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition and mode of administration, without being toxic to the patient. It may therefore be necessary where appropriate to deviate from the stated amounts, in particular as a function of age, gender, body weight, diet and general health status of the patient, route of administration, individual response to the active ingredient, nature of the preparation, and time or interval over which administration takes place. Thus, it may be satisfactory in some cases to manage with less than the aforementioned minimum amount, whereas in other cases the stated upper limit must be exceeded. It may in the event of administration of larger amounts be advisable to divide these into multiple individual doses spread over the day.

For the treatment and/or prevention of ocular disorders, as described above, the preferred route for administering the compounds of the invention is topically at the eye or by an ocular drug delivery system. Intraocular injections are another way to administer the compounds of the present invention that is suitable for such purposes.

Delivery to areas within the eye can be accomplished by injection, employing a cannula or another invasive device designed to introduce precisely metered amounts of a desired formulation to a particular compartment or tissue within the eye (*e.g.*, posterior chamber or retina). An intraocular injection may be into the vitreous (intravitreal), under the conjunctiva (subconjunctival), behind the eye (retrobulbar), into the sclera, or under the Capsule of Tenon (sub-Tenon), and may be in a depot form. Other intraocular routes of administration and injection sites and forms are also contemplated and are within the scope of the invention.

The compounds according to the invention may be formulated in a manner known to those skilled in the art so as to give adequate delivery to the back of the eye, which may be by regular dosing, such as with eye drops, or by using a delivery system to give a controlled release, such as slow release, of the compounds according to the invention.

Preferred ocular formulations for the compounds of the present invention include aqueous solutions, suspensions or gels of these compounds in the form of drops of liquid, liquid washes, sprays, ointments or gels, in admixture with excipients suitable for the manufacture and use of such appli-

cation forms. Alternatively, the compounds of the present invention may be applied to the eye via liposomes or other ocular delivery systems that are known in the art.

Appropriate dosage levels may be determined by any suitable method known to one skilled in the art of treating eye diseases. Preferably, the active substance is administered at a frequency of 1 to 4 times per day for topical administration, or less often if a drug delivery system is used. Typically, an ocular formulation intended for topical application contains the active ingredient in a concentration range of about 0.001% to 10%.

The following exemplary embodiments illustrate the invention. The invention is not restricted to the examples.

The percentages in the following tests and examples are, unless stated otherwise, by weight; parts are by weight. Solvent ratios, dilution ratios and concentrations reported for liquid/liquid solutions are each based on volume.

A. Examples

Abbreviations and Acronyms:

Ac	acetyl
aq.	aqueous (solution)
Boc	*tert*-butoxycarbonyl
br.	broad (^{1}H NMR signal)
Cbz	benzyloxycarbonyl
Celite®	registered trademark of Celite Corp. brand of diatomaceous earth
conc.	concentrated
DCI	direct chemical ionization (MS)
DCM	dichloromethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
e.e.	enantiomeric excess
EI	electron impact ionization (MS)
ent	enantiomer, enantiomerically pure
eq.	equivalent(s)
ESI	electro-spray ionization (MS)
Et	ethyl
EtOAc	ethyl acetate
Fmoc	(9*H*-fluoren-9-ylmethoxy)carbonyl
GC/MS	gas chromatography-coupled mass spectroscopy
h	hour(s)
Hal	halogen
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
HPLC	high performance liquid chromatography
LC/MS	liquid chromatography-coupled mass spectroscopy
Me	methyl
MeOH	methanol
min	minute(s)
MS	mass spectroscopy
of th.	of theory (chemical yield)
$PdCl_2$(dppf)	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
Ph	phenyl
rac	racemic, racemate

R_f	TLC retention factor
rt	room temperature
R_t	retention time (HPLC)
satd.	saturated
TBAF	tetrabutylammonium fluoride
tBu	*tert*-butyl
tert	tertiary
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography

Preparative HPLC purification methods:

Method 1:

Device: Gilson Abimed HPLC, binary pump system; column: ReproSil C18, 250 mm x 30 mm; eluent A: water / 1% ammonia, eluent B: acetonitrile; gradient: 0-3 min 10% B, 5.01-31 min 95% B, 31 min 95% B; flow rate: 50 mL/min; UV detection: 210 nm.

Method 2:

Device: Gilson Abimed HPLC, binary pump system; column: Kromasil-100A C18, 5 µm, 250 mm x 30 mm; eluent A: water / 0.05-0.5% TFA, eluent B: acetonitrile; gradient: 0-5 min 5% B, 5.01-10 min 10% B, 10.01-20 min 40% B, 20.01-27 min 50% B, 27.01-40 min 60% B, 40.01-45 min 90% B, 45.01-60 min 100% B; flow rate: 15-60 mL/min; UV detection: 210 nm.

Method 3:

Device: Gilson Abimed HPLC, binary pump system; column: Grom-Sil-120 ODS-4HE, 250 mm x 30 mm; eluent A: water, eluent B: acetonitrile; gradient: 0-3 min 10% B, 3.01-35 min 98% B, 35.01-40 min 98% B; flow rate: 50 mL/min; UV detection: 210 nm.

Method 4:

Device: Gilson Abimed HPLC, binary pump system; column: Grom-Sil-120 ODS-4HE, 250 mm x 30 mm; eluent A: water / 0.5% ammonia, eluent B: acetonitrile; gradient: 0-3 min 10% B, 3.01-35 min 98% B, 35.01-40 min 98% B; flow rate: 50 mL/min; UV detection: 210 nm.

Method 5:

Device: Gilson Abimed HPLC, binary pump system; column: Chromatorex C18 10 µm, 250 mm x 30 mm; eluent A: water, eluent B: acetonitrile; gradient: 0-3 min 10% B, 5.01-31 min 90% B, 31 min 90% B; flow rate: 50 mL/min; UV detection: 210 nm.

Method 6:

Device: Gilson Abimed HPLC, binary pump system; column: Chromatorex C18 10 µm, 250 mm x 30 mm; eluent A: water / 0.5% TFA, eluent B: acetonitrile; gradient: 0-3 min 10% B, 5.01-31 min 90% B, 31 min 90% B; flow rate: 50 mL/min; UV detection: 210 nm.

Method 7:

Device: Gilson Abimed HPLC, binary pump system; column: ReproSil C18 10 µm, 250 mm x 40 mm; eluent A: water, eluent B: acetonitrile; gradient: 0-3 min 10% B, 5.01-31 min 95% B, 31 min 95% B; flow rate: 50 mL/min; UV detection: 210 nm.

Method 8:

Device: Gilson Abimed HPLC, binary pump system; column: ReproSil C18 10 µm, 250 mm x 30 mm; eluent A: water, eluent B: acetonitrile; gradient: 0-3 min 10% B, 5.01-31 min 95% B, 31 min 95% B; flow rate: 50 mL/min; UV detection: 210 nm.

Method 9:

Device: Gilson Abimed HPLC, binary pump system; column: Waters Sunfire C18 5 µm, 250 mm x 20 mm; eluent A: water, eluent B: acetonitrile; gradient: 0 min 20% B, 15 min 60% B, 15.01-19 min 20% B; flow rate: 25 mL/min; UV detection: 210 nm.

Analytical HPLC, LC/MS and GC/MS methods:

Method 1 (HPLC):

Instrument: Agilent 1100 with DAD detection; column: Agilent Zorbax Eclipse XDB-C8 4.6, 150 mm x 5 mm; eluent A: 0.01% TFA in water, eluent B: 0.01% TFA in acetonitrile; gradient: 0-1 min 10% B, 4-5 min 90% B, 5.5 min 10% B; flow rate: 2.0 mL/min; temperature: 30°C; UV detection: 210 nm.

Method 2 (HPLC):

Instrument: HP 1100 with DAD detection; column: Kromasil 100 RP-18, 60 mm x 2.1 mm, 3.5 µm; eluent A: 5 mL perchloric acid (70%) / L water, eluent B: acetonitrile; gradient: 0 min 2% B,

0.5 min 2% B, 4.5 min 90% B, 6.5 min 90% B, 6.7 min 2% B, 7.5 min 2% B; flow rate: 0.75 mL/min; temperature: 30°C; UV detection: 210 nm.

Method 3 (HPLC):

Instrument: HP 1100 with DAD detection; column: Kromasil 100 RP-18, 60 mm x 2.1 mm, 3.5 µm; eluent A: 5 mL perchloric acid (70%) / L water, eluent B: acetonitrile; gradient: 0 min 2% B, 0.5 min 2% B, 4.5 min 90% B, 9 min 90% B, 9.2 min 2% B, 10 min 2% B; flow rate: 0.75 mL/min; temperature: 30°C; UV detection: 210 nm.

Method 4 (LC/MS):

Instrument: Micromass Platform LCZ with HPLC Agilent 1100 Series; column: Thermo Hypersil GOLD 3µ, 20 mm x 4 mm; eluent A: 1 L water + 0.5 mL 50% formic acid, eluent B: 1 L acetonitrile + 0.5 mL 50% formic acid; gradient: 0.0 min 100% A → 0.2 min 100% A → 2.9 min 30% A → 3.1 min 10% A → 5.5 min 10% A; temperature: 50°C; flow rate: 0.8 mL/min; UV detection: 210 nm.

Method 5 (LC/MS):

Instrument: Micromass ZQ with HPLC Waters Alliance 2795 / HP 1100; column: Phenomenex Synergi 2.5µ MAX-RP 100A Mercury, 20 mm x 4 mm; eluent A: 1 L water + 0.5 mL 50% formic acid, eluent B: 1 L acetonitrile + 0.5 mL 50% formic acid; gradient: 0.0 min 90% A → 2.5 min 30% A → 3.0 min 5% A → 4.0 min 5% A; flow rate: 2 mL/min; temperature: 50°C; UV detection: 210 nm.

Method 6 (LC/MS):

Instrument: Micromass Quattro Premier with Waters UPLC Acquity; column: Thermo Hypersil GOLD 1.9µ, 50 mm x 1 mm; eluent A: 1 L water + 0.5 mL 50% formic acid, eluent B: 1 L acetonitrile + 0.5 ml 50% formic acid; gradient: 0.0 min 90% A → 0.1 min 90% A → 1.5 min 10% A → 2.2 min 10% A; temperature: 50°C; flow rate: 0.33 mL/min; UV detection: 210 nm.

Method 7 (LC/MS):

Instrument: Micromass ZQ with HPLC Waters Alliance 2795; column: Phenomenex Synergi 2.5µ MAX-RP 100A Mercury, 20 mm x 4 mm; eluent A: 1 L water + 0.5 mL 50% formic acid, eluent B: 1 L acetonitrile + 0.5 mL 50% formic acid; gradient: 0.0 min 90% A → 0.1 min 90% A → 3.0 min 5% A → 4.0 min 5% A → 4.01 min 90% A; flow rate: 2 mL/min; temperature: 50°C; UV detection: 210 nm.

Method 8 (GC/MS):

Instrument: Micromass GCT, GC6890; column: Restek RTX-35, 15 m x 200 µm x 0.33 µm; constant flow with helium: 0.88 mL/min; oven: 70°C; inlet: 250°C; gradient: 70°C, 30°C/min → 310°C (keep for 3 min).

Method 9 (HPLC):

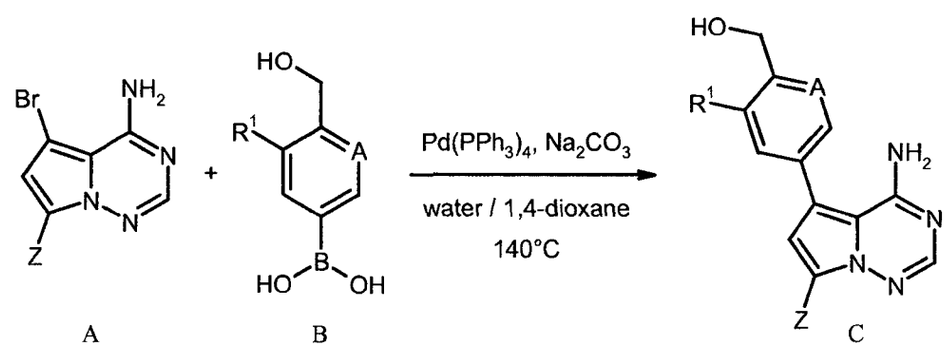
Instrument: Agilent 1100 with DAD detection; column: Merck Chromolith Speed ROD, 150 mm x 5 mm; eluent A: 0.01% formic acid in water, eluent B: acetonitrile; gradient: 0 min 5% B, 2.5 min 95% B, 3 min 95% B; flow rate: 5.0 mL/min; temperature: 40°C; UV detection: 210 nm.

Method 10 (LC/MS):

Instrument: Waters Acquity SQD UPLC System; column: Waters Acquity UPLC HSS T3 1.8µ, 50 mm x 1 mm; eluent A: 1 L water + 0.25 mL 99% formic acid, eluent B: 1 L acetonitrile + 0.25 mL 99% formic acid; gradient: 0.0 min 90% A → 1.2 min 5% A → 2.0 min 5% A; temperature: 50°C; flow rate: 0.40 mL/min; UV detection: 208-400 nm.

General synthetic method 1:

Suzuki coupling of 5-bromopyrrolo[2,1-f][1,2,4]triazine derivatives with arylboronic acids or esters:

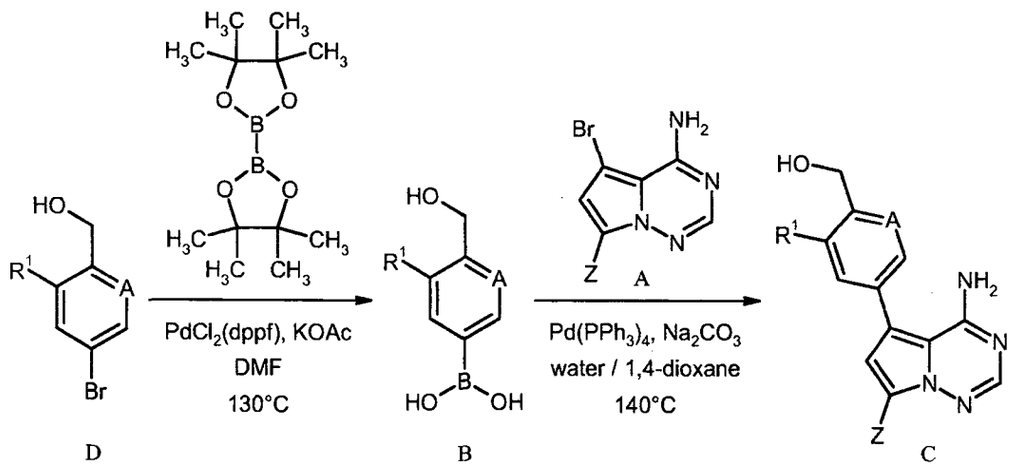


A B C

A 5-bromopyrrolo[2,1-f][1,2,4]triazine A (about 0.5 mmol), arylboronic acid B (1.2 equivalents) or a corresponding boronic ester, *e.g.*, a dimethyl boronate or pinacolato boronate, and tetrakis(triphenylphosphine)palladium(0) (0.1 equivalents) are dissolved in a mixture of 1,4-dioxane (about 4.0 mL) and 2 M aqueous sodium carbonate solution (1.5 mL) in a microwave reactor vial. The reaction vessel is crimp-capped, and the mixture is heated to 140°C for 1 h in a single-mode microwave device. After cooling, the reaction mixture is filtered over a pad of Celite which is rinsed with 1,4-dioxane to elute all organic material. The combined filtrate is evaporated to dryness under reduced pressure, and the residue is purified by preparative HPLC to give the target compound C.

General synthetic method 2:

Borylation of arylbromides and subsequent Suzuki coupling with 5-bromopyrrolo[2,1-f][1,2,4]-triazine derivatives without isolation of the intermediate arylboronic acid or ester:



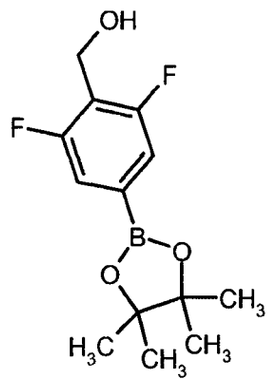
D B C

Arylbromide D (about 0.5 mmol) is dissolved in DMF (3 mL) in a microwave reactor vessel, argon is bubbled through the solution for 5 min, and [1,1'-bis(diphenylphosphino)ferrocene]dichloro-palladium(II)-dichloromethane complex (0.1 equivalents), potassium acetate (3 equivalents) and bis(pinacolato)diboron (1.2 equivalents) are added. The vessel is crimp-capped, and the mixture is heated to 130°C for 60 min in a single-mode microwave device. Then, the suspension is filtered, the filtrate is transferred to another microwave process vial, and tetrakis(triphenylphosphine)-palladium(0) (0.1 equivalents), 2 M aqueous sodium carbonate solution (4 equivalents) and the 5-bromopyrrolo[2,1-f][1,2,4]triazine A (1 equivalent) are added. The vial is crimp-capped, and the mixture is heated to 140°C for 1 h in a single-mode microwave device. The crude reaction mixture thus obtained is directly injected onto a preparative HPLC column for separation and purification of the target compound C.

Starting Materials and Intermediates:

Intermediate 1A

[2,6-Difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol

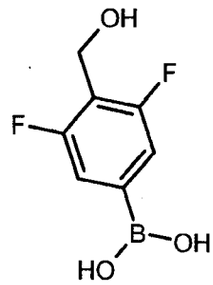


(4-Bromo-2,6-difluorophenyl)methanol (1.03 g, 4.62 mmol) was dissolved in dry 1,4-dioxane (10 mL). Argon was bubbled through the solution, then [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium-dichloromethane complex (302 mg, 0.37 mmol, 0.08 eq.), anhydrous potassium acetate (907 mg, 9.24 mmol, 2 eq.) and bis(pinacolato)diboron (1.23 g, 4.85 mmol, 1.05 eq.) were added, and the mixture was heated to 130°C for 1 h in a single-mode microwave device. Upon cooling, the mixture was filtered, and the solvent was removed under reduced pressure. Cyclohexane (200 mL) was added to the residue, and the mixture was vigorously stirred for 30 min. Undissolved material was then removed by filtration, the cyclohexane was distilled off, and the residue was purified by flash chromatography over silica gel (dichloromethane/acetonitrile gradient). Fractions containing the product were combined and evaporated. The title compound crystallized spontaneously as a brownish solid. Yield: 790 mg (63% of th.).

GC-MS (method 8): R_t = 5.36 min; MS (EI): *m/z* (%) = 270.3 (15) $[M]^+$.

Intermediate 2A

[3,5-Difluoro-4-(hydroxymethyl)phenyl]boronic acid

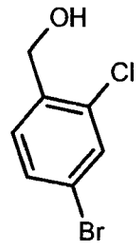


[4-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-3,5-difluorophenyl]boronic acid (19.3 g, 63.9 mmol; crude material, prepared by the method of Hattori, *Bioorg. Med. Chem.* **2006**, *14*, 3258-3262) was dissolved in 400 mL aqueous acetic acid (66%) and stirred at 40°C for 5 h. The solution was then evaporated under reduced pressure, and the residue was purified by flash chromatography over silica gel (gradient elution from 0% to 2% methanol in dichloromethane) to give 3.46 g (25% of th., LC-MS purity 87%) of the title compound.

LC-MS (method 7): R_t = 0.50 min; MS (ESIpos): *m/z* (%) = 171.2 (100) $[M\text{-}OH]^+$, MS (ESIneg): *m/z* (%) = 187.3 (100) $[M\text{-}H]^-$.

Intermediate 3A

(4-Bromo-2-chlorophenyl)methanol

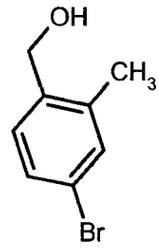


The title compound was prepared according to the procedure described in WO 2004/074270-A2 [Example A(147), step 1].

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.00 (br, 1H), 4.74 (s, 2H), 7.38 (d, 1H), 7.43 (dd, 1H), 7.53 (d, 1H).

Intermediate 4A

(4-Bromo-2-methylphenyl)methanol

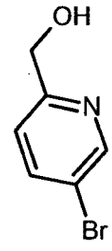


The title compound was prepared according to the procedure described in EP 1 544 208-A1 (Reference Example 14).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.62 (t, 3H), 2.32 (s, 3H), 4.64 (d, 2H), 7.23 (d, 1H), 7.32 (s, 1H), 7.33 (d, 1H).

Intermediate 5A

(5-Bromopyridin-2-yl)methanol

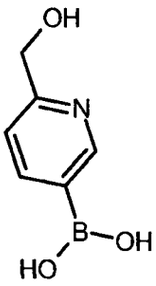


Methyl 5-bromopyridine-2-carboxylate (2.00 g, 9.27 mmol) was dissolved in ethanol (20.0 mL). Sodium borohydride (1.05 g, 27.8 mmol) was added at 0°C, and the mixture was stirred at room temperature for 18 h. The mixture was then concentrated under reduced pressure, quenched with 1 N hydrochloric acid, neutralized with solid potassium carbonate and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and evaporated to give 1.57 g (90% of th.) of the title compound.

LC-MS (method 6): R_t = 0.56 min; MS (ESIpos): *m/z* (%) = 188.0 (100) $[M+H]^+$.

Intermediate 6A

[6-(Hydroxymethyl)pyridin-3-yl]boronic acid

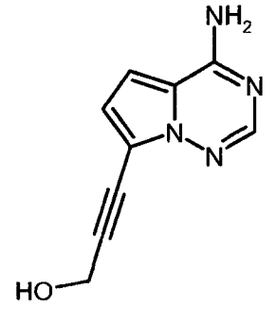


To a solution of Intermediate 5A (1.50 g, 7.98 mmol) and bis(pinacolato)diboron (2.23 g, 8.28 mmol) in degassed DMF (120 mL) was added under an argon atmosphere 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) chloride (292 mg, 0.40 mmol) and potassium acetate (2.35 g, 23.9 mmol). The mixture was heated to 80°C for 18 h and then cooled to room temperature. The suspension was filtered, and the residue was washed with dioxane. The combined filtrates were concentrated under reduced pressure, and the oily residue was taken up in 50 mL ethyl acetate and 50 mL cyclohexane and allowed to stand at room temperature overnight. The resulting precipitate was collected by filtration and discarded. The filtrate was evaporated, and the residue was dissolved again in 100 mL ethyl acetate and extracted twice with 50 mL water. The aqueous layer was concentrated to give 690 mg (56% of th.) of the title compound which was used without further purification.

LC-MS (method 6): R_t = 0.18 min; MS (ESIpos): *m/z* (%) = 154.0 (100) $[M+H]^+$.

Intermediate 7A

3-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)prop-2-yn-1-ol



The starting material 7-bromopyrrolo[2,1-f][1,2,4]triazin-4-amine was synthesized according to the procedure described in WO 2007/056170-A2 (Intermediate B).

7-Bromopyrrolo[2,1-f][1,2,4]triazin-4-amine (1.0 g, 4.69 mmol), copper(I) iodide (89 mg, 0.47 mmol, 0.1 eq.) and tetrakis(triphenylphosphine)palladium(0) (542 mg, 0.47 mmol, 0.1 eq.) were charged into a microwave reactor vial and evacuated for 1 h. The vessel was then vented with

argon, pyrrolidine (15 mL) and 2-propyn-1-ol (2.63 g, 47 mmol, 10 eq.) were added, and the vessel was crimp-capped and heated to 85°C for 120 min in a single-mode microwave device. After cooling, the reaction mixture was poured into 120 mL of concentrated aqueous ammonium chloride solution which was extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and evaporated, and the residue was purified by flash chromatography (Biotage silica column, ethyl acetate). The resulting product (222 mg) appeared pure by LC-MS (method 6) and was used for further transformations.

HPLC (method 2): R_t = 2.59 min;

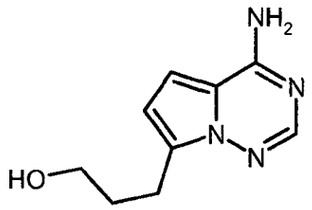
LC-MS (method 6): R_t = 0.28 min; MS (ESIpos): *m/z* (%) = 189.2 (100) $[M+H]^+$.

Intermediate 8A and Intermediate 9A

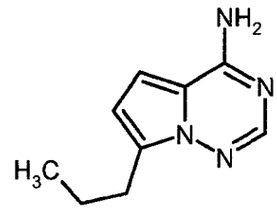
3-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)propan-1-ol

and

7-Propylpyrrolo[2,1-f][1,2,4]triazin-4-amine



and



Intermediate 7A (444 mg, 2.36 mmol) was dissolved in acetic acid (18 mL) under an argon atmosphere. Platinum(IV) oxide (40 mg, 0.18 mmol, 0.08 eq.) was added, and the mixture was vigorously stirred for 3 h at room temperature under an atmosphere of hydrogen at ambient pressure. The catalyst was then removed by filtration, the solvent was distilled off, and the residue was subjected to flash chromatography (Biotage silica column, cyclohexane/ethyl acetate gradient). The Intermediates 8A (185 mg, 41% of th.) and 9A (170 mg, 41% of th.) were obtained in two distinct chromatographic fractions:

Intermediate 8A:

HPLC (method 2): R_t = 2.68 min;

LC-MS (method 4): R_t = 0.83 min; MS (ESIpos): *m/z* (%) = 193.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 191.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.80 (m, 2H), 2.86 (t, J = 7.7 Hz, 2H), 3.45 (m, 2H), 4.49 (t, J = 5.1 Hz, 1H), 6.41 (d, J = 4.2 Hz, 1H), 6.69 (d, J = 4.2 Hz, 1H), 7.50 (br. s, 2H), 7.78 (s, 1H).

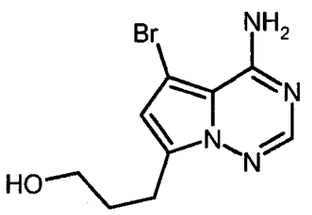
Intermediate 9A:

HPLC (method 1): R_t = 3.22 min;

LC-MS (method 4): R_t = 1.23 min; MS (ESIpos): m/z (%) = 177.1 (100) $[M+H]^+$, MS (ESIneg): m/z (%) = 175.2 (30) $[M-H]^-$.

Intermediate 10A

3-(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)propan-1-ol



Intermediate 8A (105 mg, 0.55 mmol) was dissolved in THF (8.75 mL) and cooled to -20°C. 1,3-Dibromo-5,5-dimethylhydantoin (78.1 mg, 0.5 eq.) was added, and the mixture was stirred at -20°C for 1 h. The reaction was then quenched with 0.5 mL concentrated aqueous sodium dithionite solution, warmed to room temperature and partitioned between ethyl acetate and water. The organic phase was dried over anhydrous sodium sulfate, and the solvent was distilled off. Yield: 145 mg (98% of th.).

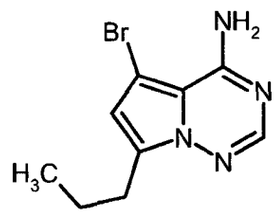
HPLC (method 1): R_t = 2.96 min; HPLC (method 2): R_t = 2.95 min;

LC-MS (method 5): R_t = 1.03 min; MS (ESIpos): m/z (%) = 271.0 (100) and 273.0 (100) $[M+H]^+$, MS (ESIneg): m/z (%) = 269.0 (99) and 271.0 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.75 (m, 2H), 2.83 (t, J = 8.1 Hz, 2H), 3.43 (m, 2H), 4.50 (t, J = 5.4 Hz, 1H), 6.62 (s, 1H), 7.81 (s, 1H).

Intermediate 11A

5-Bromo-7-propylpyrrolo[2,1-f][1,2,4]triazin-4-amine



Intermediate 9A (110 mg, 0.62 mmol) was dissolved in THF (4.44 mL) and cooled to -20°C. 1,3-Dibromo-5,5-dimethylhydantoin (89 mg, 0.5 eq.) was added, and the mixture was stirred at -20°C for 1 h. The reaction was then quenched with 0.5 mL concentrated aqueous sodium dithionite solution, warmed to room temperature and partitioned between ethyl acetate and water. The organic phase was dried over anhydrous sodium sulfate, and the solvent was distilled off. Yield: 154 mg (85% pure, 82% of th.).

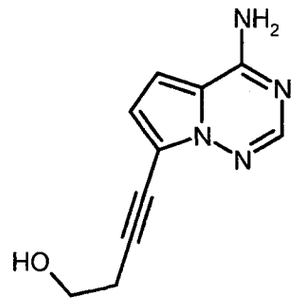
HPLC (method 1): R_t = 3.78 min;

LC-MS (method 7): R_t = 1.55 min; MS (ESIpos): *m/z* (%) = 255.0 (99) and 257.2 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.91 (t, *J* = 7.3 Hz, 3H), 1.65 (m, 2H), 2.79 (t, *J* = 7.6 Hz, 2H), 3.31 (s, 2H), 6.63 (s, 1H), 7.95 (s, 1H).

Intermediate 12A

4-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)but-3-yn-1-ol



7-Bromopyrrolo[2,1-f][1,2,4]triazin-4-amine (1.0 g, 4.69 mmol), copper(I) iodide (89 mg, 0.47 mmol, 0.1 eq.) and tetrakis(triphenylphosphine)palladium(0) (542 mg, 0.47 mmol, 0.1 eq.) were charged into a microwave reactor vial and evacuated for 1 h. The vessel was then vented with argon, pyrrolidine (15 mL) and 3-butyn-1-ol (3.36 g, 47 mmol, 10 eq.) were added, and the vessel was crimp-capped and heated to 85°C for 120 min in a single-mode microwave device. After cooling, the reaction mixture was poured into 120 mL of concentrated aqueous ammonium chloride solution and extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and evaporated, and the residue was purified by flash chromatography

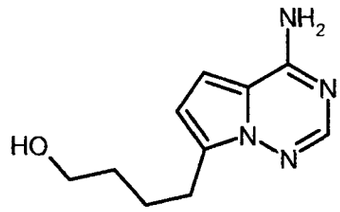
(Biotage silica column, ethyl acetate). The resulting product (735 mg) was sufficiently pure (66% by HPLC) for further transformations.

HPLC (method 2): R_t = 2.77 min;

LC-MS (method 4): R_t = 0.96 min; MS (ESIpos): *m/z* (%) = 203.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 201.1 (100) $[M-H]^-$.

Intermediate 13A

4-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)butan-1-ol



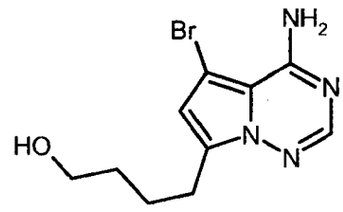
Intermediate 12A (607 mg, 3.00 mmol) was dissolved in acetic acid (64 mL), and platinum(IV) oxide (50 mg, 0.22 mmol, 0.07 eq.) was added. The mixture was stirred under an atmosphere of hydrogen at ambient pressure for 15 h. The catalyst was then removed by filtration, the filtrate was evaporated under reduced pressure, and the residue was purified by flash chromatography (Biotage silica column, ethyl acetate). Yield: 350 mg (57% of th.).

HPLC (method 2): R_t = 2.92 min;

LC-MS (method 4): R_t = 0.94 min; MS (ESIpos): *m/z* (%) = 207.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 205.3 (100) $[M-H]^-$.

Intermediate 14A

4-(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)butan-1-ol



Intermediate 13A (330 mg, 1.60 mmol) was dissolved in THF (26 mL) at -20°C, and 1,3-dibromo-5,5-dimethylhydantoin (229 mg, 0.80 mmol) was added. The mixture was stirred at -20°C for 1 h.

The reaction was then quenched with concentrated aqueous sodium sulfite solution (0.5 mL). Ethyl acetate was added, the aqueous layer was separated, and the organic layer was dried over sodium sulfate and evaporated. The crude product was subsequently purified by preparative HPLC (method 2) giving 175 mg (84% of th.) of the title compound.

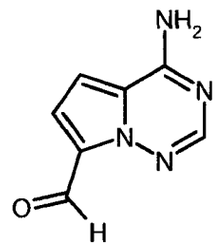
HPLC (method 1): R_t = 3.13 min;

LC-MS (method 5): R_t = 1.23 min; MS (ESIpos): *m/z* (%) = 285.0 (98) and 287.0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 283.0 (100) and 285.0 (98) $[M-H]^-$.

^{1}H-NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.39-1.48 (m, 2H), 1.60-1.69 (m, 2H), 3.31 (t, *J* = 7.3 Hz, 2H), 3.40 (m, 2H), 4.46 (br. s, 1H), 6.61 (s, 1H), 7.82 (s, 1H).

Intermediate 15A

4-Aminopyrrolo[2,1-f][1,2,4]triazine-7-carbaldehyde



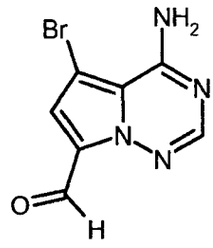
The starting material pyrrolo[2,1-f][1,2,4]triazin-4-amine was synthesized according to the procedure described in WO 2007/056170-A2 (Intermediate A).

Pyrrolo[2,1-f][1,2,4]triazin-4-amine (20.5 g, 152 mmol) was dissolved in 150 mL DMF. Under ice cooling, phosphoryl chloride (31.3 mL, 336 mmol) was added dropwise at such a rate that the internal temperature did not rise above 30°C. The mixture was then heated for 2 days at 50°C. After cooling, another portion of phosphoryl chloride (14.2 mL, 152 mmol) was added, and stirring was continued for another 24 h at 50°C. After cooling, the reaction batch was slowly poured into a mixture of 2.0 L saturated aqueous sodium bicarbonate solution and 2.0 L ethyl acetate. Solid sodium bicarbonate was added until gas evolution stopped. The layers were separated, the aqueous layer was extracted with 0.5 L ethyl acetate, and the combined organic phases were dried over sodium sulfate and concentrated. The residue was suspended in 100 mL diisopropyl ether, stirred at room temperature for 10 min and then filtered. The dried residue was stirred in 6 N hydrochloric acid (500 mL) for 1 h at 50°C and then poured into an ice/water mixture (1000 mL). The mixture was carefully neutralized with solid sodium bicarbonate, stirred for 30 min at room temperature and

then filtered again. The residue was washed with water and ligroin to yield 20.6 g (83% of th.) of white crystals which were used in the next step without further purification.

Intermediate 16A

4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazine-7-carbaldehyde

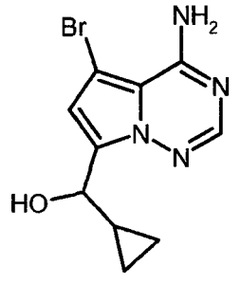


Intermediate 15A (20.6 g, 127 mmol) was dissolved in 525 mL DMF. At 0°C, 1,3-dibromo-5,5-dimethylhydantoin (21.8 g, 76.2 mmol) was added, and the mixture was stirred for 1 h under ice cooling and for further 2 h at room temperature. The resulting suspension was filtered, and the residue was washed with DMF and diethyl ether. The filtrate was discarded, and the remaining hardly soluble crystals were dried to give 20.0 g (65% of th., 80% purity by HPLC) of the title compound. This material was used without further purification.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 7.42 (s, 1H), 8.12 (s, 1H), 10.22 (s, 1H).

Intermediate 17A

(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)(cyclopropyl)methanol



Intermediate 16A (500 mg, 1.66 mmol) was suspended in dry THF (30 mL). At 0°C, a 0.5 M solution of cyclopropyl magnesium bromide in diethyl ether (10 mL, 5.0 mmol) was added. The mixture was stirred at room temperature for 1 h. Then, another portion of the Grignard solution (6.6 mL, 3.3 mmol) was added. After further stirring for 30 min at room temperature, the reaction was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine, dried over magnesium sulfate and

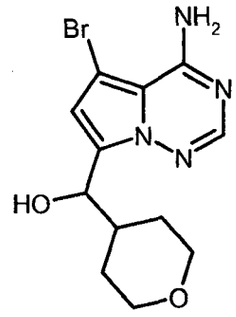
concentrated. The residue was purified by preparative HPLC (method 4). Yield: 0.14 g (29% of th.).

LC-MS (method 6): R_t = 0.75 min; MS (ESIpos): *m/z* (%) = 283.0 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.35 (m, 3H), 0.45 (m, 1H), 1.28 (m, 1H), 4.62 (t, 1H), 5.26 (d, 1H), 6.75 (s, 1H), 7.84 (s, 1H).

Intermediate 18A

(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)(tetrahydro-2*H*-pyran-4-yl)methanol

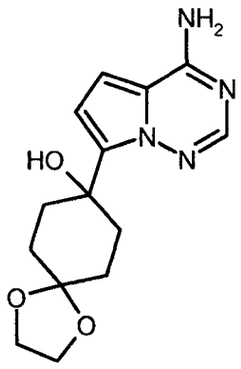


In a 50 mL three-necked flask equipped with a condenser, a thermometer and a dropping funnel, which was purged with argon, a Grignard reagent was prepared from magnesium turnings (484 mg, 19.9 mmol) and 4-chlorotetrahydropyrane (2.4 g, 19.9 mmol) in dry THF (14 mL). To this solution was added at 0°C a suspension of Intermediate 16A (1.2 g, 3.98 mmol) in THF (20 mL), and the reaction mixture was allowed to stir for 1 h at room temperature. It was then quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate (2 x 50 mL). The organic layer was washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by preparative HPLC (method 3). Yield: 0.5 g (38% of th.).

LC-MS (method 6): R_t = 0.66 min; MS (ESIpos): *m/z* (%) = 327.0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 325.1 (100) $[M-H]^-$.

Intermediate 19A

8-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-1,4-dioxaspiro[4.5]decan-8-ol



The starting material 7-bromopyrrolo[2,1-f][1,2,4]triazin-4-amine was synthesized according to the procedure described in WO 2007/056170-A2 (Intermediate B).

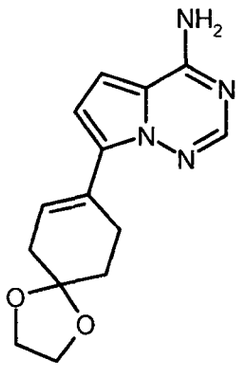
7-Bromopyrrolo[2,1-f][1,2,4]triazin-4-amine (9.20 g, 35.41 mmol) was dissolved in THF (105 mL) under argon at room temperature. Chlorotrimethylsilane (9.08 mL, 7.77 g, 70.82 mmol, 2 eq.) was added, and the mixture was stirred at room temperature for 3 h. It was then cooled to 0°C, and 2-propyl magnesium chloride (74 mL of a 2.0 M solution in THF, 149 mmol, 4.2 eq.) was added. The mixture was stirred for further 3 h while warming up to room temperature. Then, 1,4-dioxaspiro-[4.5]decan-8-one (8.38 g, 53.12 mmol, 1.5 eq.) was added, and stirring was continued for another 16 h. The reaction was quenched with a 1:1 mixture of concentrated aqueous ammonium chloride solution and ice until the pH value reached 6-7. The mixture was extracted with two portions of ethyl acetate, and the combined organic extracts were dried over anhydrous sodium carbonate and concentrated to dryness. The title compound was crystallized from diethyl ether. Yield: 6.05 g (58% of th.).

HPLC (method 1): R_t = 2.89 min;

LC-MS (method 6): R_t = 0.38 min; MS (ESIpos): *m/z* (%) = 291.2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 289.4 (100) $[M-H]^-$.

Intermediate 20A

7-(1,4-Dioxaspiro[4.5]dec-7-en-8-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



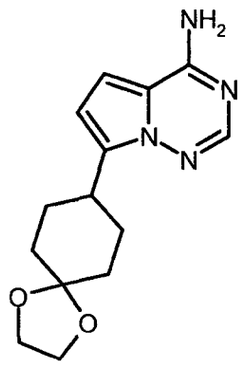
Intermediate 19A (2.81 g, 60% purity, 5.82 mmol) was dissolved in pyridine (18 mL) at 0°C. Trifluoroacetic anhydride (2.46 mL, 3.66 g, 17.45 mmol, 3 eq.) was added slowly, and the reaction mixture was stirred at ambient temperature for 16 h. The solvent was distilled off, and the residue was partitioned between water and ethyl acetate. The organic extract was dried over sodium sulfate and evaporated. The residue was triturated with diethyl ether at 0°C to yield 2.95 g (92% pure by HPLC, 99% of th.) of the title compound.

HPLC (method 1): R_t = 4.55 min;

LC-MS (method 5): R_t = 2.28 min; MS (ESIpos): *m/z* (%) = 369.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 367.1 (100) $[M-H]^-$.

Intermediate 21A

7-(1,4-Dioxaspiro[4.5]dec-8-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



Intermediate 20A (2.95 g, 10.8 mmol) was dissolved in methanol (1.07 L) under argon. Palladium on charcoal (10%, 400 mg) was added, and the mixture was vigorously stirred for 24 h under an atmosphere of hydrogen at ambient pressure and room temperature. The catalyst was removed by

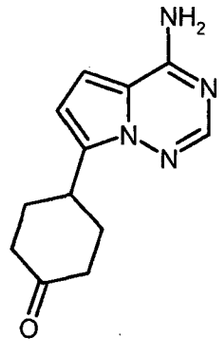
filtration, and the solvent was distilled off under reduced pressure to give 2.11 g (71% of th.) of the title compound.

HPLC (method 1): R_t = 3.14 min;

LC-MS (method 6): R_t = 0.68 min; MS (ESIpos): *m/z* (%) = 275.3 (100) $[M+H]^+$.

Intermediate 22A

4-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)cyclohexanone



Intermediate 21A (2.11 g, 7.69 mmol) was dissolved in a mixture of 1 M hydrochloric acid (23 mL) and methanol (6.80 mL) at 0°C and stirred under ice cooling for 3 h. Then, the pH value was adjusted to 6-7 by addition of concentrated aqueous sodium bicarbonate solution. The mixture was extracted with three portions of dichloromethane, and the combined organic extracts were dried over anhydrous sodium sulfate, filtered and evaporated. The residue (923 mg, 52% of th.) was used without further purification in the next synthetic step.

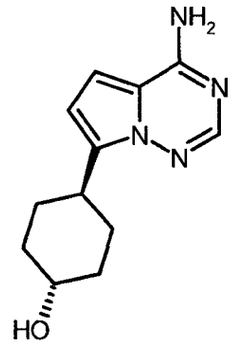
HPLC (method 2): R_t = 3.06 min;

LC-MS (method 4): R_t = 1.02 min; MS (ESIpos): *m/z* (%) = 231.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 229.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.86 (ddd, 2H), 2.25-2.36 (m, 4H), 2.59 (ddd, 2H), 3.59 (m, 1H), 6.45 (d, 1H), 6.82 (d, 1H), 7.60 (br. s, 1H), 7.82 (s, 1H).

Intermediate 23A

trans-4-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)cyclohexanol



Intermediate 22A (452 mg, 1.96 mmol) was dissolved in THF (15 mL), and the solution was cooled to 0°C. Lithium aluminium hydride solution (1 M in THF, 2.94 mL, 2.94 mmol) was added dropwise. Subsequently, the solution was stirred at 0°C for 10 min and then quenched by addition of concentrated aqueous ammonium chloride solution. The mixture was extracted with 3 portions of dichloromethane, and the combined organic extracts were dried over anhydrous sodium sulfate, filtered and evaporated. The residue (360 mg, 77% purity, 61% of th.) was used in the next synthetic step without further purification.

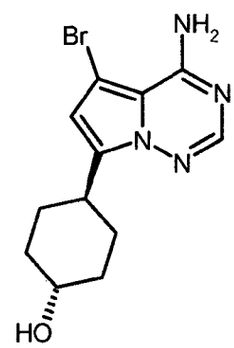
HPLC (method 1): R_t = 2.62 min;

LC-MS (method 6): R_t = 0.29 min; MS (ESIpos): *m/z* (%) = 233.2 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.30 (m, 2H), 1.42 (m, 2H), 1.91 (m, 2H), 1.99 (m, 2H), 2.97 (tt, 1H), 3.45 (m, 1H), 4.60 (d, 1H), 6.39 (d, 1H), 6.79 (d, 1H), 7.53 (br. s, 2H), 7.80 (s, 1H).

Intermediate 24A

trans-4-(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)cyclohexanol



Intermediate 23A (360 mg, 85% purity, 1.19 mmol) was dissolved in THF (8 mL) at -20°C, and 1,3-dibromo-5,5-dimethylhydantoin (188 mg, 0.66 mmol, 0.55 eq.) was added. The mixture was

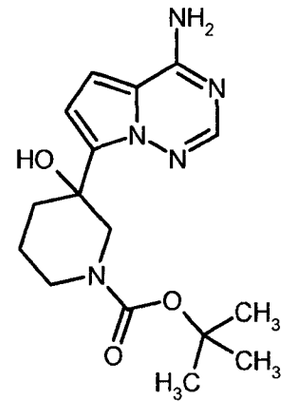
stirred at -20°C for 1 h, then 0.5 mL concentrated aqueous sodium dithionite solution was added, and the mixture was extracted with ethyl acetate. The organic extract was dried over anhydrous sodium sulfate, filtered and evaporated. The crude product (463 mg, 66% purity, 83% of th.) was used in the next synthetic step without further purification.

HPLC (method 1): R_t = 3.22 min;

LC-MS (method 7): R_t = 1.03 min; MS (ESIpos): *m/z* (%) = 311.2 and 313.0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 309.2 (50) and 311.2 (40) $[M-H]^-$.

Intermediate 25A

tert-Butyl 3-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3-hydroxypiperidine-1-carboxylate



The starting material 7-bromopyrrolo[2,1-f][1,2,4]triazin-4-amine was synthesized according to the procedure described in WO 2007/056170-A2 (Intermediate B).

7-Bromopyrrolo[2,1-f][1,2,4]triazin-4-amine (17.29 g, 81 mmol) was dissolved in THF (214 mL) under argon at room temperature. Chlorotrimethylsilane (20.60 mL, 17.63 g, 162 mmol, 2 eq.) was added, and the mixture was stirred at room temperature for 3 h. Then, it was cooled to 0°C, and 2-propyl magnesium chloride (170 mL of a 2.0 M solution in THF, 340 mmol, 4.2 eq.) was added. The mixture was stirred for further 3 h while warming up to room temperature. Then, *tert*-butyl 3-oxopiperidine-1-carboxylate (25.00 g, 121 mmol, 1.5 eq.) was added, and stirring was continued for another 16 h. The reaction was quenched with a 1:1 mixture of concentrated aqueous ammonium chloride solution and ice until the pH value reached 6-7. The mixture was extracted with two portions of ethyl acetate, and the combined organic extracts were dried over anhydrous sodium carbonate and concentrated to dryness. The title compound crystallized upon trituration of the residue with diethyl ether (50 mL). The crystals were washed with diethyl ether and dried to give 17.20 g (64% of th.).

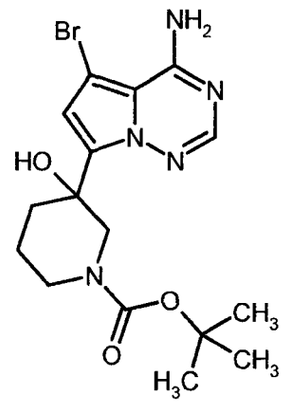
HPLC (method 2): R_t = 3.53 min;

LC-MS (method 5): R_t = 1.36 min; MS (ESIpos): *m/z* (%) = 334.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 332.0 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.19-1.43 (m, 9H), 1.72-1.88 (m, 2H), 2.38-2.46 (m, 1H), 3.02-3.20 (m, 1H), 3.44-3.96 (m, 4H), 6.58 (d, 1H), 6.81 (d, 1H), 7.82 (s, 1H).

Intermediate 26A

rac-tert-Butyl 3-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3-hydroxypiperidine-1-carboxylate



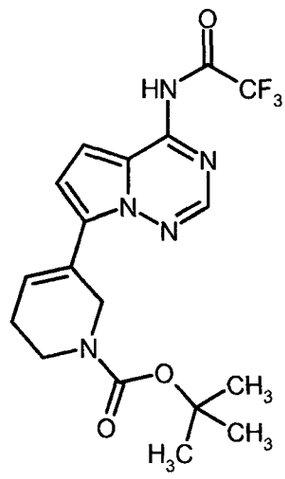
Intermediate 25A (120 mg, 0.36 mmol) was dissolved in THF (6.0 mL) at -20°C, and 1,3-dibromo-5,5-dimethylhydantoin (51 mg, 0.18 mmol, 0.5 eq.) was added. The mixture was stirred at -20°C for 2 h and then quenched with concentrated aqueous sodium sulfite solution (0.5 mL). Ethyl acetate was added, the aqueous layer was separated, and the organic extract was dried over sodium sulfate and evaporated. The title compound (148 mg, 95% of th.) was obtained as a light yellow solid.

HPLC (method 1): R_t = 4.03 min;

LC-MS (method 5): R_t = 1.99 min; MS (ESIpos): *m/z* (%) = 412.0 (90) and 414.0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 410.0 (100) and 412.0 (85) $[M-H]^-$.

Intermediate 27A

tert-Butyl 5-{4-[(trifluoroacetyl)amino]pyrrolo[2,1-f][1,2,4]triazin-7-yl}-3,6-dihydropyridine-1(2*H*)-carboxylate



Intermediate 25A (8.32 g, 24.95 mmol) was dissolved in pyridine (116 mL) at 0°C. Trifluoroacetic anhydride (8.81 mL, 13.10 g, 62.36 mmol, 2.5 eq.) was added slowly, and the reaction mixture was stirred at ambient temperature for 16 h. Then, it was cooled again to 0°C, and 150 mL of diethyl ether were added. The mixture was stirred at 0°C while the title compound slowly precipitated. The product was finally filtered off and washed with diethyl ether. The filtrate was evaporated *in vacuo*, and the residue was triturated with diethyl ether at 0°C giving a second crop of the title compound after washing with diethyl ether. The two crops were combined to yield 7.80 g (92% pure by HPLC, 76% of th.) of the title compound as yellow crystals.

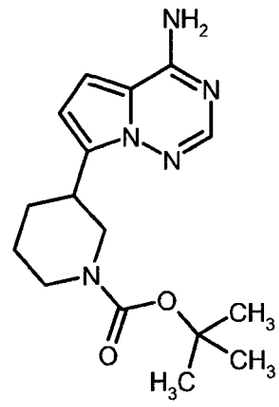
HPLC (method 1): R_t = 3.91 min;

LC-MS (method 7): R_t = 2.45 min; MS (ESIpos): *m/z* (%) = 412.2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 410.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.48 (s, 9H), 1.92 (m, 2H), 3.58 (m, 2H), 6.90 (d, 1H), 7.30 (d, 1H), 8.03-8.10 (m, 1H), 8.42 (s, 1H).

Intermediate 28A

rac-tert-Butyl 3-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidine-1-carboxylate



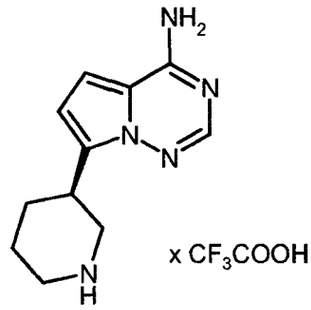
Intermediate 27A (7.80 g, 92% purity, 17.54 mmol) was dissolved in methanol (400 mL). Trifluoroacetic acid (6.76 mL, 10.0 g, 88 mmol, 5 eq.), water (3.16 mL, 175 mmol, 10 eq.) and 10% palladium on charcoal (30 mg) were added, and the mixture was hydrogenated for 24 h at room temperature and ambient pressure. The catalyst was then removed by filtration, and the solvent was evaporated *in vacuo*. The crude product (8.79 g, 75% pure, quantitative yield) was used in the next synthetic step without further purification.

HPLC (method 1): R_t = 3.64 min;

LC-MS (method 7): R_t = 1.26 min; MS (ESIpos): *m/z* (%) = 318.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 316.4 (100) $[M-H]^-$.

Intermediate 29A

7-[(3*R*)-Piperidin-3-yl]pyrrolo[2,1-f][1,2,4]triazin-4-amine trifluoroacetate



The starting material benzyl (*R*)-3-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidine-1-carboxylate has been described in WO 2007/056170-A2 (Intermediate DDD).

1.50 g (3.49 mmol) of this material were hydrogenated for 16 h at room temperature and ambient pressure in the presence of 10% palladium on charcoal (30 mg) in a mixture of methanol (50 mL)

and trifluoroacetic acid (2.70 mL). Subsequently, the catalyst was removed by filtration, and all volatiles were evaporated *in vacuo* to give 1.10 g (95% of th.) of the title compound.

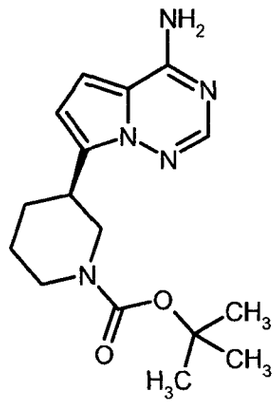
HPLC (method 2): R_t = 2.17 min;

LC-MS (method 6): R_t = 0.17 min; MS (ESIpos): *m/z* (%) = 218 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.75 (m, 2H), 1.92 (m, 1H), 2.05 (m, 1H), 2.93 (m, 1H), 3.06 (m, 1H), 3.31 (d, 1H), 3.50 (d, 1H), 3.57 (m, 1H), 6.78 (d, 1H), 7.20 (m, 1H), 8.10 (s, 1H), 8.63 (m, 1H), 8.82 (m, 1H), 9.02 (br. s, 1H).

Intermediate 30A

tert-Butyl (3*R*)-3-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidine-1-carboxylate



Intermediate 29A (1.10 g, 5.06 mmol) was suspended in dichloromethane (6.60 mL), triethylamine (1.55 mL, 1.13 g, 11.14 mmol, 2.20 eq.) was added, and the mixture was stirred for 30 min until the starting material was completely dissolved. Then, di-*tert*-butyl dicarbonate (1.22 g, 5.57 mmol, 1.1 eq.) was added, and the reaction mixture was stirred for 16 h. Subsequently, 5% aqueous citric acid was added, the phases were separated, and the organic layer was dried over sodium sulfate and evaporated. The residue was purified by preparative HPLC (method 2). Yield: 595 mg (37% of th.).

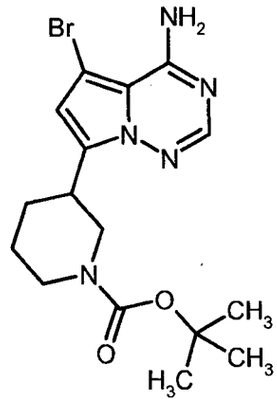
HPLC (method 2): R_t = 4.01 min;

LC-MS (method 5): R_t = 1.54 min; MS (ESIpos): *m/z* (%) = 318.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 316.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.38 (s, 9H), 1.45 (m, 2H), 1.72 (m, 2H), 2.02 (m, 2H), 2.90 (m, 1H), 3.17 (m, 1H), 3.85 (m, 1H), 4.08 (m, 1H), 6.47 (d, 1H), 6.80 (d, 1H), 7.58 (br. s, 1H), 7.81 (s, 1H).

Intermediate 31A

rac-tert-Butyl 3-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidine-1-carboxylate



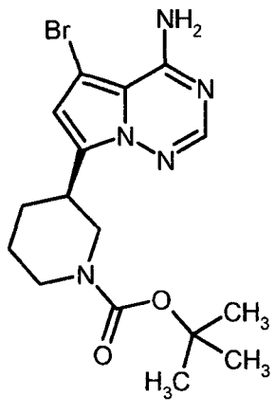
Intermediate 28A (8.28 g, 75% purity, 14.39 mmol) was dissolved in THF (222 mL) at -20°C, and 1,3-dibromo-5,5-dimethylhydantoin (2.06 g, 7.19 mmol, 0.5 eq.) was added. The mixture was stirred at -20°C for 2 h and then quenched with concentrated aqueous sodium sulfite solution (0.5 mL). Ethyl acetate was added, the aqueous layer was separated, and the organic extract was dried over sodium sulfate and evaporated. The title compound (6.30 g, 86% of th.) was obtained as a light yellow solid.

LC-MS (method 5): R_t = 2.27 min; MS (ESIpos): *m/z* (%) = 396.0 (80) and 397.9 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 394.0 (90) and 396.0 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.35 (s, 9H), 1.40-1.44 (m, 2H), 1.71 (m, 1H), 1.98 (m, 1H), 2.95 (m, 1H), 3.20 (m, 1H), 3.75 (m, 1H), 4.00 (m, 1H), 6.67 (s, 1H), 7.86 (s, 1H).

Intermediate 32A

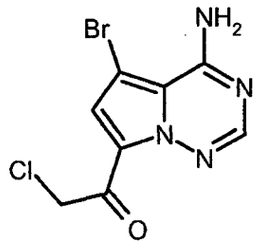
tert-Butyl (3*R*)-3-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidine-1-carboxylate



The title compound was prepared in the same way as the racemic mixture (Intermediate 31A), starting from Intermediate 30A. Analytical data were identical to those shown for Intermediate 31A.

Intermediate 33A

1-(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)-2-chloroethanone



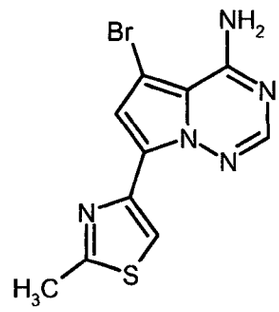
The compound was prepared according to the procedure described in WO 2007/056170-A2 (Intermediate N, step 1).

HPLC (method 1): R_t = 4.27 min;

LC-MS (method 5): R_t = 1.70 min; MS (ESIpos): *m/z* (%) = 289.0 (75) and 290.9 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 287.0 (75) and 288.9 (100) $[M-H]^-$.

Intermediate 34A

5-Bromo-7-(2-methyl-1,3-thiazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



Intermediate 33A (100 mg, 0.35 mmol) and thioacetamide (30 mg, 0.40 mmol, 1.15 eq.) were dissolved in 1,4-dioxane (3.0 mL) in a microwave reaction vial. The vial was crimp-capped, and the mixture was heated to 130°C for 60 min in a single-mode microwave device. After cooling, the solvent was distilled off, and the residue was triturated with acetonitrile and filtered. The filtrate was discarded. The title compound was isolated as crystalline solid. Yield: 99 mg (92% of th.).

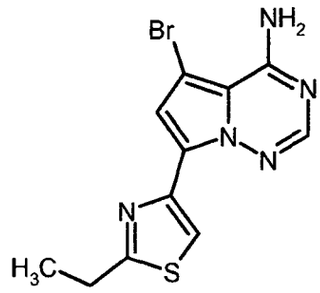
HPLC (method 1): R_t = 4.00 min;

LC-MS (method 6): R_t = 1.05 min; MS (ESIpos): *m/z* (%) = 310.0 (90) and 312 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.71 (s, 3H), 7.20 (s, 1H), 8.02 (s, 1H), 8.28 (s, 1H).

Intermediate 35A

5-Bromo-7-(2-ethyl-1,3-thiazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



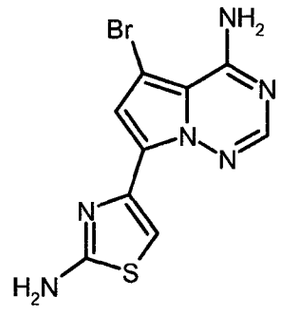
Intermediate 33A (100 mg, 0.35 mmol) and thiopropionamide (32 mg, 0.36 mmol, 1.05 eq.) were refluxed in ethanol (3.0 mL) over a period of 4.5 h. After cooling, the mixture was partitioned between ethyl acetate and aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off. The product was dried under vacuum to give 91 mg (0.28 mmol, 81% of th.) of the title compound as off-white solid.

HPLC (method 1): R_t = 4.30 min;

LC-MS (method 7): R_t = 1.84 min; MS (ESIpos): *m/z* (%) = 324.2 (100) and 325.8 (98) $[M+H]^+$.

Intermediate 36A

7-(2-Amino-1,3-thiazol-4-yl)-5-bromopyrrolo[2,1-f][1,2,4]triazin-4-amine



Intermediate 33A (100 mg, 0.35 mmol) and thiourea (32 mg, 0.41 mmol, 1.2 eq.) were suspended in 1,4-dioxane (3 mL) in a microwave reaction vial which was then crimp-capped. The mixture was heated to 120°C for 60 min in a single-mode microwave device. Upon cooling, water was added, and the resulting precipitate was collected by filtration and washed with dioxane. The off-white solid was dried under vacuum to give 98 mg (91% of th.) of the title compound.

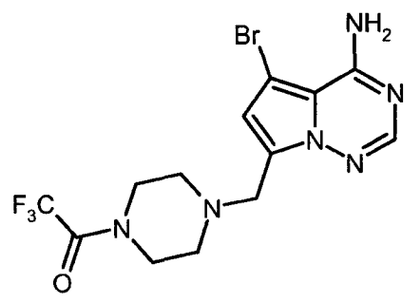
HPLC (method 1): R_t = 3.19 min;

LC-MS (method 5): R_t = 1.25 min; MS (ESIpos): *m/z* (%) = 310.9 (95) and 312.9 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 309.0 (100) and 310.9 (70) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 7.17 (s, 1H), 7.52 (s, 1H), 8.07 (s, 1H).

Intermediate 37A

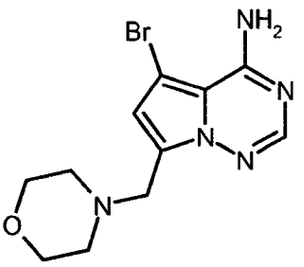
1-{4-[(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]piperazin-1-yl}-2,2,2-trifluoro-ethanone



The compound was prepared according to the procedure described in WO 2007/056170-A2 (Example 416, step 6).

Intermediate 38A

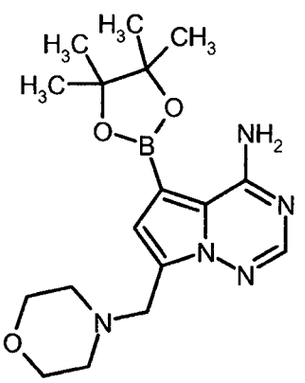
5-Bromo-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



The compound was prepared according to the procedure described in WO 2007/064931-A2 (Intermediate C).

Intermediate 39A

7-(Morpholin-4-ylmethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-4-amine

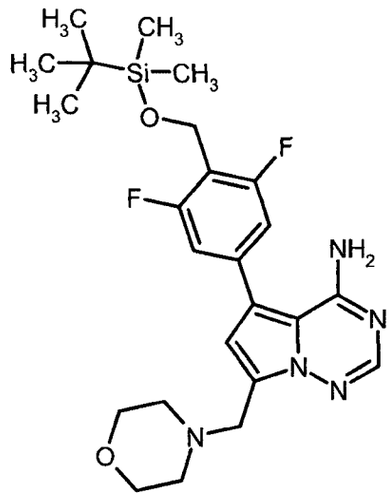


To a solution of Intermediate 38A (5.59 g, 17.9 mmol) and bis(pinacolato)diboron (10.0 g, 39.4 mmol) in degassed DMF (120 mL) was added under an argon atmosphere 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) chloride (786 mg, 1.07 mmol) and potassium acetate (7.03 g, 71.6 mmol). The mixture was heated to 80°C for 5 h and then cooled to room temperature. *tert*-Butyl methyl ether (100 mL) was added, and the suspension was filtered. The filtrate was evaporated to dryness under reduced pressure, and the residue was purified by flash chromatography over silica gel (gradient elution from 2% to 5% methanol in dichloromethane) to give 1.30 g (20% of th.) of the title compound containing some of the corresponding boronic acid derivative. This product was used without further purification.

LC-MS (method 6): R_t = 0.73 min; MS (ESIpos): *m/z* (%) = 360.3 (30) $[M+H]^+$.

Intermediate 40A

5-[4-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-3,5-difluorophenyl]-7-(morpholin-4-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-amine

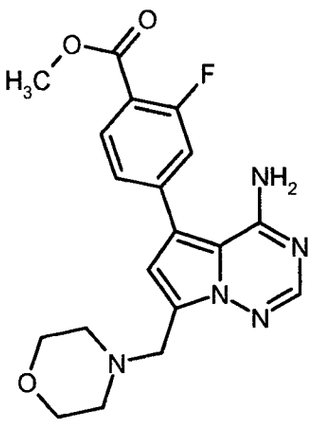


The title compound was obtained by general synthetic method 1 from Intermediate 38A (200 mg, 0.64 mmol) and [4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3,5-difluorophenyl]boronic acid (314 mg, 0.77 mmol, 74% purity; prepared by the method of Hattori, *Bioorg. Med. Chem.* **2006**, *14*, 3258-3262). Purification of the crude product was carried out by preparative HPLC (method 3). Yield: 110 mg (32% of th., LC-MS purity 92%).

LC-MS (method 6): R_t = 1.18 min; MS (ESIpos): *m/z* (%) = 490.1 (30) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 488.3 (100) $[M-H]^-$.

Intermediate 41A

Methyl 4-[4-amino-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluorobenzoate

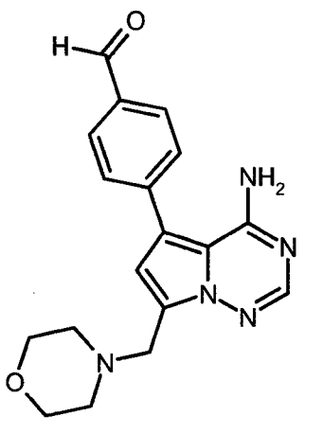


The title compound was obtained by general synthetic method 1 from Intermediate 38A (200 mg, 0.64 mmol) and [3-fluoro-4-(methoxycarbonyl)phenyl]boronic acid (139 mg, 0.71 mmol). Purification of the crude product was carried out by preparative HPLC (method 3). Yield: 80 mg (32% of th.).

LC-MS (method 6): R_t = 0.66 min; MS (ESIpos): *m/z* (%) = 386.1 (80) $[M+H]^+$.

Intermediate 42A

4-[4-Amino-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]benzaldehyde

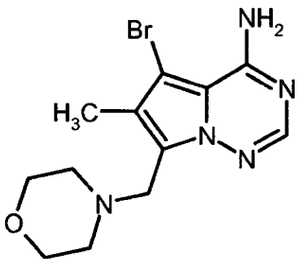


To a solution of Intermediate 38A (300 mg, 0.96 mmol) in degassed DMF (9.0 mL) was added (4-formylphenyl)boronic acid (216 mg, 1.44 mmol), tetrakis(triphenylphosphine)palladium(0) (111 mg, 0.1 mmol) and 2 M aqueous sodium carbonate solution (2.4 mL). The mixture was heated to 90°C under argon for 17 h, then cooled to room temperature and directly purified by preparative HPLC (method 3). Yield: 150 mg (46% of th.).

LC-MS (method 6): R_t = 0.44 min; MS (ESIpos): *m/z* (%) = 338.2 (30) $[M+H]^+$.

Intermediate 43A

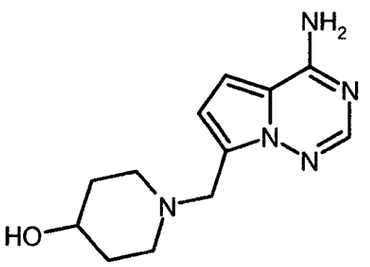
5-Bromo-6-methyl-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



The compound was prepared according to the procedure described in WO 2007/056170-A2 (Intermediate O).

Intermediate 44A

1-[(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]piperidin-4-ol



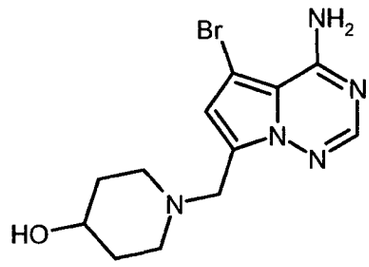
4-Hydroxypiperidine (3.62 g, 35.8 mmol) and 37% formalin solution (2.9 g, 35.8 mmol) were dissolved in acetic acid (150 mL) and stirred at room temperature for 1 h. To this solution was added a solution of pyrrolo[2,1-f][1,2,4]triazin-4-amine (2.0 g, 14.9 mmol; prepared according to the procedure described in WO 2007/056170-A2, Intermediate A) in acetic acid (150 mL), and the mixture was stirred at 60°C for 2 h. The solvent was then evaporated, and the residue was taken up in 200 mL of half-concentrated aqueous potassium bicarbonate solution and extracted with 200 mL dichloromethane. The organic layer was washed with water (2 x 50 mL) and discarded. The combined aqueous layers were evaporated to dryness, and the residue was treated with a 10:1 mixture of dichloromethane and methanol (2 x 100 mL). The organic extracts were evaporated, and the residue was purified by preparative HPLC (method 4) to give 1.16 g (15% of th.) of the title compound.

LC-MS (method 7): R_t = 0.18 min; MS (ESIpos): *m/z* (%) = 248.3 (30) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 246.5 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.35 (br. m, 2H), 1.67 (br. m, 2H), 2.07 (t, 2H), 2.70 (br. m, 2H), 3.38 (br. m, 1H), 3.75 (s, 2H), 4.51 (br, 1H), 6.52 (d, 1H), 6.84 (d, 1H), 7.62 (br, 2H), 7.82 (s, 1H).

Intermediate 45A

1-[(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]piperidin-4-ol



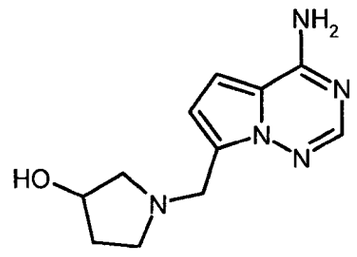
Intermediate 44A (1.10 g, 4.45 mmol) was dissolved in DMF (16.5 mL) and cooled to -20°C. 1,3-Dibromo-5,5-dimethylhydantoin (636 mg, 2.22 mmol) was added every 10 min in about 100 mg portions. Subsequently, the mixture was stirred at room temperature for a further hour and was then directly purified by preparative HPLC (method 4). Yield: 0.61 g (42% of th.).

LC-MS (method 4): R_t = 0.75 min; MS (ESIpos): *m/z* (%) = 326.0 (30) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 324.0 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.35 (br. m, 2H), 1.67 (br. m, 2H), 2.08 (t, 2H), 2.68 (br. m, 2H), 3.39 (br. m, 1H), 3.74 (s, 2H), 4.51 (br, 1H), 6.69 (s, 1H), 7.86 (s, 1H).

Intermediate 46A

1-[(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]pyrrolidin-3-ol



3-Pyrrolidinol (1.56 g, 17.9 mmol) and 37% formalin solution (1.45 g, 17.9 mmol) were dissolved in acetic acid (75 mL) and stirred at room temperature for 10 min. To this solution was added a solution of pyrrolo[2,1-f][1,2,4]triazin-4-amine (2.0 g, 14.9 mmol) in acetic acid (75 mL), and the

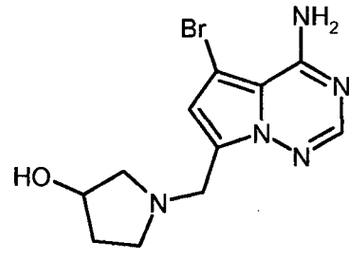
mixture was stirred at 60°C for 4 h. After evaporation, the residue was taken up in 200 mL of 1 N aqueous potassium carbonate solution and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by preparative HPLC (method 4) to give 390 mg (11% of th.) of the title compound.

LC-MS (method 4): R_t = 0.22 min; MS (ESIpos): *m/z* (%) = 234.2 (20) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 223.0 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.50 (br. m, 1H), 1.94 (m, 1H), 2.34 (dd, 1H), 2.44 (dd, 1H), 2.60 (dd, 1H), 2.71 (dd, 1H), 3.84 (dd, 2H), 4.15 (br, 1H), 4.65 (d, 1H), 6.52 (d, 1H), 6.83 (d, 1H), 7.61 (br, 2H), 7.82 (s, 1H).

Intermediate 47A

1-[(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]pyrrolidin-3-ol



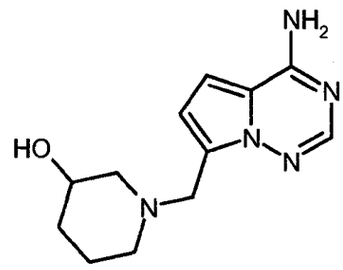
Intermediate 46A (0.9 g, 3.86 mmol) was dissolved in DMF (14.2 mL) and cooled to -20°C. 1,3-Dibromo-5,5-dimethylhydantoin (606 mg, 2.12 mmol) was added every 10 min in about 100 mg portions, and stirring was continued at room temperature for 1 h. The mixture was partitioned between 10% aqueous potassium bicarbonate solution (50 mL) and ethyl acetate (100 mL). The aqueous layer was extracted with another portion of ethyl acetate (100 mL) and then with dichloromethane (100 mL). The combined organic layers were dried over magnesium sulfate and evaporated, and the residue was purified by preparative HPLC (method 4). Yield: 0.44 g (37% of th.).

LC-MS (method 6): R_t = 0.21 min; MS (ESIpos): *m/z* (%) = 314.0 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.50 (br. m, 1H), 1.95 (m, 1H), 2.34 (dd, 1H), 2.45 (m, 1H), 2.60 (m, 1H), 2.70 (dd, 1H), 3.84 (dd, 2H), 4.15 (br, 1H), 4.65 (d, 1H), 6.71 (s, 1H), 7.86 (s, 1H).

Intermediate 48A

1-[(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]piperidin-3-ol



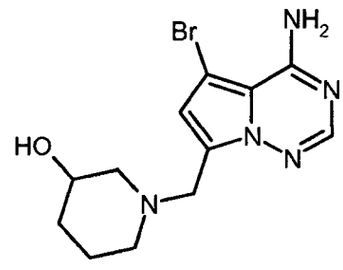
The title compound was prepared in analogy to Intermediate 46A with 3-hydroxypiperidine (1.80 g, 17.9 mmol) as starting material. After concentration of the reaction mixture, the residue was taken up in saturated aqueous potassium carbonate solution and extracted with 300 mL dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by preparative HPLC (method 4) to give 650 mg (18% of th.) of the title compound.

LC-MS (method 6): R_t = 0.16 min; MS (ESIpos): *m/z* (%) = 248.2 (60) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.99 (m, 1H), 1.37 (br. m, 1H), 1.57 (br. m, 1H), 1.74 (m, 2H), 1.88 (t, 1H), 2.68 (br. m, 1H), 2.83 (br. dd, 1H), 3.41 (br. m, 1H), 3.78 (dd, 2H), 4.54 (d, 1H), 6.52 (d, 1H), 6.84 (d, 1H), 7.61 (br, 2H), 7.82 (s, 1H).

Intermediate 49A

1-[(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]piperidin-3-ol



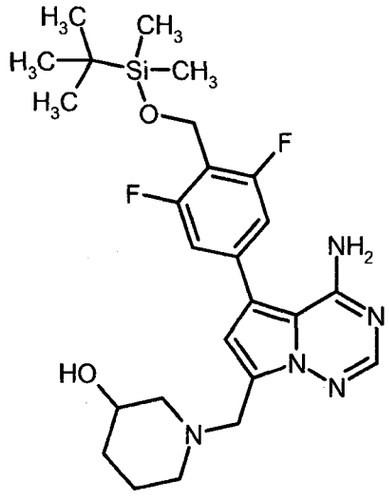
In analogy to the preparation of Intermediate 47A, the title compound was prepared from Intermediate 48A (690 mg, 2.79 mmol) to give 348 mg (93% LC-MS purity, 36% of th.) of the product after purification by preparative HPLC (method 4).

LC-MS (method 4): R_t = 0.85 min; MS (ESIpos): *m/z* (%) = 226.0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 223.9 (70) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.99 (m, 1H), 1.37 (m, 1H), 1.57 (br. m, 1H), 1.74 (m, 2H), 1.89 (m, 1H), 2.66 (br. m, 1H), 2.81 (br. m, 1H), 3.41 (br. m, 1H), 3.77 (dd, 2H), 4.54 (d, 1H), 6.70 (s, 1H), 7.86 (s, 1H).

Intermediate 50A

1-({4-Amino-5-[4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3,5-difluorophenyl]pyrrolo[2,1-f]-[1,2,4]triazin-7-yl}methyl)piperidin-3-ol



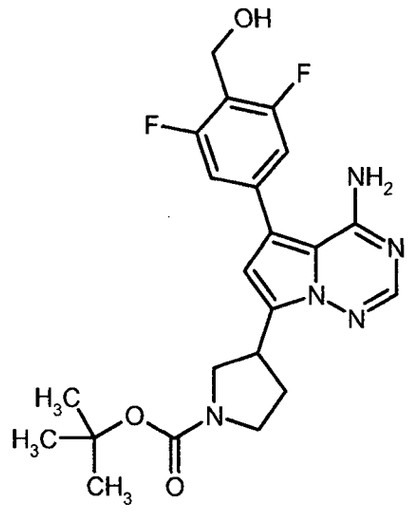
The title compound was obtained by general synthetic method 1 from Intermediate 49A (200 mg, 0.61 mmol) and [4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3,5-difluorophenyl]boronic acid (222 mg, 0.74 mmol; prepared by the method of Hattori, *Bioorg. Med. Chem.* **2006**, *14*, 3258-3262). Purification of the crude product was carried out by preparative HPLC (method 3). Yield: 153 mg (50% of th.).

LC-MS (method 7): R_t = 1.55 min; MS (ESIpos): *m/z* (%) = 504.1 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.11 (s, 6H), 0.86 (s, 9H), 1.01 (m, 1H), 1.40 (br. m, 1H), 1.59 (br. m, 1H), 1.77 (m, 2H), 1.94 (m, 1H), 2.72 (br. m, 1H), 2.87 (br. m, 1H), 3.43 (m, 1H), 3.82 (dd, 2H), 4.55 (d, 1H), 4.74 (s, 2H), 6.75 (s, 1H), 7.18 (dd, 2H), 7.95 (s, 1H).

Intermediate 51A

rac-tert-Butyl 3-{4-amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyrrolidine-1-carboxylate



The preparation of the starting material *tert*-butyl 3-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)pyrrolidine-1-carboxylate has been described in WO 2007/056170-A2 (Intermediate I).

This compound (60 mg, 0.16 mmol) was coupled according to general synthetic method 1 with Intermediate 2A (47 mg, 0.17 mmol, 1.1 eq.). The crude product was purified by preparative HPLC (method 2) to give 67 mg (84% of th.) of the title compound.

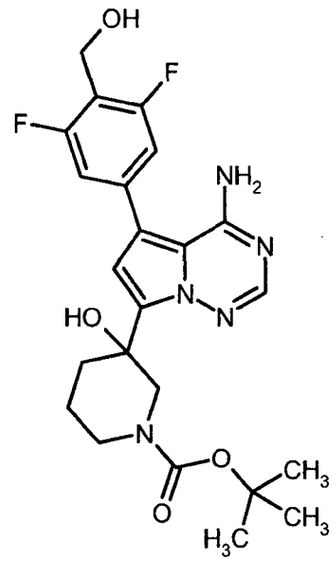
HPLC (method 2): R_t = 4.08 min;

LC-MS (method 7): R_t = 1.66 min; MS (ESIpos): *m/z* (%) = 446.2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 444.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.39 (s, 9H), 2.10 (m, 1H), 2.33 (m, 1H), 3.37 (m, 2H), 3.46 (m, 1H), 3.70-3.89 (m, 2H), 4.51 (s, 2H), 6.80 (s, 1H), 7.15 (m, 2H), 8.03 (s, 1H).

Intermediate 52A

rac-tert-Butyl 3-{4-amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}-3-hydroxypiperidine-1-carboxylate



Intermediate 26A (148 mg, 0.35 mmol) and (4-bromo-2,6-difluorophenyl)methanol (75 mg, 0.34 mmol) were coupled according to general synthetic method 2. Purification of the crude product was carried out using preparative HPLC (method 2). Yield: 46 mg (28% of th.).

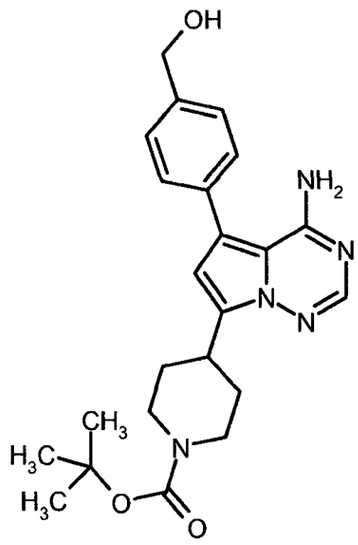
HPLC (method 3): R_t = 3.90 min;

LC-MS (method 7): R_t = 1.56 min; MS (ESIpos): *m/z* (%) = 476.2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 474.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.22-1.58 (m, 10H), 1.80 (m, 2H), 3.19 (m, 1H), 3.48 (m, 1H), 3.62 (m, 1H), 3.74 (m, 1H), 4.00 (m, 1H), 4.52 (m, 2H), 5.39 (t, 1H), 6.78 (s, 1H), 7.10 (m, 2H), 7.94 (s, 1H).

Intermediate 53A

tert-Butyl 4-{4-amino-5-[4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}piperidine-1-carboxylate



The starting material *tert*-butyl 4-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidine-1-carboxylate was prepared according to the procedure described in WO 2007/056170-A2 (Example 1, step 3).

This compound (400 mg, 1.01 mmol) was then reacted with 4-(hydroxymethyl)phenylboronic acid (184 mg, 1.21 mmol, 1.2 eq.) according to general synthetic method 1. The crude product was purified by preparative HPLC (method 2) to give 326 mg (76% of th.) of the title compound.

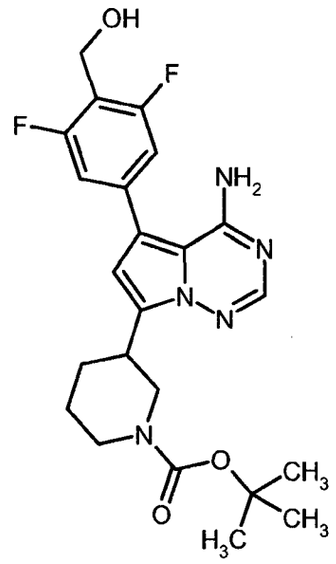
HPLC (method 2): R_t = 4.07 min;

LC-MS (method 6): R_t = 1.06 min; MS (ESIpos): *m/z* (%) = 424.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 422.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.52-1.65 (m, 2H), 1.92-2.00 (m, 2H), 2.89 (br. s, 2H), 3.10 (m, 1H), 3.28-3.37 (m, 2H), 4.06 (d, 2H), 4.60 (s, 2H), 6.68 (s, 1H), 7.47 (s, 5H), 8.02 (s, 1H).

Intermediate 54A

rac-tert-Butyl 3-{4-amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}piperidine-1-carboxylate



Intermediate 31A (200 mg, 0.39 mmol) and Intermediate 2A (138 mg, 0.51 mmol, 1.3 eq.) were reacted according to general synthetic method 1 yielding 130 mg (72% of th.) of the title compound after purification by preparative HPLC (method 2).

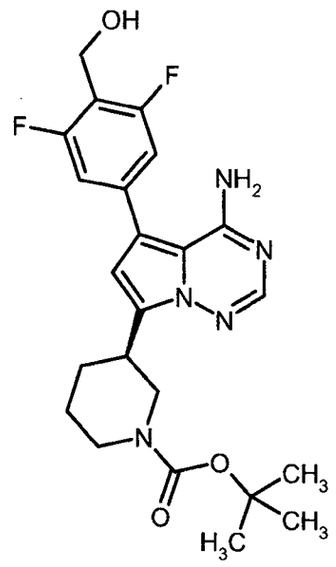
HPLC (method 3): R_t = 4.23 min;

LC-MS (method 6): R_t = 1.17 min; MS (ESIpos): *m/z* (%) = 460.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 458.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.39 (s, 9H), 1.48 (m, 2H), 1.74 (m, 2H), 2.93 (m, 1H), 3.22 (m, 1H), 3.85 (m, 1H), 4.11 (m, 1H), 4.53 (s, 2H), 6.78 (s, 1H), 7.12 (m, 2H), 8.02 (s, 1H).

Intermediate 55A

tert-Butyl (3*R*)-3-{4-amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}piperidine-1-carboxylate



The enantiomerically pure *R*-isomer was synthesized by coupling Intermediate 32A (115 mg, 0.28 mmol) with (4-bromo-2,6-difluorophenyl)methanol (76 mg, 0.33 mmol, 1.2 eq.) according to general synthetic method 2. Yield: 48 mg (38% of th.).

Alternatively, the title compound was obtained by separation of the racemic compound from Intermediate 54A (40 mg) using preparative chiral HPLC [column: chiral silica gel phase based on the selector poly(*N*-methacryloyl-L-leucine-*tert*-butylamide), 250 mm x 20 mm; eluent: ethyl acetate/isohexane 4:1; flow rate: 20 mL/min; UV detection: 260 nm]. Yield: 20 mg (*R*-isomer).

Analytical chiral HPLC [column: chiral silica gel phase based on the selector poly(*N*-methacryloyl-L-leucine-*tert*-butylamide), 250 mm x 4 mm; eluent: ethyl acetate/isohexane 4:1; flow rate: 1 mL/min; UV detection: 260 nm]: R_t = 5.68 min; e.e. >99.5.

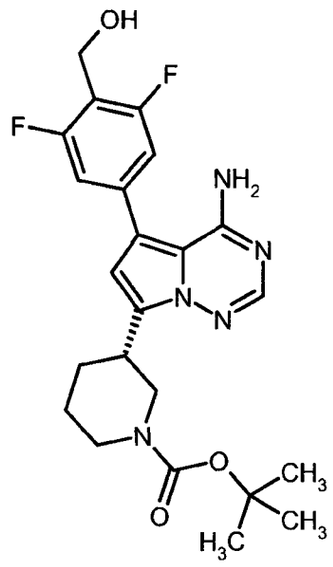
HPLC (method 3): R_t = 4.23 min;

LC-MS (method 6): R_t = 1.17 min; MS (ESIpos): *m/z* (%) = 460.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 458.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.39 (s, 9H), 1.48 (m, 2H), 1.74 (m, 2H), 2.93 (m, 1H), 3.22 (m, 1H), 3.85 (m, 1H), 4.11 (m, 1H), 4.53 (s, 2H), 6.78 (s, 1H), 7.12 (m, 2H), 8.02 (s, 1H).

Intermediate 56A

tert-Butyl (3*S*)-3-{4-amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}piperidine-1-carboxylate



The enantiomerically pure *S*-isomer was obtained by separation of the racemic compound from Intermediate 54A (40 mg) using preparative chiral HPLC as described for Intermediate 55A. Yield: 19 mg (*S*-isomer).

Analytical chiral HPLC [column: chiral silica gel phase based on the selector poly(*N*-methacryloyl-L-leucine-*tert*-butylamide), 250 mm x 4 mm; eluent: ethyl acetate/isohexane 4:1; flow rate: 1 mL/min; UV detection: 260 nm]: R_t = 7.87 min; e.e. >99.5.

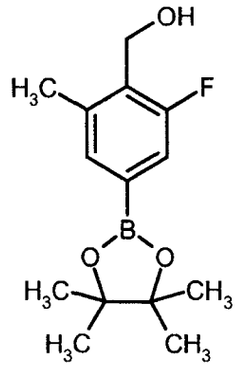
HPLC (method 3): R_t = 4.23 min;

LC-MS (method 6): R_t = 1.17 min; MS (ESIpos): *m/z* (%) = 460.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 458.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.39 (s, 9H), 1.48 (m, 2H), 1.74 (m, 2H), 2.93 (m, 1H), 3.22 (m, 1H), 3.85 (m, 1H), 4.11 (m, 1H), 4.53 (s, 2H), 6.78 (s, 1H), 7.12 (m, 2H), 8.02 (s, 1H).

Intermediate 57A

[2-Fluoro-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol

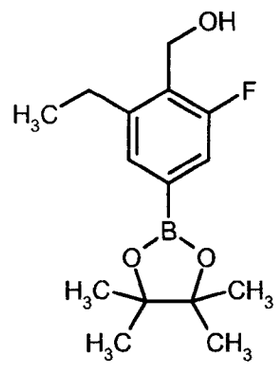


(4-Bromo-2-fluoro-6-methylphenyl)methanol (2.0 g, 9.13 mmol) was dissolved in 1,4-dioxane (20.0 mL) in a microwave reactor vial, and the solution was flushed with argon. Then, bis(pinacolato)diboron (2.43 g, 9.59 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) chloride (298 mg, 0.37 mmol) and potassium acetate (1.34 g, 13.7 mmol) were added, the reaction vessel was crimp-capped, and the mixture was heated to 130°C for 1 h in a single-mode microwave device. After cooling, the reaction mixture was filtered and the filtrate was evaporated. The residue was treated with cyclohexane (100 mL) and stirred for 10 min. The solution was filtered again, the filtrate was evaporated, and the residue was purified by chromatography (Biotage 25M silica cartridge, dichloromethane at 15 mL/min flow rate). Fractions containing the title compound were combined and evaporated, and the title compound crystallized spontaneously as a yellow solid (2.18 g, 90% of th.).

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.30 (s, 12H), 2.39 (s, 3H), 4.51 (m, 2H), 5.01 (t, 1H), 7.14 (d, 1H), 7.31 (s, 1H).

Intermediate 58A

[2-Ethyl-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol

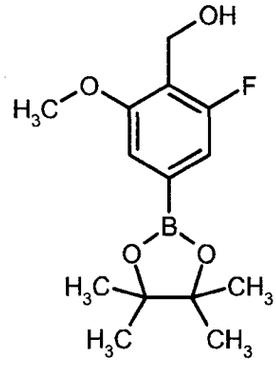


The title compound was synthesized and purified in analogy to Intermediate 57A using (4-bromo-2-ethyl-6-fluorophenyl)methanol (2.00 g, 8.58 mmol), bis(pinacolato)diboron (2.29 g, 9.01 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) chloride (280 mg, 0.34 mmol) and potassium acetate (1.26 g, 12.87 mmol) in 1,4-dioxane (20 mL). Yield: 2.16 g (90% of th.) as yellow crystals.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.17 (t, 3H), 1.30 (s, 12H), 2.76 (q, 2H), 4.50 (m, 2H), 5.03 (t, 1H), 7.14 (d, 1H), 7.32 (s, 1H).

Intermediate 59A

[2-Fluoro-6-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol

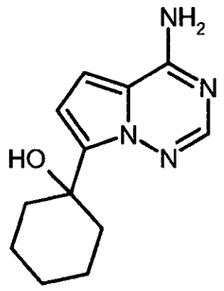


The title compound was synthesized and purified in analogy to Intermediate 57A using (4-bromo-2-methoxy-6-fluorophenyl)methanol (2.00 g, 8.51 mmol), bis(pinacolato)diboron (2.27 g, 8.90 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) chloride (278 mg, 0.34 mmol) and potassium acetate (1.25 g, 12.76 mmol) in 1,4-dioxane (20 mL). Yield: 1.81 g (75% of th.) as yellow crystals.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.30 (s, 12H), 3.83 (s, 3H), 4.47 (m, 2H), 4.86 (t, 1H), 6.97 (d, 1H), 7.02 (s, 1H).

Intermediate 60A

1-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)cyclohexanol



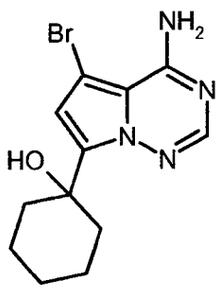
7-Bromopyrrolo[2,1-f][1,2,4]triazin-4-amine (1.20 g, 5.63 mmol) was dissolved in THF (25 mL) under argon at room temperature. Chlorotrimethylsilane (1.43 mL, 11.27 mmol) was added, and the mixture was stirred at room temperature for 3 h. Then, it was cooled to 0°C, 2-propyl magnesium chloride (11.8 mL of a 2.0 M solution in THF, 23.7 mmol) was added, and stirring was maintained for another 3 h while the reaction mixture was allowed to warm to room temperature. Then, cyclohexanone (0.88 mL, 8.45 mmol) was added, and stirring was continued for 16 h. The reaction was quenched with a mixture (1:1) of concentrated aqueous ammonium chloride solution and ice until the pH reached 6-7. The mixture was extracted with two portions of ethyl acetate, and the combined organic extracts were dried over anhydrous sodium carbonate and concentrated to dryness. The product thus obtained was used without further purification (purity ~68% by HPLC). Yield: 1.87 g (97% of th.).

LC-MS (method 5): R_t = 1.10 min; MS (ESIpos): *m/z* (%) = 233 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 231 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.28-1.33 (m, 1H), 1.42-1.50 (m, 2H), 1.58-1.63 (m, 1H), 1.67-1.78 (m, 4H), 2.13-2.23 (m, 2H), 6.69 (d, 1H), 7.20 (d, 1H), 8.02 (s, 1H), 8.58 (br. s, 1H), 9.00 (br. s, 1H).

Intermediate 61A

1-(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)cyclohexanol



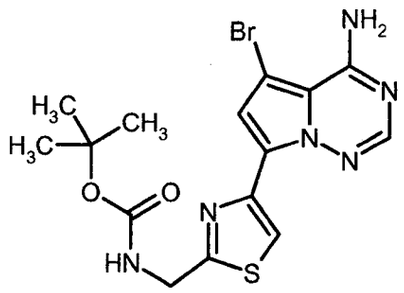
Intermediate 60A (80 mg, 0.34 mmol) was dissolved in THF (5.0 mL), and the mixture was cooled to -20°C. 1,3-Dibromo-5,5-dimethylhydantoin (49 mg, 0.17 mmol) was added at once, and stirring was continued for 1 h. The reaction was quenched with conc. aqueous sodium dithionite solution (0.5 mL), and the mixture was extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, and the solvent was distilled off to give 98 mg (91% of th.) of the title compound.

LC-MS (method 4): R_t = 1.90 min; MS (ESIpos): *m/z* (%) = 311 (95) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 309 (90) $[M-H]^-$.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.20-1.33 (m, 1H), 1.42-1.52 (m, 2H), 1.58-1.78 (m, 5H), 2.15-2.23 (m, 2H), 5.01 (br. s, 2H), 6.63 (s, 1H), 7.82 (s, 1H).

Intermediate 62A

tert-Butyl {[4-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)-1,3-thiazol-2-yl]methyl}-carbamate

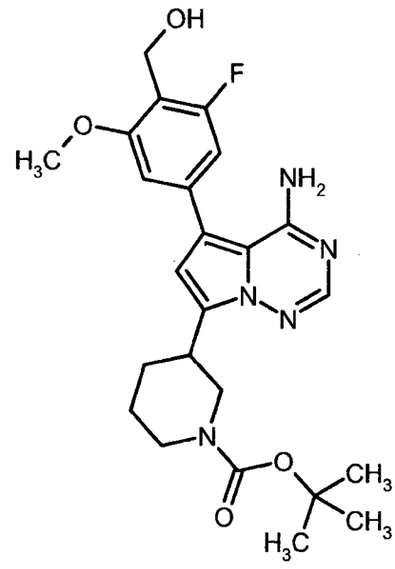


Intermediate 33A (109 mg, 0.38 mmol) and *tert*-butyl (2-amino-2-thioxoethyl)carbamate (79 mg, 0.41 mmol) were dissolved in ethanol (6.5 mL). The mixture was heated to reflux for 20 h. The mixture was then filtered, and the filtrate was evaporated. The residue was triturated with acetonitrile to give 67 mg (42% of th.) of the title compound as a brownish-grey crystalline solid.

LC-MS (method 7): R_t = 1.81 min; MS (ESIpos): *m/z* (%) = 425 (80) and 427 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 423 (50) and 425 (100) $[M-H]^-$.

Intermediate 63A

tert-Butyl 3-{4-amino-5-[3-fluoro-4-(hydroxymethyl)-5-methoxyphenyl]pyrrolo[2,1-f][1,2,4]-triazin-7-yl}piperidine-1-carboxylate



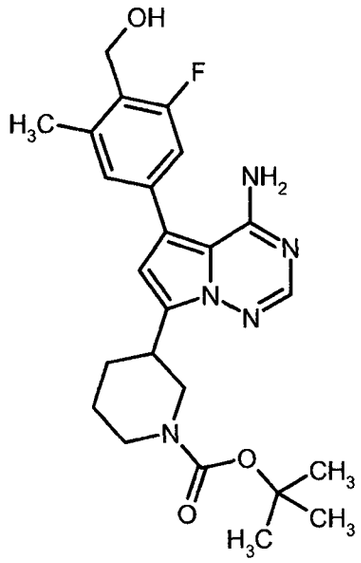
Intermediate 31A (120 mg, 0.30 mmol) and Intermediate 59A (104 mg, 0.36 mmol) were dissolved in acetonitrile (2.0 mL) in a microwave reactor vial and flushed with argon. Tetrakis(triphenylphosphine)palladium(0) (35 mg, 0.03 mmol) and 2.0 M aq. sodium carbonate solution (0.5 mL) were added, and the mixture was heated to 150°C for 1 h in a single-mode microwave device. After cooling, the mixture was filtered, and the filtrate was evaporated. The residue was purified by flash chromatography (Biotage 25M silica cartridge, dichloromethane + 2-5% methanol, flow rate 10 mL/min) to give 51 mg (36% of th.) of the title compound.

LC-MS (method 6): R_t = 1.16 min; MS (ESIpos): *m/z* (%) = 472 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 470 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.31-2.10 (m, 13H), 2.88-2.91 (m, 2H), 3.19-3.27 (m, 2H), 3.87 (s, 1H), 4.12 (m, 1H), 4.50 (m, 1H), 4.82 (t, 1H), 6.68 (s, 1H), 6.83 (d, 1H), 6.90 (s, 1H), 7.92 (s, 1H).

Intermediate 64A

tert-Butyl 3-{4-amino-5-[3-fluoro-4-(hydroxymethyl)-5-methylphenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}piperidine-1-carboxylate



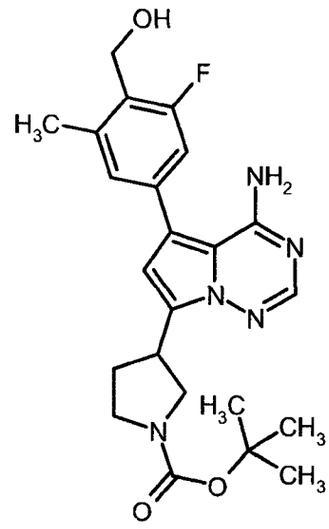
Intermediate 31A (120 mg, 0.30 mmol) and Intermediate 57A (97 mg, 0.36 mmol) were dissolved in acetonitrile (2.0 mL) in a microwave reactor vial and flushed with argon. Tetrakis(triphenylphosphine)palladium(0) (35 mg, 0.03 mmol) and 2.0 M aq. sodium carbonate solution (0.5 mL) were added, and the mixture was heated to 150°C for 1 h in a single-mode microwave device. After cooling, the mixture was filtered, and the filtrate was evaporated. The residue was purified by flash chromatography (Biotage 25M silica cartridge, dichloromethane + 2-5% methanol, flow rate 10 mL/min) to give 110 mg (71% of th.) of the title compound.

LC-MS (method 4): R_t = 2.03 min; MS (ESIpos): *m/z* (%) = 456 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 454 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.31-2.11 (m, 13H), 2.42 (s, 3H), 2.88-2.91 (m, 2H), 3.17-3.30 (m, 2H), 3.80 (m, 1H), 4.54 (m, 1H), 4.82 (t, 1H), 6.64 (s, 1H), 7.04 (d, 1H), 7.12 (s, 1H), 7.93 (s, 1H).

Intermediate 65A

tert-Butyl 3-{4-amino-5-[3-fluoro-4-(hydroxymethyl)-5-methylphenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyrrolidine-1-carboxylate



The starting material *tert*-Butyl 3-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)pyrrolidine-1-carboxylate was synthesized according to the procedure described in WO 2007/056170-A2 (Intermediate I).

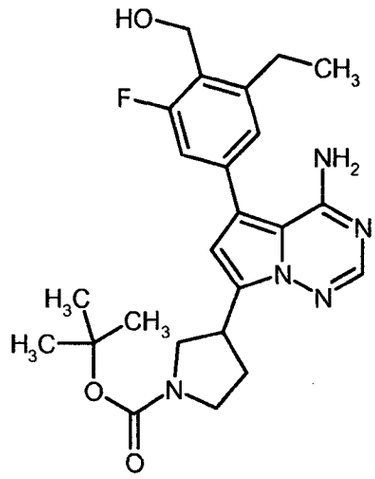
tert-Butyl 3-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)pyrrolidine-1-carboxylate (120 mg, 0.31 mmol) was dissolved in acetonitrile (2.2 mL) in a microwave reactor vial and flushed with argon. Intermediate 57A (100 mg, 0.38 mmol), tetrakis(triphenylphosphine)palladium(0) (36 mg, 0.03 mmol) and 2.0 M aq. sodium carbonate solution (0.5 mL) were added, and the mixture was heated to 150°C for 1 h in a single-mode microwave device. After cooling, the mixture was filtered, and the filtrate was evaporated. The residue was purified by flash chromatography (Biotage 25M silica cartridge, dichloromethane + 2-5% methanol, flow rate 10 mL/min) to give 91 mg (54% of th.) of the title compound.

LC-MS (method 5): R_t = 2.00 min; MS (ESIpos): *m/z* (%) = 442 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 440 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.41 (m, 9H), 2.00-2.48 (m, 2H), 3.29-3.53 (m, 3H), 3.71-3.90 (m, 2H), 4.55 (m, 2H), 4.99 (t, 1H), 6.63 (s, 1H), 7.06 (d, 1H), 7.12 (s, 1H), 7.92 (s, 1H).

Intermediate 66A

rac-tert-Butyl 3-{4-amino-5-[3-ethyl-5-fluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]-triazin-7-yl}pyrrolidine-1-carboxylate



The starting material *tert*-Butyl 3-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)pyrrolidine-1-carboxylate was synthesized according to the procedure described in WO 2007/056170-A2 (Intermediate I).

tert-Butyl 3-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)pyrrolidine-1-carboxylate (111 mg, 0.29 mmol), Intermediate 58A (98 mg, 0.35 mmol) and tetrakis(triphenylphosphine)palladium(0) (17 mg, 0.015 mmol) were dissolved in a mixture of acetonitrile (2.3 mL) and 2 M aqueous sodium carbonate solution (0.53 mL) in a microwave reactor vial. After degassing for 5 min using argon, the reaction vessel was crimp-capped, and the mixture was heated to 150°C for 1 h in a single-mode microwave device. After cooling to room temperature, saturated aqueous sodium bicarbonate solution was added, and the mixture was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by preparative HPLC (method 5). Yield: 83 mg (63% of th.).

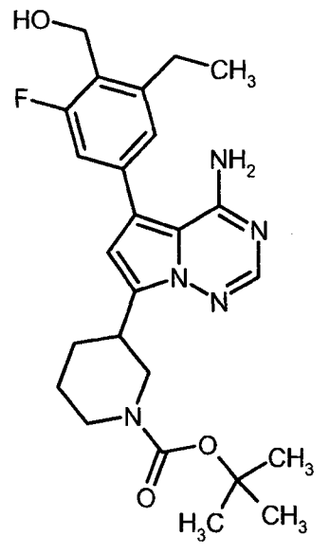
HPLC (method 9): R_t = 1.61 min;

LC-MS (method 10): R_t = 1.02 min; MS (ESIpos): *m/z* (%) = 456.4 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 454.4 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.22 (t, 3H), 1.41 (s, 9H), 2.1 (m, 1H), 2.80 (q, 2H), 3.30-3.43 (m, 2H), 3.44-3.51 (m, 1H), 3.78 (m, 1H), 4.55 (d, 2H), 5.00 (t, 1H), 6.68 (s, 1H), 7.09 (d, 1H), 7.15 (s, 1H), 7.95 (s, 1H).

Intermediate 67A

rac-tert-Butyl 3-{4-amino-5-[3-ethyl-5-fluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]-triazin-7-yl}piperidine-1-carboxylate



Intermediate 31A (148 mg, 0.29 mmol), Intermediate 58A (98 mg, 0.35 mmol) and tetrakis(triphenylphosphine)palladium(0) (17 mg, 0.015 mmol) were dissolved in a mixture of acetonitrile (2.3 mL) and 2 M aqueous sodium carbonate solution (0.67 mL) in a microwave reactor vial. After degassing for 5 min using argon, the reaction vessel was crimp-capped, and the mixture was heated to 150°C for 1 h in a single-mode microwave device. After cooling to room temperature, saturated aqueous sodium bicarbonate solution was added, and the mixture was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by preparative HPLC (method 5). Yield: 105 mg (76% of th.).

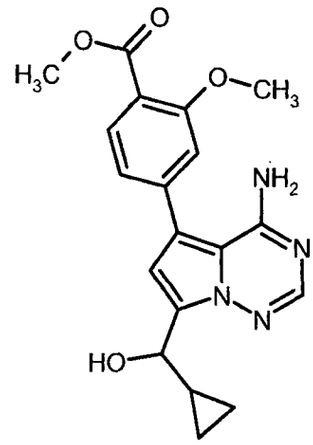
HPLC (method 9): R_t = 1.71 min;

LC-MS (method 10): R_t = 1.08 min; MS (ESIpos): *m/z* (%) = 470.4 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 468.4 (75) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.22 (t, 3H), 1.38 (s, 9H), 1.50 (m, 1H), 1.65-1.90 (m, 2H), 2.06 (m, 1H), 2.80 (q, 2H), 2.98 (m, 1H), 3.20-3.43 (m, 2H), 3.8 (m, 1H), 4.08 (m, 1H), 4.55 (d, 2H), 5.02 (t, 1H), 6.65 (s, 1H), 7.07 (d, 1H), 7.13 (s, 1H), 7.93 (s, 1H).

Intermediate 68A

rac-Methyl 4-{4-amino-7-[cyclopropyl(hydroxy)methyl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}-2-methoxybenzoate



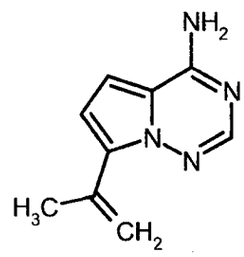
Intermediate 17A (250 mg, 0.88 mmol), [3-methoxy-4-(methoxycarbonyl)phenyl]boronic acid (223 mg, 1.06 mmol) and tetrakis(triphenylphosphine)palladium(0) (102 mg, 0.088 mmol) were dissolved in a mixture of 1,4-dioxane (5.5 mL) and 2 M aqueous sodium carbonate solution (1.32 mL) under argon and heated under reflux for 16 h. After this, another portion of tetrakis(triphenylphosphine)palladium(0) (102 mg, 0.088 mmol) was added, and heating was continued for further 24 h. After cooling to room temperature, the reaction mixture was filtered, the filtrate was concentrated, and the residue was purified by preparative HPLC (method 7). Yield: 130 mg (80% purity, 32% of th.).

LC-MS (method 10): R_t = 0.80 min; MS (ESIpos): *m/z* (%) = 369.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 367.3 (75) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.41 (m, 3H), 0.49 (m, 1H), 1.37 (m, 1H), 3.81 (s, 3H), 4.68 (d, 1H), 6.92 (s, 1H), 7.13 (dd, 1H), 7.22 (d, 1H), 7.77 (d, 1H), 8.05 (s, 1H).

Intermediate 69A

7-(Prop-1-en-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



The starting material 7-bromopyrrolo[2,1-f][1,2,4]triazin-4-amine was synthesized according to the procedure described in WO 2007/056170-A2 (Intermediate B).

Under an argon atmosphere, 7-bromopyrrolo[2,1-f][1,2,4]triazin-4-amine (426 mg, 2 mmol) and 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (420 mg, 2.5 mmol) were dissolved in a mixture of 1,2-dimethoxyethane (10 mL) and aqueous sodium carbonate solution (2 M, 4 mL). The reaction mixture was degassed, and 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) chloride (73 mg, 0.1 mmol) was added. After stirring at 90°C overnight, the reaction mixture was diluted with ethyl acetate (40 mL), water (10 mL) was added, and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 40 mL), and the combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (puriFlash, Interchim, cyclohexane/ethyl acetate 1:1 to 100% ethyl acetate gradient) to yield the title product as a slightly yellow solid. Yield: 304 mg (81% of th.).

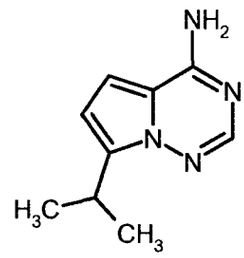
HPLC (method 10): R_t = 0.83 min;

LC-MS (method 10): R_t = 0.57 min; MS (ESIpos): *m/z* (%) = 175.1 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.15 (s, 3H), 5.22 (m, 1H), 6.30 (m, 1H), 6.73 (d, 1H), 6.91 (d, 1H), 7.69 (m, 1H), 7.91 (s, 1H).

Intermediate 70A

7-Isopropylpyrrolo[2,1-f][1,2,4]triazin-4-amine



Intermediate 69A (149 mg, 0.86 mmol) was dissolved in a mixture of ethanol and ethyl acetate (1:1, 40 mL) under argon. Palladium on charcoal (10%, 9.1 mg) was added, and the mixture was vigorously stirred for 16 h under an atmosphere of hydrogen at ambient pressure and room temperature. After this, the catalyst was removed by filtration, and the solvent was distilled off under reduced pressure to give 131 mg (80% of th.) of the title compound as a colorless solid. This product was used in the next synthetic step without further purification.

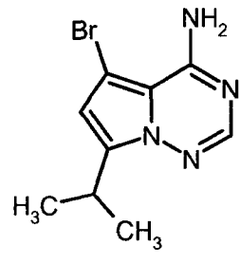
HPLC (method 10): R_t = 0.81 min;

LC-MS (method 10): R_t = 0.56 min; MS (ESIpos): *m/z* (%) = 177.0 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.27 (d, 6H), 3.36 (m, 1H), 6.41 (d, 1H), 6.80 (d, 1H), 7.48-7.59 (m, 2H), 7.80 (s, 1H).

Intermediate 71A

5-Bromo-7-isopropylpyrrolo[2,1-f][1,2,4]triazin-4-amine



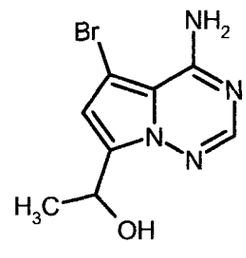
Intermediate 70A (125 mg, 0.71 mmol) was dissolved in dry THF (21 mL) and cooled to -78°C. 1,3-Dibromo-5,5-dimethylhydantoin (81 mg, 0.28 mmol) was added in two equal portions. The reaction mixture was stirred at -78°C for 1 h and then allowed to warm to room temperature overnight. After addition of water (20 mL) and further stirring for 20 min, the precipitated solid was collected by filtration and dried *in vacuo*. The crude product thus obtained (209 mg, >100% of th.) was used in the next synthetic step without further purification.

HPLC (method 9): R_t = 1.35 min.

LC-MS (method 10): R_t = 0.91 min; MS (ESIpos): *m/z* (%) = 257.0 (100) $[M+H]^+$.

Intermediate 72A

rac-1-(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)ethanol



Intermediate 16A (500 mg, 1.66 mmol) was suspended in THF (10 mL) and cooled to 0°C. Methyl magnesium bromide solution (3 N in diethylether, 1.7 mL) was added, and the reaction mixture was stirred for 30 min. Then, saturated aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried over

magnesium sulfate, filtered and concentrated to yield 235 mg (46% of th.) of the title product which was used in the next synthetic step without further purification.

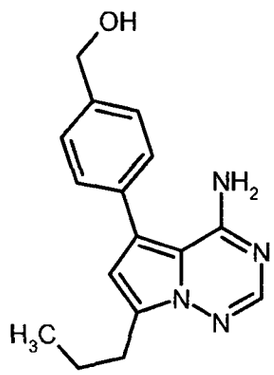
LC-MS (method 5): R_t = 0.73 min; MS (ESIpos): *m/z* (%) = 259.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 257.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.41 (d, 3H), 5.16 (m, 1H), 5.30 (m, 1H), 6.70 (s, 1H), 7.85 (s, 1H).

Preparation Examples:

Example 1

[4-(4-Amino-7-propylpyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]methanol



The title compound was obtained by general synthetic method 1 from Intermediate 11A (100 mg, 0.39 mmol) and 4-(hydroxymethyl)phenylboronic acid (60 mg, 0.39 mmol). Purification of the crude product was carried out by preparative HPLC (method 2). Yield: 33 mg (30% of th.).

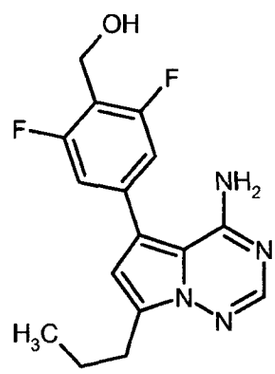
HPLC (method 1): R_t = 3.47 min; HPLC (method 2): R_t = 3.78 min;

LC-MS (method 4): R_t = 0.91 min; MS (ESIpos): *m/z* (%) = 283.2 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.97 (t, *J* = 7.4 Hz, 3H), 1.71 (m, 2H), 3.31 (s, 2H), 4.52 (s, 2H), 6.54 (s, 1H), 7.42 (s, 4H), 7.89 (s, 1H).

Example 2

[4-(4-Amino-7-propylpyrrolo[2,1-f][1,2,4]triazin-5-yl)-2,6-difluorophenyl]methanol



The title compound was obtained by general synthetic method 2 from Intermediate 11A (118 mg, 0.46 mmol) and (4-bromo-2,6-difluorophenyl)methanol (108 mg, 0.49 mmol). Purification of the crude product was carried out by preparative HPLC (method 2). Yield: 59 mg (40% of th.).

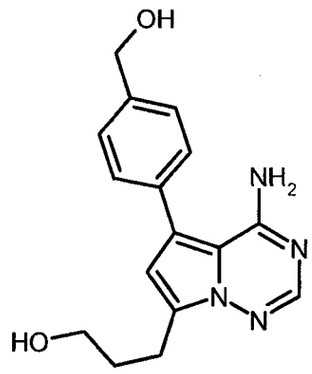
HPLC (method 2): R_t = 3.94 min;

LC-MS (method 7): R_t = 1.47 min; MS (ESIpos): *m/z* (%) = 319.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 317.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.95 (t, 3H), 1.71 (m, 2H), 4.52 (m, 2H), 5.26 (t, 1H), 6.64 (s, 1H), 7.10 (m, 2H), 7.91 (s, 1H).

Example 3

3-{4-Amino-5-[4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}propan-1-ol



The title compound was obtained from Intermediate 10A (100 mg, 0.37 mmol) and 4-(hydroxymethyl)phenylboronic acid (67 mg, 0.44 mmol, 1.2 eq.) according to general synthetic method 1. The crude product was purified by preparative HPLC (method 2) to give 73 mg (66% of th.) of the title compound as colorless solid.

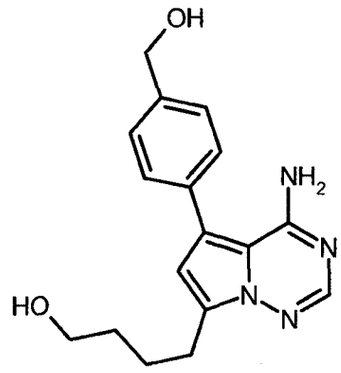
HPLC (method 1): R_t = 2.91 min; HPLC (method 2): R_t = 3.14 min;

LC-MS (method 6): R_t = 0.60 min; MS (ESIpos): *m/z* (%) = 299.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 297.4 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.84 (m, 2H), 2.95 (t, *J* = 7.6 Hz, 2H), 3.50 (m, 2H), 4.58 (s, 2H), 6.67 (s, 1H), 7.41 (s, 4H), 8.03 (s, 1H).

Example 4

4-{4-Amino-5-[4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}butan-1-ol



The title compound was obtained by general synthetic method 1 from Intermediate 14A (75 mg, 0.26 mmol) and 4-(hydroxymethyl)phenylboronic acid (48 mg, 0.32 mmol). Purification of the crude product was carried out by preparative HPLC (method 2). Yield: 66 mg (80% of th.).

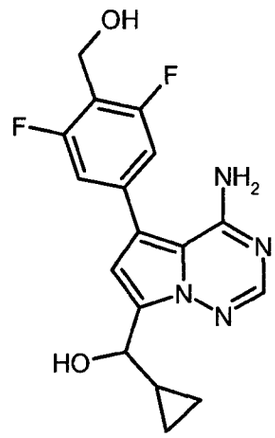
HPLC (method 2): R_t = 3.28 min;

LC-MS (method 6): R_t = 0.68 min; MS (ESIpos): *m/z* (%) = 313.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 311.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.48-1.51 (m, 2H), 1.67-1.70 (m, 2H), 2.91 (t, *J* = 7.6 Hz, 2H), 3.42 (t, *J* = 6.4 Hz, 2H), 4.58 (s, 2H), 6.67 (s, 1H), 7.42 (s, 4H), 8.03 (s, 1H).

Example 5

{4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}(cyclopropyl)methanol



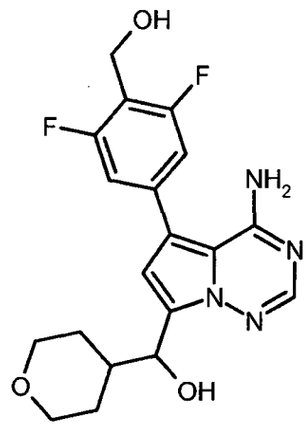
The title compound was obtained from Intermediate 17A (125 mg, 0.44 mmol) and Intermediate 2A (114 mg, 0.53 mmol) by general synthetic method 1. The crude product was purified by preparative HPLC (method 3). Yield: 73 mg (48% of th.).

LC-MS (method 7): R_t = 1.09 min; MS (ESIpos): *m/z* (%) = 347.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 345.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.39 (m, 3H), 0.48 (m, 1H), 1.35 (m, 1H), 4.54 (d, 2H), 4.67 (m, 1H), 5.26 (m, 2H), 6.80 (s, 1H), 7.14 (m, 2H), 7.92 (s, 1H).

Example 6

{4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}(tetrahydro-2*H*-pyran-4-yl)methanol



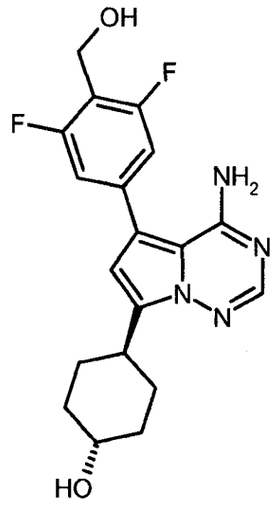
The title compound was obtained from Intermediate 18A (200 mg, 0.61 mmol) and Intermediate 2A (158 mg, 0.73 mmol) by general synthetic method 1. The crude product was purified by preparative HPLC (method 3). Yield: 125 mg (52% of th.).

LC-MS (method 5): R_t = 1.29 min; MS (ESIpos): *m/z* (%) = 391.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 389.0 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.24 (br. d, 1H), 1.36 (m, 2H), 1.68 (br. d, 1H), 2.03 (m, 1H), 2.60 (t, 2H), 3.82 (m, 2H), 4.54 (s, 2H), 4.95 (br. d, 1H), 5.28 (br, 1H), 5.33 (br, 1H), 6.73 (s, 1H), 7.14 (m, 2H), 7.93 (s, 1H).

Example 7

trans-4-{4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}-cyclohexanol



The title compound was obtained by general synthetic method 1 from Intermediate 24A (323 mg, 85% purity, 0.88 mmol) and Intermediate 1A (286 mg, 1.06 mmol, 1.2 eq.). Purification of the crude product was first carried out by flash chromatography (Biotage silica packed cartridge, eluent dichloromethane/methanol 95:5). Further purification was performed by preparative HPLC (method 2). Yield: 72 mg (21% of th.).

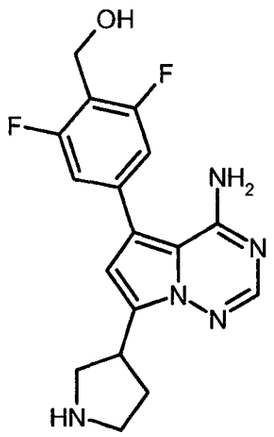
HPLC (method 2): R_t = 3.37 min;

LC-MS (method 7): R_t = 1.01 min; MS (ESIpos): *m/z* (%) = 375.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 373.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.32 (m, 2H), 1.50 (m, 2H), 1.98 (m, 2H), 2.04 (m, 2H), 3.04 (tt, 1H), 3.47 (m, 1H), 4.51 (m, 2H), 4.61 (d, 1H), 5.26 (t, 1H), 6.60 (s, 1H), 7.12 (m, 2H), 7.91 (s, 1H).

Example 8

rac-{4-[4-Amino-7-(pyrrolidin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2,6-difluorophenyl}methanol



Intermediate 51A (67 mg, 0.15 mmol) was dissolved in a 30% solution of trifluoroacetic acid in dichloromethane (6 mL) at 0°C. The reaction mixture was stirred at this temperature for 20 min, then all volatiles were removed under reduced pressure. The residue was purified by preparative HPLC (method 2). The product thus obtained was dissolved in ethyl acetate and washed with saturated aqueous sodium carbonate solution. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off to give 21 mg (41% of th.) of the title compound.

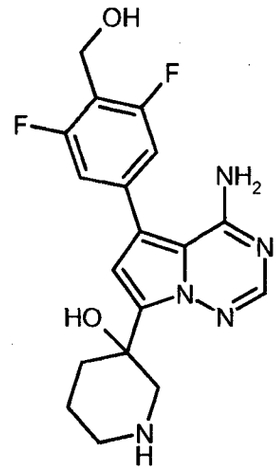
HPLC (method 2): R_t = 2.96 min;

LC-MS (method 6): R_t = 0.34 min; MS (ESIpos): *m/z* (%) = 346.1 (20) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 344.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, *d*$_6$-DMSO): δ (ppm) = 1.94 (m, 1H), 2.22 (m, 1H), 2.94 (m, 1H), 3.00-3.16 (m, 2H), 3.40 (m, 2H), 3.72 (m, 1H), 4.51 (s, 2H), 5.22 (br. s, 1H), 6.71 (s, 1H), 7.11 (m, 2H), 7.92 (s, 1H).

Example 9

rac-3-{4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}-piperidin-3-ol



Intermediate 52A (46 mg, 0.10 mmol) was dissolved in a 30% solution of trifluoroacetic acid in dichloromethane (1.5 mL) at 0°C. The reaction mixture was stirred at this temperature for 30 min, then all volatiles were removed under reduced pressure. The residue was purified by preparative HPLC (method 2). The product thus obtained was dissolved in ethyl acetate and washed with saturated aqueous sodium carbonate solution. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off to give 20 mg (55% of th.) of the title compound.

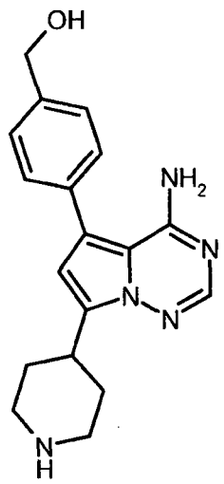
HPLC (method 2): R_t = 2.94 min;

LC-MS (method 4): R_t = 1.01 min; MS (ESIpos): *m/z* (%) = 358.1 (100) $[M-H_2O+H]^+$, MS (ESIneg): *m/z* (%) = 374.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.48 (m, 1H), 1.89 (m, 2H), 2.40-2.69 (m, 2H), 2.92 (d, 1H), 3.02 (d, 1H), 3.40 (m, 1H), 4.52 (m, 2H), 5.26 (t, 1H), 5.45 (s, 1H), 6.72 (s, 1H), 7.13 (m, 2H), 7.94 (s, 1H).

Example 10

{4-[4-Amino-7-(piperidin-4-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}methanol



Intermediate 53A (324 mg, 0.77 mmol) was dissolved in dichloromethane (15 mL). Trifluoroacetic acid (1.5 mL) was added, and the mixture was stirred at room temperature for 16 h. Another portion of trifluoroacetic acid (1.5 mL) was added, and stirring was continued until HPLC (method 1) indicated complete conversion of the starting material. All volatiles were then removed under reduced pressure, and the residue was purified by preparative HPLC (method 1) to give 226 mg (91% of th.) of the title compound.

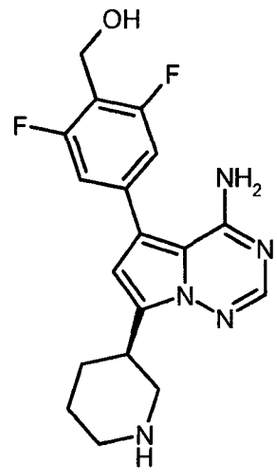
HPLC (method 1): R_t = 3.37 min; HPLC (method 2): R_t = 2.90 min;

LC-MS (method 4): R_t = 0.90 min; MS (ESIpos): *m/z* (%) = 324.1 (75) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 322.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.79-1.95 (m, 2H), 2.16-2.23 (m, 2H), 3.05-3.19 (m, 2H), 3.37-3.52 (m, 3H), 4.56 (s, 2H), 5.49 (s, 2H), 6.66 (s, 1H), 7.43 (s, 4H), 8.03 (s, 1H), 8.39-8.50 (m, 1H), 8.65-8.69 (m, 1H).

Example 11

(4-{4-Amino-7-[(3*R*)-piperidin-3-yl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}-2,6-difluorophenyl)methanol



Intermediate 55A (35 mg, 0.08 mmol) was dissolved in a 30% solution of trifluoroacetic acid in dichloromethane (1.5 mL) at 0°C. The reaction mixture was stirred at this temperature for 30 min, then all volatiles were removed under reduced pressure. The residue was purified by preparative HPLC (method 2). The product thus obtained was dissolved in ethyl acetate and washed with saturated aqueous sodium carbonate solution. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off to give 18 mg (66% of th.) of the title compound.

HPLC (method 2): R_t = 3.10 min;

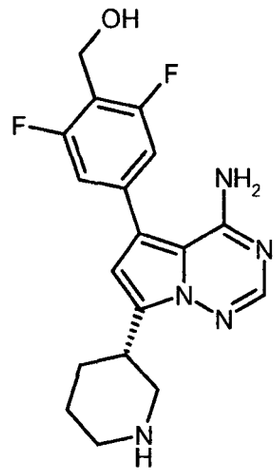
LC-MS (method 6): R_t = 0.55 min; MS (ESIpos): *m/z* (%) = 360.2 (20) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 358.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.67 (m, 2H), 1.83 (m, 1H), 2.75 (m, 1H), 2.86 (m, 1H), 3.20 (d, 1H), 3.41 (m, 2H), 4.53 (m, 2H), 5.29 (t, 1H), 6.70 (s, 1H), 7.11 (m, 1H), 7.94 (s, 1H).

$[\alpha]_{589}^{20}$ = +16.8° (c = 0.515, methanol).

Example 12

(4-{4-Amino-7-[(3*S*)-piperidin-3-yl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}-2,6-difluorophenyl)methanol

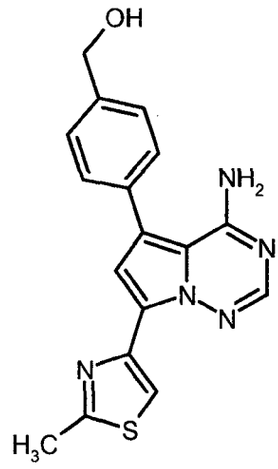


The title compound was obtained from Intermediate 56A (19 mg, 0.04 mmol) by the same method as described for the conversion of Intermediate 55A to Example 11. Yield: 12 mg (81% of th.).

HPLC, LC-MS and ^{1}H-NMR data were identical to those shown for Example 11.

Example 13

{4-[4-Amino-7-(2-methyl-1,3-thiazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}methanol



Intermediate 33A (60 mg, 0.21 mmol) and thioacetamide (15 mg, 0.20 mmol, 0.95 eq.) were dissolved in 1,4-dioxane (2 mL) and refluxed for 4.5 h. After cooling, 4-(hydroxymethyl)phenylboronic acid (38 mg, 0.25 mmol, 1.2 eq.), tetrakis(triphenylphosphine)palladium(0) (59 mg, 0.07 mmol, 0.25 eq.) and 2 M aqueous sodium carbonate solution (0.4 mL) were added. The mixture was gently stirred at 100°C for 16 h. Then, another portion of tetrakis(triphenylphosphine)-palladium(0) (24 mg, 0.1 eq.) was added, and stirring at 100°C was continued for another 4 h. The reaction mixture was then filtered, the filtrate was evaporated under reduced pressure, and the

residue was purified by preparative HPLC (method 2) to give 28 mg (40% of th.) of the title compound as off-white crystals.

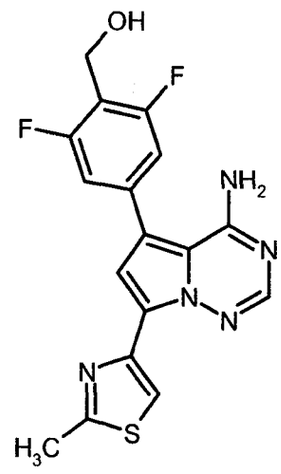
HPLC (method 1): R_t = 3.85 min; HPLC (method 2): R_t = 3.60 min;

LC-MS (method 6): R_t = 0.94 min; MS (ESIpos): *m/z* (%) = 338.2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 336.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.73 (s, 3H), 4.58 (s, 2H), 7.17 (s, 1H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 8.09 (s, 1H), 8.33 (s, 1H).

Example 14

{4-[4-Amino-7-(2-methyl-1,3-thiazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2,6-difluorophenyl}-methanol



The title compound was obtained by general synthetic method 1 from Intermediate 34A (75 mg, 0.24 mmol) and Intermediate 1A (78 mg, 0.29 mmol, 1.2 eq.). Purification of the crude product was carried out by preparative HPLC (method 2). Yield: 27 mg (30% of th.).

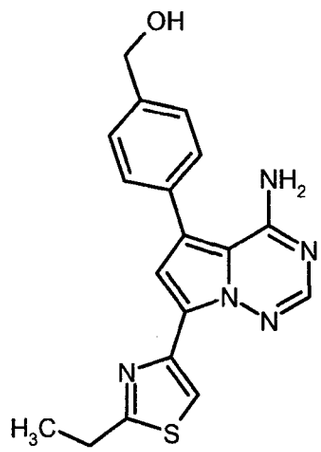
HPLC (method 1): R_t = 3.79 min;

LC-MS (method 6): R_t = 1.03 min; MS (ESIpos): *m/z* (%) = 374.0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 372.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.72 (s, 3H), 4.53 (s, 2H), 7.18-7.27 (m, 2H), 8.11 (s, 1H), 8.33 (s, 1H).

Example 15

{4-[4-Amino-7-(2-ethyl-1,3-thiazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}methanol



Intermediate 35A (91 mg, 0.28 mmol) was reacted with 4-(hydroxymethyl)phenylboronic acid (51 mg, 0.34 mmol, 1.2 eq.) according to general synthetic method 1. The crude product was purified by preparative HPLC (method 2) giving 68 mg (69% of th.) of the title compound as colorless crystals.

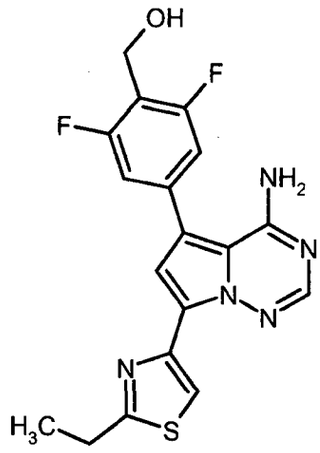
HPLC (method 1): R_t = 3.73 min;

LC-MS (method 6): R_t = 1.05 min; MS (ESIpos): *m/z* (%) = 352.2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 350.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.36 (t, *J* = 7.6 Hz, 3H), 3.06 (q, *J* = 7.6 Hz, 2H), 4.58 (s, 2H), 7.19 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 8.12 (s, 1H), 8.36 (s, 1H).

Example 16

{4-[4-Amino-7-(2-ethyl-1,3-thiazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2,6-difluorophenyl}-methanol



The title compound was obtained by general synthetic method 1 from Intermediate 35A (34 mg, 0.11 mmol) and Intermediate 1A (34 mg, 0.13 mmol, 1.2 eq.). Purification of the crude product was carried out by preparative HPLC (method 2). Yield: 16 mg (40% of th.).

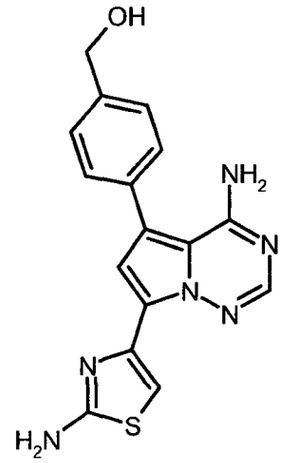
HPLC (method 1): R_t = 4.04 min;

LC-MS (method 6): R_t = 1.15 min; MS (ESIpos): *m/z* (%) = 388.0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 386.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.38 (t, 3H), 3.06 (q, 2H), 4.55 (s, 2H), 7.20-7.31 (m, 3H), 8.16 (s, 1H), 8.38 (s, 1H).

Example 17

{4-[4-Amino-7-(2-amino-1,3-thiazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}methanol



The title compound was obtained by general synthetic method 1 from Intermediate 36A (55 mg, 0.18 mmol) and 4-(hydroxymethyl)phenylboronic acid (32 mg, 0.21 mmol). Purification of the crude product was carried out by preparative HPLC (method 2). Yield: 29 mg (49% of th.).

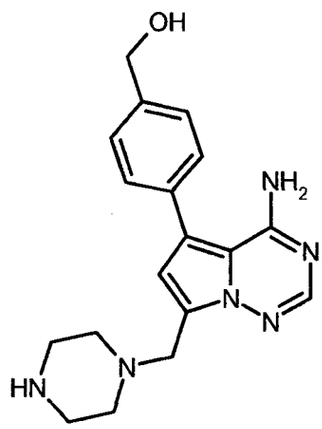
HPLC (method 1): R_t = 3.03 min;

LC-MS (method 5): R_t = 1.21 min; MS (ESIpos): *m/z* (%) = 339.1 (30) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 337.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 4.58 (m, 2H), 5.75 (m, 1H), 6.93 (s, 1H), 7.05 (m, 2H), 7.43 (m, 4H), 7.55 (s, 1H), 8.08 (s, 1H).

Example 18

{4-[4-Amino-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}methanol



Intermediate 37A (200 mg, 0.49 mmol), 4-(hydroxymethyl)phenylboronic acid (90 mg, 0.59 mmol, 1.2 eq.) and tetrakis(triphenylphosphine)palladium(0) (57 mg, 0.05 mmol, 0.1 eq.) were dissolved in a mixture of 1,4-dioxane (4.0 mL) and 2 M aqueous sodium carbonate solution (1.0 mL) in a microwave reactor vial. The reaction vessel was crimp-capped, and the mixture was heated to 140°C for 1 h in a single-mode microwave device. After cooling, the mixture was filtered over a pad of Celite which was rinsed with 1,4-dioxane to elute all organic material. The combined filtrate was evaporated to dryness under reduced pressure, and the residue was purified by preparative HPLC (method 1) to give 75 mg (45% of th.) of the title compound.

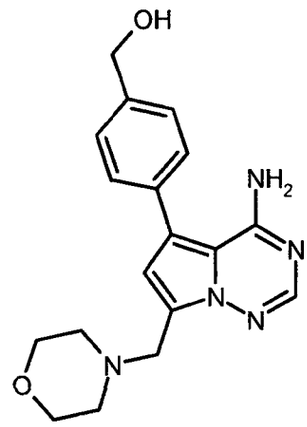
HPLC (method 1): R_t = 2.85 min;

LC-MS (method 4): R_t = 0.93 min; MS (ESIpos): *m/z* (%) = 339.1 (30) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 337.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.38 (br. s, 4H), 2.63 (m, 4H), 3.80 (s, 2H), 4.55 (s, 2H), 5.26 (br. s, 1H), 6.60 (s, 1H), 7.39 (s, 4H), 7.90 (s, 1H).

Example 19

{4-[4-Amino-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}methanol



The title compound was obtained from Intermediate 38A (200 mg, 0.64 mmol) and 4-(hydroxymethyl)phenylboronic acid (116 mg, 0.77 mmol, 1.2 eq.) according to general synthetic method 1. The crude product was purified by preparative HPLC (method 2). The material thus obtained was dissolved in a few mL of a mixture of acetonitrile and water, 2 M aqueous sodium carbonate solution was added, and the mixture was stirred for 10 min. During this time, the title compound precipitated. The crystals were isolated by filtration and dried *in vacuo* to give 95 mg (49% of th.) of a colorless solid.

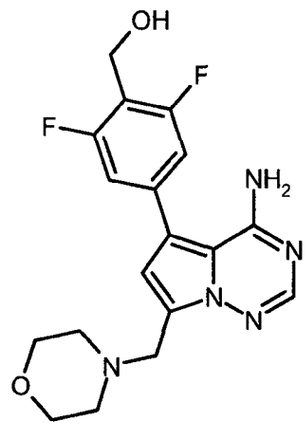
HPLC (method 1): R_t = 3.21 min;

LC-MS (method 4): R_t = 0.93 min; MS (ESIpos): *m/z* (%) = 340 (1) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 338.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.47 (m, 4H), 3.31 (s, 4H), 3.53 (t, 2H), 3.82 (s, 1H), 4.56 (d, 2H), 5.22 (t, 1H), 6.63 (s, 1H), 7.42 (s, 4H), 7.90 (s, 1H).

Example 20

{4-[4-Amino-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2,6-difluorophenyl}-methanol



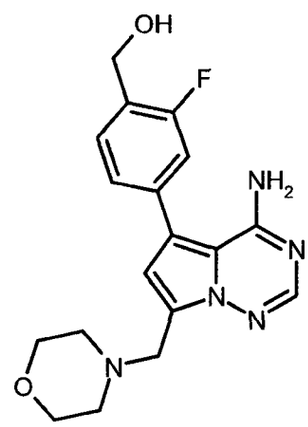
To a solution of Intermediate 40A (110 mg, 0.22 mmol) in THF (2.2 mL) was added 0.45 mL (0.45 mmol) of a 1 M solution of tetrabutylammonium fluoride (TBAF) in THF, and the mixture was stirred at room temperature for 1 h. The reaction mixture was then evaporated under reduced pressure, and the residue was suspended in 3 mL of methanol and stirred at room temperature for 5 min. The resulting precipitate was filtered, washed with a small amount of methanol and dried *in vacuo* to give 68 mg (81% of th.) of the title compound.

LC-MS (method 4): R_t = 1.03 min; MS (ESIpos): *m/z* (%) = 376.0 (80) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 374.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.45 (br. m, 4H), 3.56 (t, 4H), 3.82 (s, 2H), 4.54 (d, 2H), 5.27 (t, 1H), 6.75 (s, 1H), 7.16 (m, 2H), 7.95 (s, 1H).

Example 21

{4-[4-Amino-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluorophenyl}methanol



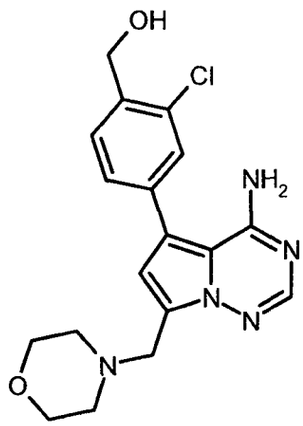
To a suspension of Intermediate 41A (65.0 mg, 0.17 mmol) in THF (2.0 mL) was added 0.2 mL (0.2 mmol) of a 1 M solution of lithium aluminium hydride in THF, and the mixture was stirred at room temperature for 1 h. The resulting solution was quenched with water and then directly purified by preparative HPLC (method 3) to give 35 mg (58% of th.) of the title compound.

LC-MS (method 6): R_t = 0.98 min; MS (ESIpos): *m/z* (%) = 358.1 (20) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 356.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.46 (br. m, 4H), 3.56 (t, 4H), 3.83 (s, 2H), 4.60 (d, 2H), 5.32 (t, 1H), 6.70 (s, 1H), 7.27 (dd, 2H), 7.55 (t, 1H), 7.94 (s, 1H).

Example 22

{4-[4-Amino-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-chlorophenyl}methanol



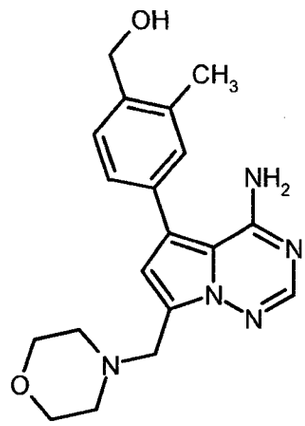
Intermediate 39A (200 mg, 0.56 mmol), Intermediate 3A (112 mg, 0.51 mmol) and tetrakis-(triphenylphosphine)palladium(0) (58 mg, 0.05 mmol) were dissolved in a mixture of 1,4-dioxane (4.0 mL) and 2 M aqueous sodium carbonate solution (1.0 mL) in a microwave reactor vial. The reaction vessel was crimp-capped, and the mixture was heated to 140°C for 1 h in a single-mode microwave device. After cooling, the mixture was filtered, and the filtrate was purified by preparative HPLC (method 3) to give 48 mg (23% of th.) of the title compound.

LC-MS (method 6): R_t = 0.53 min; MS (ESIpos): *m/z* (%) = 374.1 (80) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 372.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.46 (br. m, 4H), 3.56 (t, 4H), 3.83 (s, 2H), 4.61 (d, 2H), 5.45 (t, 1H), 6.70 (s, 1H), 7.44 (dd, 1H), 7.49 (d, 1H), 7.63 (t, 1H), 7.94 (s, 1H).

Example 23

{4-[4-Amino-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-methylphenyl}methanol



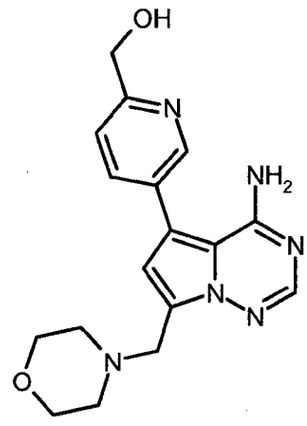
In analogy to the preparation of Example 28, Intermediate 39A (200 mg, 0.56 mmol) was reacted with Intermediate 4A (102 mg, 0.51 mmol) to give 9 mg (5% of th.) of the title compound.

LC-MS (method 4): R_t = 1.00 min; MS (ESIpos): *m/z* (%) = 354.3 (10) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 372.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.30 (s, 3H), 2.45 (br. m, 4H), 3.56 (t, 4H), 3.83 (s, 2H), 4.54 (d, 2H), 5.13 (t, 1H), 6.63 (s, 1H), 7.26 (s, 1H), 7.26 (d, 1H), 7.45 (d, 1H), 7.91 (s, 1H).

Example 24

{5-[4-Amino-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]pyridin-2-yl}methanol



The title compound was obtained from Intermediate 38A (200 mg, 0.64 mmol) and Intermediate 6A (147 mg, 0.96 mmol) by general synthetic method 1. The crude product was purified by pre-

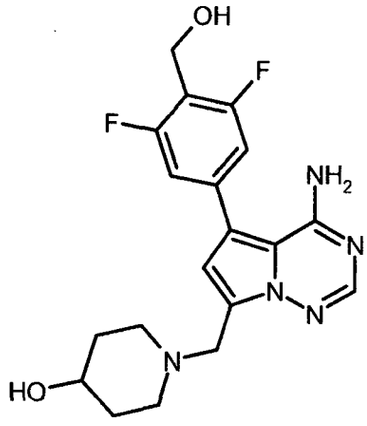
parative HPLC (method 4). Remaining impurities were removed by suspending the product in acetonitrile (2 mL) and collecting the remaining solid by filtration. Yield: 27 mg (12% of th.).

LC-MS (method 4): R_t = 0.78 min; MS (ESIpos): *m/z* (%) = 341 (10) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 339.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.46 (br. m, 4H), 3.56 (t, 4H), 3.84 (s, 2H), 4.62 (d, 2H), 5.46 (t, 1H), 6.73 (s, 1H), 7.54 (d, 1H), 7.86 (dd, 1H), 7.95 (d, 1H), 8.56 (s, 1H).

Example 25

1-({4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}methyl)-piperidin-4-ol



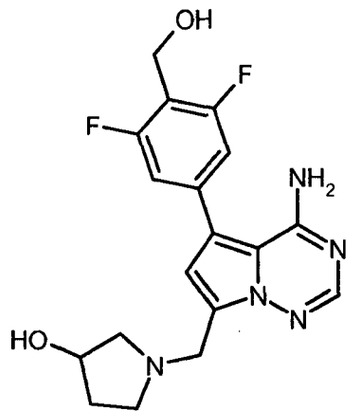
The title compound was obtained from Intermediate 45A (200 mg, 0.61 mmol) and Intermediate 2A (159 mg, 0.74 mmol) by general synthetic method 1. The crude product was purified by preparative HPLC (method 3). Yield: 103 mg (43% of th.).

LC-MS (method 4): R_t = 0.98 min; MS (ESIpos): *m/z* (%) = 390.1 (60) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 388.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.36 (br. m, 2H), 1.68 (br. m, 2H), 2.12 (br. m, 2H), 2.75 (br. m, 2H), 3.41 (br. m, 1H), 3.79 (s, 2H), 4.51 (d, 1H), 4.54 (d, 2H), 5.27 (t, 1H), 6.72 (s, 1H), 7.15 (m, 2H), 7.94 (s, 1H).

Example 26

1-({4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}methyl)-pyrrolidin-3-ol



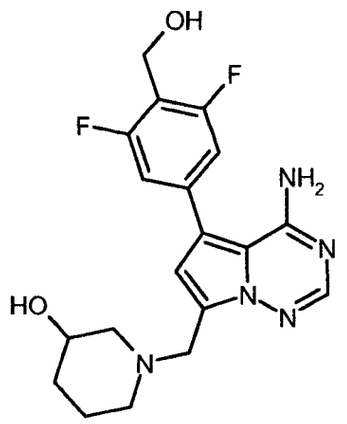
The title compound was obtained from Intermediate 47A (110 mg, 0.35 mmol) and Intermediate 2A (91.3 mg, 0.42 mmol) by general synthetic method 1. The crude product was purified by preparative HPLC (method 3). Yield: 69 mg (52% of th.).

LC-MS (method 4): R_t = 0.25 min; MS (ESIpos): *m/z* (%) = 376.1 (20) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.54 (m, 1H), 1.98 (m, 1H), 2.43 (br. d, 1H), 2.69 (m, 1H), 2.79 (dd, 1H), 3.93 (dd, 2H), 4.18 (br, 1H), 4.53 (d, 2H), 4.69 (d, 1H), 5.27 (t, 1H), 6.75 (s, 1H), 7.16 (m, 2H), 7.95 (s, 1H).

Example 27

1-({4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}methyl)-piperidin-3-ol



To a solution of Intermediate 50A (150 mg, 0.30 mmol) in THF (3.0 mL) was added 0.60 mL (0.60 mmol) of a 1 M solution of tetrabutylammonium fluoride (TBAF) in THF, and the mixture was

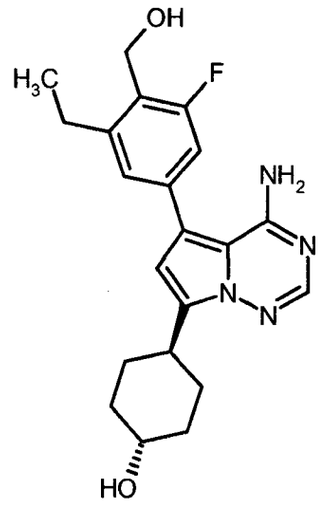
stirred at room temperature for 1 h. The reaction mixture was then concentrated, and the residue was purified by preparative HPLC (method 3) to give 65 mg (56% of th.) of the title compound.

LC-MS (method 7): R_t = 0.33 min; MS (ESIpos): *m/z* (%) = 390.3 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.02 (br. m, 1H), 1.40 (br. m, 1H), 1.60 (br. m, 1H), 1.77 (br. m, 2H), 1.95 (br. m, 1H), 2.73 (br. m, 1H), 2.88 (br. m, 1H), 3.43 (br. m, 1H), 3.83 (br. m, 2H), 4.54 (br. d, 3H), 5.27 (t, 1H), 6.74 (s, 1H), 7.15 (m, 2H), 7.95 (s, 1H).

Example 28

trans-4-{4-Amino-5-[3-ethyl-5-fluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}-cyclohexanol



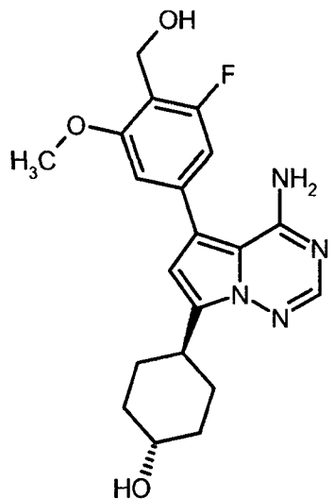
Intermediate 24A (120 mg, 0.39 mmol) and Intermediate 58A (130 mg, 0.46 mmol) were dissolved in acetonitrile (3.0 mL) in a microwave reactor vial and flushed with argon. Tetrakis(triphenylphosphine)palladium(0) (22 mg, 0.02 mmol) and 2.0 M aq. sodium carbonate solution (0.7 mL) were added, and the mixture was heated to 150°C for 1 h in a single-mode microwave device. After cooling, the mixture was filtered, and the filtrate was evaporated. The residue was purified by preparative HPLC (method 2) to give 36 mg (23% of th.) of the title compound.

LC-MS (method 6): R_t = 0.82 min; MS (ESIpos): *m/z* (%) = 385 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 383 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.24 (t, 3H), 1.28-1.38 (m, 2H), 1.46-1.54 (m, 2H), 1.94-1.97 (m, 2H), 2.01-2.05 (m, 2H), 2.82 (q, 2H), 3.03 (m, 1H), 3.47 (m, 1H), 4.53 (m, 2H), 4.61 (d, 1H), 5.02 (t, 1H), 6.58 (s, 1H), 7.08 (d, 1H), 7.15 (s, 1H), 7.90 (s, 1H).

Example 29

trans-4-{4-Amino-5-[3-fluoro-4-(hydroxymethyl)-5-methoxyphenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}cyclohexanol



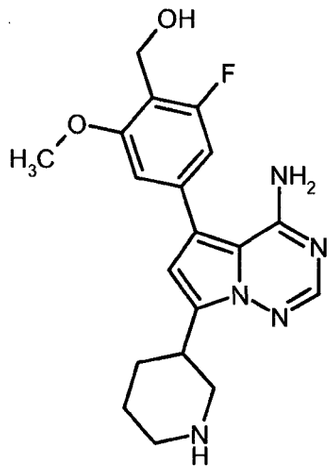
Intermediate 24A (120 mg, 0.39 mmol) and Intermediate 59A (163 mg, 80% purity, 0.46 mmol) were dissolved in acetonitrile (2.0 mL) in a microwave reactor vial and flushed with argon. Tetrakis(triphenylphosphine)palladium(0) (45 mg, 0.04 mmol) and 2.0 M aq. sodium carbonate solution (0.5 mL) were added, and the mixture was heated to 150°C for 1 h in a single-mode microwave device. After cooling, the mixture was filtered, and the filtrate was evaporated. The residue was purified by preparative HPLC (method 2) to give 6 mg (4% of th.) of the title compound.

LC-MS (method 5): R_t = 1.36 min; MS (ESIpos): *m/z* (%) = 387 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 385 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.24-1.33 (m, 2H), 1.42-1.53 (m, 2H), 1.90-1.93 (m, 2H), 2.00-2.04 (m, 2H), 3.04 (m, 1H), 3.46 (m, 1H), 3.82 (s, 3H), 4.48 (m, 2H), 4.60 (d, 1H), 4.83 (t, 1H), 6.60 (s, 1H), 6.85 (d, 1H), 6.90 (s, 1H), 7.91 (s, 1H).

Example 30

{4-[4-Amino-7-(piperidin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluoro-6-methoxyphenyl}-methanol



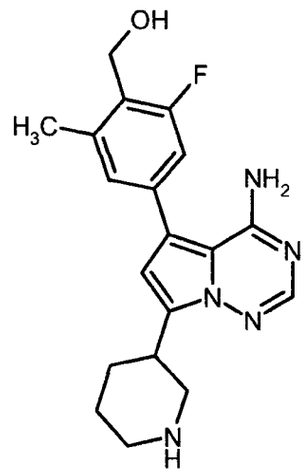
Intermediate 63A (50 mg, 0.11 mmol) was dissolved in a 30% solution of trifluoroacetic acid in dichloromethane (5.0 mL) at 0°C. The reaction mixture was stirred at this temperature for 30 min, then all volatiles were removed by distillation under reduced pressure. The residue was purified by preparative HPLC (method 2). The product thus obtained was dissolved in ethyl acetate and washed with saturated aqueous sodium carbonate solution. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off to give 30 mg (76% of th.) of the title compound.

LC-MS (method 6): R_t = 0.59 min; MS (ESIpos): *m/z* (%) = 372 (10) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 370 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.50-2.08 (m, 4H), 2.94 (m, 2H), 3.17-3.30 (m, 3H), 3.85 (s, 3H), 4.51 (m, 2H), 4.82 (t, 1H), 6.60 (s, 1H), 6.84 (d, 1H), 6.89 (s, 1H), 7.90 (s, 1H).

Example 31

{4-[4-Amino-7-(piperidin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluoro-6-methylphenyl}-methanol



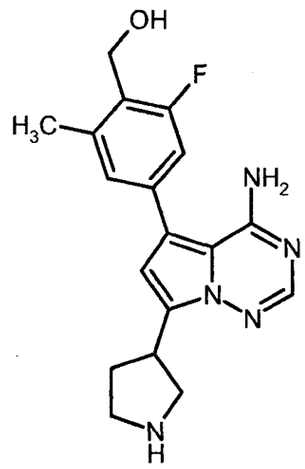
Intermediate 64A (110 mg, 0.21 mmol) was dissolved in a 30% solution of trifluoroacetic acid in dichloromethane (5.0 mL) at 0°C. The reaction mixture was stirred at this temperature for 30 min, then all volatiles were removed by distillation under reduced pressure. The residue was purified by preparative HPLC (method 2). The product thus obtained was dissolved in ethyl acetate and washed with saturated aqueous sodium carbonate solution. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off to give 59 mg (78% of th.) of the title compound.

LC-MS (method 4): R_t = 1.10 min; MS (ESIpos): *m/z* (%) = 356 (40) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 354 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.44-2.08 (m, 4H), 2.42 (s, 3H), 2.94 (m, 2H), 3.17-3.27 (m, 3H), 4.53 (m, 2H), 4.98 (t, 1H), 6.54 (s, 1H), 7.06 (d, 1H), 7.11 (s, 1H), 7.90 (s, 1H).

Example 32

{4-[4-Amino-7-(pyrrolidin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluoro-6-methylphenyl}-methanol



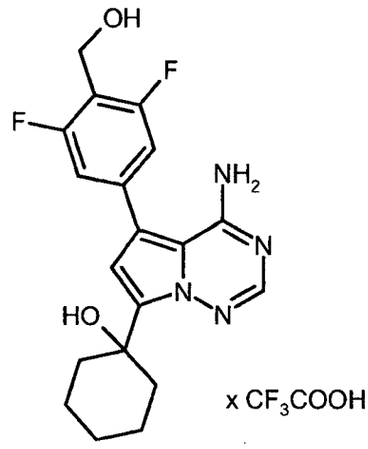
Intermediate 65A (90 mg, 0.17 mmol) was dissolved in a 30% solution of trifluoroacetic acid in dichloromethane (5.0 mL) at 0°C. The reaction mixture was stirred at this temperature for 30 min, then all volatiles were removed by distillation under reduced pressure. The residue was purified by preparative HPLC (method 2). The product thus obtained was dissolved in ethyl acetate and washed with saturated aqueous sodium carbonate solution. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off to give 27 mg (47% of th.) of the title compound.

LC-MS (method 4): R_t = 1.03 min; MS (ESIpos): *m/z* (%) = 342 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 340 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.80-2.21 (m, 2H), 2.43 (s, 3H), 2.78-2.81 (m, 1H), 2.85-3.02 (m, 2H), 3.22-3.27 (m, 1H), 3.63 (m, 1H), 4.55 (br. s, 2H), 4.98 (t, 1H), 6.63 (s, 1H), 7.06 (d, 1H), 7.11 (s, 1H), 7.90 (s, 1H).

Example 33

1-{4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}cyclohexanol trifluoroacetate



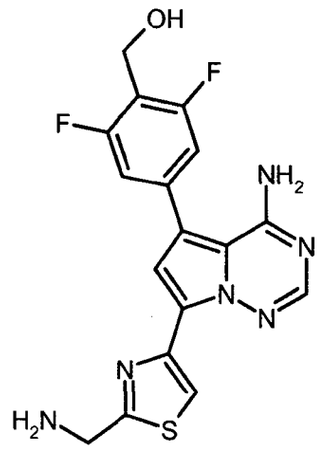
Intermediate 61A (95 mg, 0.31 mmol) and Intermediate 1A (87 mg, 0.32 mmol) were dissolved in DMF (2.0 mL) in a microwave reactor vessel and flushed with argon. Tetrakis(triphenylphosphine)palladium(0) (35 mg, 0.03 mmol) and 2.0 M aq. sodium carbonate solution (0.5 mL) were added, and the mixture was heated to 150°C for 1 h in a single-mode microwave device. After cooling, the mixture was filtered, and the filtrate was directly purified by preparative HPLC (method 2) to give 6 mg (4% of th.) of the title compound.

LC-MS (method 6): R_t = 1.05 min; MS (ESIpos): *m/z* (%) = 375 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 373 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.20-1.33 (m, 1H), 1.42-1.51 (m, 2H), 1.60-1.82 (m, 5H), 2.17-2.28 (m, 2H), 4.51 (s, 2H), 6.76 (s, 1H), 7.17 (m, 2H), 8.02 (s, 1H).

Example 34

(4-{4-Amino-7-[2-(aminomethyl)-1,3-thiazol-4-yl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}-2,6-difluorophenyl)methanol



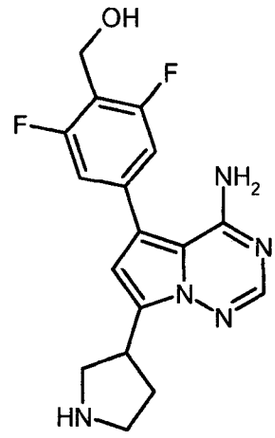
Intermediate 62A (67 mg, 0.16 mmol), Intermediate 1A (51 mg, 0.19 mmol), tetrakis(triphenylphosphine)palladium(0) (18 mg, 0.02 mmol) and 2.0 M aq. sodium carbonate solution (0.94 mL) were dissolved in 1,4-dioxane (2.50 mL) in a microwave reactor vial. The vial was crimp-capped, and the mixture was heated to 140°C for 3 h in a single-mode microwave device. Then, the reaction mixture was filtered, and the filtrate was diluted with acetonitrile and treated with diethyl ether. The resulting precipitate was collected and purified by preparative HPLC (method 2). The product thus obtained (15 mg) was subsequently treated with a 20% solution of trifluoroacetic acid in dichloromethane (2 mL) for 20 min. The volatiles were removed by distillation, and the residue was treated with conc. aqueous sodium carbonate solution and extracted with ethyl acetate. The organic extract was dried over anhydrous sodium sulfate, and the solvent was distilled off to give the title compound (10 mg, 13% of th.) as a colorless solid.

LC-MS (method 4): R_t = 1.12 min; MS (ESIpos): *m/z* (%) = 389 (25) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 387 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, *d*$_6$-DMSO): δ (ppm) = 4.24 (s, 2H), 4.53 (m, 2H), 5.30 (t, 1H), 7.18-7.23 (m, 3H), 8.11 (s, 1H), 8.40 (s, 1H).

Example 35

ent-{4-[4-Amino-7-(pyrrolidin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2,6-difluorophenyl}methanol (*enantiomer 1*)



The title compound was obtained by separation of racemic Example 8 (54 mg) using preparative chiral HPLC [column: Daicel Chiralpak AD-H, 250 mm x 20 mm; eluent: isohexane/ethanol 35:65; flow rate: 20 mL/min; UV detection: 220 nm]. Yield: 12.5 mg.

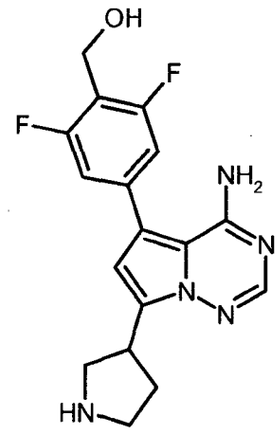
Analytical chiral HPLC [column: Daicel Chiralpak AD-H, 5 µm, 250 mm x 4.6 mm; eluent: isohexane/ethanol 50:50 + 0.2% diethylamine; flow rate: 1.0 mL/min; temperature: 40°C; UV detection: 220 nm]: R_t = 9.452 min, e.e. >99%.

HPLC (method 9): R_t = 0.70 min;

LC-MS (method 10): R_t = 0.42 min; MS (ESIpos): *m/z* (%) = 346.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 344.0 (100) $[M-H]^-$.

Example 36

ent-{4-[4-Amino-7-(pyrrolidin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2,6-difluorophenyl}methanol (*enantiomer 2*)



The title compound was obtained by separation of racemic Example 8 (54 mg) using preparative chiral HPLC [column: Daicel Chiralpak AD-H, 250 mm x 20 mm; eluent: isohexane/ethanol 35:65; flow rate: 20 mL/min; UV detection: 220 nm]. Yield: 14 mg.

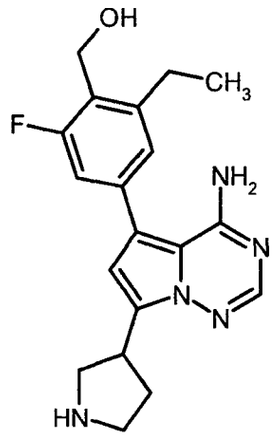
Analytical chiral HPLC [column: Daicel Chiralpak AD-H, 5 µm, 250 mm x 4.6 mm; eluent: isohexane/ethanol 50:50 + 0.2% diethylamine; flow rate: 1.0 mL/min; temperature: 40°C; UV detection: 220 nm]: R_t = 13.695 min, e.e. >99%.

HPLC (method 9): R_t = 0.71 min;

LC-MS (method 10): R_t = 0.42 min; MS (ESIpos): *m/z* (%) = 346.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 344.0 (100) $[M-H]^-$.

Example 37

rac-{4-[4-Amino-7-(pyrrolidin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-ethyl-6-fluorophenyl}-methanol



Intermediate 66A (72 mg, 0.158 mmol) was dissolved in dichloromethane (3.8 mL) at 0°C and trifluoroacetic acid (1.0 mL) was added. The reaction mixture was stirred at 0°C for 40 min, then all volatiles were removed under reduced pressure. The residue was purified by preparative HPLC (method 6). The combined product containing fractions were adjusted to basic pH using saturated aqueous sodium carbonate solution and concentrated to dryness. The resulting residue was suspended in ethyl acetate (50 mL) and filtered. The organic layer was washed with brine (5 mL), dried over anhydrous sodium sulfate, and the solvent was distilled off to give 31 mg (56% of th.) of the title compound.

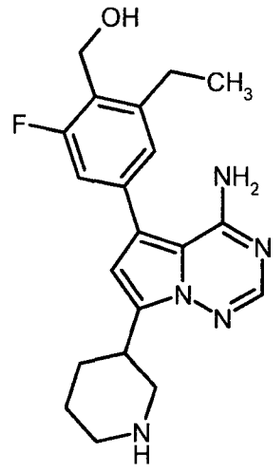
HPLC (method 9): R_t = 0.81 min;

LC-MS (method 10): R_t = 0.55 min; MS (ESIpos): *m/z* (%) = 356.3 (50) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 354.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.23 (t, 3H), 1.84-2.24 (m, 1H), 2.81 (q, 2H), 2.80-2.99 (m, 1H), 3.00-3.72 (m, 1H), 4.56 (d, 2H), 5.00 (t, 1H), 6.68 (s, 1H), 7.09 (d, 1H), 7.14 (m, 2H), 7.92 (s, 1H).

Example 38

rac-{4-[4-Amino-7-(piperidin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-ethyl-6-fluorophenyl}-methanol



Intermediate 67A (108 mg, 0.230 mmol) was dissolved in dichloromethane (5.2 mL) at 0°C and trifluoroacetic acid (1.4 mL) was added. The reaction mixture was stirred at 0°C for 40 min, then all volatiles were removed under reduced pressure. The residue was purified by preparative HPLC (method 6). The combined product containing fractions were adjusted to basic pH using saturated aqueous sodium carbonate solution and concentrated to dryness. The resulting residue was suspended in ethyl acetate (50 mL) and filtered. The organic layer was washed with brine (5 mL), dried over anhydrous sodium sulfate, and the solvent was distilled off to give 83 mg (85% of th.) of the title compound.

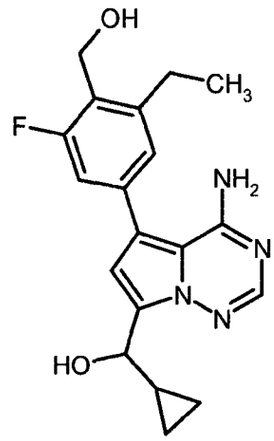
HPLC (method 9): R_t = 0.81 min;

LC-MS (method 10): R_t = 0.58 min; MS (ESIpos): *m/z* (%) = 370.3 (50) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 368.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.22 (t, 3H), 1.51-1.72 (m, 2H), 2.00-2.10 (m, 1H), 2.51-2.65 (m, 2H), 2.81 (q, 2H), 2.95-3.03 (m, 1H), 3.20-3.27 (m, 1H), 4.56 (d, 2H), 5.00 (t, 1H), 6.60 (s, 1H), 7.07 (d, 1H), 7.14 (m, 2H), 7.91 (s, 1H).

Example 39

rac-{4-Amino-5-[3-ethyl-5-fluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}-(cyclopropyl)methanol



Intermediate 17A (83 mg, 0.29 mmol), Intermediate 58A (98 mg, 0.35 mmol) and tetrakis(triphenylphosphine)palladium(0) (17 mg, 0.015 mmol) were dissolved in a mixture of acetonitrile (2.3 mL) and 2 M aqueous sodium carbonate solution (0.53 mL) in a microwave reactor vial. After degassing for 5 min using argon, the reaction vessel was crimp-capped, and the mixture was heated to 150°C for 1 h in a single-mode microwave device. After cooling to room temperature, saturated aqueous sodium bicarbonate solution was added, and the mixture was extracted three times with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by preparative HPLC (method 5) to give the title compound. Yield: 63 mg (61% of th.).

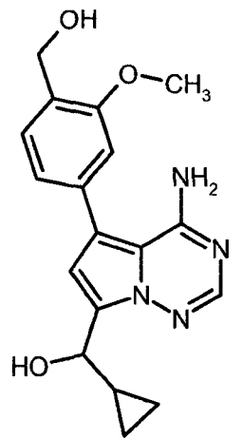
HPLC (method 9): R_t = 1.13 min;

LC-MS (method 10): R_t = 0.78 min; MS (ESIpos): *m/z* (%) = 357.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 355.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.39 (m, 3H), 0.48 (m, 1H), 1.23 (t, 3H), 1.35 (m, 1H), 2.81 (q, 2H), 4.56 (d, 2H), 4.68 (m, 1H), 5.01 (m, 1H), 5.21 (m, 1H), 6.76 (s, 1H), 7.09 (d, 1H), 7.14 (s, 1H), 7.90 (s, 1H).

Example 40

rac-{4-Amino-5-[4-(hydroxymethyl)-3-methoxyphenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}(cyclopropyl)methanol

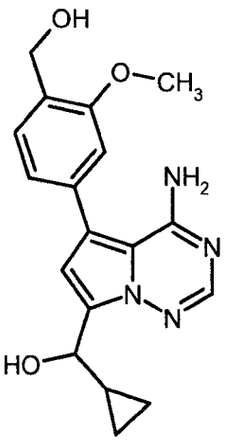


Intermediate 68A (130 mg, 0.353 mmol) was dissolved in tetrahydrofuran (6.9 mL) and cooled to 0°C. Lithium aluminium hydride solution (1 M in diethylether, 0.78 mL) was added dropwise, and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was then quenched with water and filtered. The filtrate was concentrated, and the residue was purified by preparative HPLC (method 8) to give the title compound. Yield: 63 mg (51% of th.).

LC-MS (method 10): R_t = 0.62 min; MS (ESIpos): *m/z* (%) = 341.2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 339.1 (100) $[M-H]^-$.

Example 41

ent-4-Amino-5-[4-(hydroxymethyl)-3-methoxyphenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}(cyclopropyl)methanol (*enantiomer 1*)



The title compound was obtained by separation of racemic Example 40 (63 mg) using preparative chiral HPLC [column: Daicel Chiralpak IC, 5 µm, 250 mm x 20 mm; eluent: *tert*-butyl methyl ether/methanol 85:15; flow rate: 15 mL/min; temperature: 40°C; UV detection: 220 nm]. Yield: 17 mg.

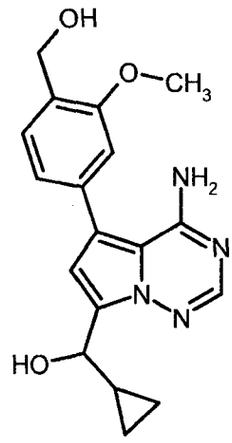
Analytical chiral HPLC [column: Daicel Chiralpak IC, 5 µm, 250 mm x 4.6 mm; eluent: *tert*-butyl methyl ether/methanol 85:15; flow rate: 1.0 mL/min; temperature: 40°C; UV detection: 220 nm]: R_t = 4.76 min, e.e. >99%.

LC-MS (method 10): R_t = 0.67 min; MS (ESIpos): *m/z* (%) = 341.2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 339.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.40 (m, 3H), 0.48 (m, 1H), 1.36 (m, 1H), 3.83 (s, 3H), 4.54 (d, 2H), 4.68 (m, 1H), 5.07 (t, 1H), 5.25 (d, 1H), 6.74 (s, 1H), 7.00 (s, 1H), 7.03 (d, 1H), 7.47 (d, 1H), 7.89 (s, 1H).

Example 42

ent-4-Amino-5-[4-(hydroxymethyl)-3-methoxyphenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}(cyclopropyl)methanol (*enantiomer 2*)



The title compound was obtained by separation of racemic Example 40 (63 mg) using preparative chiral HPLC [column: Daicel Chiralpak IC, 5 µm, 250 mm x 20 mm; eluent: *tert*-butyl methyl ether/methanol 85:15; flow rate: 15 mL/min; temperature: 40°C; UV detection: 220 nm]. Yield: 25 mg.

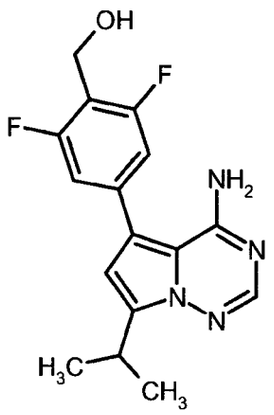
Analytical chiral HPLC [column: Daicel Chiralpak IC, 5 µm, 250 mm x 4.6 mm; eluent: *tert*-butyl methyl ether/methanol 85:15; flow rate: 1.0 mL/min; temperature: 40°C; UV detection: 220 nm]: R_t = 6.37 min, e.e. >99%.

LC-MS (method 10): R_t = 0.67 min; MS (ESIpos): *m/z* (%) = 341.2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 339.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.40 (m, 3H), 0.48 (m, 1H), 1.36 (m, 1H), 3.83 (s, 3H), 4.54 (d, 2H), 4.68 (m, 1H), 5.07 (t, 1H), 5.25 (d, 1H), 6.74 (s, 1H), 7.00 (s, 1H), 7.03 (d, 1H), 7.47 (d, 1H), 7.89 (s, 1H).

Example 43

[4-(4-Amino-7-isopropylpyrrolo[2,1-f][1,2,4]triazin-5-yl)-2,6-difluorophenyl]methanol



Intermediate 71A (181 mg, 0.709 mmol), Intermediate 1A (239 mg, 0.887 mmol) and tetrakis(triphenylphosphine)palladium(0) (41 mg, 0.035 mmol) were dissolved in a mixture of *N,N*-dimethylformamide (12.5 mL) and 2 M aqueous sodium carbonate solution (1.42 mL) in a microwave reactor vial. The reaction vessel was crimp-capped, and the mixture was heated to 130°C for 2 h in a single-mode microwave device. After cooling to room temperature, the reaction mixture was filtered through Celite and concentrated. The resulting residue was dissolved in ethyl acetate (100 mL) and washed with water and with brine (10 mL each). The organic layer was dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (puriFlash, Interchim, cyclohexane/ethyl acetate 1:1 to 100% ethyl acetate gradient) followed by preparative HPLC (method 6). The product containing fractions were combined and adjusted to basic pH using saturated aqueous sodium carbonate solution. The acetonitrile solvent was removed, and the precipitated product was collected by filtration. Yield: 69 mg (31% of th.).

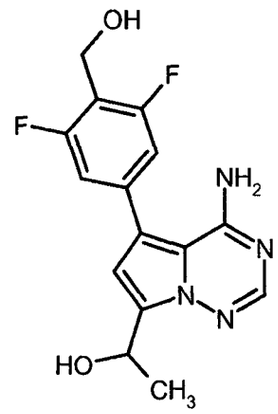
HPLC (method 9): R_t = 1.35 min;

LC-MS (method 10): R_t = 0.90 min; MS (ESIpos): *m/z* (%) = 319.0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 317.0 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.30 (d, 6H), 3.42 (m, 1H), 4.54 (s, 2H), 5.26 (s, 1H), 6.65 (s, 1H), 7.14 (m, 2H), 7.94 (s, 1H).

Example 44

rac-1-{4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}-ethanol



Intermediate 72A (230 mg, 0.743 mmol), Intermediate 2A (192 mg, 0.89 mmol) and tetrakis(triphenylphosphine)palladium(0) (86 mg, 0.074 mmol) were dissolved in a mixture of 1,4-dioxane (4.6 mL) and 2 M aqueous sodium carbonate solution (1.16 mL) in a microwave reactor vial. The reaction vessel was crimp-capped, and the mixture was heated to 140°C for 1 h in a single-mode microwave device. After cooling to room temperature, the reaction mixture was purified by preparative HPLC (method 8) to yield 48 mg of material which was further purified by preparative HPLC (method 9). Yield: 11 mg (4.6% of th.).

LC-MS (method 5): R_t = 0.89 min; MS (ESIpos): *m/z* (%) = 321.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 319.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.47 (d, 3H), 4.54 (m, 2H), 5.16-5.39 (m, 2H), 6.74 (s, 1H), 6.88 (m, 1H), 7.14 (m, 2H), 7.94 (s, 1H).

B. Evaluation of Biological Activity

Abbreviations and Acronyms:

ATCC	American Type Culture Collection
ATP	adenosine triphosphate
Bq	Bequerel
BrdU	5-bromo-2-deoxyuridine
BSA	bovine serum albumin
CHO	chinese hamster ovary
cpm	counts per minute
Ct	cycle threshold
DMEM/F12	Dulbecco's modified Eagle's medium / Ham's F12 medium (1:1)
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DTT	dithiothreitol
EDTA	ethylenediamine-tetraacetic acid
ENGS MV	microvascular endothelial cell culture medium
FAM	carboxyfluorescein succinimidyl ester
FCS	fetal calf serum
hBMP9	human bone morphogenic factor 9
HEPES	4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid
HMVEC	human microvascular endothelial cell(s)
HPMC	hydroxypropyl methyl cellulose
HTRF	homogeneous time resolved fluorescence
HUVEC	human vascular endothelial cell(s)
[I]	inhibitor concentration
IC_{50}	concentration with 50% inhibitory effect
LDH	lactate dehydrogenase
mRNA	messenger ribonucleic acid
NADH	nicotinamide adenine dinucleotide
Nonidet P40	4-ethylphenoxy-poly(ethyleneglycol)ether (*n = 11*)
PBS	phosphate buffered saline
PE	polyethylene
PEG	polyethylene glycol
PK	pyruvate kinase
p.o.	*per os*

qPCR	quantitative polymerase chain reaction
RNA	ribonucleic acid
RTL buffer	RNeasy lysis buffer
SEQ ID NO	sequence identity number
SFM	serum free medium
TAMRA	carboxytetramethylrhodamine
Tris	2-amino-2-hydroxymethylpropane-1,3-diol
Triton X-100	4-*tert*-octylphenoxy-poly(ethyleneglycol)ether (*n = 10*)

Demonstration of the activity of the compounds of the present invention may be accomplished through *in vitro, ex vivo*, and *in vivo* assays that are well known in the art. For example, to demonstrate the activity of the compounds of the present invention, the following assays may be used.

B-1a. *In vitro* enzyme inhibition using scintillation of incorporated radio label (flashplate assay)

Test principle:

Test compounds diluted in DMSO are mixed with a suitable substrate / co-substrate (here: biotinylated α-casein and ^{33}P-ATP) in a corresponding assay buffer. Addition of the enzyme of interest (here: ALK1 kinase) starts the enzyme reaction. The enzyme-catalyzed incorporation of radio label into the substrate is measured via scintillation. Incorporated radio label is separated from free radio label via specific binding of the biotinylated substrate to strepavidin-coated microtiter plates (flashplates) and concomitant washing steps. The scintillation signal intensity (counts per minutes, cpm) is proportional to the enzyme activity. Enzyme inhibition results in a decreased signal intensity. IC_{50} values of the test compounds are determined by cpm-versus-[I] plots.

Reaction buffer:

Reaction buffer contains 50 mM Tris pH 8.0 (Sigma), 1 mM $MnCl_2$ (Sigma), 0.01% Nonidet P40 (Fluka), 0.5 x Complete EDTA-free protease inhibitors (Roche; contains a mixture of several protease inhibitors for the inhibition of serine and cysteine (but not metallo-) proteases; 1 tablet contains protease inhibitors sufficient for a 50 ml cell extract; the concentration used in this assay corresponds to 1 tablet in 100 ml).

Other buffers:

1.) Stop solution: Dulbecco's PBS (PAA, Pasching, Austria), 25 mM EDTA (Sigma), 25 µM ATP (Roche), 0.05% Triton X-100 (Sigma);

2.) Saturation buffer: Dulbecco's PBS (PAA, Pasching, Austria), 100 µM ATP (Roche), 0.2% Triton X-100 (Sigma);

3.) Wash buffer: Dulbecco's PBS (PAA, Pasching, Austria).

Enzyme solution:

ALK1 (Invitrogen, Paisley, United Kingdom) stock solution (35.7 ng/µl) is diluted to 4 ng/µl; final concentration in the reaction is 1 ng/µl.

Substrate solution:

Dephosphorylated α-casein (Sigma) is biotinylated according to the manufacturer's protocol (Pierce, Bonn, Germany) resulting in a stock solution of 61.6 µM. Briefly, EZ-Link® Sulfo-NHS-Biotin reagent (sulfosuccinimidyl-6-(biotinamido)hexanoate; Pierce, Bonn, Germany) is added in equal molarity to α-casein and incubated on ice for 2 h. Afterwards, the biotin reagent is removed by dialysis (2 x 2 h and overnight).

A 100 mM solution of cold (unlabelled) ATP (Roche) is diluted 1:100 before each test. For the substrate mix, α-casein is diluted to 2.22 µM resulting in a final concentration of 1 µM α-casein in the reaction. Additionally, cold ATP is added to give a 1.11 µM solution which results in a final concentration of 500 nM in the reaction.

Radioactive ATP solution:

The stock solution (9.25 MBq/25 µl of ^{33}P-ATP; Perkin Elmer, Rodgau, Germany) is diluted to 651.2 Bq/µl. This corresponds to a final concentration of 162.8 Bq/µl.

Compound solution:

Compounds are dissolved in 100% DMSO (10 mM stock solution) and diluted to 2 mM. Further dilutions are made stepwise 1:3.16 in DMSO.

Step-by-step protocol:

A volume of 9 µl substrate solution is provided into each well of a 384 well microtiter plate (Greiner Bio-One, Solingen, Germany). 1 µl compound solution and 5 µl of the radioactive ATP solution are added. Enzyme reaction starts with addition of 5 µl of enzyme solution. The mixture is incubated for 60 minutes at room temperature and then stopped by addition of 10 µl stop solution. The 384 well microtiter flashplates (Perkin Elmer, Rodgau, Germany) are saturated with 50 µl saturation buffer per well for at least 60 minutes. Subsequently, a volume of 20 µl is discarded and replaced with 20 µl of the stopped ALK1 reaction mixture. Binding of biotinylated substrate to the flashplate is allowed for by overnight incubation at room temperature. Bound substrate is separated

from unbound components through repeated washing steps (3 x 50 µl washing buffer per well). Finally, 50 µl washing buffer is added, and the scintillation signal (cpm) is measured in a suitable counter (Perkin Elmer, Rodgau, Germany).

IC_{50} values for individual compounds of the present invention are listed in Table 1 below:

Table 1

Example No.	ALK1 IC_{50} [nM]
1	2.0
2	2.8
3	4.0
4	1.0
5	1.3
6	40
7	2.0
8	4.4
9	5.7
10	8.0
11	1.9
12	5.9
13	4.0
14	5.3
15	60
16	2.6
17	2.0
18	80
19	19
20	30
21	25

Example No.	ALK1 IC_{50} [nM]
22	17
23	30
24	140
25	65
26	30
27	70
28	170
29	1.0
30	2.0
31	4.0
32	4.0
33	15
34	4.1
40	3.2
41	3.5
42	1.2
43	1.9
44	3.8

B-1b. <u>ALK1 kinase assay (ProQinase protocol)</u>

ALK1 (Invitrogen, Carlsbad, CA, USA) kinase activity was measured at ProQinase GmbH (Freiburg, Germany) in a radiometric assay using γ-^{33}P-ATP and casein (Sigma, St. Louis, MO, USA) as substrate in 96-well PerkinElmer FlashPlates™ (Boston, MA, USA). The compounds were tested at 10 concentrations in the range of 1 x 10^{-4} M to 3 x 10^{-9} M in a total volume of 50 µl with a final DMSO concentration of 1% each. The assay components were mixed in the order:

- 20 µl assay buffer (70 mM HEPES-NaOH, pH 7.5, 3 mM $MgCl_2$, 3 mM $MnCl_2$, 2 µM sodium orthovanadate, 1.2 mM DTT);

- 5 µl γ-^{33}P-ATP (1.0 µM in water, approx. 6 x 10^5 cpm per well);
- 5 µl test compound solution (in 10% DMSO);
- 10 µl substrate (200 µg/ml, 1.0 µg/50 µl final concentration) / enzyme (4 µg/ml, 20 ng/50 µl = 5.5 nM final concentration) solution (1:1 mixture).

The reaction mixtures were incubated at 30°C for 60 minutes and stopped by adding 50 µl 2% (v/v) phosphoric acid. The plates were aspirated and washed twice with 200 µl 0.9% (w/v) sodium chloride. Incorporation of $^{33}P_i$ was determined with a microplate scintillation counter (Microbeta, Wallac). All assays were performed using a BeckmanCoulter/SAGIAN™ Core System.

Median values obtained from unspecific substrate binding of labelled ATP were set as background level, while median values measured in the absence of any inhibitor were considered to reflect full activity of ALK1 kinase. The background activity (ba) was subtracted from the full activity (fa) value as well as from the values obtained from the test compound containing samples (test compound activity, tca). The residual activity in the latter was calculated as follows:

residual activity (%) = 100 x [(tca-ba)/(fa-ba)]

The residual activities for each concentration and the compound IC_{50} values were calculated using Quattro Workflow V3.1.0 (Quattro Research GmbH, Munich, Germany). The fitting model for the IC_{50} determinations was "Sigmoidal response (variable slope)" with parameters "top" fixed at 100% and "bottom" at 0%. The fitting method used was a least-squares fit.

Representative IC_{50} values from this assay are listed in Table 2 below:

Table 2

Example No.	ALK1 IC_{50} [nM]
7	6.7
11	3.0
28	124
35	6.9
36	21
37	< 3
38	4.0

Example No.	ALK1 IC_{50} [nM]
39	5.7

B-2a. Smad7 target gene induction: HMVEC cell assay and TaqMan expression analysis

Activation of ALK1 receptors by BMP9 induces the Smad1/5 signalling pathway and enhances expression of target genes Smad6, Smad7 and Id-1. Induction of Smad7-mRNA in BMP9-stimulated endothelial cells was determined to monitor the cellular potency of ALK1 kinase inhibitors.

Human microvascular endothelial cells (HMVECadult, Cell Systems, St. Katharinen) were seeded in complete ENGS MV medium with all supplements (LifeLine Cell Technology) in 96 well plates with 10 000 cells per well. After 4 h incubation at 37°C and 7.5% CO_2 in a humidified incubator, medium was replaced with minimal medium (ENGS MV without supplements containing 0.02% FCS). After 16 h, test compounds or medium (controls) were added to the cultures, followed 30 min later by addition of hBMP9 (R&D Systems). Medium was removed 1 to 4 h later, plates were gently washed with phosphate-buffered saline, and cells were lysed with 150 µl per well of ice-cold RLT buffer (Qiagen).

Total cellular RNA was isolated with the Trizol® reagent protocol according to the manufacturer's specifications (Invitrogen, USA) and treated with DNAseI to remove genomic DNA contamination.

For relative quantitation of the mRNA distribution of hSmad7, total RNA from each sample was first reverse-transcribed using the ImProm-II Reverse Transcription System (Promega, USA) according to the manufacturer's protocol. The final volume was adjusted to 200 µl with water.

For relative quantitation of selected mRNA, the Applied Bioscience ABI 7900HT Sequence Detection System was used according to the manufacturer's specifications and protocols. PCR reactions were set up to quantitate hSmad7- and the housekeeping gene L32-mRNA. Forward and reverse primers and probes for hSmad7 and L32 were designed using the Applied Bioscience ABI Primer Express™ software and were synthesized by Eurogentec (Belgium). The hSmad7 forward primer sequence was: Primer 1 (SEQ ID NO 1). The hSmad7 reverse primer sequence was: Primer 2 (SEQ ID NO 2). Probe 1 (SEQ ID NO 3), labelled with FAM as the reporter dye and TAMRA as the quencher, was used as a probe for hSmad7. The L32 forward primer sequence was: Primer 3 (SEQ ID NO 4). The L32 reverse primer sequence was: Primer 4 (SEQ ID NO 5). Probe 2 (SEQ ID NO 6), labelled with FAM as the reporter dye and TAMRA as the quencher, was used as a probe for L32.

SEQ ID list:

		5' to 3'
SEQ ID NO 1	hSmad7 primer 1 (forward primer)	CCCTCCTTACTCCAGATACCC
SEQ ID NO 2	hSmad7 primer 2 (reverse primer)	GGAGGAAGGCACAGCATCT
SEQ ID NO 3	hSmad7 probe 1	TTTTCTCAAACCAACTGCAGACTGTCC
SEQ ID NO 4	L32 primer 3 (forward primer)	AAGTTCATCCGGCACCAGTC
SEQ ID NO 5	L32 primer 4 (reverse primer)	TGGCCCTTGAATCTTCTACGA
SEQ ID NO 6	L32 probe 2	CCCAGAGGCATTGACAACAGGG

The following reagents were prepared in a total of 20 µl added per well: 1 x qPCR-MasterMix (Eurogentec, Belgium) and hSmad7 forward and reverse primers each at 200 nM, 200 nM hSmad7 FAM/TAMRA-labelled probe 1 (SEQ ID NO 3), and 5 µl of template cDNA. Correspondingly, a second mix in a total of 20 µl was prepared using L32 FAM/TAMRA-labelled probe 2 (SEQ ID NO 6) and L32 forward and reverse primers added per well in parallel samples.

Thermal cycling parameters were 2 min at 50°C, followed by 10 min at 95°C, followed by 40 cycles of melting at 95°C for 15 sec and annealing/extending at 60°C for 1 min.

Calculation of relative expression:

The Ct (cycle threshold) values were calculated from the turning point of PCR product quantity curves by the ΔΔCt method (delta-delta Ct):

$\Delta Ct = Ct_{hSmad7} - Ct_{L32}$; relative expression = $2^{(15-\Delta Ct)}$.

IC_{50} values of test compounds were calculated on basis of relative Smad7 expressions at different compound concentrations. Representative values are listed in Table 3 below:

Table 3

Example No.	**hSmad7 IC_{50} [nM]**
1	100

Example No.	hSmad7 IC_{50} [nM]
2	125
3	180
5	150
7	130
8	60
11	90
17	120
20	4400
21	6000
22	800

B-2b. Smad7 target gene induction: HUVEC cell assay and TaqMan expression analysis

The *in vitro* potency of ALK1 inhibitors was tested in a cell-based assay. Bone morphogenetic protein 9 (BMP9) induces Smad7 mRNA expression in human vascular endothelial cells (HUVEC) via activation of ALK1.

1.5×10^4 passage 2 HUVECs (Lonza, Basel, Switzerland) per well were seeded in a 96-well plate in EBM-2 medium containing EGM-2 additives and growth factors (Lonza, CC-3156 and CC-4176). After 4 h, the medium was changed to EBM-2 with 0.2% fetal calf serum (FCS) and the cells were starved for 20 h in a humidified incubator at 37°C, 5% CO_2. Test compounds were added at 11 different concentrations between 0 and 10 000 nM one hour prior to stimulation of the cells for 3 h with recombinant human BMP9 protein at 1 ng/ml (dissolved in 4 mM hydrochloric acid, 0.1% BSA at 10 µg/ml; R&D Systems, Minneapolis, MN, USA, 3209BP). Medium was removed, and the cells were lysed in 100 µl RLT buffer (Qiagen, Hilden, Germany). RNA was isolated using the Qiagen RNeasy 96 Kit (order-No. 74182) according to manufacturer's instructions and eluted from the columns with 65 µl RNAse-free water. Reverse transcription for quantitative RT-PCR was carried out with the Omniscript Kit (Qiagen, 205113) in RNAse-free 96-well round-bottom plates. Per well, 6.8 µl of a reaction master mix containing 2 µl 10x RT-buffer, 2 µl dNTPs (5 mM each), 1.6 µl random primer N6 (125 µM), 0.25 µl Rnase Out (40 U/µl) and 1 µl Omniscript Reverse Transcriptase were added. After addition of 13.2 µl of the RNA/water mixture, plate

contents were mixed, incubated for 1 h at 37°C and the total volume adjusted to 100 µl in each well by addition of 80 µl RNAse-free water.

The quantification of human Smad7 mRNA was carried out on a TaqMan using the Eurogentec qPCR Mastermix Plus (RT-QP2X-03-075+; Cologne, Germany) and employing human L32 as housekeeping reference mRNA. Per qPCR reaction, 2.8 µl primer mix, 10 µl master mix, 2.2 µl water and 5 µl cDNA were added. Thermal cycling parameters were 2 min at 50°C, followed by 10 min at 95°C, followed by 40 cycles of melting at 95°C for 15 sec and annealing/extending at 60°C for 1 min.

Smad7 mRNA levels induced by 1 ng/ml BMP9 without the addition of any inhibitor were set at 100% induction, and % inhibition was calculated for each test compound with this value. For each test compound, every value was determined in quadruplicate. The IC_{50} values were determined using Microsoft Excel. The fitting method used was a weighted, unconstrained ML-fit.

Representative IC_{50} values from this assay are listed in Table 4 below:

Table 4

Example No.	**hSmad7 IC_{50} [nM]**
1	94
2	160
3	120
5	290
7	140
11	180
17	290
20	5900
21	790
22	3100
30	51
37	330
39	500

Example No.	hSmad7 IC_{50} [nM]
40	62
41	77
42	6.6
43	27

B-3. Systemic efficacy in the laser-induced choroidal neovascularization (CNV) model

The aim of this study was to determine whether once daily systemic administration (i.p.) of a test compound resulted in a decrease of vascular leakage and/or choroidal neovascularization in a rat model of laser-induced choroidal neovascularisation.

For this purpose, 16 pigmented Brown-Norway rats with no visible sign of ocular defects were selected and randomly divided into two groups of eight animals each. On day 0, the animals were anaesthetized by an intraperitoneal injection (15 mg/kg xylazine and 80 mg/kg ketamine). After instillation of one drop of 0.5% tropicamide to dilate the pupils, choroidal neovascularisation was induced by executing six 75 µm-sized choroidal burns around the optic disc of the right eyes using a 532 nm argon laser photocoagulation at 150 mW for 100 ms. The test compound and vehicle control (10% ethanol, 90% PEG 400) were administered once daily by intraperitoneal (i.p.) injections with dosing of the test compound at 50 mg/kg on days 0 and 1, and then continuing with 20 mg/kg from day 2 to day 23. The body weight of all animals was recorded before the start and once daily during the study.

An angiography was performed on day 21 using Heidelberg's Retinal Angiograph (HRA). After anaesthesia and pupillary dilation, 10% sodium fluorescein dye was injected subcutaneously, and images were recorded 10 min after dye injection. The vascular leakage of the fluorescein on the angiograms was evaluated by two examiners in a masked fashion and scored with 0 (no leakage) to 3 (strongly stained).

After euthanasia on day 23, the eyes were harvested and fixed in 4% paraformaldehyde solution for 1 hour at room temperature. After washing, the retina was carefully peeled, and the sclera-choroid was flat-mounted and incubated after blocking with a FITC-isolectine B4 antibody. The flat-mounted preparations were examined under a fluorescence microscope (Apotom) at 488 nm excitation wavelength. The volume of choroidal neovascularisation was scored by morphometric analysis of images using Axiovision 4.6 software.

For Example 11 as a representative of the compounds of the present invention, the following results were obtained in this model:

	vascular leakage [angiography score]	**choroidal neovascularisation lesion volume** [μm^3 x 100 000]
Example 11	0.68 ± 0.35	3.48 ± 0.40
vehicle control	1.7 ± 0.32	5.83 ± 0.55

B-4. Topical efficacy in the laser-induced choroidal neovascularization (CNV) model

The aim of this study was to determine whether twice daily topical administration (eye drops) of a test compound resulted in a decrease of vascular leakage and/or choroidal neovascularization in a rat model of laser-induced choroidal neovascularisation.

For this purpose, 65 pigmented Brown-Norway rats with no visible sign of ocular defects were selected and randomly assigned to six different groups (for n-numbers, see table below). On day 0, the animals were anaesthetized by an intraperitoneal injection (15 mg/kg xylazine and 80 mg/kg ketamine). After instillation of one drop of 0.5% tropicamide to dilate the pupils, choroidal neovascularisation was induced by burning six holes into the retina (disruption of Bruch's membrane) of one eye per animal using a 532 nm argon laser (lesion size: 50 µm; laser intensity: 150 mW; stimulus duration: 100 ms). Test compounds and vehicle controls were topically administered twice daily by instilling respective eye drops into the affected eye. The test compounds were dosed as follows: 10 µl of an eye drop formulation containing 20 mg/ml of the respective test compound suspended either in 100% liquid paraffin or in an aqueous vehicle (HPMC 15 cP 3.5%, polysorbate 80 0.5%, NaCl 0.9% in water) were applied to the affected eye twice daily at a 10 to 14 hour interval during the complete observation period of 23 days. Control animals received the respective vehicle (100% liquid paraffin or aqueous vehicle) topically twice daily. The body weight of all animals was recorded before the start and once daily during the study.

An angiography was performed on day 21 using a fluorescence fundus camera (Kowe). Here, after anaesthesia and pupillary dilation, 10% sodium fluorescein dye was injected subcutaneously, and images were recorded 2 and 10 min after dye injection. The vascular leakage of the fluorescein on the angiograms was evaluated by three different examiners who were blinded for group allocation (test compound versus vehicle), and scored with 0 (no leakage) to 3 (strongly stained).

On day 23, animals were sacrificed, and eyes were harvested and fixed in 4% paraformaldehyde solution for 1 hour at room temperature. After washing, the retina was carefully peeled, washed,

blocked and stained with a FITC-isolectine B4 antibody in order to visualize the vasculature. Then, the sclera-choroids were flat-mounted and examined under a fluorescence microscope (Keyence Biozero) at 488 nm excitation wavelength. The area (in μm^2) of choroidal neovascularization was measured using ImageTool software.

For Examples 7 and 11 as representative compounds of the present invention, the following results were obtained in this model:

	vascular leakage [HRA score]	**choroidal neovascularisation lesion size** [μm^2 x 10 000]
Example 7 (aqueous vehicle; n = 9)	1.49 ± 0.24	6.14 ± 1.60
Example 7 (paraffin vehicle; n = 8)	1.52 ± 0.21	6.21 ± 0.99
Example 11 (aqueous vehicle; n = 7)	1.66 ± 0.29	5.50 ± 1.38
Example 11 (paraffin vehicle; n = 12)	1.41 ± 0.29	6.45 ± 1.63
aqueous vehicle control (n = 12)	1.87 ± 0.27	7.84 ± 1.09
paraffin vehicle control (n = 17)	1.97 ± 0.19	7.00 ± 1.00

Although the invention has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of the invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The claims are intended to be construed to include all such embodiments and equivalent variations.

C. Examples relating to Pharmaceutical Compositions

Pharmaceutical compositions according to the present invention can be illustrated as follows:

Sterile i.v. solution:

A 5 mg/mL solution of the desired compound of the invention can be made using sterile, injectable water, and the pH is adjusted if necessary. The solution is diluted for administration to 1-2 mg/mL with sterile 5% dextrose and is administered as an i.v. infusion over about 60 minutes.

Lyophilized powder for i.v. administration:

A sterile preparation can be prepared with (*i*) 100–1000 mg of the desired compound of the invention as a lyophilized powder, (*ii*) 32–327 mg/mL sodium citrate, and (*iii*) 300–3000 mg Dextran 40. The formulation is reconstituted with sterile, injectable saline or 5% dextrose to a concentration of 10 to 20 mg/mL, which is further diluted with saline or 5% dextrose to 0.2 to 0.4 mg/mL, and is administered either as i.v. bolus or by i.v. infusion over 15–60 minutes.

Intramuscular suspension:

The following solution or suspension can be prepared for intramuscular injection:

50 mg/mL of the desired, water-insoluble compound of the invention; 5 mg/mL sodium carboxymethylcellulose; 4 mg/mL Tween 80; 9 mg/mL sodium chloride; 9 mg/mL benzyl alcohol.

Hard shell capsules:

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 mg of the desired, powdered compound of the invention, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate.

Soft gelatin capsules:

A mixture of the desired compound of the invention in a digestible oil, such as soybean oil, cottonseed oil or olive oil, is prepared and injected by means of a positive displacement pump into molten gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules are washed and dried. The desired compound of the invention can be dissolved in a mixture of polyethylene glycol, glycerin and sorbitol to prepare a water-miscible medicine mix.

Tablets:

A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 mg of the desired compound of the invention, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8 mg of lactose.

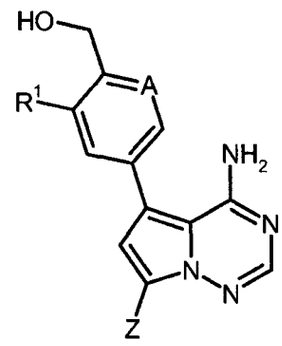
Appropriate aqueous and non-aqueous coatings may be applied to increase palatability, improve elegance and stability, or delay absorption.

Solution or suspension for topical application to the eye (eye drops):

A sterile formulation can be prepared with 100 mg of the desired compound of the invention as a lyophilized powder reconstituted in 5 mL of sterile saline. As preservative, benzalkonium chloride, thimerosal, phenylmercuric nitrate, or the like may be used in a range of about 0.001% to 1% by weight.

We claim:

1. A compound of formula (I)



(I),

wherein

A is N or C-R^2, wherein

R^2 represents hydrogen, fluoro or chloro,

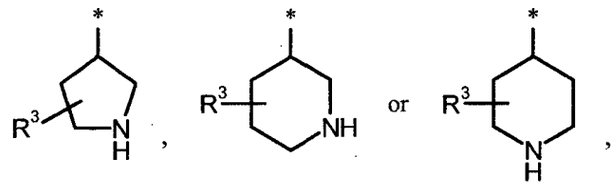
R^1 represents hydrogen, fluoro, chloro, methyl, ethyl or methoxy,

and

Z represents (C_1-C_4)-alkyl or (C_3-C_6)-cycloalkyl each of which may be substituted with hydroxy,

or

Z represents a heterocyclic group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

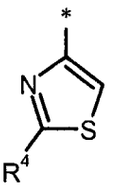
and

R^3 represents hydrogen or hydroxy,

with the proviso that when R^3 is hydroxy, this hydroxy is not attached to a ring carbon atom located adjacent to the ring nitrogen atom,

or

Z represents a thiazole group of the formula



,

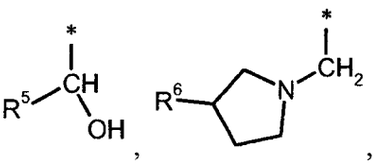
wherein * indicates the point of attachment to the pyrrolotriazine moiety,

and

R^4 represents hydrogen, methyl, ethyl, amino or aminomethyl,

or

Z represents a group of the formula



,

wherein * indicates the point of attachment to the pyrrolotriazine moiety,

R^5 represents (C_3-C_6)-cycloalkyl, oxetanyl, tetrahydrofuranyl or tetrahydropyranyl,

R^6 represents hydrogen or hydroxy,

R^7 represents hydrogen or hydroxy,

with the proviso that when R^7 is hydroxy, this hydroxy is not attached to a ring carbon atom located adjacent to the ring nitrogen atom,

and

Y is O, NH or NCH_3,

or a pharmaceutically acceptable salt, hydrate and/or solvate thereof.

2. The compound of formula (I) according to Claim 1, wherein

A is C-R^2, wherein

R^2 represents hydrogen or fluoro,

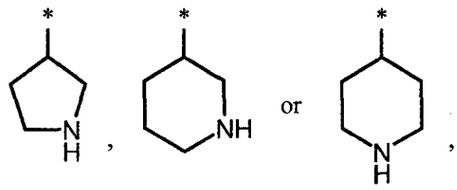
R^1 represents hydrogen, fluoro, chloro, methyl, ethyl or methoxy,

and

Z represents *n*-propyl, *n*-butyl or cyclohexyl each of which may be substituted with hydroxy,

or

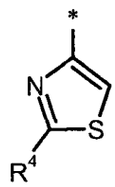
Z represents a heterocyclic group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

or

Z represents a thiazole group of the formula



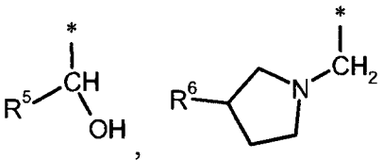
wherein * indicates the point of attachment to the pyrrolotriazine moiety,

and

R^4 represents methyl, ethyl, amino or aminomethyl,

or

Z represents a group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

R^5 represents cyclopropyl or tetrahydropyran-4-yl,

R^6 represents hydroxy,

and

Y is O,

or a pharmaceutically acceptable salt, hydrate and/or solvate thereof.

3. The compound of formula (I) according to Claim 1 or 2, wherein

A is C-R^2, wherein

R^2 represents hydrogen or fluoro,

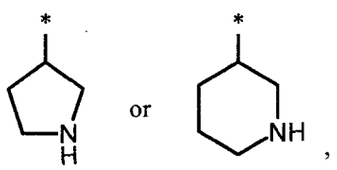
R^1 represents hydrogen, fluoro, methyl, ethyl or methoxy,

and

Z represents 4-hydroxybutyl or 4-hydroxycyclohexyl,

or

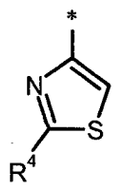
Z represents a heterocyclic group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

or

Z represents a thiazole group of the formula



,

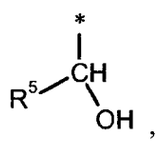
wherein * indicates the point of attachment to the pyrrolotriazine moiety,

and

R^4 represents methyl, ethyl, amino or aminomethyl,

or

Z represents a group of the formula



,

wherein * indicates the point of attachment to the pyrrolotriazine moiety,

and

R^5 represents cyclopropyl,

or a pharmaceutically acceptable salt, hydrate and/or solvate thereof.

4. A process for preparing a compound of formula (I) as defined in Claims 1 to 3, characterized in that a bromopyrrolotriazine of formula (II)

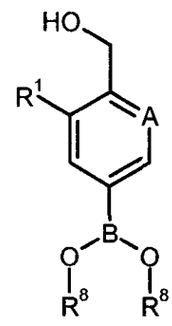


(II),

wherein Z has the meaning indicated in Claim 1 to 3,

is either

[A] coupled with an arylboronic acid or ester of formula (III)



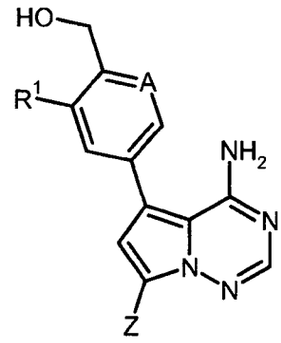
(III),

wherein A and R^1 have the meanings indicated in Claim 1 to 3,

and

R^8 represents hydrogen or (C_1-C_4)-alkyl, or both R^8 residues are linked together to form a $-(CH_2)_2-$, $-C(CH_3)_2-C(CH_3)_2-$, $-(CH_2)_3-$ or $-CH_2-C(CH_3)_2-CH_2-$ bridge,

in the presence of a suitable palladium catalyst and a base to yield the target compound of formula (I)

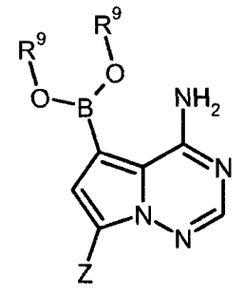


(I),

wherein A, Z and R^1 have the meanings indicated in Claim 1 to 3,

or

[B] first converted into the corresponding boronic acid or ester derivative of formula (IV)



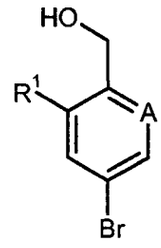
(IV),

wherein Z has the meaning indicated in Claim 1 to 3,

and

R^9 represents hydrogen or (C_1-C_4)-alkyl, or both R^9 residues are linked together to form a $-(CH_2)_2-$, $-C(CH_3)_2-C(CH_3)_2-$, $-(CH_2)_3-$ or $-CH_2-C(CH_3)_2-CH_2-$ bridge,

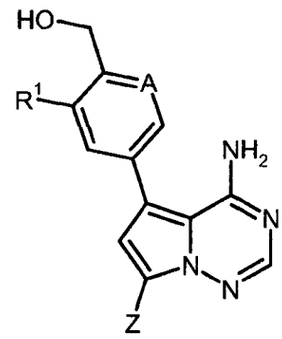
which is then coupled with an aryl bromide of formula (V)



(V),

wherein A and R^1 have the meanings indicated in Claim 1 to 3,

in the presence of a suitable palladium catalyst and a base to also give the target compound of formula (I)



(I),

wherein A, Z and R^1 have the meanings indicated in Claim 1 to 3,

optionally followed, where appropriate, by (*i*) separating the compounds of formula (I) into their respective enantiomers and/or diastereomers, and/or (*ii*) converting the compounds of formula (I) into their respective hydrates, solvates, salts and/or hydrates or solvates of the salts by treatment with the corresponding solvents and/or acids.

5. Compound as defined in any of Claims 1 to 3 for the treatment or prevention of diseases.

6. Use of a compound as defined in any of Claims 1 to 3 for the manufacture of a pharmaceutical composition for the treatment or prevention of age-related macular degeneration (AMD), choroidal neovascularisation (CNV), diabetic retinopathy and diabetic macula edema (DME).

7. A pharmaceutical composition comprising a compound as defined in any of Claims 1 to 3, or a pharmaceutically acceptable salt, hydrate and/or solvate thereof, and one or more pharmaceutically acceptable excipients.

8. The pharmaceutical composition of Claim 7 further comprising one or more additional therapeutic agents.

9. The pharmaceutical composition as defined in Claim 7 or 8 for the treatment or prevention of age-related macular degeneration (AMD), choroidal neovascularisation (CNV), diabetic retinopathy and diabetic macula edema (DME).

10. A method of treating or preventing age-related macular degeneration (AMD), choroidal neovascularisation (CNV), diabetic retinopathy and diabetic macula edema (DME) in a mammal, comprising administering to a mammal in need thereof a therapeutically effective amount of one or more compounds as defined in any of Claims 1 to 3, or of a pharmaceutical composition as defined in any of Claims 7 to 9.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/062366

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/53 A61P27/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 873 157 A1 (BAYER SCHERING PHARMA AG [DE]) 2 January 2008 (2008-01-02) claims 1-24 page 4, paragraph 17	1-10
A	WO 2007/061882 A2 (SQUIBB BRISTOL MYERS CO [US]; CHEN PING [US]; ZHAO YUFEN [US]; FINK BR) 31 May 2007 (2007-05-31) cited in the application claims 1-16	1-10
A	WO 00/71129 A1 (SQUIBB BRISTOL MYERS CO [US]) 30 November 2000 (2000-11-30) cited in the application claims 1-18	1-10

☐ 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

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

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 July 2012	02/08/2012

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2012/062366

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1873157 A1	02-01-2008	CA 2656419 A1	27-12-2007
		EP 1873157 A1	02-01-2008
		EP 2049539 A1	22-04-2009
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		WO 0071129 A1	30-11-2000

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DOCUMENT MADE AVAILABLE UNDER THE PATENT COOPERATION TREATY (PCT)

International application number:		**PCT/EP2012/062366**
International filing date:		**26 June 2012 (26.06.2012)**
Document type:		**Certified copy of priority document**
Document details:	Country/Office:	**US**
	Number:	**61/503,840**
	Filing date:	**01 July 2011 (01.07.2011)**
Date of receipt at the International Bureau:		**13 September 2012 (13.09.2012)**

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a),(b) or (b-*bis*)

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1211 Geneva 20, Switzerland
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BHC110IG

PA 1083897

THE UNITED STATES OF AMERICA

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May 23, 2012

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APPLICATION NUMBER: ***61/503,840***
FILING DATE: ***July 01, 2011***

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS ***US61/503,840***

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

E. BORNETT
Certifying Officer

Electronic Acknowledgement Receipt

EFS ID:	10440062
Application Number:	61503840
International Application Number:	
Confirmation Number:	2218
Title of Invention:	HYDROXYMETHYLARYL-SUBSTITUTED PYRROLOTRIAZINES AND USES THEREOF
First Named Inventor/Applicant Name:	Joachim Telser
Customer Number:	35969
Filer:	Thomas Christopher Blankinship
Filer Authorized By:	
Attorney Docket Number:	BHC 111016 US
Receipt Date:	01-JUL-2011
Filing Date:	
Time Stamp:	14:52:33
Application Type:	Provisional

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$220
RAM confirmation Number	1149
Deposit Account	133372
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Provisional Cover Sheet (SB16)	BHC-111016-US-20110701-Provisional-coversheet.pdf	1060517 b551bf9d3e4c4eef875e3a89cc58e28c8f462194	no	4
Warnings:					
Information:					
2		BHC-111016-US-20110701-Provisional-application.pdf	745755 1dd122f3a45708ffacf74803315696b8f0fb9557	yes	126

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	117
Claims	118	125
Abstract	126	126

Warnings:					
Information:					
3	Application Data Sheet	BHC-111016-US-20110701-ADS.pdf	1032555 30bc592d1f55cf4c79d5ada30e411bf0d6517 9c7	no	7
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	29538 8bda114fb2918 17b8caf399d77ab025c2f41 5595	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	2868365		

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National Stage of an International Application under 35 U.S.C. 371

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New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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Doc Code: TR.PROV
Document Description: Provisional Cover Sheet (SB16)

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Approved for use through 09/30/2010 OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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Provisional Application for Patent Cover Sheet

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c)

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Doc Code: **TR.PROV**
Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (11-08)
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All Inventors Must Be Listed – Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Title of Invention	HYDROXYMETHYLARYL-SUBSTITUTED PYRROLOTRIAZINES AND USES THEREOF
Attorney Docket Number (if applicable)	BHC 111016 US

Correspondence Address

Direct all correspondence to (select one):

◉ The address corresponding to Customer Number	○ Firm or Individual Name
Customer Number	35969

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

◉ No.

○ Yes, the name of the U.S. Government agency and the Government contract number are:

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Doc Code: **TR.PROV**
Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (11-08)
Approved for use through 09/30/2010 OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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Entity Status

Applicant claims small entity status under 37 CFR 1.27

○ Yes, applicant qualifies for small entity status under 37 CFR 1.27

◉ No

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Signature

Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/THOMAS C. BLANKINSHIP/			Date (YYYY-MM-DD)	2011-07-01
First Name	Thomas	Last Name	Blankinship	Registration Number (If appropriate)	39909

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BHC 11 1 016-US

HYDROXYMETHYLARYL-SUBSTITUTED PYRROLOTRIAZINES AND USES THEREOF

This invention relates to novel 5-[(hydroxymethyl)aryl]-substituted pyrrolo[2,1-f][1,2,4]triazin-4-amines, to processes for the preparation of such compounds, to pharmaceutical compositions containing such compounds, and to the use of such compounds or compositions for treating angiogenesis-related disorders, in particular angiogenesis-related ocular disorders.

The term angiogenesis, also called neovascularisation, signifies the process of forming new blood vessels. It is involved in normal development as well as in numerous pathological states including, for example, cancer, rheumatoid arthritis, wound healing following injury to a tissue, atherosclerosis, psoriasis, and diseases of the eye.

Various ocular disorders which are responsible for the majority of visual morbidities and blindness in the developed countries are characterized by, caused by and/or result in choroidal, retinal or iris neovascularisation or retinal edema [Campochiaro (2004), *Exp. Opin. Biol. Ther.* 4: 1395-1402].

For example, retinopathy associated with diabetes is a leading cause of blindness in type 1 diabetes, and is also common in type 2 diabetes. Another ocular disorder involving neovascularisation is age-related macular degeneration (AMD). AMD is the most common cause of vision loss in the western world in those 50 or older, and its prevalence increases with age. AMD is classified as either wet (neovascular) or dry (non-neovascular). The wet form of the disease is responsible for the most severe loss of vision.

Several other less common, but nonetheless debilitating retinopathies include choroidal neovascular membrane (CNVM), cystoid macular edema (CME, also referred to as macular edema or macular swelling), epi-retinal membrane (ERM, macular pucker), and macular hole. In CNVM, abnormal blood vessels stemming from the choroid grow up through the retinal layers. The fragile new vessels break easily, causing blood and fluid to pool within the layers of the retina. In CME, which can occur as a result of disease, injury or surgery, fluid collects within the layers of the macula, causing blurred, distorted central vision. ERM (macular pucker) is a cellophane-like membrane that forms over the macula, affecting the central vision by causing blur and distortion.

Also related are disorders like hypertrophic and atrophic changes of the retinal pigment epithelium (RPE), retinal detachment, choroidal vein occlusion, retinal vein occlusion, corneal angiogenesis following, for example, keratitis, cornea transplantation or keratoplasty, corneal

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angiogenesis due to hypoxia (*e.g.*, as a result of extensive contact lens wearing), pterygium conjunctivae, subretinal edema, and intraretinal edema.

Vascular endothelial growth factor (VEGF) has been found to be an important modulator of angiogenesis and has been implicated in the pathology of a number of conditions including AMD and diabetic retinopathy. Furthermore, for AMD it was shown that intravitreal injection of an anti-VEGF inhibitor like pegaptanib, ranibizumab or aflibercept reduces choroidal angiogenesis and vascular leakage [Gragoudas (2004), *N. Engl. J. Med.* 351: 2805-2816; Rosenfeld (2006), *N. Engl. J. Med.* 355: 1419-1431; Dixon (2009), *Expert Opin. Investig. Drugs* 18: 1573-1580].

The current standard of care for AMD is lucentis (ranibizumab), an anti-VEGF therapy. However, only 1/3 of all AMD patients treated with lucentis show improvement in vision [Rosenfeld (2006), *N. Engl. J. Med.* 355: 1419-1431]. Therefore new anti-angiogenic therapeutic options with a VEGF-independent mode of action have the potential to improve the current standard of care in ocular diseases like diabetic retinopathy and AMD.

ALK1 (activin receptor-like kinase-1) is a Ser/Thr kinase receptor of the TGFβ receptor family preferentially expressed in endothelial cells and involved in angiogenesis. Members of this family mediate their biological activity by ligand binding to a heterotetrameric receptor complex of type I and type II serine/threonine kinase receptors TβRI and TβRII and accessory type III receptors. TGFβ as well as the high-affinity ligands BMP9 and BMP10 can activate ALK1 in receptor complexes with BMPRII or ActRII and type III receptor endoglin [Scharpfenecker (2007), *J. Cell Sci.* 120: 964-972]. Binding of BMP9 to ALK1 in microvascular endothelial cells activates the Smad1/5/8 pathway [David (2007), *Blood* 109 (5): 1953-1961]. It was postulated that BMP9 inhibits endothelial cell migration and growth. Most studies, however, find that ALK1 receptor activation promotes endothelial cell migration, proliferation, and tube formation [Goumans (2002), *EMBO Journal* 21 (7): 1743-1753; Wu (2006), *Microvasc. Res.* 71: 12-19].

BMP9 and BMP10 activate ALK1 receptor complexes. In endothelial cells, TGFβ can also activate ALK1 while in most cell types TGFβ signals through ALK5. ALK5 activation leads to phosphorylation of Smad2/3 while ALK1 activation results in phosphorylation of Smad1/5. Each Smad signalling pathway finally results in regulation of specific sets of target genes: Smad2/3 signalling induces expression of PAI-1 and repression of Id-1, while Smad1/5 signalling induces Smad6, Smad7 and Id-1 expression and reduces PAI-1 expression [Deng (2006), *J. Cell Biol.* 134: 1563-1571; Ota (2002), *J. Cell Physiol.* 193: 299-318].

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Type III receptor endoglin plays a role in fine-tuning of ALK1 and ALK5 pathways especially in endothelial cells, regulating ligand receptor interactions [ten Dijke (2008), *Angiogenesis* 11: 79-89]. Endoglin facilitates TGFβ/ALK1-interaction but reduces TGFβ/ALK5-interaction [David (2007), *Blood* 109: 1953-1961].

Mutations in endoglin and in ALK1 are linked to the autosomal dominant disorder called hereditary hemorrhagic telangiectasia (HHT1 and HHT2, respectively) with characteristics of angiogenic disturbances like arterial venous malformations and telangiectases [Fernandez-Lopez (2006), *Clin. Med. & Res.* 4: 66-78]. RIP1-Tag2 mice with only one functional copy of the ALK1 gene ($ALK1^{+/-}$) show retarded tumor progression and lower microvessel density compared to $ALK1^{wt}$ mice. Similar observations were made with the soluble ALK1-Fc receptor construct RAP-041, that inhibited tumor angiogenesis *in vivo* and limited tumor growth [Cunha (2010), *J. Exp. Med.* 207: 85-100].

The discovery of potent and selective ALK1 inhibitors is therefore highly desirable to further elucidate the role of ALK1 in blood vessel physiology and pathology, and to derive potential therapeutic options for diseases associated with angiogenesis and vascular remodelling.

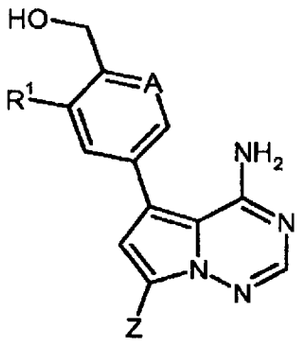
In WO 2007/147647-A1, certain 3-aryl-substituted pyrazolo[1,5-a]pyrimidine derivatives were described to be the first small molecule ALK1 kinase inhibitors published until then. These compounds were said to be useful for the treatment of diseases of dysregulated vascular growth, in particular of solid tumors and metastases thereof and also of angiogenesis-dependent diseases of the eye such as age-related macular degeneration.

Various pyrrolo[2,1-f][1,2,4]triazin-4-amine derivatives with distinctive inhibition profiles against a range of protein kinases have been disclosed in, *inter alia*, WO 00/71129-A1, WO 2005/121147-A1, WO 2007/056170-A2, WO 2007/061882-A2, WO 2007/064883-A2, WO 2007/064931-A2, WO 2007/079164-A2, WO 2008/089105-A2, WO 2009/136966-A1, and WO 2010/126960-A1. Generally, these compounds were stated to be useful for the treatment of proliferative and/or angiogenesis-related disorders such as cancer. None of these publications, however, refer to ALK1 as a potential target kinase.

Surprisingly, it has now been found that pyrrolo[2,1-f][1,2,4]triazin-4-amine derivatives having a hydroxymethylaryl substituent in 5-position exhibit potent and selective inhibition of ALK1 kinase which renders these compounds particularly useful for the treatment of angiogenesis-related ocular disorders.

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Thus, in one aspect, the present invention relates to 5-[(hydroxymethyl)aryl]-substituted pyrrolo-[2,1-f][1,2,4]triazin-4-amines of the general formula (I)



(I),

wherein

A is N or C-R^2, wherein

R^2 represents hydrogen, fluoro or chloro,

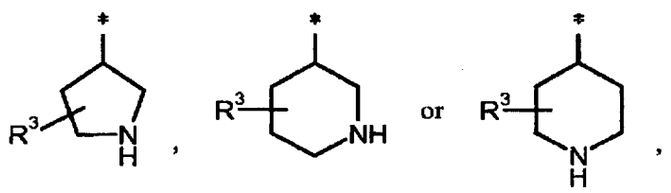
R^1 represents hydrogen, fluoro, chloro, methyl, ethyl or methoxy,

and

Z represents (C_1-C_4)-alkyl or (C_3-C_6)-cycloalkyl each of which may be substituted with hydroxy,

or

Z represents a heterocyclic group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

and

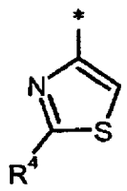
R^3 represents hydrogen or hydroxy,

with the proviso that when R^3 is hydroxy, this hydroxy is not attached to a ring carbon atom located adjacent to the ring nitrogen atom,

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or

Z represents a thiazole group of the formula



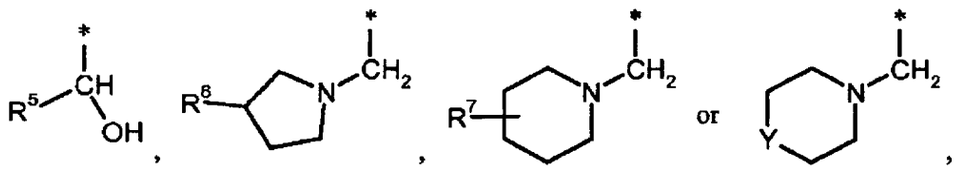
wherein * indicates the point of attachment to the pyrrolotriazine moiety,

and

R^4 represents hydrogen, methyl, ethyl, amino or aminomethyl,

or

Z represents a group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

R^5 represents (C_3-C_6)-cycloalkyl, oxetanyl, tetrahydrofuranyl or tetrahydropyranyl,

R^6 represents hydrogen or hydroxy,

R^7 represents hydrogen or hydroxy,

with the proviso that when R^7 is hydroxy, this hydroxy is not attached to a ring carbon atom located adjacent to the ring nitrogen atom,

and

Y is O, NH or NCH_3.

The compounds according to this invention can also be present in the form of their salts, solvates and/or solvates of the salts.

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Compounds according to the invention are the compounds of the formula (I) and their salts, solvates and solvates of the salts, the compounds included in the formula (I) of the formulae mentioned in the following and their salts, solvates and solvates of the salts, and the compounds included in the formula (I) and mentioned in the following as embodiment examples and their salts, solvates and solvates of the salts, where the compounds included in the formula (I) and mentioned in the following are not already salts, solvates and solvates of the salts.

Salts for the purposes of the present invention are preferably pharmaceutically acceptable salts of the compounds according to the invention (for example, see S. M. Berge *et al.*, "Pharmaceutical Salts", *J. Pharm. Sci.* **1977**, 66, 1-19). Salts which are not themselves suitable for pharmaceutical uses but can be used, for example, for isolation or purification of the compounds according to the invention are also included.

Pharmaceutically acceptable salts include acid addition salts of mineral acids, carboxylic acids and sulfonic acids, for example salts of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, naphthalenedisulfonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.

Solvates in the context of the invention are designated as those forms of the compounds according to the invention which form a complex in the solid or liquid state by stoichiometric coordination with solvent molecules. Hydrates are a specific form of solvates, in which the coordination takes place with water. Hydrates are preferred solvates in the context of the present invention.

The compounds of this invention may, either by nature of asymmetric centers or by restricted rotation, be present in the form of isomers (enantiomers, diastereomers). Any isomer may be present in which the asymmetric center is in the (*R*)-, (*S*)-, or (*R,S*)-configuration.

It will also be appreciated that when two or more asymmetric centers are present in the compounds of the invention, several diastereomers and enantiomers of the exemplified structures will often be possible, and that pure diastereomers and pure enantiomers represent preferred embodiments. It is intended that pure stereoisomers, pure diastereomers, pure enantiomers, and mixtures thereof, are within the scope of the invention.

Geometric isomers by nature of substituents about a double bond or a ring may be present in *cis* (= *Z*-) or *trans* (= *E*-) form, and both isomeric forms are encompassed within the scope of this invention.

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All isomers, whether separated, pure, partially pure, or in racemic mixture, of the compounds of this invention are encompassed within the scope of this invention. The purification of said isomers and the separation of said isomeric mixtures may be accomplished by standard techniques known in the art. For example, diastereomeric mixtures can be separated into the individual isomers by chromatographic processes or crystallization, and racemates can be separated into the respective enantiomers either by chromatographic processes on chiral phases or by resolution.

In addition, all possible tautomeric forms of the compounds described above are included according to the present invention.

Unless otherwise stated, the following definitions apply for the substituents and residues used throughout this specification and claims:

$(C_1\text{-}C_4)$-alkyl represents a straight-chain or branched saturated hydrocarbon radical having 1 to 4 carbon atoms. Examples include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl.

$(C_3\text{-}C_6)$-cycloalkyl represents a monocyclic saturated hydrocarbon radical having 3 to 6 ring carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

Throughout this document, for the sake of simplicity, the use of singular language is given preference over plural language, but is generally meant to include the plural language if not otherwise stated. *E.g.*, the expression "A method of treating a disease in a patient, comprising administering to a patient an effective amount of a compound of formula (I)" is meant to include the simultaneous treatment of more than one disease as well as the administration of more than one compound of formula (I).

In a preferred embodiment, the present invention relates to compounds of general formula (I), wherein

A is C-R^2, wherein

R^2 represents hydrogen or fluoro,

R^1 represents hydrogen, fluoro, chloro, methyl, ethyl or methoxy,

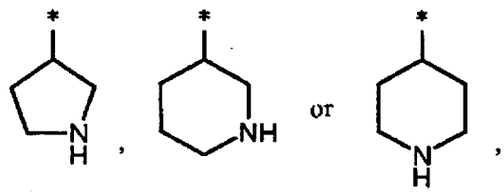
and

Z represents *n*-propyl, *n*-butyl or cyclohexyl each of which may be substituted with hydroxy,

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or

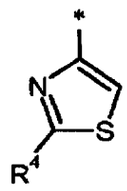
Z represents a heterocyclic group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

or

Z represents a thiazole group of the formula



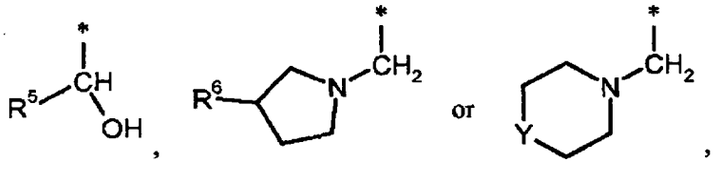
wherein * indicates the point of attachment to the pyrrolotriazine moiety,

and

R^4 represents methyl, ethyl, amino or aminomethyl,

or

Z represents a group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

R^5 represents cyclopropyl or tetrahydropyran-4-yl,

R^6 represents hydroxy,

and

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Y is O.

In a particularly preferred embodiment, the present invention relates to compounds of general formula (I), wherein

A is C-R^2, wherein

R^2 represents hydrogen or fluoro,

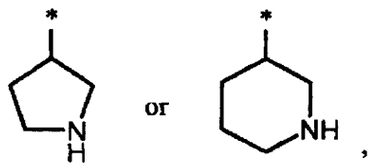
R^1 represents hydrogen, fluoro, methyl, ethyl or methoxy,

and

Z represents 4-hydroxybutyl or 4-hydroxycyclohexyl,

or

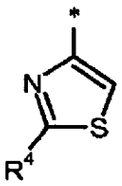
Z represents a heterocyclic group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

or

Z represents a thiazole group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

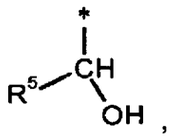
and

R^4 represents methyl, ethyl, amino or aminomethyl,

or

Z represents a group of the formula

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wherein * indicates the point of attachment to the pyrrolotriazine moiety,

and

R^5 represents cyclopropyl.

In a distinct embodiment, the present invention relates to compounds of general formula (I), wherein

A is C-R^2, wherein

R^2 represents hydrogen or fluoro.

In a further distinct embodiment, the present invention relates to compounds of general formula (I), wherein

A is C-R^2, wherein

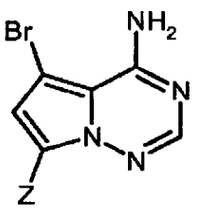
R^2 represents fluoro,

and

R^1 represents fluoro.

The definitions of residues indicated specifically in the respective combinations or preferred combinations of residues are also replaced as desired by definitions of residues of other combinations, irrespective of the particular combinations indicated for the residues. Combinations of two or more of the abovementioned preferred ranges are particularly preferred.

In another embodiment, the present invention relates to a process for preparing the compounds of general formula (I), characterized in that a bromopyrrolotriazine of formula (II)



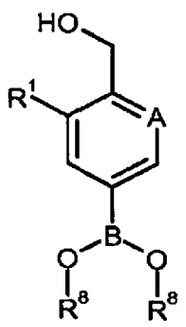
(II),

wherein Z has the meaning described above,

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is either

[A] coupled with an arylboronic acid or ester of formula (III)



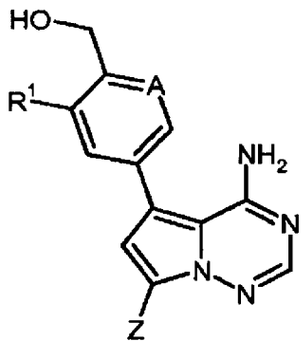
(III),

wherein A and R^1 have the meanings described above,

and

R^8 represents hydrogen or $(C_1\text{-}C_4)$-alkyl, or both R^8 residues are linked together to form a $-(CH_2)_2-$, $-C(CH_3)_2\text{-}C(CH_3)_2-$, $-(CH_2)_3-$ or $-CH_2\text{-}C(CH_3)_2\text{-}CH_2-$ bridge,

in the presence of a suitable palladium catalyst and a base to yield the target compound of formula (I)



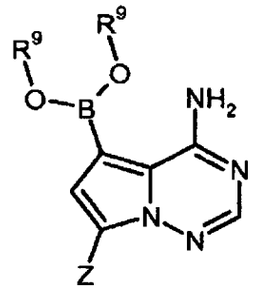
(I),

wherein A, Z and R^1 have the meanings described above,

or

[B] first converted into the corresponding boronic acid or ester derivative of formula (IV)

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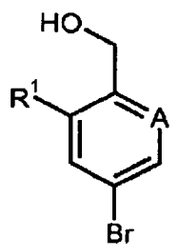
(IV),

wherein Z has the meaning described above,

and

R^9 represents hydrogen or (C_1-C_4)-alkyl, or both R^9 residues are linked together to form a $-(CH_2)_2-$, $-C(CH_3)_2-C(CH_3)_2-$, $-(CH_2)_3-$ or $-CH_2-C(CH_3)_2-CH_2-$ bridge,

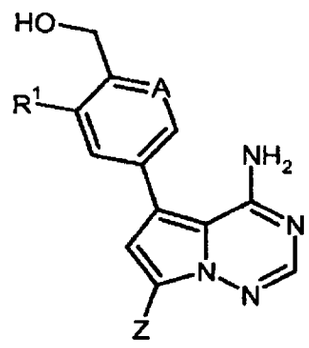
which is then coupled with an aryl bromide of formula (V)



(V),

wherein A and R^1 have the meanings described above,

in the presence of a suitable palladium catalyst and a base to also give the target compound of formula (I)



(I),

wherein A, Z and R^1 have the meanings described above,

optionally followed, where appropriate, by (*i*) separating the compounds of formula (I) into their respective enantiomers and/or diastereomers, preferably using chromatographic methods, and/or

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(*ii*) converting the compounds of formula (I) into their respective hydrates, solvates, salts and/or hydrates or solvates of the salts by treatment with the corresponding solvents and/or acids.

As outlined above, compounds of formula (I) can be synthesized by a coupling reaction ("Suzuki coupling") between the bromopyrrolotriazine (II) and an aryl boronate or boronic acid (III). This coupling is generally carried out at elevated temperature using a palladium catalyst, a base and an inert solvent. An overview of catalysts and reaction conditions can be found in the literature [see, for instance, S. Kotha *et al.*, *Tetrahedron* **2002**, *58*, 9633-9695; T. E. Barder *et al.*, *J. Am. Chem. Soc.* **2005**, *127*, 4685-4696]. The preferred catalyst in this reaction is tetrakis(triphenylphosphine)palladium(0). The preferred base is sodium carbonate employed as an aqueous solution. The reaction is carried out in organic solvents that are inert under the reaction conditions, such as 1,4-dioxane, acetonitrile, *N,N*-dimethylformamide (DMF) or dimethylsulfoxide (DMSO), or in water or in mixtures of these solvents. Preferably, the reaction is carried out in a mixture of 1,4-dioxane and water or acetonitrile and water. The reaction is generally performed at temperatures between +100°C and +250°C, preferably at +120°C to +150°C. Heating is preferably effected by a single-mode microwave device. The reactions are usually run under an inert gas atmosphere, preferably under argon.

An inverse reactivity of the reaction partners for the Suzuki coupling may sometimes be favorable. For this purpose, the bromopyrrolotriazine (II) is first converted into the corresponding boronate (IV) and then cross-coupled with an aryl bromide (V) according to one of the methods described above. The conversion of (II) to (IV) is achieved by a metal-mediated borylation reaction. The preferred method is the palladium-catalyzed "Miyaura borylation" [see, for instance, J. Takagi *et al.*, *J. Am. Chem. Soc.* **2002**, *124*, 8001-8006; T. Ishiyama *et al.*, *J. Org. Chem.* **1995**, *60*, 7508-7510; A. L. S. Thompson *et al.*, *Synthesis* **2005**, 547-550]. Procedures, reagents and solvents for the cross-coupling reaction (IV) + (V) → (I) are chosen from those mentioned in the previous section.

Arylboronic acids (III) [R^8 = H] and aryl boronates (III) [R^8 = alkyl, or both R^8 are linked together to form a cyclic boronic ester, *e.g.*, a pinacolato ester] are either commercially available, or they can be conveniently prepared from the corresponding aryl halides or aryl triflates using a metal-mediated borylation reaction (for references, see previous section). Borylation and subsequent Suzuki coupling may be carried out in two separate steps including isolation and purification of intermediate (III). Alternatively, borylation and cross-coupling may be carried out as a one-pot procedure using (III) directly without isolation and purification.

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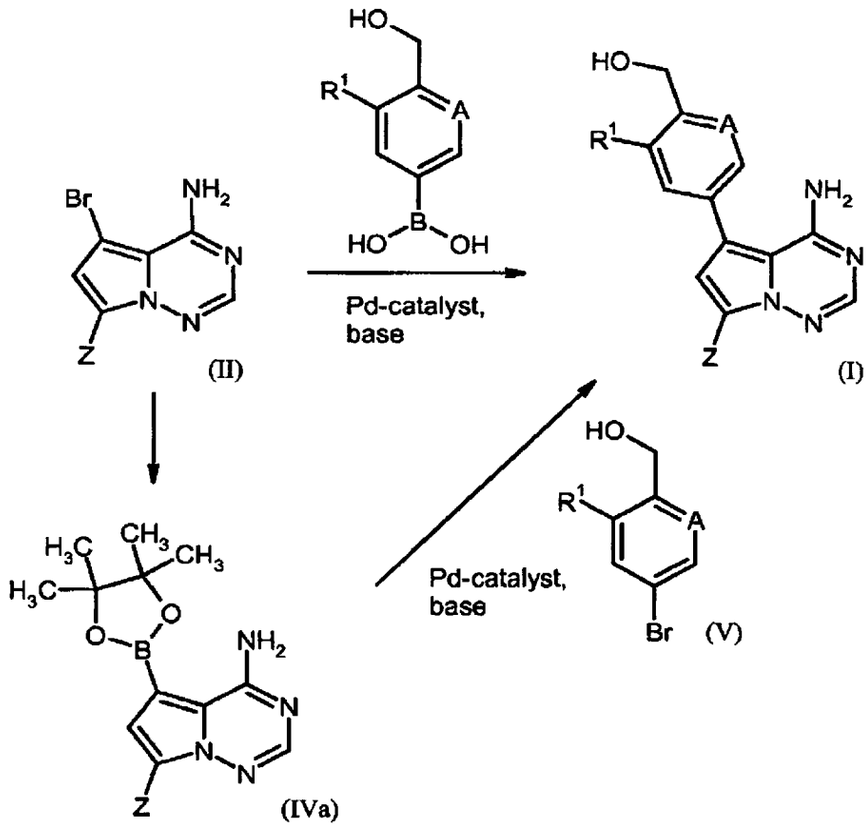
In cases where a primary or secondary amine moiety forms part of the Z group in the target compounds of formula (I), it may often be beneficial in the borylation and coupling reactions described above to use a protected derivative of this amine as the starting pyrrolotriazine (II) instead of the free amine compound. For this purpose, conventional temporary amino-protecting groups, such as acyl groups (*e.g.*, acetyl or trifluoroacetyl) or carbamate-type protecting groups (*e.g.*, a Boc-, Cbz- or Fmoc-group), may be employed. Preferably, a trifluoroacetyl or a Boc group is used. Similarly, the hydroxy function in the coupling components (III) and (V), respectively, may temporarily be blocked during the process, preferably as a silyl ether derivative such as a trimethylsilyl or *tert*-butyldimethylsilyl ether.

These protecting groups may then be cleaved off concomitantly during the aqueous work-up of the coupling reaction mixtures, or they are removed in a subsequent, separate reaction step using standard methods known in the art. The preparation of the protected intermediates described above from the corresponding free amines or alcohols of formula (II), (III) and (V), respectively, or from other precursor compounds (see section below) is also readily accomplished following general procedures described in the literature [see, for example, T. W. Greene and P. Wuts, *Protective Groups in Organic Synthesis*, Wiley, New York, 1999].

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The preparation of the compounds of the invention may be illustrated by means of the following synthesis scheme:

Scheme 1



The synthetic methodologies that may be used to prepare the bromopyrrolotriazines of formula (II) can be structured according to the chemotype of the Z group present in (II). Examples illustrating these various routes are given below (see synthesis schemes 2-6). More detailed procedures are provided in the Experimental Section describing specific intermediate and example compounds of the invention.

For example, compounds of formula (II) containing an alkyl or hydroxyalkyl residue as the Z group can be obtained by employing a coupling reaction between the bromopyrrolotriazine (VI) and a terminal alkyne of formula (VII) as the key step (scheme 2). This type of reaction ("Sonogashira reaction") is usually performed in the presence of a palladium-copper catalyst system and a base. Several examples of this reaction have been described in the literature [see, for instance, R. Chinchilla and C. Nájera, *Chem. Rev.* **2007**, *107*, 874-922]. In the present invention, the preferred copper source is copper(I) iodide, tetrakis(triphenylphosphine)palladium(0) is used as

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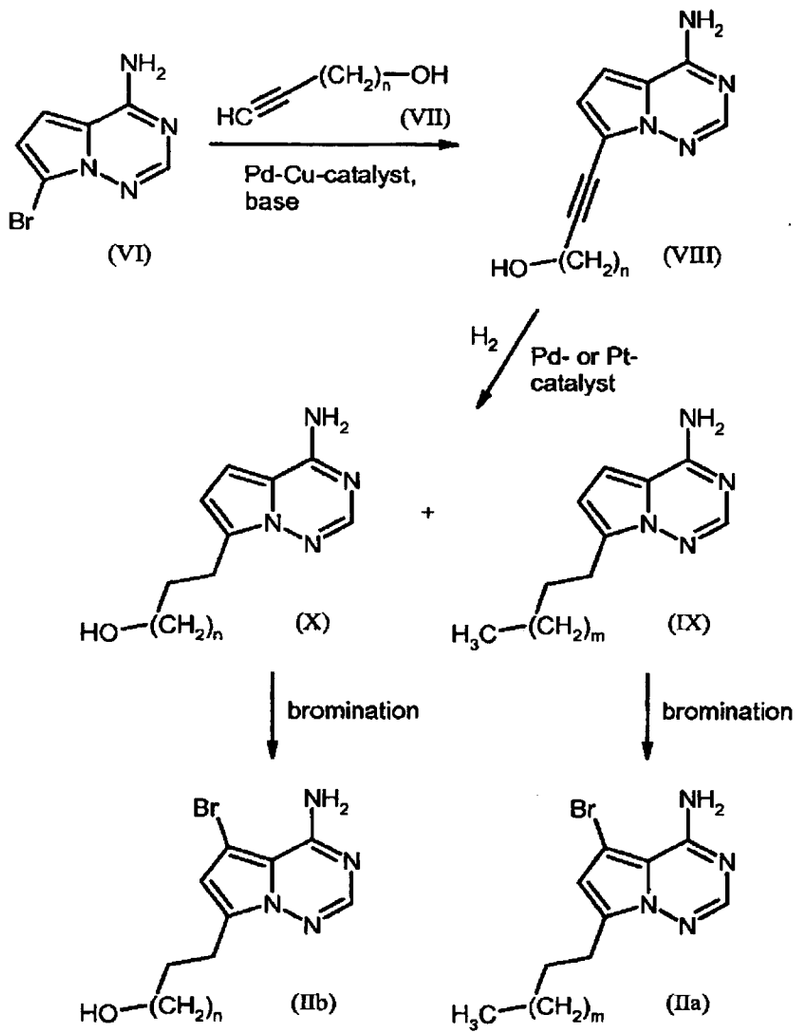
palladium catalyst, and pyrrolidine serves both as base and solvent. The coupling reaction is advantageously carried out under concurrent microwave irradiation.

The resulting alkyne (VIII) is then subjected to catalytic hydrogenation employing a customary palladium or platinum catalyst. Preferably, platinum(IV) oxide is used as the catalyst, and the reaction is run in acetic acid as the solvent. In some cases, a mixture of products (IX) and (X) is obtained by this procedure which, in any event, can be separated easily by chromatographic methods. A subsequent bromination reaction, preferably using 1,3-dibromo-5,5-dimethyl-hydantoin as the bromine source, in an inert solvent such as THF or DMF yields the target pyrrolotriazines (IIa) and (IIb), respectively.

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The preparation of the starting compound 7-bromopyrrolo[2,1-f][1,2,4]triazin-4-amine (VI) has been described previously [see WO 2007/056170-A2 (Intermediate B)].

Scheme 2



[m = 0 or 1, n = 1 or 2].

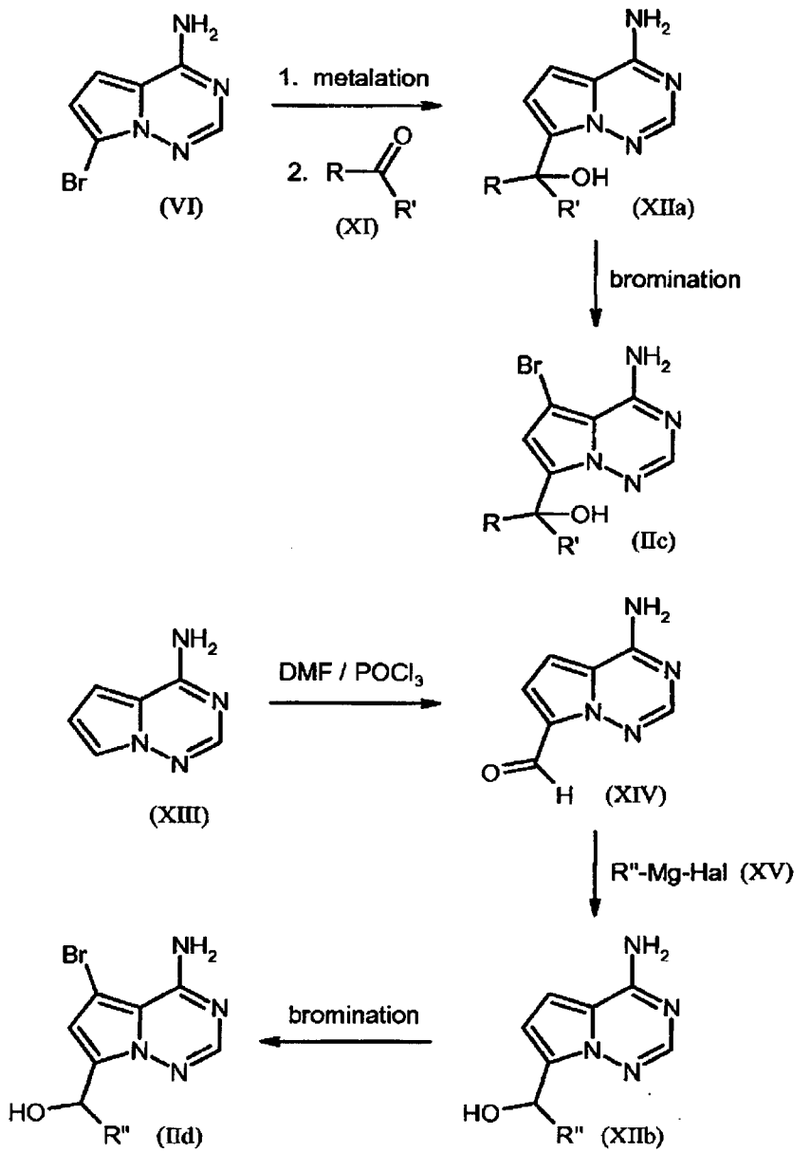
Bromopyrrolotriazine precursors of type (IIc) (scheme 3) can be prepared by metalation of compound (VI) with a metal such as magnesium or lithium or by halogen-metal exchange using an organo-magnesium or organo-lithium reagent. The preferred metal is magnesium which is introduced into (VI) by treatment with isopropylmagnesium bromide in a solvent such as THF or diethyl ether. The intermediate organo-metal species is then reacted with a cycloalkanone or heterocycloalkanone (XI) [R, R' are linked together to form a cycloalkyl or heterocycloalkyl ring] to give the tertiary alcohol (XIIa).

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A complementary route leading to secondary alcohols of formula (XIIb) utilizes a Vilsmeier formylation reaction whereby aminopyrrolotriazine (XIII) is transformed into the aldehyde (XIV) (scheme 3). Side chain introduction is accomplished by subsequent addition of an appropriate Grignard reagent (XV) [R" = alkyl or cycloalkyl] in a solvent such as THF or diethyl ether. Finally, bromination of compounds (XIIa) and (XIIb), preferably using 1,3-dibromo-5,5-dimethylhydantoin, in an inert solvent such as THF or DMF provides the target pyrrolotriazines (IIc) and (IId), respectively.

The preparation of the starting compound pyrrolo[2,1-f][1,2,4]triazin-4-amine (XIII) has been described previously [see WO 2007/056170-A2 (Intermediate A)].

Scheme 3

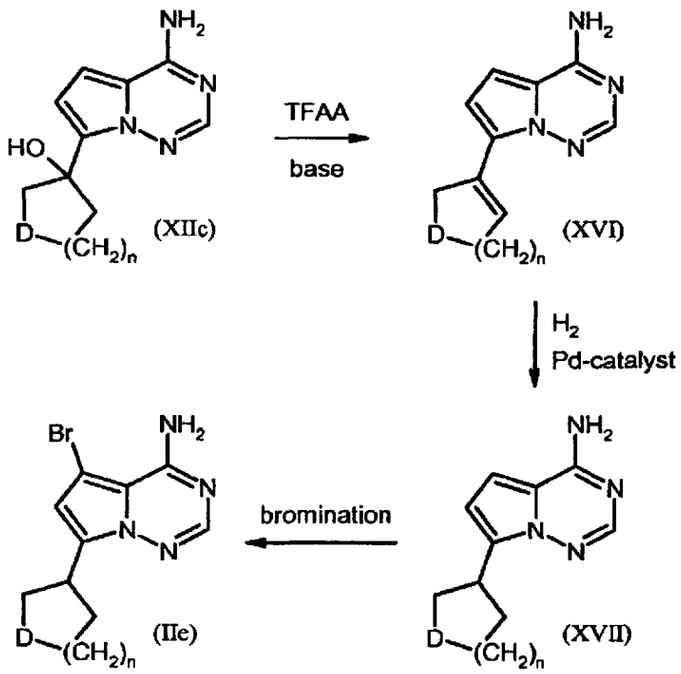


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Pyrrolotriazines of formula (II) wherein Z is representing an unsubstituted cycloalkyl or carbon-bonded aza-heterocyclyl group can be prepared by dehydration of a tertiary alcohol of formula (XIIc) to the unsaturated carbo- or heterocycle of formula (XVI), employing customary agents such as trifluoroacetic acid anhydride, trifluoromethanesulfonic acid anhydride, phosphorus(V) oxide, sulfuric acid or other strong acids (scheme 4). Subsequent catalytic hydrogenation using a conventional catalyst such as palladium on charcoal yields the saturated analog of formula (XVII). The hydrogenation step is preferably carried out in a solvent like methanol, ethanol or THF which contains a small amount of aqueous trifluoroacetic acid. Finally, bromination with 1,3-dibromo-5,5-dimethylhydantoin, as described above, provides the target pyrrolotriazine (IIe).

The alcohol precursors (XIIc) themselves are readily accessible by the synthetic route depicted in scheme 3 [*cf.* preparation of compound (XIIa)].

Scheme 4

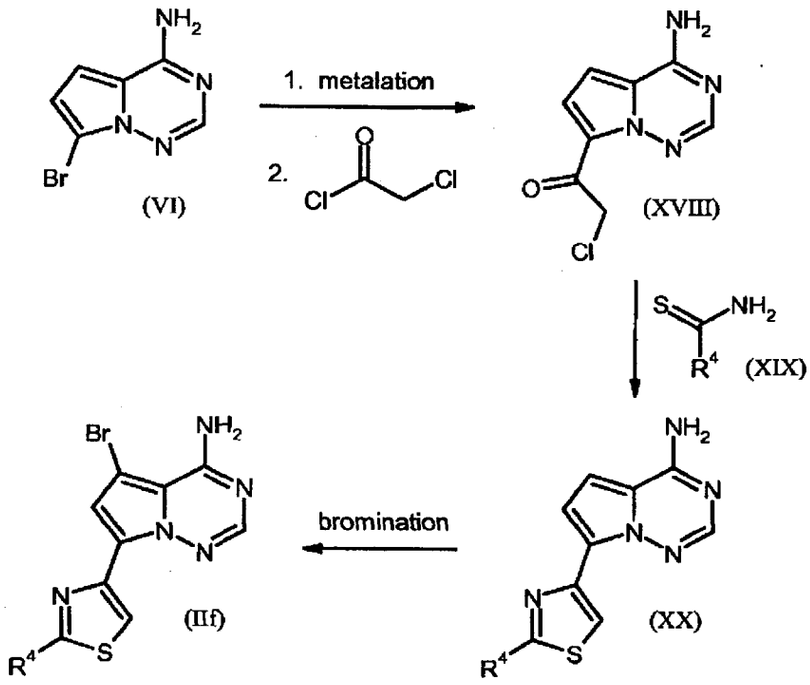


[D = *e.g.* CH_2 or N-Boc; n = 1 or 2].

Pyrrolotriazines of formula (II) wherein Z is representing a 1,3-thiazol-4-yl group can be prepared by metalation of compound (VI), as described above, followed by reaction with chloroacetyl chloride to give the intermediate (XVIII), and then condensation with a thioamide or thiourea (XIX) [with R^4 as defined above] to yield the precursor compound (XX) (scheme 5). Bromination with 1,3-dibromo-5,5-dimethylhydantoin, as described above, finally provides the target pyrrolotriazine (IIf).

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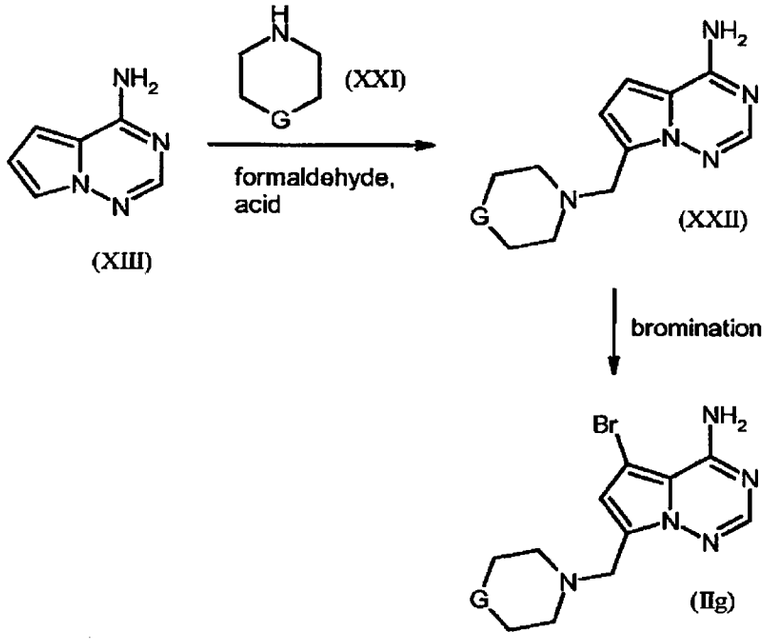
Scheme 5



Pyrrolotriazines of formula (II) wherein Z is representing an *N*-cyclic aminomethyl group can be obtained by reacting pyrrolotriazine (XIII) with formaldehyde and a cyclic amine of type (XXI) in an acidic solvent, such as acetic acid, or in a mixture of an acid with an organic solvent (scheme 6). Bromination of the resulting product (XXII) with 1,3-dibromo-5,5-dimethyl-hydantoin, as described above, then provides the target pyrrolotriazine (IIg).

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Scheme 6



[G = *e.g.* CH_2, CH(OH), O or N-Boc].

The compounds of the formulae (V), (VII), (XI), (XV), (XIX) and (XXI) are either commercially available, known from the literature, or can be prepared from readily available starting materials by adaptation of standard methods described in the literature.

The compounds of the present invention have valuable pharmacological properties and can be used for the prevention and treatment of disorders in humans and animals.

The compounds of the present invention are potent and selective inhibitors of ALK1 kinase. They can therefore be used for the treatment and/or prevention of angiogenesis-related disorders, in particular of angiogenesis-related ocular disorders.

For the present invention, the term "treatment" or "treating" includes: inhibiting, delaying, relieving, mitigating, arresting, reducing, or causing the regression of a disease, disorder, condition, or state, the development and/or progression thereof, and/or the symptoms thereof. The term "prevention" or "preventing" includes: reducing the risk of having, contracting, or experiencing, a disease, disorder, condition, or state, the development and/or progression thereof, and/or the symptoms thereof. The term prevention includes prophylaxis. Treatment or prevention of a disease, disorder, condition, or state may be partial or complete.

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Angiogenesis-related ocular disorders that may be treated and/or prevented with the compounds of the present invention include, but are not limited to, age-related macular degeneration (AMD), diabetic retinopathy, other retinopathies such as choroidal neovascularisation (CNV), choroidal neovascular membrane (CNVM), cystoid macular edema (CME), epi-retinal membrane (ERM) and macular hole, hypertrophic changes of the retinal pigment epithelium (RPE), atrophic changes of the retinal pigment epithelium, retinal detachment, choroidal vein occlusion, retinal vein occlusion, corneal angiogenesis following, for example, keratitis, cornea transplantation or keratoplasty, corneal angiogenesis due to hypoxia (*e.g.*, induced by extensive contact lens wearing), pterygium conjunctivae, subretinal edema, and intraretinal edema.

In the context of the present invention, the term age-related macular degeneration (AMD) encompasses both wet (or exudative, neovascular) and dry (or non-exudative, non-neovascular) manifestations of AMD.

The compounds of the present invention can additionally be used for the treatment and/or prevention of inflammatory diseases associated with angiogenesis, such as rheumatoid arthritis, psoriasis, contact dermatitis, asthma, pulmonary hypertension, multiple sclerosis, and inflammatory diseases of the bowel such as Crohn's disease. Fibrotic diseases, such as fibrosis and cirrhosis, may also be treated and/or prevented with the compounds of the present invention.

By virtue of their activity profile, the compounds of the present invention are particularly suitable for the treatment and/or prevention of ocular disorders, such as age-related macular degeneration (AMD), choroidal neovascularisation (CNV) and diabetic retinopathy.

The disorders mentioned above have been well characterized in humans, but also exist with a similar etiology in other animals, including mammals, and can be treated in these with the compounds of the present invention.

Thus, the present invention further relates to the use of the compounds according to the invention for the treatment and/or prevention of disorders, especially of the aforementioned disorders.

The present invention further relates to the use of the compounds according to the invention for preparing a pharmaceutical composition for the treatment and/or prevention of disorders, especially of the aforementioned disorders.

The present invention further relates to the use of the compounds according to the invention in a method for the treatment and/or prevention of disorders, especially of the aforementioned disorders.

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The present invention further relates to a method for the treatment and/or prevention of disorders, especially of the aforementioned disorders, by using an effective amount of at least one of the compounds according to the invention.

Compounds of the present invention may be administered as the sole pharmaceutical agent or in combination with one or more additional therapeutic agents where the combination causes no unacceptable adverse effects. This combination therapy includes administration of a single pharmaceutical dosage formulation which contains a compound of formula (I), as defined above, and one or more additional therapeutic agents, as well as administration of a compound of formula (I) and each additional therapeutic agent in its own separate pharmaceutical dosage formulation. For example, a compound of formula (I) and a therapeutic agent may be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent may be administered in separate dosage formulations.

Where separate dosage formulations are used, the compound of formula (I) and one or more additional therapeutic agents may be administered at essentially the same time (*i.e.*, concurrently) or at separately staggered times (*i.e.*, sequentially).

In particular, the compounds of the present invention may be used in fixed or separate combination with inhibitors of VEGF-mediated angiogenesis, such as, for example, ACTB-1003, aflibercept, apatinib, axitinib, bevacizumab, bevasiranib, BMS-690514, brivanib, cediranib, CT-322, dovitinib, E7080, foretinib, KH-902, linifanib, MGCD-265, motesanib, OTS-102, pazopanib, pegaptanib, ranibizumab, regorafenib, ruboxystaurin, sorafenib, SU-14813, sunitinib, telatinib, TG-100801, tivozanib, TSU-68, vandetanib, vargatef, vatalanib and XL-184, or with inhibitors of other signaling pathways, such as, for example, ACU-4429, disulfiram, E-10030, fenretinide, mecamylamine, PF-04523655, sirolimus, sonepcizumab, tandospirone and volociximab.

Thus, in a further embodiment, the present invention relates to pharmaceutical compositions comprising at least one of the compounds according to the invention and one or more additional therapeutic agents for the treatment and/or prevention of disorders, especially of the aforementioned disorders.

The compounds of the present invention may also be utilized, as such or in compositions, in research and diagnostics, or as analytical reference standards and the like.

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In another aspect, the present invention relates to pharmaceutical compositions comprising at least one of the compounds according to the invention together with one or more inert, non-toxic, pharmaceutically suitable excipients, and to the use thereof for the aforementioned purposes.

The compounds according to the invention can act systemically and/or locally. For this purpose, they can be administered in a suitable way such as, for example, by the oral, parenteral, pulmonary, nasal, lingual, sublingual, buccal, rectal, dermal, transdermal, conjunctival, subconjunctival, intravitreal, otic or topical routes.

The compounds according to the invention can be administered in application forms suitable for these administration routes.

Suitable for oral administration are application forms which function according to the prior art and deliver the compounds according to the invention rapidly and/or in modified fashion, and which contain the compounds according to the invention in crystalline, amorphous and/or dissolved form, such as, for example, tablets (uncoated or coated tablets, for example having enteric coatings or coatings which are insoluble or dissolve with a delay and control the release of the compound according to the invention), tablets which disintegrate rapidly in the mouth, or films/wafers, films/lyophilisates, capsules (*e.g.*, hard or soft gelatin capsules), sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, aerosols or solutions.

Parenteral administration can take place with avoidance of an absorption step (*e.g.*, intravenous, intraarterial, intracardiac, intraspinal or intralumbar) or with inclusion of an absorption (*e.g.*, intramuscular, subcutaneous, intracutaneous, percutaneous or intraperitoneal). Application forms suitable for parenteral administration are, *inter al.*, preparations for injection and infusion in the form of solutions, suspensions, emulsions, lyophilisates or sterile powders.

Forms suitable for other administration routes include, for example, pharmaceutical forms for inhalation (*e.g.*, powder inhalers, nebulizers), nasal drops, solutions or sprays, tablets or capsules for lingual, sublingual or buccal administration (*e.g.*, troches, lozenges), suppositories, ear and eye preparations (*e.g.*, drops, ointments), vaginal capsules, aqueous suspensions (lotions, shaking mixtures), lipophilic suspensions, ointments, creams, milk, pastes, foams, dusting powders, and transdermal therapeutic systems (*e.g.*, patches).

The compounds according to the invention can be converted into the recited application forms in a manner known *per se* by mixing with inert, non-toxic, pharmaceutically suitable excipients. These excipients include, *inter al.*, carriers (*e.g.*, microcrystalline cellulose, lactose, mannitol), solvents (*e.g.*, liquid polyethylene glycols), emulsifiers (*e.g.*, sodium dodecyl sulfate), surfactants

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(*e.g.*, polyoxysorbitan oleate), dispersants (*e.g.*, polyvinylpyrrolidone), synthetic and natural polymers (*e.g.*, albumin), stabilizers (*e.g.*, antioxidants such as, for example, ascorbic acid), colorants (*e.g.*, inorganic pigments such as, for example, iron oxides), and taste and/or odour masking agents.

It has generally proved advantageous to administer on parenteral administration amounts of about 0.001 to 1 mg/kg, preferably about 0.01 to 0.5 mg/kg, of body weight to achieve effective results. On oral administration, an exemplary dose range is about 0.01 to 100 mg/kg, preferably about 0.01 to 20 mg/kg, and more preferably about 0.1 to 10 mg/kg of body weight.

Nevertheless, actual dosage levels and time course of administration of the active ingredients in the pharmaceutical compositions of the invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition and mode of administration, without being toxic to the patient. It may therefore be necessary where appropriate to deviate from the stated amounts, in particular as a function of age, gender, body weight, diet and general health status of the patient, route of administration, individual response to the active ingredient, nature of the preparation, and time or interval over which administration takes place. Thus, it may be satisfactory in some cases to manage with less than the aforementioned minimum amount, whereas in other cases the stated upper limit must be exceeded. It may in the event of administration of larger amounts be advisable to divide these into multiple individual doses spread over the day.

For the treatment and/or prevention of ocular disorders, as described above, the preferred route for administering the compounds of the invention is topically at the eye or by an ocular drug delivery system. Intraocular injections are another way to administer the compounds of the present invention that is suitable for such purposes.

Delivery to areas within the eye can be accomplished by injection, employing a cannula or another invasive device designed to introduce precisely metered amounts of a desired formulation to a particular compartment or tissue within the eye (*e.g.*, posterior chamber or retina). An intraocular injection may be into the vitreous (intravitreal), under the conjunctiva (subconjunctival), behind the eye (retrobulbar), into the sclera, or under the Capsule of Tenon (sub-Tenon), and may be in a depot form. Other intraocular routes of administration and injection sites and forms are also contemplated and are within the scope of the invention.

The compounds according to the invention may be formulated in a manner known to those skilled in the art so as to give adequate delivery to the back of the eye, which may be by regular

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dosing, such as with eye drops, or by using a delivery system to give a controlled release, such as slow release, of the compounds according to the invention.

Preferred ocular formulations for the compounds of the present invention include aqueous solutions, suspensions or gels of these compounds in the form of drops of liquid, liquid washes, sprays, ointments or gels, in admixture with excipients suitable for the manufacture and use of such application forms. Alternatively, the compounds of the present invention may be applied to the eye via liposomes or other ocular delivery systems that are known in the art.

Appropriate dosage levels may be determined by any suitable method known to one skilled in the art of treating eye diseases. Preferably, the active substance is administered at a frequency of 1 to 4 times per day for topical administration, or less often if a drug delivery system is used. Typically, an ocular formulation intended for topical application contains the active ingredient in a concentration range of about 0.001% to 10%.

The following exemplary embodiments illustrate the invention. The invention is not restricted to the examples.

The percentages in the following tests and examples are, unless stated otherwise, by weight; parts are by weight. Solvent ratios, dilution ratios and concentrations reported for liquid/liquid solutions are each based on volume.

A. Examples

Abbreviations and Acronyms:

Ac	acetyl
aq.	aqueous (solution)
Boc	*tert*-butoxycarbonyl
br.	broad (^{1}H NMR signal)
Cbz	benzyloxycarbonyl
Celite®	registered trademark of Celite Corp. brand of diatomaceous earth
conc.	concentrated

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DCI	direct chemical ionization (MS)
DCM	dichloromethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
e.e.	enantiomeric excess
EI	electron impact ionization (MS)
eq.	equivalent(s)
ESI	electro-spray ionization (MS)
Et	ethyl
EtOAc	ethyl acetate
Fmoc	(9*H*-fluoren-9-ylmethoxy)carbonyl
GC/MS	gas chromatography-coupled mass spectroscopy
h	hour(s)
Hal	halogen
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
HPLC	high performance liquid chromatography
LC/MS	liquid chromatography-coupled mass spectroscopy
Me	methyl
MeOH	methanol
min	minute(s)
MS	mass spectroscopy
of th.	of theory (chemical yield)
$PdCl_2$(dppf)	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
Ph	phenyl
rac	racemic

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R_f	TLC retention factor
rt	room temperature
R_t	retention time (HPLC)
satd.	saturated
TBAF	tetrabutylammonium fluoride
tBu	*tert*-butyl
tert	tertiary
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography

Preparative HPLC purification methods:

Method 1:

Device: Gilson Abimed HPLC, binary pump system; column: ReproSil C18, 250 mm x 30 mm; eluent A: water / 1% ammonia, eluent B: acetonitrile; gradient: 0-3 min 10% B, 5.01-31 min 95% B, 31 min 95% B; flow rate: 50 mL/min; UV detection: 210 nm.

Method 2:

Device: Gilson Abimed HPLC, binary pump system; column: Kromasil-100A C18, 5 µm, 250 mm x 30 mm; eluent A: water / 0.05-0.5% TFA, eluent B: acetonitrile; gradient: 0-5 min 5% B, 5.01-10 min 10% B, 10.01-20 min 40% B, 20.01-27 min 50% B, 27.01-40 min 60% B, 40.01-45 min 90% B, 45.01-60 min 100% B; flow rate: 15-60 mL/min; UV detection: 210 nm.

Method 3:

Device: Gilson Abimed HPLC, binary pump system; column: Grom-Sil-120 ODS-4HE, 250 mm x 30 mm; eluent A: water, eluent B: acetonitrile; gradient: 0-3 min 10% B, 3.01-35 min 98% B, 35.01-40 min 98% B; flow rate: 50 mL/min; UV detection: 210 nm.

Method 4:

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Device: Gilson Abimed HPLC, binary pump system; column: Grom-Sil-120 ODS-4HE, 250 mm x 30 mm; eluent A: water / 0.5% ammonia, eluent B: acetonitrile; gradient: 0-3 min 10% B, 3.01-35 min 98% B, 35.01-40 min 98% B; flow rate: 50 mL/min; UV detection: 210 nm.

Analytical HPLC, LC/MS and GC/MS methods:

Method 1 (HPLC):

Instrument: Agilent 1100 with DAD detection; column: Agilent Zorbax Eclipse XDB-C8 4.6, 150 mm x 5 mm; eluent A: 0.01% TFA in water; eluent B: 0.01% TFA in acetonitrile; gradient: 0-1 min 10% B, 4-5 min 90% B, 5.5 min 10% B; flow rate: 2.0 mL/min; temperature: 30°C; UV detection: 210 nm.

Method 2 (HPLC):

Instrument: HP 1100 with DAD detection; column: Kromasil 100 RP-18, 60 mm x 2.1 mm, 3.5 µm; eluent A: 5 mL perchloric acid (70%) / L water, eluent B: acetonitrile; gradient: 0 min 2% B, 0.5 min 2% B, 4.5 min 90% B, 6.5 min 90% B, 6.7 min 2% B, 7.5 min 2% B; flow rate: 0.75 mL/min; temperature: 30°C; UV detection: 210 nm.

Method 3 (HPLC):

Instrument: HP 1100 with DAD detection; column: Kromasil 100 RP-18, 60 mm x 2.1 mm, 3.5 µm; eluent A: 5 mL perchloric acid (70%) / L water, eluent B: acetonitrile; gradient: 0 min 2% B, 0.5 min 2% B, 4.5 min 90% B, 9 min 90% B, 9.2 min 2% B, 10 min 2% B; flow rate: 0.75 mL/min; temperature: 30°C; UV detection: 210 nm.

Method 4 (LC/MS):

Instrument: Micromass Platform LCZ with HPLC Agilent 1100 Series; column: Thermo Hypersil GOLD 3µ, 20 mm x 4 mm; eluent A: 1 L water + 0.5 mL 50% formic acid, eluent B: 1 L acetonitrile + 0.5 mL 50% formic acid; gradient: 0.0 min 100% A → 0.2 min 100% A → 2.9 min 30% A → 3.1 min 10% A → 5.5 min 10% A; temperature: 50°C; flow rate: 0.8 mL/min; UV detection: 210 nm.

Method 5 (LC/MS):

Instrument: Micromass ZQ with HPLC Waters Alliance 2795 / HP 1100; column: Phenomenex Synergi 2.5µ MAX-RP 100A Mercury, 20 mm x 4 mm; eluent A: 1 L water + 0.5 mL 50% formic acid, eluent B: 1 L acetonitrile + 0.5 mL 50% formic acid; gradient: 0.0 min 90% A →

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2.5 min 30% A → 3.0 min 5% A → 4.0 min 5% A; flow rate: 2 mL/min; temperature: 50°C; UV detection: 210 nm.

Method 6 (LC/MS):

Instrument: Micromass Quattro Premier with Waters UPLC Acquity; column: Thermo Hypersil GOLD 1.9µ, 50 mm x 1 mm; eluent A: 1 L water + 0.5 mL 50% formic acid, eluent B: 1 L acetonitrile + 0.5 ml 50% formic acid; gradient: 0.0 min 90% A → 0.1 min 90% A → 1.5 min 10% A → 2.2 min 10% A; temperature: 50°C; flow rate: 0.33 mL/min; UV detection: 210 nm.

Method 7 (LC/MS):

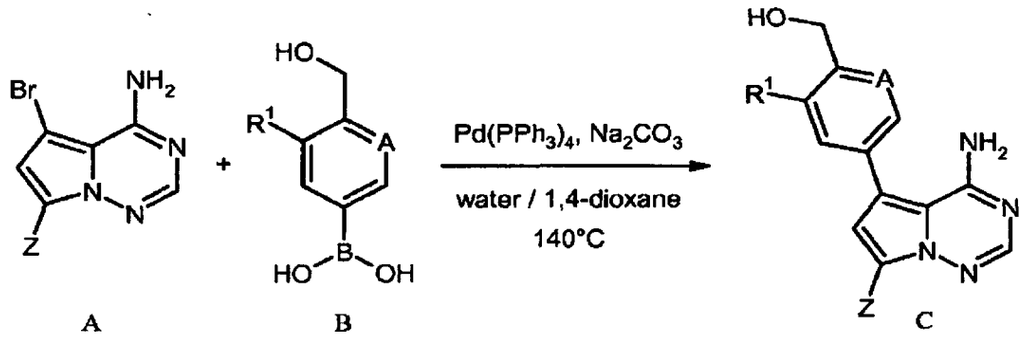
Instrument: Micromass ZQ with HPLC Waters Alliance 2795; column: Phenomenex Synergi 2.5µ MAX-RP 100A Mercury, 20 mm x 4 mm; eluent A: 1 L water + 0.5 mL 50% formic acid, eluent B: 1 L acetonitrile + 0.5 mL 50% formic acid; gradient: 0.0 min 90% A → 0.1 min 90% A → 3.0 min 5% A → 4.0 min 5% A → 4.01 min 90% A; flow rate: 2 mL/min; temperature: 50°C; UV detection: 210 nm.

Method 8 (GC/MS):

Instrument: Micromass GCT, GC6890; column: Restek RTX-35, 15 m x 200 µm x 0.33 µm; constant flow with helium: 0.88 mL/min; oven: 70°C; inlet: 250°C; gradient: 70°C, 30°C/min → 310°C (keep for 3 min).

General synthetic method 1:

Suzuki coupling of 5-bromopyrrolo[2,1-f][1,2,4]triazine derivatives with arylboronic acids or esters:



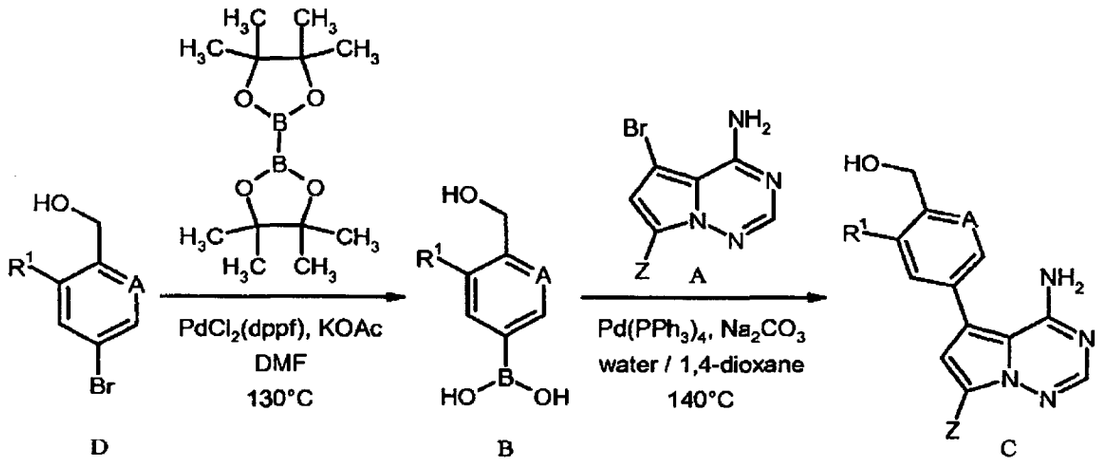
A 5-bromopyrrolo[2,1-f][1,2,4]triazine A (about 0.5 mmol), arylboronic acid B (1.2 equivalents) or a corresponding boronic ester, *e.g.*, a dimethyl boronate or pinacolato boronate, and tetrakis-(triphenylphosphine)palladium(0) (0.1 equivalents) are dissolved in a mixture of 1,4-dioxane

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(about 4.0 mL) and 2 M aqueous sodium carbonate solution (1.5 mL) in a microwave reactor vial. The reaction vessel is crimp-capped, and the mixture is heated to 140°C for 1 h in a single-mode microwave device. After cooling, the reaction mixture is filtered over a pad of Celite which is rinsed with 1,4-dioxane to elute all organic material. The combined filtrate is evaporated to dryness under reduced pressure, and the residue is purified by preparative HPLC to give the target compound C.

General synthetic method 2:

Borylation of arylbromides and subsequent Suzuki coupling with 5-bromopyrrolo[2,1-f][1,2,4]-triazine derivatives without isolation of the intermediate arylboronic acid or ester:



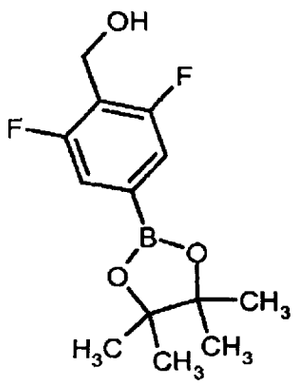
Arylbromide D (about 0.5 mmol) is dissolved in DMF (3 mL) in a microwave reactor vessel, argon is bubbled through the solution for 5 min, and [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II)-dichloromethane complex (0.1 equivalents), potassium acetate (3 equivalents) and bis(pinacolato)diboron (1.2 equivalents) are added. The vessel is crimp-capped, and the mixture is heated to 130°C for 60 min in a single-mode microwave device. Then, the suspension is filtered, the filtrate is transferred to another microwave process vial, and tetrakis(triphenylphosphine)palladium(0) (0.1 equivalents), 2 M aqueous sodium carbonate solution (4 equivalents) and the 5-bromopyrrolo[2,1-f][1,2,4]triazine A (1 equivalent) are added. The vial is crimp-capped, and the mixture is heated to 140°C for 1 h in a single-mode microwave device. The crude reaction mixture thus obtained is directly injected onto a preparative HPLC column for separation and purification of the target compound C.

Starting Materials and Intermediates:

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Intermediate 1A

[2,6-Difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol

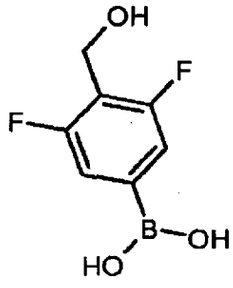


(4-Bromo-2,6-difluorophenyl)methanol (1.03 g, 4.62 mmol) was dissolved in dry 1,4-dioxane (10 mL). Argon was bubbled through the solution, then [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium-dichloromethane complex (302 mg, 0.37 mmol, 0.08 eq.), anhydrous potassium acetate (907 mg, 9.24 mmol, 2 eq.) and bis(pinacolato)diboron (1.23 g, 4.85 mmol, 1.05 eq.) were added, and the mixture was heated to 130°C for 1 h in a single-mode microwave device. Upon cooling, the mixture was filtered, and the solvent was removed under reduced pressure. Cyclohexane (200 mL) was added to the residue, and the mixture was vigorously stirred for 30 min. Undissolved material was then removed by filtration, the cyclohexane was distilled off, and the residue was purified by flash chromatography over silica gel (dichloromethane/acetonitrile gradient). Fractions containing the product were combined and evaporated. The title compound crystallized spontaneously as a brownish solid. Yield: 790 mg (63% of th.).

GC-MS (method 8): R_t = 5.36 min; MS (EI): *m/z* (%) = 270.3 (15) $[M]^+$.

Intermediate 2A

[3,5-Difluoro-4-(hydroxymethyl)phenyl]boronic acid



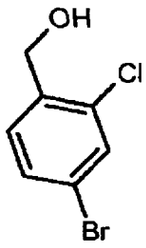
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[4-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-3,5-difluorophenyl]boronic acid (19.3 g, 63.9 mmol; crude material, prepared by the method of Hattori, *Bioorg. Med. Chem.* **2006**, *14*, 3258-3262) was dissolved in 400 mL aqueous acetic acid (66%) and stirred at 40°C for 5 h. The solution was then evaporated under reduced pressure, and the residue was purified by flash chromatography over silica gel (gradient elution from 0% to 2% methanol in dichloromethane) to give 3.46 g (25% of th., LC-MS purity 87%) of the title compound.

LC-MS (method 7): R_t = 0.50 min; MS (ESIpos): *m/z* (%) = 171.2 (100) $[M-OH]^+$, MS (ESIneg): *m/z* (%) = 187.3 (100) $[M-H]^-$.

Intermediate 3A

(4-Bromo-2-chlorophenyl)methanol



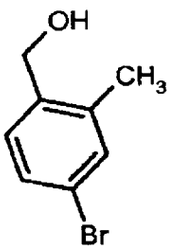
The title compound was prepared according to the procedure described in WO 2004/074270-A2 [Example A(147), step 1].

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.00 (br, 1H), 4.74 (s, 2H), 7.38 (d, 1H), 7.43 (dd, 1H), 7.53 (d, 1H).

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Intermediate 4A

(4-Bromo-2-methylphenyl)methanol

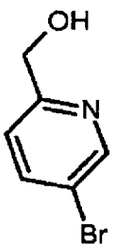


The title compound was prepared according to the procedure described in EP 1 544 208-A1 (Reference Example 14).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.62 (t, 3H), 2.32 (s, 3H), 4.64 (d, 2H), 7.23 (d, 1H), 7.32 (s, 1H), 7.33 (d, 1H).

Intermediate 5A

(5-Bromopyridin-2-yl)methanol



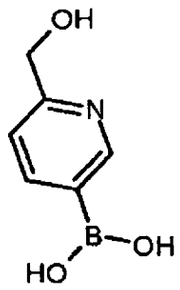
Methyl 5-bromopyridine-2-carboxylate (2.00 g, 9.27 mmol) was dissolved in ethanol (20.0 mL). Sodium borohydride (1.05 g, 27.8 mmol) was added at 0°C, and the mixture was stirred at room temperature for 18 h. The mixture was then concentrated under reduced pressure, quenched with 1 N hydrochloric acid, neutralized with solid potassium carbonate and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and evaporated to give 1.57 g (90% of th.) of the title compound.

LC-MS (method 6): R_t = 0.56 min; MS (ESIpos): *m/z* (%) = 188.0 (100) $[M+H]^+$.

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Intermediate 6A

[6-(Hydroxymethyl)pyridin-3-yl]boronic acid

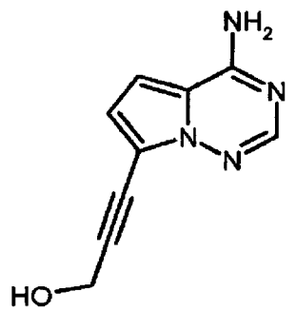


To a solution of Intermediate 5A (1.50 g, 7.98 mmol) and bis(pinacolato)diboron (2.23 g, 8.28 mmol) in degassed DMF (120 mL) was added under an argon atmosphere 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) chloride (292 mg, 0.40 mmol) and potassium acetate (2.35 g, 23.9 mmol). The mixture was heated to 80°C for 18 h and then cooled to room temperature. The suspension was filtered, and the residue was washed with dioxane. The combined filtrates were concentrated under reduced pressure, and the oily residue was taken up in 50 mL ethyl acetate and 50 mL cyclohexane and allowed to stand at room temperature overnight. The resulting precipitate was collected by filtration and discarded. The filtrate was evaporated, and the residue was dissolved again in 100 mL ethyl acetate and extracted twice with 50 mL water. The aqueous layer was concentrated to give 690 mg (56% of th.) of the title compound which was used without further purification.

LC-MS (method 6): R_t = 0.18 min; MS (ESIpos): *m/z* (%) = 154.0 (100) $[M+H]^+$.

Intermediate 7A

3-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)prop-2-yn-1-ol



The starting material 7-bromopyrrolo[2,1-f][1,2,4]triazin-4-amine was synthesized according to the procedure described in WO 2007/056170-A2 (Intermediate B).

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7-Bromopyrrolo[2,1-f][1,2,4]triazin-4-amine (1.0 g, 4.69 mmol), copper(I) iodide (89 mg, 0.47 mmol, 0.1 eq.) and tetrakis(triphenylphosphine)palladium(0) (542 mg, 0.47 mmol, 0.1 eq.) were charged into a microwave reactor vial and evacuated for 1 h. The vessel was then vented with argon, pyrrolidine (15 mL) and 2-propyn-1-ol (2.63 g, 47 mmol, 10 eq.) were added, and the vessel was crimp-capped and heated to 85°C for 120 min in a single-mode microwave device. After cooling, the reaction mixture was poured into 120 mL of concentrated aqueous ammonium chloride solution which was extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and evaporated, and the residue was purified by flash chromatography (Biotage silica column, ethyl acetate). The resulting product (222 mg) appeared pure by LC-MS (method 6) and was used for further transformations.

HPLC (method 2): R_t = 2.59 min;

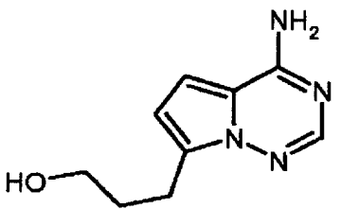
LC-MS (method 6): R_t = 0.28 min; MS (ESIpos): *m/z* (%) = 189.2 (100) $[M+H]^+$.

Intermediate 8A and Intermediate 9A

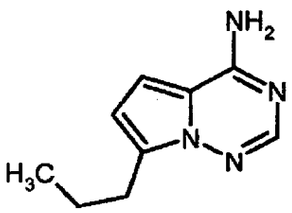
3-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)propan-1-ol

and

7-Propylpyrrolo[2,1-f][1,2,4]triazin-4-amine



and



Intermediate 7A (444 mg, 2.36 mmol) was dissolved in acetic acid (18 mL) under an argon atmosphere. Platinum(IV) oxide (40 mg, 0.18 mmol, 0.08 eq.) was added, and the mixture was vigorously stirred for 3 h at room temperature under an atmosphere of hydrogen at ambient pressure. The catalyst was then removed by filtration, the solvent was distilled off, and the residue was subjected to flash chromatography (Biotage silica column, cyclohexane/ethyl acetate gradient). The Intermediates 8A (185 mg, 41% of th.) and 9A (170 mg, 41% of th.) were obtained in two distinct chromatographic fractions:

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Intermediate 8A:

HPLC (method 2): R_t = 2.68 min;

LC-MS (method 4): R_t = 0.83 min; MS (ESIpos): *m/z* (%) = 193.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 191.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.80 (m, 2H), 2.86 (t, *J* = 7.7 Hz, 2H), 3.45 (m, 2H), 4.49 (t, *J* = 5.1 Hz, 1H), 6.41 (d, *J* = 4.2 Hz, 1H), 6.69 (d, *J* = 4.2 Hz, 1H), 7.50 (br. s, 2H), 7.78 (s, 1H).

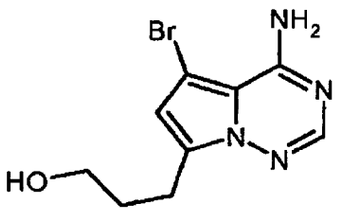
Intermediate 9A:

HPLC (method 1): R_t = 3.22 min;

LC-MS (method 4): R_t = 1.23 min; MS (ESIpos): *m/z* (%) = 177.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 175.2 (30) $[M-H]^-$.

Intermediate 10A

3-(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)propan-1-ol



Intermediate 8A (105 mg, 0.55 mmol) was dissolved in THF (8.75 mL) and cooled to -20°C. 1,3-Dibromo-5,5-dimethylhydantoin (78.1 mg, 0.5 eq.) was added, and the mixture was stirred at -20°C for 1 h. The reaction was then quenched with 0.5 mL concentrated aqueous sodium dithionite solution, warmed to room temperature and partitioned between ethyl acetate and water. The organic phase was dried over anhydrous sodium sulfate, and the solvent was distilled off. Yield: 145 mg (98% of th.).

HPLC (method 1): R_t = 2.96 min; HPLC (method 2): R_t = 2.95 min;

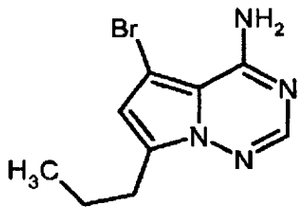
LC-MS (method 5): R_t = 1.03 min; MS (ESIpos): *m/z* (%) = 271.0 (100) and 273.0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 269.0 (99) and 271.0 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.75 (m, 2H), 2.83 (t, *J* = 8.1 Hz, 2H), 3.43 (m, 2H), 4.50 (t, *J* = 5.4 Hz, 1H), 6.62 (s, 1H), 7.81 (s, 1H).

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Intermediate 11A

5-Bromo-7-propylpyrrolo[2,1-f][1,2,4]triazin-4-amine



Intermediate 9A (110 mg, 0.62 mmol) was dissolved in THF (4.44 mL) and cooled to -20°C. 1,3-Dibromo-5,5-dimethylhydantoin (89 mg, 0.5 eq.) was added, and the mixture was stirred at -20°C for 1 h. The reaction was then quenched with 0.5 mL concentrated aqueous sodium dithionite solution, warmed to room temperature and partitioned between ethyl acetate and water. The organic phase was dried over anhydrous sodium sulfate, and the solvent was distilled off. Yield: 154 mg (85% pure, 82% of th.).

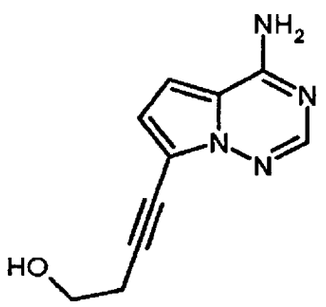
HPLC (method 1): R_t = 3.78 min;

LC-MS (method 7): R_t = 1.55 min; MS (ESIpos): *m/z* (%) = 255.0 (99) and 257.2 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.91 (t, *J* = 7.3 Hz, 3H), 1.65 (m, 2H), 2.79 (t, *J* = 7.6 Hz, 2H), 3.31 (s, 2H), 6.63 (s, 1H), 7.95 (s, 1H).

Intermediate 12A

4-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)but-3-yn-1-ol



7-Bromopyrrolo[2,1-f][1,2,4]triazin-4-amine (1.0 g, 4.69 mmol), copper(I) iodide (89 mg, 0.47 mmol, 0.1 eq.) and tetrakis(triphenylphosphine)palladium(0) (542 mg, 0.47 mmol, 0.1 eq.) were charged into a microwave reactor vial and evacuated for 1 h. The vessel was then vented with argon, pyrrolidine (15 mL) and 3-butyn-1-ol (3.36 g, 47 mmol, 10 eq.) were added, and the vessel was crimp-capped and heated to 85°C for 120 min in a single-mode microwave device.

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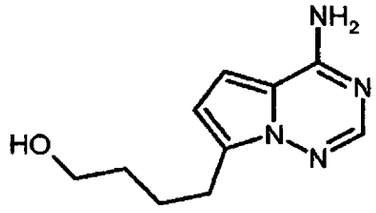
After cooling, the reaction mixture was poured into 120 mL of concentrated aqueous ammonium chloride solution and extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and evaporated, and the residue was purified by flash chromatography (Biotage silica column, ethyl acetate). The resulting product (735 mg) was sufficiently pure (66% by HPLC) for further transformations.

HPLC (method 2): R_t = 2.77 min;

LC-MS (method 4): R_t = 0.96 min; MS (ESIpos): *m/z* (%) = 203.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 201.1 (100) $[M-H]^-$.

Intermediate 13A

4-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)butan-1-ol



Intermediate 12A (607 mg, 3.00 mmol) was dissolved in acetic acid (64 mL), and platinum(IV) oxide (50 mg, 0.22 mmol, 0.07 eq.) was added. The mixture was stirred under an atmosphere of hydrogen at ambient pressure for 15 h. The catalyst was then removed by filtration, the filtrate was evaporated under reduced pressure, and the residue was purified by flash chromatography (Biotage silica column, ethyl acetate). Yield: 350 mg (57% of th.).

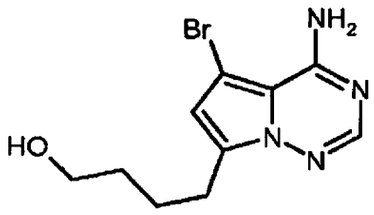
HPLC (method 2): R_t = 2.92 min;

LC-MS (method 4): R_t = 0.94 min; MS (ESIpos): *m/z* (%) = 207.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 205.3 (100) $[M-H]^-$.

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Intermediate 14A

4-(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)butan-1-ol



Intermediate 13A (330 mg, 1.60 mmol) was dissolved in THF (26 mL) at -20°C, and 1,3-dibromo-5,5-dimethylhydantoin (229 mg, 0.80 mmol) was added. The mixture was stirred at -20°C for 1 h. The reaction was then quenched with concentrated aqueous sodium sulfite solution (0.5 mL). Ethyl acetate was added, the aqueous layer was separated, and the organic layer was dried over sodium sulfate and evaporated. The crude product was subsequently purified by preparative HPLC (method 2) giving 175 mg (84% of th.) of the title compound.

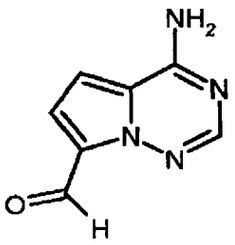
HPLC (method 1): R_t = 3.13 min;

LC-MS (method 5): R_t = 1.23 min; MS (ESIpos): *m/z* (%) = 285.0 (98) and 287.0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 283.0 (100) and 285.0 (98) $[M-H]^-$.

^{1}H-NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.39-1.48 (m, 2H), 1.60-1.69 (m, 2H), 3.31 (t, *J* = 7.3 Hz, 2H), 3.40 (m, 2H), 4.46 (br. s, 1H), 6.61 (s, 1H), 7.82 (s, 1H).

Intermediate 15A

4-Aminopyrrolo[2,1-f][1,2,4]triazine-7-carbaldehyde



The starting material pyrrolo[2,1-f][1,2,4]triazin-4-amine was synthesized according to the procedure described in WO 2007/056170-A2 (Intermediate A).

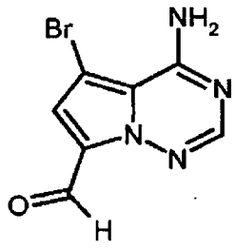
Pyrrolo[2,1-f][1,2,4]triazin-4-amine (20.5 g, 152 mmol) was dissolved in 150 mL DMF. Under ice cooling, phosphoryl chloride (31.3 mL, 336 mmol) was added dropwise at such a rate that the internal temperature did not rise above 30°C. The mixture was then heated for 2 days at 50°C.

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After cooling, another portion of phosphoryl chloride (14.2 mL, 152 mmol) was added, and stirring was continued for another 24 h at 50°C. After cooling, the reaction batch was slowly poured into a mixture of 2.0 L saturated aqueous sodium bicarbonate solution and 2.0 L ethyl acetate. Solid sodium bicarbonate was added until gas evolution stopped. The layers were separated, the aqueous layer was extracted with 0.5 L ethyl acetate, and the combined organic phases were dried over sodium sulfate and concentrated. The residue was suspended in 100 mL diisopropyl ether, stirred at room temperature for 10 min and then filtered. The dried residue was stirred in 6 N hydrochloric acid (500 mL) for 1 h at 50°C and then poured into an ice/water mixture (1000 mL). The mixture was carefully neutralized with solid sodium bicarbonate, stirred for 30 min at room temperature and then filtered again. The residue was washed with water and ligroin to yield 20.6 g (83% of th.) of white crystals which were used in the next step without further purification.

Intermediate 16A

4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazine-7-carbaldehyde



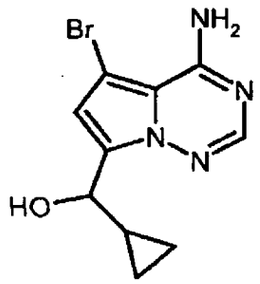
Intermediate 15A (20.6 g, 127 mmol) was dissolved in 525 mL DMF. At 0°C, 1,3-dibromo-5,5-dimethylhydantoin (21.8 g, 76.2 mmol) was added, and the mixture was stirred for 1 h under ice cooling and for further 2 h at room temperature. The resulting suspension was filtered, and the residue was washed with DMF and diethyl ether. The filtrate was discarded, and the remaining hardly soluble crystals were dried to give 20.0 g (65% of th., 80% purity by HPLC) of the title compound. This material was used without further purification.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 7.42 (s, 1H), 8.12 (s, 1H), 10.22 (s, 1H).

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Intermediate 17A

(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)(cyclopropyl)methanol



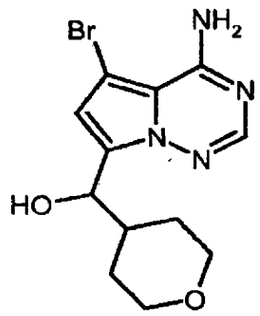
Intermediate 16A (500 mg, 1.66 mmol) was suspended in dry THF (30 mL). At 0°C, a 0.5 M solution of cyclopropyl magnesium bromide in diethyl ether (10 mL, 5.0 mmol) was added. The mixture was stirred at room temperature for 1 h. Then, another portion of the Grignard solution (6.6 mL, 3.3 mmol) was added. After further stirring for 30 min at room temperature, the reaction was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by preparative HPLC (method 4). Yield: 0.14 g (29% of th.).

LC-MS (method 6): R_t = 0.75 min; MS (ESIpos): *m/z* (%) = 283.0 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.35 (m, 3H), 0.45 (m, 1H), 1.28 (m, 1H), 4.62 (t, 1H), 5.26 (d, 1H), 6.75 (s, 1H), 7.84 (s, 1H).

Intermediate 18A

(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)(tetrahydro-2*H*-pyran-4-yl)methanol



In a 50 mL three-necked flask equipped with a condenser, a thermometer and a dropping funnel, which was purged with argon, a Grignard reagent was prepared from magnesium turnings (484 mg, 19.9 mmol) and 4-chlorotetrahydropyrane (2.4 g, 19.9 mmol) in dry THF (14 mL). To this

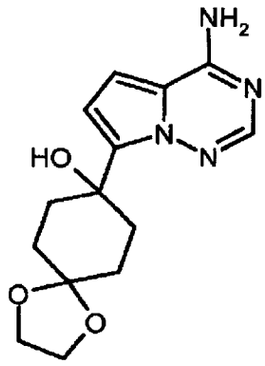
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solution was added at 0°C a suspension of Intermediate 16A (1.2 g, 3.98 mmol) in THF (20 mL), and the reaction mixture was allowed to stir for 1 h at room temperature. It was then quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate (2 x 50 mL). The organic layer was washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by preparative HPLC (method 3). Yield: 0.5 g (38% of th.).

LC-MS (method 6): R_t = 0.66 min; MS (ESIpos): *m/z* (%) = 327.0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 325.1 (100) $[M-H]^-$.

Intermediate 19A

8-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-1,4-dioxaspiro[4.5]decan-8-ol



The starting material 7-bromopyrrolo[2,1-f][1,2,4]triazin-4-amine was synthesized according to the procedure described in WO 2007/056170-A2 (Intermediate B).

7-Bromopyrrolo[2,1-f][1,2,4]triazin-4-amine (9.20 g, 35.41 mmol) was dissolved in THF (105 mL) under argon at room temperature. Chlorotrimethylsilane (9.08 mL, 7.77 g, 70.82 mmol, 2 eq.) was added, and the mixture was stirred at room temperature for 3 h. It was then cooled to 0°C, and 2-propyl magnesium chloride (74 mL of a 2.0 M solution in THF, 149 mmol, 4.2 eq.) was added. The mixture was stirred for further 3 h while warming up to room temperature. Then, 1,4-dioxaspiro[4.5]decan-8-one (8.38 g, 53.12 mmol, 1.5 eq.) was added, and stirring was continued for another 16 h. The reaction was quenched with a 1:1 mixture of concentrated aqueous ammonium chloride solution and ice until the pH value reached 6-7. The mixture was extracted with two portions of ethyl acetate, and the combined organic extracts were dried over anhydrous sodium carbonate and concentrated to dryness. The title compound was crystallized from diethyl ether. Yield: 6.05 g (58% of th.).

HPLC (method 1): R_t = 2.89 min;

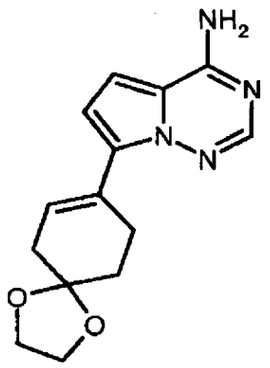
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LC-MS (method 6): R_t = 0.38 min; MS (ESIpos): *m/z* (%) = 291.2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 289.4 (100) $[M-H]^-$.

Intermediate 20A

7-(1,4-Dioxaspiro[4.5]dec-7-en-8-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



Intermediate 19A (2.81 g, 60% purity, 5.82 mmol) was dissolved in pyridine (18 mL) at 0°C. Trifluoroacetic anhydride (2.46 mL, 3.66 g, 17.45 mmol, 3 eq.) was added slowly, and the reaction mixture was stirred at ambient temperature for 16 h. The solvent was distilled off, and the residue was partitioned between water and ethyl acetate. The organic extract was dried over sodium sulfate and evaporated. The residue was triturated with diethyl ether at 0°C to yield 2.95 g (92% pure by HPLC, 99% of th.) of the title compound.

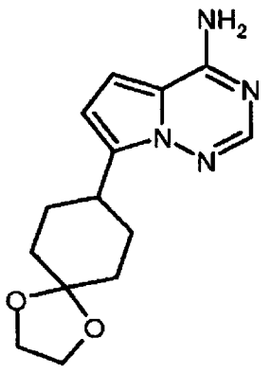
HPLC (method 1): R_t = 4.55 min;

LC-MS (method 5): R_t = 2.28 min; MS (ESIpos): *m/z* (%) = 369.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 367.1 (100) $[M-H]^-$.

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Intermediate 21A

7-(1,4-Dioxaspiro[4.5]dec-8-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



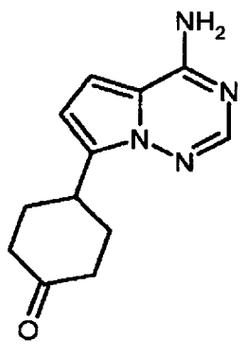
Intermediate 20A (2.95 g, 10.8 mmol) was dissolved in methanol (1.07 L) under argon. Palladium on charcoal (10%, 400 mg) was added, and the mixture was vigorously stirred for 24 h under an atmosphere of hydrogen at ambient pressure and room temperature. The catalyst was removed by filtration, and the solvent was distilled off under reduced pressure to give 2.11 g (71% of th.) of the title compound.

HPLC (method 1): R_t = 3.14 min;

LC-MS (method 6): R_t = 0.68 min; MS (ESIpos): *m/z* (%) = 275.3 (100) $[M+H]^+$.

Intermediate 22A

4-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)cyclohexanone



Intermediate 21A (2.11 g, 7.69 mmol) was dissolved in a mixture of 1 M hydrochloric acid (23 mL) and methanol (6.80 mL) at 0°C and stirred under ice cooling for 3 h. Then, the pH value was adjusted to 6-7 by addition of concentrated aqueous sodium bicarbonate solution. The mixture was extracted with three portions of dichloromethane, and the combined organic extracts

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were dried over anhydrous sodium sulfate, filtered and evaporated. The residue (923 mg, 52% of th.) was used without further purification in the next synthetic step.

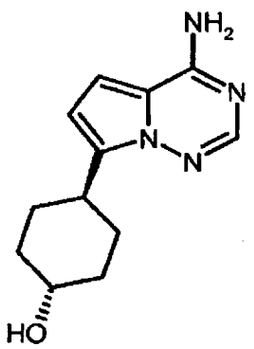
HPLC (method 2): R_t = 3.06 min;

LC-MS (method 4): R_t = 1.02 min; MS (ESIpos): *m/z* (%) = 231.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 229.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.86 (ddd, 2H), 2.25-2.36 (m, 4H), 2.59 (ddd, 2H), 3.59 (m, 1H), 6.45 (d, 1H), 6.82 (d, 1H), 7.60 (br. s, 1H), 7.82 (s, 1H).

Intermediate 23A

trans-4-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)cyclohexanol



Intermediate 22A (452 mg, 1.96 mmol) was dissolved in THF (15 mL), and the solution was cooled to 0°C. Lithium aluminium hydride solution (1 M in THF, 2.94 mL, 2.94 mmol) was added dropwise. Subsequently, the solution was stirred at 0°C for 10 min and then quenched by addition of concentrated aqueous ammonium chloride solution. The mixture was extracted with 3 portions of dichloromethane, and the combined organic extracts were dried over anhydrous sodium sulfate, filtered and evaporated. The residue (360 mg, 77% purity, 61% of th.) was used in the next synthetic step without further purification.

HPLC (method 1): R_t = 2.62 min;

LC-MS (method 6): R_t = 0.29 min; MS (ESIpos): *m/z* (%) = 233.2 (100) $[M+H]^+$.

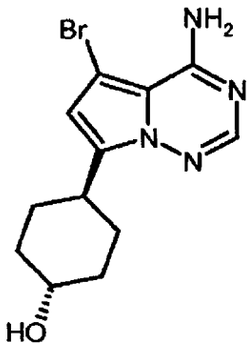
^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.30 (m, 2H), 1.42 (m, 2H), 1.91 (m, 2H), 1.99 (m, 2H), 2.97 (tt, 1H), 3.45 (m, 1H), 4.60 (d, 1H), 6.39 (d, 1H), 6.79 (d, 1H), 7.53 (br. s, 2H), 7.80 (s, 1H).

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Intermediate 24A

trans-4-(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)cyclohexanol



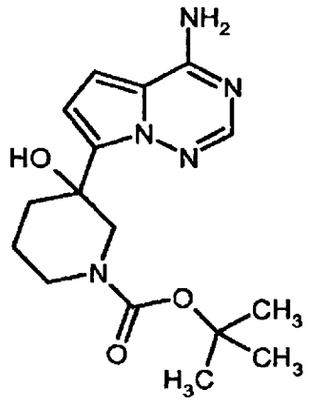
Intermediate 23A (360 mg, 85% purity, 1.19 mmol) was dissolved in THF (8 mL) at -20°C, and 1,3-dibromo-5,5-dimethylhydantoin (188 mg, 0.66 mmol, 0.55 eq.) was added. The mixture was stirred at -20°C for 1 h, then 0.5 mL concentrated aqueous sodium dithionite solution was added, and the mixture was extracted with ethyl acetate. The organic extract was dried over anhydrous sodium sulfate, filtered and evaporated. The crude product (463 mg, 66% purity, 83% of th.) was used in the next synthetic step without further purification.

HPLC (method 1): R_t = 3.22 min;

LC-MS (method 7): R_t = 1.03 min; MS (ESIpos): *m/z* (%) = 311.2 and 313.0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 309.2 (50) and 311.2 (40) $[M-H]^-$.

Intermediate 25A

tert-Butyl 3-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3-hydroxypiperidine-1-carboxylate



The starting material 7-bromopyrrolo[2,1-f][1,2,4]triazin-4-amine was synthesized according to the procedure described in WO 2007/056170-A2 (Intermediate B).

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7-Bromopyrrolo[2,1-f][1,2,4]triazin-4-amine (17.29 g, 81 mmol) was dissolved in THF (214 mL) under argon at room temperature. Chlorotrimethylsilane (20.60 mL, 17.63 g, 162 mmol, 2 eq.) was added, and the mixture was stirred at room temperature for 3 h. Then, it was cooled to 0°C, and 2-propyl magnesium chloride (170 mL of a 2.0 M solution in THF, 340 mmol, 4.2 eq.) was added. The mixture was stirred for further 3 h while warming up to room temperature. Then, *tert*-butyl 3-oxopiperidine-1-carboxylate (25.00 g, 121 mmol, 1.5 eq.) was added, and stirring was continued for another 16 h. The reaction was quenched with a 1:1 mixture of concentrated aqueous ammonium chloride solution and ice until the pH value reached 6-7. The mixture was extracted with two portions of ethyl acetate, and the combined organic extracts were dried over anhydrous sodium carbonate and concentrated to dryness. The title compound crystallized upon trituration of the residue with diethyl ether (50 mL). The crystals were washed with diethyl ether and dried to give 17.20 g (64% of th.).

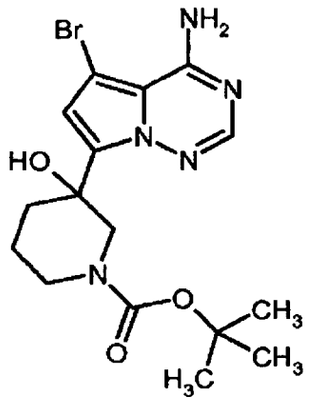
HPLC (method 2): R_t = 3.53 min;

LC-MS (method 5): R_t = 1.36 min; MS (ESIpos): *m/z* (%) = 334.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 332.0 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.19-1.43 (m, 9H), 1.72-1.88 (m, 2H), 2.38-2.46 (m, 1H), 3.02-3.20 (m, 1H), 3.44-3.96 (m, 4H), 6.58 (d, 1H), 6.81 (d, 1H), 7.82 (s, 1H).

Intermediate 26A

rac-tert-Butyl 3-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3-hydroxypiperidine-1-carboxylate



Intermediate 25A (120 mg, 0.36 mmol) was dissolved in THF (6.0 mL) at -20°C, and 1,3-dibromo-5,5-dimethylhydantoin (51 mg, 0.18 mmol, 0.5 eq.) was added. The mixture was stirred at -20°C for 2 h and then quenched with concentrated aqueous sodium sulfite solution (0.5 mL).

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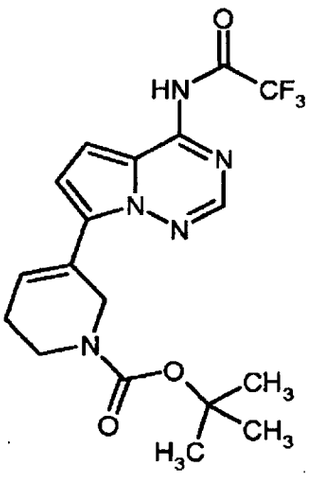
Ethyl acetate was added, the aqueous layer was separated, and the organic extract was dried over sodium sulfate and evaporated. The title compound (148 mg, 95% of th.) was obtained as a light yellow solid.

HPLC (method 1): R_t = 4.03 min;

LC-MS (method 5): R_t = 1.99 min; MS (ESIpos): *m/z* (%) = 412.0 (90) and 414.0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 410.0 (100) and 412.0 (85) $[M-H]^-$.

Intermediate 27A

tert-Butyl 5-{4-[(trifluoroacetyl)amino]pyrrolo[2,1-f][1,2,4]triazin-7-yl}-3,6-dihydropyridine-1(2*H*)-carboxylate



Intermediate 25A (8.32 g, 24.95 mmol) was dissolved in pyridine (116 mL) at 0°C. Trifluoroacetic anhydride (8.81 mL, 13.10 g, 62.36 mmol, 2.5 eq.) was added slowly, and the reaction mixture was stirred at ambient temperature for 16 h. Then, it was cooled again to 0°C, and 150 mL of diethyl ether were added. The mixture was stirred at 0°C while the title compound slowly precipitated. The product was finally filtered off and washed with diethyl ether. The filtrate was evaporated *in vacuo*, and the residue was triturated with diethyl ether at 0°C giving a second crop of the title compound after washing with diethyl ether. The two crops were combined to yield 7.80 g (92% pure by HPLC, 76% of th.) of the title compound as yellow crystals.

HPLC (method 1): R_t = 3.91 min;

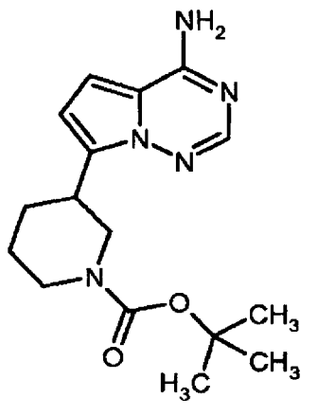
LC-MS (method 7): R_t = 2.45 min; MS (ESIpos): *m/z* (%) = 412.2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 410.2 (100) $[M-H]^-$.

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^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.48 (s, 9H), 1.92 (m, 2H), 3.58 (m, 2H), 6.90 (d, 1H), 7.30 (d, 1H), 8.03-8.10 (m, 1H), 8.42 (s, 1H).

Intermediate 28A

rac-tert-Butyl 3-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidine-1-carboxylate



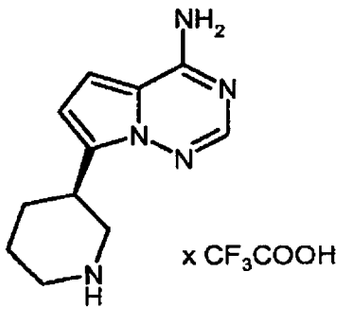
Intermediate 27A (7.80 g, 92% purity, 17.54 mmol) was dissolved in methanol (400 mL). Trifluoroacetic acid (6.76 mL, 10.0 g, 88 mmol, 5 eq.), water (3.16 mL, 175 mmol, 10 eq.) and 10% palladium on charcoal (30 mg) were added, and the mixture was hydrogenated for 24 h at room temperature and ambient pressure. The catalyst was then removed by filtration, and the solvent was evaporated *in vacuo*. The crude product (8.79 g, 75% pure, quantitative yield) was used in the next synthetic step without further purification.

HPLC (method 1): R_t = 3.64 min;

LC-MS (method 7): R_t = 1.26 min; MS (ESIpos): *m/z* (%) = 318.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 316.4 (100) $[M-H]^-$.

Intermediate 29A

7-[(3*R*)-Piperidin-3-yl]pyrrolo[2,1-f][1,2,4]triazin-4-amine trifluoroacetate



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The starting material benzyl (*R*)-3-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidine-1-carboxylate has been described in WO 2007/056170-A2 (Intermediate DDD).

1.50 g (3.49 mmol) of this material were hydrogenated for 16 h at room temperature and ambient pressure in the presence of 10% palladium on charcoal (30 mg) in a mixture of methanol (50 mL) and trifluoroacetic acid (2.70 mL). Subsequently, the catalyst was removed by filtration, and all volatiles were evaporated *in vacuo* to give 1.10 g (95% of th.) of the title compound.

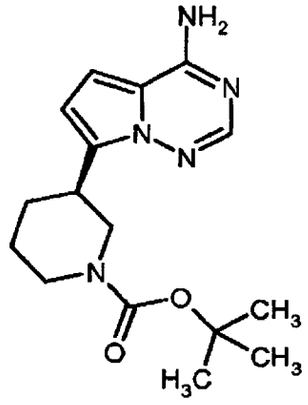
HPLC (method 2): R_t = 2.17 min;

LC-MS (method 6): R_t = 0.17 min; MS (ESIpos): *m/z* (%) = 218 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.75 (m, 2H), 1.92 (m, 1H), 2.05 (m, 1H), 2.93 (m, 1H), 3.06 (m, 1H), 3.31 (d, 1H), 3.50 (d, 1H), 3.57 (m, 1H), 6.78 (d, 1H), 7.20 (m, 1H), 8.10 (s, 1H), 8.63 (m, 1H), 8.82 (m, 1H), 9.02 (br. s, 1H).

Intermediate 30A

tert-Butyl (3*R*)-3-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidine-1-carboxylate



Intermediate 29A (1.10 g, 5.06 mmol) was suspended in dichloromethane (6.60 mL), triethylamine (1.55 mL, 1.13 g, 11.14 mmol, 2.20 eq.) was added, and the mixture was stirred for 30 min until the starting material was completely dissolved. Then, di-*tert*-butyl dicarbonate (1.22 g, 5.57 mmol, 1.1 eq.) was added, and the reaction mixture was stirred for 16 h. Subsequently, 5% aqueous citric acid was added, the phases were separated, and the organic layer was dried over sodium sulfate and evaporated. The residue was purified by preparative HPLC (method 2). Yield: 595 mg (37% of th.).

HPLC (method 2): R_t = 4.01 min;

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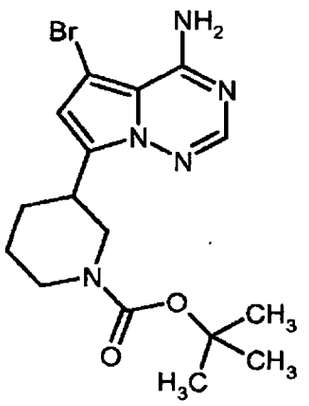
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LC-MS (method 5): R_t = 1.54 min; MS (ESIpos): *m/z* (%) = 318.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 316.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.38 (s, 9H), 1.45 (m, 2H), 1.72 (m, 2H), 2.02 (m, 2H), 2.90 (m, 1H), 3.17 (m, 1H), 3.85 (m, 1H), 4.08 (m, 1H), 6.47 (d, 1H), 6.80 (d, 1H), 7.58 (br. s, 1H), 7.81 (s, 1H).

Intermediate 31A

rac-tert-Butyl 3-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidine-1-carboxylate



Intermediate 28A (8.28 g, 75% purity, 14.39 mmol) was dissolved in THF (222 mL) at -20°C, and 1,3-dibromo-5,5-dimethylhydantoin (2.06 g, 7.19 mmol, 0.5 eq.) was added. The mixture was stirred at -20°C for 2 h and then quenched with concentrated aqueous sodium sulfite solution (0.5 mL). Ethyl acetate was added, the aqueous layer was separated, and the organic extract was dried over sodium sulfate and evaporated. The title compound (6.30 g, 86% of th.) was obtained as a light yellow solid.

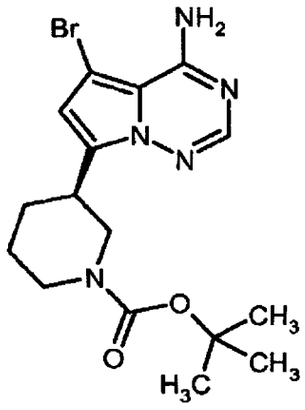
LC-MS (method 5): R_t = 2.27 min; MS (ESIpos): *m/z* (%) = 396.0 (80) and 397.9 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 394.0 (90) and 396.0 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.35 (s, 9H), 1.40-1.44 (m, 2H), 1.71 (m, 1H), 1.98 (m, 1H), 2.95 (m, 1H), 3.20 (m, 1H), 3.75 (m, 1H), 4.00 (m, 1H), 6.67 (s, 1H), 7.86 (s, 1H).

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Intermediate 32A

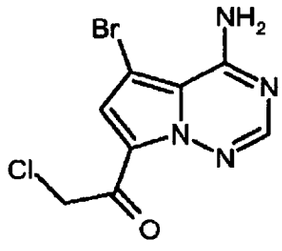
tert-Butyl (3*R*)-3-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidine-1-carboxylate



The title compound was prepared in the same way as the racemic mixture (Intermediate 31A), starting from Intermediate 30A. Analytical data were identical to those shown for Intermediate 31A.

Intermediate 33A

1-(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)-2-chloroethanone



The compound was prepared according to the procedure described in WO 2007/056170-A2 (Intermediate N, step 1).

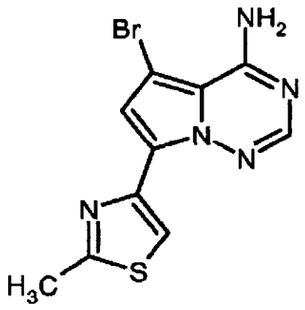
HPLC (method 1): R_t = 4.27 min;

LC-MS (method 5): R_t = 1.70 min; MS (ESIpos): *m/z* (%) = 289.0 (75) and 290.9 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 287.0 (75) and 288.9 (100) $[M-H]^-$.

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Intermediate 34A

5-Bromo-7-(2-methyl-1,3-thiazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



Intermediate 33A (100 mg, 0.35 mmol) and thioacetamide (30 mg, 0.40 mmol, 1.15 eq.) were dissolved in 1,4-dioxane (3.0 mL) in a microwave reaction vial. The vial was crimp-capped, and the mixture was heated to 130°C for 60 min in a single-mode microwave device. After cooling, the solvent was distilled off, and the residue was triturated with acetonitrile and filtered. The filtrate was discarded. The title compound was isolated as crystalline solid. Yield: 99 mg (92% of th.).

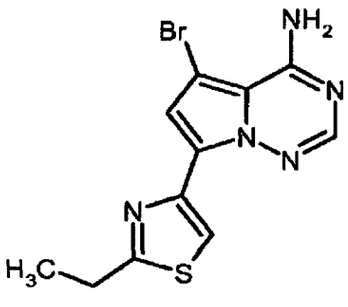
HPLC (method 1): R_t = 4.00 min;

LC-MS (method 6): R_t = 1.05 min; MS (ESIpos): *m/z* (%) = 310.0 (90) and 312 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.71 (s, 3H), 7.20 (s, 1H), 8.02 (s, 1H), 8.28 (s, 1H).

Intermediate 35A

5-Bromo-7-(2-ethyl-1,3-thiazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



Intermediate 33A (100 mg, 0.35 mmol) and thiopropionamide (32 mg, 0.36 mmol, 1.05 eq.) were refluxed in ethanol (3.0 mL) over a period of 4.5 h. After cooling, the mixture was partitioned between ethyl acetate and aqueous sodium bicarbonate solution. The organic layer was dried

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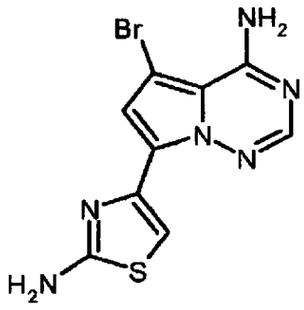
over anhydrous sodium sulfate, and the solvent was distilled off. The product was dried under vacuum to give 91 mg (0.28 mmol, 81% of th.) of the title compound as off-white solid.

HPLC (method 1): R_t = 4.30 min;

LC-MS (method 7): R_t = 1.84 min; MS (ESIpos): *m/z* (%) = 324.2 (100) and 325.8 (98) $[M+H]^+$.

Intermediate 36A

7-(2-Amino-1,3-thiazol-4-yl)-5-bromopyrrolo[2,1-f][1,2,4]triazin-4-amine



Intermediate 33A (100 mg, 0.35 mmol) and thiourea (32 mg, 0.41 mmol, 1.2 eq.) were suspended in 1,4-dioxane (3 mL) in a microwave reaction vial which was then crimp-capped. The mixture was heated to 120°C for 60 min in a single-mode microwave device. Upon cooling, water was added, and the resulting precipitate was collected by filtration and washed with dioxane. The off-white solid was dried under vacuum to give 98 mg (91% of th.) of the title compound.

HPLC (method 1): R_t = 3.19 min;

LC-MS (method 5): R_t = 1.25 min; MS (ESIpos): *m/z* (%) = 310.9 (95) and 312.9 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 309.0 (100) and 310.9 (70) $[M-H]^-$.

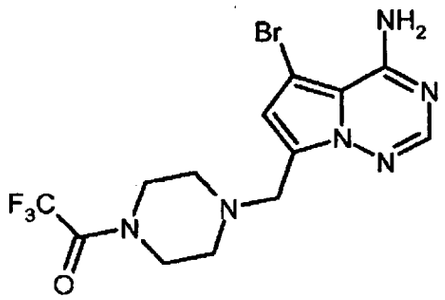
^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 7.17 (s, 1H), 7.52 (s, 1H), 8.07 (s, 1H).

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Intermediate 37A

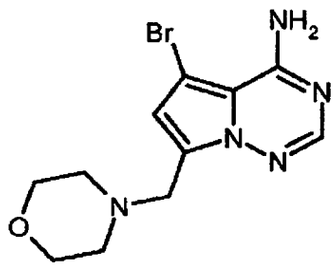
1-{4-[(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]piperazin-1-yl}-2,2,2-trifluoro-ethanone



The compound was prepared according to the procedure described in WO 2007/056170-A2 (Example 416, step 6).

Intermediate 38A

5-Bromo-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine

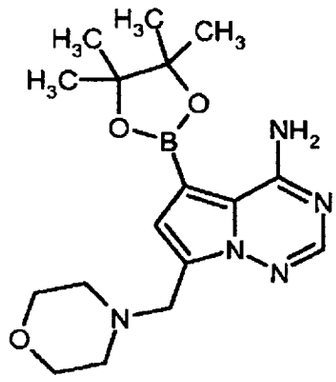


The compound was prepared according to the procedure described in WO 2007/064931-A2 (Intermediate C).

Intermediate 39A

7-(Morpholin-4-ylmethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-4-amine

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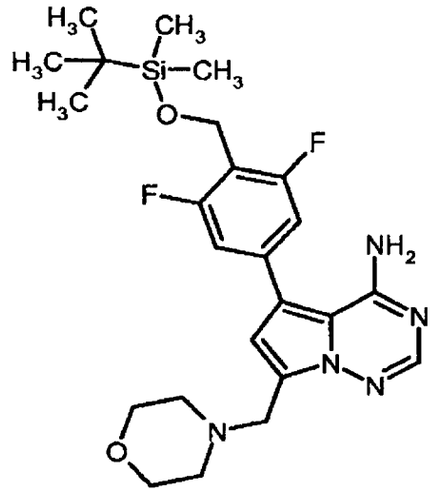


To a solution of Intermediate 38A (5.59 g, 17.9 mmol) and bis(pinacolato)diboron (10.0 g, 39.4 mmol) in degassed DMF (120 mL) was added under an argon atmosphere 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) chloride (786 mg, 1.07 mmol) and potassium acetate (7.03 g, 71.6 mmol). The mixture was heated to 80°C for 5 h and then cooled to room temperature. *tert*-Butyl methyl ether (100 mL) was added, and the suspension was filtered. The filtrate was evaporated to dryness under reduced pressure, and the residue was purified by flash chromatography over silica gel (gradient elution from 2% to 5% methanol in dichloromethane) to give 1.30 g (20% of th.) of the title compound containing some of the corresponding boronic acid derivative. This product was used without further purification.

LC-MS (method 6): R_t = 0.73 min; MS (ESIpos): *m/z* (%) = 360.3 (30) $[M+H]^+$.

Intermediate 40A

5-[4-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-3,5-difluorophenyl]-7-(morpholin-4-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-amine



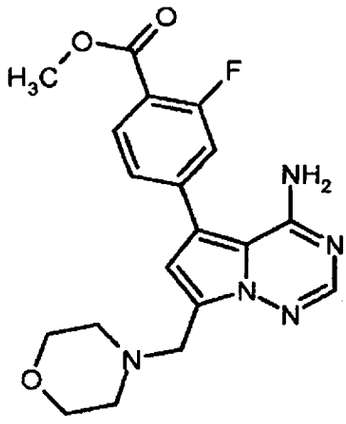
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The title compound was obtained by general synthetic method 1 from Intermediate 38A (200 mg, 0.64 mmol) and [4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3,5-difluorophenyl]boronic acid (314 mg, 0.77 mmol, 74% purity; prepared by the method of Hattori, *Bioorg. Med. Chem.* **2006**, *14*, 3258-3262). Purification of the crude product was carried out by preparative HPLC (method 3). Yield: 110 mg (32% of th., LC-MS purity 92%).

LC-MS (method 6): R_t = 1.18 min; MS (ESIpos): *m/z* (%) = 490.1 (30) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 488.3 (100) $[M-H]^-$.

Intermediate 41A

Methyl 4-[4-amino-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluorobenzoate



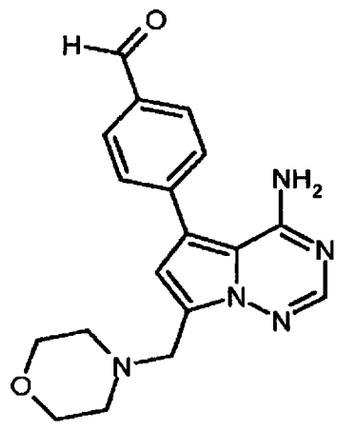
The title compound was obtained by general synthetic method 1 from Intermediate 38A (200 mg, 0.64 mmol) and [3-fluoro-4-(methoxycarbonyl)phenyl]boronic acid (139 mg, 0.71 mmol). Purification of the crude product was carried out by preparative HPLC (method 3). Yield: 80 mg (32% of th.).

LC-MS (method 6): R_t = 0.66 min; MS (ESIpos): *m/z* (%) = 386.1 (80) $[M+H]^+$.

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Intermediate 42A

4-[4-Amino-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]benzaldehyde

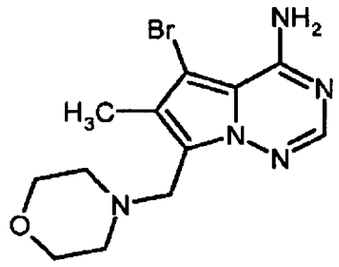


To a solution of Intermediate 38A (300 mg, 0.96 mmol) in degassed DMF (9.0 mL) was added (4-formylphenyl)boronic acid (216 mg, 1.44 mmol), tetrakis(triphenylphosphine)palladium(0) (111 mg, 0.1 mmol) and 2 M aqueous sodium carbonate solution (2.4 mL). The mixture was heated to 90°C under argon for 17 h, then cooled to room temperature and directly purified by preparative HPLC (method 3). Yield: 150 mg (46% of th.).

LC-MS (method 6): R_t = 0.44 min; MS (ESIpos): *m/z* (%) = 338.2 (30) $[M+H]^+$.

Intermediate 43A

5-Bromo-6-methyl-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



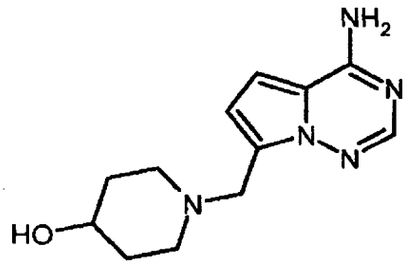
The compound was prepared according to the procedure described in WO 2007/056170-A2 (Intermediate O).

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Intermediate 44A

1-[(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]piperidin-4-ol



4-Hydroxypiperidine (3.62 g, 35.8 mmol) and 37% formalin solution (2.9 g, 35.8 mmol) were dissolved in acetic acid (150 mL) and stirred at room temperature for 1 h. To this solution was added a solution of pyrrolo[2,1-f][1,2,4]triazin-4-amine (2.0 g, 14.9 mmol; prepared according to the procedure described in WO 2007/056170-A2, Intermediate A) in acetic acid (150 mL), and the mixture was stirred at 60°C for 2 h. The solvent was then evaporated, and the residue was taken up in 200 mL of half-concentrated aqueous potassium bicarbonate solution and extracted with 200 mL dichloromethane. The organic layer was washed with water (2 x 50 mL) and discarded. The combined aqueous layers were evaporated to dryness, and the residue was treated with a 10:1 mixture of dichloromethane and methanol (2 x 100 mL). The organic extracts were evaporated, and the residue was purified by preparative HPLC (method 4) to give 1.16 g (15% of th.) of the title compound.

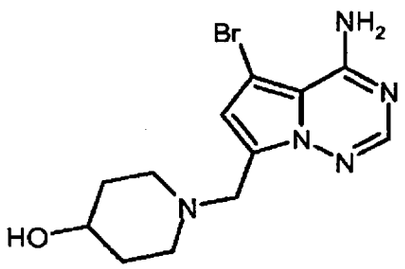
LC-MS (method 7): R_t = 0.18 min; MS (ESIpos): *m/z* (%) = 248.3 (30) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 246.5 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.35 (br. m, 2H), 1.67 (br. m, 2H), 2.07 (t, 2H), 2.70 (br. m, 2H), 3.38 (br. m, 1H), 3.75 (s, 2H), 4.51 (br, 1H), 6.52 (d, 1H), 6.84 (d, 1H), 7.62 (br, 2H), 7.82 (s, 1H).

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Intermediate 45A

1-[(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]piperidin-4-ol



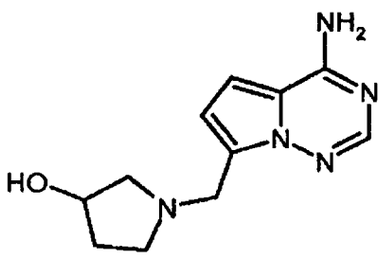
Intermediate 44A (1.10 g, 4.45 mmol) was dissolved in DMF (16.5 mL) and cooled to -20°C. 1,3-Dibromo-5,5-dimethylhydantoin (636 mg, 2.22 mmol) was added every 10 min in about 100 mg portions. Subsequently, the mixture was stirred at room temperature for a further hour and was then directly purified by preparative HPLC (method 4). Yield: 0.61 g (42% of th.).

LC-MS (method 4): R_t = 0.75 min; MS (ESIpos): *m/z* (%) = 326.0 (30) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 324.0 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.35 (br. m, 2H), 1.67 (br. m, 2H), 2.08 (t, 2H), 2.68 (br. m, 2H), 3.39 (br. m, 1H), 3.74 (s, 2H), 4.51 (br, 1H), 6.69 (s, 1H), 7.86 (s, 1H).

Intermediate 46A

1-[(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]pyrrolidin-3-ol



3-Pyrrolidinol (1.56 g, 17.9 mmol) and 37% formalin solution (1.45 g, 17.9 mmol) were dissolved in acetic acid (75 mL) and stirred at room temperature for 10 min. To this solution was added a solution of pyrrolo[2,1-f][1,2,4]triazin-4-amine (2.0 g, 14.9 mmol) in acetic acid (75 mL), and the mixture was stirred at 60°C for 4 h. After evaporation, the residue was taken up in 200 mL of 1 N aqueous potassium carbonate solution and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine, dried over magnesium sulfate and

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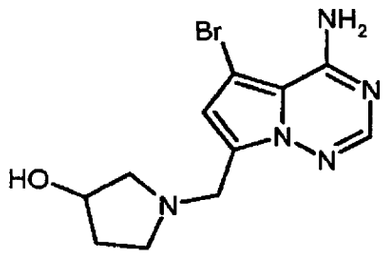
concentrated under reduced pressure. The residue was purified by preparative HPLC (method 4) to give 390 mg (11% of th.) of the title compound.

LC-MS (method 4): R_t = 0.22 min; MS (ESIpos): *m/z* (%) = 234.2 (20) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 223.0 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.50 (br. m, 1H), 1.94 (m, 1H), 2.34 (dd, 1H), 2.44 (dd, 1H), 2.60 (dd, 1H), 2.71 (dd, 1H), 3.84 (dd, 2H), 4.15 (br, 1H), 4.65 (d, 1H), 6.52 (d, 1H), 6.83 (d, 1H), 7.61 (br, 2H), 7.82 (s, 1H).

Intermediate 47A

1-[(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]pyrrolidin-3-ol



Intermediate 46A (0.9 g, 3.86 mmol) was dissolved in DMF (14.2 mL) and cooled to -20°C. 1,3-Dibromo-5,5-dimethylhydantoin (606 mg, 2.12 mmol) was added every 10 min in about 100 mg portions, and stirring was continued at room temperature for 1 h. The mixture was partitioned between 10% aqueous potassium bicarbonate solution (50 mL) and ethyl acetate (100 mL). The aqueous layer was extracted with another portion of ethyl acetate (100 mL) and then with dichloromethane (100 mL). The combined organic layers were dried over magnesium sulfate and evaporated, and the residue was purified by preparative HPLC (method 4). Yield: 0.44 g (37% of th.).

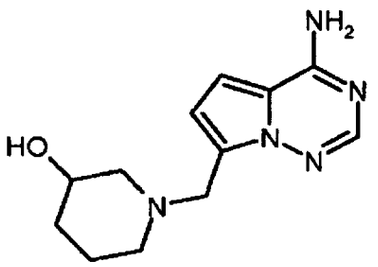
LC-MS (method 6): R_t = 0.21 min; MS (ESIpos): *m/z* (%) = 314.0 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.50 (br. m, 1H), 1.95 (m, 1H), 2.34 (dd, 1H), 2.45 (m, 1H), 2.60 (m, 1H), 2.70 (dd, 1H), 3.84 (dd, 2H), 4.15 (br, 1H), 4.65 (d, 1H), 6.71 (s, 1H), 7.86 (s, 1H).

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Intermediate 48A

1-[(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]piperidin-3-ol



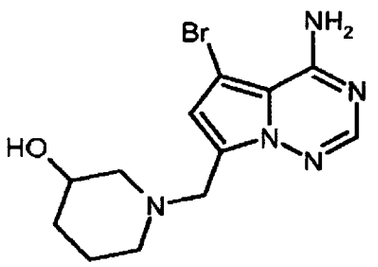
The title compound was prepared in analogy to Intermediate 46A with 3-hydroxypiperidine (1.80 g, 17.9 mmol) as starting material. After concentration of the reaction mixture, the residue was taken up in saturated aqueous potassium carbonate solution and extracted with 300 mL dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by preparative HPLC (method 4) to give 650 mg (18% of th.) of the title compound.

LC-MS (method 6): R_t = 0.16 min; MS (ESIpos): *m/z* (%) = 248.2 (60) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.99 (m, 1H), 1.37 (br. m, 1H), 1.57 (br. m, 1H), 1.74 (m, 2H), 1.88 (t, 1H), 2.68 (br. m, 1H), 2.83 (br. dd, 1H), 3.41 (br. m, 1H), 3.78 (dd, 2H), 4.54 (d, 1H), 6.52 (d, 1H), 6.84 (d, 1H), 7.61 (br, 2H), 7.82 (s, 1H).

Intermediate 49A

1-[(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]piperidin-3-ol



In analogy to the preparation of Intermediate 47A, the title compound was prepared from Intermediate 48A (690 mg, 2.79 mmol) to give 348 mg (93% LC-MS purity, 36% of th.) of the product after purification by preparative HPLC (method 4).

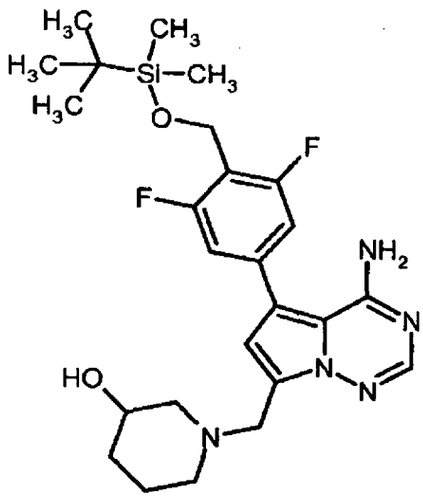
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LC-MS (method 4): R_t = 0.85 min; MS (ESIpos): *m/z* (%) = 226.0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 223.9 (70) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.99 (m, 1H), 1.37 (m, 1H), 1.57 (br. m, 1H), 1.74 (m, 2H), 1.89 (m, 1H), 2.66 (br. m, 1H), 2.81 (br. m, 1H), 3.41 (br. m, 1H), 3.77 (dd, 2H), 4.54 (d, 1H), 6.70 (s, 1H), 7.86 (s, 1H).

Intermediate 50A

1-({4-Amino-5-[4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3,5-difluorophenyl]pyrrolo[2,1-f]-[1,2,4]triazin-7-yl}methyl)piperidin-3-ol



The title compound was obtained by general synthetic method 1 from Intermediate 49A (200 mg, 0.61 mmol) and [4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3,5-difluorophenyl]boronic acid (222 mg, 0.74 mmol; prepared by the method of Hattori, *Bioorg. Med. Chem.* **2006**, *14*, 3258-3262). Purification of the crude product was carried out by preparative HPLC (method 3). Yield: 153 mg (50% of th.).

LC-MS (method 7): R_t = 1.55 min; MS (ESIpos): *m/z* (%) = 504.1 (100) $[M+H]^+$.

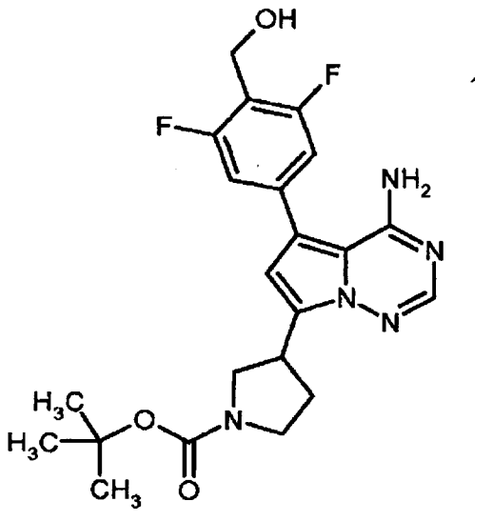
^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.11 (s, 6H), 0.86 (s, 9H), 1.01 (m, 1H), 1.40 (br. m, 1H), 1.59 (br. m, 1H), 1.77 (m, 2H), 1.94 (m, 1H), 2.72 (br. m, 1H), 2.87 (br. m, 1H), 3.43 (m, 1H), 3.82 (dd, 2H), 4.55 (d, 1H), 4.74 (s, 2H), 6.75 (s, 1H), 7.18 (dd, 2H), 7.95 (s, 1H).

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Intermediate 51A

rac-tert-Butyl 3-{4-amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyrrolidine-1-carboxylate



The preparation of the starting material *tert*-butyl 3-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]-triazin-7-yl)pyrrolidine-1-carboxylate has been described in WO 2007/056170-A2 (Intermediate I).

This compound (60 mg, 0.16 mmol) was coupled according to general synthetic method 1 with Intermediate 2A (47 mg, 0.17 mmol, 1.1 eq.). The crude product was purified by preparative HPLC (method 2) to give 67 mg (84% of th.) of the title compound.

HPLC (method 2): R_t = 4.08 min;

LC-MS (method 7): R_t = 1.66 min; MS (ESIpos): *m/z* (%) = 446.2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 444.3 (100) $[M-H]^-$.

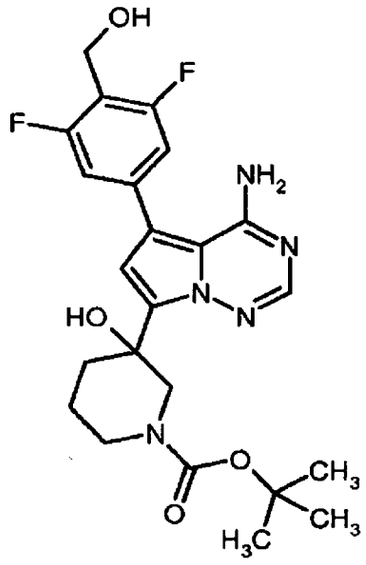
^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.39 (s, 9H), 2.10 (m, 1H), 2.33 (m, 1H), 3.37 (m, 2H), 3.46 (m, 1H), 3.70-3.89 (m, 2H), 4.51 (s, 2H), 6.80 (s, 1H), 7.15 (m, 2H), 8.03 (s, 1H).

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Intermediate 52A

rac-tert-Butyl 3-{4-amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}-3-hydroxypiperidine-1-carboxylate



Intermediate 26A (148 mg, 0.35 mmol) and (4-bromo-2,6-difluorophenyl)methanol (75 mg, 0.34 mmol) were coupled according to general synthetic method 2. Purification of the crude product was carried out using preparative HPLC (method 2). Yield: 46 mg (28% of th.).

HPLC (method 3): R_t = 3.90 min;

LC-MS (method 7): R_t = 1.56 min; MS (ESIpos): *m/z* (%) = 476.2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 474.2 (100) $[M-H]^-$.

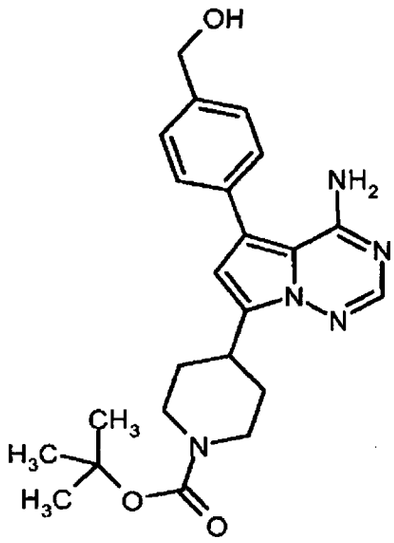
^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.22-1.58 (m, 10H), 1.80 (m, 2H), 3.19 (m, 1H), 3.48 (m, 1H), 3.62 (m, 1H), 3.74 (m, 1H), 4.00 (m, 1H), 4.52 (m, 2H), 5.39 (t, 1H), 6.78 (s, 1H), 7.10 (m, 2H), 7.94 (s, 1H).

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Intermediate 53A

tert-Butyl 4-{4-amino-5-[4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}piperidine-1-carboxylate



The starting material *tert*-butyl 4-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidine-1-carboxylate was prepared according to the procedure described in WO 2007/056170-A2 (Example 1, step 3).

This compound (400 mg, 1.01 mmol) was then reacted with 4-(hydroxymethyl)phenylboronic acid (184 mg, 1.21 mmol, 1.2 eq.) according to general synthetic method 1. The crude product was purified by preparative HPLC (method 2) to give 326 mg (76% of th.) of the title compound.

HPLC (method 2): R_t = 4.07 min;

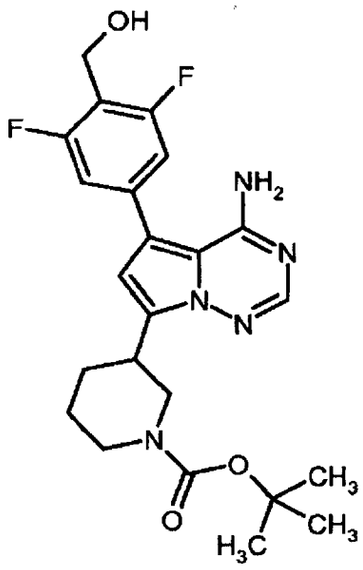
LC-MS (method 6): R_t = 1.06 min; MS (ESIpos): *m/z* (%) = 424.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 422.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.52-1.65 (m, 2H), 1.92-2.00 (m, 2H), 2.89 (br. s, 2H), 3.10 (m, 1H), 3.28-3.37 (m, 2H), 4.06 (d, 2H), 4.60 (s, 2H), 6.68 (s, 1H), 7.47 (s, 5H), 8.02 (s, 1H).

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Intermediate 54A

rac-tert-Butyl 3-{4-amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}piperidine-1-carboxylate



Intermediate 31A (200 mg, 0.39 mmol) and Intermediate 2A (138 mg, 0.51 mmol, 1.3 eq.) were reacted according to general synthetic method 1 yielding 130 mg (72% of th.) of the title compound after purification by preparative HPLC (method 2).

HPLC (method 3): R_t = 4.23 min;

LC-MS (method 6): R_t = 1.17 min; MS (ESIpos): *m/z* (%) = 460.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 458.1 (100) $[M-H]^-$.

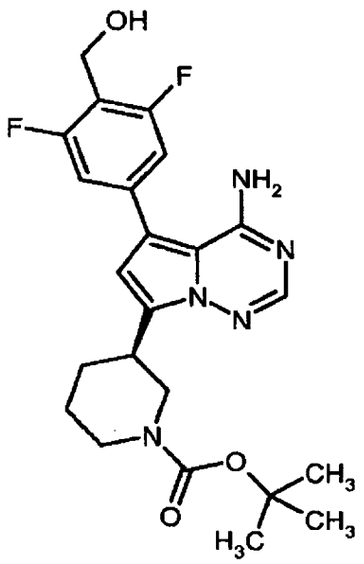
^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.39 (s, 9H), 1.48 (m, 2H), 1.74 (m, 2H), 2.93 (m, 1H), 3.22 (m, 1H), 3.85 (m, 1H), 4.11 (m, 1H), 4.53 (s, 2H), 6.78 (s, 1H), 7.12 (m, 2H), 8.02 (s, 1H).

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Intermediate 55A

tert-Butyl (3*R*)-3-{4-amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}piperidine-1-carboxylate



The enantiomerically pure *R*-isomer was synthesized by coupling Intermediate 32A (115 mg, 0.28 mmol) with (4-bromo-2,6-difluorophenyl)methanol (76 mg, 0.33 mmol, 1.2 eq.) according to general synthetic method 2. Yield: 48 mg (38% of th.).

Alternatively, the title compound was obtained by separation of the racemic compound from Intermediate 54A (40 mg) using preparative chiral HPLC [column: chiral silica gel phase based on the selector poly(*N*-methacryloyl-L-leucine-*tert*-butylamide), 250 mm x 20 mm; eluent: ethyl acetate/isohexane 4:1; flow rate: 20 mL/min; UV detection: 260 nm]. Yield: 20 mg (*R*-isomer).

Analytical chiral HPLC [column: chiral silica gel phase based on the selector poly(*N*-methacryloyl-L-leucine-*tert*-butylamide), 250 mm x 4 mm; eluent: ethyl acetate/isohexane 4:1; flow rate: 1 mL/min; UV detection: 260 nm]: R_t = 5.68 min; e.e. >99.5.

HPLC (method 3): R_t = 4.23 min;

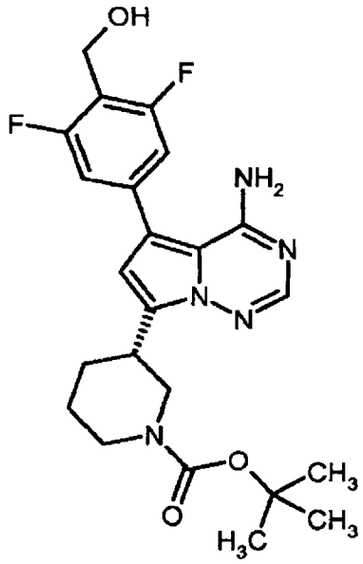
LC-MS (method 6): R_t = 1.17 min; MS (ESIpos): *m/z* (%) = 460.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 458.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.39 (s, 9H), 1.48 (m, 2H), 1.74 (m, 2H), 2.93 (m, 1H), 3.22 (m, 1H), 3.85 (m, 1H), 4.11 (m, 1H), 4.53 (s, 2H), 6.78 (s, 1H), 7.12 (m, 2H), 8.02 (s, 1H).

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Intermediate 56A

tert-Butyl (3*S*)-3-{4-amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}piperidine-1-carboxylate



The enantiomerically pure *S*-isomer was obtained by separation of the racemic compound from Intermediate 54A (40 mg) using preparative chiral HPLC as described for Intermediate 55A. Yield: 19 mg (*S*-isomer).

Analytical chiral HPLC [column: chiral silica gel phase based on the selector poly(*N*-meth-acryloyl-L-leucine-*tert*-butylamide), 250 mm x 4 mm; eluent: ethyl acetate/isohexane 4:1; flow rate: 1 mL/min; UV detection: 260 nm]: R_t = 7.87 min; e.e. >99.5.

HPLC (method 3): R_t = 4.23 min;

LC-MS (method 6): R_t = 1.17 min; MS (ESIpos): *m/z* (%) = 460.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 458.1 (100) $[M-H]^-$.

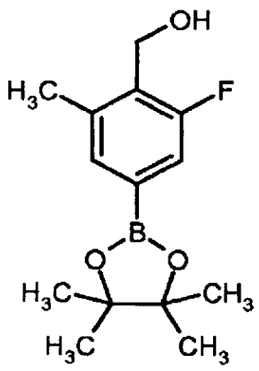
^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.39 (s, 9H), 1.48 (m, 2H), 1.74 (m, 2H), 2.93 (m, 1H), 3.22 (m, 1H), 3.85 (m, 1H), 4.11 (m, 1H), 4.53 (s, 2H), 6.78 (s, 1H), 7.12 (m, 2H), 8.02 (s, 1H).

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Intermediate 57A

[2-Fluoro-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol



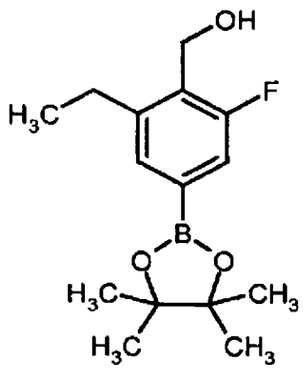
(4-Bromo-2-fluoro-6-methylphenyl)methanol (2.0 g, 9.13 mmol) was dissolved in 1,4-dioxane (20.0 mL) in a microwave reactor vial, and the solution was flushed with argon. Then, bis(pinacolato)diboron (2.43 g, 9.59 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) chloride (298 mg, 0.37 mmol) and potassium acetate (1.34 g, 13.7 mmol) were added, the reaction vessel was crimp-capped, and the mixture was heated to 130°C for 1 h in a single-mode microwave device. After cooling, the reaction mixture was filtered and the filtrate was evaporated. The residue was treated with cyclohexane (100 mL) and stirred for 10 min. The solution was filtered again, the filtrate was evaporated, and the residue was purified by chromatography (Biotage 25M silica cartridge, dichloromethane at 15 mL/min flow rate). Fractions containing the title compound were combined and evaporated, and the title compound crystallized spontaneously as a yellow solid (2.18 g, 90% of th.).

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.30 (s, 12H), 2.39 (s, 3H), 4.51 (m, 2H), 5.01 (t, 1H), 7.14 (d, 1H), 7.31 (s, 1H).

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Intermediate 58A

[2-Ethyl-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol

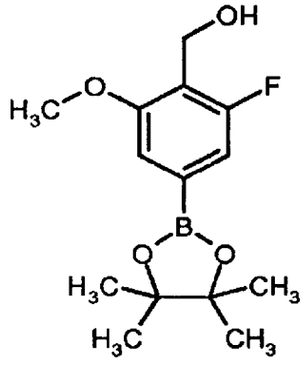


The title compound was synthesized and purified in analogy to Intermediate 57A using (4-bromo-2-ethyl-6-fluorophenyl)methanol (2.00 g, 8.58 mmol), bis(pinacolato)diboron (2.29 g, 9.01 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) chloride (280 mg, 0.34 mmol) and potassium acetate (1.26 g, 12.87 mmol) in 1,4-dioxane (20 mL). Yield: 2.16 g (90% of th.) as yellow crystals.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.17 (t, 3H), 1.30 (s, 12H), 2.76 (q, 2H), 4.50 (m, 2H), 5.03 (t, 1H), 7.14 (d, 1H), 7.32 (s, 1H).

Intermediate 59A

[2-Fluoro-6-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol



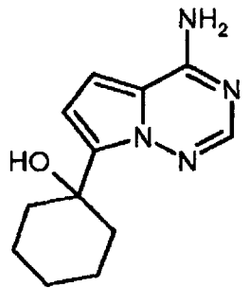
The title compound was synthesized and purified in analogy to Intermediate 57A using (4-bromo-2-methoxy-6-fluorophenyl)methanol (2.00 g, 8.51 mmol), bis(pinacolato)diboron (2.27 g, 8.90 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) chloride (278 mg, 0.34 mmol) and potassium acetate (1.25 g, 12.76 mmol) in 1,4-dioxane (20 mL). Yield: 1.81 g (75% of th.) as yellow crystals.

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^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.30 (s, 12H), 3.83 (s, 3H), 4.47 (m, 2H), 4.86 (t, 1H), 6.97 (d, 1H), 7.02 (s, 1H).

Intermediate 60A

1-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)cyclohexanol



7-Bromopyrrolo[2,1-f][1,2,4]triazin-4-amine (1.20 g, 5.63 mmol) was dissolved in THF (25 mL) under argon at room temperature. Chlorotrimethylsilane (1.43 mL, 11.27 mmol) was added, and the mixture was stirred at room temperature for 3 h. Then, it was cooled to 0°C, 2-propyl magnesium chloride (11.8 mL of a 2.0 M solution in THF, 23.7 mmol) was added, and stirring was maintained for another 3 h while the reaction mixture was allowed to warm to room temperature. Then, cyclohexanone (0.88 mL, 8.45 mmol) was added, and stirring was continued for 16 h. The reaction was quenched with a mixture (1:1) of concentrated aqueous ammonium chloride solution and ice until the pH reached 6-7. The mixture was extracted with two portions of ethyl acetate, and the combined organic extracts were dried over anhydrous sodium carbonate and concentrated to dryness. The product thus obtained was used without further purification (purity ~68% by HPLC). Yield: 1.87 g (97% of th.).

LC-MS (method 5): R_t = 1.10 min; MS (ESIpos): *m/z* (%) = 233 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 231 (100) $[M-H]^-$.

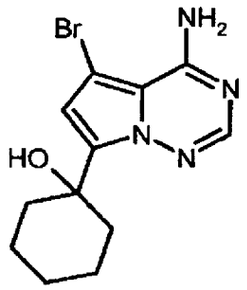
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.28-1.33 (m, 1H), 1.42-1.50 (m, 2H), 1.58-1.63 (m, 1H), 1.67-1.78 (m, 4H), 2.13-2.23 (m, 2H), 6.69 (d, 1H), 7.20 (d, 1H), 8.02 (s, 1H), 8.58 (br. s, 1H), 9.00 (br. s, 1H).

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Intermediate 61A

1-(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)cyclohexanol



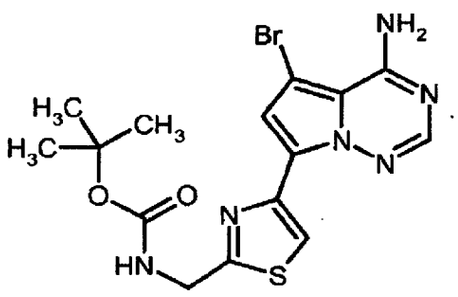
Intermediate 60A (80 mg, 0.34 mmol) was dissolved in THF (5.0 mL), and the mixture was cooled to -20°C. 1,3-Dibromo-5,5-dimethylhydantoin (49 mg, 0.17 mmol) was added at once, and stirring was continued for 1 h. The reaction was quenched with conc. aqueous sodium dithionite solution (0.5 mL), and the mixture was extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, and the solvent was distilled off to give 98 mg (91% of th.) of the title compound.

LC-MS (method 4): R_t = 1.90 min; MS (ESIpos): *m/z* (%) = 311 (95) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 309 (90) $[M-H]^-$.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.20-1.33 (m, 1H), 1.42-1.52 (m, 2H), 1.58-1.78 (m, 5H), 2.15-2.23 (m, 2H), 5.01 (br. s, 2H), 6.63 (s, 1H), 7.82 (s, 1H).

Intermediate 62A

tert-Butyl {[4-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)-1,3-thiazol-2-yl]methyl}-carbamate



Intermediate 33A (109 mg, 0.38 mmol) and *tert*-butyl (2-amino-2-thioxoethyl)carbamate (79 mg, 0.41 mmol) were dissolved in ethanol (6.5 mL). The mixture was heated to reflux for 20 h. The

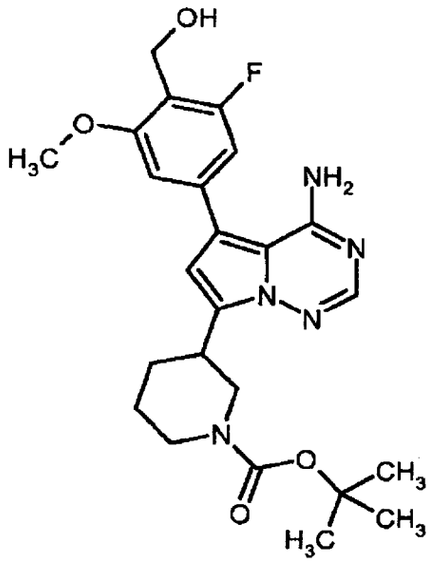
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mixture was then filtered, and the filtrate was evaporated. The residue was triturated with acetonitrile to give 67 mg (42% of th.) of the title compound as a brownish-grey crystalline solid.

LC-MS (method 7): R_t = 1.81 min; MS (ESIpos): *m/z* (%) = 425 (80) and 427 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 423 (50) and 425 (100) $[M-H]^-$.

Intermediate 63A

tert-Butyl 3-{4-amino-5-[3-fluoro-4-(hydroxymethyl)-5-methoxyphenyl]pyrrolo[2,1-f][1,2,4]-triazin-7-yl}piperidine-1-carboxylate



Intermediate 31A (120 mg, 0.30 mmol) and Intermediate 59A (104 mg, 0.36 mmol) were dissolved in acetonitrile (2.0 mL) in a microwave reactor vial and flushed with argon. Tetrakis-(triphenylphosphine)palladium(0) (35 mg, 0.03 mmol) and 2.0 M aq. sodium carbonate solution (0.5 mL) were added, and the mixture was heated to 150°C for 1 h in a single-mode microwave device. After cooling, the mixture was filtered, and the filtrate was evaporated. The residue was purified by flash chromatography (Biotage 25M silica cartridge, dichloromethane + 2-5% methanol, flow rate 10 mL/min) to give 51 mg (36% of th.) of the title compound.

LC-MS (method 6): R_t = 1.16 min; MS (ESIpos): *m/z* (%) = 472 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 470 (100) $[M-H]^-$.

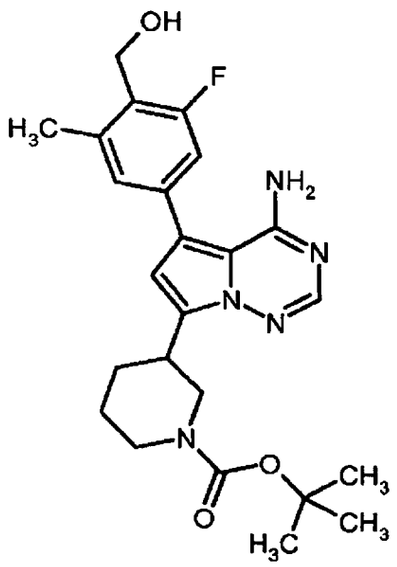
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.31-2.10 (m, 13H), 2.88-2.91 (m, 2H), 3.19-3.27 (m, 2H), 3.87 (s, 1H), 4.12 (m, 1H), 4.50 (m, 1H), 4.82 (t, 1H), 6.68 (s, 1H), 6.83 (d, 1H), 6.90 (s, 1H), 7.92 (s, 1H).

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Intermediate 64A

tert-Butyl 3-{4-amino-5-[3-fluoro-4-(hydroxymethyl)-5-methylphenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}piperidine-1-carboxylate



Intermediate 31A (120 mg, 0.30 mmol) and Intermediate 57A (97 mg, 0.36 mmol) were dissolved in acetonitrile (2.0 mL) in a microwave reactor vial and flushed with argon. Tetrakis(triphenylphosphine)palladium(0) (35 mg, 0.03 mmol) and 2.0 M aq. sodium carbonate solution (0.5 mL) were added, and the mixture was heated to 150°C for 1 h in a single-mode microwave device. After cooling, the mixture was filtered, and the filtrate was evaporated. The residue was purified by flash chromatography (Biotage 25M silica cartridge, dichloromethane + 2-5% methanol, flow rate 10 mL/min) to give 110 mg (71% of th.) of the title compound.

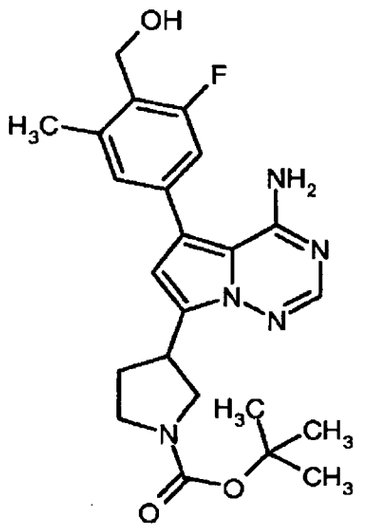
LC-MS (method 4): R_t = 2.03 min; MS (ESIpos): *m/z* (%) = 456 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 454 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.31-2.11 (m, 13H), 2.42 (s, 3H), 2.88-2.91 (m, 2H), 3.17-3.30 (m, 2H), 3.80 (m, 1H), 4.54 (m, 1H), 4.82 (t, 1H), 6.64 (s, 1H), 7.04 (d, 1H), 7.12 (s, 1H), 7.93 (s, 1H).

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Intermediate 65A

tert-Butyl 3-{4-amino-5-[3-fluoro-4-(hydroxymethyl)-5-methylphenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyrrolidine-1-carboxylate



The starting material *tert*-Butyl 3-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)pyrrolidine-1-carboxylate was synthesized according to the procedure described in WO 2007/056170-A2 (Intermediate I).

tert-Butyl 3-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)pyrrolidine-1-carboxylate (120 mg, 0.31 mmol) was dissolved in acetonitrile (2.2 mL) in a microwave reactor vial and flushed with argon. Intermediate 57A (100 mg, 0.38 mmol), tetrakis(triphenylphosphine)palladium(0) (36 mg, 0.03 mmol) and 2.0 M aq. sodium carbonate solution (0.5 mL) were added, and the mixture was heated to 150°C for 1 h in a single-mode microwave device. After cooling, the mixture was filtered, and the filtrate was evaporated. The residue was purified by flash chromatography (Biotage 25M silica cartridge, dichloromethane + 2-5% methanol, flow rate 10 mL/min) to give 91 mg (54% of th.) of the title compound.

LC-MS (method 5): R_t = 2.00 min; MS (ESIpos): *m/z* (%) = 442 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 440 (100) $[M-H]^-$.

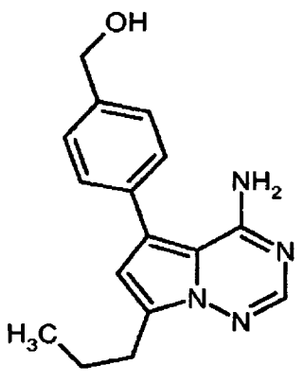
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.41 (m, 9H), 2.00-2.48 (m, 2H), 3.29-3.53 (m, 3H), 3.71-3.90 (m, 2H), 4.55 (m, 2H), 4.99 (t, 1H), 6.63 (s, 1H), 7.06 (d, 1H), 7.12 (s, 1H), 7.92 (s, 1H).

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Preparation Examples:

Example 1

[4-(4-Amino-7-propylpyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]methanol



The title compound was obtained by general synthetic method 1 from Intermediate 11A (100 mg, 0.39 mmol) and 4-(hydroxymethyl)phenylboronic acid (60 mg, 0.39 mmol). Purification of the crude product was carried out by preparative HPLC (method 2). Yield: 33 mg (30% of th.).

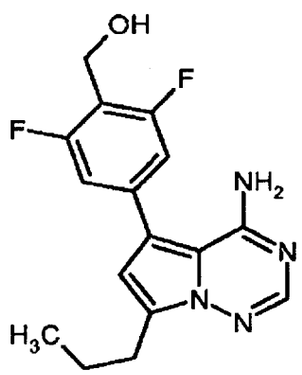
HPLC (method 1): R_t = 3.47 min; HPLC (method 2): R_t = 3.78 min;

LC-MS (method 4): R_t = 0.91 min; MS (ESIpos): *m/z* (%) = 283.2 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.97 (t, *J* = 7.4 Hz, 3H), 1.71 (m, 2H), 3.31 (s, 2H), 4.52 (s, 2H), 6.54 (s, 1H), 7.42 (s, 4H), 7.89 (s, 1H).

Example 2

[4-(4-Amino-7-propylpyrrolo[2,1-f][1,2,4]triazin-5-yl)-2,6-difluorophenyl]methanol



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The title compound was obtained by general synthetic method 2 from Intermediate 11A (118 mg, 0.46 mmol) and (4-bromo-2,6-difluorophenyl)methanol (108 mg, 0.49 mmol). Purification of the crude product was carried out by preparative HPLC (method 2). Yield: 59 mg (40% of th.).

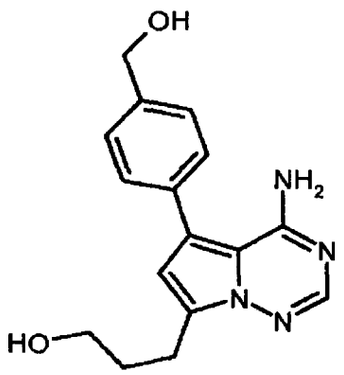
HPLC (method 2): R_t = 3.94 min;

LC-MS (method 7): R_t = 1.47 min; MS (ESIpos): *m/z* (%) = 319.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 317.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.95 (t, 3H), 1.71 (m, 2H), 4.52 (m, 2H), 5.26 (t, 1H), 6.64 (s, 1H), 7.10 (m, 2H), 7.91 (s, 1H).

Example 3

3-{4-Amino-5-[4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}propan-1-ol



The title compound was obtained from Intermediate 10A (100 mg, 0.37 mmol) and 4-(hydroxymethyl)phenylboronic acid (67 mg, 0.44 mmol, 1.2 eq.) according to general synthetic method 1. The crude product was purified by preparative HPLC (method 2) to give 73 mg (66% of th.) of the title compound as colorless solid.

HPLC (method 1): R_t = 2.91 min; HPLC (method 2): R_t = 3.14 min;

LC-MS (method 6): R_t = 0.60 min; MS (ESIpos): *m/z* (%) = 299.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 297.4 (100) $[M-H]^-$.

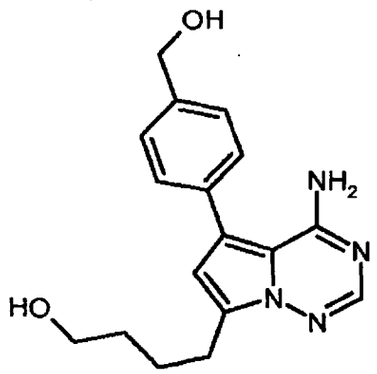
^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.84 (m, 2H), 2.95 (t, *J* = 7.6 Hz, 2H), 3.50 (m, 2H), 4.58 (s, 2H), 6.67 (s, 1H), 7.41 (s, 4H), 8.03 (s, 1H).

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Example 4

4-{4-Amino-5-[4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}butan-1-ol



The title compound was obtained by general synthetic method 1 from Intermediate 14A (75 mg, 0.26 mmol) and 4-(hydroxymethyl)phenylboronic acid (48 mg, 0.32 mmol). Purification of the crude product was carried out by preparative HPLC (method 2). Yield: 66 mg (80% of th.).

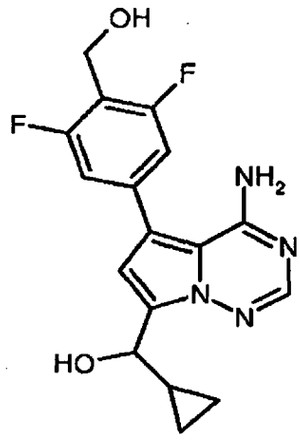
HPLC (method 2): R_t = 3.28 min;

LC-MS (method 6): R_t = 0.68 min; MS (ESIpos): *m/z* (%) = 313.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 311.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.48-1.51 (m, 2H), 1.67-1.70 (m, 2H), 2.91 (t, *J* = 7.6 Hz, 2H), 3.42 (t, *J* = 6.4 Hz, 2H), 4.58 (s, 2H), 6.67 (s, 1H), 7.42 (s, 4H), 8.03 (s, 1H).

Example 5

{4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}(cyclopropyl)methanol



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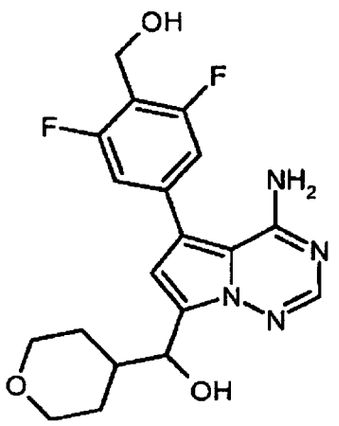
The title compound was obtained from Intermediate 17A (125 mg, 0.44 mmol) and Intermediate 2A (114 mg, 0.53 mmol) by general synthetic method 1. The crude product was purified by preparative HPLC (method 3). Yield: 73 mg (48% of th.).

LC-MS (method 7): R_t = 1.09 min; MS (ESIpos): *m/z* (%) = 347.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 345.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.39 (m, 3H), 0.48 (m, 1H), 1.35 (m, 1H), 4.54 (d, 2H), 4.67 (m, 1H), 5.26 (m, 2H), 6.80 (s, 1H), 7.14 (m, 2H), 7.92 (s, 1H).

Example 6

{4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}(tetrahydro-2*H*-pyran-4-yl)methanol



The title compound was obtained from Intermediate 18A (200 mg, 0.61 mmol) and Intermediate 2A (158 mg, 0.73 mmol) by general synthetic method 1. The crude product was purified by preparative HPLC (method 3). Yield: 125 mg (52% of th.).

LC-MS (method 5): R_t = 1.29 min; MS (ESIpos): *m/z* (%) = 391.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 389.0 (100) $[M-H]^-$.

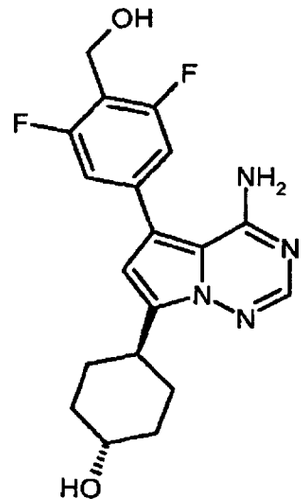
^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.24 (br. d, 1H), 1.36 (m, 2H), 1.68 (br. d, 1H), 2.03 (m, 1H), 2.60 (t, 2H), 3.82 (m, 2H), 4.54 (s, 2H), 4.95 (br. d, 1H), 5.28 (br, 1H), 5.33 (br, 1H), 6.73 (s, 1H), 7.14 (m, 2H), 7.93 (s, 1H).

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Example 7

trans-4-{4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}-cyclohexanol



The title compound was obtained by general synthetic method 1 from Intermediate 24A (323 mg, 85% purity, 0.88 mmol) and Intermediate 1A (286 mg, 1.06 mmol, 1.2 eq.). Purification of the crude product was first carried out by flash chromatography (Biotage silica packed cartridge, eluent dichloromethane/methanol 95:5). Further purification was performed by preparative HPLC (method 2). Yield: 72 mg (21% of th.).

HPLC (method 2): R_t = 3.37 min;

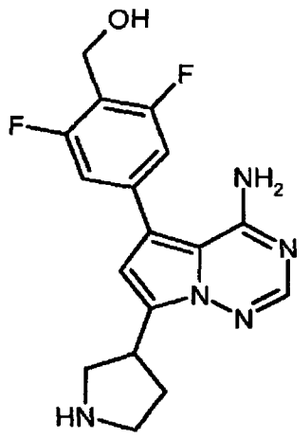
LC-MS (method 7): R_t = 1.01 min; MS (ESIpos): *m/z* (%) = 375.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 373.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.32 (m, 2H), 1.50 (m, 2H), 1.98 (m, 2H), 2.04 (m, 2H), 3.04 (tt, 1H), 3.47 (m, 1H), 4.51 (m, 2H), 4.61 (d, 1H), 5.26 (t, 1H), 6.60 (s, 1H), 7.12 (m, 2H), 7.91 (s, 1H).

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Example 8

rac-{4-[4-Amino-7-(pyrrolidin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2,6-difluorophenyl}-methanol



Intermediate 51A (67 mg, 0.15 mmol) was dissolved in a 30% solution of trifluoroacetic acid in dichloromethane (6 mL) at 0°C. The reaction mixture was stirred at this temperature for 20 min, then all volatiles were removed under reduced pressure. The residue was purified by preparative HPLC (method 2). The product thus obtained was dissolved in ethyl acetate and washed with saturated aqueous sodium carbonate solution. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off to give 21 mg (41% of th.) of the title compound.

HPLC (method 2): R_t = 2.96 min;

LC-MS (method 6): R_t = 0.34 min; MS (ESIpos): *m/z* (%) = 346.1 (20) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 344.2 (100) $[M-H]^-$.

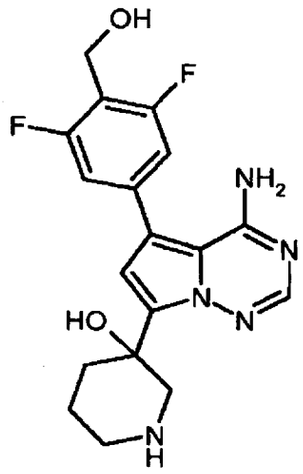
^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.94 (m, 1H), 2.22 (m, 1H), 2.94 (m, 1H), 3.00-3.16 (m, 2H), 3.40 (m, 2H), 3.72 (m, 1H), 4.51 (s, 2H), 5.22 (br. s, 1H), 6.71 (s, 1H), 7.11 (m, 2H), 7.92 (s, 1H).

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Example 9

rac-3-{4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}-piperidin-3-ol



Intermediate 52A (46 mg, 0.10 mmol) was dissolved in a 30% solution of trifluoroacetic acid in dichloromethane (1.5 mL) at 0°C. The reaction mixture was stirred at this temperature for 30 min, then all volatiles were removed under reduced pressure. The residue was purified by preparative HPLC (method 2). The product thus obtained was dissolved in ethyl acetate and washed with saturated aqueous sodium carbonate solution. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off to give 20 mg (55% of th.) of the title compound.

HPLC (method 2): R_t = 2.94 min;

LC-MS (method 4): R_t = 1.01 min; MS (ESIpos): *m/z* (%) = 358.1 (100) $[M-H_2O+H]^+$, MS (ESIneg): *m/z* (%) = 374.1 (100) $[M-H]^-$.

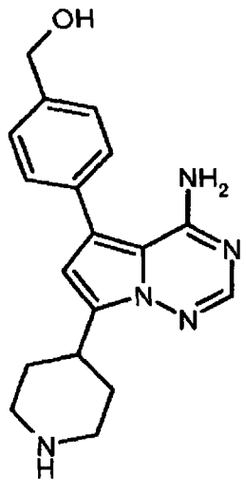
^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.48 (m, 1H), 1.89 (m, 2H), 2.40-2.69 (m, 2H), 2.92 (d, 1H), 3.02 (d, 1H), 3.40 (m, 1H), 4.52 (m, 2H), 5.26 (t, 1H), 5.45 (s, 1H), 6.72 (s, 1H), 7.13 (m, 2H), 7.94 (s, 1H).

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Example 10

{4-[4-Amino-7-(piperidin-4-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}methanol



Intermediate 53A (324 mg, 0.77 mmol) was dissolved in dichloromethane (15 mL). Trifluoroacetic acid (1.5 mL) was added, and the mixture was stirred at room temperature for 16 h. Another portion of trifluoroacetic acid (1.5 mL) was added, and stirring was continued until HPLC (method 1) indicated complete conversion of the starting material. All volatiles were then removed under reduced pressure, and the residue was purified by preparative HPLC (method 1) to give 226 mg (91% of th.) of the title compound.

HPLC (method 1): R_t = 3.37 min; HPLC (method 2): R_t = 2.90 min;

LC-MS (method 4): R_t = 0.90 min; MS (ESIpos): *m/z* (%) = 324.1 (75) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 322.2 (100) $[M-H]^-$.

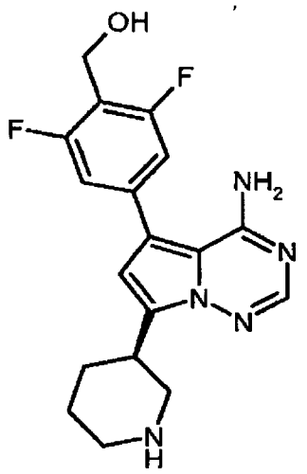
^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.79-1.95 (m, 2H), 2.16-2.23 (m, 2H), 3.05-3.19 (m, 2H), 3.37-3.52 (m, 3H), 4.56 (s, 2H), 5.49 (s, 2H), 6.66 (s, 1H), 7.43 (s, 4H), 8.03 (s, 1H), 8.39-8.50 (m, 1H), 8.65-8.69 (m, 1H).

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Example 11

(4-{4-Amino-7-[(3*R*)-piperidin-3-yl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}-2,6-difluorophenyl)-methanol



Intermediate 55A (35 mg, 0.08 mmol) was dissolved in a 30% solution of trifluoroacetic acid in dichloromethane (1.5 mL) at 0°C. The reaction mixture was stirred at this temperature for 30 min, then all volatiles were removed under reduced pressure. The residue was purified by preparative HPLC (method 2). The product thus obtained was dissolved in ethyl acetate and washed with saturated aqueous sodium carbonate solution. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off to give 18 mg (66% of th.) of the title compound.

HPLC (method 2): R_t = 3.10 min;

LC-MS (method 6): R_t = 0.55 min; MS (ESIpos): *m/z* (%) = 360.2 (20) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 358.3 (100) $[M-H]^-$.

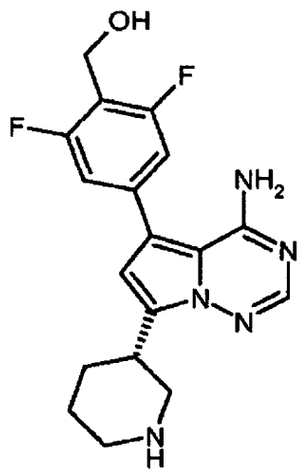
^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.67 (m, 2H), 1.83 (m, 1H), 2.75 (m, 1H), 2.86 (m, 1H), 3.20 (d, 1H), 3.41 (m, 2H), 4.53 (m, 2H), 5.29 (t, 1H), 6.70 (s, 1H), 7.11 (m, 1H), 7.94 (s, 1H).

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Example 12

(4-{4-Amino-7-[(3*S*)-piperidin-3-yl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}-2,6-difluorophenyl)-methanol

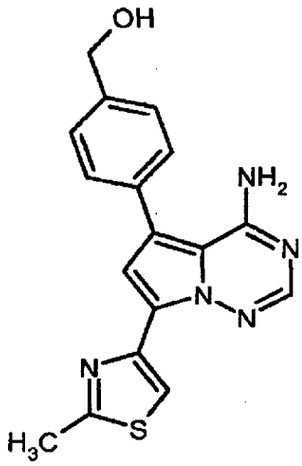


The title compound was obtained from Intermediate 56A (19 mg, 0.04 mmol) by the same method as described for the conversion of Intermediate 55A to Example 11. Yield: 12 mg (81% of th.).

HPLC, LC-MS and ^{1}H-NMR data were identical to those shown for Example 11.

Example 13

{4-[4-Amino-7-(2-methyl-1,3-thiazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}methanol



Intermediate 33A (60 mg, 0.21 mmol) and thioacetamide (15 mg, 0.20 mmol, 0.95 eq.) were dissolved in 1,4-dioxane (2 mL) and refluxed for 4.5 h. After cooling, 4-(hydroxymethyl)phenyl-

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boronic acid (38 mg, 0.25 mmol, 1.2 eq.), tetrakis(triphenylphosphine)palladium(0) (59 mg, 0.07 mmol, 0.25 eq.) and 2 M aqueous sodium carbonate solution (0.4 mL) were added. The mixture was gently stirred at 100°C for 16 h. Then, another portion of tetrakis(triphenylphosphine)-palladium(0) (24 mg, 0.1 eq.) was added, and stirring at 100°C was continued for another 4 h. The reaction mixture was then filtered, the filtrate was evaporated under reduced pressure, and the residue was purified by preparative HPLC (method 2) to give 28 mg (40% of th.) of the title compound as off-white crystals.

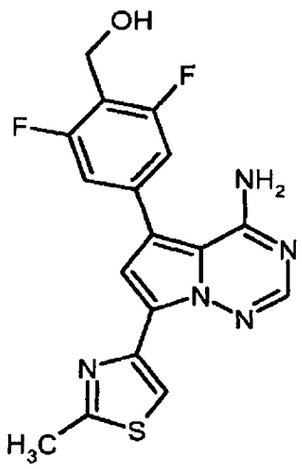
HPLC (method 1): R_t = 3.85 min; HPLC (method 2): R_t = 3.60 min;

LC-MS (method 6): R_t = 0.94 min; MS (ESIpos): *m/z* (%) = 338.2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 336.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.73 (s, 3H), 4.58 (s, 2H), 7.17 (s, 1H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 8.09 (s, 1H), 8.33 (s, 1H).

Example 14

{4-[4-Amino-7-(2-methyl-1,3-thiazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2,6-difluorophenyl}-methanol



The title compound was obtained by general synthetic method 1 from Intermediate 34A (75 mg, 0.24 mmol) and Intermediate 1A (78 mg, 0.29 mmol, 1.2 eq.). Purification of the crude product was carried out by preparative HPLC (method 2). Yield: 27 mg (30% of th.).

HPLC (method 1): R_t = 3.79 min;

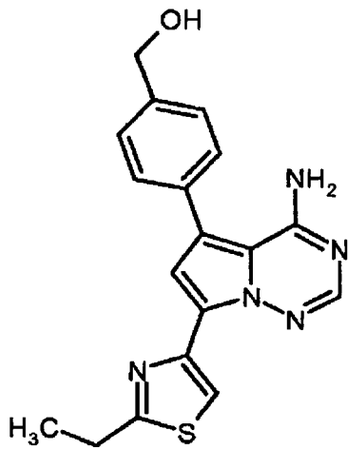
LC-MS (method 6): R_t = 1.03 min; MS (ESIpos): *m/z* (%) = 374.0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 372.2 (100) $[M-H]^-$.

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^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.72 (s, 3H), 4.53 (s, 2H), 7.18-7.27 (m, 2H), 8.11 (s, 1H), 8.33 (s, 1H).

Example 15

{4-[4-Amino-7-(2-ethyl-1,3-thiazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}methanol



Intermediate 35A (91 mg, 0.28 mmol) was reacted with 4-(hydroxymethyl)phenylboronic acid (51 mg, 0.34 mmol, 1.2 eq.) according to general synthetic method 1. The crude product was purified by preparative HPLC (method 2) giving 68 mg (69% of th.) of the title compound as colorless crystals.

HPLC (method 1): R_t = 3.73 min;

LC-MS (method 6): R_t = 1.05 min; MS (ESIpos): *m/z* (%) = 352.2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 350.3 (100) $[M-H]^-$.

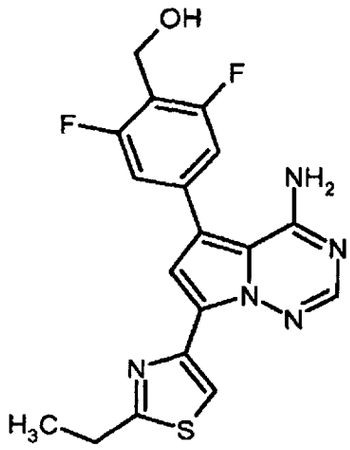
^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.36 (t, J = 7.6 Hz, 3H), 3.06 (q, J = 7.6 Hz, 2H), 4.58 (s, 2H), 7.19 (s, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 8.0 Hz, 2H), 8.12 (s, 1H), 8.36 (s, 1H).

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Example 16

{4-[4-Amino-7-(2-ethyl-1,3-thiazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2,6-difluorophenyl}-methanol



The title compound was obtained by general synthetic method 1 from Intermediate 35A (34 mg, 0.11 mmol) and Intermediate 1A (34 mg, 0.13 mmol, 1.2 eq.). Purification of the crude product was carried out by preparative HPLC (method 2). Yield: 16 mg (40% of th.).

HPLC (method 1): R_t = 4.04 min;

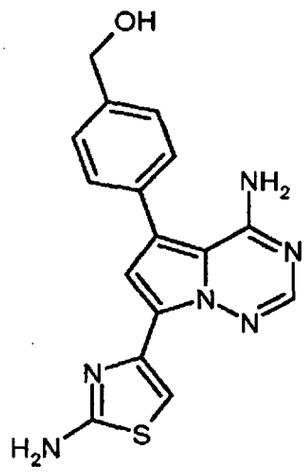
LC-MS (method 6): R_t = 1.15 min; MS (ESIpos): *m/z* (%) = 388.0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 386.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.38 (t, 3H), 3.06 (q, 2H), 4.55 (s, 2H), 7.20-7.31 (m, 3H), 8.16 (s, 1H), 8.38 (s, 1H).

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Example 17

{4-[4-Amino-7-(2-amino-1,3-thiazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}methanol



The title compound was obtained by general synthetic method 1 from Intermediate 36A (55 mg, 0.18 mmol) and 4-(hydroxymethyl)phenylboronic acid (32 mg, 0.21 mmol). Purification of the crude product was carried out by preparative HPLC (method 2). Yield: 29 mg (49% of th.).

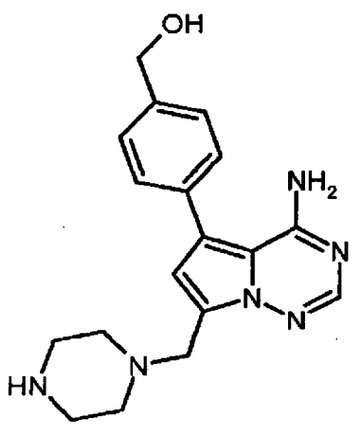
HPLC (method 1): R_t = 3.03 min;

LC-MS (method 5): R_t = 1.21 min; MS (ESIpos): *m/z* (%) = 339.1 (30) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 337.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 4.58 (m, 2H), 5.75 (m, 1H), 6.93 (s, 1H), 7.05 (m, 2H), 7.43 (m, 4H), 7.55 (s, 1H), 8.08 (s, 1H).

Example 18

{4-[4-Amino-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}methanol



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Intermediate 37A (200 mg, 0.49 mmol), 4-(hydroxymethyl)phenylboronic acid (90 mg, 0.59 mmol, 1.2 eq.) and tetrakis(triphenylphosphine)palladium(0) (57 mg, 0.05 mmol, 0.1 eq.) were dissolved in a mixture of 1,4-dioxane (4.0 mL) and 2 M aqueous sodium carbonate solution (1.0 mL) in a microwave reactor vial. The reaction vessel was crimp-capped, and the mixture was heated to 140°C for 1 h in a single-mode microwave device. After cooling, the mixture was filtered over a pad of Celite which was rinsed with 1,4-dioxane to elute all organic material. The combined filtrate was evaporated to dryness under reduced pressure, and the residue was purified by preparative HPLC (method 1) to give 75 mg (45% of th.) of the title compound.

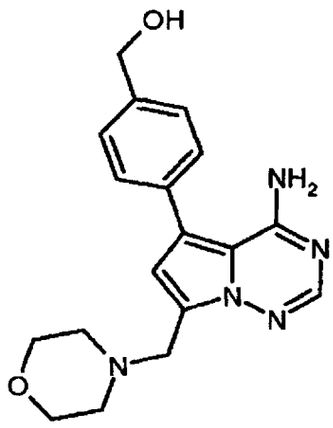
HPLC (method 1): R_t = 2.85 min;

LC-MS (method 4): R_t = 0.93 min; MS (ESIpos): *m/z* (%) = 339.1 (30) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 337.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.38 (br. s, 4H), 2.63 (m, 4H), 3.80 (s, 2H), 4.55 (s, 2H), 5.26 (br. s, 1H), 6.60 (s, 1H), 7.39 (s, 4H), 7.90 (s, 1H).

Example 19

{4-[4-Amino-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}methanol



The title compound was obtained from Intermediate 38A (200 mg, 0.64 mmol) and 4-(hydroxymethyl)phenylboronic acid (116 mg, 0.77 mmol, 1.2 eq.) according to general synthetic method 1. The crude product was purified by preparative HPLC (method 2). The material thus obtained was dissolved in a few mL of a mixture of acetonitrile and water, 2 M aqueous sodium carbonate solution was added, and the mixture was stirred for 10 min. During this time, the title compound precipitated. The crystals were isolated by filtration and dried *in vacuo* to give 95 mg (49% of th.) of a colorless solid.

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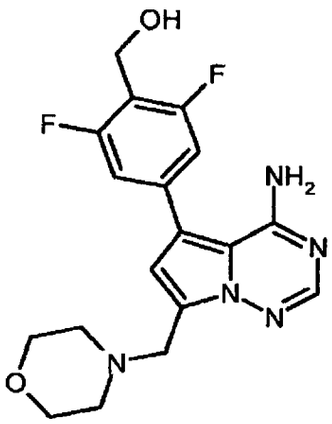
HPLC (method 1): R_t = 3.21 min;

LC-MS (method 4): R_t = 0.93 min; MS (ESIpos): *m/z* (%) = 340 (1) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 338.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.47 (m, 4H), 3.31 (s, 4H), 3.53 (t, 2H), 3.82 (s, 1H), 4.56 (d, 2H), 5.22 (t, 1H), 6.63 (s, 1H), 7.42 (s, 4H), 7.90 (s, 1H).

Example 20

{4-[4-Amino-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2,6-difluorophenyl}-methanol



To a solution of Intermediate 40A (110 mg, 0.22 mmol) in THF (2.2 mL) was added 0.45 mL (0.45 mmol) of a 1 M solution of tetrabutylammonium fluoride (TBAF) in THF, and the mixture was stirred at room temperature for 1 h. The reaction mixture was then evaporated under reduced pressure, and the residue was suspended in 3 mL of methanol and stirred at room temperature for 5 min. The resulting precipitate was filtered, washed with a small amount of methanol and dried *in vacuo* to give 68 mg (81% of th.) of the title compound.

LC-MS (method 4): R_t = 1.03 min; MS (ESIpos): *m/z* (%) = 376.0 (80) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 374.1 (100) $[M-H]^-$.

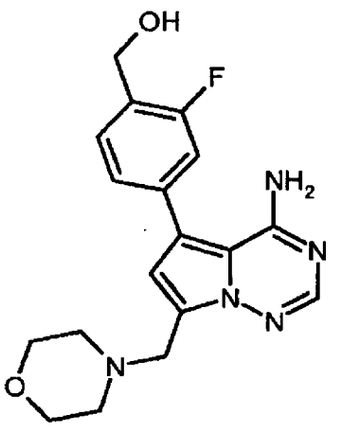
^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.45 (br. m, 4H), 3.56 (t, 4H), 3.82 (s, 2H), 4.54 (d, 2H), 5.27 (t, 1H), 6.75 (s, 1H), 7.16 (m, 2H), 7.95 (s, 1H).

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Example 21

{4-[4-Amino-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluorophenyl}-methanol



To a suspension of Intermediate 41A (65.0 mg, 0.17 mmol) in THF (2.0 mL) was added 0.2 mL (0.2 mmol) of a 1 M solution of lithium aluminium hydride in THF, and the mixture was stirred at room temperature for 1 h. The resulting solution was quenched with water and then directly purified by preparative HPLC (method 3) to give 35 mg (58% of th.) of the title compound.

LC-MS (method 6): R_t = 0.98 min; MS (ESIpos): *m/z* (%) = 358.1 (20) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 356.2 (100) $[M-H]^-$.

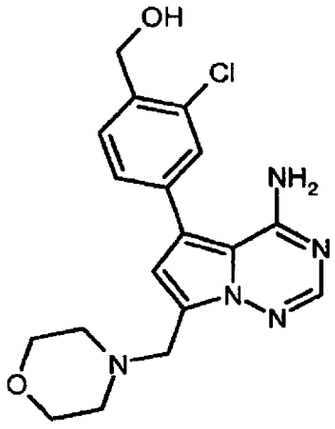
^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.46 (br. m, 4H), 3.56 (t, 4H), 3.83 (s, 2H), 4.60 (d, 2H), 5.32 (t, 1H), 6.70 (s, 1H), 7.27 (dd, 2H), 7.55 (t, 1H), 7.94 (s, 1H).

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Example 22

{4-[4-Amino-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-chlorophenyl}-methanol



Intermediate 39A (200 mg, 0.56 mmol), Intermediate 3A (112 mg, 0.51 mmol) and tetrakis-(triphenylphosphine)palladium(0) (58 mg, 0.05 mmol) were dissolved in a mixture of 1,4-dioxane (4.0 mL) and 2 M aqueous sodium carbonate solution (1.0 mL) in a microwave reactor vial. The reaction vessel was crimp-capped, and the mixture was heated to 140°C for 1 h in a single-mode microwave device. After cooling, the mixture was filtered, and the filtrate was purified by preparative HPLC (method 3) to give 48 mg (23% of th.) of the title compound.

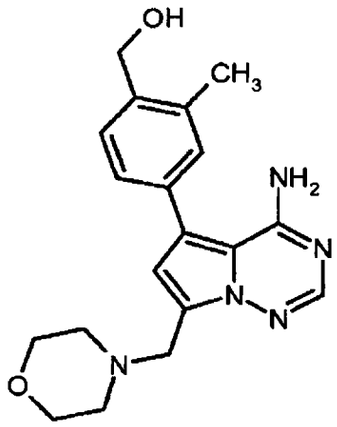
LC-MS (method 6): R_t = 0.53 min; MS (ESIpos): *m/z* (%) = 374.1 (80) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 372.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.46 (br. m, 4H), 3.56 (t, 4H), 3.83 (s, 2H), 4.61 (d, 2H), 5.45 (t, 1H), 6.70 (s, 1H), 7.44 (dd, 1H), 7.49 (d, 1H), 7.63 (t, 1H), 7.94 (s, 1H).

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Example 23

{4-[4-Amino-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-methylphenyl}-methanol



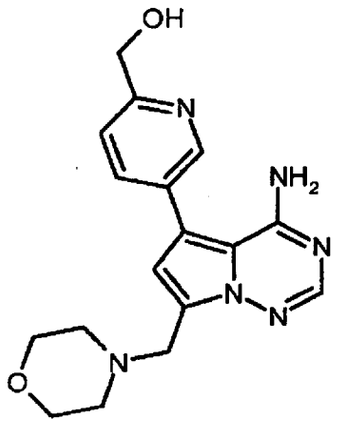
In analogy to the preparation of Example 28, Intermediate 39A (200 mg, 0.56 mmol) was reacted with Intermediate 4A (102 mg, 0.51 mmol) to give 9 mg (5% of th.) of the title compound.

LC-MS (method 4): R_t = 1.00 min; MS (ESIpos): *m/z* (%) = 354.3 (10) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 372.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.30 (s, 3H), 2.45 (br. m, 4H), 3.56 (t, 4H), 3.83 (s, 2H), 4.54 (d, 2H), 5.13 (t, 1H), 6.63 (s, 1H), 7.26 (s, 1H), 7.26 (d, 1H), 7.45 (d, 1H), 7.91 (s, 1H).

Example 24

{5-[4-Amino-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]pyridin-2-yl}methanol



The title compound was obtained from Intermediate 38A (200 mg, 0.64 mmol) and Intermediate 6A (147 mg, 0.96 mmol) by general synthetic method 1. The crude product was purified by pre-

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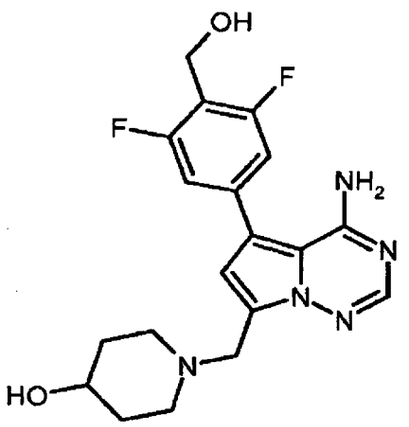
parative HPLC (method 4). Remaining impurities were removed by suspending the product in acetonitrile (2 mL) and collecting the remaining solid by filtration. Yield: 27 mg (12% of th.).

LC-MS (method 4): R_t = 0.78 min; MS (ESIpos): *m/z* (%) = 341 (10) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 339.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.46 (br. m, 4H), 3.56 (t, 4H), 3.84 (s, 2H), 4.62 (d, 2H), 5.46 (t, 1H), 6.73 (s, 1H), 7.54 (d, 1H), 7.86 (dd, 1H), 7.95 (d, 1H), 8.56 (s, 1H).

Example 25

1-({4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}methyl)piperidin-4-ol



The title compound was obtained from Intermediate 45A (200 mg, 0.61 mmol) and Intermediate 2A (159 mg, 0.74 mmol) by general synthetic method 1. The crude product was purified by preparative HPLC (method 3). Yield: 103 mg (43% of th.).

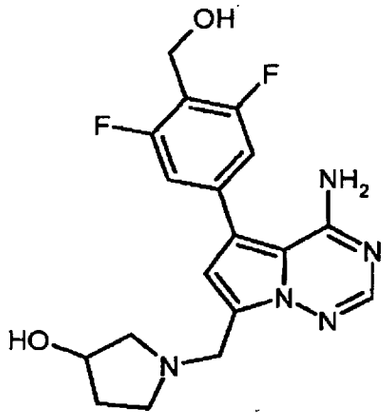
LC-MS (method 4): R_t = 0.98 min; MS (ESIpos): *m/z* (%) = 390.1 (60) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 388.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.36 (br. m, 2H), 1.68 (br. m, 2H), 2.12 (br. m, 2H), 2.75 (br. m, 2H), 3.41 (br. m, 1H), 3.79 (s, 2H), 4.51 (d, 1H), 4.54 (d, 2H), 5.27 (t, 1H), 6.72 (s, 1H), 7.15 (m, 2H), 7.94 (s, 1H).

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Example 26

1-({4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}-methyl)pyrrolidin-3-ol



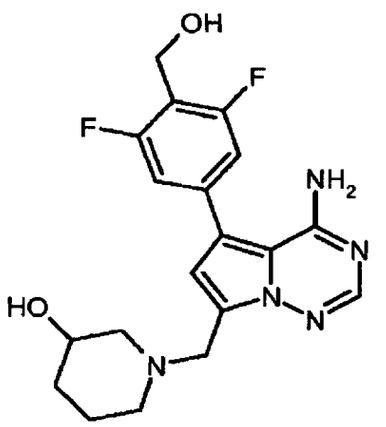
The title compound was obtained from Intermediate 47A (110 mg, 0.35 mmol) and Intermediate 2A (91.3 mg, 0.42 mmol) by general synthetic method 1. The crude product was purified by preparative HPLC (method 3). Yield: 69 mg (52% of th.).

LC-MS (method 4): R_t = 0.25 min; MS (ESIpos): *m/z* (%) = 376.1 (20) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.54 (m, 1H), 1.98 (m, 1H), 2.43 (br. d, 1H), 2.69 (m, 1H), 2.79 (dd, 1H), 3.93 (dd, 2H), 4.18 (br, 1H), 4.53 (d, 2H), 4.69 (d, 1H), 5.27 (t, 1H), 6.75 (s, 1H), 7.16 (m, 2H), 7.95 (s, 1H).

Example 27

1-({4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}methyl)piperidin-3-ol



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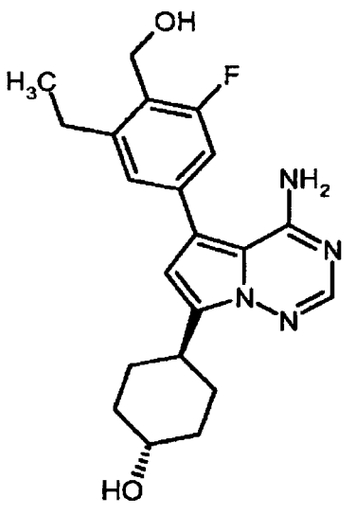
To a solution of Intermediate 50A (150 mg, 0.30 mmol) in THF (3.0 mL) was added 0.60 mL (0.60 mmol) of a 1 M solution of tetrabutylammonium fluoride (TBAF) in THF, and the mixture was stirred at room temperature for 1 h. The reaction mixture was then concentrated, and the residue was purified by preparative HPLC (method 3) to give 65 mg (56% of th.) of the title compound.

LC-MS (method 7): R_t = 0.33 min; MS (ESIpos): *m/z* (%) = 390.3 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.02 (br. m, 1H), 1.40 (br. m, 1H), 1.60 (br. m, 1H), 1.77 (br. m, 2H), 1.95 (br. m, 1H), 2.73 (br. m, 1H), 2.88 (br. m, 1H), 3.43 (br. m, 1H), 3.83 (br. m, 2H), 4.54 (br. d, 3H), 5.27 (t, 1H), 6.74 (s, 1H), 7.15 (m, 2H), 7.95 (s, 1H).

Example 28

trans-4-{4-Amino-5-[3-ethyl-5-fluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}cyclohexanol



Intermediate 24A (120 mg, 0.39 mmol) and Intermediate 58A (130 mg, 0.46 mmol) were dissolved in acetonitrile (3.0 mL) in a microwave reactor vial and flushed with argon. Tetrakis(triphenylphosphine)palladium(0) (22 mg, 0.02 mmol) and 2.0 M aq. sodium carbonate solution (0.7 mL) were added, and the mixture was heated to 150°C for 1 h in a single-mode microwave device. After cooling, the mixture was filtered, and the filtrate was evaporated. The residue was purified by preparative HPLC (method 2) to give 36 mg (23% of th.) of the title compound.

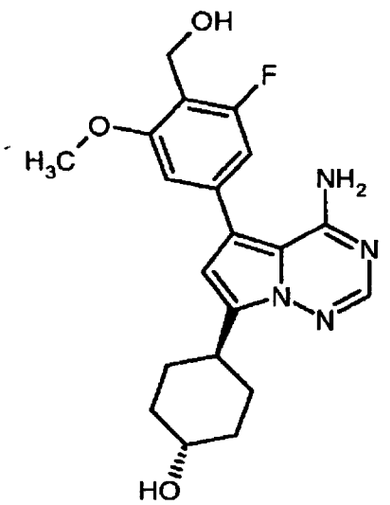
LC-MS (method 6): R_t = 0.82 min; MS (ESIpos): *m/z* (%) = 385 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 383 (100) $[M-H]^-$.

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^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.24 (t, 3H), 1.28-1.38 (m, 2H), 1.46-1.54 (m, 2H), 1.94-1.97 (m, 2H), 2.01-2.05 (m, 2H), 2.82 (q, 2H), 3.03 (m, 1H), 3.47 (m, 1H), 4.53 (m, 2H), 4.61 (d, 1H), 5.02 (t, 1H), 6.58 (s, 1H), 7.08 (d, 1H), 7.15 (s, 1H), 7.90 (s, 1H).

Example 29

trans-4-{4-Amino-5-[3-fluoro-4-(hydroxymethyl)-5-methoxyphenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}cyclohexanol



Intermediate 24A (120 mg, 0.39 mmol) and Intermediate 59A (163 mg, 80% purity, 0.46 mmol) were dissolved in acetonitrile (2.0 mL) in a microwave reactor vial and flushed with argon. Tetrakis(triphenylphosphine)palladium(0) (45 mg, 0.04 mmol) and 2.0 M aq. sodium carbonate solution (0.5 mL) were added, and the mixture was heated to 150°C for 1 h in a single-mode microwave device. After cooling, the mixture was filtered, and the filtrate was evaporated. The residue was purified by preparative HPLC (method 2) to give 6 mg (4% of th.) of the title compound.

LC-MS (method 5): R_t = 1.36 min; MS (ESIpos): *m/z* (%) = 387 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 385 (100) $[M-H]^-$.

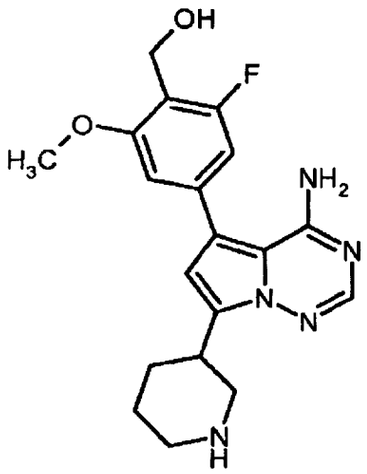
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.24-1.33 (m, 2H), 1.42-1.53 (m, 2H), 1.90-1.93 (m, 2H), 2.00-2.04 (m, 2H), 3.04 (m, 1H), 3.46 (m, 1H), 3.82 (s, 3H), 4.48 (m, 2H), 4.60 (d, 1H), 4.83 (t, 1H), 6.60 (s, 1H), 6.85 (d, 1H), 6.90 (s, 1H), 7.91 (s, 1H).

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Example 30

{4-[4-Amino-7-(piperidin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluoro-6-methoxyphenyl}-methanol



Intermediate 63A (50 mg, 0.11 mmol) was dissolved in a 30% solution of trifluoroacetic acid in dichloromethane (5.0 mL) at 0°C. The reaction mixture was stirred at this temperature for 30 min, then all volatiles were removed by distillation under reduced pressure. The residue was purified by preparative HPLC (method 2). The product thus obtained was dissolved in ethyl acetate and washed with saturated aqueous sodium carbonate solution. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off to give 30 mg (76% of th.) of the title compound.

LC-MS (method 6): R_t = 0.59 min; MS (ESIpos): *m/z* (%) = 372 (10) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 370 (100) $[M-H]^-$.

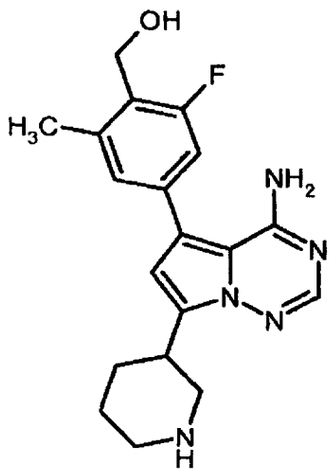
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.50-2.08 (m, 4H), 2.94 (m, 2H), 3.17-3.30 (m, 3H), 3.85 (s, 3H), 4.51 (m, 2H), 4.82 (t, 1H), 6.60 (s, 1H), 6.84 (d, 1H), 6.89 (s, 1H), 7.90 (s, 1H).

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Example 31

{4-[4-Amino-7-(piperidin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluoro-6-methylphenyl}-methanol



Intermediate 64A (110 mg, 0.21 mmol) was dissolved in a 30% solution of trifluoroacetic acid in dichloromethane (5.0 mL) at 0°C. The reaction mixture was stirred at this temperature for 30 min, then all volatiles were removed by distillation under reduced pressure. The residue was purified by preparative HPLC (method 2). The product thus obtained was dissolved in ethyl acetate and washed with saturated aqueous sodium carbonate solution. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off to give 59 mg (78% of th.) of the title compound.

LC-MS (method 4): R_t = 1.10 min; MS (ESIpos): *m/z* (%) = 356 (40) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 354 (100) $[M-H]^-$.

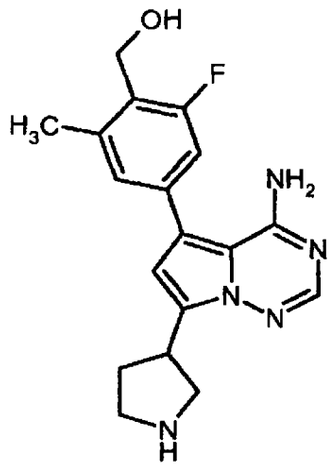
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.44-2.08 (m, 4H), 2.42 (s, 3H), 2.94 (m, 2H), 3.17-3.27 (m, 3H), 4.53 (m, 2H), 4.98 (t, 1H), 6.54 (s, 1H), 7.06 (d, 1H), 7.11 (s, 1H), 7.90 (s, 1H).

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Example 32

{4-[4-Amino-7-(pyrrolidin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluoro-6-methylphenyl}-methanol



Intermediate 65A (90 mg, 0.17 mmol) was dissolved in a 30% solution of trifluoroacetic acid in dichloromethane (5.0 mL) at 0°C. The reaction mixture was stirred at this temperature for 30 min, then all volatiles were removed by distillation under reduced pressure. The residue was purified by preparative HPLC (method 2). The product thus obtained was dissolved in ethyl acetate and washed with saturated aqueous sodium carbonate solution. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off to give 27 mg (47% of th.) of the title compound.

LC-MS (method 4): R_t = 1.03 min; MS (ESIpos): *m/z* (%) = 342 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 340 (100) $[M-H]^-$.

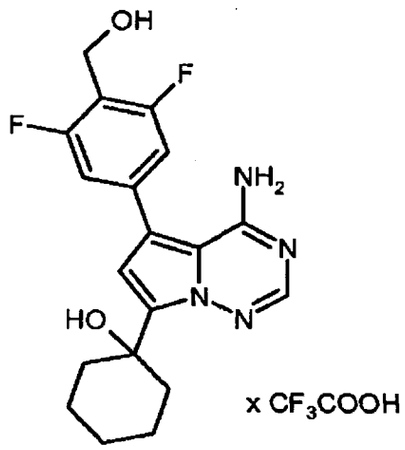
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.80-2.21 (m, 2H), 2.43 (s, 3H), 2.78-2.81 (m, 1H), 2.85-3.02 (m, 2H), 3.22-3.27 (m, 1H), 3.63 (m, 1H), 4.55 (br. s, 2H), 4.98 (t, 1H), 6.63 (s, 1H), 7.06 (d, 1H), 7.11 (s, 1H), 7.90 (s, 1H).

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Example 33

1-{4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}cyclohexanol trifluoroacetate



Intermediate 61A (95 mg, 0.31 mmol) and Intermediate 1A (87 mg, 0.32 mmol) were dissolved in DMF (2.0 mL) in a microwave reactor vessel and flushed with argon. Tetrakis(triphenylphosphine)palladium(0) (35 mg, 0.03 mmol) and 2.0 M aq. sodium carbonate solution (0.5 mL) were added, and the mixture was heated to 150°C for 1 h in a single-mode microwave device. After cooling, the mixture was filtered, and the filtrate was directly purified by preparative HPLC (method 2) to give 6 mg (4% of th.) of the title compound.

LC-MS (method 6): R_t = 1.05 min; MS (ESIpos): *m/z* (%) = 375 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 373 (100) $[M-H]^-$.

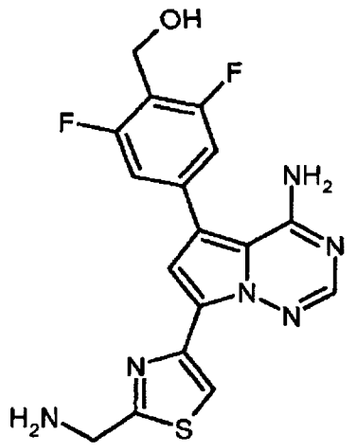
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.20-1.33 (m, 1H), 1.42-1.51 (m, 2H), 1.60-1.82 (m, 5H), 2.17-2.28 (m, 2H), 4.51 (s, 2H), 6.76 (s, 1H), 7.17 (m, 2H), 8.02 (s, 1H).

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Example 34

(4-{4-Amino-7-[2-(aminomethyl)-1,3-thiazol-4-yl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}-2,6-difluorophenyl)methanol



Intermediate 62A (67 mg, 0.16 mmol), Intermediate 1A (51 mg, 0.19 mmol), tetrakis(triphenylphosphine)palladium(0) (18 mg, 0.02 mmol) and 2.0 M aq. sodium carbonate solution (0.94 mL) were dissolved in 1,4-dioxane (2.50 mL) in a microwave reactor vial. The vial was crimp-capped, and the mixture was heated to 140°C for 3 h in a single-mode microwave device. Then, the reaction mixture was filtered, and the filtrate was diluted with acetonitrile and treated with diethyl ether. The resulting precipitate was collected and purified by preparative HPLC (method 2). The product thus obtained (15 mg) was subsequently treated with a 20% solution of trifluoroacetic acid in dichloromethane (2 mL) for 20 min. The volatiles were removed by distillation, and the residue was treated with conc. aqueous sodium carbonate solution and extracted with ethyl acetate. The organic extract was dried over anhydrous sodium sulfate, and the solvent was distilled off to give the title compound (10 mg, 13% of th.) as a colorless solid.

LC-MS (method 4): R_t = 1.12 min; MS (ESIpos): *m/z* (%) = 389 (25) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 387 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 4.24 (s, 2H), 4.53 (m, 2H), 5.30 (t, 1H), 7.18-7.23 (m, 3H), 8.11 (s, 1H), 8.40 (s, 1H).

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B. Evaluation of Biological Activity

Abbreviations and Acronyms:

ATCC	American Type Culture Collection
ATP	adenosine triphosphate
Bq	Becquerel
BrdU	5-bromo-2-deoxyuridine
BSA	bovine serum albumin
CHO	chinese hamster ovary
cpm	counts per minute
Ct	cycle threshold
DMEM/F12	Dulbecco's modified Eagle's medium / Ham's F12 medium (1:1)
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
EDTA	ethylenediamine-tetraacetic acid
ENGS MV	microvascular endothelial cell culture medium
FAM	carboxyfluorescein succinimidyl ester
FCS	fetal calf serum
hBMP9	human bone morphogenic factor 9
HMVEC	human microvascular endothelial cell(s)
HTRF	homogeneous time resolved fluorescence
[I]	inhibitor concentration
IC_{50}	concentration with 50% inhibitory effect
LDH	lactate dehydrogenase
mRNA	messenger ribonucleic acid

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NADH	nicotinamide adenine dinucleotide
Nonidet P40	4-ethylphenoxy-poly(ethyleneglycol)ether (*n = 11*)
PBS	phosphate buffered saline
PE	polyethylene
PK	pyruvate kinase
p.o.	*per os*
qPCR	quantitative polymerase chain reaction
RNA	ribonucleic acid
RTL buffer	RNeasy lysis buffer
SEQ ID NO	sequence identity number
SFM	serum free medium
TAMRA	carboxytetramethylrhodamine
Tris	2-amino-2-hydroxymethylpropane-1,3-diol
Triton X-100	4-*tert*-octylphenoxy-poly(ethyleneglycol)ether (*n = 10*)

Demonstration of the activity of the compounds of the present invention may be accomplished through *in vitro, ex vivo*, and *in vivo* assays that are well known in the art. For example, to demonstrate the activity of the compounds of the present invention, the following assays may be used.

B-1. *In vitro* enzyme inhibition using scintillation of incorporated radio label (flashplate assay)

Test principle:

Test compounds diluted in DMSO are mixed with a suitable substrate / co-substrate (here: biotinylated α-casein and ^{33}P-ATP) in a corresponding assay buffer. Addition of the enzyme of interest (here: ALK1 kinase) starts the enzyme reaction. The enzyme-catalyzed incorporation of radio label into the substrate is measured via scintillation. Incorporated radio label is separated from free radio label via specific binding of the biotinylated substrate to strepavidin-coated

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microtiter plates (flashplates) and concomitant washing steps. The scintillation signal intensity (counts per minutes, cpm) is proportional to the enzyme activity. Enzyme inhibition results in a decreased signal intensity. IC_{50} values of the test compounds are determined by cpm-versus-[I] plots.

Reaction buffer:

Reaction buffer contains 50 mM Tris pH 8.0 (Sigma), 1 mM $MnCl_2$ (Sigma), 0.01% Nonidet P40 (Fluka), 0.5 x Complete EDTA-free protease inhibitors (Roche; contains a mixture of several protease inhibitors for the inhibition of serine and cysteine (but not metallo-) proteases; 1 tablet contains protease inhibitors sufficient for a 50 ml cell extract; the concentration used in this assay corresponds to 1 tablet in 100 ml).

Other buffers:

1.) Stop solution: Dulbecco's PBS (PAA, Pasching, Austria), 25 mM EDTA (Sigma), 25 µM ATP (Roche), 0.05% Triton X-100 (Sigma);

2.) Saturation buffer: Dulbecco's PBS (PAA, Pasching, Austria), 100 µM ATP (Roche), 0.2% Triton X-100 (Sigma);

3.) Wash buffer: Dulbecco's PBS (PAA, Pasching, Austria).

Enzyme solution:

ALK1 (Invitrogen, Paisley, United Kingdom) stock solution (35.7 ng/µl) is diluted to 4 ng/µl; final concentration in the reaction is 1 ng/µl.

Substrate solution:

Dephosphorylated α-casein (Sigma) is biotinylated according to the manufacturer's protocol (Pierce, Bonn, Germany) resulting in a stock solution of 61.6 µM. Briefly, EZ-Link® Sulfo-NHS-Biotin reagent (sulfosuccinimidyl-6-(biotinamido)hexanoate; Pierce, Bonn, Germany) is added in equal molarity to α-casein and incubated on ice for 2 h. Afterwards, the biotin reagent is removed by dialysis (2 x 2 h and overnight).

A 100 mM solution of cold (unlabelled) ATP (Roche) is diluted 1:100 before each test. For the substrate mix, α-casein is diluted to 2.22 µM resulting in a final concentration of 1 µM α-casein in the reaction. Additionally, cold ATP is added to give a 1.11 µM solution which results in a final concentration of 500 nM in the reaction.

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Radioactive ATP solution:

The stock solution (9.25 MBq/25 µl of ^{33}P-ATP; Perkin Elmer, Rodgau, Germany) is diluted to 651.2 Bq/µl. This corresponds to a final concentration of 162.8 Bq/µl.

Compound solution:

Compounds are dissolved in 100% DMSO (10 mM stock solution) and diluted to 2 mM. Further dilutions are made stepwise 1:3.16 in DMSO.

Step-by-step protocol:

A volume of 9 µl substrate solution is provided into each well of a 384 well microtiter plate (Greiner Bio-One, Solingen, Germany). 1 µl compound solution and 5 µl of the radioactive ATP solution are added. Enzyme reaction starts with addition of 5 µl of enzyme solution. The mixture is incubated for 60 minutes at room temperature and then stopped by addition of 10 µl stop solution. The 384 well microtiter flashplates (Perkin Elmer, Rodgau, Germany) are saturated with 50 µl saturation buffer per well for at least 60 minutes. Subsequently, a volume of 20 µl is discarded and replaced with 20 µl of the stopped ALK1 reaction mixture. Binding of biotinylated substrate to the flashplate is allowed for by overnight incubation at room temperature. Bound substrate is separated from unbound components through repeated washing steps (3 x 50 µl washing buffer per well). Finally, 50 µl washing buffer is added, and the scintillation signal (cpm) is measured in a suitable counter (Perkin Elmer, Rodgau, Germany).

IC_{50} values for individual compounds of the present invention are listed in Table 1 below:

Table 1

Example No.	**ALK1 IC_{50} [nM]**
1	2.0
2	2.8
3	4.0
4	1.0
5	1.3
6	40

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Example No.	ALK1 IC_{50} [nM]
7	2.0
8	4.4
9	5.7
10	8.0
11	1.9
12	5.9
13	4.0
14	5.3
15	60
16	2.6
17	2.0
18	80
19	19
20	30
21	25
22	17
23	30
24	140
25	65
26	30
27	70
28	0.5

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Example No.	ALK1 IC_{50} [nM]
29	1.0
30	2.0
31	4.0
32	4.0
33	15
34	4.1

B-2. Smad7 target gene induction: Cell assay and TaqMan expression analysis

Activation of ALK1 receptors by BMP9 induces the Smad1/5 signalling pathway and enhances expression of target genes Smad6, Smad7 and Id-1. Induction of Smad7-mRNA in BMP9-stimulated endothelial cells was determined to monitor the cellular potency of ALK1 kinase inhibitors.

Human microvascular endothelial cells (HMVECadult, Cell Systems, St. Katharinen) were seeded in complete ENGS MV medium with all supplements (LifeLine Cell Technology) in 96 well plates with 10 000 cells per well. After 4 h incubation at 37°C and 7.5% CO_2 in a humidified incubator, medium was replaced with minimal medium (ENGS MV without supplements containing 0.02% FCS). After 16 h, test compounds or medium (controls) were added to the cultures, followed 30 min later by addition of hBMP9 (R&D Systems). Medium was removed 1 to 4 h later, plates were gently washed with phosphate-buffered saline, and cells were lysed with 150 µl per well of ice-cold RLT buffer (Qiagen).

Total cellular RNA was isolated with the Trizol® reagent protocol according to the manufacturer's specifications (Invitrogen, USA) and treated with DNAseI to remove genomic DNA contamination.

For relative quantitation of the mRNA distribution of hSmad7, total RNA from each sample was first reverse-transcribed using the ImProm-II Reverse Transcription System (Promega, USA) according to the manufacturer's protocol. The final volume was adjusted to 200 µl with water.

For relative quantitation of selected mRNA, the Applied Bioscience ABI 7900HT Sequence Detection System was used according to the manufacturer's specifications and protocols. PCR

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reactions were set up to quantitate hSmad7- and the housekeeping gene L32-mRNA. Forward and reverse primers and probes for hSmad7 and L32 were designed using the Applied Bioscience ABI Primer Express™ software and were synthesized by Eurogentec (Belgium). The hSmad7 forward primer sequence was: Primer 1 (SEQ ID NO 1). The hSmad7 reverse primer sequence was: Primer 2 (SEQ ID NO 2). Probe 1 (SEQ ID NO 3), labelled with FAM as the reporter dye and TAMRA as the quencher, was used as a probe for hSmad7. The L32 forward primer sequence was: Primer 3 (SEQ ID NO 4). The L32 reverse primer sequence was: Primer 4 (SEQ ID NO 5). Probe 2 (SEQ ID NO 6), labelled with FAM as the reporter dye and TAMRA as the quencher, was used as a probe for L32.

SEQ ID list:

		5' to 3'
SEQ ID NO 1	hSmad7 primer 1 (forward primer)	CCCTCCTTACTCCAGATACCC
SEQ ID NO 2	hSmad7 primer 2 (reverse primer)	GGAGGAAGGCACAGCATCT
SEQ ID NO 3	hSmad7 probe 1	TTTTCTCAAACCAACTGCAGACTGTCC
SEQ ID NO 4	L32 primer 3 (forward primer)	AAGTTCATCCGGCACCAGTC
SEQ ID NO 5	L32 primer 4 (reverse primer)	TGGCCCTTGAATCTTCTACGA
SEQ ID NO 6	L32 probe 2	CCCAGAGGCATTGACAACAGGG

The following reagents were prepared in a total of 20 µl added per well: 1 x qPCR-MasterMix (Eurogentec, Belgium) and hSmad7 forward and reverse primers each at 200 nM, 200 nM hSmad7 FAM/TAMRA-labelled probe 1 (SEQ ID NO 3), and 5 µl of template cDNA. Correspondingly, a second mix in a total of 20 µl was prepared using L32 FAM/TAMRA-labelled probe 2 (SEQ ID NO 6) and L32 forward and reverse primers added per well in parallel samples.

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Thermal cycling parameters were 2 min at 50°C, followed by 10 min at 95°C, followed by 40 cycles of melting at 95°C for 15 sec and annealing/extending at 60°C for 1 min.

Calculation of relative expression:

The Ct (cycle threshold) values were calculated from the turning point of PCR product quantity curves by the ΔΔCt method (delta-delta Ct):

$\Delta Ct = Ct_{hSmad7} - Ct_{L32}$; relative expression = $2^{(15-\Delta Ct)}$.

IC_{50} values of test compounds were calculated on basis of relative Smad7 expressions at different compound concentrations. Representative values are listed in Table 2 below:

Table 2

Example No.	**hSmad7 IC_{50} [nM]**
1	100
3	180
5	150
7	130
8	60
11	90
17	120
20	4400
21	6000
22	800

B-3. Systemic efficacy in the laser-induced choroidal neovascularization (CNV) model

The aim of this study was to determine whether once daily systemic administration (i.p.) of a test compound resulted in a decrease of choroidal neovascularization in a rat model of laser-induced choroidal neovascularisation.

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For this purpose, 16 pigmented Brown-Norway rats with no visible sign of ocular defects were selected and randomly divided into two groups of eight animals each. On day 0, the animals were anaesthetized by an intramuscular injection (15 mg/kg xylazine and 80 mg/kg ketamine). After instillation of one drop of 0.5% tropicamide to dilate the pupils, choroidal neovascularisation was induced by executing six 75 µm-sized choroidal burns around the optic disc of the right eyes using a 532 nm argon laser photocoagulation at 150 mW for 100 ms. The test compound and vehicle control were administered once daily by intraperitoneal (i.p.) injections with dosing of the test compound at 50 mg/kg on day 0 and then continuing with 20 mg/kg from day 1 to day 23. The body weight of all animals was recorded before the start and once daily during the study.

An angiography was performed on day 21 using Heidelberg's Retinal Angiograph (HRA). After anaesthesia and pupillary dilation, 10% sodium fluorescein dye was injected subcutaneously, and images were recorded 10 min after dye injection. The vascular leakage of the fluorescein on the angiograms was evaluated by two examiners in a masked fashion and scored with 0 (no leakage) to 3 (strongly stained).

After euthanasia on day 23, the eyes were harvested and fixed in 4% paraformaldehyde solution for 1 hour at room temperature. After washing, the retina was carefully peeled, and the sclera-choroid was flat-mounted and incubated after blocking with a FITC-isolectine B4 antibody. The flat-mounted preparations were examined under a fluorescence microscope (Apotom) at 488 nm excitation wavelength. The size of choroidal neovascularisation was scored by morphometric analysis of images using Axiovision 4.6 software.

For Example 11 as a representative of the compounds of the present invention, the following results were obtained in this model:

	vascular leakage [HRA score]	**choroidal neovascularisation lesion size** [μm^2 x 100 000]
Example 11	0.68 ± 0.35	3.48 ± 0.40
vehicle control	1.7 ± 0.32	5.83 ± 0.55

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B-4. Topical efficacy in the laser-induced choroidal neovascularization (CNV) model

The aim of this study was to determine whether twice daily topical administration (eye drops) of a test compound resulted in a decrease of vascular leakage and/or choroidal neovascularization in a rat model of laser-induced choroidal neovascularisation.

For this purpose, 16 pigmented Brown-Norway rats with no visible sign of ocular defects were selected and randomly assigned to two groups of eight animals each. On day 0, the animals were anaesthetized by an intraperitoneal injection (15 mg/kg xylazine and 80 mg/kg ketamine). After instillation of one drop of 0.5% tropicamide to dilate the pupils, choroidal neovascularisation was induced by burning six holes into the retina (disruption of Bruch's membrane) of one eye per animal using a 532 nm argon laser (lesion size: 50 µm; laser intensity: 150 mW; stimulus duration: 100 ms). The test compound and vehicle control were topically administered twice daily by instilling respective eye drops into the affected eye. The test compound was dosed as follows: 10 µl of an eye drop formulation containing 50 mg/ml of the test compound suspended in 100% liquid paraffin were applied to the affected eye twice daily at a 10 to 14 hour interval during the complete observation period of 23 days. The remaining eight animals received the respective vehicle (100% liquid paraffin) topically twice daily. The body weight of all animals was recorded before the start and once daily during the study.

An angiography was performed on day 21 using a fluorescence fundus camera (Kowe). Here, after anaesthesia and pupillary dilation, 10% sodium fluorescein dye was injected subcutaneously, and images were recorded 2 and 10 min after dye injection. The vascular leakage of the fluorescein on the angiograms was evaluated by three different examiners who were blinded for group allocation (test compound versus vehicle), and scored with 0 (no leakage) to 3 (strongly stained).

On day 23, animals were sacrificed, and eyes were harvested and fixed in 4% paraformaldehyde solution for 1 hour at room temperature. After washing, the retina was carefully peeled, washed, blocked and stained with a FITC-isolectine B4 antibody in order to visualize the vasculature. Then, the sclera-choroids were flat-mounted and examined under a fluorescence microscope (Keyence Biozero) at 488 nm excitation wavelength. The area (in μm^2) of choroidal neovascularization was measured using ImageTool software.

Although the invention has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of the invention may be devised by others skilled in the art

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without departing from the true spirit and scope of the invention. The claims are intended to be construed to include all such embodiments and equivalent variations.

C. Examples relating to Pharmaceutical Compositions

Pharmaceutical compositions according to the present invention can be illustrated as follows:

Sterile i.v. solution:

A 5 mg/mL solution of the desired compound of the invention can be made using sterile, injectable water, and the pH is adjusted if necessary. The solution is diluted for administration to 1-2 mg/mL with sterile 5% dextrose and is administered as an i.v. infusion over about 60 minutes.

Lyophilized powder for i.v. administration:

A sterile preparation can be prepared with (*i*) 100–1000 mg of the desired compound of the invention as a lyophilized powder, (*ii*) 32–327 mg/mL sodium citrate, and (*iii*) 300–3000 mg Dextran 40. The formulation is reconstituted with sterile, injectable saline or 5% dextrose to a concentration of 10 to 20 mg/mL, which is further diluted with saline or 5% dextrose to 0.2 to 0.4 mg/mL, and is administered either as i.v. bolus or by i.v. infusion over 15–60 minutes.

Intramuscular suspension:

The following solution or suspension can be prepared for intramuscular injection:

50 mg/mL of the desired, water-insoluble compound of the invention; 5 mg/mL sodium carboxymethylcellulose; 4 mg/mL Tween 80; 9 mg/mL sodium chloride; 9 mg/mL benzyl alcohol.

Hard shell capsules:

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 mg of the desired, powdered compound of the invention, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate.

Soft gelatin capsules:

A mixture of the desired compound of the invention in a digestible oil, such as soybean oil, cottonseed oil or olive oil, is prepared and injected by means of a positive displacement pump into molten gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The

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capsules are washed and dried. The desired compound of the invention can be dissolved in a mixture of polyethylene glycol, glycerin and sorbitol to prepare a water-miscible medicine mix.

Tablets:

A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 mg of the desired compound of the invention, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8 mg of lactose. Appropriate aqueous and non-aqueous coatings may be applied to increase palatability, improve elegance and stability, or delay absorption.

Solution or suspension for topical application to the eye (eye drops):

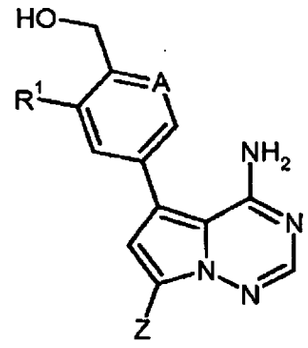
A sterile formulation can be prepared with 100 mg of the desired compound of the invention as a lyophilized powder reconstituted in 5 mL of sterile saline. As preservative, benzalkonium chloride, thimerosal, phenylmercuric nitrate, or the like may be used in a range of about 0.001% to 1% by weight.

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We claim:

1. A compound of formula (I)



(I),

wherein

A is N or C-R^2, wherein

R^2 represents hydrogen, fluoro or chloro,

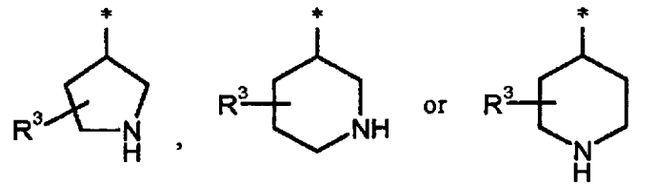
R^1 represents hydrogen, fluoro, chloro, methyl, ethyl or methoxy,

and

Z represents (C_1-C_4)-alkyl or (C_3-C_6)-cycloalkyl each of which may be substituted with hydroxy,

or

Z represents a heterocyclic group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

and

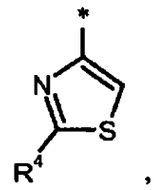
R^3 represents hydrogen or hydroxy,

with the proviso that when R^3 is hydroxy, this hydroxy is not attached to a ring carbon atom located adjacent to the ring nitrogen atom,

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or

Z represents a thiazole group of the formula



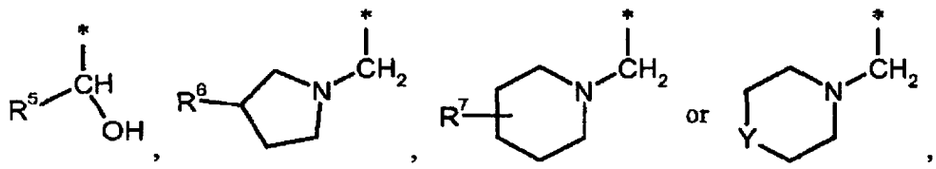
wherein * indicates the point of attachment to the pyrrolotriazine moiety,

and

R^4 represents hydrogen, methyl, ethyl, amino or aminomethyl,

or

Z represents a group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

R^5 represents (C_3-C_6)-cycloalkyl, oxetanyl, tetrahydrofuranyl or tetrahydropyranyl,

R^6 represents hydrogen or hydroxy,

R^7 represents hydrogen or hydroxy,

with the proviso that when R^7 is hydroxy, this hydroxy is not attached to a ring carbon atom located adjacent to the ring nitrogen atom,

and

Y is O, NH or NCH_3,

or a pharmaceutically acceptable salt, hydrate and/or solvate thereof.

2. The compound of formula (I) according to Claim 1, wherein

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A is C-R^2, wherein

R^2 represents hydrogen or fluoro,

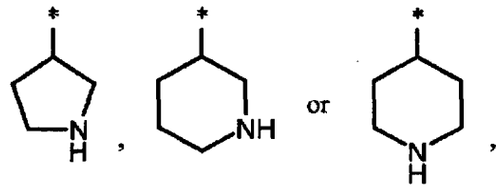
R^1 represents hydrogen, fluoro, chloro, methyl, ethyl or methoxy,

and

Z represents *n*-propyl, *n*-butyl or cyclohexyl each of which may be substituted with hydroxy,

or

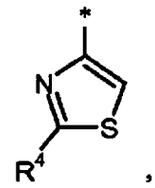
Z represents a heterocyclic group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

or

Z represents a thiazole group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

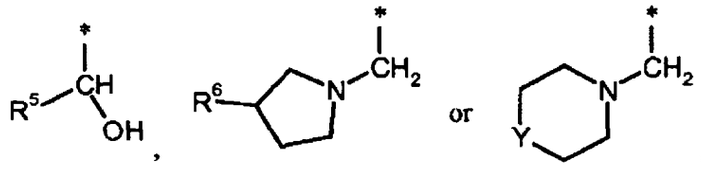
and

R^4 represents methyl, ethyl, amino or aminomethyl,

or

Z represents a group of the formula

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wherein * indicates the point of attachment to the pyrrolotriazine moiety,

R^5 represents cyclopropyl or tetrahydropyran-4-yl,

R^6 represents hydroxy,

and

Y is O,

or a pharmaceutically acceptable salt, hydrate and/or solvate thereof.

3. The compound of formula (I) according to Claim 1 or 2, wherein

A is C-R^2, wherein

R^2 represents hydrogen or fluoro,

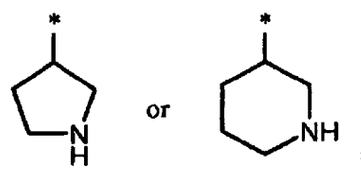
R^1 represents hydrogen, fluoro, methyl, ethyl or methoxy,

and

Z represents 4-hydroxybutyl or 4-hydroxycyclohexyl,

or

Z represents a heterocyclic group of the formula

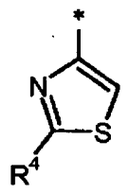


wherein * indicates the point of attachment to the pyrrolotriazine moiety,

or

Z represents a thiazole group of the formula

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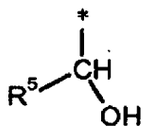
wherein * indicates the point of attachment to the pyrrolotriazine moiety,

and

R^4 represents methyl, ethyl, amino or aminomethyl,

or

Z represents a group of the formula



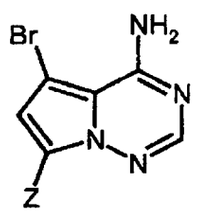
wherein * indicates the point of attachment to the pyrrolotriazine moiety,

and

R^5 represents cyclopropyl,

or a pharmaceutically acceptable salt, hydrate and/or solvate thereof.

4. A process for preparing a compound of formula (I) as defined in Claims 1 to 3, characterized in that a bromopyrrolotriazine of formula (II)



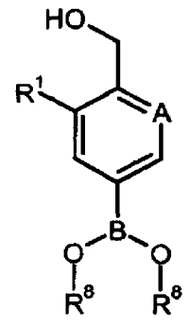
(II),

wherein Z has the meaning indicated in Claim 1 to 3,

is either

[A] coupled with an arylboronic acid or ester of formula (III)

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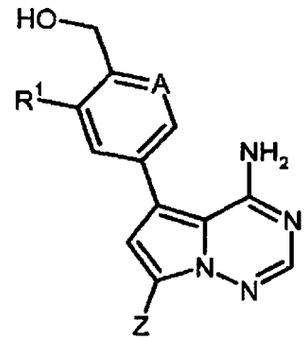
(III),

wherein A and R^1 have the meanings indicated in Claim 1 to 3,

and

R^8 represents hydrogen or (C_1-C_4)-alkyl, or both R^8 residues are linked together to form a $-(CH_2)_2-$, $-C(CH_3)_2-C(CH_3)_2-$, $-(CH_2)_3-$ or $-CH_2-C(CH_3)_2-CH_2-$ bridge,

in the presence of a suitable palladium catalyst and a base to yield the target compound of formula (I)

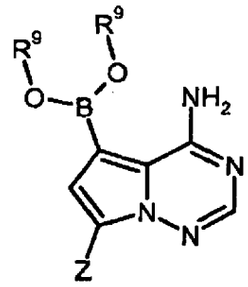


(I),

wherein A, Z and R^1 have the meanings indicated in Claim 1 to 3,

or

[B] first converted into the corresponding boronic acid or ester derivative of formula (IV)



(IV),

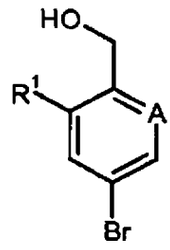
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wherein Z has the meaning indicated in Claim 1 to 3,

and

R^9 represents hydrogen or (C_1-C_4)-alkyl, or both R^9 residues are linked together to form a $-(CH_2)_2-$, $-C(CH_3)_2-C(CH_3)_2-$, $-(CH_2)_3-$ or $-CH_2-C(CH_3)_2-CH_2-$ bridge,

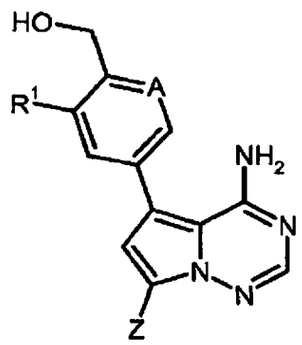
which is then coupled with an aryl bromide of formula (V)



(V),

wherein A and R^1 have the meanings indicated in Claim 1 to 3,

in the presence of a suitable palladium catalyst and a base to also give the target compound of formula (I)



(I),

wherein A, Z and R^1 have the meanings indicated in Claim 1 to 3,

optionally followed, where appropriate, by (*i*) separating the compounds of formula (I) into their respective enantiomers and/or diastereomers, and/or (*ii*) converting the compounds of formula (I) into their respective hydrates, solvates, salts and/or hydrates or solvates of the salts by treatment with the corresponding solvents and/or acids.

5. Compound as defined in any of Claims 1 to 3 for the treatment or prevention of diseases.

6. Use of a compound as defined in any of Claims 1 to 3 for the manufacture of a pharmaceutical composition for the treatment or prevention of age-related macular degeneration (AMD), choroidal neovascularisation (CNV) and diabetic retinopathy.

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7. A pharmaceutical composition comprising a compound as defined in any of Claims 1 to 3, or a pharmaceutically acceptable salt, hydrate and/or solvate thereof, and one or more pharmaceutically acceptable excipients.

8. The pharmaceutical composition of Claim 7 further comprising one or more additional therapeutic agents.

9. The pharmaceutical composition as defined in Claim 7 or 8 for the treatment or prevention of age-related macular degeneration (AMD), choroidal neovascularisation (CNV) and diabetic retinopathy.

10. A method of treating or preventing age-related macular degeneration (AMD), choroidal neovascularisation (CNV) and diabetic retinopathy in a mammal, comprising administering to a mammal in need thereof a therapeutically effective amount of one or more compounds as defined in any of Claims 1 to 3, or of a pharmaceutical composition as defined in any of Claims 7 to 9.

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BHC 11 1 016-US

Hydroxymethylaryl-substituted pyrrolotriazines and uses thereof

Abstract

This invention relates to novel 5-[(hydroxymethyl)aryl]-substituted pyrrolo[2,1-f][1,2,4]triazin-4-amines, to processes for the preparation of such compounds, to pharmaceutical compositions containing such compounds, and to the use of such compounds or compositions for treating angiogenesis-related disorders, in particular angiogenesis-related ocular disorders.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	BHC 111016 US
	Application Number	
Title of Invention	HYDROXYMETHYLARYL-SUBSTITUTED PYRROLOTRIAZINES AND USES THEREOF	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Applicant Information:

Applicant 1 [Remove]

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
Dr.	Joachim		TELSER	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Wuppertal	Country Of Residence[i]	DE

Citizenship under 37 CFR 1.41(b) [i] DE

Mailing Address of Applicant:

Address 1	Müllerstrasse 178		
Address 2			
City	Berlin	State/Province	
Postal Code	13353	Country[i]	DE

Applicant 2 [Remove]

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
Dr.	Jürgen		KLAR	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Wuppertal	Country Of Residence[i]	DE

Citizenship under 37 CFR 1.41(b) [i] DE

Mailing Address of Applicant:

Address 1	Müllerstrasse 178		
Address 2			
City	Berlin	State/Province	
Postal Code	13353	Country[i]	DE

Applicant 3 [Remove]

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
Dr.	Verena		VOEHRINGER	

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	BHC 111016 US
	Application Number	
Title of Invention	HYDROXYMETHYLARYL-SUBSTITUTED PYRROLOTRIAZINES AND USES THEREOF	

Citizenship under 37 CFR 1.41(b) i	DE		
Mailing Address of Applicant:			
Address 1	Müllerstrasse 178		
Address 2			
City	Berlin	**State/Province**	
Postal Code	13353	**Country**i	DE

Applicant 4 Remove

Applicant Authority (•) Inventor ( ) Legal Representative under 35 U.S.C. 117 ( ) Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
Dr.	Mario		LOBELL	

Residence Information (Select One) ( ) US Residency (•) Non US Residency ( ) Active US Military Service

City	Wuppertal	**Country Of Residence**i	DE
Citizenship under 37 CFR 1.41(b) i	DE		
Mailing Address of Applicant:			
Address 1	Müllerstrasse 178		
Address 2			
City	Berlin	**State/Province**	
Postal Code	13353	**Country**i	DE

Applicant 5 Remove

Applicant Authority (•) Inventor ( ) Legal Representative under 35 U.S.C. 117 ( ) Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Frank		SÜßMEIER	

Residence Information (Select One) ( ) US Residency (•) Non US Residency ( ) Active US Military Service

City	München	**Country Of Residence**i	DE
Citizenship under 37 CFR 1.41(b) i	DE		
Mailing Address of Applicant:			
Address 1	Müllerstrasse 178		
Address 2			
City	Berlin	**State/Province**	
Postal Code	13353	**Country**i	DE

Applicant 6 Remove

Applicant Authority (•) Inventor ( ) Legal Representative under 35 U.S.C. 117 ( ) Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
Dr.	Volkhart Min-Jian		LI	

Residence Information (Select One) ( ) US Residency (•) Non US Residency ( ) Active US Military Service

City	Velbert	**Country Of Residence**i	DE
Citizenship under 37 CFR 1.41(b) i	DE		

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	BHC 111016 US
	Application Number	
Title of Invention	HYDROXYMETHYLARYL-SUBSTITUTED PYRROLOTRIAZINES AND USES THEREOF	

Mailing Address of Applicant:			
Address 1	Müllerstrasse 178		
Address 2			
City	Berlin	State/Province	
Postal Code	13353	Country[i]	DE

Applicant 7 — Remove

Applicant Authority: (•) Inventor ( ) Legal Representative under 35 U.S.C. 117 ( ) Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
Dr.	Michael		BÖTTGER	

Residence Information (Select One): ( ) US Residency (•) Non US Residency ( ) Active US Military Service

City	Wuppertal	Country Of Residence[i]	DE
Citizenship under 37 CFR 1.41(b)[i]	DE		

Mailing Address of Applicant:			
Address 1	Müllerstrasse 178		
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City	Berlin	State/Province	
Postal Code	13353	Country[i]	DE

Applicant 8 — Remove

Applicant Authority: (•) Inventor ( ) Legal Representative under 35 U.S.C. 117 ( ) Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
Dr.	Stefan		GOLZ	

Residence Information (Select One): ( ) US Residency (•) Non US Residency ( ) Active US Military Service

City	Mülheim an der Ruhr	Country Of Residence[i]	DE
Citizenship under 37 CFR 1.41(b)[i]	DE		

Mailing Address of Applicant:			
Address 1	Müllerstrasse 178		
Address 2			
City	Berlin	State/Province	
Postal Code	13353	Country[i]	DE

Applicant 9 — Remove

Applicant Authority: (•) Inventor ( ) Legal Representative under 35 U.S.C. 117 ( ) Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
Dr.	Dieter		LANG	

Residence Information (Select One): ( ) US Residency (•) Non US Residency ( ) Active US Military Service

City	Velbert	Country Of Residence[i]	DE
Citizenship under 37 CFR 1.41(b)[i]	DE		

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	BHC 111016 US
	Application Number	
Title of Invention	HYDROXYMETHYLARYL-SUBSTITUTED PYRROLOTRIAZINES AND USES THEREOF	

Mailing Address of Applicant:

Address 1	Müllerstrasse 178		
Address 2			
City	Berlin	**State/Province**	
Postal Code	13353	**Country**i	DE

Applicant 10 Remove

Applicant Authority (•) Inventor ( ) Legal Representative under 35 U.S.C. 117 ( ) Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
Dr.	Karl-Heinz		SCHLEMMER	

Residence Information (Select One) ( ) US Residency (•) Non US Residency ( ) Active US Military Service

City	Wuppertal	**Country Of Residence**i	DE
Citizenship under 37 CFR 1.41(b) i	DE		

Mailing Address of Applicant:

Address 1	Müllerstrasse 178		
Address 2			
City	Berlin	**State/Province**	
Postal Code		**Country**i	DE

Applicant 11 Remove

Applicant Authority (•) Inventor ( ) Legal Representative under 35 U.S.C. 117 ( ) Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Wenlang		FU	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Florham Park	**State/Province**	NJ	**Country of Residence** i	US
Citizenship under 37 CFR 1.41(b) i	CN				

Mailing Address of Applicant:

Address 1	609 Sun Valley Way		
Address 2			
City	Florham Park	**State/Province**	NJ
Postal Code	07932	**Country**i	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	35969		
Email Address	phplus@bayer.com	Add Email	Remove Email

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	BHC 111016 US
	Application Number	
Title of Invention	HYDROXYMETHYLARYL-SUBSTITUTED PYRROLOTRIAZINES AND USES THEREOF	

Application Information:

Title of the Invention	HYDROXYMETHYLARYL-SUBSTITUTED PYRROLOTRIAZINES AND USES THEREOF		
Attorney Docket Number	BHC 111016 US	**Small Entity Status Claimed** ☐	
Application Type	Provisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)		**Suggested Figure for Publication (if any)**	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

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Enter either Customer Number or complete the Representative Name section below. If both sections are completed the Customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	35969		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of		

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	BHC 111016 US
	Application Number	
Title of Invention	HYDROXYMETHYLARYL-SUBSTITUTED PYRROLOTRIAZINES AND USES THEREOF	

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Application Number	Country i	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			○ Yes ○ No

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Assignee Information:

Providing this information in the application data sheet does not substitute for compliance with any requirement of part 3 of Title 37 of the CFR to have an assignment recorded in the Office.

Assignee 1 Remove

If the Assignee is an Organization check here. ☒

Organization Name	BAYER SCHERING PHARMA AKTIENGESELLSCHAFT		
Mailing Address Information:			
Address 1	Müllerstrasse 178		
Address 2			
City	Berlin	**State/Province**	
Country i	DE	**Postal Code**	13353
Phone Number		Fax Number	
Email Address			

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Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/THOMAS C. BLANKINSHIP/			Date (YYYY-MM-DD)	2011-07-01
First Name	Thomas	Last Name	Blankinship	Registration Number	39909

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

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DOCUMENT MADE AVAILABLE UNDER THE PATENT COOPERATION TREATY (PCT)

International application number:		**PCT/EP2012/062366**
International filing date:		**26 June 2012 (26.06.2012)**
Document type:		**Certified copy of priority document**
Document details:	Country/Office:	**EP**
	Number:	**12161547.0**
	Filing date:	**27 March 2012 (27.03.2012)**
Date of receipt at the International Bureau:		**23 July 2012 (23.07.2012)**

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a),(b) or (b-*bis*)

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1211 Geneva 20, Switzerland
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Europäisches Patentamt
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Bescheinigung	Certificate	Attestation
Die angehefteten Unterlagen stimmen mit der als ursprünglich eingereicht geltenden Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.	The attached documents are exact copies of the text in which the European patent application described on the following page is deemed to have been filed.	Les documents joints à la présente attestation sont conformes au texte, considéré comme initialement déposé, de la demande de brevet européen qui est spécifiée à la page suivante.

Patentanmeldung Nr.	**Patent application No.**	**Demande de brevet n°**
12161547.0 / EP12161547		

The organization code and number of your priority application, to be used for filing abroad under the Paris Convention, is EP12161547.

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le President de l'Office européen des brevets
p.o.

U. Ingmann

Anmeldung Nr:
Application no.: 12161547.0
Demande no :

Anmeldetag:
Date of filing: 27.03.12
Date de dépôt :

Anmelder / Applicant(s) / Demandeur(s):

Bayer Pharma Aktiengesellschaft
Müllerstrasse 178
13353 Berlin/DE

Bezeichnung der Erfindung / Title of the invention / Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se référer à la description.)

Hydroxymethylaryl-substituted pyrrolotriazines and uses thereof

In Anspruch genommene Priorität(en) / Priority(Priorities) claimed / Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen / State/Date/File no. / Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation / International Patent Classification / Classification internationale de brevets:

C07D487/00

Am Anmeldetag benannte Vertragstaaten / Contracting States designated at date of filing / Etats contractants désignées lors du dépôt:

AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR

Hydroxymethylaryl-substituted pyrrolotriazines and uses thereof

This invention relates to novel 5-[(hydroxymethyl)aryl]-substituted pyrrolo[2,1-f][1,2,4]triazin-4-amines, to processes for the preparation of such compounds, to pharmaceutical compositions containing such compounds, and to the use of such compounds or compositions for treating angiogenesis-related disorders, in particular angiogenesis-related ocular disorders.

The term angiogenesis, also called neovascularisation, signifies the process of forming new blood vessels. It is involved in normal development as well as in numerous pathological states including, for example, cancer, rheumatoid arthritis, wound healing following injury to a tissue, atherosclerosis, psoriasis, and diseases of the eye.

Various ocular disorders which are responsible for the majority of visual morbidities and blindness in the developed countries are characterized by, caused by and/or result in choroidal, retinal or iris neovascularisation or retinal edema [Campochiaro (2004), *Exp. Opin. Biol. Ther.* 4: 1395-1402].

For example, retinopathy associated with diabetes is a leading cause of blindness in type 1 diabetes, and is also common in type 2 diabetes. Another ocular disorder involving neovascularisation is age-related macular degeneration (AMD). AMD is the most common cause of vision loss in the western world in those 50 or older, and its prevalence increases with age. AMD is classified as either wet (neovascular) or dry (non-neovascular). The wet form of the disease is responsible for the most severe loss of vision.

Several other less common, but nonetheless debilitating retinopathies include choroidal neovascular membrane (CNVM), cystoid macular edema (CME, also referred to as macular edema or macular swelling), epi-retinal membrane (ERM, macular pucker), and macular hole. In CNVM, abnormal blood vessels stemming from the choroid grow up through the retinal layers. The fragile new vessels break easily, causing blood and fluid to pool within the layers of the retina. In CME, which can occur as a result of disease, injury or surgery, fluid collects within the layers of the macula, causing blurred, distorted central vision. ERM (macular pucker) is a cellophane-like membrane that forms over the macula, affecting the central vision by causing blur and distortion.

Also related are disorders like hypertrophic and atrophic changes of the retinal pigment epithelium (RPE), retinal detachment, choroidal vein occlusion, retinal vein occlusion, corneal angiogenesis following, for example, keratitis, cornea transplantation or keratoplasty, corneal angiogenesis due to hypoxia (*e.g.*, as a result of extensive contact lens wearing), pterygium conjunctivae, subretinal edema, and intraretinal edema.

Vascular endothelial growth factor (VEGF) has been found to be an important modulator of angiogenesis and has been implicated in the pathology of a number of conditions including AMD and diabetic retinopathy. Furthermore, for AMD it was shown that intravitreal injection of an anti-VEGF inhibitor like pegaptanib, ranibizumab or aflibercept reduces choroidal angiogenesis and vascular leakage [Gragoudas (2004), *N. Engl. J. Med.* 351: 2805-2816; Rosenfeld (2006), *N. Engl. J. Med.* 355: 1419-1431; Dixon (2009), *Expert Opin. Investig. Drugs* 18: 1573-1580].

The current standard of care for AMD is lucentis (ranibizumab), an anti-VEGF therapy. However, only 1/3 of all AMD patients treated with lucentis show improvement in vision [Rosenfeld (2006), *N. Engl. J. Med.* 355: 1419-1431]. Therefore new anti-angiogenic therapeutic options with a VEGF-independent mode of action have the potential to improve the current standard of care in ocular diseases like diabetic retinopathy and AMD.

ALK1 (activin receptor-like kinase-1) is a Ser/Thr kinase receptor of the TGFβ receptor family preferentially expressed in endothelial cells and involved in angiogenesis. Members of this family mediate their biological activity by ligand binding to a heterotetrameric receptor complex of type I and type II serine/threonine kinase receptors TβRI and TβRII and accessory type III receptors. TGFβ as well as the high-affinity ligands BMP9 and BMP10 can activate ALK1 in receptor complexes with BMPRII or ActRII and type III receptor endoglin [Scharpfenecker (2007), *J. Cell Sci.* 120: 964-972]. Binding of BMP9 to ALK1 in microvascular endothelial cells activates the Smad1/5/8 pathway [David (2007), *Blood* 109 (5): 1953-1961]. It was postulated that BMP9 inhibits endothelial cell migration and growth. Most studies, however, find that ALK1 receptor activation promotes endothelial cell migration, proliferation, and tube formation [Goumans (2002), *EMBO Journal* 21 (7): 1743-1753; Wu (2006), *Microvasc. Res.* 71: 12-19].

BMP9 and BMP10 activate ALK1 receptor complexes. In endothelial cells, TGFβ can also activate ALK1 while in most cell types TGFβ signals through ALK5. ALK5 activation leads to phosphorylation of Smad2/3 while ALK1 activation results in phosphorylation of Smad1/5. Each Smad signalling pathway finally results in regulation of specific sets of target genes: Smad2/3 signalling induces expression of PAI-1 and repression of Id-1, while Smad1/5 signalling induces Smad6, Smad7 and Id-1 expression and reduces PAI-1 expression [Deng (2006), *J. Cell Biol.* 134: 1563-1571; Ota (2002), *J. Cell Physiol.* 193: 299-318].

Type III receptor endoglin plays a role in fine-tuning of ALK1 and ALK5 pathways especially in endothelial cells, regulating ligand receptor interactions [ten Dijke (2008), *Angiogenesis* 11: 79-89]. Endoglin facilitates TGFβ/ALK1-interaction but reduces TGFβ/ALK5-interaction [David (2007), *Blood* 109: 1953-1961].

Mutations in endoglin and in ALK1 are linked to the autosomal dominant disorder called hereditary hemorrhagic telangiectasia (HHT1 and HHT2, respectively) with characteristics of angiogenic disturbances like arterial venous malformations and telangiectases [Fernandez-Lopez (2006), *Clin. Med. & Res.* 4: 66-78]. RIP1-Tag2 mice with only one functional copy of the ALK1 gene ($ALK1^{+/-}$) show retarded tumor progression and lower microvessel density compared to $ALK1^{wt}$ mice. Similar observations were made with the soluble ALK1-Fc receptor construct RAP-041, that inhibited tumor angiogenesis *in vivo* and limited tumor growth [Cunha (2010), *J. Exp. Med.* 207: 85-100].

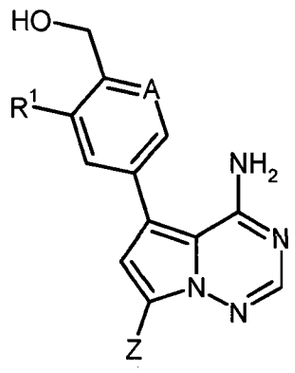
The discovery of potent and selective ALK1 inhibitors is therefore highly desirable to further elucidate the role of ALK1 in blood vessel physiology and pathology, and to derive potential therapeutic options for diseases associated with angiogenesis and vascular remodelling.

In WO 2007/147647-A1, certain 3-aryl-substituted pyrazolo[1,5-a]pyrimidine derivatives were described to be the first small molecule ALK1 kinase inhibitors published until then. These compounds were said to be useful for the treatment of diseases of dysregulated vascular growth, in particular of solid tumors and metastases thereof and also of angiogenesis-dependent diseases of the eye such as age-related macular degeneration.

Various pyrrolo[2,1-f][1,2,4]triazin-4-amine derivatives with distinctive inhibition profiles against a range of protein kinases have been disclosed in, *inter alia*, WO 00/71129-A1, WO 2005/121147-A1, WO 2007/056170-A2, WO 2007/061882-A2, WO 2007/064883-A2, WO 2007/064931-A2, WO 2007/079164-A2, WO 2008/089105-A2, WO 2009/136966-A1, and WO 2010/126960-A1. Generally, these compounds were stated to be useful for the treatment of proliferative and/or angiogenesis-related disorders such as cancer. None of these publications, however, refer to ALK1 as a potential target kinase.

Surprisingly, it has now been found that pyrrolo[2,1-f][1,2,4]triazin-4-amine derivatives having a hydroxymethylaryl substituent in 5-position exhibit potent and selective inhibition of ALK1 kinase which renders these compounds particularly useful for the treatment of angiogenesis-related ocular disorders.

Thus, in one aspect, the present invention relates to 5-[(hydroxymethyl)aryl]-substituted pyrrolo-[2,1-f][1,2,4]triazin-4-amines of the general formula (I)



(I),

wherein

A is N or C-R^2, wherein

R^2 represents hydrogen, fluoro or chloro,

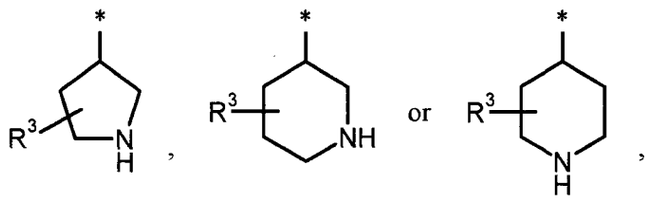
R^1 represents hydrogen, fluoro, chloro, methyl, ethyl or methoxy,

and

Z represents (C_1-C_4)-alkyl or (C_3-C_6)-cycloalkyl each of which may be substituted with hydroxy,

or

Z represents a heterocyclic group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

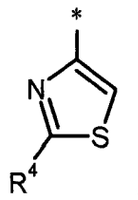
and

R^3 represents hydrogen or hydroxy,

with the proviso that when R^3 is hydroxy, this hydroxy is not attached to a ring carbon atom located adjacent to the ring nitrogen atom,

or

Z represents a thiazole group of the formula



,

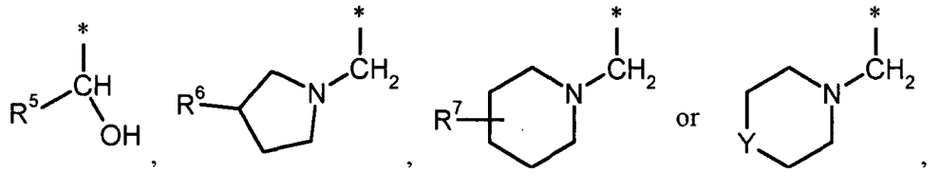
wherein * indicates the point of attachment to the pyrrolotriazine moiety,

and

R^4 represents hydrogen, methyl, ethyl, amino or aminomethyl,

or

Z represents a group of the formula



,

wherein * indicates the point of attachment to the pyrrolotriazine moiety,

R^5 represents (C_3-C_6)-cycloalkyl, oxetanyl, tetrahydrofuranyl or tetrahydropyranyl,

R^6 represents hydrogen or hydroxy,

R^7 represents hydrogen or hydroxy,

with the proviso that when R^7 is hydroxy, this hydroxy is not attached to a ring carbon atom located adjacent to the ring nitrogen atom,

and

Y is O, NH or NCH_3.

The compounds according to this invention can also be present in the form of their salts, solvates and/or solvates of the salts.

Compounds according to the invention are the compounds of the formula (I) and their salts, solvates and solvates of the salts, the compounds included in the formula (I) of the formulae mentioned in the following and their salts, solvates and solvates of the salts, and the compounds included in the formula (I) and mentioned in the following as embodiment examples and their salts, solvates and solvates of the salts, where the compounds included in the formula (I) and mentioned in the following are not already salts, solvates and solvates of the salts.

Salts for the purposes of the present invention are preferably pharmaceutically acceptable salts of the compounds according to the invention (for example, see S. M. Berge *et al.*, "Pharmaceutical Salts", *J. Pharm. Sci.* **1977**, 66, 1-19). Salts which are not themselves suitable for pharmaceutical uses but can be used, for example, for isolation or purification of the compounds according to the invention are also included.

Pharmaceutically acceptable salts include acid addition salts of mineral acids, carboxylic acids and sulfonic acids, for example salts of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, naphthalenedisulfonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.

Solvates in the context of the invention are designated as those forms of the compounds according to the invention which form a complex in the solid or liquid state by stoichiometric coordination with solvent molecules. Hydrates are a specific form of solvates, in which the coordination takes place with water. Hydrates are preferred solvates in the context of the present invention.

The compounds of this invention may, either by nature of asymmetric centers or by restricted rotation, be present in the form of isomers (enantiomers, diastereomers). Any isomer may be present in which the asymmetric center is in the (*R*)-, (*S*)-, or (*R,S*)-configuration.

It will also be appreciated that when two or more asymmetric centers are present in the compounds of the invention, several diastereomers and enantiomers of the exemplified structures will often be possible, and that pure diastereomers and pure enantiomers represent preferred embodiments. It is intended that pure stereoisomers, pure diastereomers, pure enantiomers, and mixtures thereof, are within the scope of the invention.

Geometric isomers by nature of substituents about a double bond or a ring may be present in *cis* (= *Z*-) or *trans* (= *E*-) form, and both isomeric forms are encompassed within the scope of this invention.

All isomers, whether separated, pure, partially pure, or in racemic mixture, of the compounds of this invention are encompassed within the scope of this invention. The purification of said isomers and the separation of said isomeric mixtures may be accomplished by standard techniques known in the art. For example, diastereomeric mixtures can be separated into the individual isomers by chromatographic processes or crystallization, and racemates can be separated into the respective enantiomers either by chromatographic processes on chiral phases or by resolution.

In addition, all possible tautomeric forms of the compounds described above are included according to the present invention.

Unless otherwise stated, the following definitions apply for the substituents and residues used throughout this specification and claims:

$(C_1\text{-}C_4)$-alkyl represents a straight-chain or branched saturated hydrocarbon radical having 1 to 4 carbon atoms. Examples include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl.

$(C_3\text{-}C_6)$-cycloalkyl represents a monocyclic saturated hydrocarbon radical having 3 to 6 ring carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

Throughout this document, for the sake of simplicity, the use of singular language is given preference over plural language, but is generally meant to include the plural language if not otherwise stated. *E.g.*, the expression "A method of treating a disease in a patient, comprising administering to a patient an effective amount of a compound of formula (I)" is meant to include the simultaneous treatment of more than one disease as well as the administration of more than one compound of formula (I).

In a preferred embodiment, the present invention relates to compounds of general formula (I), wherein

A is C-R^2, wherein

R^2 represents hydrogen or fluoro,

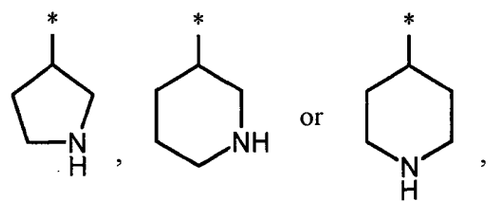
R^1 represents hydrogen, fluoro, chloro, methyl, ethyl or methoxy,

and

Z represents *n*-propyl, *n*-butyl or cyclohexyl each of which may be substituted with hydroxy,

or

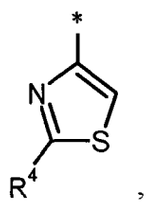
Z represents a heterocyclic group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

or

Z represents a thiazole group of the formula



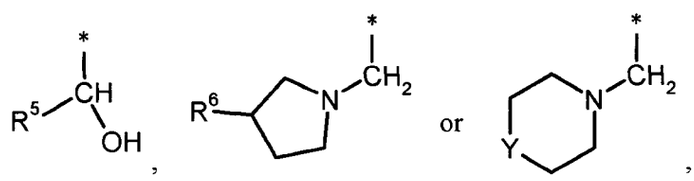
wherein * indicates the point of attachment to the pyrrolotriazine moiety,

and

R^4 represents methyl, ethyl, amino or aminomethyl,

or

Z represents a group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

R^5 represents cyclopropyl or tetrahydropyran-4-yl,

R^6 represents hydroxy,

and

Y is O.

In a particularly preferred embodiment, the present invention relates to compounds of general formula (I), wherein

A is C-R^2, wherein

R^2 represents hydrogen or fluoro,

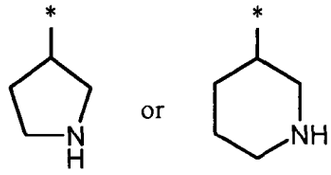
R^1 represents hydrogen, fluoro, methyl, ethyl or methoxy,

and

Z represents 4-hydroxybutyl or 4-hydroxycyclohexyl,

or

Z represents a heterocyclic group of the formula

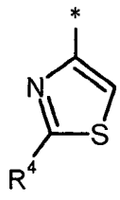


,

wherein * indicates the point of attachment to the pyrrolotriazine moiety,

or

Z represents a thiazole group of the formula



,

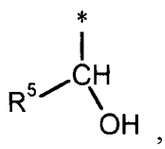
wherein * indicates the point of attachment to the pyrrolotriazine moiety,

and

R^4 represents methyl, ethyl, amino or aminomethyl,

or

Z represents a group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

and

R^5 represents cyclopropyl.

In a distinct embodiment, the present invention relates to compounds of general formula (I), wherein

A is C-R^2, wherein

R^2 represents hydrogen or fluoro.

In a further distinct embodiment, the present invention relates to compounds of general formula (I), wherein

A is C-R^2, wherein

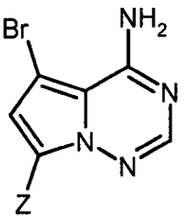
R^2 represents fluoro,

and

R^1 represents fluoro.

The definitions of residues indicated specifically in the respective combinations or preferred combinations of residues are also replaced as desired by definitions of residues of other combinations, irrespective of the particular combinations indicated for the residues. Combinations of two or more of the abovementioned preferred ranges are particularly preferred.

In another embodiment, the present invention relates to a process for preparing the compounds of general formula (I), characterized in that a bromopyrrolotriazine of formula (II)

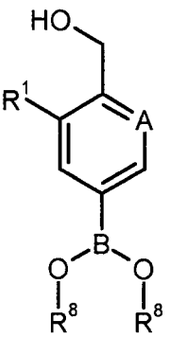


(II),

wherein Z has the meaning described above,

is either

[A] coupled with an arylboronic acid or ester of formula (III)



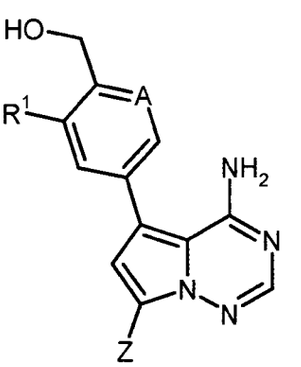
(III),

wherein A and R^1 have the meanings described above,

and

R^8 represents hydrogen or $(C_1$-$C_4)$-alkyl, or both R^8 residues are linked together to form a $-(CH_2)_2-$, $-C(CH_3)_2-C(CH_3)_2-$, $-(CH_2)_3-$ or $-CH_2-C(CH_3)_2-CH_2-$ bridge,

in the presence of a suitable palladium catalyst and a base to yield the target compound of formula (I)

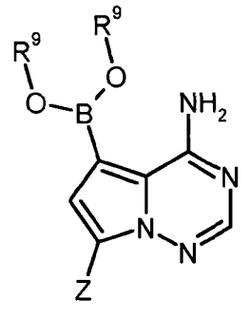


(I),

wherein A, Z and R^1 have the meanings described above,

or

[B] first converted into the corresponding boronic acid or ester derivative of formula (IV)



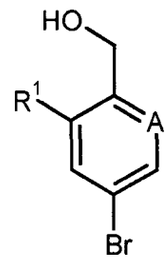
(IV),

wherein Z has the meaning described above,

and

R^9 represents hydrogen or $(C_1$-$C_4)$-alkyl, or both R^9 residues are linked together to form a $-(CH_2)_2-$, $-C(CH_3)_2-C(CH_3)_2-$, $-(CH_2)_3-$ or $-CH_2-C(CH_3)_2-CH_2-$ bridge,

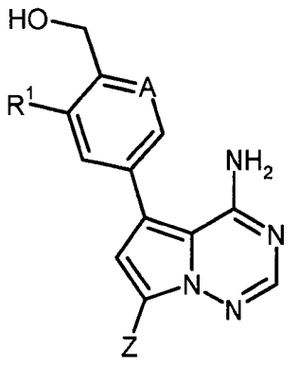
which is then coupled with an aryl bromide of formula (V)



(V),

wherein A and R^1 have the meanings described above,

in the presence of a suitable palladium catalyst and a base to also give the target compound of formula (I)



(I),

wherein A, Z and R^1 have the meanings described above,

optionally followed, where appropriate, by (*i*) separating the compounds of formula (I) into their respective enantiomers and/or diastereomers, preferably using chromatographic methods, and/or (*ii*) converting the compounds of formula (I) into their respective hydrates, solvates, salts and/or hydrates or solvates of the salts by treatment with the corresponding solvents and/or acids.

As outlined above, compounds of formula (I) can be synthesized by a coupling reaction ("Suzuki coupling") between the bromopyrrolotriazine (II) and an aryl boronate or boronic acid (III). This coupling is generally carried out at elevated temperature using a palladium catalyst, a base and an inert solvent. An overview of catalysts and reaction conditions can be found in the literature [see, for instance, S. Kotha *et al.*, *Tetrahedron* **2002**, *58*, 9633-9695; T. E. Barder *et al.*, *J. Am. Chem. Soc.* **2005**, *127*, 4685-4696]. The preferred catalyst in this reaction is tetrakis(triphenylphosphine)-palladium(0). The preferred base is sodium carbonate employed as an aqueous solution. The reaction is carried out in organic solvents that are inert under the reaction conditions, such as 1,4-dioxane, acetonitrile, *N,N*-dimethylformamide (DMF) or dimethylsulfoxide (DMSO), or in water or in mixtures of these solvents. Preferably, the reaction is carried out in a mixture of 1,4-dioxane and water or acetonitrile and water. The reaction is generally performed at temperatures between +100°C and +250°C, preferably at +120°C to +150°C. Heating is preferably effected by a single-mode microwave device. The reactions are usually run under an inert gas atmosphere, preferably under argon.

An inverse reactivity of the reaction partners for the Suzuki coupling may sometimes be favorable. For this purpose, the bromopyrrolotriazine (II) is first converted into the corresponding boronate (IV) and then cross-coupled with an aryl bromide (V) according to one of the methods described above. The conversion of (II) to (IV) is achieved by a metal-mediated borylation reaction. The preferred method is the palladium-catalyzed "Miyaura borylation" [see, for instance, J. Takagi *et al.*, *J. Am. Chem. Soc.* **2002**, *124*, 8001-8006; T. Ishiyama *et al.*, *J. Org. Chem.* **1995**, *60*, 7508-7510;

A. L. S. Thompson *et al.*, *Synthesis* **2005**, 547-550]. Procedures, reagents and solvents for the cross-coupling reaction (IV) + (V) → (I) are chosen from those mentioned in the previous section.

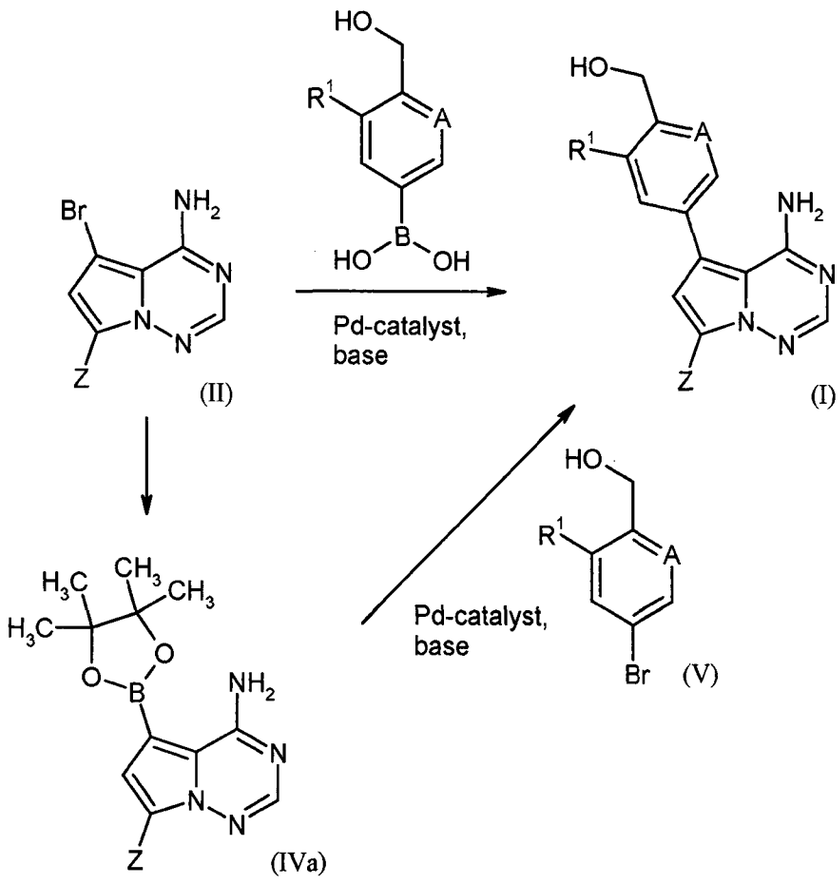
Arylboronic acids (III) [R^8 = H] and aryl boronates (III) [R^8 = alkyl, or both R^8 are linked together to form a cyclic boronic ester, *e.g.*, a pinacolato ester] are either commercially available, or they can be conveniently prepared from the corresponding aryl halides or aryl triflates using a metal-mediated borylation reaction (for references, see previous section). Borylation and subsequent Suzuki coupling may be carried out in two separate steps including isolation and purification of intermediate (III). Alternatively, borylation and cross-coupling may be carried out as a one-pot procedure using (III) directly without isolation and purification.

In cases where a primary or secondary amine moiety forms part of the Z group in the target compounds of formula (I), it may often be beneficial in the borylation and coupling reactions described above to use a protected derivative of this amine as the starting pyrrolotriazine (II) instead of the free amine compound. For this purpose, conventional temporary amino-protecting groups, such as acyl groups (*e.g.*, acetyl or trifluoroacetyl) or carbamate-type protecting groups (*e.g.*, a Boc-, Cbz- or Fmoc-group), may be employed. Preferably, a trifluoroacetyl or a Boc group is used. Similarly, the hydroxy function in the coupling components (III) and (V), respectively, may temporarily be blocked during the process, preferably as a silyl ether derivative such as a trimethylsilyl or *tert*-butyldimethylsilyl ether.

These protecting groups may then be cleaved off concomitantly during the aqueous work-up of the coupling reaction mixtures, or they are removed in a subsequent, separate reaction step using standard methods known in the art. The preparation of the protected intermediates described above from the corresponding free amines or alcohols of formula (II), (III) and (V), respectively, or from other precursor compounds (see section below) is also readily accomplished following general procedures described in the literature [see, for example, T. W. Greene and P. Wuts, *Protective Groups in Organic Synthesis*, Wiley, New York, 1999].

The preparation of the compounds of the invention may be illustrated by means of the following synthesis scheme:

Scheme 1



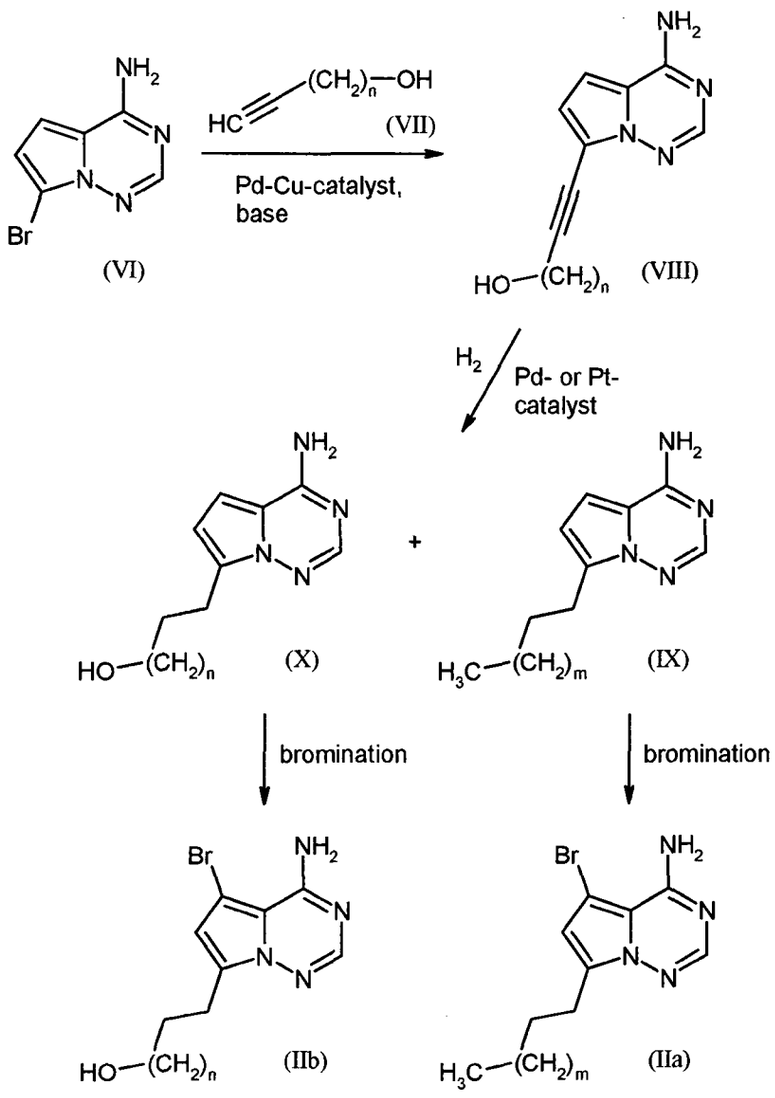
The synthetic methodologies that may be used to prepare the bromopyrrolotriazines of formula (II) can be structured according to the chemotype of the Z group present in (II). Examples illustrating these various routes are given below (see synthesis schemes 2-6). More detailed procedures are provided in the Experimental Section describing specific intermediate and example compounds of the invention.

For example, compounds of formula (II) containing an alkyl or hydroxyalkyl residue as the Z group can be obtained by employing a coupling reaction between the bromopyrrolotriazine (VI) and a terminal alkyne of formula (VII) as the key step (scheme 2). This type of reaction ("Sonogashira reaction") is usually performed in the presence of a palladium-copper catalyst system and a base. Several examples of this reaction have been described in the literature [see, for instance, R. Chinchilla and C. Nájera, *Chem. Rev.* **2007**, *107*, 874-922]. In the present invention, the preferred copper source is copper(I) iodide, tetrakis(triphenylphosphine)palladium(0) is used as palladium catalyst, and pyrrolidine serves both as base and solvent. The coupling reaction is advantageously carried out under concurrent microwave irradiation.

The resulting alkyne (VIII) is then subjected to catalytic hydrogenation employing a customary palladium or platinum catalyst. Preferably, platinum(IV) oxide is used as the catalyst, and the reaction is run in acetic acid as the solvent. In some cases, a mixture of products (IX) and (X) is obtained by this procedure which, in any event, can be separated easily by chromatographic methods. A subsequent bromination reaction, preferably using 1,3-dibromo-5,5-dimethylhydantoin as the bromine source, in an inert solvent such as THF or DMF yields the target pyrrolotriazines (IIa) and (IIb), respectively.

The preparation of the starting compound 7-bromopyrrolo[2,1-f][1,2,4]triazin-4-amine (VI) has been described previously [see WO 2007/056170-A2 (Intermediate B)].

Scheme 2



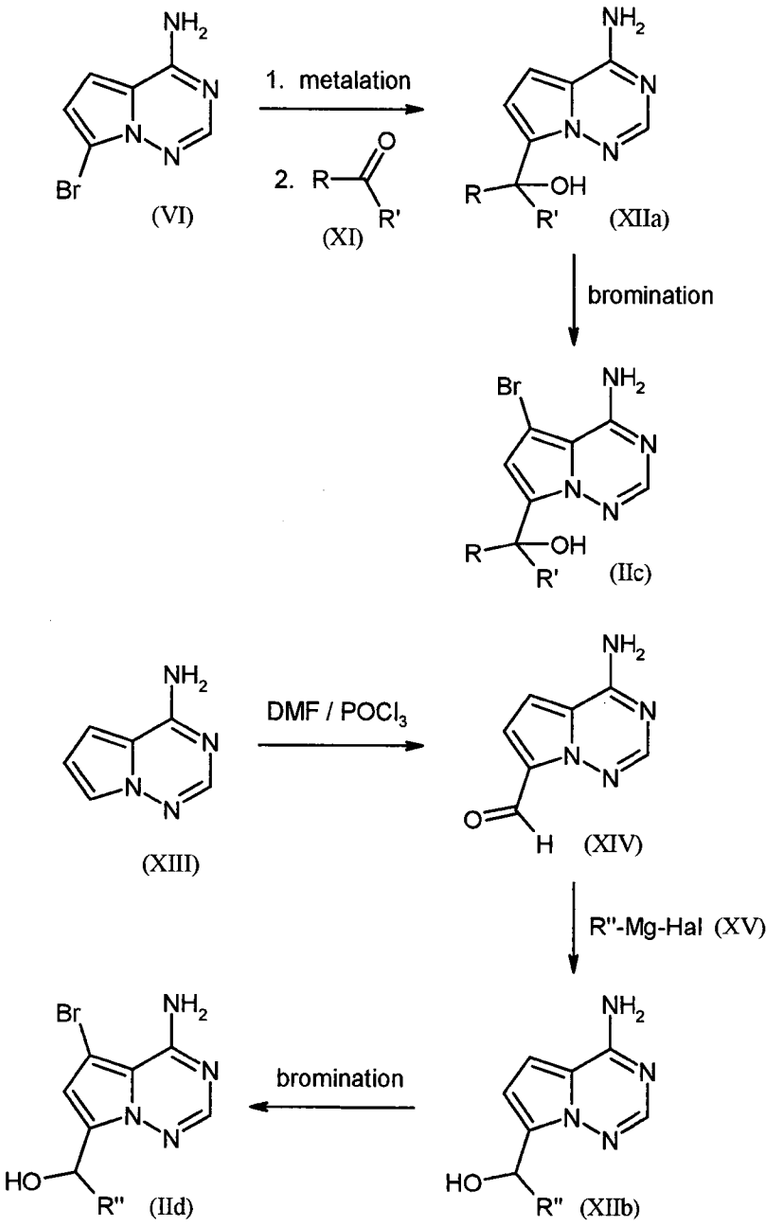
[m = 0 or 1, n = 1 or 2].

Bromopyrrolotriazine precursors of type (IIc) (scheme 3) can be prepared by metalation of compound (VI) with a metal such as magnesium or lithium or by halogen-metal exchange using an organo-magnesium or organo-lithium reagent. The preferred metal is magnesium which is introduced into (VI) by treatment with isopropylmagnesium bromide in a solvent such as THF or diethyl ether. The intermediate organo-metal species is then reacted with a cycloalkanone or heterocycloalkanone (XI) [R, R' are linked together to form a cycloalkyl or heterocycloalkyl ring] to give the tertiary alcohol (XIIa).

A complementary route leading to secondary alcohols of formula (XIIb) utilizes a Vilsmeier formylation reaction whereby aminopyrrolotriazine (XIII) is transformed into the aldehyde (XIV) (scheme 3). Side chain introduction is accomplished by subsequent addition of an appropriate Grignard reagent (XV) [R'' = alkyl or cycloalkyl] in a solvent such as THF or diethyl ether. Finally, bromination of compounds (XIIa) and (XIIb), preferably using 1,3-dibromo-5,5-dimethylhydantoin, in an inert solvent such as THF or DMF provides the target pyrrolotriazines (IIc) and (IId), respectively.

The preparation of the starting compound pyrrolo[2,1-f][1,2,4]triazin-4-amine (XIII) has been described previously [see WO 2007/056170-A2 (Intermediate A)].

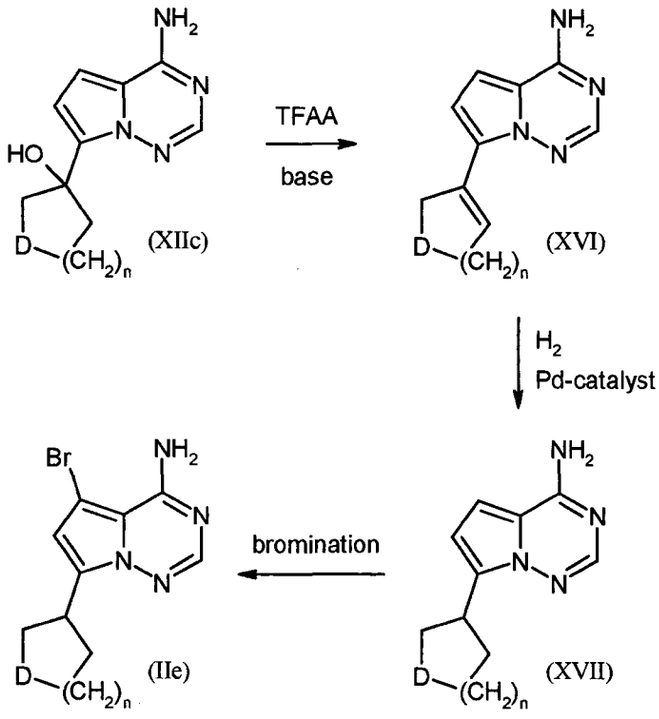
Scheme 3



Pyrrolotriazines of formula (II) wherein Z is representing an unsubstituted cycloalkyl or carbon-bonded aza-heterocyclyl group can be prepared by dehydration of a tertiary alcohol of formula (XIIc) to the unsaturated carbo- or heterocycle of formula (XVI), employing customary agents such as trifluoroacetic acid anhydride, trifluoromethanesulfonic acid anhydride, phosphorus(V) oxide, sulfuric acid or other strong acids (scheme 4). Subsequent catalytic hydrogenation using a conventional catalyst such as palladium on charcoal yields the saturated analog of formula (XVII). The hydrogenation step is preferably carried out in a solvent like methanol, ethanol or THF which contains a small amount of aqueous trifluoroacetic acid. Finally, bromination with 1,3-dibromo-5,5-dimethylhydantoin, as described above, provides the target pyrrolotriazine (IIe).

The alcohol precursors (XIIc) themselves are readily accessible by the synthetic route depicted in scheme 3 [*cf.* preparation of compound (XIIa)].

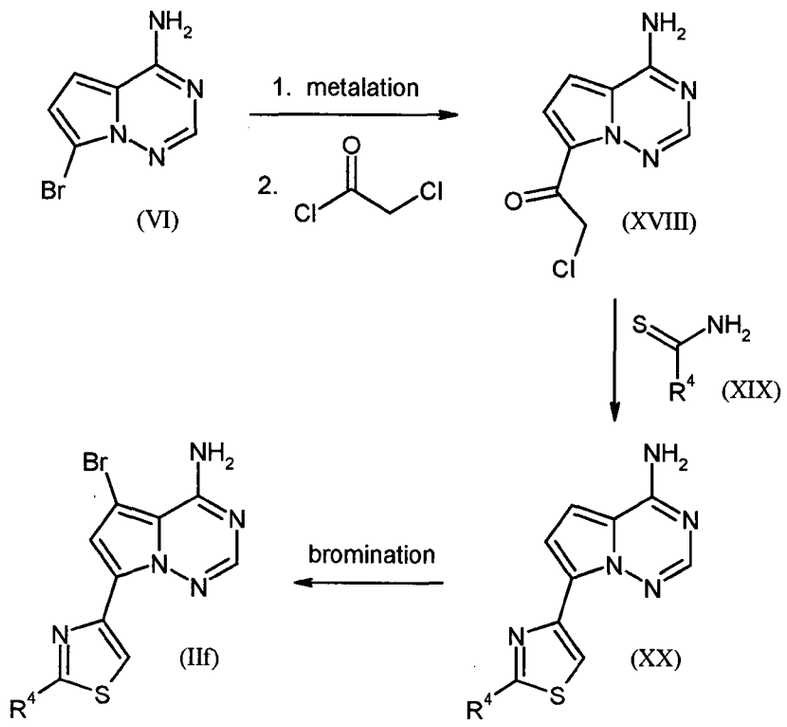
Scheme 4



[D = *e.g.* CH_2 or N-Boc; n = 1 or 2].

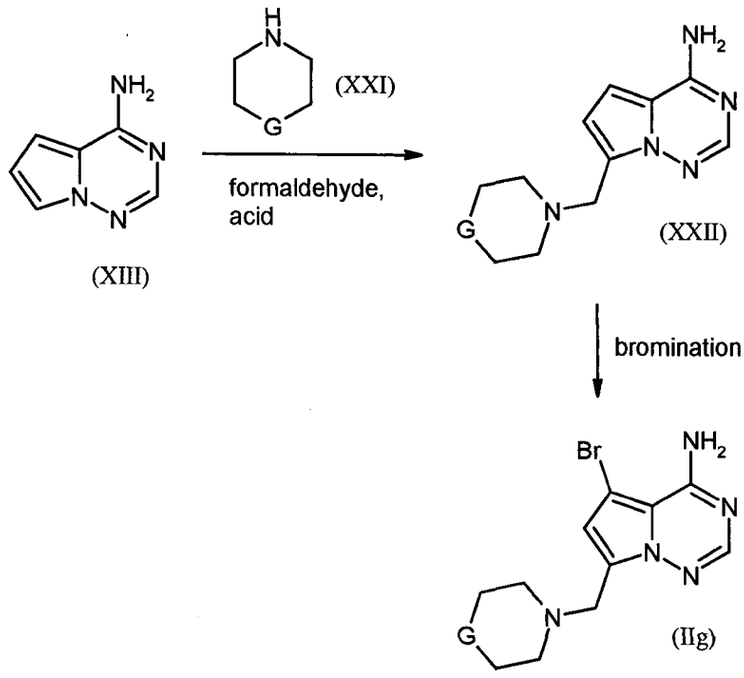
Pyrrolotriazines of formula (II) wherein Z is representing a 1,3-thiazol-4-yl group can be prepared by metalation of compound (VI), as described above, followed by reaction with chloroacetyl chloride to give the intermediate (XVIII), and then condensation with a thioamide or thiourea (XIX) [with R^4 as defined above] to yield the precursor compound (XX) (scheme 5). Bromination with 1,3-dibromo-5,5-dimethylhydantoin, as described above, finally provides the target pyrrolotriazine (IIf).

Scheme 5



Pyrrolotriazines of formula (II) wherein Z is representing an *N*-cyclic aminomethyl group can be obtained by reacting pyrrolotriazine (XIII) with formaldehyde and a cyclic amine of type (XXI) in an acidic solvent, such as acetic acid, or in a mixture of an acid with an organic solvent (scheme 6). Bromination of the resulting product (XXII) with 1,3-dibromo-5,5-dimethylhydantoin, as described above, then provides the target pyrrolotriazine (IIg).

Scheme 6



[G = *e.g.* CH_2, CH(OH), O or N-Boc].

The compounds of the formulae (V), (VII), (XI), (XV), (XIX) and (XXI) are either commercially available, known from the literature, or can be prepared from readily available starting materials by adaptation of standard methods described in the literature.

The compounds of the present invention have valuable pharmacological properties and can be used for the prevention and treatment of diseases in humans and animals.

The compounds of the present invention are potent and selective inhibitors of ALK1 kinase. They can therefore be used for the treatment and/or prevention of angiogenesis-related disorders, in particular angiogenesis-related ocular disorders.

For the present invention, the term "treatment" or "treating" includes inhibiting, delaying, relieving, mitigating, arresting, reducing or causing the regression of a disease, disorder, condition or state, the development and/or progression thereof, and/or the symptoms thereof. The term "prevention" or "preventing" includes reducing the risk of having, contracting or experiencing a disease, disorder, condition or state, the development and/or progression thereof, and/or the symptoms thereof. The term prevention includes prophylaxis. Treatment or prevention of a disease, disorder, condition or state may be partial or complete.

Angiogenesis-related ocular disorders that may be treated and/or prevented with the compounds of the present invention include, but are not limited to, age-related macular degeneration (AMD), diabetic retinopathy, in particular diabetic macula edema (DME), other retinopathies such as choroidal neovascularisation (CNV), choroidal neovascular membrane (CNVM), cystoid macular edema (CME), epi-retinal membrane (ERM) and macular hole, hypertrophic changes of the retinal pigment epithelium (RPE), atrophic changes of the retinal pigment epithelium, retinal detachment, choroidal vein occlusion, retinal vein occlusion, corneal angiogenesis following, for example, keratitis, cornea transplantation or keratoplasty, corneal angiogenesis due to hypoxia (*e.g.*, induced by extensive contact lens wearing), pterygium conjunctivae, subretinal edema, and intraretinal edema.

In the context of the present invention, the term age-related macular degeneration (AMD) encompasses both wet (or exudative, neovascular) and dry (or non-exudative, non-neovascular) manifestations of AMD.

The compounds of the present invention can additionally be used for the treatment and/or prevention of inflammatory diseases associated with angiogenesis, such as rheumatoid arthritis, psoriasis, contact dermatitis, asthma, pulmonary hypertension, multiple sclerosis, and inflammatory diseases of the bowel such as Crohn's disease. Fibrotic diseases, such as fibrosis and cirrhosis, may also be treated and/or prevented with the compounds of the present invention.

By virtue of their activity profile, the compounds of the present invention are particularly suitable for the treatment and/or prevention of ocular disorders, such as age-related macular degeneration (AMD), choroidal neovascularisation (CNV), diabetic retinopathy, and diabetic macula edema (DME).

The disorders mentioned above have been well characterized in humans, but also exist with a similar etiology in other animals, including mammals, and can be treated in these with the compounds of the present invention.

Thus, the present invention further relates to the use of the compounds according to the invention for the treatment and/or prevention of disorders, especially of the aforementioned disorders.

The present invention further relates to the use of the compounds according to the invention for preparing a pharmaceutical composition for the treatment and/or prevention of disorders, especially of the aforementioned disorders.

The present invention further relates to the use of the compounds according to the invention in a method for the treatment and/or prevention of disorders, especially of the aforementioned disorders.

The present invention further relates to a method for the treatment and/or prevention of disorders, especially of the aforementioned disorders, by using an effective amount of at least one of the compounds according to the invention.

Compounds of the present invention may be administered as the sole pharmaceutical agent or in combination with one or more additional therapeutic agents where the combination causes no unacceptable adverse effects. This combination therapy includes administration of a single pharmaceutical dosage formulation which contains a compound of formula (I), as defined above, and one or more additional therapeutic agents, as well as administration of a compound of formula (I) and each additional therapeutic agent in its own separate pharmaceutical dosage formulation. For example, a compound of formula (I) and a therapeutic agent may be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent may be administered in separate dosage formulations.

Where separate dosage formulations are used, the compound of formula (I) and one or more additional therapeutic agents may be administered at essentially the same time (*i.e.*, concurrently) or at separately staggered times (*i.e.*, sequentially).

In particular, the compounds of the present invention may be used in fixed or separate combination with inhibitors of VEGF-mediated angiogenesis, such as, for example, ACTB-1003, aflibercept, apatinib, axitinib, bevacizumab, bevasiranib, BMS-690514, brivanib, cediranib, CT-322, dovitinib, E7080, foretinib, KH-902, linifanib, MGCD-265, motesanib, OTS-102, pazopanib, pegaptanib, ranibizumab, regorafenib, ruboxystaurin, sorafenib, SU-14813, sunitinib, telatinib, TG-100801, tivozanib, TSU-68, vandetanib, vargatef, vatalanib and XL-184, or with inhibitors of other signaling pathways, such as, for example, ACU-4429, disulfiram, E-10030, fenretinide, mecamylamine, PF-04523655, sirolimus, sonepcizumab, tandospirone and volociximab.

Thus, in a further embodiment, the present invention relates to pharmaceutical compositions comprising at least one of the compounds according to the invention and one or more additional therapeutic agents for the treatment and/or prevention of disorders, especially of the aforementioned disorders.

The compounds of the present invention may also be utilized, as such or in compositions, in research and diagnostics, or as analytical reference standards and the like.

In another aspect, the present invention relates to pharmaceutical compositions comprising at least one of the compounds according to the invention together with one or more inert, non-toxic, pharmaceutically suitable excipients, and to the use thereof for the aforementioned purposes.

The compounds according to the invention can act systemically and/or locally. For this purpose, they can be administered in a suitable way such as, for example, by the oral, parenteral, pulmonary, nasal, lingual, sublingual, buccal, rectal, dermal, transdermal, conjunctival, subconjunctival, intravitreal, otic or topical routes.

The compounds according to the invention can be administered in application forms suitable for these administration routes.

Suitable for oral administration are application forms which function according to the prior art and deliver the compounds according to the invention rapidly and/or in modified fashion, and which contain the compounds according to the invention in crystalline, amorphous and/or dissolved form, such as, for example, tablets (uncoated or coated tablets, for example having enteric coatings or coatings which are insoluble or dissolve with a delay and control the release of the compound according to the invention), tablets which disintegrate rapidly in the mouth, or films/wafers, films/lyophilisates, capsules (*e.g.*, hard or soft gelatin capsules), sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, aerosols or solutions.

Parenteral administration can take place with avoidance of an absorption step (*e.g.*, intravenous, intraarterial, intracardiac, intraspinal or intralumbar) or with inclusion of an absorption (*e.g.*, intramuscular, subcutaneous, intracutaneous, percutaneous or intraperitoneal). Application forms suitable for parenteral administration are, *inter al.*, preparations for injection and infusion in the form of solutions, suspensions, emulsions, lyophilisates or sterile powders.

Forms suitable for other administration routes include, for example, pharmaceutical forms for inhalation (*e.g.*, powder inhalers, nebulizers), nasal drops, solutions or sprays, tablets or capsules for lingual, sublingual or buccal administration (*e.g.*, troches, lozenges), suppositories, ear and eye preparations (*e.g.*, drops, ointments), vaginal capsules, aqueous suspensions (lotions, shaking mixtures), lipophilic suspensions, ointments, creams, milk, pastes, foams, dusting powders, and transdermal therapeutic systems (*e.g.*, patches).

The compounds according to the invention can be converted into the recited application forms in a manner known *per se* by mixing with inert, non-toxic, pharmaceutically suitable excipients. These excipients include, *inter al.*, carriers (*e.g.*, microcrystalline cellulose, lactose, mannitol), solvents (*e.g.*, liquid polyethylene glycols), emulsifiers (*e.g.*, sodium dodecyl sulfate), surfactants (*e.g.*, polyoxysorbitan oleate), dispersants (*e.g.*, polyvinylpyrrolidone), synthetic and natural polymers (*e.g.*, albumin), stabilizers (*e.g.*, antioxidants such as, for example, ascorbic acid), colorants (*e.g.*, inorganic pigments such as, for example, iron oxides), and taste and/or odour masking agents.

It has generally proved advantageous to administer on parenteral administration amounts of about 0.001 to 1 mg/kg, preferably about 0.01 to 0.5 mg/kg, of body weight to achieve effective results. On oral administration, an exemplary dose range is about 0.01 to 100 mg/kg, preferably about 0.01 to 20 mg/kg, and more preferably about 0.1 to 10 mg/kg of body weight.

Nevertheless, actual dosage levels and time course of administration of the active ingredients in the pharmaceutical compositions of the invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition and mode of administration, without being toxic to the patient. It may therefore be necessary where appropriate to deviate from the stated amounts, in particular as a function of age, gender, body weight, diet and general health status of the patient, route of administration, individual response to the active ingredient, nature of the preparation, and time or interval over which administration takes place. Thus, it may be satisfactory in some cases to manage with less than the aforementioned minimum amount, whereas in other cases the stated upper limit must be exceeded. It may in the event of administration of larger amounts be advisable to divide these into multiple individual doses spread over the day.

For the treatment and/or prevention of ocular disorders, as described above, the preferred route for administering the compounds of the invention is topically at the eye or by an ocular drug delivery system. Intraocular injections are another way to administer the compounds of the present invention that is suitable for such purposes.

Delivery to areas within the eye can be accomplished by injection, employing a cannula or another invasive device designed to introduce precisely metered amounts of a desired formulation to a particular compartment or tissue within the eye (*e.g.*, posterior chamber or retina). An intraocular injection may be into the vitreous (intravitreal), under the conjunctiva (subconjunctival), behind the eye (retrobulbar), into the sclera, or under the Capsule of Tenon (sub-Tenon), and may be in a depot form. Other intraocular routes of administration and injection sites and forms are also contemplated and are within the scope of the invention.

The compounds according to the invention may be formulated in a manner known to those skilled in the art so as to give adequate delivery to the back of the eye, which may be by regular dosing, such as with eye drops, or by using a delivery system to give a controlled release, such as slow release, of the compounds according to the invention.

Preferred ocular formulations for the compounds of the present invention include aqueous solutions, suspensions or gels of these compounds in the form of drops of liquid, liquid washes, sprays,

ointments or gels, in admixture with excipients suitable for the manufacture and use of such application forms. Alternatively, the compounds of the present invention may be applied to the eye via liposomes or other ocular delivery systems that are known in the art.

Appropriate dosage levels may be determined by any suitable method known to one skilled in the art of treating eye diseases. Preferably, the active substance is administered at a frequency of 1 to 4 times per day for topical administration, or less often if a drug delivery system is used. Typically, an ocular formulation intended for topical application contains the active ingredient in a concentration range of about 0.001% to 10%.

The following exemplary embodiments illustrate the invention. The invention is not restricted to the examples.

The percentages in the following tests and examples are, unless stated otherwise, by weight; parts are by weight. Solvent ratios, dilution ratios and concentrations reported for liquid/liquid solutions are each based on volume.

A. Examples

Abbreviations and Acronyms:

Ac	acetyl
aq.	aqueous (solution)
Boc	*tert*-butoxycarbonyl
br.	broad (^{1}H NMR signal)
Cbz	benzyloxycarbonyl
Celite®	registered trademark of Celite Corp. brand of diatomaceous earth
conc.	concentrated
DCI	direct chemical ionization (MS)
DCM	dichloromethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
e.e.	enantiomeric excess
EI	electron impact ionization (MS)
ent	enantiomer, enantiomerically pure
eq.	equivalent(s)
ESI	electro-spray ionization (MS)
Et	ethyl
EtOAc	ethyl acetate
Fmoc	(9*H*-fluoren-9-ylmethoxy)carbonyl
GC/MS	gas chromatography-coupled mass spectroscopy
h	hour(s)
Hal	halogen
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
HPLC	high performance liquid chromatography
LC/MS	liquid chromatography-coupled mass spectroscopy
Me	methyl
MeOH	methanol
min	minute(s)
MS	mass spectroscopy
of th.	of theory (chemical yield)
$PdCl_2$(dppf)	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
Ph	phenyl

rac	racemic, racemate
R_f	TLC retention factor
rt	room temperature
R_t	retention time (HPLC)
satd.	saturated
TBAF	tetrabutylammonium fluoride
tBu	*tert*-butyl
tert	tertiary
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography

Preparative HPLC purification methods:

Method 1:

Device: Gilson Abimed HPLC, binary pump system; column: ReproSil C18, 250 mm x 30 mm; eluent A: water / 1% ammonia, eluent B: acetonitrile; gradient: 0-3 min 10% B, 5.01-31 min 95% B, 31 min 95% B; flow rate: 50 mL/min; UV detection: 210 nm.

Method 2:

Device: Gilson Abimed HPLC, binary pump system; column: Kromasil-100A C18, 5 µm, 250 mm x 30 mm; eluent A: water / 0.05-0.5% TFA, eluent B: acetonitrile; gradient: 0-5 min 5% B, 5.01-10 min 10% B, 10.01-20 min 40% B, 20.01-27 min 50% B, 27.01-40 min 60% B, 40.01-45 min 90% B, 45.01-60 min 100% B; flow rate: 15-60 mL/min; UV detection: 210 nm.

Method 3:

Device: Gilson Abimed HPLC, binary pump system; column: Grom-Sil-120 ODS-4HE, 250 mm x 30 mm; eluent A: water, eluent B: acetonitrile; gradient: 0-3 min 10% B, 3.01-35 min 98% B, 35.01-40 min 98% B; flow rate: 50 mL/min; UV detection: 210 nm.

Method 4:

Device: Gilson Abimed HPLC, binary pump system; column: Grom-Sil-120 ODS-4HE, 250 mm x 30 mm; eluent A: water / 0.5% ammonia, eluent B: acetonitrile; gradient: 0-3 min 10% B, 3.01-35 min 98% B, 35.01-40 min 98% B; flow rate: 50 mL/min; UV detection: 210 nm.

Method 5:

Device: Gilson Abimed HPLC, binary pump system; column: Chromatorex C18 10 µm, 250 mm x 30 mm; eluent A: water, eluent B: acetonitrile; gradient: 0-3 min 10% B, 5.01-31 min 90% B, 31 min 90% B; flow rate: 50 mL/min; UV detection: 210 nm.

Method 6:

Device: Gilson Abimed HPLC, binary pump system; column: Chromatorex C18 10 µm, 250 mm x 30 mm; eluent A: water / 0.5% TFA, eluent B: acetonitrile; gradient: 0-3 min 10% B, 5.01-31 min 90% B, 31 min 90% B; flow rate: 50 mL/min; UV detection: 210 nm.

Method 7:

Device: Gilson Abimed HPLC, binary pump system; column: ReproSil C18 10 µm, 250 mm x 40 mm; eluent A: water, eluent B: acetonitrile; gradient: 0-3 min 10% B, 5.01-31 min 95% B, 31 min 95% B; flow rate: 50 mL/min; UV detection: 210 nm.

Method 8:

Device: Gilson Abimed HPLC, binary pump system; column: ReproSil C18 10 µm, 250 mm x 30 mm; eluent A: water, eluent B: acetonitrile; gradient: 0-3 min 10% B, 5.01-31 min 95% B, 31 min 95% B; flow rate: 50 mL/min; UV detection: 210 nm.

Method 9:

Device: Gilson Abimed HPLC, binary pump system; column: Waters Sunfire C18 5 µm, 250 mm x 20 mm; eluent A: water, eluent B: acetonitrile; gradient: 0 min 20% B, 15 min 60% B, 15.01-19 min 20% B; flow rate: 25 mL/min; UV detection: 210 nm.

Analytical HPLC, LC/MS and GC/MS methods:

Method 1 (HPLC):

Instrument: Agilent 1100 with DAD detection; column: Agilent Zorbax Eclipse XDB-C8 4.6, 150 mm x 5 mm; eluent A: 0.01% TFA in water, eluent B: 0.01% TFA in acetonitrile; gradient: 0-1 min 10% B, 4-5 min 90% B, 5.5 min 10% B; flow rate: 2.0 mL/min; temperature: 30°C; UV detection: 210 nm.

Method 2 (HPLC):

Instrument: HP 1100 with DAD detection; column: Kromasil 100 RP-18, 60 mm x 2.1 mm, 3.5 µm; eluent A: 5 mL perchloric acid (70%) / L water, eluent B: acetonitrile; gradient: 0 min 2% B, 0.5

min 2% B, 4.5 min 90% B, 6.5 min 90% B, 6.7 min 2% B, 7.5 min 2% B; flow rate: 0.75 mL/min; temperature: 30°C; UV detection: 210 nm.

Method 3 (HPLC):

Instrument: HP 1100 with DAD detection; column: Kromasil 100 RP-18, 60 mm x 2.1 mm, 3.5 µm; eluent A: 5 mL perchloric acid (70%) / L water, eluent B: acetonitrile; gradient: 0 min 2% B, 0.5 min 2% B, 4.5 min 90% B, 9 min 90% B, 9.2 min 2% B, 10 min 2% B; flow rate: 0.75 mL/min; temperature: 30°C; UV detection: 210 nm.

Method 4 (LC/MS):

Instrument: Micromass Platform LCZ with HPLC Agilent 1100 Series; column: Thermo Hypersil GOLD 3µ, 20 mm x 4 mm; eluent A: 1 L water + 0.5 mL 50% formic acid, eluent B: 1 L acetonitrile + 0.5 mL 50% formic acid; gradient: 0.0 min 100% A → 0.2 min 100% A → 2.9 min 30% A → 3.1 min 10% A → 5.5 min 10% A; temperature: 50°C; flow rate: 0.8 mL/min; UV detection: 210 nm.

Method 5 (LC/MS):

Instrument: Micromass ZQ with HPLC Waters Alliance 2795 / HP 1100; column: Phenomenex Synergi 2.5µ MAX-RP 100A Mercury, 20 mm x 4 mm; eluent A: 1 L water + 0.5 mL 50% formic acid, eluent B: 1 L acetonitrile + 0.5 mL 50% formic acid; gradient: 0.0 min 90% A → 2.5 min 30% A → 3.0 min 5% A → 4.0 min 5% A; flow rate: 2 mL/min; temperature: 50°C; UV detection: 210 nm.

Method 6 (LC/MS):

Instrument: Micromass Quattro Premier with Waters UPLC Acquity; column: Thermo Hypersil GOLD 1.9µ, 50 mm x 1 mm; eluent A: 1 L water + 0.5 mL 50% formic acid, eluent B: 1 L acetonitrile + 0.5 ml 50% formic acid; gradient: 0.0 min 90% A → 0.1 min 90% A → 1.5 min 10% A → 2.2 min 10% A; temperature: 50°C; flow rate: 0.33 mL/min; UV detection: 210 nm.

Method 7 (LC/MS):

Instrument: Micromass ZQ with HPLC Waters Alliance 2795; column: Phenomenex Synergi 2.5µ MAX-RP 100A Mercury, 20 mm x 4 mm; eluent A: 1 L water + 0.5 mL 50% formic acid, eluent B: 1 L acetonitrile + 0.5 mL 50% formic acid; gradient: 0.0 min 90% A → 0.1 min 90% A → 3.0 min 5% A → 4.0 min 5% A → 4.01 min 90% A; flow rate: 2 mL/min; temperature: 50°C; UV detection: 210 nm.

Method 8 (GC/MS):

Instrument: Micromass GCT, GC6890; column: Restek RTX-35, 15 m x 200 µm x 0.33 µm; constant flow with helium: 0.88 mL/min; oven: 70°C; inlet: 250°C; gradient: 70°C, 30°C/min → 310°C (keep for 3 min).

Method 9 (HPLC):

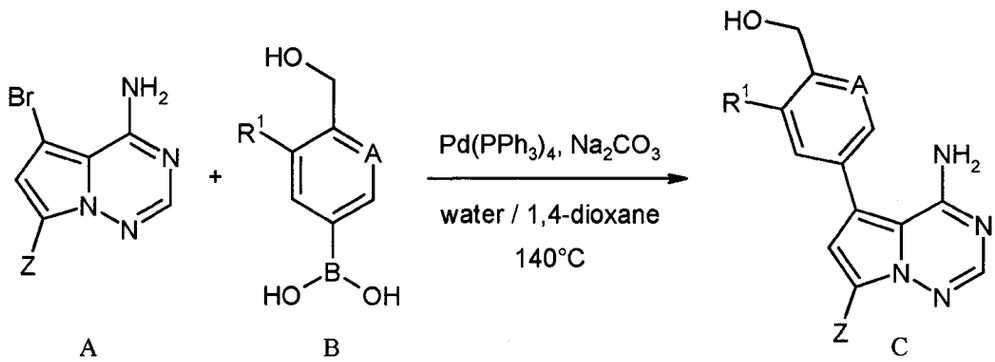
Instrument: Agilent 1100 with DAD detection; column: Merck Chromolith Speed ROD, 150 mm x 5 mm; eluent A: 0.01% formic acid in water, eluent B: acetonitrile; gradient: 0 min 5% B, 2.5 min 95% B, 3 min 95% B; flow rate: 5.0 mL/min; temperature: 40°C; UV detection: 210 nm.

Method 10 (LC/MS):

Instrument: Waters Acquity SQD UPLC System; column: Waters Acquity UPLC HSS T3 1.8µ, 50 mm x 1 mm; eluent A: 1 L water + 0.25 mL 99% formic acid, eluent B: 1 L acetonitrile + 0.25 mL 99% formic acid; gradient: 0.0 min 90% A → 1.2 min 5% A → 2.0 min 5% A; temperature: 50°C; flow rate: 0.40 mL/min; UV detection: 208-400 nm.

General synthetic method 1:

Suzuki coupling of 5-bromopyrrolo[2,1-f][1,2,4]triazine derivatives with arylboronic acids or esters:

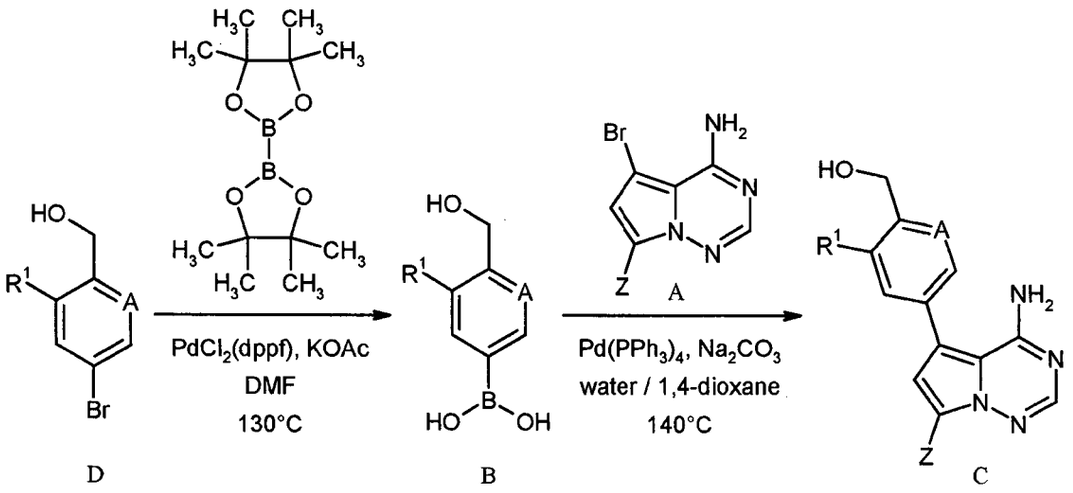


A B C

A 5-bromopyrrolo[2,1-f][1,2,4]triazine A (about 0.5 mmol), arylboronic acid B (1.2 equivalents) or a corresponding boronic ester, *e.g.*, a dimethyl boronate or pinacolato boronate, and tetrakis(triphenylphosphine)palladium(0) (0.1 equivalents) are dissolved in a mixture of 1,4-dioxane (about 4.0 mL) and 2 M aqueous sodium carbonate solution (1.5 mL) in a microwave reactor vial. The reaction vessel is crimp-capped, and the mixture is heated to 140°C for 1 h in a single-mode microwave device. After cooling, the reaction mixture is filtered over a pad of Celite which is rinsed with 1,4-dioxane to elute all organic material. The combined filtrate is evaporated to dryness under reduced pressure, and the residue is purified by preparative HPLC to give the target compound C.

General synthetic method 2:

Borylation of arylbromides and subsequent Suzuki coupling with 5-bromopyrrolo[2,1-f][1,2,4]-triazine derivatives without isolation of the intermediate arylboronic acid or ester:



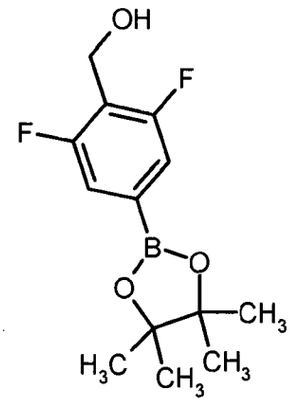
D B C

Arylbromide D (about 0.5 mmol) is dissolved in DMF (3 mL) in a microwave reactor vessel, argon is bubbled through the solution for 5 min, and [1,1'-bis(diphenylphosphino)ferrocene]dichloro-palladium(II)-dichloromethane complex (0.1 equivalents), potassium acetate (3 equivalents) and bis-(pinacolato)diboron (1.2 equivalents) are added. The vessel is crimp-capped, and the mixture is heated to 130°C for 60 min in a single-mode microwave device. Then, the suspension is filtered, the filtrate is transferred to another microwave process vial, and tetrakis(triphenylphosphine)-palladium(0) (0.1 equivalents), 2 M aqueous sodium carbonate solution (4 equivalents) and the 5-bromopyrrolo[2,1-f][1,2,4]triazine A (1 equivalent) are added. The vial is crimp-capped, and the mixture is heated to 140°C for 1 h in a single-mode microwave device. The crude reaction mixture thus obtained is directly injected onto a preparative HPLC column for separation and purification of the target compound C.

Starting Materials and Intermediates:

Intermediate 1A

[2,6-Difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol

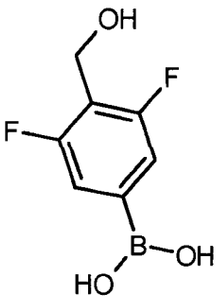


(4-Bromo-2,6-difluorophenyl)methanol (1.03 g, 4.62 mmol) was dissolved in dry 1,4-dioxane (10 mL). Argon was bubbled through the solution, then [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium-dichloromethane complex (302 mg, 0.37 mmol, 0.08 eq.), anhydrous potassium acetate (907 mg, 9.24 mmol, 2 eq.) and bis(pinacolato)diboron (1.23 g, 4.85 mmol, 1.05 eq.) were added, and the mixture was heated to 130°C for 1 h in a single-mode microwave device. Upon cooling, the mixture was filtered, and the solvent was removed under reduced pressure. Cyclohexane (200 mL) was added to the residue, and the mixture was vigorously stirred for 30 min. Undissolved material was then removed by filtration, the cyclohexane was distilled off, and the residue was purified by flash chromatography over silica gel (dichloromethane/acetonitrile gradient). Fractions containing the product were combined and evaporated. The title compound crystallized spontaneously as a brownish solid. Yield: 790 mg (63% of th.).

GC-MS (method 8): R_t = 5.36 min; MS (EI): *m/z* (%) = 270.3 (15) $[M]^+$.

Intermediate 2A

[3,5-Difluoro-4-(hydroxymethyl)phenyl]boronic acid

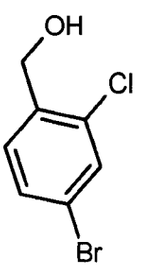


[4-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-3,5-difluorophenyl]boronic acid (19.3 g, 63.9 mmol; crude material, prepared by the method of Hattori, *Bioorg. Med. Chem.* **2006**, *14*, 3258-3262) was dissolved in 400 mL aqueous acetic acid (66%) and stirred at 40°C for 5 h. The solution was then evaporated under reduced pressure, and the residue was purified by flash chromatography over silica gel (gradient elution from 0% to 2% methanol in dichloromethane) to give 3.46 g (25% of th., LC-MS purity 87%) of the title compound.

LC-MS (method 7): R_t = 0.50 min; MS (ESIpos): *m/z* (%) = 171.2 (100) $[M\text{-}OH]^+$, MS (ESIneg): *m/z* (%) = 187.3 (100) $[M\text{-}H]^-$.

Intermediate 3A

(4-Bromo-2-chlorophenyl)methanol

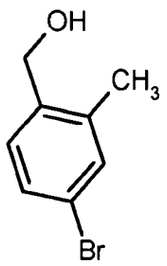


The title compound was prepared according to the procedure described in WO 2004/074270-A2 [Example A(147), step 1].

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.00 (br, 1H), 4.74 (s, 2H), 7.38 (d, 1H), 7.43 (dd, 1H), 7.53 (d, 1H).

Intermediate 4A

(4-Bromo-2-methylphenyl)methanol

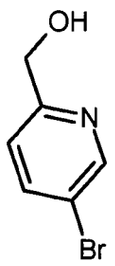


The title compound was prepared according to the procedure described in EP 1 544 208-A1 (Reference Example 14).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.62 (t, 3H), 2.32 (s, 3H), 4.64 (d, 2H), 7.23 (d, 1H), 7.32 (s, 1H), 7.33 (d, 1H).

Intermediate 5A

(5-Bromopyridin-2-yl)methanol

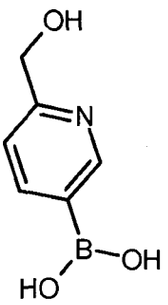


Methyl 5-bromopyridine-2-carboxylate (2.00 g, 9.27 mmol) was dissolved in ethanol (20.0 mL). Sodium borohydride (1.05 g, 27.8 mmol) was added at 0°C, and the mixture was stirred at room temperature for 18 h. The mixture was then concentrated under reduced pressure, quenched with 1 N hydrochloric acid, neutralized with solid potassium carbonate and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and evaporated to give 1.57 g (90% of th.) of the title compound.

LC-MS (method 6): R_t = 0.56 min; MS (ESIpos): *m/z* (%) = 188.0 (100) $[M+H]^+$.

Intermediate 6A

[6-(Hydroxymethyl)pyridin-3-yl]boronic acid

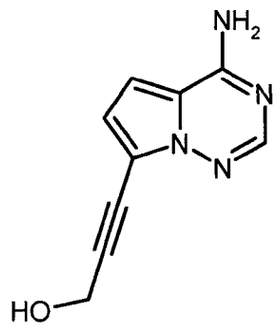


To a solution of Intermediate 5A (1.50 g, 7.98 mmol) and bis(pinacolato)diboron (2.23 g, 8.28 mmol) in degassed DMF (120 mL) was added under an argon atmosphere 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) chloride (292 mg, 0.40 mmol) and potassium acetate (2.35 g, 23.9 mmol). The mixture was heated to 80°C for 18 h and then cooled to room temperature. The suspension was filtered, and the residue was washed with dioxane. The combined filtrates were concentrated under reduced pressure, and the oily residue was taken up in 50 mL ethyl acetate and 50 mL cyclohexane and allowed to stand at room temperature overnight. The resulting precipitate was collected by filtration and discarded. The filtrate was evaporated, and the residue was dissolved again in 100 mL ethyl acetate and extracted twice with 50 mL water. The aqueous layer was concentrated to give 690 mg (56% of th.) of the title compound which was used without further purification.

LC-MS (method 6): R_t = 0.18 min; MS (ESIpos): *m/z* (%) = 154.0 (100) $[M+H]^+$.

Intermediate 7A

3-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)prop-2-yn-1-ol



The starting material 7-bromopyrrolo[2,1-f][1,2,4]triazin-4-amine was synthesized according to the procedure described in WO 2007/056170-A2 (Intermediate B).

7-Bromopyrrolo[2,1-f][1,2,4]triazin-4-amine (1.0 g, 4.69 mmol), copper(I) iodide (89 mg, 0.47 mmol, 0.1 eq.) and tetrakis(triphenylphosphine)palladium(0) (542 mg, 0.47 mmol, 0.1 eq.) were

charged into a microwave reactor vial and evacuated for 1 h. The vessel was then vented with argon, pyrrolidine (15 mL) and 2-propyn-1-ol (2.63 g, 47 mmol, 10 eq.) were added, and the vessel was crimp-capped and heated to 85°C for 120 min in a single-mode microwave device. After cooling, the reaction mixture was poured into 120 mL of concentrated aqueous ammonium chloride solution which was extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and evaporated, and the residue was purified by flash chromatography (Biotage silica column, ethyl acetate). The resulting product (222 mg) appeared pure by LC-MS (method 6) and was used for further transformations.

HPLC (method 2): R_t = 2.59 min;

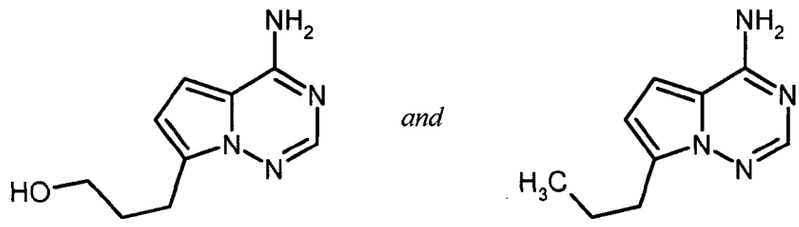
LC-MS (method 6): R_t = 0.28 min; MS (ESIpos): *m/z* (%) = 189.2 (100) $[M+H]^+$.

Intermediate 8A and Intermediate 9A

3-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)propan-1-ol

and

7-Propylpyrrolo[2,1-f][1,2,4]triazin-4-amine



Intermediate 7A (444 mg, 2.36 mmol) was dissolved in acetic acid (18 mL) under an argon atmosphere. Platinum(IV) oxide (40 mg, 0.18 mmol, 0.08 eq.) was added, and the mixture was vigorously stirred for 3 h at room temperature under an atmosphere of hydrogen at ambient pressure. The catalyst was then removed by filtration, the solvent was distilled off, and the residue was subjected to flash chromatography (Biotage silica column, cyclohexane/ethyl acetate gradient). The Intermediates 8A (185 mg, 41% of th.) and 9A (170 mg, 41% of th.) were obtained in two distinct chromatographic fractions:

Intermediate 8A:

HPLC (method 2): R_t = 2.68 min;

LC-MS (method 4): R_t = 0.83 min; MS (ESIpos): *m/z* (%) = 193.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 191.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.80 (m, 2H), 2.86 (t, J = 7.7 Hz, 2H), 3.45 (m, 2H), 4.49 (t, J = 5.1 Hz, 1H), 6.41 (d, J = 4.2 Hz, 1H), 6.69 (d, J = 4.2 Hz, 1H), 7.50 (br. s, 2H), 7.78 (s, 1H).

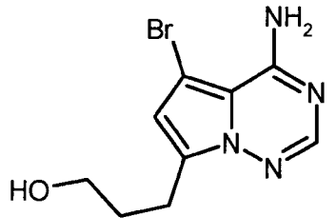
Intermediate 9A:

HPLC (method 1): R_t = 3.22 min;

LC-MS (method 4): R_t = 1.23 min; MS (ESIpos): *m/z* (%) = 177.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 175.2 (30) $[M-H]^-$.

Intermediate 10A

3-(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)propan-1-ol



Intermediate 8A (105 mg, 0.55 mmol) was dissolved in THF (8.75 mL) and cooled to -20°C. 1,3-Dibromo-5,5-dimethylhydantoin (78.1 mg, 0.5 eq.) was added, and the mixture was stirred at -20°C for 1 h. The reaction was then quenched with 0.5 mL concentrated aqueous sodium dithionite solution, warmed to room temperature and partitioned between ethyl acetate and water. The organic phase was dried over anhydrous sodium sulfate, and the solvent was distilled off. Yield: 145 mg (98% of th.).

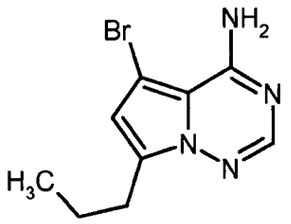
HPLC (method 1): R_t = 2.96 min; HPLC (method 2): R_t = 2.95 min;

LC-MS (method 5): R_t = 1.03 min; MS (ESIpos): *m/z* (%) = 271.0 (100) and 273.0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 269.0 (99) and 271.0 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.75 (m, 2H), 2.83 (t, J = 8.1 Hz, 2H), 3.43 (m, 2H), 4.50 (t, J = 5.4 Hz, 1H), 6.62 (s, 1H), 7.81 (s, 1H).

Intermediate 11A

5-Bromo-7-propylpyrrolo[2,1-f][1,2,4]triazin-4-amine



Intermediate 9A (110 mg, 0.62 mmol) was dissolved in THF (4.44 mL) and cooled to -20°C. 1,3-Dibromo-5,5-dimethylhydantoin (89 mg, 0.5 eq.) was added, and the mixture was stirred at -20°C for 1 h. The reaction was then quenched with 0.5 mL concentrated aqueous sodium dithionite solution, warmed to room temperature and partitioned between ethyl acetate and water. The organic phase was dried over anhydrous sodium sulfate, and the solvent was distilled off. Yield: 154 mg (85% pure, 82% of th.).

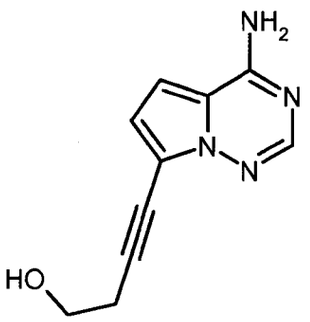
HPLC (method 1): R_t = 3.78 min;

LC-MS (method 7): R_t = 1.55 min; MS (ESIpos): *m/z* (%) = 255.0 (99) and 257.2 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.91 (t, *J* = 7.3 Hz, 3H), 1.65 (m, 2H), 2.79 (t, *J* = 7.6 Hz, 2H), 3.31 (s, 2H), 6.63 (s, 1H), 7.95 (s, 1H).

Intermediate 12A

4-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)but-3-yn-1-ol



7-Bromopyrrolo[2,1-f][1,2,4]triazin-4-amine (1.0 g, 4.69 mmol), copper(I) iodide (89 mg, 0.47 mmol, 0.1 eq.) and tetrakis(triphenylphosphine)palladium(0) (542 mg, 0.47 mmol, 0.1 eq.) were charged into a microwave reactor vial and evacuated for 1 h. The vessel was then vented with argon, pyrrolidine (15 mL) and 3-butyn-1-ol (3.36 g, 47 mmol, 10 eq.) were added, and the vessel was crimp-capped and heated to 85°C for 120 min in a single-mode microwave device. After cooling, the reaction mixture was poured into 120 mL of concentrated aqueous ammonium chloride solution and extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous sodium

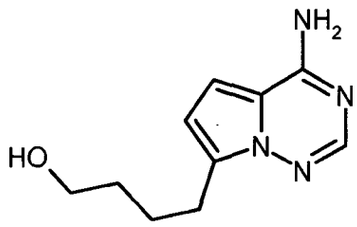
sulfate and evaporated, and the residue was purified by flash chromatography (Biotage silica column, ethyl acetate). The resulting product (735 mg) was sufficiently pure (66% by HPLC) for further transformations.

HPLC (method 2): R_t = 2.77 min;

LC-MS (method 4): R_t = 0.96 min; MS (ESIpos): *m/z* (%) = 203.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 201.1 (100) $[M-H]^-$.

Intermediate 13A

4-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)butan-1-ol



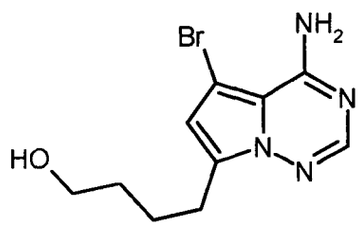
Intermediate 12A (607 mg, 3.00 mmol) was dissolved in acetic acid (64 mL), and platinum(IV) oxide (50 mg, 0.22 mmol, 0.07 eq.) was added. The mixture was stirred under an atmosphere of hydrogen at ambient pressure for 15 h. The catalyst was then removed by filtration, the filtrate was evaporated under reduced pressure, and the residue was purified by flash chromatography (Biotage silica column, ethyl acetate). Yield: 350 mg (57% of th.).

HPLC (method 2): R_t = 2.92 min;

LC-MS (method 4): R_t = 0.94 min; MS (ESIpos): *m/z* (%) = 207.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 205.3 (100) $[M-H]^-$.

Intermediate 14A

4-(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)butan-1-ol



Intermediate 13A (330 mg, 1.60 mmol) was dissolved in THF (26 mL) at -20°C, and 1,3-dibromo-5,5-dimethylhydantoin (229 mg, 0.80 mmol) was added. The mixture was stirred at -20°C for 1 h. The reaction was then quenched with concentrated aqueous sodium sulfite solution (0.5 mL). Ethyl acetate was added, the aqueous layer was separated, and the organic layer was dried over sodium sulfate and evaporated. The crude product was subsequently purified by preparative HPLC (method 2) giving 175 mg (84% of th.) of the title compound.

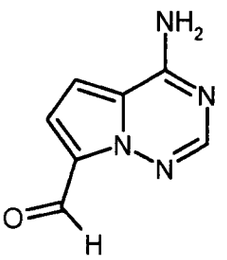
HPLC (method 1): R_t = 3.13 min;

LC-MS (method 5): R_t = 1.23 min; MS (ESIpos): *m/z* (%) = 285.0 (98) and 287.0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 283.0 (100) and 285.0 (98) $[M-H]^-$.

^{1}H-NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.39-1.48 (m, 2H), 1.60-1.69 (m, 2H), 3.31 (t, *J* = 7.3 Hz, 2H), 3.40 (m, 2H), 4.46 (br. s, 1H), 6.61 (s, 1H), 7.82 (s, 1H).

Intermediate 15A

4-Aminopyrrolo[2,1-f][1,2,4]triazine-7-carbaldehyde



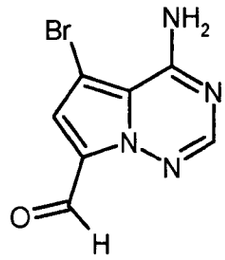
The starting material pyrrolo[2,1-f][1,2,4]triazin-4-amine was synthesized according to the procedure described in WO 2007/056170-A2 (Intermediate A).

Pyrrolo[2,1-f][1,2,4]triazin-4-amine (20.5 g, 152 mmol) was dissolved in 150 mL DMF. Under ice cooling, phosphoryl chloride (31.3 mL, 336 mmol) was added dropwise at such a rate that the internal temperature did not rise above 30°C. The mixture was then heated for 2 days at 50°C. After cooling, another portion of phosphoryl chloride (14.2 mL, 152 mmol) was added, and stirring was continued for another 24 h at 50°C. After cooling, the reaction batch was slowly poured into a mixture of 2.0 L saturated aqueous sodium bicarbonate solution and 2.0 L ethyl acetate. Solid sodium bicarbonate was added until gas evolution stopped. The layers were separated, the aqueous layer was extracted with 0.5 L ethyl acetate, and the combined organic phases were dried over sodium sulfate and concentrated. The residue was suspended in 100 mL diisopropyl ether, stirred at room temperature for 10 min and then filtered. The dried residue was stirred in 6 N hydrochloric

acid (500 mL) for 1 h at 50°C and then poured into an ice/water mixture (1000 mL). The mixture was carefully neutralized with solid sodium bicarbonate, stirred for 30 min at room temperature and then filtered again. The residue was washed with water and ligroin to yield 20.6 g (83% of th.) of white crystals which were used in the next step without further purification.

Intermediate 16A

4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazine-7-carbaldehyde

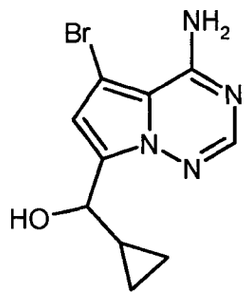


Intermediate 15A (20.6 g, 127 mmol) was dissolved in 525 mL DMF. At 0°C, 1,3-dibromo-5,5-dimethylhydantoin (21.8 g, 76.2 mmol) was added, and the mixture was stirred for 1 h under ice cooling and for further 2 h at room temperature. The resulting suspension was filtered, and the residue was washed with DMF and diethyl ether. The filtrate was discarded, and the remaining hardly soluble crystals were dried to give 20.0 g (65% of th., 80% purity by HPLC) of the title compound. This material was used without further purification.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 7.42 (s, 1H), 8.12 (s, 1H), 10.22 (s, 1H).

Intermediate 17A

(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)(cyclopropyl)methanol



Intermediate 16A (500 mg, 1.66 mmol) was suspended in dry THF (30 mL). At 0°C, a 0.5 M solution of cyclopropyl magnesium bromide in diethyl ether (10 mL, 5.0 mmol) was added. The mixture was stirred at room temperature for 1 h. Then, another portion of the Grignard solution (6.6

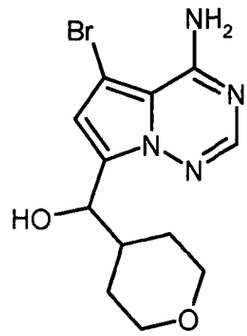
mL, 3.3 mmol) was added. After further stirring for 30 min at room temperature, the reaction was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by preparative HPLC (method 4). Yield: 0.14 g (29% of th.).

LC-MS (method 6): R_t = 0.75 min; MS (ESIpos): *m/z* (%) = 283.0 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.35 (m, 3H), 0.45 (m, 1H), 1.28 (m, 1H), 4.62 (t, 1H), 5.26 (d, 1H), 6.75 (s, 1H), 7.84 (s, 1H).

Intermediate 18A

(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)(tetrahydro-2*H*-pyran-4-yl)methanol

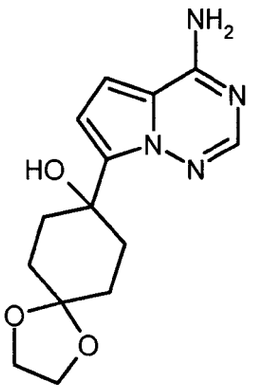


In a 50 mL three-necked flask equipped with a condenser, a thermometer and a dropping funnel, which was purged with argon, a Grignard reagent was prepared from magnesium turnings (484 mg, 19.9 mmol) and 4-chlorotetrahydropyrane (2.4 g, 19.9 mmol) in dry THF (14 mL). To this solution was added at 0°C a suspension of Intermediate 16A (1.2 g, 3.98 mmol) in THF (20 mL), and the reaction mixture was allowed to stir for 1 h at room temperature. It was then quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate (2 x 50 mL). The organic layer was washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by preparative HPLC (method 3). Yield: 0.5 g (38% of th.).

LC-MS (method 6): R_t = 0.66 min; MS (ESIpos): *m/z* (%) = 327.0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 325.1 (100) $[M-H]^-$.

Intermediate 19A

8-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-1,4-dioxaspiro[4.5]decan-8-ol



The starting material 7-bromopyrrolo[2,1-f][1,2,4]triazin-4-amine was synthesized according to the procedure described in WO 2007/056170-A2 (Intermediate B).

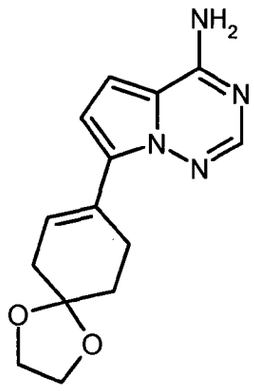
7-Bromopyrrolo[2,1-f][1,2,4]triazin-4-amine (9.20 g, 35.41 mmol) was dissolved in THF (105 mL) under argon at room temperature. Chlorotrimethylsilane (9.08 mL, 7.77 g, 70.82 mmol, 2 eq.) was added, and the mixture was stirred at room temperature for 3 h. It was then cooled to 0°C, and 2-propyl magnesium chloride (74 mL of a 2.0 M solution in THF, 149 mmol, 4.2 eq.) was added. The mixture was stirred for further 3 h while warming up to room temperature. Then, 1,4-dioxaspiro-[4.5]decan-8-one (8.38 g, 53.12 mmol, 1.5 eq.) was added, and stirring was continued for another 16 h. The reaction was quenched with a 1:1 mixture of concentrated aqueous ammonium chloride solution and ice until the pH value reached 6-7. The mixture was extracted with two portions of ethyl acetate, and the combined organic extracts were dried over anhydrous sodium carbonate and concentrated to dryness. The title compound was crystallized from diethyl ether. Yield: 6.05 g (58% of th.).

HPLC (method 1): R_t = 2.89 min;

LC-MS (method 6): R_t = 0.38 min; MS (ESIpos): *m/z* (%) = 291.2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 289.4 (100) $[M-H]^-$.

Intermediate 20A

7-(1,4-Dioxaspiro[4.5]dec-7-en-8-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



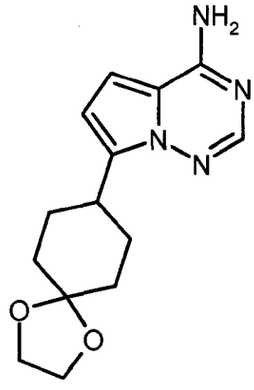
Intermediate 19A (2.81 g, 60% purity, 5.82 mmol) was dissolved in pyridine (18 mL) at 0°C. Trifluoroacetic anhydride (2.46 mL, 3.66 g, 17.45 mmol, 3 eq.) was added slowly, and the reaction mixture was stirred at ambient temperature for 16 h. The solvent was distilled off, and the residue was partitioned between water and ethyl acetate. The organic extract was dried over sodium sulfate and evaporated. The residue was triturated with diethyl ether at 0°C to yield 2.95 g (92% pure by HPLC, 99% of th.) of the title compound.

HPLC (method 1): R_t = 4.55 min;

LC-MS (method 5): R_t = 2.28 min; MS (ESIpos): *m/z* (%) = 369.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 367.1 (100) $[M-H]^-$.

Intermediate 21A

7-(1,4-Dioxaspiro[4.5]dec-8-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



Intermediate 20A (2.95 g, 10.8 mmol) was dissolved in methanol (1.07 L) under argon. Palladium on charcoal (10%, 400 mg) was added, and the mixture was vigorously stirred for 24 h under an atmosphere of hydrogen at ambient pressure and room temperature. The catalyst was removed by

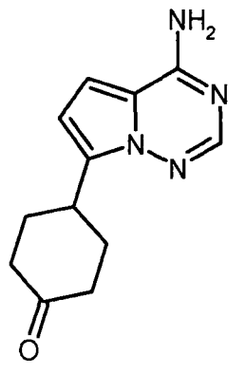
filtration, and the solvent was distilled off under reduced pressure to give 2.11 g (71% of th.) of the title compound.

HPLC (method 1): R_t = 3.14 min;

LC-MS (method 6): R_t = 0.68 min; MS (ESIpos): *m/z* (%) = 275.3 (100) $[M+H]^+$.

Intermediate 22A

4-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)cyclohexanone



Intermediate 21A (2.11 g, 7.69 mmol) was dissolved in a mixture of 1 M hydrochloric acid (23 mL) and methanol (6.80 mL) at 0°C and stirred under ice cooling for 3 h. Then, the pH value was adjusted to 6-7 by addition of concentrated aqueous sodium bicarbonate solution. The mixture was extracted with three portions of dichloromethane, and the combined organic extracts were dried over anhydrous sodium sulfate, filtered and evaporated. The residue (923 mg, 52% of th.) was used without further purification in the next synthetic step.

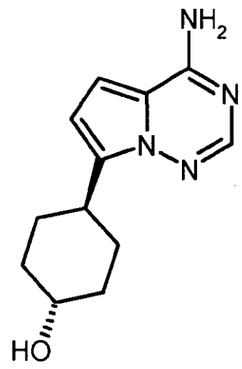
HPLC (method 2): R_t = 3.06 min;

LC-MS (method 4): R_t = 1.02 min; MS (ESIpos): *m/z* (%) = 231.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 229.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.86 (ddd, 2H), 2.25-2.36 (m, 4H), 2.59 (ddd, 2H), 3.59 (m, 1H), 6.45 (d, 1H), 6.82 (d, 1H), 7.60 (br. s, 1H), 7.82 (s, 1H).

Intermediate 23A

trans-4-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)cyclohexanol



Intermediate 22A (452 mg, 1.96 mmol) was dissolved in THF (15 mL), and the solution was cooled to 0°C. Lithium aluminium hydride solution (1 M in THF, 2.94 mL, 2.94 mmol) was added dropwise. Subsequently, the solution was stirred at 0°C for 10 min and then quenched by addition of concentrated aqueous ammonium chloride solution. The mixture was extracted with 3 portions of dichloromethane, and the combined organic extracts were dried over anhydrous sodium sulfate, filtered and evaporated. The residue (360 mg, 77% purity, 61% of th.) was used in the next synthetic step without further purification.

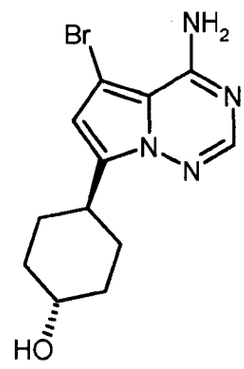
HPLC (method 1): R_t = 2.62 min;

LC-MS (method 6): R_t = 0.29 min; MS (ESIpos): *m/z* (%) = 233.2 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.30 (m, 2H), 1.42 (m, 2H), 1.91 (m, 2H), 1.99 (m, 2H), 2.97 (tt, 1H), 3.45 (m, 1H), 4.60 (d, 1H), 6.39 (d, 1H), 6.79 (d, 1H), 7.53 (br. s, 2H), 7.80 (s, 1H).

Intermediate 24A

trans-4-(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)cyclohexanol



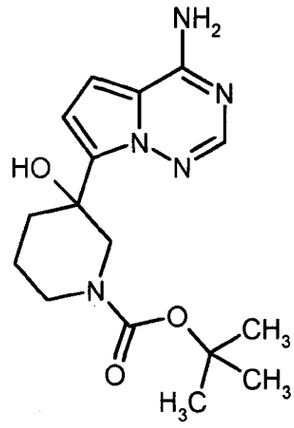
Intermediate 23A (360 mg, 85% purity, 1.19 mmol) was dissolved in THF (8 mL) at -20°C, and 1,3-dibromo-5,5-dimethylhydantoin (188 mg, 0.66 mmol, 0.55 eq.) was added. The mixture was stirred at -20°C for 1 h, then 0.5 mL concentrated aqueous sodium dithionite solution was added, and the mixture was extracted with ethyl acetate. The organic extract was dried over anhydrous sodium sulfate, filtered and evaporated. The crude product (463 mg, 66% purity, 83% of th.) was used in the next synthetic step without further purification.

HPLC (method 1): R_t = 3.22 min;

LC-MS (method 7): R_t = 1.03 min; MS (ESIpos): *m/z* (%) = 311.2 and 313.0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 309.2 (50) and 311.2 (40) $[M-H]^-$.

Intermediate 25A

tert-Butyl 3-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3-hydroxypiperidine-1-carboxylate



The starting material 7-bromopyrrolo[2,1-f][1,2,4]triazin-4-amine was synthesized according to the procedure described in WO 2007/056170-A2 (Intermediate B).

7-Bromopyrrolo[2,1-f][1,2,4]triazin-4-amine (17.29 g, 81 mmol) was dissolved in THF (214 mL) under argon at room temperature. Chlorotrimethylsilane (20.60 mL, 17.63 g, 162 mmol, 2 eq.) was added, and the mixture was stirred at room temperature for 3 h. Then, it was cooled to 0°C, and 2-propyl magnesium chloride (170 mL of a 2.0 M solution in THF, 340 mmol, 4.2 eq.) was added. The mixture was stirred for further 3 h while warming up to room temperature. Then, *tert*-butyl 3-oxopiperidine-1-carboxylate (25.00 g, 121 mmol, 1.5 eq.) was added, and stirring was continued for another 16 h. The reaction was quenched with a 1:1 mixture of concentrated aqueous ammonium chloride solution and ice until the pH value reached 6-7. The mixture was extracted with two portions of ethyl acetate, and the combined organic extracts were dried over anhydrous sodium

carbonate and concentrated to dryness. The title compound crystallized upon trituration of the residue with diethyl ether (50 mL). The crystals were washed with diethyl ether and dried to give 17.20 g (64% of th.).

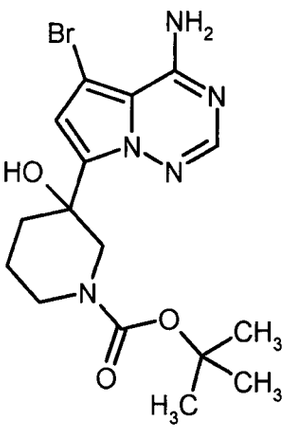
HPLC (method 2): R_t = 3.53 min;

LC-MS (method 5): R_t = 1.36 min; MS (ESIpos): *m/z* (%) = 334.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 332.0 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.19-1.43 (m, 9H), 1.72-1.88 (m, 2H), 2.38-2.46 (m, 1H), 3.02-3.20 (m, 1H), 3.44-3.96 (m, 4H), 6.58 (d, 1H), 6.81 (d, 1H), 7.82 (s, 1H).

Intermediate 26A

rac-tert-Butyl 3-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3-hydroxypiperidine-1-carboxylate



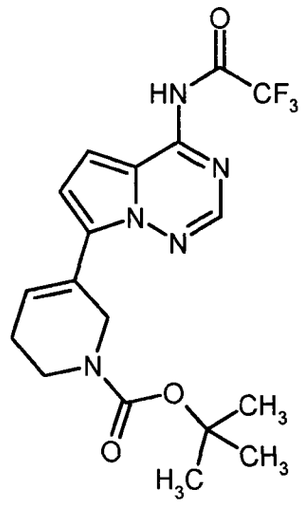
Intermediate 25A (120 mg, 0.36 mmol) was dissolved in THF (6.0 mL) at -20°C, and 1,3-dibromo-5,5-dimethylhydantoin (51 mg, 0.18 mmol, 0.5 eq.) was added. The mixture was stirred at -20°C for 2 h and then quenched with concentrated aqueous sodium sulfite solution (0.5 mL). Ethyl acetate was added, the aqueous layer was separated, and the organic extract was dried over sodium sulfate and evaporated. The title compound (148 mg, 95% of th.) was obtained as a light yellow solid.

HPLC (method 1): R_t = 4.03 min;

LC-MS (method 5): R_t = 1.99 min; MS (ESIpos): *m/z* (%) = 412.0 (90) and 414.0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 410.0 (100) and 412.0 (85) $[M-H]^-$.

Intermediate 27A

tert-Butyl 5-{4-[(trifluoroacetyl)amino]pyrrolo[2,1-f][1,2,4]triazin-7-yl}-3,6-dihydropyridine-1(2*H*)-carboxylate



Intermediate 25A (8.32 g, 24.95 mmol) was dissolved in pyridine (116 mL) at 0°C. Trifluoroacetic anhydride (8.81 mL, 13.10 g, 62.36 mmol, 2.5 eq.) was added slowly, and the reaction mixture was stirred at ambient temperature for 16 h. Then, it was cooled again to 0°C, and 150 mL of diethyl ether were added. The mixture was stirred at 0°C while the title compound slowly precipitated. The product was finally filtered off and washed with diethyl ether. The filtrate was evaporated *in vacuo*, and the residue was triturated with diethyl ether at 0°C giving a second crop of the title compound after washing with diethyl ether. The two crops were combined to yield 7.80 g (92% pure by HPLC, 76% of th.) of the title compound as yellow crystals.

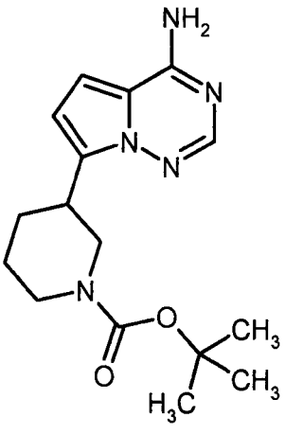
HPLC (method 1): R_t = 3.91 min;

LC-MS (method 7): R_t = 2.45 min; MS (ESIpos): *m/z* (%) = 412.2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 410.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.48 (s, 9H), 1.92 (m, 2H), 3.58 (m, 2H), 6.90 (d, 1H), 7.30 (d, 1H), 8.03-8.10 (m, 1H), 8.42 (s, 1H).

Intermediate 28A

rac-tert-Butyl 3-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidine-1-carboxylate



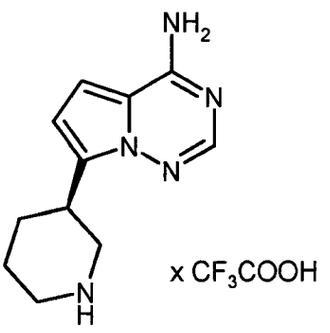
Intermediate 27A (7.80 g, 92% purity, 17.54 mmol) was dissolved in methanol (400 mL). Trifluoroacetic acid (6.76 mL, 10.0 g, 88 mmol, 5 eq.), water (3.16 mL, 175 mmol, 10 eq.) and 10% palladium on charcoal (30 mg) were added, and the mixture was hydrogenated for 24 h at room temperature and ambient pressure. The catalyst was then removed by filtration, and the solvent was evaporated *in vacuo*. The crude product (8.79 g, 75% pure, quantitative yield) was used in the next synthetic step without further purification.

HPLC (method 1): R_t = 3.64 min;

LC-MS (method 7): R_t = 1.26 min; MS (ESIpos): *m/z* (%) = 318.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 316.4 (100) $[M-H]^-$.

Intermediate 29A

7-[(3*R*)-Piperidin-3-yl]pyrrolo[2,1-f][1,2,4]triazin-4-amine trifluoroacetate



The starting material benzyl (*R*)-3-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidine-1-carboxylate has been described in WO 2007/056170-A2 (Intermediate DDD).

1.50 g (3.49 mmol) of this material were hydrogenated for 16 h at room temperature and ambient pressure in the presence of 10% palladium on charcoal (30 mg) in a mixture of methanol (50 mL)

and trifluoroacetic acid (2.70 mL). Subsequently, the catalyst was removed by filtration, and all volatiles were evaporated *in vacuo* to give 1.10 g (95% of th.) of the title compound.

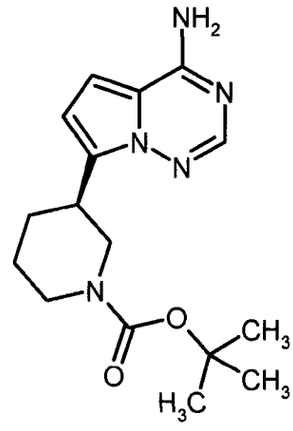
HPLC (method 2): R_t = 2.17 min;

LC-MS (method 6): R_t = 0.17 min; MS (ESIpos): *m/z* (%) = 218 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.75 (m, 2H), 1.92 (m, 1H), 2.05 (m, 1H), 2.93 (m, 1H), 3.06 (m, 1H), 3.31 (d, 1H), 3.50 (d, 1H), 3.57 (m, 1H), 6.78 (d, 1H), 7.20 (m, 1H), 8.10 (s, 1H), 8.63 (m, 1H), 8.82 (m, 1H), 9.02 (br. s, 1H).

Intermediate 30A

tert-Butyl (3*R*)-3-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidine-1-carboxylate



Intermediate 29A (1.10 g, 5.06 mmol) was suspended in dichloromethane (6.60 mL), triethylamine (1.55 mL, 1.13 g, 11.14 mmol, 2.20 eq.) was added, and the mixture was stirred for 30 min until the starting material was completely dissolved. Then, di-*tert*-butyl dicarbonate (1.22 g, 5.57 mmol, 1.1 eq.) was added, and the reaction mixture was stirred for 16 h. Subsequently, 5% aqueous citric acid was added, the phases were separated, and the organic layer was dried over sodium sulfate and evaporated. The residue was purified by preparative HPLC (method 2). Yield: 595 mg (37% of th.).

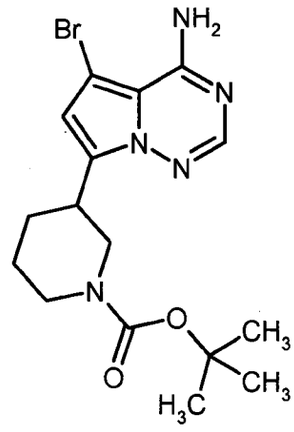
HPLC (method 2): R_t = 4.01 min;

LC-MS (method 5): R_t = 1.54 min; MS (ESIpos): *m/z* (%) = 318.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 316.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.38 (s, 9H), 1.45 (m, 2H), 1.72 (m, 2H), 2.02 (m, 2H), 2.90 (m, 1H), 3.17 (m, 1H), 3.85 (m, 1H), 4.08 (m, 1H), 6.47 (d, 1H), 6.80 (d, 1H), 7.58 (br. s, 1H), 7.81 (s, 1H).

Intermediate 31A

rac-tert-Butyl 3-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidine-1-carboxylate



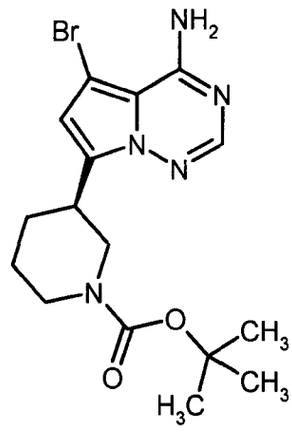
Intermediate 28A (8.28 g, 75% purity, 14.39 mmol) was dissolved in THF (222 mL) at -20°C, and 1,3-dibromo-5,5-dimethylhydantoin (2.06 g, 7.19 mmol, 0.5 eq.) was added. The mixture was stirred at -20°C for 2 h and then quenched with concentrated aqueous sodium sulfite solution (0.5 mL). Ethyl acetate was added, the aqueous layer was separated, and the organic extract was dried over sodium sulfate and evaporated. The title compound (6.30 g, 86% of th.) was obtained as a light yellow solid.

LC-MS (method 5): R_t = 2.27 min; MS (ESIpos): *m/z* (%) = 396.0 (80) and 397.9 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 394.0 (90) and 396.0 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.35 (s, 9H), 1.40-1.44 (m, 2H), 1.71 (m, 1H), 1.98 (m, 1H), 2.95 (m, 1H), 3.20 (m, 1H), 3.75 (m, 1H), 4.00 (m, 1H), 6.67 (s, 1H), 7.86 (s, 1H).

Intermediate 32A

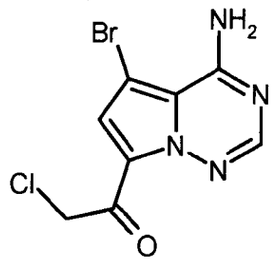
tert-Butyl (3*R*)-3-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidine-1-carboxylate



The title compound was prepared in the same way as the racemic mixture (Intermediate 31A), starting from Intermediate 30A. Analytical data were identical to those shown for Intermediate 31A.

Intermediate 33A

1-(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)-2-chloroethanone



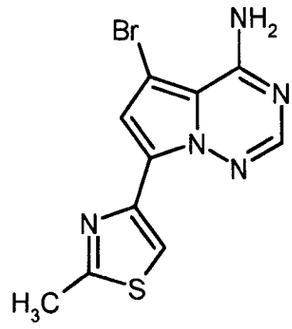
The compound was prepared according to the procedure described in WO 2007/056170-A2 (Intermediate N, step 1).

HPLC (method 1): R_t = 4.27 min;

LC-MS (method 5): R_t = 1.70 min; MS (ESIpos): *m/z* (%) = 289.0 (75) and 290.9 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 287.0 (75) and 288.9 (100) $[M-H]^-$.

Intermediate 34A

5-Bromo-7-(2-methyl-1,3-thiazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



Intermediate 33A (100 mg, 0.35 mmol) and thioacetamide (30 mg, 0.40 mmol, 1.15 eq.) were dissolved in 1,4-dioxane (3.0 mL) in a microwave reaction vial. The vial was crimp-capped, and the mixture was heated to 130°C for 60 min in a single-mode microwave device. After cooling, the solvent was distilled off, and the residue was triturated with acetonitrile and filtered. The filtrate was discarded. The title compound was isolated as crystalline solid. Yield: 99 mg (92% of th.).

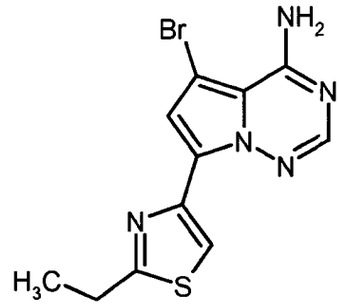
HPLC (method 1): R_t = 4.00 min;

LC-MS (method 6): R_t = 1.05 min; MS (ESIpos): *m/z* (%) = 310.0 (90) and 312 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.71 (s, 3H), 7.20 (s, 1H), 8.02 (s, 1H), 8.28 (s, 1H).

Intermediate 35A

5-Bromo-7-(2-ethyl-1,3-thiazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



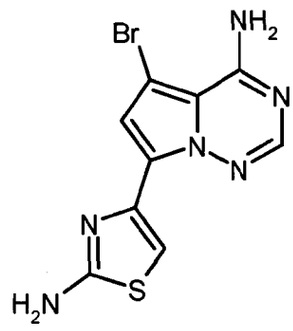
Intermediate 33A (100 mg, 0.35 mmol) and thiopropionamide (32 mg, 0.36 mmol, 1.05 eq.) were refluxed in ethanol (3.0 mL) over a period of 4.5 h. After cooling, the mixture was partitioned between ethyl acetate and aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off. The product was dried under vacuum to give 91 mg (0.28 mmol, 81% of th.) of the title compound as off-white solid.

HPLC (method 1): R_t = 4.30 min;

LC-MS (method 7): R_t = 1.84 min; MS (ESIpos): *m/z* (%) = 324.2 (100) and 325.8 (98) $[M+H]^+$.

Intermediate 36A

7-(2-Amino-1,3-thiazol-4-yl)-5-bromopyrrolo[2,1-f][1,2,4]triazin-4-amine



Intermediate 33A (100 mg, 0.35 mmol) and thiourea (32 mg, 0.41 mmol, 1.2 eq.) were suspended in 1,4-dioxane (3 mL) in a microwave reaction vial which was then crimp-capped. The mixture was heated to 120°C for 60 min in a single-mode microwave device. Upon cooling, water was added, and the resulting precipitate was collected by filtration and washed with dioxane. The off-white solid was dried under vacuum to give 98 mg (91% of th.) of the title compound.

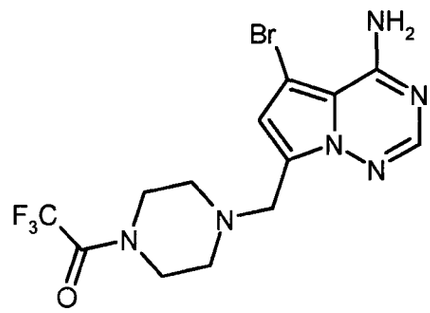
HPLC (method 1): R_t = 3.19 min;

LC-MS (method 5): R_t = 1.25 min; MS (ESIpos): *m/z* (%) = 310.9 (95) and 312.9 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 309.0 (100) and 310.9 (70) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 7.17 (s, 1H), 7.52 (s, 1H), 8.07 (s, 1H).

Intermediate 37A

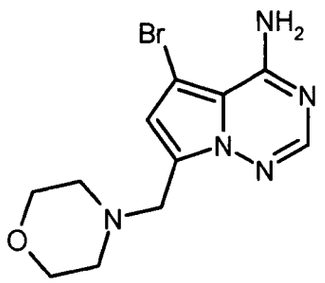
1-{4-[(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]piperazin-1-yl}-2,2,2-trifluoro-ethanone



The compound was prepared according to the procedure described in WO 2007/056170-A2 (Example 416, step 6).

Intermediate 38A

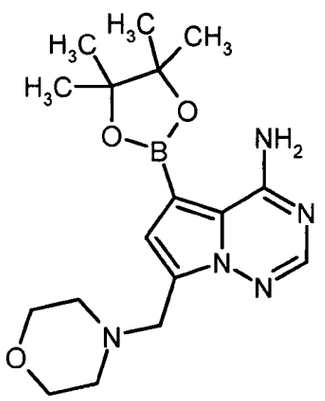
5-Bromo-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



The compound was prepared according to the procedure described in WO 2007/064931-A2 (Intermediate C).

Intermediate 39A

7-(Morpholin-4-ylmethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-4-amine



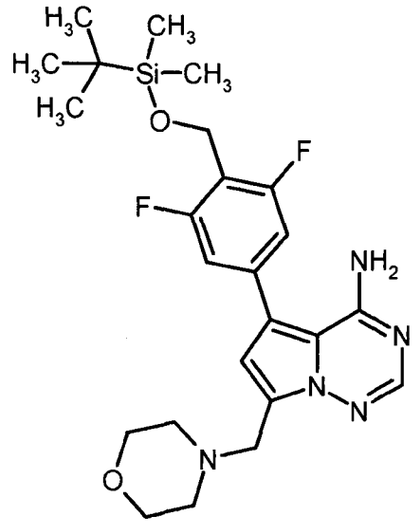
To a solution of Intermediate 38A (5.59 g, 17.9 mmol) and bis(pinacolato)diboron (10.0 g, 39.4 mmol) in degassed DMF (120 mL) was added under an argon atmosphere 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) chloride (786 mg, 1.07 mmol) and potassium acetate (7.03 g, 71.6 mmol). The mixture was heated to 80°C for 5 h and then cooled to room temperature. *tert*-Butyl methyl ether (100 mL) was added, and the suspension was filtered. The filtrate was evaporated to dryness under reduced pressure, and the residue was purified by flash chromatography over silica gel (gradient elution from 2% to 5% methanol in dichloromethane) to give 1.30 g (20% of th.) of the title

compound containing some of the corresponding boronic acid derivative. This product was used without further purification.

LC-MS (method 6): R_t = 0.73 min; MS (ESIpos): *m/z* (%) = 360.3 (30) $[M+H]^+$.

Intermediate 40A

5-[4-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-3,5-difluorophenyl]-7-(morpholin-4-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-4-amine

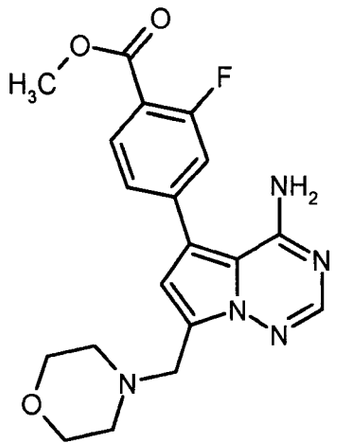


The title compound was obtained by general synthetic method 1 from Intermediate 38A (200 mg, 0.64 mmol) and [4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3,5-difluorophenyl]boronic acid (314 mg, 0.77 mmol, 74% purity; prepared by the method of Hattori, *Bioorg. Med. Chem.* **2006**, *14*, 3258-3262). Purification of the crude product was carried out by preparative HPLC (method 3). Yield: 110 mg (32% of th., LC-MS purity 92%).

LC-MS (method 6): R_t = 1.18 min; MS (ESIpos): *m/z* (%) = 490.1 (30) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 488.3 (100) $[M-H]^-$.

Intermediate 41A

Methyl 4-[4-amino-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluorobenzoate

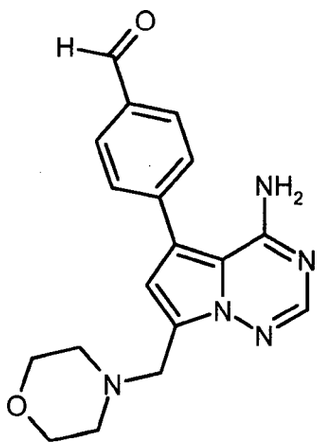


The title compound was obtained by general synthetic method 1 from Intermediate 38A (200 mg, 0.64 mmol) and [3-fluoro-4-(methoxycarbonyl)phenyl]boronic acid (139 mg, 0.71 mmol). Purification of the crude product was carried out by preparative HPLC (method 3). Yield: 80 mg (32% of th.).

LC-MS (method 6): R_t = 0.66 min; MS (ESIpos): *m/z* (%) = 386.1 (80) $[M+H]^+$.

Intermediate 42A

4-[4-Amino-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]benzaldehyde

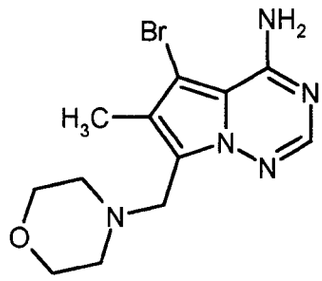


To a solution of Intermediate 38A (300 mg, 0.96 mmol) in degassed DMF (9.0 mL) was added (4-formylphenyl)boronic acid (216 mg, 1.44 mmol), tetrakis(triphenylphosphine)palladium(0) (111 mg, 0.1 mmol) and 2 M aqueous sodium carbonate solution (2.4 mL). The mixture was heated to 90°C under argon for 17 h, then cooled to room temperature and directly purified by preparative HPLC (method 3). Yield: 150 mg (46% of th.).

LC-MS (method 6): R_t = 0.44 min; MS (ESIpos): *m/z* (%) = 338.2 (30) $[M+H]^+$.

Intermediate 43A

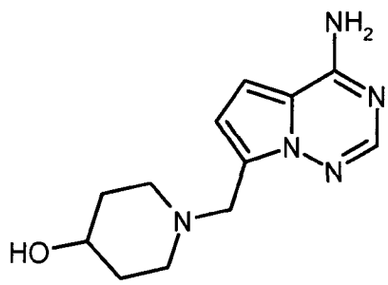
5-Bromo-6-methyl-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



The compound was prepared according to the procedure described in WO 2007/056170-A2 (Intermediate O).

Intermediate 44A

1-[(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]piperidin-4-ol



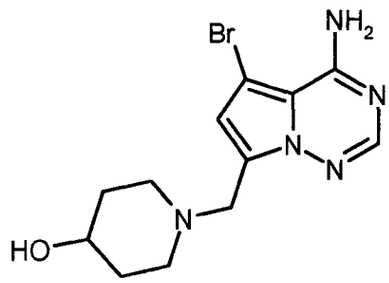
4-Hydroxypiperidine (3.62 g, 35.8 mmol) and 37% formalin solution (2.9 g, 35.8 mmol) were dissolved in acetic acid (150 mL) and stirred at room temperature for 1 h. To this solution was added a solution of pyrrolo[2,1-f][1,2,4]triazin-4-amine (2.0 g, 14.9 mmol; prepared according to the procedure described in WO 2007/056170-A2, Intermediate A) in acetic acid (150 mL), and the mixture was stirred at 60°C for 2 h. The solvent was then evaporated, and the residue was taken up in 200 mL of half-concentrated aqueous potassium bicarbonate solution and extracted with 200 mL dichloromethane. The organic layer was washed with water (2 x 50 mL) and discarded. The combined aqueous layers were evaporated to dryness, and the residue was treated with a 10:1 mixture of dichloromethane and methanol (2 x 100 mL). The organic extracts were evaporated, and the residue was purified by preparative HPLC (method 4) to give 1.16 g (15% of th.) of the title compound.

LC-MS (method 7): R_t = 0.18 min; MS (ESIpos): *m/z* (%) = 248.3 (30) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 246.5 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.35 (br. m, 2H), 1.67 (br. m, 2H), 2.07 (t, 2H), 2.70 (br. m, 2H), 3.38 (br. m, 1H), 3.75 (s, 2H), 4.51 (br, 1H), 6.52 (d, 1H), 6.84 (d, 1H), 7.62 (br, 2H), 7.82 (s, 1H).

Intermediate 45A

1-[(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]piperidin-4-ol



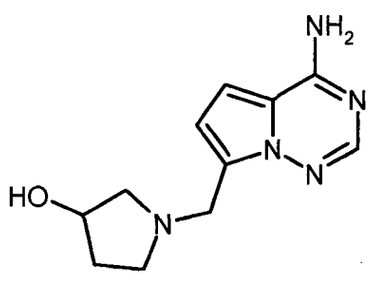
Intermediate 44A (1.10 g, 4.45 mmol) was dissolved in DMF (16.5 mL) and cooled to -20°C. 1,3-Dibromo-5,5-dimethylhydantoin (636 mg, 2.22 mmol) was added every 10 min in about 100 mg portions. Subsequently, the mixture was stirred at room temperature for a further hour and was then directly purified by preparative HPLC (method 4). Yield: 0.61 g (42% of th.).

LC-MS (method 4): R_t = 0.75 min; MS (ESIpos): *m/z* (%) = 326.0 (30) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 324.0 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.35 (br. m, 2H), 1.67 (br. m, 2H), 2.08 (t, 2H), 2.68 (br. m, 2H), 3.39 (br. m, 1H), 3.74 (s, 2H), 4.51 (br, 1H), 6.69 (s, 1H), 7.86 (s, 1H).

Intermediate 46A

1-[(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]pyrrolidin-3-ol



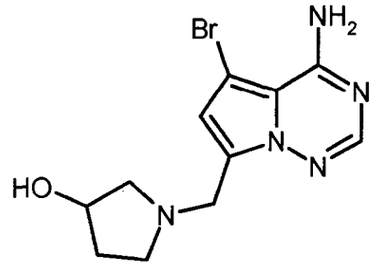
3-Pyrrolidinol (1.56 g, 17.9 mmol) and 37% formalin solution (1.45 g, 17.9 mmol) were dissolved in acetic acid (75 mL) and stirred at room temperature for 10 min. To this solution was added a solution of pyrrolo[2,1-f][1,2,4]triazin-4-amine (2.0 g, 14.9 mmol) in acetic acid (75 mL), and the mixture was stirred at 60°C for 4 h. After evaporation, the residue was taken up in 200 mL of 1 N aqueous potassium carbonate solution and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by preparative HPLC (method 4) to give 390 mg (11% of th.) of the title compound.

LC-MS (method 4): R_t = 0.22 min; MS (ESIpos): *m/z* (%) = 234.2 (20) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 223.0 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.50 (br. m, 1H), 1.94 (m, 1H), 2.34 (dd, 1H), 2.44 (dd, 1H), 2.60 (dd, 1H), 2.71 (dd, 1H), 3.84 (dd, 2H), 4.15 (br, 1H), 4.65 (d, 1H), 6.52 (d, 1H), 6.83 (d, 1H), 7.61 (br, 2H), 7.82 (s, 1H).

Intermediate 47A

1-[(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]pyrrolidin-3-ol



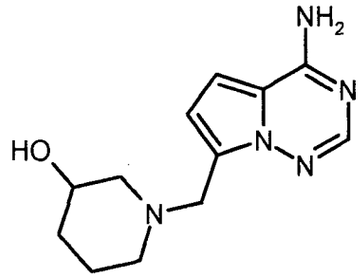
Intermediate 46A (0.9 g, 3.86 mmol) was dissolved in DMF (14.2 mL) and cooled to -20°C. 1,3-Dibromo-5,5-dimethylhydantoin (606 mg, 2.12 mmol) was added every 10 min in about 100 mg portions, and stirring was continued at room temperature for 1 h. The mixture was partitioned between 10% aqueous potassium bicarbonate solution (50 mL) and ethyl acetate (100 mL). The aqueous layer was extracted with another portion of ethyl acetate (100 mL) and then with dichloromethane (100 mL). The combined organic layers were dried over magnesium sulfate and evaporated, and the residue was purified by preparative HPLC (method 4). Yield: 0.44 g (37% of th.).

LC-MS (method 6): R_t = 0.21 min; MS (ESIpos): *m/z* (%) = 314.0 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.50 (br. m, 1H), 1.95 (m, 1H), 2.34 (dd, 1H), 2.45 (m, 1H), 2.60 (m, 1H), 2.70 (dd, 1H), 3.84 (dd, 2H), 4.15 (br, 1H), 4.65 (d, 1H), 6.71 (s, 1H), 7.86 (s, 1H).

Intermediate 48A

1-[(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]piperidin-3-ol



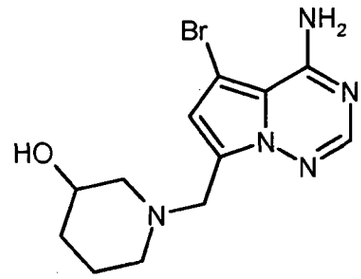
The title compound was prepared in analogy to Intermediate 46A with 3-hydroxypiperidine (1.80 g, 17.9 mmol) as starting material. After concentration of the reaction mixture, the residue was taken up in saturated aqueous potassium carbonate solution and extracted with 300 mL dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by preparative HPLC (method 4) to give 650 mg (18% of th.) of the title compound.

LC-MS (method 6): R_t = 0.16 min; MS (ESIpos): *m/z* (%) = 248.2 (60) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.99 (m, 1H), 1.37 (br. m, 1H), 1.57 (br. m, 1H), 1.74 (m, 2H), 1.88 (t, 1H), 2.68 (br. m, 1H), 2.83 (br. dd, 1H), 3.41 (br. m, 1H), 3.78 (dd, 2H), 4.54 (d, 1H), 6.52 (d, 1H), 6.84 (d, 1H), 7.61 (br, 2H), 7.82 (s, 1H).

Intermediate 49A

1-[(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]piperidin-3-ol



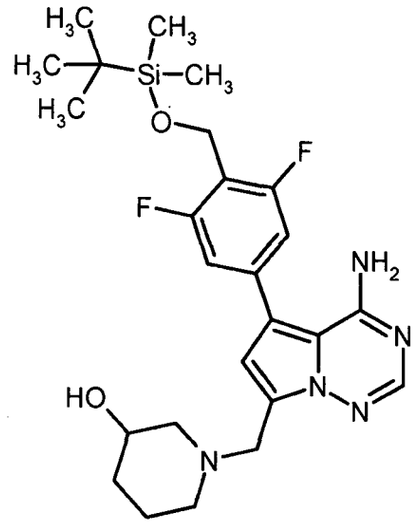
In analogy to the preparation of Intermediate 47A, the title compound was prepared from Intermediate 48A (690 mg, 2.79 mmol) to give 348 mg (93% LC-MS purity, 36% of th.) of the product after purification by preparative HPLC (method 4).

LC-MS (method 4): R_t = 0.85 min; MS (ESIpos): *m/z* (%) = 226.0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 223.9 (70) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.99 (m, 1H), 1.37 (m, 1H), 1.57 (br. m, 1H), 1.74 (m, 2H), 1.89 (m, 1H), 2.66 (br. m, 1H), 2.81 (br. m, 1H), 3.41 (br. m, 1H), 3.77 (dd, 2H), 4.54 (d, 1H), 6.70 (s, 1H), 7.86 (s, 1H).

Intermediate 50A

1-({4-Amino-5-[4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3,5-difluorophenyl]pyrrolo[2,1-f]-[1,2,4]triazin-7-yl}methyl)piperidin-3-ol



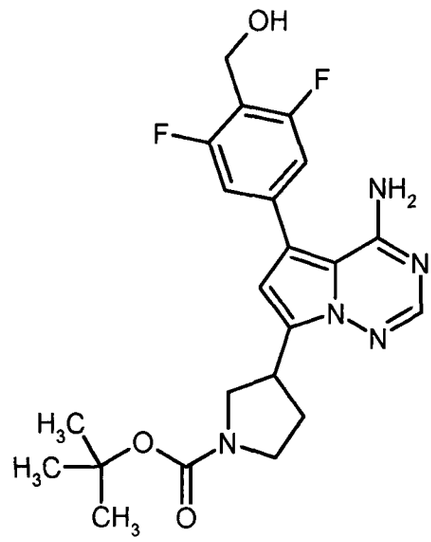
The title compound was obtained by general synthetic method 1 from Intermediate 49A (200 mg, 0.61 mmol) and [4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3,5-difluorophenyl]boronic acid (222 mg, 0.74 mmol; prepared by the method of Hattori, *Bioorg. Med. Chem.* **2006**, *14*, 3258-3262). Purification of the crude product was carried out by preparative HPLC (method 3). Yield: 153 mg (50% of th.).

LC-MS (method 7): R_t = 1.55 min; MS (ESIpos): *m/z* (%) = 504.1 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.11 (s, 6H), 0.86 (s, 9H), 1.01 (m, 1H), 1.40 (br. m, 1H), 1.59 (br. m, 1H), 1.77 (m, 2H), 1.94 (m, 1H), 2.72 (br. m, 1H), 2.87 (br. m, 1H), 3.43 (m, 1H), 3.82 (dd, 2H), 4.55 (d, 1H), 4.74 (s, 2H), 6.75 (s, 1H), 7.18 (dd, 2H), 7.95 (s, 1H).

Intermediate 51A

rac-tert-Butyl 3-{4-amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyrrolidine-1-carboxylate



The preparation of the starting material *tert*-butyl 3-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)pyrrolidine-1-carboxylate has been described in WO 2007/056170-A2 (Intermediate I).

This compound (60 mg, 0.16 mmol) was coupled according to general synthetic method 1 with Intermediate 2A (47 mg, 0.17 mmol, 1.1 eq.). The crude product was purified by preparative HPLC (method 2) to give 67 mg (84% of th.) of the title compound.

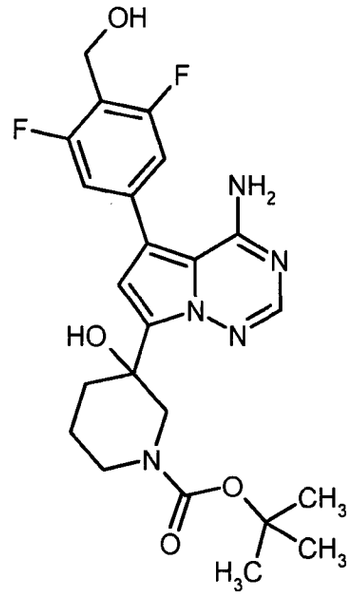
HPLC (method 2): R_t = 4.08 min;

LC-MS (method 7): R_t = 1.66 min; MS (ESIpos): *m/z* (%) = 446.2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 444.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.39 (s, 9H), 2.10 (m, 1H), 2.33 (m, 1H), 3.37 (m, 2H), 3.46 (m, 1H), 3.70-3.89 (m, 2H), 4.51 (s, 2H), 6.80 (s, 1H), 7.15 (m, 2H), 8.03 (s, 1H).

Intermediate 52A

rac-tert-Butyl 3-{4-amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}-3-hydroxypiperidine-1-carboxylate



Intermediate 26A (148 mg, 0.35 mmol) and (4-bromo-2,6-difluorophenyl)methanol (75 mg, 0.34 mmol) were coupled according to general synthetic method 2. Purification of the crude product was carried out using preparative HPLC (method 2). Yield: 46 mg (28% of th.).

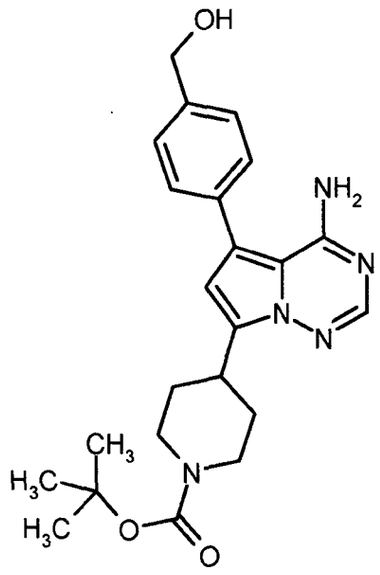
HPLC (method 3): R_t = 3.90 min;

LC-MS (method 7): R_t = 1.56 min; MS (ESIpos): *m/z* (%) = 476.2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 474.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.22-1.58 (m, 10H), 1.80 (m, 2H), 3.19 (m, 1H), 3.48 (m, 1H), 3.62 (m, 1H), 3.74 (m, 1H), 4.00 (m, 1H), 4.52 (m, 2H), 5.39 (t, 1H), 6.78 (s, 1H), 7.10 (m, 2H), 7.94 (s, 1H).

Intermediate 53A

tert-Butyl 4-{4-amino-5-[4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}piperidine-1-carboxylate



The starting material *tert*-butyl 4-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)piperidine-1-carboxylate was prepared according to the procedure described in WO 2007/056170-A2 (Example 1, step 3).

This compound (400 mg, 1.01 mmol) was then reacted with 4-(hydroxymethyl)phenylboronic acid (184 mg, 1.21 mmol, 1.2 eq.) according to general synthetic method 1. The crude product was purified by preparative HPLC (method 2) to give 326 mg (76% of th.) of the title compound.

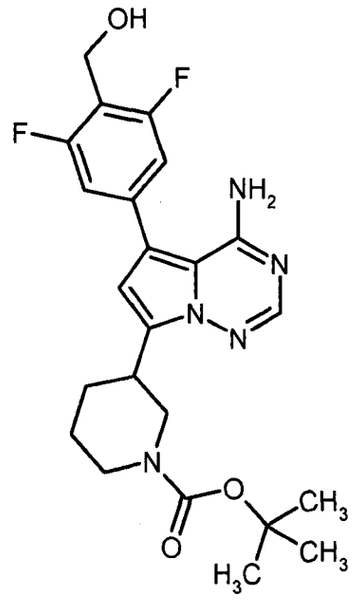
HPLC (method 2): R_t = 4.07 min;

LC-MS (method 6): R_t = 1.06 min; MS (ESIpos): *m/z* (%) = 424.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 422.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.52-1.65 (m, 2H), 1.92-2.00 (m, 2H), 2.89 (br. s, 2H), 3.10 (m, 1H), 3.28-3.37 (m, 2H), 4.06 (d, 2H), 4.60 (s, 2H), 6.68 (s, 1H), 7.47 (s, 5H), 8.02 (s, 1H).

Intermediate 54A

rac-tert-Butyl 3-{4-amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}piperidine-1-carboxylate



Intermediate 31A (200 mg, 0.39 mmol) and Intermediate 2A (138 mg, 0.51 mmol, 1.3 eq.) were reacted according to general synthetic method 1 yielding 130 mg (72% of th.) of the title compound after purification by preparative HPLC (method 2).

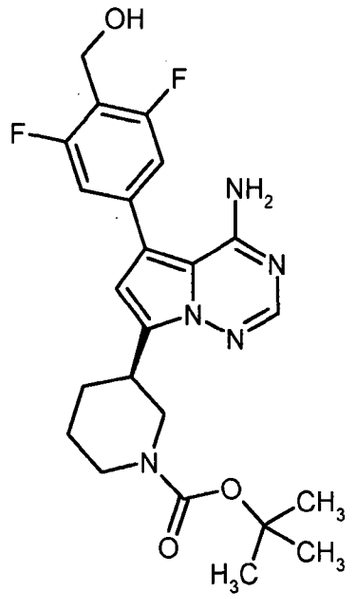
HPLC (method 3): R_t = 4.23 min;

LC-MS (method 6): R_t = 1.17 min; MS (ESIpos): *m/z* (%) = 460.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 458.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.39 (s, 9H), 1.48 (m, 2H), 1.74 (m, 2H), 2.93 (m, 1H), 3.22 (m, 1H), 3.85 (m, 1H), 4.11 (m, 1H), 4.53 (s, 2H), 6.78 (s, 1H), 7.12 (m, 2H), 8.02 (s, 1H).

Intermediate 55A

tert-Butyl (3*R*)-3-{4-amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}piperidine-1-carboxylate



The enantiomerically pure *R*-isomer was synthesized by coupling Intermediate 32A (115 mg, 0.28 mmol) with (4-bromo-2,6-difluorophenyl)methanol (76 mg, 0.33 mmol, 1.2 eq.) according to general synthetic method 2. Yield: 48 mg (38% of th.).

Alternatively, the title compound was obtained by separation of the racemic compound from Intermediate 54A (40 mg) using preparative chiral HPLC [column: chiral silica gel phase based on the selector poly(*N*-methacryloyl-L-leucine-*tert*-butylamide), 250 mm x 20 mm; eluent: ethyl acetate/isohexane 4:1; flow rate: 20 mL/min; UV detection: 260 nm]. Yield: 20 mg (*R*-isomer).

Analytical chiral HPLC [column: chiral silica gel phase based on the selector poly(*N*-methacryloyl-L-leucine-*tert*-butylamide), 250 mm x 4 mm; eluent: ethyl acetate/isohexane 4:1; flow rate: 1 mL/min; UV detection: 260 nm]: R_t = 5.68 min; e.e. >99.5.

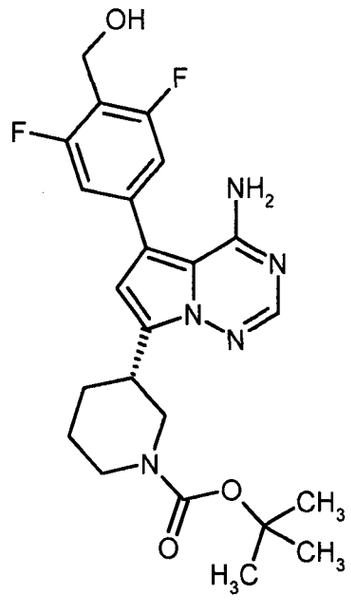
HPLC (method 3): R_t = 4.23 min;

LC-MS (method 6): R_t = 1.17 min; MS (ESIpos): *m/z* (%) = 460.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 458.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.39 (s, 9H), 1.48 (m, 2H), 1.74 (m, 2H), 2.93 (m, 1H), 3.22 (m, 1H), 3.85 (m, 1H), 4.11 (m, 1H), 4.53 (s, 2H), 6.78 (s, 1H), 7.12 (m, 2H), 8.02 (s, 1H).

Intermediate 56A

tert-Butyl (3*S*)-3-{4-amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}piperidine-1-carboxylate



The enantiomerically pure *S*-isomer was obtained by separation of the racemic compound from Intermediate 54A (40 mg) using preparative chiral HPLC as described for Intermediate 55A. Yield: 19 mg (*S*-isomer).

Analytical chiral HPLC [column: chiral silica gel phase based on the selector poly(*N*-methacryloyl-L-leucine-*tert*-butylamide), 250 mm x 4 mm; eluent: ethyl acetate/isohexane 4:1; flow rate: 1 mL/min; UV detection: 260 nm]: R_t = 7.87 min; e.e. >99.5.

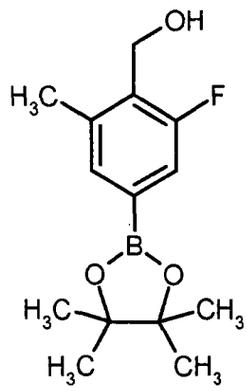
HPLC (method 3): R_t = 4.23 min;

LC-MS (method 6): R_t = 1.17 min; MS (ESIpos): *m/z* (%) = 460.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 458.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, *d*$_6$-DMSO): δ (ppm) = 1.39 (s, 9H), 1.48 (m, 2H), 1.74 (m, 2H), 2.93 (m, 1H), 3.22 (m, 1H), 3.85 (m, 1H), 4.11 (m, 1H), 4.53 (s, 2H), 6.78 (s, 1H), 7.12 (m, 2H), 8.02 (s, 1H).

Intermediate 57A

[2-Fluoro-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol

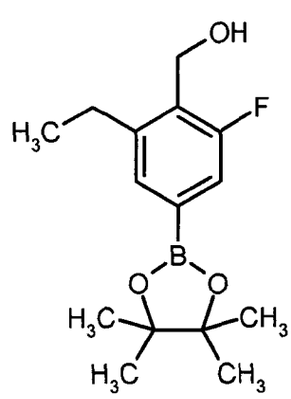


(4-Bromo-2-fluoro-6-methylphenyl)methanol (2.0 g, 9.13 mmol) was dissolved in 1,4-dioxane (20.0 mL) in a microwave reactor vial, and the solution was flushed with argon. Then, bis(pinacolato)-diboron (2.43 g, 9.59 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) chloride (298 mg, 0.37 mmol) and potassium acetate (1.34 g, 13.7 mmol) were added, the reaction vessel was crimp-capped, and the mixture was heated to 130°C for 1 h in a single-mode microwave device. After cooling, the reaction mixture was filtered and the filtrate was evaporated. The residue was treated with cyclohexane (100 mL) and stirred for 10 min. The solution was filtered again, the filtrate was evaporated, and the residue was purified by chromatography (Biotage 25M silica cartridge, dichloro-methane at 15 mL/min flow rate). Fractions containing the title compound were combined and evaporated, and the title compound crystallized spontaneously as a yellow solid (2.18 g, 90% of th.).

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.30 (s, 12H), 2.39 (s, 3H), 4.51 (m, 2H), 5.01 (t, 1H), 7.14 (d, 1H), 7.31 (s, 1H).

Intermediate 58A

[2-Ethyl-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol

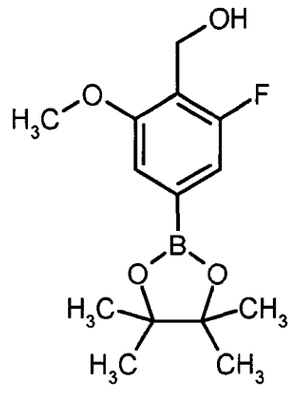


The title compound was synthesized and purified in analogy to Intermediate 57A using (4-bromo-2-ethyl-6-fluorophenyl)methanol (2.00 g, 8.58 mmol), bis(pinacolato)diboron (2.29 g, 9.01 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) chloride (280 mg, 0.34 mmol) and potassium acetate (1.26 g, 12.87 mmol) in 1,4-dioxane (20 mL). Yield: 2.16 g (90% of th.) as yellow crystals.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.17 (t, 3H), 1.30 (s, 12H), 2.76 (q, 2H), 4.50 (m, 2H), 5.03 (t, 1H), 7.14 (d, 1H), 7.32 (s, 1H).

Intermediate 59A

[2-Fluoro-6-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol

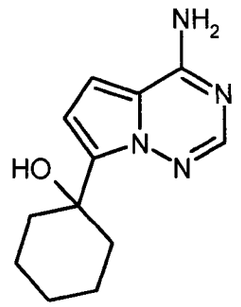


The title compound was synthesized and purified in analogy to Intermediate 57A using (4-bromo-2-methoxy-6-fluorophenyl)methanol (2.00 g, 8.51 mmol), bis(pinacolato)diboron (2.27 g, 8.90 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) chloride (278 mg, 0.34 mmol) and potassium acetate (1.25 g, 12.76 mmol) in 1,4-dioxane (20 mL). Yield: 1.81 g (75% of th.) as yellow crystals.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.30 (s, 12H), 3.83 (s, 3H), 4.47 (m, 2H), 4.86 (t, 1H), 6.97 (d, 1H), 7.02 (s, 1H).

Intermediate 60A

1-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)cyclohexanol



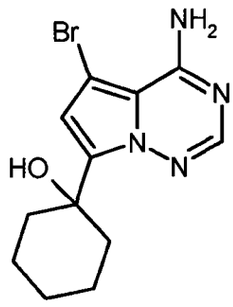
7-Bromopyrrolo[2,1-f][1,2,4]triazin-4-amine (1.20 g, 5.63 mmol) was dissolved in THF (25 mL) under argon at room temperature. Chlorotrimethylsilane (1.43 mL, 11.27 mmol) was added, and the mixture was stirred at room temperature for 3 h. Then, it was cooled to 0°C, 2-propyl magnesium chloride (11.8 mL of a 2.0 M solution in THF, 23.7 mmol) was added, and stirring was maintained for another 3 h while the reaction mixture was allowed to warm to room temperature. Then, cyclohexanone (0.88 mL, 8.45 mmol) was added, and stirring was continued for 16 h. The reaction was quenched with a mixture (1:1) of concentrated aqueous ammonium chloride solution and ice until the pH reached 6-7. The mixture was extracted with two portions of ethyl acetate, and the combined organic extracts were dried over anhydrous sodium carbonate and concentrated to dryness. The product thus obtained was used without further purification (purity ~68% by HPLC). Yield: 1.87 g (97% of th.).

LC-MS (method 5): R_t = 1.10 min; MS (ESIpos): *m/z* (%) = 233 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 231 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.28-1.33 (m, 1H), 1.42-1.50 (m, 2H), 1.58-1.63 (m, 1H), 1.67-1.78 (m, 4H), 2.13-2.23 (m, 2H), 6.69 (d, 1H), 7.20 (d, 1H), 8.02 (s, 1H), 8.58 (br. s, 1H), 9.00 (br. s, 1H).

Intermediate 61A

1-(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)cyclohexanol



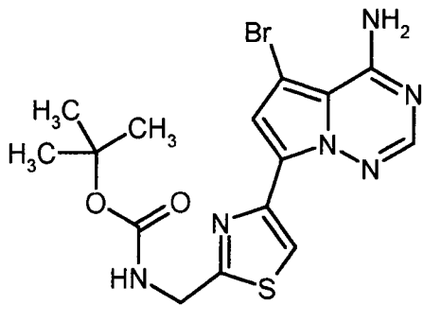
Intermediate 60A (80 mg, 0.34 mmol) was dissolved in THF (5.0 mL), and the mixture was cooled to -20°C. 1,3-Dibromo-5,5-dimethylhydantoin (49 mg, 0.17 mmol) was added at once, and stirring was continued for 1 h. The reaction was quenched with conc. aqueous sodium dithionite solution (0.5 mL), and the mixture was extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, and the solvent was distilled off to give 98 mg (91% of th.) of the title compound.

LC-MS (method 4): R_t = 1.90 min; MS (ESIpos): *m/z* (%) = 311 (95) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 309 (90) $[M-H]^-$.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.20-1.33 (m, 1H), 1.42-1.52 (m, 2H), 1.58-1.78 (m, 5H), 2.15-2.23 (m, 2H), 5.01 (br. s, 2H), 6.63 (s, 1H), 7.82 (s, 1H).

Intermediate 62A

tert-Butyl {[4-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)-1,3-thiazol-2-yl]methyl}-carbamate

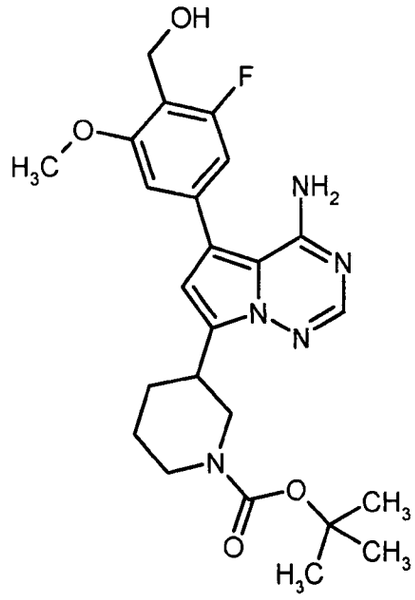


Intermediate 33A (109 mg, 0.38 mmol) and *tert*-butyl (2-amino-2-thioxoethyl)carbamate (79 mg, 0.41 mmol) were dissolved in ethanol (6.5 mL). The mixture was heated to reflux for 20 h. The mixture was then filtered, and the filtrate was evaporated. The residue was triturated with acetonitrile to give 67 mg (42% of th.) of the title compound as a brownish-grey crystalline solid.

LC-MS (method 7): R_t = 1.81 min; MS (ESIpos): *m/z* (%) = 425 (80) and 427 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 423 (50) and 425 (100) $[M-H]^-$.

Intermediate 63A

tert-Butyl 3-{4-amino-5-[3-fluoro-4-(hydroxymethyl)-5-methoxyphenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}piperidine-1-carboxylate



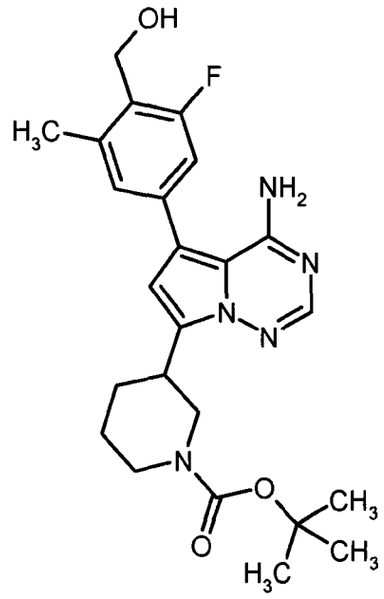
Intermediate 31A (120 mg, 0.30 mmol) and Intermediate 59A (104 mg, 0.36 mmol) were dissolved in acetonitrile (2.0 mL) in a microwave reactor vial and flushed with argon. Tetrakis(triphenylphosphine)palladium(0) (35 mg, 0.03 mmol) and 2.0 M aq. sodium carbonate solution (0.5 mL) were added, and the mixture was heated to 150°C for 1 h in a single-mode microwave device. After cooling, the mixture was filtered, and the filtrate was evaporated. The residue was purified by flash chromatography (Biotage 25M silica cartridge, dichloromethane + 2-5% methanol, flow rate 10 mL/min) to give 51 mg (36% of th.) of the title compound.

LC-MS (method 6): R_t = 1.16 min; MS (ESIpos): *m/z* (%) = 472 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 470 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.31-2.10 (m, 13H), 2.88-2.91 (m, 2H), 3.19-3.27 (m, 2H), 3.87 (s, 1H), 4.12 (m, 1H), 4.50 (m, 1H), 4.82 (t, 1H), 6.68 (s, 1H), 6.83 (d, 1H), 6.90 (s, 1H), 7.92 (s, 1H).

Intermediate 64A

tert-Butyl 3-{4-amino-5-[3-fluoro-4-(hydroxymethyl)-5-methylphenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}piperidine-1-carboxylate



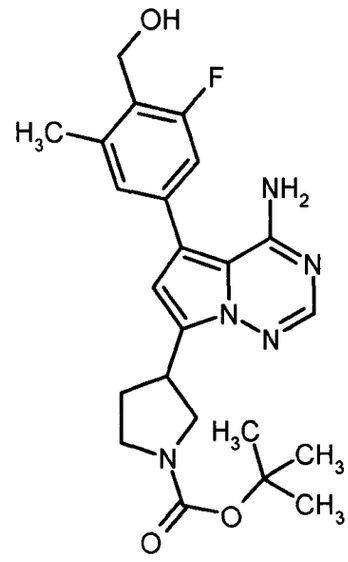
Intermediate 31A (120 mg, 0.30 mmol) and Intermediate 57A (97 mg, 0.36 mmol) were dissolved in acetonitrile (2.0 mL) in a microwave reactor vial and flushed with argon. Tetrakis(triphenylphosphine)palladium(0) (35 mg, 0.03 mmol) and 2.0 M aq. sodium carbonate solution (0.5 mL) were added, and the mixture was heated to 150°C for 1 h in a single-mode microwave device. After cooling, the mixture was filtered, and the filtrate was evaporated. The residue was purified by flash chromatography (Biotage 25M silica cartridge, dichloromethane + 2-5% methanol, flow rate 10 mL/min) to give 110 mg (71% of th.) of the title compound.

LC-MS (method 4): R_t = 2.03 min; MS (ESIpos): *m/z* (%) = 456 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 454 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.31-2.11 (m, 13H), 2.42 (s, 3H), 2.88-2.91 (m, 2H), 3.17-3.30 (m, 2H), 3.80 (m, 1H), 4.54 (m, 1H), 4.82 (t, 1H), 6.64 (s, 1H), 7.04 (d, 1H), 7.12 (s, 1H), 7.93 (s, 1H).

Intermediate 65A

tert-Butyl 3-{4-amino-5-[3-fluoro-4-(hydroxymethyl)-5-methylphenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyrrolidine-1-carboxylate



The starting material *tert*-Butyl 3-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)pyrrolidine-1-carboxylate was synthesized according to the procedure described in WO 2007/056170-A2 (Intermediate I).

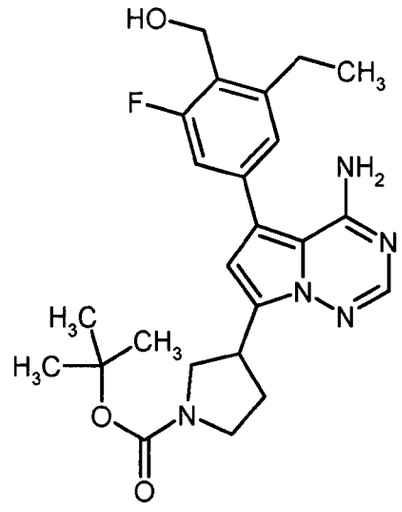
tert-Butyl 3-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)pyrrolidine-1-carboxylate (120 mg, 0.31 mmol) was dissolved in acetonitrile (2.2 mL) in a microwave reactor vial and flushed with argon. Intermediate 57A (100 mg, 0.38 mmol), tetrakis(triphenylphosphine)palladium(0) (36 mg, 0.03 mmol) and 2.0 M aq. sodium carbonate solution (0.5 mL) were added, and the mixture was heated to 150°C for 1 h in a single-mode microwave device. After cooling, the mixture was filtered, and the filtrate was evaporated. The residue was purified by flash chromatography (Biotage 25M silica cartridge, dichloromethane + 2-5% methanol, flow rate 10 mL/min) to give 91 mg (54% of th.) of the title compound.

LC-MS (method 5): R_t = 2.00 min; MS (ESIpos): *m/z* (%) = 442 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 440 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.41 (m, 9H), 2.00-2.48 (m, 2H), 3.29-3.53 (m, 3H), 3.71-3.90 (m, 2H), 4.55 (m, 2H), 4.99 (t, 1H), 6.63 (s, 1H), 7.06 (d, 1H), 7.12 (s, 1H), 7.92 (s, 1H).

Intermediate 66A

rac-tert-Butyl 3-{4-amino-5-[3-ethyl-5-fluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}pyrrolidine-1-carboxylate



The starting material *tert*-Butyl 3-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)pyrrolidine-1-carboxylate was synthesized according to the procedure described in WO 2007/056170-A2 (Intermediate I).

tert-Butyl 3-(4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)pyrrolidine-1-carboxylate (111 mg, 0.29 mmol), Intermediate 58A (98 mg, 0.35 mmol) and tetrakis(triphenylphosphine)palladium(0) (17 mg, 0.015 mmol) were dissolved in a mixture of acetonitrile (2.3 mL) and 2 M aqueous sodium carbonate solution (0.53 mL) in a microwave reactor vial. After degassing for 5 min using argon, the reaction vessel was crimp-capped, and the mixture was heated to 150°C for 1 h in a single-mode microwave device. After cooling to room temperature, saturated aqueous sodium bicarbonate solution was added, and the mixture was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by preparative HPLC (method 5). Yield: 83 mg (63% of th.).

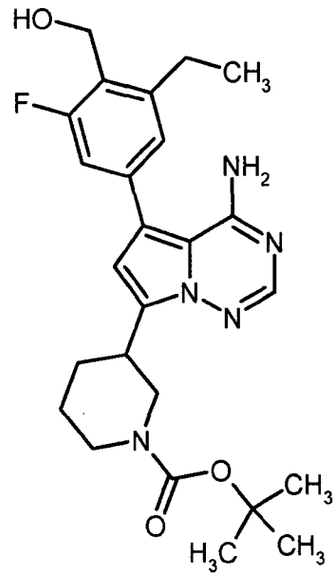
HPLC (method 9): R_t = 1.61 min;

LC-MS (method 10): R_t = 1.02 min; MS (ESIpos): *m/z* (%) = 456.4 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 454.4 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.22 (t, 3H), 1.41 (s, 9H), 2.1 (m, 1H), 2.80 (q, 2H), 3.30-3.43 (m, 2H), 3.44-3.51 (m, 1H), 3.78 (m, 1H), 4.55 (d, 2H), 5.00 (t, 1H), 6.68 (s, 1H), 7.09 (d, 1H), 7.15 (s, 1H), 7.95 (s, 1H).

Intermediate 67A

rac-tert-Butyl 3-{4-amino-5-[3-ethyl-5-fluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}piperidine-1-carboxylate



Intermediate 31A (148 mg, 0.29 mmol), Intermediate 58A (98 mg, 0.35 mmol) and tetrakis(triphenylphosphine)palladium(0) (17 mg, 0.015 mmol) were dissolved in a mixture of acetonitrile (2.3 mL) and 2 M aqueous sodium carbonate solution (0.67 mL) in a microwave reactor vial. After degassing for 5 min using argon, the reaction vessel was crimp-capped, and the mixture was heated to 150°C for 1 h in a single-mode microwave device. After cooling to room temperature, saturated aqueous sodium bicarbonate solution was added, and the mixture was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by preparative HPLC (method 5). Yield: 105 mg (76% of th.).

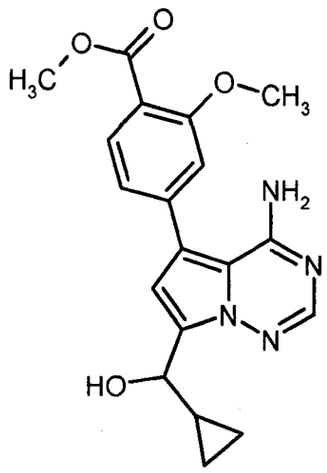
HPLC (method 9): R_t = 1.71 min;

LC-MS (method 10): R_t = 1.08 min; MS (ESIpos): *m/z* (%) = 470.4 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 468.4 (75) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.22 (t, 3H), 1.38 (s, 9H), 1.50 (m, 1H), 1.65-1.90 (m, 2H), 2.06 (m, 1H), 2.80 (q, 2H), 2.98 (m, 1H), 3.20-3.43 (m, 2H), 3.8 (m, 1H), 4.08 (m, 1H), 4.55 (d, 2H), 5.02 (t, 1H), 6.65 (s, 1H), 7.07 (d, 1H), 7.13 (s, 1H), 7.93 (s, 1H).

Intermediate 68A

rac-Methyl 4-{4-amino-7-[cyclopropyl(hydroxy)methyl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}-2-methoxybenzoate



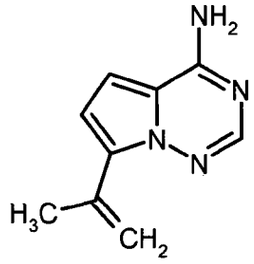
Intermediate 17A (250 mg, 0.88 mmol), [3-methoxy-4-(methoxycarbonyl)phenyl]boronic acid (223 mg, 1.06 mmol) and tetrakis(triphenylphosphine)palladium(0) (102 mg, 0.088 mmol) were dissolved in a mixture of 1,4-dioxane (5.5 mL) and 2 M aqueous sodium carbonate solution (1.32 mL) under argon and heated under reflux for 16 h. After this, another portion of tetrakis(triphenylphosphine)palladium(0) (102 mg, 0.088 mmol) was added, and heating was continued for further 24 h. After cooling to room temperature, the reaction mixture was filtered, the filtrate was concentrated, and the residue was purified by preparative HPLC (method 7). Yield: 130 mg (80% purity, 32% of th.).

LC-MS (method 10): R_t = 0.80 min; MS (ESIpos): *m/z* (%) = 369.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 367.3 (75) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.41 (m, 3H), 0.49 (m, 1H), 1.37 (m, 1H), 3.81 (s, 3H), 4.68 (d, 1H), 6.92 (s, 1H), 7.13 (dd, 1H), 7.22 (d, 1H), 7.77 (d, 1H), 8.05 (s, 1H).

Intermediate 69A

7-(Prop-1-en-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



The starting material 7-bromopyrrolo[2,1-f][1,2,4]triazin-4-amine was synthesized according to the procedure described in WO 2007/056170-A2 (Intermediate B).

Under an argon atmosphere, 7-bromopyrrolo[2,1-f][1,2,4]triazin-4-amine (426 mg, 2 mmol) and 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (420 mg, 2.5 mmol) were dissolved in a mixture of 1,2-dimethoxyethane (10 mL) and aqueous sodium carbonate solution (2 M, 4 mL). The reaction mixture was degassed, and 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) chloride (73 mg, 0.1 mmol) was added. After stirring at 90°C overnight, the reaction mixture was diluted with ethyl acetate (40 mL), water (10 mL) was added, and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 40 mL), and the combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (puriFlash, Interchim, cyclohexane/ethyl acetate 1:1 to 100% ethyl acetate gradient) to yield the title product as a slightly yellow solid. Yield: 304 mg (81% of th.).

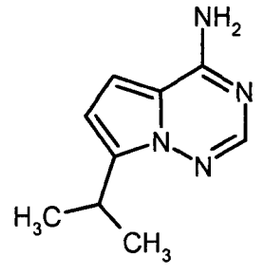
HPLC (method 10): R_t = 0.83 min;

LC-MS (method 10): R_t = 0.57 min; MS (ESIpos): *m/z* (%) = 175.1 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.15 (s, 3H), 5.22 (m, 1H), 6.30 (m, 1H), 6.73 (d, 1H), 6.91 (d, 1H), 7.69 (m, 1H), 7.91 (s, 1H).

Intermediate 70A

7-Isopropylpyrrolo[2,1-f][1,2,4]triazin-4-amine



Intermediate 69A (149 mg, 0.86 mmol) was dissolved in a mixture of ethanol and ethyl acetate (1:1, 40 mL) under argon. Palladium on charcoal (10%, 9.1 mg) was added, and the mixture was vigorously stirred for 16 h under an atmosphere of hydrogen at ambient pressure and room temperature. After this, the catalyst was removed by filtration, and the solvent was distilled off under reduced pressure to give 131 mg (80% of th.) of the title compound as a colorless solid. This product was used in the next synthetic step without further purification.

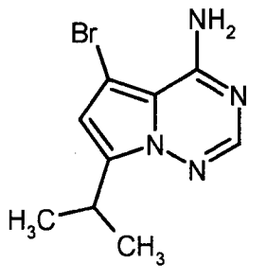
HPLC (method 10): R_t = 0.81 min;

LC-MS (method 10): R_t = 0.56 min; MS (ESIpos): *m/z* (%) = 177.0 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.27 (d, 6H), 3.36 (m, 1H), 6.41 (d, 1H), 6.80 (d, 1H), 7.48-7.59 (m, 2H), 7.80 (s, 1H).

Intermediate 71A

5-Bromo-7-isopropylpyrrolo[2,1-f][1,2,4]triazin-4-amine



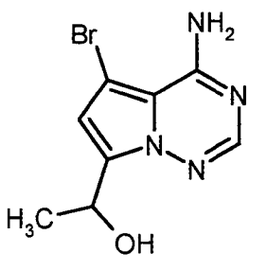
Intermediate 70A (125 mg, 0.71 mmol) was dissolved in dry THF (21 mL) and cooled to -78°C. 1,3-Dibromo-5,5-dimethylhydantoin (81 mg, 0.28 mmol) was added in two equal portions. The reaction mixture was stirred at -78°C for 1 h and then allowed to warm to room temperature overnight. After addition of water (20 mL) and further stirring for 20 min, the precipitated solid was collected by filtration and dried *in vacuo*. The crude product thus obtained (209 mg, >100% of th.) was used in the next synthetic step without further purification.

HPLC (method 9): R_t = 1.35 min.

LC-MS (method 10): R_t = 0.91 min; MS (ESIpos): *m/z* (%) = 257.0 (100) $[M+H]^+$.

Intermediate 72A

rac-1-(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-7-yl)ethanol



Intermediate 16A (500 mg, 1.66 mmol) was suspended in THF (10 mL) and cooled to 0°C. Methyl magnesium bromide solution (3 N in diethylether, 1.7 mL) was added, and the reaction mixture was stirred for 30 min. Then, saturated aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to yield 235 mg (46% of th.) of the title product which was used in the next synthetic step without further purification.

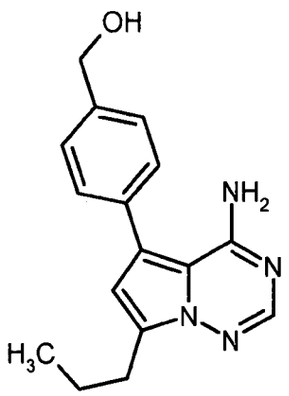
LC-MS (method 5): R_t = 0.73 min; MS (ESIpos): *m/z* (%) = 259.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 257.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.41 (d, 3H), 5.16 (m, 1H), 5.30 (m, 1H), 6.70 (s, 1H), 7.85 (s, 1H).

Preparation Examples:

Example 1

[4-(4-Amino-7-propylpyrrolo[2,1-f][1,2,4]triazin-5-yl)phenyl]methanol



The title compound was obtained by general synthetic method 1 from Intermediate 11A (100 mg, 0.39 mmol) and 4-(hydroxymethyl)phenylboronic acid (60 mg, 0.39 mmol). Purification of the crude product was carried out by preparative HPLC (method 2). Yield: 33 mg (30% of th.).

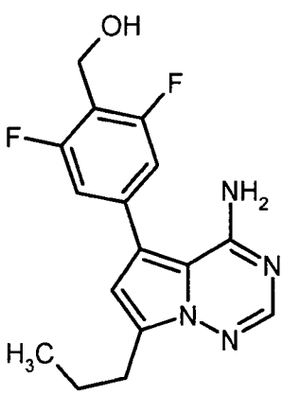
HPLC (method 1): R_t = 3.47 min; HPLC (method 2): R_t = 3.78 min;

LC-MS (method 4): R_t = 0.91 min; MS (ESIpos): *m/z* (%) = 283.2 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.97 (t, *J* = 7.4 Hz, 3H), 1.71 (m, 2H), 3.31 (s, 2H), 4.52 (s, 2H), 6.54 (s, 1H), 7.42 (s, 4H), 7.89 (s, 1H).

Example 2

[4-(4-Amino-7-propylpyrrolo[2,1-f][1,2,4]triazin-5-yl)-2,6-difluorophenyl]methanol



The title compound was obtained by general synthetic method 2 from Intermediate 11A (118 mg, 0.46 mmol) and (4-bromo-2,6-difluorophenyl)methanol (108 mg, 0.49 mmol). Purification of the crude product was carried out by preparative HPLC (method 2). Yield: 59 mg (40% of th.).

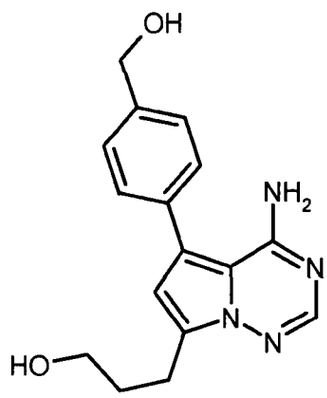
HPLC (method 2): R_t = 3.94 min;

LC-MS (method 7): R_t = 1.47 min; MS (ESIpos): *m/z* (%) = 319.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 317.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.95 (t, 3H), 1.71 (m, 2H), 4.52 (m, 2H), 5.26 (t, 1H), 6.64 (s, 1H), 7.10 (m, 2H), 7.91 (s, 1H).

Example 3

3-{4-Amino-5-[4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}propan-1-ol



The title compound was obtained from Intermediate 10A (100 mg, 0.37 mmol) and 4-(hydroxymethyl)phenylboronic acid (67 mg, 0.44 mmol, 1.2 eq.) according to general synthetic method 1. The crude product was purified by preparative HPLC (method 2) to give 73 mg (66% of th.) of the title compound as colorless solid.

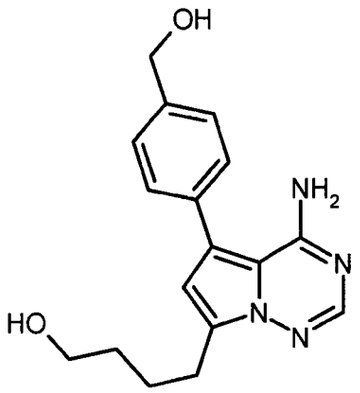
HPLC (method 1): R_t = 2.91 min; HPLC (method 2): R_t = 3.14 min;

LC-MS (method 6): R_t = 0.60 min; MS (ESIpos): *m/z* (%) = 299.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 297.4 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.84 (m, 2H), 2.95 (t, J = 7.6 Hz, 2H), 3.50 (m, 2H), 4.58 (s, 2H), 6.67 (s, 1H), 7.41 (s, 4H), 8.03 (s, 1H).

Example 4

4-{4-Amino-5-[4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}butan-1-ol



The title compound was obtained by general synthetic method 1 from Intermediate 14A (75 mg, 0.26 mmol) and 4-(hydroxymethyl)phenylboronic acid (48 mg, 0.32 mmol). Purification of the crude product was carried out by preparative HPLC (method 2). Yield: 66 mg (80% of th.).

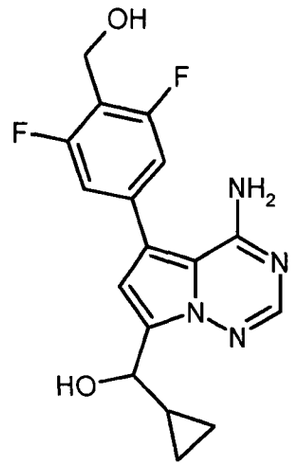
HPLC (method 2): R_t = 3.28 min;

LC-MS (method 6): R_t = 0.68 min; MS (ESIpos): *m/z* (%) = 313.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 311.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.48-1.51 (m, 2H), 1.67-1.70 (m, 2H), 2.91 (t, *J* = 7.6 Hz, 2H), 3.42 (t, *J* = 6.4 Hz, 2H), 4.58 (s, 2H), 6.67 (s, 1H), 7.42 (s, 4H), 8.03 (s, 1H).

Example 5

{4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}(cyclopropyl)-methanol



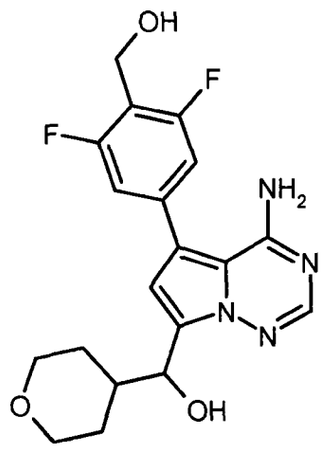
The title compound was obtained from Intermediate 17A (125 mg, 0.44 mmol) and Intermediate 2A (114 mg, 0.53 mmol) by general synthetic method 1. The crude product was purified by preparative HPLC (method 3). Yield: 73 mg (48% of th.).

LC-MS (method 7): R_t = 1.09 min; MS (ESIpos): *m/z* (%) = 347.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 345.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.39 (m, 3H), 0.48 (m, 1H), 1.35 (m, 1H), 4.54 (d, 2H), 4.67 (m, 1H), 5.26 (m, 2H), 6.80 (s, 1H), 7.14 (m, 2H), 7.92 (s, 1H).

Example 6

{4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}(tetrahydro-2*H*-pyran-4-yl)methanol



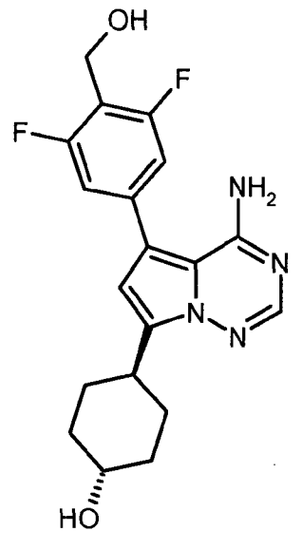
The title compound was obtained from Intermediate 18A (200 mg, 0.61 mmol) and Intermediate 2A (158 mg, 0.73 mmol) by general synthetic method 1. The crude product was purified by preparative HPLC (method 3). Yield: 125 mg (52% of th.).

LC-MS (method 5): R_t = 1.29 min; MS (ESIpos): *m/z* (%) = 391.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 389.0 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.24 (br. d, 1H), 1.36 (m, 2H), 1.68 (br. d, 1H), 2.03 (m, 1H), 2.60 (t, 2H), 3.82 (m, 2H), 4.54 (s, 2H), 4.95 (br. d, 1H), 5.28 (br, 1H), 5.33 (br, 1H), 6.73 (s, 1H), 7.14 (m, 2H), 7.93 (s, 1H).

Example 7

trans-4-{4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}-cyclohexanol



The title compound was obtained by general synthetic method 1 from Intermediate 24A (323 mg, 85% purity, 0.88 mmol) and Intermediate 1A (286 mg, 1.06 mmol, 1.2 eq.). Purification of the crude product was first carried out by flash chromatography (Biotage silica packed cartridge, eluent dichloromethane/methanol 95:5). Further purification was performed by preparative HPLC (method 2). Yield: 72 mg (21% of th.).

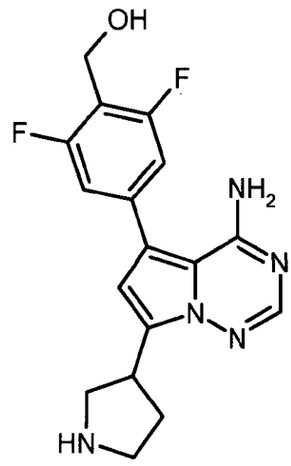
HPLC (method 2): R_t = 3.37 min;

LC-MS (method 7): R_t = 1.01 min; MS (ESIpos): *m/z* (%) = 375.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 373.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.32 (m, 2H), 1.50 (m, 2H), 1.98 (m, 2H), 2.04 (m, 2H), 3.04 (tt, 1H), 3.47 (m, 1H), 4.51 (m, 2H), 4.61 (d, 1H), 5.26 (t, 1H), 6.60 (s, 1H), 7.12 (m, 2H), 7.91 (s, 1H).

Example 8

rac-{4-[4-Amino-7-(pyrrolidin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2,6-difluorophenyl}methanol



Intermediate 51A (67 mg, 0.15 mmol) was dissolved in a 30% solution of trifluoroacetic acid in dichloromethane (6 mL) at 0°C. The reaction mixture was stirred at this temperature for 20 min, then all volatiles were removed under reduced pressure. The residue was purified by preparative HPLC (method 2). The product thus obtained was dissolved in ethyl acetate and washed with saturated aqueous sodium carbonate solution. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off to give 21 mg (41% of th.) of the title compound.

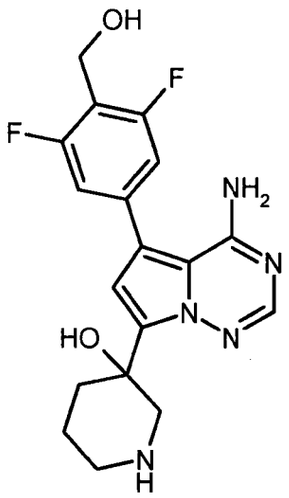
HPLC (method 2): R_t = 2.96 min;

LC-MS (method 6): R_t = 0.34 min; MS (ESIpos): *m/z* (%) = 346.1 (20) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 344.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.94 (m, 1H), 2.22 (m, 1H), 2.94 (m, 1H), 3.00-3.16 (m, 2H), 3.40 (m, 2H), 3.72 (m, 1H), 4.51 (s, 2H), 5.22 (br. s, 1H), 6.71 (s, 1H), 7.11 (m, 2H), 7.92 (s, 1H).

Example 9

rac-3-{4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}-piperidin-3-ol



Intermediate 52A (46 mg, 0.10 mmol) was dissolved in a 30% solution of trifluoroacetic acid in dichloromethane (1.5 mL) at 0°C. The reaction mixture was stirred at this temperature for 30 min, then all volatiles were removed under reduced pressure. The residue was purified by preparative HPLC (method 2). The product thus obtained was dissolved in ethyl acetate and washed with saturated aqueous sodium carbonate solution. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off to give 20 mg (55% of th.) of the title compound.

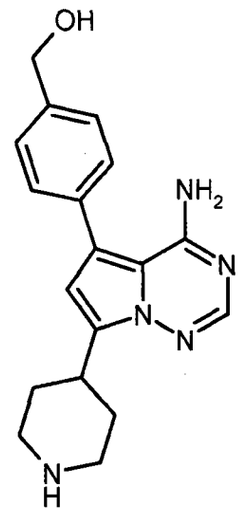
HPLC (method 2): R_t = 2.94 min;

LC-MS (method 4): R_t = 1.01 min; MS (ESIpos): *m/z* (%) = 358.1 (100) $[M-H_2O+H]^+$, MS (ESIneg): *m/z* (%) = 374.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.48 (m, 1H), 1.89 (m, 2H), 2.40-2.69 (m, 2H), 2.92 (d, 1H), 3.02 (d, 1H), 3.40 (m, 1H), 4.52 (m, 2H), 5.26 (t, 1H), 5.45 (s, 1H), 6.72 (s, 1H), 7.13 (m, 2H), 7.94 (s, 1H).

Example 10

{4-[4-Amino-7-(piperidin-4-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}methanol



Intermediate 53A (324 mg, 0.77 mmol) was dissolved in dichloromethane (15 mL). Trifluoroacetic acid (1.5 mL) was added, and the mixture was stirred at room temperature for 16 h. Another portion of trifluoroacetic acid (1.5 mL) was added, and stirring was continued until HPLC (method 1) indicated complete conversion of the starting material. All volatiles were then removed under reduced pressure, and the residue was purified by preparative HPLC (method 1) to give 226 mg (91% of th.) of the title compound.

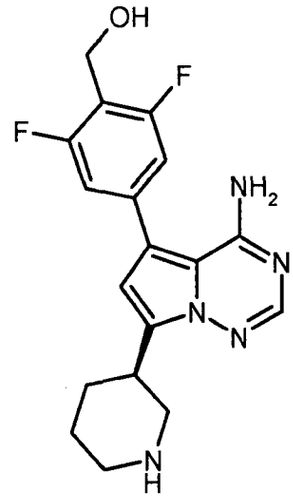
HPLC (method 1): R_t = 3.37 min; HPLC (method 2): R_t = 2.90 min;

LC-MS (method 4): R_t = 0.90 min; MS (ESIpos): *m/z* (%) = 324.1 (75) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 322.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.79-1.95 (m, 2H), 2.16-2.23 (m, 2H), 3.05-3.19 (m, 2H), 3.37-3.52 (m, 3H), 4.56 (s, 2H), 5.49 (s, 2H), 6.66 (s, 1H), 7.43 (s, 4H), 8.03 (s, 1H), 8.39-8.50 (m, 1H), 8.65-8.69 (m, 1H).

Example 11

(4-{4-Amino-7-[(3*R*)-piperidin-3-yl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}-2,6-difluorophenyl)methanol



Intermediate 55A (35 mg, 0.08 mmol) was dissolved in a 30% solution of trifluoroacetic acid in dichloromethane (1.5 mL) at 0°C. The reaction mixture was stirred at this temperature for 30 min, then all volatiles were removed under reduced pressure. The residue was purified by preparative HPLC (method 2). The product thus obtained was dissolved in ethyl acetate and washed with saturated aqueous sodium carbonate solution. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off to give 18 mg (66% of th.) of the title compound.

HPLC (method 2): R_t = 3.10 min;

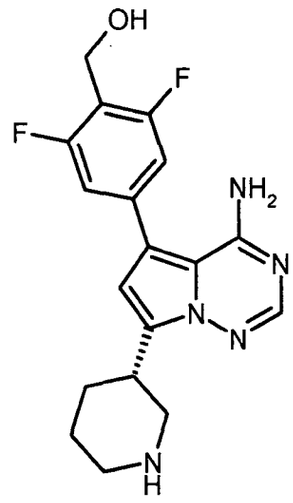
LC-MS (method 6): R_t = 0.55 min; MS (ESIpos): *m/z* (%) = 360.2 (20) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 358.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.67 (m, 2H), 1.83 (m, 1H), 2.75 (m, 1H), 2.86 (m, 1H), 3.20 (d, 1H), 3.41 (m, 2H), 4.53 (m, 2H), 5.29 (t, 1H), 6.70 (s, 1H), 7.11 (m, 1H), 7.94 (s, 1H).

$[\alpha]_{589}^{20}$ = +16.8° (c = 0.515, methanol).

Example 12

(4-{4-Amino-7-[(3*S*)-piperidin-3-yl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}-2,6-difluorophenyl)methanol

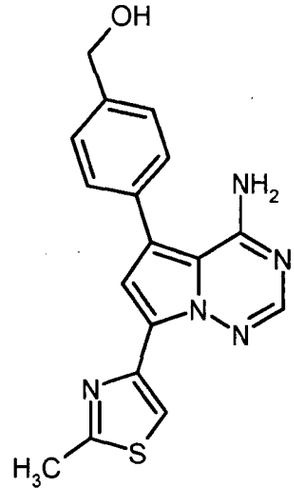


The title compound was obtained from Intermediate 56A (19 mg, 0.04 mmol) by the same method as described for the conversion of Intermediate 55A to Example 11. Yield: 12 mg (81% of th.).

HPLC, LC-MS and ^{1}H-NMR data were identical to those shown for Example 11.

Example 13

{4-[4-Amino-7-(2-methyl-1,3-thiazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}methanol



Intermediate 33A (60 mg, 0.21 mmol) and thioacetamide (15 mg, 0.20 mmol, 0.95 eq.) were dissolved in 1,4-dioxane (2 mL) and refluxed for 4.5 h. After cooling, 4-(hydroxymethyl)phenylboronic acid (38 mg, 0.25 mmol, 1.2 eq.), tetrakis(triphenylphosphine)palladium(0) (59 mg, 0.07 mmol, 0.25 eq.) and 2 M aqueous sodium carbonate solution (0.4 mL) were added. The mixture was gently stirred at 100°C for 16 h. Then, another portion of tetrakis(triphenylphosphine)palladium(0) (24 mg, 0.1 eq.) was added, and stirring at 100°C was continued for another 4 h. The reaction mixture was

then filtered, the filtrate was evaporated under reduced pressure, and the residue was purified by preparative HPLC (method 2) to give 28 mg (40% of th.) of the title compound as off-white crystals.

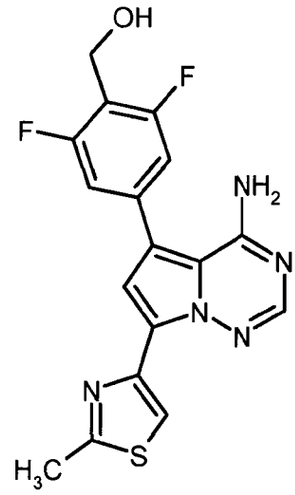
HPLC (method 1): R_t = 3.85 min; HPLC (method 2): R_t = 3.60 min;

LC-MS (method 6): R_t = 0.94 min; MS (ESIpos): *m/z* (%) = 338.2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 336.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.73 (s, 3H), 4.58 (s, 2H), 7.17 (s, 1H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 8.09 (s, 1H), 8.33 (s, 1H).

Example 14

{4-[4-Amino-7-(2-methyl-1,3-thiazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2,6-difluorophenyl}-methanol



The title compound was obtained by general synthetic method 1 from Intermediate 34A (75 mg, 0.24 mmol) and Intermediate 1A (78 mg, 0.29 mmol, 1.2 eq.). Purification of the crude product was carried out by preparative HPLC (method 2). Yield: 27 mg (30% of th.).

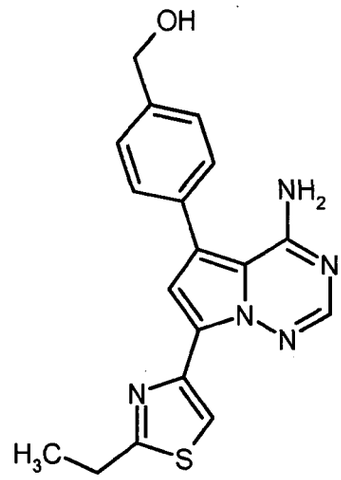
HPLC (method 1): R_t = 3.79 min;

LC-MS (method 6): R_t = 1.03 min; MS (ESIpos): *m/z* (%) = 374.0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 372.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.72 (s, 3H), 4.53 (s, 2H), 7.18-7.27 (m, 2H), 8.11 (s, 1H), 8.33 (s, 1H).

Example 15

{4-[4-Amino-7-(2-ethyl-1,3-thiazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}methanol



Intermediate 35A (91 mg, 0.28 mmol) was reacted with 4-(hydroxymethyl)phenylboronic acid (51 mg, 0.34 mmol, 1.2 eq.) according to general synthetic method 1. The crude product was purified by preparative HPLC (method 2) giving 68 mg (69% of th.) of the title compound as colorless crystals.

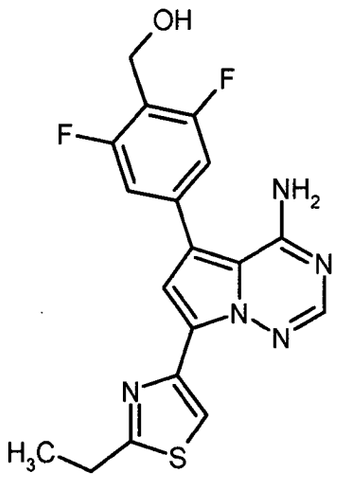
HPLC (method 1): R_t = 3.73 min;

LC-MS (method 6): R_t = 1.05 min; MS (ESIpos): *m/z* (%) = 352.2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 350.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.36 (t, *J* = 7.6 Hz, 3H), 3.06 (q, *J* = 7.6 Hz, 2H), 4.58 (s, 2H), 7.19 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 8.12 (s, 1H), 8.36 (s, 1H).

Example 16

{4-[4-Amino-7-(2-ethyl-1,3-thiazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2,6-difluorophenyl}-methanol



The title compound was obtained by general synthetic method 1 from Intermediate 35A (34 mg, 0.11 mmol) and Intermediate 1A (34 mg, 0.13 mmol, 1.2 eq.). Purification of the crude product was carried out by preparative HPLC (method 2). Yield: 16 mg (40% of th.).

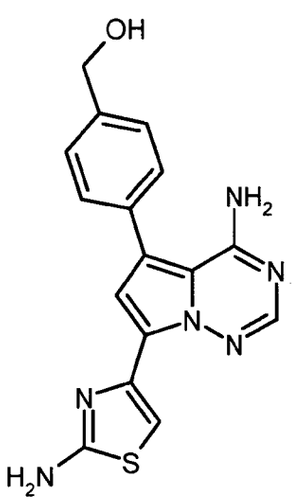
HPLC (method 1): R_t = 4.04 min;

LC-MS (method 6): R_t = 1.15 min; MS (ESIpos): *m/z* (%) = 388.0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 386.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.38 (t, 3H), 3.06 (q, 2H), 4.55 (s, 2H), 7.20-7.31 (m, 3H), 8.16 (s, 1H), 8.38 (s, 1H).

Example 17

{4-[4-Amino-7-(2-amino-1,3-thiazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}methanol



The title compound was obtained by general synthetic method 1 from Intermediate 36A (55 mg, 0.18 mmol) and 4-(hydroxymethyl)phenylboronic acid (32 mg, 0.21 mmol). Purification of the crude product was carried out by preparative HPLC (method 2). Yield: 29 mg (49% of th.).

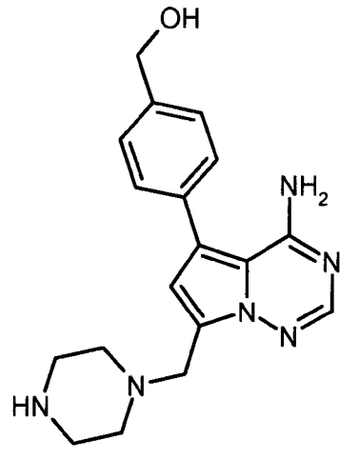
HPLC (method 1): R_t = 3.03 min;

LC-MS (method 5): R_t = 1.21 min; MS (ESIpos): *m/z* (%) = 339.1 (30) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 337.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 4.58 (m, 2H), 5.75 (m, 1H), 6.93 (s, 1H), 7.05 (m, 2H), 7.43 (m, 4H), 7.55 (s, 1H), 8.08 (s, 1H).

Example 18

{4-[4-Amino-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}methanol



Intermediate 37A (200 mg, 0.49 mmol), 4-(hydroxymethyl)phenylboronic acid (90 mg, 0.59 mmol, 1.2 eq.) and tetrakis(triphenylphosphine)palladium(0) (57 mg, 0.05 mmol, 0.1 eq.) were dissolved in a mixture of 1,4-dioxane (4.0 mL) and 2 M aqueous sodium carbonate solution (1.0 mL) in a microwave reactor vial. The reaction vessel was crimp-capped, and the mixture was heated to 140°C for 1 h in a single-mode microwave device. After cooling, the mixture was filtered over a pad of Celite which was rinsed with 1,4-dioxane to elute all organic material. The combined filtrate was evaporated to dryness under reduced pressure, and the residue was purified by preparative HPLC (method 1) to give 75 mg (45% of th.) of the title compound.

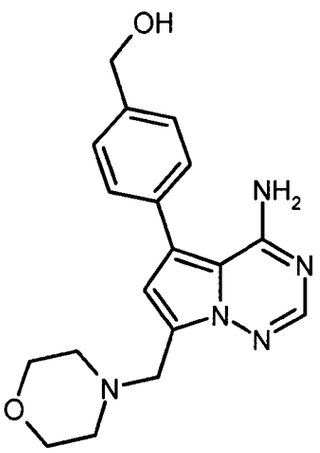
HPLC (method 1): R_t = 2.85 min;

LC-MS (method 4): R_t = 0.93 min; MS (ESIpos): *m/z* (%) = 339.1 (30) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 337.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.38 (br. s, 4H), 2.63 (m, 4H), 3.80 (s, 2H), 4.55 (s, 2H), 5.26 (br. s, 1H), 6.60 (s, 1H), 7.39 (s, 4H), 7.90 (s, 1H).

Example 19

{4-[4-Amino-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]phenyl}methanol



The title compound was obtained from Intermediate 38A (200 mg, 0.64 mmol) and 4-(hydroxymethyl)phenylboronic acid (116 mg, 0.77 mmol, 1.2 eq.) according to general synthetic method 1. The crude product was purified by preparative HPLC (method 2). The material thus obtained was dissolved in a few mL of a mixture of acetonitrile and water, 2 M aqueous sodium carbonate solution was added, and the mixture was stirred for 10 min. During this time, the title compound precipitated. The crystals were isolated by filtration and dried *in vacuo* to give 95 mg (49% of th.) of a colorless solid.

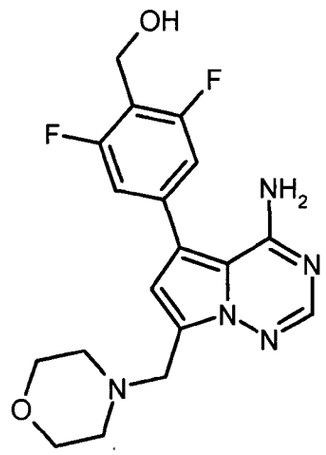
HPLC (method 1): R_t = 3.21 min;

LC-MS (method 4): R_t = 0.93 min; MS (ESIpos): *m/z* (%) = 340 (1) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 338.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.47 (m, 4H), 3.31 (s, 4H), 3.53 (t, 2H), 3.82 (s, 1H), 4.56 (d, 2H), 5.22 (t, 1H), 6.63 (s, 1H), 7.42 (s, 4H), 7.90 (s, 1H).

Example 20

{4-[4-Amino-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2,6-difluorophenyl}-methanol



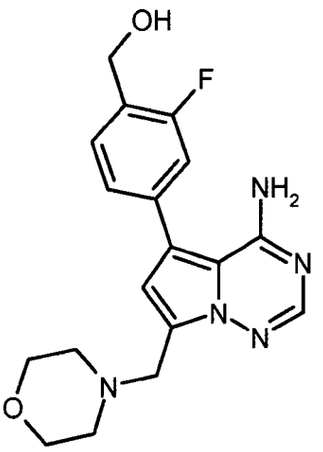
To a solution of Intermediate 40A (110 mg, 0.22 mmol) in THF (2.2 mL) was added 0.45 mL (0.45 mmol) of a 1 M solution of tetrabutylammonium fluoride (TBAF) in THF, and the mixture was stirred at room temperature for 1 h. The reaction mixture was then evaporated under reduced pressure, and the residue was suspended in 3 mL of methanol and stirred at room temperature for 5 min. The resulting precipitate was filtered, washed with a small amount of methanol and dried *in vacuo* to give 68 mg (81% of th.) of the title compound.

LC-MS (method 4): R_t = 1.03 min; MS (ESIpos): *m/z* (%) = 376.0 (80) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 374.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.45 (br. m, 4H), 3.56 (t, 4H), 3.82 (s, 2H), 4.54 (d, 2H), 5.27 (t, 1H), 6.75 (s, 1H), 7.16 (m, 2H), 7.95 (s, 1H).

Example 21

{4-[4-Amino-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluorophenyl}methanol



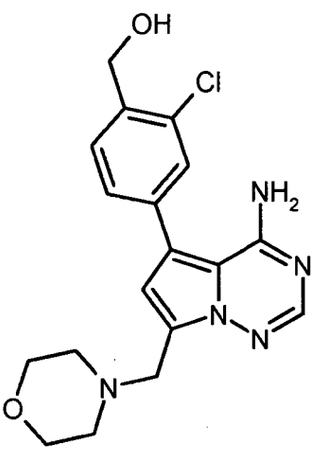
To a suspension of Intermediate 41A (65.0 mg, 0.17 mmol) in THF (2.0 mL) was added 0.2 mL (0.2 mmol) of a 1 M solution of lithium aluminium hydride in THF, and the mixture was stirred at room temperature for 1 h. The resulting solution was quenched with water and then directly purified by preparative HPLC (method 3) to give 35 mg (58% of th.) of the title compound.

LC-MS (method 6): R_t = 0.98 min; MS (ESIpos): *m/z* (%) = 358.1 (20) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 356.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.46 (br. m, 4H), 3.56 (t, 4H), 3.83 (s, 2H), 4.60 (d, 2H), 5.32 (t, 1H), 6.70 (s, 1H), 7.27 (dd, 2H), 7.55 (t, 1H), 7.94 (s, 1H).

Example 22

{4-[4-Amino-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-chlorophenyl}methanol



Intermediate 39A (200 mg, 0.56 mmol), Intermediate 3A (112 mg, 0.51 mmol) and tetrakis-(triphenylphosphine)palladium(0) (58 mg, 0.05 mmol) were dissolved in a mixture of 1,4-dioxane

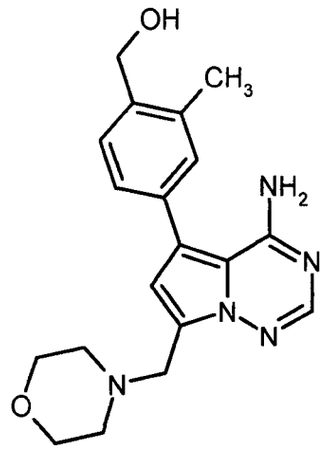
(4.0 mL) and 2 M aqueous sodium carbonate solution (1.0 mL) in a microwave reactor vial. The reaction vessel was crimp-capped, and the mixture was heated to 140°C for 1 h in a single-mode microwave device. After cooling, the mixture was filtered, and the filtrate was purified by preparative HPLC (method 3) to give 48 mg (23% of th.) of the title compound.

LC-MS (method 6): R_t = 0.53 min; MS (ESIpos): *m/z* (%) = 374.1 (80) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 372.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.46 (br. m, 4H), 3.56 (t, 4H), 3.83 (s, 2H), 4.61 (d, 2H), 5.45 (t, 1H), 6.70 (s, 1H), 7.44 (dd, 1H), 7.49 (d, 1H), 7.63 (t, 1H), 7.94 (s, 1H).

Example 23

{4-[4-Amino-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-methylphenyl}methanol



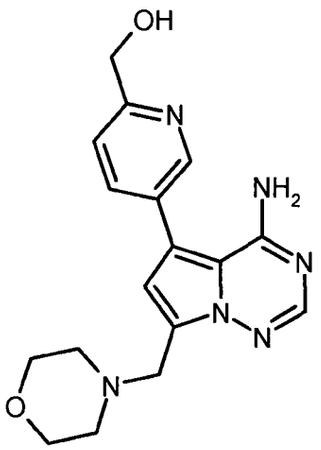
In analogy to the preparation of Example 28, Intermediate 39A (200 mg, 0.56 mmol) was reacted with Intermediate 4A (102 mg, 0.51 mmol) to give 9 mg (5% of th.) of the title compound.

LC-MS (method 4): R_t = 1.00 min; MS (ESIpos): *m/z* (%) = 354.3 (10) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 372.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.30 (s, 3H), 2.45 (br. m, 4H), 3.56 (t, 4H), 3.83 (s, 2H), 4.54 (d, 2H), 5.13 (t, 1H), 6.63 (s, 1H), 7.26 (s, 1H), 7.26 (d, 1H), 7.45 (d, 1H), 7.91 (s, 1H).

Example 24

{5-[4-Amino-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]pyridin-2-yl}methanol



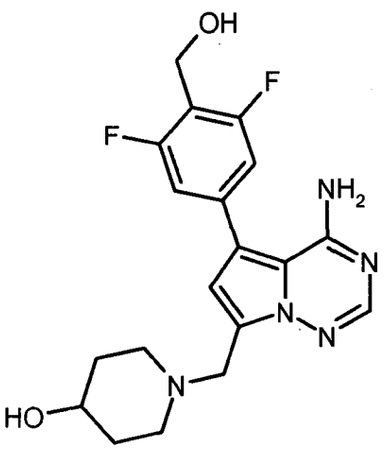
The title compound was obtained from Intermediate 38A (200 mg, 0.64 mmol) and Intermediate 6A (147 mg, 0.96 mmol) by general synthetic method 1. The crude product was purified by preparative HPLC (method 4). Remaining impurities were removed by suspending the product in acetonitrile (2 mL) and collecting the remaining solid by filtration. Yield: 27 mg (12% of th.).

LC-MS (method 4): R_t = 0.78 min; MS (ESIpos): *m/z* (%) = 341 (10) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 339.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 2.46 (br. m, 4H), 3.56 (t, 4H), 3.84 (s, 2H), 4.62 (d, 2H), 5.46 (t, 1H), 6.73 (s, 1H), 7.54 (d, 1H), 7.86 (dd, 1H), 7.95 (d, 1H), 8.56 (s, 1H).

Example 25

1-({4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}methyl)-piperidin-4-ol



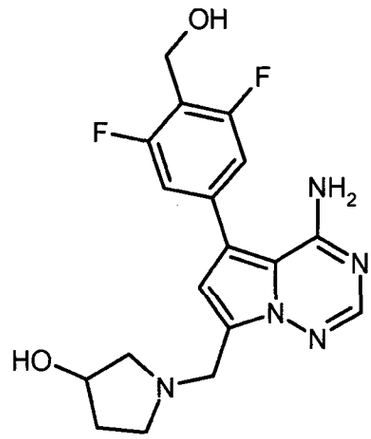
The title compound was obtained from Intermediate 45A (200 mg, 0.61 mmol) and Intermediate 2A (159 mg, 0.74 mmol) by general synthetic method 1. The crude product was purified by preparative HPLC (method 3). Yield: 103 mg (43% of th.).

LC-MS (method 4): R_t = 0.98 min; MS (ESIpos): *m/z* (%) = 390.1 (60) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 388.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.36 (br. m, 2H), 1.68 (br. m, 2H), 2.12 (br. m, 2H), 2.75 (br. m, 2H), 3.41 (br. m, 1H), 3.79 (s, 2H), 4.51 (d, 1H), 4.54 (d, 2H), 5.27 (t, 1H), 6.72 (s, 1H), 7.15 (m, 2H), 7.94 (s, 1H).

Example 26

1-({4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}methyl)-pyrrolidin-3-ol



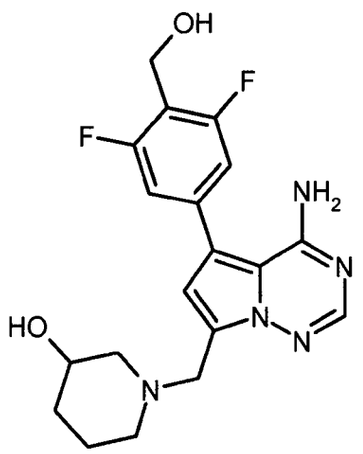
The title compound was obtained from Intermediate 47A (110 mg, 0.35 mmol) and Intermediate 2A (91.3 mg, 0.42 mmol) by general synthetic method 1. The crude product was purified by preparative HPLC (method 3). Yield: 69 mg (52% of th.).

LC-MS (method 4): R_t = 0.25 min; MS (ESIpos): *m/z* (%) = 376.1 (20) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.54 (m, 1H), 1.98 (m, 1H), 2.43 (br. d, 1H), 2.69 (m, 1H), 2.79 (dd, 1H), 3.93 (dd, 2H), 4.18 (br, 1H), 4.53 (d, 2H), 4.69 (d, 1H), 5.27 (t, 1H), 6.75 (s, 1H), 7.16 (m, 2H), 7.95 (s, 1H).

Example 27

1-({4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}methyl)-piperidin-3-ol



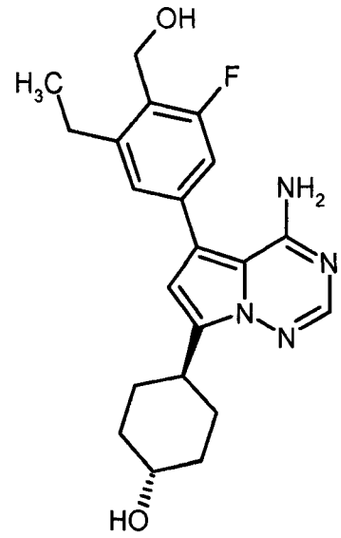
To a solution of Intermediate 50A (150 mg, 0.30 mmol) in THF (3.0 mL) was added 0.60 mL (0.60 mmol) of a 1 M solution of tetrabutylammonium fluoride (TBAF) in THF, and the mixture was stirred at room temperature for 1 h. The reaction mixture was then concentrated, and the residue was purified by preparative HPLC (method 3) to give 65 mg (56% of th.) of the title compound.

LC-MS (method 7): R_t = 0.33 min; MS (ESIpos): *m/z* (%) = 390.3 (100) $[M+H]^+$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.02 (br. m, 1H), 1.40 (br. m, 1H), 1.60 (br. m, 1H), 1.77 (br. m, 2H), 1.95 (br. m, 1H), 2.73 (br. m, 1H), 2.88 (br. m, 1H), 3.43 (br. m, 1H), 3.83 (br. m, 2H), 4.54 (br. d, 3H), 5.27 (t, 1H), 6.74 (s, 1H), 7.15 (m, 2H), 7.95 (s, 1H).

Example 28

trans-4-{4-Amino-5-[3-ethyl-5-fluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}-cyclohexanol



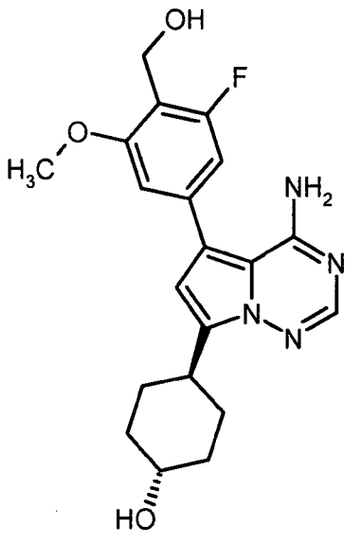
Intermediate 24A (120 mg, 0.39 mmol) and Intermediate 58A (130 mg, 0.46 mmol) were dissolved in acetonitrile (3.0 mL) in a microwave reactor vial and flushed with argon. Tetrakis(triphenylphosphine)palladium(0) (22 mg, 0.02 mmol) and 2.0 M aq. sodium carbonate solution (0.7 mL) were added, and the mixture was heated to 150°C for 1 h in a single-mode microwave device. After cooling, the mixture was filtered, and the filtrate was evaporated. The residue was purified by preparative HPLC (method 2) to give 36 mg (23% of th.) of the title compound.

LC-MS (method 6): R_t = 0.82 min; MS (ESIpos): *m/z* (%) = 385 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 383 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.24 (t, 3H), 1.28-1.38 (m, 2H), 1.46-1.54 (m, 2H), 1.94-1.97 (m, 2H), 2.01-2.05 (m, 2H), 2.82 (q, 2H), 3.03 (m, 1H), 3.47 (m, 1H), 4.53 (m, 2H), 4.61 (d, 1H), 5.02 (t, 1H), 6.58 (s, 1H), 7.08 (d, 1H), 7.15 (s, 1H), 7.90 (s, 1H).

Example 29

trans-4-{4-Amino-5-[3-fluoro-4-(hydroxymethyl)-5-methoxyphenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}cyclohexanol



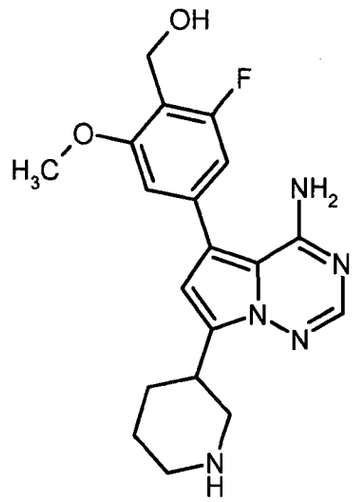
Intermediate 24A (120 mg, 0.39 mmol) and Intermediate 59A (163 mg, 80% purity, 0.46 mmol) were dissolved in acetonitrile (2.0 mL) in a microwave reactor vial and flushed with argon. Tetrakis-(triphenylphosphine)palladium(0) (45 mg, 0.04 mmol) and 2.0 M aq. sodium carbonate solution (0.5 mL) were added, and the mixture was heated to 150°C for 1 h in a single-mode microwave device. After cooling, the mixture was filtered, and the filtrate was evaporated. The residue was purified by preparative HPLC (method 2) to give 6 mg (4% of th.) of the title compound.

LC-MS (method 5): R_t = 1.36 min; MS (ESIpos): *m/z* (%) = 387 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 385 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.24-1.33 (m, 2H), 1.42-1.53 (m, 2H), 1.90-1.93 (m, 2H), 2.00-2.04 (m, 2H), 3.04 (m, 1H), 3.46 (m, 1H), 3.82 (s, 3H), 4.48 (m, 2H), 4.60 (d, 1H), 4.83 (t, 1H), 6.60 (s, 1H), 6.85 (d, 1H), 6.90 (s, 1H), 7.91 (s, 1H).

Example 30

{4-[4-Amino-7-(piperidin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluoro-6-methoxyphenyl}-methanol



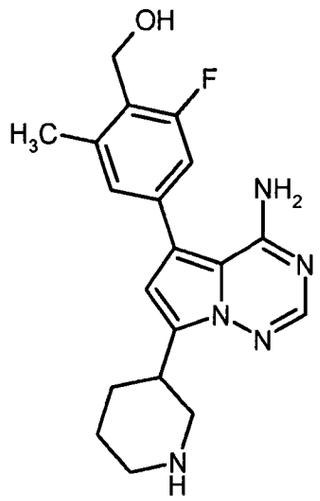
Intermediate 63A (50 mg, 0.11 mmol) was dissolved in a 30% solution of trifluoroacetic acid in dichloromethane (5.0 mL) at 0°C. The reaction mixture was stirred at this temperature for 30 min, then all volatiles were removed by distillation under reduced pressure. The residue was purified by preparative HPLC (method 2). The product thus obtained was dissolved in ethyl acetate and washed with saturated aqueous sodium carbonate solution. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off to give 30 mg (76% of th.) of the title compound.

LC-MS (method 6): R_t = 0.59 min; MS (ESIpos): *m/z* (%) = 372 (10) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 370 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.50-2.08 (m, 4H), 2.94 (m, 2H), 3.17-3.30 (m, 3H), 3.85 (s, 3H), 4.51 (m, 2H), 4.82 (t, 1H), 6.60 (s, 1H), 6.84 (d, 1H), 6.89 (s, 1H), 7.90 (s, 1H).

Example 31

{4-[4-Amino-7-(piperidin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluoro-6-methylphenyl}methanol



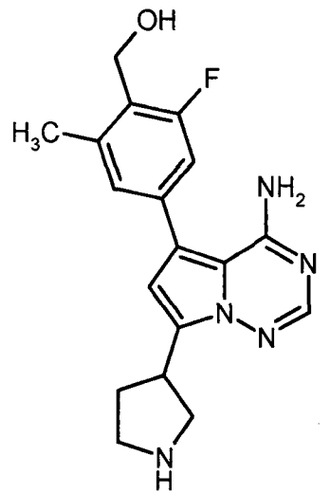
Intermediate 64A (110 mg, 0.21 mmol) was dissolved in a 30% solution of trifluoroacetic acid in dichloromethane (5.0 mL) at 0°C. The reaction mixture was stirred at this temperature for 30 min, then all volatiles were removed by distillation under reduced pressure. The residue was purified by preparative HPLC (method 2). The product thus obtained was dissolved in ethyl acetate and washed with saturated aqueous sodium carbonate solution. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off to give 59 mg (78% of th.) of the title compound.

LC-MS (method 4): R_t = 1.10 min; MS (ESIpos): *m/z* (%) = 356 (40) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 354 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.44-2.08 (m, 4H), 2.42 (s, 3H), 2.94 (m, 2H), 3.17-3.27 (m, 3H), 4.53 (m, 2H), 4.98 (t, 1H), 6.54 (s, 1H), 7.06 (d, 1H), 7.11 (s, 1H), 7.90 (s, 1H).

Example 32

{4-[4-Amino-7-(pyrrolidin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-fluoro-6-methylphenyl}methanol



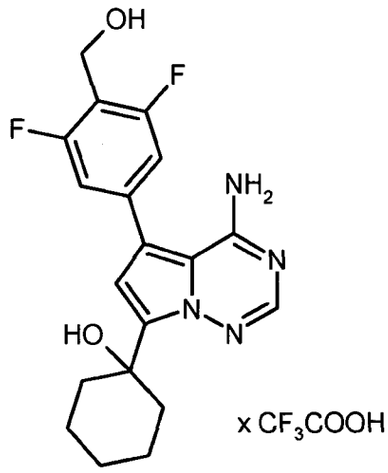
Intermediate 65A (90 mg, 0.17 mmol) was dissolved in a 30% solution of trifluoroacetic acid in dichloromethane (5.0 mL) at 0°C. The reaction mixture was stirred at this temperature for 30 min, then all volatiles were removed by distillation under reduced pressure. The residue was purified by preparative HPLC (method 2). The product thus obtained was dissolved in ethyl acetate and washed with saturated aqueous sodium carbonate solution. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off to give 27 mg (47% of th.) of the title compound.

LC-MS (method 4): R_t = 1.03 min; MS (ESIpos): *m/z* (%) = 342 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 340 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.80-2.21 (m, 2H), 2.43 (s, 3H), 2.78-2.81 (m, 1H), 2.85-3.02 (m, 2H), 3.22-3.27 (m, 1H), 3.63 (m, 1H), 4.55 (br. s, 2H), 4.98 (t, 1H), 6.63 (s, 1H), 7.06 (d, 1H), 7.11 (s, 1H), 7.90 (s, 1H).

Example 33

1-{4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}cyclohexanol trifluoroacetate



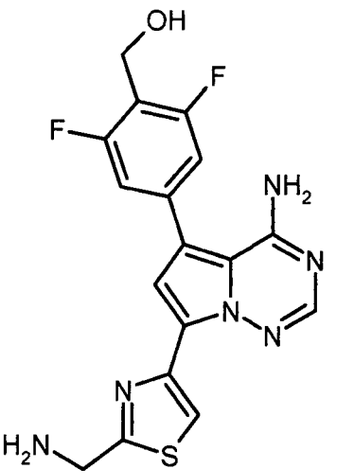
Intermediate 61A (95 mg, 0.31 mmol) and Intermediate 1A (87 mg, 0.32 mmol) were dissolved in DMF (2.0 mL) in a microwave reactor vessel and flushed with argon. Tetrakis(triphenylphosphine)-palladium(0) (35 mg, 0.03 mmol) and 2.0 M aq. sodium carbonate solution (0.5 mL) were added, and the mixture was heated to 150°C for 1 h in a single-mode microwave device. After cooling, the mixture was filtered, and the filtrate was directly purified by preparative HPLC (method 2) to give 6 mg (4% of th.) of the title compound.

LC-MS (method 6): R_t = 1.05 min; MS (ESIpos): *m/z* (%) = 375 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 373 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.20-1.33 (m, 1H), 1.42-1.51 (m, 2H), 1.60-1.82 (m, 5H), 2.17-2.28 (m, 2H), 4.51 (s, 2H), 6.76 (s, 1H), 7.17 (m, 2H), 8.02 (s, 1H).

Example 34

(4-{4-Amino-7-[2-(aminomethyl)-1,3-thiazol-4-yl]pyrrolo[2,1-f][1,2,4]triazin-5-yl}-2,6-difluoro-phenyl)methanol



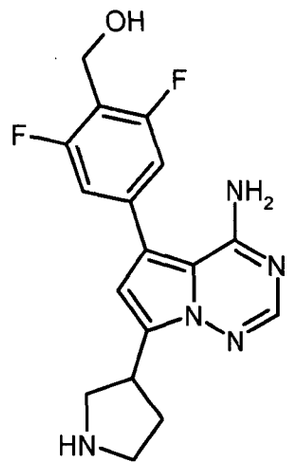
Intermediate 62A (67 mg, 0.16 mmol), Intermediate 1A (51 mg, 0.19 mmol), tetrakis(triphenylphosphine)palladium(0) (18 mg, 0.02 mmol) and 2.0 M aq. sodium carbonate solution (0.94 mL) were dissolved in 1,4-dioxane (2.50 mL) in a microwave reactor vial. The vial was crimp-capped, and the mixture was heated to 140°C for 3 h in a single-mode microwave device. Then, the reaction mixture was filtered, and the filtrate was diluted with acetonitrile and treated with diethyl ether. The resulting precipitate was collected and purified by preparative HPLC (method 2). The product thus obtained (15 mg) was subsequently treated with a 20% solution of trifluoroacetic acid in dichloromethane (2 mL) for 20 min. The volatiles were removed by distillation, and the residue was treated with conc. aqueous sodium carbonate solution and extracted with ethyl acetate. The organic extract was dried over anhydrous sodium sulfate, and the solvent was distilled off to give the title compound (10 mg, 13% of th.) as a colorless solid.

LC-MS (method 4): R_t = 1.12 min; MS (ESIpos): *m/z* (%) = 389 (25) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 387 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 4.24 (s, 2H), 4.53 (m, 2H), 5.30 (t, 1H), 7.18-7.23 (m, 3H), 8.11 (s, 1H), 8.40 (s, 1H).

Example 35

ent-{4-[4-Amino-7-(pyrrolidin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2,6-difluorophenyl}methanol (*enantiomer 1*)



The title compound was obtained by separation of racemic Example 8 (54 mg) using preparative chiral HPLC [column: Daicel Chiralpak AD-H, 250 mm x 20 mm; eluent: isohexane/ethanol 35:65; flow rate: 20 mL/min; UV detection: 220 nm]. Yield: 12.5 mg.

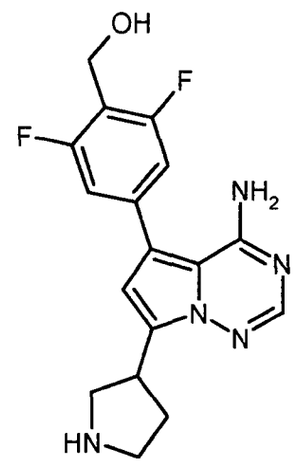
Analytical chiral HPLC [column: Daicel Chiralpak AD-H, 5 µm, 250 mm x 4.6 mm; eluent: isohexane/ethanol 50:50 + 0.2% diethylamine; flow rate: 1.0 mL/min; temperature: 40°C; UV detection: 220 nm]: R_t = 9.452 min, e.e. >99%.

HPLC (method 9): R_t = 0.70 min;

LC-MS (method 10): R_t = 0.42 min; MS (ESIpos): *m/z* (%) = 346.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 344.0 (100) $[M-H]^-$.

Example 36

ent-{4-[4-Amino-7-(pyrrolidin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2,6-difluorophenyl}methanol (*enantiomer 2*)



The title compound was obtained by separation of racemic Example 8 (54 mg) using preparative chiral HPLC [column: Daicel Chiralpak AD-H, 250 mm x 20 mm; eluent: isohexane/ethanol 35:65; flow rate: 20 mL/min; UV detection: 220 nm]. Yield: 14 mg.

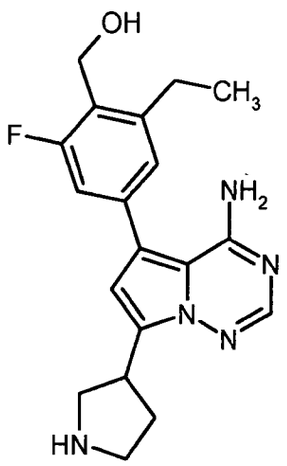
Analytical chiral HPLC [column: Daicel Chiralpak AD-H, 5 µm, 250 mm x 4.6 mm; eluent: isohexane/ethanol 50:50 + 0.2% diethylamine; flow rate: 1.0 mL/min; temperature: 40°C; UV detection: 220 nm]: R_t = 13.695 min, e.e. >99%.

HPLC (method 9): R_t = 0.71 min;

LC-MS (method 10): R_t = 0.42 min; MS (ESIpos): *m/z* (%) = 346.1 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 344.0 (100) $[M-H]^-$.

Example 37

rac-{4-[4-Amino-7-(pyrrolidin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-ethyl-6-fluorophenyl}-methanol



Intermediate 66A (72 mg, 0.158 mmol) was dissolved in dichloromethane (3.8 mL) at 0°C and trifluoroacetic acid (1.0 mL) was added. The reaction mixture was stirred at 0°C for 40 min, then all volatiles were removed under reduced pressure. The residue was purified by preparative HPLC (method 6). The combined product containing fractions were adjusted to basic pH using saturated aqueous sodium carbonate solution and concentrated to dryness. The resulting residue was suspended in ethyl acetate (50 mL) and filtered. The organic layer was washed with brine (5 mL), dried over anhydrous sodium sulfate, and the solvent was distilled off to give 31 mg (56% of th.) of the title compound.

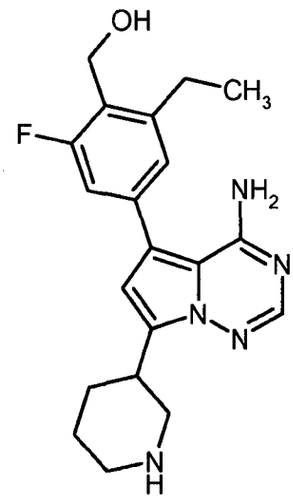
HPLC (method 9): R_t = 0.81 min;

LC-MS (method 10): R_t = 0.55 min; MS (ESIpos): *m/z* (%) = 356.3 (50) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 354.2 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.23 (t, 3H), 1.84-2.24 (m, 1H), 2.81 (q, 2H), 2.80-2.99 (m, 1H), 3.00-3.72 (m, 1H), 4.56 (d, 2H), 5.00 (t, 1H), 6.68 (s, 1H), 7.09 (d, 1H), 7.14 (m, 2H), 7.92 (s, 1H).

Example 38

rac-{4-[4-Amino-7-(piperidin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-5-yl]-2-ethyl-6-fluorophenyl}-methanol



Intermediate 67A (108 mg, 0.230 mmol) was dissolved in dichloromethane (5.2 mL) at 0°C and trifluoroacetic acid (1.4 mL) was added. The reaction mixture was stirred at 0°C for 40 min, then all volatiles were removed under reduced pressure. The residue was purified by preparative HPLC (method 6). The combined product containing fractions were adjusted to basic pH using saturated aqueous sodium carbonate solution and concentrated to dryness. The resulting residue was suspended in ethyl acetate (50 mL) and filtered. The organic layer was washed with brine (5 mL), dried over anhydrous sodium sulfate, and the solvent was distilled off to give 83 mg (85% of th.) of the title compound.

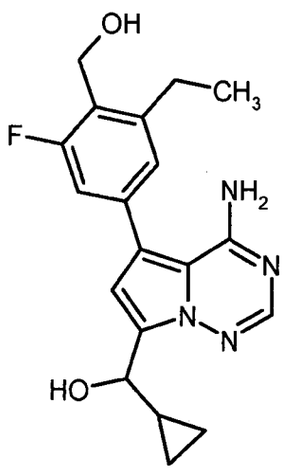
HPLC (method 9): R_t = 0.81 min;

LC-MS (method 10): R_t = 0.58 min; MS (ESIpos): *m/z* (%) = 370.3 (50) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 368.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.22 (t, 3H), 1.51-1.72 (m, 2H), 2.00-2.10 (m, 1H), 2.51-2.65 (m, 2H), 2.81 (q, 2H), 2.95-3.03 (m, 1H), 3.20-3.27 (m, 1H), 4.56 (d, 2H), 5.00 (t, 1H), 6.60 (s, 1H), 7.07 (d, 1H), 7.14 (m, 2H), 7.91 (s, 1H).

Example 39

rac-{4-Amino-5-[3-ethyl-5-fluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}(cyclopropyl)methanol



Intermediate 17A (83 mg, 0.29 mmol), Intermediate 58A (98 mg, 0.35 mmol) and tetrakis(triphenylphosphine)palladium(0) (17 mg, 0.015 mmol) were dissolved in a mixture of acetonitrile (2.3 mL) and 2 M aqueous sodium carbonate solution (0.53 mL) in a microwave reactor vial. After degassing for 5 min using argon, the reaction vessel was crimp-capped, and the mixture was heated to 150°C for 1 h in a single-mode microwave device. After cooling to room temperature, saturated aqueous sodium bicarbonate solution was added, and the mixture was extracted three times with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by preparative HPLC (method 5) to give the title compound. Yield: 63 mg (61% of th.).

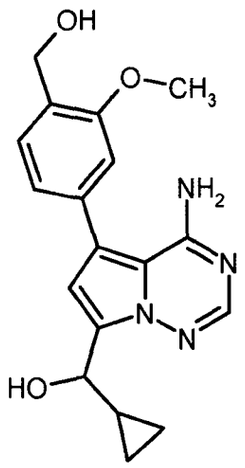
HPLC (method 9): R_t = 1.13 min;

LC-MS (method 10): R_t = 0.78 min; MS (ESIpos): *m/z* (%) = 357.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 355.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.39 (m, 3H), 0.48 (m, 1H), 1.23 (t, 3H), 1.35 (m, 1H), 2.81 (q, 2H), 4.56 (d, 2H), 4.68 (m, 1H), 5.01 (m, 1H), 5.21 (m, 1H), 6.76 (s, 1H), 7.09 (d, 1H), 7.14 (s, 1H), 7.90 (s, 1H).

Example 40

rac-{4-Amino-5-[4-(hydroxymethyl)-3-methoxyphenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}(cyclopropyl)methanol

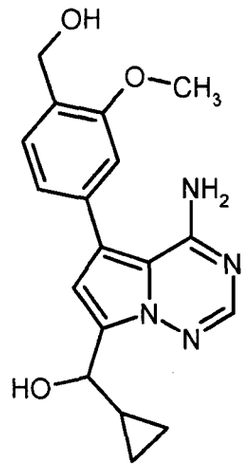


Intermediate 68A (130 mg, 0.353 mmol) was dissolved in tetrahydrofuran (6.9 mL) and cooled to 0°C. Lithium aluminium hydride solution (1 M in diethylether, 0.78 mL) was added dropwise, and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was then quenched with water and filtered. The filtrate was concentrated, and the residue was purified by preparative HPLC (method 8) to give the title compound. Yield: 63 mg (51% of th.).

LC-MS (method 10): R_t = 0.62 min; MS (ESIpos): *m/z* (%) = 341.2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 339.1 (100) $[M-H]^-$.

Example 41

ent-4-Amino-5-[4-(hydroxymethyl)-3-methoxyphenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}(cyclopropyl)methanol (*enantiomer 1*)



The title compound was obtained by separation of racemic Example 40 (63 mg) using preparative chiral HPLC [column: Daicel Chiralpak IC, 5 µm, 250 mm x 20 mm; eluent: *tert*-butyl methyl ether/methanol 85:15; flow rate: 15 mL/min; temperature: 40°C; UV detection: 220 nm]. Yield: 17 mg.

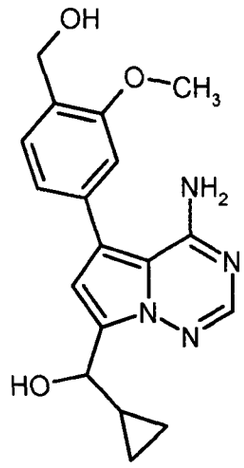
Analytical chiral HPLC [column: Daicel Chiralpak IC, 5 µm, 250 mm x 4.6 mm; eluent: *tert*-butyl methyl ether/methanol 85:15; flow rate: 1.0 mL/min; temperature: 40°C; UV detection: 220 nm]: R_t = 4.76 min, e.e. >99%.

LC-MS (method 10): R_t = 0.67 min; MS (ESIpos): *m/z* (%) = 341.2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 339.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.40 (m, 3H), 0.48 (m, 1H), 1.36 (m, 1H), 3.83 (s, 3H), 4.54 (d, 2H), 4.68 (m, 1H), 5.07 (t, 1H), 5.25 (d, 1H), 6.74 (s, 1H), 7.00 (s, 1H), 7.03 (d, 1H), 7.47 (d, 1H), 7.89 (s, 1H).

Example 42

ent-4-Amino-5-[4-(hydroxymethyl)-3-methoxyphenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}(cyclopropyl)methanol (*enantiomer 2*)



The title compound was obtained by separation of racemic Example 40 (63 mg) using preparative chiral HPLC [column: Daicel Chiralpak IC, 5 µm, 250 mm x 20 mm; eluent: *tert*-butyl methyl ether/methanol 85:15; flow rate: 15 mL/min; temperature: 40°C; UV detection: 220 nm]. Yield: 25 mg.

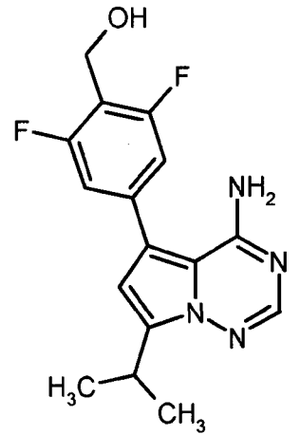
Analytical chiral HPLC [column: Daicel Chiralpak IC, 5 µm, 250 mm x 4.6 mm; eluent: *tert*-butyl methyl ether/methanol 85:15; flow rate: 1.0 mL/min; temperature: 40°C; UV detection: 220 nm]: R_t = 6.37 min, e.e. >99%.

LC-MS (method 10): R_t = 0.67 min; MS (ESIpos): *m/z* (%) = 341.2 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 339.1 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 0.40 (m, 3H), 0.48 (m, 1H), 1.36 (m, 1H), 3.83 (s, 3H), 4.54 (d, 2H), 4.68 (m, 1H), 5.07 (t, 1H), 5.25 (d, 1H), 6.74 (s, 1H), 7.00 (s, 1H), 7.03 (d, 1H), 7.47 (d, 1H), 7.89 (s, 1H).

Example 43

[4-(4-Amino-7-isopropylpyrrolo[2,1-f][1,2,4]triazin-5-yl)-2,6-difluorophenyl]methanol



Intermediate 71A (181 mg, 0.709 mmol), Intermediate 1A (239 mg, 0.887 mmol) and tetrakis(triphenylphosphine)palladium(0) (41 mg, 0.035 mmol) were dissolved in a mixture of *N,N*-dimethylformamide (12.5 mL) and 2 M aqueous sodium carbonate solution (1.42 mL) in a microwave reactor vial. The reaction vessel was crimp-capped, and the mixture was heated to 130°C for 2 h in a single-mode microwave device. After cooling to room temperature, the reaction mixture was filtered through Celite and concentrated. The resulting residue was dissolved in ethyl acetate (100 mL) and washed with water and with brine (10 mL each). The organic layer was dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (puriFlash, Interchim, cyclohexane/ethyl acetate 1:1 to 100% ethyl acetate gradient) followed by preparative HPLC (method 6). The product containing fractions were combined and adjusted to basic pH using saturated aqueous sodium carbonate solution. The acetonitrile solvent was removed, and the precipitated product was collected by filtration. Yield: 69 mg (31% of th.).

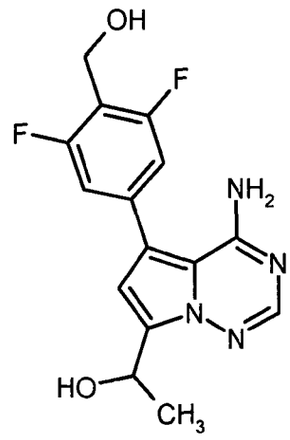
HPLC (method 9): R_t = 1.35 min;

LC-MS (method 10): R_t = 0.90 min; MS (ESIpos): *m/z* (%) = 319.0 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 317.0 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.30 (d, 6H), 3.42 (m, 1H), 4.54 (s, 2H), 5.26 (s, 1H), 6.65 (s, 1H), 7.14 (m, 2H), 7.94 (s, 1H).

Example 44

rac-1-{4-Amino-5-[3,5-difluoro-4-(hydroxymethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}ethanol



Intermediate 72A (230 mg, 0.743 mmol), Intermediate 2A (192 mg, 0.89 mmol) and tetrakis(triphenylphosphine)palladium(0) (86 mg, 0.074 mmol) were dissolved in a mixture of 1,4-dioxane (4.6 mL) and 2 M aqueous sodium carbonate solution (1.16 mL) in a microwave reactor vial. The reaction vessel was crimp-capped, and the mixture was heated to 140°C for 1 h in a single-mode microwave device. After cooling to room temperature, the reaction mixture was purified by preparative HPLC (method 8) to yield 48 mg of material which was further purified by preparative HPLC (method 9). Yield: 11 mg (4.6% of th.).

LC-MS (method 5): R_t = 0.89 min; MS (ESIpos): *m/z* (%) = 321.3 (100) $[M+H]^+$, MS (ESIneg): *m/z* (%) = 319.3 (100) $[M-H]^-$.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) = 1.47 (d, 3H), 4.54 (m, 2H), 5.16-5.39 (m, 2H), 6.74 (s, 1H), 6.88 (m, 1H), 7.14 (m, 2H), 7.94 (s, 1H).

B. Evaluation of Biological Activity

Abbreviations and Acronyms:

ATCC	American Type Culture Collection
ATP	adenosine triphosphate
Bq	Bequerel
BrdU	5-bromo-2-deoxyuridine
BSA	bovine serum albumin
CHO	chinese hamster ovary
cpm	counts per minute
Ct	cycle threshold
DMEM/F12	Dulbecco's modified Eagle's medium / Ham's F12 medium (1:1)
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DTT	dithiothreitol
EDTA	ethylenediamine-tetraacetic acid
ENGS MV	microvascular endothelial cell culture medium
FAM	carboxyfluorescein succinimidyl ester
FCS	fetal calf serum
hBMP9	human bone morphogenic factor 9
HEPES	4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid
HMVEC	human microvascular endothelial cell(s)
HPMC	hydroxypropyl methyl cellulose
HTRF	homogeneous time resolved fluorescence
HUVEC	human vascular endothelial cell(s)
[I]	inhibitor concentration
IC_{50}	concentration with 50% inhibitory effect
LDH	lactate dehydrogenase
mRNA	messenger ribonucleic acid
NADH	nicotinamide adenine dinucleotide
Nonidet P40	4-ethylphenoxy-poly(ethyleneglycol)ether (*n = 11*)
PBS	phosphate buffered saline
PE	polyethylene
PEG	polyethylene glycol
PK	pyruvate kinase

p.o.	*per os*
qPCR	quantitative polymerase chain reaction
RNA	ribonucleic acid
RTL buffer	RNeasy lysis buffer
SEQ ID NO	sequence identity number
SFM	serum free medium
TAMRA	carboxytetramethylrhodamine
Tris	2-amino-2-hydroxymethylpropane-1,3-diol
Triton X-100	4-*tert*-octylphenoxy-poly(ethyleneglycol)ether (*n = 10*)

Demonstration of the activity of the compounds of the present invention may be accomplished through *in vitro, ex vivo,* and *in vivo* assays that are well known in the art. For example, to demonstrate the activity of the compounds of the present invention, the following assays may be used.

B-1a. *In vitro* enzyme inhibition using scintillation of incorporated radio label (flashplate assay)

Test principle:

Test compounds diluted in DMSO are mixed with a suitable substrate / co-substrate (here: biotinylated α-casein and ^{33}P-ATP) in a corresponding assay buffer. Addition of the enzyme of interest (here: ALK1 kinase) starts the enzyme reaction. The enzyme-catalyzed incorporation of radio label into the substrate is measured via scintillation. Incorporated radio label is separated from free radio label via specific binding of the biotinylated substrate to strepavidin-coated microtiter plates (flashplates) and concomitant washing steps. The scintillation signal intensity (counts per minutes, cpm) is proportional to the enzyme activity. Enzyme inhibition results in a decreased signal intensity. IC_{50} values of the test compounds are determined by cpm-versus-[I] plots.

Reaction buffer:

Reaction buffer contains 50 mM Tris pH 8.0 (Sigma), 1 mM $MnCl_2$ (Sigma), 0.01% Nonidet P40 (Fluka), 0.5 x Complete EDTA-free protease inhibitors (Roche; contains a mixture of several protease inhibitors for the inhibition of serine and cysteine (but not metallo-) proteases; 1 tablet contains protease inhibitors sufficient for a 50 ml cell extract; the concentration used in this assay corresponds to 1 tablet in 100 ml).

Other buffers:

1.) Stop solution: Dulbecco's PBS (PAA, Pasching, Austria), 25 mM EDTA (Sigma), 25 µM ATP (Roche), 0.05% Triton X-100 (Sigma);

2.) Saturation buffer: Dulbecco's PBS (PAA, Pasching, Austria), 100 µM ATP (Roche), 0.2% Triton X-100 (Sigma);

3.) Wash buffer: Dulbecco's PBS (PAA, Pasching, Austria).

Enzyme solution:

ALK1 (Invitrogen, Paisley, United Kingdom) stock solution (35.7 ng/µl) is diluted to 4 ng/µl; final concentration in the reaction is 1 ng/µl.

Substrate solution:

Dephosphorylated α-casein (Sigma) is biotinylated according to the manufacturer's protocol (Pierce, Bonn, Germany) resulting in a stock solution of 61.6 µM. Briefly, EZ-Link® Sulfo-NHS-Biotin reagent (sulfosuccinimidyl-6-(biotinamido)hexanoate; Pierce, Bonn, Germany) is added in equal molarity to α-casein and incubated on ice for 2 h. Afterwards, the biotin reagent is removed by dialysis (2 x 2 h and overnight).

A 100 mM solution of cold (unlabelled) ATP (Roche) is diluted 1:100 before each test. For the substrate mix, α-casein is diluted to 2.22 µM resulting in a final concentration of 1 µM α-casein in the reaction. Additionally, cold ATP is added to give a 1.11 µM solution which results in a final concentration of 500 nM in the reaction.

Radioactive ATP solution:

The stock solution (9.25 MBq/25 µl of ^{33}P-ATP; Perkin Elmer, Rodgau, Germany) is diluted to 651.2 Bq/µl. This corresponds to a final concentration of 162.8 Bq/µl.

Compound solution:

Compounds are dissolved in 100% DMSO (10 mM stock solution) and diluted to 2 mM. Further dilutions are made stepwise 1:3.16 in DMSO.

Step-by-step protocol:

A volume of 9 µl substrate solution is provided into each well of a 384 well microtiter plate (Greiner Bio-One, Solingen, Germany). 1 µl compound solution and 5 µl of the radioactive ATP solution are

added. Enzyme reaction starts with addition of 5 µl of enzyme solution. The mixture is incubated for 60 minutes at room temperature and then stopped by addition of 10 µl stop solution. The 384 well microtiter flashplates (Perkin Elmer, Rodgau, Germany) are saturated with 50 µl saturation buffer per well for at least 60 minutes. Subsequently, a volume of 20 µl is discarded and replaced with 20 µl of the stopped ALK1 reaction mixture. Binding of biotinylated substrate to the flashplate is allowed for by overnight incubation at room temperature. Bound substrate is separated from unbound components through repeated washing steps (3 x 50 µl washing buffer per well). Finally, 50 µl washing buffer is added, and the scintillation signal (cpm) is measured in a suitable counter (Perkin Elmer, Rodgau, Germany).

IC_{50} values for individual compounds of the present invention are listed in Table 1 below:

Table 1

Example No.	**ALK1 IC_{50} [nM]**
1	2.0
2	2.8
3	4.0
4	1.0
5	1.3
6	40
7	2.0
8	4.4
9	5.7
10	8.0
11	1.9
12	5.9
13	4.0
14	5.3
15	60
16	2.6

Example No.	ALK1 IC_{50} [nM]
17	2.0
18	80
19	19
20	30
21	25
22	17
23	30
24	140
25	65
26	30
27	70
28	170
29	1.0
30	2.0
31	4.0
32	4.0
33	15
34	4.1
40	3.2
41	3.5
42	1.2
43	1.9
44	3.8

B-1b. ALK1 kinase assay (ProQinase protocol)

ALK1 (Invitrogen, Carlsbad, CA, USA) kinase activity was measured at ProQinase GmbH (Freiburg, Germany) in a radiometric assay using γ-^{33}P-ATP and casein (Sigma, St. Louis, MO, USA) as substrate in 96-well PerkinElmer FlashPlates™ (Boston, MA, USA). The compounds were tested at 10 concentrations in the range of 1 x 10^{-4} M to 3 x 10^{-9} M in a total volume of 50 µl with a final DMSO concentration of 1% each. The assay components were mixed in the order:

- 20 µl assay buffer (70 mM HEPES-NaOH, pH 7.5, 3 mM $MgCl_2$, 3 mM $MnCl_2$, 2 µM sodium orthovanadate, 1.2 mM DTT);
- 5 µl γ-^{33}P-ATP (1.0 µM in water, approx. 6 x 10^5 cpm per well);
- 5 µl test compound solution (in 10% DMSO);
- 10 µl substrate (200 µg/ml, 1.0 µg/50 µl final concentration) / enzyme (4 µg/ml, 20 ng/50 µl = 5.5 nM final concentration) solution (1:1 mixture).

The reaction mixtures were incubated at 30°C for 60 minutes and stopped by adding 50 µl 2% (v/v) phosphoric acid. The plates were aspirated and washed twice with 200 µl 0.9% (w/v) sodium chloride. Incorporation of $^{33}P_i$ was determined with a microplate scintillation counter (Microbeta, Wallac). All assays were performed using a BeckmanCoulter/SAGIAN™ Core System.

Median values obtained from unspecific substrate binding of labelled ATP were set as background level, while median values measured in the absence of any inhibitor were considered to reflect full activity of ALK1 kinase. The background activity (ba) was subtracted from the full activity (fa) value as well as from the values obtained from the test compound containing samples (test compound activity, tca). The residual activity in the latter was calculated as follows:

residual activity (%) = 100 x [(tca-ba)/(fa-ba)]

The residual activities for each concentration and the compound IC_{50} values were calculated using Quattro Workflow V3.1.0 (Quattro Research GmbH, Munich, Germany). The fitting model for the IC_{50} determinations was "Sigmoidal response (variable slope)" with parameters "top" fixed at 100% and "bottom" at 0%. The fitting method used was a least-squares fit.

Representative IC_{50} values from this assay are listed in Table 2 below:

Table 2

Example No.	ALK1 IC_{50} [nM]
7	6.7
11	3.0
28	124
35	6.9
36	21
37	< 3
38	4.0
39	5.7

B-2a. Smad7 target gene induction: HMVEC cell assay and TaqMan expression analysis

Activation of ALK1 receptors by BMP9 induces the Smad1/5 signalling pathway and enhances expression of target genes Smad6, Smad7 and Id-1. Induction of Smad7-mRNA in BMP9-stimulated endothelial cells was determined to monitor the cellular potency of ALK1 kinase inhibitors.

Human microvascular endothelial cells (HMVECadult, Cell Systems, St. Katharinen) were seeded in complete ENGS MV medium with all supplements (LifeLine Cell Technology) in 96 well plates with 10 000 cells per well. After 4 h incubation at 37°C and 7.5% CO_2 in a humidified incubator, medium was replaced with minimal medium (ENGS MV without supplements containing 0.02% FCS). After 16 h, test compounds or medium (controls) were added to the cultures, followed 30 min later by addition of hBMP9 (R&D Systems). Medium was removed 1 to 4 h later, plates were gently washed with phosphate-buffered saline, and cells were lysed with 150 µl per well of ice-cold RLT buffer (Qiagen).

Total cellular RNA was isolated with the Trizol® reagent protocol according to the manufacturer's specifications (Invitrogen, USA) and treated with DNAseI to remove genomic DNA contamination.

For relative quantitation of the mRNA distribution of hSmad7, total RNA from each sample was first reverse-transcribed using the ImProm-II Reverse Transcription System (Promega, USA) according to the manufacturer's protocol. The final volume was adjusted to 200 µl with water.

For relative quantitation of selected mRNA, the Applied Bioscience ABI 7900HT Sequence Detection System was used according to the manufacturer's specifications and protocols. PCR reactions were set up to quantitate hSmad7- and the housekeeping gene L32-mRNA. Forward and reverse primers and probes for hSmad7 and L32 were designed using the Applied Bioscience ABI Primer Express™ software and were synthesized by Eurogentec (Belgium). The hSmad7 forward primer sequence was: Primer 1 (SEQ ID NO 1). The hSmad7 reverse primer sequence was: Primer 2 (SEQ ID NO 2). Probe 1 (SEQ ID NO 3), labelled with FAM as the reporter dye and TAMRA as the quencher, was used as a probe for hSmad7. The L32 forward primer sequence was: Primer 3 (SEQ ID NO 4). The L32 reverse primer sequence was: Primer 4 (SEQ ID NO 5). Probe 2 (SEQ ID NO 6), labelled with FAM as the reporter dye and TAMRA as the quencher, was used as a probe for L32.

SEQ ID list:

		5' to 3'
SEQ ID NO 1	hSmad7 primer 1 (forward primer)	CCCTCCTTACTCCAGATACCC
SEQ ID NO 2	hSmad7 primer 2 (reverse primer)	GGAGGAAGGCACAGCATCT
SEQ ID NO 3	hSmad7 probe 1	TTTTCTCAAACCAACTGCAGACTGTCC
SEQ ID NO 4	L32 primer 3 (forward primer)	AAGTTCATCCGGCACCAGTC
SEQ ID NO 5	L32 primer 4 (reverse primer)	TGGCCCTTGAATCTTCTACGA
SEQ ID NO 6	L32 probe 2	CCCAGAGGCATTGACAACAGGG

The following reagents were prepared in a total of 20 µl added per well: 1 x qPCR-MasterMix (Eurogentec, Belgium) and hSmad7 forward and reverse primers each at 200 nM, 200 nM hSmad7 FAM/TAMRA-labelled probe 1 (SEQ ID NO 3), and 5 µl of template cDNA. Correspondingly, a second mix in a total of 20 µl was prepared using L32 FAM/TAMRA-labelled probe 2 (SEQ ID NO 6) and L32 forward and reverse primers added per well in parallel samples.

Thermal cycling parameters were 2 min at 50°C, followed by 10 min at 95°C, followed by 40 cycles of melting at 95°C for 15 sec and annealing/extending at 60°C for 1 min.

Calculation of relative expression:

The Ct (cycle threshold) values were calculated from the turning point of PCR product quantity curves by the ΔΔCt method (delta-delta Ct):

$\Delta Ct = Ct_{hSmad7} - Ct_{L32}$; relative expression = $2^{(15-\Delta Ct)}$.

IC_{50} values of test compounds were calculated on basis of relative Smad7 expressions at different compound concentrations. Representative values are listed in Table 3 below:

Table 3

Example No.	hSmad7 IC_{50} [nM]
1	100
2	125
3	180
5	150
7	130
8	60
11	90
17	120
20	4400
21	6000
22	800

B-2b. Smad7 target gene induction: HUVEC cell assay and TaqMan expression analysis

The *in vitro* potency of ALK1 inhibitors was tested in a cell-based assay. Bone morphogenetic protein 9 (BMP9) induces Smad7 mRNA expression in human vascular endothelial cells (HUVEC) via activation of ALK1.

1.5×10^4 passage 2 HUVECs (Lonza, Basel, Switzerland) per well were seeded in a 96-well plate in EBM-2 medium containing EGM-2 additives and growth factors (Lonza, CC-3156 and CC-4176). After 4 h, the medium was changed to EBM-2 with 0.2% fetal calf serum (FCS) and the cells were

starved for 20 h in a humidified incubator at 37°C, 5% CO_2. Test compounds were added at 11 different concentrations between 0 and 10 000 nM one hour prior to stimulation of the cells for 3 h with recombinant human BMP9 protein at 1 ng/ml (dissolved in 4 mM hydrochloric acid, 0.1% BSA at 10 µg/ml; R&D Systems, Minneapolis, MN, USA, 3209BP). Medium was removed, and the cells were lysed in 100 µl RLT buffer (Qiagen, Hilden, Germany). RNA was isolated using the Qiagen RNeasy 96 Kit (order-No. 74182) according to manufacturer's instructions and eluted from the columns with 65 µl RNAse-free water. Reverse transcription for quantitative RT-PCR was carried out with the Omniscript Kit (Qiagen, 205113) in RNAse-free 96-well round-bottom plates. Per well, 6.8 µl of a reaction master mix containing 2 µl 10x RT-buffer, 2 µl dNTPs (5 mM each), 1.6 µl random primer N6 (125 µM), 0.25 µl Rnase Out (40 U/µl) and 1 µl Omniscript Reverse Transcriptase were added. After addition of 13.2 µl of the RNA/water mixture, plate contents were mixed, incubated for 1 h at 37°C and the total volume adjusted to 100 µl in each well by addition of 80 µl RNAse-free water.

The quantification of human Smad7 mRNA was carried out on a TaqMan using the Eurogentec qPCR Mastermix Plus (RT-QP2X-03-075+; Cologne, Germany) and employing human L32 as housekeeping reference mRNA. Per qPCR reaction, 2.8 µl primer mix, 10 µl master mix, 2.2 µl water and 5 µl cDNA were added. Thermal cycling parameters were 2 min at 50°C, followed by 10 min at 95°C, followed by 40 cycles of melting at 95°C for 15 sec and annealing/extending at 60°C for 1 min.

Smad7 mRNA levels induced by 1 ng/ml BMP9 without the addition of any inhibitor were set at 100% induction, and % inhibition was calculated for each test compound with this value. For each test compound, every value was determined in quadruplicate. The IC_{50} values were determined using Microsoft Excel. The fitting method used was a weighted, unconstrained ML-fit.

Representative IC_{50} values from this assay are listed in Table 4 below:

Table 4

Example No.	**hSmad7 IC_{50} [nM]**
1	94
2	160
3	120
5	290

Example No.	hSmad7 IC_{50} [nM]
7	140
11	180
17	290
20	5900
21	790
22	3100
30	51
37	330
39	500
40	62
41	77
42	6.6
43	27

B-3. Systemic efficacy in the laser-induced choroidal neovascularization (CNV) model

The aim of this study was to determine whether once daily systemic administration (i.p.) of a test compound resulted in a decrease of vascular leakage and/or choroidal neovascularization in a rat model of laser-induced choroidal neovascularisation.

For this purpose, 16 pigmented Brown-Norway rats with no visible sign of ocular defects were selected and randomly divided into two groups of eight animals each. On day 0, the animals were anaesthetized by an intraperitoneal injection (15 mg/kg xylazine and 80 mg/kg ketamine). After instillation of one drop of 0.5% tropicamide to dilate the pupils, choroidal neovascularisation was induced by executing six 75 µm-sized choroidal burns around the optic disc of the right eyes using a 532 nm argon laser photocoagulation at 150 mW for 100 ms. The test compound and vehicle control (10% ethanol, 90% PEG 400) were administered once daily by intraperitoneal (i.p.) injections with dosing of the test compound at 50 mg/kg on days 0 and 1, and then continuing with 20 mg/kg from day 2 to day 23. The body weight of all animals was recorded before the start and once daily during the study.

An angiography was performed on day 21 using Heidelberg's Retinal Angiograph (HRA). After anaesthesia and pupillary dilation, 10% sodium fluorescein dye was injected subcutaneously, and images were recorded 10 min after dye injection. The vascular leakage of the fluorescein on the angiograms was evaluated by two examiners in a masked fashion and scored with 0 (no leakage) to 3 (strongly stained).

After euthanasia on day 23, the eyes were harvested and fixed in 4% paraformaldehyde solution for 1 hour at room temperature. After washing, the retina was carefully peeled, and the sclera-choroid was flat-mounted and incubated after blocking with a FITC-isolectine B4 antibody. The flat-mounted preparations were examined under a fluorescence microscope (Apotom) at 488 nm excitation wavelength. The volume of choroidal neovascularisation was scored by morphometric analysis of images using Axiovision 4.6 software.

For Example 11 as a representative of the compounds of the present invention, the following results were obtained in this model:

	vascular leakage [angiography score]	**choroidal neovascularisation lesion volume** [μm^3 x 100 000]
Example 11	0.68 ± 0.35	3.48 ± 0.40
vehicle control	1.7 ± 0.32	5.83 ± 0.55

B-4. <u>Topical efficacy in the laser-induced choroidal neovascularization (CNV) model</u>

The aim of this study was to determine whether twice daily topical administration (eye drops) of a test compound resulted in a decrease of vascular leakage and/or choroidal neovascularization in a rat model of laser-induced choroidal neovascularisation.

For this purpose, 65 pigmented Brown-Norway rats with no visible sign of ocular defects were selected and randomly assigned to six different groups (for n-numbers, see table below). On day 0, the animals were anaesthetized by an intraperitoneal injection (15 mg/kg xylazine and 80 mg/kg ketamine). After instillation of one drop of 0.5% tropicamide to dilate the pupils, choroidal neovascularisation was induced by burning six holes into the retina (disruption of Bruch's membrane) of one eye per animal using a 532 nm argon laser (lesion size: 50 µm; laser intensity: 150 mW; stimulus duration: 100 ms). Test compounds and vehicle controls were topically administered twice daily by instilling respective eye drops into the affected eye. The test compounds were dosed as

follows: 10 µl of an eye drop formulation containing 20 mg/ml of the respective test compound suspended either in 100% liquid paraffin or in an aqueous vehicle (HPMC 15 cP 3.5%, polysorbate 80 0.5%, NaCl 0.9% in water) were applied to the affected eye twice daily at a 10 to 14 hour interval during the complete observation period of 23 days. Control animals received the respective vehicle (100% liquid paraffin or aqueous vehicle) topically twice daily. The body weight of all animals was recorded before the start and once daily during the study.

An angiography was performed on day 21 using a fluorescence fundus camera (Kowe). Here, after anaesthesia and pupillary dilation, 10% sodium fluorescein dye was injected subcutaneously, and images were recorded 2 and 10 min after dye injection. The vascular leakage of the fluorescein on the angiograms was evaluated by three different examiners who were blinded for group allocation (test compound versus vehicle), and scored with 0 (no leakage) to 3 (strongly stained).

On day 23, animals were sacrificed, and eyes were harvested and fixed in 4% paraformaldehyde solution for 1 hour at room temperature. After washing, the retina was carefully peeled, washed, blocked and stained with a FITC-isolectine B4 antibody in order to visualize the vasculature. Then, the sclera-choroids were flat-mounted and examined under a fluorescence microscope (Keyence Biozero) at 488 nm excitation wavelength. The area (in μm^2) of choroidal neovascularization was measured using ImageTool software.

For Examples 7 and 11 as representative compounds of the present invention, the following results were obtained in this model:

	vascular leakage [HRA score]	**choroidal neovascularisation lesion size** [μm^2 x 10 000]
Example 7 (aqueous vehicle; n = 9)	1.49 ± 0.24	6.14 ± 1.60
Example 7 (paraffin vehicle; n = 8)	1.52 ± 0.21	6.21 ± 0.99
Example 11 (aqueous vehicle; n = 7)	1.66 ± 0.29	5.50 ± 1.38
Example 11 (paraffin vehicle; n = 12)	1.41 ± 0.29	6.45 ± 1.63
aqueous vehicle control (n = 12)	1.87 ± 0.27	7.84 ± 1.09

	vascular leakage [HRA score]	**choroidal neovascularisation lesion size** [μm^2 x 10 000]
paraffin vehicle control (n = 17)	1.97 ± 0.19	7.00 ± 1.00

Although the invention has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of the invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The claims are intended to be construed to include all such embodiments and equivalent variations.

C. Examples relating to Pharmaceutical Compositions

Pharmaceutical compositions according to the present invention can be illustrated as follows:

Sterile i.v. solution:

A 5 mg/mL solution of the desired compound of the invention can be made using sterile, injectable water, and the pH is adjusted if necessary. The solution is diluted for administration to 1-2 mg/mL with sterile 5% dextrose and is administered as an i.v. infusion over about 60 minutes.

Lyophilized powder for i.v. administration:

A sterile preparation can be prepared with (*i*) 100–1000 mg of the desired compound of the invention as a lyophilized powder, (*ii*) 32–327 mg/mL sodium citrate, and (*iii*) 300–3000 mg Dextran 40. The formulation is reconstituted with sterile, injectable saline or 5% dextrose to a concentration of 10 to 20 mg/mL, which is further diluted with saline or 5% dextrose to 0.2 to 0.4 mg/mL, and is administered either as i.v. bolus or by i.v. infusion over 15–60 minutes.

Intramuscular suspension:

The following solution or suspension can be prepared for intramuscular injection:

50 mg/mL of the desired, water-insoluble compound of the invention; 5 mg/mL sodium carboxymethylcellulose; 4 mg/mL Tween 80; 9 mg/mL sodium chloride; 9 mg/mL benzyl alcohol.

Hard shell capsules:

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 mg of the desired, powdered compound of the invention, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate.

Soft gelatin capsules:

A mixture of the desired compound of the invention in a digestible oil, such as soybean oil, cottonseed oil or olive oil, is prepared and injected by means of a positive displacement pump into molten gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules are washed and dried. The desired compound of the invention can be dissolved in a mixture of polyethylene glycol, glycerin and sorbitol to prepare a water-miscible medicine mix.

Tablets:

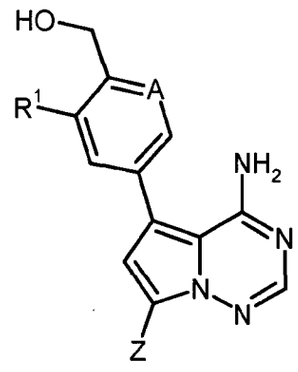
A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 mg of the desired compound of the invention, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8 mg of lactose. Appropriate aqueous and non-aqueous coatings may be applied to increase palatability, improve elegance and stability, or delay absorption.

Solution or suspension for topical application to the eye (eye drops):

A sterile formulation can be prepared with 100 mg of the desired compound of the invention as a lyophilized powder reconstituted in 5 mL of sterile saline. As preservative, benzalkonium chloride, thimerosal, phenylmercuric nitrate, or the like may be used in a range of about 0.001% to 1% by weight.

We claim:

1. A compound of formula (I)



(I),

wherein

A is N or C-R^2, wherein

R^2 represents hydrogen, fluoro or chloro,

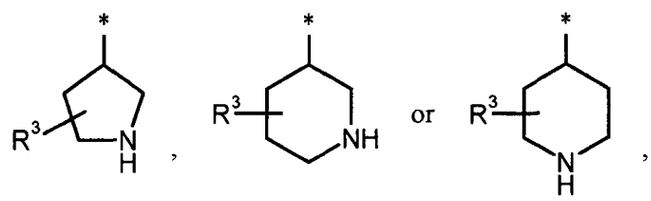
R^1 represents hydrogen, fluoro, chloro, methyl, ethyl or methoxy,

and

Z represents (C_1-C_4)-alkyl or (C_3-C_6)-cycloalkyl each of which may be substituted with hydroxy,

or

Z represents a heterocyclic group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

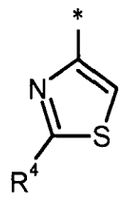
and

R^3 represents hydrogen or hydroxy,

with the proviso that when R^3 is hydroxy, this hydroxy is not attached to a ring carbon atom located adjacent to the ring nitrogen atom,

or

Z represents a thiazole group of the formula



,

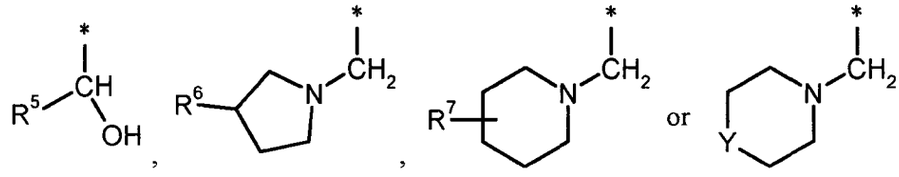
wherein * indicates the point of attachment to the pyrrolotriazine moiety,

and

R^4 represents hydrogen, methyl, ethyl, amino or aminomethyl,

or

Z represents a group of the formula



,

wherein * indicates the point of attachment to the pyrrolotriazine moiety,

R^5 represents (C_3-C_6)-cycloalkyl, oxetanyl, tetrahydrofuranyl or tetrahydropyranyl,

R^6 represents hydrogen or hydroxy,

R^7 represents hydrogen or hydroxy,

with the proviso that when R^7 is hydroxy, this hydroxy is not attached to a ring carbon atom located adjacent to the ring nitrogen atom,

and

Y is O, NH or NCH_3,

or a pharmaceutically acceptable salt, hydrate and/or solvate thereof.

2. The compound of formula (I) according to Claim 1, wherein

A is C-R^2, wherein

R^2 represents hydrogen or fluoro,

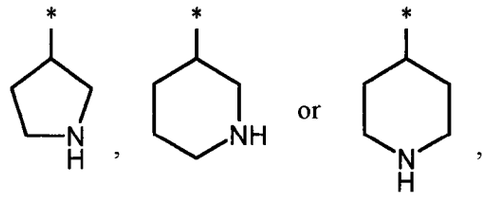
R^1 represents hydrogen, fluoro, chloro, methyl, ethyl or methoxy,

and

Z represents *n*-propyl, *n*-butyl or cyclohexyl each of which may be substituted with hydroxy,

or

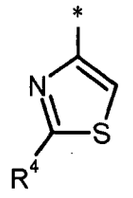
Z represents a heterocyclic group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

or

Z represents a thiazole group of the formula



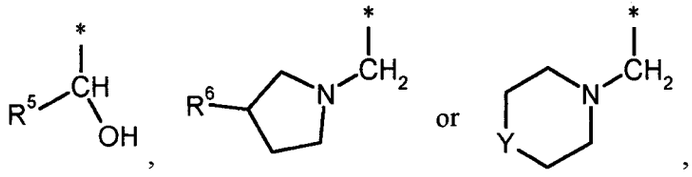
wherein * indicates the point of attachment to the pyrrolotriazine moiety,

and

R^4 represents methyl, ethyl, amino or aminomethyl,

or

Z represents a group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

R^5 represents cyclopropyl or tetrahydropyran-4-yl,

R^6 represents hydroxy,

and

Y is O,

or a pharmaceutically acceptable salt, hydrate and/or solvate thereof.

3. The compound of formula (I) according to Claim 1 or 2, wherein

A is C-R^2, wherein

R^2 represents hydrogen or fluoro,

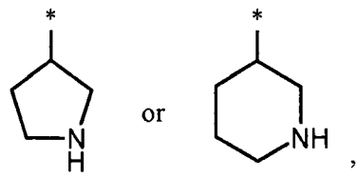
R^1 represents hydrogen, fluoro, methyl, ethyl or methoxy,

and

Z represents 4-hydroxybutyl or 4-hydroxycyclohexyl,

or

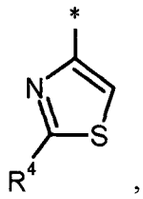
Z represents a heterocyclic group of the formula



wherein * indicates the point of attachment to the pyrrolotriazine moiety,

or

Z represents a thiazole group of the formula



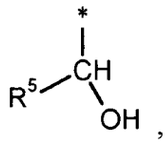
wherein * indicates the point of attachment to the pyrrolotriazine moiety,

and

R^4 represents methyl, ethyl, amino or aminomethyl,

or

Z represents a group of the formula



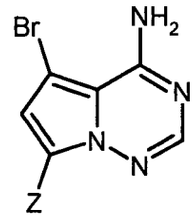
wherein * indicates the point of attachment to the pyrrolotriazine moiety,

and

R^5 represents cyclopropyl,

or a pharmaceutically acceptable salt, hydrate and/or solvate thereof.

4. A process for preparing a compound of formula (I) as defined in Claims 1 to 3, characterized in that a bromopyrrolotriazine of formula (II)

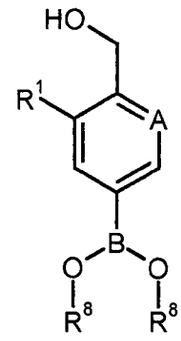


(II),

wherein Z has the meaning indicated in Claim 1 to 3,

is either

[A] coupled with an arylboronic acid or ester of formula (III)



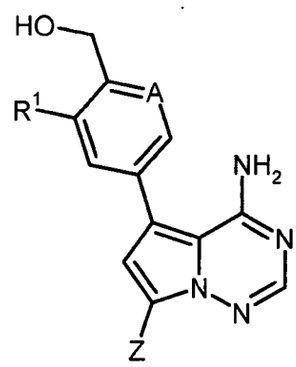
(III),

wherein A and R^1 have the meanings indicated in Claim 1 to 3,

and

R^8 represents hydrogen or (C_1-C_4)-alkyl, or both R^8 residues are linked together to form a -$(CH_2)_2$-, -$C(CH_3)_2$-$C(CH_3)_2$-, -$(CH_2)_3$- or -CH_2-$C(CH_3)_2$-CH_2- bridge,

in the presence of a suitable palladium catalyst and a base to yield the target compound of formula (I)

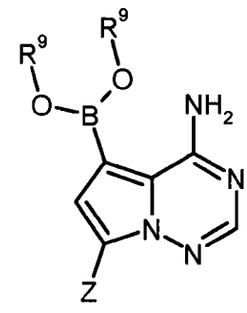


(I),

wherein A, Z and R^1 have the meanings indicated in Claim 1 to 3,

or

[B] first converted into the corresponding boronic acid or ester derivative of formula (IV)



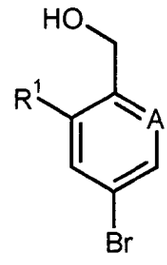
(IV),

wherein Z has the meaning indicated in Claim 1 to 3,

and

R^9 represents hydrogen or $(C_1$-$C_4)$-alkyl, or both R^9 residues are linked together to form a $-(CH_2)_2-$, $-C(CH_3)_2-C(CH_3)_2-$, $-(CH_2)_3-$ or $-CH_2-C(CH_3)_2-CH_2-$ bridge,

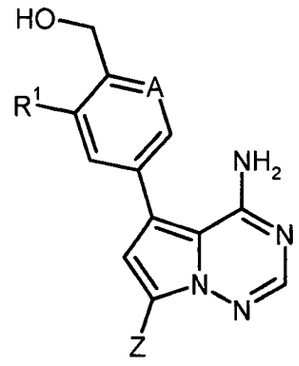
which is then coupled with an aryl bromide of formula (V)



(V),

wherein A and R^1 have the meanings indicated in Claim 1 to 3,

in the presence of a suitable palladium catalyst and a base to also give the target compound of formula (I)



(I),

wherein A, Z and R^1 have the meanings indicated in Claim 1 to 3,

optionally followed, where appropriate, by (*i*) separating the compounds of formula (I) into their respective enantiomers and/or diastereomers, and/or (*ii*) converting the compounds of formula (I) into their respective hydrates, solvates, salts and/or hydrates or solvates of the salts by treatment with the corresponding solvents and/or acids.

5. Compound as defined in any of Claims 1 to 3 for the treatment or prevention of diseases.

6. Use of a compound as defined in any of Claims 1 to 3 for the manufacture of a pharmaceutical composition for the treatment or prevention of age-related macular degeneration (AMD), choroidal neovascularisation (CNV), diabetic retinopathy and diabetic macula edema (DME).

7. A pharmaceutical composition comprising a compound as defined in any of Claims 1 to 3, or a pharmaceutically acceptable salt, hydrate and/or solvate thereof, and one or more pharmaceutically acceptable excipients.

8. The pharmaceutical composition of Claim 7 further comprising one or more additional therapeutic agents.

9. The pharmaceutical composition as defined in Claim 7 or 8 for the treatment or prevention of age-related macular degeneration (AMD), choroidal neovascularisation (CNV), diabetic retinopathy and diabetic macula edema (DME).

10. A method of treating or preventing age-related macular degeneration (AMD), choroidal neovascularisation (CNV), diabetic retinopathy and diabetic macula edema (DME) in a mammal, comprising administering to a mammal in need thereof a therapeutically effective amount of one or more compounds as defined in any of Claims 1 to 3, or of a pharmaceutical composition as defined in any of Claims 7 to 9.

Hydroxymethylaryl-substituted pyrrolotriazines and uses thereof

Abstract

This invention relates to novel 5-[(hydroxymethyl)aryl]-substituted pyrrolo[2,1-f][1,2,4]triazin-4-amines, to processes for the preparation of such compounds, to pharmaceutical compositions containing such compounds, and to the use of such compounds or compositions for treating angiogenesis-related disorders, in particular angiogenesis-related ocular disorders.

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PATENT COOPERATION TREATY PCT/EP2012/062366

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION, OBTENTION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

Bayer Intellectual Property GmbH
Creative Campus Monheim, Geb. 4865
Alfred-Nobel-Str. 10
40789 Monheim
ALLEMAGNE

Date of mailing *(day/month/year)* 17 September 2012 (17.09.2012)	
Applicant's or agent's file reference BHC111016-WO	**IMPORTANT NOTIFICATION**
International application No. PCT/EP2012/062366	International filing date *(day/month/year)* 26 June 2012 (26.06.2012)
International publication date *(day/month/year)* **Not yet published**	Priority date *(day/month/year)* 01 July 2011 (01.07.2011)
Applicant Bayer Intellectual Property GmbH et al	

The applicant is hereby notified of the date of receipt (or of obtaining by the International Bureau) of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to the date of receipt, **the priority document concerned was submitted or transmitted to or obtained by the International Bureau in compliance with Rule 17.1(a), (b) or (b-*bis*)**. This Form replaces any previously issued notification concerning submission, transmittal or obtaining of priority documents.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
01 July 2011 (01.07.2011)	61/503,840	US	13 September 2012 (13.09.2012)
27 March 2012 (27.03.2012)	12161547.0	EP	23 July 2012 (23.07.2012)

The letters "NR" denote a priority document which, on the date of mailing of this Form, had not yet been received or obtained by the International Bureau in compliance with Rule 17.1(a), (b) or (b-*bis*). Where the applicant has failed to either submit, request to prepare and transmit, or to request the International Bureau to obtain the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

An asterisk "*" next to a date of receipt, denotes a priority document submitted or transmitted to or obtained by the International Bureau but not in compliance with Rule 17.1(a), (b) or (b-*bis*) (the priority document was received after the time limit prescribed in Rule 17.1(a); the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b) or the request to the International Bureau to obtain the priority document was made after the applicable time limit under Rule 17.1(b-*bis*)). Even though the priority document was not furnished in compliance with Rule 17.1(a), (b) or (b-*bis*), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

The International Bureau of WIPO
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1211 Geneva 20, Switzerland

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Agnès Wittmann-Regis
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Telephone No. +41 22 338 74 06

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PATENT COOPERATION TREATY PCT/EP2012/062366

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

BAYER INTELLECTUAL PROPERTY GMBH
Creative Campus Monheim, Geb. 4865
Alfred-Nobel-Str. 10
40789 Monheim
ALLEMAGNE

Date of mailing *(day/month/year)*
24 October 2013 (24.10.2013)

Applicant's or agent's file reference
BHC111016-WO

IMPORTANT NOTIFICATION

International application No.
PCT/EP2012/062366

International filing date *(day/month/year)*
26 June 2012 (26.06.2012)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
SCHLANGE, Thomas
Rietmacherweg 1
42781 Haan
Germany

State of Nationality: DE
State of Residence: DE
Telephone No.:
Facsimile No.:
E-mail address:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

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Dinkelweg 14
42781 Haan
Germany

State of Nationality: DE
State of Residence: DE
Telephone No.:
Facsimile No.:
E-mail address:
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

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1211 Geneva 20, Switzerland

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PATENT COOPERATION TREATY PCT/EP2012/062366

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26 June 2012 (26.06.2012)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
SCHALL, Andreas
Straßburger Str. 15
42107 Wuppertal
Germany

State of Nationality: DE
State of Residence: DE
Telephone No.:
Facsimile No.:
E-mail address:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
SCHALL, Andreas
Wettinerstr. 4a
42287 Wuppertal
Germany

State of Nationality: DE
State of Residence: DE
Telephone No.:
Facsimile No.:
E-mail address:
☐ Notifications by e-mail authorized

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☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
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1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 89 70

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

Industria y Comercio
SUPERINTENDENCIA

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Bogotá D.C., Diciembre 05 de 2013 - 14:34:20

RECIBIDO DE : POSSE HERRERA & RUIZ S.A. NI 830.022.196

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
RECIBO DE CA	999999999	125556	05/12/2013		502.400.00

*** Conceptos Pagados ***

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

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

Responsable: _____
-******-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 13-285797- -00000-0000
Fecha: 2013-12-05 14:44:06 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: ~~598~~ 599

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 13-285797- -00000-0000

Fecha: 2013-12-05 14:44:06 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: ~~598~~ 599

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 ☐