SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 14-123802- -00000-0000
Fecha: 2014-06-09 14:44:51 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 773

POSSE HERRERA RUIZ

1000 2013 CHAMBERS
-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: BENZOTIENILO-PIRROLOTRIAZINAS DISUSTITUIDAS Y SUS USOS

51. CLASIFICACION INTERNACIONAL:

C07D 487/04 (2006.01) A61K 31/53 (2006.01)
A61P 35/00 (2006.01)

71. SOLICITANTE:

1. BAYER INTELLECTUAL PROPERTY GMBH
2. BAYER PHARMA AKTIENGESELLSCHAFT

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22. BOGOTÁ D.C., JUNIO 09 DE 2014

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO — radicación
No. 14-123802- -00000-0000
Fecha: 2014-06-09 14:44:51 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 772 773

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/EP2012/074977**	**Fecha** 10/12/2012
	Publicación Internacional No.	**WO 2013/087578A1**	**Fecha** 20/06/2013

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

BENZOTIENILO-PIRROLOTRIAZINAS DISUSTITUIDAS Y SUS USOS

4 CLASIFICACIÓN INTERNACIONAL (CIP)

C07D 487/04 (2006.01) ***A61K 31/53*** (2006.01) ***A61P 35/00*** (2006.01)

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

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3. COLLIN	**3. Marie-Pierre**	
4. HÜBSCH	**4. Walter**	
5. LOBELL	**5. Mario**	
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9. VÖHRINGER	**9. Verena**	

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	3. ALEMANIA		3. Wuppertal	3. Katernberger Schulweg 52, 42113
	4. ALEMANIA		4. Wuppertal	4. Wildsteig 22, 42113
	5. ALEMANIA		5. Wuppertal	5. Am Eigenbach 16, 42113
	6. ALEMANIA		6. Wuppertal	6. Falkenberg 159, 42113
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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
CAMARGO WILLIAMSON	**HELENA**	**C.C 35.455.268 de Bogota T.P 76985**

DIRECCIÓN	**CARRERA 7 Nº 71 – 52, TORRE A, PISO 5**	No. TELÉFONO	**3257300**
CIUDAD	**BOGOTÁ**	CORREO ELECTRÓNICO	**helena.camargo@phrlegal.com**
PAÍS	**COLOMBIA**	No. RADICACIÓN DE PROTOCOLO DE PODER GENERAL	**PROT. PODER 13-102341** **PROT. PODER 14-044503**

10 **DECLARACIONES DE PRIORIDAD** ☒ SI ☐ NO

(33) PAÍS DE ORIGEN	CÓDIGO PAÍS	(31) NÚMERO	(32) FECHA (AAAA/MM/DD)
1. **COMUNIDAD EUROPEA**		**11193841.1**	**15/12/2011**

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 ☐

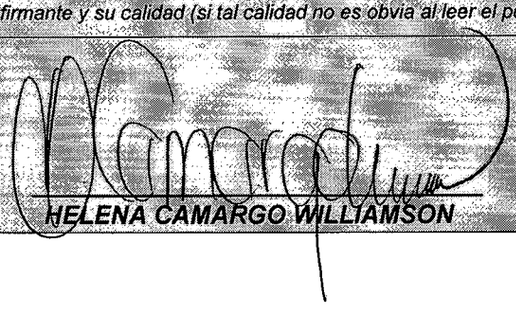
Debe aportar los documentos que se indican en el numeral 17 de anexos

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)



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, PROT. PODER 13-102341
   PROT. PODER 14-044503
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.

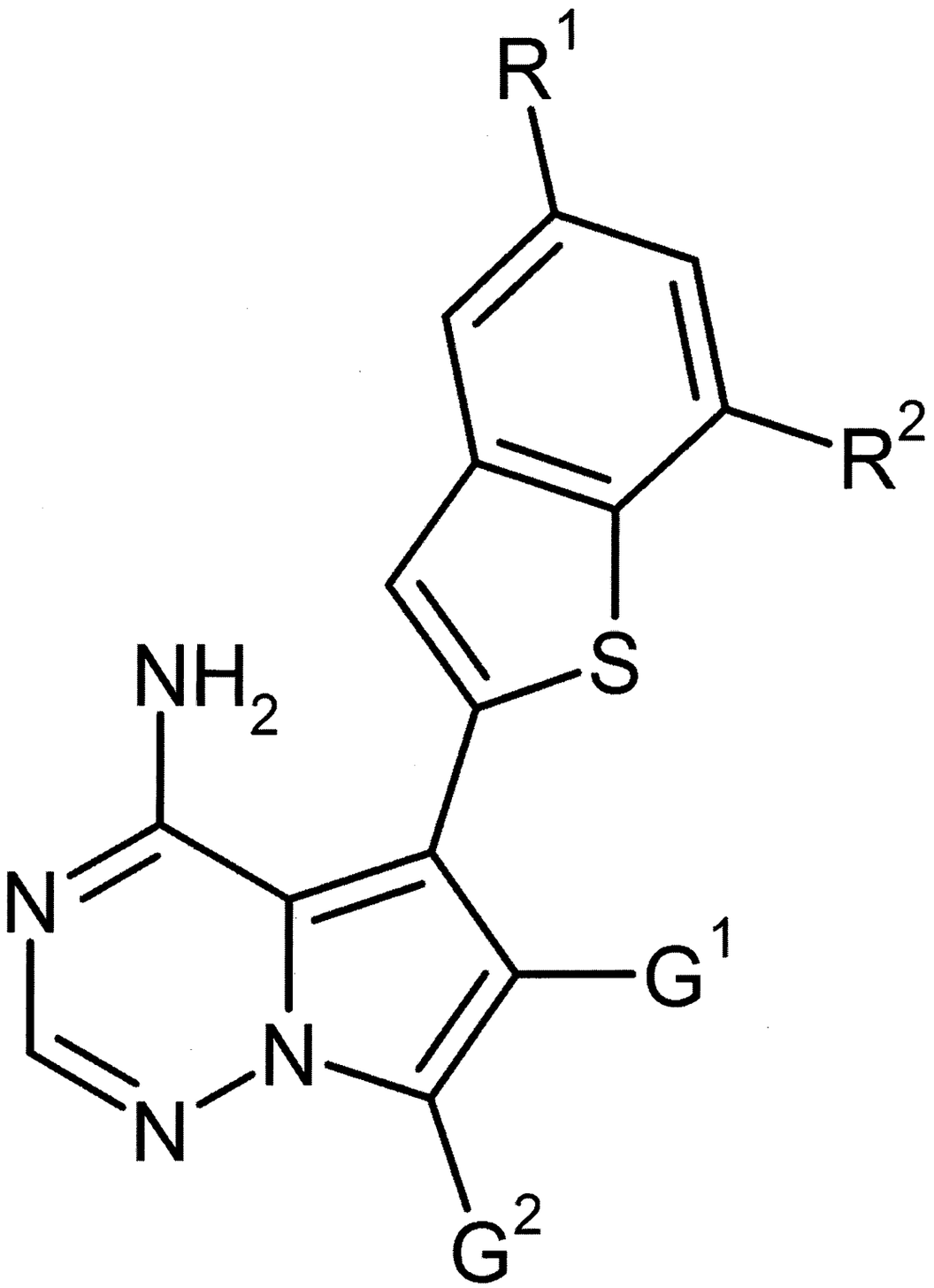
Universidades públicas o privadas

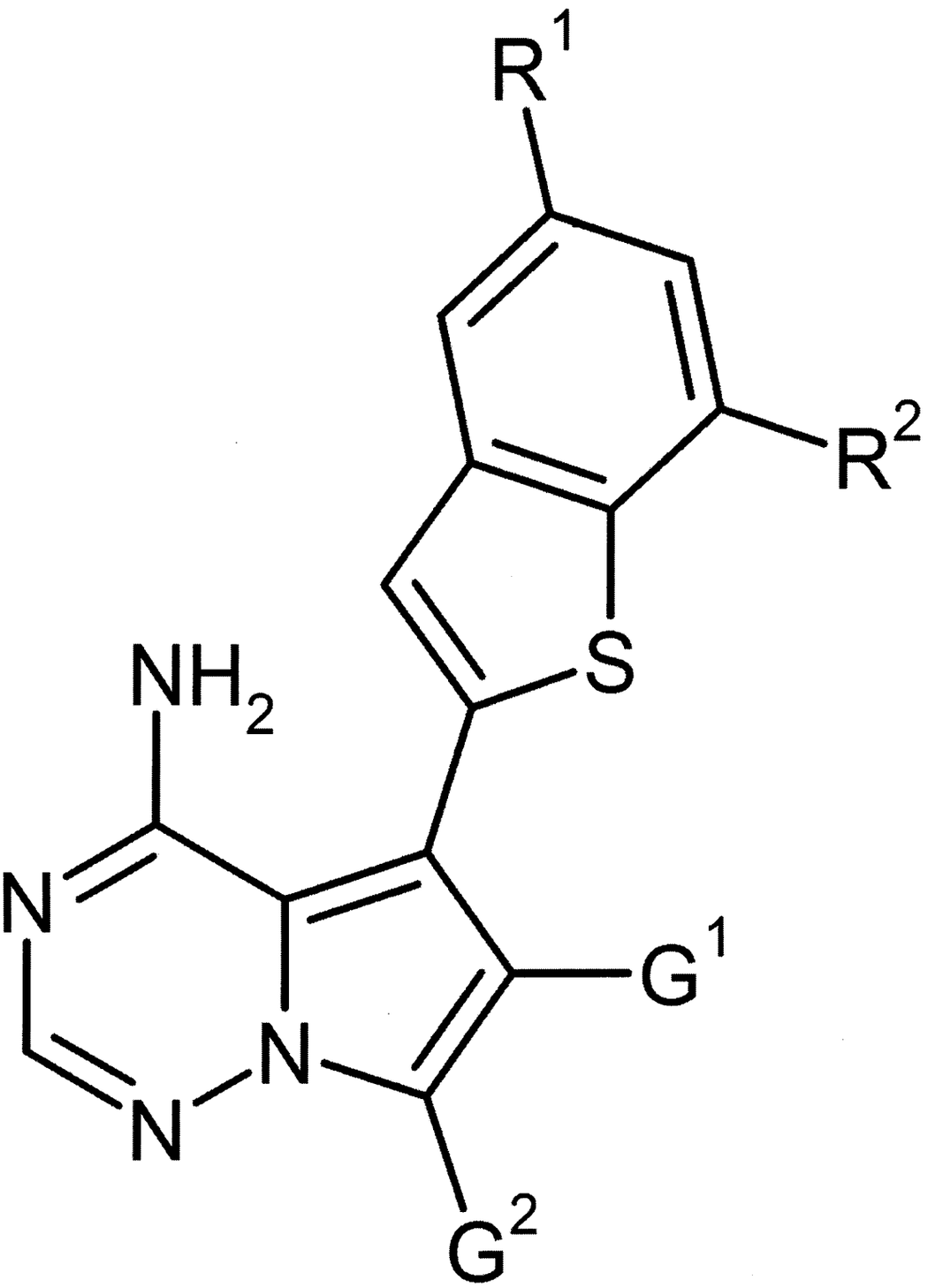
☐ Copia acto de reconocimiento institucional emitido por el Ministerio de Educación

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.


R1
R2
S
NH2
N
N
N
G1
G2


R1
R2
S
NH2
N
N
N
G1
G2

Benzotienilo-pirrolotriazinas disustituidas y sus usos

La presente invención se refiere a derivados de 5-(1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-4-amina novedosos que tienen actividades inhibidoras de la proteína tirosina quinasa, a procesos para la preparación de estos compuestos, a composiciones farmacéuticas que contienen estos compuestos, y al uso de estos compuestos o composiciones para tratar trastornos proliferativos, en particular, cáncer y enfermedades tumorales.

El cáncer es la mayor causa de muerte a nivel mundial y representó 7,6 millones de muertes (alrededor del 13% de todas las muertes) en 2008. Se prevé que las muertes por cáncer continuarán elevándose en el mundo hasta más de 11 millones en 2030 (fuente de la OMS, Hoja informativa Nº. 297, febrero 2011).

Existen muchas formas en las que puede aparecer el cáncer, lo cual es una de las razones por las que su terapia es difícil. Una de las formas en que se puede producir la transformación de las células es después de una alteración genética. La terminación del proyecto del genoma humano mostró inestabilidad genómica y heterogeneidad de los genes del cáncer humano. Las recientes estrategias para identificar estas alteraciones genéticas aceleraron el proceso para descubrir el gen cancerígeno. Por ejemplo, la anormalidad genética puede conducir a la sobreexpresión de proteínas, y por lo tanto a una activación no fisiológica de estas proteínas. Una familia de proteínas de la cual deriva un número de oncoproteínas son las tirosina quinasas y en particular las tirosina quinasas receptoras (RTKs). En las últimas dos décadas, numerosas vías de investigación han demostrado la importancia de la señalización mediada por RTK en el desarrollo celular adverso que conduce al cáncer. En los últimos años, se han obtenido resultados promisorios en la clínica con inhibidores de pequeñas moléculas selectivos de las tirosina quinasas como una nueva clase de agentes anti-tumorales [Swinney and Anthony, *Nature Rev. Drug Disc.* 10 (7), 507-519 (2011)].

Los factores de crecimiento de los fibroblastos (FGFs) y sus receptores (FGFRs) forman parte de un único y diverso sistema de señalización, el cual cumple una función clave en una variedad de procesos biológicos que abarcan varios aspectos del desarrollo embriónico y la patofisiología adulta [Itoh and Ornitz, *J. Biochem.* 149 (2), 121-130 (2011)]. De una manera espacio-temporal, los FGFs estimulan a través de la unión del FGFR un amplio intervalo de funciones celulares que incluyen la migración, proliferación, diferenciación y supervivencia.

La familia de los FGF comprende 18 factores de crecimiento polipeptídico secretados que se unen a cuatro tirosina quinasas del receptor muy conservadas (FGFR-1 a -4) que se expresan en la superficie celular. Además, el FGRF-5 puede unirse a los FGFs pero no tiene un dominio quinasa, y por lo tanto está privado de la señalización intracelular. La especificidad de la interacción del ligando/receptor es potenciada por un número de procesos de transcripción y de traducción que da lugar a múltiples isoformas por la iniciación transcripcional alternativa, el corte y empalme alternativo, y los truncamientos del terminal C. Varios proteoglicanos de sulfato heparan (por ej., syndecans) pueden ser parte del complejo FGF/FGFR e influir con fuerza en la capacidad de los FGFs para inducir las respuestas de señalización [Polanska *et al.*, *Developmental Dynamics* 238 (2), 277-293 (2009)]. Los FGFRs son receptores de la superficie celular que consisten de tres dominios de tipo inmunoglobulina extracelulares, un dominio de transmembrana de único paso, y un dominio de tirosina quinasa dimerizado intracelular. La unión del FGF le aporta a las quinasas intracelulares una íntima proximidad, permitiéndoles transfosforilarse una con otra. Se han identificado siete sitios de fosforilación (por ej. en el FGFR-1 Tyr463, Tyr583, Tyr585, Tyr653, Tyr654, Tyr730, y Tyr766).

Algunos de estos grupos de fosfotirosina actúan como sitios de acoplamiento para las moléculas de señalización corriente abajo, las cuales en sí mismas también pueden ser directamente fosforiladas por el FGFR, conduciendo a la

activación de múltiples vías de transducción de señal. De este modo, la cascada de señalización MAPK está involucrada en el crecimiento y la diferenciación celular, la cascada de señalización PI3K/Akt está involucrada en la supervivencia celular y la determinación del destino de la célula, mientras que las cascadas de señalización PI3K y PKC cumplen una función en el control de la polaridad celular. Varios inhibidores de retroalimentación de la señalización del FGF han sido identificados recientemente e incluyen los miembros de las familias Spry (Sprouty) y Sef (expresión similar al FGF). Además, en ciertas condiciones, el FGFR es liberado de las membranas pre-Golgi en el citosol. El receptor y su ligando, FGF-2, son cotransportados en el núcleo mediante un mecanismo que involucra la importancia, y están comprometidos en el complejo de la proteína que se une al CREB (CBP), un coactivador transcripcional esencial y común que actúa como factor de entrada de la activación génica. Se han observado múltiples correlaciones entre la expresión inmuno-histoquímica del FGF-2, el FGFR-1 y el FGFR-2 y sus localizaciones celulares tumorales nucleares y citoplásmicas. Por ejemplo, en los adenocarcinomas de pulmón esta asociación también se encontró en el nivel nuclear, enfatizando una función activa del complejo en el núcleo [Korc and Friesel, *Curr. Cancer Drugs Targets* 5, 639-651 (2009)].

Los FGFs se expresan ampliamente tanto en los tejidos en desarrollo y adultos y cumplen importantes funciones en una variedad de procesos normales y patológicos, incluyendo el desarrollo tisular, la regeneración del tejido, angiogénesis, transformación neoplásica, migración celular, diferenciación celular, y supervivencia celular. Además, los FGFs como factores proangiogénicos han estado implicados además en el fenómeno de aparición de la resistencia a la inhibición del receptor-2 del factor de crecimiento endotelial vascular (VEGFR-2) [Bergers and Hanahan, *Nat. Rev. Cancer* 8, 592-603 (2008)].

Los recientes perfiles oncogenómicos de las redes de señalización mostraron

una importante función para la señalización del FGF aberrante en la aparición de algunos cánceres humanos [Wesche *et al.*, *Biochem. J.* 437 (2), 199-213 (2011)]. La señalización constitutiva del FGFR independiente del ligandos ha sido descripta en muchos cánceres humanos, tales como cáncer de cerebro, cáncer de cabeza y cuello, cáncer gástrico y cáncer de ovario. Las formas mutadas del FGFR como también las traslocaciones intragénicas del FGFR han sido identificadas en malignidades tales como enfermedades mieloproliferativas. De interés, las mismas mutaciones que se descubrieron como la causa de muchos trastornos del desarrollo también se hallaron en las células tumorales (por ej., las mutaciones halladas en acondroplasia y displasia tanatofórica, las cuales causan la dimerización y de este modo la activación constitutiva del FGFR-3, también se hallan con frecuencia en el cáncer de vesícula). Una mutación que promueve la dimerización es sólo un mecanismo que puede incrementar la señalización independiente del ligando de los FGFRs. Otras mutaciones localizadas dentro o fuera del dominio quinasa de los FGFRs pueden cambiar la conformación del dominio dando lugar a las quinasas permanentemente activas.

La amplificación de la región cromosómica 8p11-12, la locación genómica del FGRF-1, es una amplificación focal común en el cáncer de pecho y se produce en aproximadamente el 10% de los cánceres de pecho, predominantemente en los cánceres positivos del receptor de estrógenos. Las amplificaciones del FGFR-1 también han sido informadas en el carcinoma escamoso de pulmón de células no pequeñas y se hallan a una baja incidencia en el cáncer de ovarios, cáncer de vesícula y rabdomiosarcoma. De manera similar, aproximadamente el 10% de los cánceres gástricos muestran la amplificación del FGFR-2, el cual está asociado con cánceres del tipo difuso, de pobre pronóstico. Además, se halló que múltiples polimorfismos de nucleótidos simples (SNPs) localizados en los FGFR-1 a -4 se correlacionan con un riesgo incrementado de desarrollar cánceres selectivos, o se informó que están asociados con bajo pronóstico (por

ej., el alelo FGFR-4 G388R en el cáncer de pecho, cáncer de colon y adenocarcinoma de pulmón). La función directa de estos SNPs para promover el cáncer todavía es controvertida.

En síntesis, se ha realizado un gran número de estudios in vitro e in vivo que validan a los FGFR-1 a -4 como dianas del cáncer importantes, y las revisiones exhaustivas han sintetizado estos hallazgos (véase, por ejemplo, Heinzle *et al.*, *Expert Opin. Ther. Targets* 15 (7), 829-846 (2011); Wesche *et al.*, *Biochem. J.* 437 (2), 199-213 (2011); Greulich and Pollock, *Trends in Molecular Medicine* 17 (5), 283-292 (2011); Haugsten *et al.*, *Mol. Cancer Res.* 8 (11), 1439-1452 (2010)]. Se han seguido varias estrategias para atenuar la señalización de los FGFR-1 a -4 aberrantes en tumores humanos incluyendo anticuerpos de bloqueo e inhibidores de pequeñas moléculas, entre otros. Actualmente un número selectivo de inhibidores del FGFR de pequeñas moléculas están en desarrollo clínico, tales como AZD-4547 (AstraZeneca) y BJG-398 (Novartis).

No obstante los avances significativos que se han logrado en general en la terapia cancerosa en los últimos años, hay una constante necesidad de identificar nuevos compuestos anticancerosos con propiedades mejoradas, tales como mayor potencia, mayor selectividad, toxicidad reducida y/o mejor tolerancia. Por lo tanto, el problema técnico a ser resuelto de acuerdo con la presente invención puede ser visto al suministrar compuestos alternativos que tengan actividad inhibidora sobre las quinasas del FGFR, ofreciendo de este modo nuevas opciones terapéuticas para el tratamiento de las enfermedades mediadas por el FGFR, en particular el cáncer y otros trastornos proliferativos.

Los inhibidores de la quinasa hetero-5,6-bicíclica fusionada que portan un sustituyente heteroarilo bicíclico de 9 miembros o uno de 10 miembros han sido divulgados en los documentos WO 2007/061737-A2 y WO 2005/097800-A1, respectivamente. Se estableció que estos compuestos son útiles para el tratamiento del cáncer y otras enfermedades que debido a su acción inhibidora sobre las quinasas de mTOR (blanco mamífero de rapamicina) y/o el IGF-1R

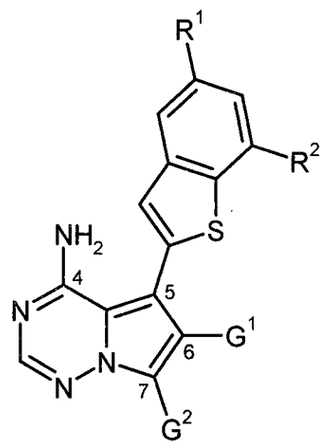
(receptor del factor de crecimiento del tipo insulina tipo 1). Además, las estructuras del molde hetero-5,6-bicíclico asociadas con la inhibición de las quinasas se han descripto en, entre otros, los documentos WO 01/19828-A2, WO 2007/079164-A2 y WO 2010/051043-A1.

Los derivados de 4-aminopirrolo[2,1-f][1,2,4]triazina con perfiles de inhibición diferentes contra un número de proteína quinasas han sido divulgados en , *inter alia*, WO 00/71129-A1, WO 2007/056170-A2, WO 2007/061882-A2, WO 2007/064932-A2, WO 2009/136966-A1, y WO 2010/126960-A1.

En los documentos WO 2005/121147-A1, WO 2007/064883-A2 y WO 2007/064931-A2, los derivados de 4-aminopirrolo[2,1-f][1,2,4]triazina que contienen un grupo diarilurea sustituido en la posición 5 se describieron como que tienen actividad de inhibición del FGFR-1. Sin embargo, otras tirosinas quinasas del receptor, notablemente el VEGFR, PDGFR y Tie-2 quinasas, también son significativamente inhibidas por esta clase particular de compuesto. Como se planteó como hipótesis que esta actividad multi quinasa podría conducir a un aumento de los efectos colaterales potenciales durante el tratamiento, el objetivo de la presente invención fue identificar nuevos agentes que tengan una selectividad mejorada para las FGFR quinasas, proporcionando de este modo nuevas opciones para una terapia contra el cáncer más tolerable.

Sorprendentemente se ha hallado ahora que ciertos derivados de 4-aminopirrolo[2,1-f][1,2,4]triazina que portan un residuo bentotiofen-2-ilo específicamente sustituido en la posición 5 exhiben una potente y selectiva inhibición de las FGFR quinasas, notablemente de las FGFR-1 y FGFR-3 quinasas, lo cual hace que estos compuestos sean particularmente útiles para el tratamiento de trastornos proliferativos, tales como cáncer y enfermedades tumorales.

De este modo, en un aspecto, la presente invención se refiere a derivados de 5-(1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-4-amina 6,7-disustituidos de la fórmula general (I)



(I),

en la que

R^1 es hidrógeno, cloro, metilo o metoxi,

R^2 es hidrógeno o metoxi,

a condición de que al menos uno de R^1 y R^2 sea diferente de hidrógeno,

G^1 representa cloro, alquilo (C_1-C_4), alcoxicarbonilo (C_1-C_4), aza-heteroarilo de 5 miembros, o el grupo $-CH_2-OR^3$, $-CH_2-NR^4R^5$ o $-C(=O)-NR^4R^6$, en la que

R^3 es hidrógeno, alquilo (C_1-C_4) o cicloalquilo (C_3-C_6) o fenilo, en la que

(*i*) dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi, alcoxi (C_1-C_4), hidroxicarbonilo, alcoxicarbonilo (C_1-C_4), amino, aminocarbonilo, mono-(C_1-C_4)-alquil-aminocarbonilo, di-alquilaminocarbonilo (C_1-C_4)-, cicloalquilo (C_3-C_6) o hasta tres átomos de flúor,

y

(*ii*) dicho cicloalquilo (C_3-C_6) está opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados del grupo que consiste en alquilo (C_1-C_4), hidroxi y amino,

y

(*iii*) dicho fenilo está opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados del grupo que consiste en flúor, cloro, bromo, ciano, trifluorometilo,

trifluorometoxi, alquilo (C_1-C_4) y alcoxi (C_1-C_4),

R^4 es hidrógeno o alquilo (C_1-C_4),

R^5 es hidrógeno, alquilo (C_1-C_4), alquilcarbonilo (C_1-C_4), cicloalquilo (C_3-C_6) o heterocicloalquilo de 4 a 6 miembros, en la que

(*i*) dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi, alcoxi (C_1-C_4), hidroxicarbonilo, alcoxicarbonilo (C_1-C_4), aminocarbonilo, mono-(C_1-C_4)-alquil-aminocarbonilo, di-alquilaminocarbonilo (C_1-C_4), o cicloalquilo (C_3-C_6),

y

(*ii*) dicho cicloalquilo (C_3-C_6) está opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados del grupo que consiste en alquilo (C_1-C_4), hidroxi y amino,

y

(*iii*) dicho heterocicloalquilo de 4 a 6 miembros está opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados del grupo que consiste en alquilo (C_1-C_4), hidroxi, oxo y amino,

R^6 es hidrógeno, alquilo (C_1-C_4), cicloalquilo (C_3-C_6) o heterocicloalquilo de 4 a 6 miembros, en la que

(*i*) dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi, alcoxi (C_1-C_4), hidroxicarbonilo, alcoxicarbonilo (C_1-C_4), amino, aminocarbonilo, mono-(C_1-C_4)-alquil-aminocarbonilo, di-alquilaminocarbonilo (C_1-C_4), o cicloalquilo (C_3-C_6),

y

(*ii*) dicho cicloalquilo (C_3-C_6) está opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados del grupo que consiste en alquilo (C_1-C_4), hidroxi y amino,

y

(*iii*) dicho heterocicloalquilo de 4 a 6 miembros está opcionalmente

sustituido con uno o dos sustituyentes independientemente seleccionados del grupo que consiste en alquilo (C_1-C_4), hidroxi, oxo y amino,

o

R^4 y R^5, o R^4 y R^6, respectivamente, se unen y, tomados junto con el átomo de nitrógeno al cual están unidos, forman un anillo heterocicloalquilo monocíclico, saturado de 4 a 7 miembros el cual puede contener un segundo heteroátomo del anillo seleccionado de $N(R^7)$ y O, y el cual puede estar sustituido en los átomos de carbono del anillo con uno o dos sustituyentes independientemente seleccionados del grupo que consiste en alquilo (C_1-C_4), oxo, hidroxi, amino y aminocarbonilo, y en la que

R^7 es hidrógeno, alquilo (C_1-C_4), formilo o alquilcarbonilo (C_1-C_4),

y

G^2 representa cloro, ciano, alquilo (C_1-C_4), o el grupo $-CR^{8A}R^{8B}$-OH, $-CH_2$-NR^9R^{10}, $-C(=O)$-$NR^{11}R^{12}$ o $-CH_2$-OR^{15}, en la que

R^{8A} and R^{8B} se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo (C_1-C_4), ciclopropilo y ciclobutilo,

R^9 es hidrógeno o alquilo (C_1-C_4),

R^{10} es hidrógeno, alquilo (C_1-C_4), alquilcarbonilo (C_1-C_4), cicloalquilo (C_3-C_6) o heterocicloalquilo de 4 a 6 miembros, en la que

(*i*) dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi, amino, aminocarbonilo, mono-(C_1-C_4)-alquilaminocarbonilo, o di-alquilaminocarbonilo (C_1-C_4),

y

(*ii*) dicho cicloalquilo (C_3-C_6) está opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados del grupo que consiste en alquilo (C_1-C_4), hidroxi y amino,

y

(*iii*) dicho heterocicloalquilo de 4 a 6 miembros está opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados del grupo que consiste en alquilo (C_1-C_4), hidroxi, oxo y amino,

R^{11} es hidrógeno o alquilo (C_1-C_4),

R^{12} es hidrógeno, alquilo (C_1-C_4), cicloalquilo (C_3-C_6) o heterocicloalquilo de 4 a 6 miembros, en la que

(*i*) dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi, amino, aminocarbonilo, mono-(C_1-C_4)-alquilaminocarbonilo, o di-alquilaminocarbonilo (C_1-C_4),

y

(*ii*) dicho cicloalquilo (C_3-C_6) está opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados del grupo que consiste en alquilo (C_1-C_4), hidroxi y amino,

y

(*iii*) dicho heterocicloalquilo de 4 a 6 miembros está opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados del grupo que consiste en alquilo (C_1-C_4), hidroxi, oxo y amino,

o

R^9 y R^{10}, o R^{11} y R^{12}, respectivamente, se unen y, tomados junto con el átomo de nitrógeno al cual están unidos, forman un anillo heterocicloalquilo monocíclico, saturado de 4 a 7 miembros el cual puede contener un segundo heteroátomo del anillo seleccionado de $N(R^{13})$, O, S y $S(O)_2$, y el cual puede estar sustituido en los átomos de carbono del anillo con hasta tres sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo (C_1-C_4), oxo, hidroxi, amino y aminocarbonilo, y en la

que

R^{13} es hidrógeno, alquilo (C_1-C_4) o cicloalquilo (C_3-C_6), formilo o alquilcarbonilo (C_1-C_4),

y

R^{15} es alquilo (C_1-C_4),

a condición de que G^1 no sea cloro cuando G^2 es cloro o ciano.

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

Los compuestos de acuerdo con esta invención son los compuestos de fórmula (I) y sus sales, solvatos, y solvatos de las sales, los compuestos incluidos en la fórmula (I) de las fórmulas (I-A), (I-B), (I-C), (I-D) y (I-E) mencionados a continuación y sus sales, solvatos, y solvatos de las sales, y los compuestos incluidos en la fórmula (I) y mencionados a continuación como los productos del proceso y/o los ejemplos de realización y sus sales, solvatos, y solvatos de las sales, donde los compuestos incluidos en la fórmula (I) mencionados a continuación ya no son sales, solvatos, y solvatos de las sales,

Las sales con el fin 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). Las sales que no son adecuadas por sí mismas para usos farmacéuticos, pero se pueden usar por ejemplo para el aislamiento y la purificación de los compuestos de acuerdo con la invención, también se incluyen.

Las sales farmacéuticamente aceptables incluyen sales de adición de ácido de ácidos minerales, ácidos carboxílicos y ácidos sulfónicos, por ejemplo sales de ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido fosfórico, ácido metanosulfónico, ácido etanosulfónico, ácido bencenosulfónico, ácido toluenosulfónico, ácido nafatlenodisulfónico, ácido fórmico, ácido acético, ácido trifluoroacético, ácido propiónico, ácido láctico, acido tartárico, ácido málico,

ácido cítrico, ácido fumárico, ácido maleico, y ácido benzoico.

Las sales farmacéuticamente aceptables incluyen también sales de bases tradicionales, tales como por ejemplo y preferentemente sales de dianal alcalino (por ejemplo sales de sodio y potasio), sales de dianal alcalinotérreo (por ejemplo sales de calcio y magnesio), y sales de amonio que derivan de amoníaco o aminas orgánicas, tales como las que se ilustran y preferentemente etilamina, dietilamina, trietilamina, N,N-diisopropiletilamina, monoetanolamina, dietanolamina, trietanolamina, dimetilaminoetanol, dietilaminoetanol, procaína, diciclohexilamina, dibencilamina, N-metilmorfolina, N-metilpiperidina, arginina, lisina, y 1,2-etilendiamina.

Se designan solvatos en el contexto de la invención 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 solvente. Los hidratos son una forma específica de solvatos, en los cuales la coordinación tiene lugar con agua. Los hidratos son solvatos preferentes en el contexto de la presente invención.

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

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

Los isómeros geométricos por naturaleza de los sustituyentes alrededor de un

enlace doble o un anillo pueden estar presentes en la forma cis (=Z) o trans (=E-), y ambas formas isoméricas están dentro del alcance de esta invención.

Todos los isómeros, ya sea separados, puros, parcialmente puros, o en mezcla racémica, de los compuestos de esta invención están dentro del alcance de esta invención. La purificación de dichos isómeros y la separación de dichas mezclas isoméricas pueden obtenerse mediante técnicas estándares conocidas en la técnica. Por ejemplo, las mezclas diastereoméricas se pueden separar en los isómeros individuales por procesos cromatográficos o cristalización, y los racematos se pueden separar en los respectivos enantiómeros ya sea por procesos cromatográficos sobre fases quirales o por resolución.

Además, todas las formas tautoméricas posibles de los compuestos que se describieron anteriormente se incluyen de acuerdo con la presente invención.

La presente invención abarca además todas las variantes isotópicas adecuadas de los compuestos de acuerdo con la invención. Una variante isotópica de un compuesto de acuerdo con la invención se entiende que significa un compuesto en el cual al menos un átomo dentro del compuesto de acuerdo con la invención ha sido intercambiado por otro átomo del mismo número atómico, pero con una masa atómica diferente a la masa atómica que usual o predominantemente se produce en la naturaleza. Ejemplos de isótopos que se pueden incorporar a los compuestos de la invención incluyen isótopos de hidrógeno, carbono, nitrógeno, oxígeno, flúor, cloro, bromo, y yodo, tales como ^{2}H (deuterio), ^{3}H (tritio), ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{18}F, ^{36}Cl, ^{82}Br, ^{123}I, ^{124}I, ^{129}I and ^{131}I. Las variantes isotrópicas particulares de un compuesto de acuerdo con la invención, especialmente aquéllas en las cuales se han incorporado uno o más isótopos radioactivos, pueden ser beneficiosas, por ejemplo, para el examen del mecanismo de acción o de la distribución del compuesto activo en el cuerpo. Debido a la preparación y detección comparativamente fácil, especialmente los compuestos etiquetados con isótopos ^{3}H o ^{14}C son adecuados para este fin. Además, la incorporación de isótopos, por ejemplo de deuterio, puede conducir

a beneficios terapéuticos particulares como consecuencia de una mayor estabilidad dianabólica del compuesto, por ejemplo una extensión de la vida media en el cuerpo o una reducción en la dosis activa requerida. Estas modificaciones de los compuestos de acuerdo con la invención pueden, por lo tanto, en algunos casos, constituir además una realización preferente de la presente invención. Las variantes isotópicas de los compuestos de acuerdo con la invención se pueden preparar mediante procesos conocidos por los expertos en la técnica, por ejemplo, mediante los procedimientos descriptos a continuación y los procedimientos que se describen en los ejemplos de trabajo, mediante el uso de las correspondientes modificaciones isotópicas de los reactivos particulares y/o los compuestos de partida en los mismos.

En el contexto de la presente invención los sustituyentes y los residuos tienen el siguiente significado, a menos que se especifique de otro modo:

Alquilo (C_1-C_4) en el contexto de la invención representa un radical alquilo de cadena recta o ramificada que tiene 1 a 4 átomos de carbono. Puede mencionarse a modo de ejemplo y preferentemente: metilo, etilo, n-propilo, isopropilo, n-butilo, iso-butilo, sec-butilo, y ter-butilo.

Alcoxi (C_1-C_4) en el contexto de la invención representa un radical alcoxi de cadena recta o ramificada que tiene 1 a 4 átomos de carbono. Puede mencionarse a modo de ejemplo y preferentemente: metoxi, etoxi, n-propoxi, isopropoxi, n-butoxi, iso-butoxi, sec-butoxi, y ter-butoxi.

Mono-alquilamino (C_1-C_4) en el contexto de la invención representa un grupo amino con un sustituyente alquilo de cadena recta o ramificada que contiene 1 a 4 átomos de carbono. Puede mencionarse a modo de ejemplo y preferentemente: metilamino, etilamino, n-propilamino, isopropilamino, n-butilamino, y ter-butilamino.

Di-alquilamino (C_1-C_4) en el contexto de la invención representa un grupo amino con dos sustituyentes alquilo de cadena recta o ramificada idénticos o diferentes que contiene cada uno de ellos 1 a 4 átomos de carbono. Puede

mencionarse a modo de ejemplo y preferentemente: *N,N*-dimetilamino, *N,N*-dietilamino, *N*-etil-*N*-metilamino, *N*-metil-*N*-*n*-propilamino, *N*-isopropil-*N*-metilamino, *N*-isopropil-*N*-*n*-propilamino, *N,N*-diisopropilamino, *N*-*n*-butil-*N*-metilamino, y N-ter-butil-N-metilamino.

Alquilcarbonilo (C_1-C_4) en el contexto de la invención representa un radical alquilo de cadena recta o ramificada que tiene 1 a 4 átomos de carbono, el cual está unido al resto de la molécula mediante un grupo carbonilo [-C(=O)-]. Puede mencionarse a modo de ejemplo y preferentemente: acetilo, propionilo, n-butirilo, iso-butirilo, n-pentanoílo, y pivaloílo.

Alcoxicarbonilo (C_1-C_4) en el contexto de la invención representa un radical alcoxi de cadena recta o ramificada que tiene 1 a 4 átomos de carbono el cual está unido al resto de la molécula mediante un grupo carbonilo [-C(=O)-]. Puede mencionarse a modo de ejemplo y preferentemente: metoxicarbonilo, etoxicarbonilo, etoxicarbonilo; y etoxicarbonilo, n-propoxicarbonilo, isopropoxicarbonilo, n-butoxicarbonilo, y ter-butoxicarbonilo.

Mono-alquilaminocarbonilo (C_1-C_4) en el contexto de la invención representa un grupo amino, el cual está unido al resto de la molécula mediante un grupo carbonilo [-C(=O)-] y el cual tiene un sustituyente alquilo de cadena recta o ramificada que tiene 1 a 4 átomos de carbono. Puede mencionarse a modo de ejemplo y preferentemente: metilaminocarbonilo, etilaminocarbonilo, *n*-propilaminocarbonilo, isopropilaminocarbonilo, *n*-butilaminocarbonilo, y *ter*-butilaminocarbonilo.

Di-alquilaminocarbonilo (C_1-C_4) en el contexto de la invención representa un grupo amino, el cual está unido al resto de la molécula mediante un grupo carbonilo [-C(=O)-] y el cual tiene dos sustituyentes alquilo de cadena recta o ramificada idénticos o diferentes que tiene 1 a 4 átomos de carbono. Puede mencionarse a modo de ejemplo y preferentemente: *N,N*-dimetilaminocarbonilo, *N,N*-dietilaminocarbonilo, *N-etil-N*-metilaminocarbonilo, *N*-metil-*N*-*n*-propilaminocarbonilo, *N*-isopropil-*N*-metilaminocarbonilo, *N,N*-diisopropilaminocarbonilo, *N*-

n-butil-*N*-metilaminocarbonilo, y *N*-*ter*-butil-*N*-metilaminocarbonilo.

Cicloalquilo (C_3-C_6) en el contexto de la invención representa un carbociclo monocíclico, saturado que tiene 3 a 6 átomos de carbono. Puede mencionarse a modo de ejemplo; ciclopropilo, ciclobutilo, ciclopentilo, y ciclohexilo. Se prefieren ciclopropilo y ciclobutilo.

Heterocicloalquilo de 4 a 7 miembros y heterocicloalquilo de 4 a 6 miembros en el contexto de la invención representan un heterociclo monocíclico, saturado con 4 a 7 o, respectivamente, 4 a 6 átomos del anillo en total, el cual contiene uno o más heteroátomos del anillo idénticos o diferentes de las series N, O, S y $S(O)_2$, y el cual puede estar unido mediante un átomo de carbono del anillo o mediante un átomo de nitrógeno del anillo (si está presente). Se prefiere el heterocicloalquilo de 4 a 6 miembros que contiene un átomo de nitrógeno del anillo y opcionalmente otro heteroátomo del anillo de las series N, O o $S(O)_2$. Se prefiere particularmente el heterocicloalquilo de 5 o 6 miembros que contiene un átomo de nitrógeno del anillo y opcionalmente otro heteroátomo del anillo de las series N u O. Puede mencionarse a modo de ejemplo: azetidinilo, oxetanilo, tietanilo, pirrolidinilo, pirazolidinilo, imidazolidinilo, tetrahidrofuranilo, tiolanilo, 1,1-dioxidotiolanilo, 1,2-oxazolidinilo, 1,3-oxazolidinilo, 1,3-tiazolidinilo, piperidinilo, piperazinilo, tetrahidropiranilo, tetrahidrotiopiranilo, 1,3-dioxanilo, 1,4-dioxanilo, 1,2-oxazinanilo, morfolinilo, tiomorfolinilo, 1,1-dioxidotiomorfolinilo, azepanilo, 1,4-diazepanilo, y 1,4-oxazepanilo. Se prefieren azetidinilo, pirrolidinilo, pirazolidinilo, imidazolidinilo, 1,2-oxazolidinilo, 1,3-oxazolidinilo, piperidinilo, piperazinilo, 1,2-oxazinanilo, morfolinilo, y tiomorfolinilo. Se prefieren particularmente pirrolidinilo, piperidinilo, piperazinilo, y morfolinilo.

Azaheteroarilo de 5 miembros en el contexto de la invención representa un radical heterocíclico aromático (heteroaromático) que tiene 5 átomos del anillo en total, el cual contiene al menos un átomo de nitrógeno del anillo y opcionalmente uno o dos otros heteroátomos del anillo de la serie N, O y/o S, y el cual está unido mediante un átomo de carbono del anillo u opcionalmente

mediante un átomo de nitrógeno del anillo (cuando lo permite la valencia). Se prefiere el azaheteroarilo de 5 miembros que contiene un átomo de nitrógeno del anillo y uno o dos otros heteroátomos del anillo de la serie N y/u O. Puede mencionarse a modo de ejemplo: pirrolilo, pirazolilo, imidazolilo, oxazolilo, tiazolilo, isoxazolilo, isotiazolilo, triazolilo, oxadiazolilo, y tiadiazolilo. Se prefieren pirazolilo, imidazolilo, oxazolilo, isoxazolilo, y oxadiazolilo.

Un sustituyente oxo en el contexto de la invención represente un átomo de oxígeno, el cual está unido a un átomo de carbono mediante un enlace doble.

En el contexto de la presente invención, para todos los radicales que aparecen varias veces, su significado es independiente uno de otro. Si los radicales en los compuestos de acuerdo con la invención están sustituidos, los radicales pueden ser mono- o poli-sustituido, a menos que se especifique lo contrario. Se prefiere la sustitución con uno o con dos o tres sustituyentes idénticos o diferentes. Se prefiere particularmente la sustitución con uno o con dos sustituyentes idénticos o diferentes.

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

R^1 es cloro, metilo o metoxi,

R^2 es hidrógeno o metoxi,

G^1 representa cloro, alquilo (C_1-C_4), alcoxicarbonilo (C_1-C_4) o azaheteroarilo de 5 miembros seleccionado del grupo que consiste en pirazolilo, imidazolilo, oxazolilo, isoxazolilo y oxadiazolilo, o representa el grupo -CH_2-OR^3 o -CH_2-NR^4R^5, en la que

R^3 es hidrógeno, alquilo (C_1-C_4) o cicloalquilo (C_3-C_6),

en la que dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi, alcoxi (C_1-C_4), hidroxicarbonilo, alcoxicarbonilo (C_1-C_4), amino, aminocarbonilo, cicloalquilo (C_3-C_6) o hasta tres átomos de flúor,

R^4 es hidrógeno o alquilo (C_1-C_4),

R^5 es hidrógeno, alquilo (C_1-C_4), alquilcarbonilo (C_1-C_4), cicloalquilo (C_3-C_6) o heterocicloalquilo de 5 o 6 miembros, en la que

(*i*) dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi, hidroxicarbonilo, o cicloalquilo (C_3-C_6),

y

(*ii*) dicho heterocicloalquilo de 5 o 6 miembros está opcionalmente sustituido con oxo,

o

R^4 y R^5 se unen y, tomados junto con el átomo de nitrógeno al cual están unidos, forman un anillo heterocicloalquilo monocíclico, saturado de 4 a 6 miembros, el cual puede contener un segundo heteroátomo del anillo seleccionado de $N(R^7)$ y O, y el cual puede estar sustituido en un átomo de carbono del anillo con oxo o hidroxi, y en la que

R^7 es hidrógeno o alquilo (C_1-C_4),

y

G^2 representa cloro, ciano, alquilo (C_1-C_4), o el grupo $-CR^{8A}R^{8B}$-OH, $-CH_2$-NR^9R^{10}, $-C(=O)$-$NR^{11}R^{12}$ o $-CH_2$-OR^{15}, en la que

R^{8A} and R^{8B} se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo (C_1-C_4), y ciclopropilo,

R^9 es hidrógeno o metilo,

R^{10} es hidrógeno, alquilo (C_1-C_4), alquilcarbonilo (C_1-C_4), cicloalquilo (C_3-C_6) o heterocicloalquilo de 5 o 6 miembros, en la que

(*i*) dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi o aminocarbonilo,

y

(*ii*) dicho heterocicloalquilo de 5 o 6 miembros está opcionalmente sustituido con oxo,

R^{11} es hidrógeno o metilo,

R^{12} es hidrógeno, alquilo (C_1-C_4), cicloalquilo (C_3-C_6) o heterocicloalquilo de 5 o 6 miembros, en la que

(*i*) dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi, y

(*ii*) dicho heterocicloalquilo de 5 o 6 miembros está opcionalmente sustituido con oxo,

o

R^9 y R^{10}, o R^{11} y R^{12}, respectivamente, se unen y, tomados junto con el átomo de nitrógeno al cual están unidos, forman un anillo heterocicloalquilo monocíclico, saturado de 4 a 6 miembros el cual puede contener un segundo heteroátomo del anillo seleccionado de $N(R^{13})$, O, S y $S(O)_2$, y el cual puede estar sustituido en los átomos de carbono del anillo con hasta tres sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo (C_1-C_4), oxo, hidroxi, amino y aminocarbonilo, y en la que

R^{13} es hidrógeno, alquilo (C_1-C_4), ciclopropilo, ciclobutilo, formilo o alquilcarbonilo (C_1-C_4),

y

R^{15} es metilo o etilo,

a condición de que G^1 no sea cloro cuando G^2 es cloro o ciano.

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

R^1 es metilo,

R^2 es metoxi,

G^1 representa metilo, oxazol-5-ilo o el grupo $-CH_2-OR^3$ o $-CH_2-NR^4R^5$, en la que

R^3 es hidrógeno, alquilo (C_1-C_4), ciclopropilo o ciclobutilo,

en la que dicho alquilo (C_1-C_4) está opcionalmente sustituido con

hidroxi, metoxi, etoxi, hidroxicarbonilo, metoxicarbonilo, etoxicarbonilo, amino, aminocarbonilo, ciclopropilo, ciclobutilo o hasta tres átomos de flúor,

R^4 es hidrógeno, metilo o etilo,

R^5 es hidrógeno, alquilo (C_1-C_4), acetilo, ciclopropilo, ciclobutilo o 2-oxopirrolidin-3-ilo,

en la que dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi, hidroxicarbonilo, ciclopropilo o ciclobutilo,

o

R^4 y R^5 se unen y, tomados junto con el átomo de nitrógeno al cual están unidos, forman un anillo heterocicloalquilo monocíclico, saturado de 5 o 6 miembros, el cual puede contener un segundo heteroátomo del anillo seleccionado de NH y O, y el cual puede estar sustituido en un átomo de carbono del anillo con oxo o hidroxi,

y

G^2 representa metilo o el grupo $-CR^{8A}R^{8B}$-OH, $-CH_2-NR^9R^{10}$ o $-C(=O)-NR^{11}R^{12}$, en la que

R^{8A} y R^{8B} son independientemente hidrógeno o metilo,

R^9 es hidrógeno,

R^{10} es hidrógeno, alquilo (C_1-C_4), acetilo, ciclopropilo, ciclobutilo o 2-oxopirrolidin-3-ilo,

en la que dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi o aminocarbonilo,

R^{11} es hidrógeno o metilo,

R^{12} es hidrógeno, alquilo (C_1-C_4), ciclopropilo, ciclobutilo o 2-oxopirrolidin-3-ilo,

en la que dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi,

o

R^9 y R^{10}, o R^{11} y R^{12}, respectivamente, se unen y, tomados junto con el átomo de nitrógeno al cual están unidos, forman un anillo heterocicloalquilo monocíclico, saturado de 4 a 6 miembros, el cual puede contener un segundo heteroátomo del anillo seleccionado de $N(R^{13})$, O, y $S(O)_2$, y el cual puede estar sustituido en los átomos de carbono del anillo con hasta tres sustituyentes independientemente seleccionados del grupo que consiste en flúor, metilo, oxo, hidroxi, amino y aminocarbonilo, y en la que

R^{13} es hidrógeno, formilo o acetilo.

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

R^1 es metilo,

y

R^2 es metoxi.

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

G^1 representa el grupo $-CH_2-OR^3$, en la que

R^3 es hidrógeno o alquilo (C_1-C_4) opcionalmente sustituido con hidroxi, metoxi, amino, aminocarbonilo o hasta tres átomos de flúor.

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

G^1 representa el grupo $-CH_2-NR^4R^5$, en la que

R^4 es hidrógeno o metilo,

R^5 es alquilo (C_1-C_4), acetilo, ciclopropilo, ciclobutilo o 2-oxopirrolidin-3-ilo,

en la que dicho alquilo (C_1-C_4) está opcionalmente sustituido con

hidroxi,

o

R^4 y R^5 se unen y, tomados junto con el átomo de nitrógeno al cual están unidos, forman un anillo heterocicloalquilo monocíclico, saturado de 5 o 6 miembros, el cual puede contener un segundo heteroátomo del anillo seleccionado de NH y O, y el cual puede estar sustituido en un átomo de carbono del anillo con oxo o hidroxi.

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

G^2 representa el grupo $-CH_2-NR^9R^{10}$, en la que

R^9 es hidrógeno,

R^{10} es acetilo o 2-oxopirrolidin-3-ilo,

o

R^9 y R^{10} se unen y, tomados junto con el átomo de nitrógeno al cual están unidos, forman un anillo heterocicloalquilo monocíclico, saturado de 5 o 6 miembros, el cual puede contener un segundo heteroátomo del anillo seleccionado de $N(R^{13})$ y O, y el cual puede estar sustituido en los átomos de carbono del anillo con hasta dos sustituyentes independientemente seleccionados del grupo que consiste en metilo, oxo y amino, y en la que

R^{13} es hidrógeno, formilo o acetilo.

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

G^2 representa el grupo $-C(=O)-NR^{11}R^{12}$, en la que

R^{11} es hidrógeno,

R^{12} es alquilo (C_1-C_4) o 2-oxopirrolidin-3-ilo,

en la que dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi,

o

R^{11} y R^{12} se unen y, tomados junto con el átomo de nitrógeno al cual están unidos, forman un anillo heterocicloalquilo monocíclico, saturado de 4 a 6 miembros, el cual puede contener un segundo heteroátomo del anillo seleccionado de NH y O, y el cual puede estar sustituido en un átomo de carbono del anillo con oxo o hidroxi.

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

R^1 es metilo,

R^2 es metoxi,

G^1 representa el grupo $-CH_2-OR^3$, en la que

R^3 es alquilo (C_1-C_4) opcionalmente sustituido con hidroxi, amino o aminocarbonilo,

y

G^2 representa el grupo $-CH_2-NR^9R^{10}$ o $-C(=O)-NR^{11}R^{12}$, en la que

R^9 es hidrógeno,

R^{10} es 2-oxopirrolidin-3-ilo,

o

R^9 y R^{10} se unen y, tomados junto con el átomo de nitrógeno al cual están unidos, forman un anillo piperazin-1-ilo, 3-oxopiperazin-1-ilo o 4-acetilpiperazin-1-ilo.

R^{11} es hidrógeno,

R^{12} es 2-oxopirrolidin-3-ilo,

o

R^{11} y R^{12} se unen y, tomados junto con el átomo de nitrógeno al cual están unidos, forman un anillo 3-hidroxiazetidin-1-ilo, 4-hidroxipiperidin-1-ilo o 3-oxopiperazin-1-ilo.

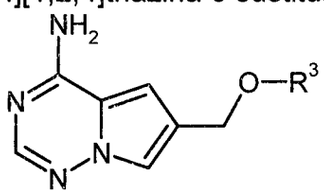
Las definiciones de los residuos indicados específicamente en las

combinaciones respectivas o las combinaciones preferentes de los residuos también se reemplazan según se desee por las definiciones de los residuos de otras combinaciones, sin importar las combinaciones particulares indicadas para los residuos. Las combinaciones de dos o más de los intervalos preferentes antes mencionados son particularmente preferentes.

Los compuestos de la fórmula general (I) se pueden preparar a través de varias vías de síntesis, las cuales están regidas esencialmente por la naturaleza de los grupos G^1 y G^2 particulares que han sido elegidos (véase las definiciones anteriores).

De este modo, en otra realización, la presente invención se refiere a un procedimiento para preparar los compuestos de la presente fórmula general (I), caracterizada porque

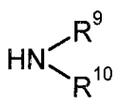
[A] una 4-aminopirrolo[2,1-f][1,2,4]triazina 6 sustituida de fórmula (II)



(II),

en la que R^3 tiene el significado que se describió anteriormente,

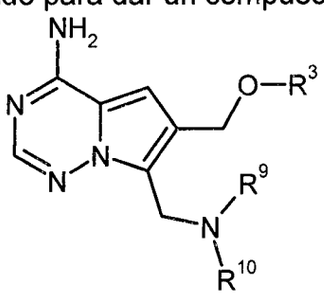
se hace reaccionar primero con formaldehído y una amina de fórmula (III)



(III),

en la que R^9 y R^{10} tienen los significados que se describieron anteriormente,

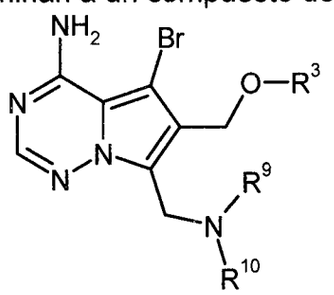
en presencia de un ácido para dar un compuesto de fórmula (IV)



(IV),

en la que R^3, R^9 y R^{10} tienen los significados que se describieron anteriormente,

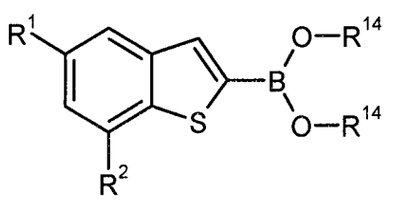
posteriormente se brominan a un compuesto de fórmula (V)



(V),

en la que R^3, R^9 y R^{10} tienen los significados que se describieron anteriormente,

y posteriormente se acoplan con un benzotiofeno-2-il boronato de fórmula (VI)



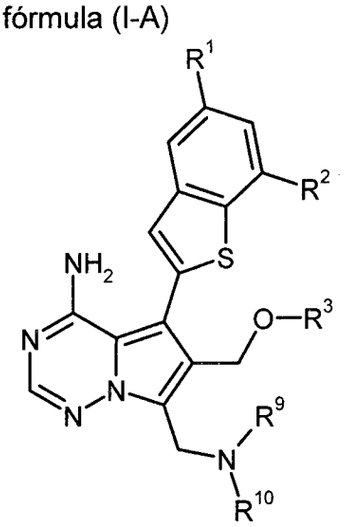
(VI),

en la que R^1 y R^2 tienen los significados que se describieron anteriormente,

y

R^{14} representa hidrógeno o alquilo (C_1-C_4), o ambos residuos R^{14} se enlazan juntos para formar un puente -$(CH_2)_2$-, -$C(CH_3)_2$-$C(CH_3)_2$-, -$(CH_2)_3$-, -CH_2-$C(CH_3)_2$-CH_2- o -C(=O)-CH_2-$N(CH_3)$-CH_2-C(=O)-,

en presencia de un catalizador de paladio y una base para dar el compuesto diana de fórmula (I-A)



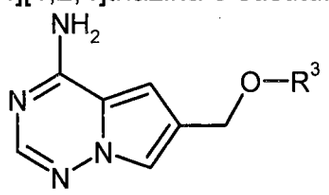
(I-A),

en la que R^1, R^2, R^3, R^9 y R^{10} tienen los significados que se describieron

anteriormente,

o

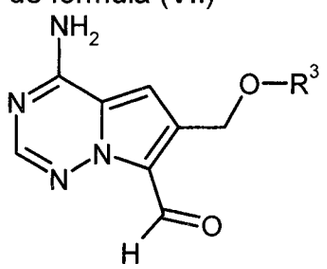
[B] una 4-aminopirrolo[2,1-f][1,2,4]triazina 6 sustituida de fórmula (II)



(II),

en la que R^3 tiene el significado que se describió anteriormente,

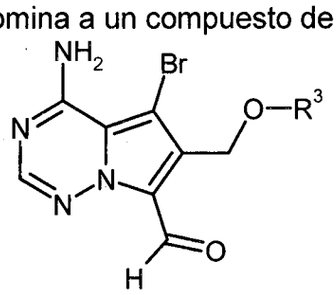
se formila primero con N,N-dimetilformamida en presencia de cloruro de fosforilo a un aldehído de fórmula (VII)



(VII),

en la que R^3 tiene el significado que se describió anteriormente,

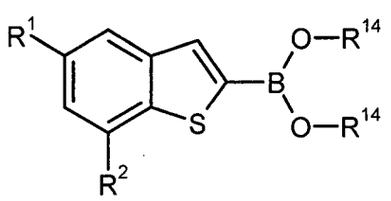
posteriormente se bromina a un compuesto de fórmula (VIII)



(VIII),

en la que R^3 tiene el significado que se describió anteriormente,

y posteriormente se acopla con un benzotiofeno-2-il boronato de fórmula (VI)

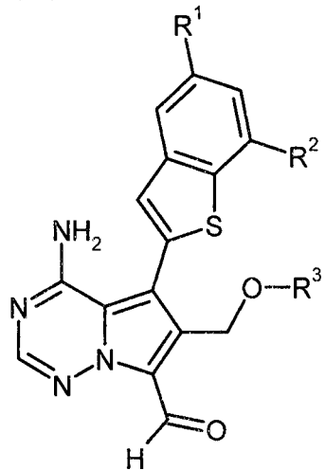


(VI),

en la que R^1, R^2 y R^{14} tienen los significados que se describieron anteriormente,

en presencia de un catalizador de paladio y una base para dar un

compuesto de fórmula (IX)

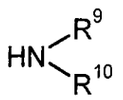


(IX),

en la que R^1, R^2 y R^3 tienen los significados que se describieron anteriormente,

el cual posteriormente o bien

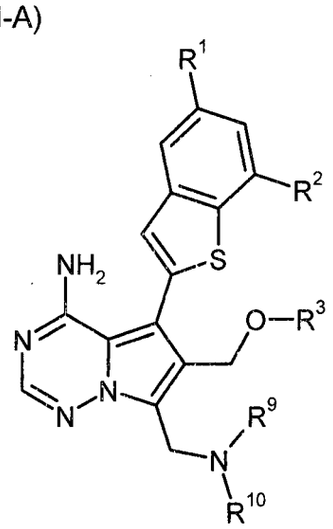
[B-1] se hace reaccionar con una amina de fórmula (III)



(III),

en la que R^9 y R^{10} tienen los significados que se describieron anteriormente,

en presencia de un ácido y un agente reductor para dar el compuesto diana de fórmula (I-A)

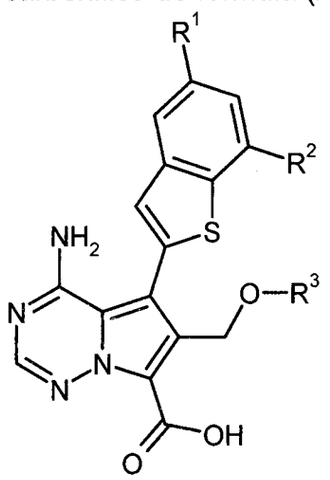


(I-A),

en la que R^1, R^2, R^3, R^9 y R^{10} tienen los significados que se describieron anteriormente,

o

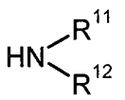
[B-2] se oxida a un ácido carboxílico de fórmula (X)



(X),

en la que R^1, R^2 y R^3 tienen los significados que se describieron anteriormente,

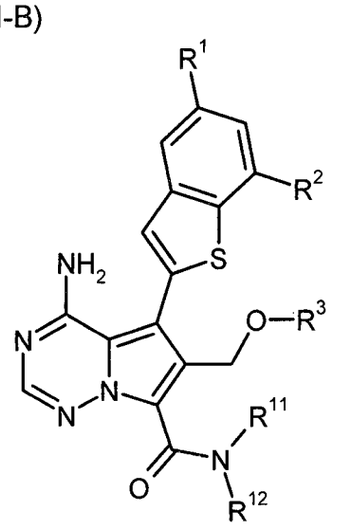
y finalmente se acopla con una amina de fórmula (XI)



(XI),

en la que R^{11} y R^{12} tienen los significados que se describieron anteriormente,

en presencia de un agente de condensación para dar el compuesto diana de fórmula (I-B)

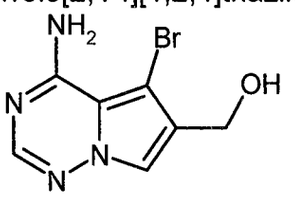


(I-B),

en la que R^1, R^2, R^3, R^{11} y R^{12} tienen los significados que se describieron anteriormente,

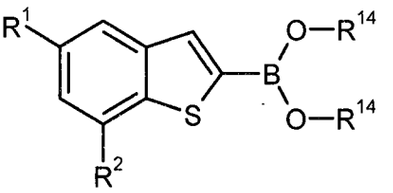
o

[C] una 4-amino-5-bromopirrolo[2,1-f][1,2,4]triazina 6 sustituida de fórmula (XII)



(XII)

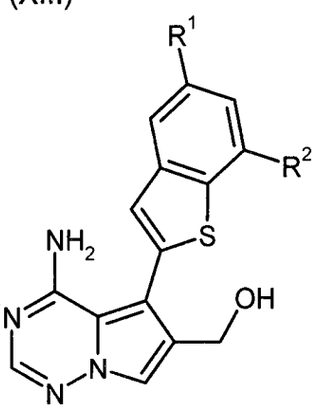
se acopla primero con un benzotiofeno-2-il boronato de fórmula (VI)



(VI),

en la que R^1, R^2 y R^{14} tienen los significados que se describieron anteriormente,

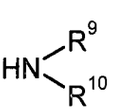
en presencia de un catalizador de paladio y una base para dar un compuesto de fórmula (XIII)



(XIII),

en la que R^1 y R^2 tienen los significados que se describieron anteriormente,

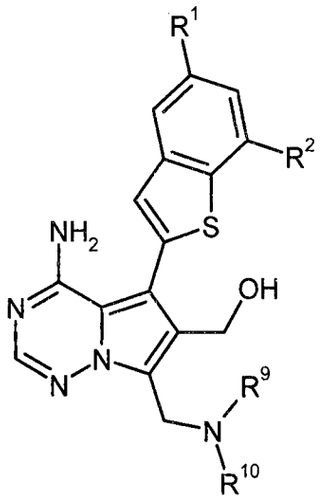
y posteriormente se hace reaccionar con formaldehído y una amina de fórmula (III)



(III),

en la que R^9 y R^{10} tienen los significados que se describieron anteriormente,

en presencia de un ácido para dar el compuesto de fórmula (I-C)

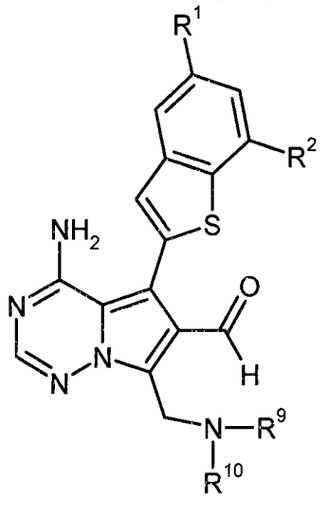


(I-C),

en la que R^1, R^2 R^9 y R^{10} tienen los significados que se describieron anteriormente,

el cual posteriormente o bien

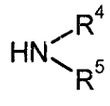
[C-1] se oxida a un aldehído de fórmula (XIV)



(XIV),

en la que R^1, R^2 R^9 y R^{10} tienen los significados que se describieron anteriormente,

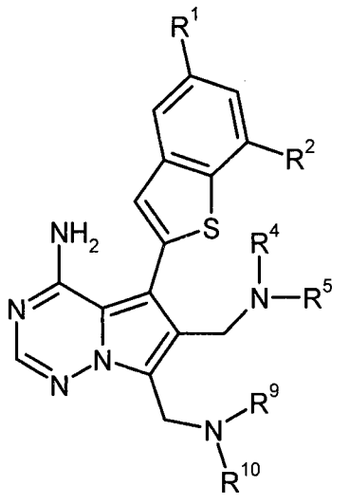
y se trata con una amina de fórmula (XV)



(XV),

en la que R^4 y R^5 tienen los significados que se describieron anteriormente,

en presencia de un ácido y un agente reductor para dar el compuesto diana de fórmula (I-D)

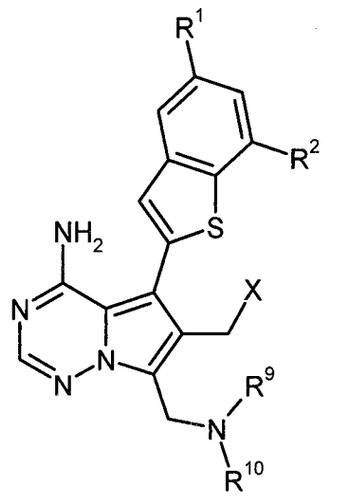


(I-D),

en la que R^1, R^2, R^4, R^5, R^9 y R^{10} tienen los significados que se describieron anteriormente,

o

[C-2] se convierte en el correspondiente derivado 6-(halometilo) de fórmula (XVI)



(XVI),

en la que R^1, R^2 R^9 y R^{10} tienen los significados que se describieron anteriormente,

y

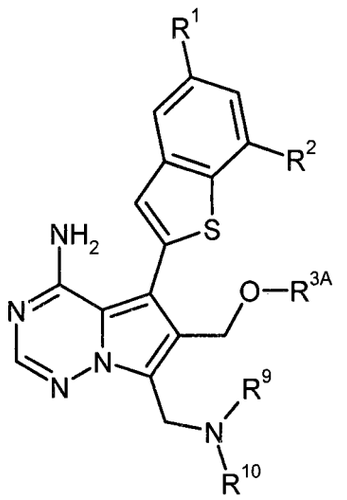
X es cloro, bromo o yodo,

y se trata con un alcohol de fórmula (XVII)

R^{3A}—OH (XVII),

en la que R^{3A} tiene el significado de R^3 como se describió anteriormente salvo hidrógeno,

en presencia de una base para dar el compuesto diana de fórmula (I-E)



(I-E),

en la que R^1, R^2, R^{3A}, R^9 y R^{10} tienen los significados que se describieron anteriormente, seguido opcionalmente, donde sea apropiado, por (i) separación de los compuestos de fórmula (I) obtenidos de este modo en sus respectivos enantiómeros y/o diastereómeros, preferentemente usando procedimientos cromatográficos, y/o (ii) conversión los compuestos de fórmula (I) en sus respectivos hidratos, solvatos, sales y/o hidratos o solvatos de las sales mediante el tratamiento con los correspondientes solventes y/o ácidos o bases.

Los compuestos de las fórmulas (I-A), (I-B), (I-C), (I-D) y (I-E), los cuales se pueden preparar mediante los procedimientos descriptos anteriormente, representan cada uno de ellos un subconjunto particular de los compuestos de la fórmula general (I).

Los pasos del procedimiento [A] (II) → (IV) and [C] (XIII) → (I-C), que representan las reacciones de aminometilación del tipo Mannich, se llevan a cabo en la forma usual mediante el tratamiento del compuesto de partida respectivo con una mezcla de formaldehído acuoso y el componente amina (III) en presencia de un catalizador de ácido tal como ácido fórmico o ácido acético. Preferentemente, el ácido acético se usa tanto como catalizador como solvente. La reacción usualmente se realiza a una temperatura que oscila desde +20°C a +80°C.

Como agente de brominación para las etapas del procedimiento [A] (IV) → (V) and [B] (VII) → (VIII), preferentemente se usan N-bromo-succinimida (NBS), 1,3-dibromo-5,5-dimetildantoína (DBDMH) o bromo elemental. Las reacciones se llevan a cabo generalmente en un solvente inerte, tales como diclorometano, cloroformo, tetrahidrofurano, acetonitrilo o N,N-dimetilformamida (DMF), dentro de un intervalo de temperatura desde -78°C a +20°C.

Las reacciones de acoplamiento [A] (V) + (VI) → (I-A), [B] (VIII) + (VI) → (IX) and [C] (XII) + (VI) → (XIII) ["acoplamiento Suzuki-Miyaura"] se llevan a cabo generalmente en un solvente inerte con la ayuda de un catalizador de paladio y una base acuosa. Los catalizadores de paladio adecuados para este fin incluyen, por ejemplo, acetato de paladio (II), cloruro de paladio (II), cloruro de bis(trifenilfosfina)paladio(II), cloruro de bis(acetonitrilo)paladio(II), cloruro de [1,1'-bis(difenilfosfino)ferroceno]paladio(II), tetrakis(trifenilfosfina)paladio(0), bis-(dibencilidenacetona)paladio(0), y tris(dibencilidenacetona)dipaladio(0), opcionalmente en combinación con otros ligandos de fosfina, tales como por ejemplo, 2-diciclohexilfosfino-2',4',6'-triisopropilbifenilo (X-Phos), 2-diciclohexil-fosfino-2',6'-dimethoxibifenilo (S-Fos), 4,5-bis(difenilfosfino)-9,9-dimetilxanteno (Xantphos), o 4-(di-*ter*-butilfosfino)-*N,N*-dimetilanilina. Además, se pueden usar precatalizadores de paladio a partir de los cuales se genera la especie catalíticamente activa bajo condiciones de reacción, tales como (2'-aminobifenil-2-il)(cloro)paladio-diciclohexil(2',4',6'-triisopropilbifenil-2-il)fosfina, [véase, por ejemplo, S. Kotha *et al.*, *Tetrahedron* 58, 9633-9695 (2002); T. E. Barder *et al.*, *J. Am. Chem. Soc.* 127 (13), 4685-4696 (2005); S. L. Buchwald *et al., J. Am. Chem. Soc.* 132 (40), 14073-14075 (2010), y otras referencias mencionadas en los mismos].

Las bases adecuadas para estas reacciones de acoplamiento son en particular los carbonatos alcalinos, tales como sodio, potasio o carbonato de cesio, fosfatos alcalinos, tales como fosfato de sodio o potasio, o fluoruros alcalinos, tales como fluoruro de potasio o cesio. Usualmente, estas bases se emplean

como soluciones acuosas. Las reacciones se llevan a cabo en solventes orgánicos que son inertes bajo las condiciones de reacción. Preferentemente, se emplean solventes orgánicos miscibles en agua, tales como 1,22-dimetoxietano, tetrahidrofurano, 1,4-dioxano, acetonitrilo, N,N-dimetilformamida (DMF) o dimetilsulfóxido (DMSO), pero también se pueden usar otros solventes inertes tales como diclorometano o tolueno.

La etapa del procedimiento [B] (II) → (VII) ["formilación Vilsmeier-Haack"] se lleva a cabo de la manera usual mediante el tratamiento de la pirrolotriazina (II) en solvente de N,N-dimetilformamida (DMF) con cloruro de fosforilo. La reacción se realiza usualmente a una temperatura desde 0ºC hasta +80ºC.

Los agentes de reducción para las reacciones de aminación reductoras [B-1] (IX) + (III) → (I-A) y [C-1] (XIV) + (XV) → (I-D) son borohidruros alcalinos convencionales, tales como borohidruro de litio, borohidruro de sodio, borohidruro de potasio, cianoborohidruro de sodio o triacetoxiborohidruro de sodio. Las transformaciones se llevan a cabo generalmente en presencia de un ácido, preferentemente ácido acético, en un alcohol o solvente de éter, tales como metanol, etanol, isopropanol, tetrahidrofurano o 1,4-dioxano, dentro de un intervalo de temperatura desde 0°C a +80°C, dependiendo de la reactividad de los componentes amina (III) y (XV), respectivamente, y/o el borohidruro particular usado.

Para la reacción de oxidación en la etapa del procedimiento [B-2] (IX) → (X), la oxidación con clorito de sodio en presencia de un limpiador de hipoclorito tal como 2-metil-2-buteno representa el procedimiento de elección [*cf.* H. W. Pinnick *et al.*, *Tetrahedron* 37, 2091-2096 (1981); A. Raach and O. Reiser, *J. Prakt. Chem.* 342 (6), 605-608 (2000), y las referencias citadas en el mismo]. La reacción usualmente se lleva a cabo en una mezcla de tetrahidrofurano/agua a una temperatura entre 0ºC y temperatura ambiente.

Los agentes de condensación adecuados para la etapa del procedimiento B-2] (X) + (XI) → (I-B) [formación de amida] incluyen, por ejemplo, carbodiimidas

tales como N,N'-dietil-, N,N'-dipropil-, N,N'-diisopropil-, N,N'-diciclohexilcarbodiimida (DCC) o N-(3-dimetilaminopropil)-N'-etilcarbodiimida (EDC), Derivados de fosgeno tales como N,N'-carbonildiimidazol (CDI) o isobutil cloroformiato, α-cloroenaminas tales como 1-cloro-2-metil-1-dimetilamino-1-propeno, compuestos de fósforo tales como anhídrido propanofosfónico, dietil cianofosfonato, bis(2-oxo-3-oxazolidinil)fosforil cloruro, benzotriazol-1-iloxi-tris-(dimetilamino)fosfonio hexafluorofosfato (BOP) o benzotriazol-1-iloxi-tris(pirrolidino)fosfonio hexafluorofosfato (PyBOP), y compuestos de uronio tales como *O*-(benzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio tetrafluoroborato (TBTU), *O*-(benzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio hexafluorofosfato (HBTU), 2-(2-oxo-1-(2*H*)-piridil)-1,1,3,3-tetrametiluronio tetrafluoroborato (TPTU), *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio hexafluorofosfato (HATU) o *O*-(1*H*-6-chlorobenzotriazol-1-il)-1,1,3,3-tetrametiluronio tetrafluoroborato (TCTU), si fuera apropiado en combinación con otros auxiliares, tales como 1-hidroxibenzotriazol (HOBt) o N-hidroxisuccinimida (HOSu), y/o bases tales como carbonatos alcalinos, por ejemplo carbonato de sodio o potasio, o bases de amina orgánica, tales como trietilamina, N-metilpiperidina, N-metilmorfolina (NMM), N,N-diisopropiletilamina (DIPEA), piridina o 4-N,N-dimetilaminopiridina (DMAP). Se da preferencia a usar *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio hexafluorofosfato (HATU) o *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetrametiluronio tetrafluoroborato (TBTU) en combinación con N,N-diisopropiletilamina (DIPEA) y opcionalmente 1-hidroxibenzotriazol (HOBt).

Los solventes inertes para la etapa del procedimiento [B-2] (X) + (XI) → (I-B) son, por ejemplo, éteres tales como éter dietílico, ter-butil metil éter, tetrahidrofurano, 1,4-dioxano, o 1,2-dimetoxietano, hidrocarburos tales como benceno, tolueno, xileno, hexano o ciclohexano, hidrocarburos halogenados tales como diclorometano, triclorometano, tetracloruro de carbono, 1,2-dicloroetano, tricloroetileno o clorobenceno, u otros solventes tales como acetona, acetonitrilo, acetato de etilo, piridina, dimetilsulfóxido (DMSO), N,N-

dimetilformamida (DMF), N,N'-dimetilpropileno urea (DMPU) o N-metilpirrolidinona (NMP). Además es posible usar mezclas de estos solventes. Se da preferencia al uso de diclorometano, tetrahidrofurano, N,N-dimetilformamida o mezclas de los mismos. Las reacciones se llevan a cabo generalmente a una temperatura que oscila desde 0°C a +60°C. preferentemente a +10°C hasta +40°C.

Los agentes de oxidación que son capaces de convertir el alcohol primario (I-C) en el aldehído (XIV) (procedimiento [C-1] en condiciones suaves incluyen 1,1,1-triacetoxi-1,1-dihidro-1,2-benzodioxol-3-(1H)-ona ("periodinano Dess-Martin"), 2,2,6,6-tetrametilpiperidin-1-oxilo (TEMPO) en combinación con oxidantes secundarios tales como yodosobenceno-I,I-diacetato o hipoclorito de sodio, y los sistemas de oxidación basados en dimetilsulfóxido (DMSO) tales como DMSO/anhídrido trifluoroacético o DMSO/ N,N'-diciclohexil-carbodiimida (DCC). Se da preferencia a 1,1,1-triacetoxi-1,1,-dihidro-1,2-benciodoxol-3-(1H)-ona. La reacción se lleva a cabo generalmente en un solvente inerte, preferentemente usando diclorometano.

Para la transformación de hidroxi a halógeno en la etapa del procedimiento [C-2] (I-C) $\rightarrow$ (XVI), se pueden emplear varios procedimientos estándares y reactivos que son bien conocidos en la técnica. Los reactivos de elección son cloruro de tionilo [para X = Cl], tetrabromometano/trifenilfosfina [para X = Br], y yodo/trifenilfosfina [para X = I]. Se prefiere la preparación de los derivados de 6-(clorometilo) (XVI) [X = Cl] por razones de conveniencia de elaboración y estabilidad del compuesto.

Las bases adecuadas para la etapa del procedimiento [C-2] (XVI) + (XVII) $\rightarrow$ (I-E) [formación de éter] son en particular carbonatos alcalinos tales como litio, sodio, potasio o carbonato de cesio, acetatos alcalino tales como acetato de sodio o potasio, o bases de amina terciaria convencionales tales como trietilamina, N-metilmorfolina, N-metilpiperidina, N,N-diisopropiletilamina o piridina. Se da preferencia a N,N-diisopropiletilamina (DIPEA). La reacción (XVI)

+ (XVII) → (I-E) se realiza en un solvente inerte, tal como tetrahidrofurano, o sin solvente, usando un exceso de alcohol (XVII), a una temperatura que oscila desde +20°C a +200°C, preferentemente a +50°C hasta +150°C. Ventajosamente, la conversión se lleva a cabo por medio de un dispositivo de reactor de microondas.

La secuencia de la reacción (I-C) → (XVI) → (I-E) puede llevarse a cabo en dos etapas separadas, es decir con aislamiento y purificación del compuesto intermediario (XVI), o se puede llevar a cabo usando un procedimiento directo. es decir empleando el intermediario bruto (XVI) como se obtiene en la reacción de preparación.

En los casos donde un resto de amina primaria o secundaria forma parte del grupo G^1 o G^2 en los compuestos diana de fórmula (I), algunas veces puede ser apropiado en las reacciones de preparación descriptas anteriormente usar un derivado protegido de esta amina como compuesto de reacción en lugar de la amina libre. A este fin, se pueden emplear grupos de protección amino temporarios convencionales, tales como los grupos de acilo (por ej., acetilo o trifluoroacetilo) o grupos de protección del tipo carbamato (por ej., un grupo Boc, Cbz o Fmoc). Preferentemente se usa un grupo Boc (ter-butoxicarbonilo). De manera similar, una función hidroxi que es parte del grupo G^1 o G^2 puede ser bloqueada temporalmente en los compuestos precursores y en los intermediarios del procedimiento, por ejemplo, como un éter tetrahidropiranilo (THP) o como un derivado de silil éter, tal como trimetilsililo o ter-butildimetilsililo éter.

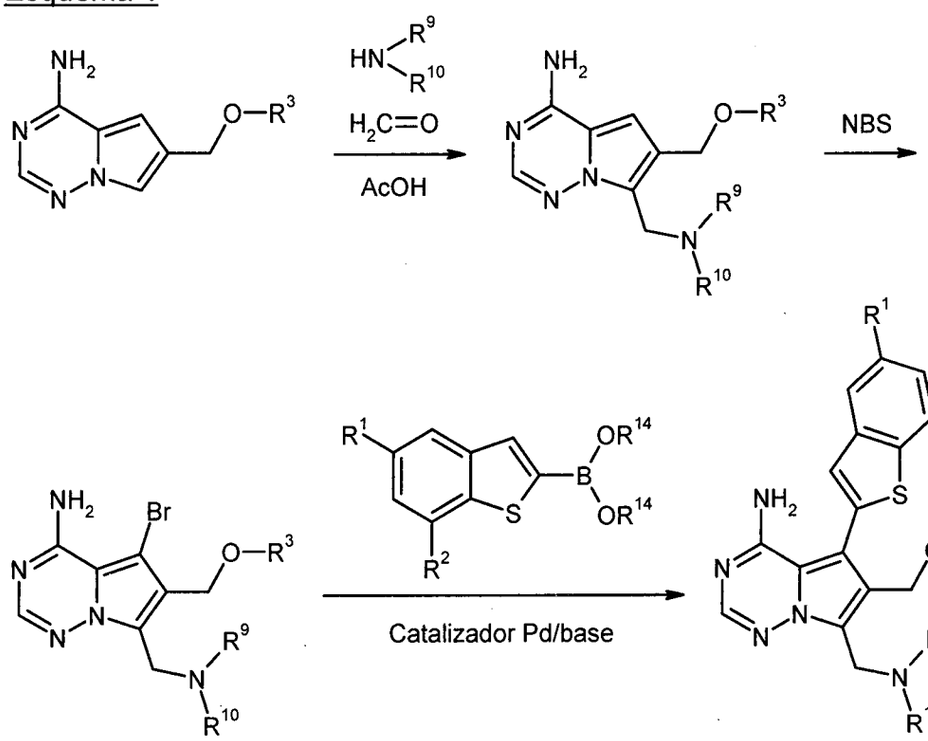
Estos grupos de protección se pueden escindir posteriormente de forma concomitante durante los procedimientos de elaboración acuosa y purificación, o se pueden remover en una etapa de reacción posterior, separada usando procedimientos estándares bien conocidos en la técnica. La preparación de estos intermediarios protegidos a partir de las correspondientes aminas libres o alcoholes se obtiene de igual modo fácilmente siguiendo los procedimientos

generales descriptos en la literatura [véase, por ejemplo, T. W. Greene and P. Wuts, *Protective Groups in Organic Synthesis*, Wiley, New York, 1999].

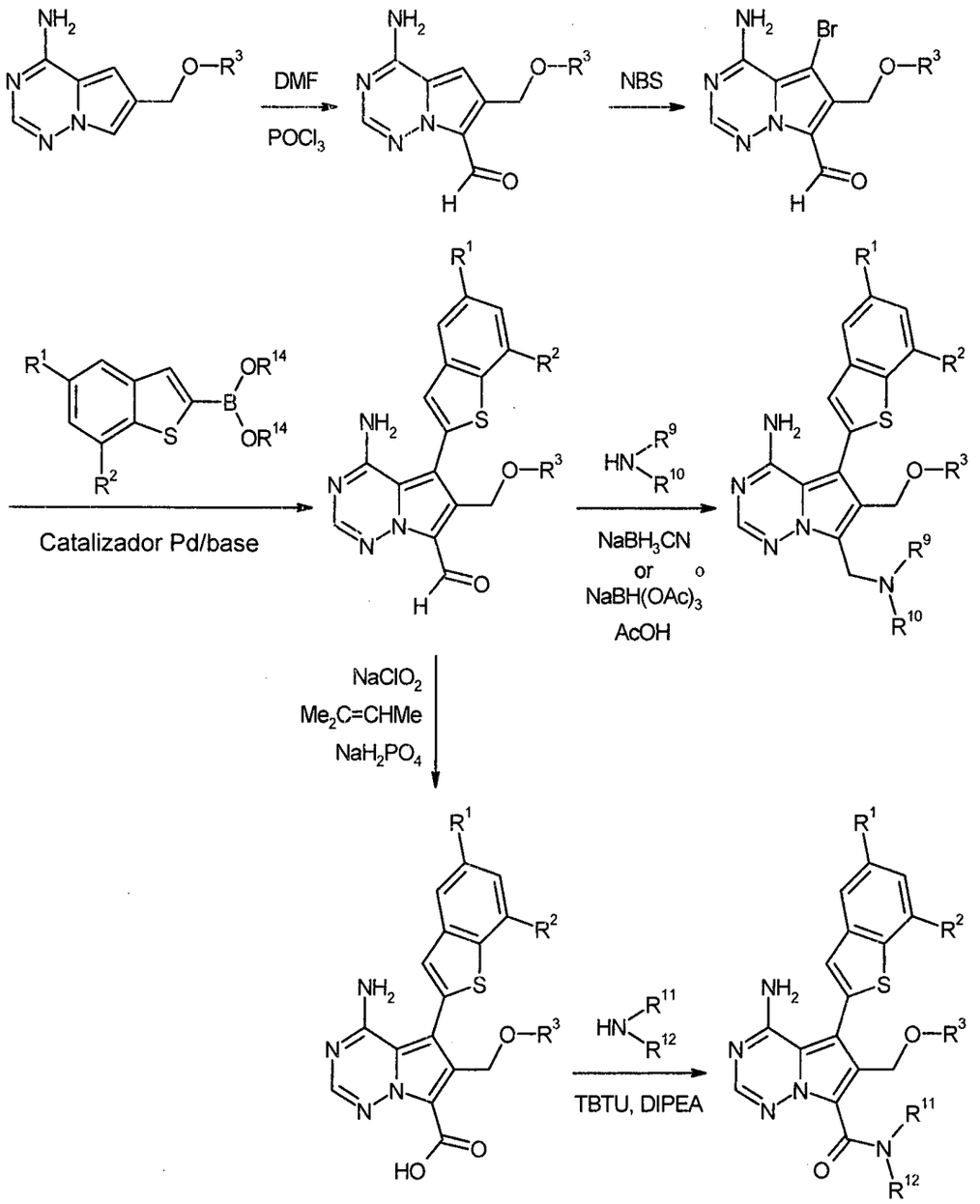
Ciertos tipos de derivados de amina protegidos (es decir, acilados) ejercen actividad inhibidora del FGFR significativa por sí mismos. En consecuencia, estos compuestos también están comprendidos en la fórmula general (I) como se definió anteriormente.

La preparación de los compuestos de la invención se puede ilustrar por medio de los siguientes esquemas de reacción:

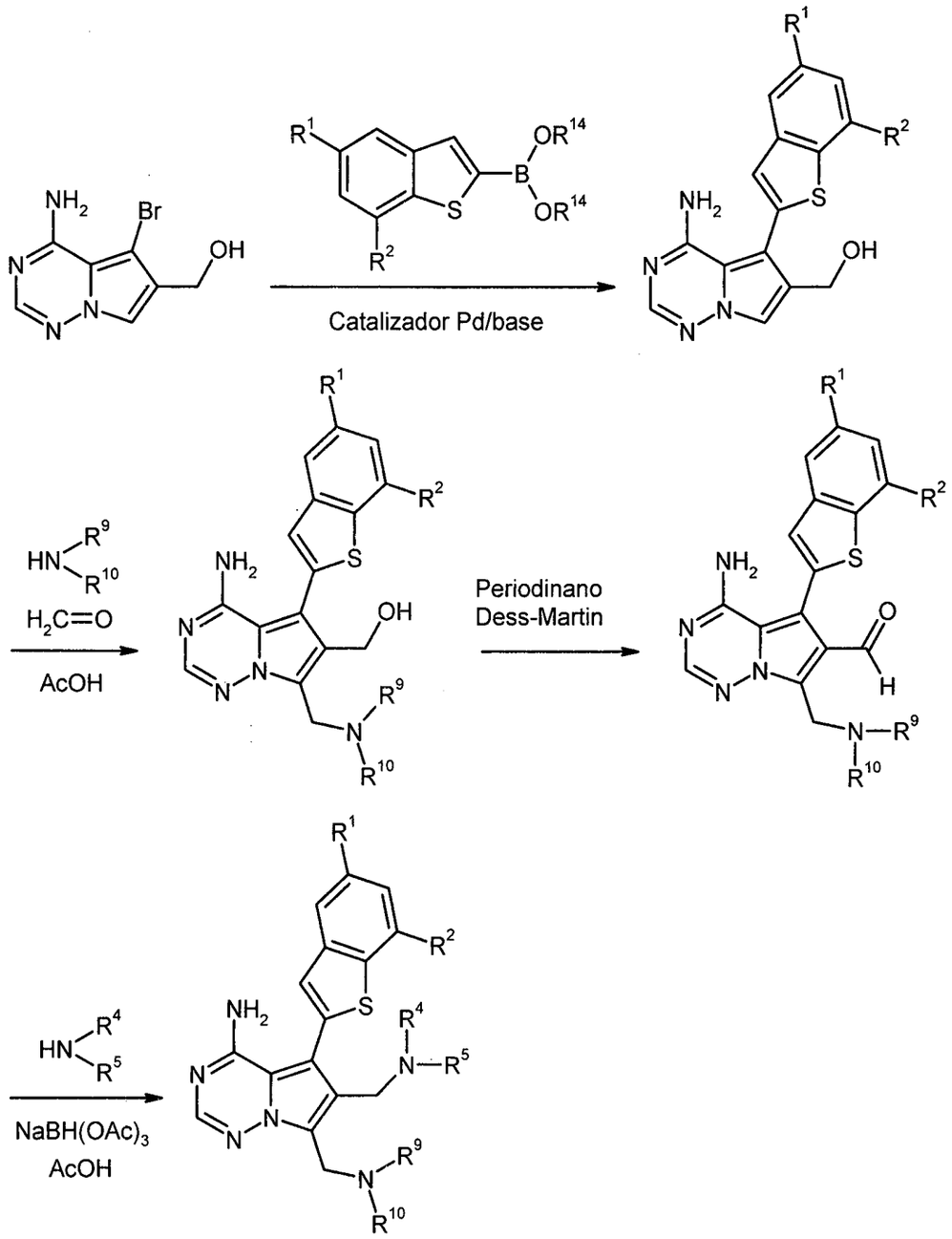
Esquema 1



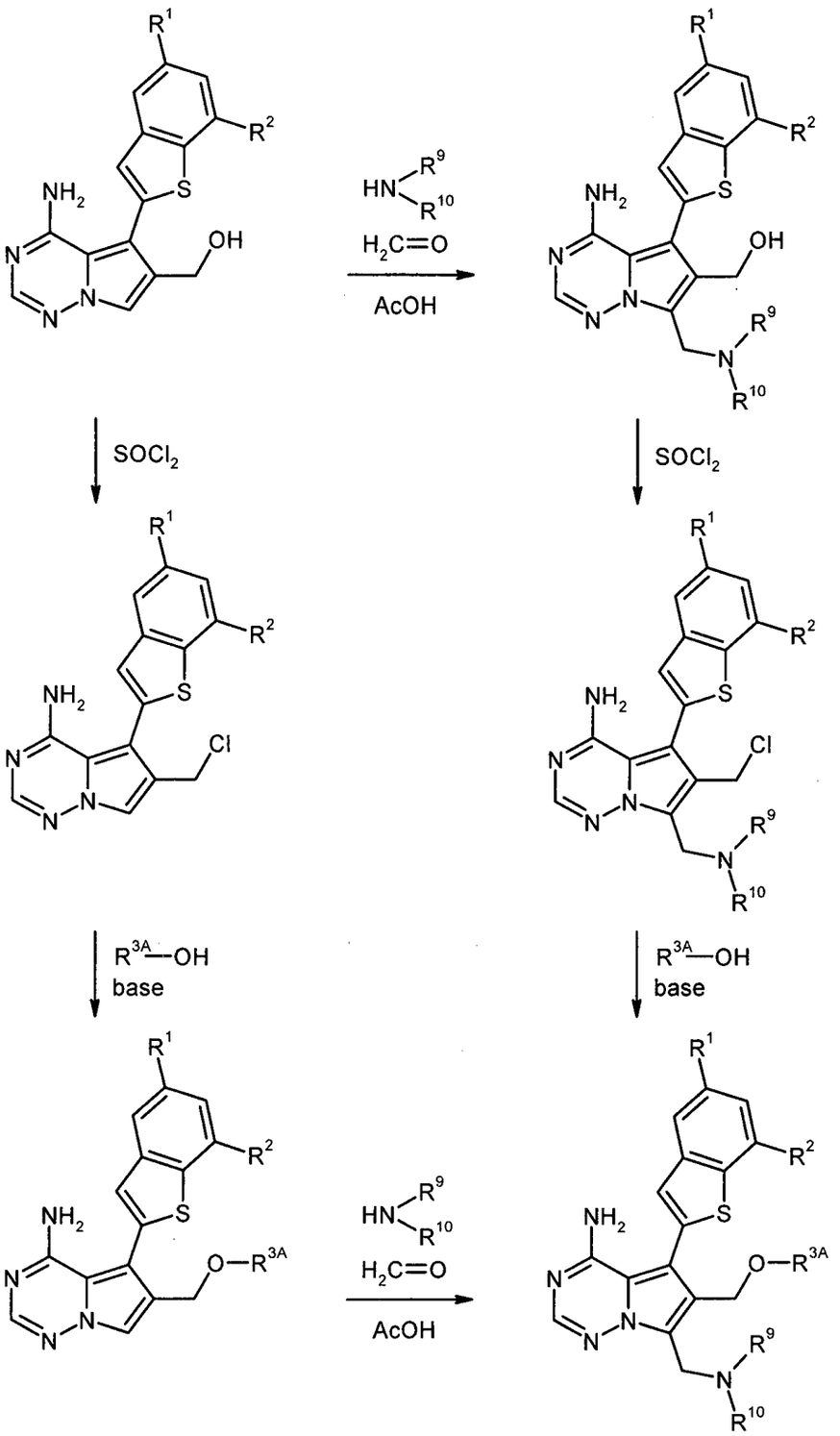
Esquema 2


DMF
POCl3
NBS
Catalizador Pd/base
NaBH3CN
or
NaBH(OAc)3
AcOH
NaClO2
Me2C=CHMe
NaH2PO4
TBTU, DIPEA

Esquema 3



Esquema 4

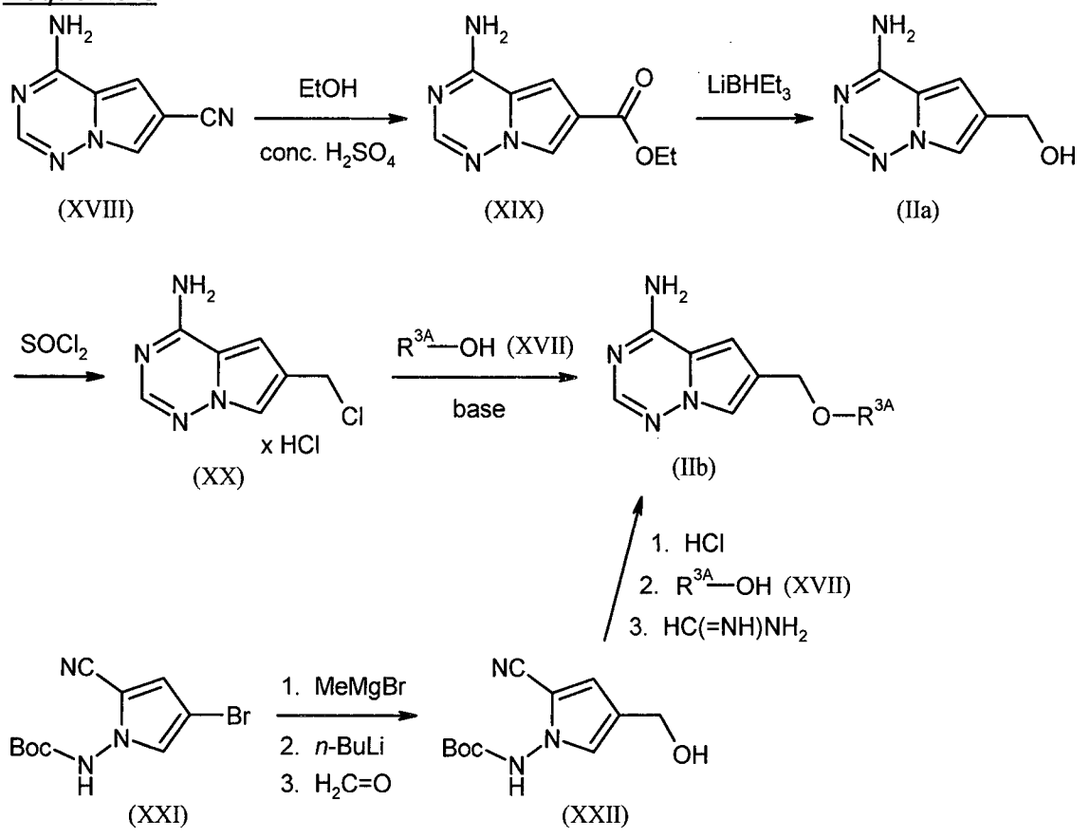


La 4-aminopirrolo[2,1-f][1,2,4]triazina 6 sustituida de fórmula (II) puede, por ejemplo, prepararse mediante dos vías diferentes, las cuales se describen en el esquema 5 a continuación. En la primera vía, la 4-amino-6-cianopirrolo[2,1-f]-[1,2,4]triazina (XVIII) se convierte en el éster (XIX) mediante la alcoholísis mediada por ácido y posteriormente se reduce al compuesto 6-(hidroximetilo)

(IIa) [R^3 en (II) = H] usando trietil-borohidruro de litio. La transformación estándar en la correspondiente 6-(halometil)pirrolotriazina, tal como el compuesto cloro (XX), seguido del tratamiento con un alcohol de fórmula (XVII) en presencia de una base proporciona fácilmente los derivados de éter de fórmula (IIb) [R^3 en (II) ≠ H]. La preparación del compuesto de partida (XVIII) ha sido descripta previamente [véase la Solicitud de Patente Internacional WO 2007/ 064883 (Intermediario AX / Etapa 3)].

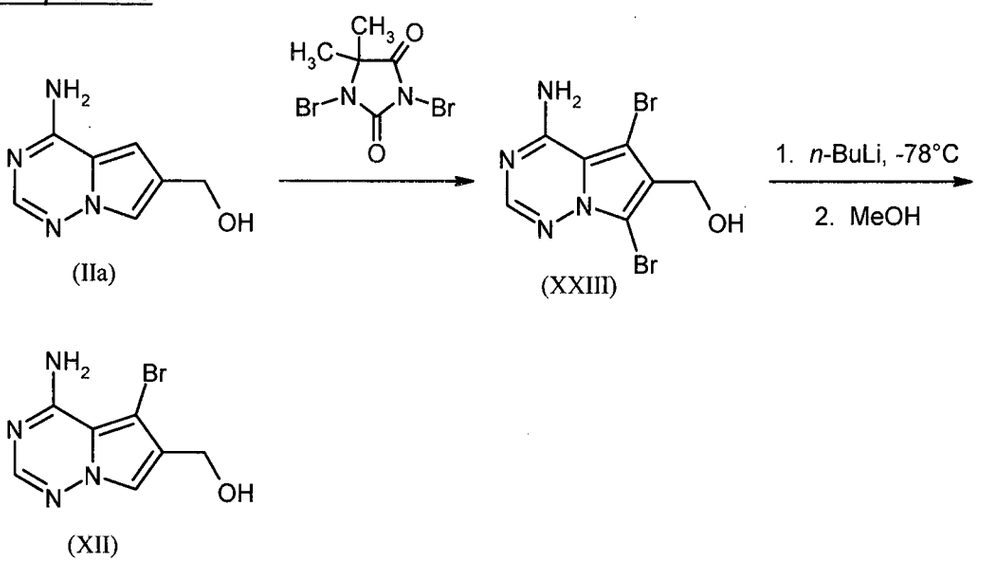
La segunda vía comienza a partir del 1-amino-4-bromo-2-cianopirrol protegido (XXI) [la preparación se da en la Solicitud de Patente Internacional WO 2007/064883 (Intermediario AAE, Etapa 3)]. La deprotonación del nitrógeno uretano, la subsiguiente dianalación en la posición 4 y la reacción con formaldehído da el derivado 4-(hidroximetilo) (XXII). El tratamiento con cloruro de hidrógeno seguido de la adición de alcohol (XVII) y la condensación con formamidina usando un procedimiento directo proporciona posteriormente el compuesto diana de fórmula (IIb). Esta vía es especialmente adecuada para la preparación de los derivados de alquil éter [R^{3A} en (IIb) = (C_1-C_4)-alquilo] en que el reactivo de alcohol (XVII) también puede ser útil como el solvente de reacción en estos casos.

Esquema 5



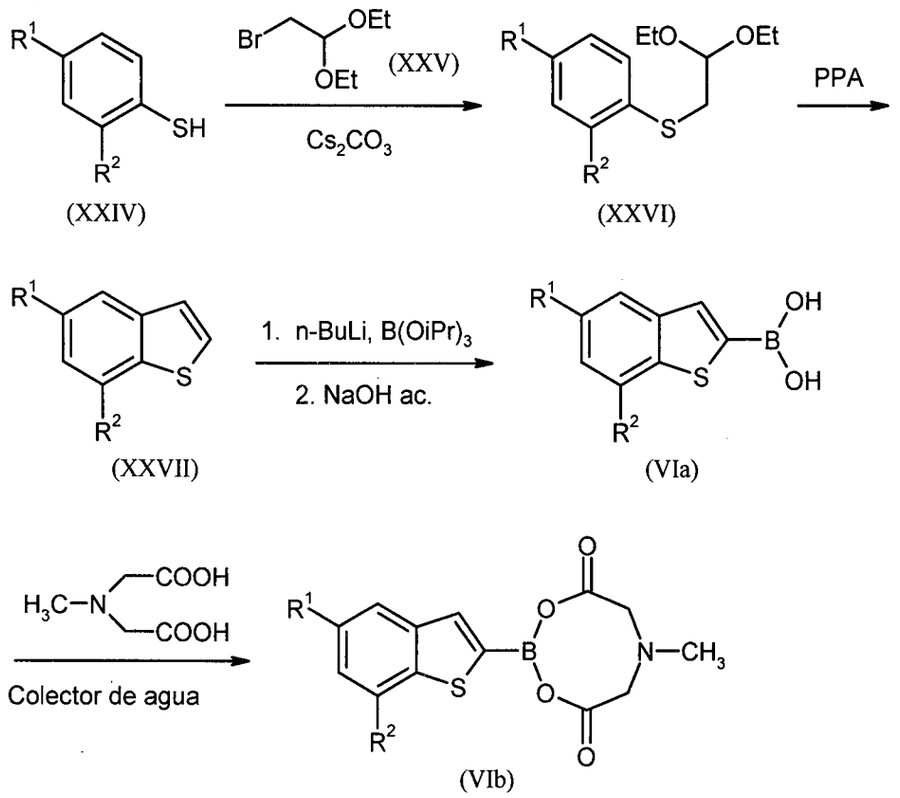
El derivado 4-amino-5-bromopirrolo[2,1-f][1,2,4]triazina de fórmula (XII) está disponible fácilmente a partir de 4-amino-6-(hidroximetil)pirrolo[2,1-f][1,2,4]-triazina (IIa) (véase el esquema 5) por la 5,7-dibrominacióin inicial usando 1,3-dibromo-5,5-dimetilhidantoína y la subsiguiente 7-debromination selectiva mediante un intercambio de halógeno-dianal con n-butillitio seguido del templado de metanol (véase el esquema 6 a continuación).

Esquema 6



Los benzotiofeno-2-il boronatos de fórmula (VI) pueden ser preparados de forma conveniente partiendo de los derivados de tiofenol sustituidos de fórmula (XXIV) (véase el esquema 7 a continuación). La alquilación con bromo-acetal (XXV) y la posterior ciclización mediada por el ácido polifosfórico proporciona los intermediarios de benzotiofeno de fórmula (XXVII) los cuales posteriormente se dianalizan en la posición 2 y se hacen reaccionar con trialquil borato. La elaboración alcalina da los ácidos (benzotiofen-2-il)borónico libres de fórmula (VIa) los cuales pueden ser transformados, si se desea, en boronatos cíclicos, por ej., los denominados boronatos MIDA de fórmula (VIb), mediante procedimientos estándares conocidos en la técnica [véase, por ejemplo, D. M. Knapp *et al.*, *J. Am. Chem. Soc.* 131 (20), 6961-6963 (2009)].

Esquema 7



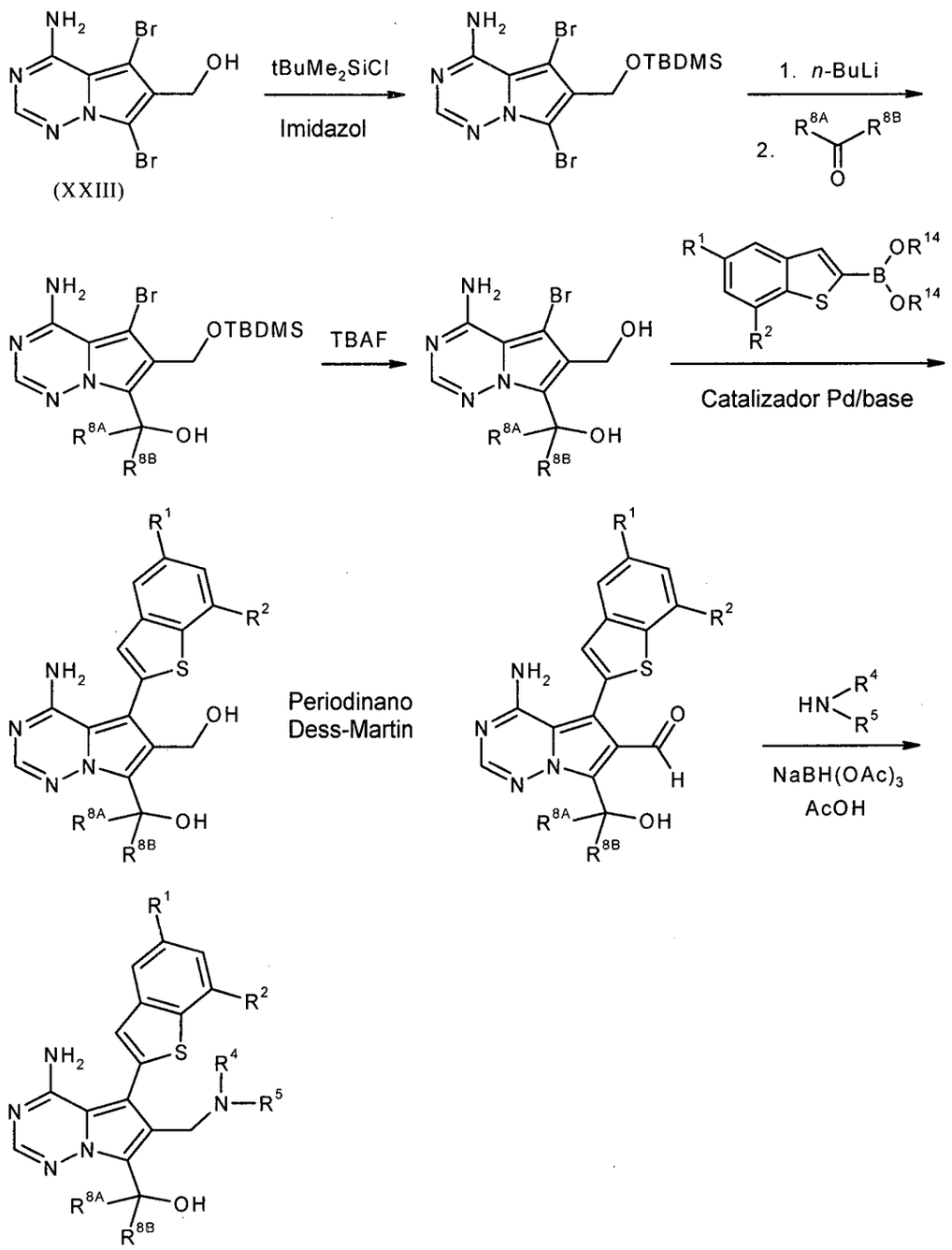
[*cf.* P. A. Plé and L. J. Marnett, *J. Heterocyclic Chem.* 25 (4), 1271-1272 (1988); A. Venturelli *et al.*, *J. Med. Chem.* 50 (23), 5644-5654 (2007)].

Los compuestos de las fórmulas (III), (XI), (XV), (XVII), (XXIV) y (XXV) están disponibles en el comercio, se conocen a partir de la literatura, o se pueden preparar a partir de los materiales de partida fácilmente disponibles por la adaptación de los procedimientos estándares descriptos en la literatura. Los procedimientos detallados y las referencias de literatura para preparar los materiales de partida también se pueden hallar en la Parte Experimental en la sección sobre la preparación de los materiales de partida y los intermediarios.

La preparación de otros subgrupos de los compuestos de fórmula general (I) se ilustra en los siguientes esquemas de reacción 8-14. Los precursores de pirrolotriazina requeridos se pueden sintetizar fácilmente mediante procedimientos habituales bien conocidos en la técnica, y otras transformaciones sintéticas, en muchos casos, siguen las vías de preparación que han sido delineadas en la sección del procedimiento anterior, usando tipos

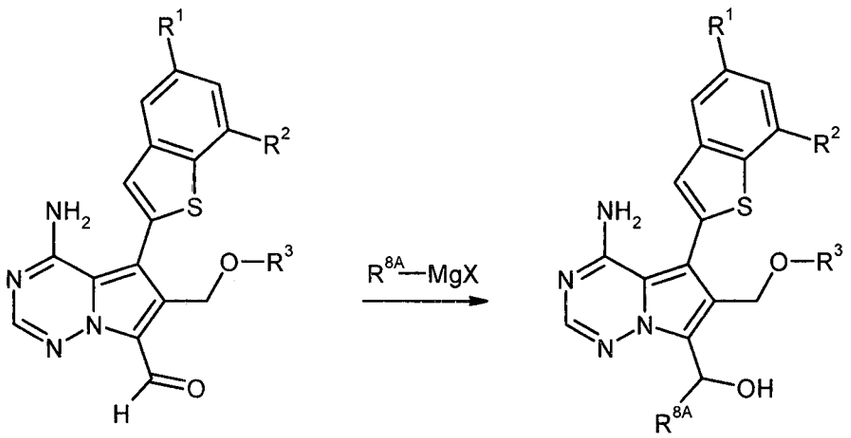
similares de reacciones, tales como, por ejemplo, bromination, acoplamiento de boronato, aminometilación, aminación reductora, oxidación y/o reacciones formadoras de éter o amida. Se proporcionan otros detalles en la Parte Experimental sobre la preparación de las realizaciones de ejemplo y sus respectivos compuestos precursores.

Esquema 8



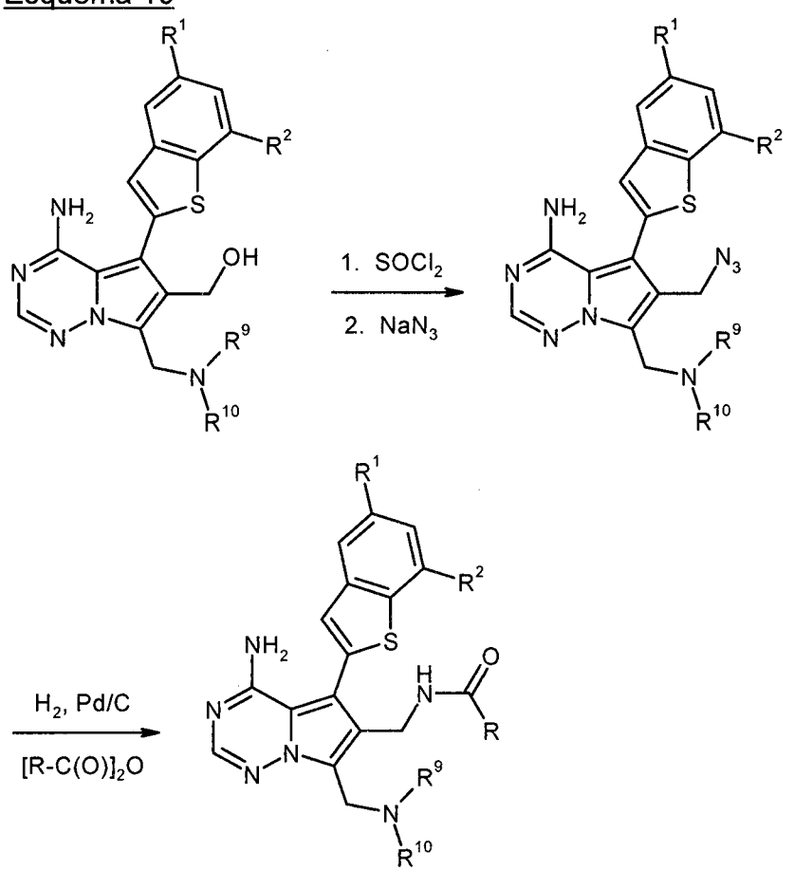
[R^{8A}, R^{8B} = alquilo (C_1-C_4), ciclopropilo o ciclobutilo].

Esquema 9



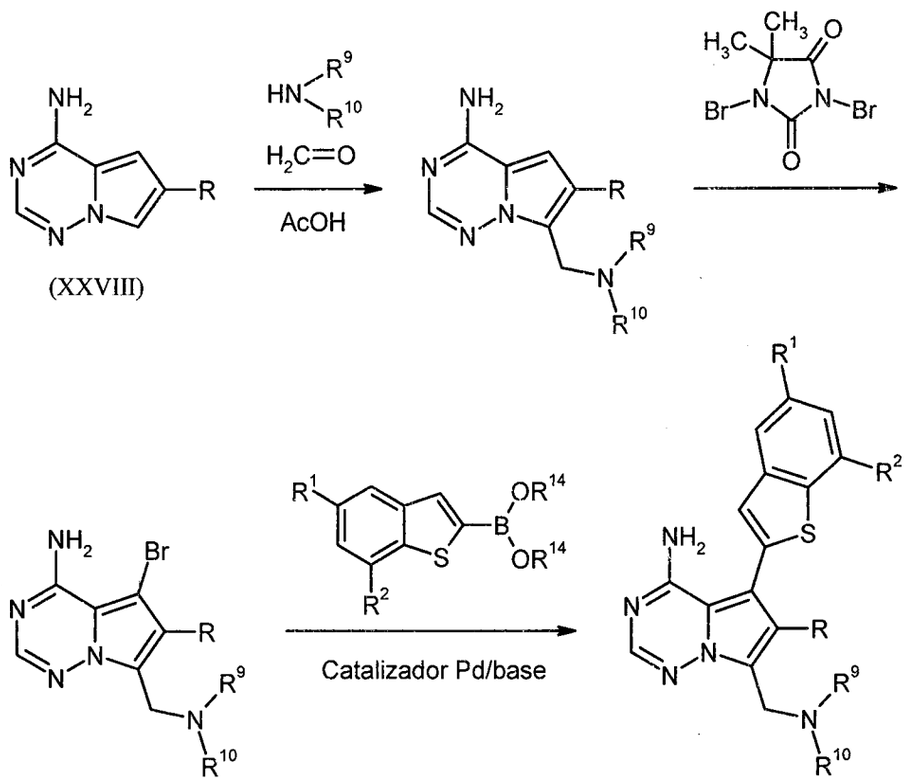
[R^{8A} = alquilo (C_1-C_4), ciclopropilo o ciclobutilo; X = Cl, Br o I].

Esquema 10



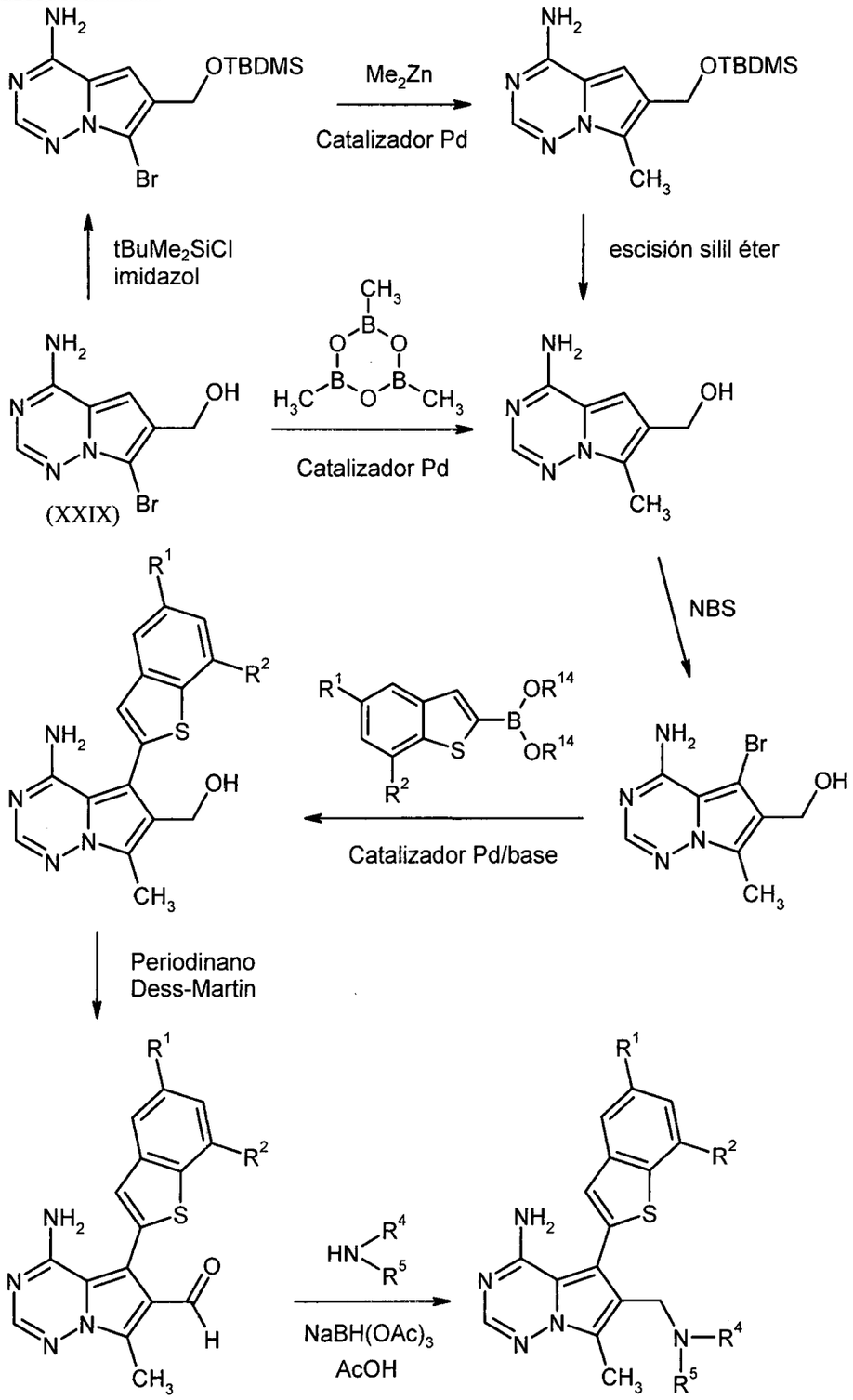
[R = alquilo (C_1-C_4)].

Esquema 11



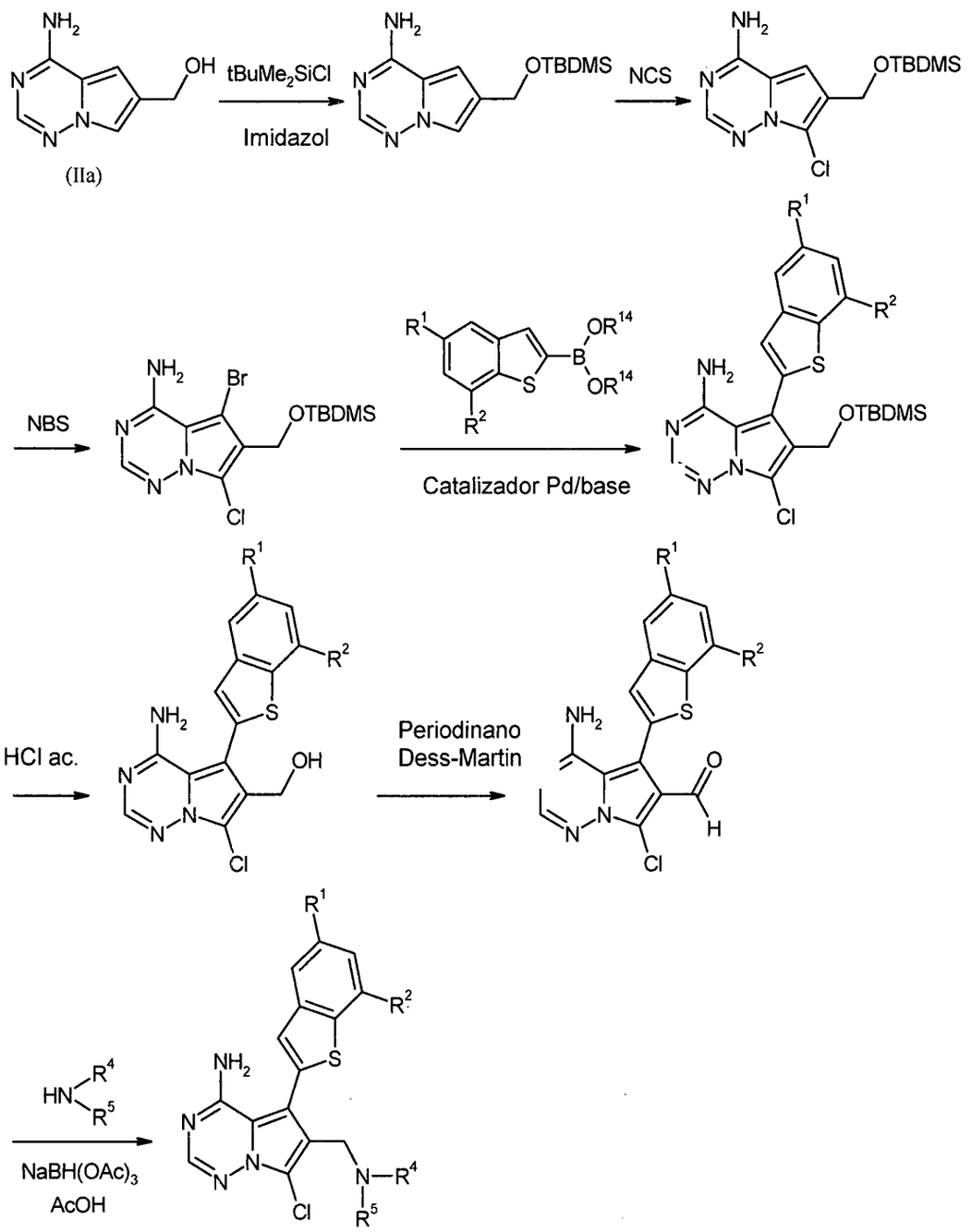
[R = cloro o alquilo (C_1-C_4); para la preparación del material de partida (XXVIII), véase la Solicitud de Patente Internacional WO 2007/064883 y WO 2007/056170, respectivamente].

Esquema 12

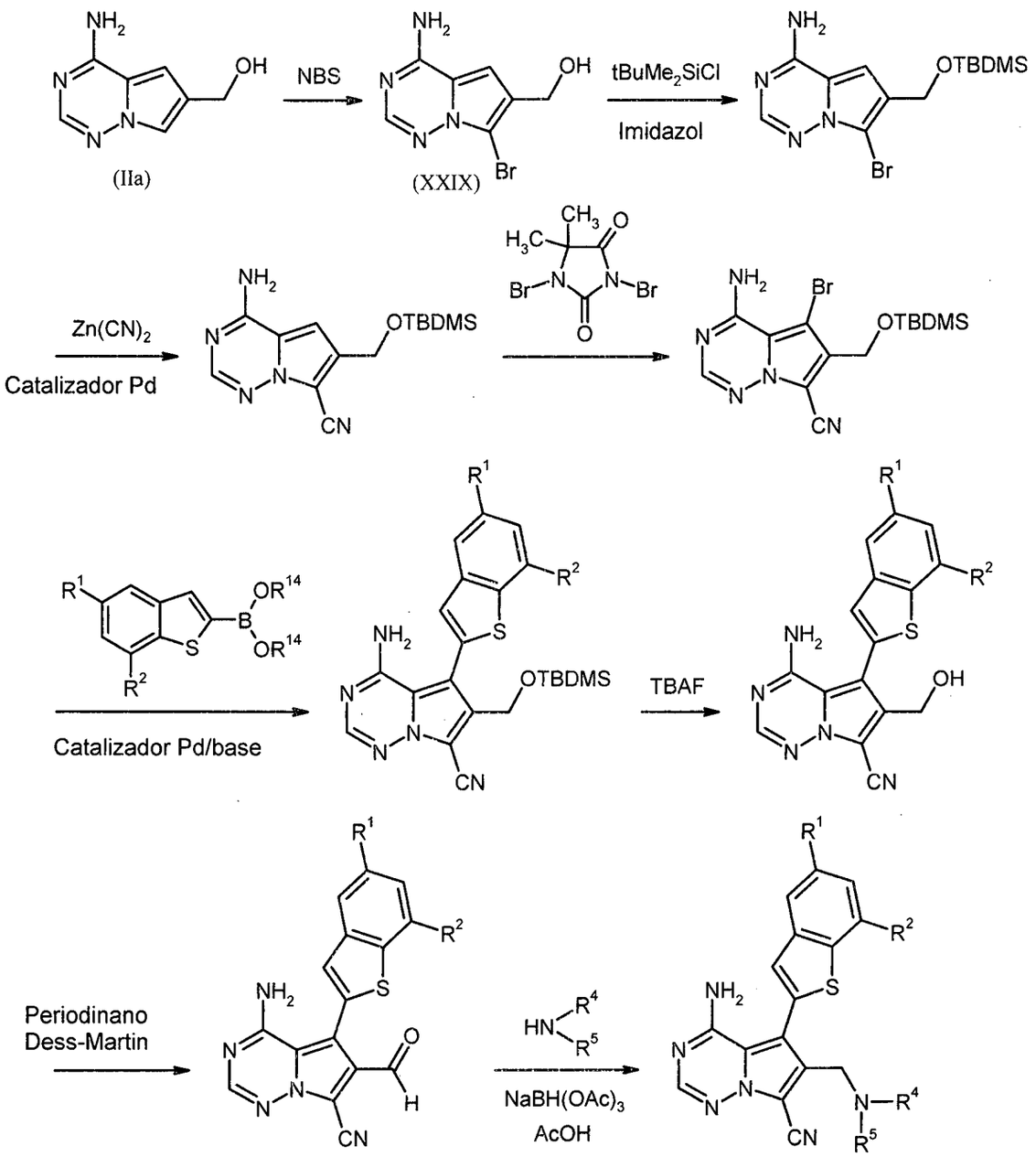


[para la preparación del compuesto de partida (XXIX), véase el esquema 14 a continuación].

Esquema 13


NH2
OH
tBuMe2SiCl
Imidazol
OTBDMS
NCS
Cl
(IIa)
NBS
Br
R1
R2
OR14
B
S
N
Catalizador Pd/base
HCl ac.
Periodinano
Dess-Martin
O
H
HN
R4
R5
NaBH(OAc)3
AcOH

Esquema 14



Los compuestos de la presente invención tienen propiedades farmacológicas valiosas y se pueden usar para la prevención y el tratamiento de trastornos en humanos y otros mamíferos.

Los compuestos de la presente invención son potentes inhibidores de la actividad o la expresión de las tirosina quinasas del receptor, particularmente de las quinasas del FGFR, y de forma más notable de las quinasas del FGFR-1 y el FGFR-3. En consecuencia, en otra realización, la presente invención proporciona un procedimiento para trastornos que se relacionan a o están

mediados por la actividad de las quinasas del FGFR en un paciente que necesita de ese tratamiento, que comprende administrar al paciente una cantidad eficaz de un compuesto de fórmula (I) como se definió anteriormente. En ciertas realizaciones, los trastornos que se refieren a la actividad de las quinasas del FGFR son trastornos proliferativos, en particular cáncer y enfermedades tumorales.

En el contexto de la presente invención, el término "tratamiento" o "que trata" incluye inhibir, retardar, aliviar, mitigar, detener, reducir, o causar la regresión de una enfermedad, trastorno, afección, o estado, el desarrollo y/o el avance de la misma, y/o sus síntomas. El término "prevención" o "que previene" incluye reducir los riesgos de tener, contraer, o experimentar una enfermedad, trastorno, afección, o estado, el desarrollo y/o el avance de la misma, y/o sus síntomas. El término prevención incluye la profilaxis. El tratamiento o la prevención de un trastorno, enfermedad, afección, o estado puede ser parcial o completo.

El término "trastorno proliferativo" incluye los trastornos que involucran la proliferación no deseada o sin control de una célula. Los compuestos de la presente invención se pueden utilizar para prevenir, inhibir, bloquear, reducir, disminuir, controlar, etc., la proliferación celular y/o la división celular, y/o producir apoptosis. Este procedimiento comprende administrar a un sujeto que lo necesita, incluyendo un mamífero, incluyendo un humano, una cantidad de un compuesto de esta invención, o una sal, isómero, polimorfo, dianabolito, hidrato o solvato del mismo aceptable para uso farmacéutico, el cual es eficaz para tratar o prevenir el trastorno.

A lo largo de este documento, con el fin de simplificar, se da preferencia al uso de un lenguaje singular sobre el plural, pero en general significa incluir el lenguaje plural si no se establece lo contrario. Por ejemplo, la expresión "Un procedimiento para tratar una enfermedad en un paciente, que comprende administrar a un paciente una cantidad eficaz de un compuesto de fórmula (I)

significa incluir el tratamiento simultáneo de más de una enfermedad como también la administración de más de un compuesto de fórmula (I).

Los trastornos proliferativos que se pueden tratar y/o prevenir con los compuestos de la presente invención incluyen particularmente, pero sin limitación, el grupo de cáncer y enfermedades tumorales. Se entiende que éstos son en particular, las siguientes enfermedades, pero sin estar limitado a éstos: carcinomas de mamas y tumores de mamas (formas ductal y lobular, también *in situ*), tumores del tracto respiratorio (carcinoma de pulmón de células pequeñas y no pequeñas, carcinoma parvicelular y no-parvicelular, carcinoma broncogénico, adenoma broncogénico, blastoma pleuropulmonar), tumores cerebrales (por ej., del tronco encefálico y del hipotálamo, astrocitoma, glioblastoma, meduloblastoma, ependimoma, y neuro-ectodérmico y tumores pineales), tumores de los órganos digestivos (esófago, estómago, vesícula biliar, intestino delgado, intestino grueso, recto, ano), tumores hepáticos (entre otros carcinoma hepatocelular, carcinoma colangiocelular y una mezcla del carcinoma hepatocelular y colangiocelular), tumores de la cabeza y la región del cuello (laringe, hipofaringe, nasofaringe, orofaringe, labios y cavidad oral), tumores cutáneos (carcinoma epitelial escamoso, sarcoma de Kaposi, melanoma maligno, cáncer cutáneo de células Merkel y cáncer cutáneo no melanomatoso), tumores de tejido blando (entre otros sarcomas de tejido blando, osteosarcomas, histiocitomas fibrosos malignos, linfosarcomas y rabdomiosarcomas), tumores de los ojos (entre otros melanoma intraocular, melanoma maligno uveal y retinoblastoma), tumores de las glándulas endócrinas y exocrinas (por ej., tiroides y glándulas paratiroideas, páncreas y glándula salivar), tumores del tracto urinario (tumores de la vesícula, pene, riñón, pelvis renal y uréter), tumores de los órganos reproductivos (carcinomas del endometrio, cuello del útero, ovario, vagina, vulva y útero en las mujeres, y carcinomas de próstata y testículos en los hombres), como también sus metástasis distantes. Estos trastornos además incluyen hemopatías

proliferativas en forma sólida y en forma de glóbulos rojos en circulación, tales como linfomas, leucemias y enfermedades mieloproliferativas, por ej., mieloide agudo, leucemia linfoblástica aguda, linfocítica crónica, mielógena crónica y tricoleucemia, y linfomas relacionados con SIDA, linfomas de Hodgkin, linfomas de no Hodgkin, linfomas de células T cutáneas, linfomas de Burkitt, y linfomas en el sistema nervioso central.

Debido a su actividad y perfil de selectividad, se cree que los compuestos de la presente invención son particularmente adecuados para el tratamiento del cáncer de pecho (de mama), pulmón, estómago (gástrico), vesícula y ovario y las enfermedades tumorales. Además, los compuestos de la presente invención pueden ser especialmente adecuados para la prevención o eliminación de la metástasis tumoral en general.

Otros trastornos proliferativos que se pueden tratar y/o prevenir con los compuestos y los procedimientos de la presente invención incluyen psoriasis, queloides y otras hiperplasias que afectan la piel, trastornos bullosos asociados con la formación del ampollas subepidérmicas incluyen penfigoide ampolloso, eritema multiforme y dermatitis herpetiformis, trastornos fibróticos tales como fibrosis de pulmón, aterosclerosis, restenosis y cirrosis hepática, Enfermedades renales incluyendo los trastornos proliferativos de células mesangiales, glomerulopatías, glomerulonefritis, nefropatía diabética, nefroesclerosis maligna y enfermedad del riñón poliquístico, hiperplasia prostática benigna (BPH)). trastornos proliferativos angiogénicos y de vasos sanguíneos, y síndromes de la microangiopatía trombótica.

Los compuestos de la presente invención además son útiles para el tratamiento y/o la prevención de enfermedades oftalmológicas tales como, por ejemplo, degeneración macular relacionada con la edad (AMD), degeneración macular seca, oclusión de la vena de la retina isquémica, edema macular diabético, retinopatía diabética, retinopatía del prematuro, y otras retinopatías.

Otras afecciones que se pueden tratar y/o prevenir mediante la administración

de un compuesto de la presente invención incluyen enfermedades ginecológicas tales como endometriosis, mioma y quistes ováricos, trastornos dianabólicos relacionados con la adipogénesis, dianabolismo biliar, dianabolismo del fosfato, dianabolismo del calcio y/o mineralización ósea, trastornos del esqueleto tales como, por ejemplo, microsomia, acondrodisplasia y síndrome de Pfeiffer, enfermedades cartilaginosas tales como osteoartritis y poliartritis, artritis reumatoide, calvicies, y rechazo al trasplante.

Las enfermedades antes mencionadas han sido bien caracterizadas en humanos, pero además existen con una etiología comparable en otros mamíferos, y se pueden tratar en aquéllos con los compuestos y los procedimientos de la presente invención.

De este modo, la presente invención además se refiere al uso de los compuestos de acuerdo con la invención para el tratamiento y/o la prevención de trastornos, especialmente de los trastornos antes mencionados.

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 la prevención de trastornos, especialmente de los trastornos antes mencionados.

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

La presente invención además se refiere a un procedimiento para el tratamiento y/o prevención de trastornos, especialmente de los trastornos antes mencionados, mediante el uso de una cantidad eficaz de al menos uno de los compuestos de acuerdo con la invención.

Los compuestos de la presente invención se pueden administrar como el único agente farmacéutico o en combinación con uno o más agentes terapéuticos adicionales en la medida en que esta combinación no conduzca a efectos colaterales indeseables y/o inaceptables. Esta terapia de combinación incluye la

administración de una formulación de dosificación farmacéutica única que contiene un compuesto de fórmula (I), como se define anteriormente, y uno o más agentes terapéuticos adicionales, como también la administración de un compuesto de fórmula (I) y cada agente terapéutico adicional en su propia formulación de dosificación farmacéutica separada. Por ejemplo, un compuesto de fórmula (I) y un agente terapéutico se pueden administrar al paciente juntos en una sola composición de dosificación oral (fija) tal como un comprimido o cápsula, o cada agente se puede administrar en formulaciones de dosificación separadas.

Donde se usan formulaciones de dosificación separadas, el compuesto de formula (I) y uno o más agentes terapéuticos adicionales se pueden administrar esencialmente a la misma vez (es decir, de forma concurrente) o en tiempos escalonados separados (es decir, de forma secuencial).

En particular, los compuestos de la presente invención se pueden usar en combinación fija o separada con otros agentes anticancerosos tales como agentes alquilantes, antidianabolitos, agentes antitumorales que derivan de las plantas, agentes de terapia hormonal, inhibidores de topoisomerasa, inhibidores de tubulin, inhibidores de quinasa, fármacos específicos, anticuerpos, conjugados de anticuerpo-fármaco (ADCs), compuestos inmunológicos, modificadores de respuesta biológica, compuestos anti-angiogénicos, y otras sustancias antiproliferativas, citostáticas y/o citotóxicas. A este respecto, el siguiente es un listado no limitante de ejemplos de agentes secundarios que se pueden usar en combinación con los compuestos de la presente invención.

Abarelix, abiraterone, aclarubicin, afatinib, aflibercept, aldesleukin, alemtuzumab, alitretinoin, alfaradin, altretamina, aminoglutethimida, amonafida, amrubicin, amsacrine, anastrozol, andromustine, arglabin, asparaginasa, axitinib, 5-azacitidina, basiliximab, belotecan, bendamustine, bevacizumab, bexaroteno, bicalutamida, bisantreno, bleomicina, bortezomib, bosutinib, brivanib alaninato, buserelin, busulfan, cabazitaxel, CAL-101, folinato de calcio,

levofolinato de calcio, camptotecin, capecitabina, carboplatino, carmofur, carmustine, catumaxomab, cediranib, celmoleuquina, cetuximab, clorambucil, clormadinona, chlormetina, cidofovir, cisplatino, cladribina, ácido clodrónico, clofarabine, combretastatina, crisantaspase, crizotinib, ciclofosfamida cyproterone, citarabina, dacarbazine, dactinomicina, darbepoetin alfa, darinaparsin, dasatinib, daunorubicin, decitabine, degarelix, denileuquina diftitox, denosumab, deslorelin, cloruro de dibrospidio, docetaxel, dovitinib, doxifluridina, doxorubicin, dutasteride, eculizumab, edrecolomab, eflornitina, acetato de eliptinio, eltrombopag, endostatina, enocitabina epimbicin, epirubicin, epitiostanol, epoetin alfa, epoetin beta, epotilona, eptaplatin, eribulin, erlotinib, estradiol, estramustine, etoposide, everolimus, exatecan, exemestane, exisulind, fadrozol, fenretinide, filgrastim, finasteride, flavopiridol, fludarabine, 5-fluorouracil, fluoximesterone, flutamide, foretinib, formestane, fotemustine, fulvestrant, ganirelix, gefitinib, gemcitabina, gemtuzumab, gimatecan, gimeracil, glufosfamide, glutoxim, goserelin, histrelin, hidroxi-urea, ácido ibandrónico, ibritumomab tiuxetan, idarubicin, ifosfamida, imatinib, imiquimod, improsulfan, intedanib, interferón alfa, interferón alfa-2a, interferón alfa-2b, interferón beta, interferón gamma, interleuquin-2, ipilimumab, irinotecan, ixabepilone, lanreotide, lapatinib, lasofoxifeno, lenalidomide, lenograstim, lentinan, lenvatinib, lestaurtinib, letrozol, leuprorelin, levamisol, linifanib, linsitinib, lisuride, lobaplatin, lomustine, lonidamina, lurtotecan, mafosfamide, mapatumumab, masitinib, masoprocol, medroxiprogesterona, megestrol, melarsoprol, mefalan, mepitiostane, mercaptopurina, metotrexato, aminolevulinato de metilo, metiltestosterona, mifamurtide, mifepristone, miltefosine, miriplatin, mitobronitol, mitoguazona, mitolactol, mitomicinas, mitotane, mitoxantrone, molgramostim, motesanib, nandrolone, nedaplatin, nelarabine, neratinib, nilotinib, nilutamida, nimotuzumab, nimustine, nitracrine, nolatrexed, ofatumumab, oprelvekin, oxaliplatino, paclitaxel, palifermin, ácido pamidrónico, panitumumab, pazopanib, pegaspargase, pegepoetin beta, pegfilgastrim, peg-interferón alfa-2b, pelitrexol, pemetrexed,

pemtumomab, pentostatin, peplomicina, perfosfamide, perifosine, pertuzumab, picibanil, pirambicin, pirarubicin, plerixafor, plicamicin, poliglusam, poliestradiol fosfato, ponatinib, porfimer sodio, pralatrexato, prednimustine, procarbazina, procodazol, PX-866, quinagolide, raloxifeno, raltitrexed, ranibizumab, ranimustine, razoxane, regorafenib, ácido risedrónico, rituximab, romidepsin, romiplostim, rubitecan, saracatinib, sargramostim, satraplatin, selumetinib, sipuleucel-T, sirolimus, sizofiran, sobuzoxane, sorafenib, estreptozocina, sunitinib, talaporfin, tamibaroteno, tamoxifeno, tandutinib, tasonermin, teceleukin, tegafur, telatinib, temoporfin, temozolomide, temsirolimus, teniposide, testolactona, testosterona, tetrofosmin, talidomide, tiotepa, timalfasin, tioguanina, tipifarnib, tivozanib, toceranib, tocilizumab, topotecan, toremifeno, tositumomab, trabectedin, trastuzumab, treosulfan, tretinoin, triapine, trilostane, trimetrexato, triptorelin, trofosfamida, ubenimex, valrubicin, vandetanib, vapreotide, varlitinib, vatalanib, vemurafenib, vidarabine, vinblastine, vincristine, vindesine, vinflunine, vinorelbine, volociximab, vorinostat, zinostatin, ácido zoledrónico, y zorubicin.

En general, los siguientes objetivos se pueden alcanzar con la combinación de los compuestos de la presente invención con otros agentes anticancerosos:

- actividad mejorada en la disminución del crecimiento de un tumor, en la reducción de su tamaño o incluso en su completa eliminación en comparación con el tratamiento con un solo compuesto activo;
- posibilidad de emplear los quimioterapéuticos usados en una dosificación menor que en la monoterapia;
- posibilidad de una terapia más tolerable con pocos efectos colaterales en comparación con la administración individual;
- posibilidad de tratamiento de un espectro más amplio de cáncer y enfermedades tumorales;
- obtención de un índice más alto de respuesta a la terapia;
- tiempo de supervivencia más prolongado del paciente en comparación con la terapia estándar.

De este modo, en otra realización, la presente invención se refiere a composiciones farmacéuticas que comprende al menos uno de los compuestos de acuerdo con la invención y uno o más agentes terapéuticos adicionales para el tratamiento y/o la prevención de trastornos, especialmente de los trastornos antes mencionados.

En el tratamiento del cáncer, los compuestos de la presente invención también se pueden emplear junto con la radioterapia y/o intervención quirúrgica.

Más aún, los compuestos de fórmula (I) se pueden utilizar, como tal o en composiciones, en investigación y diagnóstico, o como criterios de referencia analítica, y similares, los cuales son bien conocidos en la técnica.

Cuando los compuestos de la presente invención se administran como productos farmacéuticos, a humanos y otros mamíferos, se puede administrar per se o en forma de una composición farmacéutica que contiene, por ejemplo, 0,1% a 99,5% (más preferentemente, 0,5% a 90%) del ingrediente activo en combinación con uno o más excipientes aceptables para uso farmacéutico.

De este modo, en otro aspecto, la presente invención se refiere a composiciones farmacéuticas que comprenden al menos uno de los compuestos de acuerdo con la invención, convencionalmente junto con uno o más excipientes inertes, no tóxicos, adecuados para uso farmacéutico y al uso de los mismos para el tratamiento y/o la prevención de trastornos, especialmente de los trastornos antes mencionados.

Los compuestos de acuerdo con la invención pueden actuar de forma sistémica y/o local. A este fin, se pueden administrar en una forma adecuada tal como, por ejemplo, por vía oral, pulmonar, nasal, lingual, sublingual, bucal, rectal, dérmica, transdérmica, conjuntival, ótica o tópica, o en forma de un implante o stent.

Para estas vías de aplicación, los compuestos de la invención se pueden administrar en formas de aplicación adecuadas.

Las formas de aplicación adecuadas para administración oral que funcionan de

acuerdo con la técnica anterior y administran los compuestos de acuerdo con la invención de forma rápida y/o modificada, y que contienen los compuestos de acuerdo con la invención en forma cristalina, amorfa y/o disuelta, tales como, por ejemplo, comprimidos (comprimidos sin recubrir o recubiertos, por ejemplo que tienen recubrimientos entéricos o recubrimientos que son insolubles o se disuelven con un retraso o controlan la liberación del compuesto de acuerdo con la invención), comprimidos que se desintegran de forma rápida en la boca, o películas/obleas, películas/ liofilisados, cápsulas (por ej., cápsulas de gelatina dura o blanda), comprimidos recubiertos con azúcar, gránulos, pellets, polvos, emulsiones, suspensiones, aerosoles o soluciones.

La aplicación parenteral se puede llevar a cabo evitando el paso de absorción (por vía intravenosa, intraarterial, intracardial, intraespinal o intralumbar) o con la inclusión de una absorción (por vía intramuscular, subcutánea, intracutánea, percutánea o intraperitoneal). Las formas de aplicación parenteral útiles incluyen preparaciones de inyección e infusión en la forma de soluciones, suspensiones, emulsiones, liofilisados y polvos estériles.

Las formas adecuadas para otras vías de aplicación incluyen, por ejemplo, formas farmacéuticas inhaladoras (por ej., inhaladores de polvo, nebulizadores), gotas nasales, soluciones o pulverizaciones, comprimidos o cápsulas a ser administradas por vía lingual, sublingual o bucal (por ej., pastillas, píldoras), supositorios, preparaciones para oídos y ojos (por ej., gotas, ungüentos), cápsulas vaginales, suspensiones acuosas (lociones, mezclas para agitar), suspensiones lipofílicas, ungüentos, cremas, leches, pastas, espumas, polvos para espolvorear, sistemas terapéuticos transdérmicos (por ej., parches), implantes y stents.

En una realización preferente, la composición farmacéutica que comprende un compuesto de fórmula (I) como se definió anteriormente se proporciona en una forma adecuada para la administración oral. En otra realización preferente, la composición farmacéutica que comprende un compuesto de fórmula (I) como se

definió anteriormente se proporciona en una forma adecuada para la administración intravenosa.

Los compuestos de acuerdo con la invención se pueden convertir en las formas de aplicación mencionadas de manera conocida per se mezclando con excipientes adecuados inertes, no tóxicos, farmacéuticamente aceptables. Estos excipientes incluyen, entre otros, vehículos (por ej., celulosa microcristalina, lactosa, manitol), solventes (por ej., polietilenglicoles líquidos), emulsionantes (por ej., dodecil sulfato sódico), tensioactivos (por ej., polioxosorbitán oleato), dispersantes (por ej., polivinilpirrolidona), polímeros sintéticos y naturales (por ej., albúmina), estabilizantes (por ej., antioxidantes tales como, por ejemplo, ácido ascórbico), colorantes (por ej., pigmentos inorgánicos tales como, por ejemplo, óxidos de hierro), y agentes enmascaradores del gusto y/o el olor.

Una dosis preferente del compuesto de la presente invención es la máxima que un paciente pueda tolerar y no desarrollar serios efectos colaterales. De manera ilustrativa, el compuesto de la presente invención se puede administrar por vía parenteral a una dosis de aproximadamente 0,001 mg/kg hasta aproximadamente 1 mg/kg, preferentemente de aproximadamente 0,01 mg/kg a aproximadamente 0,5 mg/kg de peso corporal. En la administración oral, un intervalo de dosis ejemplar es aproximadamente 0,01 a 100 mg/kg, preferentemente aproximadamente 0,01 a 20 mg/kg, y más preferentemente aproximadamente 0,1 a 10 mg/kg de peso corporal. Los intervalos intermedios a los valores antes mencionados además intentan ser parte de la invención.

No obstante, los niveles de dosificación reales y el tiempo de administración de los principios activos en las composiciones farmacéuticas de la invención pueden variar para obtener una cantidad del ingrediente activo el cual es eficaz para obtener la respuesta terapéutica deseada para un paciente particular, la composición y el modo de administración, sin ser tóxica al paciente. Por lo tanto, puede ser necesario donde sea apropiado desviarse de las cantidades

establecidas, en particular como una función de la edad, el género, el peso corporal, la dieta y el estado de salud general del paciente, la biodisponibilidad y las características farmacodinámicas del compuesto particular y su modo y la vía de administración, el tiempo o el intervalo en el cual tiene lugar la administración, el régimen de dosis seleccionado, la respuesta del paciente individual al ingrediente activo, la enfermedad específica involucrada, el grado o la implicancia o la severidad de la enfermedad, la clase de tratamiento concurrente (es decir, la interacción del compuesto de la invención con otros terapéuticos coadministrados), y otras circunstancias relevantes.

De este modo, puede ser satisfactorio en algunos casos administrar menos de la cantidad mínima antes mencionada, por lo que en otros casos el límite superior establecido puede ser excedido. El tratamiento puede iniciarse con dosificaciones más pequeñas, las cuales son inferiores a la dosis óptima del compuesto. De ahí en adelante, la dosificación puede incrementarse mediante pequeños incrementos hasta que se alcance el efecto óptimo bajo las circunstancias. Por conveniencia, la dosificación diaria total puede dividirse y administrarse en porciones individuales distribuidas a lo largo del día.

Las siguientes realizaciones de ejemplo ilustran la invención. La invención no está limitada a los ejemplos.

Los porcentajes en los siguientes ensayos y ejemplos, a menos que se indique lo contrario, son en peso, las partes son en peso. Las relaciones de solvente, las relaciones y concentraciones de dilución informadas para el líquido/ soluciones líquidas se basan cada una de ellas en el volumen.

A. Ejemplos

Abreviaturas y acrónimos:

Ac	acetilo
Ac_2O	anhídrido acético
AcOH	ácido acético
Ac.	acuoso (solución)
Boc	ter-butoxicarbonilo
br.	ancho (^{1}H-RMN señal)
Bu	butilo
cat.	catalítico
conc.	concentrado
d:	doblete (^{1}H-RMN señal)
DBDMH	1,3-dibromo-5,5-dimetildantoína
DCI	ionizacíon química directa (EM)
DCM	diclorometano
Periodinano Dess-Martin	1,1,1-triacetoxi-1,1-dihidro-1,2-benzodioxol-3-(1H)-ona
DIPEA	*N,N-diisopropiletilamina*
DMF	N,N-dimetilformamida
DMSO	dimetilsulfóxido
EI	ionización por impacto de electrones (EM)
eq.	equivalente(s)
ESI	ionización por electro aspersión (EM)
Et	etilo
EtOAc	acetato de etilo
GC-MS	Cromatográfica gaseosa-espectroscopía de masa acoplada
h	hora(s)
Hal	halógeno

^{1}H-RMN	espectroscopía de resonancia magnética nuclear protónica
HPLC	cromatografía líquida de alta resolución
iPr	isopropilo
LC-MS	Cromatográfica líquida-espectroscopía de masa acoplada
Me	metilo
MeOH	metanol
min...	minuto(s)
EM	espectroscopía de masa
m/z	relación masa a carga (EM)
NBS	N-bromosuccinimida
n-Bu	n-butilo
NCS	N-clorosuccinimida
de teo.	de teoría (rendimiento químico)
Pd/C	paladio sobre carbón
$PdCl_2(dppf)$	[1,1'-bis(difenilfosfino)ferro-ceno]dicloropaladio(II)
$Pd(dba)_2$	bis(dibencilidenacetona)paladio
Ph	Fenilo
PPA	ácido polifosfórico
q	cuarteto (^{1}H-RMN señal)
Cuant.	cuantitativo (rendimiento)
rac	racémico
R_f	factor de retención TLC
RP	fase inversa (HPLC)
ta	temperatura ambiente
T_r	tiempo de retención (HPLC)
s	singulete (^{1}H-RMN señal)

sat.	saturada (solución)
t	triplete (^{1}H-RMN señal)
TBAF	*tetra-n-butilamonio fluoruro*
TBDMS	*ter-butildimetilsililo*
TBTU	tetrafluoroborato *N*-[(1*H*-benzotriazol-1-iloxi)(dimetilamino)metileno]-*N*-metil-metanaminio
tBu	ter-butilo
ter	terciario
TFA	ácido trifluoroacético
THF	tetrahidrofurano
TLC	cromatografía de capa delgada

Procedimientos LC-MS y GC-MS:

Procedimiento 1 (LC-MS):

Instrumento: Micromass Quattro Premier con Waters UPLC Acquity; columna: Thermo Hypersil GOLD 1.9µ, 50 mm x 1 mm; eluyente A: 1 litro de agua + 0,5 ml 50% de ácido fórmico acuoso, eluyente B: 1 litro de acetonitrilo + 0,5 ml 50% de ácido fórmico ac.; gradiente: 0,0 min 90% A → 0,1 min 90% A → 1,5 min 10% A → 2,2 min 10% A; temperatura: 50°C; caudal: 0,33 ml/min; detección UV: 210 nm.

Procedimiento 2 (LC-MS):

Instrumento: Sistema Waters Acquity SQD UPLC; columna: Waters Acquity UPLC HSS T3 1,8µ, 50 mm x 1 mm; eluyente A: 1 litro de agua + 0,25 ml 99% de ácido fórmico, eluyente B: 1 litro de acetonitrilo + 0,25 99% ml 50% de ácido fórmico; gradiente: 0,0 min 90% A → 1,2 min 5% A → 2,0 min 5% A; horno: 50°C; caudal: 0,40 ml/min; detección UV: 210-400 nm.

Procedimiento 3 (LC-MS):

Instrumento: Micromass Quattro Micro con HPLC Agilent 1100 Series; columna:

YMC-Triart C18 3µ, 50 mm x 3 mm; eluyente A: 1 litro de agua + 0,01 mol carbonato de amonio, eluyente B: 1 litro de acetonitrilo; gradiente: 0,0 min 100% A → 2,75 min 5% A → 4,5 min 5% A; horno: 40°C; caudal: 1,25 ml/min; detección UV: 210 nm.

Procedimiento 4 (LC-MS):

Instrumento: Sistema Waters Acquity SQD UPLC; columna: Waters Acquity UPLC HSS T3 1,8µ, 30 mm x 2 mm; eluyente A: 1 litro de agua + 0,25 ml 99% de ácido fórmico, eluyente B: 1 litro de acetonitrilo + 0,25 99% ml 50% de ácido fórmico; gradiente: 0,0 min 90% A → 1,2 min 5% A → 2,0 min 5% A; horno: 50°C; caudal: 0,60 ml/min; detección UV: 208-400 nm.

Procedimiento 5 (LC-MS):

Instrumento: Micromass Quattro Premier con Waters UPLC Acquity; columna: Thermo Hypersil GOLD 1.9µ, 50 mm x 1 mm; eluyente A: 1 litro de agua + 0,5 ml 50% de ácido fórmico acuoso, eluyente B: 1 litro de acetonitrilo + 0,5 ml 50% de ácido fórmico ac.; gradiente: 0,0 min 97% A → 0,5 min 97% A → 3,2 min 5% A → 4,0 min 5% A; temperatura: 50°C; caudal: 0,3 ml/min; detección UV: 210 nm.

Procedimiento 6 (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 7 (LC-MS):

Instrumento EM: Waters Micromass QM; Instrumento HPLC: Agilent 1100 series; columna: Agilent ZORBAX Extend-C18 3,0 mm x 50 mm, 3.5µ; eluyente A: 1 litro de agua + 0,01 mol carbonato de amonio, eluyente B: 1 litro de acetonitrilo; gradiente: 0,0 min 98% A → 0,2 min 98% A → 3,0 min 5% A → 4,5 min 5% A; temperatura: 40°C; caudal: 1,75 ml/min; detección UV: 210 nm.

Procedimiento 8 (LC-MS):

Instrumento EM: Waters Micromass ZQ; Instrumento HPLC: Agilent 1100

series; columna: Agilent ZORBAX Extend-C18 3,0 mm x 50 mm, 3.5µ; eluyente A: 1 litro de agua + 0,01 mol carbonato de amonio, eluyente B: 1 litro de acetonitrilo; gradiente: 0,0 min 98% A → 0,2 min 98% A → 3,0 min 5% A → 4,5 min 5% A; temperatura: 40°C; caudal: 1,75 ml/min; detección UV: 210 nm.

Procedimientos generales de purificación (Véase tabla I y II a continuación):

Procedimiento P1:

RP-HPLC preparativa (Reprosil C18, gradiente acetonitrilo/ 0,2% ácido trifluoroacético ac.).

Procedimiento P2:

RP-HPLC preparativa (XBridge C18, gradiente acetonitrilo/ agua + 0,1% amoníaco ac.).

Procedimiento P3:

RP-HPLC preparativa (Sunfire C18, gradiente acetonitrilo/ agua).

Procedimiento P4:

RP-HPLC preparativa (XBridge C18, gradiente acetonitrilo/ agua + 0,05% amoníaco ac.).

Procedimiento P5:

El producto obtenido a partir de la purificación por RP-HPLC precedente se disuelve en metanol y se filtra a través de un cartucho de intercambio aniónico (Stratospheres SPE, PL-HCO_3 MP-resina). El cartucho se eluye con metanol, y el filtrado se evapora.

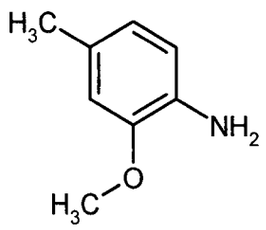
Procedimiento P6:

Una solución del producto en acetato de etilo se lava con solución de hidrógeno carbonato de sodio seguido de solución de cloruro de sodio acuoso saturada, se seca sobre sulfato de magnesio, se filtra y se evapora.

Materiales de partida e intermediarios:

Intermediario 1A

2-metoxi-4-metilanilina



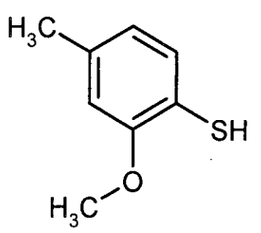
Una mezcla de 5-metil-2-nitroanisol (265 g, 1,58 moles) y 10% Pd/C (39,75 g) en THF (1,32 L) se agitó durante toda la noche a ta bajo 1 atm de hidrógeno. La filtración sobre kieselguhr y la evaporación dieron 216,1 g del producto bruto el cual se usó en el próximo paso sin purificación posterior.

LC-MS (procedimiento 3): Tr = 2,39 min; MS (ESIpos): m/z = 138 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 6,45-6,63 (m, 3H), 4,46 (s, 2H), 3,72 (s, 3H), 2,16 (s, 3H) ppm.

Intermediario 2A

2-metoxi-4-metilbencenotiol



Procedimiento 1:

Una solución de nitrito de sodio (7 g, 101,4 mmoles) en agua (25 ml) se agregó gota a gota a una solución enfriada (0°-5°C) del intermediario 1A (13,7 g, 100 mmoles) en ácido clorhídrico concentrado (30 ml) y agua (85 ml). Después de agitar a 0°C durante 10 min, se agregó acetato de sodio (15 g, 182,8 mmoles). La mezcla resultante se agregó gota a gota a una solución caliente (70°-80°C) de *O*-etil ditiocarbonato de potasio (30 g, 187,1 mmoles) en agua (140 ml), se agitó entre 70°C y 80°C durante 1 h y posteriormente se enfrió hasta ta. La mezcla se extrajo dos veces con acetato de etilo, y los extractos orgánicos combinados se secaron sobre sulfato de sodio y se evaporaron. El residuo se colocó en una solución 1,3 M de hidróxido de potasio en etanol (300 ml). Se agregó glucosa (8 g), y la mezcla resultante se sometió a reflujo durante 3 h. Posteriormente, el solvente de etanol se evaporó, y el residuo se diluyó con

agua y se acidificó con ácido sulfúrico acuoso 6N. Se agregó polvo de zinc (15 g) cuidadosamente, y la mezcla resultante se calentó hasta 50°C durante 30 min. La mezcla posteriormente se enfrió hasta ta, se diluyó con diclorometano y se filtró. El filtrado se extrajo dos veces con diclorometano, y los extractos orgánicos combinados se secaron sobre sulfato de sodio y se evaporaron dando 14,3 g del producto bruto el cual se usó en el próximo paso sin purificación posterior.

Procedimiento 2:

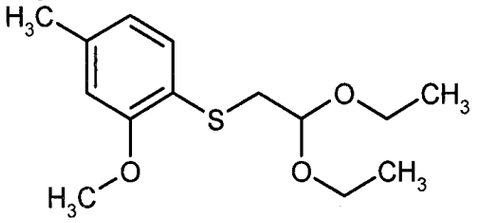
A 2,9 litros de THF se agregó una solución tibia de 355 ml (6,67 moles) ácido sulfúrico concentrado en 1,1 litro de agua. A 50°C, se agregaron 293 g (1,33 moles) cloruro 2-metoxi-4-metilbencenosulfonilo bajo agitación. Posteriormente, 521 g (7,97 moles) de polvo de zinc se agregaron cuidadosamente en porciones (espumando), y la reacción levemente exotérmica se enfrió en un baño acuoso para mantener una temperatura de 50°-55°C. La mezcla posteriormente se agitó a 55°C durante 3 h. El avance de la reacción se controló por TLC (gel de sílice, éter de petróleo/acetato de etilo 95:5). La mezcla de reacción se vertió en 13,6 litros de agua, 6,8 litros diclorometano se agregaron, y la mezcla se agitó durante 5 min. Después de decantar del zinc remanente y separación de fase, la fase acuosa se extrajo una vez más con 6,8 litros diclorometano. Las fases orgánicas combinadas se lavaron con 10% de salmuera, se secaron y se evaporaron a 40°C a presión reducida dando 237 g de producto bruto. Este material se usó en el próximo paso sin purificación posterior. Una muestra analítica se obtuvo por cromatografía de gel de sílice con éter de petróleo/acetato de etilo (97:3) como eluyente.

LC-MS (procedimiento 1): Tr = 1,21 min; MS (ESIneg): m/z = 153 $(M-H)^-$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,17 (d, 1H), 6,81 (s, 1H), 6,66 (d, 1H), 4,63 (br. s, 1H), 3,80 (s, 3H), 2,26 (s, 3H) ppm.

Intermediario 3A

1-[(2,2-dietoxietil)sulfanil]-2-metoxi-4-metilbenceno



Se suspendieron 237 g material bruto del intermediario 2A, 287 g (1,46 moles) bromoacetaldehído-dietilacetal y 862 g (2,65 moles) carbonato de cesio en 2 litros de DMF. La temperatura de reacción aumentó inicialmente hasta 40°C, posteriormente se continuó con la agitación durante toda la noche a temperatura ambiente. La mezcla de reacción se dividió entre 10 litros de agua y 2,7 litros de acetato de etilo. La fase acuosa se extrajo con otra porción de 2,7 litros acetato de etilo. Las fases orgánicas combinadas se lavaron con 10% salmuera, se secaron y se evaporaron. El residuo oleoso resultante se purificó por cromatografía de gel de sílice con éter de petróleo/acetato de etilo (95:5) como eluyente.

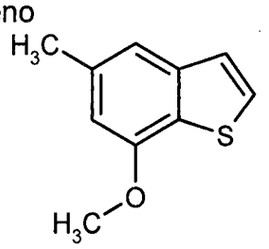
Rendimiento: 236 g de un aceite (66% de teor.)

GC-MS (procedimiento 6): Tr = 6,03 min; MS (Elpos): m/z = 270 $(M)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,16 (d, 1H), 6,82 (s, 1H), 6,73 (d, 1H), 4,55 (t, 1H), 3,80 (s, 3H), 3,52-3,64 (m, 2H), 3,39-3,51 (m, 2H), 2,96 (d, 2H), 2,33 (s, 3H), 1,09 (t, 6H) ppm.

Intermediario 4A

7-metoxi-5-metil-1-benzotiofeno



A una mezcla de reflujo de 13 g ácido polifosfórico y 150 ml clorobenceno se agregó gota a gota una solución de 5,2 g (19,2 mmoles) del intermediario 3A, y se continuó con el reflujo durante toda la noche. Después de enfriar, la capa orgánica se decantó, y el residuo y el matraz se enjuagaron dos veces con

DCM. Las fases orgánicas combinadas se evaporaron a presión reducida. El residuo (3,76 g) se cromatografió sobre gel de sílice con isohexano/0-10% acetato de etilo como eluyente.

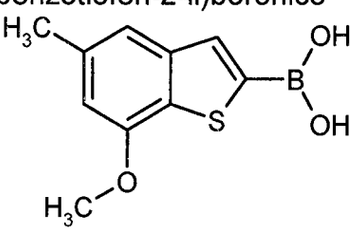
Rendimiento: 1,69 g de un aceite (49% de teor.)

GC-MS (procedimiento 6): Tr = 5,20 min; MS (Elpos): m/z = 178 $(M)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,68 (d, 1H), 7,34 (d, 1H), 7,28 (s, 1H), 6,78 (s, 1H), 3,93 (s, 3H), 2,43 (s, 3H) ppm.

Intermediario 5A

Ácido (7-metoxi-5-metil-1-benzotiofen-2-il)borónico



Bajo atmósfera de argón, 26,7 g (150 mmoles) del intermediario 4A se disolvieron en 270 ml de THF y se enfriaron hasta -70°C. Entre -70°C y -65°C, 66 ml (165 mmoles) de una solución 2,5 N de *n*-butilitio en hexano se agregaron gota a gota dentro de 20 min, dando por resultado la formación de un precipitado de color blanco. Después de agitar durante 1 h a -70°C, 41,5 ml (180 mmoles) tri isopropil borato se agregaron a esta temperatura dentro de 10 min (dando por resultado una suspensión espesa). Se continuó con la agitación durante 1 h a -70°C, antes que la mezcla de reacción se dejara entibiar hasta ta durante toda la noche. Posteriormente, se agregaron 400 ml de solución de cloruro de amonio acuosa saturada, las capas se separaron, y la capa acuosa se extrajo una vez más con THF. Las fases orgánicas combinadas se evaporaron a presión reducida. Al residuo obtenido de este modo, se agregaron 200 ml de agua y 86 ml de solución de hidróxido de sodio acuoso 2 N. La solución se lavó dos veces con DCM, posteriormente se acidificó con 35 ml de 3 M ácido sulfúrico, y la suspensión resultante se agitó vigorosamente durante 1 h. El precipitado se filtró por succión y se secó

durante toda la noche a 45°C al vacío.

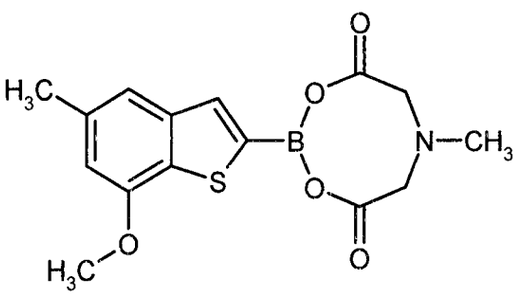
Rendimiento: 28,25 g de un sólido incoloro (94% puro por LC-MS, 80% de teor.)

LC-MS (procedimiento 2): Tr = 0,87 min; MS (ESIpos): m/z = 223 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,17 (d, 1H), 6,81 (s, 1H), 6,66 (d, 1H), 4,63 (br. s, 1H), 3,80 (s, 3H), 2,26 (s, 3H) ppm.

Intermediario 6A

2-(7-metoxi-5-metil-1-benzotiofen-2-il)-6-metil-1,3,6,2-dioxazaborocano-4,8-diona



Se disolvieron 6,3 g (28,4 mmoles) del intermediario 5A y 4,2 g (28,4 mmoles) ácido 2,2'-(metilimino)diacético en una mezcla de 45 ml DMSO y 400 ml tolueno y se sometió a reflujo durante 16 h usando una trampa Dean-Stark. Después de la evaporación, el residuo se colocó en acetato de etilo y se lavó tres veces con agua y una vez con salmuera. La fase orgánica se secó sobre sulfato de magnesio y se evaporó hasta un volumen de aproximadamente 200 ml. Un sólido de color blanco precipitó el cual se filtró, se lavó con acetato de etilo y se secó al vacío para dar un primer cultivo (5,52 g) del compuesto del título. Un segundo cultivo (3,32 g) se obtuvo después de la evaporación de la lejía madre y de la cromatografía flash sobre una capa de gel de sílice usando ciclohexano/0-100% acetato de etilo en forma de eluyente.

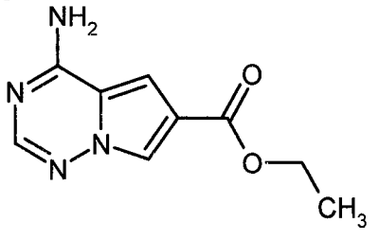
Rendimiento: 8,84 g (pureza total 92,5% por LC-MS, 87% de teor.)

LC-MS (procedimiento 2): Tr = 0,93 min; MS (ESIpos): m/z = 334 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,42 (s, 1H), 7,26 (s, 1H), 6,76 (s, 1H), 4,40 (d, 2H), 4,17 (d, 2H), 3,92 (s, 3H), 2,63 (s, 3H), 2,42 (s, 3H) ppm.

Intermediario 7A

4-aminopirrolo[2,1-f][1,2,4]triazin-6-carboxilato de etilo



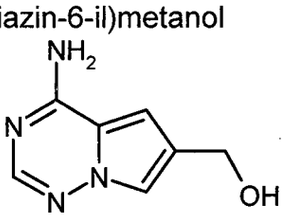
Una solución de 4-aminopirrolo[2,1-f][1,2,4]triazin-6-carbonitrilo (3,9 g, 24,5 mmoles; preparación descripta en Solicitud de Patente Internacional PCT WO 2007/064883) en etanol (124,8 ml) se agitó con ácido sulfúrico concentrado (62,4 ml) a 80°C durante toda la noche. Después de enfriar hasta ta, la mezcla de reacción se vertió en 800 g de hielo y se llevó hasta pH 6-7 con solución de hidróxido de sodio acuoso concentrado. Se agregaron acetato de etilo (500 ml) y diclorometano (500 ml) a la suspensión, y la mezcla resultante se filtró sobre kieselguhr. La capa orgánica se separó de la capa acuosa. El sólido se disolvió en agua caliente (1 l), y la capa acuosa se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se secaron sobre sulfato de sodio y se evaporaron. El residuo se trituró con una mezcla de isopropanol/éter dietílico, y el sólido se filtró dando 2,5 g (49% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,59 min; MS (ESIpos): m/z = 206 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,11-7,97 (m, 3H), 7,88 (s, 1H), 7,34 (br. s, 1H), 4,27 (q, 2H), 1,30 (t, 3H) ppm.

Intermediario 8A

(4-aminopirrolo[2,1-f][1,2,4]triazin-6-il)metanol



Una solución helada del intermediario 7A (3,0 g, 14,5 mmoles) en THF (30 ml) se trató con una solución 1M de trietilborohidruro de litio 1M en THF (58 ml) y se agitó a ta durante 45 min. La mezcla de reacción se enfrió posteriormente

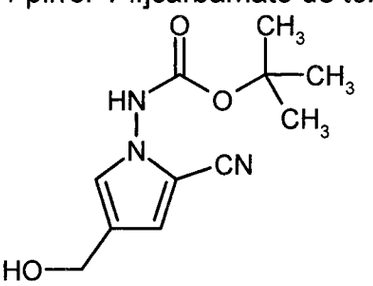
hasta 0°C, se templó con metanol, se entibió lentamente hasta ta y se adsorbió sobre kieselguhr. La purificación por cromatografía de columna sobre gel de sílice (diclorometano/metanol 20:1 → 4:1 gradiente) dio 2,21 g (92,5% de teor.) del compuesto del título.

LC-MS (procedimiento 3): Tr = 1,46 min; MS (ESIpos): m/z = 164 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,75 (s, 1H), 7,64 (br. s, 2H), 7,50 (br. d, 1H), 6,79 (br. d, 1H), 5,01 (t, 1H), 4,50 (d, 2H) ppm.

Intermediario 9A

[2-ciano-4-(hidroximetil)-1*H*-pirrol-1-il]carbamato de *ter*-butilo



Bajo argón, una solución 1M de bromuro de metilmagnesio en THF (13,3 ml) se agregó durante 15 min a una solución de (4-bromo-2-ciano-1*H*-pirrol-1-il)carbamato de *ter*-butilo (3,7 g, 12,09 mmoles; preparación descripta en Solicitud de Patente Internacional PCT WO 2007/064883, Intermediario AAE, Etapa 3) en THF (37 ml) se enfrió hasta -60°C. Después de 30 min, una solución 1,6M de *n*-butilitio en hexano (15,1 ml, 24,2 mmoles) se agregó durante 10 min a la reacción, y la mezcla resultante se agitó entre -60°C y -40°C durante 1 h. Posteriormente, se agregó paraformaldehído (1,09 g, 36,3 mmoles) a la reacción, y la mezcla de reacción se entibió lentamente hasta ta y se agitó durante toda la noche. Después de templar con solución de cloruro de amonio acuosa saturada, la capa acuosa se extrajo dos veces con acetato de etilo. Las fases orgánicas combinadas se lavaron con solución de cloruro de sodio acuosa saturada, se secaron sobre sulfato de sodio y se evaporaron. La purificación por cromatografía de columna sobre gel de sílice (ciclohexano/acetato de etilo 2:1 → 1:1) dio 2,04 g (69% de teor.) del

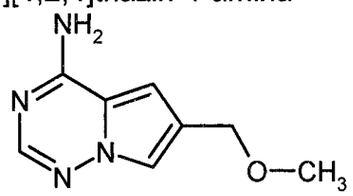
compuesto del título.

LC-MS (procedimiento 4): Tr = 0,70 min; MS (ESIpos): m/z = 238 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 10,79 (br. s, 1H), 7,09 (d, 1H), 6,86 (d, 1H), 4,97 (t, 1H), 4,28 (d, 2H), 1,45 (s, 9H) ppm.

Intermediario 10A

6-(metoximetil)pirrolo[2,1-f][1,2,4]triazin-4-amina



Procedimiento 1:

Una solución del intermediario 8A (1,3 g, 7,9 mmoles) en THF (25 ml) se trató con cloruro de tionilo (1,15 ml, 15,8 mmoles) y se agitó a ta durante 2 h. Después de la evaporación, el residuo se disolvió en metanol (25 ml) y se trató con acetato de sodio (1,3 g, 15,8 mmoles). La mezcla se agitó durante 3 h a 65°C y posteriormente se evaporó nuevamente. La purificación por cromatografía de columna sobre gel de sílice (diclorometano/metanol 100:2) dio 787 mg (55% de teor.) del compuesto del título.

Procedimiento 2:

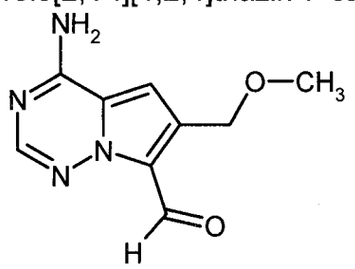
Una solución del intermediario 9A (6,14 g, 25,88 mmoles) en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (15 ml) se agitó a ta durante 5 h. Después de diluir con metanol (73 ml), se continuó con la agitación a ta durante toda la noche. Posteriormente, se agregaron fosfato de potasio (54,9 g, 258,65 mmoles) y acetato formamidinio (13,46 g, 129,32 mmoles), y la mezcla resultante se agitó a 65°C durante 17 h. La mezcla de reacción se evaporó, se agregó solución de cloruro de sodio acuosa saturada, y la mezcla se extrajo con diclorometano seguido de acetato de etilo. Las fases orgánicas combinadas se secaron sobre sulfato de sodio y se evaporaron. La purificación por cromatografía de columna sobre gel de sílice (diclorometano/metanol 40:1 → 20:1) dio 2,36 g (49% de teor.) del compuesto del título.

LC-MS (procedimiento 3): Tr = 1,72 min; MS (ESIpos): m/z = 179 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,77 (s, 1H), 7,69 (br. s, 2H), 7,57 (s, 1H), 6,81 (s, 1H), 4,42 (s, 2H), 3,25 (s, 3H) ppm.

Intermediario 11A

4-Amino-6-(metoximetil)pirrolo[2,1-f][1,2,4]triazin-7-carbaldehído



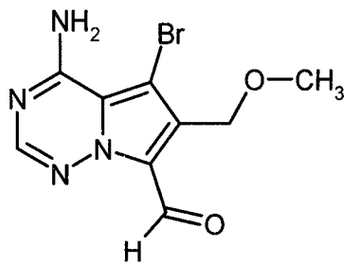
Se agregó cloruro de fosforilo (13,7 ml, 147,18 mmoles) a una solución del intermediario 10A (5,24 g, 29,43 mmoles) en DMF (80 ml) a 0°C. La mezcla resultante se agitó a 60°C durante 8 h, posteriormente cuidadosamente se templó con agua y se neutralizó con solución de hidróxido de sodio acuoso 4 M. La capa acuosa se extrajo con acetato de etilo. Las fases orgánicas combinadas se lavaron con solución de cloruro de sodio acuosa saturada, se secaron sobre sulfato de magnesio y se evaporaron. Una solución del residuo en metanol (50 ml) se trató con acetato de sodio (2,41 g, 29,43 mmoles) y se sometió a reflujo durante toda la noche. La mezcla de reacción se diluyó con agua y se extrajo con acetato de etilo. Las fases orgánicas combinadas se lavaron con solución de cloruro de sodio acuosa saturada, se secaron sobre sulfato de magnesio y se evaporaron, dando 2,66 g del producto bruto el cual se usó en el próximo paso sin purificación posterior.

LC-MS (procedimiento 4): Tr = 0,50 min; MS (ESIpos): m/z = 207 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 10,35 (s, 1H), 8,20 (br. s, 2H), 8,07 (s, 1H), 7,06 (s, 1H), 4,72 (s, 2H), 3,39 (s, 3H) ppm.

Intermediario 12A

4-amino-5-bromo-6-(metoximetil)pirrolo[2,1-f][1,2,4]triazin-7-carbaldehído



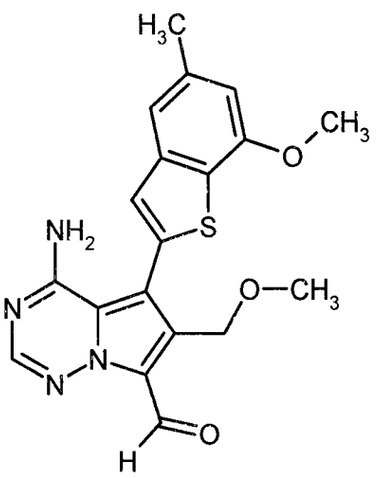
Una solución del intermediario 11A (bruto, 2,66 g) en DMF (30 ml), se enfrió hasta -30°C, se trató con una solución de *N*-bromosuccinimida (NBS; 2,52 g, 14,19 mmoles) en DMF (14 ml). La mezcla resultante se entibió lentamente hasta 0°C. Después de 1 hora, la mezcla se entibió hasta ta, se agitó durante otros 15 min y posteriormente se templó con solución de tiosulfato de sodio acuoso 1 M. El precipitado se filtró y se lavó con acetato de etilo, dando 1,1 g (100% de pureza, 30% de teor.) en forma de un primer cultivo del compuesto del título. El filtrado restante se extrajo con acetato de etilo. Las fases orgánicas combinadas se lavaron con solución de cloruro de sodio acuosa saturada, se secaron sobre sulfato de sodio y se evaporaron. La purificación del residuo por cromatografía de columna sobre gel de sílice (ciclohexano/acetato de etilo 1:1 → 1:3) dio otros 1,39 g (70% de pureza, 26% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,67 min; MS (ESIpos): m/z = 283/285 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 10,36 (s, 1H), 8,63 (br. s, 1H), 8,13 (s, 1H), 7,23 (br. s, 1H), 4,64 (s, 2H), 3,26 (s, 3H) ppm.

Intermediario 13A

4-amino-6-(metoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f]-[1,2,4]triazin-7-carbaldehído



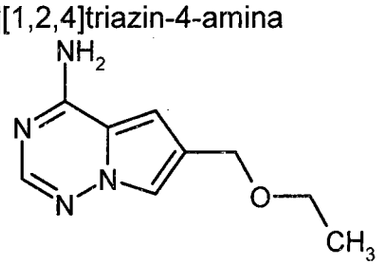
Bajo argón, una solución de fosfato de potasio acuoso 0,5 M desgasificada (9,9 ml) se agregó a una solución del intermediario 12A (710 mg, 2,49 mmoles), el intermediario 5A (921 mg, 3,73 mmoles) y (2'-aminobifenil-2-il)-(cloro)paladio-diciclohexil(2',4',6'-triisopropilbifenil-2-il)fosfina (1:1; 196 mg, 249 µmoles; véase S. L. Buchwald *et al.*, *J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)) en THF desgasificado (28,4 ml). La mezcla resultante se agitó a 60°C durante 2 h y posteriormente se evaporó. La purificación del residuo por cromatografía de columna sobre gel de sílice (ciclohexano/acetato de etilo 5:1 → 1:1) dio 550 mg (51% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 1,06 min; MS (ESIpos): m/z = 383 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 10,50 (s, 1H), 8,43 (br. s, 1H), 8,21 (s, 1H), 7,42 (s, 1H), 7,33 (s, 1H), 6,87 (s, 1H), 6,09 (br. s, 1H), 4,58 (s, 2H), 3,96 (s, 3H), 3,19 (s, 3H), 2,46 (s, 3H) ppm.

Intermediario 14A

6-(etoximetil)pirrolo[2,1-f][1,2,4]triazin-4-amina



Procedimiento 1:

A una suspensión de 2 g (12,2 mmoles) del intermediario 8A en 40 ml de THF

se agregaron 1,78 ml (24,4 mmoles) cloruro de tionilo a ta dentro de 20 seg. La mezcla se agitó durante 1,5 h, posteriormente se evaporó hasta sequedad, y el residuo se disolvió en 40 ml etanol. Se agregaron 2 g (24,4 mmoles) acetato de sodio, y la mezcla se agitó a 70°C durante 1 h 45 min. La mezcla de reacción se evaporó nuevamente, y se agregó solución de hidrógeno carbonato de sodio acuosa saturada. La mezcla se extrajo cinco veces con acetato de etilo. Las fases orgánicas combinadas se lavaron con solución de cloruro de sodio acuosa saturada, se secaron con sulfato de magnesio y se evaporaron hasta sequedad, dando 2,02 g de producto bruto el cual se purificó por cromatografía de columna sobre gel de sílice con diclorometano/metanol (0-2%) en forma de eluyente.

Rendimiento: 1,37 g (58% de teor.).

Procedimiento 2:

Etapa 1: Una solución del intermediario 9A (2,3 g, 9,69 mmoles) en 1,4-dioxano (5 ml) se trató con una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (24 ml, 96,9 mmoles) y se agitó a ta durante 130 min. Posteriormente, la suspensión se filtró, y el precipitado se lavó con 1,4-dioxano (5 ml) y se secó al vacío dando 1,01 g (54% de teor.) del compuesto intermediario clorhidrato 1-amino-4-(clorometil)-1*H*-pirrol-2-carbonitrilo.

Etapa 2: se disolvió 1-amino-4-(clorometil)-1*H*-pirrol-2-carbonitrilo clorhidrato recién preparado de la etapa 1 (0,3 g, 1,82 mmoles) en etanol (10 ml) y se agitó a ta durante 5 min. La solución transparente se trató con acetato de formamidina (813 mg, 7,81 mmoles) y fosfato de potasio (1,66 g, 7,81 mmoles) y se agitó primero a ta durante 3 días, posteriormente a 80°C durante 10,5 h. S e agregó más acetato de formamidina (488 mg, 4,69 mmoles), y la mezcla se agitó durante otros 18 h a 80°C. La mezcla posteriormente se enfrió hasta ta, y se agregaron agua y acetato de etilo. La fase orgánica se separó, y la fase acuosa se extrajo dos veces con acetato de etilo. Las fases orgánicas combinadas se lavaron con solución de cloruro de sodio acuosa saturada, se

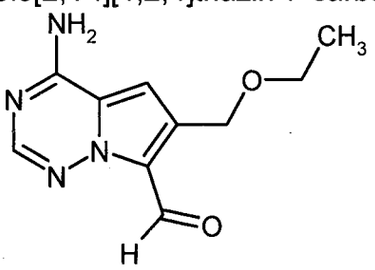
secaron con sulfato de magnesio y se evaporaron. El residuo se disolvió en una mezcla de metanol y diclorometano, se adsorbió sobre tierra de diatomea, se secaron al vacío y finalmente se purificó por cromatografía sobre gel de sílice (gradiente 0-10% metanol/diclorometano) dando 260 mg (78% de teor.) del compuesto del título.

LC-MS (procedimiento 3): Tr = 2,02 min; MS (ESIpos): m/z = 193 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,77 (s, 1H), 7,59-7,74 (br. s, 2H), 7,56 (s, 1H), 6,82 (s, 1H), 5,76 (s, 1H), 4,46 (s, 2H), 3,46 (q, 2H), 1,13 (t, 3H) ppm.

Intermediario 15A

4-amino-6-(etoximetil)pirrolo[2,1-f][1,2,4]triazin-7-carbaldehído



A una solución de 2,1 g (10,9 mmoles) del intermediario 14A en 40 ml de DMF seco, se agregaron 5,1 ml (54,6 mmoles) de cloruro de fosforilo gota a gota a 0°C bajo una atmósfera de argón. La mezcla se agitó a 60°C durante 10 h. Posteriormente, se agrego agua cuidadosamente, y la mezcla se agitó a temperatura ambiente hasta que todos los intermediarios reactivos se destruyeron (Control por HPLC). La solución ácida se neutralizó con solución de hidróxido de sodio acuoso 1 M y se extrajo tres veces con acetato de etilo. Las fases orgánicas combinadas se lavaron con solución de cloruro de sodio acuosa saturada, se secaron sobre sulfato de magnesio y se evaporaron a presión reducida.

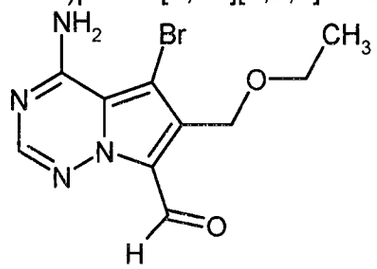
Rendimiento: 1,94 g (pureza 90%, 81% de teor.)

LC-MS (procedimiento 5): Tr = 1,49 min; MS (ESIpos): m/z = 221 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 10,35 (s, 1H), 8,14-8,26 (m, 2H), 8,07 (s, 1H), 7,07 (s, 1H), 4,76 (s, 2H), 3,58 (q, 2H), 1,20 (t, 3H) ppm.

Intermediario 16A

4-amino-5-bromo-6-(etoximetil)pirrolo[2,1-f][1,2,4]triazin-7-carbaldehído



A una solución de 73 g (0,33 moles) del intermediario 15A en 1,9 litros de DMF se agregó gota a gota una solución de 65 g (0,37 moles) de NBS en 200 ml de DMF a -15°C. La mezcla se dejó entibiar hasta 0°C y se agitó durante 3 h a esta temperatura. La mezcla de reacción se vertió en 2% de solución de tiosulfato de sodio acuoso bajo agitación, y el precipitado se filtró, se lavó con agua y se secó sobre pentóxido de fósforo al vacío.

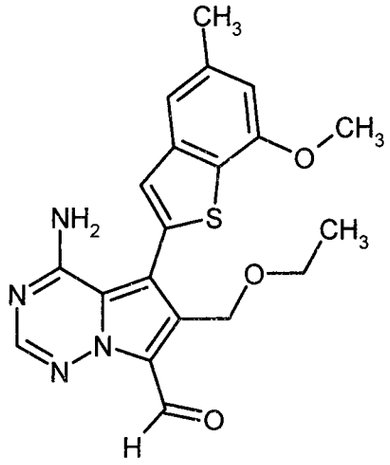
Rendimiento: 85,6 g (86% de teor.)

LC-MS (procedimiento 2): Tr = 0,76 min; MS (ESIpos): m/z = 299/301 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 10,36 (s, 1H), 8,62 (br. s, 1H), 8,13 (s, 1H), 7,22 (br. s, 1H), 4,68 (s, 2H), 3,49 (q, 2H), 1,10 (t, 3H) ppm.

Intermediario 17A

4-amino-6-(etoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-7-carbaldehído



Bajo una atmósfera de argón, 714 mg (pureza 85%, 2,03 mmoles) del intermediario 16A, 946 mg (2,84 mmoles) del intermediario 6A y 160 mg (0,2

mmoles) (2'-aminobifenil-2-il)(cloro)paladio-diciclohexil(2',4',6'-triisopropilbifenil-2-il)fosfina (1:1; véase S. L. Buchwald *et al.*, *J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)) se suspendieron en 15,5 ml de THF. Posteriormente, se agregaron 15,5 ml de una solución de fosfato de potasio acuoso 0,5 M desgasificada, y la mezcla se agitó a 50°C durante 16 h. Después de la adición de agua, la mezcla se extrajo con acetato de etilo, y las fases orgánicas combinadas se secaron sobre sulfato de magnesio y se evaporaron a presión reducida. El residuo se purificó por cromatografía de columna sobre gel de sílice (100 g) con 10-50% acetato de etilo/ ciclohexano en forma de eluyente.

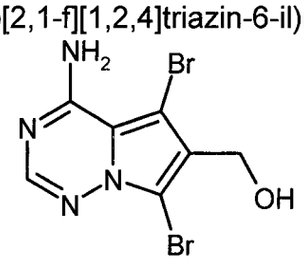
Rendimiento: 452 mg (75% puro por HPLC, 42% de teor.)

LC-MS (procedimiento 5): Tr = 2,38 min; MS (ESIpos): m/z = 397 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 10,50 (s, 1H), 8,42 (br. s, 1H), 8,21 (s, 1H), 7,43 (s, 1H), 7,33 (s, 1H), 6,87 (s, 1H), 6,07 (br. s, 1H), 4,63 (s, 2H), 3,96 (s, 3H), 3,40 (q, 2H), 2,46 (s, 3H), 1,02 (t, 3H) ppm.

Intermediario 18A

(4-amino-5,7-dibromopirrolo[2,1-f][1,2,4]triazin-6-il)metanol



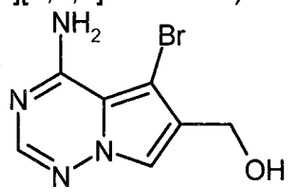
Una solución del intermediario 8A (5 g, 30,4 mmoles) en THF (100 ml) se trató con 1,3-dibromo-5,5-dimetilhidantoína (9,58 g, 33,5 mmoles) y se agitó a ta durante 2 h. El precipitado se filtró y se secó al vacío para dar 6,60 g (64% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,56 min; MS (ESIpos): m/z = 321/323/325 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,23 (br. s, 1H), 7,96 (s, 1H), 6,94 (br. s, 1H), 5,09 (br. s, 1H), 4,43 (s, 2H) ppm.

Intermediario 19A

(4-amino-5-bromopirrolo[2,1-f][1,2,4]triazin-6-il)metanol



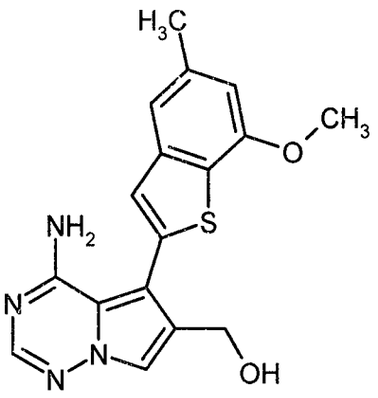
Una suspensión del intermediario 18A (3,7 g, 11,5 mmoles) en THF (800 ml) se calentó bajo agitación hasta disolución completa. La mezcla se enfrió posteriormente hasta -78°C, y una solución 1,6M de *n*-butilitio en hexanos (20 ml, 32,1 mmoles) se agregó gota a gota. Después de 5 min, se agregó otra porción de solución de n-butillitio 1,6 M (1,5 ml, 2,29 mmoles). La mezcla resultante se agitó a -78°C durante 5 min, posteriormente se templó con metanol (5 ml) y se entibió hasta ta. La mezcla de reacción se diluyó con solución de cloruro de amonio acuosa saturada, solución de hidrógeno carbonato de sodio acuosa saturada, solución de cloruro de sodio acuosa saturada y acetato de etilo. Después de la separación de fase, la capa orgánica se lavó con solución de cloruro de sodio acuosa saturada. Las fases acuosas combinadas se extrajeron nuevamente con acetato de etilo. Las fases orgánicas combinadas se lavaron nuevamente con solución de cloruro de sodio acuosa saturada, se secaron sobre sulfato de magnesio y se evaporaron para dar 2,87 g del producto bruto el cual se usó en etapas subsiguientes sin purificación posterior.

LC-MS (procedimiento 3): Tr = 1,73 min; MS (ESIpos): m/z = 243/245 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,41-7,89 (br. s, 1H), 7,82 (s, 1H), 7,66 (s, 1H), 7,13-6,48 (br. s, 1H), 5,11 (t, 1H), 4,45 (d, 2H) ppm.

Intermediario 20A

[4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-6-il]-metanol



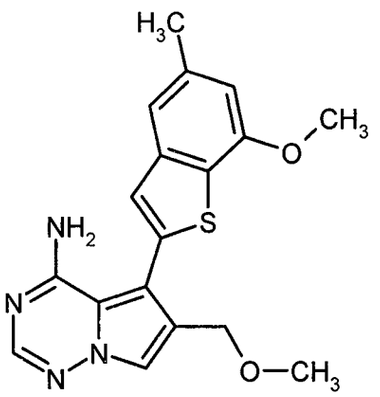
Una suspensión del intermediario 19A (70% de pureza, 2,52 g, 7,26 mmoles), el intermediario 6A (3,63 g, 10,9 mmoles) y fluoruro de cesio (5,51 g, 36,3 mmoles) en una mezcla de THF/agua (10:1; 80 ml) se desgasificó bajo argón. Se agregó 4-(di-*ter*-butilfosfino)-*N,N*-dimetilanilina-dicloropaladio (2:1; 176 mg, 0,248 mmoles) , y la mezcla resultante se desgasificó nuevamente y se agitó a 50°C durante 16 h. La mezcla de reacción posteriormente se lavó con solución de cloruro de sodio acuosa saturada, y la capa orgánica se separó, se secó sobre sulfato de magnesio, se filtró y se evaporó. El residuo se suspendió en metanol, y el sólido resultante se filtró y se secó al vacío para dar 1,97 g (90% de pureza, 72% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,85 min; MS (ESIpos): m/z = 340 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,91 (s, 1H), 7,5-8,1 (br. s, 1H), 7,72 (s, 1H), 7,35 (s, 1H), 7,30 (s, 1H), 6,84 (s, 1H), 5,5-6,0 (br. s, 1H), 5,06 (t, 1H), 4,49 (d, 2H), 3,95 (s, 3H), 2,45 (s, 3H) ppm.

Intermediario 21A

6-(metoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-4-amina



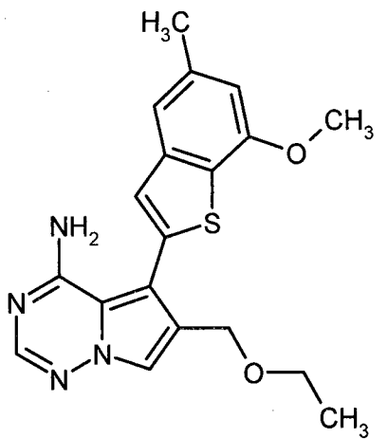
Una solución del intermediario 20A (400 mg, 1,17 mmoles) en diclorometano (12 ml) se trató con cloruro de tionilo (128 µl, 1,76 mmoles) y se agitó a ta durante 15 min. Después de la evaporación, el residuo se colocó en metanol (12 ml) y se trató con DIPEA (409 µl, 2,35 mmoles). La mezcla se sometió a reflujo durante toda la noche y posteriormente se evaporó nuevamente. La purificación por cromatografía de columna sobre gel de sílice (diclorometano/metanol 98:2 → 95:5) dio 388 mg (93% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 1,00 min; MS (ESIpos): m/z = 355 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,93 (s, 1H), 7,82 (s, 1H), 7,35 (s, 1H), 7,31 (s, 1H), 6,84 (s, 1H), 4,38 (s, 2H), 3,95 (s, 3H), 3,22 (s, 3H), 2,45 (s, 3H) ppm.

Intermediario 22A

6-(etoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-4-amina



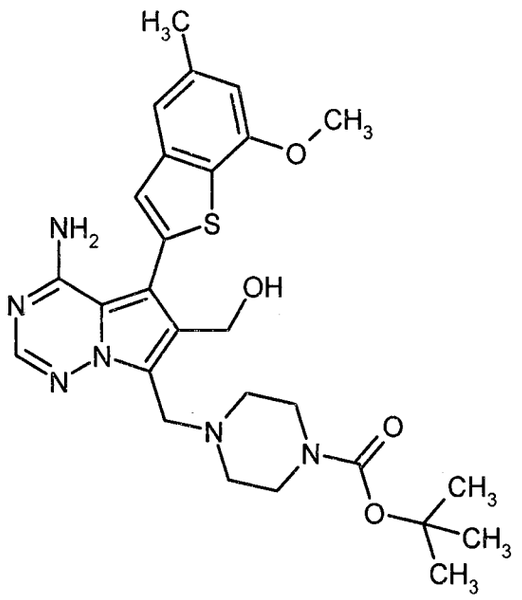
El intermediario 20A (200 mg, 587 µmoles) en diclorometano (5 ml) se trató con cloruro de tionilo (64 µl, 881 µmoles) y se agitó a ta durante 15 min. Después de la evaporación, el residuo se sometió a reflujo en etanol (5 ml) durante 1 h, posteriormente se trató con DIPEA (204 µl, 1,17 mmoles) y se sometió a reflujo nuevamente durante toda la noche. La mezcla de reacción se evaporó, y el producto bruto se purificó por cromatografía de columna sobre gel de sílice (diclorometano/metanol 98:2 → 95:5) dando 202 mg (90% de teor.) del compuesto del título.

LC-MS (procedimiento 5): Tr = 2,32 min; MS (ESIpos): m/z = 369 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,31-7,59 (br. s, 1H), 7,93 (s, 1H), 7,81 (s, 1H), 7,35 (s, 1H), 7,30 (s, 1H), 6,84 (s, 1H), 6,20-5,50 (br. s, 1H), 4,41 (s, 2H), 3,95 (s, 3H), 3,41 (q, 2H), 2,45 (s, 3H), 1,08 (t, 3H) ppm.

Intermediario 23A

4-{[4-amino-6-(hidroximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f]-[1,2,4]triazin-7-il]metil}piperazin-1-carboxilato de *ter*-butilo



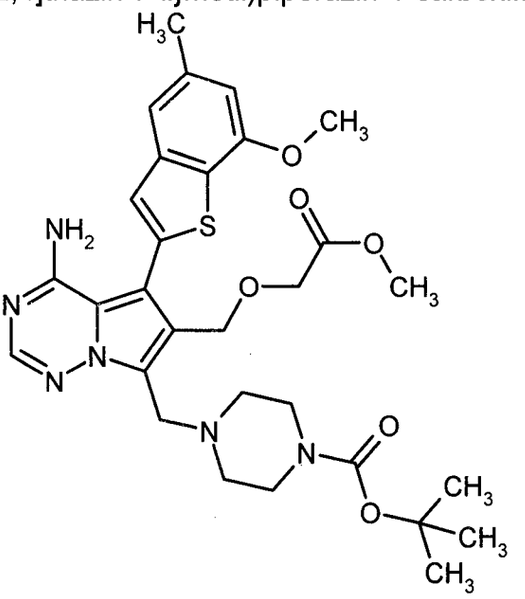
Una solución del intermediario 20A (9,5 g, 27,9 mmoles) en ácido acético (136,8 ml) se trató con piperazin-1-carboxilato de *ter*-butilo (6,24 g, 33,49 mmoles) y 37% de solución de formaldehído acuosa (2,5 ml, 33,49 mmoles). La mezcla se agitó a 60°C durante 2,5 h. Después de la evaporación, el residuo se colocó en acetato de etilo, y la mezcla se lavó dos veces con solución de hidrógeno carbonato de sodio acuosa saturada, se secó sobre sulfato de sodio y se evaporó. El residuo se trituró en etanol en ebullición (100 ml). El sólido se filtró y se lavó con etanol y éter dietílico dando 9,70 g (58% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,88 min; MS (ESIpos): m/z = 539 $(M+H)^+$

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 7,94 (s, 1H), 7,13-7,35 (m, 2H, superposición con pico de $CHCl_3$), 6,67 (s, 1H), 5,86 (br. s, 1H), 5,54 (br. s, 2H), 4,68 (s, 2H), 4,08 (s, 2H), 4,00 (s, 3H), 3,45 (br. s, 4H), 2,59-2,48 (m, 7H), 1,45 (s, 9H) ppm.

Intermediario 24A

4-({4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-6-[(2-metoxi-2-oxoetoxi)-metil]pirrolo[2,1-f][1,2,4]triazin-7-il}metil)piperazin-1-carboxilato de *ter*-butilo



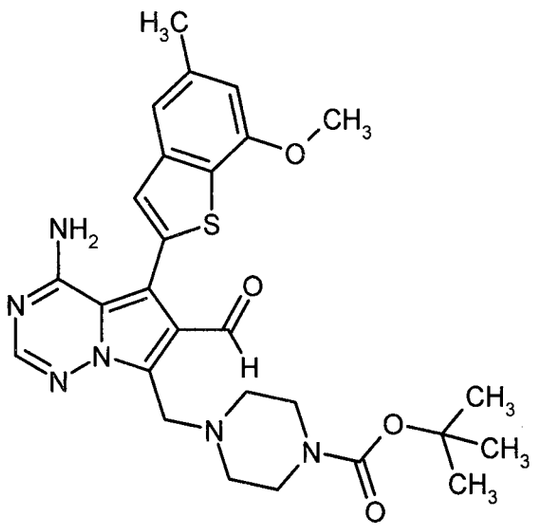
Una solución del intermediario 23A (300 mg, 556 µmoles) en diclorometano (12 ml) se trató con cloruro de tionilo (81 µl, 1,11 mmoles) y se agitó a ta durante 15 min. Después de la evaporación, el residuo se disolvió en metilglicolato recién destilado (2,5 ml) y se trató con DIPEA (485 µl, 2,78 mmoles). La mezcla se agitó a 70°C durante 2 h, posteriormente se evaporó nuevamente, y metilglicolato en exceso se removió por destilación. La purificación del residuo por cromatografía de columna sobre gel de sílice (ciclohexano/acetato de etilo 1:5) dio 136 mg (33% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,88 min; MS (ESIpos): m/z = 611 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,99 (s, 1H), 7,39 (s, 1H), 7,31 (s, 1H), 6,85 (s, 1H), 4,58 (s, 2H), 4,11 (s, 2H), 3,96 (s, 3H), 3,93 (s, 2H), 3,57 (s, 3H), 3,30-3,24 (m, 4H), 2,45-2,38 (m, 7H), 1,39 (s, 9H) ppm.

Intermediario 25A

4-{[4-amino-6-formil-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]-triazin-7-il]metil}piperazin-1-carboxilato de *ter*-butilo



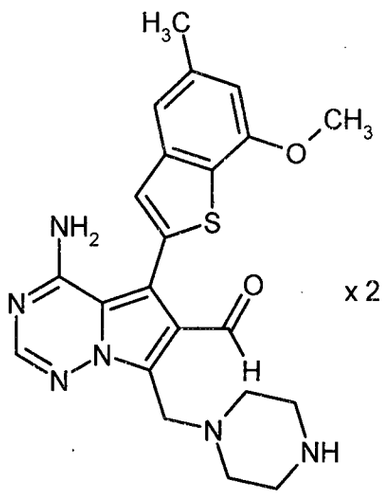
Una solución del intermediario 23A (300 mg, 556 µmoles) en diclorometano (4,2 ml) se trató con Periodinano Dess-Martin (1,1,1-triacetoxi-1,1-dihidro-1,2-benziodoxol-3(1*H*)-ona; 307 mg, 724 µmoles) y se agitó a ta durante 2 h. La mezcla de reacción se templó con solución de hidrógeno carbonato de sodio acuosa saturada y solución de tiosulfato de sodio acuosa saturada (1:1) y se agitó a ta durante 30 min. La capa acuosa se extrajo tres veces con diclorometano, y las capas orgánicas combinadas se secaron sobre sulfato de magnesio y se evaporaron. La purificación por cromatografía de columna sobre gel de sílice (ciclohexano/acetato de etilo 1:1 → 100% acetato de etilo) dio 273 mg (87% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,87 min; MS (ESIpos): m/z = 537 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 10,02 (s, 1H), 8,44-8,18 (br. s, 1H), 8,08 (s, 1H), 7,51 (s, 1H), 7,32 (s, 1H), 6,88 (s, 1H), 6,01-5,74 (br. s, 1H), 4,16 (s, 2H), 3,96 (s, 3H), 3,30-3,22 (m, 4H), 2,48-2,40 (m, 7H), 1,38 (s, 9H) ppm.

Intermediario 26A

4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-6-carbaldehído bis(formiato)



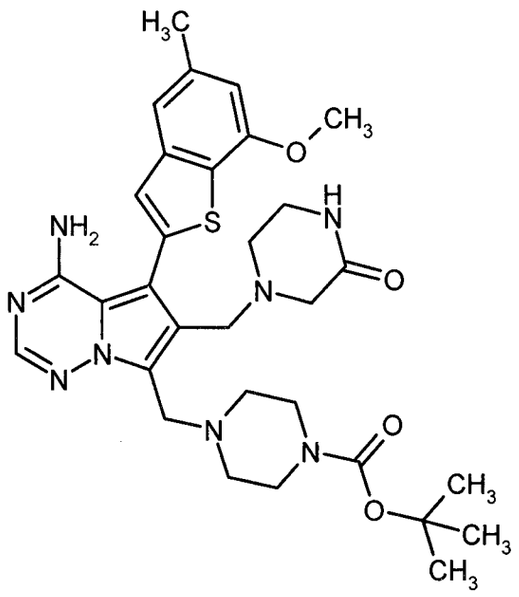
Una solución del intermediario 23A (80 mg, 148 µmoles) en THF (3,9 ml) se trató con Periodinano Dess-Martin (1,1,1-triacetoxi-1,1-dihidro-1,2-benziodoxol-3(1*H*)-ona; 94 mg, 222 µmoles) y se agitó a ta durante 30 min. La mezcla de reacción se templó con solución de hidrógeno carbonato de sodio acuosa saturada y solución de tiosulfato de sodio acuosa saturada (1:1). La capa acuosa se extrajo tres veces con acetato de etilo, y las capas orgánicas combinadas se secaron sobre sulfato de magnesio y se evaporaron. El residuo se disolvió en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (4 ml) y se agitó a ta durante 1 h. Después de la evaporación, el residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) dando 34 mg (52% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,78 min; MS (ESIpos): m/z = 437 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 10,02 (s, 1H), 8,29 (br. s, 2H), 8,09 (s, 1H), 7,50 (s, 1H), 7,33 (s, 1H), 6,88 (s, 1H), 4,17 (s, 2H), 3,96 (s, 3H), 2,90-2,81 (m, 4H), 2,63-2,56 (m, 4H), 2,46 (s, 3H) ppm.

Intermediario 27A

4-({4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-6-[(3-oxopiperazin-1-il)-metil]pirrolo[2,1-f][1,2,4]triazin-7-il}metil)piperazin-1-carboxilato de *ter*-butilo

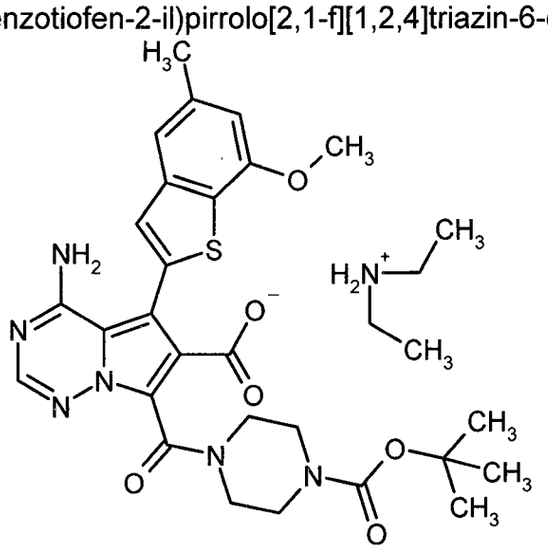


Una solución del intermediario 25A (185 mg, 344 µmoles) en THF (4,6 ml) se trató con 2-oxopiperazina (344 mg, 3,4 mmoles), triacetoxiborohidruro de sodio (365 mg, 1,7 mmoles) y ácido acético (39 µl, 689 µmoles). La mezcla resultante se agitó a ta durante 2 h, posteriormente se adsorbió sobre kieselguhr y se purificó por cromatografía de columna sobre gel de sílice (diclorometano → diclorometano/metanol 100:8) dando 221 mg (cuant.) del compuesto del título.

LC-MS (procedimiento 4): Tr = 0,77 min; MS (ESIpos): m/z = 621 $(M+H)^+$.

Intermediario 28A

N-etiletanaminio 4-amino-7-{[4-(*ter*-butoxicarbonil)piperazin-1-il]carbonil}-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-6-carboxilato



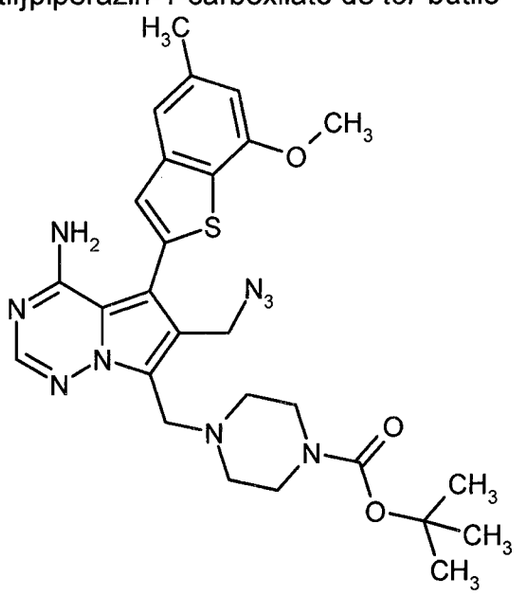
Una solución del intermediario 25A (70 mg, 130 µmoles) en THF/agua (10:1, 4,85 ml) se trató con una solución 2 M de 2-metil-2-buten en THF (521 µl, 1,04 mmoles) y dihidrógenofosfato de sodio (107 mg, 783 µmoles) y se agitó a ta durante 5 min. Se agregó clorito de sodio (70 mg, 783 µmoles), y la mezcla resultante se agitó a ta durante toda la noche. Después de diluir con agua, la fase acuosa se extrajo tres veces con acetato de etilo. Las capas orgánicas combinadas se secaron sobre sulfato de sodio y se evaporaron, y el residuo se purificó por RP-HPLC preparativa (XBridge C18, gradiente 5-50% acetonitrilo/agua + 0,05% dietilamina) dando 18 mg (21% de teor.) del compuesto del título.

LC-MS (procedimiento 1): Tr = 1,14 min; MS (ESIpos): m/z = 567 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): *inter al.* δ = 8,26-7,89 (br. s, 1H), 7,94 (s, 1H), 7,33 (s, 1H), 7,28 (s, 1H), 6,83 (s, 1H), 5,64-5,33 (br. s, 1H), 3,95 (s, 3H), 2,80 (q, 4H), 2,45 (s, 3H), 1,40 (s, 9H), 1,09 (t, 6H) ppm.

Intermediario 29A

4-{[4-amino-6-(azidometil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f]-[1,2,4]triazin-7-il]metil}piperazin-1-carboxilato de *ter*-butilo



Una solución del intermediario 23A (150 mg, 0,278 mmoles) en diclorometano (7,5 ml) se trató con cloruro de tionilo (40 µl, 0,56 mmoles) y se agitó a ta

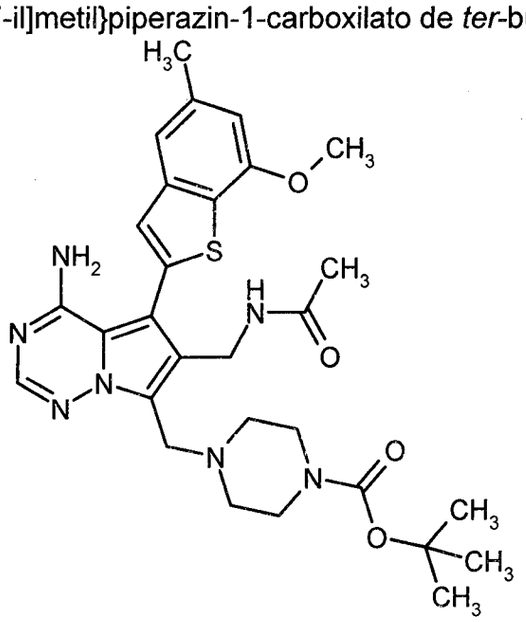
durante 15 min. Después de la evaporación, el residuo se disolvió en DMF (6 ml) y se trató con azida de sodio (362 mg, 5,57 mmoles) y yoduro de sodio (208 mg, 1,39 mmoles). La mezcla se calentó hasta 80°C durante 1 h, posteriormente se diluyó con agua y se extrajo tres veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con agua y con solución de cloruro de sodio acuosa saturada, se secaron sobre sulfato de magnesio y se evaporaron. La purificación por cromatografía de columna sobre gel de sílice (ciclohexano/acetato de etilo 98:2 → 100% acetato de etilo) dio 95,8 mg (57% de teor.) del compuesto del título.

LC-MS (procedimiento 4): Tr = 0,99 min; MS (ESIpos): m/z = 564 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,20-7,80 (br. s, 1H), 8,01 (s, 1H), 7,39 (s, 1H), 7,33 (s, 1H), 6,86 (s, 1H), 6,05-5,55 (br. s, 1H), 4,50 (s, 2H), 3,96 (s, 3H), 3,94 (s, 2H), 3,32-3,25 (m, 4H), 2,45 (s, 3H), 2,43-2,36 (m, 4H), 1,39 (s, 9H) ppm.

Intermediario 30A

4-{[6-(acetamidometil)-4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo-[2,1-f][1,2,4]triazin-7-il]metil}piperazin-1-carboxilato de *ter*-butilo



Una mezcla del intermediario 29A (320 mg, 567 µmoles), 10% Pd/C (320 mg) y anhídrido acético (106 µl, 1,13 mmoles) en metanol (32 ml) se agitó durante 90

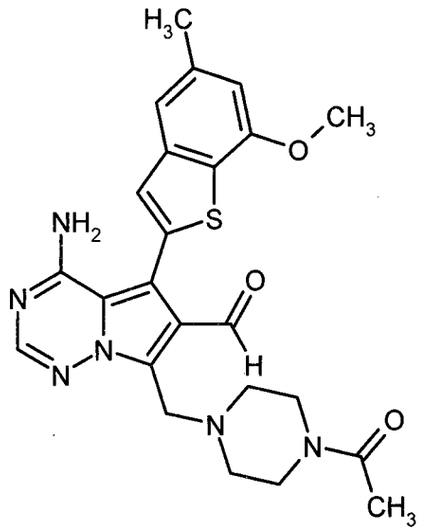
min bajo 1 atm de hidrógeno a ta. La mezcla posteriormente se filtró a través de kieselguhr, y el filtrado se evaporó. La purificación por cromatografía de columna sobre gel de sílice (ciclohexano/acetato de etilo 1:1 → 100% acetato de etilo) dio 440 mg (cuant.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,91 min; MS (ESIpos): m/z = 580 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,02-7,97 (m, 2H), 7,38 (s, 1H), 7,31 (s, 1H), 6,85 (s, 1H), 4,27 (br. d, 2H), 3,95 (s, 3H), 3,89 (s, 2H), 3,31-3,24 (m, 4H), 2,45 (s, 3H), 2,43-2,36 (m, 4H), 1,74 (s, 3H), 1,39 (s, 9H) ppm.

Intermediario 31A

7-[(4-acetilpiperazin-1-il)metil]-4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-pirrolo[2,1-f][1,2,4]triazin-6-carbaldehído

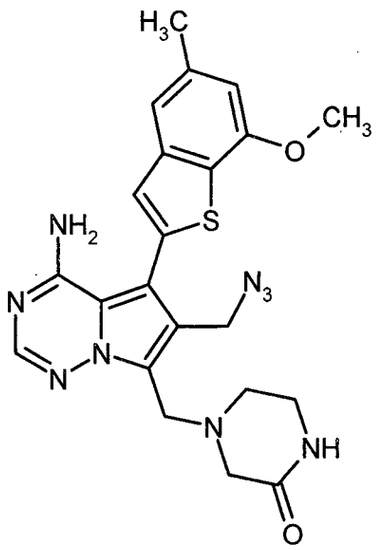


Una solución del ejemplo 55 (678 mg, pureza 89%, 1,26 mmoles) en diclorometano (4 ml) que contiene tamices moleculares (4Å) se trató con Periodinano Dess-Martin (1,1,1-triacetoxi-1,1-dihidro-1,2-benziodoxol-3(1*H*)-ona; 623 mg; 1,47 mmoles) y se agitó a ta durante 5 min. La mezcla de reacción posteriormente se adsorbió sobre tierra de diatomea y se purificó por cromatografía de columna sobre gel de sílice (gradiente de 30-100% de acetato de etilo/ciclohexano, posteriormente 0-10% de metanol/diclorometano) dando 449 mg (49% de teor.) del compuesto del título.

LC-MS (procedimiento 4): Tr = 0,70 min; MS (ESIpos): m/z = 479 $(M+H)^+$.

Intermediario 32A

4-{[4-amino-6-(azidometil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f]-[1,2,4]triazin-7-il]metil}piperazin-2-ona



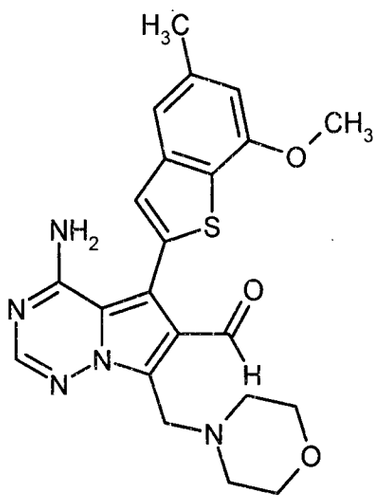
Una solución del ejemplo 13 (59 mg, 130 μmoles) en diclorometano (3,5 ml) se trató con cloruro de tionilo (19 μl, 261 μmoles) y se agitó a ta durante 15 min. Después de la evaporación, el residuo se disolvió en DMF (2,8 ml) y se trató con yoduro de sodio (97 mg, 652 μmoles) y azida de sodio (169 mg, 2,6 mmoles). La mezcla se agitó a 80°C durante 1 h. Después de diluir con solución de cloruro de sodio acuosa saturada, la fase acuosa se extrajo cuatro veces con acetato de etilo, y las capas orgánicas combinadas se secaron sobre sulfato de magnesio y se evaporaron. La purificación por cromatografía de columna sobre gel de sílice (diclorometano/metanol 98:2 → 90:10) dio 35 mg (56% de teor.) del compuesto del título.

LC-MS (procedimiento 5): Tr = 2,04 min; MS (ESIpos): m/z = 478 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,02 (s, 1H), 7,75 (br. s, 1H), 7,41 (s, 1H), 7,33 (s, 1H), 6,86 (s, 1H), 4,51 (s, 2H), 4,01 (s, 2H), 3,96 (s, 3H), 3,16-3,08 (m, 2H), 3,04-2,98 (m, 2H), 2,65-2,58 (m, 2H), 2,45 (s, 3H) ppm.

Intermediario 33A

4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(morfolin-4-ilmetil)pirrolo-[2,1-f][1,2,4]triazin-6-carbaldehído

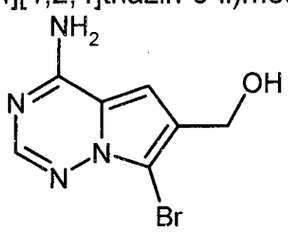


Una solución del ejemplo 50 (710 mg, pureza 70%, 1,13 mmoles) en diclorometano (5 ml) que contiene tamices moleculares (4Å) se trató con Periodinano Dess-Martin (1,1,1-triacetoxi-1,1-dihidro-1,2-benziodoxol-3(1*H*)-ona; 623 mg, 1,47 mmoles) y se agitó a ta durante 5 min. La mezcla de reacción posteriormente se adsorbió sobre tierra de diatomea y se purificó por cromatografía de columna sobre gel de sílice (gradiente de 30-100% acetato de etilo/ciclohexano) dando 386 mg (72% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,76 min; MS (ESIpos): m/z = 438 $(M+H)^+$.

Intermediario 34A

(4-amino-7-bromopirrolo[2,1-f][1,2,4]triazin-6-il)metanol



Una solución de 1,3-dibromo-5,5-dimetilhidantoína (87 mg, 0,305 mmoles) en THF (1 ml) se agregó gota a gota a una solución del intermediario 8A (100 mg, 0,609 mmoles) en THF (4 ml) y metanol (2 ml) a -78°C. La mezcla se agitó a -78°C durante 16 h, posteriormente se diluyó con agua y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con solución de cloruro de sodio acuosa saturada, se secaron sobre sulfato de magnesio y se evaporaron. La purificación por cromatografía de columna sobre gel de sílice

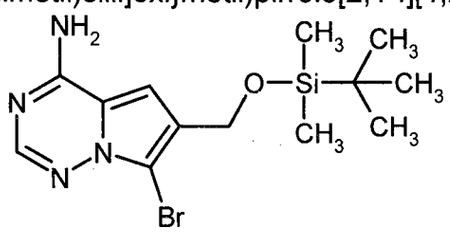
(diclorometano/metanol 20:1 → 10:1) dio 55 mg (32% de teor.) del compuesto del título.

LC-MS (procedimiento 3): Tr = 1,71 min; MS (ESIpos): m/z = 243/245 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,74-7,94 (m, 3H), 7,04 (s, 1H), 5,12 (t, 1H), 4,48 (d, 2H) ppm.

Intermediario 35A

7-bromo-6-({[*ter*-butil(dimetil)silil]oxi}metil)pirrolo[2,1-f][1,2,4]triazin-4-amina



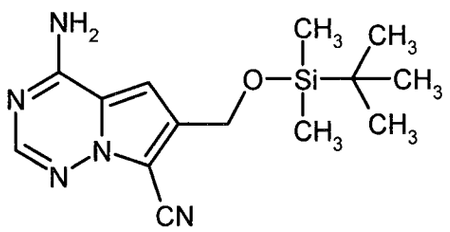
Una solución del intermediario 34A (885 mg, 3,64 mmoles) en DMF (11 ml) se trató con *ter*-butildimetilsilil cloruro (823 mg, 5,46 mmoles) e imidazol (743 mg, 10,92 mmoles) y se agitó a ta durante 2 h. La mezcla de reacción se combinó con la mezcla de reacción de una serie analítica de 100 mg, se diluyó con agua y se extrajo dos veces con acetato de etilo. Las fases orgánicas combinadas se lavaron con agua y solución de cloruro de sodio acuosa saturada, se secaron sobre sulfato de magnesio y se evaporaron. La purificación por cromatografía de columna sobre gel de sílice (ciclohexano/acetato de etilo 2:1 → 100% acetato de etilo) dio 1,36 g (93% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 1,13 min; MS (ESIpos): m/z = 357/359 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,98-7,68 (m, 3H), 7,04 (s, 1H), 4,68 (s, 2H), 0,89 (s, 9H), 0,09 (s, 6H) ppm.

Intermediario 36A

4-amino-6-({[*ter*-butil(dimetil)silil]oxi}metil)pirrolo[2,1-f][1,2,4]triazin-7-carbonitrilo



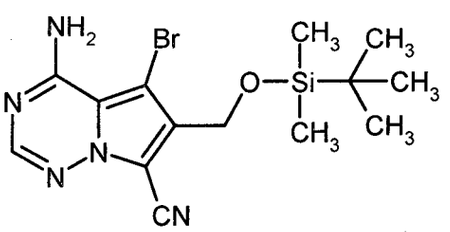
Bajo argón, una mezcla del intermediario 35A (880 mg, 2,46 mmoles), complejo [1,1'-bis(difenilfosfino)ferroceno]dicloropaladio(II)-diclorometano [$PdCl_2$(dppf) x DCM] (120 mg, 0,148 mmoles), bis(dibencilidenacetona)paladio [$Pd(dba)_2$] (135 mg, 0,148 mmoles), cianuro de zinc (578 mg, 4,92 mmoles), polvo de zinc (64 mg, 0,985 mmoles) y acetato de zinc (180 mg, 0,985 mmoles) en DMF desgasificado/agua (100:1, 9,2 ml) se agitó a 160°C durante toda la noche. La mezcla de reacción posteriormente se combinó con la mezcla de reacción de una serie analítica de 100 mg, y las mezclas combinadas se adsorbieron sobre kieselguhr, se filtró sobre otra capa de kieselguhr y eluyó con *ter-butil metil éter*. El filtrado se lavó con solución de hidrógeno carbonato de sodio acuosa saturada, y la capa acuosa se extrajo nuevamente tres veces con *ter-butil metil éter*. Las fases orgánicas combinadas se secaron sobre sulfato de sodio y se evaporaron. La purificación por cromatografía de columna sobre gel de sílice (ciclohexano/acetato de etilo 1:1) dio 453 mg (44% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 1,09 min; MS (ESIpos): m/z = 304 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,22-8,35 (m, 2H), 8,06 (s, 1H), 6,95 (s, 1H), 4,83 (s, 2H), 0,91 (s, 9H), 0,11 (s, 6H) ppm.

Intermediario 37A

4-amino-5-bromo-6-({[*ter*-butil(dimetil)silil]oxi}metil)pirrolo[2,1-f][1,2,4]triazin-7-carbonitrilo



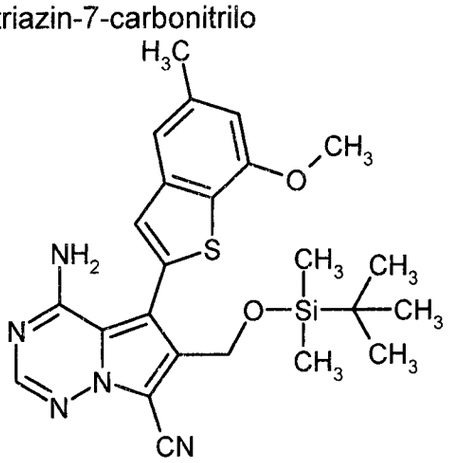
Una solución de 1,3-dibromo-5,5-dimetilhidantoína (621 mg, 2,17 mmoles) en THF (20 ml) se agregó gota a gota a una solución del intermediario 36A (1,1 g, 3,62 mmoles) en THF (80 ml) a -50°C. La mezcla resultante se entibió lentamente hasta ta, se agitó durante 2 h y posteriormente se templó con 10% de solución de tiosulfato de sodio acuoso y solución de hidrógeno carbonato de sodio acuosa saturada. La fase acuosa se extrajo tres veces con acetato de etilo. Un precipitado sólido de la solución de acetato de etilo se filtró y se lavó con acetato de etilo, dando 508 mg (100% de pureza, 36% de teor.) en forma de un primer cultivo del compuesto del título. El filtrado restante se secó sobre sulfato de sodio y se evaporaron. El residuo se precipitó a partir de DMSO y se lavó con DMSO y acetato de etilo dando otros 498 mg (85% de pureza, 26% de teor.) del compuesto del título.

LC-MS (procedimiento 5): Tr = 2,70 min; MS (ESIpos): m/z = 382/384 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,10 (s, 1H), 4,76 (s, 2H), 0,90 (s, 9H), 0,12 (s, 6H) ppm.

Intermediario 38A

4-amino-6-({[*ter*-butil(dimetil)silil]oxi}metil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-7-carbonitrilo



Bajo argón, una solución del intermediario 37A (459 mg, 1,29 mmoles) en THF desgasificado (14,8 ml) se agregó a (2'-aminobifenil-2-il)(cloro)paladio-diciclohexil(2',4',6'-triisopropilbifenil-2-il)fosfina (1:1; 152 mg, 0,19 mmoles; véase S. L. Buchwald *et al.*, *J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)) y el

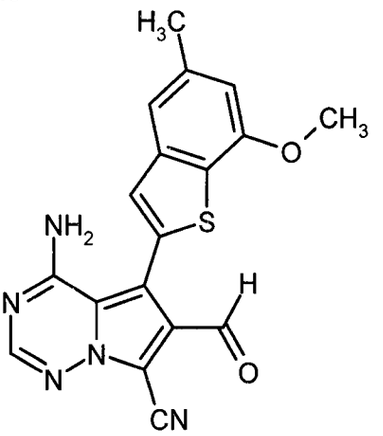
intermediario 6A (647 mg, 1,94 mmoles). La solución de fosfato de potasio 0,5 M desgasificado (5,1 ml) se agregó gota a gota, y la mezcla resultante se agitó a 60°C durante 2 h. La mezcla de reacción posteriormente se combinó con las mezclas de reacción de las anteriores series analíticas de 70 mg, 90 mg y 500 mg y se evaporaron. La purificación del residuo por cromatografía de columna sobre gel de sílice (ciclohexano/acetato de etilo 3:1 → 100% acetato de etilo) dio 1,0 g (58% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 1,49 min; MS (ESIpos): m/z = 480 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,57-8,35 (br. s, 1H), 8,18 (s, 1H), 7,41 (s, 1H), 7,30 (s, 1H), 6,86 (s, 1H), 6,28-6,03 (br. s, 1H), 4,74 (s, 2H), 3,95 (s, 3H), 2,44 (s, 3H), 0,83 (s, 9H), 0,00 (s, 6H) ppm.

Intermediario 39A

4-amino-6-formil-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-7-carbonitrilo



Una solución del ejemplo 68 (250 mg, 0,684 mmoles) en diclorometano (5 ml) se trató con periodinano Dess-Martin (1,1,1-triacetoxi-1,1-dihidro-1,2-benziodoxol-3(1*H*)-ona; 377 mg, 0,889 mmoles) y se agitó a ta durante 1 h. La mezcla de reacción se combinó con la mezcla de reacción de una serie analítica de 50 mg, se templó con solución de hidrógeno carbonato de sodio acuosa saturada y solución de tiosulfato de sodio acuosa saturada (1:1) y se agitó a ta durante 30 min. La fase acuosa se extrajo tres veces con acetato de etilo, y las fases orgánicas combinadas se secaron sobre sulfato de sodio y se

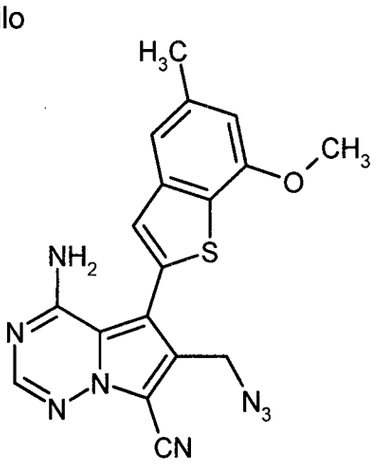
evaporaron. La purificación por cromatografía de columna sobre gel de sílice (ciclohexano/25% acetato de etilo → 100% acetato de etilo) dio 102 mg (24% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 1,02 min; MS (ESIpos): m/z = 364 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 9,86 (s, 1H), 8,78 (br. s, 1H), 8,30 (s, 1H), 7,62 (s, 1H), 7,36 (s, 1H), 6,91 (s, 1H), 6,51 (br. s, 1H), 3,97 (s, 3H), 2,46 (s, 3H) ppm.

Intermediario 40A

4-amino-6-(azidometil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-7-carbonitrilo



Una solución del ejemplo 68 (100 mg, 273 µmoles) en diclorometano (5 ml) se trató con cloruro de tionilo (39 µl, 547 µmoles) y se agitó a ta durante 15 min. Después de la evaporación, el residuo se disolvió en DMF (6 ml) y se trató con yoduro de sodio (205 mg, 1,36 mmoles) y azida de sodio (355 mg, 5,47 mmoles). La mezcla se agitó a 80°C durante toda la noche, posteriormente se diluyó con agua y se extrajo tres veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con agua, seguido de solución de cloruro de sodio acuosa saturada, se secaron sobre sulfato de sodio y se evaporaron dando 91 mg del producto bruto el cual se usó en el próximo paso sin purificación posterior.

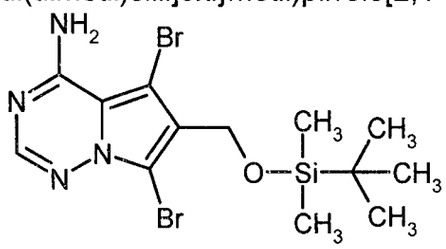
LC-MS (procedimiento 2): Tr = 1,13 min; MS (ESIpos): m/z = 391 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): d = 8,65-8,45 (br. s, 1H), 8,23 (s, 1H), 7,46 (s,

1H), 7,34 (s, 1H), 6,88 (s, 1H), 6,41-6,10 (br. s, 1H), 4,57 (s, 2H), 3,96 (s, 3H), 2,46 (s, 3H) ppm.

Intermediario 41A

5,7-dibromo-6-({[*ter*-butil(dimetil)silil]oxi}metil)pirrolo[2,1-f][1,2,4]triazin-4-amina



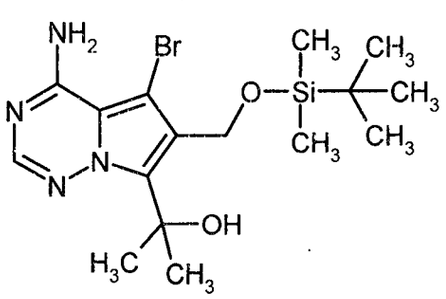
Una solución del intermediario 18A (2 g, 6,21 mmoles) en DMF (20 ml) se trató con imidazol (846 mg, 12,4 mmoles) y *ter*-butildimetilsilil cloruro (1,12 g, 7,45 mmoles) y se agitó a ta durante 20 h. La mezcla de reacción posteriormente se diluyó con agua (200 ml) y se agitó a ta durante otros 2 h. La filtración del sólido dio 2,46 g (88% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 1,37 min; MS (ESIpos): m/z = 437 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,49-8,05 (br. s, 1H), 7,96 (s, 1H), 7,15-6,76 (br. s, 1H), 4,64 (s, 2H), 0,87 (s, 9H), 0,09 (s, 6H) ppm.

Intermediario 42A

2-[4-amino-5-bromo-6-({[*ter*-butil(dimetil)silil]oxi}metil)pirrolo[2,1-f][1,2,4]triazin-7-il]propan-2-ol



Bajo argón, una solución del intermediario 41A (1 g, 2,29 mmoles) en THF (40 ml) se enfrió hasta -78°C y se trató con una solución 1,6M de metillitio en éter dietílico (1,5 ml, 2,40 mmoles). Después de agitar durante 10 min a -78°C, se agregó una solución 1,6M de *n*-butilitio en hexanos (1,58 ml, 2,52 mmoles), y se continuó con la agitación durante 10 min. Se agregó acetona (1,68 ml,

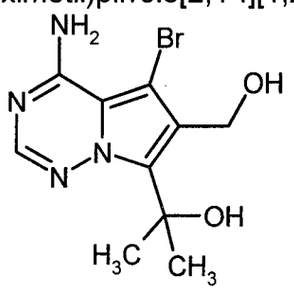
22,92 mmoles), y la mezcla resultante se entibió lentamente hasta ta y se agitó a ta durante 18 h. La reacción posteriormente se templó con agua, y la fase acuosa se extrajo dos veces con acetato de etilo. Las fases orgánicas combinadas se lavaron con solución de cloruro de sodio acuosa saturada, se secaron sobre sulfato de magnesio y se evaporaron. La purificación por cromatografía flash sobre gel de sílice (ciclohexano/acetato de etilo 2:1) dio 306 mg (30% de teor.) del compuesto del título.

LC-MS (procedimiento 4): Tr = 1,39 min; MS (ESIpos): m/z = 415/417 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,23-7,85 (br. s, 1H), 7,89 (s, 1H), 7,05-6,82 (br. s, 1H), 5,49 (s, 1H), 4,88 (s, 2H), 1,66 (s, 6H), 0,87 (s, 9H), 0,08 (s, 6H) ppm.

Intermediario 43A

2-[4-Amino-5-bromo-6-(hidroximetil)pirrolo[2,1-f][1,2,4]triazin-7-il]propan-2-ol



Una solución del intermediario 42A (304 mg, 0,732 mmoles) en THF (15 ml) se trató con una solución 1M de fluoruro de tetra-n-butilamonio en THF (768 µl, 768 µmoles) y se agitó a ta durante 2 min. La mezcla de reacción se diluyó con acetonitrilo (20 ml), posteriormente se evaporó, y el residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-30% acetonitrilo/0,2% TFA ac.). El producto obtenido de este modo se disolvió en metanol y se filtró a través de un cartucho de intercambio aniónico (Stratospheres SPE, PL-HCO_3 MP-resina). El cartucho se eluyó con metanol, y el filtrado se evaporó dando 180 mg (67% de teor.) del compuesto del título.

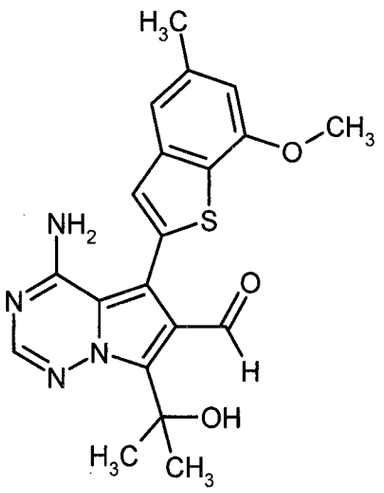
LC-MS (procedimiento 2): Tr = 0,55 min; MS (ESIpos): m/z = 301/303 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,21-7,90 (m, 1H), 7,87 (s, 1H), 7,09-6,60

(br. s, 1H), 5,90 (br. s, 1H), 5,03 (br. s, 1H), 4,63 (s, 2H), 1,66 (s, 6H) ppm.

Intermediario 44A

4-amino-7-(2-hidroxipropan-2-il)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo-[2,1-f][1,2,4]triazin-6-carbaldehído

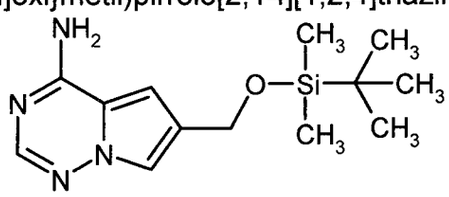


Una solución del ejemplo 73 (135 mg, pureza 89%, 302 µmoles) en diclorometano (7 ml) se trató con Periodinano Dess-Martin (1,1,1-triacetoxi-1,1-dihidro-1,2-benziodoxol-3(1*H*)-ona; 166 mg, 392 µmoles) y se agitó a ta durante 70 min. La mezcla de reacción se combinó con la mezcla de reacción de una serie analítica de 18 mg (45 µmoles) y se templó con solución de hidrógeno carbonato de sodio acuosa saturada y solución de tiosulfato de sodio acuosa saturada (1:1). La fase acuosa se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se lavaron con solución de cloruro de sodio acuosa saturada, se secaron sobre sulfato de magnesio y se evaporaron dando 143 mg (pureza 77%, 92% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 1,08 min; MS (ESIpos): m/z = 397 $(M+H)^+$.

Intermediario 45A

6-({[*ter*-butil(dimetil)silil]oxi}metil)pirrolo[2,1-f][1,2,4]triazin-4-amina

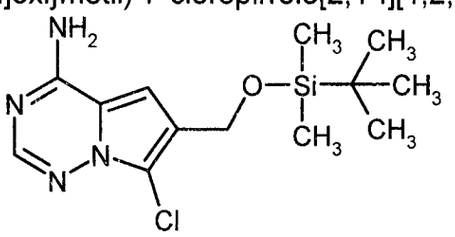


Una solución de 1,5 g (9,14 mmoles) del intermediario 8A en 15 ml DMF seco se trató con 1,65 g (10,96 mmoles) *ter*-butildimetilsilil cloruro y 1,24 g (18,27 mmoles) imidazol y se agitó a ta durante toda la noche. La mezcla de reacción se vertió en 250 ml agua y se agitó durante 5 min. El precipitado resultante se filtró y se secó al vacío a 45°C. Rendimiento: 2,28 g (90% de teor.).

LC-MS (procedimiento 5): Tr = 2,12 min; MS (ESIpos): m/z = 279 $(M+H)^+$.

Intermediario 46A

6-({[*ter*-Butil(dimetil)silil]oxi}metil)-7-cloropirrolo[2,1-f][1,2,4]triazin-4-amina



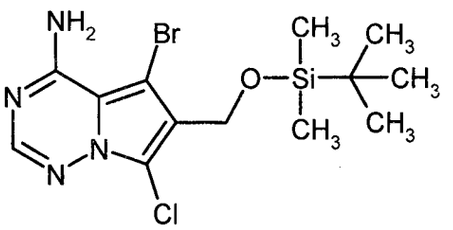
Una solución de 2 g (7,18 mmoles) del intermediario 45A en 20 ml de THF se trató con 893 mg (6,47 mmoles) *N*-clorosuccinimida en 6 porciones durante 60 min a -10°C. Se continuó con la agitación durante 15 min a -10°C, posteriormente la mezcla se dejó entibiar hasta ta. Otros 192 mg (1,44 mmoles) *N*-clorosuccinimida se agregaron a ta, y se continuó con la agitación durante toda la noche. Aproximadamente un décimo de la mezcla de reacción se evaporó hasta sequedad, y el residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) dando 94 mg (4% de teor.) del compuesto del título. La mayor parte de la mezcla de reacción se adsorbió sobre gel de sílice y se sometió a cromatografía sobre gel de sílice con isohexano/acetato de etilo 5-66% como eluyente, dando 899 mg (40% de teor.) del compuesto del título. Total rendimiento: 993 mg (44% de teor.).

LC-MS (procedimiento 5): Tr = 2,45 min; MS (ESIpos): m/z = 313 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,69-8,04 (m, 3H), 7,0 (s, 1H), 4,70 (s, 2H), 0,88 (s, 9H), 0,08 (s, 6H) ppm.

Intermediario 47A

5-Bromo-6-({[*ter*-butil(dimetil)silil]oxi}metil)-7-cloropirrolo[2,1-f][1,2,4]triazin-4-amina



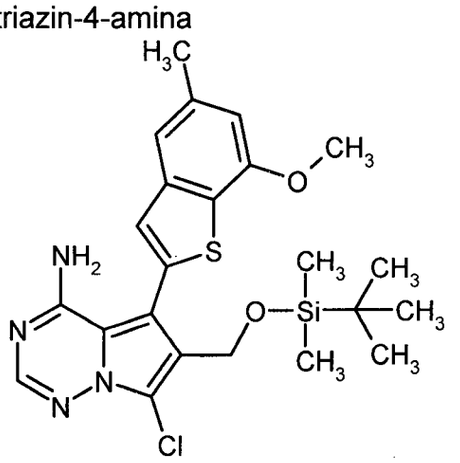
Una solución de 890 mg (2,85 mmoles) del intermediario 46A en 20 ml DMF se trató con 506 mg (2,85 mmoles) *N*-bromosuccinimida en porciones durante 1 h a -10°C. Se continuó con la agitación durante 3 h a -10°C y posteriormente durante toda la noche a ta. Se agregó agua (200 ml) , y la mezcla se agitó durante 2 h. El sólido precipitado se filtró, se lavó con agua y se secó al vacío a 45°C. Rendimiento: 997 mg (89% de teor.).

LC-MS (procedimiento 5): Tr = 2,82 min; MS (ESIpos): m/z = 391/393/395 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,32 (br. s, 1H), 7,97 (s, 1H), 6,97 (br. s, 1H), 4,66 (s, 2H), 0,87 (s, 9H), 0,09 (s, 6H) ppm.

Intermediario 48A

6-({[*ter*-butil(dimetil)silil]oxi}metil)-7-cloro-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-4-amina



Bajo una atmósfera de argón, un matraz se cargó con 800 mg (2,04 mmoles) del intermediario 47A, 680 mg (2,04 mmoles) del intermediario 6A, 80 mg (0,1 mmoles) (2'-aminobifenil-2-il)(cloro)paladio-diciclohexil(2',4',6'-triisopropilbifenil-

2-il)fosfina (1:1; véase S. L. Buchwald *et al.*, *J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)) y 1,3 g (6,13 mmoles) fosfato de potasio. Posteriormente, 30 ml de una mezcla de 1,4-dioxano/agua desgasificada (5:1) se agregaron, y la solución se agitó a 70°C durante 1 h. Otros 680 mg (2,04 mmoles) del intermediario 6A y 32 mg (0,04 mmoles) (2'-aminobifenil-2-il)(cloro)paladio-diciclohexil(2',4',6'-triisopropilbifenil-2-il)fosfina (1:1) se agregaron, y la agitación a 70°C continuó durante 1 h. Este procedimiento se repitió tres veces hasta que el material de partida se consumió (control por LC-MS). Con la última porción de reactivos, además se agregaron 1,6 ml de solución 5 M de hidróxido de sodio ac. para obtener un valor de pH de 8-9. Al final del período de reacción, se agregaron 30 ml agua y 5 M ácido fórmico acuoso (pH 3-4) al cabo de lo cual se separó un aceite. Una parte de este aceite se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso). Se obtuvieron dos fracciones del compuesto del título: 103 mg de un sólido (89% de pureza por LC-MS, 9% de teor.), y 23 mg de un sólido (100% de pureza por LC-MS, 2% de teor.). El resto del aceite y el sobrenadante se diluyeron con agua, se ajustó hasta pH 8-9 con solución de hidrógeno carbonato de sodio acuosa saturada y se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se lavaron con agua, se secaron y se evaporaron a presión reducida, dando 2,1 g de un aceite. Este material se purificó por cromatografía de columna sobre gel de sílice con diclorometano/0-5% metanol como eluyente para dar otros 709 mg (43% de pureza por LC-MS, 31% de teor.) del compuesto del título. Total rendimiento: 42% de teor.

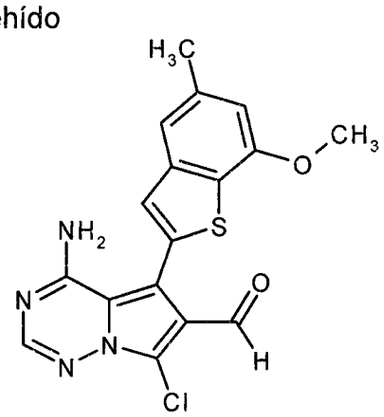
LC-MS (procedimiento 2): Tr = 1,57 min; MS (ESIpos): m/z = 489 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,08 (s, 1H), 7,43 (s, 1H), 7,32 (s, 1H), 6,88 (s, 1H), 4,66 (s, 2H), 3,98 (s, 3H), 2,47 (s, 3H), 0,84 (s, 9H), –0,03 (s, 6H) ppm.

Intermediario 49A

4-amino-7-cloro-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-

f][1,2,4]triazin-6-carbaldehído



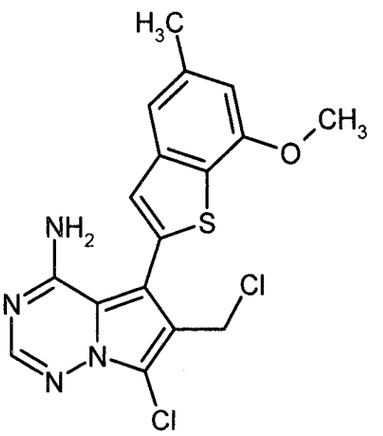
A una suspensión de 166 mg (0,44 mmoles) del ejemplo 79 y tamices moleculares (3Å) en 3 ml de diclorometano se agregaron 207 mg (0,49 mmoles) periodinano Dess-Martin (1,1,1-triacetoxi-1,1-dihidro-1,2-benziodoxol-3(1*H*)-ona) a 0-5°C. La mezcla se agitó durante 10 min a esta temperatura, posteriormente otros se agregaron 56 mg (0,13 mmoles) Periodinano Dess-Martin, y se continuó con la agitación durante 15 min a 5°C y 10 min a temperatura ambiente. Después de esto, la mezcla se adsorbió sobre tierra de diatomea y se purificó por cromatografía de columna sobre gel de sílice con diclorometano/ 0-10% metanol como eluyente. Rendimiento: 100 mg de un sólido (92,7% puro por LC-MS, 56% de teor.).

LC-MS (procedimiento 2): Tr = 1,08 min; MS (ESIpos): m/z = 373 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 9,90 (s, 1H), 8,46 (br. s, 1H), 8,15 (s, 1H), 7,54 (s, 1H), 7,34 (s, 1H), 6,89 (s, 1H), 6,07 (br. s, 1H), 3,96 (s, 3H), 2,46 (s, 3H) ppm.

Intermediario 50A

7-cloro-6-(clorometil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]-triazin-4-amina

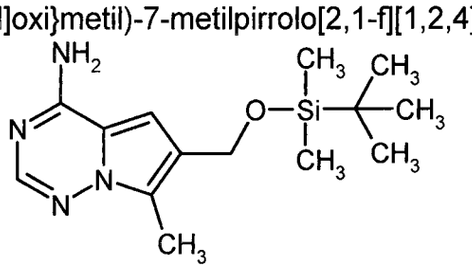


El compuesto del título se aisló en forma de subproducto en la preparación del ejemplo 79 (véase a continuación). Rendimiento: 9,2 mg (10% de teor.).

LC-MS (procedimiento 3): Tr = 2,98 min; MS (ESIpos): m/z = 393/395 $(M+H)^+$.

Intermediario 51A

6-({[*ter*-butil(dimetil)silil]oxi}metil)-7-metilpirrolo[2,1-f][1,2,4]triazin-4-amina



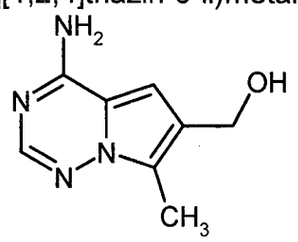
A una solución de 3 g (8,4 mmoles) del intermediario 35A en 60 ml 1,4-dioxano bajo una atmósfera de argón se agregaron 171 mg (0,21 mmoles) de $PdCl_2$(dppf) x DCM y posteriormente gota a gota durante 10 min 16,8 ml de una solución 2 M de dimetilzinc en tolueno (causando un incremento en la temperatura desde 22°C hasta 31°C). Se continuó con la agitación primero durante 10 min a temperatura ambiente, posteriormente durante 13 h a 90°C. Después de esto, se agregó agua (10 ml) a la mezcla de reacción a ta, y la suspensión se agitó durante 1 h. La mezcla se evaporó a presión reducida, y el residuo se colocó en agua y acetato de etilo y se agitó durante 1 hora más. El precipitado se filtró y se descartó, las fases se separaron, y la capa acuosa se extrajo dos veces con acetato de etilo. Las fases orgánicas combinadas se secaron y se evaporaron dando 2,45 g (92% de pureza por LC-MS, 92% de teor.) del compuesto del título.

LC-MS (procedimiento 5): Tr = 2,18 min; MS (ESIpos): m/z = 293 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,98-7,78 (m, 3H), 7,04 (s, 1H), 4,68 (s, 2H), 0,89 (s, 9H), 0,09 (s, 6H) ppm.

Intermediario 52A

(4-amino-7-metilpirrolo[2,1-f][1,2,4]triazin-6-il)metanol



Procedimiento 1:

A una solución de 100 mg (0,28 mmoles) del intermediario 35A en 2 ml 1,4-dioxano bajo una atmósfera de argón se agregaron 6 mg (0,01 mmoles) de $PdCl_2$(dppf) x DCM y posteriormente gota a gota durante 10 min 0,56 ml de una solución 2 M de dimetilzinc en tolueno. La mezcla se agitó a 90°C durante toda la noche, posteriormente se evaporó, y el residuo se trató con acetonitrilo y 5 M ácido fórmico acuoso. El precipitado se filtró, el filtrado se evaporó, y el residuo se colocó en DMSO/acetonitrilo y se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso). Rendimiento: 33 mg (66% de teor.).

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,79 (s, 1H), 7,47 (br. s, 2H), 6,80 (s, 1H), 4,84 (t, 1H), 4,49 (d, 2H), 2,36 (s, 3H) ppm.

Procedimiento 2:

Bajo una atmósfera de argón, un recipiente de reacción de microondas se cargó con 750 mg (3,1 mmoles) del intermediario 34A, 515 µl (3,7 mmoles) trimetilboroxina, 786 mg (3,7 mmoles) fosfato de potasio y 73 mg (0,09 mmoles) (2'-aminobifenil-2-il)(cloro)paladio-diciclohexil(2',4',6'-triisopropilbifenil-2-il)fosfina (1:1; véase S. L. Buchwald *et al.*, *J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)). Posteriormente, 13 ml de una mezcla de 1,4-dioxano/agua desgasificada (5:1) se agregaron, el recipiente se cerró, y la

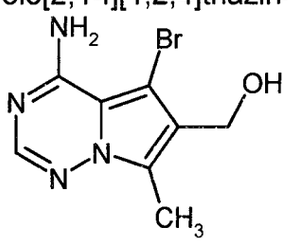
mezcla se calentó hasta 140°C durante 20 min en las microondas (4 bar, 50 wat). Otros 50 mg (2'-aminobifenil-2-il)(cloro)paladio-diciclohexil(2',4',6'-triisopropilbifenil-2-il)fosfina (1:1) se agregaron, y la mezcla se calentó nuevamente hasta 140°C durante 20 min en las microondas. Se agregó otra porción de 515 µl de trimetilboroxina, y el recipiente se calentó nuevamente hasta 140°C durante 20 min. Este último procedimiento se repitió dos veces más con períodos de calentamiento de 30 min cada uno hasta que la LC-MS mostró que sólo quedaron pequeñas cantidades del material de partida. La mezcla se filtró sobre kieselguhr, se lavó con 1,4-dioxano, y los filtrados combinados se evaporaron hasta sequedad. Este residuo se combinó con una serie analítica de 100 mg anterior y se purificó por RP-HPLC preparativa (XBridge C18, gradiente 5-42% acetonitrilo/0,05% solución de hidróxido de amonio ac.). Rendimiento: 238 mg (38% de teor.).

LC-MS (procedimiento 5): Tr = 0,51 min; MS (ESIneg): m/z = 177 $(M-H)^-$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,79 (s, 1H), 7,48 (br. s, 2H), 6,80 (s, 1H), 4,84 (t, 1H), 4,49 (d, 2H), 2,36 (s, 3H) ppm.

Intermediario 53A

(4-amino-5-bromo-7-metilpirrolo[2,1-f][1,2,4]triazin-6-il)metanol



Una solución de 245 mg (1,38 mmoles) del intermediario 52A en 8,8 ml DMF se trató con 288 mg (1,62 mmoles) *N*-bromosuccinimida en porciones durante 2 h a -10°C. Se continuó con la agitación a -10°C durante 30 min y posteriormente durante 2 h a temperatura ambiente. La mezcla se vertió en 50 ml agua y se extrajo con acetato de etilo. Las fases orgánicas combinadas se secaron y se evaporaron. El residuo se cromatografió flash sobre gel de sílice con diclorometano/0-15% metanol como eluyente. Rendimiento: 148 mg (42%

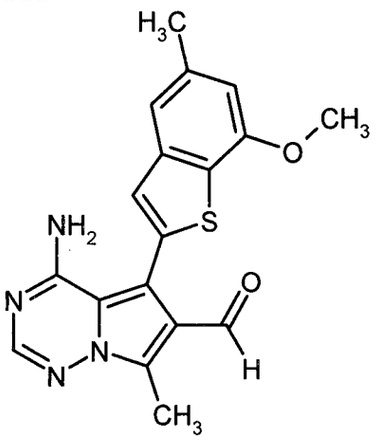
de teor.).

LC-MS (procedimiento 4): Tr = 0,42 min; MS (ESIpos): m/z = 257/259 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,85 (s, 1H), 6,14-8,22 (ancho, 2H), 4,88 (t, 1H), 4,45 (d, 2H), 2,43 (s, 3H) ppm.

Intermediario 54A

4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-metilpirrolo[2,1-f][1,2,4]triazin-6-carbaldehído



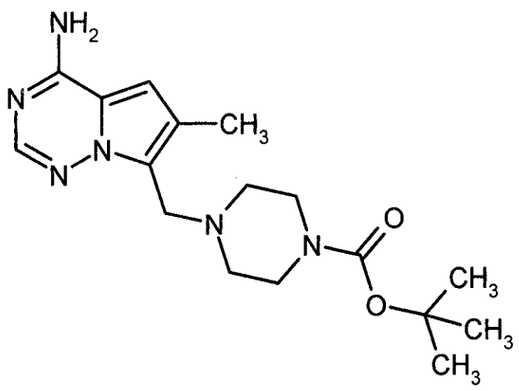
A una suspensión de 175 mg (0,49 mmoles) del ejemplo 75 y tamices moleculares (3Å) en 3,5 ml diclorometano se agregaron 230 mg (0,54 mmoles) Periodinano Dess-Martin (1,1,1-triacetoxi-1,1-dihidro-1,2-benziodoxol-3(1*H*)-ona) a 0-5°C. La mezcla se agitó durante 5 min a esta temperatura, seguido de 30 min a ta. Después de esto, la mezcla se adsorbió sobre tierra de diatomea y se purificó por cromatografía flash sobre gel de sílice con isohexano/10-100% acetato de etilo como eluyente. Rendimiento: 139 mg de un sólido (79% de teor.).

LC-MS (procedimiento 5): Tr = 2,34 min; MS (ESIpos): m/z = 353 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 9,93 (s, 1H), 8,06 (s, 1H), 7,50 (s, 1H), 7,33 (s, 1H), 6,88 (s, 1H), 3,96 (s, 3H), 2,71 (s, 3H), 2,46 (s, 3H) ppm.

Intermediario 55A

ter-butilo 4-[(4-amino-6-metilpirrolo[2,1-f][1,2,4]triazin-7-il)metil]piperazin-1-carboxilato



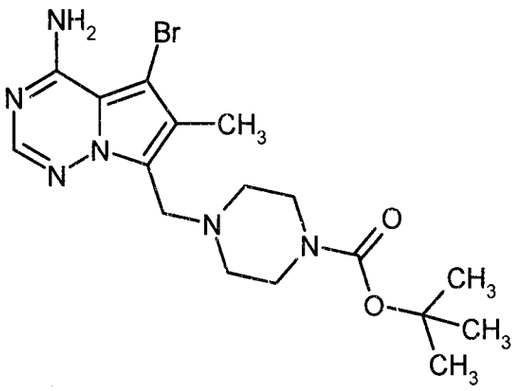
Una solución de 6-metilpirrolo[2,1-f][1,2,4]triazin-4-amina (500 mg, 3,3 mmoles; preparación descripta en Solicitud de Patente Internacional PCT WO 2007/056170) en ácido acético (8 ml) se trató con 37% de solución de formaldehído acuosa (328 µl, 4,04 mmoles) y piperazin-1-carboxilato de *ter*-butilo (754 mg, 4,04 mmoles). La mezcla se agitó a 60°C durante toda la noche. Después de la evaporación, el residuo se colocó en acetato de etilo y se lavó con solución de hidrógeno carbonato de sodio acuosa saturada. La capa acuosa se extrajo dos veces con acetato de etilo. Las fases orgánicas combinadas se secaron sobre sulfato de magnesio y se evaporaron dando 1,2 g del producto bruto el cual se usó en el próximo paso sin purificación posterior.

LC-MS (procedimiento 2): Tr = 0,56 min; MS (ESIpos): m/z = 347 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,79 (s, 1H), 7,51 (br. s, 2H), 6,67 (s, 1H), 3,76 (br. s, 2H), 3,29-3,17 (m, 4H), 2,36-2,29 (m, 4H), 2,22 (s, 3H), 1,37 (s, 9H) ppm.

Intermediario 56A

4-[(4-amino-5-bromo-6-metilpirrolo[2,1-f][1,2,4]triazin-7-il)metil]piperazin-1-carboxilato de *ter*-butilo



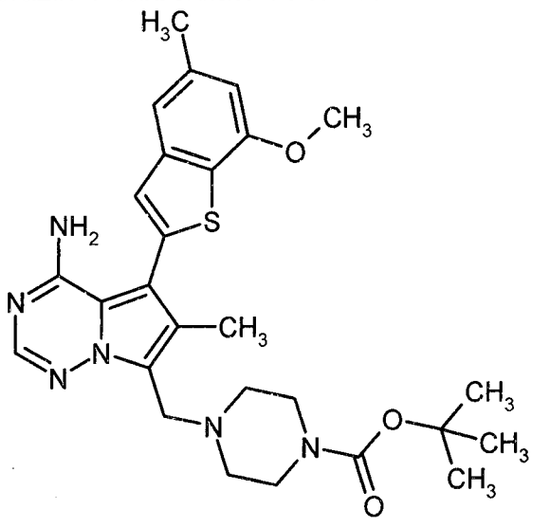
Una solución del intermediario 55A (1,17 g, 3,37 mmoles) en THF (20 ml) se enfrió hasta -60°C y se trató con 1,3-dibromo-5,5-dimetilhidantoína (5,78 mg, 2,02 mmoles). La mezcla se agitó durante 4 h a -60°C hasta -20°C. Después de esto, la mezcla de reacción se templó con 10% de solución de tiosulfato de sodio acuoso. La mayoría del solvente THF se evaporó al cabo de lo cual un sólido precipitó. La filtración y recristalización a partir de acetona dio 862 mg (59% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,66 min; MS (ESIpos): m/z = 425/427 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,29-7,62 (br. s, 1H), 7,85 (s, 1H), 7,17-6,44 (br. s, 1H), 3,80 (s, 2H), 3,29-3,22 (m, 4H), 2,37-2,27 (m, 4H), 2,16 (s, 3H), 1,37 (s, 9H) ppm.

Intermediario 57A

4-{[4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-6-metilpirrolo[2,1-f][1,2,4]-triazin-7-il]metil}piperazin-1-carboxilato de *ter*-butilo



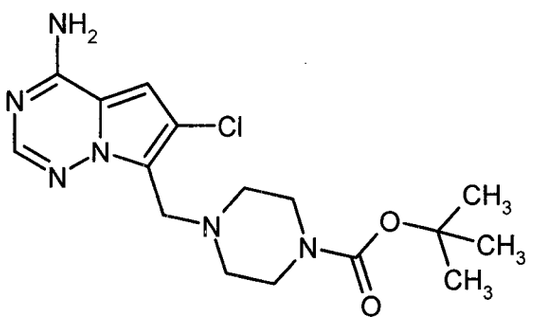
Una solución del intermediario 56A (100 mg, 235 µmoles) en 1,4-dioxano desgasificado (3 ml) se trató con Intermediario 6A (93 mg, 282 µmoles), diciclohexil(2',6'-dimetoxibifenil-2-il)fosfina (S-Phos; 9,6 mg, 23 µmoles) y paladio diacetato (2,6 mg, 11 µmoles). Se agregó solución de fosfato de potasio ac. 3 M desgasificado (588 µl), y la mezcla resultante se agitó a 60°C durante 1 h. Se agregó otra porción del intermediario 6A (78 mg, 235 µmoles), y la agitación a 60°C continuó durante toda la noche. La mezcla de reacción se templó con solución de hidróxido de sodio 2 M ac., y la fase acuosa se extrajo con acetato de etilo. Las fases orgánicas combinadas se lavaron con solución de cloruro de sodio acuosa saturada, se secaron sobre sulfato de magnesio y se evaporaron. La purificación por cromatografía de columna sobre gel de sílice (ciclohexano/acetato de etilo 3:2) dio 82 mg (62% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,97 min; MS (ESIpos): m/z = 523 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,94 (s, 1H), 7,34 (s, 1H), 7,30 (s, 1H), 6,84 (s, 1H), 3,95 (s, 3H), 3,84 (s, 2H), 3,30-3,23 (m, 4H, superposición con pico de agua), 2,45 (s, 3H), 2,42-2,33 (m, 4H), 2,19 (s, 3H), 1,39 (s, 9H) ppm.

Intermediario 58A

4-[(4-amino-6-cloropirrolo[2,1-f][1,2,4]triazin-7-il)metil]piperazin-1-carboxilato de *ter*-butilo



Siguiendo el procedimiento del intermediario 55A, 4 g (23,7 mmoles) 6-cloropirrolo[2,1-f][1,2,4]triazin-4-amina (preparación descripta en Solicitud de Patente Internacional PCT WO 2007/064883) se hicieron reaccionar para dar 11,2 g del compuesto del título como material bruto, el cual se usó en el

próximo paso sin purificación posterior.

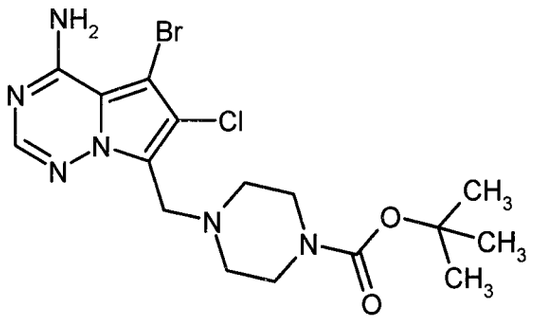
LC-MS (procedimiento 5): Tr = 0,74 min; MS (ESIpos): m/z = 367 $(M+H)^+$

Una muestra de 67 mg de la correspondiente sal formiato, formiato 4-[(4-amino-6-cloropirrolo[2,1-f][1,2,4]triazin-7-il)metil]piperazin-1-carboxilato de *ter*-butilo, se aisló después de la RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) de 100 mg del material bruto obtenido anteriormente.

^{1}H-RMN (400 MHz, DMSO-d_6): *inter al.* δ = 8,14 (s, 1H), 7,91 (s, 1H), 7,83 (br. s, 2H), 6,95 (s, 1H), 3,80 (s, 2H), 3,17 (s, 2H), 2,38 (br. s, 4H), 1,37 (s, 9H) ppm.

Intermediario 59A

4-[(4-amino-5-bromo-6-cloropirrolo[2,1-f][1,2,4]triazin-7-il)metil]piperazin-1-carboxilato de *ter*-butilo



Siguiendo el procedimiento del intermediario 56A, 11 g (30 mmoles) del intermediario 58A se hicieron reaccionar para dar 1,17 g (9% de teor.) del compuesto del título después de la cromatografía flash sobre gel de sílice (diclorometano/metanol 10:1) y subsiguiente RP-HPLC preparativa (Daiso C18, gradiente 40-65% acetonitrilo/agua).

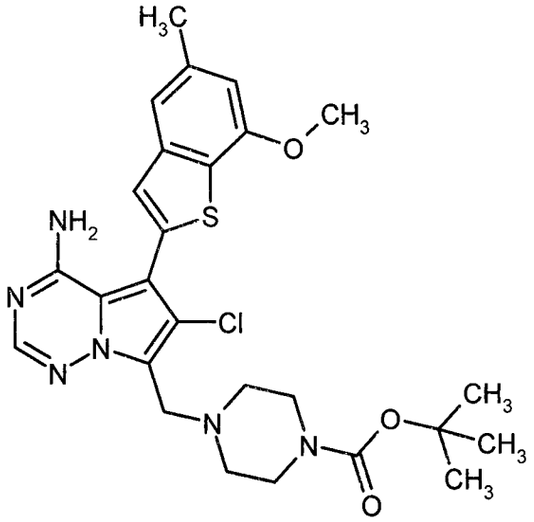
LC-MS (procedimiento 2): Tr = 0,74 min; MS (ESIpos): m/z = 445/447/449 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): *inter al.* δ = 7,96 (s, 1H), 3,84 (s, 2H), 2,37 (br. s, 4H), 1,37 (s, 9H) ppm.

Intermediario 60A

4-{[4-amino-6-cloro-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]-

triazin-7-il]metil}piperazin-1-carboxilato de *ter*-butilo



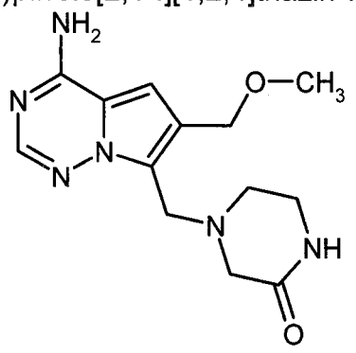
Bajo una atmósfera de argón, un matraz se cargó con 140 mg (0,31 mmoles) del intermediario 59A, 102 mg (0,46 mmoles) del intermediario 5A, 16 mg (0,02 mmoles) $PdCl_2$(dppf) x DCM y 122 mg (1,15 mmoles) carbonato de sodio. Después de la adición de 3 ml de 1,2-dimetoxietano desgasificado/agua (3:1), la suspensión se agitó a 60°C durante 2,5 h. Otras porciones del intermediario 5A (50 mg, 0,23 mmoles) y $PdCl_2$(dppf) x DCM (8 mg, 0,01 mmoles) se agregaron, y se continuó con la agitación a 40°C durante 2,5 h. Este último procedimiento se repitió una vez más hasta que el material de partida se consumió. Posteriormente, la mezcla de reacción se evaporó parcialmente a presión reducida, se agregó agua, y la mezcla se extrajo con diclorometano. Las fases orgánicas combinadas se lavaron con agua y solución de cloruro de sodio acuosa saturada, se secaron y se evaporaron a presión reducida. El residuo (322 mg) se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) para dar 49 mg de una mezcla del compuesto del título y el derivado Boc desprotegido, 6-cloro-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-amina. Esta mezcla se usó como tal en la próxima etapa de reacción (véase el ejemplo 85).

LC-MS (procedimiento 2): Tr = 1,00 min; MS (ESIpos): m/z = 543 $(M+H)^+$, y Tr

= 0,81 min; MS (ESIpos): m/z = 443 $(M+H)^+$.

Intermediario 61A

4-{[4-amino-6-(metoximetil)pirrolo[2,1-f][1,2,4]triazin-7-il]metil}piperazin-2-ona

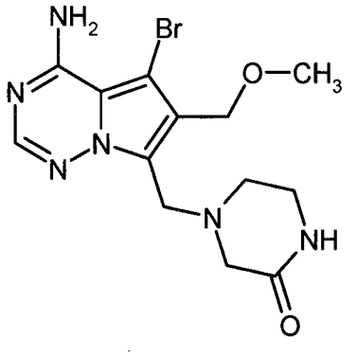


Una solución del intermediario 10A (5 g, 28,1 mmoles) y piperazin-2-ona (3,09 g, 30,9 mmoles) en ácido acético (85 ml) se trató con 37% de solución de formaldehído acuosa (3,15 ml, 42,1 mmoles) y se agitó a 60°C durante 16 h. Los volátiles se evaporaron a presión reducida, y el residuo se disolvió en metanol y se adsorbió sobre tierra de diatomea. La purificación por cromatografía de columna sobre gel de sílice (5-10% metanol/diclorometano) dio 3,91 g (46% de teor.) del compuesto del título.

LC-MS (procedimiento 3): Tr = 1,68 min; MS (ESIpos): m/z = 291 $(M+H)^+$.

Intermediario 62A

4-{[4-amino-5-bromo-6-(metoximetil)pirrolo[2,1-f][1,2,4]triazin-7-il]metil}piperazin-2-ona



Una solución del intermediario 61A (3,9 g, 13,4 mmoles) en DMF (50 ml) se enfrió hasta 0°C y se trató con una solución de *N*-bromosuccinimida (2,63 g, 14,8 mmoles) en DMF (6 ml). La mezcla se agitó a 0°C durante 1 h. Posteriormente, el solvente se evaporó, y el residuo se disolvió en metanol y

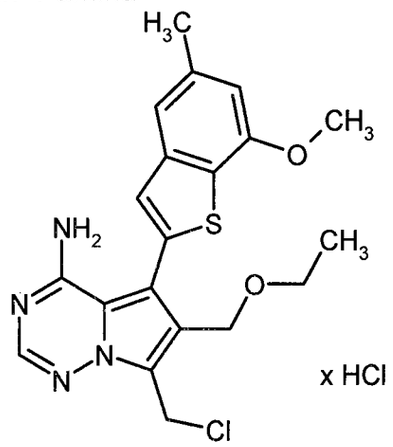
se adsorbió sobre tierra de diatomea. La purificación por cromatografía de columna sobre gel de sílice (5-10% metanol/diclorometano) dio 1,99 g (39% de teor.) del compuesto del título.

LC-MS (procedimiento 3): Tr = 1,86 min; MS (ESIpos): m/z = 369/371 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,96-8,23 (br. s, 1H), 7,90 (s, 1H), 7,71 (s, 1H), 6,72-6,98 (br. s, 1H), 4,45 (s, 2H), 3,91 (s, 2H), 3,27 (s, 3H), 3,07 (br. s, 2H), 2,96 (s, 2H), 2,56 (br. s, 2H) ppm.

Intermediario 63A

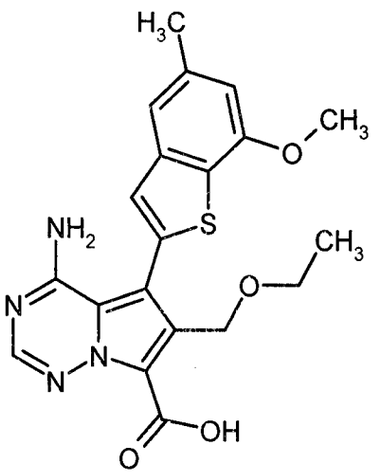
Clorhidrato 7-(clorometil)-6-(etoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-4-amina



Una suspensión del ejemplo 86 (1 g, 2,51 mmoles) en tolueno (60 ml) se trató gota a gota con cloruro de tionilo (1,83 ml, 25,1 mmoles), y la mezcla se agitó a ta durante toda la noche. Los volátiles se evaporaron a presión reducida. El residuo se coevaporó con tolueno a presión reducida tres veces dando 0,85 g (74% de teor.) del compuesto del título el cual se usó inmediatamente para la próxima etapa sin purificación posterior.

Intermediario 64A

Ácido 4-amino-6-(etoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-7-carboxílico



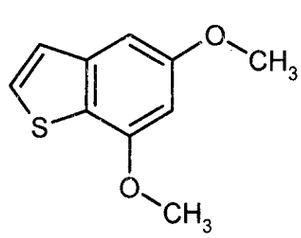
Una suspensión del intermediario 17A (5 g, 12,6 mmoles) en THF/agua (10:1, 220 ml) se trató con una solución 2 M de 2-metil-2-buteno en THF (31,5 ml, 63,1 mmoles) y con dihidrógenofosfato de sodio (6,96 g, 50,4 mmoles). La mezcla se agitó a ta durante 5 min. Posteriormente, se agregó clorito de sodio (4,56 g, 50,44 mmoles) , y la mezcla resultante se agitó a ta durante 20 h. La suspensión se filtró, y el sólido resultante se lavó con agua dando 4,24 g (74% de teor.) del compuesto del título el cual se usó en el próximo paso sin purificación posterior.

LC-MS (procedimiento 4): Tr = 1,06 min; MS (ESIpos): m/z = 413 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 13,22 (br. s, 1H), 8,53-8,00 (br. s, 1H), 8,14 (s, 1H), 7,41 (s, 1H), 7,33 (s, 1H), 6,86 (s, 1H), 6,28-5,65 (br. s, 1H), 4,61 (s, 2H), 3,96 (s, 3H), 3,36 (q, 2H), 2,46 (s, 3H), 1,01 (t, 3H) ppm.

Intermediario 65A

5,7-dimetoxi-1-benzotiofeno



A una solución de 1-benzotiofeno-5,7-diol (1,16 g, 6,98 mmoles) en acetona (20 ml) bajo argón se agregaron carbonato de potasio (2,89 g, 20,9 mmoles) y yodometano (912 µl, 14,6 mmoles). La mezcla resultante se agitó bajo reflujo durante 18 h. Después de enfriar hasta ta, la mezcla se trató con una solución

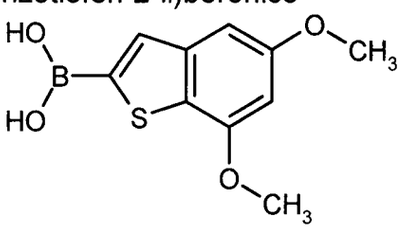
7 M de amoníaco en metanol (10 ml) durante 30 min y posteriormente se adsorbió sobre gel de sílice. La purificación por cromatografía de columna sobre gel de sílice (ciclohexano/acetato de etilo 40:1) dio 0,52 g (32% de teor.) del compuesto del título.

LC-MS (procedimiento 4): Tr = 1,02 min; MS (ESIpos): m/z = 195 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,69 (d, 1H), 7,35 (d, 1H), 7,02 (d, 1H), 6,57 (d, 1H), 3,92 (s, 3H), 3,81 (s, 3H) ppm.

Intermediario 66A

Ácido (5,7-dimetoxi-1-benzotiofen-2-il)borónico

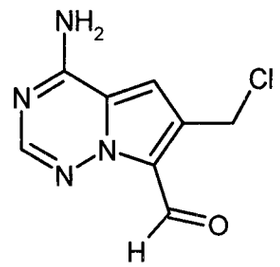


Bajo una atmósfera de argón, una solución 1,6M de *n*-butilitio en hexano (1,84 ml, 2,95 mmoles) se agregó gota a gota a una solución del intermediario 65A (520 mg, 2,68 mmoles) en THF seco (5 ml) a -70°C. Después de 1 hora a -70°C, se agregó triisopropil borato (742 µl, 3,21 mmoles), y la mezcla se agitó durante 16 h mientras se entibiaba lentamente hasta ta. Diclorometano y solución de cloruro de amonio acuosa saturada se agregaron, y el valor de pH se ajustó hasta 6 por la adición de 1 M ácido clorhídrico. La fase orgánica se separó, y la fase acuosa se extrajo con diclorometano. Las fases orgánicas combinadas se secaron con sulfato de magnesio, se filtraron y se evaporaron. El residuo resultante se purificó por cromatografía de columna sobre gel de sílice (primero eluyendo con diclorometano/metanol 40:1, posteriormente metanol, finalmente metanol/4 M cloruro de hidrógeno en 1,4-dioxano 10:1) dando 631 mg (71% de pureza, 71% de teor.) del compuesto del título.

LC-MS (procedimiento 4): Tr = 0,83 min; MS (ESIpos): m/z = 239 $(M+H)^+$.

Intermediario 67A

4-amino-6-(clorometil)pirrolo[2,1-f][1,2,4]triazin-7-carbaldehído

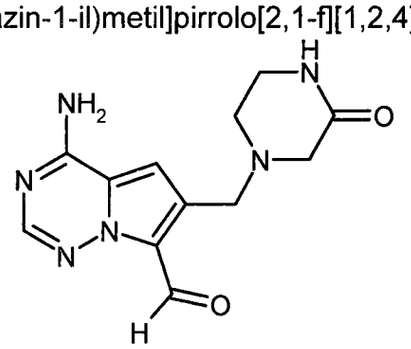


El intermediario 67A se aisló como un subproducto de la síntesis del intermediario 11A después de la cromatografía de columna sobre gel de sílice (diclorometano/acetona 8:2 → 7:3).

LC-MS (procedimiento 2): Tr = 0,6 min; MS (ESIpos): m/z = 211/213 $(M+H)^+$.

Intermediario 68A

4-Amino-6-[(3-oxopiperazin-1-il)metil]pirrolo[2,1-f][1,2,4]triazin-7-carbaldehído

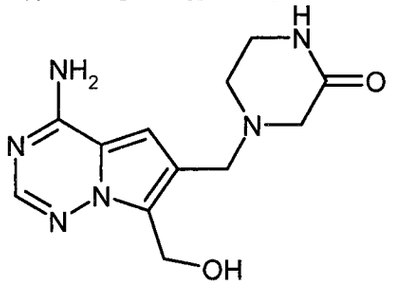


Una solución del intermediario 67A (11,03 g, 52,4 mmoles) y 2-oxopiperazina (6,82 g, 68,1 mmoles) en 331 ml DMF se trató a ta con DIPEA (13,7 ml, 78,6 mmoles) y se agitó durante toda la noche. El precipitado se filtró, se lavó con DMF y éter dietílico y posteriormente se secaron al vacío para dar 11,64 g del compuesto del título (89% de pureza, 72% de teor.).

LC-MS (procedimiento 7): Tr = 1,30 min; MS (ESIpos): m/z = 275 $(M+H)^+$.

Intermediario 69A

4-{[4-Amino-7-(hidroximetil)pirrolo[2,1-f][1,2,4]triazin-6-il]metil}piperazin-2-ona



A una solución del intermediario 68A (10,17 g, 89% de pureza, 33,01 mmoles)

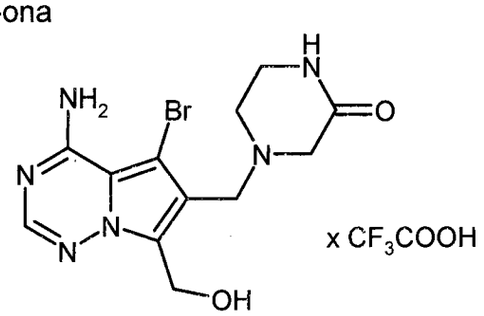
en 1 M ácido clorhídrico (370 ml) y metanol (370 ml) a ta se agregó polvo de zinc (12,1 g, 185 mmoles), y la mezcla se agitó a ta durante 18 h. Se agregó gel de sílice (100 g), y los volátiles se evaporaron a presión reducida. El residuo se suspendió en metanol, los volátiles se evaporaron a presión reducida nuevamente, y el residuo se secó al vacío. El sólido se sometió a cromatografía de columna sobre gel de sílice (gradiente diclorometano/7 M amoníaco en metanol 10:1 → 3:1) para dar 6,39 g del compuesto del título (60% de teor.).

LC-MS (procedimiento 8): Tr = 1,12 min; MS (ESIpos): m/z = 277 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,83 (s, 1H), 7,76 (br. s, 1H), 7,64 (br. s, 2H), 6,83 (s, 1H), 5,01 (br. s, 1H), 4,74 (s, 2H), 3,64 (br. s, 2H), 3,14 (br. s, 2H), 2,95 (br. s, 2H), 2,58 (br. s, 2H) ppm.

Intermediario 70A

Trifluoroacetato 4-{[4-amino-5-bromo-7-(hidroximetil)pirrolo[2,1-f][1,2,4]triazin-6-il]metil}piperazin-2-ona



Una suspensión del intermediario 69A (1 g) en metanol/agua (10:1, 33 ml) se trató con ácido trifluoroacético (0,56 ml, 7,24 mmoles) para dar por resultado una solución transparente. Una solución de *N*-bromosuccinimida (708 mg, 3,98 mmoles) en metanol (30 ml) se agregó gota a gota a 0°C, y la mezcla se agitó a 0°C durante 1 h. El precipitado formado se filtró y se secó al vacío para dar 700 mg del compuesto del título (41% de teor.).

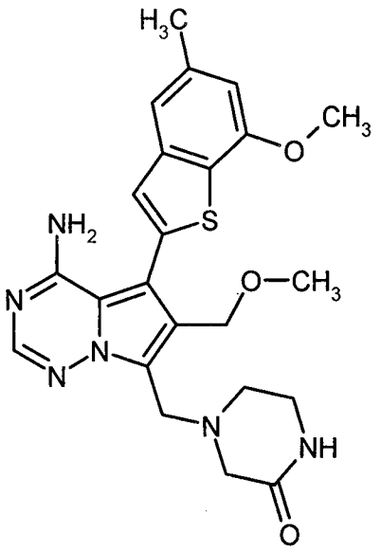
LC-MS (procedimiento 7): Tr = 1,38 min; MS (ESIpos): m/z = 355/357 $(M+H)^+$

^{1}H-RMN (400 MHz, D_2O): δ = 7,90 (s, 1H), 5,00 (s, 2H), 4,44 (s, 2H), 3,85 (s, 2H), 3,58 (br. t, 2H), 3,50 (br. t, 2H) ppm.

Ejemplos de preparación:

Ejemplo 1

4-{[4-amino-6-(metoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f]-[1,2,4]triazin-7-il]metil}piperazin-2-ona



Procedimiento 1:

Una solución del intermediario 13A (3 g, 7,84 mmoles) en metanol (87 ml) se trató con ácido acético (0,898 ml, 15,68 mmoles), 2-oxopiperazina (1,17 g, 11,76 mmoles) y triacetoxiborohidruro de sodio (4,98 g, 23,53 mmoles). La mezcla se agitó a ta durante 4,5 h. Se agregaron otras porciones de 2-oxo-piperazina (392 mg, 3,9 mmoles) y triacetoxiborohidruro de sodio (3,3 g, 15,68 mmoles), y la mezcla resultante se agitó a 60°C durante toda la noche. Después de la evaporación, el residuo se colocó en solución de hidrógeno carbonato de sodio acuosa saturada y se extrajo con acetato de etilo. Las fases orgánicas combinadas se secaron sobre sulfato de sodio y se evaporaron, y el residuo se purificó por cromatografía de columna sobre gel de sílice (diclorometano/metanol 40:1 → 10:1). El producto obtenido de este modo se trituró en metanol y se filtró dando 540 mg (14% de teor.) del compuesto del título. El licor madre metanólico se evaporó y el residuo se purificó por RP-HPLC dos veces (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido

fórmico acuoso). Las fracciones que contienen el producto bruto se combinaron y se neutralizó con solución de hidrógeno carbonato de sodio acuosa saturada. El solvente de acetonitrilo se evaporó, y la fase acuosa se extrajo con acetato de etilo. Las fases orgánicas combinadas se secaron sobre sulfato de sodio y se evaporaron dando 395 mg (13% de teor.) en forma de un segundo lote del compuesto del título.

Procedimiento 2:

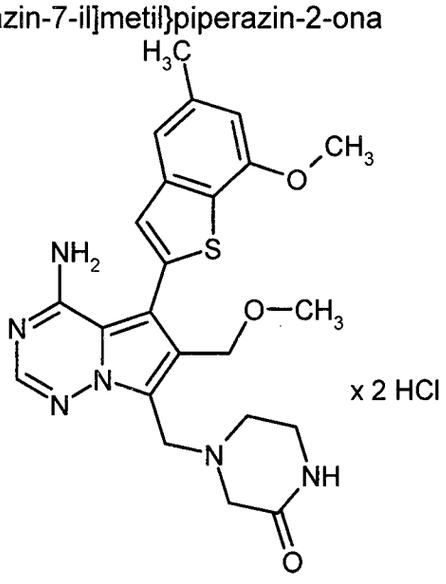
Una solución del intermediario 21A (291 mg, 0,82 mmoles) en ácido acético (2,9 ml) se trató con 37% de solución de formaldehído acuosa (104 µl, 1,39 mmoles) y 2-oxopiperazina (139 mg, 1,39 mmoles). La mezcla se agitó a 60°C durante 3 h y posteriormente se evaporó. La purificación por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) dio 184 mg (44% de teor.) del compuesto del título.

LC-MS (procedimiento 4): Tr = 0,77 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,00 (s, 1H), 7,73 (br. s, 1H), 7,37 (s, 1H), 7,31 (s, 1H), 6,84 (s, 1H), 4,41 (s, 2H), 3,97 (s, 2H), 3,96 (s, 3H), 3,20 (s, 3H), 3,15-3,08 (br. s, 2H), 3,01 (s, 2H), 2,64 (br. t, 2H), 2,45 (s, 3H) ppm.

Ejemplo 2

Diclorhidrato 4-{[4-amino-6-(metoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-7-il]metil}piperazin-2-ona



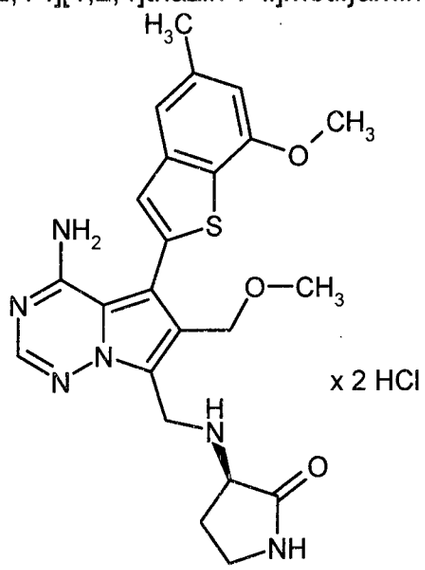
Una solución del ejemplo 1 (100 mg, 214 µmoles) en 1,4-dioxano (2 ml) se trató con una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (2 ml, 8 mmoles). El solvente se evaporó dejando 130 mg (cuant.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,79 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,39 (br. s, 1H), 8,31-8,53 (br. s, 1H), 8,17 (s, 1H), 7,38 (s, 1H), 7,34 (s, 1H), 6,87 (s, 1H), 6,21-6,42 (br. s, 1H), 4,81 (br. s, 2H), 4,52 (br. s, 2H), 3,96 (s, 3H), 3,57 (s, 2H), 3,32-3,72 (m, 4H), 3,26 (s, 3H), 2,46 (s, 3H) ppm.

Ejemplo 3

Diclorhidrato (*3R*)-3-({[4-amino-6-(metoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-7-il]metil}amino)pirrolidin-2-ona



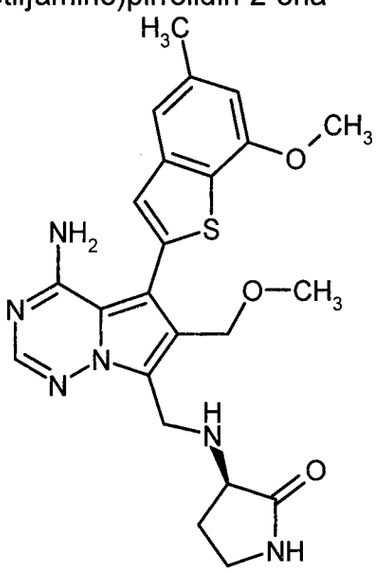
Una solución del intermediario 13A (520 mg, 1,36 mmoles) en metanol (15 ml) y ácido acético (156 µl, 2,7 mmoles) se trató con (*R*)-3-aminopirrolidin-2-ona (503 mg, 5,0 mmoles) y triacetoxiborohidruro (1,06 g, 5,0 mmoles). La mezcla se agitó a ta durante toda la noche y posteriormente se evaporó. La purificación por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) y liofilización del producto obtenido de este modo a partir de una solución 4 M de cloruro de hidrógeno en 1,4-dioxano dio 272 mg (36% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,70 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): d = 9,62 (br. s, 1H), 9,46 (br. s, 1H), 8,56-8,22 (br. s, 1H), 8,44 (s, 1H), 8,19 (s, 1H), 7,38 (s, 1H), 7,34 (s, 1H), 6,87 (s, 1H), 6,54-6,12 (br. s, 1H), 4,89-4,65 (m, 2H), 4,58-4,46 (m, 2H), 4,17-4,07 (br. s, 1H, superposición con pico de agua), 3,96 (s, 3H), 3,36-3,16 (m, 2H), 3,25 (s, 3H), 2,48-2,39 (m, 1H), 2,46 (s, 3H), 2,23-2,06 (m, 1H) ppm.

Ejemplo 4

(*3R*)-3-({[4-amino-6-(metoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo-[2,1-f][1,2,4]triazin-7-il]metil}amino)pirrolidin-2-ona



Una solución del intermediario 13A (2,0 g, 5,2 mmoles) en metanol (58 ml) y ácido acético (0,6 ml) se trató con (*R*)-3-aminopirrolidin-2-ona (785 mg, 7,8 mmoles) y triacetoxiborohidruro (3,32 g, 15,6 mmoles). La mezcla se agitó a ta durante toda la noche. Después de esto, la mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio acuosa saturada y se extrajo tres veces con acetato de etilo. Las fases orgánicas combinadas se secaron sobre sulfato de sodio y se evaporaron. El residuo se purificó por cromatografía de columna dos veces sobre gel de sílice (diclorometano/metanol 40:1 hasta 10:1) para dar 957 mg (37% de teor.) del compuesto del título.

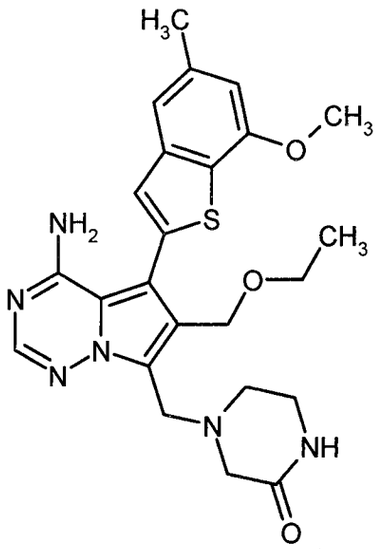
LC-MS (procedimiento 4): Tr = 0,72 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,01 (s, 1H), 7,75 (s, 1H), 7,35 (s, 1H), 7,31

(s, 1H), 6,85 (s, 1H), 4,46-4,34 (m, 2H), 4,24-4,02 (m, 2H), 3,96 (s, 3H), 3,24-3,04 (m, 3H), 3,21 (s, 3H), 2,45 (s, 3H), 2,40-2,27 (m, 1H), 1,80-1,65 (m, 1H) ppm.

Ejemplo 5

4-{[4-amino-6-(etoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f]-[1,2,4]triazin-7-il]metil}piperazin-2-ona



Procedimiento 1:

Una solución del intermediario 17A (2 g, 5,05 mmoles) en THF (100 ml) se trató a 0°C con 2-oxopiperazina (1,01 g, 10,1 mmoles), triacetoxiborohidruro de sodio (1,07 g, 5,04 mmoles) y ácido acético (0,29 ml, 5,04 mmoles). La mezcla resultante se agitó a 0°C durante 30 min. Cuatro porciones adicionales de triacetoxiborohidruro de sodio (1,07 g, 5,04 mmoles) y de ácido acético (0,29 ml, 5,04 mmoles) se agregaron cada 30 minutos, y la mezcla resultante se agitó durante otros 30 min a 0°C, posteriormente durante 25 min a 35°C y finalmente a ta durante toda la noche. La reacción se templó con 10% de solución de cloruro de sodio ac. y se extrajo dos veces con acetato de etilo. Las capas orgánicas combinadas se evaporaron. El residuo se purificó por cromatografía de columna sobre gel de sílice (diclorometano/ metanol 95:5 → 90:10) dando 360 mg (17% de teor.) del compuesto descripta en Ejemplo 86 (véase a continuación) y 1,82 g del compuesto del título en fracciones

separadas. El producto del título obtenido de este modo se suspendió en etanol (20 ml), se sometió a reflujo durante 2 h y posteriormente se enfrió hasta 15°C. El sólido se filtró y se lavó con etanol dando 1,63 g (67% de teor.) del compuesto del título puro.

Procedimiento 2:

Una solución del ejemplo 13 (930 mg, 1,9 mmoles) en diclorometano (18 ml) se trató con cloruro de tionilo (210 µl, 2,8 mmoles) y se agitó a ta durante 15 min. Después de la evaporación, el residuo se disolvió en etanol (18 ml) y se trató con DIPEA (670 µl, 3,8 mmoles). La mezcla se agitó a 70°C durante 2 h y posteriormente se evaporó. El residuo se purificó por cromatografía de columna sobre gel de sílice (diclorometano/metanol 98:2 → 90:10). El producto obtenido de este modo se trituró en una mezcla de acetonitrilo/éter dietílico y se filtró. El filtrado se evaporó, y el residuo se purificó nuevamente por cromatografía de columna sobre gel de sílice (diclorometano/metanol 98:2 → 90:10). Nuevamente, el producto obtenido de este modo se trituró en acetonitrilo/éter dietílico y se filtró. Este procedimiento se repitió una vez más. Los tres lotes de sólidos obtenidos de esta manera se combinaron, se trituraron en acetonitrilo/éter dietílico una vez nuevamente y finalmente se filtró dando 600 mg (62% de teor.) del compuesto del título.

Procedimiento 3:

Una solución del intermediario 22A (720 mg, pureza 89%, 1,74 mmoles) en ácido acético (10 ml) se agitó con piperazin-2-ona (261 mg, 2,61 mmoles) a 60°C. A esto, se agregó 37% de solución de formaldehído acuosa (260 µl, 3,48 mmoles) en tres porciones después de 0, 3 y 12 h, respectivamente, y la mezcla se agitó a 60°C durante un total de 24 h. Posteriormente, los volátiles se removieron a presión reducida, y el residuo se dividió entre acetato de etilo y solución de hidrógeno carbonato de sodio acuosa saturada. La fase orgánica se lavó con solución de cloruro de sodio acuosa saturada, se secaron con sulfato de magnesio y se evaporaron. El residuo se disolvió en una mezcla de

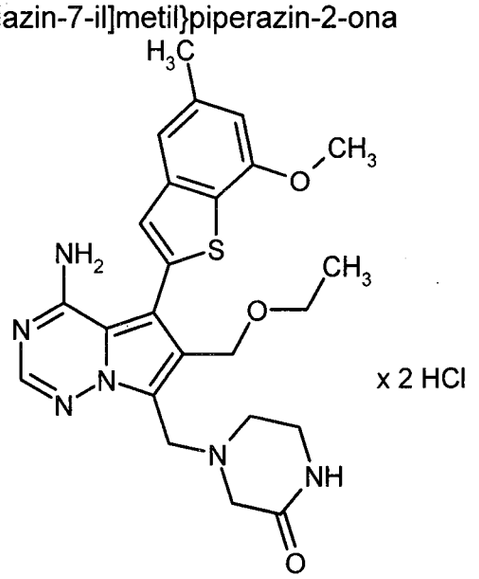
metanol y diclorometano, se adsorbió sobre tierra de diatomea, se secaron al vacío y se purificó por cromatografía flash sobre gel de sílice (gradiente 0-6% metanol/diclorometano). Las fracciones del producto se combinaron, se evaporó y re-se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 30-50% acetonitrilo/0,2% TFA ac.). Las fracciones del producto se combinaron nuevamente, se diluyó con solución de hidrógeno carbonato de sodio acuosa saturada y se extrajo con acetato de etilo. La fase orgánica se lavó con solución de cloruro de sodio acuosa saturada, se secaron con sulfato de magnesio y se evaporaron dando 281 mg (31% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,86 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,01 (s, 1H), 7,8-8,05 (br. s, 1H), 7,74 (br. s, 1H), 7,38 (s, 1H), 7,31 (s, 1H), 6,85 (s, 1H), 5,6-5,9 (br. s, 1H), 4,45 (s, 2H), 3,97 (s, 2H), 3,94 (s, 3H), 3,41 (q, 2H), 3,09-3,13 (m, 2H), 3,02 (s, 2H), 2,63-2,69 (br. s, 2H), 2,45 (s, 3H), 1,07 (t, 3H) ppm.

Ejemplo 6

Diclorhidrato 4-{[4-amino-6-(etoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-7-il]metil}piperazin-2-ona



Una solución del intermediario 17A (60 mg, pureza 69%, 104 µmoles) en metanol (6 ml) se trató con 2-oxopiperazina (22 mg, 209 µmoles),

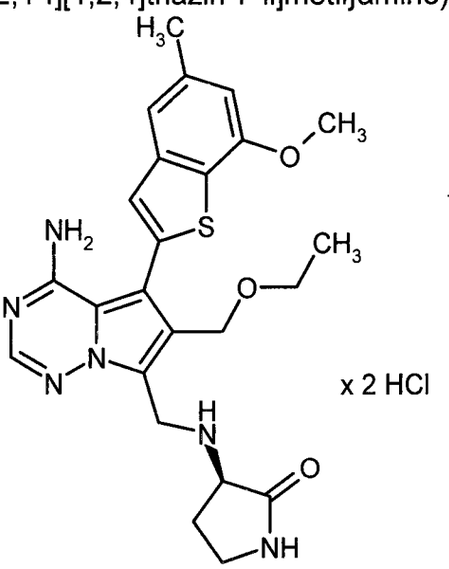
cianoborohidruro de sodio (33 mg, 522 mmoles) y ácido acético (12 µl, 209 µmoles). La mezcla se agitó a 60°C durante 16 h y posteriormente se filtró. El filtrado y el residuo se purificaron de forma separada por RP-HPLC preparativa (Reprosil C18, gradiente 40-60% acetonitrilo/0,2% TFA ac.). Las fracciones del producto se combinaron, se diluyó con 1 M ácido clorhídrico (3 ml) y se evaporaron hasta sequedad dando 46 mg (79% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,87 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,37 (br. s, 1H), 8,31 (br. s, 1H), 8,14 (s, 1H), 7,38 (s, 1H), 7,33 (s, 1H), 6,87 (s, 1H), 6,13 (br. s, 1H), 4,80 (br. s, 2H), 4,52 (s, 2H), 3,96 (s, 3H), 3,86 (br. s, 2H), 3,36-3,51 (m, 5H), 2,46 (s, 3H), 1,11 (t, 3H) ppm.

Ejemplo 7

Diclorhidrato (*3R*)-3-({[4-amino-6-(etoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-7-il]metil}amino)pirrolidin-2-ona



x 2 HCl

Una solución del intermediario 17A (60 mg, pureza 69%, 104 µmoles) en metanol (3 ml) se trató con (*R*)-3-aminopirrolidin-2-ona (22 mg, 209 µmoles), cianoborohidruro de sodio (33 mg, 522 µmoles) y ácido acético (12 µl, 209 µmoles). La mezcla se agitó a 60°C durante 4 h y posteriormente se filtró. El filtrado se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 40-60%

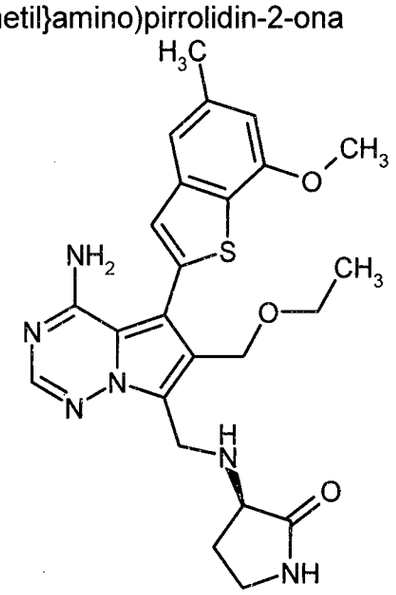
acetonitrilo/ 0,2% TFA ac.). Las fracciones del producto se combinaron, se diluyó con 1 M ácido clorhídrico y se evaporaron hasta sequedad dando 46 mg (79% de teor.) del compuesto del título.

LC-MS (procedimiento 4): Tr = 0,74 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 9,58-9,75 (m, 1H), 9,33-9,54 (m, 1H), 8,44 (s, 1H), 8,27-8,71 (br. s, 1H), 8,19 (s, 1H), 7,38 (s, 1H), 7,34 (s, 1H), 6,87 (s, 1H), 6,18-6,48 (br. s, 1H), 4,68-4,87 (m, 2H), 4,49-4,62 (q, 2H), 3,96 (s, 3H), 3,45 (q, 2H), 3,18-3,35 (m, 2H), 2,46 (s, 4H), 2,08-2,22 (m, 1H), 1,10 (t, 3H) ppm.

Ejemplo 8

(*3R*)-3-({[4-amino-6-(etoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo-[2,1-f][1,2,4]triazin-7-il]metil}amino)pirrolidin-2-ona



Una solución del intermediario 17A (226 mg, pureza 75%, 428 µmoles) en metanol (4 ml) se trató con (*R*)-3-aminopirrolidin-2-ona (85 mg, 855 µmoles), cianoborohidruro de sodio (134 mg, 2,14 mmoles) y ácido acético (49 µl, 855 µmoles). La mezcla se agitó a ta durante 1,5 h. Después de esto, la mezcla se separó directamente por RP-HPLC preparativa (Reprosil C18, gradiente 40-60% acetonitrilo/0,2% TFA ac.). Las fracciones del producto se combinaron, se diluyó con solución de hidrógeno carbonato de sodio acuosa saturada y se extrajo con acetato de etilo. Las fases orgánicas combinadas se lavaron con

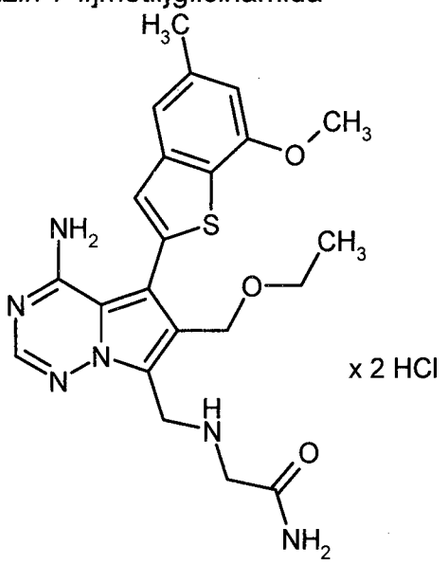
solución de cloruro de sodio acuosa saturada, se secaron sobre sulfato de magnesio y se evaporaron hasta sequedad dando 180 mg (88% de teor.) del compuesto del título.

LC-MS (procedimiento 4): Tr = 0,74 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,00 (s, 1H), 7,76 (s, 1H), 7,8-8,1 (br. s, 1H), 7,35 (s, 1H), 7,31 (s, 1H), 6,84 (s, 1H), 5,6-5,9 (br. s, 1H), 4,39-4,49 (m, 2H), 4,04-4,23 (m, 2H), 3,96 (s, 3H), 3,41 (q, 2H), 3,05-3,23 (m, 3H), 2,45 (s, 3H), 2,31-2,40 (m, 1H), 1,68-1,79 (m, 1H), 1,08 (t, 3H) ppm.

Ejemplo 9

Diclorhidrato N^2-{[4-amino-6-(etoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-7-il]metil}glicinamida



Una solución del intermediario 17A (60 mg, pureza 69%, 104 µmoles) en metanol (3 ml) se trató con clorhidrato glicinamida (23 mg, 209 µmoles), cianoborohidruro de sodio (32 mg, 522 mmoles) y ácido acético (12 µl, 209 µmoles). La mezcla se agitó a 60°C durante 16 h. Después de la filtración, el filtrado se separó por RP-HPLC preparativa (Reprosil C18, gradiente 20-40% acetonitrilo/0,2% TFA ac.). Las fracciones del producto se combinaron, se diluyeron con 1 M ácido clorhídrico, se evaporaron hasta sequedad y se combinaron con el residuo a partir de la etapa de filtración. Este material se purificó nuevamente por RP-HPLC preparativa dos veces (Reprosil C18,

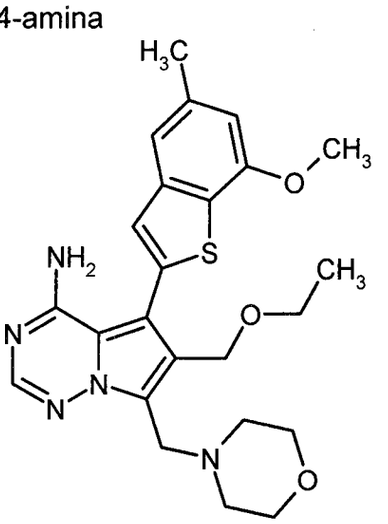
gradiente 20-40% acetonitrilo/0,2% TFA ac.). Las fracciones del producto se combinaron nuevamente, se diluyeron con 1 M ácido clorhídrico y se evaporaron hasta sequedad dando 7,4 mg (13% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,80 min; MS (ESIpos): m/z = 455 $(M+H)^+$

^{1}H-RMN (500 MHz, DMSO-d_6): δ = 9,33 (br. s, 2H), 9,05 (br. s, 1H), 8,31 (s, 1H), 7,93 (br. s, 1H), 7,58 (br. s, 1H), 7,40 (s, 1H), 7,35 (s, 1H), 7,05 (br. s, 1H), 6,88 (s, 1H), 4,65 (br. m, 2H), 4,56 (s, 2H), 3,96 (s, 3H), 3,74 (br. m, 2H), 3,46 (q, 2H), 2,46 (s, 3H), 1,10 (t, 3H) ppm.

Ejemplo 10

6-(etoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(morfolin-4-ilmetil)-pirrolo[2,1-f][1,2,4]triazin-4-amina



Una solución del intermediario 17A (55 mg, pureza 73%, 101 µmoles) en metanol (3 ml) se trató con morfolina (18 mg, 202 µmoles), cianoborohidruro de sodio (19 mg, 303 mmoles) y ácido acético (18 µl, 304 µmoles). La mezcla se agitó a 60°C durante 18 h. Otras cantidades de morfolina (18 mg, 202 µmoles), cianoborohidruro de sodio (19 mg, 303 mmoles) y ácido acético (18 µl, 304 µmoles) se agregaron, y la agitación a 60°C continuó durante otra 3 h. La mezcla resultante se diluyó con THF para disolver los precipitados y se separó por RP-HPLC preparativa (Reprosil C18, gradiente 20-40% acetonitrilo/0,2% TFA ac.). Las fracciones del producto se combinaron y se

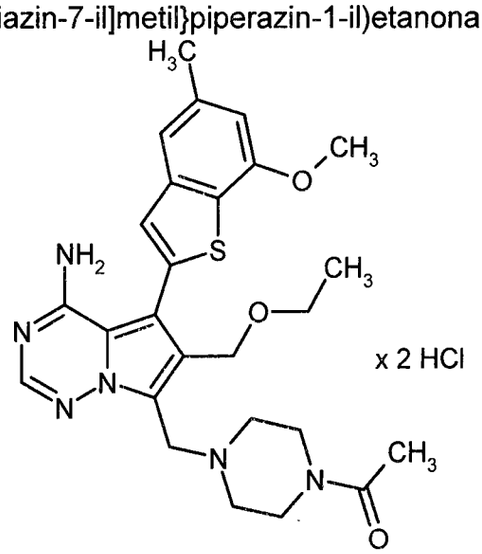
evaporaron hasta sequedad. El residuo se disolvió en metanol y se filtró a través de un cartucho de intercambio aniónico (Stratospheres SPE, PL-HCO_3 MP-resina). El cartucho se eluyó con metanol, y el filtrado se evaporó dando 32 mg (68% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,78 min; MS (ESIpos): m/z = 468 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,98 (s, 1H), 7,9 (br. s, 1H), 7,37 (s, 1H), 7,31 (s, 1H), 6,84 (s, 1H), 5,75 (br. s, 1H), 4,45 (s, 2H), 3,95 (s, 3H), 3,88 (s, 2H), 3,51-3,56 (m, 4H), 3,40 (q, 2H), 2,4-2,5 (m, 4H), 2,45 (s, 3H), 1,06 (t, 3H) ppm.

Ejemplo 11

Diclorhidrato 1-(4-{[4-amino-6-(etoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-7-il]metil}piperazin-1-il)etanona



Una solución del intermediario 17A (130 mg, 0,328 mmoles) en metanol (8 ml) se trató con *N*-acetilpiperazina (63 mg, 0,492 mmoles), cianoborohidruro de sodio (103 mg, 1,63 mmoles) y ácido acético (37 µl, 0,655 mmoles). La mezcla se agitó a 60°C durante 3 h. Posteriormente se combinó con la mezcla de reacción de una serie analítica de 30 mg, se evaporó y se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso). El producto obtenido de este modo se liofilizó a partir de 1,4-dioxano, posteriormente se disolvió en acetato de etilo y se lavó con solución

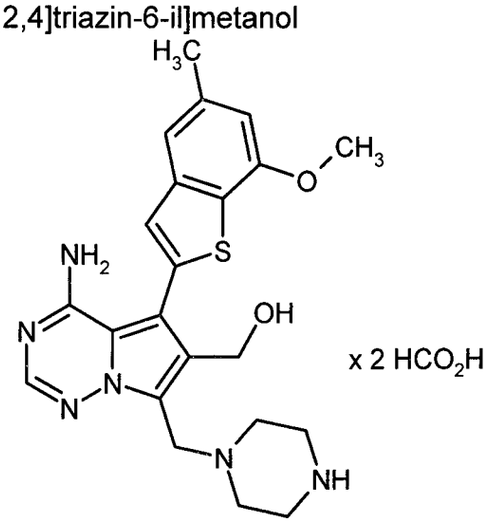
de hidrógeno carbonato de sodio acuosa saturada. La capa orgánica se secó sobre sulfato de magnesio, se evaporó y se liofilizó nuevamente a partir de 1,4-dioxano. Re-la purificación por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso), seguido de cromatografía de columna dos veces sobre gel de sílice (diclorometano/metanol 98:2 → 4:1) y la liofilización a partir de una solución 4 M de cloruro de hidrógeno en 1,4-dioxano dio 49 mg (18% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,82 min; MS (ESIpos): m/z = 509 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): *inter al.* δ = 8,65-8,26 (br. s, 1H), 8,17 (s, 1H), 7,38 (s, 1H), 7,34 (s, 1H), 6,87 (s, 1H), 6,53-6,05 (br. s, 1H), 4,75 (br. s, 2H), 4,56 (br. s, 2H), 3,96 (s, 3H), 3,45 (q, 2H, superposición con pico de agua), 2,46 (s, 3H), 2,03 (s, 3H), 1,09 (t, 3H) ppm.

Ejemplo 12

bis(formiato) [4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-6-il]metanol



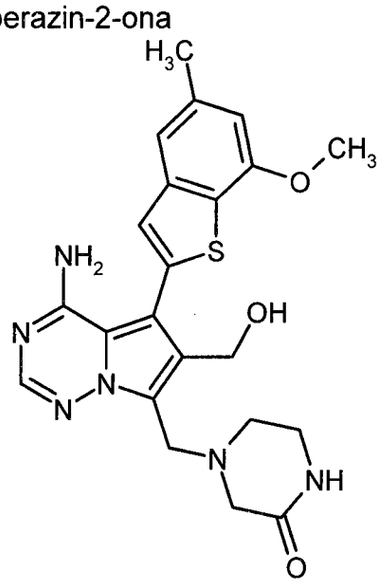
Una solución del intermediario 23A (95 mg, 152 μmoles) en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (3,7 ml) se agitó a ta durante 2 h. Después de la evaporación, el residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) dando 44 mg (62% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,63 min; MS (ESIpos): m/z = 439 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,28 (br. s, 2H), 7,98 (s, 1H), 7,37 (s, 1H), 7,31 (s, 1H), 6,85 (s, 1H), 4,50 (s, 2H, superposición con pico de agua), 3,98 (s, 2H, superposición con pico de agua), 3,95 (s, 3H, superposición con pico de agua), 2,95-2,84 (m, 4H), 2,61-2,55 (m, 4H, superposición con pico de DMSO), 2,45 (s, 3H) ppm.

Ejemplo 13

4-{[4-amino-6-(hidroximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f]-[1,2,4]triazin-7-il]metil}piperazin-2-ona



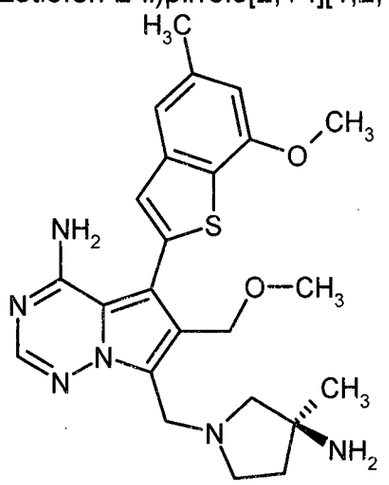
Una solución del intermediario 20A (1,34 g, 3,96 mmoles) en ácido acético (13,9 ml) se trató con 37% de solución de formaldehído acuosa (501 µl, 6,6 mmoles) y 2-oxopiperazina (670 mg, 6,6 mmoles). La mezcla se agitó a 50°C durante 2 h y posteriormente se evaporó. La purificación por cromatografía de columna sobre gel de sílice (diclorometano/metanol 98:2 → 90:10) dio 942 mg (49% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,67 min; MS (ESIpos): m/z = 453 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,99 (s, 1H), 7,76 (br. s, 1H), 7,39 (s, 1H), 7,31 (s, 1H), 6,84 (s, 1H), 4,51 (s, 2H), 4,03 (br. s, 2H), 3,95 (s, 3H), 3,18-3,13 (m, 2H), 3,07-2,98 (m, 2H), 2,72-2,60 (m, 2H), 2,45 (s, 3H) ppm.

Ejemplo 14

Triclorhidrato 7-{[(3*S*)-3-amino-3-metilpirrolidin-1-il]metil}-6-(metoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-4-amina



x 3 HCl

Una solución del intermediario 21A (100 mg, 0,28 mmoles) en ácido acético (1 ml) se trató con 37% de solución de formaldehído acuosa (25 µl, 0,33 mmoles) y [(3*S*)-3-metilpirrolidin-3-il]carbamato de *ter*-butilo (Yoshida *et al.*, *Chem. Pharm. Bull.* 1996, 44 (7), 1376-1386; 67 mg, 0,33 mmoles). La mezcla se agitó a ta durante 3 h y posteriormente se evaporó. El residuo se diluyó con solución de hidrógeno carbonato de sodio acuosa saturada, y se agregó carbonato de potasio sólido hasta que no se produjo más generación de gas. La fase acuosa se extrajo tres veces con acetato de etilo. Las fases orgánicas combinadas se secaron sobre sulfato de sodio y se evaporaron. El residuo se disolvió en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (2 ml) y se agitó a ta durante 2 h. Después de la evaporación, el residuo se purificó por RP-HPLC preparativa dos veces (primero Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso; posteriormente Shield RP18, gradiente 5-50% metanol + 0,1% TFA ac./0,1% TFA ac.). El producto obtenido de este modo se liofilizó a partir de una solución 4 M de cloruro de hidrógeno en 1,4-dioxano dando 14 mg (8% de teor.) del compuesto del título.

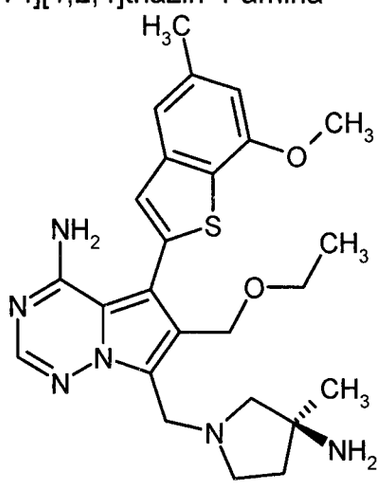
LC-MS (procedimiento 2): Tr = 0,67 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): *inter al.* δ = 8,50-8,22 (br. s, 1H), 8,14 (s, 1H), 7,36 (s, 1H), 7,34 (s, 1H), 6,87 (s, 1H), 6,36-6,01 (br. s, 1H), 4,88 (br. s, 2H),

4,56 (br. s, 2H), 3,96 (s, 3H, superposición con pico de agua), 3,26 (s, 3H), 2,46 (s, 3H), 1,52 (s, 3H) ppm.

Ejemplo 15

7-{[(*3S*)-3-amino-3-metilpirrolidin-1-il]metil}-6-(etoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-4-amina



Una solución del intermediario 17A (100 mg, 271 µmoles) en ácido acético (1 ml) se trató con 37% de solución de formaldehído acuosa (24 µl, 326 µmoles) y [(*3S*)-3-metilpirrolidin-3-il]carbamato de *ter*-butilo (Yoshida *et al.*, *Chem. Pharm. Bull.* 1996, 44 (7), 1376-1386; 65 mg, 326 µmoles). La mezcla se agitó a 60°C durante 4 h. Posteriormente, se agregaron otras cantidades de 37% de solución de formaldehído acuosa (10 µl, 136 µmoles) y [(*3S*)-3-metilpirrolidin-3-il]carbamato de *ter*-butilo (27 mg, 136 µmoles), y la agitación a 60°C continuó durante toda la noche. Después de la evaporación, el residuo se dividió entre acetato de etilo y solución de hidrógeno carbonato de sodio acuosa saturada. Se agregó carbonato de potasio sólido hasta que no se produjo más generación de gas. La fase acuosa se extrajo tres veces con acetato de etilo. Las fases orgánicas combinadas se secaron sobre sulfato de sodio, se evaporaron y se purificaron por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso). El producto obtenido de este modo se disolvió en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (2 ml) y se agitó a ta durante 1 h. Después de la evaporación, el

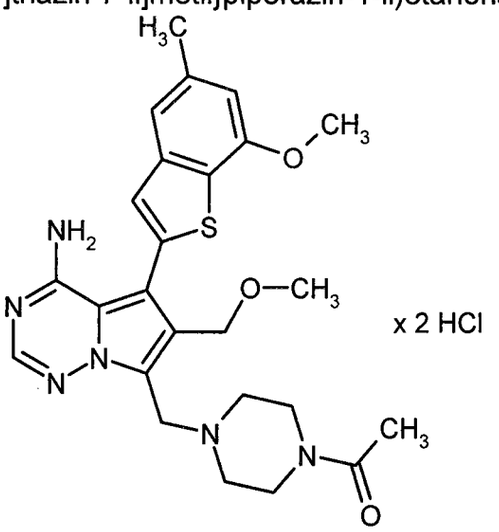
residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) dando 24 mg (18% de teor.) del compuesto del título.

LC-MS (procedimiento 4): Tr = 0,70 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): *inter al.* δ = 8,19 (s, 1H), 7,38 (s, 1H), 7,34 (s, 1H), 6,87 (s, 1H), 4,90 (br. s, 2H), 3,96 (s, 3H), 3,46 (q, 3H), 2,46 (s, 3H), 1,54 (s, 3H), 1,14-1,05 (m, 3H) ppm.

Ejemplo 16

Diclorhidrato 1-(4-{[4-amino-6-(metoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-7-il]metil}piperazin-1-il)etanona



x 2 HCl

Una solución del intermediario 21A (50 mg, 141 μmoles) en ácido acético (1 ml) se trató con 37% de solución de formaldehído acuosa (4,6 μl, 169 μmoles) y *N*-acetilpiperazina (21,6 mg, 169 μmoles). La mezcla se agitó a 75°C durante 3 h. Después de la evaporación, el residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso). La liofilización a partir de una solución 4 M de cloruro de hidrógeno en 1,4-dioxano dio 34 mg (39% de teor.) del compuesto del título.

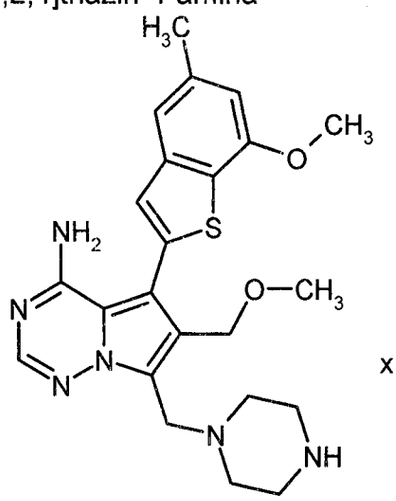
LC-MS (procedimiento 5): Tr = 1,78 min; MS (ESIpos): m/z = 495 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): *inter al.* δ = 8,70-8,35 (br. s, 1H), 8,18 (s, 1H), 7,37 (s, 1H), 7,34 (s, 1H), 6,86 (s, 1H), 6,61-6,19 (br. s, 1H), 4,74 (br. s, 2H),

4,54 (br. s, 2H), 3,96 (s, 3H), 3,25 (s, 3H), 2,46 (s, 3H), 2,03 (s, 3H) ppm.

Ejemplo 17

Formiato 6-(metoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-amina



x HCOOH

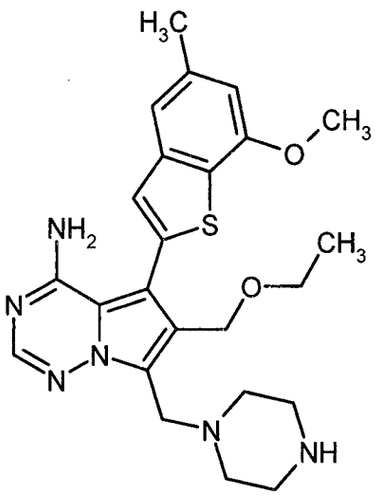
Una solución del intermediario 23A (110 mg, 204 µmoles) en diclorometano (2,2 ml) se trató con cloruro de tionilo (29 µl, 408 µmoles) y se agitó a ta durante 15 min. Después de la evaporación, el residuo se disolvió en metanol (2,2 ml) y se trató con DIPEA (39 µl, 224 µmoles). La mezcla se agitó a 70°C durante 1 h y posteriormente se evaporó. El residuo se colocó en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (2,2 ml) y se agitó a ta durante 2 h. La evaporación y la purificación por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) dio 44,9 mg (46% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,73 min; MS (ESIpos): m/z = 453 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,28 (br. s, 1H), 8,00 (s, 1H), 7,35 (s, 1H), 7,31 (s, 1H), 6,85 (s, 1H), 4,41 (s, 2H), 4,00-3,90 (m, 5H), 3,00-2,90 (m, 4H), 2,65-2,56 (m, 4H), 2,45 (s, 3H) ppm.

Ejemplo 18

6-(etoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)-pirrolo[2,1-f][1,2,4]triazin-4-amina



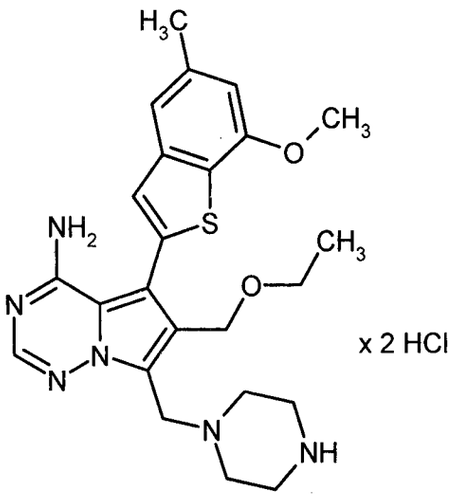
Una solución del intermediario 23A (80 mg, 317 µmoles) en diclorometano (2 ml) se trató con cloruro de tionilo (22 µl, 297 µmoles) y se agitó a ta durante 15 min. Después de la evaporación, el residuo se disolvió en etanol (2 ml) y se trató con DIPEA (28 µl, 163 µmoles). La mezcla se agitó a 70°C durante 1 h y posteriormente se evaporó. El residuo se colocó en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (2 ml) y se agitó a ta durante 1 h. La evaporación y la purificación por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) dio 35 mg (50% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,82 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): *inter al.* δ = 8,09 (br. s, 1H), 7,36 (s, 1H), 7,32 (s, 1H), 6,86 (s, 1H), 4,50 (br. s, 2H), 3,96 (s, 3H), 3,42 (q, 2H, superposición con pico de agua), 2,45 (s, 3H), 1,05 (t, 3H) ppm.

Ejemplo 19

Diclorhidrato 6-(etoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-amina



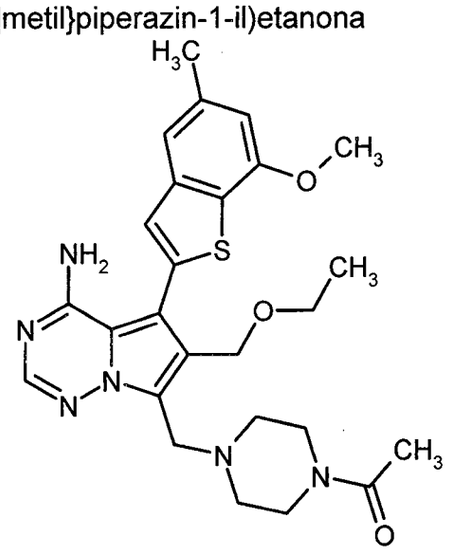
Una solución del ejemplo 18 (50 mg, 107 μmoles) en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (1 ml) se agitó a ta durante 15 min. Después de la evaporación se obtuvieron 55 mg (93% de teor.) del compuesto del título.

LC-MS (procedimiento 4): Tr = 0,74 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): *inter al.* δ = 8,18 (s, 1H), 7,37 (s, 1H), 7,34 (s, 1H), 6,87 (s, 1H), 4,76 (br. s, 2H), 4,60 (br. s, 2H), 3,96 (s, 3H), 3,45 (q, 2H), 2,46 (s, 3H), 1,09 (t, 3H) ppm.

Ejemplo 20

1-(4-{[4-amino-6-(etoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo-[2,1-f][1,2,4]triazin-7-il]metil}piperazin-1-il)etanona



Una solución del ejemplo 18 (70 mg, 150 μmoles) en diclorometano (2 ml) y

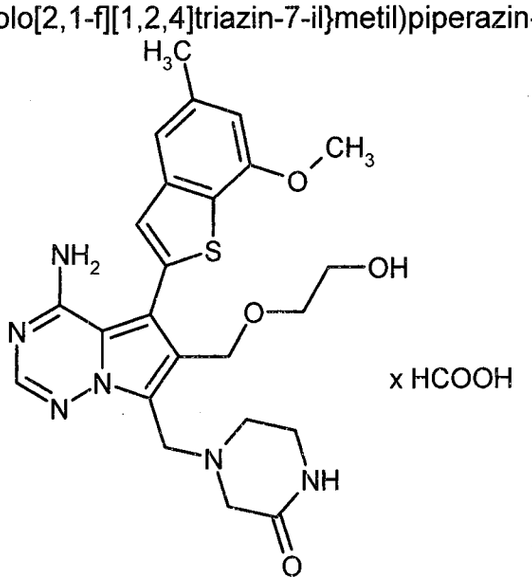
THF (0,8 ml) se trató con cloruro de acetilo (21 µl, 300 µmoles) y carbonato de sodio (127 mg, 1,2 mmoles). La mezcla se agitó a ta durante toda la noche. Después de la evaporación, el residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) dando 27 mg (31% de teor.) del compuesto del título.

LC-MS (procedimiento 4): Tr = 0,77 min; MS (ESIpos): m/z = 509 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,98 (s, 1H), 7,37 (s, 1H), 7,31 (s, 1H), 6,84 (s, 1H), 4,45 (s, 2H), 3,95 (s, 3H), 3,92 (s, 2H), 3,45-3,36 (m, 6H), 2,48-2,38 (m, 7H, superposición con Pico de DMSO), 1,97 (s, 3H), 1,06 (t, 3H) ppm.

Ejemplo 21

Formiato 4-({4-Amino-6-[(2-hidroxietoxi)metil]-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-7-il}metil)piperazin-2-ona



Una solución del ejemplo 13 (60 mg, 132 µmoles) en diclorometano (2 ml) se trató con cloruro de tionilo (14 µl, 198 µmoles). La mezcla se agitó a ta durante 15 min y posteriormente se evaporó. El residuo se disolvió en etilenglicol (500 µl) y se agitó a 100°C durante 90 min. La purificación por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) dio 34 mg (47% de teor.) del compuesto del título.

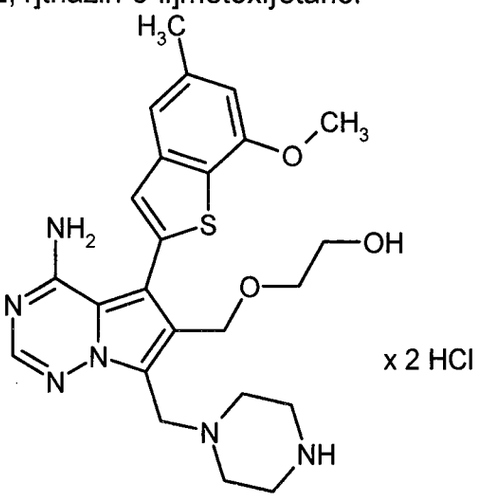
LC-MS (procedimiento 2): Tr = 0,69 min; MS (ESIpos): m/z = 497 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,14 (s, 1H), 8,00 (s, 1H), 7,74 (br. s, 1H),

7,42 (s, 1H), 7,31 (s, 1H), 6,84 (s, 1H), 4,49 (s, 2H), 3,99 (s, 2H), 3,96 (s, 3H), 3,50-3,43 (m, 2H), 3,42-3,36 (m, 2H, superposición con pico de agua), 3,15-3,07 (m, 2H), 3,03 (s, 2H), 2,69-2,61 (m, 2H), 2,45 (s, 3H) ppm.

Ejemplo 22

Diclorhidrato 2-{[4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-6-il]metoxi}etanol



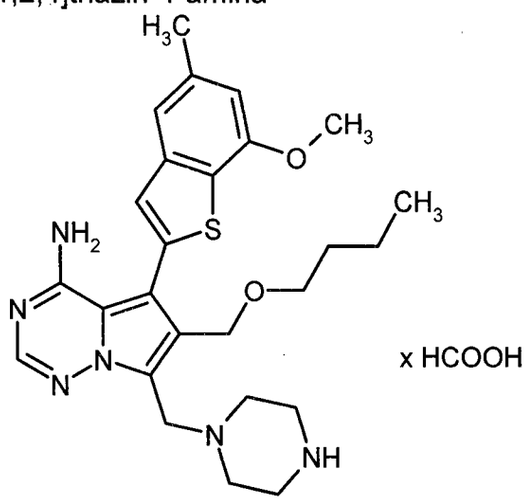
Una solución del intermediario 23A (100 mg, 185 µmoles) en diclorometano (4 ml) se trató con cloruro de tionilo (27 µl, 371 µmoles). La mezcla se agitó a ta durante 20 min y posteriormente se evaporó. El residuo se disolvió en etilenglicol/THF (2:1, 1,5 ml) y se agitó a 100°C durante 2 h. Después de la evaporación, el residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso), seguido de cromatografía de columna sobre gel de sílice (diclorometano/metanol + 0,1% de amoníaco ac. 98:2 → 90:10). La liofilización a partir de una solución 4 M de cloruro de hidrógeno en 1,4-dioxano dio 67 mg (64% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,66 min; MS (ESIpos): m/z = 483 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,16 (s, 1H), 7,49 (s, 1H), 7,43 (s, 1H), 6,98 (s, 1H), 4,86 (s, 2H), 4,69 (s, 2H), 4,03 (s, 3H), 3,81-3,49 (m, 12H), 2,50 (s, 3H) ppm.

Ejemplo 23

Formiato 6-(butoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-amina



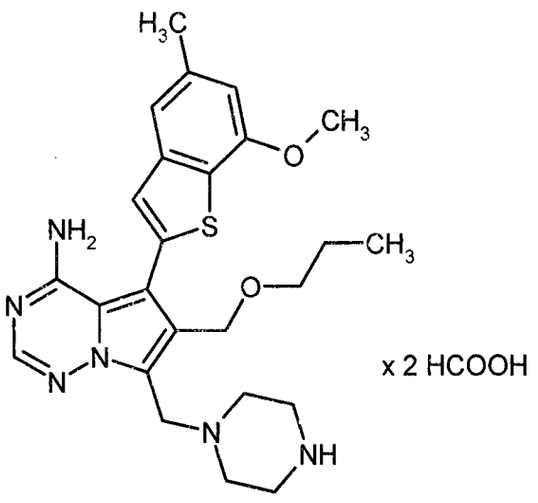
Una solución del intermediario 23A (100 mg, 185 µmoles) en diclorometano (2 ml) se trató con cloruro de tionilo (27 µl, 371 µmoles). La mezcla se agitó a ta durante 15 min y posteriormente se evaporó. El residuo se disolvió en 1-butanol (2 ml) y se calentó hasta 70°C durante 1 h. Después de la evaporación, el residuo se colocó en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (2 ml) y se agitó a ta durante 2 h. La evaporación y la purificación por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) dio 22 mg (24% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,82 min; MS (ESIpos): m/z = 495 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,29 (s, 1H), 7,99 (s, 1H), 7,35 (s, 1H), 7,29 (s, 1H), 6,84 (s, 1H), 4,43 (s, 2H), 3,95 (s, 3H), 3,92 (s, 2H), 3,35 (t, 2H), 2,90-2,79 (m, 4H), 2,45 (s, 3H), 1,47-1,37 (m, 2H), 1,31-1,18 (m, 2H), 0,80 (t, 3H) ppm.

Ejemplo 24

bis(formiato) 5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)-6-(propoximetil)pirrolo[2,1-f][1,2,4]triazin-4-amina



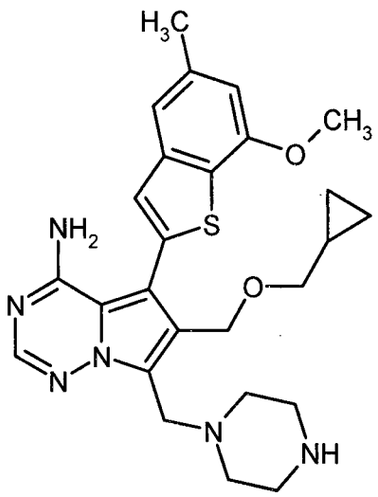
Una solución del intermediario 23A (100 mg, 185 µmoles) en diclorometano (2 ml) se trató con cloruro de tionilo (27 µl, 371 µmoles). La mezcla se agitó a ta durante 15 min y posteriormente se evaporó. El residuo se disolvió en 1-propanol (2 ml), se trató con DIPEA (48 µl, 278 µmoles) y se agitó a ta durante 1 h. Después de la evaporación, el residuo se colocó en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (2 ml) y se agitó a ta durante 2 h. La evaporación y la purificación por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) dio 15 mg (16% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,78 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,26 (br. s, 2H), 7,98 (s, 1H), 7,36 (s, 1H), 7,30 (s, 1H), 6,84 (s, 1H), 4,44 (s, 2H), 3,95 (s, 3H), 3,92 (s, 2H), 3,32 (t, 2H), 2,87-2,79 (m, 4H), 1,52-1,39 (m, 2H), 0,81 (t, 3H) ppm.

Ejemplo 25

bis(formiato) 6-[(ciclopropilmetoxi)metil]-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-amina



x 2 HCOOH

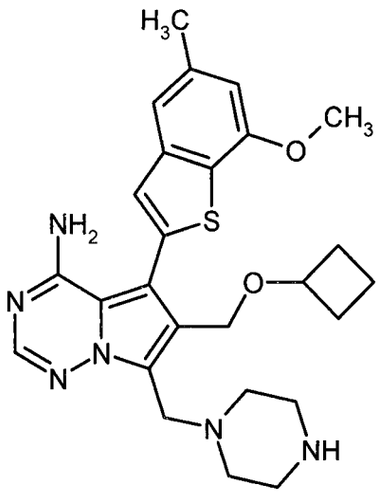
Una solución del intermediario 23A (100 mg, 185 µmoles) en diclorometano (2 ml) se trató con cloruro de tionilo (27 µl, 371 µmoles). La mezcla se agitó a ta durante 15 min y posteriormente se evaporó. El residuo se disolvió en ciclopropilmetanol (2 ml), se trató con DIPEA (48 µl, 278 µmoles) y se agitó a 70°C durante 2 h. Después de la evaporación, el residuo se colocó en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (2 ml) y se agitó a ta durante 2 h. La evaporación y la purificación por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) dio 29 mg (30% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,78 min; MS (ESIpos): m/z = 493 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,28 (br. s, 2H), 7,99 (s, 1H), 7,37 (s, 1H), 7,30 (s, 1H), 6,84 (s, 1H), 4,45 (s, 2H), 3,95 (s, 3H), 3,93 (s, 2H), 3,21 (d, 2H), 2,95-2,83 (m, 4H), 2,61-2,56 (m, 4H), 2,45 (s, 3H), 1,01-0,91 (m, 1H), 0,46-0,37 (m, 2H), 0,15-0,08 (m, 2H) ppm.

Ejemplo 26

6-[(ciclobutiloxi)metil]-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-il-metil)pirrolo[2,1-f][1,2,4]triazin-4-amina



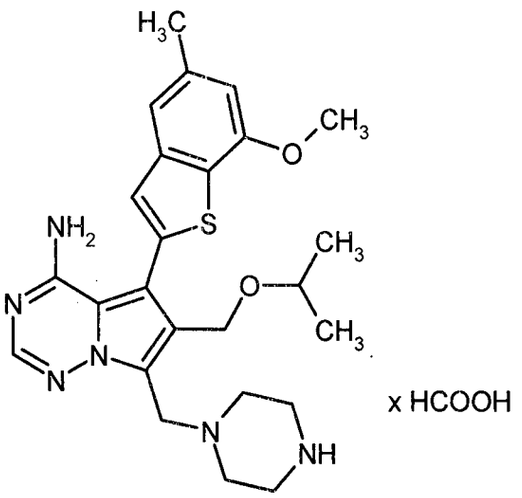
Una solución del intermediario 23A (85 mg, 157 µmoles) en diclorometano (1,7 ml) se trató con cloruro de tionilo (23 µl, 315 µmoles). La mezcla se agitó a ta durante 15 min y posteriormente se evaporó. El residuo se disolvió en ciclobutanol (1,7 ml), se trató con DIPEA (41 µl, 236 µmoles) y se agitó a 70°C durante 2 h. Después de la evaporación, el residuo se colocó en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (1,7 ml) y se agitó a ta durante 2 h. La evaporación y la purificación por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) dio 23 mg (28% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,82 min; MS (ESIpos): m/z = 493 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,01 (s, 1H), 7,37 (s, 1H), 7,32 (s, 1H), 6,85 (s, 1H), 4,37 (s, 2H), 4,06-3,86 (m, 6H), 3,14-2,97 (m, 4H), 2,80-2,62 (m, 4H), 2,45 (s, 3H), 2,10-1,96 (m, 2H), 1,83-1,69 (m, 2H), 1,65-1,52 (m, 1H), 1,49-1,33 (m, 1H) ppm.

Ejemplo 27

Formiato 6-(isopropoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-amina



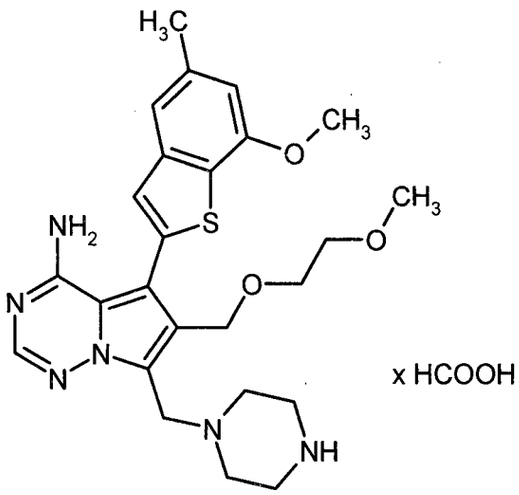
Una solución del intermediario 23A (65 mg, 120 µmoles) en diclorometano (1,3 ml) se trató con cloruro de tionilo (17 µl, 241 µmoles). La mezcla se agitó a ta durante 15 min y posteriormente se evaporó. El residuo se disolvió en 2-propanol (1,3 ml), se trató con DIPEA (23 µl, 132 µmoles) y se agitó a 70°C durante 1 h. S e agregó más DIPEA (23 µl, 132 µmoles), y la mezcla se agitó nuevamente a 70°C durante 1 h. Posteriormente, otra porción de DIPEA (63 µl, 362 µmoles) se agregó, y se continuó con la agitación a 90°C durante 3 h. Después de la evaporación, el residuo se colocó en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (1,3 ml) y se agitó a ta durante 2 h. La evaporación y la purificación por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) dio 23 mg (34% de teor.) del compuesto del título.

LC-MS (procedimiento 4): Tr = 0,74 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,30 (s, 1H), 7,98 (s, 1H), 7,37 (s, 1H), 7,30 (s, 1H), 6,84 (s, 1H), 4,43 (s, 2H), 3,95 (s, 3H), 3,90 (s, 2H), 3,57 (m, 1H, superposición con pico de agua), 2,88-2,78 (m, 4H), 2,45 (s, 3H), 1,04 (d, 6H) ppm.

Ejemplo 28

Formiato 6-[(2-metoxietoxi)metil]-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-amina



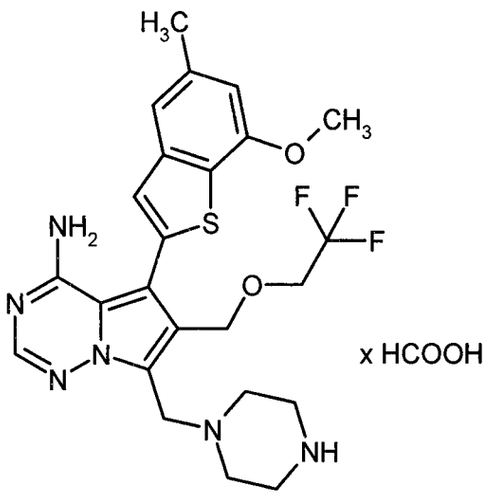
Una solución del intermediario 23A (100 mg, 185 µmoles) en diclorometano (2 ml) se trató con cloruro de tionilo (27 µl, 371 µmoles). La mezcla se agitó a ta durante 15 min y posteriormente se evaporó. El residuo se disolvió en 2-metoxietanol (2 ml), se trató con DIPEA (35 µl, 204 µmoles) y se agitó a 70°C durante 1 h. Después de la evaporación, el residuo se colocó en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (2 ml) y se agitó a ta durante 2 h. La evaporación y la purificación por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) dio 50 mg (50% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,75 min; MS (ESIpos): m/z = 497 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,26 (br. s, 1H), 7,99 (s, 1H), 7,39 (s, 1H), 7,30 (s, 1H), 6,84 (s, 1H), 4,48 (s, 2H), 3,95 (s, 3H), 3,94 (s, 2H), 3,52-3,46 (m, 2H, superposición con pico de agua), 3,44-3,37 (m, 2H, superposición con pico de agua), 3,20 (s, 3H), 2,94-2,84 (m, 4H), 2,61-2,54 (m, 4H, superposición con Pico de DMSO), 2,45 (s, 3H) ppm.

Ejemplo 29

Formiato 5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)-6-[(2,2,2-trifluoroetoxi)metil]pirrolo[2,1-f][1,2,4]triazin-4-amina



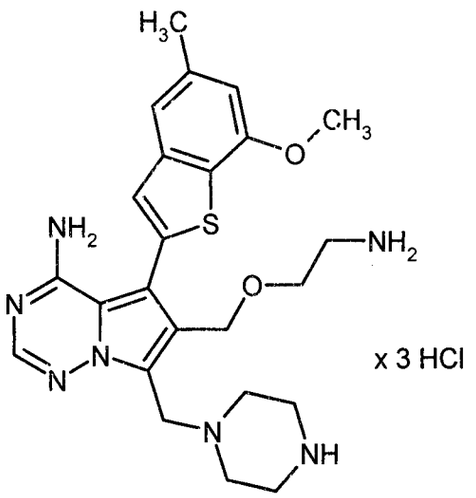
Una solución del intermediario 23A (100 mg, 185 µmoles) en diclorometano (2 ml) se trató con cloruro de tionilo (27 µl, 371 µmoles). La mezcla se agitó a ta durante 15 min y posteriormente se evaporó. El residuo se disolvió en 2,2,2-trifluoroetanol (2 ml), se trató con DIPEA (35 µl, 204 µmoles) y se agitó a 70°C durante 1 h. Se agregó más DIPEA (35 µl, 204 µmoles), y se continuó con la agitación a ta durante 1 h. Después de la evaporación, el residuo se colocó en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (2 ml) y se agitó a ta durante 2 h. La evaporación y la purificación por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) dio 23 mg (23% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,79 min; MS (ESIpos): m/z = 521 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,28 (br. s, 1H), 8,00 (s, 1H), 7,37 (s, 1H), 7,30 (s, 1H), 6,85 (s, 1H), 4,66 (s, 2H), 4,08 (q, 2H), 3,95 (s, 3H), 3,92 (s, 2H), 2,85-2,75 (m, 4H), 2,45 (s, 3H) ppm.

Ejemplo 30

Triclorhidrato 6-[(2-aminoetoxi)metil]-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-amina



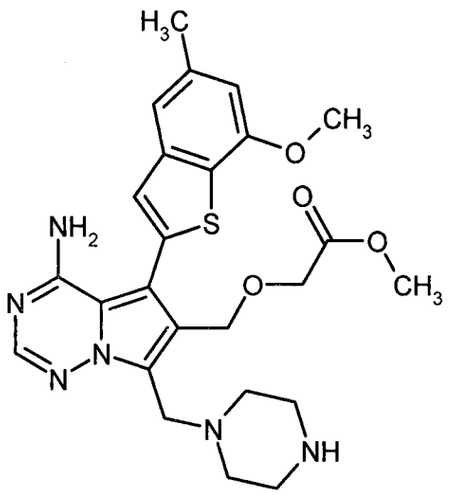
Una solución del intermediario 23A (150 mg, 278 μmoles) en diclorometano (5 ml) se trató con cloruro de tionilo (40 μl, 556 μmoles). La mezcla se agitó a ta durante 15 min y posteriormente se evaporó. El residuo se disolvió en THF (0,5 ml) y se trató con (2-hidroxietil)carbamato de *ter*-butilo (1 ml) y DIPEA (242 μl, 1,39 mmoles). La mezcla se agitó a 100°C durante toda la noche. Después de la evaporación, el residuo se colocó en 1,4-dioxano (10 ml), se trató con una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (10 ml) y se agitó a ta durante 1 h. Los volátiles se removieron a presión reducida, y el residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso). Además la purificación por RP-HPLC preparativa (Shield RP18, 25% acetonitrilo/75% 0,01% TFA ac.) seguida de liofilización a partir de una solución 4 M de cloruro de hidrógeno en 1,4-dioxano dio 10 mg (6% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,58 min; MS (ESIpos): m/z = 482 $(M+H)^+$

^{1}H-RMN (400 MHz, D_2O): δ = 8,12 (s, 1H), 7,50 (s, 1H), 7,44 (s, 1H), 6,99 (s, 1H), 4,61 (s, 2H), 4,04 (s, 3H), 3,88-3,80 (m, 1H), 3,70-3,60 (m, 3H), 3,52-3,46 (m, 4H), 3,40-3,34 (m, 4H), 3,07 (t, 2H), 2,51 (s, 3H) ppm.

Ejemplo 31

{[4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo-[2,1-f][1,2,4]triazin-6-il]metoxi}acetato de metilo



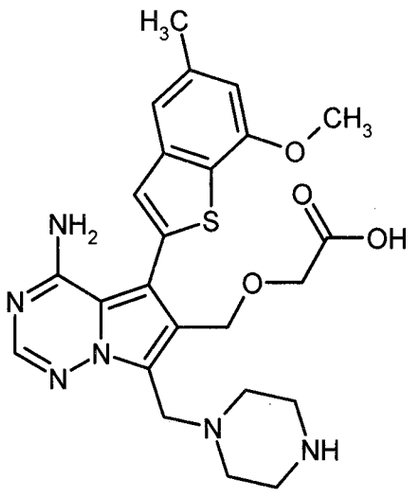
Una solución del intermediario 23A (50 mg, 92 μmoles) en diclorometano (2 ml) se trató con cloruro de tionilo (13 μl, 186 μmoles). La mezcla se agitó a ta durante 15 min y posteriormente se evaporó. El residuo se disolvió en metilglicolato (1 ml), se trató con DIPEA (80 μl, 464 μmoles) y se agitó a 70°C durante 2 h. Después de la evaporación, el residuo se colocó en diclorometano (1,6 ml), se trató con ácido trifluoroacético (400 μl, 5,19 mmoles) y se agitó a ta durante 1 h. Posteriormente, la mezcla se evaporó, y el residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% TFA ac.). Las fracciones que contienen el compuesto del título se neutralizaron con solución de hidrógeno carbonato de sodio acuosa saturada y se evaporaron. El residuo se colocó en agua, y la mezcla se extrajo tres veces con diclorometano. Las fases orgánicas combinadas se secaron sobre sulfato de sodio y se evaporaron dando 21 mg (43% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,72 min; MS (ESIpos): m/z = 511 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,99 (s, 1H), 7,39 (s, 1H), 7,31 (s, 1H), 6,85 (s, 1H), 4,59 (s, 2H), 4,11 (s, 2H), 3,95 (s, 3H), 3,90 (s, 2H), 3,57 (s, 3H), 2,81-2,69 (m, 4H), 2,48-2,39 (m, 7H) ppm.

Ejemplo 32

Ácido {[4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-6-il]metoxi}acético



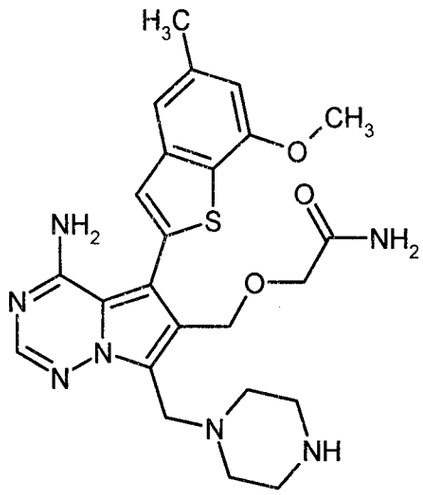
Una solución del intermediario 24A (200 mg, 327 µmoles) en THF (14 ml) se trató con solución 2,5 M de hidróxido de litio ac. (16 ml) y se agitó a 80°C durante 2 h. La mezcla posteriormente se combinó con la mezcla de reacción de una serie analítica de 27 mg. La fase acuosa se extrajo dos veces con THF, y las fases orgánicas combinadas se evaporaron. El residuo se disolvió en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (2 ml) y se agitó a ta durante 3 h. Después de la evaporación, el residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% TFA ac.). la liofilización a partir de una solución 4 M de cloruro de hidrógeno en 1,4-dioxano y re-la purificación por RP-HPLC preparativa (XBridge C18, gradiente 5-95% acetonitrilo/0,1% solución de hidróxido de amonio ac.) dio 13 mg (7% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,69 min; MS (ESIpos): m/z = 497 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,00 (s, 1H), 7,38 (s, 1H), 7,30 (s, 1H), 6,84 (s, 1H), 4,54 (s, 2H), 4,08 (s, 2H), 3,95 (s, 3H), 3,79 (s, 2H), 2,99-2,89 (m, 4H), 2,73-2,63 (m, 4H), 2,44 (s, 3H) ppm.

Ejemplo 33

2-{[4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo-[2,1-f][1,2,4]triazin-6-il]metoxi}acetamida



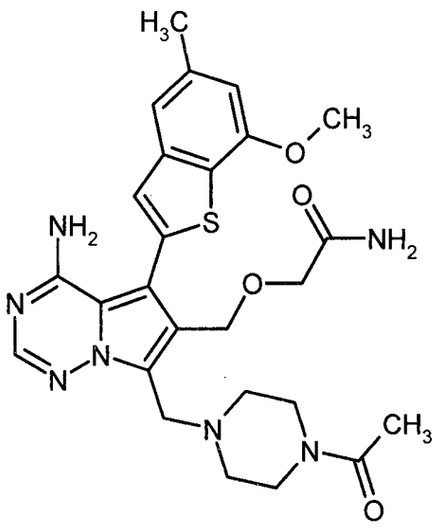
El intermediario 24A (200 mg, 327 µmoles) se trató con una solución 7 M de amoníaco en metanol (10 ml) y se agitó a ta durante toda la noche. La mezcla posteriormente se combinó con la mezcla de reacción de una serie analítica de 20 mg, y los solventes se evaporaron. El residuo se trató con una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (2 ml) y se agitó a ta durante 2 h. La evaporación y subsiguientes purificaciones por RP-HPLC preparativa (primero Reprosil C18, gradiente 10-95% acetonitrilo/0,1% TFA ac.; posteriormente XBridge C18, gradiente 5-95% acetonitrilo/0,1% de solución de hidróxido de amonio ac.) dio 5,5 mg (3% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,69 min; MS (ESIpos): m/z = 496 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,14-7,59 (br. s, 1H), 7,99 (s, 1H), 7,39 (s, 1H), 7,35-7,22 (m, 3H), 6,85 (s, 1H), 4,54 (s, 2H), 3,95 (s, 3H), 3,90 (s, 2H), 3,79 (s, 2H), 2,73-2,66 (m, 4H), 2,45 (s, 3H), 2,43-2,35 (m, 4H) ppm.

Ejemplo 34

2-({7-[(4-acetilpiperazin-1-il)metil]-4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-6-il}metoxi)acetamida



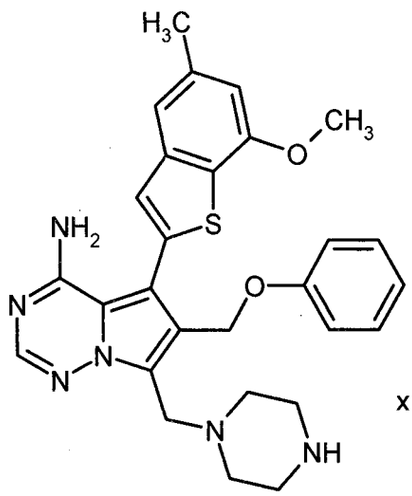
Una solución del ejemplo 33 (105 mg, 68% de pureza, 144 µmoles) en THF/diclorometano (1:2,5, 3,9 ml) se trató con carbonato de sodio (179 mg, 1,6 mmoles) y se agitó a ta durante 30 min. Se agregó cloruro de acetilo (30 µl, 424 µmoles), y la mezcla resultante se agitó a ta durante 30 min, posteriormente se templó con metanol (2 ml) y se evaporó. La purificación por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) dio 30 mg (85% de pureza, 34% de teor.) del compuesto del título.

LC-MS (procedimiento 5): Tr = 1,67 min; MS (ESIpos): m/z = 538 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,99 (s, 1H), 7,40 (s, 1H), 7,33-7,19 (m, 3H), 6,85 (s, 1H), 4,55 (s, 2H), 3,96 (s, 5H), 3,80 (s, 2H), 3,43-3,36 (m, 4H), 2,47-2,38 (m, 7H), 1,97 (s, 3H) ppm.

Ejemplo 35

bis(formiato) 5-(7-metoxi-5-metil-1-benzotiofen-2-il)-6-(phenoximetil)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-amina



x 2 HCOOH

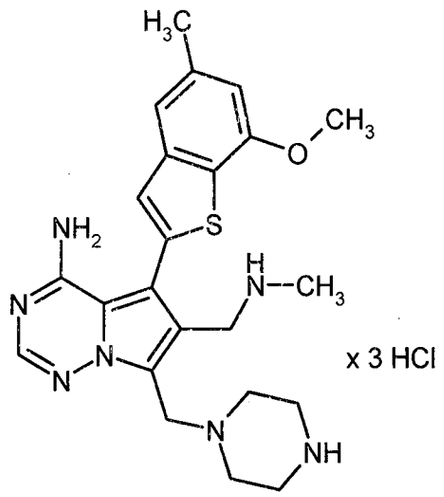
Una solución del intermediario 23A (100 mg, 185 μmoles) en diclorometano (2 ml) se trató con cloruro de tionilo (27 μl, 371 μmoles). La mezcla se agitó a ta durante 15 min y posteriormente se evaporó. El residuo se disolvió en THF (2 ml), se trató con fenol (174 mg, 1,85 mmoles) y DIPEA (48 μl, 278 μmoles) y se agitó a 70°C durante 2 h. Otras cantidades de fenol (174 mg, 1,85 mmoles) y DIPEA (64 μl, 371 μmoles) se agregaron, y se continuó con la agitación a 70°C durante toda la noche. Después de la evaporación, el residuo se colocó en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (2 ml) y se agitó a ta durante 2 h. La evaporación y la purificación por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) dio 8 mg (8% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,84 min; MS (ESIpos): m/z = 515 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,26 (s, 2H), 8,02 (s, 1H), 7,36 (s, 1H), 7,30-7,22 (m, 3H), 6,99-6,89 (m, 3H), 6,81 (m, 1H), 5,04 (s, 2H), 3,93 (s, 5H), 2,78-2,71 (m, 4H), 2,42 (s, 3H) ppm.

Ejemplo 36

Triclorhidrato 5-(7-metoxi-5-metil-1-benzotiofen-2-il)-6-[(metilamino)metil]-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-amina



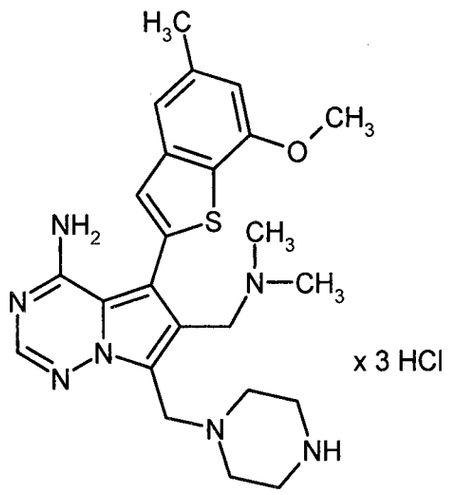
El intermediario 25A (150 mg, 279 µmoles) en THF (3 ml) se trató con ácido acético (32 µl, 559 µmoles), una solución 2 M de metilamina en THF (698 µl, 1,39 mmoles) y triacetoxiborohidruro de sodio (296 mg, 1,39 mmoles). La mezcla se agitó a 60°C durante 2 h y posteriormente se evaporó. El residuo se disolvió en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (1,87 ml) y se agitó a ta durante 2 h. Después de la evaporación, el residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% TFA ac.). La liofilización a partir de una solución 4 M de cloruro de hidrógeno en 1,4-dioxano dio 79 mg (49% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,56 min; MS (ESIpos): m/z = 452 $(M+H)^+$

^{1}H-RMN (400 MHz, D_2O): δ = 8,17 (s, 1H), 7,57 (s, 1H), 7,46 (s, 1H), 7,01 (s, 1H), 4,52 (s, 2H), 4,46 (s, 2H), 4,04 (s, 3H), 3,48-3,39 (m, 4H), 3,25-3,15 (m, 4H), 2,59 (s, 3H), 2,51 (s, 3H) ppm.

Ejemplo 37

Triclorhidrato 6-[(dimetilamino)metil]-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-amina



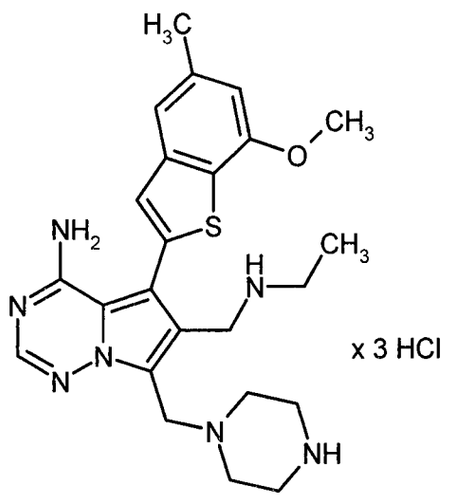
Una solución del intermediario 25A (150 mg, 279 μmoles) en THF (3 ml) se trató con ácido acético (32 μl, 559 μmoles), una solución 2 M de dimetilamina en THF (698 μl, 1,39 mmoles) y triacetoxiborohidruro de sodio (296 mg, 1,39 mmoles). La mezcla se agitó a 60°C durante 2 h y posteriormente se evaporó. El residuo se disolvió en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (1,88 ml) y se agitó a ta durante 2 h. Después de la evaporación, el residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% TFA ac.). La liofilización a partir de una solución 4 M de cloruro de hidrógeno en 1,4-dioxano dio 83 mg (50% de teor.) del compuesto del título.

LC-MS (procedimiento 4): Tr = 0,50 min; MS (ESIpos): m/z = 466 $(M+H)^+$

^{1}H-RMN (400 MHz, D_2O): δ = 8,17 (s, 1H), 7,57 (s, 1H), 7,45 (s, 1H), 7,01 (s, 1H), 4,57 (s, 2H), 4,50 (s, 2H), 4,04 (s, 3H), 3,47-3,36 (m, 4H), 3,21-3,12 (m, 4H), 2,80 (s, 6H), 2,51 (s, 3H) ppm.

Ejemplo 38

Triclorhidrato 6-[(etilamino)metil]-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-amina



Una solución del intermediario 25A (60 mg, 111,8 µmoles) en THF (1 ml) se trató con una solución 2 M de etilamina en THF (83 µl, 167 µmoles), triacetoxiborohidruro de sodio (118 mg, 559 µmoles) y ácido acético (83 µl, 167 µmoles). La mezcla se agitó a 60°C durante 90 min. Se agregaron otras cantidades de solución 2 M de etilamina (83 µl, 167 µmoles) y triacetoxiborohidruro de sodio (71 mg, 335 µmoles), y la agitación a 60°C continuó durante otras 2 h. Después de la evaporación, el residuo se disolvió en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (3 ml) y se agitó a ta durante toda la noche. La mezcla se evaporó, y el residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) y se liofilizó a partir de una solución 4 M de cloruro de hidrógeno en 1,4-dioxano. La repurificación por RP-HPLC preparativa (Sunfire C18, 20% acetonitrilo/80% 0,02% TFA ac.) y la re-liofilización a partir de una solución 4 M de cloruro de hidrógeno en 1,4-dioxano dio 19 mg (29% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,56 min; MS (ESIpos): m/z = 466 $(M+H)^+$

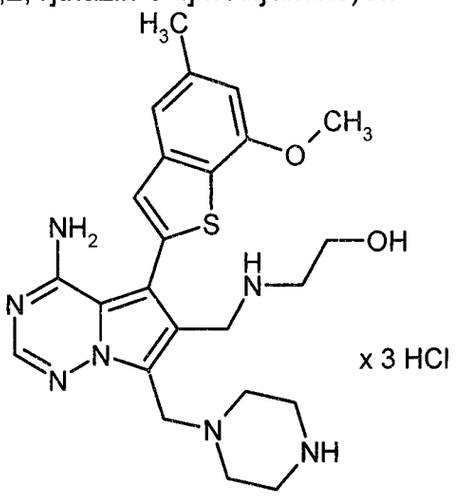
^{1}H-RMN (400 MHz, D_2O): δ = 8,14 (s, 1H), 7,56 (s, 1H), 7,45 (s, 1H), 7,01 (s, 1H), 4,45 (s, 4H), 4,04 (s, 3H), 3,45-3,32 (m, 4H), 3,18-3,05 (m, 4H), 2,99 (q, 2H), 2,51 (s, 3H), 1,10 (t, 3H) ppm.

Ejemplo 39

Triclorhidrato 2-({[4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-

168

1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-6-il]metil}amino)etanol



Una solución del intermediario 25A (150 mg, 279 µmoles) en THF (3 ml) se trató con 2-aminoetanol (84 µl, 1,39 mmoles), triacetoxiborohidruro de sodio (296 mg, 1,39 mmoles) y ácido acético (32 µl, 559 µmoles). La mezcla se agitó a 60°C durante 2 h y posteriormente se evaporó. El residuo se disolvió en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (1,87 ml) y se agitó a ta durante 2 h. Después de la evaporación, el residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% TFA ac.). La liofilización a partir de una solución 4 M de cloruro de hidrógeno en 1,4-dioxano dio 140 mg (80% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,54 min; MS (ESIpos): m/z = 482 $(M+H)^+$

^{1}H-RMN (400 MHz, D_2O): δ = 8,15 (s, 1H), 7,56 (s, 1H), 7,45 (s, 1H), 7,00 (s, 1H), 4,47 (s, 2H), 4,37 (s, 2H), 4,04 (s, 3H), 3,79-3,71 (m, 2H), 3,42-3,34 (m, 4H), 3,19-3,12 (m, 2H), 3,06-2,97 (m, 4H), 2,51 (s, 3H) ppm.

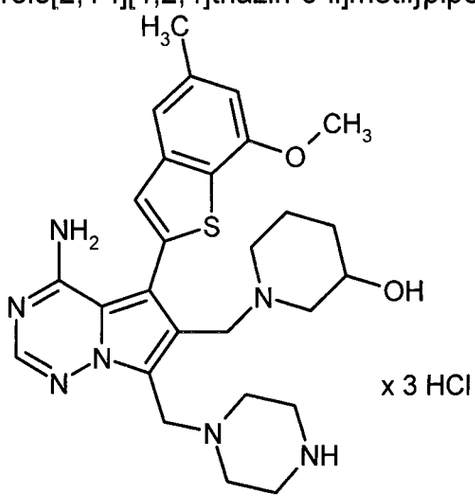
Procedimiento general para las reacciones de aminación reductora con el intermediario 25A (GP1):

Una solución 0,1 M del intermediario 25A en THF se trató con 5 eq. del respectivo componente de amina, 5 eq. de triacetoxiborohidruro de sodio y 2 eq. de ácido acético. La mezcla resultante se agitó a 60°C durante 2 h y posteriormente se evaporó. Una solución 0,15 M del residuo obtenido de este modo en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano se agitó a

ta durante 1-2 h. Después de la evaporación, el residuo se purificó como se describe a continuación.

Ejemplo 40

Triclorhidrato *rac*-1-{[4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-6-il]metil}piperidin-3-ol



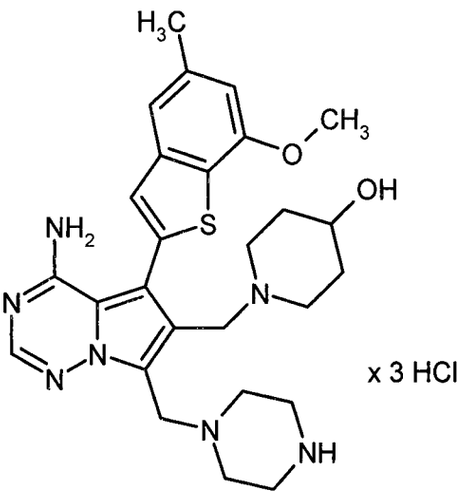
De acuerdo con el GP1, el intermediario 25A (150 mg, 279 μmoles) se hizo reaccionar con 3-hidroxipiperidina (141 mg, 1,39 mmoles). La purificación por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% TFA ac.) y la liofilización a partir de una solución 4 M de cloruro de hidrógeno en 1,4-dioxano dio 178 mg (cuant.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,54 min; MS (ESIpos): m/z = 522 $(M+H)^+$

^{1}H-RMN (400 MHz, D_2O): δ = 8,16 (s, 1H), 7,55 (s, 1H), 7,45 (s, 1H), 7,01 (s, 1H), 4,66-4,16 (m, 5H), 4,04 (s, 3H), 3,55-2,71 (m, 11H), 2,51 (s, 3H), 1,96-1,42 (m, 4H), 1,64-1,50 (m, 1H) ppm.

Ejemplo 41

Triclorhidrato 1-{[4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-6-il]metil}piperidin-4-ol



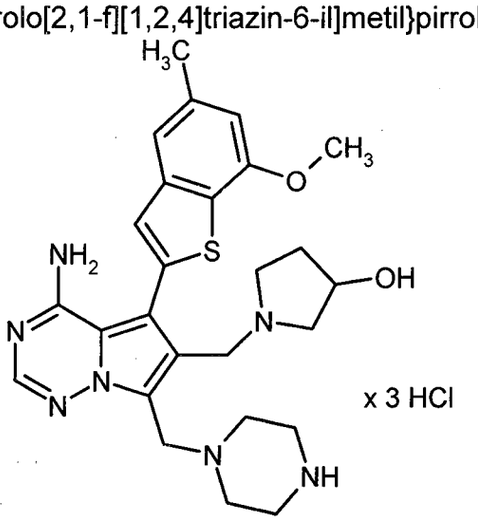
De acuerdo con GP1, el intermediario 25A (150 mg, 279 µmoles) se hizo reaccionar con 4-hidroxipiperidina (141 mg, 1,39 mmoles). La purificación por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% TFA ac.) y la liofilización a partir de una solución 4 M de cloruro de hidrógeno en 1,4-dioxano dio 162 mg (91% de teor.) del compuesto del título.

LC-MS (procedimiento 4): Tr = 0,48 min; MS (ESIpos): m/z = 522 $(M+H)^+$

^{1}H-RMN (400 MHz, D_2O): δ = 8,16 (s, 1H), 7,58 (br. s, 1H), 7,46 (s, 1H), 7,01 (s, 1H), 4,67-4,48 (m, 4H), 4,04 (s, 4H), 3,59-2,78 (m, 12H), 2,51 (s, 3H), 2,14-1,38 (m, 4H) ppm.

Ejemplo 42

Triclorhidrato *rac*-1-{[4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-6-il]metil}pirrolidin-3-ol



De acuerdo con GP1, el intermediario 25A (150 mg, 279 µmoles) se hizo

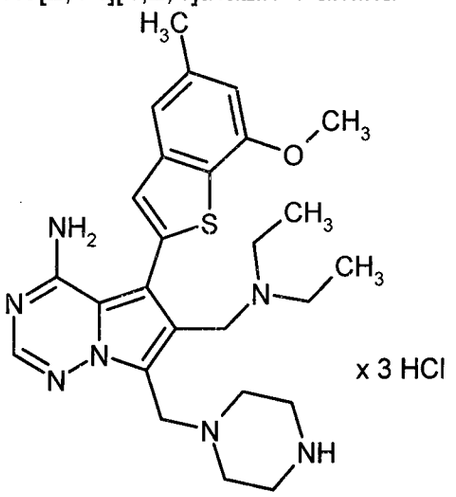
reaccionar con 3-hidroxipirrolidina (113 µl, 1,39 mmoles). La purificación por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% TFA ac.) y la liofilización a partir de una solución 4 M de cloruro de hidrógeno en 1,4-dioxano dio 148 mg (85% de teor.) del compuesto del título.

LC-MS (procedimiento 4): Tr = 0,46 min; MS (ESIpos): m/z = 508 $(M+H)^+$

^{1}H-RMN (400 MHz, D_2O): δ = 8,18 (s, 1H), 7,58 (s, 1H), 7,46 (s, 1H), 7,01 (s, 1H), 4,71-4,30 (m, 5H), 4,04 (s, 3H), 3,70-2,95 (m, 12H), 2,51 (s, 3H), 2,32-2,14 (m, 1H), 2,03-1,87 (m, 1H) ppm.

Ejemplo 43

Triclorhidrato 6-[(dietilamino)metil]-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-amina



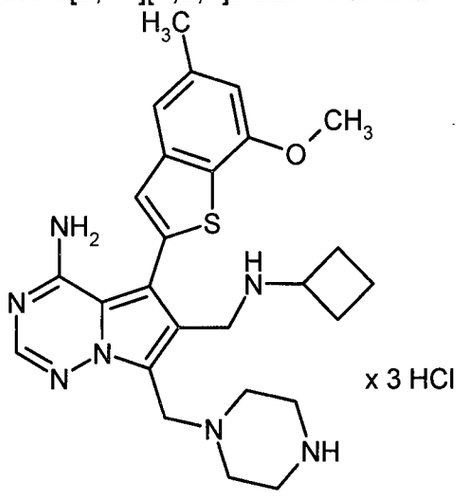
De acuerdo con GP1, el intermediario 25A (150 mg, 279 µmoles) se hizo reaccionar con dietilamina (144 µl, 1,39 mmoles). La purificación por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/ 0,1% TFA ac.) y la liofilización a partir de una solución 4 M de cloruro de hidrógeno en 1,4-dioxano dio 127 mg (69% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,55 min; MS (ESIpos): m/z = 494 $(M+H)^+$

^{1}H-RMN (400 MHz, D_2O): δ = 8,19 (s, 1H), 7,61 (s, 1H), 7,47 (s, 1H), 7,01 (s, 1H), 4,59 (s, 2H), 4,51 (s, 2H), 4,04 (s, 3H), 3,47-3,35 (m, 4H), 3,29-3,00 (m, 8H), 2,51 (s, 3H), 1,07 (t, 6H) ppm.

Ejemplo 44

Triclorhidrato 6-[(ciclobutilamino)metil]-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-amina



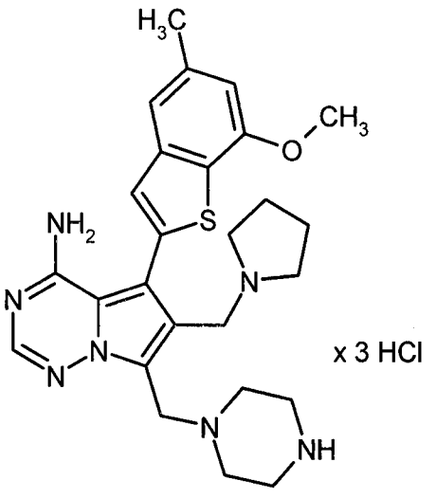
De acuerdo con GP1, el intermediario 25A (150 mg, 279 µmoles) se hizo reaccionar con ciclobutilamina (119 µl, 1,39 mmoles). La purificación por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% TFA ac.) y la liofilización a partir de una solución 4 M de cloruro de hidrógeno en 1,4-dioxano dio 127 mg (72% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,58 min; MS (ESIpos): m/z = 492 $(M+H)^+$

^{1}H-RMN (400 MHz, D_2O): δ = 8,16 (s, 1H), 7,59 (s, 1H), 7,47 (s, 1H), 7,00 (s, 1H), 4,40 (s, 2H), 4,37 (s, 2H), 4,04 (s, 3H), 3,69-3,58 (m, 1H), 3,44-3,33 (m, 4H), 3,21-3,12 (m, 4H), 2,51 (s, 3H), 2,02-1,87 (m, 4H), 1,81-1,62 (m, 2H) ppm.

Ejemplo 45

Triclorhidrato 5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)-6-(pirrolidin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-amina



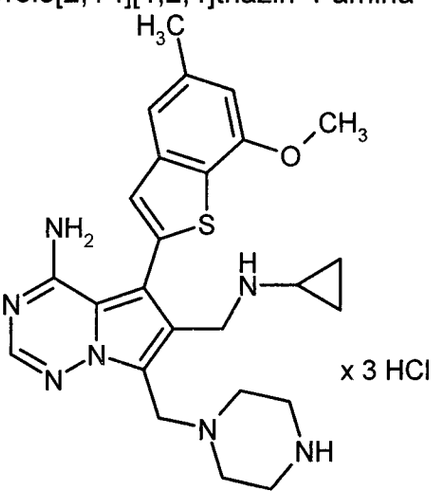
De acuerdo con GP1, el intermediario 25A (150 mg, 279 µmoles) se hizo reaccionar con pirrolidina (116 µl, 1,39 mmoles). La purificación por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/ 0,1% TFA ac.) y la liofilización a partir de una solución 4 M de cloruro de hidrógeno en 1,4-dioxano dio 112 mg (64% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,54 min; MS (ESIpos): m/z = 492 $(M+H)^+$

^{1}H-RMN (400 MHz, D_2O): δ = 8,19 (s, 1H), 7,60 (s, 1H), 7,46 (s, 1H), 7,01 (s, 1H), 4,70-4,61 (m, 4H), 4,04 (s, 3H), 3,55-3,40 (m, 6H), 3,35-3,26 (m, 4H), 3,02-2,87 (m, 2H), 2,51 (s, 3H), 1,97-1,83 (m, 4H) ppm.

Ejemplo 46

Triclorhidrato 6-[(ciclopropilamino)metil]-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-amina



De acuerdo con GP1, el intermediario 25A (200 mg, 372 µmoles) se hizo

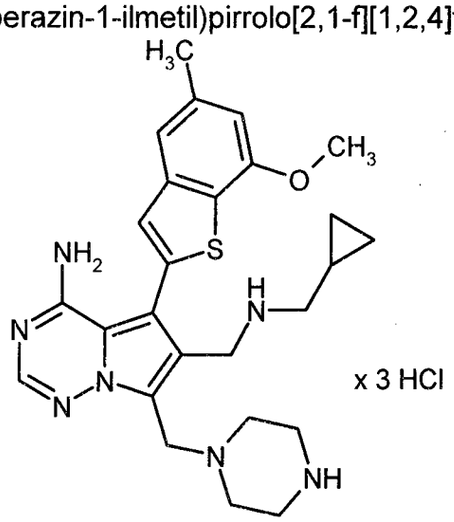
reaccionar con ciclopropilamina (129 µl, 1,86 mmoles). La purificación por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% TFA ac.) y la liofilización a partir de una solución 4 M de cloruro de hidrógeno en 1,4-dioxano dio 140 mg (62% de teor.) del compuesto del título.

LC-MS (procedimiento 5): Tr = 1,42 min; MS (ESIpos): m/z = 478 $(M+H)^+$

^{1}H-RMN (400 MHz, D_2O): δ = 8,16 (s, 1H), 7,56 (s, 1H), 7,46 (s, 1H), 7,01 (s, 1H), 4,57 (s, 2H), 4,47 (s, 2H), 4,04 (s, 3H), 3,46-3,34 (m, 4H), 3,19-3,07 (m, 4H), 2,61-2,54 (m, 1H), 2,51 (s, 3H), 0,75-0,64 (m, 4H) ppm.

Ejemplo 47

Triclorhidrato 6-{[(ciclopropilmetil)amino]metil}-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-amina



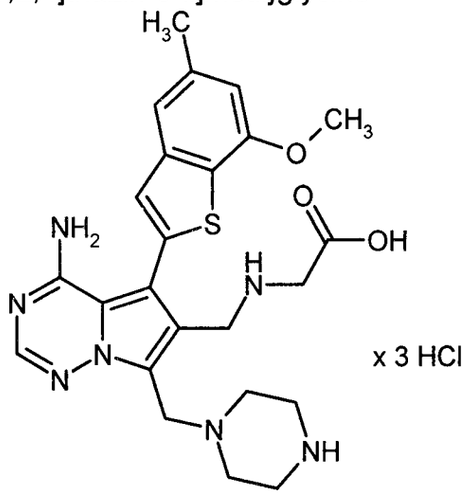
De acuerdo con GP1, el intermediario 25A (200 mg, 372 µmoles) se hizo reaccionar con ciclopropilmetilamina (161 µl, 1,86 mmoles). La purificación por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% TFA ac.) y la liofilización a partir de una solución 4 M de cloruro de hidrógeno en 1,4-dioxano dio 163 mg (69% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,60 min; MS (ESIpos): m/z = 492 $(M+H)^+$

^{1}H-RMN (400 MHz, D_2O): δ = 8,14 (s, 1H), 7,57 (s, 1H), 7,45 (s, 1H), 7,00 (s, 1H), 4,50 (s, 2H), 4,44 (s, 2H), 4,04 (s, 3H), 3,42-3,34 (m, 4H), 3,16-3,07 (m, 4H), 2,86 (d, 2H), 2,50 (s, 3H), 0,89-0,76 (m, 1H), 0,55-0,45 (m, 2H), 0,23-0,14 (m, 2H) ppm.

Ejemplo 48

Triclorhidrato *N*-{[4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-6-il]metil}glycine



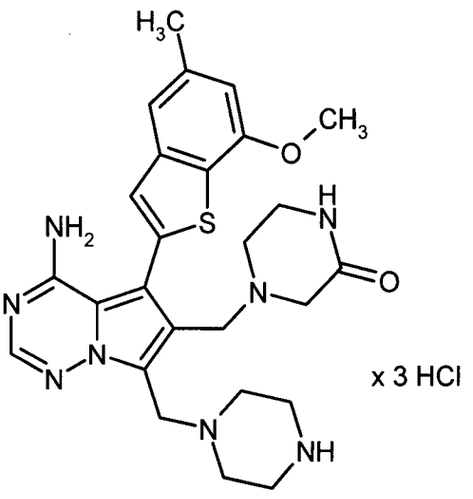
Una solución del intermediario 25A (161 mg, 300 µmoles) en THF (3,2 ml) se trató con 2-aminoácido acético (112 mg, 1,5 mmoles), triacetoxiborohidruro de sodio (317 mg, 1,5 mmoles) y ácido acético (34 µl, 600 µmoles). La mezcla resultante se agitó a 60°C durante 2 h y posteriormente se evaporó. El residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% TFA ac.). El producto obtenido de este modo se disolvió en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (2 ml) y se agitó a ta durante 1 h. Después de la evaporación, el residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% TFA ac.). La posterior liofilización a partir de una solución 4 M de cloruro de hidrógeno en 1,4-dioxano dio 18 mg (9% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,63 min; MS (ESIpos): m/z = 496 $(M+H)^+$

^{1}H-RMN (400 MHz, D_2O): δ = 8,14 (s, 1H), 7,54 (s, 1H), 7,45 (s, 1H), 6,99 (s, 1H), 4,42 (s, 2H), 4,36 (s, 2H), 4,03 (s, 3H), 3,64 (s, 2H), 3,42-3,33 (m, 4H), 3,07-2,96 (m, 4H), 2,50 (s, 3H) ppm.

Ejemplo 49

Triclorhidrato 4-{[4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-6-il]metil}piperazin-2-ona



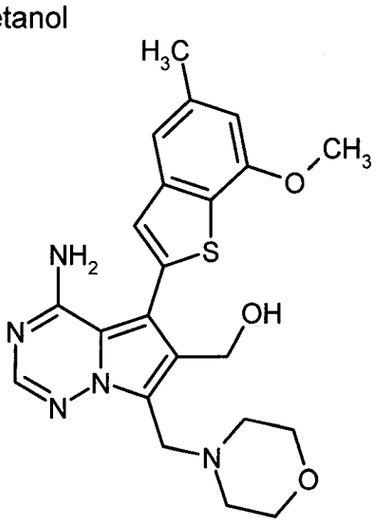
x 3 HCl

Una solución del intermediario 27A (220 mg, 354 μmoles) en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (2 ml) se agitó a ta durante 2 h. Posteriormente, la mezcla se evaporó dejando 235 mg del producto bruto el cual se usó en el próximo paso sin purificación posterior.

LC-MS (procedimiento 4): Tr = 0,60 min; MS (ESIpos): m/z = 521 $(M+H)^+$.

Ejemplo 50

[4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(morfolin-4-ilmetil)pirrolo-[2,1-f][1,2,4]triazin-6-il]metanol



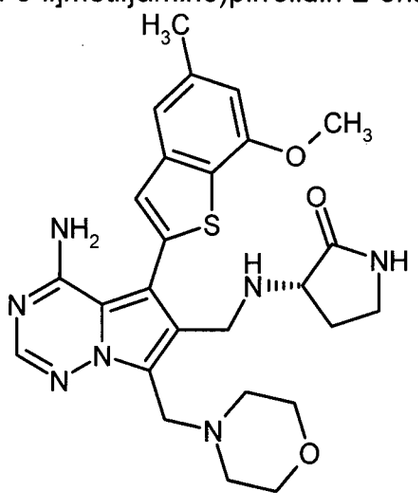
Una solución del intermediario 20A (500 mg, pureza 87%, 1,28 mmoles) y 4-metilenemorfolin-4-ium cloruro (347 mg, 2,56 mmoles) en DMF (28 ml) se agitó a 70°C durante 1,5 h. La mezcla se diluyó con acetato de etilo y se lavó con solución de hidrógeno carbonato de sodio acuosa saturada y solución de cloruro de sodio acuosa saturada. La capa orgánica se secaron con sulfato de

magnesio y se evaporaron a presión reducida dando 710 mg (pureza 78%, 99% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,65 min; MS (ESIpos): m/z = 440 $(M+H)^+$.

Ejemplo 51

(*3S*)-3-({[4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(morfolin-4-ilmetil)-pirrolo[2,1-f][1,2,4]triazin-6-il]metil}amino)pirrolidin-2-ona



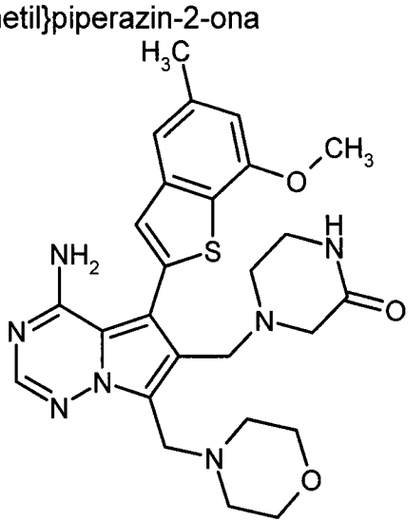
Una solución del intermediario 33A (65 mg, 149 µmoles) en metanol (2 ml) se trató con (*3S*)-3-aminopirrolidin-2-ona (45 mg, 446 µmoles), cianoborohidruro de sodio (47 mg, 743 µmoles) y ácido acético (26 µl, 446 µmoles). Después de agitar a 60°C durante 16 h, la mezcla resultante se separó por RP-HPLC preparativa (Reprosil C18, gradiente 20-40% acetonitrilo/0,2% TFA ac.). El producto obtenido de este modo se disolvió en metanol y se filtró a través de un cartucho de intercambio aniónico (Stratospheres SPE, PL-HCO_3 MP-resina). El cartucho se eluyó con metanol, y el filtrado se evaporó dando 49 mg (63% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,71 min; MS (ESIpos): m/z = 522 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,96 (s, 1H), 7,66 (s, 1H), 7,5-8,1 (br. s, 1H), 7,44 (s, 1H), 7,31 (s, 1H), 6,84 (s, 1H), 5,4-6,0 (br. s, 1H), 3,95 (s, 3H), 3,91 (s, 2H), 3,75 (d, 2H), 3,50-3,66 (m, 4H), 3,06-3,19 (m, 3H), 2,94-3,05 (m, 1H), 2,61 (t, 1H), 2,45 (t, 3H), 2,38-2,44 (m, 4H), 1,89-1,99 (m, 1H), 1,49-1,60 (m, 1H) ppm.

Ejemplo 52

4-{[4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(morfolin-4-ilmetil)pirrolo-[2,1-f][1,2,4]triazin-6-il]metil}piperazin-2-ona



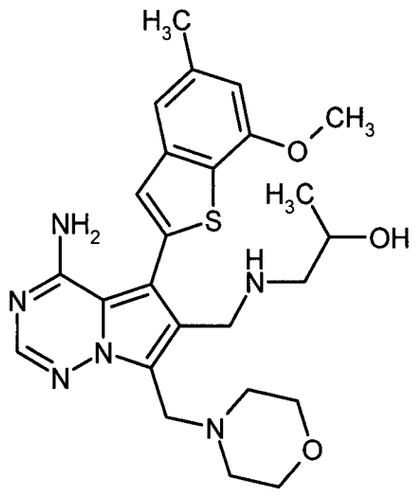
Una solución del intermediario 33A (65 mg, 149 µmoles) en metanol (2 ml) se trató con 2-oxopiperazina (45 mg, 446 µmoles), cianoborohidruro de sodio (47 mg, 743 µmoles) y ácido acético (26 µl, 446 µmoles). Después de agitar a 60°C durante 16 h, la mezcla resultante se separó por RP-HPLC preparativa (Reprosil C18, gradiente 20-40% acetonitrilo/0,2% TFA ac.). El producto obtenido de este modo se disolvió en metanol y se filtró a través de un cartucho de intercambio aniónico (Stratospheres SPE, PL-HCO_3 MP-resina). El cartucho se eluyó con metanol, y el filtrado se evaporó dando 41 mg (53% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,70 min; MS (ESIpos): m/z = 522 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,97 (s, 1H), 7,67 (br. s, 1H), 7,55-8,05 (br. s, 1H), 7,38 (s, 1H), 7,30 (s, 1H), 6,84 (s, 1H), 5,29-5,88 (br. s, 1H), 3,95 (s, 3H), 3,92 (s, 2H), 3,58 (s, 2H), 3,51-3,56 (m, 4H), 3,00-3,06 (m, 2H), 2,85 (s, 2H), 2,45 (s, 3H), 2,43-2,48 (m, 5H) ppm.

Ejemplo 53

rac-1-({[4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(morfolin-4-ilmetil)-pirrolo[2,1-f][1,2,4]triazin-6-il]metil}amino)propan-2-ol



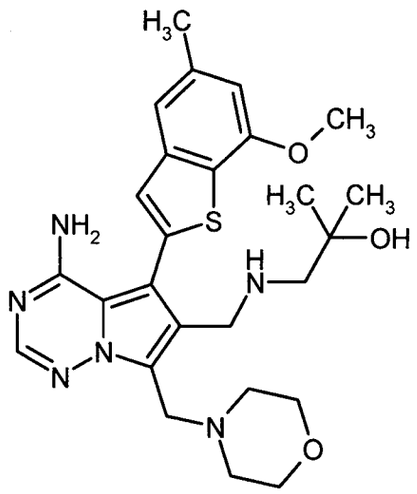
Una solución del intermediario 33A (64 mg, 146 µmoles) en metanol (2 ml) se trató con *rac*-1-aminopropan-2-ol (33 mg, 439 µmoles), cianoborohidruro de sodio (46 mg, 731 µmoles) y ácido acético (25 µl, 439 µmoles). Después de agitar a 60°C durante 16 h, la mezcla resultante se separó por RP-HPLC preparativa (Reprosil C18, gradiente 20-40% acetonitrilo/0,2% TFA ac.). El producto obtenido de este modo se disolvió en metanol y se filtró a través de un cartucho de intercambio aniónico (Stratospheres SPE, PL-HCO_3 MP-resina). El cartucho se eluyó con metanol, y el filtrado se evaporó dando 42 mg (57% de teor.) del compuesto del título.

LC-MS (procedimiento 5): Tr = 1,63 min; MS (ESIpos): m/z = 497 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,96 (s, 1H), 7,47-7,92 (br. s, 1H), 7,39 (s, 1H), 7,30 (s, 1H), 6,84 (s, 1H), 5,36-5,92 (br. s, 1H), 4,36 (d, 1H), 3,95 (s, 3H), 3,90 (s, 2H), 3,64-3,75 (m, 2H), 3,49-3,61 (m, 5H), 2,45 (s, 3H), 2,39-2,47 (m, 4H), 2,31-2,38 (m, 2H), 0,97 (d, 3H) ppm.

Ejemplo 54

1-({[4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(morfolin-4-ilmetil)pirrolo-[2,1-f][1,2,4]triazin-6-il]metil}amino)-2-metilpropan-2-ol



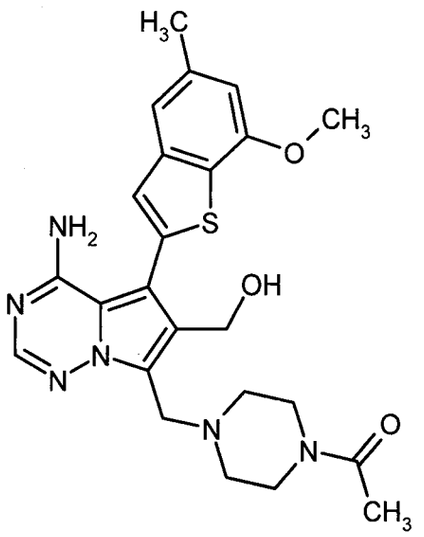
Una solución del intermediario 33A (80 mg, 183 µmoles) en metanol (2 ml) se trató con 1-amino-2-metilpropan-2-ol (34 mg, 274 µmoles), cianoborohidruro de sodio (57 mg, 914 µmoles) y ácido acético (21 µl, 366 µmoles). Después de agitar a 60°C durante 16 h, la mezcla resultante se separó por RP-HPLC preparativa (Reprosil C18, gradiente 20-40% acetonitrilo/0,2% TFA ac.). El producto obtenido de este modo se disolvió en metanol y se filtró a través de un cartucho de intercambio aniónico (Stratospheres SPE, PL-HCO_3 MP-resina). El cartucho se eluyó con metanol, y el filtrado se evaporó dando 29 mg (31% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,65 min; MS (ESIpos): m/z = 511 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,96 (s, 1H), 7,50-8,02 (br. s, 1H), 7,42 (s, 1H), 7,28 (s, 1H), 6,84 (s, 1H), 5,4-6,0 (br. s, 1H), 4,11 (s, 1H), 3,95 (s, 3H), 3,90 (s, 2H), 3,70 (d, 2H), 3,51-3,58 (m, 4H), 2,45 (s, 3H), 2,39-2,46 (m, 4H), 2,33 (d, 2H), 1,83-1,92 (m, 1H), 1,03 (s, 6H) ppm.

Ejemplo 55

1-(4-{[4-amino-6-(hidroximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo-[2,1-f][1,2,4]triazin-7-il]metil}piperazin-1-il)etanona

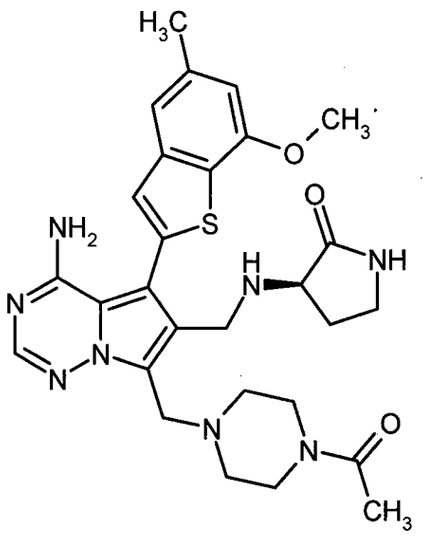


Una solución del intermediario 20A (345 mg, 1,01 mmoles) en ácido acético (5 ml) se trató con 37% de solución de formaldehído acuosa (91 µl, 1,22 mmoles) y 1-acetilpiperazina (160 mg, 1,22 mmoles). La mezcla se agitó a 60°C durante 6 h y posteriormente se evaporó. El residuo se disolvió en una mezcla de THF/solución 1 M de hidróxido de litio ac. (1:1, 10 ml) y se agitó a ta durante 2 h. La mezcla posteriormente se combinó con la mezcla de reacción de una serie analítica de 100 mg, y se agregó solución de cloruro de amonio acuosa saturada. La mezcla se extrajo con acetato de etilo, y la fase orgánica se lavó con solución de cloruro de sodio acuosa saturada, se secó sobre sulfato de magnesio y se evaporó a presión reducida dando 678 mg (pureza 87%, 94% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,71 min; MS (ESIpos): m/z = 481 $(M+H)^+$.

Ejemplo 56

(*3R*)-3-[({7-[(4-acetilpiperazin-1-il)metil]-4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-6-il}metil)amino]pirrolidin-2-ona



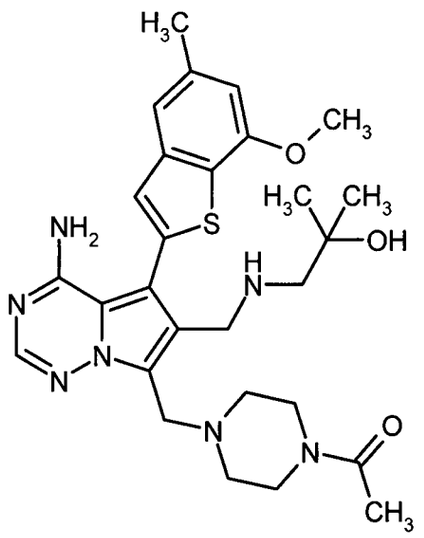
Una solución del intermediario 31A (80 mg, 167 µmoles) en metanol (1,4 ml) se trató con (*3R*)-3-aminopirrolidin-2-ona (21 mg, 251 µmoles), cianoborohidruro de sodio (52 mg, 836 µmoles) y ácido acético (19 µl, 334 µmoles). Después de agitar a 60°C durante 16 h, la mezcla resultante se separó por RP-HPLC preparativa (Reprosil C18, gradiente 20-40% acetonitrilo/0,2% TFA ac.). El producto obtenido de este modo se disolvió en metanol y se filtró a través de un cartucho de intercambio aniónico (Strato-spheres SPE, PL-HCO_3 MP-resina). El cartucho se eluyó con metanol, y el filtrado se evaporó dando 46 mg (49% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,70 min; MS (ESIpos): m/z = 563 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,42 (s, 1H), 8,05 (s, 1H), 7,93-8,24 (br. s, 1H), 7,51 (s, 1H), 7,34 (s, 1H), 6,88 (s, 1H), 5,75-6,07 (br. s, 1H), 4,21-4,37 (m, 2H), 4,19 (s, 2H), 4,10 (t, 1H), 3,96 (s, 3H), 3,56-3,66 (m, 2H), 3,44-3,54 (m, 4H), 3,11-3,27 (m, 4H), 2,47 (s, 4H), 2,16-2,25 (m, 1H), 2,00 (s, 3H), 1,86-1,95 (m, 1H) ppm.

Ejemplo 57

1-(4-{[4-amino-6-{[(2-hidroxi-2-metilpropil)amino]metil}-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-7-il]metil}piperazin-1-il)etanona



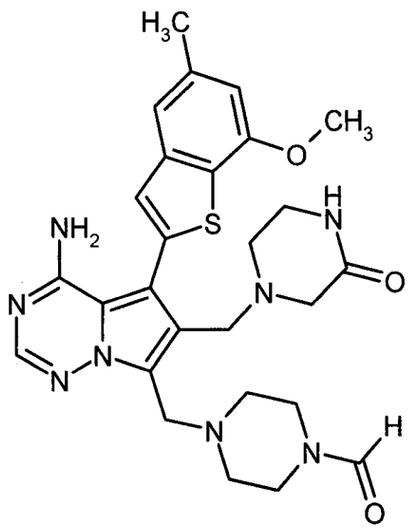
Una solución del intermediario 31A (80 mg, 183 µmoles) en metanol (2 ml) se trató con 1-amino-2-metilpropan-2-ol (31 mg, 251 µmoles), cianoborohidruro de sodio (53 mg, 836 µmoles) y ácido acético (19 µl, 334 µmoles). Después de agitar a 60°C durante 16 h, la mezcla resultante se separó por RP-HPLC preparativa (Reprosil C18, gradiente 20-40% acetonitrilo/0,2% TFA ac.). El producto obtenido de este modo se disolvió en metanol y se filtró a través de un cartucho de intercambio aniónico (Stratospheres SPE, PL-HCO_3 MP-resina). El cartucho se eluyó con metanol, y el filtrado se evaporó dando 29 mg (31% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,71 min; MS (ESIpos): m/z = 552 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,96 (s, 1H), 7,59-8,02 (br. s, 1H), 7,42 (s, 1H), 7,28 (s, 1H), 6,84 (s, 1H), 5,45-5,93 (br. s, 1H), 4,13 (br. s, 1H), 3,95 (s, 3H), 3,93 (s, 2H), 3,71 (s, 2H), 3,37-3,44 (m, 4H), 2,45 (s, 3H), 2,32-2,43 (m, 6H), 1,97 (s, 3H), 1,03 (s, 6H) ppm.

Ejemplo 58

Formiato 4-({4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-6-[(3-oxopiperazin-1-il)metil]pirrolo[2,1-f][1,2,4]triazin-7-il}metil)piperazin-1-carbaldehído



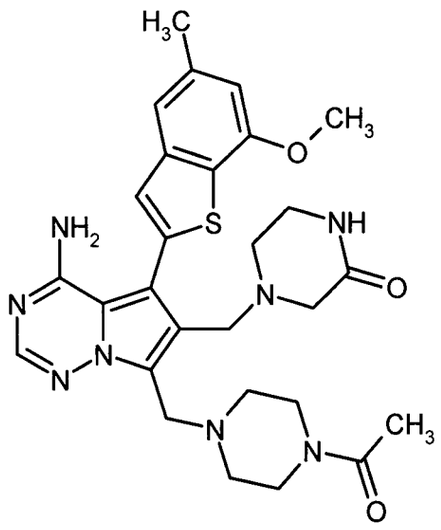
Se agitaron ácido anhídrido acético (498 µl, 5,17 mmoles) y ácido fórmico (237 µl, 6,28 mmoles) primero 2 h a 50°C y posteriormente durante toda la noche a ta. A continuación, la mezcla se diluyó con diclorometano (5,1 ml), y 1,16 ml de esta solución se agregaron a una solución del ejemplo 49 (233 mg, 370 µmoles) en piridina (89 µl). Después de agitar a ta durante 2 h, la mezcla se diluyó con metanol y posteriormente se evaporó. El residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) dando 77 mg (35% de teor.) del compuesto del título.

LC-MS (procedimiento 4): Tr = 0,62 min; MS (ESIpos): m/z = 549 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): *inter al.* δ = 8,14 (s, 1H), 7,97 (s, 2H), 7,67 (s, 1H), 7,38 (s, 1H), 7,30 (s, 1H), 6,84 (s, 1H), 3,96 (s, 2H), 3,95 (s, 3H), 3,58 (s, 2H), 3,04 (br. t, 2H), 2,86 (s, 2H), 2,45 (s, 3H), 2,42 (br. t, 2H) ppm.

Ejemplo 59

4-({7-[(4-acetilpiperazin-1-il)metil]-4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-6-il}metil)piperazin-2-ona



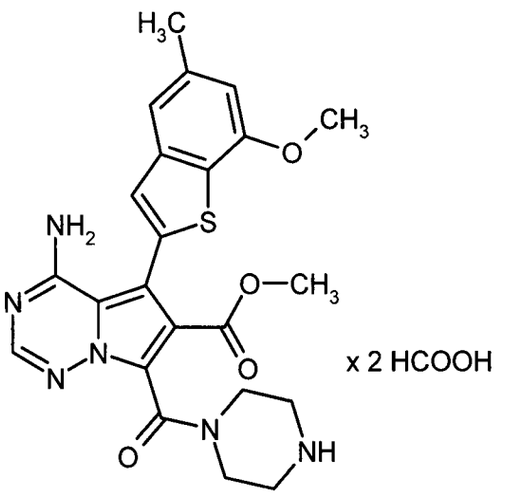
Una suspensión del ejemplo 49 (310 mg, 522 μmoles) en diclorometano/THF (2,5:1, 9,64 ml) se trató con carbonato de sodio (442 mg, 4,17 mmoles) y se agitó a ta durante 30 min. Se agregó cloruro de acetilo (74 μl, 1,04 mmoles), y la mezcla resultante se agitó a ta durante 2 h. Después de templar con metanol, la mezcla se evaporó, y el residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) dando 133 mg (45% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,69 min; MS (ESIpos): m/z = 563 $(M+H)^+$

^{1}H-RMN (400 MHz, metanol-d_4): δ = 7,89 (s, 1H), 7,30 (s, 1H), 7,28 (s, 1H), 6,79 (s, 1H), 4,13 (s, 2H), 3,98 (s, 3H), 3,74 (s, 2H), 3,59 (t, 2H), 3,54 (t, 2H), 3,18 (t, 2H), 3,02 (s, 2H), 2,68-2,55 (m, 6H), 2,48 (s, 3H), 2,08 (s, 3H) ppm.

Ejemplo 60

bis(formiato) 4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilcarbonil)pirrolo[2,1-f][1,2,4]triazin-6-carboxilato de metilo



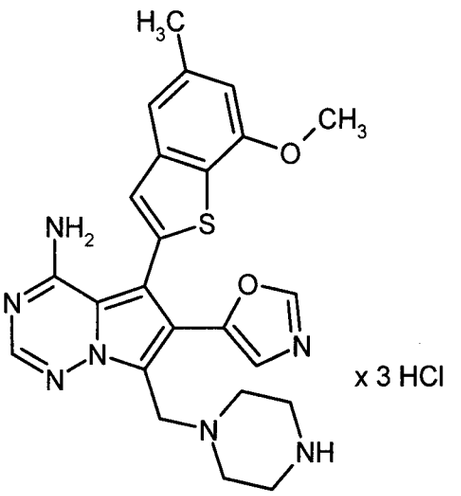
A una solución del intermediario 28A (15 mg, 26 μmoles) en a THF/metanol mixture (5:1, 180 μl), se enfrió hasta 0°C, se agregó (trimetilsilil)diazometano (solución 2 M en hexano, 15 μl, 32 μmoles). La mezcla resultante se entibió lentamente hasta ta durante 30 min y posteriormente se evaporó. El residuo se disolvió en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (0,5 ml) y se agitó a ta durante 1 h. Después de la evaporación, el residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) dando 4,8 mg (35% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,66 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): *inter al.* δ = 8,17 (s, 2H), 8,38-8,23 (br. s, 1H), 8,04 (s, 1H), 7,43 (s, 1H), 7,31 (s, 1H), 6,86 (s, 1H), 5,71-5,58 (br. s, 1H), 3,96 (s, 3H), 3,60 (s, 3H, superposición con pico de agua), 2,46 (s, 3H) ppm.

Ejemplo 61

Triclorhidrato 5-(7-metoxi-5-metil-1-benzotiofen-2-il)-6-(1,3-oxazol-5-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-amina



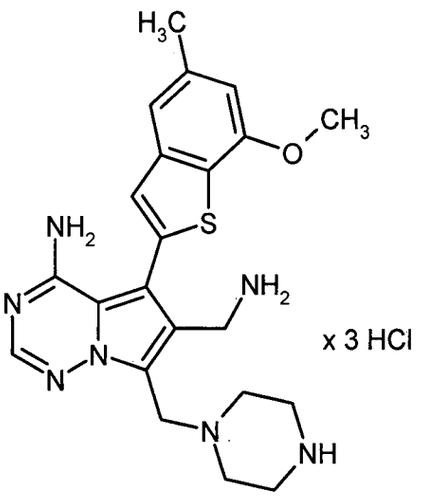
Una solución del intermediario 25A (100 mg, 0,19 mmoles) en metanol (3,33 ml) se trató con (4-toluenosulfonilo)metilisocianuro (36 mg, 0,19 mmoles) y carbonato de potasio (25 mg, 186 µmoles). La mezcla se sometió a reflujo durante 6 h. Posteriormente se combinó con las mezclas de reacción de tres series analíticas de 30 mg y se evaporaron. El residuo se disolvió en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (10 ml) y se agitó a ta durante 2 h. Después de la evaporación, el residuo se purificó por RP-HPLC preparativa dos veces (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% TFA ac.). Además, la purificación por cromatografía de columna sobre gel de sílice (diclorometano/metanol 5:1 con 0,5% de amoníaco ac.) y la liofilización a partir de una solución 4 M de cloruro de hidrógeno en 1,4-dioxano dio 75 mg (34% de teor.) del compuesto del título.

LC-MS (procedimiento 4): Tr = 0,69 min; MS (ESIpos): m/z = 476 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): *inter al.* δ = 8,40 (s, 1H), 8,20 (s, 1H), 7,46 (s, 1H), 7,35 (s, 1H), 6,96 (s, 1H), 6,89 (s, 1H), 3,95 (s, 3H), 2,46 (s, 3H) ppm.

Ejemplo 62

Triclorhidrato 6-(aminometil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-amina



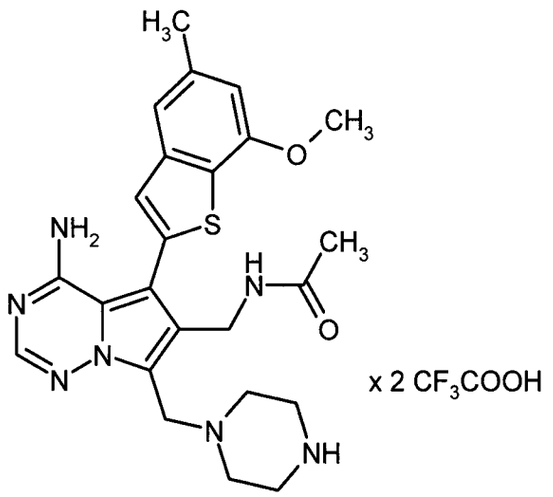
Una suspensión del intermediario 29A (76 mg, 134 μmoles) y 10% Pd/C (60 mg) en una solución 0,5 M de cloruro de hidrógeno en metanol (20 ml) se agitó a ta durante 3 h bajo 1 atm de hidrógeno. La mezcla posteriormente se filtró a través de kieselguhr, el filtrado se evaporó, y el residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% TFA ac.). El producto obtenido de este modo se liofilizó a partir de una solución 4 M de cloruro de hidrógeno en 1,4-dioxano dando 34 mg (46% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,55 min; MS (ESIpos): m/z = 438 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): *inter al.* δ = 8,24 (br. s, 3H), 8,12 (s, 1H), 7,52 (s, 1H), 7,34 (s, 1H), 6,89 (s, 1H), 3,96 (s, 3H), 3,76-3,63 (m, 1H), 3,52-3,42 (m, 1H), 2,47 (s, 3H) ppm.

Ejemplo 63

bis(trifluoroacetato) *N*-{[4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-6-il]metil}acetamida



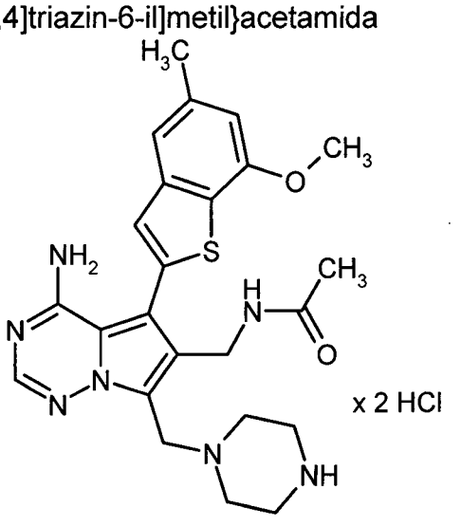
Una solución del intermediario 30A (210 mg, 362 μmoles) en diclorometano (26 ml) se trató con ácido trifluoroacético (5,2 ml) y se agitó a ta durante 1 h. Después de la evaporación a ta, el residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% TFA ac.) dando 163 mg (63% de teor.) del compuesto del título.

LC-MS (procedimiento 3): Tr = 2,42 min; MS (ESIpos): m/z = 480 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): *inter al.* δ = 9,00-8,75 (br. s, 1H), 8,30-8,16 (br. s, 1H), 8,08 (s, 1H), 7,38 (s, 1H), 7,33 (s, 1H), 6,87 (s, 1H), 4,32 (br. d, 2H), 3,96 (s, 3H), 3,40-2,98 (m, 8H), 2,46 (s, 3H), 1,77 (s, 3H) ppm.

Ejemplo 64

Diclorhidrato *N*-{[4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-6-il]metil}acetamida



Una solución del intermediario 30A (80 mg, 0,14 mmoles) en diclorometano

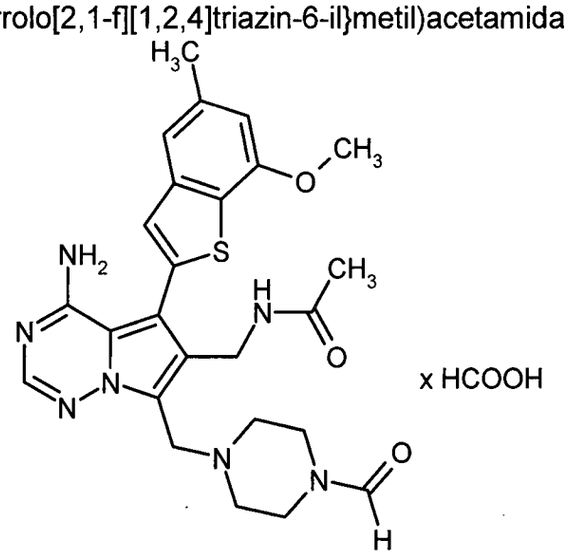
(10 ml) y ácido trifluoroacético (2 ml) se agitó a ta durante 1 h y posteriormente se evaporó. La purificación por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) y la liofilización a partir de una mezcla de metanol y solución 4 M de cloruro de hidrógeno en 1,4-dioxano dio 39 mg (50% de teor.) del compuesto del título.

LC-MS (procedimiento 5): Tr = 1,56 min; MS (ESIpos): m/z = 480 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): *inter al.* δ = 8,12 (s, 1H), 7,38 (s, 1H), 7,33 (s, 1H), 6,87 (s, 1H), 4,37 (br. d, 2H), 3,96 (s, 3H), 3,85-3,20 (m, 8H, superposición con pico de agua), 2,46 (s, 3H), 1,76 (s, 3H) ppm.

Ejemplo 65

Formiato *N*-({4-amino-7-[(4-formilpiperazin-1-il)metil]-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-6-il}metil)acetamida



Se agitaron ácido anhídrido acético (304 µl, 3,16 mmoles) y ácido fórmico (145 µl, 3,16 mmoles) primero 2 h a 50°C y posteriormente durante toda la noche a ta. A continuación, la mezcla se diluyó con diclorometano (3,1 ml), y 663 µl de esta solución se agregaron a una solución del ejemplo 63 (160 mg, 226 µmoles) en piridina (54 µl). La mezcla se agitó a ta durante 2 h, posteriormente se diluyó con metanol (1 ml), y se continuó con la agitación a 40°C durante otra 2 h. Después de la evaporación, el residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico

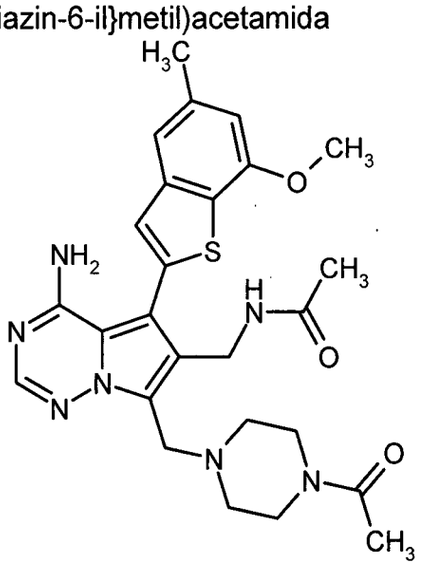
acuoso) dando 74 mg (61% de teor.) del compuesto del título.

LC-MS (procedimiento 4): Tr = 0,65 min; MS (ESIpos): m/z = 508 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,13 (s, 1H), 8,06-7,89 (m, 3H), 7,38 (s, 1H), 7,31 (s, 1H), 6,85 (s, 1H), 4,28 (d, 2H), 4,01-3,88 (m, 5H), 2,47-2,34 (m, 7H), 1,75 (s, 3H) ppm.

Ejemplo 66

N-({7-[(4-acetilpiperazin-1-il)metil]-4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-6-il}metil)acetamida



Una solución del ejemplo 63 (110 mg, 229 μmoles) y cloruro de acetilo (32 μl, 458 μmoles) en THF/ diclorometano (1:2, 3 ml) se trató con carbonato de sodio (194 mg, 1,83 mmoles) y se agitó a ta durante toda la noche. Posteriormente, la mezcla se diluyó con metanol (2 ml) y agua (1 ml) y se agitó a ta durante 1 h. Después de la evaporación, el residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso). La liofilización a partir de 1,4-dioxano y la re-purificación por cromatografía de columna sobre gel de sílice (diclorometano/metanol 50:1 → 100% metanol) dio 35 mg (28% de teor.) del compuesto del título.

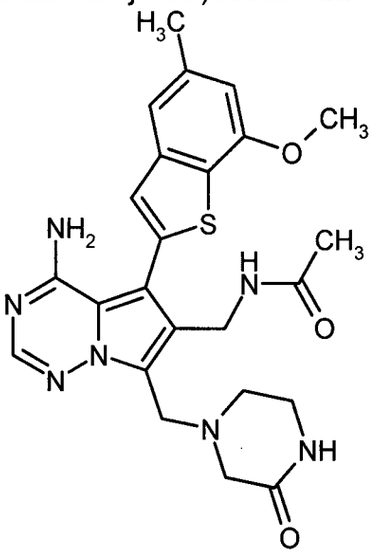
LC-MS (procedimiento 2): Tr = 0,70 min; MS (ESIpos): m/z = 522 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,04-7,98 (m, 2H), 7,38 (s, 1H), 7,31 (s, 1H), 6,85 (s, 1H), 4,27 (d, 2H), 3,95 (s, 3H), 3,91 (s, 2H), 3,44-3,36 (m, 4H),

2,48-2,35 (m, 7H), 1,98 (s, 3H), 1,75 (s, 3H) ppm.

Ejemplo 67

N-({4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-[(3-oxopiperazin-1-il)metil]pirrolo[2,1-f][1,2,4]triazin-6-il}metil)acetamida



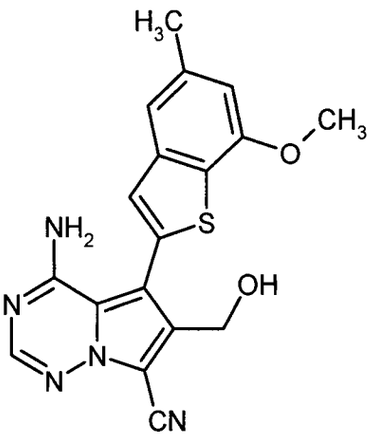
Una suspensión del intermediario 32A (35 mg, 73 µmoles) en metanol (4,1 ml) se trató con anhídrido acético (13 µl, 146 µmoles) y 10% Pd/C (41 mg) y se agitó a ta durante 1 h bajo 1 atm de hidrógeno. La filtración sobre kieselguhr y la evaporación del filtrado dio 30 mg (79% de teor.) del compuesto del título.

LC-MS (procedimiento 5): Tr = 1,65 min; MS (ESIpos): m/z = 494 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,99 (s, 2H), 7,75 (br. s, 1H), 7,39 (s, 1H), 7,31 (s, 1H), 6,85 (s, 1H), 4,27 (s, 1H), 4,26 (s, 1H), 3,95 (s, 5H), 3,19-3,08 (m, 2H), 3,05-2,96 (m, 2H), 2,66-2,57 (m, 2H), 2,45 (s, 3H), 1,72 (s, 3H) ppm.

Ejemplo 68

4-amino-6-(hidroximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f]-[1,2,4]triazin-7-carbonitrilo



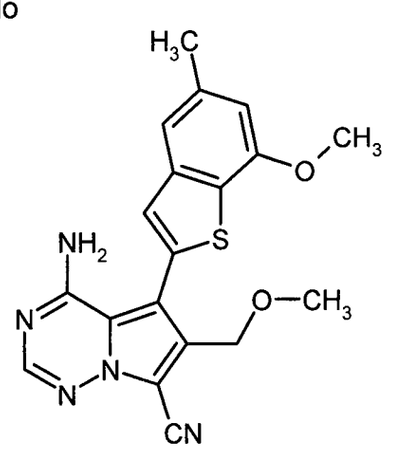
Una solución del intermediario 38A (1 g, 2,08 mmoles) en THF (10 ml) se trató con una solución 1M de fluoruro de tetra-n-butilamonio en THF (12 ml, 12 mmoles). La mezcla se agitó a ta durante toda la noche y posteriormente se evaporó. El residuo se colocó en agua y se extrajo tres veces con acetato de etilo. Las fases orgánicas combinadas se secaron sobre sulfato de magnesio y se evaporaron. El residuo se trituró en ter-butil metil éter, y el sólido se filtró dando 680 mg (78% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,95 min; MS (ESIpos): m/z = 366 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,61-8,29 (br. s, 1H), 8,18 (s, 1H), 7,43 (s, 1H), 7,32 (s, 1H), 6,87 (s, 1H), 6,32-6,03 (br. s, 1H), 5,46 (t, 1H), 4,55 (d, 2H), 3,96 (s, 3H), 2,45 (s, 3H) ppm.

Ejemplo 69

4-amino-6-(metoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f]-[1,2,4]triazin-7-carbonitrilo



Una solución del ejemplo 68 (60 mg, 164 μmoles) en diclorometano (5 ml) se

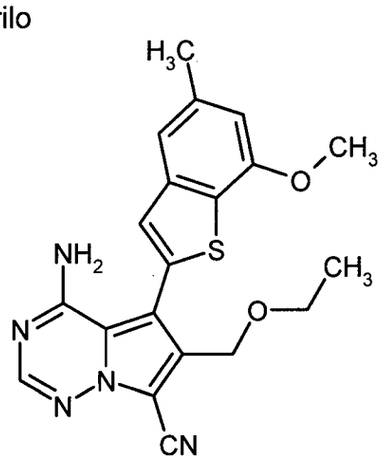
trató con cloruro de tionilo (18 µl, 246 µmoles). La mezcla se agitó a ta durante 15 min y posteriormente se evaporó. El residuo se disolvió en metanol (2 ml) y se trató con DIPEA (57 µl, 328 µmoles). La mezcla se agitó primero 2 h a 60°C, posteriormente se sometió a reflujo durante toda la noche y finalmente se calentó hasta 150°C durante 30 min en un dispositivo de microondas. Después de esto, la mezcla se evaporó, y el residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% TFA ac.). El producto obtenido de este modo se disolvió en metanol y se filtró a través de un cartucho de intercambio aniónico (Stratospheres SPE, PL-HCO_3 MP-resina). El cartucho se eluyó con metanol, y el filtrado se evaporó dando 18 mg (28% de teor.) del compuesto del título.

LC-MS (procedimiento 4): Tr = 1,12 min; MS (ESIpos): m/z = 379 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,61-8,40 (br. s, 1H), 8,21 (s, 1H), 7,42 (s, 1H), 7,33 (s, 1H), 6,87 (s, 1H), 6,34-6,09 (br. s, 1H), 4,47 (s, 2H), 3,96 (s, 3H), 3,26 (s, 3H), 2,45 (s, 3H) ppm.

Ejemplo 70

4-amino-6-(etoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-7-carbonitrilo



Una solución del ejemplo 68 (60 mg, 164 µmoles) en diclorometano (5 ml) se trató con cloruro de tionilo (18 µl, 246 µmoles). La mezcla se agitó a ta durante 15 min y posteriormente se evaporó. El residuo se disolvió en etanol (2 ml) y se trató con DIPEA (57 µl, 328 µmoles). La mezcla se agitó a 60°C durante

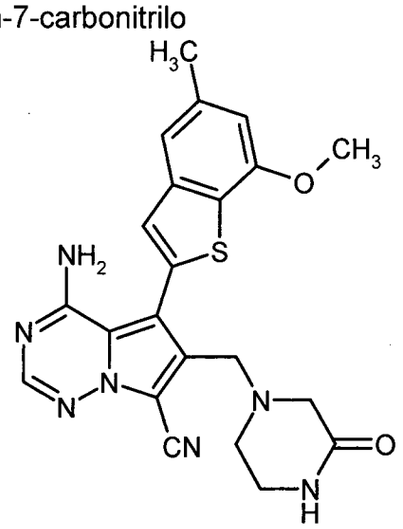
toda la noche y posteriormente se calentó hasta 150°C durante 30 min en un dispositivo de microondas. Después de esto, la mezcla se evaporó, y el residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% TFA ac.). El producto obtenido de este modo se disolvió en etanol (2 ml) y nuevamente se calentó hasta 150°C durante 30 min en las microondas oven. Se agregó DIPEA (57 µl, 328 µmoles), y el calentamiento hasta 150°C en las microondas oven continuó durante otros 30 min. Después de la evaporación, el residuo se purificó por cromatografía de columna sobre gel de sílice (diclorometano/ metanol 95:5) dando 16 mg (23% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 1,18 min; MS (ESIpos): m/z = 393 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,61-8,38 (br. s, 1H), 8,20 (s, 1H), 7,42 (s, 1H), 7,33 (s, 1H), 6,87 (s, 1H), 6,33-6,08 (br. s, 1H), 4,51 (s, 2H), 3,96 (s, 3H), 3,45 (q, 2H), 2,45 (s, 3H), 1,10 (t, 3H) ppm.

Ejemplo 71

4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-6-[(3-oxopiperazin-1-il)metil]-pirrolo[2,1-f][1,2,4]triazin-7-carbonitrilo



Una solución del intermediario 39A (20 mg, 55 µmoles) en THF (0,73 ml) se trató con ácido acético (6 µl, 110 µmoles), 2-oxopiperazina (27 mg, 275 µmoles) y triacetoxiborohidruro de sodio (58 mg, 275 µmoles). Después de agitar a ta durante 3 h, otras cantidades de THF (1 ml), ácido acético (6 µl, 110

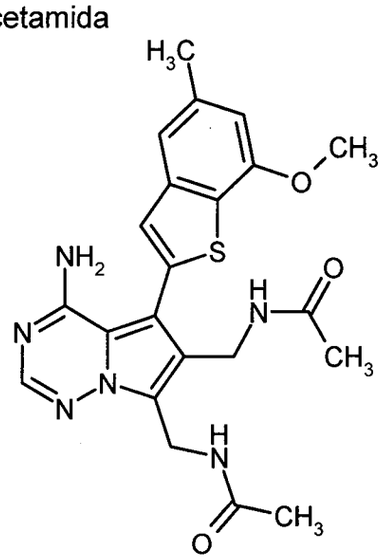
μmoles), se agregaron 2-oxopiperazina (27 mg, 275 μmoles) y triacetoxiborohidruro de sodio (58 mg, 275 μmoles), y se continuó con la agitación a ta durante toda la noche. Después de la evaporación, el residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% TFA ac.). El producto obtenido de este modo se disolvió en metanol y se filtró a través de un cartucho de intercambio aniónico (Strato-spheres SPE, PL-HCO_3 MP-resina). El cartucho se eluyó con metanol, y el filtrado se evaporó dando 13 mg (52% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,86 min; MS (ESIpos): m/z = 447 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,60-8,31 (br. s, 1H), 8,19 (s, 1H), 7,74 (s, 1H), 7,44 (s, 1H), 7,33 (s, 1H), 6,87 (s, 1H), 6,25-5,98 (br. s, 1H), 3,96 (s, 3H), 3,62 (s, 2H), 3,13-3,07 (m, 2H), 2,91 (s, 2H), 2,45 (s, 3H) ppm.

Ejemplo 72

N,N'-{[4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-6,7-diil]bis(metilene)}diacetamida



Una suspensión del intermediario 40A (bruto, 85 mg), 10% Pd/C (115 mg) y anhídrido acético (40 μl, 435 μmoles) en metanol (12 ml) se agitó a ta bajo 1 atm de hidrógeno. Después de 4 h, se agregaron otras cantidades de 10% Pd/C (115 mg) y anhídrido acético (40 μl, 435 μmoles), y la agitación a ta bajo 1 atm de hidrógeno continuó durante 2 h. La mezcla resultante se filtró a través

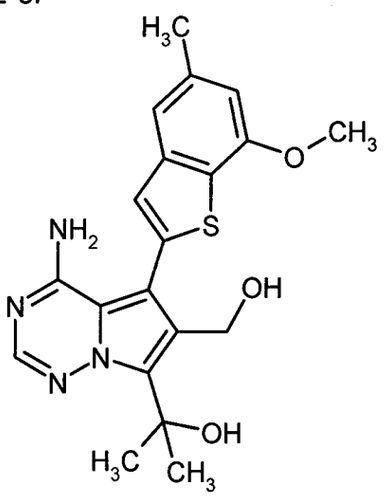
de kieselguhr, el filtrado se evaporó, y el residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% TFA ac.). El producto obtenido de este modo se disolvió en metanol y se filtró a través de un cartucho de intercambio aniónico (Stratospheres SPE, PL-HCO_3 MP-resina). El cartucho se eluyó con metanol, y el filtrado se evaporó dando 18 mg (18% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,73 min; MS (ESIpos): m/z = 452 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,29 (br. t, 1H), 8,04 (br. t, 1H), 8,00 (s, 1H), 7,34 (s, 1H), 7,31 (s, 1H), 6,85 (s, 1H), 4,58 (d, 2H), 4,26 (d, 2H), 3,95 (s, 3H), 2,45 (s, 3H), 1,81 (s, 3H), 1,74 (s, 3H) ppm.

Ejemplo 73

2-[4-amino-6-(hidroximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f]-[1,2,4]triazin-7-il]propan-2-ol



Un matraz que contiene una suspensión del intermediario 43A (180 mg, 598 µmoles), el intermediario 6A (299 mg, 897 µmoles) y fluoruro de cesio (454 mg, 2,99 mmoles) en THF/agua (10:1, 11 ml) se desgasificó a presión reducida y posteriormente se rellenó con argón. Se agregó 4-(di-*ter*-butilfosfino)-*N,N*-dimetilanilina-dicloropaladio (2:1; 13 mg, 18 µmoles) . La mezcla resultante se desgasificó nuevamente y se agitó bajo argón a 50°C durante 16 h. Después de esto, la mezcla de reacción se separó por RP-HPLC preparativa (Reprosil C18, gradiente 30-50% acetonitrilo/0,2% de TFA ac.). Las fracciones del

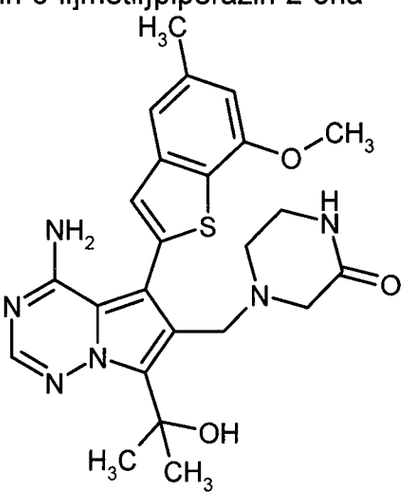
producto se diluyeron con una solución 7 M de amoníaco en metanol y posteriormente se concentró a presión reducida. El precipitado se filtró, se lavó con agua y se secó al vacío dando 99 mg (42% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,89 min; MS (ESIpos): m/z = 399 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,96 (s, 1H), 7,51-8,02 (br. s, 1H), 7,37 (s, 1H), 7,31 (s, 1H), 6,86 (s, 1H), 5,99 (s, 1H), 5,23-5,82 (br. s, 1H), 5,04 (t, 1H), 4,53 (d, 2H), 3,96 (s, 3H), 2,45 (s, 3H), 1,73 (s, 6H) ppm.

Ejemplo 74

4-{[4-amino-7-(2-hidroxipropan-2-il)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-6-il]metil}piperazin-2-ona



Una solución del intermediario 44A (50 mg, 73% de pureza, 92 µmoles) en metanol (4 ml) se trató con 2-oxopiperazina (28 mg, 276 µmoles), cianoborohidruro de sodio (23 mg, 368 µmoles) y ácido acético (21 µl, 368 µmoles). La mezcla se agitó primero 18 h a 60°C y posteriormente 3 días a ta. Después de esto, la mezcla se separó por RP-HPLC preparativa (Reprosil C18, gradiente 20-40% acetonitrilo/0,2% TFA ac.). Las fracciones del producto se diluyeron con una solución 7 M de amoníaco en metanol y se evaporaron a presión reducida. El residuo se disolvió en acetato de etilo y se lavó con agua. La fase orgánica se secó con sulfato de sodio y se concentró a presión reducida. El residuo se disolvió en 1,4-dioxano y se liofilizó dando 24 mg (52%

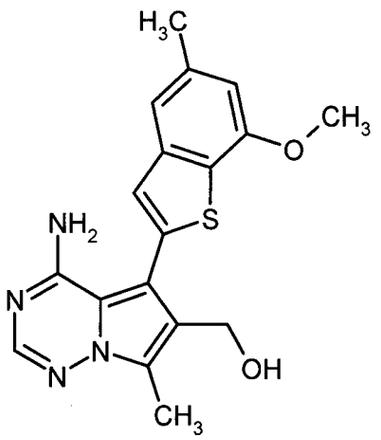
de teor.) del compuesto del título.

LC-MS (procedimiento 5): Tr = 1,85 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,99 (s, 1H), 7,73-8,01 (br. s, 1H), 7,41 (s, 1H), 7,33 (s, 1H), 6,87 (s, 1H), 5,2-5,7 (br. s, 1H), 3,95 (s, 3H), 3,57 (s, 2H), 3,14 (br. s, 2H), 2,60 (br. s, 4H), 2,46 (s, 3H), 1,70 (br. s, 6H) ppm.

Ejemplo 75

[4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-metilpirrolo[2,1-f][1,2,4]triazin-6-il]metanol



Bajo una atmósfera de argón, un matraz se cargó con 165 mg (0,64 mmoles) del intermediario 53A, 143 mg (0,64 mmoles) del intermediario 5A, 25 mg (0,03 mmoles) (2'-aminobifenil-2-il)(cloro)paladio-diciclohexil(2',4',6'-triisopropilbifenil-2-il)fosfina (1:1; véase S. L. Buchwald *et al.*, *J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)) y 409 mg (1,93 mmoles) fosfato de potasio. Posteriormente, se agregaron 7 ml de una mezcla desgasificada de 1,4-dioxano y agua (5:1), y la solución se agitó a 70°C durante 1 h. Se agregó otra porción del intermediario 5A (142 mg, 0,64 mmoles) y de (2'-aminobifenil-2-il)-(cloro)paladio-diciclohexil(2',4',6'-triisopropilbifenil-2-il)fosfina (10 mg, 0,012 mmoles), y se continuó con la agitación durante 1 h. Después de esto, la mezcla de reacción se evaporó parcialmente a presión reducida, se agregó agua, y la mezcla se extrajo con acetato de etilo. Las fases orgánicas combinadas se evaporaron a presión reducida, y el residuo se trituró con acetonitrilo. El precipitado se filtró y se secó al vacío dando 180 mg (92% de

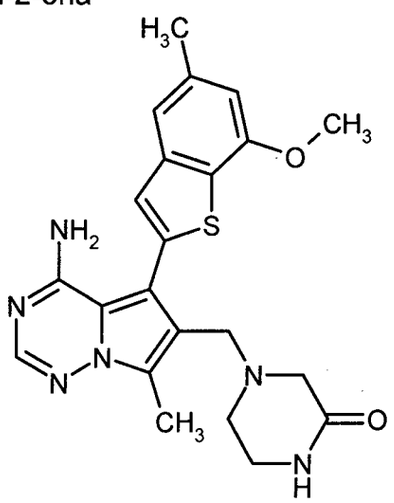
pureza por LC-MS, 73% de teor.) del compuesto del título. A partir del filtrado se obtuvo un segundo lote (41 mg, 18% de teor.) por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso). Total rendimiento: 91% de teor.

LC-MS (procedimiento 5): Tr = 1,92 min; MS (ESIpos): m/z = 355 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,95 (s, 1H), 7,35 (s, 1H), 7,30 (s, 1H), 6,83 (s, 1H), 4,82 (t, 1H), 4,44 (d, 2H), 3,95 (s, 3H), 2,45 (s, 3H) ppm.

Ejemplo 76

4-{[4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-metilpirrolo[2,1-f][1,2,4]-triazin-6-il]metil}piperazin-2-ona



Una suspensión de 55 mg (0,16 mmoles) del intermediario 54A en THF (1,5 ml) se trató con 78 mg (0,78 mmoles) piperazin-2-ona, 18 µl (0,31 mmoles) ácido acético y 166 mg (0,78 mmoles) triacetoxiborohidruro. La mezcla se agitó a temperatura ambiente durante toda la noche. Posteriormente, se agregaron 1,5 ml agua, y la mayoría del solvente THF se evaporó a presión reducida. La mezcla restante se diluyó con más agua, y el sólido precipitado se filtró y se secó (35 mg). Este material se purificó además por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso). Las fracciones del producto se ajustaron hasta pH 9 con carbonato de potasio sólido y se concentraron parcialmente a presión reducida. El sólido precipitado se filtró y se secó a 45°C al vacío para dar 16 mg (24% de teor.)

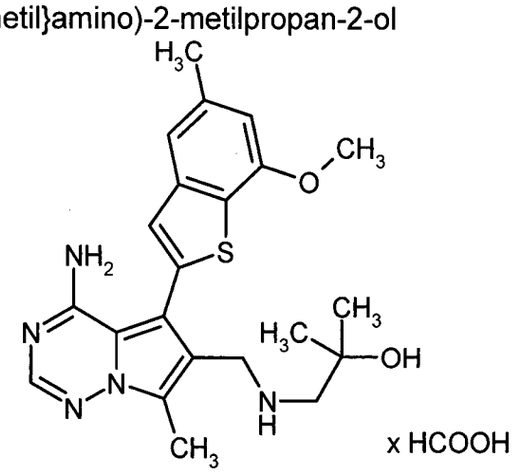
del compuesto del título.

LC-MS (procedimiento 5): Tr = 1,74 min; MS (ESIpos): m/z = 437 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,95 (s, 1H), 7,66 (br. s, 1H), 7,35 (s, 1H), 7,30 (s, 1H), 6,83 (s, 1H), 3,95 (s, 3H), 3,50 (s, 2H), 3,05 (m, 2H), 2,84 (s, 2H), 2,45 (m, 5H) ppm.

Ejemplo 77

Formiato 1-({[4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-metilpirrolo[2,1-f][1,2,4]triazin-6-il]metil}amino)-2-metilpropan-2-ol



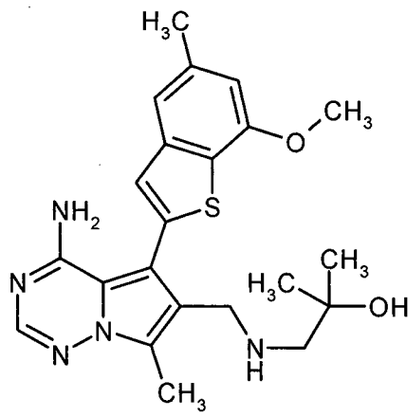
Una suspensión de 55 mg (0,16 mmoles) del intermediario 54A en THF (1,5 ml) se trató con 98 mg (0,78 mmoles) clorhidrato 1-amino-2-metilpropan-2-ol, 39 mg (0,47 mmoles) de acetato de sodio y 166 mg (0,78 mmoles) de triacetoxiborohidruro de sodio. La mezcla se agitó a temperatura ambiente durante toda la noche. Posteriormente, se agregaron 1,5 ml agua, y la mezcla se evaporó a presión reducida. El residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) para dar 38 mg (52% de teor.) del compuesto del título.

LC-MS (procedimiento 5): Tr = 1,68 min; MS (ESIpos): m/z = 426 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,19 (s, 1H), 7,94 (s, 1H), 7,38 (s, 1H), 7,29 (s, 1H), 6,84 (s, 1H), 3,95 (s, 3H), 2,45 (s, 3H), 2,34 (s, 2H), 1,02 (s, 6H) ppm.

Ejemplo 78

1-({[4-amino-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-metilpirrolo[2,1-f][1,2,4]-triazin-6-il]metil}amino)-2-metilpropan-2-ol



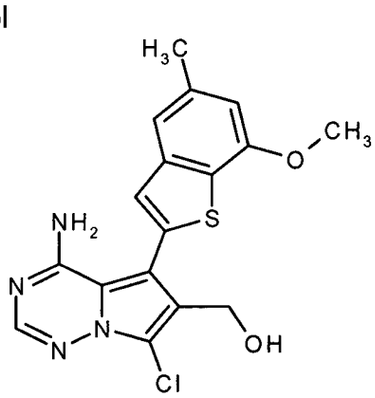
Una solución de 29 mg (0,06 mmoles) del ejemplo 77 en 3 ml de metanol se corrió a través de un cartucho Stratospheres SPE PL-HCO_3 MP-resina, preacondicionado con 2 ml de metanol. El cartucho se lavó con 4 ml de metanol, y el eluado se evaporó para dar 21,5 mg (82% de teor.) del compuesto del título.

LC-MS (procedimiento 4): Tr = 0,68 min; MS (ESIpos): m/z = 426 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,94 (s, 1H), 7,37 (s, 1H), 7,28 (s, 1H), 6,83 (s, 1H), 4,07 (s, 1H), 3,95 (s, 3H), 3,63-3,75 (m, 2H), 2,45 (s, 3H), 2,32 (m, 3H), 1,42-1,56 (m, 1H), 1,02 (s, 6H) ppm.

Ejemplo 79

[4-amino-7-cloro-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-6-il]metanol



Una solución del intermediario 48A (117 mg, 0,24 mmoles) en 5 ml de THF se trató con 5 ml de ácido clorhídrico conc. y se agitó a temperatura ambiente durante toda la noche. Posteriormente, se agregaron 12 ml de solución 5 M de hidróxido de sodio ac. como también acetato de etilo, las capas se separaron,

y la capa acuosa se extrajo dos veces con acetato de etilo. Las fases orgánicas combinadas se lavaron con solución de cloruro de sodio acuosa saturada, se secaron y se evaporaron. El residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) para dar 30 mg (34% de teor.) del compuesto del título.

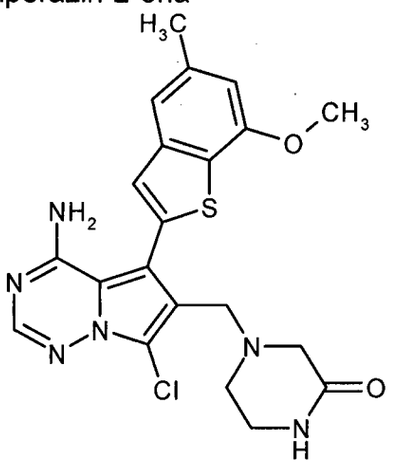
LC-MS (procedimiento 2): Tr = 0,90 min; MS (ESIpos): m/z = 375 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,04 (s, 1H), 7,43 (s, 1H), 7,32 (s, 1H), 6,85 (s, 1H), 5,02 (t, 1H), 4,43 (d, 2H), 3,96 (s, 3H), 2,45 (s, 3H) ppm.

9,2 mg (10% de teor.) de 7-cloro-6-(clorometil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-4-amina se aislaron en forma de un subproducto (*cf.* Intermediario 50A).

Ejemplo 80

4-{[4-amino-7-cloro-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-6-il]metil}piperazin-2-ona



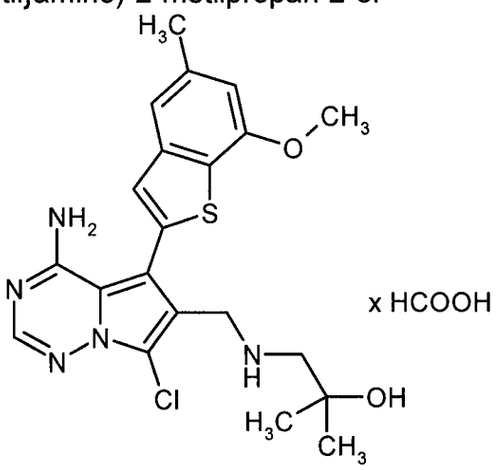
El compuesto del título se preparó de acuerdo con el procedimiento del ejemplo 76 partiendo de 40 mg (0,11 mmoles) del intermediario 49A. Rendimiento: 27 mg (55% de teor.).

LC-MS (procedimiento 2): Tr = 0,86 min; MS (ESIpos): m/z = 457 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,05 (s, 1H), 7,68 (br. s, 1H), 7,44 (s, 1H), 7,31 (s, 1H), 6,85 (s, 1H), 3,96 (s, 3H), 3,52 (s, 2H), 3,05 (br. s, 2H), 2,86 (s, 2H), 2,45 (s, 3H) ppm.

Ejemplo 81

Formiato 1-({[4-amino-7-cloro-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-6-il]metil}amino)-2-metilpropan-2-ol



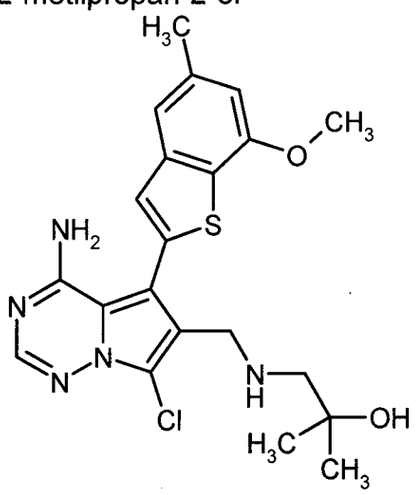
El compuesto del título se preparó de acuerdo con el procedimiento del ejemplo 77 partiendo de 40 mg (0,11 mmoles) del intermediario 49A. Rendimiento: 24 mg (45% de teor.).

LC-MS (procedimiento 2): Tr = 0,73 min; MS (ESIpos): m/z = 446 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,15 (s, 1H), 8,04 (s, 1H), 7,45 (s, 1H), 7,30 (s, 1H), 6,85 (s, 1H), 3,96 (s, 3H), 3,73 (s, 2H), 2,45 (s, 3H), 2,32 (s, 2H), 1,00 (s, 6H) ppm.

Ejemplo 82

1-({[4-amino-7-cloro-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]-triazin-6-il]metil}amino)-2-metilpropan-2-ol



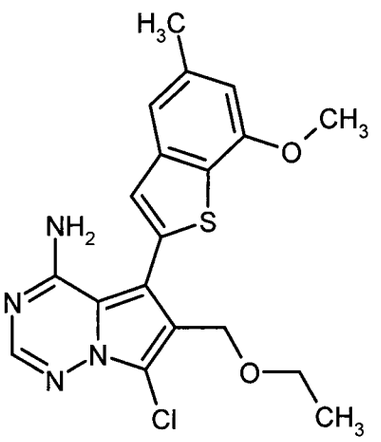
El compuesto del título se preparó a partir del ejemplo 81 de acuerdo con el procedimiento del ejemplo 78.

LC-MS (procedimiento 2): Tr = 0,72 min; MS (ESIpos): m/z = 446 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,04 (s, 1H), 7,45 (s, 1H), 7,30 (s, 1H), 6,85 (s, 1H), 4,09 (br. s, 1H), 3,95 (s, 3H), 3,71 (s, 2H), 2,45 (s, 3H), 2,31 (s, 2H), 1,44-1,64 (m, 1H), 1,00 (s, 6H) ppm.

Ejemplo 83

7-cloro-6-(etoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]-triazin-4-amina



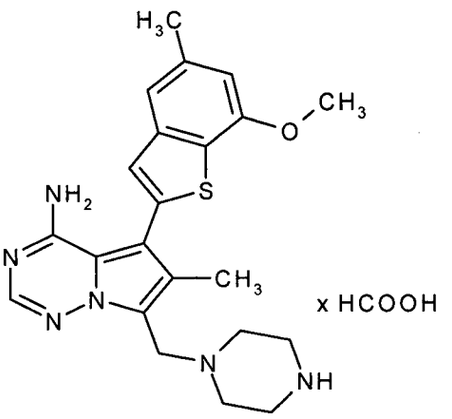
Se suspendieron 8,2 mg (0,02 mmoles) del intermediario 50A en 1 ml de etanol, se trató con 41 µl (0,11 mmoles) de una solución 2,68 M de etanolato de sodio en etanol y se sometió a reflujo durante 1 min. La solución transparente posteriormente se evaporó, y el producto bruto se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) para dar 5 mg (56% de teor.) del compuesto del título.

LC-MS (procedimiento 4): Tr = 1,25 min; MS (ESIpos): m/z = 402 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,06 (s, 1H), 7,40 (s, 1H), 7,32 (s, 1H), 6,86 (s, 1H), 4,40 (s, 2H), 3,96 (s, 3H), 3,40 (q, 2H), 2,45 (s, 3H), 1,06 (t, 3H) ppm.

Ejemplo 84

Formiato 5-(7-metoxi-5-metil-1-benzotiofen-2-il)-6-metil-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-amina



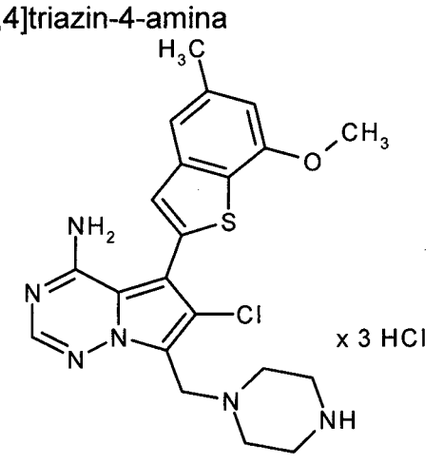
Una solución del intermediario 57A (100 mg, 191 μmoles) en una solución 4 M de cloruro de hidrógeno en 1,4-dioxano (2 ml) se agitó a ta durante 3 h y posteriormente se evaporó. La purificación por RP-HPLC preparativa dos veces (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido fórmico acuoso) dio 71 mg (67% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,81 min; MS (ESIpos): m/z = 423 $(M+H)^+$

^{1}H-RMN (400 MHz, $CDCl_3$): δ = 8,46 (br. s, 1H), 7,89 (s, 1H), 7,27 (s, 1H, superposición con pico de $CHCl_3$), 7,18 (s, 1H), 6,67 (s, 1H), 4,01 (s, 3H), 3,97 (s, 2H), 3,18-3,09 (m, 4H), 2,82-2,73 (m, 4H), 2,50 (s, 3H), 2,24 (s, 3H) ppm.

Ejemplo 85

Triclorhidrato 6-cloro-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-7-(piperazin-1-ilmetil)pirrolo[2,1-f][1,2,4]triazin-4-amina



El intermediario 60A (65 mg, 0,12 mmoles) se agitó en 1 ml de una solución 4 M de cloruro de hidrógeno en 1,4-dioxano durante 2 h a ta. La suspensión se evaporó hasta sequedad, y el producto bruto se purificó por RP-HPLC

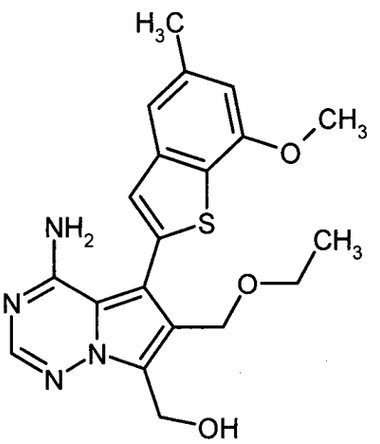
preparativa (Reprosil C18, gradiente 10-95% acetonitrilo/0,1% de ácido clorhídrico ac.) dando 49 mg (74% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,81 min; MS (ESIpos): m/z = 443 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): *inter al.* δ = 9,56 (br. s, 1H), 8,45 (br. s, 1H), 8,19 (s, 1H), 7,44 (s, 1H), 7,36 (s, 1H), 6,89 (s, 1H), 6,30 (br. s, 1H), 4,63 (br. s, 1H), 3,40 (br. s, 8H), 2,46 (s, 3H) ppm.

Ejemplo 86

[4-amino-6-(etoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f]-[1,2,4]triazin-7-il]metanol



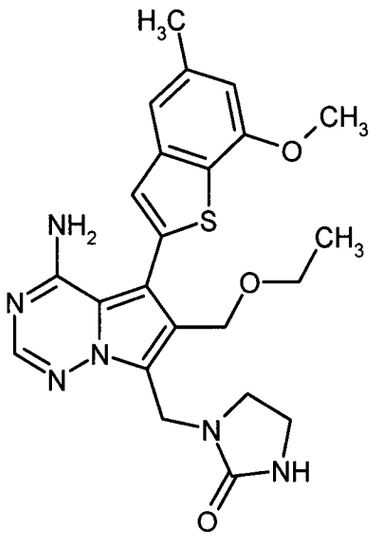
El compuesto del título (360 mg) se obtuvo en forma de un subproducto en la preparación del ejemplo 5 por el procedimiento de preparación 1.

LC-MS (procedimiento 2): Tr = 0,99 min; MS (ESIpos): m/z = 399 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,09-7,72 (br. s, 1H), 7,99 (s, 1H), 7,35 (s, 1H), 7,31 (s, 1H), 6,84 (s, 1H), 6,05-5,48 (br. s, 1H), 5,04 (br. s, 1H), 4,81 (d, 2H), 4,47 (s, 2H), 3,96 (s, 3H), 3,39 (q, 3H), 2,45 (s, 3H), 1,05 (t, 3H) ppm.

Ejemplo 87

1-{[4-amino-6-(etoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f]-[1,2,4]triazin-7-il]metil}imidazolidin-2-ona



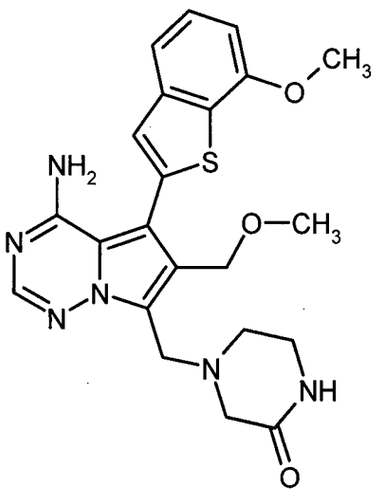
Una suspensión del intermediario 63A (100 mg, 0,221 mmoles) en THF (5 ml) se trató con imidazolidin-2-ona (57 mg, 0,662 mmoles) y *N,N*-diisopropiletilamina (153 µl, 0,926 mmoles), y la mezcla se calentó hasta 150°C durante 90 min en un horno de microondas. Después de esto, la mezcla de reacción se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 40-60% acetonitrilo/0,2% de ácido trifluoroacético ac.). El producto obtenido de este modo se disolvió en metanol y se filtró a través de un cartucho de intercambio aniónico (Stratospheres SPE, PL-HCO_3 MP-resina). El cartucho se eluyó con metanol, y el filtrado se evaporó. El producto se purificó una vez nuevamente por cromatografía de capa delgada preparativa sobre gel de sílice (ciclohexano/acetato de etilo 3:1) dando 24 mg (22% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,99 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,21-7,65 (br. s, 1H), 7,99 (s, 1H), 7,36 (s, 1H), 7,31 (s, 1H), 6,84 (s, 1H), 6,38 (s, 1H), 6,04-5,56 (br. s, 1H), 4,65 (s, 2H), 4,46 (s, 2H), 3,95 (s, 3H), 3,38 (q, 2H), 3,31-3,10 (m, 4H), 2,45 (s, 3H), 1,06 (t, 3H) ppm.

Ejemplo 88

4-{[4-amino-5-(7-metoxi-1-benzotiofen-2-il)-6-(metoximetil)pirrolo[2,1-f][1,2,4]-triazin-7-il]metil}piperazin-2-ona



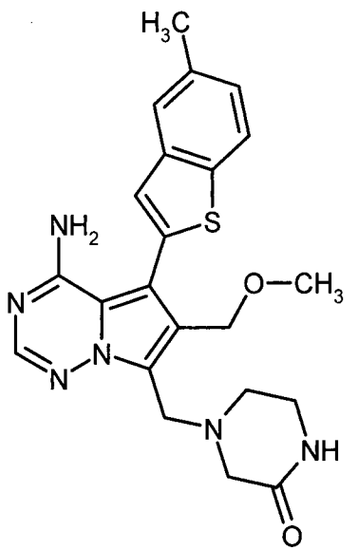
A una solución del intermediario 62A (72,6 mg, 197 µmoles), el ácido (7-metoxi-1-benzotiofen-2-il)borónico (45 mg, 216 µmoles) y fluoruro de cesio (149 mg, 983 µmoles) en THF desgasificado/agua (10:1, 2,2 ml) bajo argón se agregó (2'-aminobifenil-2-il)(cloro)paladio-diciclohexil(2',4',6'-triisopropilbifenil-2-il)fosfina (1:1; 7,7 mg, 9,8 µmoles; véase S. L. Buchwald *et al.*, *J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)). La mezcla resultante se desgasificó nuevamente y se agitó bajo argón a 60°C durante 3 h. Después de esto, la mezcla se separó por RP-HPLC preparativa (Reprosil C18, gradiente 20-40% acetonitrilo/0,1% TFA ac.). Las fracciones del producto se combinaron y se evaporaron hasta sequedad. El residuo se disolvió en metanol y se filtró a través de un cartucho de intercambio aniónico (Stratospheres SPE, PL-HCO_3 MP-resina). El cartucho se eluyó con metanol, y el filtrado se evaporó dando 31 mg (35% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,71 min; MS (ESIpos): m/z = 453 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,00 (s, 1H), 7,72 (s, 1H), 7,61-8,23 (br. s, 1H), 7,51 (d, 1H), 7,46 (s, 1H), 7,40 (t, 1H), 6,99 (d, 1H), 5,57-6,11 (br. s, 1H), 4,42 (s, 2H), 3,98 (s, 5H), 3,20 (s, 3H), 3,11 (br. m, 2H), 3,01 (s, 2H), 2,62-2,67 (m, 2H) ppm.

Ejemplo 89

4-{[4-amino-6-(metoximetil)-5-(5-metil-1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]-triazin-7-il]metil}piperazin-2-ona



A una solución del intermediario 62A (50 mg, 135 µmoles), el ácido (5-metil-1-benzotiofen-2-il)borónico (28,6 mg, 149 µmoles) y fluoruro de cesio (103 mg, 677 µmoles) en THF desgasificado/agua (10:1, 4,4 ml) bajo argón se agregó (2'-aminobifenil-2-il)(cloro)paladio-diciclohexil(2',4',6'-triisopropilbifenil-2-il)fosfina (1:1; 5,3 mg, 6,8 µmoles; véase S. L. Buchwald *et al.*, *J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)). La mezcla resultante se desgasificó nuevamente y se agitó bajo argón a 60°C durante 16 h. Después de esto, la mezcla se separó por RP-HPLC preparativa (Reprosil C18, gradiente 30-50% acetonitrilo/0,1% TFA ac.). Las fracciones del producto se combinaron y se evaporaron hasta sequedad. El residuo se disolvió en metanol y se filtró a través de un cartucho de intercambio aniónico (StratoSpheres SPE, PL-HCO_3 MP-resina). El cartucho se eluyó con metanol, y el filtrado se evaporó dando 27 mg (45% de teor.) del compuesto del título.

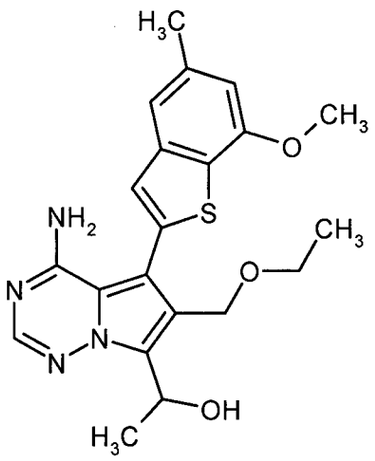
LC-MS (procedimiento 2): Tr = 0,79 min; MS (ESIpos): m/z = 437 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,00 (s, 1H), 7,89 (d, 1H), 7,73 (s, 1H), 7,71 (s, 1H), 7,58-8,18 (br. s, 1H), 7,40 (s, 1H), 7,24 (dd, 1H), 5,58-6,03 (m, 1H), 4,42 (s, 2H), 3,97 (s, 2H), 3,21 (s, 3H), 3,11 (br. t, 2H), 3,01 (s, 2H), 2,64 (t, 2H), 2,44 (s, 3H) ppm.

Ejemplo 90

1-[4-amino-6-(etoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f]-

[1,2,4]triazin-7-il]etanol



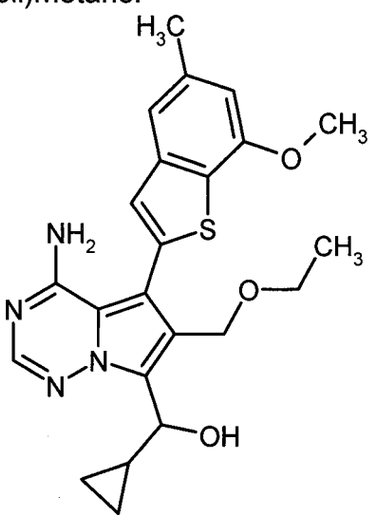
Bajo argón, una solución 1M de bromuro de metilmagnesio en THF (630 µl, 630 µmoles) se agregó gota a gota a ta a una solución del intermediario 17A (100 mg, 252 µmoles) en THF (10 ml). La mezcla se agitó a ta durante 3 h y posteriormente se trató con otra porción de bromuro de metilmagnesio en THF (177 µl, 177 µmoles). La mezcla de reacción se agitó durante otras 16 h, posteriormente se templó con solución de cloruro de amonio acuosa saturada y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron con sulfato de magnesio, se filtraron y se evaporaron. El residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 40-60% acetonitrilo/0,1% TFA ac.). Las fracciones del producto se diluyeron con solución de hidrógeno carbonato de sodio acuosa saturada y se extrajeron con acetato de etilo. La fase orgánica se lavó con solución de cloruro de sodio acuosa saturada, se secó con sulfato de magnesio, se filtró y se evaporó dando 39 mg (36% de teor.) del compuesto del título.

LC-MS (procedimiento 4): Tr = 1,07 min; MS (ESIpos): m/z = 413 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,95 (s, 1H), 7,56-8,07 (br. s, 1H), 7,35 (s, 1H), 7,31 (s, 1H), 6,84 (s, 1H), 5,46-5,54 (m, 1H), 5,37-5,95 (br. s, 1H), 5,26 (d, 1H), 4,67 (d, 1H), 4,38 (d, 1H), 3,95 (s, 3H), 3,38 (q, 2H), 2,45 (s, 3H), 1,52 (d, 3H), 1,05 (t, 3H) ppm.

Ejemplo 91

[4-amino-6-(etoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f]-[1,2,4]triazin-7-il](ciclopropil)metanol



Bajo argón, una solución 0,5 M de bromuro de ciclopropilmagnesio en THF (1,26 ml, 630 µmoles) se agregó gota a gota a ta a una solución del intermediario 17A (100 mg, 252 µmoles) en THF (5 ml). La mezcla se agitó a ta durante 1 h, posteriormente se templó con solución de cloruro de amonio acuosa saturada y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secaron con sulfato de magnesio, se filtraron y se evaporaron. El residuo se purificó por RP-HPLC preparativa (Reprosil C18, gradiente 50-70% acetonitrilo/0,1% TFA ac.). Las fracciones del producto se diluyeron con solución de hidrógeno carbonato de sodio acuosa saturada y se extrajeron con acetato de etilo. La fase orgánica se lavó con solución de cloruro de sodio acuosa saturada, se secó con sulfato de magnesio, se filtró y se evaporó dando 10 mg (10% de teor.) del compuesto del título.

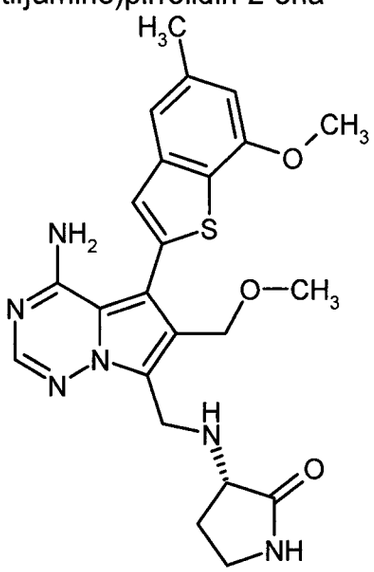
LC-MS (procedimiento 2): Tr = 1,13 min; MS (ESIpos): m/z = 439 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,94 (s, 1H), 7,68-8,04 (br. s, 1H), 7,36 (s, 1H), 7,31 (s, 1H), 6,84 (s, 1H), 5,47-5,89 (br. s, 1H), 5,30 (d, 1H), 4,64 (d, 1H), 4,59-4,67 (m, 1H), 4,39 (d, 1H), 3,96 (s, 3H), 3,38 (q, 2H), 2,45 (s, 3H), 1,54-1,64 (m, 1H), 1,04 (t, 3H), 0,51-0,59 (m, 1H), 0,40-0,47 (m, 1H), 0,28-0,38 (m,

2H) ppm.

Ejemplo 92

(*3S*)-3-({[4-amino-6-(metoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo-[2,1-f][1,2,4]triazin-7-il]metil}amino)pirrolidin-2-ona



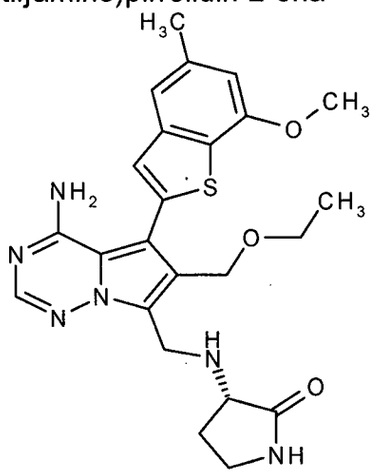
Una suspensión del intermediario 13A (100 mg, 0,233 mmoles) en THF (2 ml) se trató con (*S*)-3-aminopirrolidin-2-ona (35 mg, 0,349 mmoles), triacetoxiborohidruro de sodio (148 mg, 0,698 mmoles) y ácido acético (26,6 µl, 0,465 mmoles). La mezcla resultante se agitó a ta durante 3 h y posteriormente se purificó directamente por RP-HPLC preparativa (Reprosil C18, gradiente 40-60% acetonitrilo/0,2% ácido trifluoroacético ac.). Las fracciones del producto se combinaron y se evaporaron hasta sequedad. El residuo se disolvió en metanol y se filtró a través de un cartucho de intercambio aniónico (Stratospheres SPE, PL-HCO_3 MP-resina). El cartucho se eluyó con metanol, y el filtrado se evaporó dando 56 mg (51% de teor.) del compuesto del título.

LC-MS (procedimiento 4): Tr = 0,72 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,01 (s, 1H), 7,76 (s, 1H), 7,35 (s, 1H), 7,31 (s, 1H), 6,85 (s, 1H), 4,48 (d, 2H), 4,43 (d, 2H), 4,24-4,02 (m, 2H), 3,96 (s, 3H), 3,26-2,99 (m, 6H), 2,45 (s, 3H), 2,40-2,27 (m, 1H), 1,82-1,64 (m, 1H) ppm.

Ejemplo 93

(*3S*)-3-({[4-amino-6-(etoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo-[2,1-f][1,2,4]triazin-7-il]metil}amino)pirrolidin-2-ona



Una suspensión del intermediario 17A (100 mg, 0,252 mmoles) en THF (2 ml) se trató con (*S*)-3-aminopirrolidin-2-ona (38 mg, 378 µmoles), triacetoxiborohidruro de sodio (160 mg, 757 µmoles) y ácido acético (30 µl, 504 µmoles). La mezcla resultante se agitó a ta durante 3 h y posteriormente se purificó directamente por RP-HPLC preparativa (Reprosil C18, gradiente 30-50% acetonitrilo/0,2% de ácido trifluoroacético ac.). Las fracciones del producto se combinaron y se evaporaron hasta sequedad. El residuo se disolvió en metanol y se filtró a través de un cartucho de intercambio aniónico (Stratospheres SPE, PL-HCO_3 MP-resina). El cartucho se eluyó con metanol, y el filtrado se evaporó dando 84 mg (69% de teor.) del compuesto del título.

LC-MS (procedimiento 4): Tr = 0,75 min; MS (ESIpos): m/z = 481 $(M+H)^+$

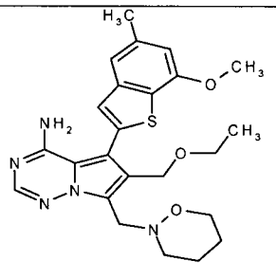
^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,00 (s, 1H), 7,75 (s, 1H), 7,67-8,11 (br. s, 1H), 7,35 (s, 1H), 7,31 (s, 1H), 6,85 (s, 1H), 5,5-6,0 (br. s, 1H), 4,44 (q, 2H), 4,14-4,21 (m, 1H), 4,02-4,11 (m, 1H), 3,38-3,45 (q, 2H), 3,16-3,24 (m, 1H), 3,05-3,16 (m, 2H), 2,45 (s, 3H), 2,31-2,40 (m, 1H), 1,67-1,79 (m, 1H), 1,08 (t, 3H) ppm.

Procedimiento general para la preparación de los ejemplos 94–105 en la tabla I:

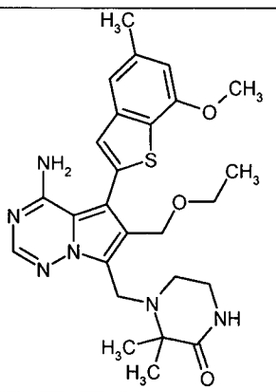
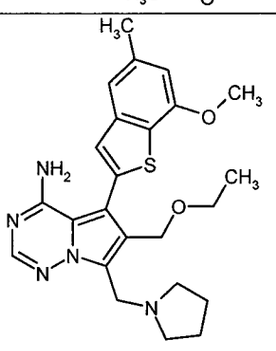
Una suspensión 0,13 M del intermediario 17A en THF se trató con 1,5 eq. del

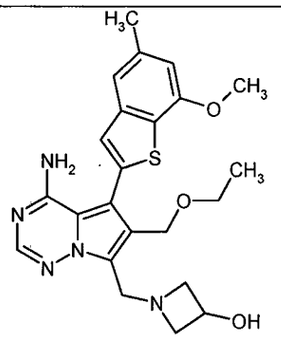
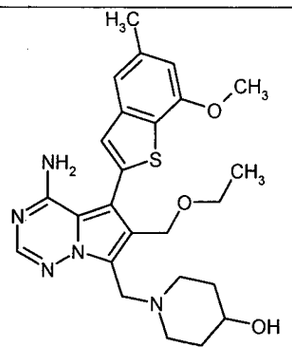
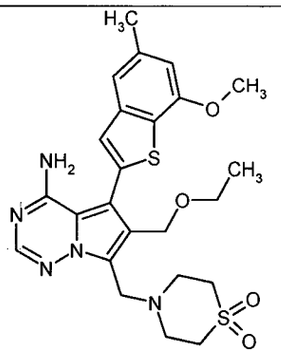
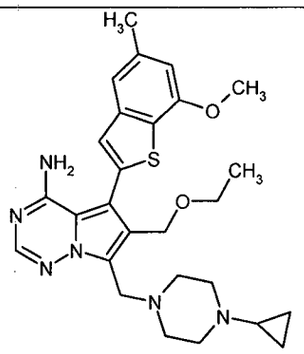
respectivo componente de amina, 3 eq. de triacetoxiborohidruro de sodio y 1,5 eq. de ácido acético. La mezcla resultante se agitó a 60°C durante 3–20 h. Después de esto, se llevó a cabo la purificación de acuerdo con los procedimientos indicados.

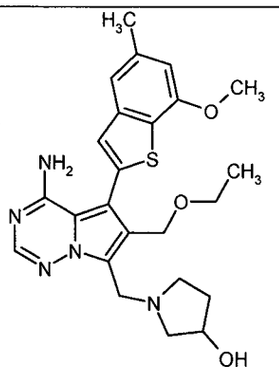
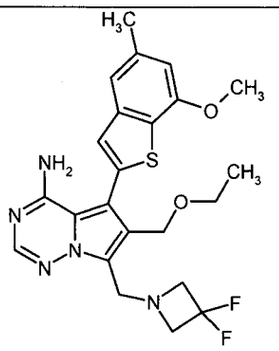
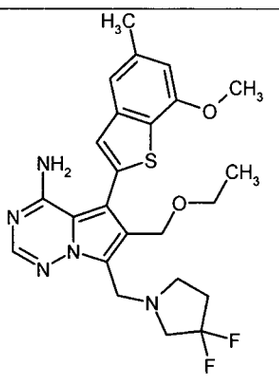
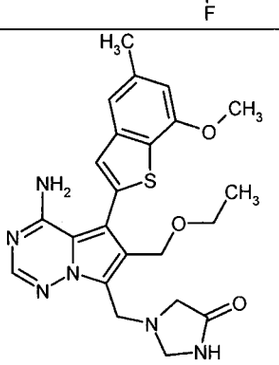
Tabla I

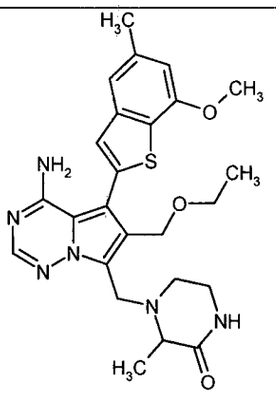
Ejemplo Nº.	Estructura	Procedimiento(s) de purificación	Datos de LC-MS
94		P1, P5	Procedimiento 4: Tr = 1,22 min; MS (ESIpos): m/z = 468 $(M+H)^+$

(Continuación)

Ejemplo Nº.	Estructura	Procedimiento(s) de purificación	Datos de LC-MS
95		P6, P3	Procedimiento 2: Tr = 0,92 min; MS (ESIpos): m/z = 509 $(M+H)^+$
96		P1, P5	Procedimiento 4: Tr = 0,83 min; MS (ESIpos): m/z = 452 $(M+H)^+$

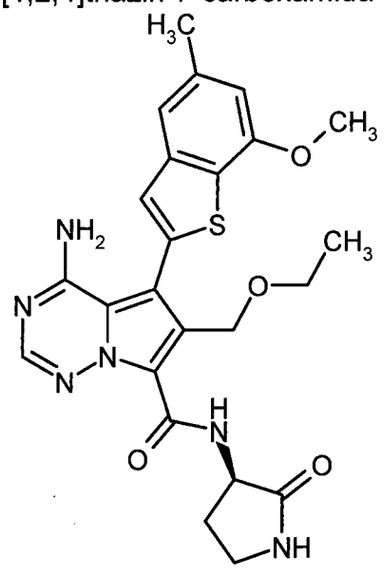
(Continuación)			
Ejemplo Nº.	**Estructura**	**Procedimiento(s) de purificación**	**Datos de LC-MS**
97		P1, P5	Procedimiento 5: Tr = 1,84 min; MS (ESIpos): m/z = 454 $(M+H)^+$
98		P1, P5	Procedimiento 5: Tr = 1,82 min; MS (ESIpos): m/z = 482 $(M+H)^+$
99		P1, P5	Procedimiento 5: Tr = 2,21 min; MS (ESIpos): m/z = 516 $(M+H)^+$
100		P1, P5	Procedimiento 2: Tr = 0,86 min; MS (ESIpos): m/z = 507 $(M+H)^+$

(Continuación)			
Ejemplo Nº.	**Estructura**	**Procedimiento(s) de purificación**	**Datos de LC-MS**
101		P1, P5	Procedimiento 2: Tr = 0,81 min; MS (ESIpos): m/z = 468 $(M+H)^+$
102		P1, P5, P4	Procedimiento 2: Tr = 1,03 min; MS (ESIpos): m/z = 474 $(M+H)^+$
103		P1, P5, P2	Procedimiento 2: Tr = 1,05 min; MS (ESIpos): m/z = 460 $(M+H)^+$
104		P1, P6	Procedimiento 2: Tr = 0,91 min; MS (ESIpos): m/z = 467 $(M+H)^+$

(Continuación)			
Ejemplo Nº.	**Estructura**	**Procedimiento(s) de purificación**	**Datos de LC-MS**
105		P1, P6	Procedimiento 2: Tr = 0,89 min; MS (ESIpos): m/z = 495 $(M+H)^+$

Ejemplo 106

4-amino-6-(etoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)-*N*-[(*3R*)-2-oxo-pirrolidin-3-il]pirrolo[2,1-f][1,2,4]triazin-7-carboxamida



Una solución agitada del intermediario 64A (50 mg, 121 µmoles) en DMF (2 ml) se trató a ta con *N*-[(1*H*-benzotriazol-1-iloxi)(dimetilamino)metilene]-*N*-metilmetanaminio tetrafluoroborato (TBTU) (43 mg, 133 µmoles) y DIPEA (53 µl, 303 µmoles). Después de 15 min, se agregó (*3R*)-3-aminopirrolidin-2-ona (24 mg, 242 µmoles) , y la mezcla resultante se agitó a ta durante otros 2 h. Después de esto, la mezcla se separó por RP-HPLC preparativa (Reprosil

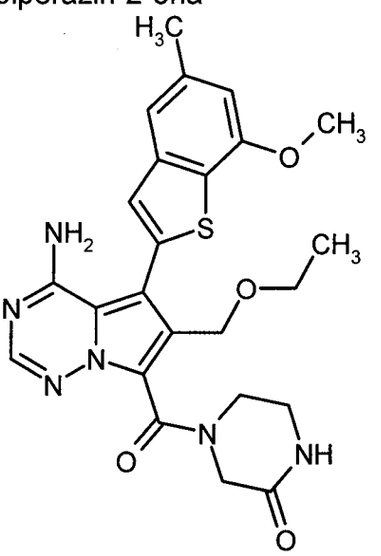
C18, gradiente 30-50% acetonitrilo/0,2% de ácido trifluoroacético ac.). Las fracciones del producto se combinaron y se evaporaron hasta sequedad. El residuo se disolvió en metanol y se filtró a través de un cartucho de intercambio aniónico (Stratospheres SPE, PL-HCO_3 MP-resina). El cartucho se eluyó con metanol, y el filtrado se evaporó dando 36 mg (60% de teor.) del compuesto del título.

LC-MS (procedimiento 2): Tr = 0,91 min; MS (ESIpos): m/z = 495 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 9,50 (d, 1H), 8,21-8,45 (br. s, 1H), 8,17 (s, 1H), 7,97 (s, 1H), 7,41 (s, 1H), 7,33 (s, 1H), 6,86 (s, 1H), 5,84-6,09 (br. s, 1H), 4,74 (dd, 2H), 4,47-4,56 (m, 1H), 3,96 (s, 3H), 3,37 (q, 2H), 3,22-3,29 (m, 2H), 2,54-2,61 (m, 1H), 2,46 (s, 3H), 1,90-2,03 (m, 1H), 1,00 (t, 3H) ppm.

Ejemplo 107

4-{[4-amino-6-(etoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f]-[1,2,4]triazin-7-il]carbonil}piperazin-2-ona



Una solución agitada del intermediario 64A (50 mg, 121 µmoles) en DMF (2 ml) se trató a ta con TBTU (43 mg, 133 µmoles) y DIPEA (53 µl, 303 µmoles). Después de 15 min, piperazin-2-ona (24 mg, 242 µmoles) se agregó, y la mezcla resultante se agitó a ta durante otros 16 h. Después de esto, la mezcla se separó por RP-HPLC preparativa (Reprosil C18, gradiente 40-60% acetonitrilo/0,2% ácido trifluoroacético ac.). Las fracciones del producto se

combinaron y se evaporaron hasta sequedad. El residuo se disolvió en metanol y se filtró a través de un cartucho de intercambio aniónico (Strato-spheres SPE, PL-HCO_3 MP-resina). El cartucho se eluyó con metanol, y el filtrado se evaporó dando 45 mg (68% de teor.) del compuesto del título.

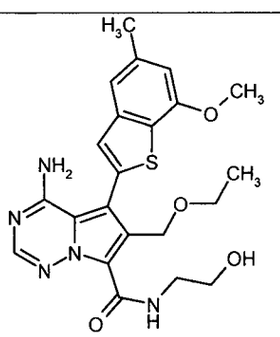
LC-MS (procedimiento 2): Tr = 0,92 min; MS (ESIpos): m/z = 495 $(M+H)^+$

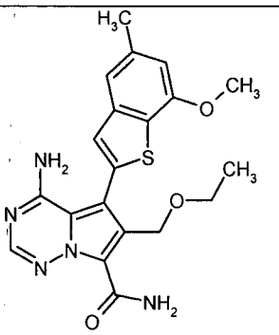
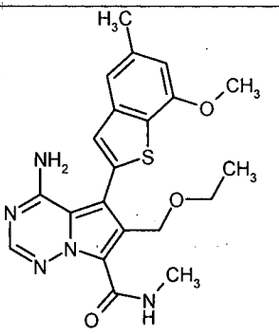
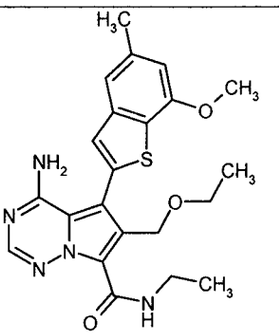
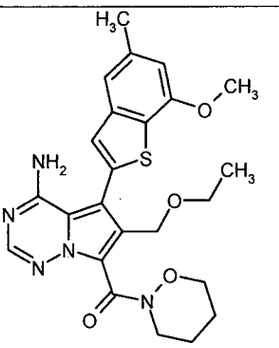
^{1}H-RMN (400 MHz, DMSO-d_6): δ = 8,14 (br. s, 1H), 7,99-8,01 (m, 1H), 7,9-8,3 (br. s, 1H), 7,41 (d, 1H), 7,32 (s, 1H), 6,86 (s, 1H), 5,78-6,05 (br. s, 1H), 4,30-4,49 (m, 2H), 4,13-4,23 (m, 1H), 4,03-4,10 (m, 1H), 3,96 (s, 3H), 3,76-3,87 (m, 1H), 3,57-3,74 (m, 1H), 3,35-3,43 (m, 2H), 3,14-3,25 (m, 1H), 2,45 (s, 3H), 0,96-1,05 (m, 3H) ppm.

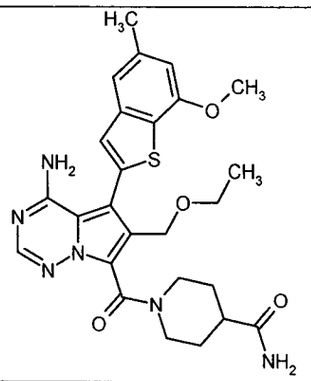
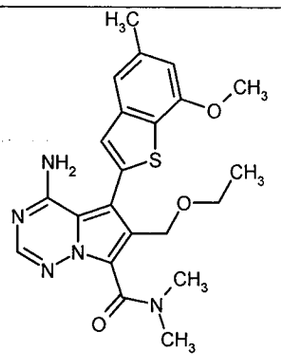
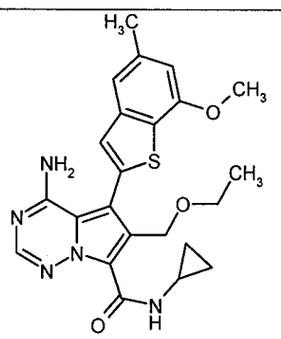
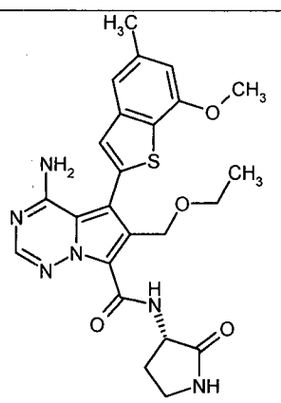
Procedimiento general para la preparación de los ejemplos 108–123 en la tabla II:

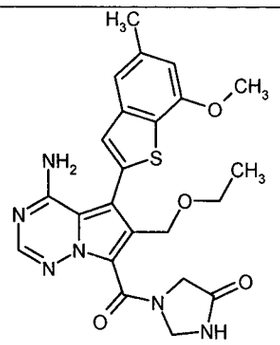
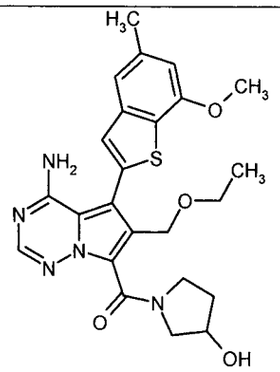
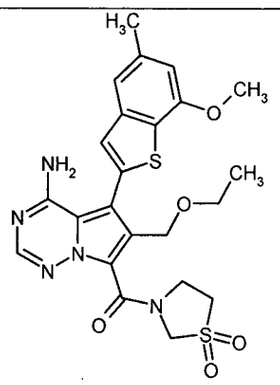
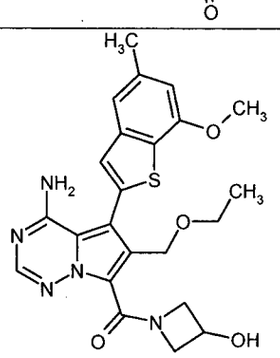
Una solución 0,13 M del intermediario 64A en DMF se trató con 1,1 eq. TBTU y 2,5 eq. DIPEA y se agitó a ta durante 15 min. Se agregaron 2 eq. de la respectiva amina, y la mezcla resultante se agitó a ta durante otros 18 h. Después de esto, se llevó a cabo la purificación de acuerdo con los procedimientos indicados.

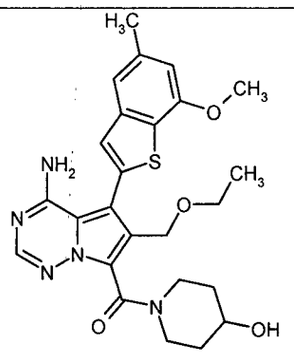
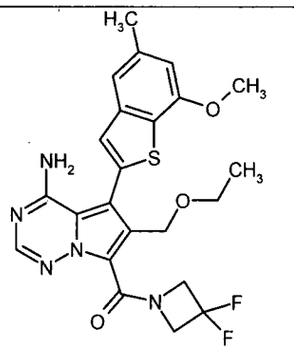
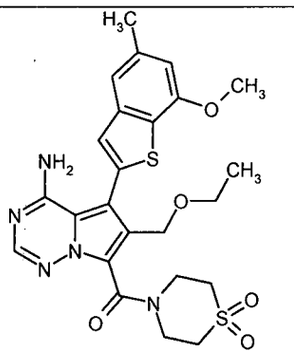
Tabla II

Ejemplo Nº.	Estructura	Procedimiento(s) de purificación	Datos de LC-MS
108		P1	Procedimiento 2: Tr = 1,02 min; MS (ESIpos): m/z = 456 $(M+H)^+$

(Continuación)			
Ejemplo Nº.	**Estructura**	**Procedimiento(s) de purificación**	**Datos de LC-MS**
109		P1	Procedimiento 4: Tr = 0,97 min; MS (ESIpos): m/z = 412 $(M+H)^+$
110		P1, P5	Procedimiento 2: Tr = 1,01 min; MS (ESIpos): m/z = 426 $(M+H)^+$
111		P1, P5	Procedimiento 4: Tr = 1,11 min; MS (ESIpos): m/z = 440 $(M+H)^+$
112		P1	Procedimiento 4: Tr = 1,07 min; MS (ESIpos): m/z = 482 $(M+H)^+$

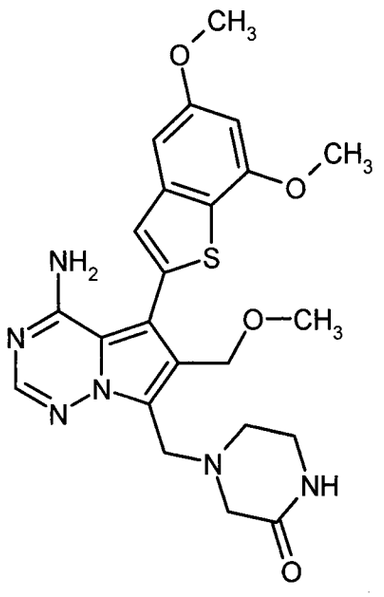
(Continuación)			
Ejemplo Nº.	**Estructura**	**Procedimiento(s) de purificación**	**Datos de LC-MS**
113		P1, P5	Procedimiento 2: Tr = 0,84 min; MS (ESIpos): m/z = 523 $(M+H)^+$
114		P1, P5	Procedimiento 2: Tr = 0,96 min; MS (ESIpos): m/z = 440 $(M+H)^+$
115		P1, P5	Procedimiento 2: Tr = 1,09 min; MS (ESIpos): m/z = 452 $(M+H)^+$
116		P1, P5	Procedimiento 4: Tr = 0,95 min; MS (ESIpos): m/z = 495 $(M+H)^+$

(Continuación)			
Ejemplo Nº.	**Estructura**	**Procedimiento(s) de purificación**	**Datos de LC-MS**
117		P1, P5	Procedimiento 4: Tr = 0,93 min; MS (ESIpos): m/z = 481 $(M+H)^+$
118		P1, P5	Procedimiento 2: Tr = 0,93 min; MS (ESIpos): m/z = 482 $(M+H)^+$
119		P1, P5	Procedimiento 2: Tr = 1,04 min; MS (ESIpos): m/z = 516 $(M+H)^+$
120		P1, P5	Procedimiento 4: Tr = 0,88 min; MS (ESIpos): m/z = 468 $(M+H)^+$

(Continuación)			
Ejemplo Nº.	**Estructura**	**Procedimiento(s) de purificación**	**Datos de LC-MS**
121		P1, P5	Procedimiento 4: Tr = 0,91 min; MS (ESIpos): m/z = 496 $(M+H)^+$
122		P1, P5	Procedimiento 4: Tr = 1,09 min; MS (ESIpos): m/z = 488 $(M+H)^+$
123		P1, P5	Procedimiento 4: Tr = 0,98 min; MS (ESIpos): m/z = 530 $(M+H)^+$

Ejemplo 124

4-{[4-amino-5-(5,7-dimetoxi-1-benzotiofen-2-il)-6-(metoximetil)pirrolo[2,1-f]-[1,2,4]triazin-7-il]metil}piperazin-2-ona



A una solución del intermediario 62A (100 mg, 271 µmoles), el Intermediario 66A (77 mg, 325 µmoles) y fluoruro de cesio (206 mg, 1,35 mmoles) en THF desgasificado/agua (10:1; 5 ml) bajo argón se agregó (2'-aminobifenil-2-il)-(cloro)paladio-diciclohexil(2',4',6'-triisopropilbifenil-2-il)fosfina (1:1; 42,6 mg, 54 µmoles; véase S. L. Buchwald *et al.*, *J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)). La mezcla resultante se desgasificó nuevamente y se agitó bajo argón a 60°C durante 6 h. Posteriormente, se agregó otra porción del intermediario 66A (39 mg, 162 µmoles), y la agitación a 60°C continuó durante 10 h. Después de esto, la mezcla de reacción se separó por RP-HPLC preparativa (Reprosil C18, gradiente 30-50% acetonitrilo/0,1% TFA ac.). Las fracciones del producto se combinaron y se evaporaron hasta sequedad. El residuo se disolvió en metanol y se filtró a través de un cartucho de intercambio aniónico (Stratospheres SPE, PL-HCO_3 MP-resina). El cartucho se eluyó con metanol, y el filtrado se evaporó dando 40 mg (28% de teor.) del compuesto del título.

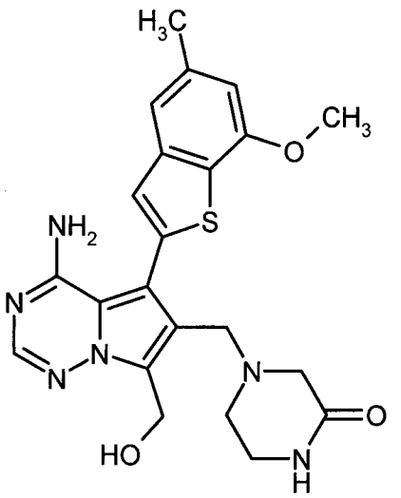
LC-MS (procedimiento 2): Tr = 0,78 min; MS (ESIpos): m/z = 483 $(M+H)^+$

^{1}H-RMN (500 MHz, DMSO-d_6): δ = 7,99 (s, 1H), 7,68 (br. s, 1H), 7,49-8,17 (br. s, 1H), 7,37 (s, 1H), 7,05 (d, 1H), 6,63 (d, 1H), 5,5-6,0 (br. s, 1H), 4,42 (s, 2H), 3,97 (s, 2H), 3,94 (s, 3H), 3,84 (s, 3H), 3,20 (s, 3H), 3,09-3,14 (m, 2H), 3,01 (s,

2H), 2,62-2,67 (m, 2H) ppm.

Ejemplo 125

4-{[4-amino-7-(hidroximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f]-[1,2,4]triazin-6-il]metil}piperazin-2-ona



A una suspensión del intermediario 70A (700 mg, 1,49 mmoles), el intermediario 5A (497 mg, 2,24 mmoles) y fluoruro de cesio (1,36 g, 8,95 mmoles) en THF desgasificado/agua (2:1, 90 ml) bajo argón se agregó (2'-aminobifenil-2-il)(cloro)paladio-diciclohexil(2',4',6'-triisopropilbifenil-2-il)fosfina (1:1; 117 mg, 0,149 mmoles; véase S. L. Buchwald *et al.*, *J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)). La mezcla resultante se desgasificó nuevamente y se agitó bajo argón a 60°C durante toda la noche. Otra porción del intermediario 5A (231 mg, 1,04 mmoles) y (2'-aminobifenil-2-il)-(cloro)paladio-diciclohexil(2',4',6'-triisopropilbifenil-2-il)fosfina (1:1; 117 mg, 0,149 mmoles) se agregaron, y se continuó con la agitación a 60°C durante 3 h. El precipitado se filtró, se lavó con THF y se secó al vacío. El sólido se suspendió en mixture de DMF y 1 M de ácido trifluoroacético ac. y se filtró. El filtrado se separó por RP-HPLC preparativa (Reprosil C18, gradiente 20-40% acetonitrilo/0,2% de ácido trifluoroacético acuoso). Las fracciones del producto se combinaron y posteriormente se alcalizaron por la adición de solución de bicarbonato de sodio acuosa saturada. La solución se extrajo con acetato de etilo, y la capa orgánica se lavó con salmuera, se secaron sobre sulfato de

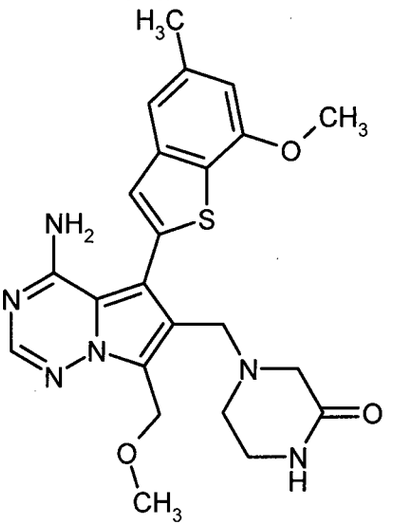
magnesio y se evaporaron para dar 88 mg del compuesto del título (13% de teor.).

LC-MS (procedimiento 2): Tr = 0,70 min; MS (ESIpos): m/z = 453 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): *inter al.* δ = 7,6-8,0 (br. s, 1H), 7,98 (s, 1H), 7,71 (s, 1H), 7,37 (s, 1H), 7,31 (s, 1H), 6,84 (s, 1H), 5,4-5,8 (br. s, 1H), 5,19 (t, 1H), 4,85 (d, 2H), 3,95 (s, 3H), 3,58 (s, 2H), 3,04 (br. m, 2H), 2,88 (s, 2H), 2,45 (s, 3H) ppm.

Ejemplo 126

4-{[4-amino-7-(metoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f]-[1,2,4]triazin-6-il]metil}piperazin-2-ona



Una suspensión del ejemplo 125 (88 mg, 194 µmoles) en diclorometano (5 ml) se trató con cloruro de tionilo (29 µl, 389 µmoles), y la mezcla se agitó a ta durante 65 min. Se agregó otra porción de cloruro de tionilo (29 µl, 389 µmoles), y se continuó con la agitación durante 1,5 h. Un exceso de metanol se agregó posteriormente, seguido de la adición gota a gota de una solución 5,4 M de metilato de sodio en metanol (84 mg, 1,56 mmoles) hasta que se alcanzó pH 8. Después de agitar durante 3 días, los volátiles se evaporaron a presión reducida, y el residuo se separó por RP-HPLC preparativa (Reprosil C18, gradiente 20-40% acetonitrilo/0,2% de ácido trifluoroacético ac.). Las fracciones del producto se evaporaron para dar 19 mg del compuesto del título

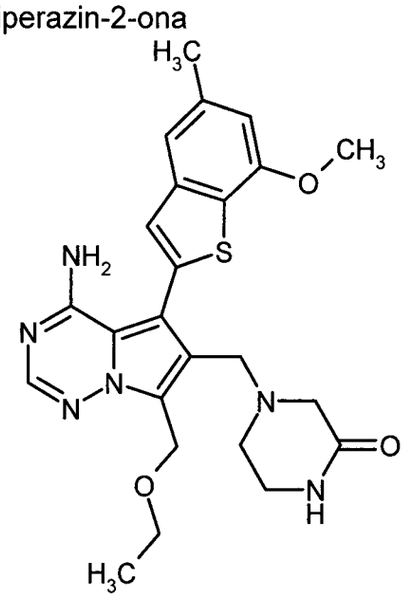
(21% de teor.).

LC-MS (procedimiento 2): Tr = 0,77 min; MS (ESIpos): m/z = 466 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,99 (s, 1H), 7,75-8,11 (br. s, 1H), 7,68 (s, 1H), 7,38 (s, 1H), 7,31 (s, 1H), 6,84 (s, 1H), 5,51-5,82 (m, 1H), 4,77 (s, 2H), 3,95 (s, 3H), 3,55 (s, 2H), 3,31 (s, 3H), 3,04 (br. s, 2H), 2,85 (s, 2H), 2,42-2,48 (m, 5H) ppm.

Ejemplo 127

4-{[4-amino-7-(etoximetil)-5-(7-metoxi-5-metil-1-benzotiofen-2-il)pirrolo[2,1-f]-[1,2,4]triazin-6-il]metil}piperazin-2-ona



Una suspensión del ejemplo 125 (100 mg, 221 µmoles) en diclorometano (10 ml) se trató con cloruro de tionilo (161 µl, 2,21 mmoles), y la mezcla se agitó a ta durante 30 min. Se agregó etanol, y los volátiles se evaporaron a presión reducida. El residuo se disolvió en etanol (10 ml), se agregó etilato de sodio (30 mg, 442 µmoles), y la mezcla se agitó a ta durante 1 h. La mezcla se separó posteriormente directamente por RP-HPLC preparativa (Reprosil C18, gradiente 20-40% acetonitrilo/0,2% de ácido trifluoroacético ac-). Las fracciones del producto se combinaron y se alcalizaron por la adición de solución de bicarbonato de sodio acuosa saturada. La solución se extrajo con acetato de etilo, y la capa orgánica se lavó con salmuera, se secó sobre sulfato de magnesio y se evaporó para dar 57 mg del compuesto del título

(54% de teor.).

LC-MS (procedimiento 2): Tr = 0,85 min; MS (ESIpos): m/z = 480 $(M+H)^+$

^{1}H-RMN (400 MHz, DMSO-d_6): δ = 7,99 (s, 1H), 7,75-8,09 (br. s, 1H), 7,64-7,71 (m, 1H), 7,38 (s, 1H), 7,31 (s, 1H), 6,84 (s, 1H), 5,38-5,91 (br. s, 1H), 4,81 (s, 2H), 3,95 (s, 3H), 3,49-3,59 (m, 4H), 2,99-3,08 (m, 2H), 2,86 (s, 2H), 1,12 (t, 3H) ppm.

B. Evaluación de la actividad biológica

Abreviaturas y acrónimos:

Ahx	ácido 6-aminohexanoico
ATP	adenosina trifosfato
BSA	albúmina de suero de bovino
CREB	proteína de unión al elemento de respuesta cAMP
DMSO	dimetilsulfóxido
EDTA	ácido etilendiaminotetraacético
EGTA	Ácido etilenglicol-bis(2-aminoetil éter)-N,N,N',N'-tetraacético
FBS	suero de bovino fetal
FGF	factor de crecimiento del fibroblasto
FGFR	receptor del factor de crecimiento del fibroblasto
GFP	proteína fluorescente verde
GST	glutationa S-transferasa
HEPES	ácido 4-(2-hidroxietil)piperazina-1-etansulfónico
HRTF	fluorescencia resuelta en tiempo homogéneo
MOPS	ácido 3-(N-morfolino)propanosulfónico
mTOR	blanco mamífero de rapamicina
PBS	solución salina tamponada con fosfato
PI3K	fosfatidilinositol 3-quinasa
RTK	receptor tirosina quinasa
SNP	polimorfismo de nucleótido simple

TR-FRET	transferencia de energía de resonancia por fluorescencia de resolución temporal
VEGF	factor de crecimiento endotelial vascular
VEGFR	receptor del factor de crecimiento endotelial vascular

La demostración de la actividad de los compuestos de la presente invención se puede obtener a través de ensayos in vitro, ex vivo, e in vivo que son bien conocidos en la técnica. Por ejemplo, para demostrar la actividad de los compuestos de la presente invención, se pueden usar los siguientes ensayos.

B-1. Ensayo de ATP quinasa alta del FGFR-1

La actividad inhibidora del FGFR-1 a elevada concentración de ATP de los compuestos de la presente invención después de su pre-incubación con FGFR-1 se cuantificó empleando el ensayo ATP alto del FGFR-1 basado en la TR-FRET como se describe en los siguientes párrafos:

Una proteína de fusión del FGFR-1 marcada recombinante [fusión de glutationa-S-transferasa (GST) (N-terminal), sitio de escisión de la trombina, marca His6, y la parte intracelular del FGFR-1 humano de los aminoácidos G400 a R800 como en la entrada del GenBank NM_015850], que se expresa en las células de insectos SF9 usando el sistema de expresión baculovirus y se purifica mediante la cromatografía por afinidad de glutationa-agarosa, se adquirió de Proqinase (producto nº. 0101-0000-1) y se usó como enzima. Como sustrato para la reacción de quinasa, se usó el péptido biotinilado biotin-Ahx-AAEEEYFFLFAKKK (C-terminal en forma de amida) el cual se adquirió, por ej., de Biosyntan (Berlin-Buch, Alemania).

Usualmente, los compuestos de ensayo se ensayaron en la misma placa de microtítulos a 11 concentraciones diferentes en el intervalo de 20 µM a 0,1 nM (por ej., 20 µM, 5,9 µM, 1,7 µM, 0,51 µM, 0,15 µM, 44 nM, 13 nM, 3,8 nM, 1,1 nM, 0,33 nM, y 0,1 nM) en duplicados para cada concentración. La serie de dilución se preparó de forma separada antes del ensayo como soluciones de

reserva 100 veces concentrada en DMSO; las concentración exactas podrían variar dependiendo de la pipeta usada. Para el ensayo, se pipetearon 50 nl de cada solución de reserva del compuesto de ensayo en DMSO en una placa de microtítulos de 384 pocillos de bajo volumen, negra (Greiner Bio-One, Frickenhausen, Alemania). Se agregaron 2 µl de una solución de la proteína de fusión del FGFR-1 anterior en tampón de ensayo acuoso [8 mM MOPS pH 7,0, 10 mM de acetato de magnesio, 1,0 mM de ditiotreitol, 0,05% (p/v) de albúmina de suero de bovino (BSA), 0,07% (v/v) de Tween-20, 0,2 mM de EDTA], y la mezcla se incubó durante 15 min a 22ºC para permitir la preunión del compuesto de ensayo a la enzima. A continuación, la reacción de quinasa se inició mediante la adición de 3 µl de una solución de adenosina trifosfato (ATP, 3,3 mM; concentración final en el volumen de ensayo de 5 µl = 2 mM) y sustrato (0,16 µM; concentración final en el volumen de ensayo de 5 µl = 0,1 µM) en tampón de ensayo, y la mezcla resultante se incubó durante un tiempo de reacción de 15 min a 22ºC. La concentración de la proteína de fusión del FGFR-1 se ajustó dependiendo de la actividad del lote de enzimas y se eligió de forma apropiada para que el ensayo esté en el intervalo lineal (las concentraciones típicas estuvieron en el intervalo de 0,05 µg/ml). La reacción se detuvo por la adición de 5 µl de una solución de reactivos de detección HTRF [25 nM de estreptavidina-XL665 (Cis Biointernational) y 1 nM PT66-Eu-quelato, un anticuerpo anti-fosfotirosina marcado con europio-quelato (Perkin-Elmer; se puede usar PT66-Tb-criptato de Cis Biointernational en su lugar), en solución de EDTA acuosa (50 mM de EDTA, 0,1% p/v) de BSA en 50 mM de HEPES/NaOH pH 7,5)].

La mezcla resultante se incubó durante 1 hora a 22ºC para permitir la formación del complejo entre el péptido biotinilado fosforilado y los reactivos de detección. Posteriormente, la cantidad de sustrato fosforilado se evaluó mediante la medición de la transferencia de energía por resonancia del Eu-quelato a la estreptavidina-XL665. Para esto, las emisiones de fluorescencia a 620 nm y 665

nm después de la excitación a 350 nm se midieron en un lector TR-FRET [por ej., Rubystar (BMG Labtechnologies, Offenburg, Alemania) o Viewlux (Perkin-Elmer)]. La relación de las emisiones a 665 nm y a 620 nm se tomó como la medición para la cantidad de sustrato fosforilado. Los datos se normalizaron (reacción enzimática sin inhibidor = 0% de inhibición, todos los otros componentes del ensayo pero sin enzima = 100% de inhibición), y los valores IC_{50} se calcularon mediante un ajuste de 4 parámetros usando un software local.

Los valores de IC_{50} para los compuestos individuales de la invención a partir de este ensayo se enumeran en la tabla 1A a continuación.

Tabla 1A

Ejemplo Nº.	FGFR-1 (ATP alta) IC_{50} [nM]
1	12,2
2	7,2
3	6,6
4	13,7
5	4,6
6	9,0
7	4,2
8	9,4
9	31,0
10	12,7
11	6,5
12	3,3
13	2,5
14	1,4
15	1,0
16	12,5
17	0,9
18	0,7
19	0,5
20	25,0
21	4,2
22	0,9
23	17,9
24	1,3
25	0,7
26	0,9

Ejemplo Nº.	FGFR-1 (ATP alta) IC_{50} [nM]
27	1,3
28	2,1
29	1,6
30	2,8
31	1,5
32	5,2
33	1,0
34	6,0
35	61,3
36	3,0
37	22,1
38	6,9
39	1,1
40	2,1
41	2,8
42	5,1
43	8,6
44	2,1
45	3,4
46	3,2
47	1,7
48	12,8
51	4,4
52	9,7
53	3,9
54	11,2

Ejemplo Nº.	FGFR-1 (ATP alta) IC_{50} [nM]
56	2,4
57	3,2
58	6,8
59	3,8
60	16,2
61	0,5
62	3,1
64	1,0
65	5,6
66	1,6
67	5,0
68	27,0
69	55,3
70	39,1
71	2,7
72	1,4
73	4,4
74	4,0
75	4,1
76	2,8
77	1,4
78	1,7
79	12,6
80	1,3
81	1,9
82	3,4

Ejemplo Nº.	FGFR-1 (ATP alta) IC_{50} [nM]
83	14,5
84	3,7
85	26,4
86	3,9
87	14,1
88	79,6
89	82,9
90	9,9
91	52,9
92	8,2
93	5,5
94	81,9
95	17,0
96	54,5
97	16,4
98	17,0
99	24,8
100	54,5
101	30,8
102	39,2
103	50,3
104	5,6
105	8,7
106	6,4
107	9,4
108	3,9

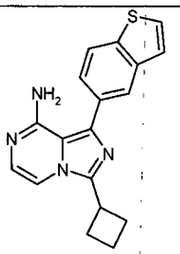
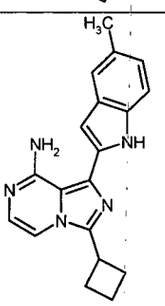
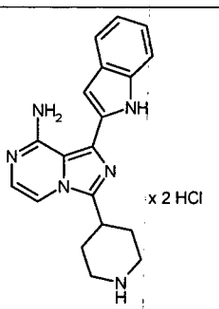
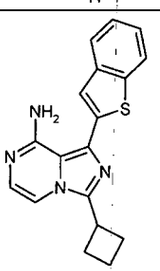
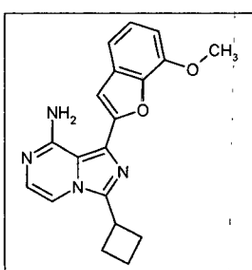
Ejemplo Nº.	FGFR-1 (ATP alta) IC_{50} [nM]
109	8,4
110	17,5
111	27,0
112	42,1
113	52,7
114	11,2
115	24,9
116	3,7
117	8,8
118	6,8

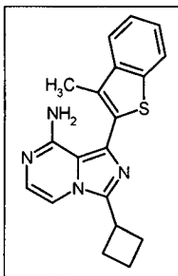
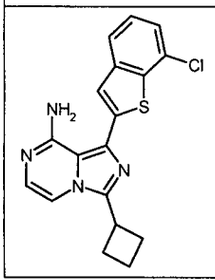
Ejemplo Nº.	FGFR-1 (ATP alta) IC_{50} [nM]
119	9,0
120	6,8
121	8,2
122	18,9
123	25,1
124	27,3
125	5,0
126	3,9
127	8,0

Los derivados de 8-amino-1-(benzotiofen-2-il)imidazo[1,5-a]pirazina seleccionados y los compuestos relacionados que se consideraron representativos de la técnica anterior más próxima (véase la Solicitud de Patente Internacional WO 2007/061737-A2 y los compuestos de ejemplo descriptos en la misma) se sintetizaron siguiendo los procedimientos publicados y además se ensayaron en el ensayo de ATP alta del FGFR-1 con fines de comparación. Los valores de IC_{50} que se obtuvieron para estos compuestos se enumeran en la tabla 1B a continuación:

Tabla 1B

Estructura del compuesto comparativa	Ejemplo Nº. en el doc. WO 2007/061737	FGFR-1 (ATP alta) IC_{50} [nM]

Estructura del compuesto comparativa	**Ejemplo Nº. en el doc. WO 2007/061737**	**FGFR-1 (ATP alta) IC_{50} [nM]**
	4	12000
	5	500
	25	880
	120	985
	205	20000

	210	456
	233	4600

Los valores de IC_{50} que se especifican en la tabla 1A y 1B muestran que los compuestos de la presente invención son aproximadamente cinco a mil veces más potentes en la inhibición de la actividad del FGFR-1 quinasa que los compuestos de la técnica anterior seleccionados.

B-2. Ensayo del FGFR-3 quinasa

La actividad inhibidora del FGFR-3 de los compuestos de la presente invención después de su pre-incubación con el FGFR-3a se cuantificó empleando el ensayo del FGFR-3 basado en la TR-FRET como se describe en los siguientes párrafos:

Una proteína de fusión del FGFR-3 marcada recombinante [fusión de glutationa-S-transferasa (GST) (N-terminal), sitio de escisión de la trombina, marca His6, y la parte intracelular del FGFR-3 humano de los aminoácidos R397 a R806 como en la entrada NCBI/Proteína NP_000133,1], que se expresa en las células de insectos SF9 usando el sistema de expresión baculovirus y se purifica mediante la cromatografía por afinidad de S-transferasa, se adquirió de Proqinase (producto nº. 1068-0000-1) y se usó como enzima. Como sustrato para la reacción de quinasa, se usó el péptido biotinilado biotin-Ahx-AAEEEYFFLFAKKK (C-terminal en forma de amida) el cual se adquirió, por ej., de Biosyntan (Berlin-Buch, Alemania).

Usualmente, los compuestos de ensayo se ensayaron en la misma placa de

microtítulos a 11 concentraciones diferentes en el intervalo de 20 µM a 0,1 nM (por ej., 20 µM, 5,9 µM, 1,7 µM, 0,51 µM, 0,15 µM, 44 nM, 13 nM, 3,8 nM, 1,1 nM, 0,33 nM, y 0,1 nM) en duplicados para cada concentración. La serie de dilución se preparó de forma separada antes del ensayo como soluciones de reserva 100 veces concentrada en DMSO; las concentración exactas podrían variar dependiendo de la pipeta usada. Para el ensayo, se pipetearon 50 nl de cada solución de reserva del compuesto de ensayo en DMSO en una placa de microtítulos de 384 pocillos de bajo volumen, negra (Greiner Bio-One, Frickenhausen, Alemania). Se agregaron 2 µl de una solución de la proteína de fusión del FGFR-3 anterior en tampón de ensayo acuoso [8 mM MOPS pH 7,0, 10 mM de acetato de magnesio, 1,0 mM de ditiotreitol, 0,05% (p/v) de albúmina de suero de bovino (BSA), 0,07% (v/v) de Tween-20, 0,2 mM de EDTA], y la mezcla se incubó durante 15 min a 22ºC para permitir la preunión del compuesto de ensayo a la enzima. A continuación, la reacción de quinasa se inició mediante la adición de 3 µl de una solución de adenosina trifosfato (ATP, 16,7 µM; concentración final en el volumen de ensayo de 5 µl = 10 µM) y sustrato (0,8 µM; concentración final en el volumen de ensayo de 5 µl = 0,5 µM) en tampón de ensayo, y la mezcla resultante se incubó durante un tiempo de reacción de 60 min a 22ºC. La concentración de la proteína de fusión del FGFR-3 se ajustó dependiendo de la actividad del lote de enzimas y se eligió de forma apropiada para que el ensayo esté en el intervalo lineal (las concentraciones típicas estuvieron en el intervalo de 0,03 µg/ml). La reacción se detuvo por la adición de 5 µl de una solución de reactivos de detección HTRF [100 nM de estreptavidina-XL665 (Cis Biointernational) y 1 nM PT66-Tb-criptato, un anticuerpo anti-fosfotirosina marcado con terbio-criptato (Cis Biointernational; se puede usar PT66-Eu-quelato de Perkin-Elmer en su lugar), en solución de EDTA acuosa (50 mM de EDTA, 0,1% p/v) de BSA en 50 mM de HEPES/NaOH pH 7,5)].

La mezcla resultante se incubó durante 1 hora a 22ºC para permitir la formación del complejo entre el péptido biotinilado fosforilado y los reactivos de detección.

Posteriormente, la cantidad de sustrato fosforilado se evaluó mediante la medición de la transferencia de energía por resonancia del Tb-quelato a la estreptavidina-XL665. Para esto, las emisiones de fluorescencia a 620 nm y 665 nm después de la excitación a 350 nm se midieron en un lector TR-FRET [por ej., Rubystar (BMG Labtechnologies, Offenburg, Alemania) o Viewlux (Perkin-Elmer)]. La relación de las emisiones a 665 nm y a 620 nm se tomó como la medición para la cantidad de sustrato fosforilado. Los datos se normalizaron (reacción enzimática si inhibidor = 0% de inhibición, todos los otros componentes del ensayo pero sin enzima = 100% de inhibición), y los valores IC_{50} se calcularon mediante un ajuste de 4 parámetros usando un software local.

Los valores IC_{50} para los compuestos individuales de la invención a partir de este ensayo se enumeran en la tabla 2A, dada a continuación.

Tabla 2A

Ejemplo Nº.	**FGFR-3 IC_{50} [nM]**	**Ejemplo Nº.**	**FGFR-3 IC_{50} [nM]**
1	24,8	15	1,0
2	29,4	16	9,4
3	46,6	17	3,3
4	24,8	18	2,8
5	12,1	19	2,7
6	28,5	20	26,1
7	10,4	21	13,0
8	17,7	22	4,7
9	63,9	23	41,9
10	8,3	24	5,7
11	13,0	25	5,2
12	14,0	26	4,9
13	10,0	27	12,6
14	2,5	28	9,7

Ejemplo Nº.	FGFR-3 IC_{50} [nM]
29	2,5
30	6,4
31	13,3
32	52,3
33	7,2
34	10,5
35	65,4
36	9,8
37	34,6
38	18,8
39	4,9
40	7,9
41	7,2
42	18,4
43	32,4
44	6,1
45	9,7
46	8,1
47	3,4
48	45,4
51	3,9
52	7,0
53	2,5
54	6,8
56	2,0
57	1,8

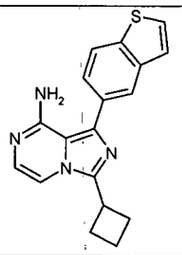
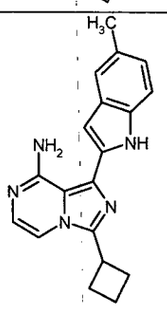
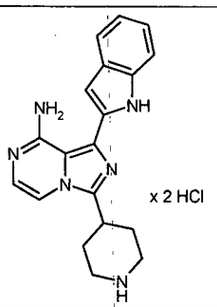
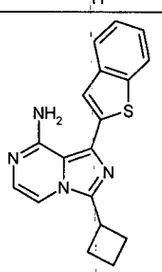
Ejemplo Nº.	FGFR-3 IC_{50} [nM]
58	9,8
59	6,8
60	77,9
61	0,9
62	11,0
64	2,9
65	3,1
66	3,7
67	9,4
68	42,7
69	58,1
71	5,4
72	0,7
73	12,2
74	1,4
75	19,8
76	1,4
77	3,8
78	2,0
79	17,9
80	0,2
81	0,5
82	16,0
83	2,1
84	16,5
85	26,0

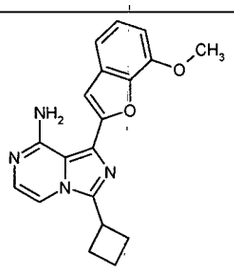
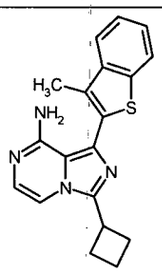
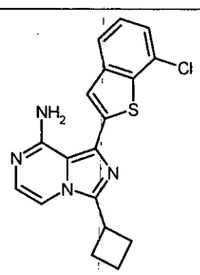
Ejemplo Nº.	FGFR-3 IC_{50} [nM]
86	6,8
87	28,1
90	11,0
91	31,1
93	8,7
95	28,7
98	26,5
99	36,9

Ejemplo Nº.	FGFR-3 IC_{50} [nM]
102	39,8
106	7,1
107	17,4
108	7,7
114	9,6
117	5,3
119	4,5
121	24,6

Los derivados de 8-amino-1-(benzotiofen-2-il)imidazo[1,5-a]pirazina seleccionados y los compuestos relacionados que se consideraron representativos de la técnica anterior más próxima (véase la Solicitud de Patente Internacional WO 2007/061737-A2 y los compuestos de ejemplo descriptos en la misma) se sintetizaron siguiendo los procedimientos publicados y además se ensayaron en el ensayo de ATP alta del FGFR-3 con fines de comparación. Los valores de IC_{50} que se obtuvieron para estos compuestos se enumeran en la tabla 2B, dada a continuación:

Tabla 2B

Estructura del compuesto comparativa	Ejemplo Nº. en el doc. WO 2007/061737	FGFR-3 IC_{50} [nM]
	4	2400
	5	250
	25	1200
	120	506

(Continuación)		
Estructura del compuesto comparativa	**Ejemplo No. en el doc. WO 2007/061737**	**FGFR-3 IC_{50} [nM]**
	205	20000
	210	554
	233	10000

Los valores de IC_{50} que se especifican en la tabla 2A y 2B muestran que los compuestos de la presente invención son aproximadamente tres a mil veces más potentes en la inhibición de la actividad del FGFR-3 quinasa que los compuestos de la técnica anterior seleccionados.

B-3. *Ensayo de ATP quinasa alta del FGFR-4*

La actividad inhibidora del FGFR-1 a elevada concentración de ATP de los compuestos de la presente invención después de su pre-incubación con FGFR-4 se cuantificó empleando el ensayo ATP alto del FGFR-4 basado en la TR-FRET como se describe en los siguientes párrafos:

Una proteína de fusión del FGFR-4 marcada recombinante [fusión de glutationa-S-transferasa (GST) (N-terminal), sitio de escisión de la trombina, marca His6, y la

parte intracelular del FGFR-4 humano de los aminoácidos R391 a R802 como en la entrada del GenBank NM_002011], que se expresa en las células de insectos SF9 usando el sistema de expresión baculovirus y se purifica mediante la cromatografía por afinidad de glutationa-agarosa, se adquirió de Proqinase (producto nº. 0101-0000-3) y se usó como enzima. Como sustrato para la reacción de quinasa, se usó el péptido biotinilado biotin-Ahx-AAEEEYFFLFAKKK (C-terminal en forma de amida) el cual se adquirió, por ej., de Biosyntan (Berlin-Buch, Alemania).

Usualmente, los compuestos de ensayo se ensayaron en la misma placa de microtítulos a 11 concentraciones diferentes en el intervalo de 20 µM a 0,1 nM (por ej., 20 µM, 5,9 µM, 1,7 µM, 0,51 µM, 0,15 µM, 44 nM, 13 nM, 3,8 nM, 1,1 nM, 0,33 nM, y 0,1 nM) en duplicados para cada concentración. La serie de dilución se preparó de forma separada antes del ensayo como soluciones de reserva 100 veces concentrada en DMSO; las concentración exactas podrían variar dependiendo de la pipeta usada. Para el ensayo, se pipetearon 50 nl de cada solución de reserva del compuesto de ensayo en DMSO en una placa de microtítulos de 384 pocillos de bajo volumen, negra (Greiner Bio-One, Frickenhausen, Alemania). Se agregaron 2 µl de una solución de la proteína de fusión del FGFR-1 anterior en tampón de ensayo acuoso [8 mM MOPS pH 7,0, 10 mM de acetato de magnesio, 1,0 mM de ditiotreitol, 0,05% (p/v) de albúmina de suero de bovino (BSA), 0,07% (v/v) de Tween-20, 0,2 mM de EDTA], y la mezcla se incubó durante15 min a 22ºC para permitir la preunión del compuesto de ensayo a la enzima. A continuación, la reacción de quinasa se inició mediante la adición de 3 µl de una solución de adenosina trifosfato (ATP, 3,3 mM; concentración final en el volumen de ensayo de 5 µl = 2 mM) y sustrato (0,8 µM; concentración final en el volumen de ensayo de 5 µl = 0,5 µM) en tampón de ensayo, y la mezcla resultante se incubó durante un tiempo de reacción de 60 min a 22ºC. La concentración de la proteína de fusión del FGFR-1 se ajustó dependiendo de la actividad del lote de enzimas y se eligió de forma apropiada

para que el ensayo esté en el intervalo lineal (las concentraciones típicas estuvieron en el intervalo de 0,03 µg/ml). La reacción se detuvo por la adición de 5 µl de una solución de reactivos de detección HTRF [100 nM de estreptavidina-XL665 (Cis Biointernational) y 1 nM PT66-Tb-criptato, un anticuerpo anti-fosfotirosina marcado con terbio-criptato (Cis Biointernational; se puede usar PT66-Eu-quelato de Perkin-Elmer en su lugar), en solución de EDTA acuosa (50 mM de EDTA, 0,1% p/v) de BSA en 50 mM de HEPES/NaOH pH 7,5)].

La mezcla resultante se incubó durante 1 hora a 22°C para permitir la formación del complejo entre el péptido biotinilado fosforilado y los reactivos de detección. Posteriormente, la cantidad de sustrato fosforilado se evaluó mediante la medición de la transferencia de energía por resonancia del Tb-quelato a la estreptavidina-XL665. Para esto, las emisiones de fluorescencia a 620 nm y 665 nm después de la excitación a 350 nm se midieron en un lector TR-FRET [por ej., Rubystar (BMG Labtechnologies, Offenburg, Alemania) o Viewlux (Perkin-Elmer)]. La relación de las emisiones a 665 nm y a 620 nm se tomó como la medición para la cantidad de sustrato fosforilado. Los datos se normalizaron (reacción enzimática si inhibidor = 0% de inhibición, todos los otros componentes del ensayo pero sin enzima = 100% de inhibición), y los valores IC_{50} se calcularon mediante un ajuste de 4 parámetros usando un software local.

B-4. *Ensayo de mTOR quinasa (con fines comparativos)*

La actividad inhibidora del mTOR de los compuestos de la presente invención se cuantificó empleando el ensayo mTOR basado en la TR-FRET como se describe en los siguientes párrafos:

Una proteína mTOR marcada de fusión recombinante [glutationa-S-transferasa (GST) fusionada a los aminoácidos mTOR humanos de 1360 a 2549], que se expresa en las células de insectos y purificada por cromatografía por afinidad de glutationa-sefarosa, se adquirió de Invitrogen (Cat.-Nº. 4753) y se usó como enzima. Como sustrato para la reacción de quinasa, se usó una proteína de fusión recombinante de GFP y 4E-BP1 (adquirida de Invitrogen, Cat.-Nº. PV4759).

Los compuestos se disolvieron en DMSO para generar soluciones de reserve de 10 mM. Estas soluciones primero se diluyeron 100 veces con 100% de DMSO para obtener soluciones 1 mM en 100% de DMSO, luego se diluyeron 100 veces en 50% de DMSO para obtener soluciones 10 µM en 50% de DMSO.

Para el ensayo, 0,5 µl de una solución 10 µM del compuesto de ensayo en 50% de DMSO se pipeteó en una placa de microtítulos de 384 pocillos de bajo volumen, negra (Greiner Bio-One, Frickenhausen, Alemania). Se agregaron 2 µl de una solución de la proteína de fusión mTOR anterior en tampón de ensayo acuoso [50 mM de HEPES/NaOH pH 7,5, 5 mM de cloruro de magnesio, 1,0 mM de ditiotreitol, 1 mM de EGTA, 0,01% (v/v) de Triton-X100, 0,01% (p/v) de albúmina de suero bovino (BSA)], y la mezcla se incubó durante 15 min a 22°C para permitir la preunión del compuesto de ensayo a la enzima. A continuación, la reacción de quinasa se inició mediante la adición de 2,5 µl de una solución de adenosina trifosfato (ATP, 80 µM; concentración final en el volumen de ensayo de 5 µl = 40 µM) y sustrato (0,6 µM; concentración final en el volumen de ensayo de 5 µl = 0,3 µM) en tampón de ensayo, y la mezcla resultante se incubó durante un tiempo de reacción de 60 min a 22°C. La concentración de la proteína de fusión mTOR se eligió de forma apropiada como para que el ensayo esté en el intervalo lineal (una concentración final típica en el volumen de ensayo de 5 µl fue 1,25 ng/µl. La reacción se detuvo por la adición de 5 µl de 30 mM de EDTA (concentración final en el volumen de ensayo de 10 µl = 15 mM) y 2 nM de anticuerpo fosfoespecífico anti-4E-BP1 [pT46] marcado con Tb-quelato [Invitrogen Cat.-Nº. PV4755] (concentración final en el volumen de ensayo de 10 µl = 1 nM) en tampón de FRET.

La mezcla resultante se incubó durante 1 hora a 22°C para permitir la formación del complejo entre el sustrato fosforilado y el anticuerpo marcado con Tb-quelato. Posteriormente, la cantidad de sustrato fosforilado se evaluó mediante la medición de la transferencia de energía por resonancia del Tb-quelato al GFP. Para esto, las emisiones de fluorescencia a 495 nm y 520 nm después de la excitación a 340

nm se midieron en un lector Envision 2104 de múltiples etiquetas (Perkin-Elmer). La relación de las emisiones a 520 nm y a 495 nm se tomó como la medición para la cantidad de sustrato fosforilado. Los datos se normalizaron (reacción enzimática sin inhibidor = 0% de inhibición, todos los otros componentes del ensayo pero sin enzima = 100% de inhibición), y o bien se calcularon valores medios (si se ensayan en replicados a una concentración simple) o los valores de IC_{50} (por un ajuste de 4 parámetros usando un software local).

Los valores de inhibición medios a 1 µM para los compuestos individuales de la presente invención se enumeran en la tabla 3, dada a continuación.

Tabla 3

Ejemplo Nº.	**mTOR % de inhibición @ 1 µM**
1	8,7
2	7,2
3	8,2
5	9,7
6	0,3
7	3,1
8	7,8
9	*sin detección del efecto inhibidor*
10	6,0
11	33,2
12	25,8
13	14,9
14	15,7
16	36,9
17	6,7

Ejemplo Nº.	**mTOR % de inhibición @ 1 µM**
18	*sin detección del efecto inhibidor*
19	17,6
20	31,3
21	5,0
22	17,6
23	11,6
24	6,3
25	3,5
26	6,8
27	5,9
28	*sin detección del efecto inhibidor*
29	28,5
30	21,1
31	16,3

Ejemplo Nº.	mTOR % de inhibición @ 1 µM
32	1,6
33	0,9
34	25,9
35	1,4
36	14,4
37	8,6
38	20,8
39	11,5
40	0,1
41	*sin detección del efecto inhibidor*
42	*sin detección del efecto inhibidor*
43	10,1
44	13,3
45	15,5
46	11,0
47	14,7
48	4,1
51	8,4
52	4,2
53	3,3
54	1,7
56	16,1
57	2,0
58	4,0

Ejemplo Nº.	mTOR % de inhibición @ 1 µM
59	0,8
60	11,1
61	15,9
62	0,2
64	1,1
65	13,9
66	15,8
67	8,4
68	8,0
69	8,7
70	5,8
71	0,1
72	8,2
73	18,5
74	18,6
75	10,2
76	8,5
77	0,7
78	5,8
79	14,7
80	3,9
81	4,1
82	7,1
83	6,3
84	9,1

Ejemplo Nº.	mTOR % de inhibición @ 1 µM
85	0,9
87	12,7
88	5,3
89	*sin detección del efecto inhibidor*
93	12,5
98	*sin detección del efecto inhibidor*
99	5,3

Ejemplo Nº.	mTOR % de inhibición @ 1 µM
103	*sin detección del efecto inhibidor*
107	*sin detección del efecto inhibidor*
108	8,5
119	*sin detección del efecto inhibidor*
121	*sin detección del efecto inhibidor*

(sin detección del efecto inhibidor = sin efecto inhibidor detectable a 1 µM).

Los datos en la tabla 3 muestran que los compuestos de la presente invención sólo tienen un efecto inhibidor débil, si existe, sobre la mTOR quinasa, el cual no se considera que contribuya a la actividad farmacológica observada con estos compuestos.

B-5. Inhibición de la proliferación celular mediada por el factor de crecimiento

Se obtuvieron células endoteliales de la vena umbilical humana (HUVEC) de Cellsystems (FC-0003) y se desarrollaron en el medio completo de Vasculife VEGF (Cellsystems, LL-1020) que contiene 2% de suero bovino fetal (FBS) a 37°C y 5% de CO_2. Las células se usaron para los ensayos de proliferación hasta el pasaje 7.

Las células HUVEC se cosecharon usando accutasa (PAA, L11-007) y se sembraron en las columnas 2 a 12 de las placas de 96 pocillos (fondo plano de 96 pocillos de la placa de cultivo tisular Falcon MICROTEST, BD 353075, o µCLEAR-PLATE, de 96 pocillos, negra, Greiner Bio-One, No. 655090) a una densidad celular de 2500 células/ pocillo en 100 µl de medio completo Vasculife VEGF quedando la columna 1 vacía como blanco. Las células se incubaron a 37°C y 5%

de CO_2 durante al menos 6 horas. A continuación, las células se lavaron una vez con PBS y se privaron de alimento durante toda la noche en el medio basal Vasculife (Cellsystems, LM-0002) que contiene heparina, ascorbato y L-glutamina (componentes del kit de Vasculife Life Factors, Cellsystemas LL-1020) como también 0,2% de FBS.

Después de aproximadamente 18 horas, se descartó el medio privado de alimento, y las células se expusieron durante 72 horas a 9 concentraciones de registro consecutivo o medio-registro del compuesto de ensayo en el intervalo de 10 pM a 30 µM y a 5, 10 o 20 ng/ml de hFGF-2 (FGF humano recombinante básico, R&D Systems, 233-FB) en 100 µl de medio privado de alimento. Las soluciones de reserva de 10 mM de los compuestos de ensayo en DMSO se diluyeron hasta 200 x concentración final en DMSO dando por resultado una concentración de DMSO final de 0,5% en todos los pocillos. Los controles consistieron de células desarrolladas en el medio privado de alimento únicamente y de células desarrolladas en el medio privado de alimento que contiene hFGF-2 con 0,5% de DMSO. Para determinar la proliferación celular, se agregó 5 µl solución de Alamar Azul (Biosource, DAL1100) a cada pocillo (dilución 1,20), y las células se dejaron incubar durante otras 4 horas a 37ºC y 5% de CO_2 antes de medir la fluorescencia (ex. 535 nm, em. 595 nm) con un lector de placa Spectrafluor Plus Tecan ((XFLUOR4 versión 4,20). En algunos experimentos, se usó un kit de determinación de ATP (BIAFFIN GmbH, LBR-T100) de acuerdo con las instrucciones del fabricante. En cada experimento, se ensayaron muestras por triplicado, y se determinaron las desviaciones estándares. Se usó el software GraphPad Prism 5 para analizar los datos y obtener los valores de IC_{50}. Todos los compuestos de ensayo se ensayaron 2 a 10 veces en experimentos independientes y se obtuvieron resultados similares.

Los datos mencionados en la tabla 4, dada a continuación, representan los valores IC_{50} para los compuestos representativos de la invención que surgen de los correspondientes valores pIC_{50} promediados:

Tabla 4

Ejemplo Nº.	Proliferación de HUVEC mediada por hFGF-2, IC_{50} [nM]
1	16,4
4	17,5
5	5,3
8	9,7
10	16,0
11	150,0
13	17,0
14	25,0
16	117,3
18	10,4
21	3,7
26	56,7
34	37,3
38	213,3
39	365,0
45	171,0
46	84,5
48	360,0
51	1,2
52	4,0
53	3,3
54	2,2
56	18,1
57	3,2

Ejemplo Nº.	Proliferación de HUVEC mediada por hFGF-2, IC_{50} [nM]
59	51,1
60	250,0
64	4,5
67	12,1
68	14,4
71	5,4
72	1,6
73	5,5
74	0,2
75	1,5
76	1,5
77	3,2
79	3,5
80	1,6
81	1,6
84	46,6
85	126,0

La mayoría de los compuestos de la presente invención representaron aproximadamente de diez a cien veces la actividad inhibidora reducida en este ensayo de proliferación cuando se usó el factor de desarrollo endotelial vascular (isoforma VEGF-A_{165}) como factor de crecimiento mediador (en lugar de FGF-2), indicando una selectividad significativa de estos compuestos para las FGFR versus las VEGFR quinasas.

B-6. Modelos de tumor humano senoinjerto y sinérgicos.

Se han conducido diferentes modelos de tumor a fin de perfilar los compuestos de la presente invención in vivo. Las células tumorales humanas, de rata o de ratón se cultivaron in vivo y se implantaron en ratones inmunodeficientes o inmunocompetentes, o ratas inmunodeficientes. El tratamiento se inició después del establecimiento del tumor, y los animales que portan el tumor se trataron con sustancias a través de diferentes vías (por ej., por vía intravenosa, intraperitoneal o subcutánea). Las sustancias se ensayaron como monoterapia o terapia de combinación con otras sustancias farmacológicas. Se condujo el tratamiento de los animales que portan el tumor hasta que los tumores alcanzaron un tamaño promedio de 120 mm^2. Los tumores se midieron en dos dimensiones usando un calibre, y el volumen del tumor se calculó de acuerdo con la fórmula (longitud x $ancho^2$)/2. La eficacia de la sustancia se evaluó al final del experimento usando la relación T/C [T = peso final del tumor en el grupo tratado; C = peso final del tumor en el grupo control]. La significancia estadística de la eficacia entre el control y los grupos tratados se determinó usando el ensayo de varianza ANOVA. Todos los estudios de animales se condujeron de acuerdo con las guías regulatorias alemanas.

Si bien la invención ha sido divulgada con referencia a realizaciones específicas, es evidente que otros expertos en la técnica pueden realizar otras realizaciones y variantes de la invención sin apartarse del verdadero espíritu y alcance de la invención. Se interpreta que las reivindicaciones incluyen todas

estas realizaciones y las variantes equivalentes.

C. Ejemplos que se refieren a las composiciones farmacéuticas

Las composiciones farmacéuticas de acuerdo con la presente invención se pueden ilustrar de la siguiente forma:

Solución i.v. estéril:

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

Polvo liofilizado para administración i.v.:

Se puede preparar una preparación estéril con (i) 100-1000 mg del compuesto deseado de la invención como polvo liofilizado, (ii) 32-327 mg/ml de citrato de sodio, y (iii) 300-3000 mg de dextrano 40. La formulación se reconstituye con solución salina estéril, inyectable o 5% de dextrosa a una concentración de 10 a 20 mg/ml, la cual además se diluye con solución salina o 5% de dextrosa hasta 0,2 hasta 0,4 mg/ml, y se administra o bien como bolo i.v. o por infusión i.v. durante 15 a 60 minutos.

Suspensión intramuscular:

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

50 mg/ml del compuesto insoluble en agua deseado de la invención, 5 mg/ml de carboximetilcelulosa sódica; 4 mg/ml de Tween 80; 9 mg/ml de cloruro de sodio; 9 mg/ml de alcohol bencílico.

Cápsulas duras:

Un gran número de cápsulas unitarias se preparan mediante el llenado de cápsulas de gelatina dura de dos piezas estándares, conteniendo cada una 100 mg del compuesto en polvo, deseado de la invención, 150 mg de lactosa, 50 mg de celulosa y 6 mg de estearato de magnesio.

Cápsulas de gelatina blanda:

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

Comprimidos:

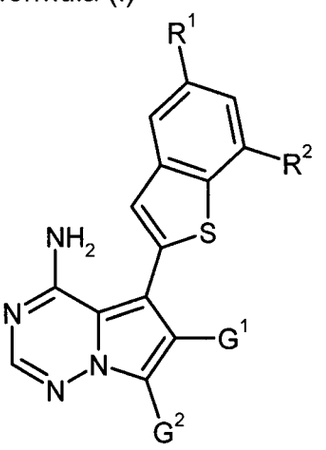
Se prepara un gran número de comprimidos mediante procedimientos convencionales de modo que la unidad de dosificación es 100 mg del compuesto deseado de la invención, 0,2 mg de dióxido de silicio coloidal, 5 mg de estearato de magnesio, 275 mg de celulosa microcristalina, 11 mg de almidón, y 98,8 mg de lactosa. Los recubrimientos acuosos y no acuosos apropiados se pueden aplicar para incrementar el sabor agradable, mejorar la elegancia y la estabilidad, o retardar la absorción.

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

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

Reivindicaciones

1. Un compuesto de fórmula (I)



(I),

en la que

R^1 es hidrógeno, cloro, metilo o metoxi,

R^2 es hidrógeno o metoxi,

a condición de que al menos uno de R^1 y R^2 sea diferente de hidrógeno,

G^1 representa cloro, alquilo (C_1-C_4), alcoxicarbonilo (C_1-C_4), aza-heteroarilo de 5 miembros, o el grupo $-CH_2-OR^3$, $-CH_2-NR^4R^5$ o $-C(=O)-NR^4R^6$, en la que

R^3 es hidrógeno, alquilo (C_1-C_4) o cicloalquilo (C_3-C_6) o fenilo,

(*i*) dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi, alcoxi (C_1-C_4), hidroxicarbonilo, alcoxicarbonilo (C_1-C_4), amino, aminocarbonilo, mono-(C_1-C_4)-alquil-aminocarbonilo, di-alquilaminocarbonilo (C_1-C_4)-, ciclo-alquilo (C_3-C_6) o hasta tres átomo de flúor,

y

(*ii*)dicho cicloalquilo (C_3-C_6) está opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados del grupo que consiste en alquilo (C_1-C_4), hidroxi y amino,

y

(*iii*) dicho fenilo está opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados del grupo que consiste en flúor, cloro, bromo, ciano, trifluorometilo, trifluorometoxi, alquilo (C_1-C_4) y alcoxi (C_1-C_4),

R^4 es hidrógeno o alquilo (C_1-C_4),

R^5 es hidrógeno, alquilo (C_1-C_4), alquilcarbonilo (C_1-C_4), cicloalquilo (C_3-C_6) o heterocicloalquilo de 4 a 6 miembros, en la que

(*i*) dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi, alcoxi (C_1-C_4), hidroxicarbonilo, alcoxicarbonilo (C_1-C_4), aminocarbonilo, mono-(C_1-C_4)-alquil-aminocarbonilo, di-alquilaminocarbonilo (C_1-C_4), o cicloalquilo (C_3-C_6),

y

(*ii*) dicho cicloalquilo (C_3-C_6) está opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados del grupo que consiste en alquilo (C_1-C_4), hidroxi y amino,

y

(*iii*) dicho heterocicloalquilo de 4 a 6 miembros está opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados del grupo que consiste en alquilo (C_1-C_4), hidroxi, oxo y amino,

R^6 es hidrógeno, alquilo (C_1-C_4), cicloalquilo (C_3-C_6) o heterocicloalquilo de 4 a 6 miembros, en la que

(*i*) dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi, alcoxi (C_1-C_4), hidroxicarbonilo, alcoxicarbonilo (C_1-C_4), amino, aminocarbonilo, mono-(C_1-C_4)-alquil-aminocarbonilo, di-alquilaminocarbonilo (C_1-C_4), o cicloalquilo (C_3-C_6),

y

(*ii*) dicho cicloalquilo (C_3-C_6) está opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados del grupo que consiste en alquilo (C_1-C_4), hidroxi y amino,

y

(*iii*) dicho heterocicloalquilo de 4 a 6 miembros está opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados del grupo que consiste en alquilo (C_1-C_4), hidroxi, oxo y amino,

o

R^4 y R^5, o R^4 y R^6, respectivamente, se unen y, tomados junto con el átomo de nitrógeno al cual están unidos, forman un anillo heterocicloalquilo monocíclico, saturado de 4 a 7 miembros el cual puede contener un segundo heteroátomo del anillo seleccionado de $N(R^7)$ y O, y el cual puede estar sustituido en los átomos de carbono del anillo con uno o dos sustituyentes independientemente seleccionados del grupo que consiste en alquilo (C_1-C_4), oxo, hidroxi, amino y aminocarbonilo, y en la que

R^7 es hidrógeno, alquilo (C_1-C_4), formilo o alquilcarbonilo (C_1-C_4),

y

G^2 representa cloro, ciano, alquilo (C_1-C_4), o el grupo $-CR^{8A}R^{8B}$-OH, $-CH_2$-NR^9R^{10}, $-C(=O)-NR^{11}R^{12}$ o $-CH_2-OR^{15}$, en la que

R^{8A} y R^{8B} se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo (C_1-C_4), ciclopropilo y ciclobutilo,

R^9 es hidrógeno o alquilo (C_1-C_4),

R^{10} es hidrógeno, alquilo (C_1-C_4), alquilcarbonilo (C_1-C_4), cicloalquilo (C_3-C_6) o heterocicloalquilo de 4 a 6 miembros, en la que

(*i*) dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi, amino, aminocarbonilo, mono-(C_1-C_4)-alquilaminocarbonilo, o di-alquilaminocarbonilo (C_1-C_4),

y

(*ii*) dicho cicloalquilo (C_3-C_6) está opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados del grupo que consiste en alquilo (C_1-C_4), hidroxi y amino,

y

(*iii*) dicho heterocicloalquilo de 4 a 6 miembros está opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados del grupo que consiste en alquilo (C_1-C_4), hidroxi, oxo y amino,

R^{11} es hidrógeno o alquilo (C_1-C_4),

R^{12} es hidrógeno, alquilo (C_1-C_4), cicloalquilo (C_3-C_6) o heterocicloalquilo de 4 a 6 miembros, en la que

(*i*) dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi, amino, aminocarbonilo, mono-(C_1-C_4)-alquilaminocarbonilo, o di-alquilaminocarbonilo (C_1-C_4),

y

(*ii*) dicho cicloalquilo (C_3-C_6) está opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados del grupo que consiste en alquilo (C_1-C_4), hidroxi y amino,

y

(*iii*) dicho heterocicloalquilo de 4 a 6 miembros está opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados del grupo que consiste en alquilo (C_1-C_4), hidroxi, oxo y amino,

o

R^9 y R^{10}, o R^{11} y R^{12}, respectivamente, se unen y, tomados junto con el átomo de nitrógeno al cual están unidos, forman un anillo heterocicloalquilo monocíclico, saturado de 4 a 7 miembros el cual puede contener un segundo heteroátomo del anillo seleccionado de $N(R^{13})$, O, S y $S(O)_2$, y el cual puede estar sustituido en los átomos de carbono del anillo con hasta tres sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo (C_1-C_4), oxo, hidroxi, amino y aminocarbonilo, y en la que

R^{13} es hidrógeno, alquilo (C_1-C_4) o cicloalquilo (C_3-C_6), formilo o alquilcarbonilo (C_1-C_4),

y

R^{15} es alquilo (C_1-C_4),

a condición de que G^1 no sea cloro cuando G^2 es cloro o ciano,

o una sal, hidrato y/o solvato del mismo aceptable para uso farmacéutico.

2. El compuesto de fórmula (I) de acuerdo con la reivindicación 1, en la que

R^1 es cloro, metilo o metoxi,

R^2 es hidrógeno o metoxi,

G^1 representa cloro, alquilo (C_1-C_4), alcoxicarbonilo (C_1-C_4) o azaheteroarilo de 5 miembros seleccionado del grupo que consiste en pirazolilo, imidazolilo, oxazolilo, isoxazolilo y oxadiazolilo, o representa el grupo $-CH_2-OR^3$ o $-CH_2-NR^4R^5$, en la que

R^3 es hidrógeno, alquilo (C_1-C_4) o cicloalquilo (C_3-C_6),

en la que dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi, alcoxi (C_1-C_4), hidroxicarbonilo, alcoxicarbonilo (C_1-C_4), amino, aminocarbonilo, cicloalquilo (C_3-C_6) o hasta tres átomos de flúor,

R^4 es hidrógeno o alquilo (C_1-C_4),

R^5 es hidrógeno, alquilo (C_1-C_4), alquilcarbonilo (C_1-C_4), cicloalquilo (C_3-C_6) o heterocicloalquilo de 5 o 6 miembros, en la que

(*i*) dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi, hidroxicarbonilo, o cicloalquilo (C_3-C_6),

y

(*ii*) dicho heterocicloalquilo de 5 o 6 miembros está opcionalmente sustituido con oxo,

o

R^4 y R^5 se unen y, tomados junto con el átomo de nitrógeno al cual están unidos, forman un anillo heterocicloalquilo monocíclico, saturado de 4 a 6 miembros el cual puede contener un segundo heteroátomo del anillo seleccionado de $N(R^7)$ y O, y el cual puede estar sustituido en un átomo de carbono del anillo con oxo o hidroxi, y en la que

R^7 es hidrógeno o alquilo (C_1-C_4),

y

G^2 representa cloro, ciano, alquilo (C_1-C_4), o el grupo $-CR^{8A}R^{8B}-OH$, $-CH_2-NR^9R^{10}$, $-C(=O)-NR^{11}R^{12}$ o $-CH_2-OR^{15}$, en la que

R^{8A} y R^{8B} se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo (C_1-C_4), y ciclopropilo,

R^9 es hidrógeno o metilo,

R^{10} es hidrógeno, alquilo (C_1-C_4), alquilcarbonilo (C_1-C_4), cicloalquilo (C_3-C_6) o heterocicloalquilo de 5 o 6 miembros, en la que

(*i*) dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi o aminocarbonilo,

y

(*ii*) dicho heterocicloalquilo de 5 o 6 miembros está opcionalmente sustituido con oxo,

R^{11} es hidrógeno o metilo,

R^{12} es hidrógeno, alquilo (C_1-C_4), cicloalquilo (C_3-C_6) o heterocicloalquilo de 5 o 6 miembros, en la que

(*i*) dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi,

y

(*ii*) dicho heterocicloalquilo de 5 o 6 miembros está opcionalmente sustituido con oxo,

o

R^9 y R^{10}, o R^{11} y R^{12}, respectivamente, se unen y, tomados junto con el átomo de nitrógeno al cual están unidos, forman un anillo heterocicloalquilo monocíclico, saturado de 4 a 6 miembros el cual puede contener un segundo heteroátomo del anillo seleccionado de $N(R^{13})$, O, S y $S(O)_2$, y el cual puede estar sustituido en los átomos de carbono del anillo con hasta tres sustituyentes independientemente seleccionados del grupo que consiste en flúor, alquilo (C_1-C_4), oxo, hidroxi, amino y aminocarbonilo, y en la que

R^{13} es hidrógeno, alquilo (C_1-C_4), ciclopropilo, ciclobutilo, formilo o alquilcarbonilo (C_1-C_4),

y

R^{15} es metilo o etilo,

a condición de que G^1 no sea cloro cuando G^2 es cloro o ciano,

o una sal, hidrato y/o solvato del mismo farmacéuticamente aceptable.

3. El compuesto de fórmula (I) de acuerdo con la reivindicación 1 o 2, en la que

R^1 es metilo,

R^2 es metoxi,

G^1 representa metilo, oxazol-5-ilo o el grupo $-CH_2-OR^3$ o $-CH_2-NR^4R^5$, en la que

R^3 es hidrógeno, alquilo (C_1-C_4), ciclopropilo o ciclobutilo,

en la que dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi, metoxi, etoxi, hidroxicarbonilo, metoxicarbonilo, etoxicarbonilo, amino, aminocarbonilo, ciclopropilo, ciclobutilo o hasta tres átomos de flúor.

R^4 es hidrógeno, metilo o etilo,

R^5 es hidrógeno, alquilo (C_1-C_4), acetilo, ciclopropilo, ciclobutilo o 2-oxopirrolidin-3-ilo,

en la que dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi, hidroxicarbonilo, ciclopropilo o ciclobutilo,

o

R^4 y R^5 se unen y, tomados junto con el átomo de nitrógeno al cual están unidos, forman un anillo heterocicloalquilo monocíclico, saturado de 5 o 6 miembros, el cual puede contener un segundo heteroátomo del anillo seleccionado de NH y O, y el cual puede estar sustituido en un átomo de carbono del anillo con oxo o hidroxi,

y

G^2 representa metilo o el grupo $-CR^{8A}R^{8B}-OH$, $-CH_2-NR^9R^{10}$ o $-C(=O)-NR^{11}R^{12}$, en la que

R^{8A} y R^{8B} son independientemente hidrógeno o metilo,

R^9 es hidrógeno,

R^{10} es hidrógeno, alquilo (C_1-C_4), acetilo, ciclopropilo, ciclobutilo o 2-oxopirrolidin-3-ilo,

en la que dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi o

aminocarbonilo,

R^{11} es hidrógeno o metilo,

R^{12} es hidrógeno, alquilo (C_1-C_4), ciclopropilo, ciclobutilo o 2-oxopirrolidin-3-ilo,

en la que dicho alquilo (C_1-C_4) está opcionalmente sustituido con hidroxi,

o

R^9 y R^{10}, o R^{11} y R^{12}, respectivamente, se unen y, tomados junto con el átomo de nitrógeno al cual están unidos, forman un anillo heterocicloalquilo monocíclico, saturado de 4 a 6 miembros el cual puede contener un segundo heteroátomo del anillo seleccionado de $N(R^{13})$, O, y $S(O)_2$, y el cual puede estar sustituido en los átomos de carbono del anillo con hasta tres sustituyentes independientemente seleccionados del grupo que consiste en flúor, metilo, oxo, hidroxi, amino y aminocarbonilo, y en la que

R^{13} es hidrógeno, formilo o acetilo,

o una sal, hidrato y/o solvato del mismo farmacéuticamente aceptable.

4. El compuesto de fórmula (I) de acuerdo con la reivindicación 1, 2 o 3, en la que

R^1 es metilo,

R^2 es metoxi,

G^1 representa el grupo -CH_2-OR^3, en la que

R^3 es alquilo (C_1-C_4) opcionalmente sustituido con hidroxi, amino o aminocarbonilo,

y

G^2 representa el grupo -CH_2-NR^9R^{10} o -C(=O)-$NR^{11}R^{12}$, en la que

R^9 es hidrógeno,

R^{10} es 2-oxopirrolidin-3-ilo,

o

R^9 y R^{10} se unen y, tomados junto con el átomo de nitrógeno al cual están unidos, forman un anillo piperazin-1-ilo, 3-oxopiperazin-1-ilo o 4-acetilpiperazin-

1-ilo.

R^{11} es hidrógeno,

R^{12} es 2-oxopirrolidin-3-ilo,

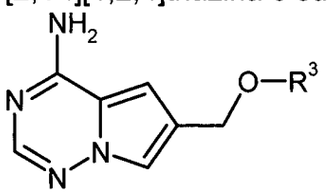
o

R^{11} y R^{12} se unen y, tomados junto con el átomo de nitrógeno al cual están unidos, forman un anillo 3-hidroxiazetidin-1-ilo, 4-hidroxipiperidin-1-ilo o 3-oxopiperazin-1-ilo,

o una sal, hidrato y/o solvato del mismo farmacéuticamente aceptable.

5. Procedimiento de preparación de un compuesto de fórmula (I) como se define en las reivindicaciones 1 a 4, caracterizado porque

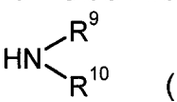
[A] una 4-aminopirrolo[2,1-f][1,2,4]triazina 6 sustituida de fórmula (II)



(II),

en la que R^3 tiene el significado que se indica en las reivindicaciones 1 a 4,

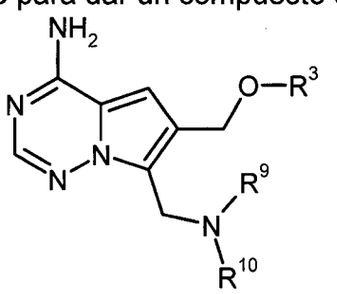
se hace reaccionar primero con formaldehído y una amina de fórmula (III)



(III),

en la que R^9 y R^{10} tienen el significado que se indica en las reivindicaciones 1 a 4,

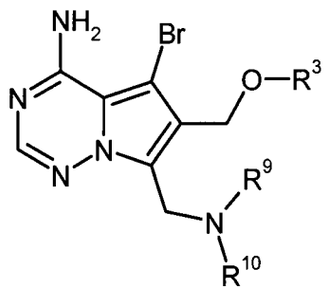
en presencia de un ácido para dar un compuesto de fórmula (IV)



(IV),

en la que R^3, R^9 y R^{10} tienen el significado que se indica en las reivindicaciones 1 a 4,

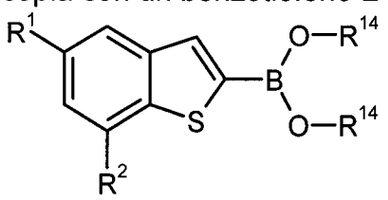
posteriormente se brominan a un compuesto de fórmula (V)



(V),

en la que R^3, R^9 y R^{10} tienen el significado que se indica en las reivindicaciones 1 a 4,

y posteriormente se acopla con un benzotiofeno-2-il boronato de fórmula (VI)



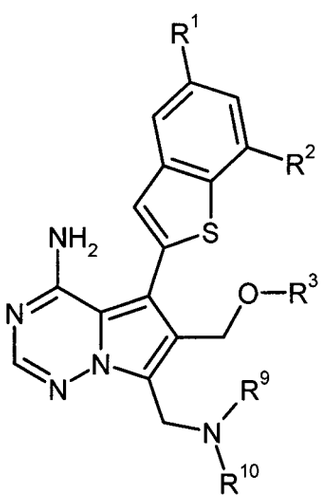
(VI),

en la que R^1 y R^2 tienen el significado que se indica en las reivindicaciones 1 a 4,

y

R^{14} representa hidrógeno o alquilo (C_1-C_4), o ambos residuos R^{14} están enlazados juntos para formar un puente -$(CH_2)_2$-, -$C(CH_3)_2$-$C(CH_3)_2$-, -$(CH_2)_3$-, -CH_2-$C(CH_3)_2$-CH_2- o -C(=O)-CH_2-$N(CH_3)$-CH_2-C(=O)-,

en presencia de un catalizador de paladio y una base para dar el compuesto diana de fórmula (I-A)

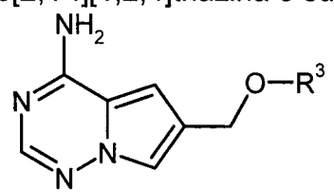


(I-A),

en la que R^1, R^2, R^3, R^9 y R^{10} tienen el significado que se indica en las reivindicaciones 1 a 4,

o

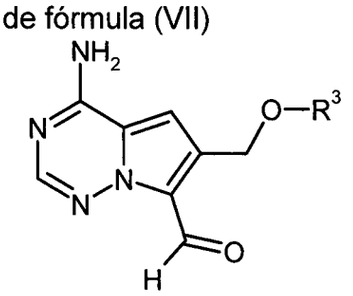
[B] una 4-aminopirrolo[2,1-f][1,2,4]triazina 6 sustituida de fórmula (II)



(II),

en la que R^3 tiene el significado que se indica en las reivindicaciones 1 a 4,

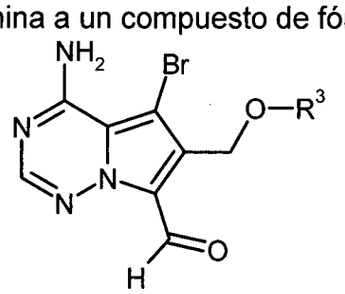
se formila primero con N,N-dimetilformamida en presencia de cloruro de fosforilo a un aldehído de fórmula (VII)



(VII),

en la que R^3 tiene el significado que se indica en las reivindicaciones 1 a 4,

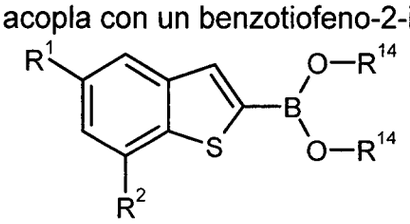
posteriormente se bromina a un compuesto de fórmula (VIII)



(VIII),

en la que R^3 tiene el significado que se indica en las reivindicaciones 1 a 4,

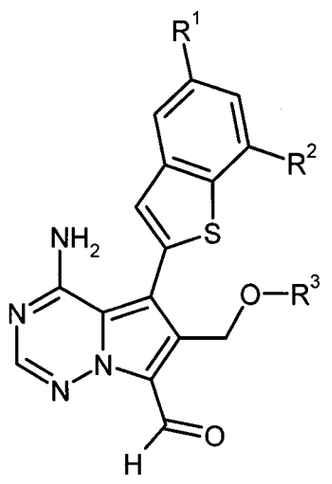
y posteriormente se acopla con un benzotiofeno-2-il boronato de fórmula (VI)



(VI),

en la que R^1, R^2 y R^{14} tienen los significados que se indicaron anteriormente,

en presencia de un catalizador de paladio y una base para dar un compuesto de fórmula (IX)

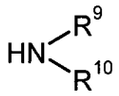


(IX),

en la que R^1, R^2 y R^3 tienen los significados que se indican en las reivindicaciones 1 a 4,

el cual posteriormente o bien

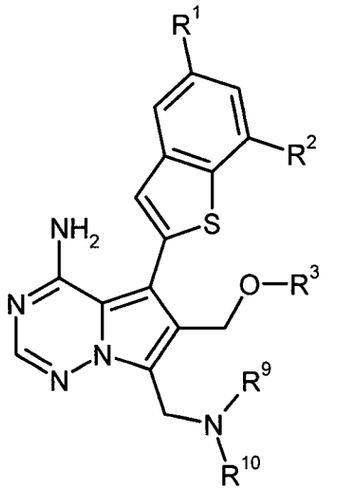
[B-1] se hace reaccionar con una amina de fórmula (III)



(III),

en la que R^9 y R^{10} tienen el significado que se indica en las reivindicaciones 1 a 4,

en presencia de un ácido y un agente reductor para dar el compuesto diana de fórmula (I-A)

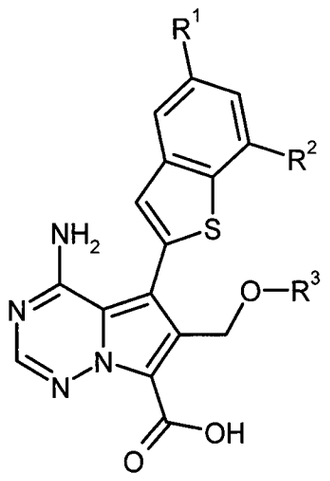


(I-A),

en la que R^1, R^2, R^3, R^9 y R^{10} tienen el significado que se indica en las reivindicaciones 1 a 4,

o

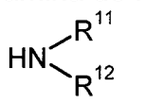
[B-2] se oxida a un ácido carboxílico de fórmula (X)



(X),

en la que R^1, R^2 y R^3 tienen los significados que se indican en las reivindicaciones 1 a 4,

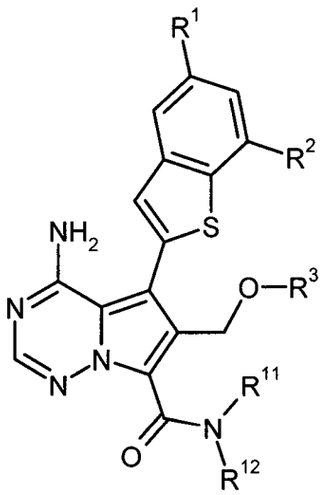
y finalmente se acopla con una amina de fórmula (XI)



(XI),

en la que R^{11} y R^{12} tienen el significado que se indica en las reivindicaciones 1 a 4,

en presencia de un agente de condensación para dar el compuesto diana de fórmula (I-B)

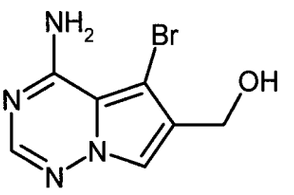


(I-B),

en la que R^1, R^2, R^3, R^{11} y R^{12} tienen el significado que se indica en las reivindicaciones 1 a 4,

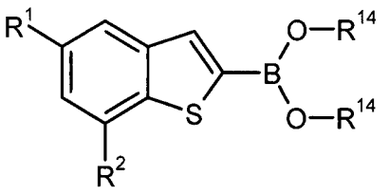
o

[C] una 4-amino-5-bromopirrolo[2,1-f][1,2,4]triazina 6 sustituida de fórmula (XII)



(XII)

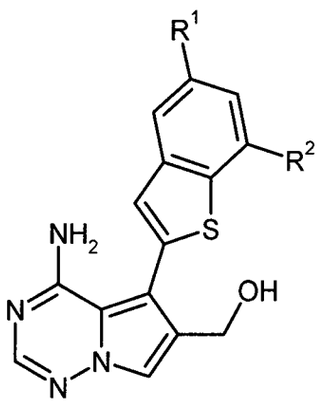
se acopla primero con un benzotiofeno-2-il boronato de fórmula (VI)



(VI),

en la que R^1, R^2 y R^{14} tienen los significados que se indicaron anteriormente,

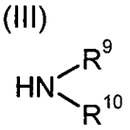
en presencia de un catalizador de paladio y una base para dar un compuesto de fórmula (XIII)



(XIII),

en la que R^1 y R^2 tienen el significado que se indica en las reivindicaciones 1 a 4,

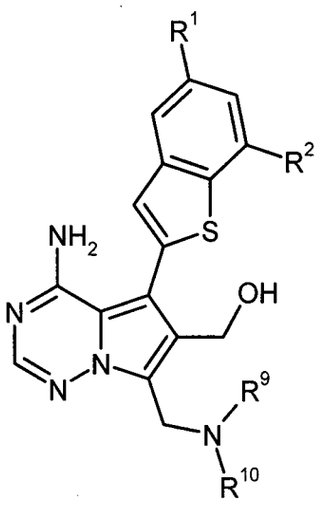
y posteriormente se hace reaccionar con formaldehído y una amina de fórmula (III)



(III),

en la que R^9 y R^{10} tienen el significado que se indica en las reivindicaciones 1 a 4,

en presencia de un ácido para dar el compuesto de fórmula (I-C)

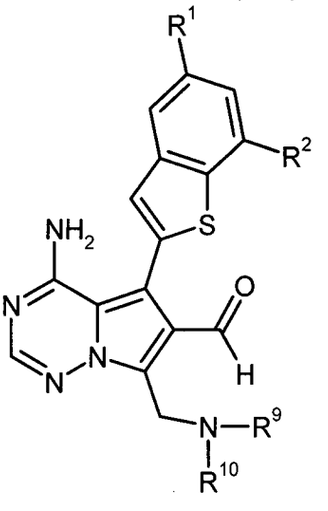


(I-C),

en la que R^1, R^2, R^9 y R^{10} tienen los significados que se indica en las reivindicaciones 1 a 4,

el cual posteriormente o bien

[C-1] se oxida a un aldehído de fórmula (XIV)



(XIV),

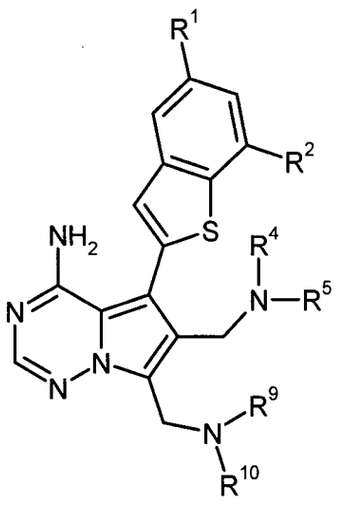
en la que R^1, R^2, R^9 y R^{10} tienen los significados que se indica en las reivindicaciones 1 a 4,

y se trata con una amina de fórmula (XV)

(XV),

en la que R^4 y R^5 tienen el significado que se indica en las reivindicaciones 1 a 4,

en presencia de un ácido y un agente reductor para dar el compuesto diana de fórmula (I-D)

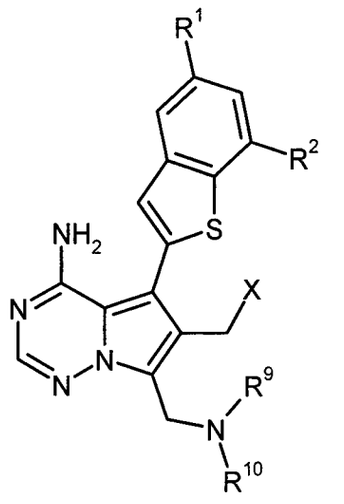


(I-D),

en la que R^1, R^2, R^4, R^5, R^9 y R^{10} tienen el significado que se indica en las reivindicaciones 1 a 4,

o

[C-2] se convierte en el correspondiente derivado 6-(halometilo) de fórmula (XVI)



(XVI),

en la que R^1, R^2, R^9 y R^{10} tienen los significados que se indica en las reivindicaciones 1 a 4,

y

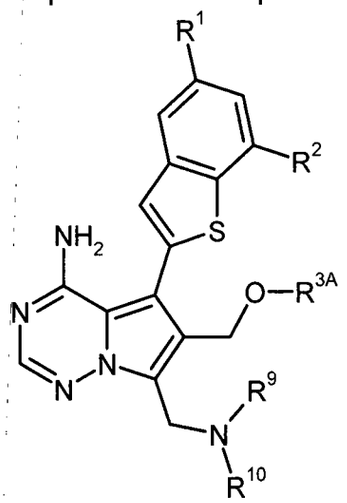
X es cloro, bromo o yodo,

y se trata con un alcohol de fórmula (XVII)

R^{3A}—OH (XVII),

en la que R^{3A} tiene el significado de R^3 como se indica en las reivindicaciones 1 a 4, salvo hidrógeno,

en presencia de una base para dar el compuesto diana de fórmula (I-E)



(I-E),

en la que R^1, R^2, R^{3A}, R^9 y R^{10} tienen los significados que se indicaron anteriormente,

seguido opcionalmente, donde sea apropiado, de (i) separar los compuestos de fórmula (I) obtenidos de este modo en sus respectivos enantiómeros y/o diastereómeros, y/o (ii) convertir los compuestos de fórmula (I) en sus respectivos hidratos, solvatos, sales y/o hidratos o solvatos de las sales mediante el tratamiento con los correspondientes solventes y/o ácidos o bases.

6. El compuesto como se define en cualquiera de las reivindicaciones 1 a 4 para el tratamiento y/o la prevención de enfermedades.

7. El compuesto como se define en cualquiera de las reivindicaciones 1 a 4 para su uso en un procedimiento para el tratamiento y/o la prevención de cáncer y enfermedades tumorales.

8. Uso de un compuesto según se define en cualquiera de las reivindicaciones 1 a 4 para la producción de una composición farmacéutica para el tratamiento y/o la prevención de cáncer y enfermedades tumorales.

9. La composición farmacéutica que comprende un compuesto según se define en cualquiera de las reivindicaciones 1 a 4 y uno o más excipientes farmacéuticamente aceptables.

10. La composición farmacéutica de la reivindicación 9 que comprende además uno o más agentes terapéuticos adicionales.

11. La composición farmacéutica según se define en la reivindicación 9 o 10 para el tratamiento y/o la prevención de cáncer y enfermedades tumorales.

12. Procedimiento para el tratamiento y/o la prevención de cáncer y enfermedades tumorales, que comprende administrar a un mamífero que lo necesita una cantidad eficaz para uso terapéutico de uno o más compuestos según se define en cualquiera de las reivindicaciones 1 a 4, o de una composición farmacéutica según se define en cualquiera de las reivindicaciones 9 a 11.

Benzotienilo-pirrolotriazinas disustituidas y sus usos

Resumen

La presente invención se refiere a novedosos derivados de 5-(1-benzotiofen-2-il)pirrolo[2,1-f][1,2,4]triazin-4-amina que tienen actividades inhibidoras de la proteína tirosina quinasa, a procedimientos de preparación de estos compuestos, a composiciones farmacéuticas que contienen estos compuestos, y al uso de estos compuestos y composiciones para tratar trastornos proliferativos, en particular, cáncer y enfermedades tumorales.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 June 2013 (20.06.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/087578 A1

(51) International Patent Classification:
C07D 487/04 (2006.01) *A61P 35/00* (2006.01)
A61K 31/53 (2006.01)

(21) International Application Number:
PCT/EP2012/074977

(22) International Filing Date:
10 December 2012 (10.12.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
11193841.1 15 December 2011 (15.12.2011) EP

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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, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,

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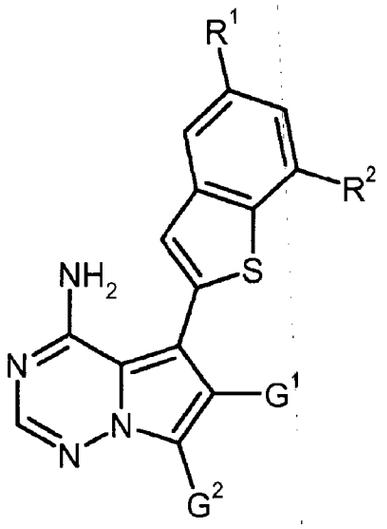
(54) Title: DISUBSTITUTED BENZOTHIENYL-PYRROLOTRIAZINES AND THEIR USE AS FGFR KINASE INHIBITORS



(I),

(57) Abstract: This invention relates to novel substituted 5-(1-benzothiophen-2-yl) pyrrolo[2,1-f][1,2,4]triazin-4-amine derivatives of formula (I) wherein R^1 is hydrogen, chloro, methyl or methoxy, R^2 is hydrogen or methoxy, with the proviso that at least one of R^1 and R^2 is other than hydrogen, G^1 represents chloro, $(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_4)$-alkoxycarbonyl, 5-membered aza-heteroaryl, or the group $-CH_2\text{-}OR^3$, $-CH_2\text{-}NR^4R^5$ or $-C(=O)\text{-}NR^4R^6$, and G^2 represents chloro, cyano, $(C_1\text{-}C_4)$-alkyl, or the group - $CR^{8A}R^{8B}\text{-}OH$, $-CH_2\text{-}NR^9R^{10}$, $-C(=O)\text{-}NR^{11}R^{12}$ or $-CH_2\text{-}OR^{15}$, having protein tyrosine kinase inhibitory activities, 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 proliferative disorders, in particular cancer and tumor diseases.

WO 2013/087578 A1

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))*

DISUBSTITUTED BENZOTHIENYL - PYRROLOTRIAZINES AND THEIR USE AS FGFR KINASE INHIBITORS

This invention relates to novel substituted 5-(1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine derivatives having protein tyrosine kinase inhibitory activities, 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 proliferative disorders, in particular cancer and tumor diseases.

Cancer is a leading cause of death worldwide and accounted for 7.6 million deaths (around 13% of all deaths) in 2008. Deaths from cancer are projected to continue to rise worldwide to over 11 million in 2030 (WHO source, Fact Sheet No. 297, February 2011).

There are many ways how cancers can arise which is one of the reasons why their therapy is difficult. One way that transformation of cells can occur is following a genetic alteration. The completion of the human genome project showed genomic instability and heterogeneity of human cancer genes. Recent strategies to identify these genetic alterations sped up the process of cancer-gene discovery. Gene abnormality can, for instance, lead to the overexpression of proteins, and hence to a non-physiological activation of these proteins. One family of proteins from which a number of onco-proteins derive are tyrosine kinases and in particular receptor tyrosine kinases (RTKs). In the past two decades, numerous avenues of research have demonstrated the importance of RTK-mediated signalling in adverse cell growth leading to cancer. In recent years, promising results have been achieved in the clinic with selective small-molecule inhibitors of tyrosine kinases as a new class of anti-tumorigenic agents [Swinney and Anthony, *Nature Rev. Drug Disc.* 10 (7), 507-519 (2011)].

Fibroblast growth factors (FGFs) and their receptors (FGFRs) form part of a unique and diverse signalling system which plays a key role in a variety of biological processes which encompass various aspects of embryonic development and adult pathophysiology [Itoh and Ornitz, *J. Biochem.* 149 (2), 121-130 (2011)]. In a spatio-temporal manner, FGFs stimulate through FGFR binding a wide range of cellular functions including migration, proliferation, differentiation, and survival.

The FGF family comprises 18 secreted polypeptidic growth factors that bind to four highly conserved receptor tyrosine kinases (FGFR-1 to -4) expressed at the cell surface. In addition, FGFR-5 can bind to FGFs but does not have a kinase domain, and therefore is devoid of intracellular signalling. The specificity of the ligand/receptor interaction is enhanced by a number of transcriptional and translational processes which give rise to multiple isoforms by alternative transcriptional initiation, alternative splicing, and C-terminal truncations. Various heparan sulfate proteoglycans (e.g. syndecans) can be part of the FGF/FGFR complex and strongly influence the ability of FGFs to

induce signalling responses [Polanska *et al.*, *Developmental Dynamics* 238 (2), 277-293 (2009)]. FGFRs are cell surface receptors consisting of three extracellular immunoglobulin-like domains, a single-pass transmembrane domain, and an intracellular dimerized tyrosine kinase domain. Binding of FGF bring the intracellular kinases into close proximity, enabling them to transphosphorylate each other. Seven phosphorylation sites have been identified (e.g., in FGFR-1 Tyr463, Tyr583, Tyr585, Tyr653, Tyr654, Tyr730, and Tyr766).

Some of these phosphotyrosine groups act as docking sites for downstream signalling molecules which themselves may also be directly phosphorylated by FGFR, leading to the activation of multiple signal transduction pathways. Thus, the MAPK signalling cascade is implicated in cell growth and differentiation, the PI3K/Akt signalling cascade is involved in cell survival and cell fate determination, while the PI3K and PKC signalling cascades have a function in the control of cell polarity. Several feedback inhibitors of FGF signalling have now been identified and include members of the Spry (Sprouty) and Sef (similar expression to FGF) families. Additionally, in certain conditions, FGFR is released from pre-Golgi membranes into the cytosol. The receptor and its ligand, FGF-2, are co-transported into the nucleus by a mechanism that involves importin, and are engaged in the CREB-binding protein (CBP) complex, a common and essential transcriptional co-activator that acts as a gene activation gating factor. Multiple correlations between the immuno-histochemical expression of FGF-2, FGFR-1 and FGFR-2 and their cytoplasmic and nuclear tumor cell localizations have been observed. For instance, in lung adenocarcinomas this association is also found at the nuclear level, emphasizing an active role of the complex at the nucleus [Korc and Friesel, *Curr. Cancer Drugs Targets* 5, 639-651 (2009)].

FGFs are widely expressed in both developing and adult tissues and play important roles in a variety of normal and pathological processes, including tissue development, tissue regeneration, angio-genesis, neoplastic transformation, cell migration, cellular differentiation, and cell survival. Additionally, FGFs as pro-angiogenic factors have also been implicated in the emerging phenomenon of resistance to vascular endothelial growth factor receptor-2 (VEGFR-2) inhibition [Bergers and Hanahan, *Nat. Rev. Cancer* 8, 592-603 (2008)].

Recent oncogenomic profiles of signalling networks demonstrated an important role for aberrant FGF signalling in the emergence of some common human cancers [Wesche *et al.*, *Biochem. J.* 437 (2), 199-213 (2011)]. Ligand-independent FGFR constitutive signalling has been described in many human cancers, such as brain cancer, head and neck cancer, gastric cancer and ovarian cancer. FGFR-mutated forms as well as FGFR-intragenic translocations have been identified in malignancies such as myeloproliferative diseases. Interestingly, the same mutations discovered to be

the cause of many developmental disorders are also found in tumor cells (e.g., the mutations found in achondroplasia and thanatophoric dysplasia, which cause dimerization and thus constitutive activation of FGFR-3, are also frequently found in bladder cancer). A mutation that promotes dimerization is just one mechanism that can increase ligand-independent signalling from FGFRs. Other mutations located inside or outside of the kinase domain of FGFRs can change the conformation of the domain giving rise to permanently active kinases.

Amplification of the chromosomal region 8p11-12, the genomic location of *FGFR-1*, is a common focal amplification in breast cancer and occurs in approximately 10% of breast cancers, predominantly in oestrogen receptor-positive cancers. *FGFR-1* amplifications have also been reported in non-small cell lung squamous carcinoma and are found at a low incidence in ovarian cancer, bladder cancer and rhabdomyosarcoma. Similarly, approximately 10% of gastric cancers show *FGFR-2* amplification, which is associated with poor prognosis, diffuse-type cancers. Moreover, multiple single nucleotide polymorphisms (SNPs) located in FGFR-1 to -4 were found to correlate with an increased risk of developing selective cancers, or were reported to be associated with poor prognosis (e.g., FGFR-4 G388R allele in breast cancer, colon cancer and lung adenocarcinoma). The direct role of these SNPs to promote cancer is still controversial.

In summary, a great number of *in vitro* and *in vivo* studies have been performed that validate FGFR-1 to -4 as important cancer targets, and comprehensive reviews have summarized these findings [see, for example, Heinzle *et al.*, *Expert Opin. Ther. Targets* 15 (7), 829-846 (2011); Wesche *et al.*, *Biochem. J.* 437 (2), 199-213 (2011); Greulich and Pollock, *Trends in Molecular Medicine* 17 (5), 283-292 (2011); Haugsten *et al.*, *Mol. Cancer Res.* 8 (11), 1439-1452 (2010)]. Several strategies have been followed to attenuate aberrant FGFR-1 to -4 signalling in human tumors including blocking antibodies and small-molecule inhibitors, amongst others. A number of selective small-molecule FGFR inhibitors are currently in clinical development, such as AZD-4547 (AstraZeneca) and BJG-398 (Novartis).

Notwithstanding the significant advancements that have generally been achieved in cancer therapy in recent years, there is a continuing need to identify new anti-cancer compounds with improved properties, such as higher potency, greater selectivity, reduced toxicity and/or better tolerability. Therefore, the technical problem to be solved according to the present invention may be seen in providing alternative compounds having inhibitory activity on the FGFR kinases, thus offering new therapeutic options for the treatment of FGFR-mediated diseases, in particular cancer and other proliferative disorders.

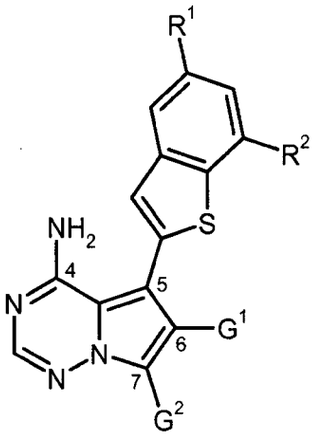
Fused hetero-5,6-bicyclic kinase inhibitors bearing a 9- or a 10-membered bicyclic heteroaryl substituent have been disclosed in WO 2007/061737-A2 and WO 2005/097800-A1, respectively. These compounds were stated to be useful for the treatment of cancer and other diseases owing to their inhibitory action on the mTOR (mammalian target of Rapamycin) and/or IGF-1R (type 1 insulin-like growth factor receptor) kinases. Further hetero-5,6-bicyclic template structures associated with the inhibition of kinases have been described in, *inter alia*, WO 01/19828-A2, WO 2007/079164-A2 and WO 2010/051043-A1.

4-Aminopyrrolo[2,1-f][1,2,4]triazine derivatives with differing inhibition profiles against a number of protein kinases have been disclosed in, *inter alia*, WO 00/71129-A1, WO 2007/056170-A2, WO 2007/061882-A2, WO 2007/064932-A2, WO 2009/136966-A1, and WO 2010/126960-A1.

In WO 2005/121147-A1, WO 2007/064883-A2 and WO 2007/064931-A2, 4-aminopyrrolo[2,1-f]-[1,2,4]triazine derivatives containing a substituted diarylurea group in 5-position were described as having FGFR-1 inhibiting activity. However, other receptor tyrosine kinases, notably the VEGFR, PDGFR and Tie-2 kinases, are also significantly inhibited by this particular class of compounds. As it was hypothesized that such multi-kinase activity might lead to an augmentation of potential side effects during treatment, it was the aim of the present invention to identify new agents having an improved selectivity for the FGFR kinases, thus providing new options for a more tolerable cancer therapy.

Surprisingly, it has now been found that certain 4-aminopyrrolo[2,1-f][1,2,4]triazine derivatives bearing a specifically substituted benzothiophen-2-yl residue in 5-position exhibit potent and selective inhibition of FGFR kinases, notably of the FGFR-1 and FGFR-3 kinases, which renders these compounds particularly useful for the treatment of proliferative disorders, such as cancer and tumor diseases.

Thus, in one aspect, the present invention relates to 6,7-disubstituted 5-(1-benzothiophen-2-yl)-pyrrolo[2,1-f][1,2,4]triazin-4-amine derivatives of the general formula (I)



(I),

wherein

R^1 is hydrogen, chloro, methyl or methoxy,

R^2 is hydrogen or methoxy,

with the proviso that at least one of R^1 and R^2 is other than hydrogen,

G^1 represents chloro, $(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_4)$-alkoxycarbonyl, 5-membered aza-heteroaryl, or the group $-CH_2\text{-}OR^3$, $-CH_2\text{-}NR^4R^5$ or $-C(=O)\text{-}NR^4R^6$, wherein

R^3 is hydrogen, $(C_1\text{-}C_4)$-alkyl, $(C_3\text{-}C_6)$-cycloalkyl or phenyl, wherein

(*i*) said $(C_1\text{-}C_4)$-alkyl is optionally substituted with hydroxy, $(C_1\text{-}C_4)$-alkoxy, hydroxycarbonyl, $(C_1\text{-}C_4)$-alkoxycarbonyl, amino, aminocarbonyl, mono-$(C_1\text{-}C_4)$-alkylaminocarbonyl, di-$(C_1\text{-}C_4)$-alkylaminocarbonyl, $(C_3\text{-}C_6)$-cycloalkyl or up to three fluoro atoms,

and

(*ii*) said $(C_3\text{-}C_6)$-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of $(C_1\text{-}C_4)$-alkyl, hydroxy and amino,

and

(*iii*) said phenyl is optionally substituted with one or two substituents independently selected from the group consisting of fluoro, chloro, bromo, cyano, trifluoromethyl, trifluoromethoxy, $(C_1\text{-}C_4)$-alkyl and $(C_1\text{-}C_4)$-alkoxy,

R^4 is hydrogen or $(C_1$-$C_4)$-alkyl,

R^5 is hydrogen, $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkylcarbonyl, $(C_3$-$C_6)$-cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein

(*i*) said $(C_1$-$C_4)$-alkyl is optionally substituted with hydroxy, $(C_1$-$C_4)$-alkoxy, hydroxycarbonyl, $(C_1$-$C_4)$-alkoxycarbonyl, aminocarbonyl, mono-$(C_1$-$C_4)$-alkyl-aminocarbonyl, di-$(C_1$-$C_4)$-alkylaminocarbonyl or $(C_3$-$C_6)$-cycloalkyl,

and

(*ii*) said $(C_3$-$C_6)$-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of $(C_1$-$C_4)$-alkyl, hydroxy and amino,

and

(*iii*) said 4- to 6-membered heterocycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of $(C_1$-$C_4)$-alkyl, hydroxy, oxo and amino,

R^6 is hydrogen, $(C_1$-$C_4)$-alkyl, $(C_3$-$C_6)$-cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein

(*i*) said $(C_1$-$C_4)$-alkyl is optionally substituted with hydroxy, $(C_1$-$C_4)$-alkoxy, hydroxycarbonyl, $(C_1$-$C_4)$-alkoxycarbonyl, amino, aminocarbonyl, mono-$(C_1$-$C_4)$-alkylaminocarbonyl, di-$(C_1$-$C_4)$-alkylaminocarbonyl or $(C_3$-$C_6)$-cycloalkyl,

and

(*ii*) said $(C_3$-$C_6)$-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of $(C_1$-$C_4)$-alkyl, hydroxy and amino,

and

(*iii*) said 4- to 6-membered heterocycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of $(C_1$-$C_4)$-alkyl, hydroxy, oxo and amino,

or

R^4 and R^5, or R^4 and R^6, respectively, are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 4- to 7-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from $N(R^7)$ and O, and which may be substituted on ring carbon atoms with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, oxo, hydroxy, amino and aminocarbonyl, and wherein

R^7 is hydrogen, (C_1-C_4)-alkyl, formyl or (C_1-C_4)-alkylcarbonyl,

and

G^2 represents chloro, cyano, (C_1-C_4)-alkyl, or the group $-CR^{8A}R^{8B}-OH$, $-CH_2-NR^9R^{10}$, $-C(=O)-NR^{11}R^{12}$ or $-CH_2-OR^{15}$, wherein

R^{8A} and R^{8B} are independently selected from the group consisting of hydrogen, (C_1-C_4)-alkyl, cyclopropyl and cyclobutyl,

R^9 is hydrogen or (C_1-C_4)-alkyl,

R^{10} is hydrogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkylcarbonyl, (C_3-C_6)-cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein

(*i*) said (C_1-C_4)-alkyl is optionally substituted with hydroxy, amino, aminocarbonyl, mono-(C_1-C_4)-alkylaminocarbonyl or di-(C_1-C_4)-alkylaminocarbonyl,

and

(*ii*) said (C_3-C_6)-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy and amino,

and

(*iii*) said 4- to 6-membered heterocycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy, oxo and amino,

R^{11} is hydrogen or (C_1-C_4)-alkyl,

R^{12} is hydrogen, $(C_1\text{-}C_4)$-alkyl, $(C_3\text{-}C_6)$-cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein

(*i*) said $(C_1\text{-}C_4)$-alkyl is optionally substituted with hydroxy, amino, aminocarbonyl, mono-$(C_1\text{-}C_4)$-alkylaminocarbonyl or di-$(C_1\text{-}C_4)$-alkylaminocarbonyl,

and

(*ii*) said $(C_3\text{-}C_6)$-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of $(C_1\text{-}C_4)$-alkyl, hydroxy and amino,

and

(*iii*) said 4- to 6-membered heterocycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of $(C_1\text{-}C_4)$-alkyl, hydroxy, oxo and amino,

or

R^9 and R^{10}, or R^{11} and R^{12}, respectively, are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 4- to 7-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from $N(R^{13})$, O, S and $S(O)_2$, and which may be substituted on ring carbon atoms with up to three substituents independently selected from the group consisting of fluoro, $(C_1\text{-}C_4)$-alkyl, oxo, hydroxy, amino and aminocarbonyl, and wherein

R^{13} is hydrogen, $(C_1\text{-}C_4)$-alkyl, $(C_3\text{-}C_6)$-cycloalkyl, formyl or $(C_1\text{-}C_4)$-alkylcarbonyl,

and

R^{15} is $(C_1\text{-}C_4)$-alkyl,

with the proviso that G^1 is not chloro when G^2 is chloro or cyano.

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 (I-A), (I-B), (I-C), (I-D) and (I-E) 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 process products and/or 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, formic acid, acetic acid, trifluoroacetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid, and benzoic acid.

Pharmaceutically acceptable salts also include salts of customary bases, such as for example and preferably alkali metal salts (for example sodium and potassium salts), alkaline earth metal salts (for example calcium and magnesium salts), and ammonium salts derived from ammonia or organic amines, such as illustratively and preferably ethylamine, diethylamine, triethylamine, *N,N*-diisopropylethylamine, monoethanolamine, diethanolamine, triethanolamine, dimethylaminoethanol, diethylaminoethanol, procaine, dicyclohexylamine, dibenzylamine, *N*-methylmorpholine, *N*-methylpiperidine, arginine, lysine, and 1,2-ethylenediamine.

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.

The present invention also encompasses all suitable isotopic variants of the compounds according to the invention. An isotopic variant of a compound according to the invention is understood to mean a compound in which at least one atom within the compound according to the invention has been exchanged for another atom of the same atomic number, but with a different atomic mass than the atomic mass which usually or predominantly occurs in nature. Examples of isotopes which can be incorporated into a compound according to the invention are those of hydrogen, carbon, nitrogen, oxygen, fluorine, chlorine, bromine and iodine, such as ^{2}H (deuterium), ^{3}H (tritium), ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{18}F, ^{36}Cl, ^{82}Br, ^{123}I, ^{124}I, ^{129}I and ^{131}I. Particular isotopic variants of a compound according to the invention, especially those in which one or more radioactive isotopes have been incorporated, may be beneficial, for example, for the examination of the mechanism of action or of the active compound distribution in the body. Due to comparatively easy preparability and detectability, especially compounds labelled with ^{3}H or ^{14}C isotopes are suitable for this purpose. In addition, the incorporation of isotopes, for example of deuterium, can lead to particular therapeutic benefits as a consequence of greater metabolic stability of the compound, for example an extension of the half-life in the body or a reduction in the active dose required. Such modifications of the compounds according to the invention may therefore in some cases also constitute a preferred embodiment of the present invention. Isotopic variants of the compounds according to the invention can be prepared by

processes known to those skilled in the art, for example by the methods described below and the methods described in the working examples, by using corresponding isotopic modifications of the particular reagents and/or starting compounds therein.

In the context of the present invention, the substituents and residues have the following meaning, unless specified otherwise:

(C1-C4)-Alkyl in the context of the invention represents a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. There may be mentioned by way of example and preferably: methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *iso*-butyl, *sec*-butyl, and *tert*-butyl.

(C1-C4)-Alkoxy in the context of the invention represents a straight-chain or branched alkoxy radical having 1 to 4 carbon atoms. There may be mentioned by way of example and preferably: methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *iso*-butoxy, *sec*-butoxy, and *tert*-butoxy.

Mono-(C1-C4)-alkylamino in the context of the invention represents an amino group with a straight-chain or branched alkyl substituent which contains 1 to 4 carbon atoms. There may be mentioned by way of example and preferably: methylamino, ethylamino, *n*-propylamino, isopropylamino, *n*-butylamino, and *tert*-butylamino.

Di-(C1-C4)-alkylamino in the context of the invention represents an amino group with two identical or different straight-chain or branched alkyl substituents which each contain 1 to 4 carbon atoms. There may be mentioned by way of example and preferably: *N,N*-dimethylamino, *N,N*-diethylamino, *N*-ethyl-*N*-methylamino, *N*-methyl-*N*-*n*-propylamino, *N*-isopropyl-*N*-methylamino, *N*-isopropyl-*N*-*n*-propylamino, *N,N*-diisopropylamino, *N*-*n*-butyl-*N*-methylamino, and *N*-*tert*-butyl-*N*-methylamino.

(C1-C4)-Alkylcarbonyl in the context of the invention represents a straight-chain or branched alkyl radical having 1 to 4 carbon atoms which is bonded to the rest of the molecule via a carbonyl group [-C(=O)-]. There may be mentioned by way of example and preferably: acetyl, propionyl, *n*-butyryl, *iso*-butyryl, *n*-pentanoyl, and pivaloyl.

(C1-C4)-Alkoxycarbonyl in the context of the invention represents a straight-chain or branched alkoxy radical having 1 to 4 carbon atoms which is bonded to the rest of the molecule via a carbonyl group [-C(=O)-]. There may be mentioned by way of example and preferably: methoxycarbonyl, ethoxycarbonyl, *n*-propoxycarbonyl, isopropoxycarbonyl, *n*-butoxycarbonyl, and *tert*-butoxycarbonyl.

Mono-(C_1-C_4)-alkylaminocarbonyl in the context of the invention represents an amino group which is bonded to the rest of the molecule via a carbonyl group [-C(=O)-] and which has a straight-chain or branched alkyl substituent having 1 to 4 carbon atoms. There may be mentioned by way of example and preferably: methylaminocarbonyl, ethylaminocarbonyl, *n*-propylaminocarbonyl, isopropylaminocarbonyl, *n*-butylaminocarbonyl, and *tert*-butylaminocarbonyl.

Di-(C_1-C_4)-alkylaminocarbonyl in the context of the invention represents an amino group which is bonded to the rest of the molecule via a carbonyl group [-C(=O)-] and which has two identical or different straight-chain or branched alkyl substituents having in each case 1 to 4 carbon atoms. There may be mentioned by way of example and preferably: *N,N*-dimethylaminocarbonyl, *N,N*-diethylaminocarbonyl, *N*-ethyl-*N*-methylaminocarbonyl, *N*-methyl-*N*-*n*-propylaminocarbonyl, *N*-isopropyl-*N*-methylaminocarbonyl, *N,N*-diisopropylaminocarbonyl, *N*-*n*-butyl-*N*-methylaminocarbonyl, and *N*-*tert*-butyl-*N*-methylaminocarbonyl.

(C_3-C_6)-Cycloalkyl in the context of the invention represents a monocyclic, saturated carbocycle having 3 to 6 ring carbon atoms. There may be mentioned by way of example: cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Preferred are cyclopropyl and cyclobutyl.

4- to 7-membered heterocycloalkyl and 4- to 6-membered heterocycloalkyl in the context of the invention represent a monocyclic, saturated heterocycle with 4 to 7 or, respectively, 4 to 6 ring atoms in total, which contains one or two identical or different ring heteroatoms from the series N, O, S and $S(O)_2$, and which can be bonded via a ring carbon atom or via a ring nitrogen atom (if present). 4- to 6-membered heterocycloalkyl containing one ring nitrogen atom and optionally one further ring heteroatom from the series N, O or $S(O)_2$ is preferred. 5- or 6-membered heterocycloalkyl containing one ring nitrogen atom and optionally one further ring heteroatom from the series N or O is particularly preferred. There may be mentioned by way of example: azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, tetrahydrofuranyl, thiolanyl, 1,1-dioxidothiolanyl, 1,2-oxazolidinyl, 1,3-oxazolidinyl, 1,3-thiazolidinyl, piperidinyl, piperazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,2-oxazinanyl, morpholinyl, thiomorpholinyl, 1,1-dioxidothiomorpholinyl, azepanyl, 1,4-diazepanyl, and 1,4-oxazepanyl. Preferred are azetidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, 1,2-oxazolidinyl, 1,3-oxazolidinyl, piperidinyl, piperazinyl, 1,2-oxazinanyl, morpholinyl, and thiomorpholinyl. Particularly preferred are pyrrolidinyl, piperidinyl, piperazinyl, and morpholinyl.

5-membered aza-heteroaryl in the context of the invention represents an aromatic heterocyclic radical (heteroaromatic) having 5 ring atoms in total, which contains at least one ring nitrogen atom and optionally one or two further ring heteroatoms from the series N, O and/or S, and which is bonded

via a ring carbon atom or optionally via a ring nitrogen atom (when allowed by valency). 5-membered aza-heteroaryl containing one ring nitrogen atom and one or two further ring hetero-atoms from the series N and/or O is preferred. There may be mentioned by way of example: pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, and thiadiazolyl. Preferred are pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, and oxadiazolyl.

An oxo substituent in the context of the invention represents an oxygen atom, which is bonded to a carbon atom via a double bond.

In the context of the present invention, for all the radicals which occur several times, the meaning thereof is independent of each other. If radicals in the compounds according to the invention are substituted, the radicals can be mono- or polysubstituted, unless specified otherwise. Substitution by one or by two or three identical or different substituents is preferred. Substitution by one or by two identical or different substituents is particularly preferred.

In a preferred embodiment, the present invention relates to compounds of general formula (I), wherein

R^1 is chloro, methyl or methoxy,

R^2 is hydrogen or methoxy,

G^1 represents chloro, $(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_4)$-alkoxycarbonyl or 5-membered aza-heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl, or represents the group $-CH_2\text{-}OR^3$ or $-CH_2\text{-}NR^4R^5$, wherein

R^3 is hydrogen, $(C_1\text{-}C_4)$-alkyl or $(C_3\text{-}C_6)$-cycloalkyl,

wherein said $(C_1\text{-}C_4)$-alkyl is optionally substituted with hydroxy, $(C_1\text{-}C_4)$-alkoxy, hydroxycarbonyl, $(C_1\text{-}C_4)$-alkoxycarbonyl, amino, aminocarbonyl, $(C_3\text{-}C_6)$-cycloalkyl or up to three fluoro atoms,

R^4 is hydrogen or $(C_1\text{-}C_4)$-alkyl,

R^5 is hydrogen, $(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_4)$-alkylcarbonyl, $(C_3\text{-}C_6)$-cycloalkyl or 5- or 6-membered heterocycloalkyl, wherein

(*i*) said $(C_1\text{-}C_4)$-alkyl is optionally substituted with hydroxy, hydroxycarbonyl or $(C_3\text{-}C_6)$-cycloalkyl,

and

(*ii*) said 5- or 6-membered heterocycloalkyl is optionally substituted with oxo,

or

R^4 and R^5 are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 4- to 6-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from $N(R^7)$ and O, and which may be substituted on a ring carbon atom with oxo or hydroxy, and wherein

R^7 is hydrogen or $(C_1\text{-}C_4)$-alkyl,

and

G^2 represents chloro, cyano, $(C_1\text{-}C_4)$-alkyl, or the group $-CR^{8A}R^{8B}\text{-}OH$, $-CH_2\text{-}NR^9R^{10}$, $-C(=O)\text{-}NR^{11}R^{12}$ or $-CH_2\text{-}OR^{15}$, wherein

R^{8A} and R^{8B} are independently selected from the group consisting of hydrogen, $(C_1\text{-}C_4)$-alkyl and cyclopropyl,

R^9 is hydrogen or methyl,

R^{10} is hydrogen, $(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_4)$-alkylcarbonyl, $(C_3\text{-}C_6)$-cycloalkyl or 5- or 6-membered heterocycloalkyl, wherein

(*i*) said $(C_1\text{-}C_4)$-alkyl is optionally substituted with hydroxy or aminocarbonyl,

and

(*ii*) said 5- or 6-membered heterocycloalkyl is optionally substituted with oxo,

R^{11} is hydrogen or methyl,

R^{12} is hydrogen, $(C_1\text{-}C_4)$-alkyl, $(C_3\text{-}C_6)$-cycloalkyl or 5- or 6-membered heterocycloalkyl, wherein

(*i*) said $(C_1\text{-}C_4)$-alkyl is optionally substituted with hydroxy,

and

(*ii*) said 5- or 6-membered heterocycloalkyl is optionally substituted with oxo,

or

R^9 and R^{10}, or R^{11} and R^{12}, respectively, are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 4- to 6-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from $N(R^{13})$, O, S and $S(O)_2$, and which may be substituted on ring carbon atoms with up to three substituents independently selected from the group consisting of fluoro, (C_1-C_4)-alkyl, oxo, hydroxy, amino and aminocarbonyl, and wherein

R^{13} is hydrogen, (C_1-C_4)-alkyl, cyclopropyl, cyclobutyl, formyl or (C_1-C_4)-alkyl-carbonyl,

and

R^{15} is methyl or ethyl,

with the proviso that G^1 is not chloro when G^2 is chloro or cyano.

In a particularly preferred embodiment, the present invention relates to compounds of general formula (I), wherein

R^1 is methyl,

R^2 is methoxy,

G^1 represents methyl, oxazol-5-yl or the group $-CH_2-OR^3$ or $-CH_2-NR^4R^5$, wherein

R^3 is hydrogen, (C_1-C_4)-alkyl, cyclopropyl or cyclobutyl,

wherein said (C_1-C_4)-alkyl is optionally substituted with hydroxy, methoxy, ethoxy, hydroxycarbonyl, methoxycarbonyl, ethoxycarbonyl, amino, aminocarbonyl, cyclopropyl, cyclobutyl or up to three fluoro atoms,

R^4 is hydrogen, methyl or ethyl,

R^5 is hydrogen, (C_1-C_4)-alkyl, acetyl, cyclopropyl, cyclobutyl or 2-oxopyrrolidin-3-yl,

wherein said (C_1-C_4)-alkyl is optionally substituted with hydroxy, hydroxycarbonyl, cyclopropyl or cyclobutyl,

or

R^4 and R^5 are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 5- or 6-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from NH and O, and which may be substituted on a ring carbon atom with oxo or hydroxy,

and

G^2 represents methyl or the group $-CR^{8A}R^{8B}-OH$, $-CH_2-NR^9R^{10}$ or $-C(=O)-NR^{11}R^{12}$, wherein

R^{8A} and R^{8B} are independently hydrogen or methyl,

R^9 is hydrogen,

R^{10} is hydrogen, (C_1-C_4)-alkyl, acetyl, cyclopropyl, cyclobutyl or 2-oxopyrrolidin-3-yl,

wherein said (C_1-C_4)-alkyl is optionally substituted with hydroxy or aminocarbonyl,

R^{11} is hydrogen or methyl,

R^{12} is hydrogen, (C_1-C_4)-alkyl, cyclopropyl, cyclobutyl or 2-oxopyrrolidin-3-yl,

wherein said (C_1-C_4)-alkyl is optionally substituted with hydroxy,

or

R^9 and R^{10}, or R^{11} and R^{12}, respectively, are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 4- to 6-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from $N(R^{13})$, O and $S(O)_2$, and which may be substituted on ring carbon atoms with up to three substituents independently selected from the group consisting of fluoro, methyl, oxo, hydroxy, amino and aminocarbonyl, and wherein

R^{13} is hydrogen, formyl or acetyl.

In a distinct embodiment, the present invention relates to compounds of general formula (I), wherein

R^1 is methyl,

and

R^2 is methoxy.

In a further distinct embodiment, the present invention relates to compounds of general formula (I), wherein

G^1 represents the group $-CH_2-OR^3$, wherein

R^3 is hydrogen or (C_1-C_4)-alkyl optionally substituted with hydroxy, methoxy, amino, aminocarbonyl or up to three fluoro atoms.

In another distinct embodiment, the present invention relates to compounds of general formula (I), wherein

G^1 represents the group $-CH_2-NR^4R^5$, wherein

R^4 is hydrogen or methyl,

R^5 is (C_1-C_4)-alkyl, acetyl, cyclopropyl, cyclobutyl or 2-oxopyrrolidin-3-yl,

wherein said (C_1-C_4)-alkyl is optionally substituted with hydroxy,

or

R^4 and R^5 are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 5- or 6-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from NH and O, and which may be substituted on a ring carbon atom with oxo or hydroxy.

In another distinct embodiment, the present invention relates to compounds of general formula (I), wherein

G^2 represents the group $-CH_2-NR^9R^{10}$, wherein

R^9 is hydrogen,

R^{10} is acetyl or 2-oxopyrrolidin-3-yl,

or

R^9 and R^{10} are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 5- or 6-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from $N(R^{13})$ and O, and which may be

substituted on ring carbon atoms with up to two substituents independently selected from the group consisting of methyl, oxo, hydroxy and amino, and wherein

R^{13} is hydrogen, formyl or acetyl.

In yet another distinct embodiment, the present invention relates to compounds of general formula (I), wherein

G^2 represents the group $-C(=O)-NR^{11}R^{12}$, wherein

R^{11} is hydrogen,

R^{12} is (C_1-C_4)-alkyl or 2-oxopyrrolidin-3-yl,

wherein said (C_1-C_4)-alkyl is optionally substituted with hydroxy,

or

R^{11} and R^{12} are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 4- to 6-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from NH and O, and which may be substituted on a ring carbon atom with oxo or hydroxy.

In an especially preferred embodiment, the present invention relates to compounds of general formula (I), wherein

R^1 is methyl,

R^2 is methoxy,

G^1 represents the group $-CH_2-OR^3$, wherein

R^3 is (C_1-C_4)-alkyl optionally substituted with hydroxy, amino or aminocarbonyl,

and

G^2 represents the group $-CH_2-NR^9R^{10}$ or $-C(=O)-NR^{11}R^{12}$, wherein

R^9 is hydrogen,

R^{10} is 2-oxopyrrolidin-3-yl,

or

R^9 and R^{10} are joined and, taken together with the nitrogen atom to which they are attached, form a piperazin-1-yl, 3-oxopiperazin-1-yl or 4-acetylpiperazin-1-yl ring,

R^{11} is hydrogen,

R^{12} is 2-oxopyrrolidin-3-yl,

or

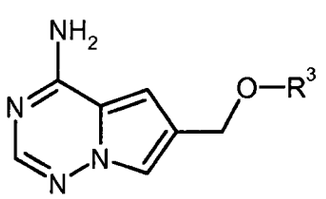
R^{11} and R^{12} are joined and, taken together with the nitrogen atom to which they are attached, form a 3-hydroxyazetidin-1-yl, 4-hydroxypiperidin-1-yl or 3-oxopiperazin-1-yl ring.

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.

The compounds of the general formula (I) can be prepared by various synthetic routes which are primarily governed by the nature of the particular G^1 and G^2 groups chosen (see definitions above).

Thus, in another embodiment, the present invention relates to a process for preparing the compounds of the general formula (I), characterized in that

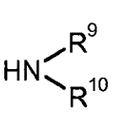
[A] a 6-substituted 4-aminopyrrolo[2,1-f][1,2,4]triazine of formula (II)



(II),

wherein R^3 has the meaning described above,

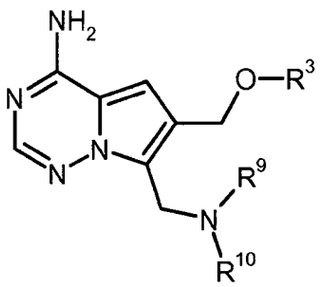
is at first reacted with formaldehyde and an amine of formula (III)



(III),

wherein R^9 and R^{10} have the meanings described above,

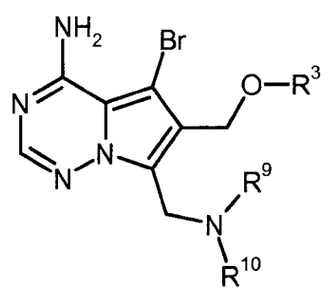
in the presence of an acid to give a compound of formula (IV)



(IV),

wherein R^3, R^9 and R^{10} have the meanings described above,

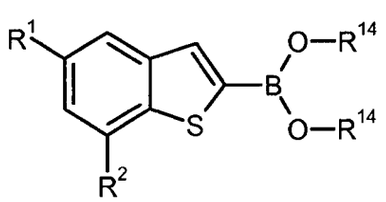
then brominated to a compound of formula (V)



(V),

wherein R^3, R^9 and R^{10} have the meanings described above,

and subsequently coupled with a benzothiophen-2-yl boronate of formula (VI)



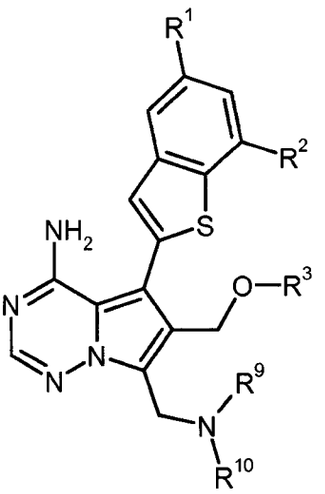
(VI),

wherein R^1 and R^2 have the meanings described above,

and

R^{14} represents hydrogen or $(C_1$-$C_4)$-alkyl, or both R^{14} residues are linked together to form a $-(CH_2)_2-$, $-C(CH_3)_2-C(CH_3)_2-$, $-(CH_2)_3-$, $-CH_2-C(CH_3)_2-CH_2-$ or $-C(=O)-CH_2-N(CH_3)-CH_2-C(=O)-$ bridge,

in the presence of a palladium catalyst and a base to yield the target compound of formula (I-A)

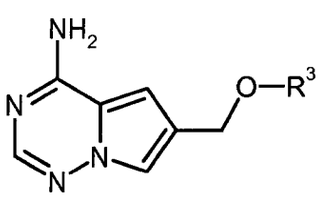


(I-A),

wherein R^1, R^2, R^3, R^9 and R^{10} have the meanings described above,

or

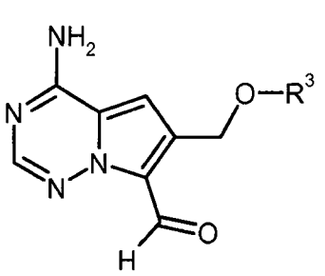
[B] a 6-substituted 4-aminopyrrolo[2,1-f][1,2,4]triazine of formula (II)



(II),

wherein R^3 has the meaning described above,

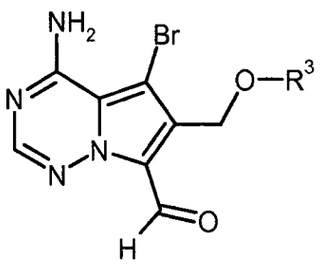
is at first formylated with *N,N*-dimethylformamide in the presence of phosphoryl chloride to an aldehyde of formula (VII)



(VII),

wherein R^3 has the meaning described above,

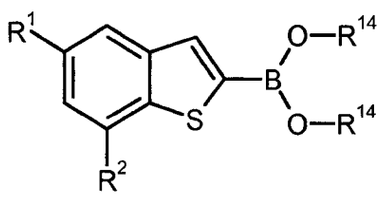
then brominated to a compound of formula (VIII)



(VIII),

wherein R^3 has the meaning described above,

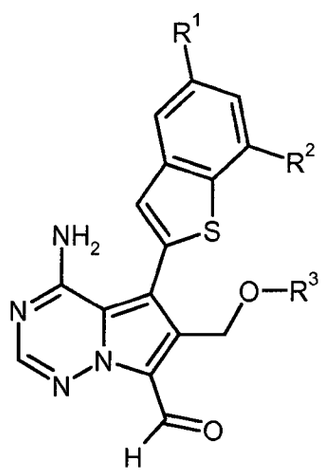
and subsequently coupled with a benzothiophen-2-yl boronate of formula (VI)



(VI),

wherein R^1, R^2 and R^{14} have the meanings described above,

in the presence of a palladium catalyst and a base to give a compound of formula (IX)

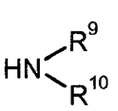


(IX),

wherein R^1, R^2 and R^3 have the meanings described above,

which then is either

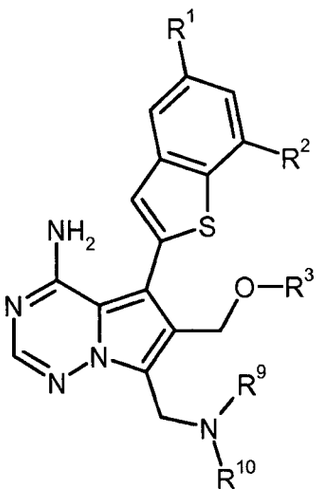
[B-1] reacted with an amine of formula (III)



(III),

wherein R^9 and R^{10} have the meanings described above,

in the presence of an acid and a reducing agent to yield the target compound of formula (I-A)

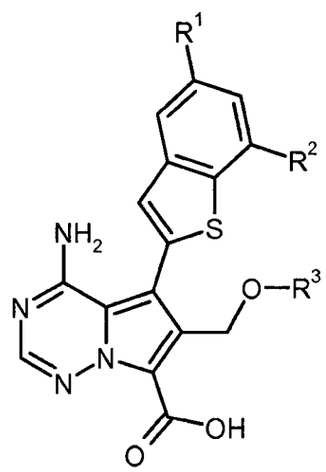


(I-A),

wherein R^1, R^2, R^3, R^9 and R^{10} have the meanings described above,

or

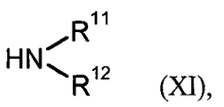
[B-2] oxidized to a carboxylic acid of formula (X)



(X),

wherein R^1, R^2 and R^3 have the meanings described above,

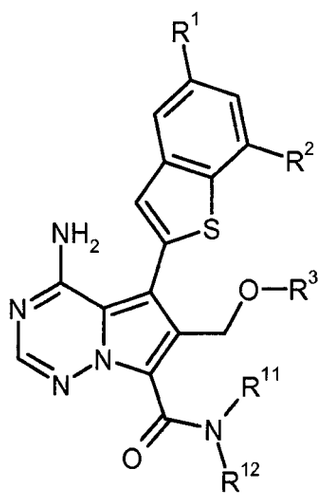
and finally coupled with an amine of formula (XI)



(XI),

wherein R^{11} and R^{12} have the meanings described above,

in the presence of a condensing agent to yield the target compound of formula (I-B)

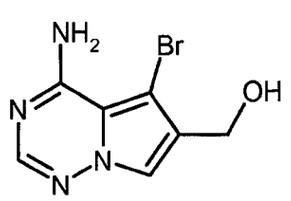


(I-B),

wherein R^1, R^2, R^3, R^{11} and R^{12} have the meanings described above,

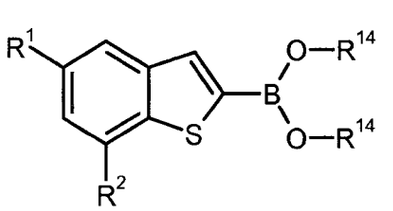
or

[C] a 6-substituted 4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazine of formula (XII)



(XII)

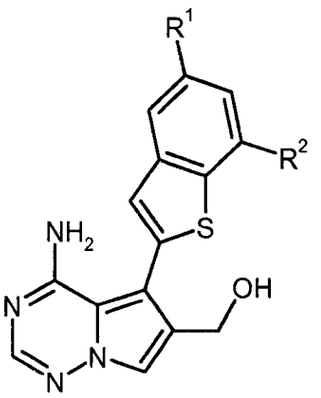
is at first coupled with a benzothiophen-2-yl boronate of formula (VI)



(VI),

wherein R^1, R^2 and R^{14} have the meanings described above,

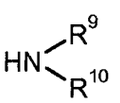
in the presence of a palladium catalyst and a base to give a compound of formula (XIII)



(XIII),

wherein R^1 and R^2 have the meanings described above,

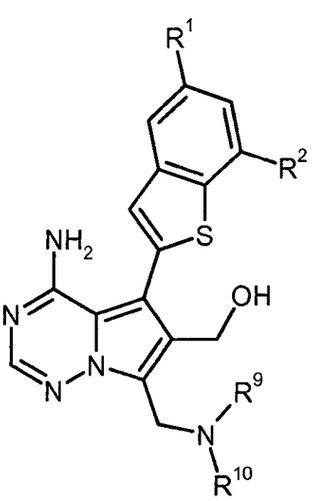
and then reacted with formaldehyde and an amine of formula (III)



(III),

wherein R^9 and R^{10} have the meanings described above,

in the presence of an acid to yield the compound of formula (I-C)



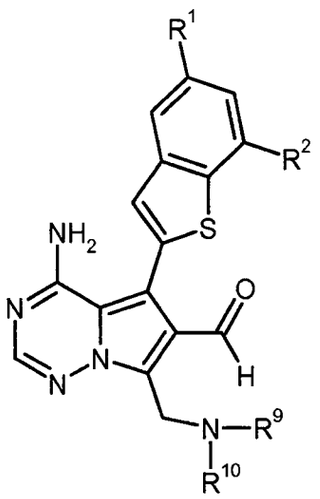
(I-C),

wherein R^1, R^2, R^9 and R^{10} have the meanings described above,

which subsequently is either

[C-1] oxidized to an aldehyde of formula (XIV)

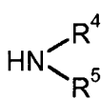
Hoja en blanco



(XIV),

wherein R^1, R^2, R^9 and R^{10} have the meanings described above,

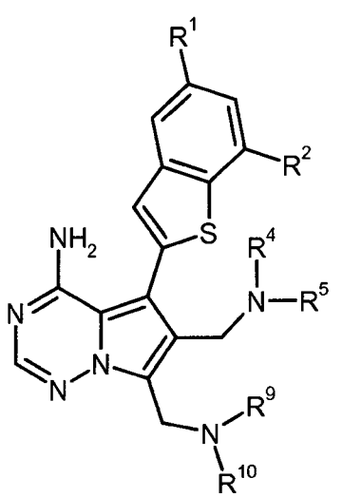
and treated with an amine of formula (XV)



(XV),

wherein R^4 and R^5 have the meanings described above,

in the presence of an acid and a reducing agent to yield the target compound of formula (I-D)

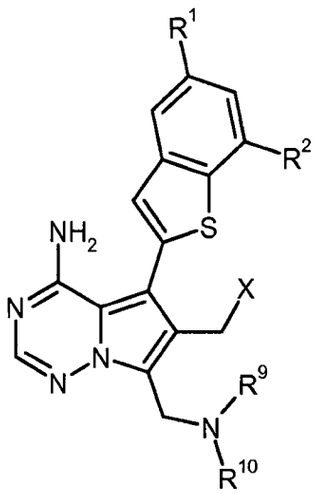


(I-D),

wherein R^1, R^2, R^4, R^5, R^9 and R^{10} have the meanings described above,

or

[C-2] converted into the corresponding 6-(halomethyl) derivative of formula (XVI)



(XVI),

wherein R^1, R^2, R^9 and R^{10} have the meanings described above,

and

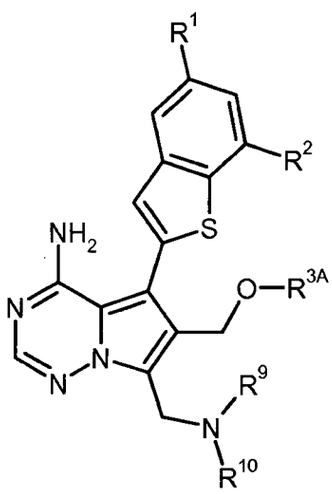
X is chloro, bromo or iodo,

and treated with an alcohol of formula (XVII)

$$R^{3A}—OH \quad (XVII),$$

wherein R^{3A} has the meaning of R^3 as described above except for hydrogen,

in the presence of a base to yield the target compound of formula (I-E)



(I-E),

wherein R^1, R^2, R^{3A}, R^9 and R^{10} have the meanings described above,

optionally followed, where appropriate, by (*i*) separating the compounds of formula (I) thus obtained 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 or bases.

The compounds of the formulae (I-A), (I-B), (I-C), (I-D) and (I-E), which can be prepared by the processes described above, each represent a particular subset of the compounds of the general formula (I).

Process steps [A] (II) → (IV) and [C] (XIII) → (I-C), representing Mannich-type aminomethylation reactions, are carried out in the usual way by treating the respective starting compound with a mixture of aqueous formaldehyde and amine component (III) in the presence of an acid catalyst such as formic acid or acetic acid. Preferably, acetic acid is used both as catalyst and solvent. The reaction is usually performed at a temperature ranging from +20°C to +80°C.

As the brominating agent for process steps [A] (IV) → (V) and [B] (VII) → (VIII), preferably *N*-bromosuccinimide (NBS), 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) or elemental bromine are used. The reactions are generally carried out in an inert solvent, such as dichloromethane, chloroform, tetrahydrofuran, acetonitrile or *N,N*-dimethylformamide (DMF), within a temperature range from -78°C to +20°C.

The coupling reactions [A] (V) + (VI) → (I-A), [B] (VIII) + (VI) → (IX) and [C] (XII) + (VI) → (XIII) ["Suzuki-Miyaura coupling"] are generally carried out in an inert solvent with the aid of a palladium catalyst and an aqueous base. Palladium catalysts suitable for this purpose include, for example, palladium(II) acetate, palladium(II) chloride, bis(triphenylphosphine)palladium(II) chloride, bis(acetonitrile)palladium(II) chloride, [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) chloride, tetrakis(triphenylphosphine)palladium(0), bis(dibenzylideneacetone)palladium(0), and tris-(dibenzylideneacetone)dipalladium(0), optionally in combination with other phosphine ligands such as, for example, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-Phos), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (S-Phos), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos), or 4-(di-*tert*-butylphosphino)-*N,N*-dimethylaniline. Also, palladium pre-catalysts from which the catalytically active species is generated under the reaction conditions, such as (2'-aminobiphenyl-2-yl)(chloro)palladium-dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine, can be used [see, for example, S. Kotha *et al.*, *Tetrahedron* 58, 9633-9695 (2002); T. E. Barder *et al.*, *J. Am.*

Chem. Soc. 127 (13), 4685-4696 (2005); S. L. Buchwald *et al.*, *J. Am. Chem. Soc.* 132 (40), 14073-14075 (2010), and further references cited therein].

Suitable bases for these coupling reactions are in particular alkali carbonates, such as sodium, potassium or caesium carbonate, alkali phosphates, such as sodium or potassium phosphate, or alkali fluorides, such as potassium or caesium fluoride. Usually, these bases are employed as aqueous solutions. The reactions are carried out in organic solvents that are inert under the reaction conditions. Preferably, water-miscible organic solvents, such as 1,2-dimethoxyethane, tetrahydrofuran, 1,4-dioxane, acetonitrile, *N,N*-dimethylformamide (DMF) or dimethylsulfoxide (DMSO), are employed but other inert solvents, such as dichloromethane or toluene, may also be used.

Process step [B] (II) → (VII) ["Vilsmeier-Haack formylation"] is carried out in the usual manner by treating the pyrrolotriazine (II) in *N,N*-dimethylformamide (DMF) solvent with phosphoryl chloride. The reaction is usually performed at a temperature from 0°C to +80°C.

Reducing agents suitable for the reductive amination reactions [B-1] (IX) + (III) → (I-A) and [C-1] (XIV) + (XV) → (I-D) are customary alkali borohydrides, such as lithium borohydride, sodium borohydride, potassium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride. The transformations are generally carried out in the presence of an acid, preferably acetic acid, in an alcohol or ether solvent, such as methanol, ethanol, isopropanol, tetrahydrofuran or 1,4-dioxane, within a temperature range from 0°C to +80°C, depending on the reactivity of the amine components (III) and (XV), respectively, and/or the particular borohydride used.

For the oxidation reaction in process step [B-2] (IX) → (X), oxidation with sodium chlorite in the presence of a hypochlorite scavenger such as 2-methyl-2-butene represents the method of choice [*cf.* H. W. Pinnick *et al.*, *Tetrahedron* 37, 2091-2096 (1981); A. Raach and O. Reiser, *J. Prakt. Chem.* 342 (6), 605-608 (2000), and references cited therein]. The reaction is usually carried out in a tetrahydrofuran/water mixture at a temperature between 0°C and ambient temperature.

Condensing agents suitable for process step [B-2] (X) + (XI) → (I-B) [amide formation] include, for example, carbodiimides such as *N,N'*-diethyl-, *N,N'*-dipropyl-, *N,N'*-diisopropyl-, *N,N'*-dicyclohexylcarbodiimide (DCC) or *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide (EDC), phosgene derivatives such as *N,N'*-carbonyldiimidazole (CDI) or isobutyl chloroformate, α-chloroenamines such as 1-chloro-2-methyl-1-dimethylamino-1-propene, phosphorus compounds such as propanephosphonic anhydride, diethyl cyanophosphonate, bis(2-oxo-3-oxazolidinyl)phosphoryl chloride, benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP) or benzotriazol-1-yloxy-tris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP), and uronium compounds such

as *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU), *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU), 2-(2-oxo-1-(2*H*)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) or *O*-(1*H*-6-chlorobenzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TCTU), if appropriate in combination with further auxiliaries, such as 1-hydroxybenzotriazole (HOBt) or *N*-hydroxysuccinimide (HOSu), and/or bases such as alkali carbonates, for example sodium or potassium carbonate, or organic amine bases, such as triethylamine, *N*-methylpiperidine, *N*-methylmorpholine (NMM), *N,N*-diisopropylethylamine (DIPEA), pyridine or 4-*N,N*-dimethylaminopyridine (DMAP). Preference is given to using *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) or *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) in combination with *N,N*-diisopropylethylamine (DIPEA) and optionally 1-hydroxybenzotriazole (HOBt).

Inert solvents for process step [B-2] (X) + (XI) → (I-B) are, for example, ethers such as diethyl ether, *tert*-butyl methyl ether, tetrahydrofuran, 1,4-dioxane or 1,2-dimethoxyethane, hydrocarbons such as benzene, toluene, xylene, hexane or cyclohexane, halogenated hydrocarbons such as dichloromethane, trichloromethane, carbon tetrachloride, 1,2-dichloroethane, trichloroethylene or chlorobenzene, or other solvents such as acetone, acetonitrile, ethyl acetate, pyridine, dimethylsulfoxide (DMSO), *N,N*-dimethylformamide (DMF), *N,N'*-dimethylpropylene urea (DMPU) or *N*-methylpyrrolidinone (NMP). It is also possible to use mixtures of these solvents. Preference is given to using dichloromethane, tetrahydrofuran, *N,N*-dimethylformamide or mixtures thereof. The reactions are generally carried out at a temperature ranging from 0°C to +60°C, preferably at +10°C to +40°C.

Oxidizing agents that are capable of converting the primary alcohol (I-C) into the aldehyde (XIV) (process [C-1]) under mild conditions include 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one ("Dess-Martin periodinane"), 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) in combination with secondary oxidants such as iodosobenzene-*I,I*-diacetate or sodium hypochlorite, and dimethylsulfoxide (DMSO)-based oxidation systems such as DMSO/trifluoroacetic anhydride or DMSO/*N,N'*-dicyclohexylcarbodiimide (DCC). Preference is given to 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one. The reaction is generally carried out in an inert solvent, preferably using dichloromethane.

For the hydroxy-to-halogen transformation in process step [C-2] (I-C) → (XVI), various standard methods and reagents that are well known in the art may be employed. Reagents of choice are thionyl chloride [for X = Cl], tetrabromomethane/triphenylphosphine [for X = Br], and iodine/triphenyl-

phosphine [for X = I]. The preparation of 6-(chloromethyl) derivatives (XVI) [X = Cl] is preferred for reasons of convenience of work-up and compound stability.

Bases suitable for the process step [C-2] (XVI) + (XVII) → (I-E) [ether formation] are in particular alkali carbonates such as lithium, sodium, potassium or caesium carbonate, alkali acetates such as sodium or potassium acetate, or customary tertiary amine bases such as triethylamine, *N*-methylmorpholine, *N*-methylpiperidine, *N,N*-diisopropylethylamine or pyridine. Preference is given to *N,N*-diisopropylethylamine (DIPEA). The reaction (XVI) + (XVII) → (I-E) is performed in an inert solvent, such as tetrahydrofuran, or without solvent, using an excess of alcohol (XVII), at a temperature ranging from +20°C to +200°C, preferably at +50°C to +150°C. Advantageously, the conversion is carried out by means of a microwave reactor device.

The reaction sequence (I-C) → (XVI) → (I-E) may be carried out in two separate steps, i.e. with isolation and purification of the intermediate compound (XVI), or it may be performed using a one-pot procedure, i.e. employing the crude intermediate (XVI) as obtained in the preparation reaction.

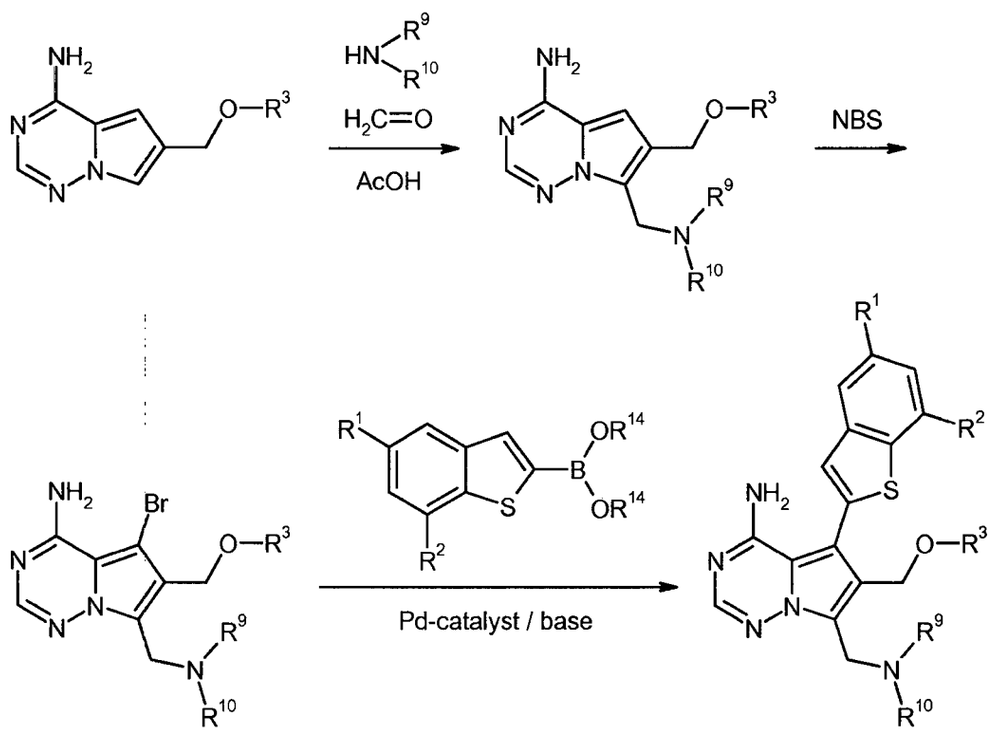
In cases where a primary or secondary amine moiety forms part of the G^1 or G^2 group in the target compounds of formula (I), it may sometimes be appropriate in the preparation reactions described above to use a protected derivative of this amine as reaction component instead of the free amine. For this 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. A Boc (*tert*-butoxycarbonyl) group is preferably used. Similarly, a hydroxy function being part of the G^1 or G^2 group may temporarily be blocked in precursor compounds and process intermediates, for example as a tetrahydropyranyl (THP) ether or as a silyl ether derivative, such as a trimethylsilyl or *tert*-butyldimethylsilyl ether.

These protecting groups may then be cleaved off concomitantly during aqueous work-up and purification procedures, or they are removed in a subsequent, separate reaction step using standard methods well known in the art. The preparation of such protected intermediates from the corresponding free amines or alcohols is likewise 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].

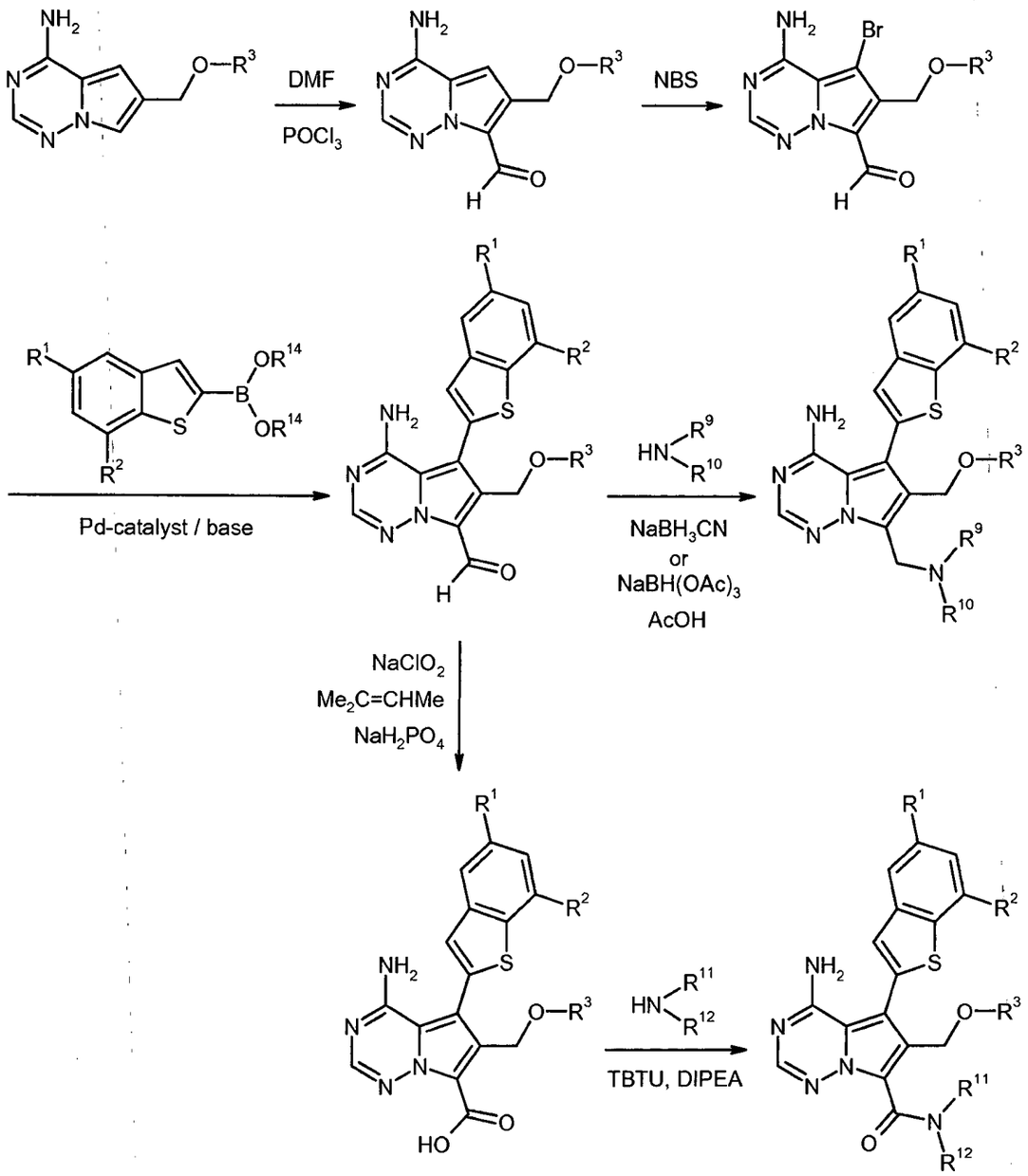
Certain types of protected (*i.e.* acylated) amine derivatives exert significant FGFR-inhibiting activity by their own. Accordingly, such compounds are also encompassed by the general formula (I) as defined above.

The preparation of the compounds of the invention may be illustrated by means of the following reaction schemes:

Scheme 1

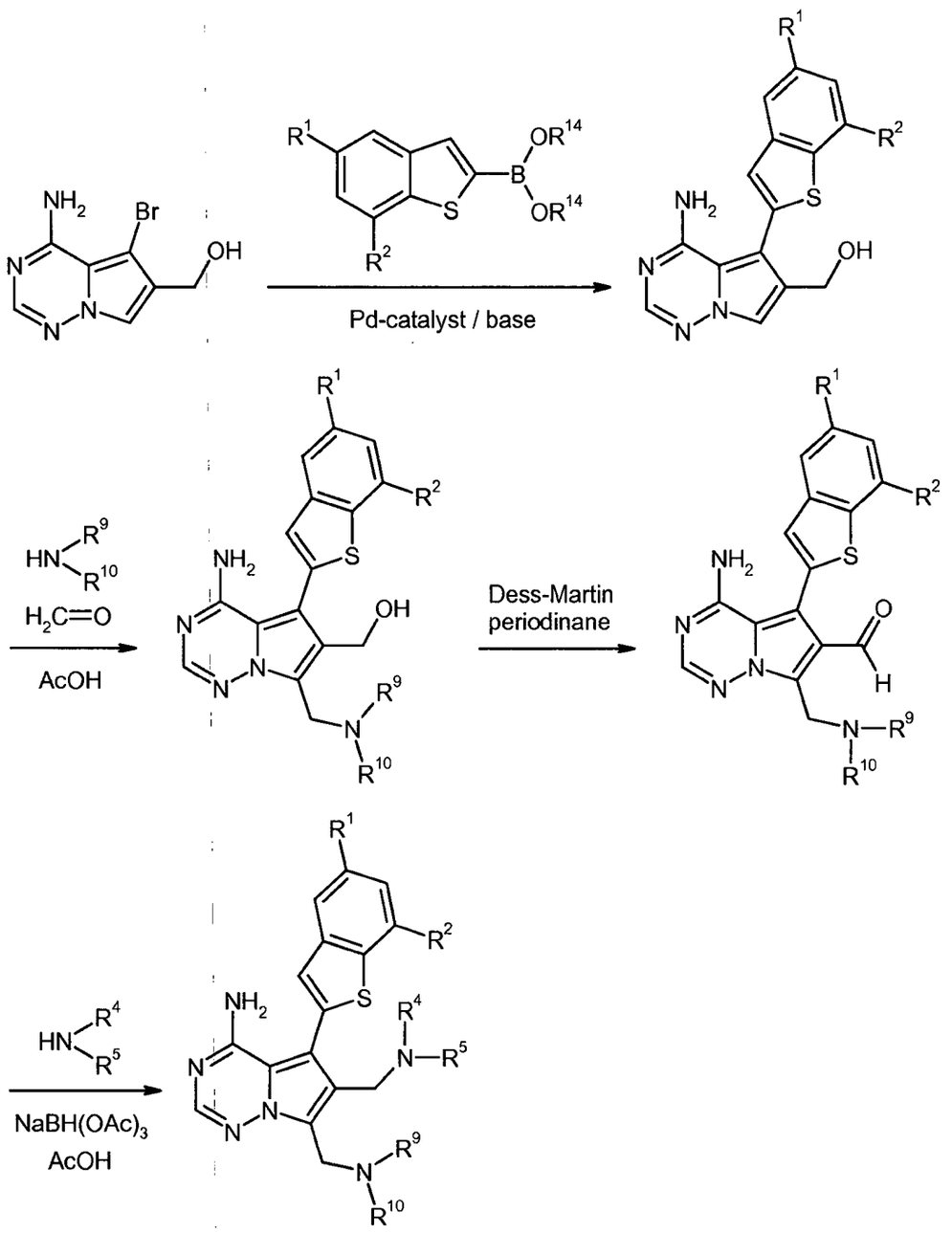


Scheme 2

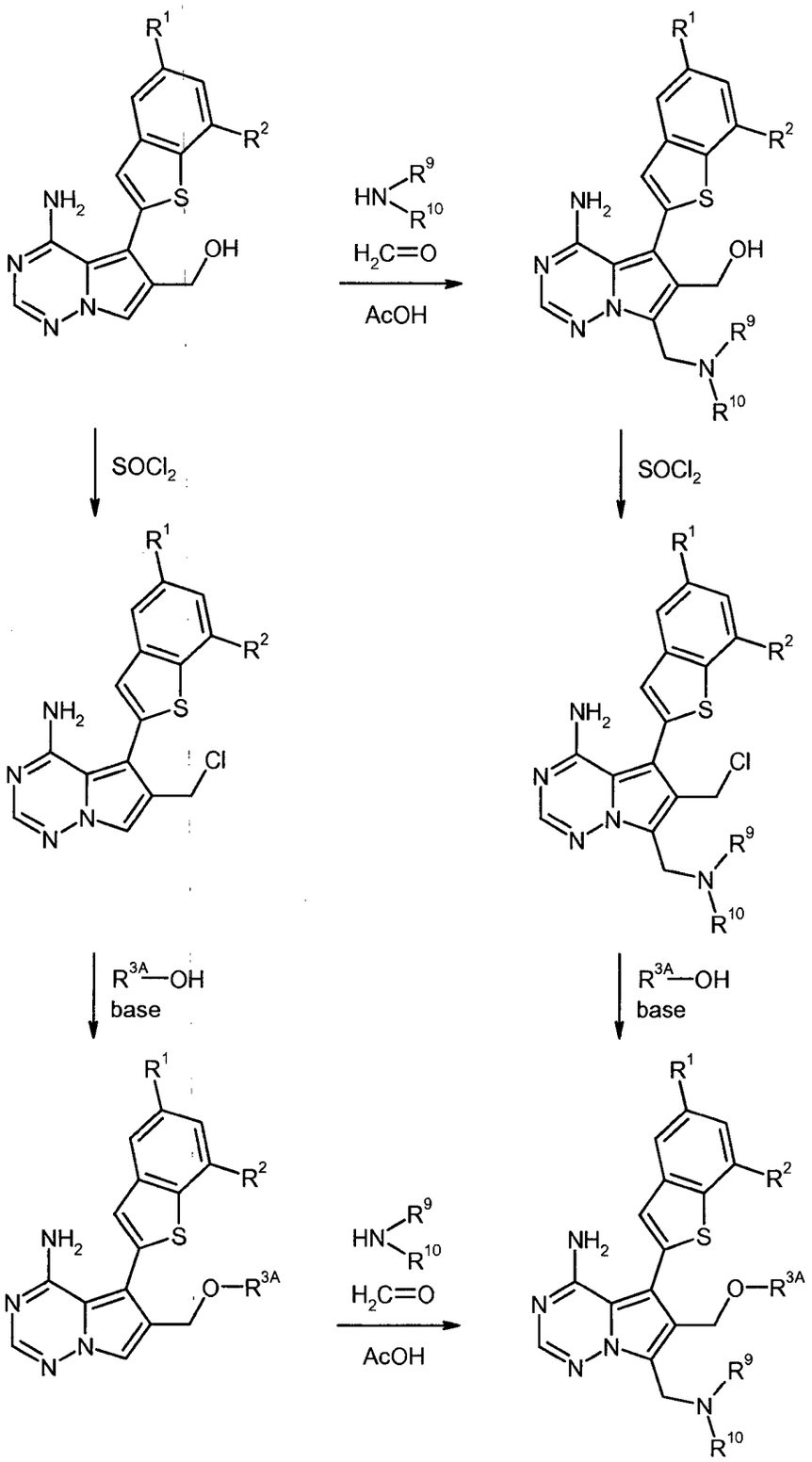

DMF
POCl3
NBS
Pd-catalyst / base
NaBH3CN
or
NaBH(OAc)3
AcOH
NaClO2
Me2C=CHMe
NaH2PO4
TBTU, DIPEA

311

Scheme 3


Pd-catalyst / base
Dess-Martin periodinane
AcOH
NaBH(OAc)3
AcOH

Scheme 4

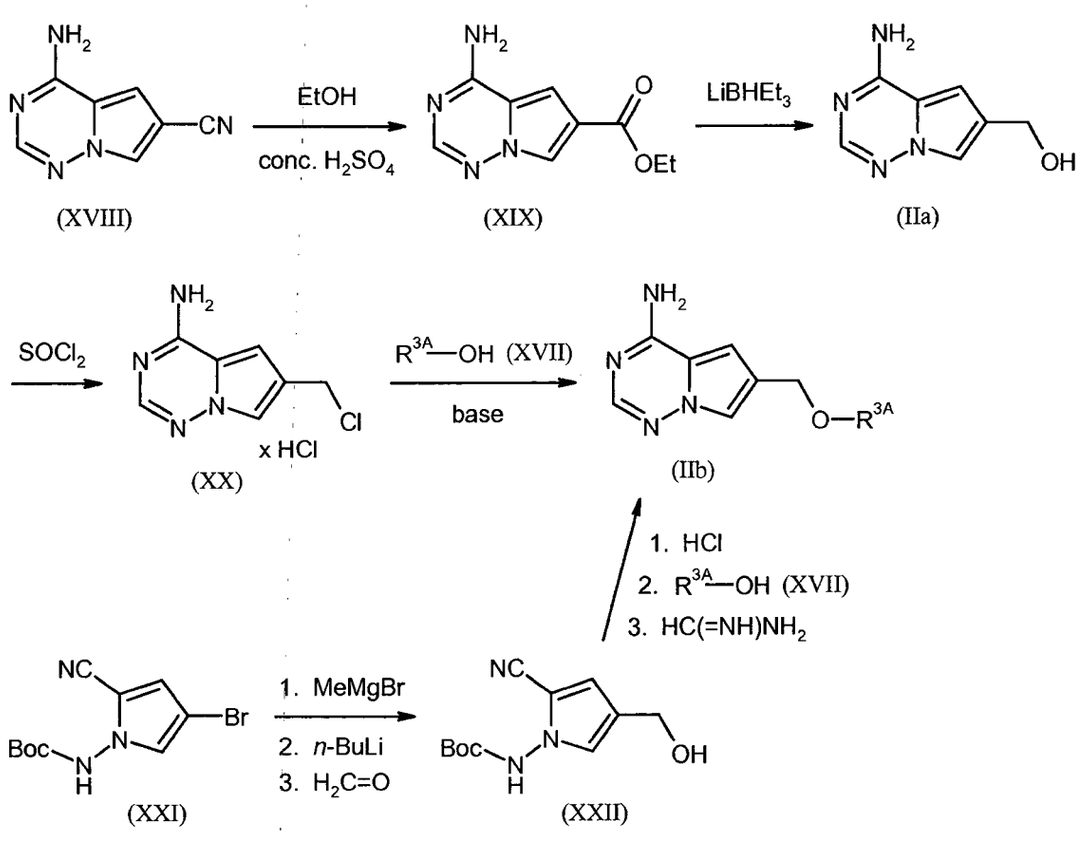


The 6-substituted 4-aminopyrrolo[2,1-f][1,2,4]triazines of formula (II) can, for example, be prepared by two different routes which are depicted in Scheme 5 below. In the first route, 4-amino-6-

cyanopyrrolo[2,1-f][1,2,4]triazine (XVIII) is converted into the ester (XIX) by acid-mediated alcoholysis and then reduced to the 6-(hydroxymethyl) compound (IIa) [R^3 in (II) = H] using lithium triethylborohydride. Standard transformation into the corresponding 6-(halomethyl)pyrrolotriazine, such as the chloro compound (XX), followed by treatment with an alcohol of formula (XVII) in the presence of a base readily provides the ether derivatives of formula (IIb) [R^3 in (II) ≠ H]. The preparation of the starting compound (XVIII) has been described previously [see Int. Pat. Appl. WO 2007/ 064883 (Intermediate AX / Step 3)].

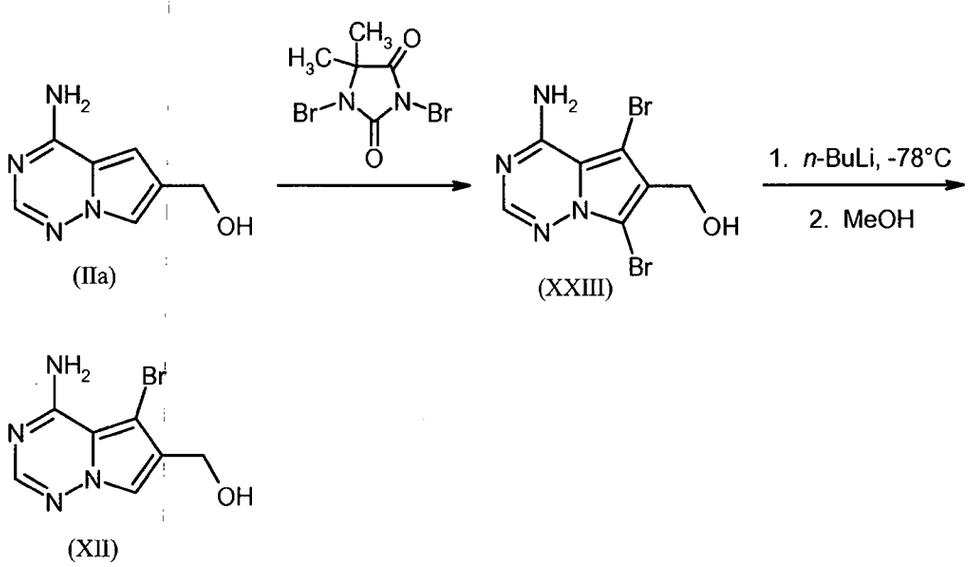
The second route starts from the protected 1-amino-4-bromo-2-cyanopyrrole (XXI) [preparation given in Int. Pat. Appl. WO 2007/064883 (Intermediate AAE, Step 3)]. Deprotonation of the urethane nitrogen, subsequent metalation in 4-position and reaction with formaldehyde affords the 4-(hydroxymethyl) derivative (XXII). Treatment with hydrogen chloride followed by addition of alcohol (XVII) and condensation with formamidine using a one-pot procedure then provides the target compound of formula (IIb). This route is especially suited for the preparation of alkyl ether derivatives [R^{3A} in (IIb) = (C_1-C_4)-alkyl] in that the alcohol reactant (XVII) may also serve as the reaction solvent in these cases.

Scheme 5



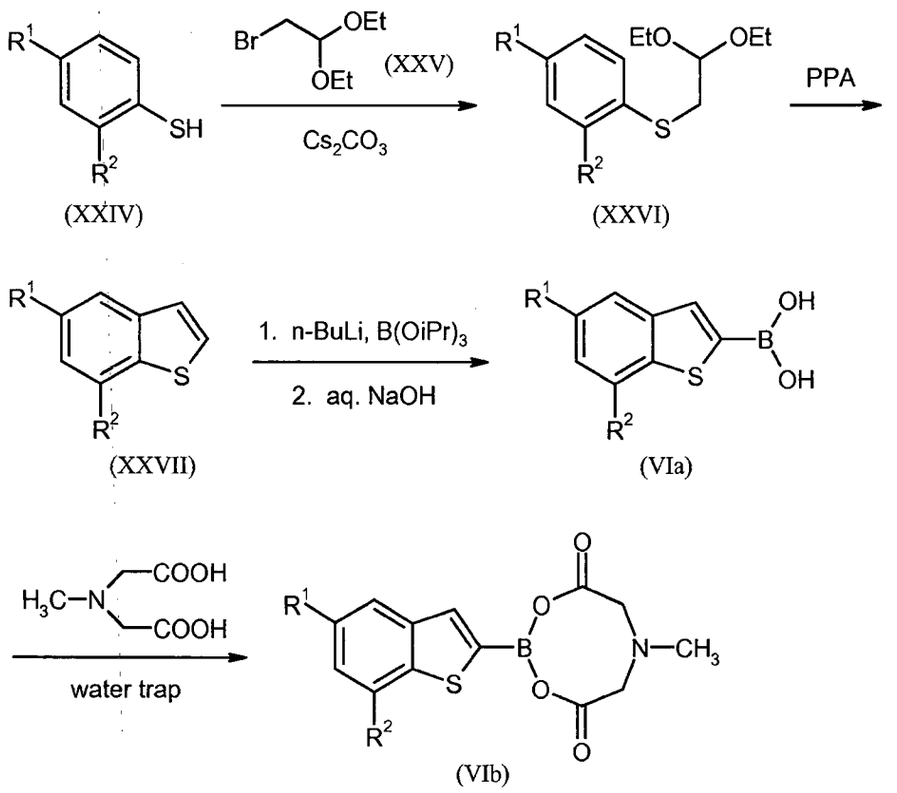
The 4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazine derivative of formula (XII) is readily available from 4-amino-6-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazine (IIa) (cf. Scheme 5) by initial 5,7-dibromination using 1,3-dibromo-5,5-dimethylhydantoin and subsequent selective 7-debromination via a halogen-metal exchange with *n*-butyllithium followed by methanol quenching (see Scheme 6 below).

Scheme 6



The benzothiophen-2-yl boronates of formula (VI) can conveniently be prepared starting from the substituted thiophenol derivatives of formula (XXIV) (see Scheme 7 below). Alkylation with bromo-acetal (XXV) and subsequent polyphosphoric acid-mediated cyclization provides the benzothiophene intermediates of formula (XXVII) which are then metalated in 2-position and reacted with a trialkyl borate. Alkaline work-up affords the free (benzothiophen-2-yl)boronic acids of formula (VIa) which may be transformed, if desired, into cyclic boronates, *e.g.* so-called MIDA boronates of formula (VIb), by standard procedures known in the art [see, for example, D. M. Knapp *et al.*, *J. Am. Chem. Soc.* 131 (20), 6961-6963 (2009)].

Scheme 7

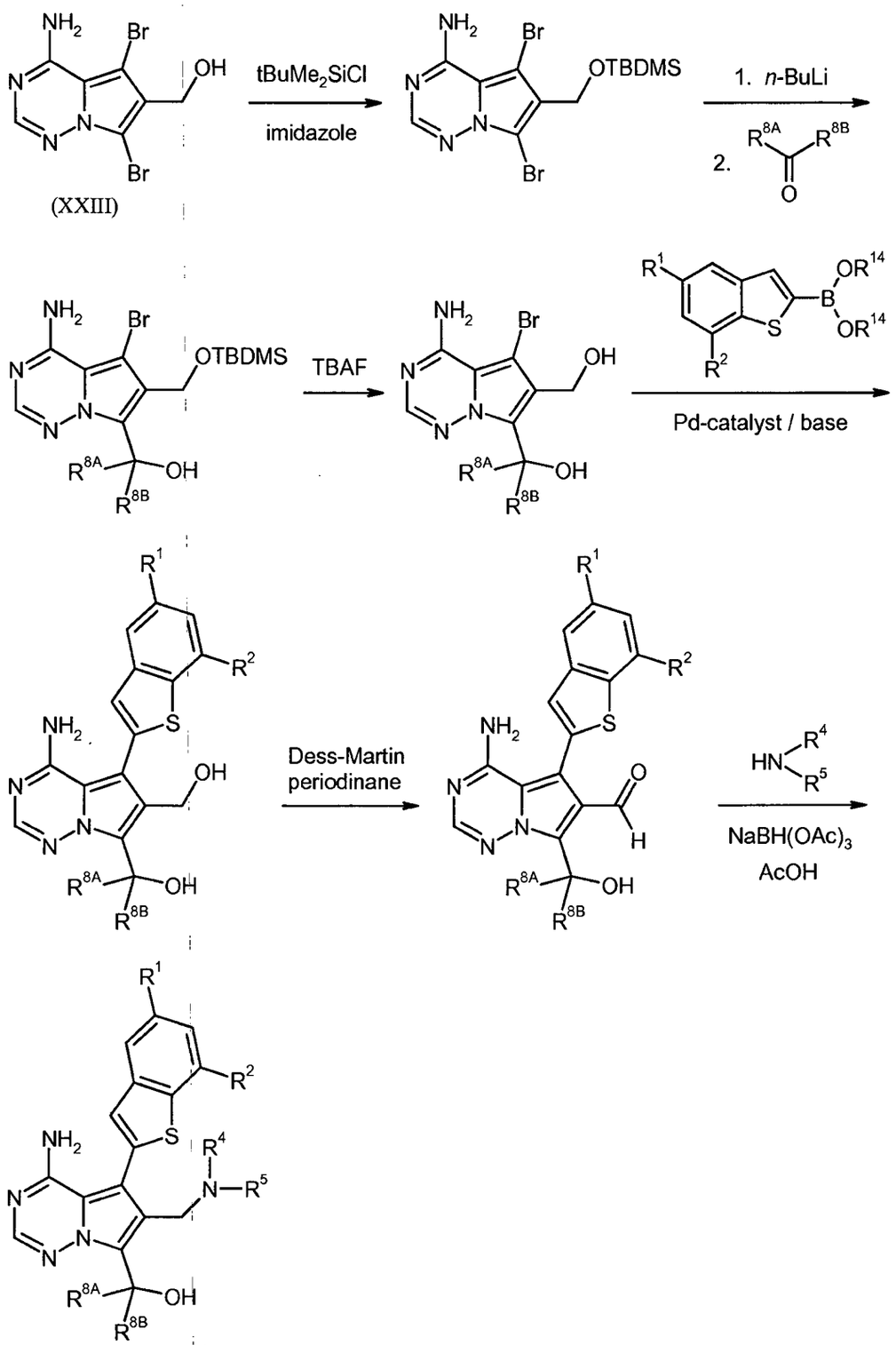


[*cf.* P. A. Plé and L. J. Marnett, *J. Heterocyclic Chem.* 25 (4), 1271-1272 (1988); A. Venturelli *et al.*, *J. Med. Chem.* 50 (23), 5644-5654 (2007)].

The compounds of the formulae (III), (XI), (XV), (XVII), (XXIV) and (XXV) 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. Detailed procedures and literature references for preparing the starting materials can also be found in the Experimental Part in the section on the preparation of the starting materials and intermediates.

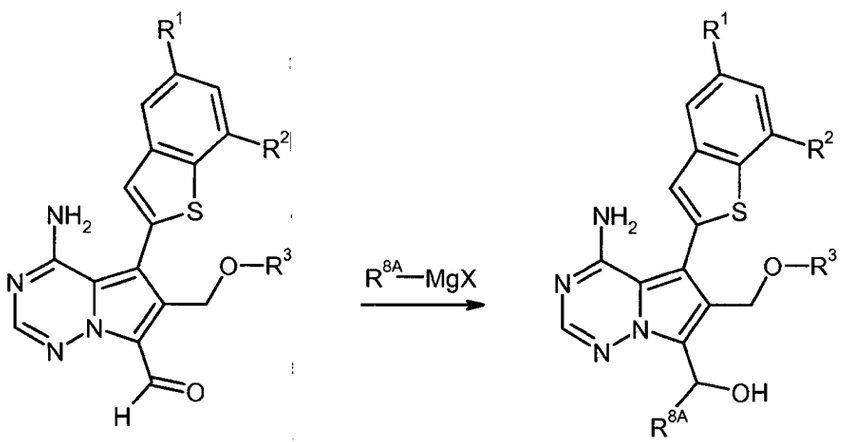
The preparation of further subgroups of the compounds of general formula (I) is illustrated in the following reaction schemes 8–14. The required pyrrolotriazine precursors can be readily synthesized by customary methods well known in the art, and further synthetic transformations, in most instances, follow the preparation routes that have been outlined in the process section above, using similar types of reactions, such as, for example, bromination, boronate coupling, aminomethylation, reductive amination, oxidation and/or ether or amide forming reactions. Further details are provided in the Experimental Part on the preparation of the exemplary embodiments and their respective precursor compounds.

Scheme 8



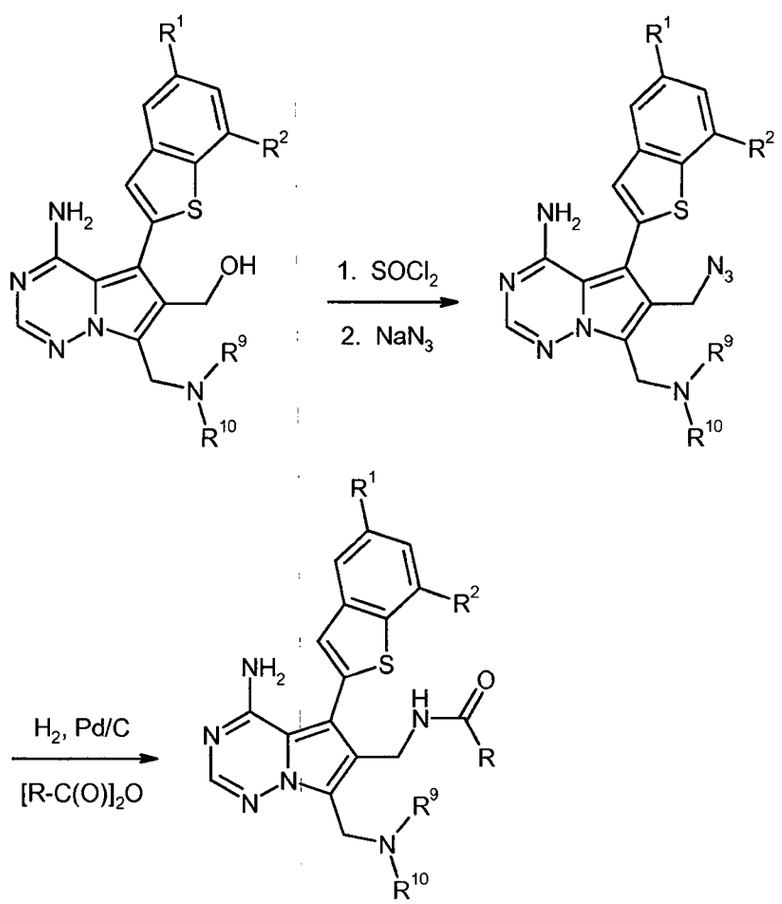
[R^{8A}, R^{8B} = (C_1-C_4)-alkyl, cyclopropyl or cyclobutyl].

Scheme 9



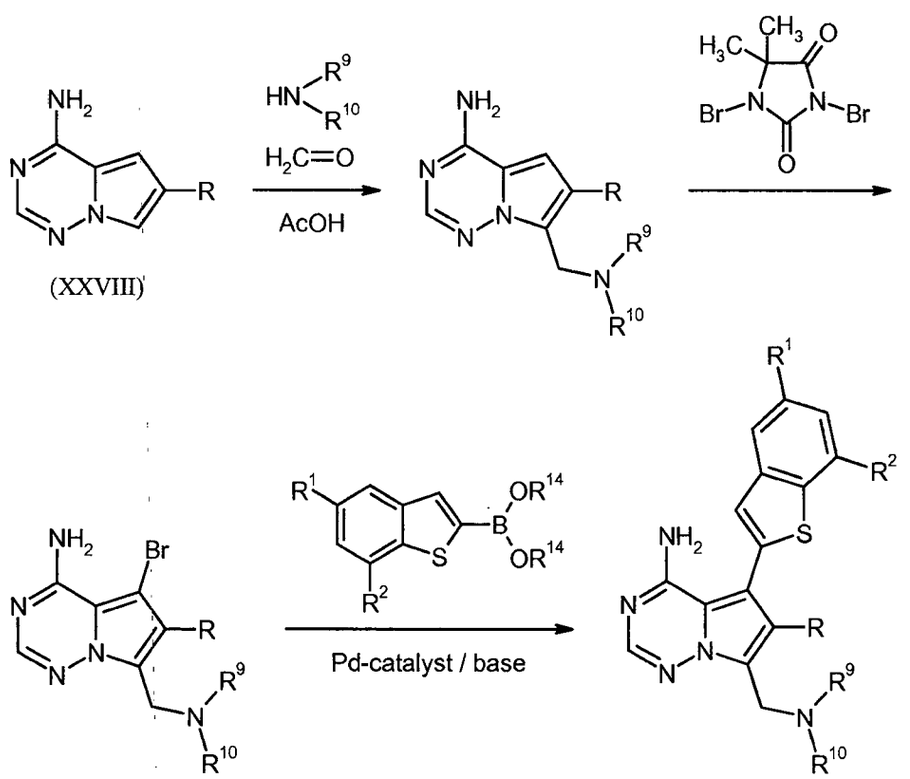
[R^{8A} = (C_1-C_4)-alkyl, cyclopropyl or cyclobutyl; X = Cl, Br or I].

Scheme 10



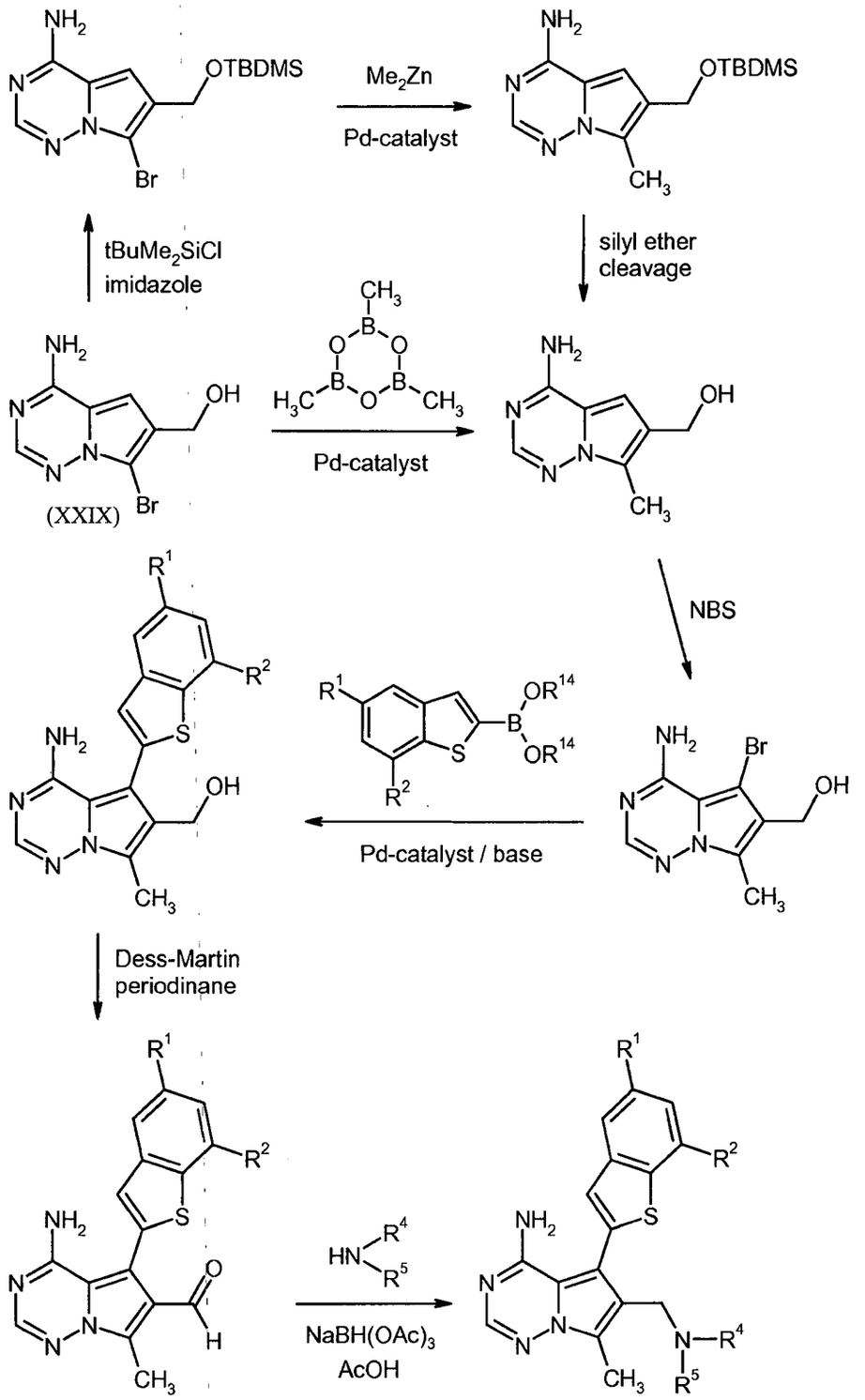
[R = (C_1-C_4)-alkyl].

Scheme 11



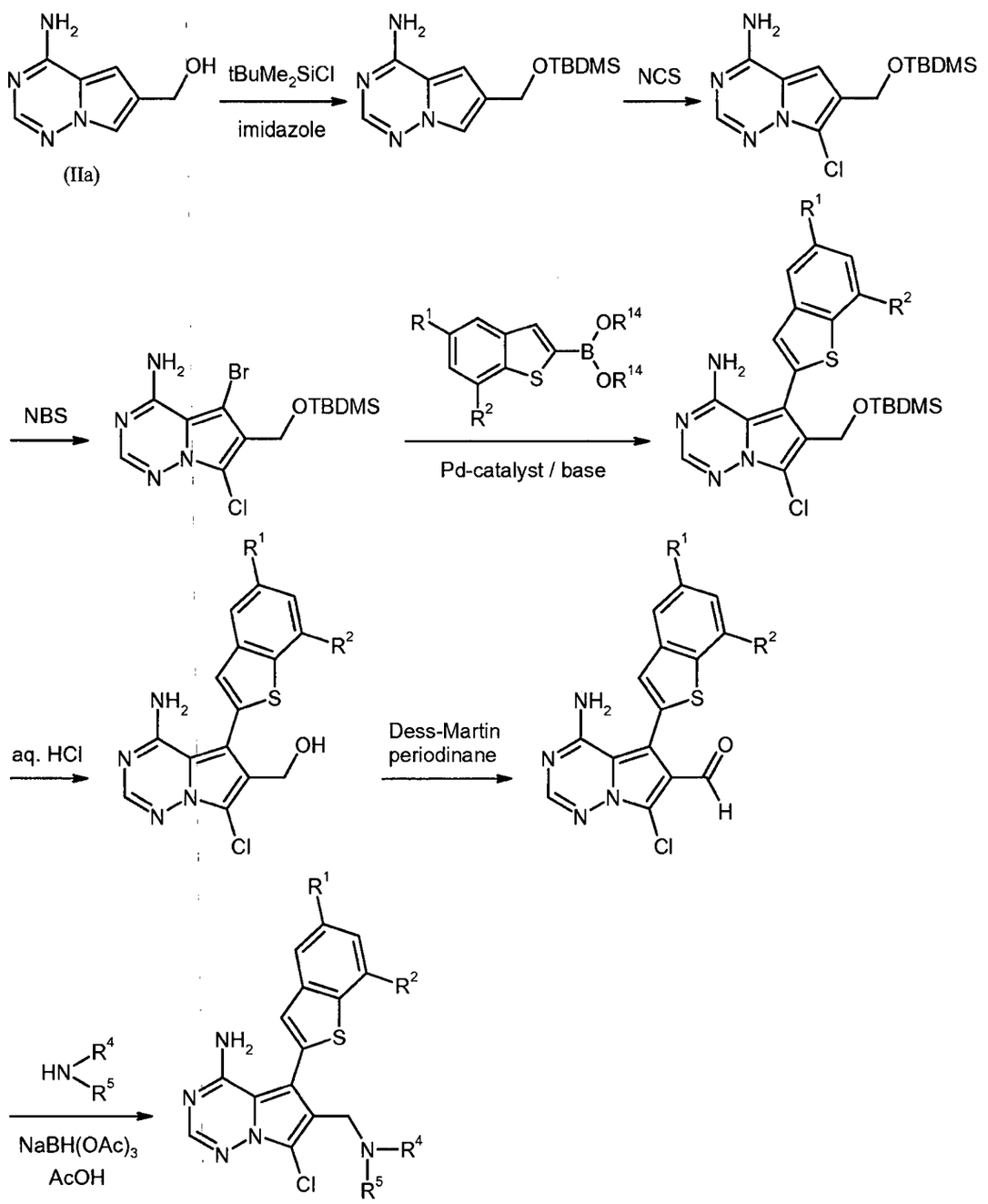
[R = chloro or (C_1-C_4)-alkyl; for the preparation of the starting material (XXVIII), see Int. Pat. Appl. WO 2007/064883 and WO 2007/056170, respectively].

Scheme 12

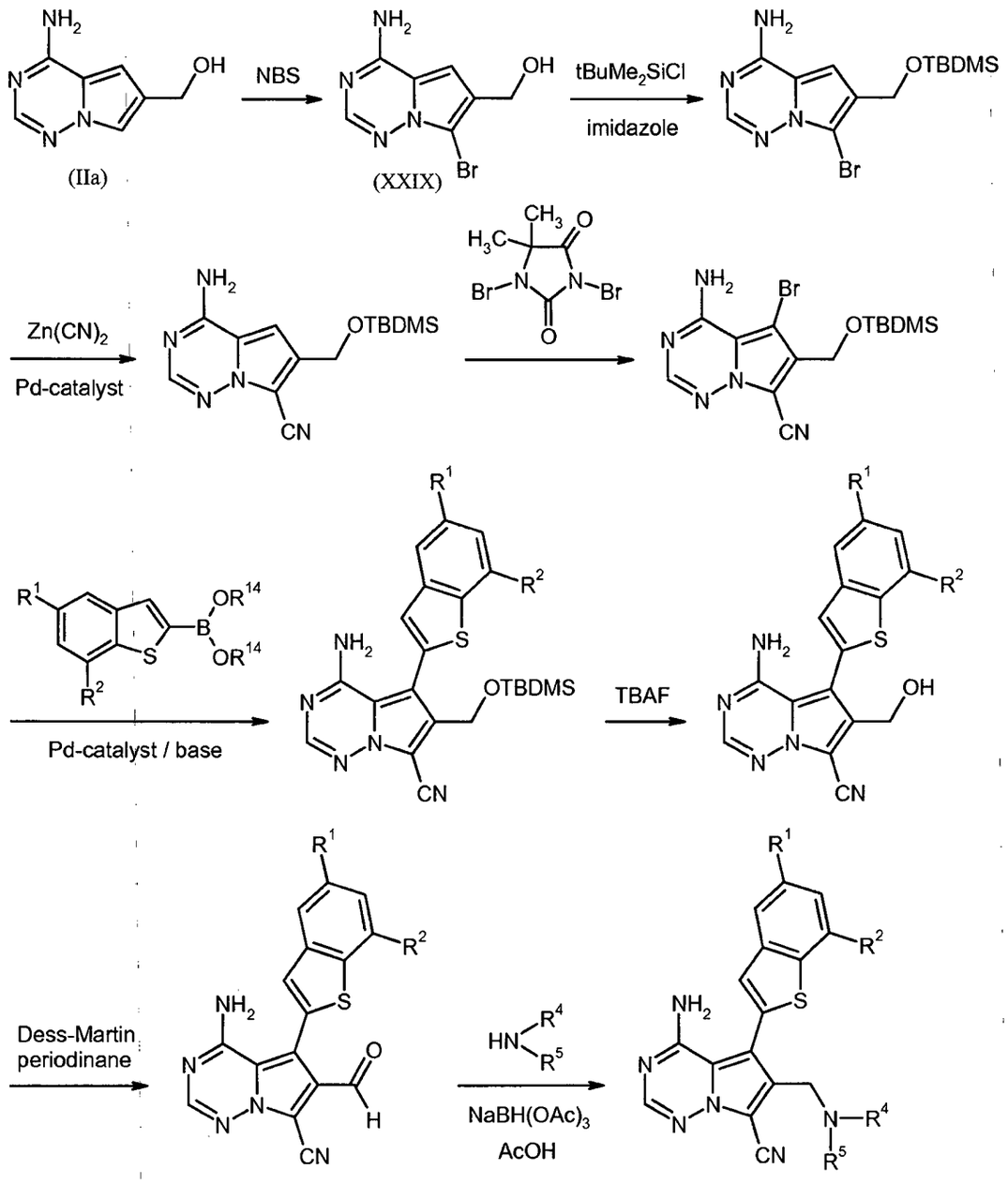


[for the preparation of the starting compound (XXIX), see Scheme 14 below].

Scheme 13


NH2
OH
(IIa)
tBuMe2SiCl
imidazole
OTBDMS
NCS
Cl
NBS
Br
R1
R2
OR14
B
S
N
Pd-catalyst / base
aq. HCl
Dess-Martin
periodinane
O
H
HN
R4
R5
NaBH(OAc)3
AcOH

Scheme 14



The compounds of the present invention have valuable pharmacological properties and can be used for the prevention and treatment of disorders in humans and other mammals.

The compounds of the present invention are potent inhibitors of the activity or expression of receptor tyrosine kinases, particularly of the FGFR kinases, and most notably of the FGFR-1 and FGFR-3 kinases. Accordingly, in another embodiment, the present invention provides a method of treating disorders relating to or mediated by the activity of FGFR kinases in a patient in need of such treatment, comprising administering to the patient an effective amount of a compound of formula (I)

as defined above. In certain embodiments, the disorders relating to the activity of FGFR kinases are proliferative disorders, in particular cancer and tumor diseases.

In the context of 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 disorder, disease, condition, or state may be partial or complete.

The term "proliferative disorder" includes disorders involving the undesired or uncontrolled proliferation of a cell. The compounds of the present invention can be utilized to prevent, inhibit, block, reduce, decrease, control, etc., cell proliferation and/or cell division, and/or produce apoptosis. This method comprises administering to a subject in need thereof, including a mammal, including a human, an amount of a compound of this invention, or a pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate or solvate thereof which is effective to treat or prevent the disorder.

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. For example, 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).

Proliferative disorders that can be treated and/or prevented with the compounds of the present invention particularly include, but are not limited to, the group of cancer and tumor diseases. These are understood as meaning, in particular, the following diseases, but without being limited to them: mammary carcinomas and mammary tumors (ductal and lobular forms, also *in situ*), tumors of the respiratory tract (small cell and non-small cell lung carcinoma, parvicellular and non-parvicellular carcinoma, bronchial carcinoma, bronchial adenoma, pleuropulmonary blastoma), cerebral tumors (e.g. of the brain stem and of the hypothalamus, astrocytoma, glioblastoma, medulloblastoma, ependymoma, and neuro-ectodermal and pineal tumors), tumors of the digestive organs (oesophagus, stomach, gall bladder, small intestine, large intestine, rectum, anus), liver tumors (inter alia hepatocellular carcinoma, cholangiocellular carcinoma and mixed hepatocellular and cholangiocellular carcinoma), tumors of the head and neck region (larynx, hypopharynx, nasopharynx, oropharynx, lips and oral cavity), skin tumors (squamous epithelial carcinoma, Kaposi sarcoma,

malignant melanoma, Merkel cell skin cancer and non-melanomatous skin cancer), tumors of soft tissue (inter alia soft tissue sarcomas, osteosarcomas, malignant fibrous histiocytomas, lymphosarcomas and rhabdomyosarcomas), tumors of the eyes (inter alia intraocular melanoma, uveal melanoma and retinoblastoma), tumors of the endocrine and exocrine glands (e.g. thyroid and parathyroid glands, pancreas and salivary gland), tumors of the urinary tract (tumors of the bladder, penis, kidney, renal pelvis and ureter), tumors of the reproductive organs (carcinomas of the endometrium, cervix, ovary, vagina, vulva and uterus in women, and carcinomas of the prostate and testicles in men), as well as distant metastases thereof. These disorders also include proliferative blood diseases in solid form and as circulating blood cells, such as lymphomas, leukaemias and myeloproliferative diseases, e.g. acute myeloid, acute lymphoblastic, chronic lymphocytic, chronic myelogenic and hairy cell leukaemia, and AIDS-related lymphomas, Hodgkin's lymphomas, non-Hodgkin's lymphomas, cutaneous T-cell lymphomas, Burkitt's lymphomas, and lymphomas in the central nervous system.

Due to their activity and selectivity profile, the compounds of the present invention are believed to be particularly suitable for the treatment of breast (mammary), lung, stomach (gastric), bladder and ovary cancer and tumor diseases. Furthermore, the compounds of the present invention may be especially suited for the prevention or suppression of tumor metastasis in general.

Other proliferative disorders that can be treated and/or prevented with the compounds and methods of the present invention include psoriasis, keloids and other hyperplasias affecting the skin, bullous disorders associated with subepidermal blister formation including bullous pemphigoid, erythema multiforme and dermatitis herpetiformis, fibrotic disorders such as lung fibrosis, atherosclerosis, restenosis and hepatic cirrhosis, renal diseases including mesangial cell proliferative disorders, glomerulopathies, glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis and polycystic kidney disease, benign prostate hyperplasia (BPH), angiogenic or blood vessel proliferative disorders, and thrombotic microangiopathy syndromes.

The compounds of the present invention are also useful for the treatment and/or prevention of ophthalmological diseases such as, for example, age-related macular degeneration (AMD), dry macular degeneration, ischemic retinal vein occlusion, diabetic macula edema, diabetic retinopathy, retinopathy of prematurity, and other retinopathies.

Other conditions that may be treated and/or prevented by administering a compound of the present invention include gynaecological diseases such as endometriosis, myoma and ovarian cysts, metabolic disorders related to adipogenesis, bile metabolism, phosphate metabolism, calcium metabolism and/or bone mineralization, skeletal disorders such as, for example, dwarfism, achondrodysplasia

and Pfeiffer syndrome, cartilage diseases such as osteoarthritis and polyarthritis, rheumatoid arthritis, calvities, and transplant rejection.

The diseases mentioned above have been well characterized in humans, but also exist with a comparable aetiology in other mammals, and can be treated in those with the compounds and methods 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 as long as this combination does not lead to undesirable and/or unacceptable side effects. Such 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 (fixed) 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 other anti-cancer agents such as alkylating agents, anti-metabolites, plant-derived anti-tumor agents, hormonal therapy agents, topoisomerase inhibitors, tubulin inhibitors, kinase inhibitors,

targeted drugs, antibodies, antibody-drug conjugates (ADCs), immunologicals, biological response modifiers, anti-angiogenic compounds, and other anti-proliferative, cytostatic and/or cytotoxic substances. In this regard, the following is a non-limiting list of examples of secondary agents that may be used in combination with the compounds of the present invention:

Abarelix, abiraterone, aclarubicin, afatinib, aflibercept, aldesleukin, alemtuzumab, alitretinoin, alpharadin, altretamine, aminoglutethimide, amonafide, amrubicin, amsacrine, anastrozole, andromustine, arglabin, asparaginase, axitinib, 5-azacitidine, basiliximab, belotecan, bendamustine, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin, bortezomib, bosutinib, brivanib alaninate, buserelin, busulfan, cabazitaxel, CAL-101, calcium folinate, calcium levofolinate, camptothecin, capecitabine, carboplatin, carmofur, carmustine, catumaxomab, cediranib, celmoleukin, cetuximab, chlorambucil, chlormadinone, chlormethine, cidofovir, cisplatin, cladribine, clodronic acid, clofarabine, combretastatin, crisantaspase, crizotinib, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, darbepoetin alfa, darinaparsin, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftitox, denosumab, deslorelin, dibrospidium chloride, docetaxel, dovitinib, doxifluridine, doxorubicin, dutasteride, eculizumab, edrecolomab, eflornithine, elliptinium acetate, eltrombopag, endostatin, enocitabine, epimbicin, epirubicin, epitiostanol, epoetin alfa, epoetin beta, epothilone, eptaplatin, eribulin, erlotinib, estradiol, estramustine, etoposide, everolimus, exatecan, exemestane, exisulind, fadrozole, fenretinide, filgrastim, finasteride, flavopiridol, fludarabine, 5-fluorouracil, fluoxymesterone, flutamide, foretinib, formestane, fotemustine, fulvestrant, ganirelix, gefitinib, gemcitabine, gemtuzumab, gimatecan, gimeracil, glufosfamide, glutoxim, goserelin, histrelin, hydroxyurea, ibandronic acid, ibritumomab tiuxetan, idarubicin, ifosfamide, imatinib, imiquimod, improsulfan, intedanib, interferon alpha, interferon alpha-2a, interferon alpha-2b, interferon beta, interferon gamma, interleukin-2, ipilimumab, irinotecan, ixabepilone, lanreotide, lapatinib, lasofoxifene, lenalidomide, lenograstim, lentinan, lenvatinib, lestaurtinib, letrozole, leuprorelin, levamisole, linifanib, linsitinib, lisuride, lobaplatin, lomustine, lonidamine, lurtotecan, mafosfamide, mapatumumab, masitinib, masoprocol, medroxyprogesterone, megestrol, melarsoprol, melphalan, mepitiostane, mercaptopurine, methotrexate, methyl aminolevulinate, methyltestosterone, mifamurtide, mifepristone, miltefosine, miriplatin, mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane, mitoxantrone, molgramostim, motesanib, nandrolone, nedaplatin, nelarabine, neratinib, nilotinib, nilutamide, nimotuzumab, nimustine, nitracrine, nolatrexed, ofatumumab, oprelvekin, oxaliplatin, paclitaxel, palifermin, pamidronic acid, panitumumab, pazopanib, pegaspargase, peg-epoetin beta, pegfilgastrim, peg-interferon alpha-2b, pelitrexol, pemetrexed, pemtumomab, pentostatin, peplomycin, perfosfamide, perifosine, pertuzumab, picibanil, pirambicin, pirarubicin, plerixafor, plicamycin, poliglusam, polyestradiol phosphate, ponatinib, porfimer sodium, pralatrexate, prednimustine, procarbazine, procodazole, PX-866, quinagolide,

raloxifene, raltitrexed, ranibizumab, ranimustine, razoxane, regorafenib, risedronic acid, rituximab, romidepsin, romiplostim, rubitecan, saracatinib, sargramostim, satraplatin, selumetinib, sipuleucel-T, sirolimus, sizofiran, sobuzoxane, sorafenib, streptozocin, sunitinib, talaporfin, tamibarotene, tamoxifen, tandutinib, tasonermin, teceleukin, tegafur, telatinib, temoporfin, temozolomide, temsirolimus, teniposide, testolactone, testosterone, tetrofosmin, thalidomide, thiotepa, thymalfasin, tioguanine, tipifarnib, tivozanib, toceranib, tocilizumab, topotecan, toremifene, tositumomab, trabectedin, trastuzumab, treosulfan, tretinoin, triapine, trilostane, trimetrexate, triptorelin, trofosfamide, ubenimex, valrubicin, vandetanib, vapreotide, varlitinib, vatalanib, vemurafenib, vidarabine, vinblastine, vincristine, vindesine, vinflunine, vinorelbine, volociximab, vorinostat, zinostatin, zoledronic acid, and zorubicin.

Generally, the following aims may be pursued with the combination of compounds of the present invention with other anti-cancer agents:

- improved activity in slowing down the growth of a tumor, in reducing its size or even in its complete elimination compared with treatment with a single active compound;
- possibility of employing the chemotherapeutics used in a lower dosage than in monotherapy;
- possibility of a more tolerable therapy with few side effects compared with individual administration;
- possibility of treatment of a broader spectrum of cancer and tumor diseases;
- achievement of a higher rate of response to therapy;
- longer survival time of the patient compared with standard therapy.

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.

In cancer treatment, the compounds of the present invention may also be employed in conjunction with radiation therapy and/or surgical intervention.

Furthermore, the compounds of formula (I) may be utilized, as such or in compositions, in research and diagnostics, or as analytical reference standards, and the like, which are well known in the art.

When the compounds of the present invention are administered as pharmaceuticals, to humans and other mammals, they can be given *per se* or as a pharmaceutical composition containing, for example, 0.1% to 99.5% (more preferably, 0.5% to 90%) of active ingredient in combination with one or more pharmaceutically acceptable excipients.

Thus, in another aspect, the present invention relates to pharmaceutical compositions comprising at least one of the compounds according to the invention, conventionally together with one or more inert, non-toxic, pharmaceutically suitable excipients, and to the use thereof for the treatment and/or prevention of disorders, especially of the aforementioned disorders.

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, otic or topical route, or as an implant or stent.

For these application routes, the compounds of the invention can be administered in suitable application forms.

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 application can be carried out with avoidance of an absorption step (intravenously, intraarterially, intracardially, intraspinally or intralumbarly) or with inclusion of an absorption (intramuscularly, subcutaneously, intracutaneously, percutaneously or intraperitoneally). Useful parenteral application forms include injection and infusion preparations in the form of solutions, suspensions, emulsions, lyophilisates and sterile powders.

Forms suitable for other application routes include, for example, inhalatory pharmaceutical forms (e.g. powder inhalers, nebulizers), nasal drops, solutions or sprays, tablets or capsules to be administered lingually, sublingually or buccally (e.g. troches, lozenges), suppositories, ear and eye preparations (e.g. drops, ointments), vaginal capsules, aqueous suspensions (lotions, shaking mix-

tures), lipophilic suspensions, ointments, creams, milks, pastes, foams, dusting powders, transdermal therapeutic systems (e.g. patches), implants and stents.

In a preferred embodiment, the pharmaceutical composition comprising a compound of formula (I) as defined above is provided in a form suitable for oral administration. In another preferred embodiment, the pharmaceutical composition comprising a compound of formula (I) as defined above is provided in a form suitable for intravenous administration.

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 alia, 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.

A preferred dose of the compound of the present invention is the maximum that a patient can tolerate and not develop serious side effects. Illustratively, the compound of the present invention may be administered parenterally at a dose of about 0.001 mg/kg to about 1 mg/kg, preferably of about 0.01 mg/kg to about 0.5 mg/kg of body weight. 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. Ranges intermediate to the above-recited values are also intended to be part of the invention.

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, the bioavailability and pharmacodynamic characteristics of the particular compound and its mode and route of administration, the time or interval over which administration takes place, the dose regimen selected, the response of the individual patient to the active ingredient, the specific disease involved, the degree of or the involvement or severity of the disease, the kind of concurrent treatment (i.e., the interaction of the compound of the invention with other co-administered therapeutics), and other relevant circumstances.

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. Treatment can be initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage may be increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in individual portions spread over the day.

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
Ac_2O	acetic anhydride
AcOH	acetic acid
aq.	aqueous (solution)
Boc	*tert*-butoxycarbonyl
br.	broad (^{1}H-NMR signal)
Bu	butyl
cat.	catalytic
conc.	concentrated
d	doublet (^{1}H-NMR signal)
DBDMH	1,3-dibromo-5,5-dimethylhydantoin
DCI	direct chemical ionization (MS)
DCM	dichloromethane
Dess-Martin periodinane	1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one
DIPEA	*N,N*-diisopropylethylamine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
EI	electron impact ionization (MS)
eq.	equivalent(s)
ESI	electro-spray ionization (MS)
Et	ethyl
EtOAc	ethyl acetate
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
iPr	isopropyl
LC-MS	liquid chromatography-coupled mass spectroscopy
Me	methyl
MeOH	methanol
min	minute(s)

MS	mass spectroscopy
m/z	mass-to-charge ratio (MS)
NBS	*N*-bromosuccinimide
n-Bu	*n*-butyl
NCS	*N*-chlorosuccinimide
of th.	of theory (chemical yield)
Pd/C	palladium on charcoal
$PdCl_2(dppf)$	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
$Pd(dba)_2$	bis(dibenzylideneacetone)palladium
Ph	phenyl
PPA	polyphosphoric acid
q	quartet (^{1}H-NMR signal)
quant.	quantitative (yield)
rac	racemic
R_f	TLC retention factor
RP	reverse phase (HPLC)
rt	room temperature
R_t	retention time (HPLC)
s	singlet (^{1}H-NMR signal)
sat.	saturated (solution)
t	triplet (^{1}H-NMR signal)
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBTU	*N*-[(1*H*-benzotriazol-1-yloxy)(dimethylamino)methylene]-*N*-methyl-methanaminium tetrafluoroborate
tBu	*tert*-butyl
tert	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

LC-MS and GC-MS methods:

Method 1 (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% aq. formic acid, eluent B: 1 L acetonitrile + 0.5 ml 50% aq. 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 2 (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; oven: 50°C; flow rate: 0.40 mL/min; UV detection: 210-400 nm.

Method 3 (LC-MS):

Instrument: Micromass Quattro Micro with HPLC Agilent 1100 Series; column: YMC-Triart C18 3µ, 50 mm x 3 mm; eluent A: 1 L water + 0.01 mol ammonium carbonate, eluent B: 1 L acetonitrile; gradient: 0.0 min 100% A → 2.75 min 5% A → 4.5 min 5% A; oven: 40°C; flow rate: 1.25 mL/min; UV detection: 210 nm.

Method 4 (LC-MS):

Instrument: Waters Acquity SQD UPLC System; column: Waters Acquity UPLC HSS T3 1.8µ, 30 mm x 2 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; oven: 50°C; flow rate: 0.60 mL/min; UV detection: 208-400 nm.

Method 5 (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% aq. formic acid, eluent B: 1 L acetonitrile + 0.5 ml 50% aq. formic acid; gradient: 0.0 min 97% A → 0.5 min 97% A → 3.2 min 5% A → 4.0 min 5% A; temperature: 50°C; flow rate: 0.3 mL/min; UV detection: 210 nm.

Method 6 (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 (maintain for 3 min).

Method 7 (LC-MS):

Instrument MS: Waters Micromass QM; Instrument HPLC: Agilent 1100 series; column: Agilent ZORBAX Extend-C18 3.0 mm x 50 mm, 3.5µ; eluent A: 1 L water + 0.01 mol ammonium carbonate, eluent B: 1 L acetonitrile; gradient: 0.0 min 98% A → 0.2 min 98% A → 3.0 min 5% A → 4.5 min 5% A; temperature: 40°C; flow rate: 1.75 mL/min; UV detection: 210 nm.

Method 8 (LC-MS):

Instrument MS: Waters Micromass ZQ; Instrument HPLC: Agilent 1100 series; column: Agilent ZORBAX Extend-C18 3.0 mm x 50 mm, 3.5µ; eluent A: 1 L water + 0.01 mol ammonium carbonate, eluent B: 1 L acetonitrile; gradient: 0.0 min 98% A → 0.2 min 98% A → 3.0 min 5% A → 4.5 min 5% A; temperature: 40°C; flow rate: 1.75 mL/min; UV detection: 210 nm.

General purification methods *(see Table I and II below)*:

Method P1:

Preparative RP-HPLC (Reprosil C18, gradient acetonitrile/0.2% aq. trifluoroacetic acid).

Method P2:

Preparative RP-HPLC (XBridge C18, gradient acetonitrile/water + 0.1% aq. ammonia).

Method P3:

Preparative RP-HPLC (Sunfire C18, gradient acetonitrile/water).

Method P4:

Preparative RP-HPLC (XBridge C18, gradient acetonitrile/water + 0.05% aq. ammonia).

Method P5:

The product obtained from the preceding RP-HPLC purification is dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge is eluted with methanol, and the filtrate is evaporated.

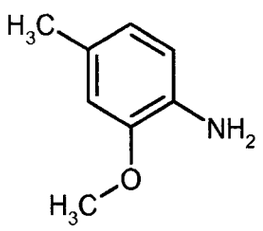
Method P6:

A solution of the product in ethyl acetate is washed with sat. aq. sodium hydrogencarbonate solution followed by sat. aq. sodium chloride solution, dried over magnesium sulfate, filtered and evaporated.

Starting Materials and Intermediates:

Intermediate 1A

2-Methoxy-4-methylaniline



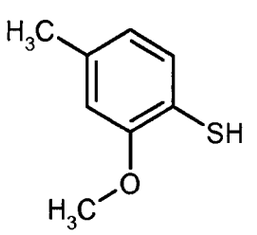
A mixture of 5-methyl-2-nitroanisol (265 g, 1.58 mol) and 10% Pd/C (39.75 g) in THF (1.32 L) was stirred overnight at rt under 1 atm of hydrogen. Filtration over kieselguhr and evaporation afforded 216.1 g of the crude product which was used in the next step without further purification.

LC-MS (method 3): R_t = 2.39 min; MS (ESIpos): m/z = 138 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 6.45-6.63 (m, 3H), 4.46 (s, 2H), 3.72 (s, 3H), 2.16 (s, 3H) ppm.

Intermediate 2A

2-Methoxy-4-methylbenzenethiol



Method 1:

A solution of sodium nitrite (7 g, 101.4 mmol) in water (25 ml) was added dropwise to a cooled (0°-5°C) solution of Intermediate 1A (13.7 g, 100 mmol) in concentrated hydrochloric acid (30 ml) and water (85 ml). After stirring at 0°C for 10 min, sodium acetate (15 g, 182.8 mmol) was added. The resulting mixture was added dropwise to a hot solution (70°-80°C) of potassium *O*-ethyl dithiocarbonate (30 g, 187.1 mmol) in water (140 ml), stirred between 70°C and 80°C for 1 h and then cooled to rt. The mixture was extracted twice with ethyl acetate, and the combined organic extracts were dried over sodium sulfate and evaporated. The residue was taken up in a 1.3 M solution of

potassium hydroxide in ethanol (300 ml). Glucose (8 g) was added, and the resulting mixture was refluxed for 3 h. Then, the ethanol solvent was evaporated, and the residue was diluted with water and acidified with 6 N aqueous sulfuric acid. Zinc powder (15 g) was added carefully, and the resulting mixture was heated to 50°C for 30 min. The mixture was then cooled to rt, diluted with dichloromethane and filtered. The filtrate was extracted twice with dichloromethane, and the combined organic extracts were dried over sodium sulfate and evaporated affording 14.3 g of the crude product which was used in the next step without further purification.

Method 2:

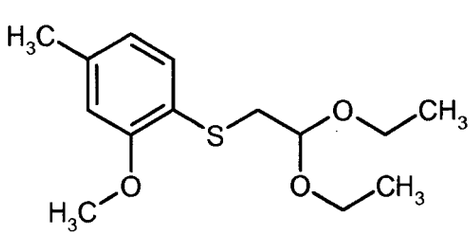
To 2.9 L of THF was added a warm solution of 355 ml (6.67 mol) concentrated sulfuric acid in 1.1 L of water. At 50°C, 293 g (1.33 mol) 2-methoxy-4-methylbenzenesulfonyl chloride were added under stirring. Then, 521 g (7.97 mol) of zinc powder were added carefully in portions (foaming), and the slightly exothermic reaction was cooled in a water bath to maintain a temperature of 50°-55°C. The mixture was subsequently stirred at 55°C for 3 h. The progress of the reaction was monitored by TLC (silica gel, petrolether/ethyl acetate 95:5). The reaction mixture was poured into 13.6 L of water, 6.8 L dichloromethane were added, and the mixture was stirred for 5 min. After decanting from remaining zinc and phase separation, the aqueous phase was extracted once more with 6.8 L dichloromethane. The combined organic phases were washed with 10% brine, dried and evaporated at 40°C under reduced pressure yielding 237 g of crude product. This material was used in the next step without further purification. An analytical sample was obtained by silica gel chromatography with petrolether/ethyl acetate (97:3) as eluent.

LC-MS (method 1): R_t = 1.21 min; MS (ESIneg): m/z = 153 $(M-H)^-$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.17 (d, 1H), 6.81 (s, 1H), 6.66 (d, 1H), 4.63 (br. s, 1H), 3.80 (s, 3H), 2.26 (s, 3H) ppm.

Intermediate 3A

1-[(2,2-Diethoxyethyl)sulfanyl]-2-methoxy-4-methylbenzene



237 g crude material from Intermediate 2A, 287 g (1.46 mol) bromoacetaldehyde-diethylacetal and 862 g (2.65 mol) caesium carbonate were suspended in 2 L DMF. The reaction temperature increased initially to 40°C, then stirring was continued overnight at ambient temperature. The reaction mixture was partitioned between 10 L of water and 2.7 L of ethyl acetate. The aqueous phase was extracted with another portion of 2.7 L ethyl acetate. The combined organic phases were washed with 10% brine, dried and evaporated. The resulting oily residue was purified by silica gel chromatography with petrolether/ethyl acetate (95:5) as eluent.

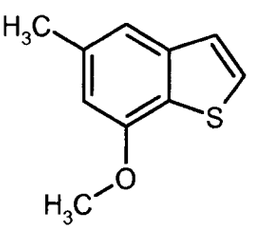
Yield: 236 g of an oil (66% of th.)

GC-MS (method 6): R_t = 6.03 min; MS (EIpos): m/z = 270 $(M)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.16 (d, 1H), 6.82 (s, 1H), 6.73 (d, 1H), 4.55 (t, 1H), 3.80 (s, 3H), 3.52-3.64 (m, 2H), 3.39-3.51 (m, 2H), 2.96 (d, 2H), 2.33 (s, 3H), 1.09 (t, 6H) ppm.

Intermediate 4A

7-Methoxy-5-methyl-1-benzothiophene



To a refluxing mixture of 13 g polyphosphoric acid and 150 ml chlorobenzene was added dropwise a solution of 5.2 g (19.2 mmol) of Intermediate 3A, and refluxing was continued overnight. After cooling, the organic layer was decanted, and the residue and flask were rinsed twice with DCM. The combined organic phases were evaporated at reduced pressure. The residue (3.76 g) was chromatographed on silica gel with isohexane/0-10% ethyl acetate as eluent.

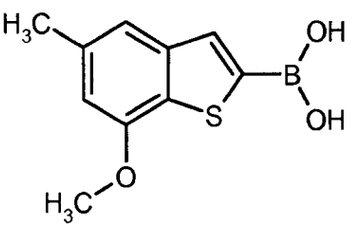
Yield: 1.69 g of an oil (49% of th.)

GC-MS (method 6): R_t = 5.20 min; MS (EIpos): m/z = 178 $(M)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.68 (d, 1H), 7.34 (d, 1H), 7.28 (s, 1H), 6.78 (s, 1H), 3.93 (s, 3H), 2.43 (s, 3H) ppm.

Intermediate 5A

(7-Methoxy-5-methyl-1-benzothiophen-2-yl)boronic acid



Under argon atmosphere, 26.7 g (150 mmol) of Intermediate 4A were dissolved in 270 ml of THF and cooled to -70°C. Between -70°C and -65°C, 66 ml (165 mmol) of a 2.5 N solution of *n*-butyl-lithium in hexane were added dropwise within 20 min, resulting in formation of a white precipitate. After stirring for 1 h at -70°C, 41.5 ml (180 mmol) triisopropyl borate were added at this temperature within 10 min (resulting in a thick suspension). Stirring was continued for 1 h at -70°C, before the reaction mixture was allowed to warm up to rt overnight. Then, 400 ml of saturated aq. ammonium chloride solution were added, the layers were separated, and the aqueous layer was extracted once more with THF. The combined organic phases were evaporated under reduced pressure. To the residue thus obtained, 200 ml of water and 86 ml of 2 N aq. sodium hydroxide solution were added. The solution was washed twice with DCM, then acidified with 35 ml of 3 M sulfuric acid, and the resulting suspension was stirred vigorously for 1 h. The precipitate was filtered off by suction and dried overnight at 45°C *in vacuo*.

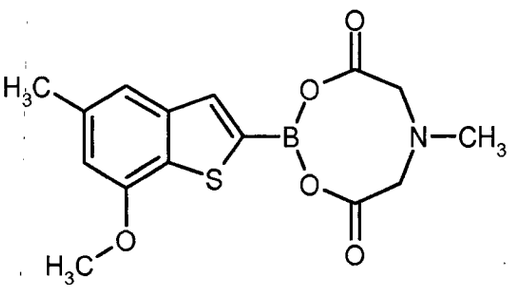
Yield: 28.25 g of a colorless solid (94% pure by LC-MS, 80% of th.)

LC-MS (method 2): R_t = 0.87 min; MS (ESIpos): m/z = 223 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.17 (d, 1H), 6.81 (s, 1H), 6.66 (d, 1H), 4.63 (br. s, 1H), 3.80 (s, 3H), 2.26 (s, 3H) ppm.

Intermediate 6A

2-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione



6.3 g (28.4 mmol) of Intermediate 5A and 4.2 g (28.4 mmol) 2,2'-(methylimino)diacetic acid were dissolved in a mixture of 45 ml DMSO and 400 ml toluene and refluxed for 16 h using a Dean-Stark trap. After evaporation, the residue was taken up in ethyl acetate and washed three times with water and once with brine. The organic phase was dried over magnesium sulfate and evaporated to a volume of about 200 ml. A white solid precipitated which was filtered, washed with ethyl acetate and dried *in vacuo* to give a first crop (5.52 g) of the title compound. A second crop (3.32 g) was obtained after evaporation of the mother liquor and flash-chromatography over a layer of silica gel using cyclohexane/0-100% ethyl acetate as the eluent.

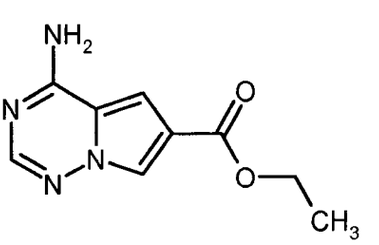
Yield: 8.84 g (overall purity 92.5% by LC-MS, 87% of th.)

LC-MS (method 2): R_t = 0.93 min; MS (ESIpos): m/z = 334 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.42 (s, 1H), 7.26 (s, 1H), 6.76 (s, 1H), 4.40 (d, 2H), 4.17 (d, 2H), 3.92 (s, 3H), 2.63 (s, 3H), 2.42 (s, 3H) ppm.

Intermediate 7A

Ethyl 4-aminopyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



A solution of 4-aminopyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile (3.9 g, 24.5 mmol; preparation described in PCT Int. Pat. Appl. WO 2007/064883) in ethanol (124.8 ml) was stirred with concentrated sulfuric acid (62.4 ml) at 80°C overnight. After cooling to rt, the reaction mixture was poured onto 800 g of ice and brought to pH 6-7 with concentrated aq. sodium hydroxide solution. Ethyl acetate (500 ml) and dichloromethane (500 ml) were added to the suspension, and the resulting

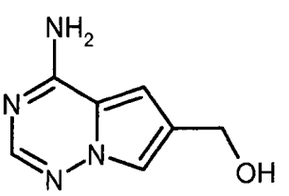
mixture was filtered over kieselguhr. The organic layer was separated from the aqueous layer. The solid was dissolved in hot water (1 L), and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over sodium sulfate and evaporated. The residue was triturated with an isopropanol/diethylether mixture, and the solid was filtered off yielding 2.5 g (49% of th.) of the title compound.

LC-MS (method 2): R_t = 0.59 min; MS (ESIpos): m/z = 206 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.11-7.97 (m, 3H), 7.88 (s, 1H), 7.34 (br. s, 1H), 4.27 (q, 2H), 1.30 (t, 3H) ppm.

Intermediate 8A

(4-Aminopyrrolo[2,1-f][1,2,4]triazin-6-yl)methanol



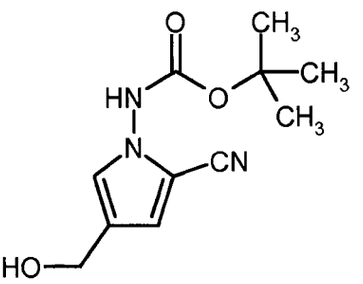
An ice-cooled solution of Intermediate 7A (3.0 g, 14.5 mmol) in THF (30 ml) was treated with a 1 M solution of lithium triethylborohydride in THF (58 ml) and stirred at rt for 45 min. The reaction mixture was then cooled to 0°C, quenched with methanol, warmed slowly to rt and adsorbed on kieselguhr. Purification by column chromatography over silica gel (dichloromethane/methanol 20:1 → 4:1 gradient) afforded 2.21 g (92.5% of th.) of the title compound.

LC-MS (method 3): R_t = 1.46 min; MS (ESIpos): m/z = 164 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.75 (s, 1H), 7.64 (br. s, 2H), 7.50 (br. d, 1H), 6.79 (br. d, 1H), 5.01 (t, 1H), 4.50 (d, 2H) ppm.

Intermediate 9A

tert-Butyl [2-cyano-4-(hydroxymethyl)-1*H*-pyrrol-1-yl]carbamate



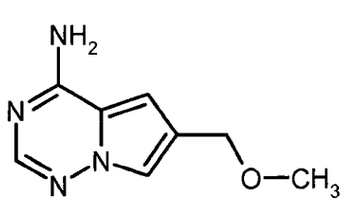
Under argon, a 1 M solution of methylmagnesium bromide in THF (13.3 ml) was added over 15 min to a solution of *tert*-butyl (4-bromo-2-cyano-1*H*-pyrrol-1-yl)carbamate (3.7 g, 12.09 mmol; preparation described in PCT Int. Pat. Appl. WO 2007/064883, Intermediate AAE, Step 3) in THF (37 ml) cooled to -60°C. After 30 min, a 1.6 M solution of *n*-butyllithium in hexane (15.1 ml, 24.2 mmol) was added over 10 min to the reaction, and the resulting mixture was stirred between -60°C and -40°C for 1 h. Then, paraformaldehyde (1.09 g, 36.3 mmol) was added to the reaction, and the reaction mixture was slowly warmed to rt and stirred overnight. After quenching with sat. aq. ammonium chloride solution, the aqueous layer was extracted twice with ethyl acetate. The combined organic phases were washed with sat. aq. sodium chloride solution, dried over sodium sulfate and evaporated. Purification by column chromatography on silica gel (cyclohexane/ethyl acetate 2:1 → 1:1) afforded 2.04 g (69% of th.) of the title compound.

LC-MS (method 4): R_t = 0.70 min; MS (ESIpos): m/z = 238 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.79 (br. s, 1H), 7.09 (d, 1H), 6.86 (d, 1H), 4.97 (t, 1H), 4.28 (d, 2H), 1.45 (s, 9H) ppm.

Intermediate 10A

6-(Methoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



Method 1:

A solution of Intermediate 8A (1.3 g, 7.9 mmol) in THF (25 ml) was treated with thionyl chloride (1.15 ml, 15.8 mmol) and stirred at rt for 2 h. After evaporation, the residue was dissolved in methanol (25 ml) and treated with sodium acetate (1.3 g, 15.8 mmol). The mixture was stirred for

3 h at 65°C and then evaporated again. Purification by column chromatography on silica gel (dichloromethane/methanol 100:2) afforded 787 mg (55% of th.) of the title compound.

Method 2:

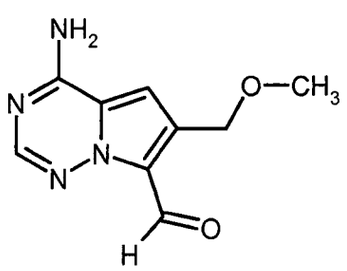
A solution of Intermediate 9A (6.14 g, 25.88 mmol) in a 4 M solution of hydrogen chloride in 1,4-dioxane (15 ml) was stirred at rt for 5 h. After dilution with methanol (73 ml), stirring at rt was continued overnight. Then, potassium phosphate (54.9 g, 258.65 mmol) and formamidinium acetate (13.46 g, 129.32 mmol) were added, and the resulting mixture was stirred at 65°C for 17 h. The reaction mixture was evaporated, sat. aq. sodium chloride solution was added, and the mixture was extracted with dichloromethane followed by ethyl acetate. The combined organic phases were dried over sodium sulfate and evaporated. Purification by column chromatography on silica gel (dichloromethane/methanol 40:1 → 20:1) afforded 2.36 g (49% of th.) of the title compound.

LC-MS (method 3): R_t = 1.72 min; MS (ESIpos): m/z = 179 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.77 (s, 1H), 7.69 (br. s, 2H), 7.57 (s, 1H), 6.81 (s, 1H), 4.42 (s, 2H), 3.25 (s, 3H) ppm.

Intermediate 11A

4-Amino-6-(methoxymethyl)pyrrolo[2,1-f][1,2,4]triazine-7-carbaldehyde



Phosphoryl chloride (13.7 ml, 147.18 mmol) was added to a solution of Intermediate 10A (5.24 g, 29.43 mmol) in DMF (80 ml) at 0°C. The resulting mixture was stirred at 60°C for 8 h, then carefully quenched with water and neutralized with 4 M aq. sodium hydroxide solution. The aqueous layer was extracted with ethyl acetate. The combined organic phases were washed with sat. aq. sodium chloride solution, dried over magnesium sulfate and evaporated. A solution of the residue in methanol (50 ml) was treated with sodium acetate (2.41 g, 29.43 mmol) and refluxed overnight. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic phases were washed with sat. aq. sodium chloride solution, dried over magnesium sulfate and

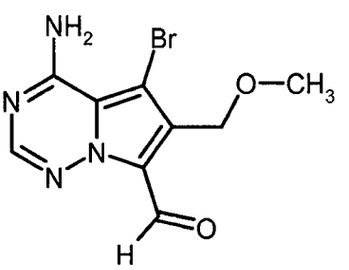
evaporated, affording 2.66 g of the crude product which was used in the next step without further purification.

LC-MS (method 4): R_t = 0.50 min; MS (ESIpos): m/z = 207 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.35 (s, 1H), 8.20 (br. s, 2H), 8.07 (s, 1H), 7.06 (s, 1H), 4.72 (s, 2H), 3.39 (s, 3H) ppm.

Intermediate 12A

4-Amino-5-bromo-6-(methoxymethyl)pyrrolo[2,1-f][1,2,4]triazine-7-carbaldehyde



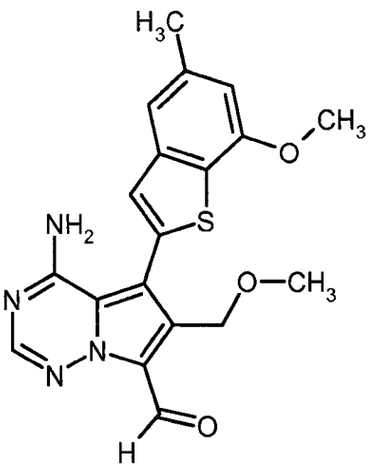
A solution of Intermediate 11A (crude, 2.66 g) in DMF (30 ml), cooled to -30°C, was treated with a solution of *N*-bromosuccinimide (NBS; 2.52 g, 14.19 mmol) in DMF (14 ml). The resulting mixture was slowly warmed to 0°C. After 1 hour, the mixture was warmed to rt, stirred for further 15 min and then quenched with 1 M aq. sodium thiosulfate solution. The precipitate was filtered off and washed with ethyl acetate, affording 1.1 g (100% purity, 30% of th.) as a first crop of the title compound. The remaining filtrate was extracted with ethyl acetate. The combined organic phases were washed with sat. aq. sodium chloride solution, dried over sodium sulfate and evaporated. Purification of the residue by column chromatography on silica gel (cyclohexane/ethyl acetate 1:1 → 1:3) afforded further 1.39 g (70% purity, 26% of th.) of the title compound.

LC-MS (method 2): R_t = 0.67 min; MS (ESIpos): m/z = 283/285 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.36 (s, 1H), 8.63 (br. s, 1H), 8.13 (s, 1H), 7.23 (br. s, 1H), 4.64 (s, 2H), 3.26 (s, 3H) ppm.

Intermediate 13A

4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazine-7-carbaldehyde



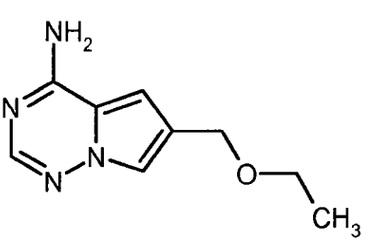
Under argon, a degassed 0.5 M aq. potassium phosphate solution (9.9 ml) was added to a solution of Intermediate 12A (710 mg, 2.49 mmol), Intermediate 5A (921 mg, 3.73 mmol) and (2'-amino-biphenyl-2-yl)(chloro)palladium-dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (1:1; 196 mg, 249 µmol; see S. L. Buchwald *et al., J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)) in degassed THF (28.4 ml). The resulting mixture was stirred at 60°C for 2 h and then evaporated. Purification of the residue by column chromatography on silica gel (cyclohexane/ethyl actetate 5:1 → 1:1) afforded 550 mg (51% of th.) of the title compound.

LC-MS (method 2): R_t = 1.06 min; MS (ESIpos): m/z = 383 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.50 (s, 1H), 8.43 (br. s, 1H), 8.21 (s, 1H), 7.42 (s, 1H), 7.33 (s, 1H), 6.87 (s, 1H), 6.09 (br. s, 1H), 4.58 (s, 2H), 3.96 (s, 3H), 3.19 (s, 3H), 2.46 (s, 3H) ppm.

Intermediate 14A

6-(Ethoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



Method 1:

To a suspension of 2 g (12.2 mmol) of Intermediate 8A in 40 ml THF were added 1.78 ml (24.4 mmol) thionyl chloride at rt within 20 sec. The mixture was stirred for 1.5 h, then evaporated to

dryness, and the residue was dissolved in 40 ml ethanol. 2 g (24.4 mmol) sodium acetate were added, and the mixture was stirred at 70°C for 1 h 45 min. The reaction mixture was evaporated again, and sat. aq. sodium hydrogencarbonate solution was added. The mixture was extracted five times with ethyl acetate. The combined organic phases were washed with sat. aq. sodium chloride solution, dried with magnesium sulfate and evaporated to dryness, giving 2.02 g of crude product which was purified by column chromatography on silica gel with dichloromethane/methanol (0-2%) as the eluent.

Yield: 1.37 g (58% of th.).

Method 2:

Step 1: A solution of Intermediate 9A (2.3 g, 9.69 mmol) in 1,4-dioxane (5 ml) was treated with a 4 M solution of hydrogen chloride in 1,4-dioxane (24 ml, 96.9 mmol) and stirred at rt for 130 min. Then, the suspension was filtered, and the precipitate was washed with 1,4-dioxane (5 ml) and dried *in vacuo* yielding 1.01 g (54% of th.) of the intermediate compound 1-amino-4-(chloromethyl)-1*H*-pyrrole-2-carbonitrile hydrochloride.

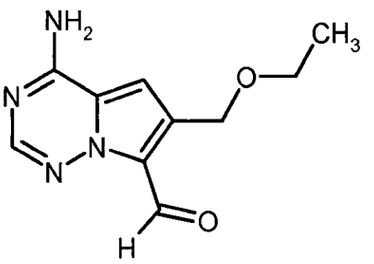
Step 2: Freshly prepared 1-amino-4-(chloromethyl)-1*H*-pyrrole-2-carbonitrile hydrochloride from Step 1 (0.3 g, 1.82 mmol) was dissolved in ethanol (10 ml) and stirred at rt for 5 min. The clear solution was treated with formamidine acetate (813 mg, 7.81 mmol) and potassium phosphate (1.66 g, 7.81 mmol) and stirred first at rt for 3 days, then at 80°C for 10.5 h. More formamidine acetate (488 mg, 4.69 mmol) was added, and the mixture was stirred for further 18 h at 80°C. The mixture was then cooled to rt, and water and ethyl acetate were added. The organic phase was separated, and the aqeous phase was extracted twice with ethyl acetate. The combined organic phases were washed with sat. aq. sodium chloride solution, dried with magnesium sulfate and evaporated. The residue was dissolved in a mixture of methanol and dichloromethane, adsorbed on diatomaceous earth, dried *in vacuo* and finally purified by chromatography on silica gel (gradient 0-10% methanol/dichloromethane) yielding 260 mg (78% of th.) of the title compound.

LC-MS (method 3): R_t = 2.02 min; MS (ESIpos): m/z = 193 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.77 (s, 1H), 7.59-7.74 (br. s, 2H), 7.56 (s, 1H), 6.82 (s, 1H), 5.76 (s, 1H), 4.46 (s, 2H), 3.46 (q, 2H), 1.13 (t, 3H) ppm.

Intermediate 15A

4-Amino-6-(ethoxymethyl)pyrrolo[2,1-f][1,2,4]triazine-7-carbaldehyde



To a solution of 2.1 g (10.9 mmol) of Intermediate 14A in 40 ml dry DMF, 5.1 ml (54.6 mmol) phosphoryl chloride were added dropwise at 0°C under an argon atmosphere. The mixture was stirred at 60°C for 10 h. Then, water was added carefully, and the mixture was stirred at ambient temperature until all reactive intermediates were destroyed (HPLC control). The acidic solution was neutralized with 1 M aq. sodium hydroxide solution and extracted three times with ethyl acetate. The combined organic phases were washed with sat. aq. sodium chloride solution, dried over magnesium sulfate and evaporated at reduced pressure.

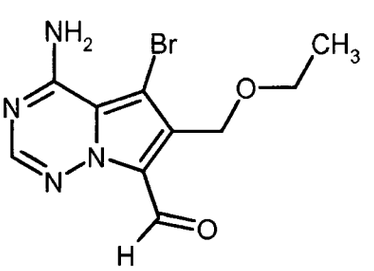
Yield: 1.94 g (purity 90%, 81% of th.)

LC-MS (method 5): R_t = 1.49 min; MS (ESIpos): m/z = 221 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.35 (s, 1H), 8.14-8.26 (m, 2H), 8.07 (s, 1H), 7.07 (s, 1H), 4.76 (s, 2H), 3.58 (q, 2H), 1.20 (t, 3H) ppm.

Intermediate 16A

4-Amino-5-bromo-6-(ethoxymethyl)pyrrolo[2,1-f][1,2,4]triazine-7-carbaldehyde



To a solution of 73 g (0.33 mol) of Intermediate 15A in 1.9 L DMF was added dropwise a solution of 65 g (0.37 mol) NBS in 200 ml DMF at -15°C. The mixture was allowed to warm to 0°C and stirred for 3 h at this temperature. The reaction mixture was poured into 2% aq. sodium thiosulfate solution under stirring, and the precipitate was filtered off, washed with water and dried over phosphorous pentoxide *in vacuo*.

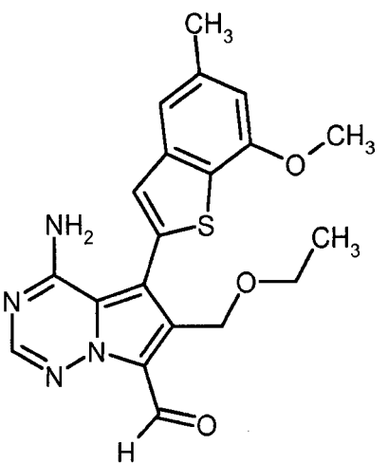
Yield: 85.6 g (86% of th.)

LC-MS (method 2): R_t = 0.76 min; MS (ESIpos): m/z = 299/301 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.36 (s, 1H), 8.62 (br. s, 1H), 8.13 (s, 1H), 7.22 (br. s, 1H), 4.68 (s, 2H), 3.49 (q, 2H), 1.10 (t, 3H) ppm.

Intermediate 17A

4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazine-7-carbaldehyde



Under an argon atmosphere, 714 mg (purity 85%, 2.03 mmol) of Intermediate 16A, 946 mg (2.84 mmol) of Intermediate 6A and 160 mg (0.2 mmol) (2'-aminobiphenyl-2-yl)(chloro)palladium-dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (1:1; see S. L. Buchwald *et al.*, *J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)) were suspended in 15.5 ml THF. Then, 15.5 ml of a degassed 0.5 M aq. potassium phosphate solution were added, and the mixture was stirred at 50°C for 16 h. After addition of water, the mixture was extracted with ethyl acetate, and the combined organic phases were dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (100 g) with 10-50% ethyl acetate/ cyclohexane as the eluent.

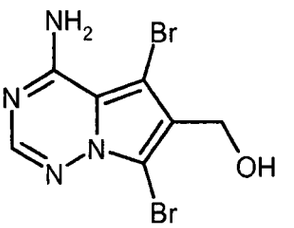
Yield: 452 mg (75% pure by HPLC, 42% of th.)

LC-MS (method 5): R_t = 2.38 min; MS (ESIpos): m/z = 397 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.50 (s, 1H), 8.42 (br. s, 1H), 8.21 (s, 1H), 7.43 (s, 1H), 7.33 (s, 1H), 6.87 (s, 1H), 6.07 (br. s, 1H), 4.63 (s, 2H), 3.96 (s, 3H), 3.40 (q, 2H), 2.46 (s, 3H), 1.02 (t, 3H) ppm.

Intermediate 18A

(4-Amino-5,7-dibromopyrrolo[2,1-f][1,2,4]triazin-6-yl)methanol



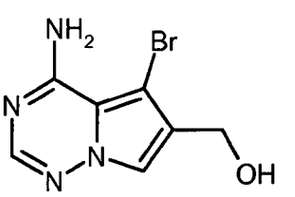
A solution of Intermediate 8A (5 g, 30.4 mmol) in THF (100 ml) was treated with 1,3-dibromo-5,5-dimethylhydantoin (9.58 g, 33.5 mmol) and stirred at rt for 2 h. The precipitate was filtered off and dried *in vacuo* to afford 6.60 g (64% of th.) of the title compound.

LC-MS (method 2): R_t = 0.56 min; MS (ESIpos): m/z = 321/323/325 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.23 (br. s, 1H), 7.96 (s, 1H), 6.94 (br. s, 1H), 5.09 (br. s, 1H), 4.43 (s, 2H) ppm.

Intermediate 19A

(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-6-yl)methanol



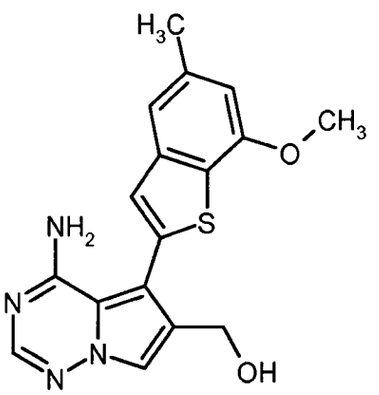
A suspension of Intermediate 18A (3.7 g, 11.5 mmol) in THF (800 ml) was heated under stirring until complete dissolution. The mixture was then cooled to -78°C, and a 1.6 M solution of *n*-butyllithium in hexanes (20 ml, 32.1 mmol) was added dropwise. After 5 min, a further portion of 1.6 M *n*-butyllithium solution (1.5 ml, 2.29 mmol) was added. The resulting mixture was stirred at -78°C for 5 min, then quenched with methanol (5 ml) and warmed to rt. The reaction mixture was diluted with sat. aq. ammonium chloride solution, sat. aq. sodium hydrogencarbonate solution, sat. aq. sodium chloride solution and ethyl acetate. After phase separation, the organic layer was washed with sat. aq. sodium chloride solution. The combined aqueous phases were re-extracted with ethyl acetate. The combined organic phases were washed again with sat. aq. sodium chloride solution, dried over magnesium sulfate and evaporated to afford 2.87 g of the crude product which was used in subsequent steps without further purification.

LC-MS (method 3): R_t = 1.73 min; MS (ESIpos): m/z = 243/245 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.41-7.89 (br. s, 1H), 7.82 (s, 1H), 7.66 (s, 1H), 7.13-6.48 (br. s, 1H), 5.11 (t, 1H), 4.45 (d, 2H) ppm.

Intermediate 20A

[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methanol



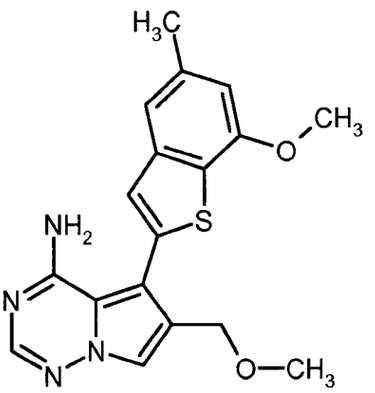
A suspension of Intermediate 19A (70% purity, 2.52 g, 7.26 mmol), Intermediate 6A (3.63 g, 10.9 mmol) and caesium fluoride (5.51 g, 36.3 mmol) in a THF/water mixture (10:1; 80 ml) was degassed under argon. 4-(Di-*tert*-butylphosphino)-*N,N*-dimethylaniline-dichloropalladium (2:1; 176 mg, 0.248 mmol) was added, and the resulting mixture was degassed again and stirred at 50°C for 16 h. The reaction mixture was then washed with sat. aq. sodium chloride solution, and the organic layer was separated, dried over magnesium sulfate, filtered and evaporated. The residue was suspended in methanol, and the resulting solid was filtered off and dried *in vacuo* to afford 1.97 g (90% purity, 72% of th.) of the title compound.

LC-MS (method 2): R_t = 0.85 min; MS (ESIpos): m/z = 340 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.91 (s, 1H), 7.5-8.1 (br. s, 1H), 7.72 (s, 1H), 7.35 (s, 1H), 7.30 (s, 1H), 6.84 (s, 1H), 5.5-6.0 (br. s, 1H), 5.06 (t, 1H), 4.49 (d, 2H), 3.95 (s, 3H), 2.45 (s, 3H) ppm.

Intermediate 21A

6-(Methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



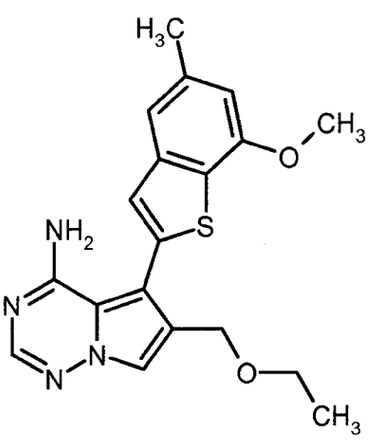
A solution of Intermediate 20A (400 mg, 1.17 mmol) in dichloromethane (12 ml) was treated with thionyl chloride (128 µl, 1.76 mmol) and stirred at rt for 15 min. After evaporation, the residue was taken up in methanol (12 ml) and treated with DIPEA (409 µl, 2.35 mmol). The mixture was refluxed overnight and then evaporated again. Purification by column chromatography on silica gel (dichloromethane/methanol 98:2 → 95:5) afforded 388 mg (93% of th.) of the title compound.

LC-MS (method 2): R_t = 1.00 min; MS (ESIpos): m/z = 355 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.93 (s, 1H), 7.82 (s, 1H), 7.35 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 4.38 (s, 2H), 3.95 (s, 3H), 3.22 (s, 3H), 2.45 (s, 3H) ppm.

Intermediate 22A

6-(Ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



Intermediate 20A (200 mg, 587 µmol) in dichloromethane (5 ml) was treated with thionyl chloride (64 µl, 881 µmol) and stirred at rt for 15 min. After evaporation, the residue was refluxed in ethanol (5 ml) for 1 h, then treated with DIPEA (204 µl, 1.17 mmol) and refluxed again overnight. The reaction mixture was evaporated, and the crude product was purified by column chromatography on

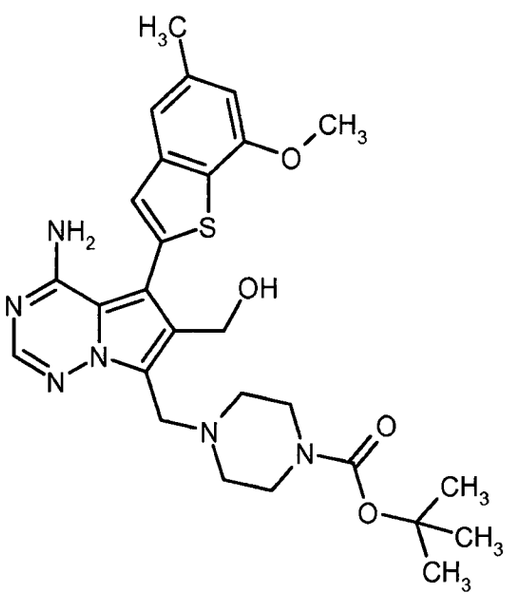
silica gel (dichloromethane/methanol 98:2 → 95:5) affording 202 mg (90% of th.) of the title compound.

LC-MS (method 5): R_t = 2.32 min; MS (ESIpos): m/z = 369 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.31-7.59 (br. s, 1H), 7.93 (s, 1H), 7.81 (s, 1H), 7.35 (s, 1H), 7.30 (s, 1H), 6.84 (s, 1H), 6.20-5.50 (br. s, 1H), 4.41 (s, 2H), 3.95 (s, 3H), 3.41 (q, 2H), 2.45 (s, 3H), 1.08 (t, 3H) ppm.

Intermediate 23A

tert-Butyl 4-{[4-amino-6-(hydroxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo-[2,1-f][1,2,4]triazin-7-yl]methyl}piperazine-1-carboxylate



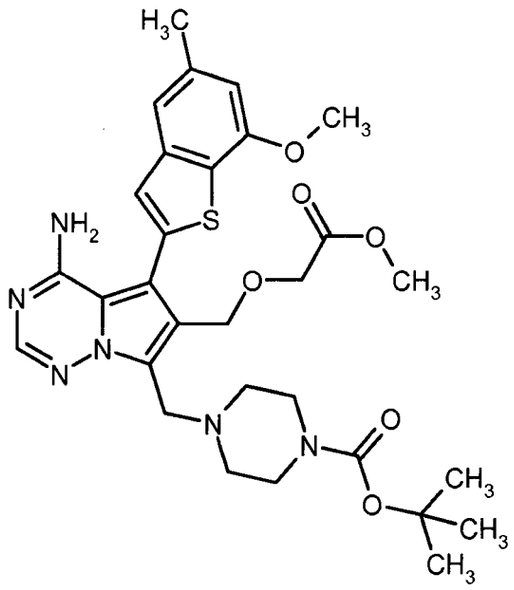
A solution of Intermediate 20A (9.5 g, 27.9 mmol) in acetic acid (136.8 ml) was treated with *tert*-butyl piperazine-1-carboxylate (6.24 g, 33.49 mmol) and 37% aq. formaldehyde solution (2.5 ml, 33.49 mmol). The mixture was stirred at 60°C for 2.5 h. After evaporation, the residue was taken up in ethyl acetate, and the mixture was washed twice with sat. aq. sodium hydrogencarbonate solution, dried over sodium sulfate and evaporated. The residue was triturated in boiling ethanol (100 ml). The solid was filtered off and washed with ethanol and diethylether affording 9.70 g (58% of th.) of the title compound.

LC-MS (method 2): R_t = 0.88 min; MS (ESIpos): m/z = 539 $(M+H)^+$

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.94 (s, 1H), 7.13-7.35 (m, 2H, overlap with $CHCl_3$ peak), 6.67 (s, 1H), 5.86 (br. s, 1H), 5.54 (br. s, 2H), 4.68 (s, 2H), 4.08 (s, 2H), 4.00 (s, 3H), 3.45 (br. s, 4H), 2.59-2.48 (m, 7H), 1.45 (s, 9H) ppm.

Intermediate 24A

tert-Butyl 4-({4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-6-[(2-methoxy-2-oxoethoxy)-methyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}methyl)piperazine-1-carboxylate



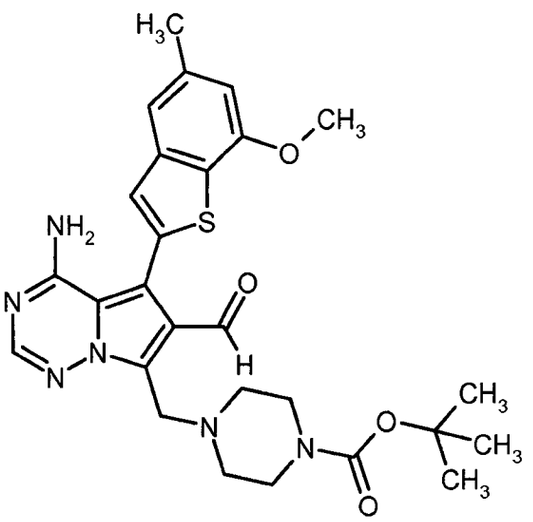
A solution of Intermediate 23A (300 mg, 556 µmol) in dichloromethane (12 ml) was treated with thionyl chloride (81 µl, 1.11 mmol) and stirred at rt for 15 min. After evaporation, the residue was dissolved in freshly distilled methylglycolate (2.5 ml) and treated with DIPEA (485 µl, 2.78 mmol). The mixture was stirred at 70°C for 2 h, then evaporated again, and excess methylglycolate was removed by distillation. Purification of the residue by column chromatography on silica gel (cyclohexane/ethyl acetate 1:5) afforded 136 mg (33% of th.) of the title compound.

LC-MS (method 2): R_t = 0.88 min; MS (ESIpos): m/z = 611 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.99 (s, 1H), 7.39 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 4.58 (s, 2H), 4.11 (s, 2H), 3.96 (s, 3H), 3.93 (s, 2H), 3.57 (s, 3H), 3.30-3.24 (m, 4H), 2.45-2.38 (m, 7H), 1.39 (s, 9H) ppm.

Intermediate 25A

tert-Butyl 4-{[4-amino-6-formyl-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-7-yl]methyl}piperazine-1-carboxylate



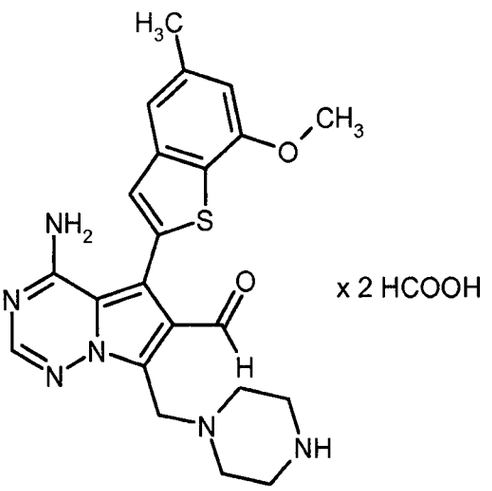
A solution of Intermediate 23A (300 mg, 556 µmol) in dichloromethane (4.2 ml) was treated with Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one; 307 mg, 724 µmol) and stirred at rt for 2 h. The reaction mixture was quenched with sat. aq. sodium hydrogencarbonate solution and sat. aq. sodium thiosulfate solution (1:1) and stirred at rt for 30 min. The aqueous layer was extracted three times with dichloromethane, and the combined organic layers were dried over magnesium sulfate and evaporated. Purification by column chromatography on silica gel (cyclohexane/ethyl acetate 1:1 → 100% ethyl acetate) afforded 273 mg (87% of th.) of the title compound.

LC-MS (method 2): R_t = 0.87 min; MS (ESIpos): m/z = 537 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.02 (s, 1H), 8.44-8.18 (br. s, 1H), 8.08 (s, 1H), 7.51 (s, 1H), 7.32 (s, 1H), 6.88 (s, 1H), 6.01-5.74 (br. s, 1H), 4.16 (s, 2H), 3.96 (s, 3H), 3.30-3.22 (m, 4H), 2.48-2.40 (m, 7H), 1.38 (s, 9H) ppm.

Intermediate 26A

4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f]-[1,2,4]triazine-6-carbaldehyde bis(formiate)



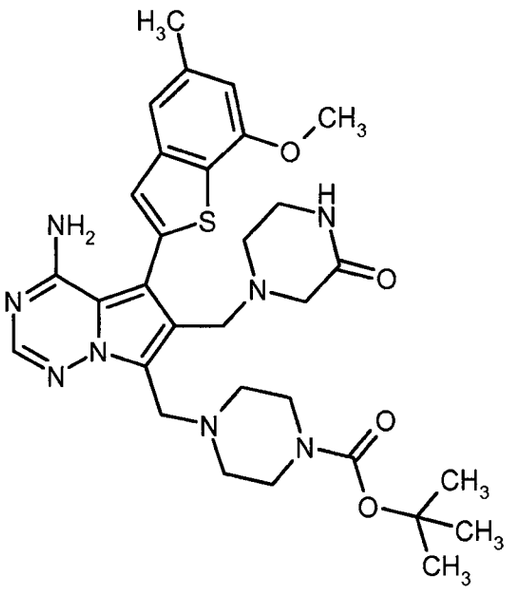
A solution of Intermediate 23A (80 mg, 148 µmol) in THF (3.9 ml) was treated with Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one; 94 mg, 222 µmol) and stirred at rt for 30 min. The reaction mixture was quenched with sat. aq. sodium hydrogencarbonate solution and sat. aq. sodium thiosulfate solution (1:1). The aqueous layer was extracted three times with ethyl acetate, and the combined organic layers were dried over magnesium sulfate and evaporated. The residue was dissolved in a 4 M solution of hydrogen chloride in 1,4-dioxane (4 ml) and stirred at rt for 1 h. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) affording 34 mg (52% of th.) of the title compound.

LC-MS (method 2): R_t = 0.78 min; MS (ESIpos): m/z = 437 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.02 (s, 1H), 8.29 (br. s, 2H), 8.09 (s, 1H), 7.50 (s, 1H), 7.33 (s, 1H), 6.88 (s, 1H), 4.17 (s, 2H), 3.96 (s, 3H), 2.90-2.81 (m, 4H), 2.63-2.56 (m, 4H), 2.46 (s, 3H) ppm.

Intermediate 27A

tert-Butyl 4-({4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-6-[(3-oxopiperazin-1-yl)-methyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}methyl)piperazine-1-carboxylate

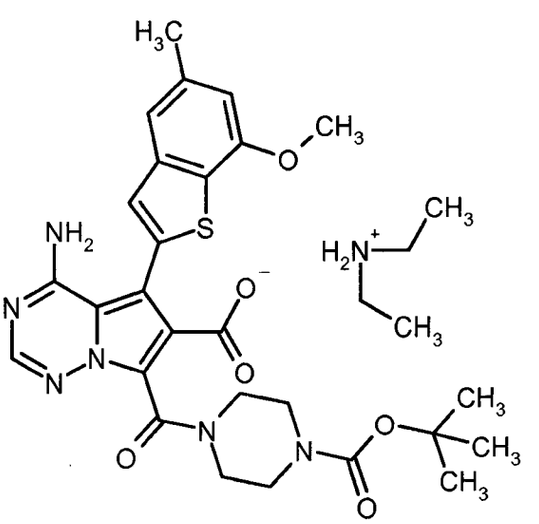


A solution of Intermediate 25A (185 mg, 344 µmol) in THF (4.6 ml) was treated with 2-oxo-piperazine (344 mg, 3.4 mmol), sodium triacetoxyborohydride (365 mg, 1.7 mmol) and acetic acid (39 µl, 689 µmol). The resulting mixture was stirred at rt for 2 h, then adsorbed on kieselguhr and purified by column chromatography on silica gel (dichloromethane → dichloromethane/methanol 100:8) affording 221 mg (quant.) of the title compound.

LC-MS (method 4): R_t = 0.77 min; MS (ESIpos): m/z = 621 $(M+H)^+$.

Intermediate 28A

N-Ethylethanaminium 4-amino-7-{[4-(*tert*-butoxycarbonyl)piperazin-1-yl]carbonyl}-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



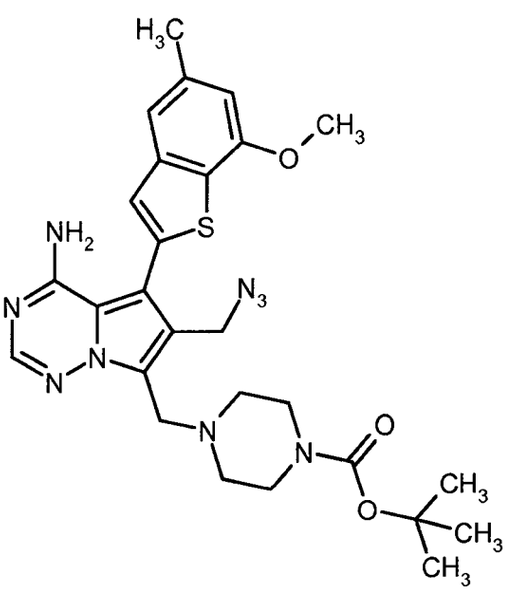
A solution of Intermediate 25A (70 mg, 130 µmol) in THF/water (10:1, 4.85 ml) was treated with a 2 M solution of 2-methyl-2-buten in THF (521 µl, 1.04 mmol) and sodium dihydrogenphosphate (107 mg, 783 µmol) and stirred at rt for 5 min. Sodium chlorite (70 mg, 783 µmol) was added, and the resulting mixture was stirred at rt overnight. After dilution with water, the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried over sodium sulfate and evaporated, and the residue was purified by preparative RP-HPLC (XBridge C18, gradient 5-50% acetonitrile/water + 0.05% diethylamine) affording 18 mg (21% of th.) of the title compound.

LC-MS (method 1): R_t = 1.14 min; MS (ESIpos): m/z = 567 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.26-7.89 (br. s, 1H), 7.94 (s, 1H), 7.33 (s, 1H), 7.28 (s, 1H), 6.83 (s, 1H), 5.64-5.33 (br. s, 1H), 3.95 (s, 3H), 2.80 (q, 4H), 2.45 (s, 3H), 1.40 (s, 9H), 1.09 (t, 6H) ppm.

Intermediate 29A

tert-Butyl 4-{[4-amino-6-(azidomethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo-[2,1-f][1,2,4]triazin-7-yl]methyl}piperazine-1-carboxylate



A solution of Intermediate 23A (150 mg, 0.278 mmol) in dichloromethane (7.5 ml) was treated with thionyl chloride (40 µl, 0.56 mmol) and stirred at rt for 15 min. After evaporation, the residue was dissolved in DMF (6 ml) and treated with sodium azide (362 mg, 5.57 mmol) and sodium iodide (208 mg, 1.39 mmol). The mixture was heated to 80°C for 1 h, then diluted with water and extracted three times with ethyl acetate. The combined organic layers were washed with water and with sat. aq. sodium chloride solution, dried over magnesium sulfate and evaporated. Purification by column

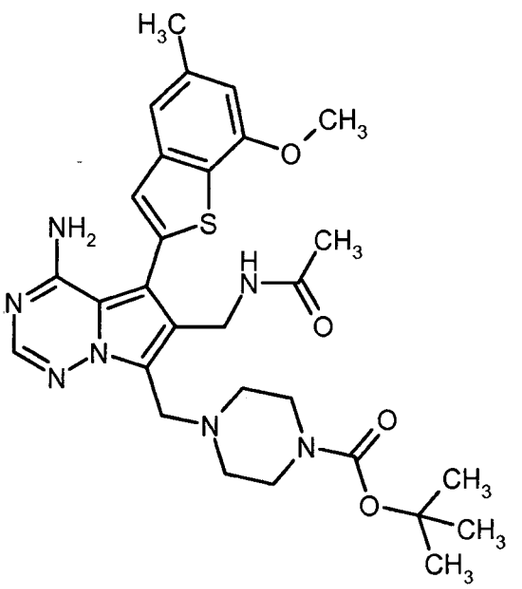
chromatography on silica gel (cyclohexane/ethyl acetate 98:2 → 100% ethyl acetate) afforded 95.8 mg (57% of th.) of the title compound.

LC-MS (method 4): R_t = 0.99 min; MS (ESIpos): m/z = 564 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.20-7.80 (br. s, 1H), 8.01 (s, 1H), 7.39 (s, 1H), 7.33 (s, 1H), 6.86 (s, 1H), 6.05-5.55 (br. s, 1H), 4.50 (s, 2H), 3.96 (s, 3H), 3.94 (s, 2H), 3.32-3.25 (m, 4H), 2.45 (s, 3H), 2.43-2.36 (m, 4H), 1.39 (s, 9H) ppm.

Intermediate 30A

tert-Butyl 4-{[6-(acetamidomethyl)-4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo-[2,1-f][1,2,4]triazin-7-yl]methyl}piperazine-1-carboxylate



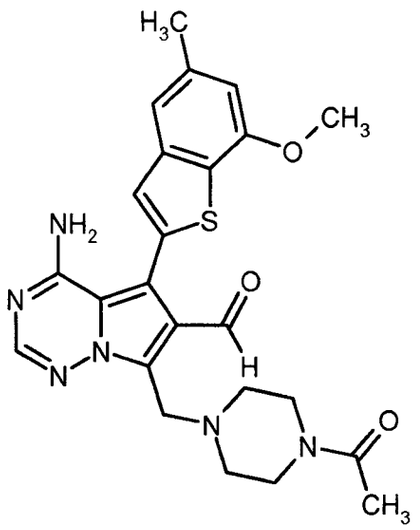
A mixture of Intermediate 29A (320 mg, 567 µmol), 10% Pd/C (320 mg) and acetic anhydride (106 µl, 1.13 mmol) in methanol (32 ml) was stirred for 90 min under 1 atm of hydrogen at rt. The mixture was then filtered through kieselguhr, and the filtrate was evaporated. Purification by column chromatography on silica gel (cyclohexane/ethyl acetate 1:1 → 100% ethyl acetate) afforded 440 mg (quant.) of the title compound.

LC-MS (method 2): R_t = 0.91 min; MS (ESIpos): m/z = 580 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.02-7.97 (m, 2H), 7.38 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 4.27 (br. d, 2H), 3.95 (s, 3H), 3.89 (s, 2H), 3.31-3.24 (m, 4H), 2.45 (s, 3H), 2.43-2.36 (m, 4H), 1.74 (s, 3H), 1.39 (s, 9H) ppm.

Intermediate 31A

7-[(4-Acetylpiperazin-1-yl)methyl]-4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo-[2,1-f][1,2,4]triazine-6-carbaldehyde

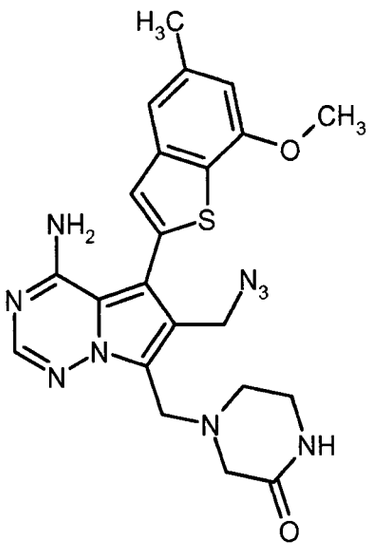


A solution of Example 55 (678 mg, purity 89%, 1.26 mmol) in dichloromethane (4 ml) containing molecular sieves (4Å) was treated with Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one; 623 mg, 1.47 mmol) and stirred at rt for 5 min. The reaction mixture was then adsorbed on diatomaceous earth and purified by column chromatography on silica gel (gradient of 30-100% ethyl acetate/cyclohexane, then 0-10% methanol/dichloromethane) yielding 449 mg (49% of th.) of the title compound.

LC-MS (method 4): R_t = 0.70 min; MS (ESIpos): m/z = 479 $(M+H)^+$.

Intermediate 32A

4-{[4-Amino-6-(azidomethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-7-yl]methyl}piperazin-2-one



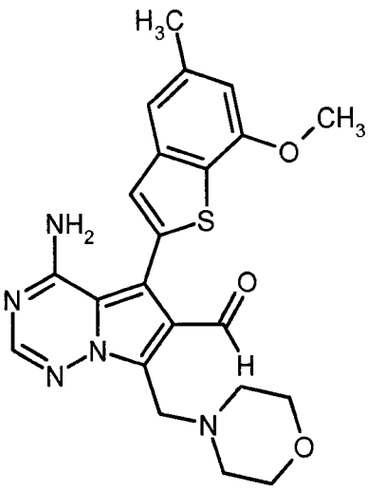
A solution of Example 13 (59 mg, 130 µmol) in dichloromethane (3.5 ml) was treated with thionyl chloride (19 µl, 261 µmol) and stirred at rt for 15 min. After evaporation, the residue was dissolved in DMF (2.8 ml) and treated with sodium iodide (97 mg, 652 µmol) and sodium azide (169 mg, 2.6 mmol). The mixture was stirred at 80°C for 1 h. After dilution with sat. aq. sodium chloride solution, the aqueous phase was extracted four times with ethyl acetate, and the combined organic layers were dried over magnesium sulfate and evaporated. Purification by column chromatography on silica gel (dichloromethane/methanol 98:2 → 90:10) afforded 35 mg (56% of th.) of the title compound.

LC-MS (method 5): R_t = 2.04 min; MS (ESIpos): m/z = 478 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.02 (s, 1H), 7.75 (br. s, 1H), 7.41 (s, 1H), 7.33 (s, 1H), 6.86 (s, 1H), 4.51 (s, 2H), 4.01 (s, 2H), 3.96 (s, 3H), 3.16-3.08 (m, 2H), 3.04-2.98 (m, 2H), 2.65-2.58 (m, 2H), 2.45 (s, 3H) ppm.

Intermediate 33A

4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f]-[1,2,4]triazine-6-carbaldehyde

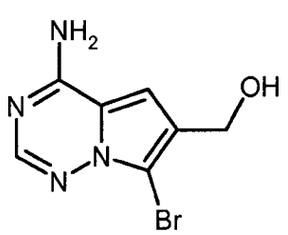


A solution of Example 50 (710 mg, purity 70%, 1.13 mmol) in dichloromethane (5 ml) containing molecular sieves (4Å) was treated with Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one; 623 mg, 1.47 mmol) and stirred at rt for 5 min. The reaction mixture was then adsorbed on diatomaceous earth and purified by column chromatography on silica gel (gradient of 30-100% ethyl acetate/cyclohexane) yielding 386 mg (72% of th.) of the title compound.

LC-MS (method 2): R_t = 0.76 min; MS (ESIpos): m/z = 438 $(M+H)^+$.

Intermediate 34A

(4-Amino-7-bromopyrrolo[2,1-f][1,2,4]triazin-6-yl)methanol



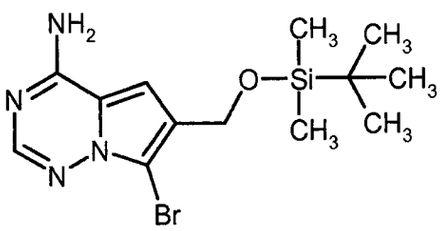
A solution of 1,3-dibromo-5,5-dimethylhydantoin (87 mg, 0.305 mmol) in THF (1 ml) was added dropwise to a solution of Intermediate 8A (100 mg, 0.609 mmol) in THF (4 ml) and methanol (2 ml) at -78°C. The mixture was stirred at -78°C for 16 h, then diluted with water and extracted with ethyl acetate. The combined organic layers were washed with sat. aq. sodium chloride solution, dried over magnesium sulfate and evaporated. Purification by column chromatography on silica gel (dichloromethane/methanol 20:1 → 10:1) afforded 55 mg (32% of th.) of the title compound.

LC-MS (method 3): R_t = 1.71 min; MS (ESIpos): m/z = 243/245 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.74-7.94 (m, 3H), 7.04 (s, 1H), 5.12 (t, 1H), 4.48 (d, 2H) ppm.

Intermediate 35A

7-Bromo-6-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



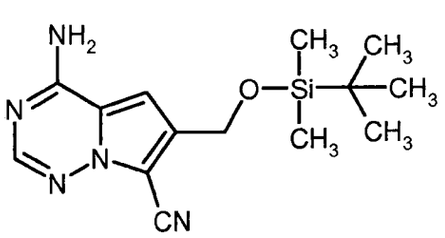
A solution of Intermediate 34A (885 mg, 3.64 mmol) in DMF (11 ml) was treated with *tert*-butyldimethylsilyl chloride (823 mg, 5.46 mmol) and imidazole (743 mg, 10.92 mmol) and stirred at rt for 2 h. The reaction mixture was combined with the reaction mixture of a 100 mg test run, diluted with water and extracted twice with ethyl acetate. The combined organic phases were washed with water and sat. aq. sodium chloride solution, dried over magnesium sulfate and evaporated. Purification by column chromatography on silica gel (cyclohexane/ethyl acetate 2:1 → 100% ethyl acetate) afforded 1.36 g (93% of th.) of the title compound.

LC-MS (method 2): R_t = 1.13 min; MS (ESIpos): m/z = 357/359 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.98-7.68 (m, 3H), 7.04 (s, 1H), 4.68 (s, 2H), 0.89 (s, 9H), 0.09 (s, 6H) ppm.

Intermediate 36A

4-Amino-6-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)pyrrolo[2,1-f][1,2,4]triazine-7-carbonitrile



Under argon, a mixture of Intermediate 35A (880 mg, 2.46 mmol), [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II)-dichloromethane complex [$PdCl_2$(dppf) x DCM] (120 mg, 0.148 mmol), bis(dibenzylideneacetone)palladium [$Pd(dba)_2$] (135 mg, 0.148 mmol), zinc cyanide (578 mg, 4.92 mmol), zinc powder (64 mg, 0.985 mmol) and zinc acetate (180 mg, 0.985 mmol) in degassed

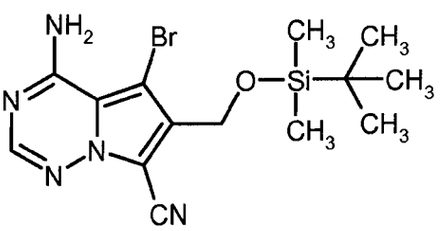
DMF/water (100:1, 9.2 ml) was stirred at 160°C overnight. The reaction mixture was then combined with the reaction mixture of a 100 mg test run, and the combined mixtures were adsorbed on kieselguhr, filtered over another layer of kieselguhr and eluted with *tert*-butyl methyl ether. The filtrate was washed with sat. aq. sodium hydrogencarbonate solution, and the aqueous layer was re-extracted three times with *tert*-butyl methyl ether. The combined organic phases were dried over sodium sulfate and evaporated. Purification by column chromatography on silica gel (cyclohexane/ethyl acetate 1:1) afforded 453 mg (44% of th.) of the title compound.

LC-MS (method 2): R_t = 1.09 min; MS (ESIpos): m/z = 304 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.22-8.35 (m, 2H), 8.06 (s, 1H), 6.95 (s, 1H), 4.83 (s, 2H), 0.91 (s, 9H), 0.11 (s, 6H) ppm.

Intermediate 37A

4-Amino-5-bromo-6-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)pyrrolo[2,1-f][1,2,4]triazine-7-carbonitrile



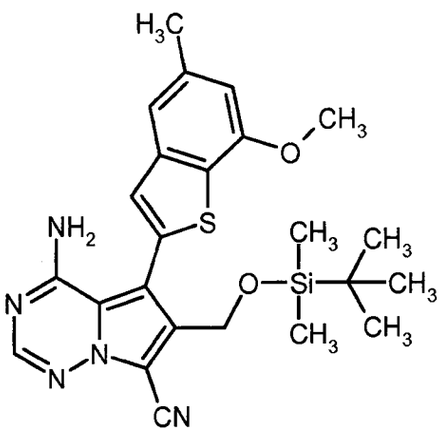
A solution of 1,3-dibromo-5,5-dimethylhydantoin (621 mg, 2.17 mmol) in THF (20 ml) was added dropwise to a solution of Intermediate 36A (1.1 g, 3.62 mmol) in THF (80 ml) at -50°C. The resulting mixture was slowly warmed to rt, stirred for 2 h and then quenched with 10% aq. sodium thiosulfate solution and sat. aq. sodium hydrogencarbonate solution. The aqueous phase was extracted three times with ethyl acetate. A solid precipitating from the ethyl acetate solution was filtered off and washed with ethyl acetate, affording 508 mg (100% purity, 36% of th.) as a first crop of the title compound. The remaining filtrate was dried over sodium sulfate and evaporated. The residue was precipitated from DMSO and washed with DMSO and ethyl acetate affording further 498 mg (85% purity, 26% of th.) of the title compound.

LC-MS (method 5): R_t = 2.70 min; MS (ESIpos): m/z = 382/384 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.10 (s, 1H), 4.76 (s, 2H), 0.90 (s, 9H), 0.12 (s, 6H) ppm.

Intermediate 38A

4-Amino-6-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-pyrrolo[2,1-f][1,2,4]triazine-7-carbonitrile



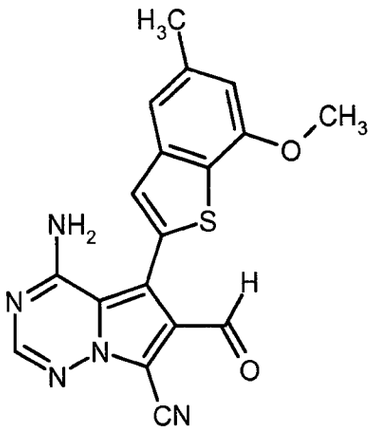
Under argon, a solution of Intermediate 37A (459 mg, 1.29 mmol) in degassed THF (14.8 ml) was added to (2'-aminobiphenyl-2-yl)(chloro)palladium-dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)-phosphine (1:1; 152 mg, 0.19 mmol; see S. L. Buchwald *et al., J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)) and Intermediate 6A (647 mg, 1.94 mmol). Degassed 0.5 M aq. potassium phosphate solution (5.1 ml) was added dropwise, and the resulting mixture was stirred at 60°C for 2 h. The reaction mixture was then combined with the reaction mixtures of previous 70 mg, 90 mg and 500 mg test runs and evaporated. Purification of the residue by column chromatography on silica gel (cyclohexane/ethyl acetate 3:1 → 100% ethyl acetate) afforded 1.0 g (58% of th.) of the title compound.

LC-MS (method 2): R_t = 1.49 min; MS (ESIpos): m/z = 480 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.57-8.35 (br. s, 1H), 8.18 (s, 1H), 7.41 (s, 1H), 7.30 (s, 1H), 6.86 (s, 1H), 6.28-6.03 (br. s, 1H), 4.74 (s, 2H), 3.95 (s, 3H), 2.44 (s, 3H), 0.83 (s, 9H), 0.00 (s, 6H) ppm.

Intermediate 39A

4-Amino-6-formyl-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazine-7-carbonitrile



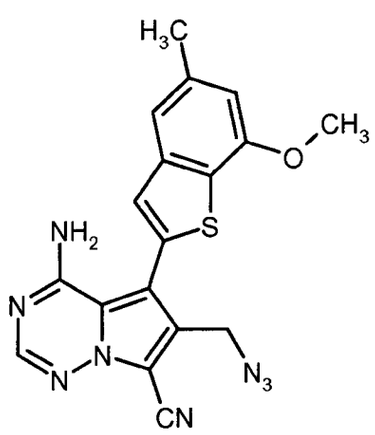
A solution of Example 68 (250 mg, 0.684 mmol) in dichloromethane (5 ml) was treated with Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one; 377 mg, 0.889 mmol) and stirred at rt for 1 h. The reaction mixture was combined with the reaction mixture from a 50 mg test run, quenched with sat. aq. sodium hydrogencarbonate solution and sat. aq. sodium thiosulfate solution (1:1) and stirred at rt for 30 min. The aqueous phase was extracted three times with ethyl acetate, and the combined organic phases were dried over sodium sulfate and evaporated. Purification by column chromatography on silica gel (cyclohexane/25% ethyl acetate → 100% ethyl acetate) afforded 102 mg (24% of th.) of the title compound.

LC-MS (method 2): R_t = 1.02 min; MS (ESIpos): m/z = 364 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 9.86 (s, 1H), 8.78 (br. s, 1H), 8.30 (s, 1H), 7.62 (s, 1H), 7.36 (s, 1H), 6.91 (s, 1H), 6.51 (br. s, 1H), 3.97 (s, 3H), 2.46 (s, 3H) ppm.

Intermediate 40A

4-Amino-6-(azidomethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazine-7-carbonitrile



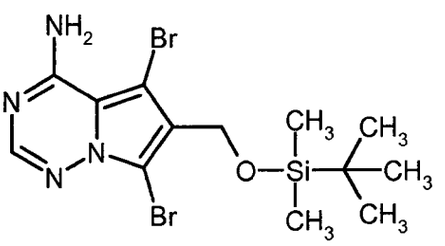
A solution of Example 68 (100 mg, 273 µmol) in dichloromethane (5 ml) was treated with thionyl chloride (39 µl, 547 µmol) and stirred at rt for 15 min. After evaporation, the residue was dissolved in DMF (6 ml) and treated with sodium iodide (205 mg, 1.36 mmol) and sodium azide (355 mg, 5.47 mmol). The mixture was stirred at 80°C overnight, then diluted with water and extracted three times with ethyl acetate. The combined organic layers were washed with water, followed by sat. aq. sodium chloride solution, dried over sodium sulfate and evaporated affording 91 mg of the crude product which was used in the next step without further purification.

LC-MS (method 2): R_t = 1.13 min; MS (ESIpos): m/z = 391 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): d = 8.65-8.45 (br. s, 1H), 8.23 (s, 1H), 7.46 (s, 1H), 7.34 (s, 1H), 6.88 (s, 1H), 6.41-6.10 (br. s, 1H), 4.57 (s, 2H), 3.96 (s, 3H), 2.46 (s, 3H) ppm.

Intermediate 41A

5,7-Dibromo-6-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



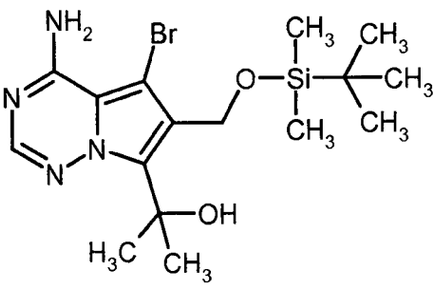
A solution of Intermediate 18A (2 g, 6.21 mmol) in DMF (20 ml) was treated with imidazole (846 mg, 12.4 mmol) and *tert*-butyldimethylsilyl chloride (1.12 g, 7.45 mmol) and stirred at rt for 20 h. The reaction mixture was then diluted with water (200 ml) and stirred at rt for further 2 h. Filtration of the solid afforded 2.46 g (88% of th.) of the title compound.

LC-MS (method 2): R_t = 1.37 min; MS (ESIpos): m/z = 437 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.49-8.05 (br. s, 1H), 7.96 (s, 1H), 7.15-6.76 (br. s, 1H), 4.64 (s, 2H), 0.87 (s, 9H), 0.09 (s, 6H) ppm.

Intermediate 42A

2-[4-Amino-5-bromo-6-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]-propan-2-ol



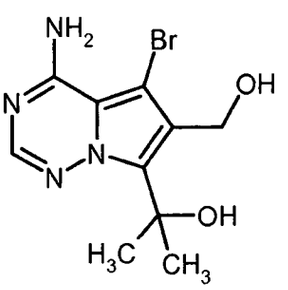
Under argon, a solution of Intermediate 41A (1 g, 2.29 mmol) in THF (40 ml) was cooled to -78°C and treated with a 1.6 M solution of methyllithium in diethylether (1.5 ml, 2.40 mmol). After stirring for 10 min at -78°C, a 1.6 M solution of *n*-butyllithium in hexanes (1.58 ml, 2.52 mmol) was added, and stirring was continued for 10 min. Acetone (1.68 ml, 22.92 mmol) was added, and the resulting mixture was slowly warmed to rt and stirred at rt for 18 h. The reaction was then quenched with water, and the aqueous phase was extracted twice with ethyl acetate. The combined organic phases were washed with sat. aq. sodium chloride solution, dried over magnesium sulfate and evaporated. Purification by flash chromatography on silica gel (cyclohexane/ethyl acetate 2:1) afforded 306 mg (30% of th.) of the title compound.

LC-MS (method 4): R_t = 1.39 min; MS (ESIpos): m/z = 415/417 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.23-7.85 (br. s, 1H), 7.89 (s, 1H), 7.05-6.82 (br. s, 1H), 5.49 (s, 1H), 4.88 (s, 2H), 1.66 (s, 6H), 0.87 (s, 9H), 0.08 (s, 6H) ppm.

Intermediate 43A

2-[4-Amino-5-bromo-6-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]propan-2-ol



A solution of Intermediate 42A (304 mg, 0.732 mmol) in THF (15 ml) was treated with a 1 M solution of tetra-*n*-butylammonium fluoride in THF (768 µl, 768 µmol) and stirred at rt for 2 min. The reaction mixture was diluted with acetonitrile (20 ml), then evaporated, and the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-30% acetonitrile/0.2% aq. TFA). The product thus obtained was dissolved in methanol and filtered through an anion exchange cartridge

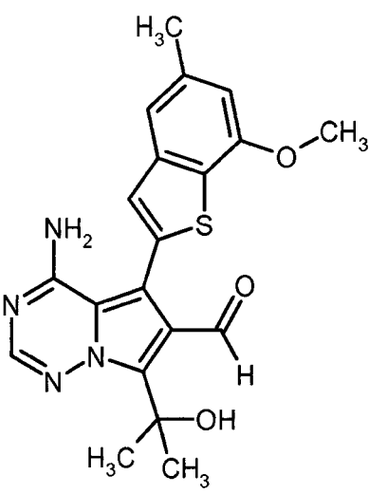
(Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated affording 180 mg (67% of th.) of the title compound.

LC-MS (method 2): R_t = 0.55 min; MS (ESIpos): m/z = 301/303 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.21-7.90 (m, 1H), 7.87 (s, 1H), 7.09-6.60 (br. s, 1H), 5.90 (br. s, 1H), 5.03 (br. s, 1H), 4.63 (s, 2H), 1.66 (s, 6H) ppm.

Intermediate 44A

4-Amino-7-(2-hydroxypropan-2-yl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazine-6-carbaldehyde

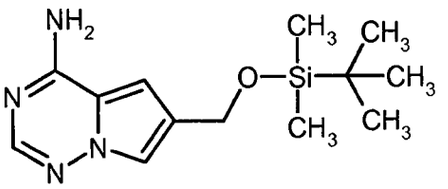


A solution of Example 73 (135 mg, purity 89%, 302 µmol) in dichloromethane (7 ml) was treated with Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one; 166 mg, 392 µmol) and stirred at rt for 70 min. The reaction mixture was combined with the reaction mixture of a 18 mg (45 µmol) test run and quenched with sat. aq. sodium hydrogencarbonate solution and sat. aq. sodium thiosulfate solution (1:1). The aqueous phase was extracted three times with dichloromethane. The combined organic phases were washed with sat. aq. sodium chloride solution, dried over magnesium sulfate and evaporated yielding 143 mg (purity 77%, 92% of th.) of the title compound.

LC-MS (method 2): R_t = 1.08 min; MS (ESIpos): m/z = 397 $(M+H)^+$.

Intermediate 45A

6-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine

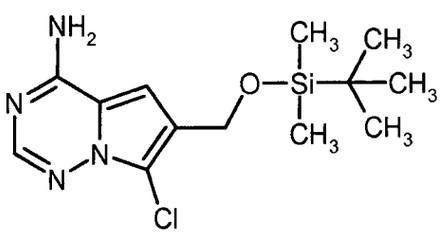


A solution of 1.5 g (9.14 mmol) of Intermediate 8A in 15 ml dry DMF was treated with 1.65 g (10.96 mmol) *tert*-butyldimethylsilyl chloride and 1.24 g (18.27 mmol) imidazole and stirred at rt overnight. The reaction mixture was poured into 250 ml water and stirred for 5 min. The resulting precipitate was filtered off and dried *in vacuo* at 45°C. Yield: 2.28 g (90% of th.).

LC-MS (method 5): R_t = 2.12 min; MS (ESIpos): m/z = 279 $(M+H)^+$.

Intermediate 46A

6-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-7-chloropyrrolo[2,1-f][1,2,4]triazin-4-amine



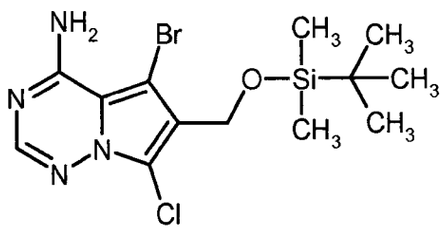
A solution of 2 g (7.18 mmol) of Intermediate 45A in 20 ml THF was treated with 893 mg (6.47 mmol) *N*-chlorosuccinimide in 6 portions over 60 min at -10°C. Stirring was continued for 15 min at -10°C, then the mixture was allowed to warm to rt. Another 192 mg (1.44 mmol) *N*-chloro-succinimide were added at rt, and stirring was continued overnight. About one-tenth of the reaction mixture was evaporated to dryness, and the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) furnishing 94 mg (4% of th.) of the title compound. The major part of the reaction mixture was adsorbed on silica gel and subjected to chromatography on silica gel with isohexane/ethyl acetate 5-66% as eluent, yielding 899 mg (40% of th.) of the title compound. Total yield: 993 mg (44% of th.).

LC-MS (method 5): R_t = 2.45 min; MS (ESIpos): m/z = 313 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.69-8.04 (m, 3H), 7.0 (s, 1H), 4.70 (s, 2H), 0.88 (s, 9H), 0.08 (s, 6H) ppm.

Intermediate 47A

5-Bromo-6-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-7-chloropyrrolo[2,1-f][1,2,4]triazin-4-amine



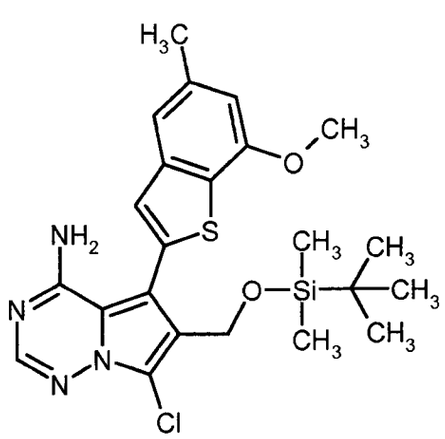
A solution of 890 mg (2.85 mmol) of Intermediate 46A in 20 ml DMF was treated with 506 mg (2.85 mmol) *N*-bromosuccinimide in portions over 1 h at -10°C. Stirring was continued for 3 h at -10°C and then overnight at rt. Water (200 ml) was added, and the mixture was stirred for 2 h. The precipitated solid was filtered off, washed with water and dried *in vacuo* at 45°C. Yield: 997 mg (89% of th.).

LC-MS (method 5): R_t = 2.82 min; MS (ESIpos): m/z = 391/393/395 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.32 (br. s, 1H), 7.97 (s, 1H), 6.97 (br. s, 1H), 4.66 (s, 2H), 0.87 (s, 9H), 0.09 (s, 6H) ppm.

Intermediate 48A

6-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-7-chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-pyrrolo[2,1-f][1,2,4]triazin-4-amine



Under an argon atmosphere, a flask was charged with 800 mg (2.04 mmol) of Intermediate 47A, 680 mg (2.04 mmol) of Intermediate 6A, 80 mg (0.1 mmol) (2'-aminobiphenyl-2-yl)(chloro)-palladium-dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (1:1; see S. L. Buchwald *et al.*,

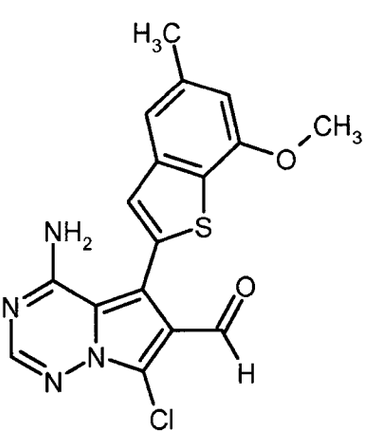
J. Am. Chem. Soc. 132 (*40*), 14073-14075 (2010)) and 1.3 g (6.13 mmol) potassium phosphate. Then, 30 ml of a degassed 1,4-dioxane/water mixture (5:1) were added, and the solution was stirred at 70°C for 1 h. Further 680 mg (2.04 mmol) of Intermediate 6A and 32 mg (0.04 mmol) (2'-amino-biphenyl-2-yl)(chloro)palladium-dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (1:1) were added, and stirring at 70°C was continued for another 1 h. This procedure was repeated three times until the starting material was consumed (control by LC-MS). With the last portion of reagents, also 1.6 ml of 5 M aq. sodium hydroxide solution were added to achieve a pH value of 8-9. At the end of the reaction period, 30 ml water and 5 M aq. formic acid were added (pH 3-4) whereupon an oil separated. A part of this oil was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid). Two fractions of the title compound were obtained: 103 mg of a solid (89% purity by LC-MS, 9% of th.), and 23 mg of a solid (100% purity by LC-MS, 2% of th.). The rest of the oil and the supernatant were diluted with water, adjusted to pH 8-9 with sat. aq. sodium hydrogencarbonate solution and extracted three times with dichloromethane. The combined organic phases were washed with water, dried and evaporated under reduced pressure, yielding 2.1 g of an oil. This material was purified by column chromatography on silica gel with dichloromethane/0-5% methanol as eluent to afford further 709 mg (43% purity by LC-MS, 31% of th.) of the title compound. Total yield: 42% of th.

LC-MS (method 2): R_t = 1.57 min; MS (ESIpos): m/z = 489 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.08 (s, 1H), 7.43 (s, 1H), 7.32 (s, 1H), 6.88 (s, 1H), 4.66 (s, 2H), 3.98 (s, 3H), 2.47 (s, 3H), 0.84 (s, 9H), −0.03 (s, 6H) ppm.

Intermediate 49A

4-Amino-7-chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde



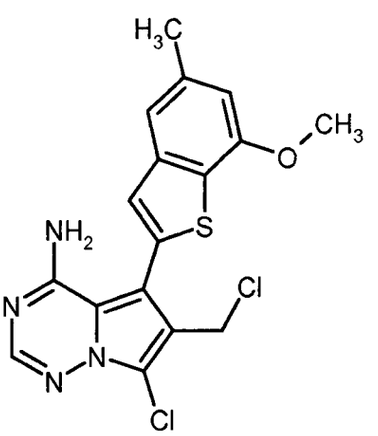
To a suspension of 166 mg (0.44 mmol) of Example 79 and molecular sieves (3Å) in 3 ml dichloromethane were added 207 mg (0.49 mmol) Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one) at 0-5°C. The mixture was stirred for 10 min at this temperature, then further 56 mg (0.13 mmol) Dess-Martin periodinane were added, and stirring was continued for 15 min at 5°C and 10 min at ambient temperature. After this, the mixture was adsorbed on diatomaceous earth and purified by column chromatography on silica gel with dichloromethane/ 0-10% methanol as eluent. Yield: 100 mg of a solid (92.7% pure by LC-MS, 56% of th.).

LC-MS (method 2): R_t = 1.08 min; MS (ESIpos): m/z = 373 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 9.90 (s, 1H), 8.46 (br. s, 1H), 8.15 (s, 1H), 7.54 (s, 1H), 7.34 (s, 1H), 6.89 (s, 1H), 6.07 (br. s, 1H), 3.96 (s, 3H), 2.46 (s, 3H) ppm.

Intermediate 50A

7-Chloro-6-(chloromethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-4-amine

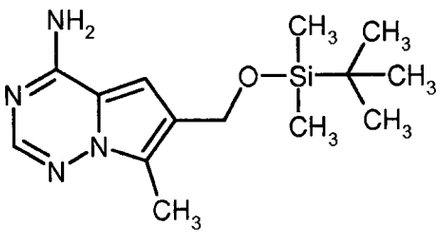


The title compound was isolated as a by-product in the preparation of Example 79 (see below). Yield: 9.2 mg (10% of th.).

LC-MS (method 3): R_t = 2.98 min; MS (ESIpos): m/z = 393/395 $(M+H)^+$.

Intermediate 51A

6-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-7-methylpyrrolo[2,1-f][1,2,4]triazin-4-amine



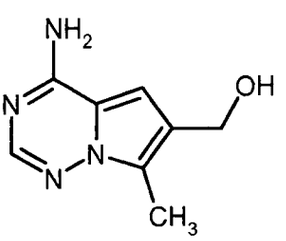
To a solution of 3 g (8.4 mmol) of Intermediate 35A in 60 ml 1,4-dioxane under an argon atmosphere were added 171 mg (0.21 mmol) of $PdCl_2$(dppf) x DCM and then dropwise over 10 min 16.8 ml of a 2 M solution of dimethylzinc in toluene (causing a rise in temperature from 22°C to 31°C). Stirring was continued first for 10 min at ambient temperature, then for 13 h at 90°C. After this, water (10 ml) was added to the reaction mixture at rt, and the suspension was stirred for 1 h. The mixture was evaporated under reduced pressure, and the residue was taken up in water and ethyl acetate and stirred for another 1 h. The precipitate was filtered off and discarded, the phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic phases were dried and evaporated affording 2.45 g (92% purity by LC-MS, 92% of th.) of the title compound.

LC-MS (method 5): R_t = 2.18 min; MS (ESIpos): m/z = 293 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.98-7.78 (m, 3H), 7.04 (s, 1H), 4.68 (s, 2H), 0.89 (s, 9H), 0.09 (s, 6H) ppm.

Intermediate 52A

(4-Amino-7-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl)methanol



Method 1:

To a solution of 100 mg (0.28 mmol) of Intermediate 35A in 2 ml 1,4-dioxane under an argon atmosphere were added 6 mg (0.01 mmol) $PdCl_2$(dppf) x DCM and then dropwise over 10 min 0.56 ml of a 2 M solution of dimethylzinc in toluene. The mixture was stirred at 90°C overnight, then evaporated, and the residue was treated with acetonitrile and 5 M aq. formic acid. The precipitate was filtered off, the filtrate was evaporated, and the residue was taken up in DMSO/aceto-

nitrile and purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid). Yield: 33 mg (66% of th.).

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.79 (s, 1H), 7.47 (br. s, 2H), 6.80 (s, 1H), 4.84 (t, 1H), 4.49 (d, 2H), 2.36 (s, 3H) ppm.

Method 2:

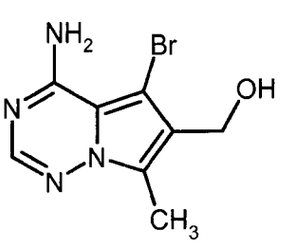
Under an argon atmosphere, a microwave reaction vessel was charged with 750 mg (3.1 mmol) of Intermediate 34A, 515 µl (3.7 mmol) trimethylboroxine, 786 mg (3.7 mmol) potassium phosphate and 73 mg (0.09 mmol) (2'-aminobiphenyl-2-yl)(chloro)palladium-dicyclohexyl(2',4',6'-triisopropyl-biphenyl-2-yl)phosphine (1:1; see S. L. Buchwald *et al., J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)). Then, 13 ml of a degassed 1,4-dioxane/water mixture (5:1) were added, the vessel was sealed, and the mixture was heated to 140°C for 20 min in the microwave (4 bar, 50 watt). Further 50 mg (2'-aminobiphenyl-2-yl)(chloro)palladium-dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)-phosphine (1:1) were added, and the mixture was heated again to 140°C for 20 min in the microwave. Another portion of 515 µl trimethylboroxine was added, and the vessel was heated again to 140°C for 20 min. The latter procedure was repeated two more times with heating periods of 30 min each until LC-MS showed only minor amounts of starting material left. The mixture was filtered over kieselguhr, washed with 1,4-dioxane, and the combined filtrates were evaporated to dryness. This residue was combined with a previous 100 mg test run and purified by preparative RP-HPLC (XBridge C18, gradient 5-42% acetonitrile/0.05% aq. ammonium hydroxide solution). Yield: 238 mg (38% of th.).

LC-MS (method 5): R_t = 0.51 min; MS (ESIneg): m/z = 177 $(M-H)^-$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.79 (s, 1H), 7.48 (br. s, 2H), 6.80 (s, 1H), 4.84 (t, 1H), 4.49 (d, 2H), 2.36 (s, 3H) ppm.

Intermediate 53A

(4-Amino-5-bromo-7-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl)methanol



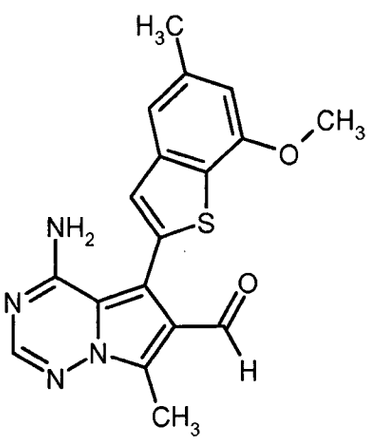
A solution of 245 mg (1.38 mmol) of Intermediate 52A in 8.8 ml DMF was treated with 288 mg (1.62 mmol) *N*-bromosuccinimide in portions over 2 h at -10°C. Stirring was continued at -10°C for 30 min and then for 2 h at ambient temperature. The mixture was poured into 50 ml water and extracted with ethyl acetate. The combined organic phases were dried and evaporated. The residue was flash-chromatographed on silica gel with dichloromethane/0-15% methanol as eluent. Yield: 148 mg (42% of th.).

LC-MS (method 4): R_t = 0.42 min; MS (ESIpos): m/z = 257/259 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.85 (s, 1H), 6.14-8.22 (broad, 2H), 4.88 (t, 1H), 4.45 (d, 2H), 2.43 (s, 3H) ppm.

Intermediate 54A

4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-methylpyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde



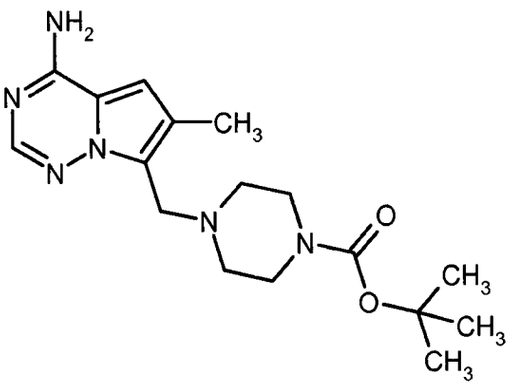
To a suspension of 175 mg (0.49 mmol) of Example 75 and molecular sieves (3Å) in 3.5 ml dichloromethane were added 230 mg (0.54 mmol) Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one) at 0-5°C. The mixture was stirred for 5 min at this temperature, followed by 30 min at rt. After this, the mixture was adsorbed on diatomaceous earth and purified by flash-chromatography on silica gel with isohexane/10-100% ethyl acetate as eluent. Yield: 139 mg of a solid (79% of th.).

LC-MS (method 5): R_t = 2.34 min; MS (ESIpos): m/z = 353 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 9.93 (s, 1H), 8.06 (s, 1H), 7.50 (s, 1H), 7.33 (s, 1H), 6.88 (s, 1H), 3.96 (s, 3H), 2.71 (s, 3H), 2.46 (s, 3H) ppm.

Intermediate 55A

tert-Butyl 4-[(4-amino-6-methylpyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]piperazine-1-carboxylate



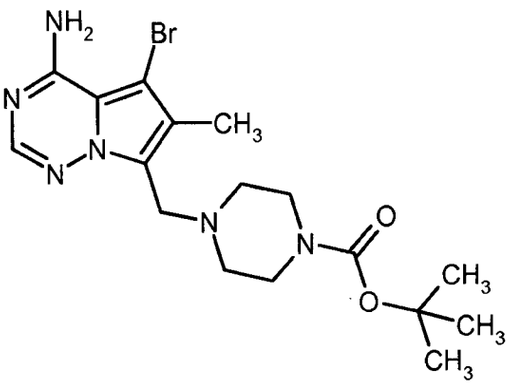
A solution of 6-methylpyrrolo[2,1-f][1,2,4]triazin-4-amine (500 mg, 3.3 mmol; preparation described in PCT Int. Pat. Appl. WO 2007/056170) in acetic acid (8 ml) was treated with 37% aq. formaldehyde solution (328 µl, 4.04 mmol) and *tert*-butyl piperazine-1-carboxylate (754 mg, 4.04 mmol). The mixture was stirred at 60°C overnight. After evaporation, the residue was taken up in ethyl acetate and washed with sat. aq. sodium hydrogencarbonate solution. The aqueous layer was extracted twice with ethyl acetate. The combined organic phases were dried over magnesium sulfate and evaporated affording 1.2 g of the crude product which was used in the next step without further purification.

LC-MS (method 2): R_t = 0.56 min; MS (ESIpos): m/z = 347 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.79 (s, 1H), 7.51 (br. s, 2H), 6.67 (s, 1H), 3.76 (br. s, 2H), 3.29-3.17 (m, 4H), 2.36-2.29 (m, 4H), 2.22 (s, 3H), 1.37 (s, 9H) ppm.

Intermediate 56A

tert-Butyl 4-[(4-amino-5-bromo-6-methylpyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]piperazine-1-carboxylate



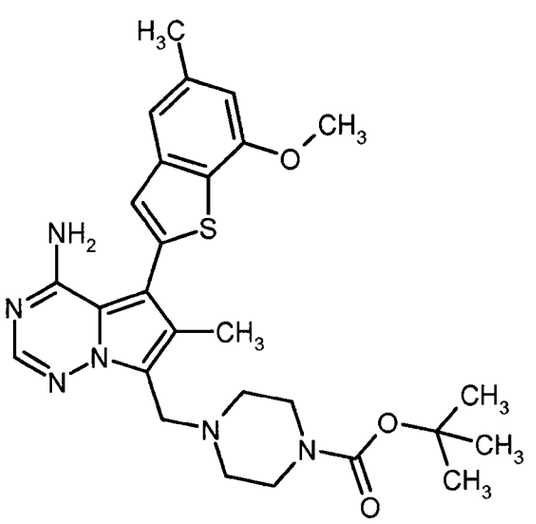
A solution of Intermediate 55A (1.17 g, 3.37 mmol) in THF (20 ml) was cooled to -60°C and treated with 1,3-dibromo-5,5-dimethylhydantoin (5.78 mg, 2.02 mmol). The mixture was stirred for 4 h at -60°C to -20°C. After this, the reaction mixture was quenched with 10% aq. sodium thiosulfate solution. Most of the THF solvent was evaporated whereupon a solid precipitated. Filtration and recrystallization from acetone afforded 862 mg (59% of th.) of the title compound.

LC-MS (method 2): R_t = 0.66 min; MS (ESIpos): m/z = 425/427 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.29-7.62 (br. s, 1H), 7.85 (s, 1H), 7.17-6.44 (br. s, 1H), 3.80 (s, 2H), 3.29-3.22 (m, 4H), 2.37-2.27 (m, 4H), 2.16 (s, 3H), 1.37 (s, 9H) ppm.

Intermediate 57A

tert-Butyl 4-{[4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-6-methylpyrrolo[2,1-f][1,2,4]-triazin-7-yl]methyl}piperazine-1-carboxylate



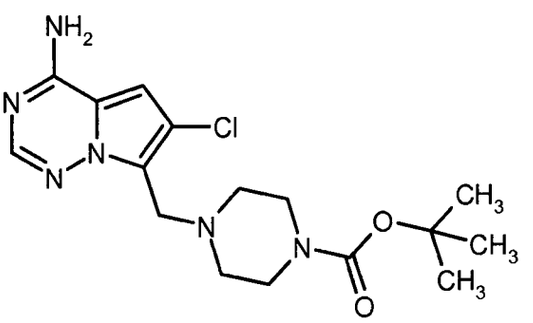
A solution of Intermediate 56A (100 mg, 235 µmol) in degassed 1,4-dioxane (3 ml) was treated with Intermediate 6A (93 mg, 282 µmol), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (S-Phos; 9.6 mg, 23 µmol) and palladium diacetate (2.6 mg, 11 µmol). Degassed 3 M aq. potassium phosphate solution (588 µl) was added, and the resulting mixture was stirred at 60°C for 1 h. A further portion of Intermediate 6A (78 mg, 235 µmol) was added, and stirring at 60°C was continued overnight. The reaction mixture was quenched with 2 M aq. sodium hydroxide solution, and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with sat. aq. sodium chloride solution, dried over magnesium sulfate and evaporated. Purification by column chromatography on silica gel (cyclohexane/ethyl acetate 3:2) afforded 82 mg (62% of th.) of the title compound.

LC-MS (method 2): R_t = 0.97 min; MS (ESIpos): m/z = 523 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.94 (s, 1H), 7.34 (s, 1H), 7.30 (s, 1H), 6.84 (s, 1H), 3.95 (s, 3H), 3.84 (s, 2H), 3.30-3.23 (m, 4H, overlap with water peak), 2.45 (s, 3H), 2.42-2.33 (m, 4H), 2.19 (s, 3H), 1.39 (s, 9H) ppm.

Intermediate 58A

tert-Butyl 4-[(4-amino-6-chloropyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]piperazine-1-carboxylate



Following the procedure of Intermediate 55A, 4 g (23.7 mmol) 6-chloropyrrolo[2,1-f][1,2,4]triazin-4-amine (preparation described in PCT Int. Pat. Appl. WO 2007/064883) were reacted to give 11.2 g of the title compound as crude material which was used in the next step without further purification.

LC-MS (method 5): R_t = 0.74 min; MS (ESIpos): m/z = 367 $(M+H)^+$

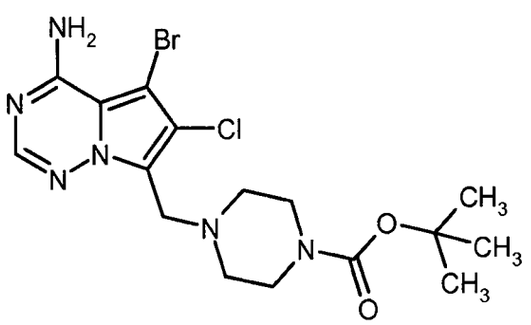
A sample of 67 mg of the corresponding formiate salt, *tert*-butyl 4-[(4-amino-6-chloropyrrolo[2,1-f]-[1,2,4]triazin-7-yl)methyl]piperazine-1-carboxylate formiate, was isolated after preparative RP-

HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) of 100 mg of the crude material obtained above.

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.14 (s, 1H), 7.91 (s, 1H), 7.83 (br. s, 2H), 6.95 (s, 1H), 3.80 (s, 2H), 3.17 (s, 2H), 2.38 (br. s, 4H), 1.37 (s, 9H) ppm.

Intermediate 59A

tert-Butyl 4-[(4-amino-5-bromo-6-chloropyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]piperazine-1-carboxylate



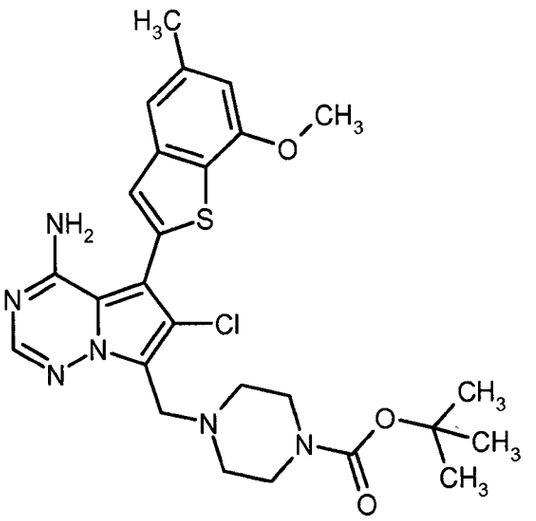
Following the procedure of Intermediate 56A, 11 g (30 mmol) of Intermediate 58A were reacted to give 1.17 g (9% of th.) of the title compound after flash-chromatography on silica gel (dichloromethane/methanol 10:1) and subsequent preparative RP-HPLC (Daiso C18, gradient 40-65% acetonitrile/water).

LC-MS (method 2): R_t = 0.74 min; MS (ESIpos): m/z = 445/447/449 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 7.96 (s, 1H), 3.84 (s, 2H), 2.37 (br. s, 4H), 1.37 (s, 9H) ppm.

Intermediate 60A

tert-Butyl 4-{[4-amino-6-chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-7-yl]methyl}piperazine-1-carboxylate

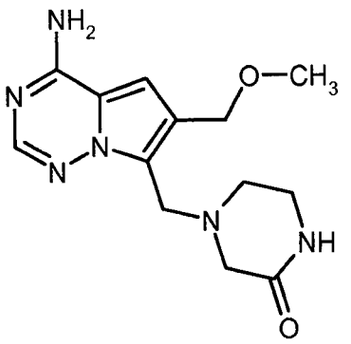


Under an argon atmosphere, a flask was charged with 140 mg (0.31 mmol) of Intermediate 59A, 102 mg (0.46 mmol) of Intermediate 5A, 16 mg (0.02 mmol) $PdCl_2$(dppf) x DCM and 122 mg (1.15 mmol) sodium carbonate. After addition of 3 ml degassed 1,2-dimethoxyethane/water (3:1), the suspension was stirred at 60°C for 2.5 h. Further portions of Intermediate 5A (50 mg, 0.23 mmol) and $PdCl_2$(dppf) x DCM (8 mg, 0.01 mmol) were added, and stirring was continued at 40°C for 2.5 h. The latter procedure was repeated once more until the starting material was consumed. Then, the reaction mixture was partially evaporated under reduced pressure, water was added, and the mixture was extracted with dichloromethane. The combined organic phases were washed with water and sat. aq. sodium chloride solution, dried and evaporated under reduced pressure. The residue (322 mg) was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) to give 49 mg of a mixture of the title compound and the Boc-deprotected derivative, 6-chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine. This mixture was used as such in the next reaction step (see Example 85).

LC-MS (method 2): R_t = 1.00 min; MS (ESIpos): m/z = 543 $(M+H)^+$, and R_t = 0.81 min; MS (ESIpos): m/z = 443 $(M+H)^+$.

Intermediate 61A

4-{[4-Amino-6-(methoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one

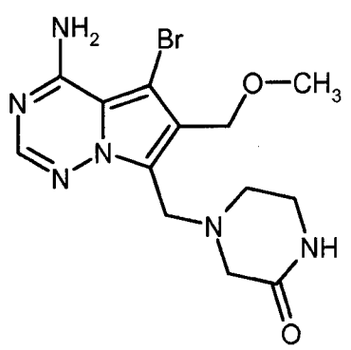


A solution of Intermediate 10A (5 g, 28.1 mmol) and piperazin-2-one (3.09 g, 30.9 mmol) in acetic acid (85 ml) was treated with 37% aq. formaldehyde solution (3.15 ml, 42.1 mmol) and stirred at 60°C for 16 h. The volatiles were evaporated under reduced pressure, and the residue was dissolved in methanol and adsorbed on diatomaceous earth. Purification by column chromatography on silica gel (5-10% methanol/dichloromethane) afforded 3.91 g (46% of th.) of the title compound.

LC-MS (method 3): R_t = 1.68 min; MS (ESIpos): m/z = 291 $(M+H)^+$.

Intermediate 62A

4-{[4-Amino-5-bromo-6-(methoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one



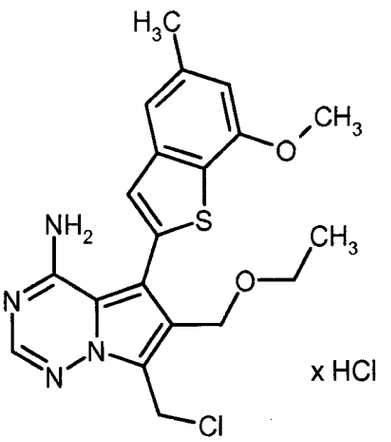
A solution of Intermediate 61A (3.9 g, 13.4 mmol) in DMF (50 ml) was cooled to 0°C and treated with a solution of *N*-bromosuccinimide (2.63 g, 14.8 mmol) in DMF (6 ml). The mixture was stirred at 0°C for 1 h. Then, the solvent was evaporated, and the residue was dissolved in methanol and adsorbed on diatomaceous earth. Purification by column chromatography on silica gel (5-10% methanol/dichloromethane) afforded 1.99 g (39% of th.) of the title compound.

LC-MS (method 3): R_t = 1.86 min; MS (ESIpos): m/z = 369/371 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.96-8.23 (br. s, 1H), 7.90 (s, 1H), 7.71 (s, 1H), 6.72-6.98 (br. s, 1H), 4.45 (s, 2H), 3.91 (s, 2H), 3.27 (s, 3H), 3.07 (br. s, 2H), 2.96 (s, 2H), 2.56 (br. s, 2H) ppm.

Intermediate 63A

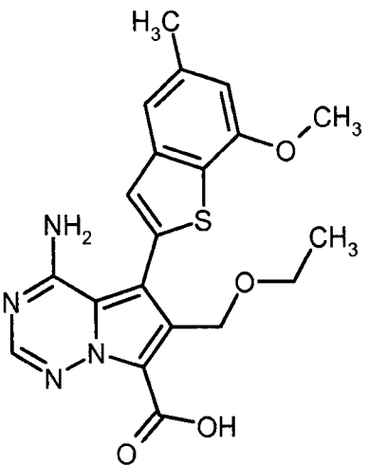
7-(Chloromethyl)-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-4-amine hydrochloride



A suspension of Example 86 (1 g, 2.51 mmol) in toluene (60 ml) was treated dropwise with thionyl chloride (1.83 ml, 25.1 mmol), and the mixture was stirred at rt overnight. The volatiles were evaporated under reduced pressure. The residue was co-evaporated with toluene under reduced pressure for three times affording 0.85 g (74% of th.) of the title compound which was immediately used for the next step without further purification.

Intermediate 64A

4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazine-7-carboxylic acid



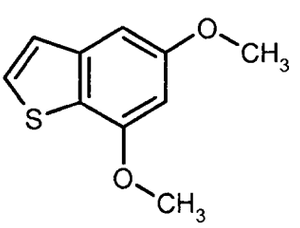
A suspension of Intermediate 17A (5 g, 12.6 mmol) in THF/water (10:1, 220 ml) was treated with a 2 M solution of 2-methyl-2-butene in THF (31.5 ml, 63.1 mmol) and with sodium dihydrogenphosphate (6.96 g, 50.4 mmol). The mixture was stirred at rt for 5 min. Then, sodium chlorite (4.56 g, 50.44 mmol) was added, and the resulting mixture was stirred at rt for 20 h. The suspension was filtered, and the resulting solid was washed with water affording 4.24 g (74% of th.) of the title compound which was used in the next step without further purification.

LC-MS (method 4): R_t = 1.06 min; MS (ESIpos): m/z = 413 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 13.22 (br. s, 1H), 8.53-8.00 (br. s, 1H), 8.14 (s, 1H), 7.41 (s, 1H), 7.33 (s, 1H), 6.86 (s, 1H), 6.28-5.65 (br. s, 1H), 4.61 (s, 2H), 3.96 (s, 3H), 3.36 (q, 2H), 2.46 (s, 3H), 1.01 (t, 3H) ppm.

Intermediate 65A

5,7-Dimethoxy-1-benzothiophene



To a solution of 1-benzothiophene-5,7-diol (1.16 g, 6.98 mmol) in acetone (20 ml) under argon were added potassium carbonate (2.89 g, 20.9 mmol) and iodomethane (912 µl, 14.6 mmol). The resulting mixture was stirred under reflux for 18 h. After cooling to rt, the mixture was treated with a 7 M solution of ammonia in methanol (10 ml) for 30 min and then adsorbed on silica gel. Purification by

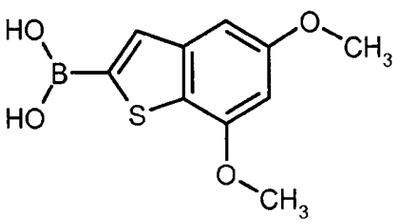
column chromatography over silica gel (cyclohexane/ethyl acetate 40:1) afforded 0.52 g (32% of th.) of the title compound.

LC-MS (method 4): R_t = 1.02 min; MS (ESIpos): m/z = 195 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.69 (d, 1H), 7.35 (d, 1H), 7.02 (d, 1H), 6.57 (d, 1H), 3.92 (s, 3H), 3.81 (s, 3H) ppm.

Intermediate 66A

(5,7-Dimethoxy-1-benzothiophen-2-yl)boronic acid

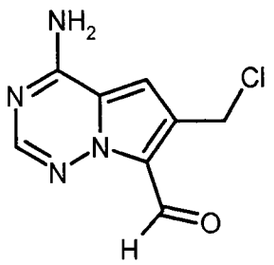


Under an argon atmosphere, a 1.6 M solution of *n*-butyllithium in hexane (1.84 ml, 2.95 mmol) was added dropwise to a solution of Intermediate 65A (520 mg, 2.68 mmol) in dry THF (5 ml) at -70°C. After 1 h at -70°C, triisopropyl borate (742 µl, 3.21 mmol) was added, and the mixture was stirred for 16 h while slowly warming up to rt. Dichloromethane and sat. aq. ammonium chloride solution were added, and the pH value was adjusted to 6 by addition of 1 M hydrochloric acid. The organic phase was separated, and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried with magnesium sulfate, filtered and evaporated. The resulting residue was purified by column chromatography over silica gel (at first eluting with dichloromethane/methanol 40:1, then methanol, finally methanol/4 M hydrogen chloride in 1,4-dioxane 10:1) yielding 631 mg (71% purity, 71% of th.) of the title compound.

LC-MS (method 4): R_t = 0.83 min; MS (ESIpos): m/z = 239 $(M+H)^+$.

Intermediate 67A

4-Amino-6-(chloromethyl)pyrrolo[2,1-f][1,2,4]triazine-7-carbaldehyde

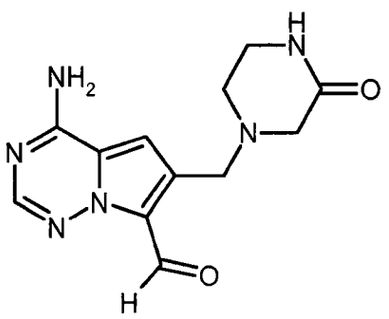


Intermediate 67A was isolated as a side-product of the synthesis of Intermediate 11A after column chromatography on silica gel (dichloromethane/acetone 8:2 → 7:3).

LC-MS (method 2): R_t = 0.6 min; MS (ESIpos): m/z = 211/213 $(M+H)^+$.

Intermediate 68A

4-Amino-6-[(3-oxopiperazin-1-yl)methyl]pyrrolo[2,1-f][1,2,4]triazine-7-carbaldehyde

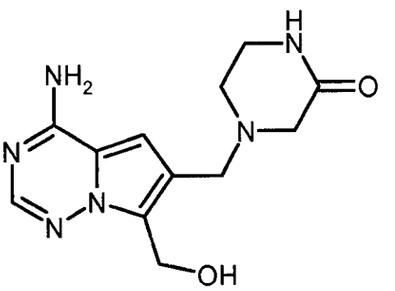


A solution of Intermediate 67A (11.03 g, 52.4 mmol) and 2-oxopiperazine (6.82 g, 68.1 mmol) in 331 ml DMF was treated at rt with DIPEA (13.7 ml, 78.6 mmol) and stirred overnight. The precipitate was filtered off, washed with DMF and diethylether and then dried *in vacuo* to yield 11.64 g of the title compound (89% purity, 72% of th.).

LC-MS (method 7): R_t = 1.30 min; MS (ESIpos): m/z = 275 $(M+H)^+$.

Intermediate 69A

4-{[4-Amino-7-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one



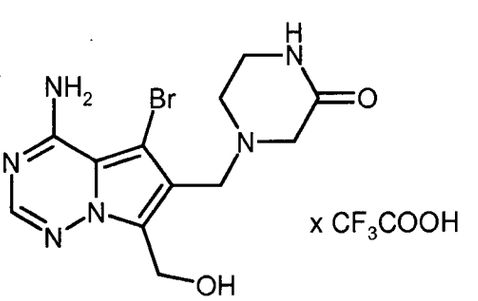
To a solution of Intermediate 68A (10.17 g, 89% purity, 33.01 mmol) in 1 M hydrochloric acid (370 ml) and methanol (370 ml) at rt was added zinc dust (12.1 g, 185 mmol), and the mixture was stirred at rt for 18 h. Silica gel (100 g) was added, and the volatiles were evaporated under reduced pressure. The residue was suspended in methanol, the volatiles were evaporated under reduced pressure again, and the residue was dried *in vacuo*. The solid was subjected to column chromatography on silica gel (gradient dichloromethane/7 M ammonia in methanol 10:1 → 3:1) to yield 6.39 g of the title compound (60% of th.).

LC-MS (method 8): R_t = 1.12 min; MS (ESIpos): m/z = 277 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.83 (s, 1H), 7.76 (br. s, 1H), 7.64 (br. s, 2H), 6.83 (s, 1H), 5.01 (br. s, 1H), 4.74 (s, 2H), 3.64 (br. s, 2H), 3.14 (br. s, 2H), 2.95 (br. s, 2H), 2.58 (br. s, 2H) ppm.

Intermediate 70A

4-{[4-Amino-5-bromo-7-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one trifluoroacetate



A suspension of Intermediate 69A (1 g) in methanol/water (10:1, 33 ml) was treated with trifluoroacetic acid (0.56 ml, 7.24 mmol) to result in a clear solution. A solution of *N*-bromosuccinimide (708 mg, 3.98 mmol) in methanol (30 ml) was added dropwise at 0°C, and the mixture was stirred at 0°C for 1 h. The formed precipitate was filtered off and dried *in vacuo* to yield 700 mg of the title compound (41% of th.).

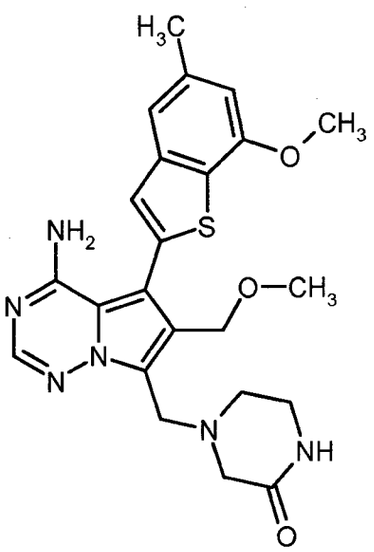
LC-MS (method 7): R_t = 1.38 min; MS (ESIpos): m/z = 355/357 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 7.90 (s, 1H), 5.00 (s, 2H), 4.44 (s, 2H), 3.85 (s, 2H), 3.58 (br. t, 2H), 3.50 (br. t, 2H) ppm.

Preparation Examples:

Example 1

4-{[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}piperazin-2-one



Method 1:

A solution of Intermediate 13A (3 g, 7.84 mmol) in methanol (87 ml) was treated with acetic acid (0.898 ml, 15.68 mmol), 2-oxopiperazine (1.17 g, 11.76 mmol) and sodium triacetoxyborohydride (4.98 g, 23.53 mmol). The mixture was stirred at rt for 4.5 h. Further portions of 2-oxopiperazine (392 mg, 3.9 mmol) and sodium triacetoxyborohydride (3.3 g, 15.68 mmol) were added, and the resulting mixture was stirred at 60°C overnight. After evaporation, the residue was taken up in sat. aq. sodium hydrogencarbonate solution and extracted with ethyl acetate. The combined organic phases were dried over sodium sulfate and evaporated, and the residue was purified by column chromatography on silica gel (dichloromethane/methanol 40:1 → 10:1). The product thus obtained was triturated in methanol and filtered off affording 540 mg (14% of th.) of the title compound. The methanolic mother liquor was evaporated and the residue purified by two-fold RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid). The fractions containing pure product

were combined and neutralized with sat. aq. sodium hydrogencarbonate solution. The acetonitrile solvent was evaporated, and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried over sodium sulfate and evaporated affording 395 mg (13% of th.) as a second batch of the title compound.

Method 2:

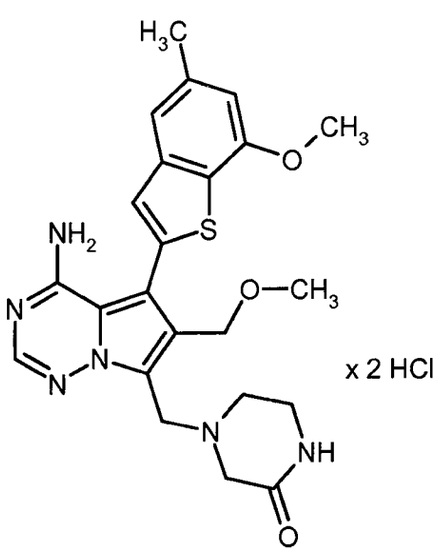
A solution of Intermediate 21A (291 mg, 0.82 mmol) in acetic acid (2.9 ml) was treated with 37% aq. formaldehyde solution (104 µl, 1.39 mmol) and 2-oxopiperazine (139 mg, 1.39 mmol). The mixture was stirred at 60°C for 3 h and then evaporated. Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 184 mg (44% of th.) of the title compound.

LC-MS (method 4): R_t = 0.77 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.00 (s, 1H), 7.73 (br. s, 1H), 7.37 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 4.41 (s, 2H), 3.97 (s, 2H), 3.96 (s, 3H), 3.20 (s, 3H), 3.15-3.08 (br. s, 2H), 3.01 (s, 2H), 2.64 (br. t, 2H), 2.45 (s, 3H) ppm.

Example 2

4-{[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}piperazin-2-one dihydrochloride



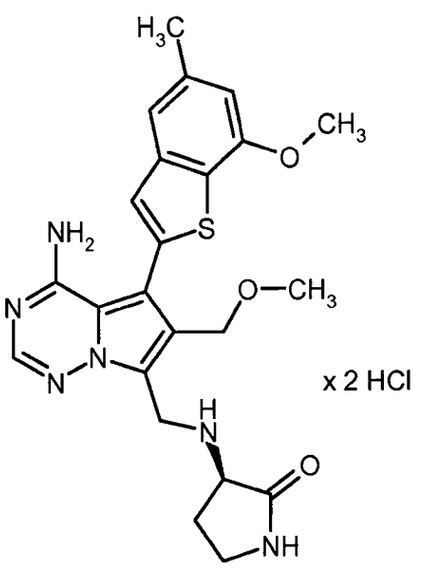
A solution of Example 1 (100 mg, 214 µmol) in 1,4-dioxane (2 ml) was treated with a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml, 8 mmol). The solvent was evaporated leaving 130 mg (quant.) of the title compound.

LC-MS (method 2): R_t = 0.79 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.39 (br. s, 1H), 8.31-8.53 (br. s, 1H), 8.17 (s, 1H), 7.38 (s, 1H), 7.34 (s, 1H), 6.87 (s, 1H), 6.21-6.42 (br. s, 1H), 4.81 (br. s, 2H), 4.52 (br. s, 2H), 3.96 (s, 3H), 3.57 (s, 2H), 3.32-3.72 (m, 4H), 3.26 (s, 3H), 2.46 (s, 3H) ppm.

Example 3

(*3R*)-3-({[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}amino)pyrrolidin-2-one dihydrochloride



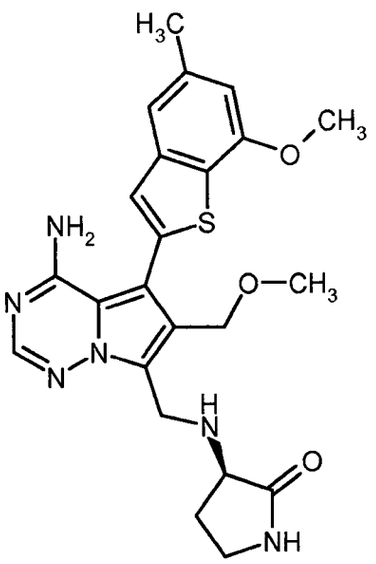
A solution of Intermediate 13A (520 mg, 1.36 mmol) in methanol (15 ml) and acetic acid (156 µl, 2.7 mmol) was treated with (*R*)-3-aminopyrrolidin-2-one (503 mg, 5.0 mmol) and triacetoxyborohydride (1.06 g, 5.0 mmol). The mixture was stirred at rt overnight and then evaporated. Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) and lyophilization of the product thus obtained from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 272 mg (36% of th.) of the title compound.

LC-MS (method 2): R_t = 0.70 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): d = 9.62 (br. s, 1H), 9.46 (br. s, 1H), 8.56-8.22 (br. s, 1H), 8.44 (s, 1H), 8.19 (s, 1H), 7.38 (s, 1H), 7.34 (s, 1H), 6.87 (s, 1H), 6.54-6.12 (br. s, 1H), 4.89-4.65 (m, 2H), 4.58-4.46 (m, 2H), 4.17-4.07 (br. s, 1H, overlap with water peak), 3.96 (s, 3H), 3.36-3.16 (m, 2H), 3.25 (s, 3H), 2.48-2.39 (m, 1H), 2.46 (s, 3H), 2.23-2.06 (m, 1H) ppm.

Example 4

(*3R*)-3-({[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}amino)pyrrolidin-2-one



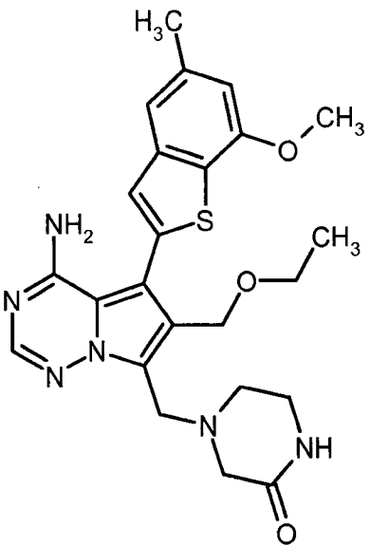
A solution of Intermediate 13A (2.0 g, 5.2 mmol) in methanol (58 ml) and acetic acid (0.6 ml) was treated with (*R*)-3-aminopyrrolidin-2-one (785 mg, 7.8 mmol) and triacetoxyborohydride (3.32 g, 15.6 mmol). The mixture was stirred at rt overnight. After this, the reaction mixture was diluted with sat. aq. sodium hydrogencarbonate solution and extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate and evaporated. The residue was purified by two-fold column chromatography on silica gel (dichloromethane/methanol 40:1 to 10:1) to afford 957 mg (37% of th.) of the title compound.

LC-MS (method 4): R_t = 0.72 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.01 (s, 1H), 7.75 (s, 1H), 7.35 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 4.46-4.34 (m, 2H), 4.24-4.02 (m, 2H), 3.96 (s, 3H), 3.24-3.04 (m, 3H), 3.21 (s, 3H), 2.45 (s, 3H), 2.40-2.27 (m, 1H), 1.80-1.65 (m, 1H) ppm.

Example 5

4-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-7-yl]methyl}piperazin-2-one



Method 1:

A solution of Intermediate 17A (2 g, 5.05 mmol) in THF (100 ml) was treated at 0°C with 2-oxopiperazine (1.01 g, 10.1 mmol), sodium triacetoxyborohydride (1.07 g, 5.04 mmol) and acetic acid (0.29 ml, 5.04 mmol). The resulting mixture was stirred at 0°C for 30 min. Four additional portions of sodium triacetoxyborohydride (1.07 g, 5.04 mmol) and of acetic acid (0.29 ml, 5.04 mmol) were added every 30 minutes, and the resulting mixture was stirred for further 30 min at 0°C, then for 25 min at 35°C and finally at rt overnight. The reaction was quenched with 10% aq. sodium chloride solution and extracted twice with ethyl acetate. The combined organic layers were evaporated. The residue was purified by column chromatography over silica gel (dichloromethane/ methanol 95:5 → 90:10) affording 360 mg (17% of th.) of the compound described in Example 86 (see below) and 1.82 g of the title compound in separate fractions. The title product thus obtained was suspended in ethanol (20 ml), refluxed for 2 h and then cooled to 15°C. The solid was filtered off and washed with ethanol affording 1.63 g (67% of th.) of the pure title compound.

Method 2:

A solution of Example 13 (930 mg, 1.9 mmol) in dichloromethane (18 ml) was treated with thionyl chloride (210 µl, 2.8 mmol) and stirred at rt for 15 min. After evaporation, the residue was dissolved in ethanol (18 ml) and treated with DIPEA (670 µl, 3.8 mmol). The mixture was stirred at 70°C for 2 h and then evaporated. The residue was purified by column chromatography on silica gel (dichloromethane/methanol 98:2 → 90:10). The product thus obtained was triturated in an aceto-nitrile/diethylether mixture and filtered. The filtrate was evaporated, and the residue was re-purified by column chromatography on silica gel (dichloromethane/methanol 98:2 → 90:10). Again, the product thus obtained was triturated in acetonitrile/diethylether and filtered. This procedure was

repeated one more time. The three batches of solids obtained in this way were combined, triturated in acetonitrile/diethylether once again and finally filtered off affording 600 mg (62% of th.) of the title compound.

Method 3:

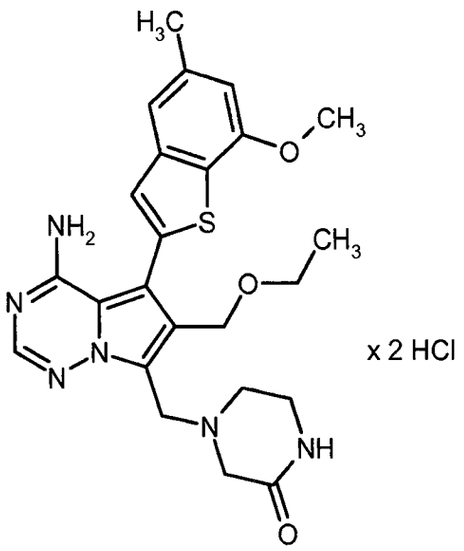
A solution of Intermediate 22A (720 mg, purity 89%, 1.74 mmol) in acetic acid (10 ml) was stirred with piperazin-2-one (261 mg, 2.61 mmol) at 60°C. To this, 37% aq. formaldehyde solution (260 µl, 3.48 mmol) was added in three portions after 0, 3 and 12 h, respectively, and the mixture was stirred at 60°C for a total of 24 h. Then, the volatiles were removed under reduced pressure, and the residue was partitioned between ethyl acetate and sat. aq. sodium hydrogencarbonate solution. The organic phase was washed with sat. aq. sodium chloride solution, dried with magnesium sulfate and evaporated. The residue was dissolved in a mixture of methanol and dichloromethane, adsorbed on diatomaceous earth, dried *in vacuo* and purified by flash-chromatography on silica gel (gradient 0-6% methanol/dichloromethane). The product fractions were combined, evaporated and re-purified by preparative RP-HPLC (Reprosil C18, gradient 30-50% acetonitrile/0.2% aq. TFA). The product fractions were combined again, diluted with sat. aq. sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic phase was washed with sat. aq. sodium chloride solution, dried with magnesium sulfate and evaporated yielding 281 mg (31% of th.) of the title compound.

LC-MS (method 2): R_t = 0.86 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.01 (s, 1H), 7.8-8.05 (br. s, 1H), 7.74 (br. s, 1H), 7.38 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 5.6-5.9 (br. s, 1H), 4.45 (s, 2H), 3.97 (s, 2H), 3.94 (s, 3H), 3.41 (q, 2H), 3.09-3.13 (m, 2H), 3.02 (s, 2H), 2.63-2.69 (br. s, 2H), 2.45 (s, 3H), 1.07 (t, 3H) ppm.

Example 6

4-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-7-yl]methyl}piperazin-2-one dihydrochloride



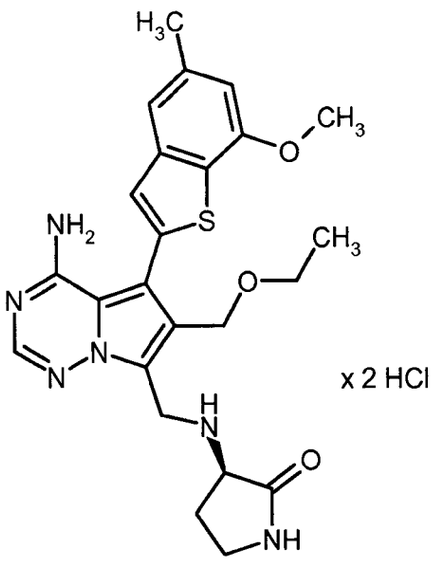
A solution of Intermediate 17A (60 mg, purity 69%, 104 µmol) in methanol (6 ml) was treated with 2-oxopiperazine (22 mg, 209 µmol), sodium cyanoborohydride (33 mg, 522 mmol) and acetic acid (12 µl, 209 µmol). The mixture was stirred at 60°C for 16 h and then filtered. The filtrate and the residue were purified separately by preparative RP-HPLC (Reprosil C18, gradient 40-60% acetonitrile/0.2% aq. TFA). The product fractions were combined, diluted with 1 M hydrochloric acid (3 ml) and evaporated to dryness yielding 46 mg (79% of th.) of the title compound.

LC-MS (method 2): R_t = 0.87 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.37 (br. s, 1H), 8.31 (br. s, 1H), 8.14 (s, 1H), 7.38 (s, 1H), 7.33 (s, 1H), 6.87 (s, 1H), 6.13 (br. s, 1H), 4.80 (br. s, 2H), 4.52 (s, 2H), 3.96 (s, 3H), 3.86 (br. s, 2H), 3.36-3.51 (m, 5H), 2.46 (s, 3H), 1.11 (t, 3H) ppm.

Example 7

(*3R*)-3-({[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}amino)pyrrolidin-2-one dihydrochloride



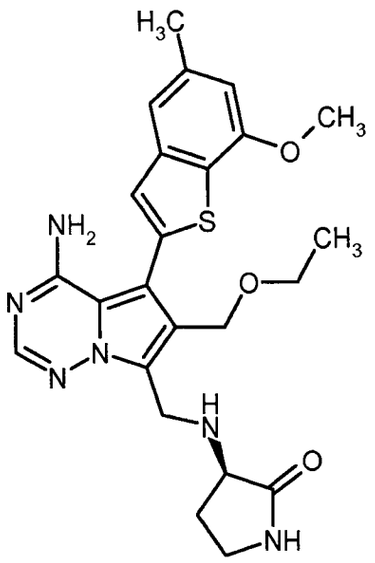
A solution of Intermediate 17A (60 mg, purity 69%, 104 µmol) in methanol (3 ml) was treated with (*R*)-3-aminopyrrolidin-2-one (22 mg, 209 µmol), sodium cyanoborohydride (33 mg, 522 µmol) and acetic acid (12 µl, 209 µmol). The mixture was stirred at 60°C for 4 h and then filtered. The filtrate was purified by preparative RP-HPLC (Reprosil C18, gradient 40-60% acetonitrile/ 0.2% aq. TFA). The product fractions were combined, diluted with 1 M hydrochloric acid and evaporated to dryness yielding 46 mg (79% of th.) of the title compound.

LC-MS (method 4): R_t = 0.74 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 9.58-9.75 (m, 1H), 9.33-9.54 (m, 1H), 8.44 (s, 1H), 8.27-8.71 (br. s, 1H), 8.19 (s, 1H), 7.38 (s, 1H), 7.34 (s, 1H), 6.87 (s, 1H), 6.18-6.48 (br. s, 1H), 4.68-4.87 (m, 2H), 4.49-4.62 (q, 2H), 3.96 (s, 3H), 3.45 (q, 2H), 3.18-3.35 (m, 2H), 2.46 (s, 4H), 2.08-2.22 (m, 1H), 1.10 (t, 3H) ppm.

Example 8

(*3R*)-3-({[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}amino)pyrrolidin-2-one



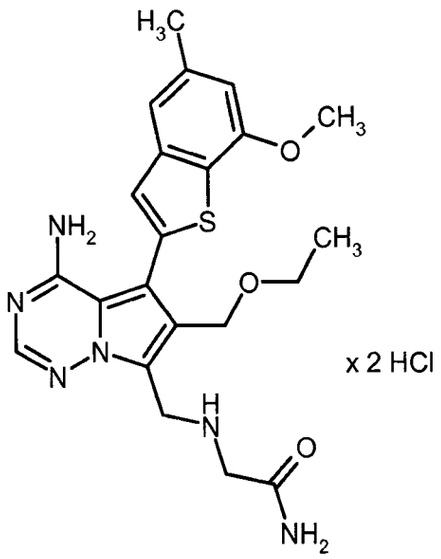
A solution of Intermediate 17A (226 mg, purity 75%, 428 µmol) in methanol (4 ml) was treated with (*R*)-3-aminopyrrolidin-2-one (85 mg, 855 µmol), sodium cyanoborohydride (134 mg, 2.14 mmol) and acetic acid (49 µl, 855 µmol). The mixture was stirred at rt for 1.5 h. After this, the mixture was directly separated by preparative RP-HPLC (Reprosil C18, gradient 40-60% acetonitrile/0.2% aq. TFA). The product fractions were combined, diluted with sat. aq. sodium hydrogencarbonate solution and extracted with ethyl acetate. The combined organic phases were washed with sat. aq. sodium chloride solution, dried over magnesium sulfate and evaporated to dryness yielding 180 mg (88% of th.) of the title compound.

LC-MS (method 4): R_t = 0.74 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.00 (s, 1H), 7.76 (s, 1H), 7.8-8.1 (br. s, 1H), 7.35 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 5.6-5.9 (br. s, 1H), 4.39-4.49 (m, 2H), 4.04-4.23 (m, 2H), 3.96 (s, 3H), 3.41 (q, 2H), 3.05-3.23 (m, 3H), 2.45 (s, 3H), 2.31-2.40 (m, 1H), 1.68-1.79 (m, 1H), 1.08 (t, 3H) ppm.

Example 9

N^2-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}glycinamide dihydrochloride



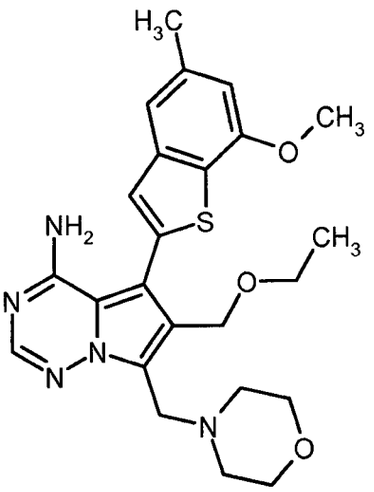
A solution of Intermediate 17A (60 mg, purity 69%, 104 µmol) in methanol (3 ml) was treated with glycinamide hydrochloride (23 mg, 209 µmol), sodium cyanoborohydride (32 mg, 522 mmol) and acetic acid (12 µl, 209 µmol). The mixture was stirred at 60°C for 16 h. After filtration, the filtrate was separated by preparative RP-HPLC (Reprosil C18, gradient 20-40% acetonitrile/0.2% aq. TFA). The product fractions were combined, diluted with 1 M hydrochloric acid, evaporated to dryness and combined with the residue from the filtration step. This material was re-purified by two-fold preparative RP-HPLC (Reprosil C18, gradient 20-40% acetonitrile/0.2% aq. TFA). The product fractions were combined again, diluted with 1 M hydrochloric acid and evaporated to dryness yielding 7.4 mg (13% of th.) of the title compound.

LC-MS (method 2): R_t = 0.80 min; MS (ESIpos): m/z = 455 $(M+H)^+$

^{1}H-NMR (500 MHz, DMSO-d_6): δ = 9.33 (br. s, 2H), 9.05 (br. s, 1H), 8.31 (s, 1H), 7.93 (br. s, 1H), 7.58 (br. s, 1H), 7.40 (s, 1H), 7.35 (s, 1H), 7.05 (br. s, 1H), 6.88 (s, 1H), 4.65 (br. m, 2H), 4.56 (s, 2H), 3.96 (s, 3H), 3.74 (br. m, 2H), 3.46 (q, 2H), 2.46 (s, 3H), 1.10 (t, 3H) ppm.

Example 10

6-(Ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-4-amine



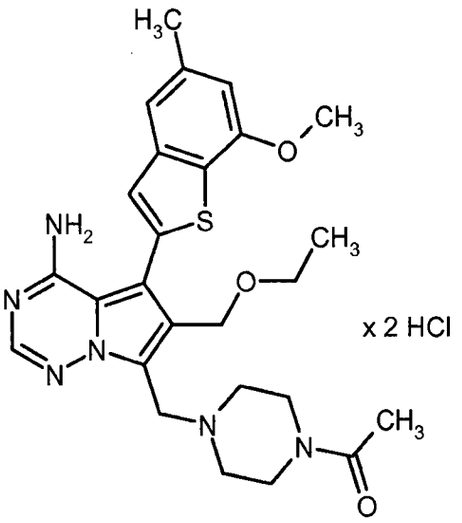
A solution of Intermediate 17A (55 mg, purity 73%, 101 µmol) in methanol (3 ml) was treated with morpholine (18 mg, 202 µmol), sodium cyanoborohydride (19 mg, 303 mmol) and acetic acid (18 µl, 304 µmol). The mixture was stirred at 60°C for 18 h. Further amounts of morpholine (18 mg, 202 µmol), sodium cyanoborohydride (19 mg, 303 mmol) and acetic acid (18 µl, 304 µmol) were added, and stirring at 60°C was continued for another 3 h. The resulting mixture was diluted with THF to dissolve precipitates and separated by preparative RP-HPLC (Reprosil C18, gradient 20-40% acetonitrile/0.2% aq. TFA). The product fractions were combined and evaporated to dryness. The residue was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated yielding 32 mg (68% of th.) of the title compound.

LC-MS (method 2): R_t = 0.78 min; MS (ESIpos): m/z = 468 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.98 (s, 1H), 7.9 (br. s, 1H), 7.37 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 5.75 (br. s, 1H), 4.45 (s, 2H), 3.95 (s, 3H), 3.88 (s, 2H), 3.51-3.56 (m, 4H), 3.40 (q, 2H), 2.4-2.5 (m, 4H), 2.45 (s, 3H), 1.06 (t, 3H) ppm.

Example 11

1-(4-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}piperazin-1-yl)ethanone dihydrochloride



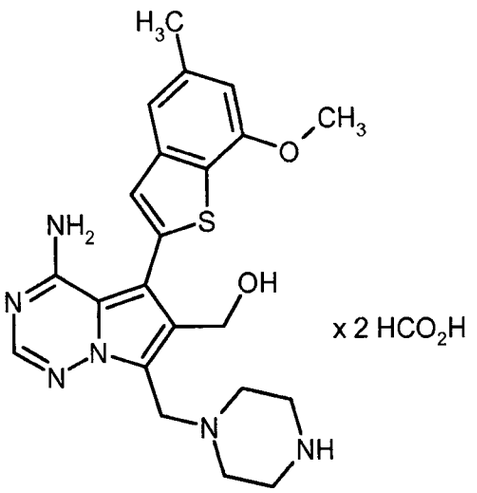
A solution of Intermediate 17A (130 mg, 0.328 mmol) in methanol (8 ml) was treated with *N*-acetylpiperazine (63 mg, 0.492 mmol), sodium cyanoborohydride (103 mg, 1.63 mmol) and acetic acid (37 µl, 0.655 mmol). The mixture was stirred at 60°C for 3 h. It was then combined with the reaction mixture of a 30 mg test run, evaporated and purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid). The product thus obtained was lyophilized from 1,4-dioxane, then dissolved in ethyl acetate and washed with sat. aq. sodium hydrogencarbonate solution. The organic layer was dried over magnesium sulfate, evaporated and lyophilized again from 1,4-dioxane. Re-purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid), followed by two-fold column chromatography on silica gel (dichloromethane/methanol 98:2 → 4:1) and lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 49 mg (18% of th.) of the title compound.

LC-MS (method 2): R_t = 0.82 min; MS (ESIpos): m/z = 509 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.65-8.26 (br. s, 1H), 8.17 (s, 1H), 7.38 (s, 1H), 7.34 (s, 1H), 6.87 (s, 1H), 6.53-6.05 (br. s, 1H), 4.75 (br. s, 2H), 4.56 (br. s, 2H), 3.96 (s, 3H), 3.45 (q, 2H, overlap with water peak), 2.46 (s, 3H), 2.03 (s, 3H), 1.09 (t, 3H) ppm.

Example 12

[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f]-[1,2,4]triazin-6-yl]methanol bis(formiate)



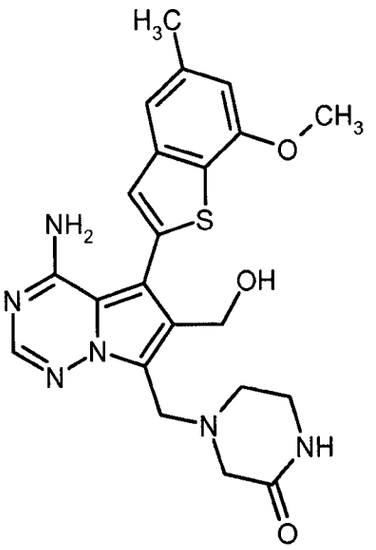
A solution of Intermediate 23A (95 mg, 152 µmol) in a 4 M solution of hydrogen chloride in 1,4-dioxane (3.7 ml) was stirred at rt for 2 h. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) affording 44 mg (62% of th.) of the title compound.

LC-MS (method 2): R_t = 0.63 min; MS (ESIpos): m/z = 439 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.28 (br. s, 2H), 7.98 (s, 1H), 7.37 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 4.50 (s, 2H, overlap with water peak), 3.98 (s, 2H, overlap with water peak), 3.95 (s, 3H, overlap with water peak), 2.95-2.84 (m, 4H), 2.61-2.55 (m, 4H, overlap with DMSO peak), 2.45 (s, 3H) ppm.

Example 13

4-{[4-Amino-6-(hydroxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-7-yl]methyl}piperazin-2-one



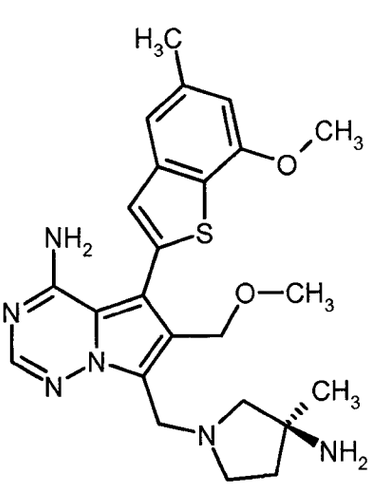
A solution of Intermediate 20A (1.34 g, 3.96 mmol) in acetic acid (13.9 ml) was treated with 37% aq. formaldehyde solution (501 µl, 6.6 mmol) and 2-oxopiperazine (670 mg, 6.6 mmol). The mixture was stirred at 50°C for 2 h and then evaporated. Purification by column chromatography on silica gel (dichloromethane/methanol 98:2 → 90:10) afforded 942 mg (49% of th.) of the title compound.

LC-MS (method 2): R_t = 0.67 min; MS (ESIpos): m/z = 453 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.99 (s, 1H), 7.76 (br. s, 1H), 7.39 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 4.51 (s, 2H), 4.03 (br. s, 2H), 3.95 (s, 3H), 3.18-3.13 (m, 2H), 3.07-2.98 (m, 2H), 2.72-2.60 (m, 2H), 2.45 (s, 3H) ppm.

Example 14

7-{[(3*S*)-3-Amino-3-methylpyrrolidin-1-yl]methyl}-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride



x 3 HCl

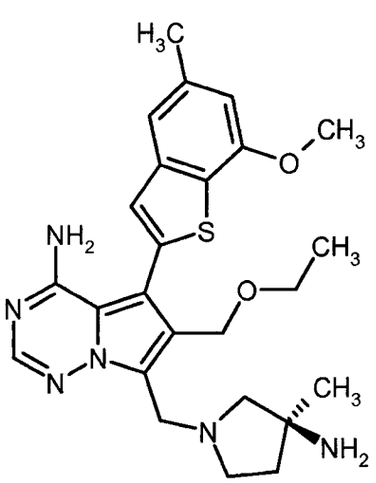
A solution of Intermediate 21A (100 mg, 0.28 mmol) in acetic acid (1 ml) was treated with 37% aq. formaldehyde solution (25 µl, 0.33 mmol) and *tert*-butyl [(*3S*)-3-methylpyrrolidin-3-yl]carbamate (Yoshida *et al.*, *Chem. Pharm. Bull.* 1996, 44 (7), 1376-1386; 67 mg, 0.33 mmol). The mixture was stirred at rt for 3 h and then evaporated. The residue was diluted with sat. aq. sodium hydrogencarbonate solution, and solid potassium carbonate was added until no more gas generation occurred. The aqueous phase was extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate and evaporated. The residue was dissolved in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) and stirred at rt for 2 h. After evaporation, the residue was purified by two-fold preparative RP-HPLC (first Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid; then Shield RP18, gradient 5-50% methanol + 0.1% aq. TFA/0.1% aq. TFA). The product thus obtained was lyophilized from a 4 M solution of hydrogen chloride in 1,4-dioxane affording 14 mg (8% of th.) of the title compound.

LC-MS (method 2): R_t = 0.67 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.50-8.22 (br. s, 1H), 8.14 (s, 1H), 7.36 (s, 1H), 7.34 (s, 1H), 6.87 (s, 1H), 6.36-6.01 (br. s, 1H), 4.88 (br. s, 2H), 4.56 (br. s, 2H), 3.96 (s, 3H, overlap with water peak), 3.26 (s, 3H), 2.46 (s, 3H), 1.52 (s, 3H) ppm.

Example 15

7-{[(*3S*)-3-Amino-3-methylpyrrolidin-1-yl]methyl}-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



A solution of Intermediate 17A (100 mg, 271 µmol) in acetic acid (1 ml) was treated with 37% aq. formaldehyde solution (24 µl, 326 µmol) and *tert*-butyl [(*3S*)-3-methylpyrrolidin-3-yl]carbamate (Yoshida *et al.*, *Chem. Pharm. Bull.* 1996, 44 (7), 1376-1386; 65 mg, 326 µmol). The mixture was

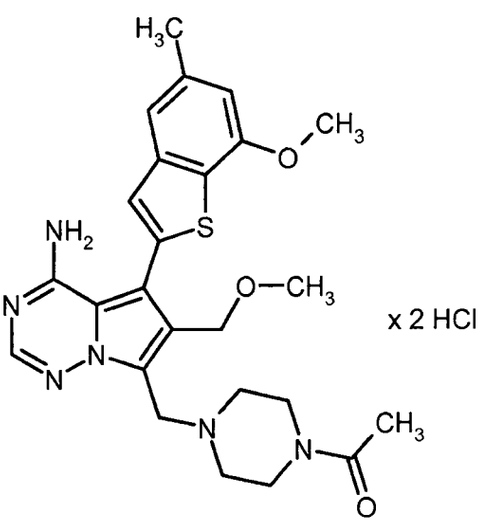
stirred at 60°C for 4 h. Then, further amounts of 37% aq. formaldehyde solution (10 µl, 136 µmol) and *tert*-butyl [(*3S*)-3-methylpyrrolidin-3-yl]carbamate (27 mg, 136 µmol) were added, and stirring at 60°C was continued overnight. After evaporation, the residue was partitioned between ethyl acetate and sat. aq. sodium hydrogencarbonate solution. Solid potassium carbonate was added until no more gas generation occurred. The aqueous phase was extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate, evaporated and purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid). The product thus obtained was dissolved in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) and stirred at rt for 1 h. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) affording 24 mg (18% of th.) of the title compound.

LC-MS (method 4): R_t = 0.70 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.19 (s, 1H), 7.38 (s, 1H), 7.34 (s, 1H), 6.87 (s, 1H), 4.90 (br. s, 2H), 3.96 (s, 3H), 3.46 (q, 3H), 2.46 (s, 3H), 1.54 (s, 3H), 1.14-1.05 (m, 3H) ppm.

Example 16

1-(4-{[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}piperazin-1-yl)ethanone dihydrochloride



A solution of Intermediate 21A (50 mg, 141 µmol) in acetic acid (1 ml) was treated with 37% aq. formaldehyde solution (4.6 µl, 169 µmol) and *N*-acetylpiperazine (21.6 mg, 169 µmol). The mixture was stirred at 75°C for 3 h. After evaporation, the residue was purified by preparative RP-HPLC

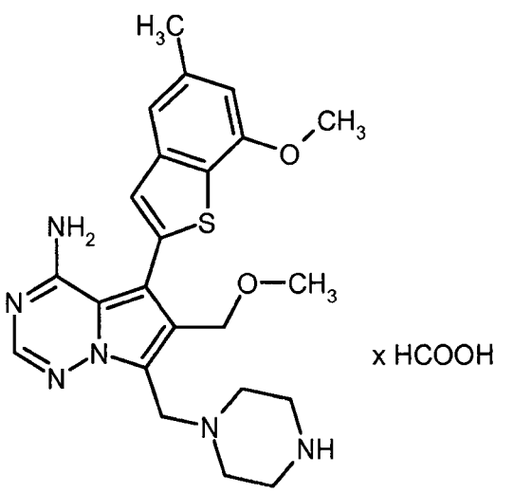
(Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid). Lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 34 mg (39% of th.) of the title compound.

LC-MS (method 5): R_t = 1.78 min; MS (ESIpos): m/z = 495 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.70-8.35 (br. s, 1H), 8.18 (s, 1H), 7.37 (s, 1H), 7.34 (s, 1H), 6.86 (s, 1H), 6.61-6.19 (br. s, 1H), 4.74 (br. s, 2H), 4.54 (br. s, 2H), 3.96 (s, 3H), 3.25 (s, 3H), 2.46 (s, 3H), 2.03 (s, 3H) ppm.

Example 17

6-(Methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-4-amine formiate



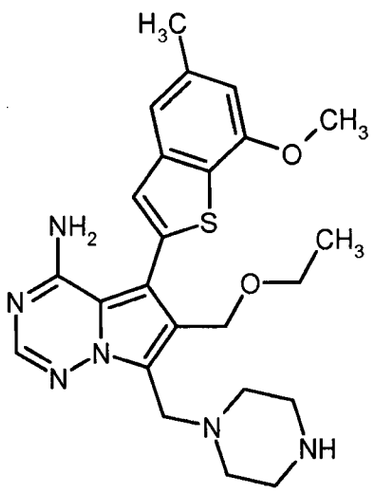
A solution of Intermediate 23A (110 mg, 204 µmol) in dichloromethane (2.2 ml) was treated with thionyl chloride (29 µl, 408 µmol) and stirred at rt for 15 min. After evaporation, the residue was dissolved in methanol (2.2 ml) and treated with DIPEA (39 µl, 224 µmol). The mixture was stirred at 70°C for 1 h and then evaporated. The residue was taken up in a 4 M solution of hydrogen chloride in 1,4-dioxane (2.2 ml) and stirred at rt for 2 h. Evaporation and purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 44.9 mg (46% of th.) of the title compound.

LC-MS (method 2): R_t = 0.73 min; MS (ESIpos): m/z = 453 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.28 (br. s, 1H), 8.00 (s, 1H), 7.35 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 4.41 (s, 2H), 4.00-3.90 (m, 5H), 3.00-2.90 (m, 4H), 2.65-2.56 (m, 4H), 2.45 (s, 3H) ppm.

Example 18

6-(Ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-4-amine



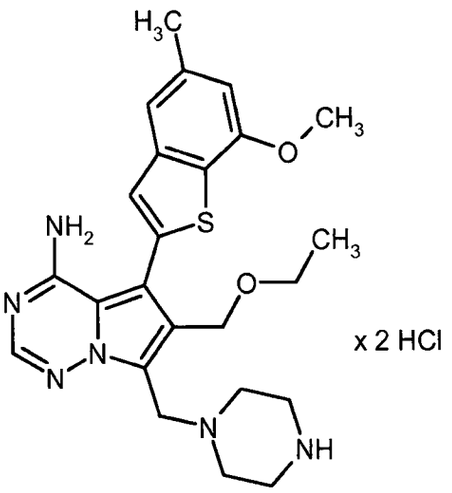
A solution of Intermediate 23A (80 mg, 317 µmol) in dichloromethane (2 ml) was treated with thionyl chloride (22 µl, 297 µmol) and stirred at rt for 15 min. After evaporation, the residue was dissolved in ethanol (2 ml) and treated with DIPEA (28 µl, 163 µmol). The mixture was stirred at 70°C for 1 h and then evaporated. The residue was taken up in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) and stirred at rt for 1 h. Evaporation and purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 35 mg (50% of th.) of the title compound.

LC-MS (method 2): R_t = 0.82 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.09 (br. s, 1H), 7.36 (s, 1H), 7.32 (s, 1H), 6.86 (s, 1H), 4.50 (br. s, 2H), 3.96 (s, 3H), 3.42 (q, 2H, overlap with water peak), 2.45 (s, 3H), 1.05 (t, 3H) ppm.

Example 19

6-(Ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-4-amine dihydrochloride



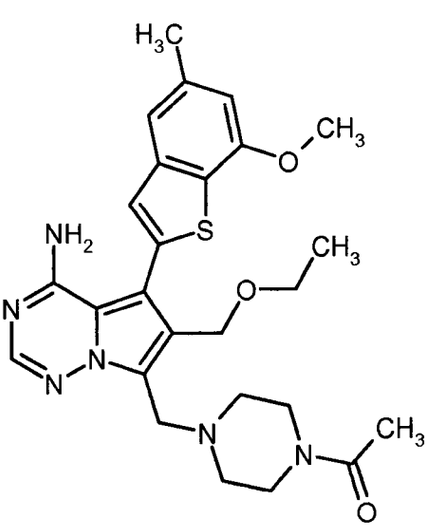
A solution of Example 18 (50 mg, 107 µmol) in a 4 M solution of hydrogen chloride in 1,4-dioxane (1 ml) was stirred at rt for 15 min. After evaporation 55 mg (93% of th.) of the title compound were obtained.

LC-MS (method 4): R_t = 0.74 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.18 (s, 1H), 7.37 (s, 1H), 7.34 (s, 1H), 6.87 (s, 1H), 4.76 (br. s, 2H), 4.60 (br. s, 2H), 3.96 (s, 3H), 3.45 (q, 2H), 2.46 (s, 3H), 1.09 (t, 3H) ppm.

Example 20

1-(4-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}piperazin-1-yl)ethanone



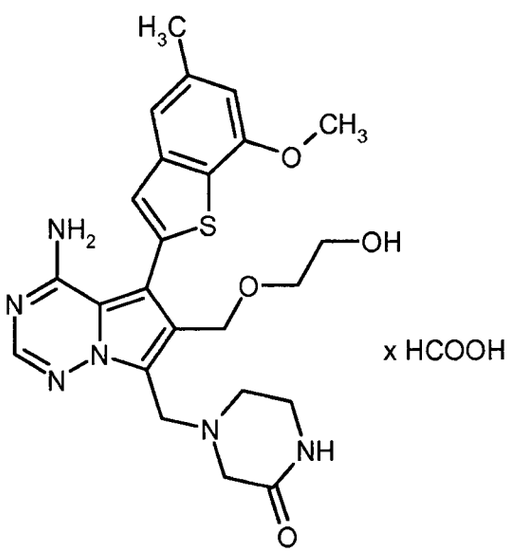
A solution of Example 18 (70 mg, 150 µmol) in dichloromethane (2 ml) and THF (0.8 ml) was treated with acetyl chloride (21 µl, 300 µmol) and sodium carbonate (127 mg, 1.2 mmol). The mixture was stirred at rt overnight. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) affording 27 mg (31% of th.) of the title compound.

LC-MS (method 4): R_t = 0.77 min; MS (ESIpos): m/z = 509 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.98 (s, 1H), 7.37 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 4.45 (s, 2H), 3.95 (s, 3H), 3.92 (s, 2H), 3.45-3.36 (m, 6H), 2.48-2.38 (m, 7H, overlap with DMSO peak), 1.97 (s, 3H), 1.06 (t, 3H) ppm.

Example 21

4-({4-Amino-6-[(2-hydroxyethoxy)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo-[2,1-f][1,2,4]triazin-7-yl}methyl)piperazin-2-one formiate



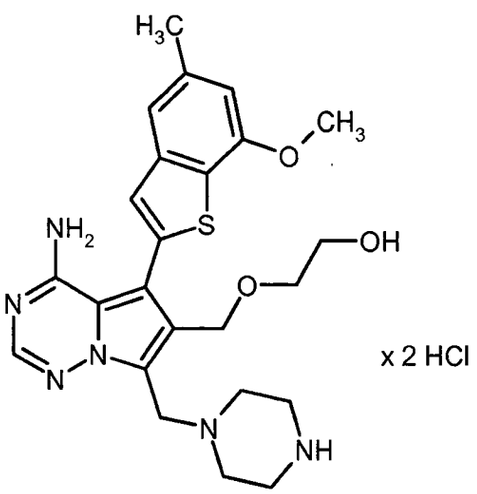
A solution of Example 13 (60 mg, 132 µmol) in dichloromethane (2 ml) was treated with thionyl chloride (14 µl, 198 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in ethylene glycol (500 µl) and stirred at 100°C for 90 min. Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 34 mg (47% of th.) of the title compound.

LC-MS (method 2): R_t = 0.69 min; MS (ESIpos): m/z = 497 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.14 (s, 1H), 8.00 (s, 1H), 7.74 (br. s, 1H), 7.42 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 4.49 (s, 2H), 3.99 (s, 2H), 3.96 (s, 3H), 3.50-3.43 (m, 2H), 3.42-3.36 (m, 2H, overlap with water peak), 3.15-3.07 (m, 2H), 3.03 (s, 2H), 2.69-2.61 (m, 2H), 2.45 (s, 3H) ppm.

Example 22

2-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f]-[1,2,4]triazin-6-yl]methoxy}ethanol dihydrochloride



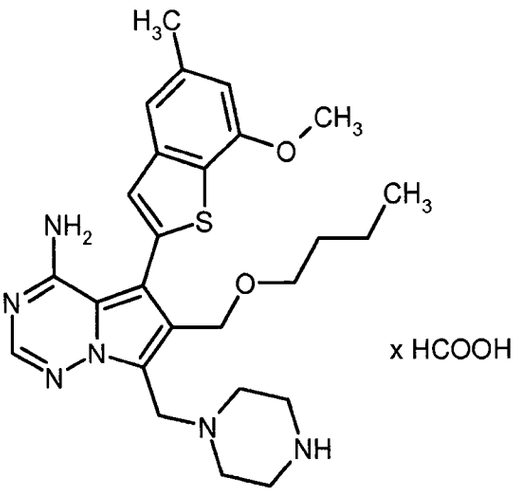
A solution of Intermediate 23A (100 mg, 185 µmol) in dichloromethane (4 ml) was treated with thionyl chloride (27 µl, 371 µmol). The mixture was stirred at rt for 20 min and then evaporated. The residue was dissolved in ethylene glycol/THF (2:1, 1.5 ml) and stirred at 100°C for 2 h. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid), followed by column chromatography on silica gel (dichloro-methane/methanol + 0.1% aq. ammonia 98:2 → 90:10). Lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 67 mg (64% of th.) of the title compound.

LC-MS (method 2): R_t = 0.66 min; MS (ESIpos): m/z = 483 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.16 (s, 1H), 7.49 (s, 1H), 7.43 (s, 1H), 6.98 (s, 1H), 4.86 (s, 2H), 4.69 (s, 2H), 4.03 (s, 3H), 3.81-3.49 (m, 12H), 2.50 (s, 3H) ppm.

Example 23

6-(Butoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-4-amine formiate



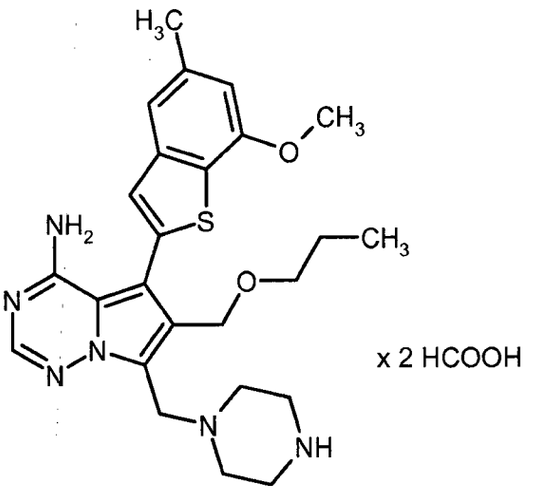
A solution of Intermediate 23A (100 mg, 185 µmol) in dichloromethane (2 ml) was treated with thionyl chloride (27 µl, 371 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in 1-butanol (2 ml) and heated to 70°C for 1 h. After evaporation, the residue was taken up in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) and stirred at rt for 2 h. Evaporation and purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 22 mg (24% of th.) of the title compound.

LC-MS (method 2): R_t = 0.82 min; MS (ESIpos): m/z = 495 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.29 (s, 1H), 7.99 (s, 1H), 7.35 (s, 1H), 7.29 (s, 1H), 6.84 (s, 1H), 4.43 (s, 2H), 3.95 (s, 3H), 3.92 (s, 2H), 3.35 (t, 2H), 2.90-2.79 (m, 4H), 2.45 (s, 3H), 1.47-1.37 (m, 2H), 1.31-1.18 (m, 2H), 0.80 (t, 3H) ppm.

Example 24

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)-6-(propoxymethyl)pyrrolo-[2,1-f][1,2,4]triazin-4-amine bis(formiate)



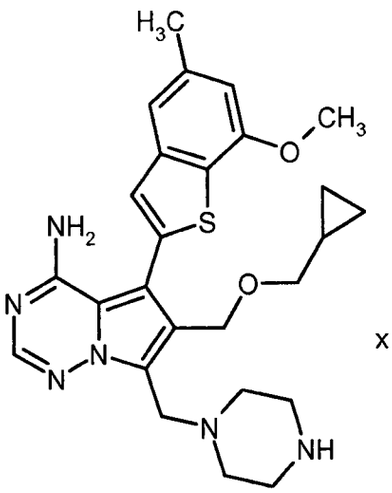
A solution of Intermediate 23A (100 mg, 185 µmol) in dichloromethane (2 ml) was treated with thionyl chloride (27 µl, 371 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in 1-propanol (2 ml), treated with DIPEA (48 µl, 278 µmol) and stirred at rt for 1 h. After evaporation, the residue was taken up in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) and stirred at rt for 2 h. Evaporation and purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 15 mg (16% of th.) of the title compound.

LC-MS (method 2): R_t = 0.78 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.26 (br. s, 2H), 7.98 (s, 1H), 7.36 (s, 1H), 7.30 (s, 1H), 6.84 (s, 1H), 4.44 (s, 2H), 3.95 (s, 3H), 3.92 (s, 2H), 3.32 (t, 2H), 2.87-2.79 (m, 4H), 1.52-1.39 (m, 2H), 0.81 (t, 3H) ppm.

Example 25

6-[(Cyclopropylmethoxy)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-yl-methyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine bis(formiate)



x 2 HCOOH

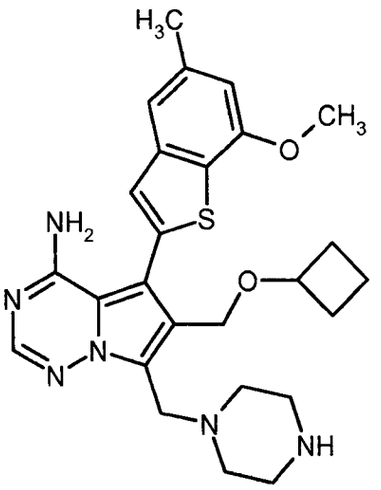
A solution of Intermediate 23A (100 mg, 185 µmol) in dichloromethane (2 ml) was treated with thionyl chloride (27 µl, 371 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in cyclopropylmethanol (2 ml), treated with DIPEA (48 µl, 278 µmol) and stirred at 70°C for 2 h. After evaporation, the residue was taken up in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) and stirred at rt for 2 h. Evaporation and purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 29 mg (30% of th.) of the title compound.

LC-MS (method 2): R_t = 0.78 min; MS (ESIpos): m/z = 493 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.28 (br. s, 2H), 7.99 (s, 1H), 7.37 (s, 1H), 7.30 (s, 1H), 6.84 (s, 1H), 4.45 (s, 2H), 3.95 (s, 3H), 3.93 (s, 2H), 3.21 (d, 2H), 2.95-2.83 (m, 4H), 2.61-2.56 (m, 4H), 2.45 (s, 3H), 1.01-0.91 (m, 1H), 0.46-0.37 (m, 2H), 0.15-0.08 (m, 2H) ppm.

Example 26

6-[(Cyclobutyloxy)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-yl-methyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



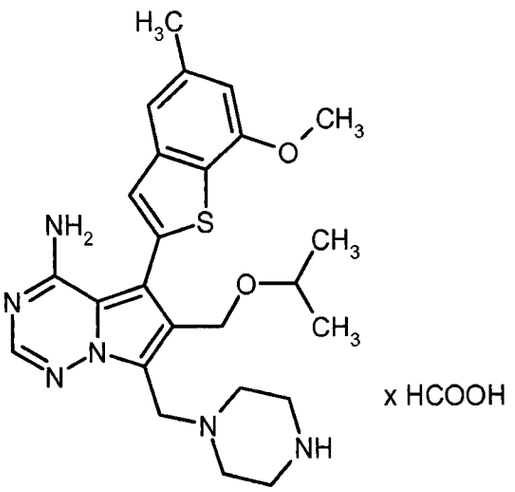
A solution of Intermediate 23A (85 mg, 157 µmol) in dichloromethane (1.7 ml) was treated with thionyl chloride (23 µl, 315 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in cyclobutanol (1.7 ml), treated with DIPEA (41 µl, 236 µmol) and stirred at 70°C for 2 h. After evaporation, the residue was taken up in a 4 M solution of hydrogen chloride in 1,4-dioxane (1.7 ml) and stirred at rt for 2 h. Evaporation and purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 23 mg (28% of th.) of the title compound.

LC-MS (method 2): R_t = 0.82 min; MS (ESIpos): m/z = 493 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.01 (s, 1H), 7.37 (s, 1H), 7.32 (s, 1H), 6.85 (s, 1H), 4.37 (s, 2H), 4.06-3.86 (m, 6H), 3.14-2.97 (m, 4H), 2.80-2.62 (m, 4H), 2.45 (s, 3H), 2.10-1.96 (m, 2H), 1.83-1.69 (m, 2H), 1.65-1.52 (m, 1H), 1.49-1.33 (m, 1H) ppm.

Example 27

6-(Isopropoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-amine formiate



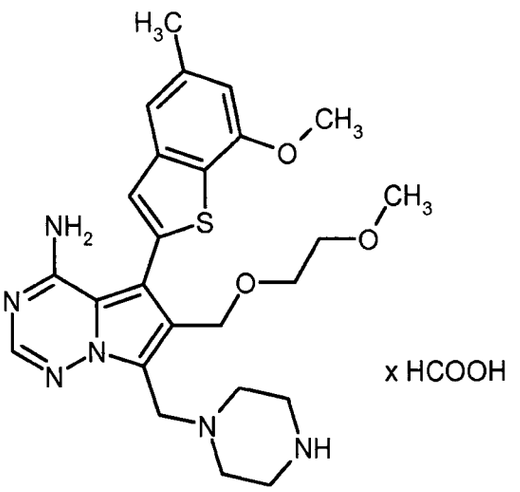
A solution of Intermediate 23A (65 mg, 120 µmol) in dichloromethane (1.3 ml) was treated with thionyl chloride (17 µl, 241 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in 2-propanol (1.3 ml), treated with DIPEA (23 µl, 132 µmol) and stirred at 70°C for 1 h. Further DIPEA (23 µl, 132 µmol) was added, and the mixture was stirred again at 70°C for 1 h. Then, another portion of DIPEA (63 µl, 362 µmol) was added, and stirring was continued at 90°C for 3 h. After evaporation, the residue was taken up in a 4 M solution of hydrogen chloride in 1,4-dioxane (1.3 ml) and stirred at rt for 2 h. Evaporation and purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 23 mg (34% of th.) of the title compound.

LC-MS (method 4): R_t = 0.74 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.30 (s, 1H), 7.98 (s, 1H), 7.37 (s, 1H), 7.30 (s, 1H), 6.84 (s, 1H), 4.43 (s, 2H), 3.95 (s, 3H), 3.90 (s, 2H), 3.57 (m, 1H, overlap with water peak), 2.88-2.78 (m, 4H), 2.45 (s, 3H), 1.04 (d, 6H) ppm.

Example 28

6-[(2-Methoxyethoxy)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine formiate



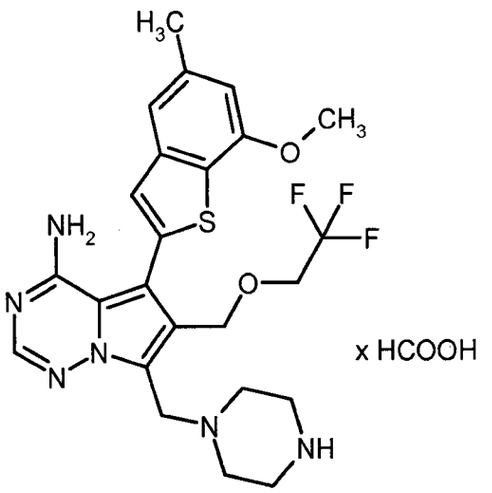
A solution of Intermediate 23A (100 mg, 185 µmol) in dichloromethane (2 ml) was treated with thionyl chloride (27 µl, 371 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in 2-methoxyethanol (2 ml), treated with DIPEA (35 µl, 204 µmol) and stirred at 70°C for 1 h. After evaporation, the residue was taken up in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) and stirred at rt for 2 h. Evaporation and purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 50 mg (50% of th.) of the title compound.

LC-MS (method 2): R_t = 0.75 min; MS (ESIpos): m/z = 497 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.26 (br. s, 1H), 7.99 (s, 1H), 7.39 (s, 1H), 7.30 (s, 1H), 6.84 (s, 1H), 4.48 (s, 2H), 3.95 (s, 3H), 3.94 (s, 2H), 3.52-3.46 (m, 2H, overlap with water peak), 3.44-3.37 (m, 2H, overlap with water peak), 3.20 (s, 3H), 2.94-2.84 (m, 4H), 2.61-2.54 (m, 4H, overlap with DMSO peak), 2.45 (s, 3H) ppm.

Example 29

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)-6-[(2,2,2-trifluoroethoxy)-methyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine formiate



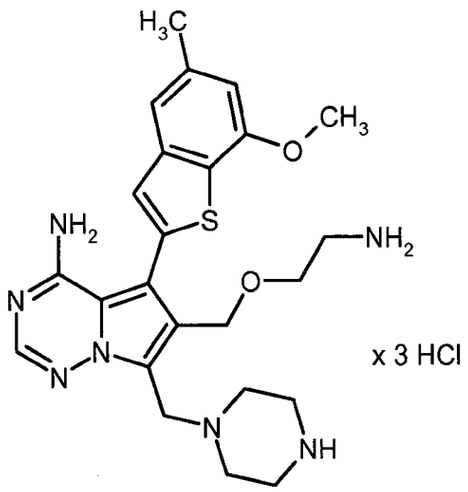
A solution of Intermediate 23A (100 mg, 185 µmol) in dichloromethane (2 ml) was treated with thionyl chloride (27 µl, 371 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in 2,2,2-trifluoroethanol (2 ml), treated with DIPEA (35 µl, 204 µmol) and stirred at 70°C for 1 h. Further DIPEA (35 µl, 204 µmol) was added, and stirring was continued at rt for 1 h. After evaporation, the residue was taken up in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) and stirred at rt for 2 h. Evaporation and purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 23 mg (23% of th.) of the title compound.

LC-MS (method 2): R_t = 0.79 min; MS (ESIpos): m/z = 521 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.28 (br. s, 1H), 8.00 (s, 1H), 7.37 (s, 1H), 7.30 (s, 1H), 6.85 (s, 1H), 4.66 (s, 2H), 4.08 (q, 2H), 3.95 (s, 3H), 3.92 (s, 2H), 2.85-2.75 (m, 4H), 2.45 (s, 3H) ppm.

Example 30

6-[(2-Aminoethoxy)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride



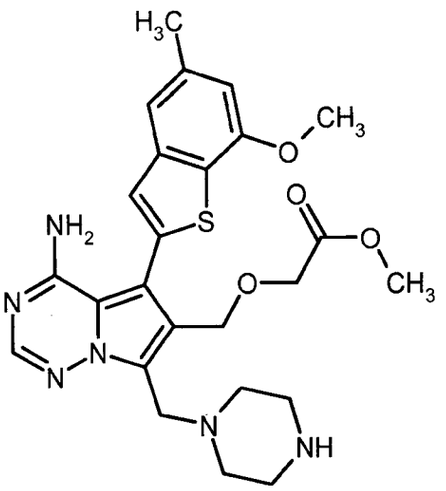
A solution of Intermediate 23A (150 mg, 278 µmol) in dichloromethane (5 ml) was treated with thionyl chloride (40 µl, 556 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in THF (0.5 ml) and treated with *tert*-butyl (2-hydroxyethyl)carbamate (1 ml) and DIPEA (242 µl, 1.39 mmol). The mixture was stirred at 100°C overnight. After evaporation, the residue was taken up in 1,4-dioxane (10 ml), treated with a 4 M solution of hydrogen chloride in 1,4-dioxane (10 ml) and stirred at rt for 1 h. The volatiles were removed under reduced pressure, and the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid). Further purification by preparative RP-HPLC (Shield RP18, 25% acetonitrile/75% 0.01% aq. TFA) followed by lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 10 mg (6% of th.) of the title compound.

LC-MS (method 2): R_t = 0.58 min; MS (ESIpos): m/z = 482 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.12 (s, 1H), 7.50 (s, 1H), 7.44 (s, 1H), 6.99 (s, 1H), 4.61 (s, 2H), 4.04 (s, 3H), 3.88-3.80 (m, 1H), 3.70-3.60 (m, 3H), 3.52-3.46 (m, 4H), 3.40-3.34 (m, 4H), 3.07 (t, 2H), 2.51 (s, 3H) ppm.

Example 31

Methyl {[4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methoxy}acetate



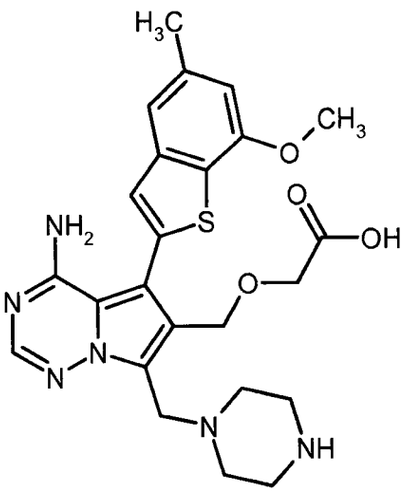
A solution of Intermediate 23A (50 mg, 92 µmol) in dichloromethane (2 ml) was treated with thionyl chloride (13 µl, 186 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in methylglycolate (1 ml), treated with DIPEA (80 µl, 464 µmol) and stirred at 70°C for 2 h. After evaporation, the residue was taken up in dichloromethane (1.6 ml), treated with trifluoroacetic acid (400 µl, 5.19 mmol) and stirred at rt for 1 h. Then, the mixture was evaporated, and the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). Fractions containing the title compound were neutralized with sat. aq. sodium hydrogencarbonate solution and evaporated. The residue was taken up in water, and the mixture was extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and evaporated affording 21 mg (43% of th.) of the title compound.

LC-MS (method 2): R_t = 0.72 min; MS (ESIpos): m/z = 511 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.99 (s, 1H), 7.39 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 4.59 (s, 2H), 4.11 (s, 2H), 3.95 (s, 3H), 3.90 (s, 2H), 3.57 (s, 3H), 2.81-2.69 (m, 4H), 2.48-2.39 (m, 7H) ppm.

Example 32

{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f]-[1,2,4]triazin-6-yl]methoxy}acetic acid



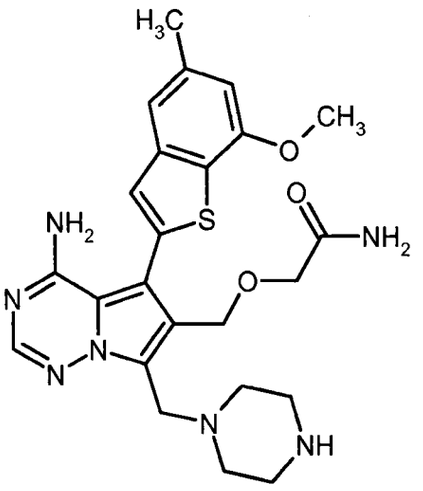
A solution of Intermediate 24A (200 mg, 327 µmol) in THF (14 ml) was treated with 2.5 M aq. lithium hydroxide solution (16 ml) and stirred at 80°C for 2 h. The mixture was then combined with the reaction mixture of a 27 mg test run. The aqueous phase was extracted twice with THF, and the combined organic phases were evaporated. The residue was dissolved in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) and stirred at rt for 3 h. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). Lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane and re-purification by preparative RP-HPLC (XBridge C18, gradient 5-95% acetonitrile/0.1% aq. ammonium hydroxide solution) afforded 13 mg (7% of th.) of the title compound.

LC-MS (method 2): R_t = 0.69 min; MS (ESIpos): m/z = 497 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.00 (s, 1H), 7.38 (s, 1H), 7.30 (s, 1H), 6.84 (s, 1H), 4.54 (s, 2H), 4.08 (s, 2H), 3.95 (s, 3H), 3.79 (s, 2H), 2.99-2.89 (m, 4H), 2.73-2.63 (m, 4H), 2.44 (s, 3H) ppm.

Example 33

2-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f]-[1,2,4]triazin-6-yl]methoxy}acetamide



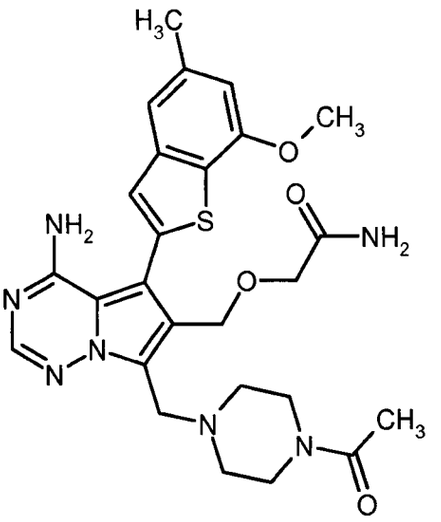
Intermediate 24A (200 mg, 327 µmol) was treated with a 7 M solution of ammonia in methanol (10 ml) and stirred at rt overnight. The mixture was then combined with the reaction mixture of a 20 mg test run, and the solvents were evaporated. The residue was treated with a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) and stirred at rt for 2 h. Evaporation and subsequent purifications by preparative RP-HPLC (first Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA; then XBridge C18, gradient 5-95% acetonitrile/0.1% aq. ammonium hydoxide solution) afforded 5.5 mg (3% of th.) of the title compound.

LC-MS (method 2): R_t = 0.69 min; MS (ESIpos): m/z = 496 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.14-7.59 (br. s, 1H), 7.99 (s, 1H), 7.39 (s, 1H), 7.35-7.22 (m, 3H), 6.85 (s, 1H), 4.54 (s, 2H), 3.95 (s, 3H), 3.90 (s, 2H), 3.79 (s, 2H), 2.73-2.66 (m, 4H), 2.45 (s, 3H), 2.43-2.35 (m, 4H) ppm.

Example 34

2-({7-[(4-Acetylpiperazin-1-yl)methyl]-4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-pyrrolo[2,1-f][1,2,4]triazin-6-yl}methoxy)acetamide



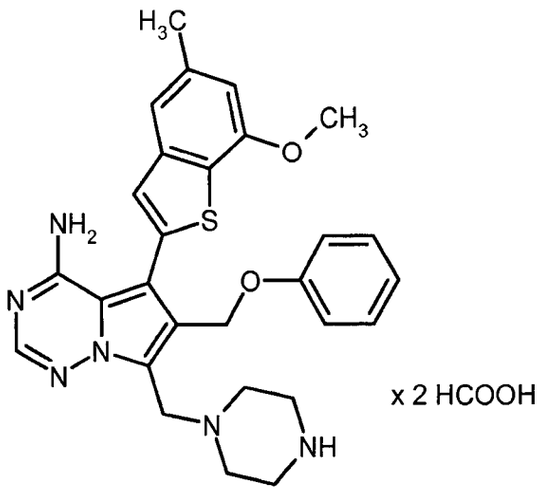
A solution of Example 33 (105 mg, 68% purity, 144 µmol) in THF/dichloromethane (1:2.5, 3.9 ml) was treated with sodium carbonate (179 mg, 1.6 mmol) and stirred at rt for 30 min. Acetyl chloride (30 µl, 424 µmol) was added, and the resulting mixture was stirred at rt for 30 min, then quenched with methanol (2 ml) and evaporated. Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 30 mg (85% purity, 34% of th.) of the title compound.

LC-MS (method 5): R_t = 1.67 min; MS (ESIpos): m/z = 538 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.99 (s, 1H), 7.40 (s, 1H), 7.33-7.19 (m, 3H), 6.85 (s, 1H), 4.55 (s, 2H), 3.96 (s, 5H), 3.80 (s, 2H), 3.43-3.36 (m, 4H), 2.47-2.38 (m, 7H), 1.97 (s, 3H) ppm.

Example 35

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-6-(phenoxymethyl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-4-amine bis(formiate)



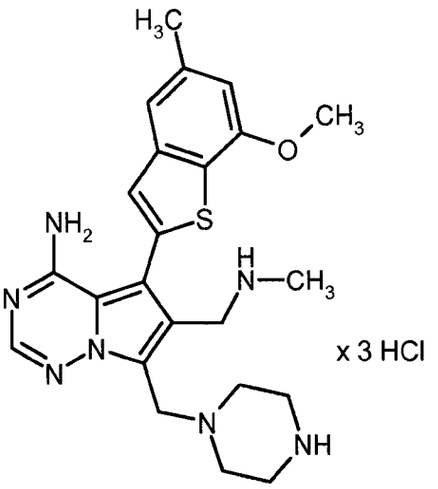
A solution of Intermediate 23A (100 mg, 185 µmol) in dichloromethane (2 ml) was treated with thionyl chloride (27 µl, 371 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in THF (2 ml), treated with phenol (174 mg, 1.85 mmol) and DIPEA (48 µl, 278 µmol) and stirred at 70°C for 2 h. Further amounts of phenol (174 mg, 1.85 mmol) and DIPEA (64 µl, 371 µmol) were added, and stirring was continued at 70°C overnight. After evaporation, the residue was taken up in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) and stirred at rt for 2 h. Evaporation and purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 8 mg (8% of th.) of the title compound.

LC-MS (method 2): R_t = 0.84 min; MS (ESIpos): m/z = 515 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.26 (s, 2H), 8.02 (s, 1H), 7.36 (s, 1H), 7.30-7.22 (m, 3H), 6.99-6.89 (m, 3H), 6.81 (m, 1H), 5.04 (s, 2H), 3.93 (s, 5H), 2.78-2.71 (m, 4H), 2.42 (s, 3H) ppm.

Example 36

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-6-[(methylamino)methyl]-7-(piperazin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride



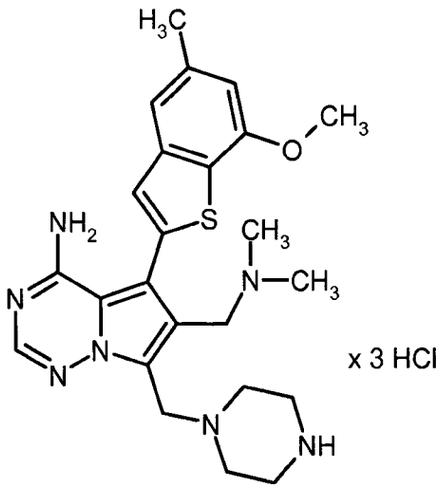
Intermediate 25A (150 mg, 279 µmol) in THF (3 ml) was treated with acetic acid (32 µl, 559 µmol), a 2 M solution of methylamine in THF (698 µl, 1.39 mmol) and sodium triacetoxyborohydride (296 mg, 1.39 mmol). The mixture was stirred at 60°C for 2 h and then evaporated. The residue was dissolved in a 4 M solution of hydrogen chloride in 1,4-dioxane (1.87 ml) and stirred at rt for 2 h. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). Lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 79 mg (49% of th.) of the title compound.

LC-MS (method 2): R_t = 0.56 min; MS (ESIpos): m/z = 452 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.17 (s, 1H), 7.57 (s, 1H), 7.46 (s, 1H), 7.01 (s, 1H), 4.52 (s, 2H), 4.46 (s, 2H), 4.04 (s, 3H), 3.48-3.39 (m, 4H), 3.25-3.15 (m, 4H), 2.59 (s, 3H), 2.51 (s, 3H) ppm.

Example 37

6-[(Dimethylamino)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride



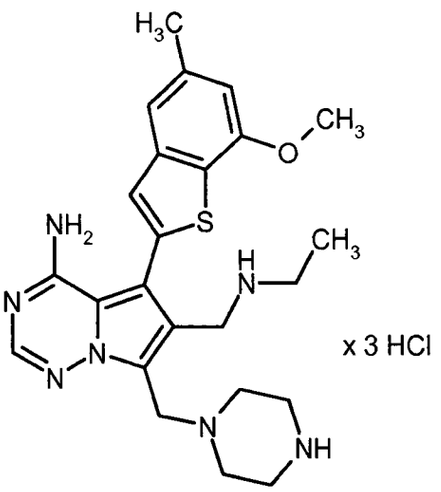
A solution of Intermediate 25A (150 mg, 279 µmol) in THF (3 ml) was treated with acetic acid (32 µl, 559 µmol), a 2 M solution of dimethylamine in THF (698 µl, 1.39 mmol) and sodium triacetoxyborohydride (296 mg, 1.39 mmol). The mixture was stirred at 60°C for 2 h and then evaporated. The residue was dissolved in a 4 M solution of hydrogen chloride in 1,4-dioxane (1.88 ml) and stirred at rt for 2 h. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). Lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 83 mg (50% of th.) of the title compound.

LC-MS (method 4): R_t = 0.50 min; MS (ESIpos): m/z = 466 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.17 (s, 1H), 7.57 (s, 1H), 7.45 (s, 1H), 7.01 (s, 1H), 4.57 (s, 2H), 4.50 (s, 2H), 4.04 (s, 3H), 3.47-3.36 (m, 4H), 3.21-3.12 (m, 4H), 2.80 (s, 6H), 2.51 (s, 3H) ppm.

Example 38

6-[(Ethylamino)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride



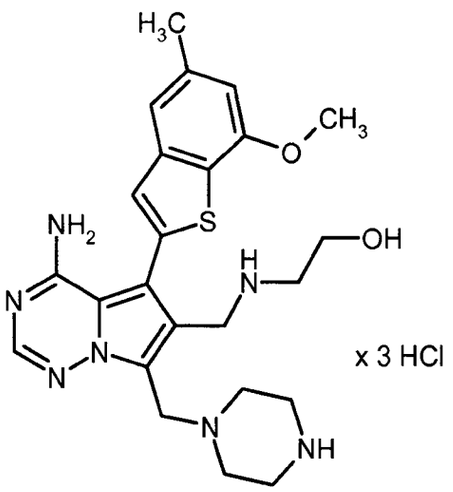
A solution of Intermediate 25A (60 mg, 111.8 µmol) in THF (1 ml) was treated with a 2 M solution of ethylamine in THF (83 µl, 167 µmol), sodium triacetoxyborohydride (118 mg, 559 µmol) and acetic acid (83 µl, 167 µmol). The mixture was stirred at 60°C for 90 min. Further amounts of 2 M ethylamine solution (83 µl, 167 µmol) and sodium triacetoxyborohydride (71 mg, 335 µmol) were added, and stirring at 60°C was continued for another 2 h. After evaporation, the residue was dissolved in a 4 M solution of hydrogen chloride in 1,4-dioxane (3 ml) and stirred at rt overnight. The mixture was evaporated, and the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) and lyophilized from a 4 M solution of hydrogen chloride in 1,4-dioxane. Re-purification by preparative RP-HPLC (Sunfire C18, 20% acetonitrile/80% 0.02% aq. TFA) and re-lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 19 mg (29% of th.) of the title compound.

LC-MS (method 2): R_t = 0.56 min; MS (ESIpos): m/z = 466 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.14 (s, 1H), 7.56 (s, 1H), 7.45 (s, 1H), 7.01 (s, 1H), 4.45 (s, 4H), 4.04 (s, 3H), 3.45-3.32 (m, 4H), 3.18-3.05 (m, 4H), 2.99 (q, 2H), 2.51 (s, 3H), 1.10 (t, 3H) ppm.

Example 39

2-({[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f]-[1,2,4]triazin-6-yl]methyl}amino)ethanol trihydrochloride



A solution of Intermediate 25A (150 mg, 279 µmol) in THF (3 ml) was treated with 2-aminoethanol (84 µl, 1.39 mmol), sodium triacetoxyborohydride (296 mg, 1.39 mmol) and acetic acid (32 µl, 559 µmol). The mixture was stirred at 60°C for 2 h and then evaporated. The residue was dissolved in a 4 M solution of hydrogen chloride in 1,4-dioxane (1.87 ml) and stirred at rt for 2 h. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). Lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 140 mg (80% of th.) of the title compound.

LC-MS (method 2): R_t = 0.54 min; MS (ESIpos): m/z = 482 $(M+H)^+$

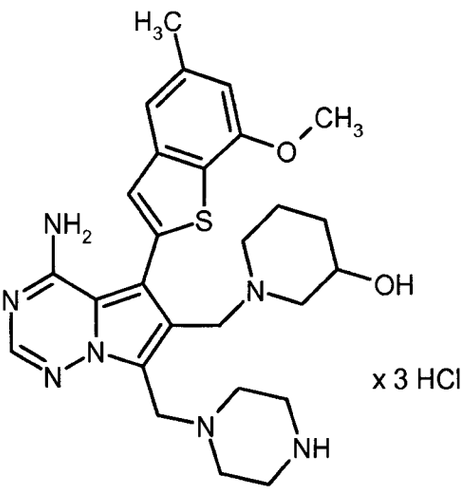
^{1}H-NMR (400 MHz, D_2O): δ = 8.15 (s, 1H), 7.56 (s, 1H), 7.45 (s, 1H), 7.00 (s, 1H), 4.47 (s, 2H), 4.37 (s, 2H), 4.04 (s, 3H), 3.79-3.71 (m, 2H), 3.42-3.34 (m, 4H), 3.19-3.12 (m, 2H), 3.06-2.97 (m, 4H), 2.51 (s, 3H) ppm.

General Procedure for reductive amination reactions with Intermediate 25A (GP1):

A 0.1 M solution of Intermediate 25A in THF was treated with 5 eq. of the respective amine component, 5 eq. of sodium triacetoxyborohydride and 2 eq. of acetic acid. The resulting mixture was stirred at 60°C for 2 h and then evaporated. A 0.15 M solution of the residue thus obtained in a 4 M solution of hydrogen chloride in 1,4-dioxane was stirred at rt for 1-2 h. After evaporation, the residue was purified as described below.

Example 40

rac-1-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methyl}piperidin-3-ol trihydrochloride



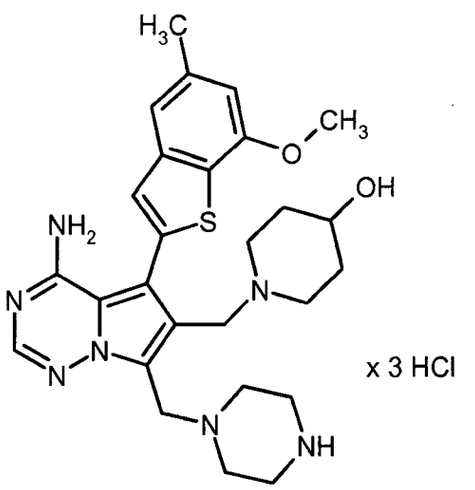
According to GP1, Intermediate 25A (150 mg, 279 µmol) was reacted with 3-hydroxypiperidine (141 mg, 1.39 mmol). Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA) and lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 178 mg (quant.) of the title compound.

LC-MS (method 2): R_t = 0.54 min; MS (ESIpos): m/z = 522 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.16 (s, 1H), 7.55 (s, 1H), 7.45 (s, 1H), 7.01 (s, 1H), 4.66-4.16 (m, 5H), 4.04 (s, 3H), 3.55-2.71 (m, 11H), 2.51 (s, 3H), 1.96-1.42 (m, 4H), 1.64-1.50 (m, 1H) ppm.

Example 41

1-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f]-[1,2,4]triazin-6-yl]methyl}piperidin-4-ol trihydrochloride



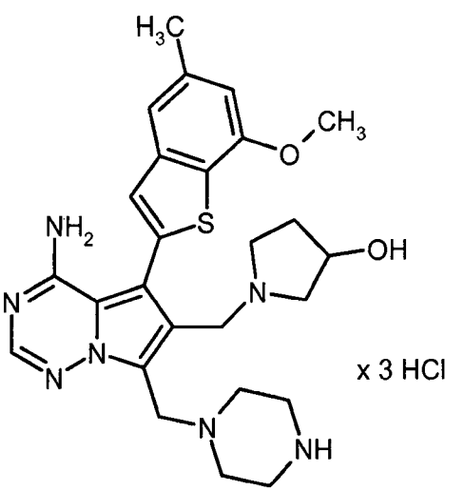
According to GP1, Intermediate 25A (150 mg, 279 µmol) was reacted with 4-hydroxypiperidine (141 mg, 1.39 mmol). Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA) and lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 162 mg (91% of th.) of the title compound.

LC-MS (method 4): R_t = 0.48 min; MS (ESIpos): m/z = 522 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.16 (s, 1H), 7.58 (br. s, 1H), 7.46 (s, 1H), 7.01 (s, 1H), 4.67-4.48 (m, 4H), 4.04 (s, 4H), 3.59-2.78 (m, 12H), 2.51 (s, 3H), 2.14-1.38 (m, 4H) ppm.

Example 42

rac-1-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methyl}pyrrolidin-3-ol trihydrochloride



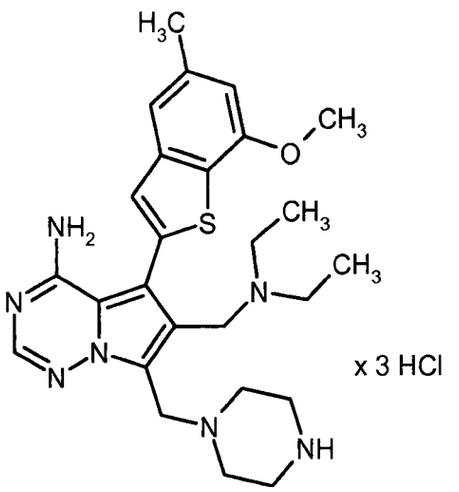
According to GP1, Intermediate 25A (150 mg, 279 µmol) was reacted with 3-hydroxypyrrolidine (113 µl, 1.39 mmol). Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA) and lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 148 mg (85% of th.) of the title compound.

LC-MS (method 4): R_t = 0.46 min; MS (ESIpos): m/z = 508 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.18 (s, 1H), 7.58 (s, 1H), 7.46 (s, 1H), 7.01 (s, 1H), 4.71-4.30 (m, 5H), 4.04 (s, 3H), 3.70-2.95 (m, 12H), 2.51 (s, 3H), 2.32-2.14 (m, 1H), 2.03-1.87 (m, 1H) ppm.

Example 43

6-[(Diethylamino)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride



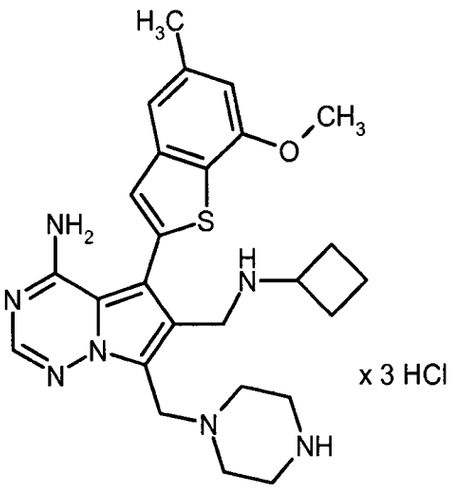
According to GP1, Intermediate 25A (150 mg, 279 µmol) was reacted with diethylamine (144 µl, 1.39 mmol). Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/ 0.1% aq. TFA) and lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 127 mg (69% of th.) of the title compound.

LC-MS (method 2): R_t = 0.55 min; MS (ESIpos): m/z = 494 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.19 (s, 1H), 7.61 (s, 1H), 7.47 (s, 1H), 7.01 (s, 1H), 4.59 (s, 2H), 4.51 (s, 2H), 4.04 (s, 3H), 3.47-3.35 (m, 4H), 3.29-3.00 (m, 8H), 2.51 (s, 3H), 1.07 (t, 6H) ppm.

Example 44

6-[(Cyclobutylamino)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-yl-methyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride



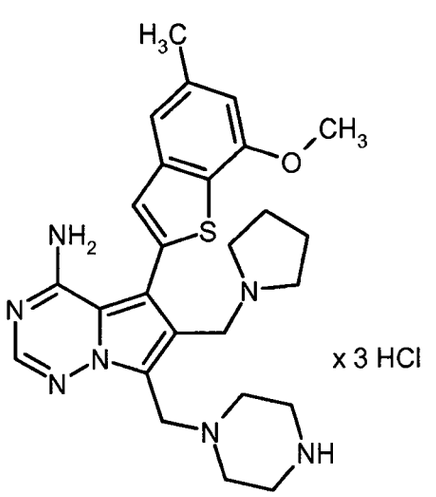
According to GP1, Intermediate 25A (150 mg, 279 µmol) was reacted with cyclobutylamine (119 µl, 1.39 mmol). Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA) and lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 127 mg (72% of th.) of the title compound.

LC-MS (method 2): R_t = 0.58 min; MS (ESIpos): m/z = 492 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.16 (s, 1H), 7.59 (s, 1H), 7.47 (s, 1H), 7.00 (s, 1H), 4.40 (s, 2H), 4.37 (s, 2H), 4.04 (s, 3H), 3.69-3.58 (m, 1H), 3.44-3.33 (m, 4H), 3.21-3.12 (m, 4H), 2.51 (s, 3H), 2.02-1.87 (m, 4H), 1.81-1.62 (m, 2H) ppm.

Example 45

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)-6-(pyrrolidin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride



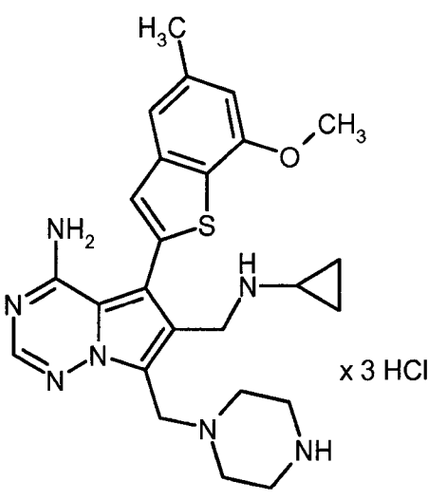
According to GP1, Intermediate 25A (150 mg, 279 µmol) was reacted with pyrrolidine (116 µl, 1.39 mmol). Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/ 0.1% aq. TFA) and lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 112 mg (64% of th.) of the title compound.

LC-MS (method 2): R_t = 0.54 min; MS (ESIpos): m/z = 492 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.19 (s, 1H), 7.60 (s, 1H), 7.46 (s, 1H), 7.01 (s, 1H), 4.70-4.61 (m, 4H), 4.04 (s, 3H), 3.55-3.40 (m, 6H), 3.35-3.26 (m, 4H), 3.02-2.87 (m, 2H), 2.51 (s, 3H), 1.97-1.83 (m, 4H) ppm.

Example 46

6-[(Cyclopropylamino)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-yl-methyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride



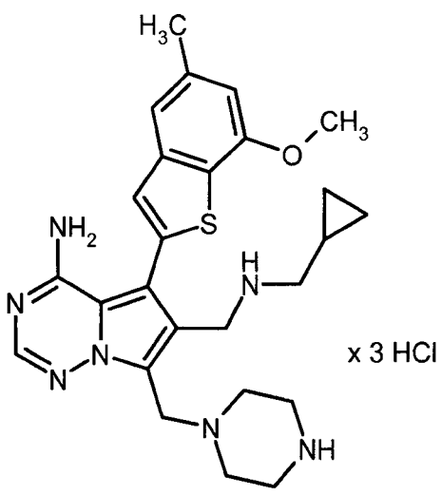
According to GP1, Intermediate 25A (200 mg, 372 µmol) was reacted with cyclopropylamine (129 µl, 1.86 mmol). Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA) and lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 140 mg (62% of th.) of the title compound.

LC-MS (method 5): R_t = 1.42 min; MS (ESIpos): m/z = 478 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.16 (s, 1H), 7.56 (s, 1H), 7.46 (s, 1H), 7.01 (s, 1H), 4.57 (s, 2H), 4.47 (s, 2H), 4.04 (s, 3H), 3.46-3.34 (m, 4H), 3.19-3.07 (m, 4H), 2.61-2.54 (m, 1H), 2.51 (s, 3H), 0.75-0.64 (m, 4H) ppm.

Example 47

6-{[(Cyclopropylmethyl)amino]methyl}-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride



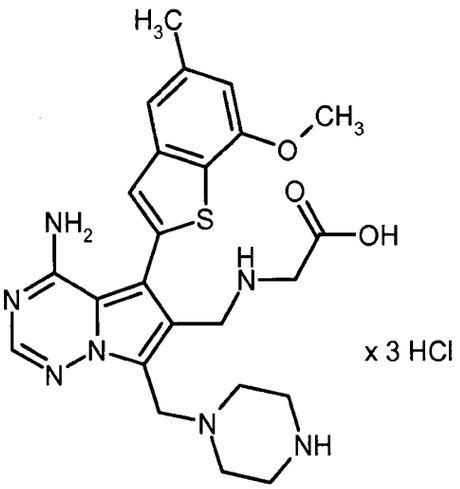
According to GP1, Intermediate 25A (200 mg, 372 µmol) was reacted with cyclopropylmethylamine (161 µl, 1.86 mmol). Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA) and lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 163 mg (69% of th.) of the title compound.

LC-MS (method 2): R_t = 0.60 min; MS (ESIpos): m/z = 492 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.14 (s, 1H), 7.57 (s, 1H), 7.45 (s, 1H), 7.00 (s, 1H), 4.50 (s, 2H), 4.44 (s, 2H), 4.04 (s, 3H), 3.42-3.34 (m, 4H), 3.16-3.07 (m, 4H), 2.86 (d, 2H), 2.50 (s, 3H), 0.89-0.76 (m, 1H), 0.55-0.45 (m, 2H), 0.23-0.14 (m, 2H) ppm.

Example 48

N-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f]-[1,2,4]triazin-6-yl]methyl}glycine trihydrochloride



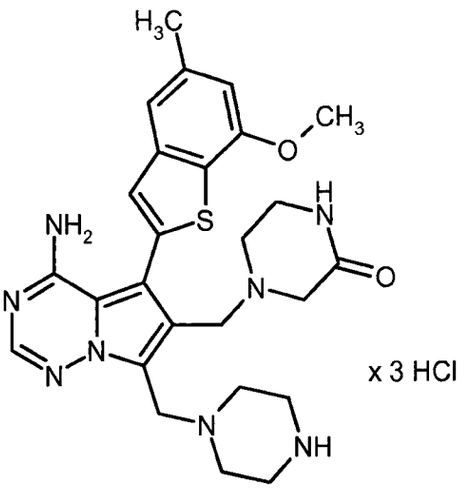
A solution of Intermediate 25A (161 mg, 300 µmol) in THF (3.2 ml) was treated with 2-aminoacetic acid (112 mg, 1.5 mmol), sodium triacetoxyborohydride (317 mg, 1.5 mmol) and acetic acid (34 µl, 600 µmol). The resulting mixture was stirred at 60°C for 2 h and then evaporated. The residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). The product thus obtained was dissolved in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) and stirred at rt for 1 h. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). Subsequent lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 18 mg (9% of th.) of the title compound.

LC-MS (method 2): R_t = 0.63 min; MS (ESIpos): m/z = 496 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.14 (s, 1H), 7.54 (s, 1H), 7.45 (s, 1H), 6.99 (s, 1H), 4.42 (s, 2H), 4.36 (s, 2H), 4.03 (s, 3H), 3.64 (s, 2H), 3.42-3.33 (m, 4H), 3.07-2.96 (m, 4H), 2.50 (s, 3H) ppm.

Example 49

4-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one trihydrochloride

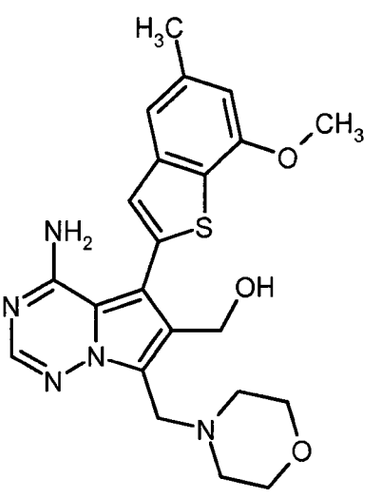


A solution of Intermediate 27A (220 mg, 354 µmol) in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) was stirred at rt for 2 h. Then, the mixture was evaporated leaving 235 mg of the crude product which was used in the next step without further purification.

LC-MS (method 4): R_t = 0.60 min; MS (ESIpos): m/z = 521 $(M+H)^+$.

Example 50

[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methanol



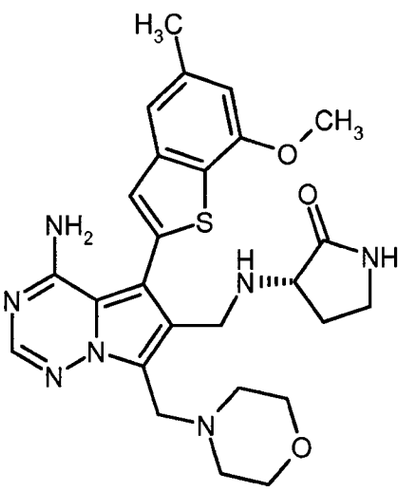
A solution of Intermediate 20A (500 mg, purity 87%, 1.28 mmol) and 4-methylenemorpholin-4-ium chloride (347 mg, 2.56 mmol) in DMF (28 ml) was stirred at 70°C for 1.5 h. The mixture was diluted with ethyl acetate and washed with sat. aq. sodium hydrogencarbonate solution and sat. aq.

sodium chloride solution. The organic layer was dried with magnesium sulfate and evaporated under reduced pressure yielding 710 mg (purity 78%, 99% of th.) of the title compound.

LC-MS (method 2): R_t = 0.65 min; MS (ESIpos): m/z = 440 $(M+H)^+$.

Example 51

(*3S*)-3-({[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)pyrrolidin-2-one



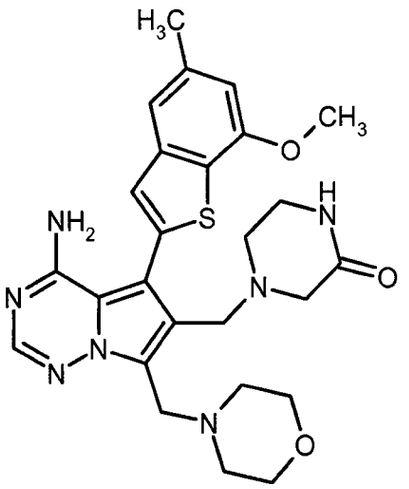
A solution of Intermediate 33A (65 mg, 149 µmol) in methanol (2 ml) was treated with (*3S*)-3-aminopyrrolidin-2-one (45 mg, 446 µmol), sodium cyanoborohydride (47 mg, 743 µmol) and acetic acid (26 µl, 446 µmol). After stirring at 60°C for 16 h, the resulting mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 20-40% acetonitrile/0.2% aq. TFA). The product thus obtained was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated yielding 49 mg (63% of th.) of the title compound.

LC-MS (method 2): R_t = 0.71 min; MS (ESIpos): m/z = 522 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.96 (s, 1H), 7.66 (s, 1H), 7.5-8.1 (br. s, 1H), 7.44 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 5.4-6.0 (br. s, 1H), 3.95 (s, 3H), 3.91 (s, 2H), 3.75 (d, 2H), 3.50-3.66 (m, 4H), 3.06-3.19 (m, 3H), 2.94-3.05 (m, 1H), 2.61 (t, 1H), 2.45 (t, 3H), 2.38-2.44 (m, 4H), 1.89-1.99 (m, 1H), 1.49-1.60 (m, 1H) ppm.

Example 52

4-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one



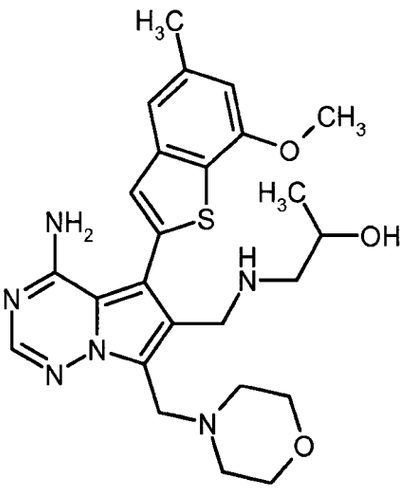
A solution of Intermediate 33A (65 mg, 149 µmol) in methanol (2 ml) was treated with 2-oxo-piperazine (45 mg, 446 µmol), sodium cyanoborohydride (47 mg, 743 µmol) and acetic acid (26 µl, 446 µmol). After stirring at 60°C for 16 h, the resulting mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 20-40% acetonitrile/0.2% aq. TFA). The product thus obtained was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated yielding 41 mg (53% of th.) of the title compound.

LC-MS (method 2): R_t = 0.70 min; MS (ESIpos): m/z = 522 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.97 (s, 1H), 7.67 (br. s, 1H), 7.55-8.05 (br. s, 1H), 7.38 (s, 1H), 7.30 (s, 1H), 6.84 (s, 1H), 5.29-5.88 (br. s, 1H), 3.95 (s, 3H), 3.92 (s, 2H), 3.58 (s, 2H), 3.51-3.56 (m, 4H), 3.00-3.06 (m, 2H), 2.85 (s, 2H), 2.45 (s, 3H), 2.43-2.48 (m, 5H) ppm.

Example 53

rac-1-({[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methyl}amino)propan-2-ol



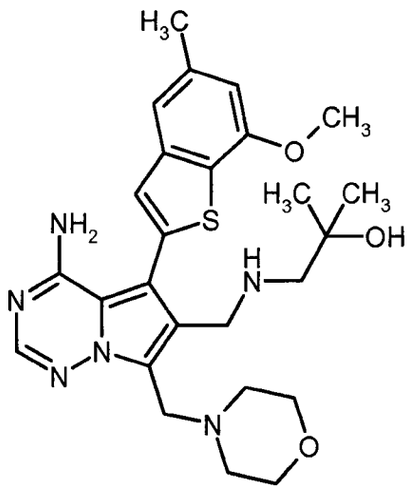
A solution of Intermediate 33A (64 mg, 146 µmol) in methanol (2 ml) was treated with *rac*-1-amino-propan-2-ol (33 mg, 439 µmol), sodium cyanoborohydride (46 mg, 731 µmol) and acetic acid (25 µl, 439 µmol). After stirring at 60°C for 16 h, the resulting mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 20-40% acetonitrile/0.2% aq. TFA). The product thus obtained was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated yielding 42 mg (57% of th.) of the title compound.

LC-MS (method 5): R_t = 1.63 min; MS (ESIpos): m/z = 497 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.96 (s, 1H), 7.47-7.92 (br. s, 1H), 7.39 (s, 1H), 7.30 (s, 1H), 6.84 (s, 1H), 5.36-5.92 (br. s, 1H), 4.36 (d, 1H), 3.95 (s, 3H), 3.90 (s, 2H), 3.64-3.75 (m, 2H), 3.49-3.61 (m, 5H), 2.45 (s, 3H), 2.39-2.47 (m, 4H), 2.31-2.38 (m, 2H), 0.97 (d, 3H) ppm.

Example 54

1-({[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methyl}amino)-2-methylpropan-2-ol



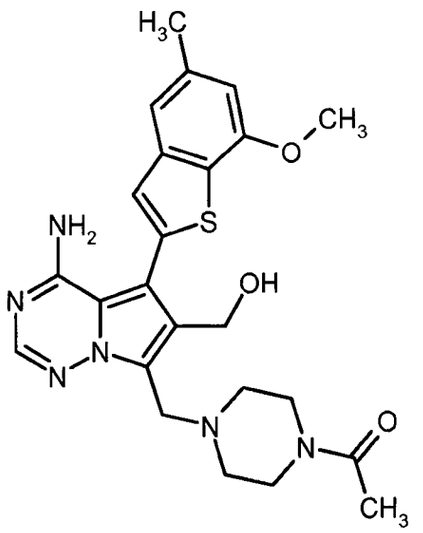
A solution of Intermediate 33A (80 mg, 183 µmol) in methanol (2 ml) was treated with 1-amino-2-methylpropan-2-ol (34 mg, 274 µmol), sodium cyanoborohydride (57 mg, 914 µmol) and acetic acid (21 µl, 366 µmol). After stirring at 60°C for 16 h, the resulting mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 20-40% acetonitrile/0.2% aq. TFA). The product thus obtained was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated yielding 29 mg (31% of th.) of the title compound.

LC-MS (method 2): R_t = 0.65 min; MS (ESIpos): m/z = 511 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.96 (s, 1H), 7.50-8.02 (br. s, 1H), 7.42 (s, 1H), 7.28 (s, 1H), 6.84 (s, 1H), 5.4-6.0 (br. s, 1H), 4.11 (s, 1H), 3.95 (s, 3H), 3.90 (s, 2H), 3.70 (d, 2H), 3.51-3.58 (m, 4H), 2.45 (s, 3H), 2.39-2.46 (m, 4H), 2.33 (d, 2H), 1.83-1.92 (m, 1H), 1.03 (s, 6H) ppm.

Example 55

1-(4-{[4-Amino-6-(hydroxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}piperazin-1-yl)ethanone

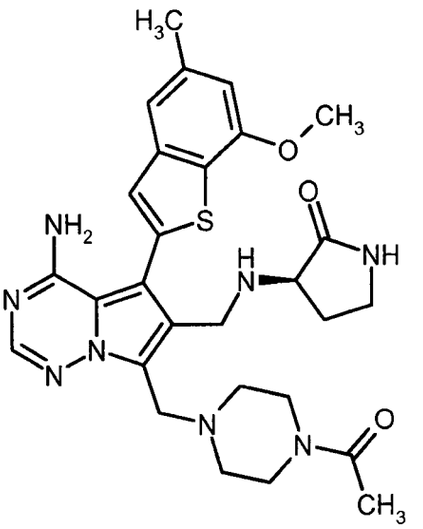


A solution of Intermediate 20A (345 mg, 1.01 mmol) in acetic acid (5 ml) was treated with 37% aq. formaldehyde solution (91 µl, 1.22 mmol) and 1-acetylpiperazine (160 mg, 1.22 mmol). The mixture was stirred at 60°C for 6 h and then evaporated. The residue was dissolved in a mixture of THF/1 M aq. lithium hydroxide solution (1:1, 10 ml) and stirred at rt for 2 h. The mixture was then combined with the reaction mixture of a 100 mg test run, and sat. aq. ammonium chloride solution was added. The mixture was extracted with ethyl acetate, and the organic phase was washed with sat. aq. sodium chloride solution, dried over magnesium sulfate and evaporated under reduced pressure yielding 678 mg (purity 87%, 94% of th.) of the title compound.

LC-MS (method 2): R_t = 0.71 min; MS (ESIpos): m/z = 481 $(M+H)^+$.

Example 56

(*3R*)-3-[({7-[(4-Acetylpiperazin-1-yl)methyl]-4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl}methyl)amino]pyrrolidin-2-one



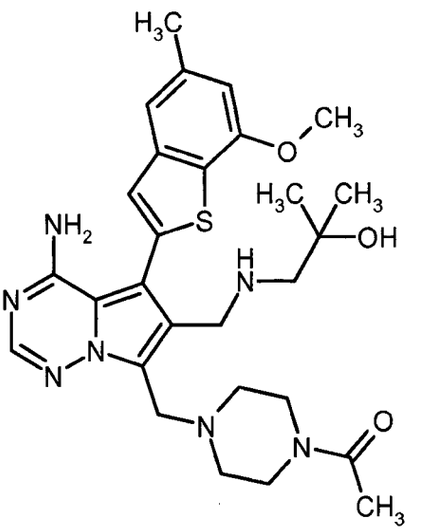
A solution of Intermediate 31A (80 mg, 167 µmol) in methanol (1.4 ml) was treated with (*3R*)-3-aminopyrrolidin-2-one (21 mg, 251 µmol), sodium cyanoborohydride (52 mg, 836 µmol) and acetic acid (19 µl, 334 µmol). After stirring at 60°C for 16 h, the resulting mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 20-40% acetonitrile/0.2% aq. TFA). The product thus obtained was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated yielding 46 mg (49% of th.) of the title compound.

LC-MS (method 2): R_t = 0.70 min; MS (ESIpos): m/z = 563 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.42 (s, 1H), 8.05 (s, 1H), 7.93-8.24 (br. s, 1H), 7.51 (s, 1H), 7.34 (s, 1H), 6.88 (s, 1H), 5.75-6.07 (br. s, 1H), 4.21-4.37 (m, 2H), 4.19 (s, 2H), 4.10 (t, 1H), 3.96 (s, 3H), 3.56-3.66 (m, 2H), 3.44-3.54 (m, 4H), 3.11-3.27 (m, 4H), 2.47 (s, 4H), 2.16-2.25 (m, 1H), 2.00 (s, 3H), 1.86-1.95 (m, 1H) ppm.

Example 57

1-(4-{[4-Amino-6-{[(2-hydroxy-2-methylpropyl)amino]methyl}-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-1-yl)ethanone



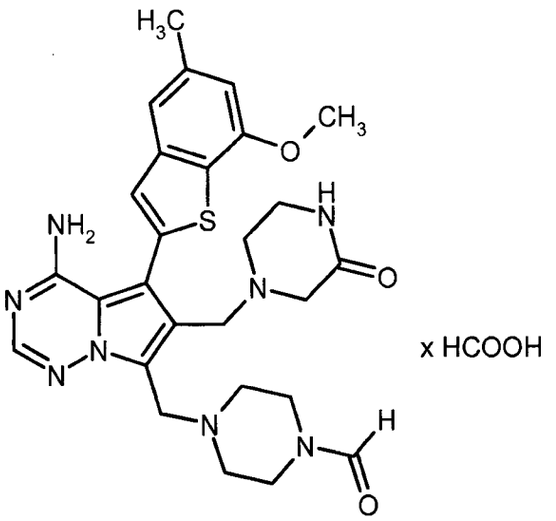
A solution of Intermediate 31A (80 mg, 183 µmol) in methanol (2 ml) was treated with 1-amino-2-methylpropan-2-ol (31 mg, 251 µmol), sodium cyanoborohydride (53 mg, 836 µmol) and acetic acid (19 µl, 334 µmol). After stirring at 60°C for 16 h, the resulting mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 20-40% acetonitrile/0.2% aq. TFA). The product thus obtained was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated yielding 29 mg (31% of th.) of the title compound.

LC-MS (method 2): R_t = 0.71 min; MS (ESIpos): m/z = 552 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.96 (s, 1H), 7.59-8.02 (br. s, 1H), 7.42 (s, 1H), 7.28 (s, 1H), 6.84 (s, 1H), 5.45-5.93 (br. s, 1H), 4.13 (br. s, 1H), 3.95 (s, 3H), 3.93 (s, 2H), 3.71 (s, 2H), 3.37-3.44 (m, 4H), 2.45 (s, 3H), 2.32-2.43 (m, 6H), 1.97 (s, 3H), 1.03 (s, 6H) ppm.

Example 58

4-({4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-6-[(3-oxopiperazin-1-yl)methyl]pyrrolo-[2,1-f][1,2,4]triazin-7-yl}methyl)piperazine-1-carbaldehyde formiate



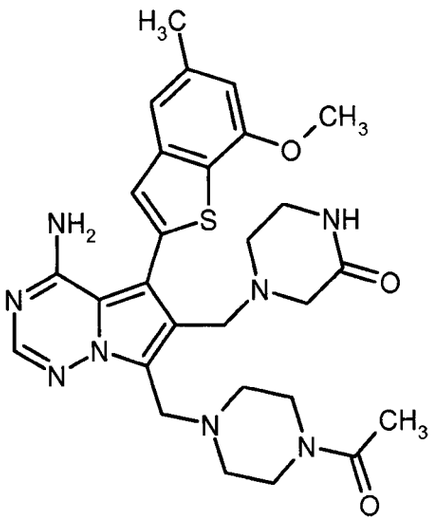
Acetic acid anhydride (498 µl, 5.17 mmol) and formic acid (237 µl, 6.28 mmol) were stirred first 2 h at 50°C and then overnight at rt. Subsequently, the mixture was diluted with dichloromethane (5.1 ml), and 1.16 ml of this solution were added to a solution of Example 49 (233 mg, 370 µmol) in pyridine (89 µl). After stirring at rt for 2 h, the mixture was diluted with methanol and then evaporated. The residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) affording 77 mg (35% of th.) of title compound.

LC-MS (method 4): R_t = 0.62 min; MS (ESIpos): m/z = 549 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.14 (s, 1H), 7.97 (s, 2H), 7.67 (s, 1H), 7.38 (s, 1H), 7.30 (s, 1H), 6.84 (s, 1H), 3.96 (s, 2H), 3.95 (s, 3H), 3.58 (s, 2H), 3.04 (br. t, 2H), 2.86 (s, 2H), 2.45 (s, 3H), 2.42 (br. t, 2H) ppm.

Example 59

4-({7-[(4-Acetylpiperazin-1-yl)methyl]-4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-pyrrolo[2,1-f][1,2,4]triazin-6-yl}methyl)piperazin-2-one



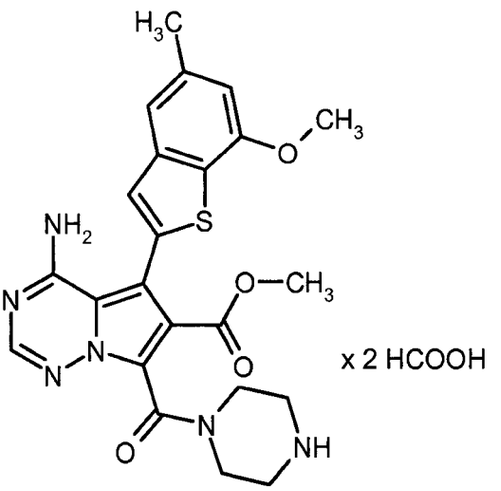
A suspension of Example 49 (310 mg, 522 µmol) in dichloromethane/THF (2.5:1, 9.64 ml) was treated with sodium carbonate (442 mg, 4.17 mmol) and stirred at rt for 30 min. Acetyl chloride (74 µl, 1.04 mmmol) was added, and the resulting mixture was stirred at rt for 2 h. After quenching with methanol, the mixture was evaporated, and the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) affording 133 mg (45% of th.) of the title compound.

LC-MS (method 2): R_t = 0.69 min; MS (ESIpos): m/z = 563 $(M+H)^+$

^{1}H-NMR (400 MHz, methanol-d_4): δ = 7.89 (s, 1H), 7.30 (s, 1H), 7.28 (s, 1H), 6.79 (s, 1H), 4.13 (s, 2H), 3.98 (s, 3H), 3.74 (s, 2H), 3.59 (t, 2H), 3.54 (t, 2H), 3.18 (t, 2H), 3.02 (s, 2H), 2.68-2.55 (m, 6H), 2.48 (s, 3H), 2.08 (s, 3H) ppm.

Example 60

Methyl 4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylcarbonyl)pyrrolo-[2,1-f][1,2,4]triazine-6-carboxylate bis(formiate)



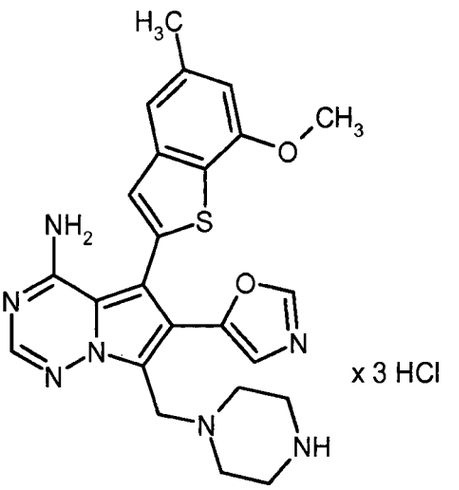
To a solution of Intermediate 28A (15 mg, 26 µmol) in a THF/methanol mixture (5:1, 180 µl), cooled to 0°C, was added (trimethylsilyl)diazomethane (2 M solution in hexane, 15 µl, 32 µmol). The resulting mixture was slowly warmed to rt over 30 min and then evaporated. The residue was dissolved in a 4 M solution of hydrogen chloride in 1,4-dioxane (0.5 ml) and stirred at rt for 1 h. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) affording 4.8 mg (35% of th.) of the title compound.

LC-MS (method 2): R_t = 0.66 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.17 (s, 2H), 8.38-8.23 (br. s, 1H), 8.04 (s, 1H), 7.43 (s, 1H), 7.31 (s, 1H), 6.86 (s, 1H), 5.71-5.58 (br. s, 1H), 3.96 (s, 3H), 3.60 (s, 3H, overlap with water peak), 2.46 (s, 3H) ppm.

Example 61

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-6-(1,3-oxazol-5-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-4-amine trihydrochloride



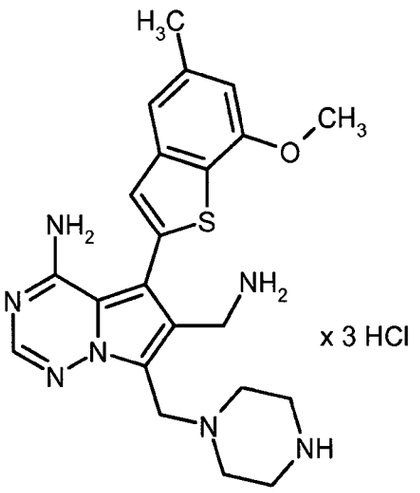
A solution of Intermediate 25A (100 mg, 0.19 mmol) in methanol (3.33 ml) was treated with (4-toluenesulfonyl)methylisocyanide (36 mg, 0.19 mmol) and potassium carbonate (25 mg, 186 µmol). The mixture was refluxed for 6 h. It was then combined with the reactions mixtures from three 30 mg test runs and evaporated. The residue was dissolved in a 4 M solution of hydrogen chloride in 1,4-dioxane (10 ml) and stirred at rt for 2 h. After evaporation, the residue was purified by two-fold preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). Further purification by column chromatography on silica gel (dichloromethane/methanol 5:1 with 0.5% aq. ammonia) and lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 75 mg (34% of th.) of the title compound.

LC-MS (method 4): R_t = 0.69 min; MS (ESIpos): m/z = 476 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.40 (s, 1H), 8.20 (s, 1H), 7.46 (s, 1H), 7.35 (s, 1H), 6.96 (s, 1H), 6.89 (s, 1H), 3.95 (s, 3H), 2.46 (s, 3H) ppm.

Example 62

6-(Aminomethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-4-amine trihydrochloride



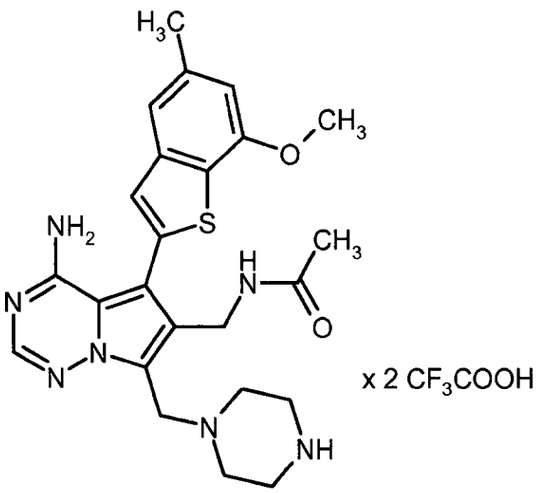
A suspension of Intermediate 29A (76 mg, 134 µmol) and 10% Pd/C (60 mg) in a 0.5 M solution of hydrogen chloride in methanol (20 ml) was stirred at rt for 3 h under 1 atm of hydrogen. The mixture was then filtered through kieselguhr, the filtrate was evaporated, and the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). The product thus obtained was lyophilized from a 4 M solution of hydrogen chloride in 1,4-dioxane affording 34 mg (46% of th.) of the title compound.

LC-MS (method 2): R_t = 0.55 min; MS (ESIpos): m/z = 438 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.24 (br. s, 3H), 8.12 (s, 1H), 7.52 (s, 1H), 7.34 (s, 1H), 6.89 (s, 1H), 3.96 (s, 3H), 3.76-3.63 (m, 1H), 3.52-3.42 (m, 1H), 2.47 (s, 3H) ppm.

Example 63

N-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methyl}acetamide bis(trifluoroacetate)



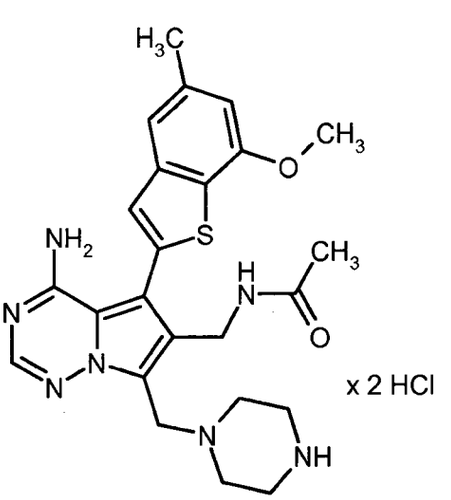
A solution of Intermediate 30A (210 mg, 362 µmol) in dichloromethane (26 ml) was treated with trifluoroacetic acid (5.2 ml) and stirred at rt for 1 h. After evaporation at rt, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA) affording 163 mg (63% of th.) of the title compound.

LC-MS (method 3): R_t = 2.42 min; MS (ESIpos): m/z = 480 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 9.00-8.75 (br. s, 1H), 8.30-8.16 (br. s, 1H), 8.08 (s, 1H), 7.38 (s, 1H), 7.33 (s, 1H), 6.87 (s, 1H), 4.32 (br. d, 2H), 3.96 (s, 3H), 3.40-2.98 (m, 8H), 2.46 (s, 3H), 1.77 (s, 3H) ppm.

Example 64

N-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methyl}acetamide dihydrochloride



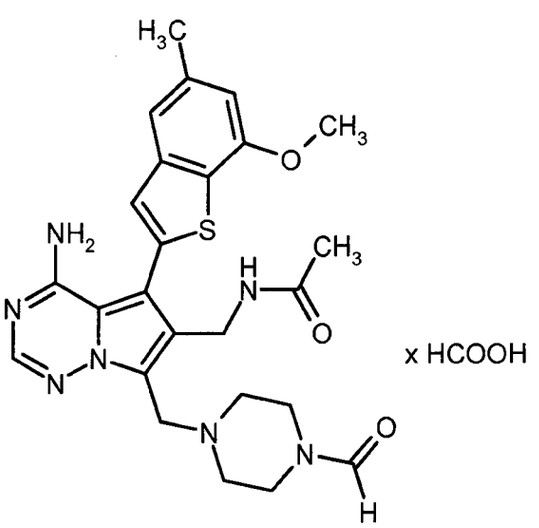
A solution of Intermediate 30A (80 mg, 0.14 mmol) in dichloromethane (10 ml) and trifluoroacetic acid (2 ml) was stirred at rt for 1 h and then evaporated. Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) and lyophilization from a mixture of methanol and 4 M solution of hydrogen chloride in 1,4-dioxane afforded 39 mg (50% of th.) of the title compound.

LC-MS (method 5): R_t = 1.56 min; MS (ESIpos): m/z = 480 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.12 (s, 1H), 7.38 (s, 1H), 7.33 (s, 1H), 6.87 (s, 1H), 4.37 (br. d, 2H), 3.96 (s, 3H), 3.85-3.20 (m, 8H, overlap with water peak), 2.46 (s, 3H), 1.76 (s, 3H) ppm.

Example 65

N-({4-Amino-7-[(4-formylpiperazin-1-yl)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-pyrrolo[2,1-f][1,2,4]triazin-6-yl}methyl)acetamide formiate



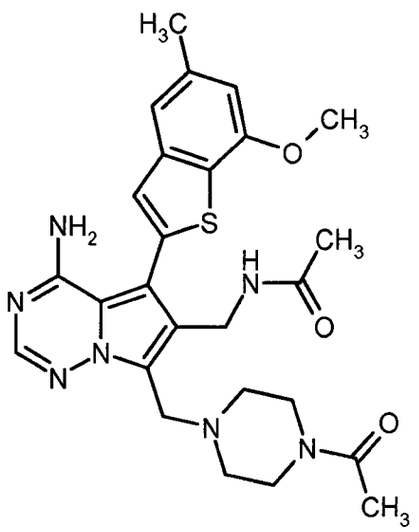
Acetic acid anhydride (304 µl, 3.16 mmol) and formic acid (145 µl, 3.16 mmol) were stirred first 2 h at 50°C and then overnight at rt. Subsequently, the mixture was diluted with dichloromethane (3.1 ml), and 663 µl of this solution were added to a solution of Example 63 (160 mg, 226 µmol) in pyridine (54 µl). The mixture was stirred at rt for 2 h, then diluted with methanol (1 ml), and stirring was continued at 40°C for another 2 h. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) affording 74 mg (61% of th.) of title compound.

LC-MS (method 4): R_t = 0.65 min; MS (ESIpos): m/z = 508 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.13 (s, 1H), 8.06-7.89 (m, 3H), 7.38 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 4.28 (d, 2H), 4.01-3.88 (m, 5H), 2.47-2.34 (m, 7H), 1.75 (s, 3H) ppm.

Example 66

N-({7-[(4-Acetylpiperazin-1-yl)methyl]-4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-pyrrolo[2,1-f][1,2,4]triazin-6-yl}methyl)acetamide



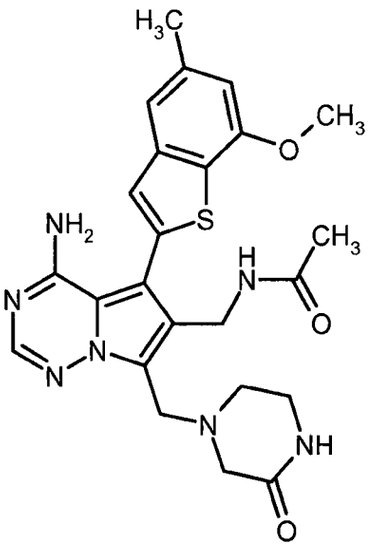
A solution of Example 63 (110 mg, 229 µmol) and acetyl chloride (32 µl, 458 µmol) in THF/dichloromethane (1:2, 3 ml) was treated with sodium carbonate (194 mg, 1.83 mmol) and stirred at rt overnight. Then, the mixture was diluted with methanol (2 ml) and water (1 ml) and stirred at rt for 1 h. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid). Lyophilization from 1,4-dioxane and re-purification by column chromatography on silica gel (dichloromethane/methanol 50:1 → 100% methanol) afforded 35 mg (28% of th.) of the title compound.

LC-MS (method 2): R_t = 0.70 min; MS (ESIpos): m/z = 522 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.04-7.98 (m, 2H), 7.38 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 4.27 (d, 2H), 3.95 (s, 3H), 3.91 (s, 2H), 3.44-3.36 (m, 4H), 2.48-2.35 (m, 7H), 1.98 (s, 3H), 1.75 (s, 3H) ppm.

Example 67

N-({4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-[(3-oxopiperazin-1-yl)methyl]-pyrrolo[2,1-f][1,2,4]triazin-6-yl}methyl)acetamide



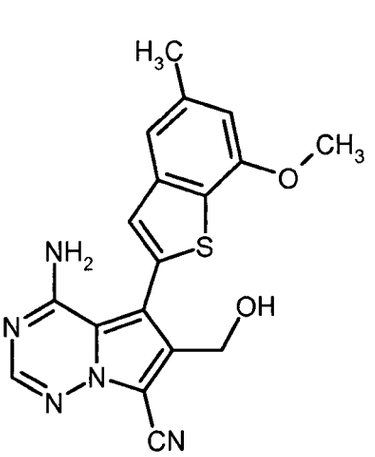
A suspension of Intermediate 32A (35 mg, 73 µmol) in methanol (4.1 ml) was treated with acetic anhydride (13 µl, 146 µmol) and 10% Pd/C (41 mg) and stirred at rt for 1 h under 1 atm of hydrogen. Filtration over kieselguhr and evaporation of the filtrate afforded 30 mg (79% of th.) of the title compound.

LC-MS (method 5): R_t = 1.65 min; MS (ESIpos): m/z = 494 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.99 (s, 2H), 7.75 (br. s, 1H), 7.39 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 4.27 (s, 1H), 4.26 (s, 1H), 3.95 (s, 5H), 3.19-3.08 (m, 2H), 3.05-2.96 (m, 2H), 2.66-2.57 (m, 2H), 2.45 (s, 3H), 1.72 (s, 3H) ppm.

Example 68

4-Amino-6-(hydroxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazine-7-carbonitrile



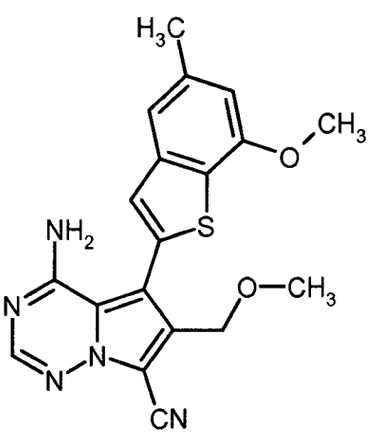
A solution of Intermediate 38A (1 g, 2.08 mmol) in THF (10 ml) was treated with a 1 M solution of tetra-*n*-butylammonium fluoride in THF (12 ml, 12 mmol). The mixture was stirred at rt overnight and then evaporated. The residue was taken up in water and extracted three times with ethyl acetate. The combined organic phases were dried over magnesium sulfate and evaporated. The residue was triturated in *tert*-butyl methyl ether, and the solid was filtered off affording 680 mg (78% of th.) of the title compound.

LC-MS (method 2): R_t = 0.95 min; MS (ESIpos): m/z = 366 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.61-8.29 (br. s, 1H), 8.18 (s, 1H), 7.43 (s, 1H), 7.32 (s, 1H), 6.87 (s, 1H), 6.32-6.03 (br. s, 1H), 5.46 (t, 1H), 4.55 (d, 2H), 3.96 (s, 3H), 2.45 (s, 3H) ppm.

Example 69

4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazine-7-carbonitrile



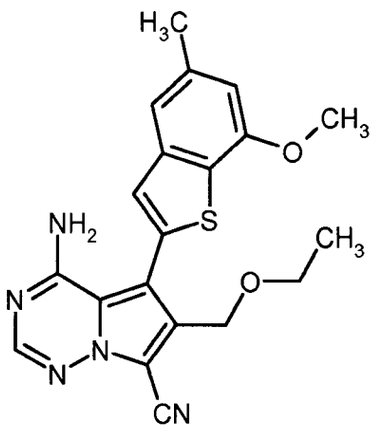
A solution of Example 68 (60 mg, 164 µmol) in dichloromethane (5 ml) was treated with thionyl chloride (18 µl, 246 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in methanol (2 ml) and treated with DIPEA (57 µl, 328 µmol). The mixture was stirred first 2 h at 60°C, then refluxed overnight and finally heated to 150°C for 30 min in a microwave device. After this, the mixture was evaporated, and the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). The product thus obtained was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated affording 18 mg (28% of th.) of the title compound.

LC-MS (method 4): R_t = 1.12 min; MS (ESIpos): m/z = 379 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.61-8.40 (br. s, 1H), 8.21 (s, 1H), 7.42 (s, 1H), 7.33 (s, 1H), 6.87 (s, 1H), 6.34-6.09 (br. s, 1H), 4.47 (s, 2H), 3.96 (s, 3H), 3.26 (s, 3H), 2.45 (s, 3H) ppm.

Example 70

4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazine-7-carbonitrile



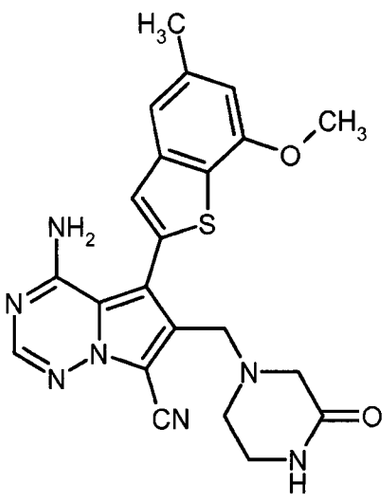
A solution of Example 68 (60 mg, 164 µmol) in dichloromethane (5 ml) was treated with thionyl chloride (18 µl, 246 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in ethanol (2 ml) and treated with DIPEA (57 µl, 328 µmol). The mixture was stirred at 60°C overnight and then heated to 150°C for 30 min in a microwave device. After this, the mixture was evaporated, and the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). The product thus obtained was dissolved in ethanol (2 ml) and again heated to 150°C for 30 min in the microwave oven. DIPEA (57 µl, 328 µmol) was added, and heating to 150°C in the microwave oven was continued for further 30 min. After evaporation, the residue was purified by column chromatography on silica gel (dichloromethane/ methanol 95:5) affording 16 mg (23% of th.) of the title compound.

LC-MS (method 2): R_t = 1.18 min; MS (ESIpos): m/z = 393 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.61-8.38 (br. s, 1H), 8.20 (s, 1H), 7.42 (s, 1H), 7.33 (s, 1H), 6.87 (s, 1H), 6.33-6.08 (br. s, 1H), 4.51 (s, 2H), 3.96 (s, 3H), 3.45 (q, 2H), 2.45 (s, 3H), 1.10 (t, 3H) ppm.

Example 71

4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-6-[(3-oxopiperazin-1-yl)methyl]pyrrolo[2,1-f][1,2,4]triazine-7-carbonitrile



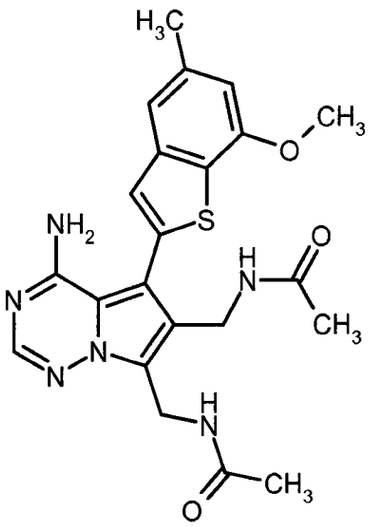
A solution of Intermediate 39A (20 mg, 55 µmol) in THF (0.73 ml) was treated with acetic acid (6 µl, 110 µmol), 2-oxopiperazine (27 mg, 275 µmol) and sodium triacetoxyborohydride (58 mg, 275 µmol). After stirring at rt for 3 h, further amounts of THF (1 ml), acetic acid (6 µl, 110 µmol), 2-oxopiperazine (27 mg, 275 µmol) and sodium triacetoxyborohydride (58 mg, 275 µmol) were added, and stirring at rt was continued overnight. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). The product thus obtained was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated affording 13 mg (52% of th.) of the title compound.

LC-MS (method 2): R_t = 0.86 min; MS (ESIpos): m/z = 447 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.60-8.31 (br. s, 1H), 8.19 (s, 1H), 7.74 (s, 1H), 7.44 (s, 1H), 7.33 (s, 1H), 6.87 (s, 1H), 6.25-5.98 (br. s, 1H), 3.96 (s, 3H), 3.62 (s, 2H), 3.13-3.07 (m, 2H), 2.91 (s, 2H), 2.45 (s, 3H) ppm.

Example 72

N,N'-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazine-6,7-diyl]bis(methylene)}diacetamide



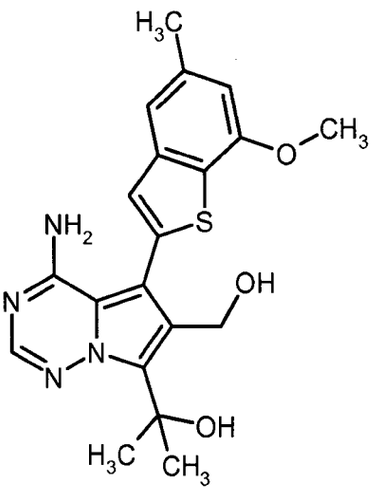
A suspension of Intermediate 40A (crude, 85 mg), 10% Pd/C (115 mg) and acetic anhydride (40 µl, 435 µmol) in methanol (12 ml) was stirred at rt under 1 atm of hydrogen. After 4 h, further amounts of 10% Pd/C (115 mg) and acetic anhydride (40 µl, 435 µmol) were added, and stirring at rt under 1 atm of hydrogen was continued for 2 h. The resulting mixture was filtered through kieselguhr, the filtrate was evaporated, and the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). The product thus obtained was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated affording 18 mg (18% of th.) of the title compound.

LC-MS (method 2): R_t = 0.73 min; MS (ESIpos): m/z = 452 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.29 (br. t, 1H), 8.04 (br. t, 1H), 8.00 (s, 1H), 7.34 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 4.58 (d, 2H), 4.26 (d, 2H), 3.95 (s, 3H), 2.45 (s, 3H), 1.81 (s, 3H), 1.74 (s, 3H) ppm.

Example 73

2-[4-Amino-6-(hydroxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-7-yl]propan-2-ol



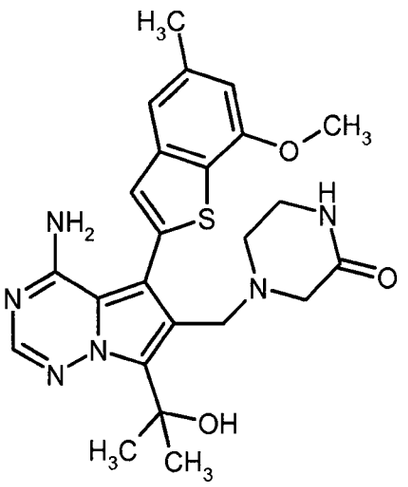
A flask containing a suspension of Intermediate 43A (180 mg, 598 µmol), Intermediate 6A (299 mg, 897 µmol) and caesium fluoride (454 mg, 2.99 mmol) in THF/water (10:1, 11 ml) was degassed under reduced pressure and then refilled with argon. 4-(Di-*tert*-butylphosphino)-*N*,*N*-dimethylaniline-dichloropalladium (2:1; 13 mg, 18 µmol) was added. The resulting mixture was degassed again and stirred under argon at 50°C for 16 h. After this, the reaction mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 30-50% acetonitrile/0.2% aq. TFA). The product fractions were diluted with a 7 M solution of ammonia in methanol and then concentrated under reduced pressure. The precipitate was filtered off, washed with water and dried *in vacuo* yielding 99 mg (42% of th.) of the title compound.

LC-MS (method 2): R_t = 0.89 min; MS (ESIpos): m/z = 399 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.96 (s, 1H), 7.51-8.02 (br. s, 1H), 7.37 (s, 1H), 7.31 (s, 1H), 6.86 (s, 1H), 5.99 (s, 1H), 5.23-5.82 (br. s, 1H), 5.04 (t, 1H), 4.53 (d, 2H), 3.96 (s, 3H), 2.45 (s, 3H), 1.73 (s, 6H) ppm.

Example 74

4-{[4-Amino-7-(2-hydroxypropan-2-yl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one



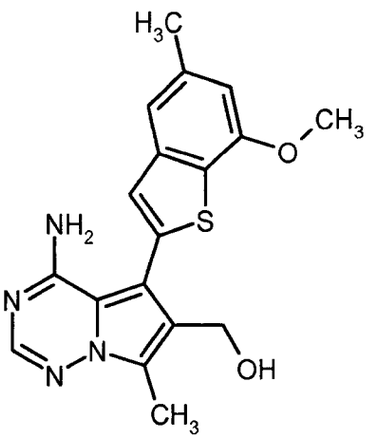
A solution of Intermediate 44A (50 mg, 73% purity, 92 µmol) in methanol (4 ml) was treated with 2-oxopiperazine (28 mg, 276 µmol), sodium cyanoborohydride (23 mg, 368 µmol) and acetic acid (21 µl, 368 µmol). The mixture was stirred first 18 h at 60°C and then 3 days at rt. After this, the mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 20-40% acetonitrile/0.2% aq. TFA). The product fractions were diluted with a 7 M solution of ammonia in methanol and evaporated under reduced pressure. The residue was dissolved in ethyl acetate and washed with water. The organic phase was dried with sodium sulfate and concentrated under reduced pressure. The residue was dissolved in 1,4-dioxane and lyophilized yielding 24 mg (52% of th.) of the title compound.

LC-MS (method 5): R_t = 1.85 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.99 (s, 1H), 7.73-8.01 (br. s, 1H), 7.41 (s, 1H), 7.33 (s, 1H), 6.87 (s, 1H), 5.2-5.7 (br. s, 1H), 3.95 (s, 3H), 3.57 (s, 2H), 3.14 (br. s, 2H), 2.60 (br. s, 4H), 2.46 (s, 3H), 1.70 (br. s, 6H) ppm.

Example 75

[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]-methanol



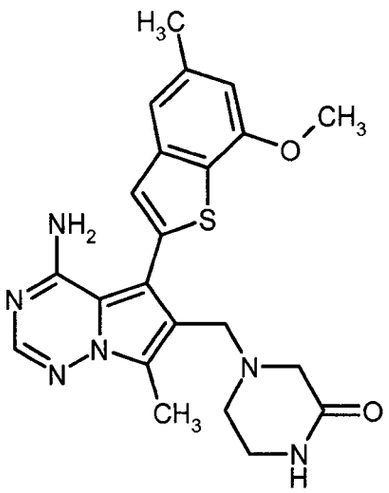
Under an argon atmosphere, a flask was charged with 165 mg (0.64 mmol) of Intermediate 53A, 143 mg (0.64 mmol) of Intermediate 5A, 25 mg (0.03 mmol) (2'-aminobiphenyl-2-yl)(chloro)palladium-dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (1:1; see S. L. Buchwald *et al.*, *J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)) and 409 mg (1.93 mmol) potassium phosphate. Then, 7 ml of a degassed mixture of 1,4-dioxane and water (5:1) were added, and the solution was stirred at 70°C for 1 h. Another portion of Intermediate 5A (142 mg, 0.64 mmol) and of (2'-aminobiphenyl-2-yl)(chloro)palladium-dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (10 mg, 0.012 mmol) were added, and stirring was continued for 1 h. After this, the reaction mixture was partially evaporated under reduced pressure, water was added, and the mixture was extracted with ethyl acetate. The combined organic phases were evaporated under reduced pressure, and the residue was triturated with acetonitrile. The precipitate was filtered off and dried *in vacuo* yielding 180 mg (92% purity by LC-MS, 73% of th.) of the title compound. From the filtrate a second batch (41 mg, 18% of th.) was obtained by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid). Total yield: 91% of th.

LC-MS (method 5): R_t = 1.92 min; MS (ESIpos): m/z = 355 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.95 (s, 1H), 7.35 (s, 1H), 7.30 (s, 1H), 6.83 (s, 1H), 4.82 (t, 1H), 4.44 (d, 2H), 3.95 (s, 3H), 2.45 (s, 3H) ppm.

Example 76

4-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one



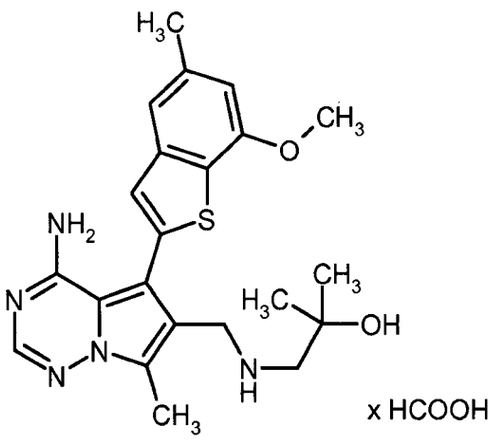
A suspension of 55 mg (0.16 mmol) of Intermediate 54A in THF (1.5 ml) was treated with 78 mg (0.78 mmol) piperazin-2-one, 18 µl (0.31 mmol) acetic acid and 166 mg (0.78 mmol) triacetoxyborohydride. The mixture was stirred at ambient temperature overnight. Then, 1.5 ml water were added, and most of the THF solvent was evaporated under reduced pressure. The remaining mixture was diluted with more water, and the precipitated solid was filtered off and dried (35 mg). This material was further purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid). The product fractions were adjusted to pH 9 with solid potassium carbonate and partially concentrated under reduced pressure. The precipitated solid was filtered off and dried at 45°C *in vacuo* to afford 16 mg (24% of th.) of the title compound.

LC-MS (method 5): R_t = 1.74 min; MS (ESIpos): m/z = 437 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.95 (s, 1H), 7.66 (br. s, 1H), 7.35 (s, 1H), 7.30 (s, 1H), 6.83 (s, 1H), 3.95 (s, 3H), 3.50 (s, 2H), 3.05 (m, 2H), 2.84 (s, 2H), 2.45 (m, 5H) ppm.

Example 77

1-({[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)-2-methylpropan-2-ol formiate



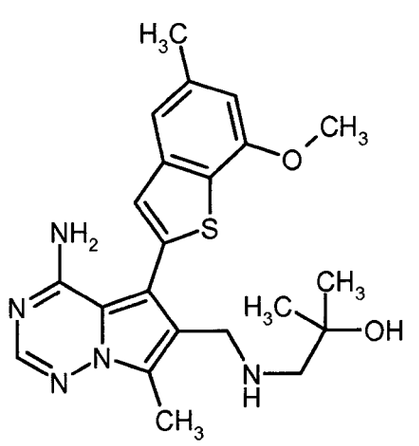
A suspension of 55 mg (0.16 mmol) of Intermediate 54A in THF (1.5 ml) was treated with 98 mg (0.78 mmol) 1-amino-2-methylpropan-2-ol hydrochloride, 39 mg (0.47 mmol) sodium acetate and 166 mg (0.78 mmol) sodium triacetoxyborohydride. The mixture was stirred at ambient temperature overnight. Then, 1.5 ml water were added, and the mixture was evaporated under reduced pressure. The residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) to afford 38 mg (52% of th.) of the title compound.

LC-MS (method 5): R_t = 1.68 min; MS (ESIpos): m/z = 426 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.19 (s, 1H), 7.94 (s, 1H), 7.38 (s, 1H), 7.29 (s, 1H), 6.84 (s, 1H), 3.95 (s, 3H), 2.45 (s, 3H), 2.34 (s, 2H), 1.02 (s, 6H) ppm.

Example 78

1-({[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)-2-methylpropan-2-ol



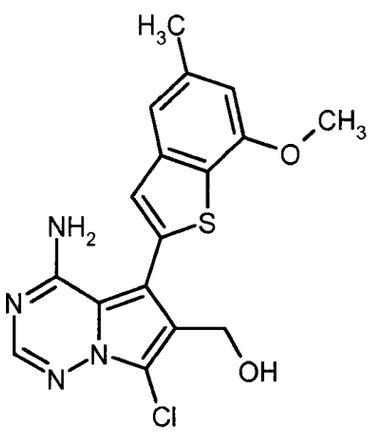
A solution of 29 mg (0.06 mmol) of Example 77 in 3 ml of methanol was run through a Strato-spheres SPE PL-HCO_3 MP-resin cartridge, preconditioned with 2 ml of methanol. The cartridge was washed with 4 ml of methanol, and the eluate was evaporated to afford 21.5 mg (82% of th.) of the title compound.

LC-MS (method 4): R_t = 0.68 min; MS (ESIpos): m/z = 426 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.94 (s, 1H), 7.37 (s, 1H), 7.28 (s, 1H), 6.83 (s, 1H), 4.07 (s, 1H), 3.95 (s, 3H), 3.63-3.75 (m, 2H), 2.45 (s, 3H), 2.32 (m, 3H), 1.42-1.56 (m, 1H), 1.02 (s, 6H) ppm.

Example 79

[4-Amino-7-chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]-methanol



A solution of Intermediate 48A (117 mg, 0.24 mmol) in 5 ml THF was treated with 5 ml conc. hydrochloric acid and stirred at ambient temperature overnight. Then, 12 ml of 5 M aq. sodium hydroxide solution as well as ethyl acetate were added, the layers were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic phases were washed with sat. aq. sodium chloride solution, dried and evaporated. The residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) to afford 30 mg (34% of th.) of the title compound.

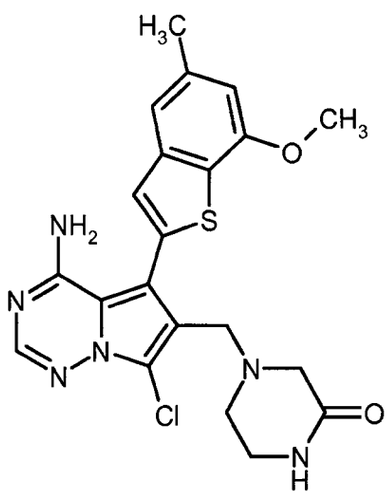
LC-MS (method 2): R_t = 0.90 min; MS (ESIpos): m/z = 375 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.04 (s, 1H), 7.43 (s, 1H), 7.32 (s, 1H), 6.85 (s, 1H), 5.02 (t, 1H), 4.43 (d, 2H), 3.96 (s, 3H), 2.45 (s, 3H) ppm.

9.2 mg (10% of th.) of 7-chloro-6-(chloromethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-pyrrolo[2,1-f][1,2,4]triazin-4-amine were isolated as a by-product (*cf.* Intermediate 50A).

Example 80

4-{[4-Amino-7-chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one



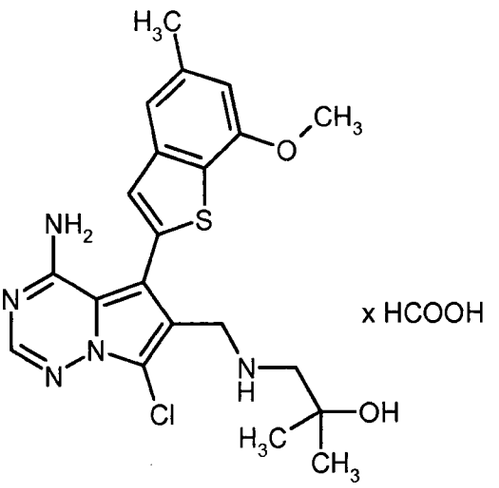
The title compound was prepared according to the procedure of Example 76 starting from 40 mg (0.11 mmol) of Intermediate 49A. Yield: 27 mg (55% of th.).

LC-MS (method 2): R_t = 0.86 min; MS (ESIpos): m/z = 457 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.05 (s, 1H), 7.68 (br. s, 1H), 7.44 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 3.96 (s, 3H), 3.52 (s, 2H), 3.05 (br. s, 2H), 2.86 (s, 2H), 2.45 (s, 3H) ppm.

Example 81

1-({[4-Amino-7-chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)-2-methylpropan-2-ol formiate



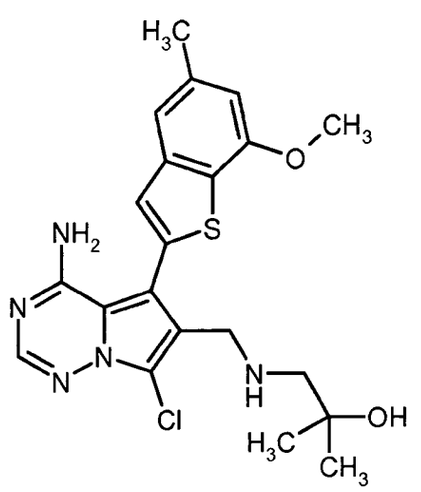
The title compound was prepared according to the procedure of Example 77 starting from 40 mg (0.11 mmol) of Intermediate 49A. Yield: 24 mg (45% of th.).

LC-MS (method 2): R_t = 0.73 min; MS (ESIpos): m/z = 446 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.15 (s, 1H), 8.04 (s, 1H), 7.45 (s, 1H), 7.30 (s, 1H), 6.85 (s, 1H), 3.96 (s, 3H), 3.73 (s, 2H), 2.45 (s, 3H), 2.32 (s, 2H), 1.00 (s, 6H) ppm.

Example 82

1-({[4-Amino-7-chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)-2-methylpropan-2-ol



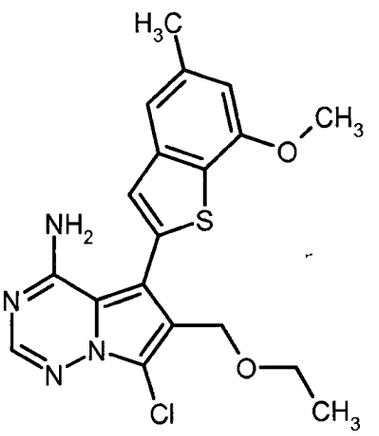
The title compound was prepared from Example 81 according to the procedure of Example 78.

LC-MS (method 2): R_t = 0.72 min; MS (ESIpos): m/z = 446 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.04 (s, 1H), 7.45 (s, 1H), 7.30 (s, 1H), 6.85 (s, 1H), 4.09 (br. s, 1H), 3.95 (s, 3H), 3.71 (s, 2H), 2.45 (s, 3H), 2.31 (s, 2H), 1.44-1.64 (m, 1H), 1.00 (s, 6H) ppm.

Example 83

7-Chloro-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-4-amine



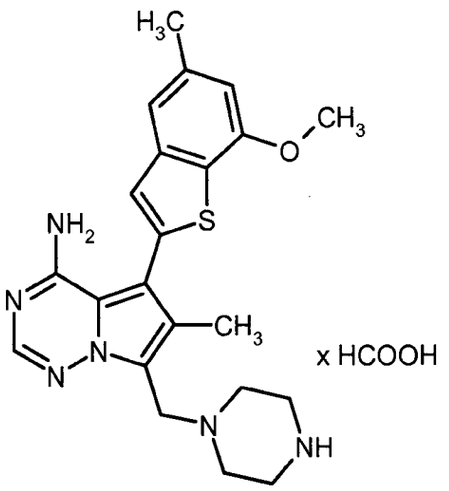
8.2 mg (0.02 mmol) of Intermediate 50A were suspended in 1 ml of ethanol, treated with 41 µl (0.11 mmol) of a 2.68 M solution of sodium ethanolate in ethanol and refluxed for 1 min. The clear solution was then evaporated, and the crude product was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) to afford 5 mg (56% of th.) of the title compound.

LC-MS (method 4): R_t = 1.25 min; MS (ESIpos): m/z = 402 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.06 (s, 1H), 7.40 (s, 1H), 7.32 (s, 1H), 6.86 (s, 1H), 4.40 (s, 2H), 3.96 (s, 3H), 3.40 (q, 2H), 2.45 (s, 3H), 1.06 (t, 3H) ppm.

Example 84

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-6-methyl-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f]-[1,2,4]triazin-4-amine formiate



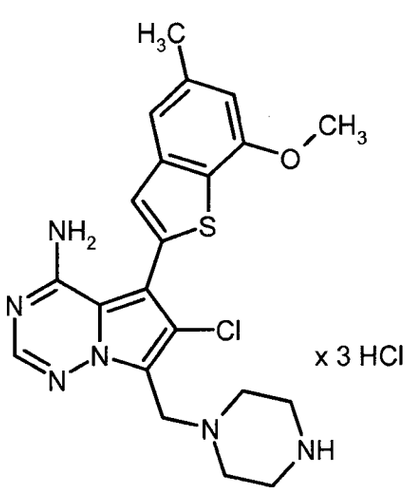
A solution of Intermediate 57A (100 mg, 191 µmol) in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) was stirred at rt for 3 h and then evaporated. Purification by two-fold preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 71 mg (67% of th.) of the title compound.

LC-MS (method 2): R_t = 0.81 min; MS (ESIpos): m/z = 423 $(M+H)^+$

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.46 (br. s, 1H), 7.89 (s, 1H), 7.27 (s, 1H, overlap with $CHCl_3$ peak), 7.18 (s, 1H), 6.67 (s, 1H), 4.01 (s, 3H), 3.97 (s, 2H), 3.18-3.09 (m, 4H), 2.82-2.73 (m, 4H), 2.50 (s, 3H), 2.24 (s, 3H) ppm.

Example 85

6-Chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f]-[1,2,4]triazin-4-amine trihydrochloride



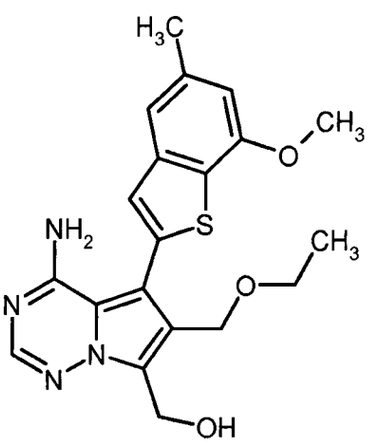
Intermediate 60A (65 mg, 0.12 mmol) was stirred in 1 ml of a 4 M solution of hydrogen chloride in 1,4-dioxane for 2 h at rt. The suspension was evaporated to dryness, and the crude product was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. hydrochloric acid) affording 49 mg (74% of th.) of the title compound.

LC-MS (method 2): R_t = 0.81 min; MS (ESIpos): m/z = 443 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 9.56 (br. s, 1H), 8.45 (br. s, 1H), 8.19 (s, 1H), 7.44 (s, 1H), 7.36 (s, 1H), 6.89 (s, 1H), 6.30 (br. s, 1H), 4.63 (br. s, 1H), 3.40 (br. s, 8H), 2.46 (s, 3H) ppm.

Example 86

[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-7-yl]methanol



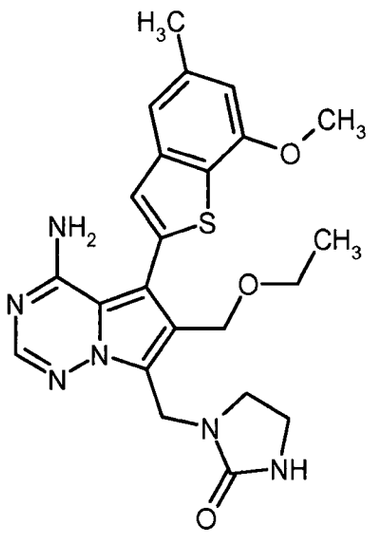
The title compound (360 mg) was obtained as a side product in the preparation of Example 5 by preparation method 1.

LC-MS (method 2): R_t = 0.99 min; MS (ESIpos): m/z = 399 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.09-7.72 (br. s, 1H), 7.99 (s, 1H), 7.35 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 6.05-5.48 (br. s, 1H), 5.04 (br. s, 1H), 4.81 (d, 2H), 4.47 (s, 2H), 3.96 (s, 3H), 3.39 (q, 3H), 2.45 (s, 3H), 1.05 (t, 3H) ppm.

Example 87

1-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-7-yl]methyl}imidazolidin-2-one



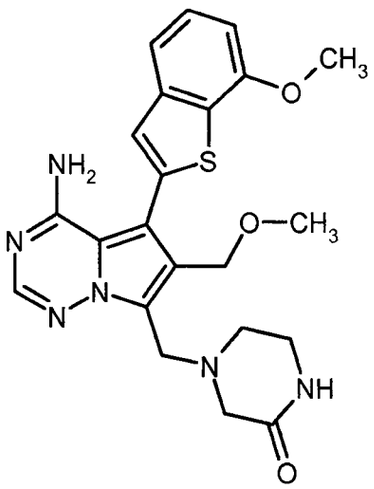
A suspension of Intermediate 63A (100 mg, 0.221 mmol) in THF (5 ml) was treated with imidazolidin-2-one (57 mg, 0.662 mmol) and *N,N*-diisopropylethylamine (153 µl, 0.926 mmol), and the mixture was heated to 150°C for 90 min in a microwave oven. After this, the reaction mixture was purified by preparative RP-HPLC (Reprosil C18, gradient 40-60% acetonitrile/0.2% aq. trifluoroacetic acid). The product thus obtained was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated. The product was purified once again by preparative thin layer chromatography over silica gel (cyclohexane/ethyl acetate 3:1) affording 24 mg (22% of th.) of the title compound.

LC-MS (method 2): R_t = 0.99 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.21-7.65 (br. s, 1H), 7.99 (s, 1H), 7.36 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 6.38 (s, 1H), 6.04-5.56 (br. s, 1H), 4.65 (s, 2H), 4.46 (s, 2H), 3.95 (s, 3H), 3.38 (q, 2H), 3.31-3.10 (m, 4H), 2.45 (s, 3H), 1.06 (t, 3H) ppm.

Example 88

4-{[4-Amino-5-(7-methoxy-1-benzothiophen-2-yl)-6-(methoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one



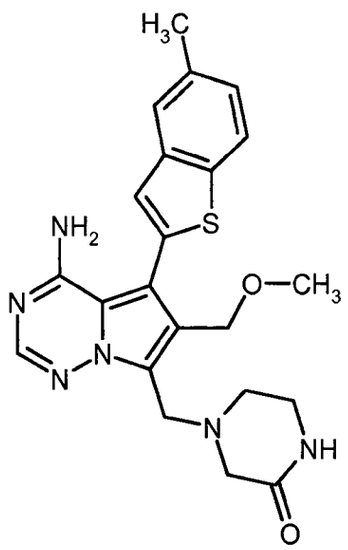
To a solution of Intermediate 62A (72.6 mg, 197 µmol), (7-methoxy-1-benzothiophen-2-yl)boronic acid (45 mg, 216 µmol) and caesium fluoride (149 mg, 983 µmol) in degassed THF/water (10:1, 2.2 ml) under argon was added (2'-aminobiphenyl-2-yl)(chloro)palladium-dicyclohexyl(2',4',6'-triiso-propylbiphenyl-2-yl)phosphine (1:1; 7.7 mg, 9.8 µmol; see S. L. Buchwald *et al.*, *J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)). The resulting mixture was degassed again and stirred under argon at 60°C for 3 h. After this, the mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 20-40% acetonitrile/0.1% aq. TFA). The product fractions were combined and evaporated to dryness. The residue was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated affording 31 mg (35% of th.) of the title compound.

LC-MS (method 2): R_t = 0.71 min; MS (ESIpos): m/z = 453 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.00 (s, 1H), 7.72 (s, 1H), 7.61-8.23 (br. s, 1H), 7.51 (d, 1H), 7.46 (s, 1H), 7.40 (t, 1H), 6.99 (d, 1H), 5.57-6.11 (br. s, 1H), 4.42 (s, 2H), 3.98 (s, 5H), 3.20 (s, 3H), 3.11 (br. m, 2H), 3.01 (s, 2H), 2.62-2.67 (m, 2H) ppm.

Example 89

4-{[4-Amino-6-(methoxymethyl)-5-(5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one



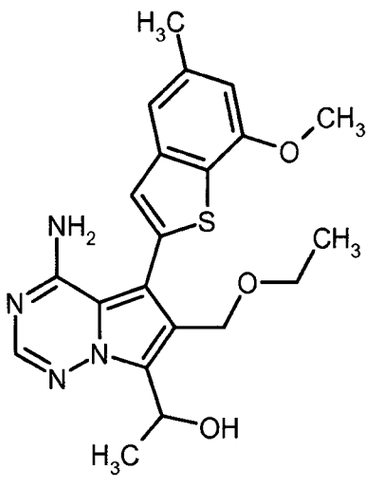
To a solution of Intermediate 62A (50 mg, 135 µmol), (5-methyl-1-benzothiophen-2-yl)boronic acid (28.6 mg, 149 µmol) and caesium fluoride (103 mg, 677 µmol) in degassed THF/water (10:1, 4.4 ml) under argon was added (2'-aminobiphenyl-2-yl)(chloro)palladium-dicyclohexyl(2',4',6'-triiso-propylbiphenyl-2-yl)phosphine (1:1; 5.3 mg, 6.8 µmol; see S. L. Buchwald *et al.*, *J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)). The resulting mixture was degassed again and stirred under argon at 60°C for 16 h. After this, the mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 30-50% acetonitrile/0.1% aq. TFA). The product fractions were combined and evaporated to dryness. The residue was dissolved in methanol and filtered through an anion exchange cartridge (StratoSpheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated affording 27 mg (45% of th.) of the title compound.

LC-MS (method 2): R_t = 0.79 min; MS (ESIpos): m/z = 437 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.00 (s, 1H), 7.89 (d, 1H), 7.73 (s, 1H), 7.71 (s, 1H), 7.58-8.18 (br. s, 1H), 7.40 (s, 1H), 7.24 (dd, 1H), 5.58-6.03 (m, 1H), 4.42 (s, 2H), 3.97 (s, 2H), 3.21 (s, 3H), 3.11 (br. t, 2H), 3.01 (s, 2H), 2.64 (t, 2H), 2.44 (s, 3H) ppm.

Example 90

1-[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-7-yl]ethanol



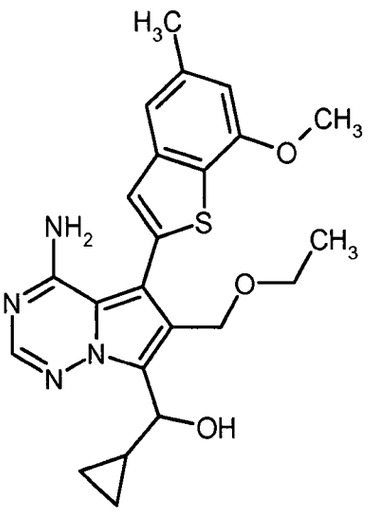
Under argon, a 1 M solution of methylmagnesium bromide in THF (630 µl, 630 µmol) was added dropwise at rt to a solution of Intermediate 17A (100 mg, 252 µmol) in THF (10 ml). The mixture was stirred at rt for 3 h and then treated with another portion of methylmagnesium bromide in THF (177 µl, 177 µmol). The reaction mixture was stirred for further 16 h, then quenched with sat. aq. ammonium chloride solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried with magnesium sulfate, filtered and evaporated. The residue was purified by preparative RP-HPLC (Reprosil C18, gradient 40-60% acetonitrile/0.1% aq. TFA). The product fractions were diluted with sat. aq. sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic phase was washed with sat. aq. sodium chloride solution, dried with magnesium sulfate, filtered and evaporated yielding 39 mg (36% of th.) of the title compound.

LC-MS (method 4): R_t = 1.07 min; MS (ESIpos): m/z = 413 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.95 (s, 1H), 7.56-8.07 (br. s, 1H), 7.35 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 5.46-5.54 (m, 1H), 5.37-5.95 (br. s, 1H), 5.26 (d, 1H), 4.67 (d, 1H), 4.38 (d, 1H), 3.95 (s, 3H), 3.38 (q, 2H), 2.45 (s, 3H), 1.52 (d, 3H), 1.05 (t, 3H) ppm.

Example 91

[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-7-yl](cyclopropyl)methanol



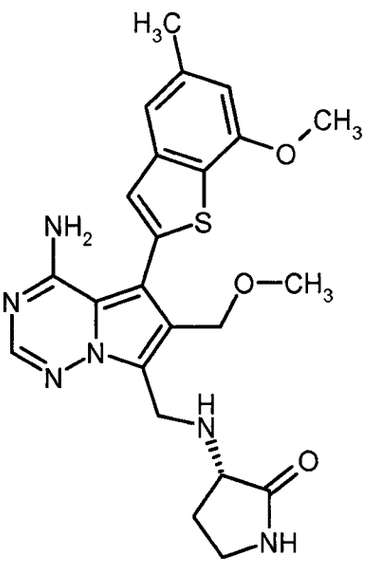
Under argon, a 0.5 M solution of cyclopropylmagnesium bromide in THF (1.26 ml, 630 µmol) was added dropwise at rt to a solution of Intermediate 17A (100 mg, 252 µmol) in THF (5 ml). The mixture was stirred at rt for 1 h, then quenched with sat. aq. ammonium chloride solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried with magnesium sulfate, filtered and evaporated. The residue was purified by preparative RP-HPLC (Reprosil C18, gradient 50-70% acetonitrile/0.1% aq. TFA). The product fractions were diluted with sat. aq. sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic phase was washed with sat. aq. sodium chloride solution, dried with magnesium sulfate, filtered and evaporated yielding 10 mg (10% of th.) of the title compound.

LC-MS (method 2): R_t = 1.13 min; MS (ESIpos): m/z = 439 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.94 (s, 1H), 7.68-8.04 (br. s, 1H), 7.36 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 5.47-5.89 (br. s, 1H), 5.30 (d, 1H), 4.64 (d, 1H), 4.59-4.67 (m, 1H), 4.39 (d, 1H), 3.96 (s, 3H), 3.38 (q, 2H), 2.45 (s, 3H), 1.54-1.64 (m, 1H), 1.04 (t, 3H), 0.51-0.59 (m, 1H), 0.40-0.47 (m, 1H), 0.28-0.38 (m, 2H) ppm.

Example 92

(*3S*)-3-({[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}amino)pyrrolidin-2-one



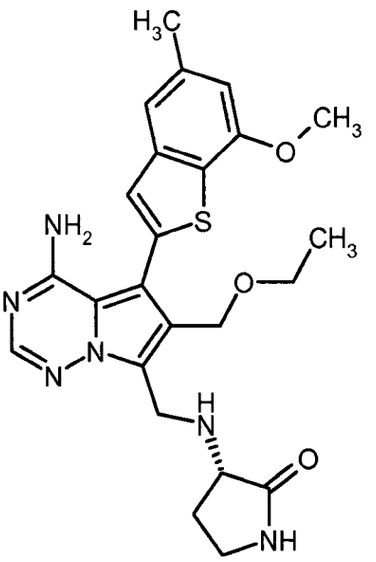
A suspension of Intermediate 13A (100 mg, 0.233 mmol) in THF (2 ml) was treated with (*S*)-3-aminopyrrolidin-2-one (35 mg, 0.349 mmol), sodium triacetoxyborohydride (148 mg, 0.698 mmol) and acetic acid (26.6 µl, 0.465 mmol). The resulting mixture was stirred at rt for 3 h and then directly purified by preparative RP-HPLC (Reprosil C18, gradient 40-60% acetonitrile/0.2% aq. trifluoroacetic acid). The product fractions were combined and evaporated to dryness. The residue was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated affording 56 mg (51% of th.) of the title compound.

LC-MS (method 4): R_t = 0.72 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.01 (s, 1H), 7.76 (s, 1H), 7.35 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 4.48 (d, 2H), 4.43 (d, 2H), 4.24-4.02 (m, 2H), 3.96 (s, 3H), 3.26-2.99 (m, 6H), 2.45 (s, 3H), 2.40-2.27 (m, 1H), 1.82-1.64 (m, 1H) ppm.

Example 93

(*3S*)-3-({[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}amino)pyrrolidin-2-one



A suspension of Intermediate 17A (100 mg, 0.252 mmol) in THF (2 ml) was treated with (*S*)-3-aminopyrrolidin-2-one (38 mg, 378 µmol), sodium triacetoxyborohydride (160 mg, 757 µmol) and acetic acid (30 µl, 504 µmol). The resulting mixture was stirred at rt for 3 h and then directly purified by preparative RP-HPLC (Reprosil C18, gradient 30-50% acetonitrile/0.2% aq. trifluoroacetic acid). The product fractions were combined and evaporated to dryness. The residue was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated affording 84 mg (69% of th.) of the title compound.

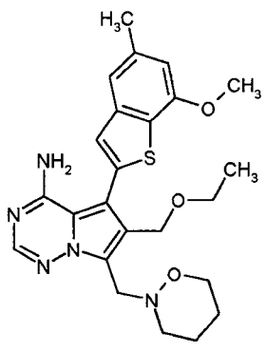
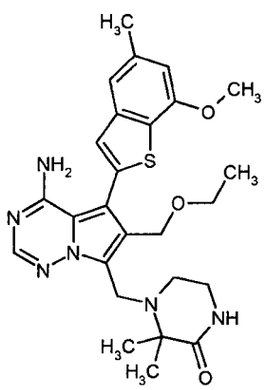
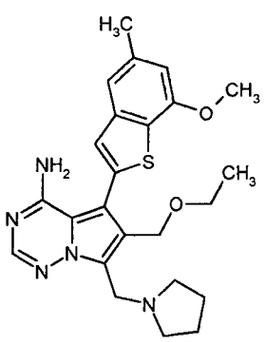
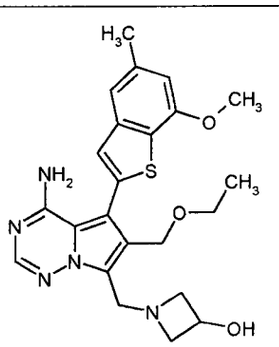
LC-MS (method 4): R_t = 0.75 min; MS (ESIpos): m/z = 481 $(M+H)^+$

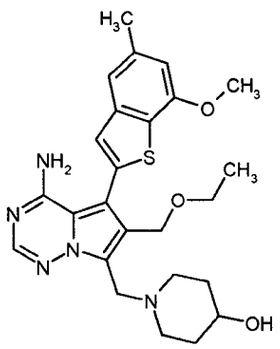
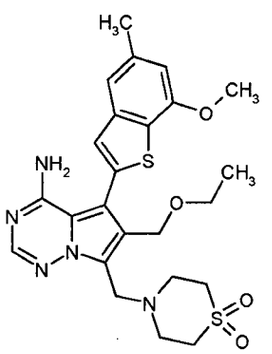
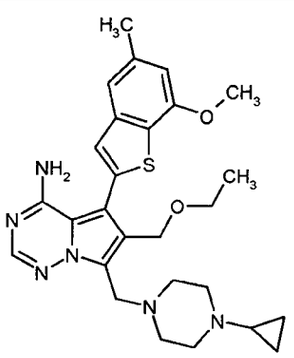
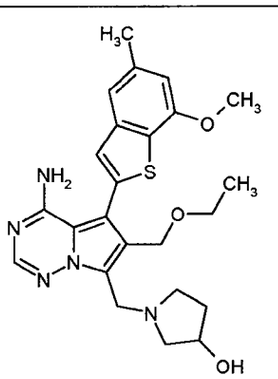
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.00 (s, 1H), 7.75 (s, 1H), 7.67-8.11 (br. s, 1H), 7.35 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 5.5-6.0 (br. s, 1H), 4.44 (q, 2H), 4.14-4.21 (m, 1H), 4.02-4.11 (m, 1H), 3.38-3.45 (q, 2H), 3.16-3.24 (m, 1H), 3.05-3.16 (m, 2H), 2.45 (s, 3H), 2.31-2.40 (m, 1H), 1.67-1.79 (m, 1H), 1.08 (t, 3H) ppm.

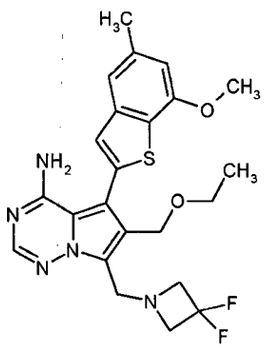
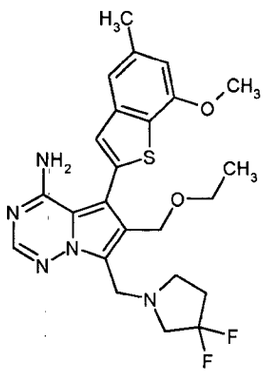
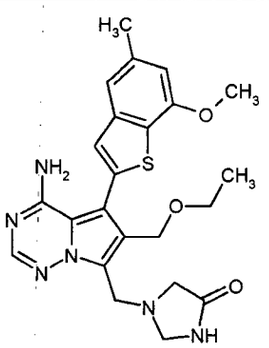
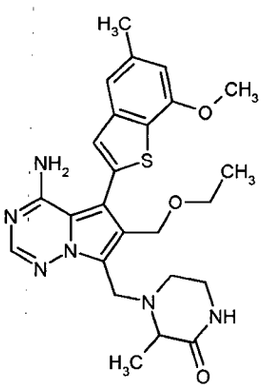
General procedure for the preparation of Examples 94–105 in Table I:

A 0.13 M suspension of Intermediate 17A in THF was treated with 1.5 eq. of the respective amine component, 3 eq. of sodium triacetoxyborohydride and 1.5 eq. of acetic acid. The resulting mixture was stirred at 60°C for 3–20 h. After this, purification was carried out according to the methods indicated.

Table I

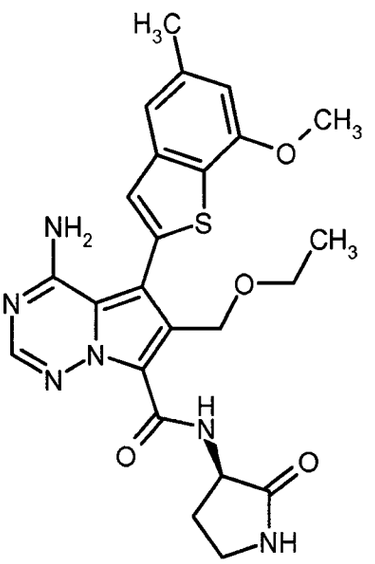
Example No.	Structure	Purification method(s)	LC-MS data
94		P1, P5	Method 4: R_t = 1.22 min; MS (ESIpos): m/z = 468 $(M+H)^+$
95		P6, P3	Method 2: R_t = 0.92 min; MS (ESIpos): m/z = 509 $(M+H)^+$
96		P1, P5	Method 4: R_t = 0.83 min; MS (ESIpos): m/z = 452 $(M+H)^+$
97		P1, P5	Method 5: R_t = 1.84 min; MS (ESIpos): m/z = 454 $(M+H)^+$

Example No.	Structure	Purification method(s)	LC-MS data
98		P1, P5	Method 5: R_t = 1.82 min; MS (ESIpos): m/z = 482 $(M+H)^+$
99		P1, P5	Method 5: R_t = 2.21 min; MS (ESIpos): m/z = 516 $(M+H)^+$
100		P1, P5	Method 2: R_t = 0.86 min; MS (ESIpos): m/z = 507 $(M+H)^+$
101		P1, P5	Method 2: R_t = 0.81 min; MS (ESIpos): m/z = 468 $(M+H)^+$

Example No.	Structure	Purification method(s)	LC-MS data
102		P1, P5, P4	Method 2: R_t = 1.03 min; MS (ESIpos): m/z = 474 $(M+H)^+$
103		P1, P5, P2	Method 2: R_t = 1.05 min; MS (ESIpos): m/z = 460 $(M+H)^+$
104		P1, P6	Method 2: R_t = 0.91 min; MS (ESIpos): m/z = 467 $(M+H)^+$
105		P1, P6	Method 2: R_t = 0.89 min; MS (ESIpos): m/z = 495 $(M+H)^+$

Example 106

4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-*N*-[(*3R*)-2-oxopyrrolidin-3-yl]pyrrolo[2,1-f][1,2,4]triazine-7-carboxamide



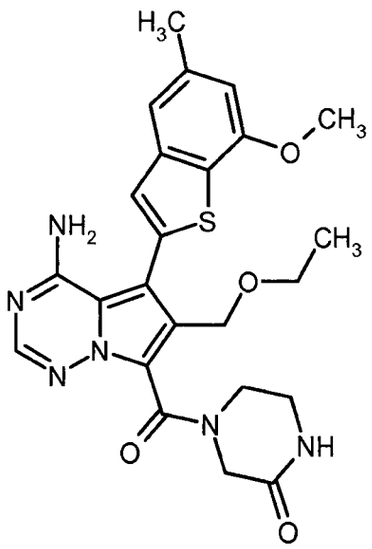
A stirred solution of Intermediate 64A (50 mg, 121 µmol) in DMF (2 ml) was treated at rt with *N*-[(1*H*-benzotriazol-1-yloxy)(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate (TBTU) (43 mg, 133 µmol) and DIPEA (53 µl, 303 µmol). After 15 min, (*3R*)-3-aminopyrrolidin-2-one (24 mg, 242 µmol) was added, and the resulting mixture was stirred at rt for further 2 h. After this, the mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 30-50% acetonitrile/0.2% aq. trifluoroacetic acid). The product fractions were combined and evaporated to dryness. The residue was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated affording 36 mg (60% of th.) of the title compound.

LC-MS (method 2): R_t = 0.91 min; MS (ESIpos): m/z = 495 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 9.50 (d, 1H), 8.21-8.45 (br. s, 1H), 8.17 (s, 1H), 7.97 (s, 1H), 7.41 (s, 1H), 7.33 (s, 1H), 6.86 (s, 1H), 5.84-6.09 (br. s, 1H), 4.74 (dd, 2H), 4.47-4.56 (m, 1H), 3.96 (s, 3H), 3.37 (q, 2H), 3.22-3.29 (m, 2H), 2.54-2.61 (m, 1H), 2.46 (s, 3H), 1.90-2.03 (m, 1H), 1.00 (t, 3H) ppm.

Example 107

4-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-7-yl]carbonyl}piperazin-2-one



A stirred solution of Intermediate 64A (50 mg, 121 µmol) in DMF (2 ml) was treated at rt with TBTU (43 mg, 133 µmol) and DIPEA (53 µl, 303 µmol). After 15 min, piperazin-2-one (24 mg, 242 µmol) was added, and the resulting mixture was stirred at rt for further 16 h. After this, the mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 40-60% acetonitrile/0.2% aq. trifluoroacetic acid). The product fractions were combined and evaporated to dryness. The residue was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated affording 45 mg (68% of th.) of the title compound.

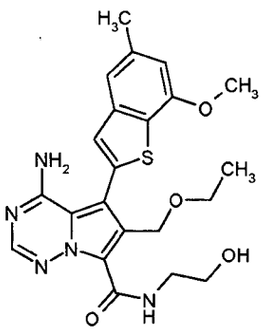
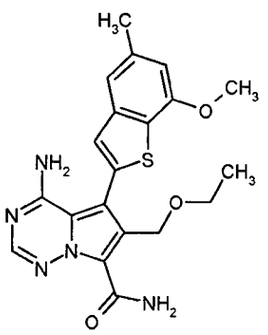
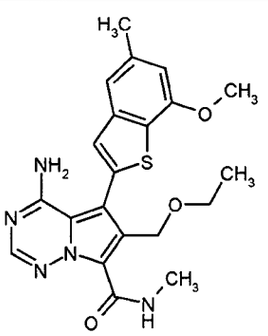
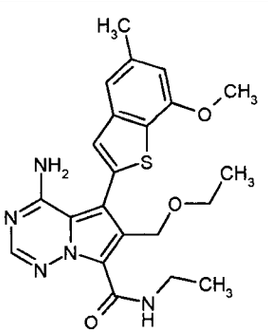
LC-MS (method 2): R_t = 0.92 min; MS (ESIpos): m/z = 495 $(M+H)^+$

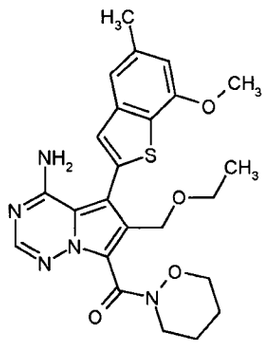
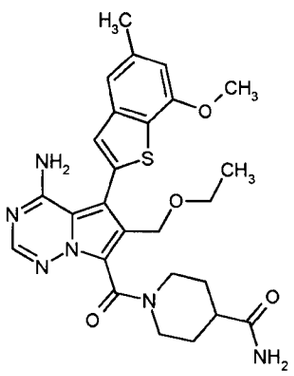
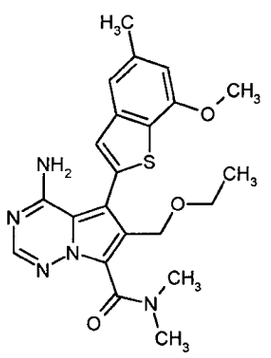
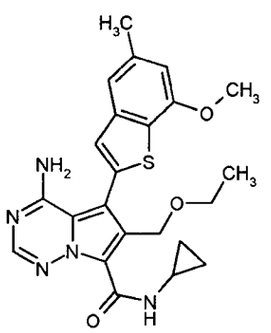
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.14 (br. s, 1H), 7.99-8.01 (m, 1H), 7.9-8.3 (br. s, 1H), 7.41 (d, 1H), 7.32 (s, 1H), 6.86 (s, 1H), 5.78-6.05 (br. s, 1H), 4.30-4.49 (m, 2H), 4.13-4.23 (m, 1H), 4.03-4.10 (m, 1H), 3.96 (s, 3H), 3.76-3.87 (m, 1H), 3.57-3.74 (m, 1H), 3.35-3.43 (m, 2H), 3.14-3.25 (m, 1H), 2.45 (s, 3H), 0.96-1.05 (m, 3H) ppm.

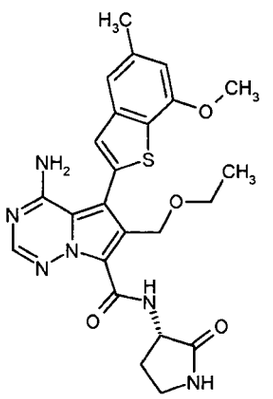
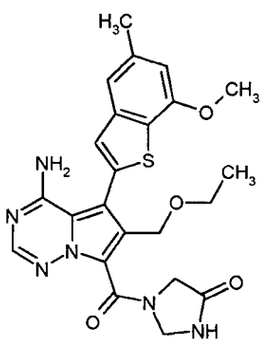
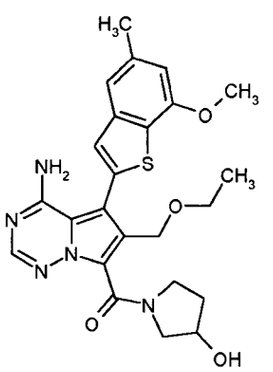
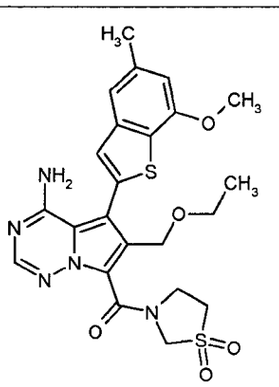
General procedure for the preparation of Examples 108–123 in Table II:

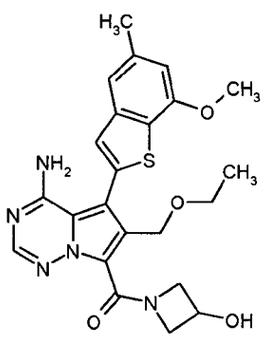
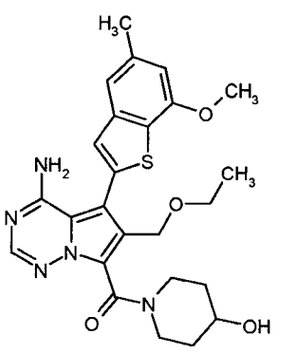
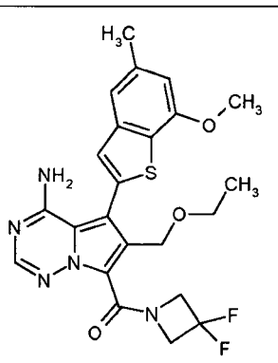
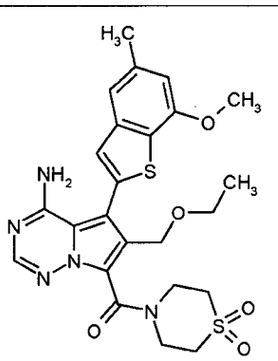
A 0.13 M solution of Intermediate 64A in DMF was treated with 1.1 eq. TBTU and 2.5 eq. DIPEA and stirred at rt for 15 min. 2 eq. of the respective amine were added, and the resulting mixture was stirred at rt for further 18 h. After this, purification was carried out according to the methods indicated.

Table II

Example No.	Structure	Purification method(s)	LC-MS data
108		P1	Method 2: R_t = 1.02 min; MS (ESIpos): m/z = 456 $(M+H)^+$
109		P1	Method 4: R_t = 0.97 min; MS (ESIpos): m/z = 412 $(M+H)^+$
110		P1, P5	Method 2: R_t = 1.01 min; MS (ESIpos): m/z = 426 $(M+H)^+$
111		P1, P5	Method 4: R_t = 1.11 min; MS (ESIpos): m/z = 440 $(M+H)^+$

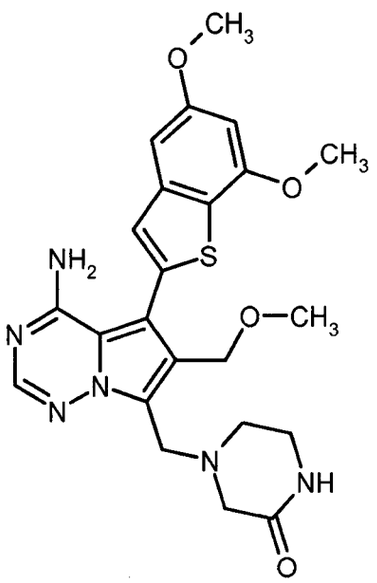
Example No.	Structure	Purification method(s)	LC-MS data
112		P1	Method 4: R_t = 1.07 min; MS (ESIpos): m/z = 482 $(M+H)^+$
113		P1, P5	Method 2: R_t = 0.84 min; MS (ESIpos): m/z = 523 $(M+H)^+$
114		P1, P5	Method 2: R_t = 0.96 min; MS (ESIpos): m/z = 440 $(M+H)^+$
115		P1, P5	Method 2: R_t = 1.09 min; MS (ESIpos): m/z = 452 $(M+H)^+$

Example No.	Structure	Purification method(s)	LC-MS data
116		P1, P5	Method 4: R_t = 0.95 min; MS (ESIpos): m/z = 495 $(M+H)^+$
117		P1, P5	Method 4: R_t = 0.93 min; MS (ESIpos): m/z = 481 $(M+H)^+$
118		P1, P5	Method 2: R_t = 0.93 min; MS (ESIpos): m/z = 482 $(M+H)^+$
119		P1, P5	Method 2: R_t = 1.04 min; MS (ESIpos): m/z = 516 $(M+H)^+$

Example No.	Structure	Purification method(s)	LC-MS data
120		P1, P5	Method 4: R_t = 0.88 min; MS (ESIpos): m/z = 468 $(M+H)^+$
121		P1, P5	Method 4: R_t = 0.91 min; MS (ESIpos): m/z = 496 $(M+H)^+$
122		P1, P5	Method 4: R_t = 1.09 min; MS (ESIpos): m/z = 488 $(M+H)^+$
123		P1, P5	Method 4: R_t = 0.98 min; MS (ESIpos): m/z = 530 $(M+H)^+$

Example 124

4-{[4-Amino-5-(5,7-dimethoxy-1-benzothiophen-2-yl)-6-(methoxymethyl)pyrrolo[2,1-f][1,2,4]-triazin-7-yl]methyl}piperazin-2-one



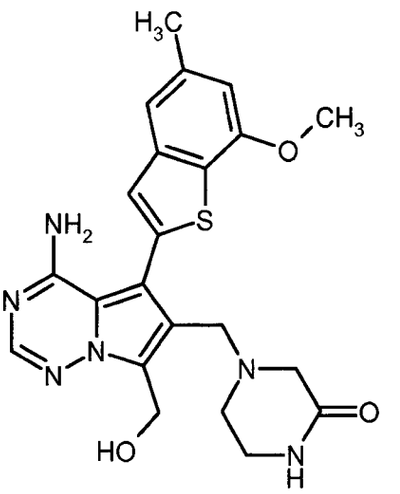
To a solution of Intermediate 62A (100 mg, 271 µmol), Intermediate 66A (77 mg, 325 µmol) and caesium fluoride (206 mg, 1.35 mmol) in degassed THF/water (10:1; 5 ml) under argon was added (2'-aminobiphenyl-2-yl)(chloro)palladium-dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (1:1; 42.6 mg, 54 µmol; see S. L. Buchwald *et al., J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)). The resulting mixture was degassed again and stirred under argon at 60°C for 6 h. Then, another portion of Intermediate 66A (39 mg, 162 µmol) was added, and stirring at 60°C was continued for 10 h. After this, the reaction mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 30-50% acetonitrile/0.1% aq. TFA). The product fractions were combined and evaporated to dryness. The residue was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated affording 40 mg (28% of th.) of the title compound.

LC-MS (method 2): R_t = 0.78 min; MS (ESIpos): m/z = 483 $(M+H)^+$

^{1}H-NMR (500 MHz, DMSO-d_6): δ = 7.99 (s, 1H), 7.68 (br. s, 1H), 7.49-8.17 (br. s, 1H), 7.37 (s, 1H), 7.05 (d, 1H), 6.63 (d, 1H), 5.5-6.0 (br. s, 1H), 4.42 (s, 2H), 3.97 (s, 2H), 3.94 (s, 3H), 3.84 (s, 3H), 3.20 (s, 3H), 3.09-3.14 (m, 2H), 3.01 (s, 2H), 2.62-2.67 (m, 2H) ppm.

Example 125

4-{[4-Amino-7-(hydroxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-6-yl]methyl}piperazin-2-one



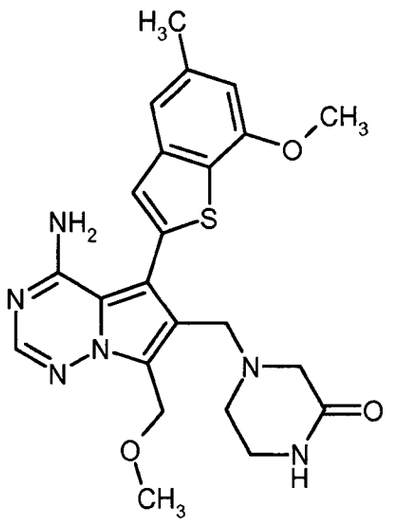
To a suspension of Intermediate 70A (700 mg, 1.49 mmol), Intermediate 5A (497 mg, 2.24 mmol) and caesium fluoride (1.36 g, 8.95 mmol) in degassed THF/water (2:1, 90 ml) under argon was added (2'-aminobiphenyl-2-yl)(chloro)palladium-dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (1:1; 117 mg, 0.149 mmol; see S. L. Buchwald *et al.*, *J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)). The resulting mixture was degassed again and stirred under argon at 60°C overnight. Another portion of Intermediate 5A (231 mg, 1.04 mmol) and (2'-aminobiphenyl-2-yl)-(chloro)palladium-dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (1:1; 117 mg, 0.149 mmol) were added, and stirring was continued at 60°C for 3 h. The precipitate was filtered off, washed with THF and dried *in vacuo*. The solid was suspended in mixture of DMF and 1 M aq. trifluoroacetic acid and filtered. The filtrate was separated by preparative RP-HPLC (Reprosil C18, gradient 20-40% acetonitrile/0.2% aq. trifluoroacetic acid). The product fractions were combined and then alkalized by addition of sat. aq. sodium bicarbonate solution. The solution was extracted with ethyl acetate, and the organic layer was washed with brine, dried over magnesium sulfate and evaporated to yield 88 mg of the title compound (13% of th.).

LC-MS (method 2): R_t = 0.70 min; MS (ESIpos): m/z = 453 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 7.6-8.0 (br. s, 1H), 7.98 (s, 1H), 7.71 (s, 1H), 7.37 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 5.4-5.8 (br. s, 1H), 5.19 (t, 1H), 4.85 (d, 2H), 3.95 (s, 3H), 3.58 (s, 2H), 3.04 (br. m, 2H), 2.88 (s, 2H), 2.45 (s, 3H) ppm.

Example 126

4-{[4-Amino-7-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-6-yl]methyl}piperazin-2-one



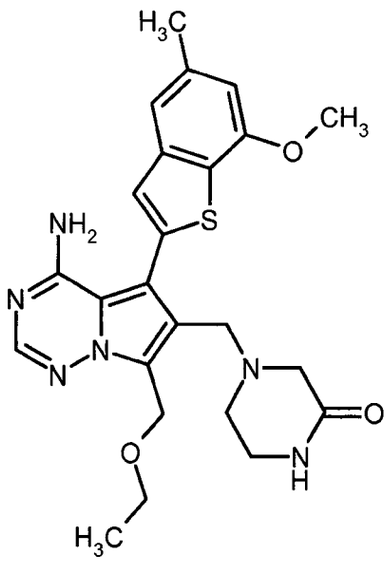
A suspension of Example 125 (88 mg, 194 µmol) in dichloromethane (5 ml) was treated with thionyl chloride (29 µl, 389 µmol), and the mixture was stirred at rt for 65 min. Another portion of thionyl chloride (29 µl, 389 µmol) was added, and stirring was continued for 1.5 h. An excess of methanol was then added, followed by dropwise addition of a 5.4 M solution of sodium methylate in methanol (84 mg, 1.56 mmol) until pH 8 was reached. After stirring for 3 days, the volatiles were evaporated under reduced pressure, and the residue was separated by preparative RP-HPLC (Reprosil C18, gradient 20-40% acetonitrile/0.2% aq. trifluoroacetic acid). The product fractions were evaporated to yield 19 mg of the title compound (21% of th.).

LC-MS (method 2): R_t = 0.77 min; MS (ESIpos): m/z = 466 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.99 (s, 1H), 7.75-8.11 (br. s, 1H), 7.68 (s, 1H), 7.38 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 5.51-5.82 (m, 1H), 4.77 (s, 2H), 3.95 (s, 3H), 3.55 (s, 2H), 3.31 (s, 3H), 3.04 (br. s, 2H), 2.85 (s, 2H), 2.42-2.48 (m, 5H) ppm.

Example 127

4-{[4-Amino-7-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-6-yl]methyl}piperazin-2-one



A suspension of Example 125 (100 mg, 221 µmol) in dichloromethane (10 ml) was treated with thionyl chloride (161 µl, 2.21 mmol), and the mixture was stirred at rt for 30 min. Ethanol was added, and the volatiles were evaporated under reduced pressure. The residue was dissolved in ethanol (10 ml), sodium ethylate (30 mg, 442 µmol) was added, and the mixture was stirred at rt for 1 h. The mixture was then directly separated by preparative RP-HPLC (Reprosil C18, gradient 20-40% acetonitrile/0.2% aq. trifluoroacetic acid). The product fractions were combined and alkalized by addition of sat. aq. sodium bicarbonate solution. The solution was extracted with ethyl acetate, and the organic layer was washed with brine, dried over magnesium sulfate and evaporated to yield 57 mg of the title compound (54% of th.).

LC-MS (method 2): R_t = 0.85 min; MS (ESIpos): m/z = 480 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.99 (s, 1H), 7.75-8.09 (br. s, 1H), 7.64-7.71 (m, 1H), 7.38 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 5.38-5.91 (br. s, 1H), 4.81 (s, 2H), 3.95 (s, 3H), 3.49-3.59 (m, 4H), 2.99-3.08 (m, 2H), 2.86 (s, 2H), 1.12 (t, 3H) ppm.

B. Evaluation of Biological Activity

Abbreviations and Acronyms:

Ahx	6-aminohexanoic acid
ATP	adenosine triphosphate
BSA	bovine serum albumin
CREB	cAMP-response element-binding protein
DMSO	dimethylsulfoxide
EDTA	ethylenediaminetetraacetic acid
EGTA	ethyleneglycol-bis(2-aminoethylether)-*N,N,N',N'*-tetraacetic acid
FBS	fetal bovine serum
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
GFP	green fluorescent protein
GST	glutathione S-transferase
HEPES	4-(2-hydroxyethyl)piperazine-1-ethansulfonic acid
HRTF	homogeneous time-resolved fluorescence
MOPS	3-(*N*-morpholino)propanesulfonic acid
mTOR	mammalian target of Rapamycin
PBS	phosphate buffered saline
PI3K	phosphatidylinositol 3-kinase
RTK	receptor tyrosine kinase
SNP	single nucleotide polymorphism
TR-FRET	time-resolved fluorescence resonance energy transfer
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

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. FGFR-1 high ATP kinase assay

FGFR-1 inhibitory activity at high ATP concentration of the compounds of the present invention after their pre-incubation with FGFR-1 was quantified employing the TR-FRET based FGFR-1 high ATP assay as described in the following paragraphs:

A recombinant tagged FGFR-1 fusion protein [fusion of glutathione-*S*-transferase (GST) (N-terminally), His6-tag, thrombin cleavage site, and the intracellular part of human FGFR-1 from amino acids G400 to R800 as in GenBank entry NM_015850], expressed in SF9 insect cells using baculovirus expression system and purified via glutathione-agarose affinity chromatography, was purchased from Proqinase (product no. 0101-0000-1) and used as enzyme. As substrate for the kinase reaction, the biotinylated peptide biotin-Ahx-AAEEEYFFLFAKKK (C-terminus in amide form) was used which can be purchased, e.g., from Biosyntan (Berlin-Buch, Germany).

Usually, test compounds were tested on the same microtiter plate at 11 different concentrations in the range of 20 µM to 0.1 nM (e.g. 20 µM, 5.9 µM, 1.7 µM, 0.51 µM, 0.15 µM, 44 nM, 13 nM, 3.8 nM, 1.1 nM, 0.33 nM, and 0.1 nM) in duplicates for each concentration. The dilution series was prepared separately prior to the assay as 100-fold concentrated stock solutions in DMSO; exact concentrations could vary depending on the pipettor used. For the assay, 50 nl of each stock solution of the test compound in DMSO was pipetted into a black, low-volume 384-well microtiter plate (Greiner Bio-One, Frickenhausen, Germany). 2 µl of a solution of the above FGFR-1 fusion protein in aqueous assay buffer [8 mM MOPS pH 7.0, 10 mM magnesium acetate, 1.0 mM dithiothreitol, 0.05% (w/v) bovine serum albumin (BSA), 0.07% (v/v) Tween-20, 0.2 mM EDTA] was added, and the mixture was incubated for 15 min at 22°C to allow pre-binding of the test compound to the enzyme. Then, the kinase reaction was started by the addition of 3 µl of a solution of adenosine triphosphate (ATP, 3.3 mM; final concentration in the 5 µl assay volume = 2 mM) and substrate (0.16 µM; final concentration in the 5 µl assay volume = 0.1 µM) in assay buffer, and the resulting mixture was incubated for a reaction time of 15 min at 22°C. The concentration of FGFR-1 fusion protein was adjusted depending on the activity of the enzyme lot and was chosen appropriately to have the assay in the linear range (typical concentrations were in the range of 0.05 µg/ml). The reaction was stopped by the addition of 5 µl of a solution of HTRF detection reagents [25 nM streptavidin-XL665 (Cis Biointernational) and 1 nM PT66-Eu-chelate, an europium-chelate labelled anti-phosphotyrosine antibody (Perkin-Elmer; PT66-Tb-cryptate from Cis Biointernational may be used instead), in an aqueous EDTA solution (50 mM EDTA, 0.1% (w/v) BSA in 50 mM HEPES/NaOH pH 7.5)].

The resulting mixture was incubated for 1 h at 22°C to allow formation of the complex between the phosphorylated biotinylated peptide and the detection reagents. Subsequently, the amount of phosphorylated substrate was evaluated by measurement of the resonance energy transfer from the Eu-chelate to the streptavidin-XL665. For this, the fluorescence emissions at 620 nm and 665 nm after excitation at 350 nm were measured in a TR-FRET reader [e.g. Rubystar (BMG Labtechnologies, Offenburg, Germany) or Viewlux (Perkin-Elmer)]. The ratio of the emissions at 665 nm and at 620 nm was taken as the measure for the amount of phosphorylated substrate. Data were normalised (enzyme reaction without inhibitor = 0% inhibition, all other assay components but no enzyme = 100% inhibition), and IC_{50} values were calculated by a 4-parameter fit using an in-house software.

IC_{50} values for individual compounds of the invention from this assay are listed in Table 1A below:

Table 1A

Example No.	FGFR-1 (high ATP) IC_{50} [nM]
1	12.2
2	7.2
3	6.6
4	13.7
5	4.6
6	9.0
7	4.2
8	9.4
9	31.0
10	12.7
11	6.5
12	3.3
13	2.5
14	1.4

Example No.	FGFR-1 (high ATP) IC_{50} [nM]
15	1.0
16	12.5
17	0.9
18	0.7
19	0.5
20	25.0
21	4.2
22	0.9
23	17.9
24	1.3
25	0.7
26	0.9
27	1.3
28	2.1

Example No.	FGFR-1 (high ATP) IC_{50} [nM]
29	1.6
30	2.8
31	1.5
32	5.2
33	1.0
34	6.0
35	61.3
36	3.0
37	22.1
38	6.9
39	1.1
40	2.1
41	2.8
42	5.1
43	8.6
44	2.1
45	3.4
46	3.2
47	1.7
48	12.8
51	4.4
52	9.7
53	3.9
54	11.2

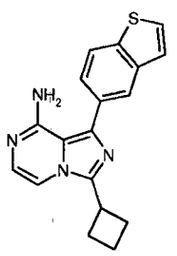
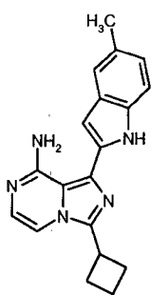
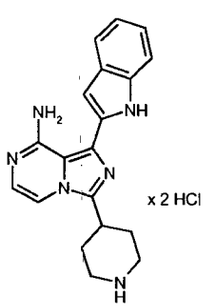
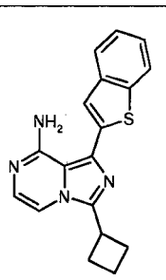
Example No.	FGFR-1 (high ATP) IC_{50} [nM]
56	2.4
57	3.2
58	6.8
59	3.8
60	16.2
61	0.5
62	3.1
64	1.0
65	5.6
66	1.6
67	5.0
68	27.0
69	55.3
70	39.1
71	2.7
72	1.4
73	4.4
74	4.0
75	4.1
76	2.8
77	1.4
78	1.7
79	12.6
80	1.3

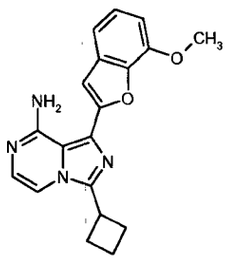
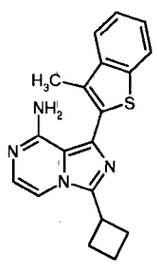
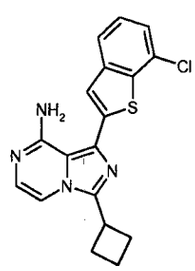
Example No.	FGFR-1 (high ATP) IC_{50} [nM]
81	1.9
82	3.4
83	14.5
84	3.7
85	26.4
86	3.9
87	14.1
88	79.6
89	82.9
90	9.9
91	52.9
92	8.2
93	5.5
94	81.9
95	17.0
96	54.5
97	16.4
98	17.0
99	24.8
100	54.5
101	30.8
102	39.2
103	50.3
104	5.6

Example No.	FGFR-1 (high ATP) IC_{50} [nM]
105	8.7
106	6.4
107	9.4
108	3.9
109	8.4
110	17.5
111	27.0
112	42.1
113	52.7
114	11.2
115	24.9
116	3.7
117	8.8
118	6.8
119	9.0
120	6.8
121	8.2
122	18.9
123	25.1
124	27.3
125	5.0
126	3.9
127	8.0

Selected 8-amino-1-(benzothiophen-2-yl)imidazo[1,5-a]pyrazine derivatives and related compounds which were regarded to be representative of closest prior art (see Int. Pat. Appl. WO 2007/061737-A2 and example compounds described therein) were synthesized following the published procedures and also tested in the FGFR-1 high ATP assay for comparative purposes. IC_{50} values that were obtained for these compounds are listed in Table 1B below:

Table 1B

Structure of comparative compound	Example No. in WO 2007/061737	FGFR-1 (high ATP) IC_{50} [nM]
	4	12000
	5	500
	25	880
	120	985

Structure of comparative compound	Example No. in WO 2007/061737	FGFR-1 (high ATP) IC_{50} [nM]
	205	20000
	210	456
	233	4600

The IC_{50} values specified in Table 1A and 1B demonstrate that the compounds of the present invention are about five to a thousand times more potent in inhibiting FGFR-1 kinase activity than the selected prior art compounds.

B-2. FGFR-3 kinase assay

FGFR-3 inhibitory activity of the compounds of the present invention after their pre-incubation with FGFR-3 was quantified employing the TR-FRET based FGFR-3 assay as described in the following paragraphs:

A recombinant tagged FGFR-3 fusion protein [fusion of glutathione-*S*-transferase (GST) (N-terminally), His6-tag, thrombin cleavage site, and the intracellular part of human FGFR-3 from amino acids R397 to T806 as in NCBI/Protein entry NP_000133.1], expressed in SF9 insect cells using baculovirus expression system and purified via glutathione-S-transferase affinity chromatography, was purchased from Proqinase (product no. 1068-0000-1) and used as enzyme. As substrate for the

kinase reaction, the biotinylated peptide biotin-Ahx-AAEEEYFFLFAKKK (C-terminus in amide form) was used which can be purchased, e.g., from Biosyntan (Berlin-Buch, Germany).

Usually, test compounds were tested on the same microtiter plate at 11 different concentrations in the range of 20 µM to 0.1 nM (e.g. 20 µM, 5.9 µM, 1.7 µM, 0.51 µM, 0.15 µM, 44 nM, 13 nM, 3.8 nM, 1.1 nM, 0.33 nM, and 0.1 nM) in duplicates for each concentration. The dilution series was prepared separately prior to the assay as 100-fold concentrated stock solutions in DMSO; exact concentrations could vary depending on the pipettor used. For the assay, 50 nl of each stock solution of the test compound in DMSO was pipetted into a black, low-volume 384-well microtiter plate (Greiner Bio-One, Frickenhausen, Germany). 2 µl of a solution of the above FGFR-3 fusion protein in aqueous assay buffer [8 mM MOPS pH 7.0, 10 mM magnesium acetate, 1.0 mM dithiothreitol, 0.05% (w/v) bovine serum albumin (BSA), 0.07% (v/v) Tween-20, 0.2 mM EDTA] was added, and the mixture was incubated for 15 min at 22°C to allow pre-binding of the test compound to the enzyme. Then, the kinase reaction was started by the addition of 3 µl of a solution of adenosine triphosphate (ATP, 16.7 µM; final concentration in the 5 µl assay volume = 10 µM) and substrate (0.8 µM; final concentration in the 5 µl assay volume = 0.5 µM) in assay buffer, and the resulting mixture was incubated for a reaction time of 60 min at 22°C. The concentration of FGFR-3 fusion protein was adjusted depending on the activity of the enzyme lot and was chosen appropriately to have the assay in the linear range (typical concentrations were in the range of 0.03 µg/ml). The reaction was stopped by the addition of 5 µl of a solution of HTRF detection reagents [100 nM streptavidin-XL665 (Cis Biointernational) and 1 nM PT66-Tb-cryptate, a terbium-cryptate labelled anti-phosphotyrosine antibody (Cis Biointernational; PT66-Eu-chelate from Perkin-Elmer may be used instead), in an aqueous EDTA solution (50 mM EDTA, 0.1% (w/v) BSA in 50 mM HEPES/NaOH pH 7.5)].

The resulting mixture was incubated for 1 h at 22°C to allow formation of the complex between the phosphorylated biotinylated peptide and the detection reagents. Subsequently, the amount of phosphorylated substrate was evaluated by measurement of the resonance energy transfer from the Tb-chelate to the streptavidin-XL665. For this, the fluorescence emissions at 620 nm and 665 nm after excitation at 350 nm were measured in a TR-FRET reader [e.g. Rubystar (BMG Labtechnologies, Offenburg, Germany) or Viewlux (Perkin-Elmer)]. The ratio of the emissions at 665 nm and at 620 nm was taken as the measure for the amount of phosphorylated substrate. Data were normalised (enzyme reaction without inhibitor = 0% inhibition, all other assay components but no enzyme = 100% inhibition), and IC_{50} values were calculated by a 4-parameter fit using an in-house software.

IC_{50} values for individual compounds of the invention from this assay are listed in Table 2A below:

Table 2A

Example No.	FGFR-3 IC_{50} [nM]
1	24.8
2	29.4
3	46.6
4	24.8
5	12.1
6	28.5
7	10.4
8	17.7
9	63.9
10	8.3
11	13.0
12	14.0
13	10.0
14	2.5
15	1.0
16	9.4
17	3.3
18	2.8
19	2.7
20	26.1
21	13.0
22	4.7
23	41.9

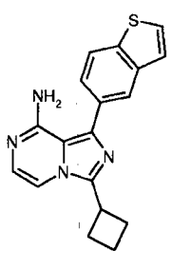
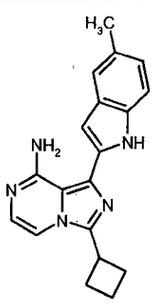
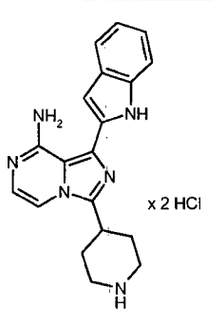
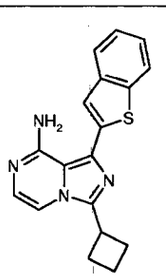
Example No.	FGFR-3 IC_{50} [nM]
24	5.7
25	5.2
26	4.9
27	12.6
28	9.7
29	2.5
30	6.4
31	13.3
32	52.3
33	7.2
34	10.5
35	65.4
36	9.8
37	34.6
38	18.8
39	4.9
40	7.9
41	7.2
42	18.4
43	32.4
44	6.1
45	9.7
46	8.1

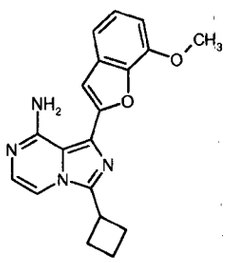
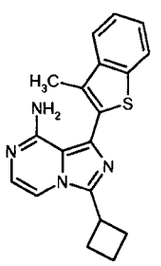
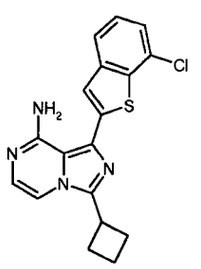
Example No.	FGFR-3 IC_{50} [nM]
47	3.4
48	45.4
51	3.9
52	7.0
53	2.5
54	6.8
56	2.0
57	1.8
58	9.8
59	6.8
60	77.9
61	0.9
62	11.0
64	2.9
65	3.1
66	3.7
67	9.4
68	42.7
69	58.1
71	5.4
72	0.7
73	12.2
74	1.4
75	19.8
76	1.4

Example No.	FGFR-3 IC_{50} [nM]
77	3.8
78	2.0
79	17.9
80	0.2
81	0.5
82	16.0
83	2.1
84	16.5
85	26.0
86	6.8
87	28.1
90	11.0
91	31.1
93	8.7
95	28.7
98	26.5
99	36.9
102	39.8
106	7.1
107	17.4
108	7.7
114	9.6
117	5.3
119	4.5
121	24.6

Selected 8-amino-1-(benzothiophen-2-yl)imidazo[1,5-a]pyrazine derivatives and related compounds which were regarded to be representative of closest prior art (see Int. Pat. Appl. WO 2007/061737-A2 and example compounds described therein) were synthesized following the published procedures and also tested in the FGFR-3 assay for comparative purposes. IC_{50} values that were obtained for these compounds are listed in Table 2B below:

Table 2B

Structure of comparative compound	**Example No. in WO 2007/061737**	**FGFR-3 IC_{50} [nM]**
	4	2400
	5	250
	25	1200
	120	506

Structure of comparative compound	Example No. in WO 2007/061737	FGFR-3 IC_{50} [nM]
	205	20000
	210	554
	233	10000

The IC_{50} values specified in Table 2A and 2B demonstrate that the compounds of the present invention are about three to a thousand times more potent in inhibiting FGFR-3 kinase activity than the selected prior art compounds.

B-3. <u>FGFR-4 high ATP kinase assay</u>

FGFR-4 inhibitory activity at high ATP concentration of the compounds of the present invention after their pre-incubation with FGFR-4 was quantified employing the TR-FRET based FGFR-4 high ATP assay as described in the following paragraphs:

A recombinant tagged FGFR-4 fusion protein [fusion of glutathione-*S*-transferase (GST) (N-terminally), His6-tag, thrombin cleavage site, and the intracellular part of human FGFR-4 from amino acids R391 to T802 as in GenBank entry NM_002011], expressed in SF9 insect cells using baculovirus expression system and purified via glutathione-agarose affinity chromatography, was purchased from Proqinase (product no. 0127-0000-3) and used as enzyme. As substrate for the kinase

reaction, the biotinylated peptide biotin-Ahx-AAEEEYFFLFAKKK (C-terminus in amide form) was used which can be purchased, e.g., from Biosyntan (Berlin-Buch, Germany).

Usually, test compounds were tested on the same microtiter plate at 11 different concentrations in the range of 20 µM to 0.1 nM (e.g. 20 µM, 5.9 µM, 1.7 µM, 0.51 µM, 0.15 µM, 44 nM, 13 nM, 3.8 nM, 1.1 nM, 0.33 nM, and 0.1 nM) in duplicates for each concentration. The dilution series was prepared separately prior to the assay as 100-fold concentrated stock solutions in DMSO; exact concentrations could vary depending on the pipettor used. For the assay, 50 nl of each stock solution of the test compound in DMSO was pipetted into a black, low-volume 384-well microtiter plate (Greiner Bio-One, Frickenhausen, Germany). 2 µl of a solution of the above FGFR-4 fusion protein in aqueous assay buffer [8 mM MOPS pH 7.0, 10 mM magnesium acetate, 1.0 mM dithiothreitol, 0.05% (w/v) bovine serum albumin (BSA), 0.07% (v/v) Tween-20, 0.2 mM EDTA] was added, and the mixture was incubated for 15 min at 22°C to allow pre-binding of the test compound to the enzyme. Then, the kinase reaction was started by the addition of 3 µl of a solution of adenosine triphosphate (ATP, 3.3 mM; final concentration in the 5 µl assay volume = 2 mM) and substrate (0.8 µM; final concentration in the 5 µl assay volume = 0.5 µM) in assay buffer, and the resulting mixture was incubated for a reaction time of 60 min at 22°C. The concentration of FGFR-4 fusion protein was adjusted depending on the activity of the enzyme lot and was chosen appropriately to have the assay in the linear range (typical concentrations were in the range of 0.03 µg/ml). The reaction was stopped by the addition of 5 µl of a solution of HTRF detection reagents [100 nM streptavidin-XL665 (Cis Biointernational) and 1 nM PT66-Tb-cryptate, a terbium-cryptate labelled anti-phosphotyrosine antibody (Cis Biointernational; PT66-Eu-chelate from Perkin-Elmer may be used instead), in an aqueous EDTA solution (50 mM EDTA, 0.1% (w/v) BSA in 50 mM HEPES/NaOH pH 7.5)].

The resulting mixture was incubated for 1 h at 22°C to allow formation of the complex between the phosphorylated biotinylated peptide and the detection reagents. Subsequently, the amount of phosphorylated substrate was evaluated by measurement of the resonance energy transfer from the Tb-chelate to the streptavidin-XL665. For this, the fluorescence emissions at 620 nm and 665 nm after excitation at 350 nm were measured in a TR-FRET reader [e.g. Rubystar (BMG Labtechnologies, Offenburg, Germany) or Viewlux (Perkin-Elmer)]. The ratio of the emissions at 665 nm and at 620 nm was taken as the measure for the amount of phosphorylated substrate. Data were normalised (enzyme reaction without inhibitor = 0% inhibition, all other assay components but no enzyme = 100% inhibition), and IC_{50} values were calculated by a 4-parameter fit using an in-house software.

B-4. mTOR kinase assay (*for comparative purposes*)

mTOR inhibitory activity of the compounds of the present invention was quantified employing the TR-FRET based mTOR assay as described in the following paragraphs:

Recombinant fusion tagged mTOR protein [glutathione-*S*-transferase (GST) fused to human mTOR amino acids from 1360 to 2549], expressed in insect cells and purified by glutathione-sepharose affinity chromatography, was purchased from Invitrogen (Cat.-No. 4753) and used as enzyme. As substrate for the kinase reaction, a recombinant fusion protein of GFP and 4E-BP1 (purchased from Invitrogen, Cat.-No. PV4759) was used.

Test compounds were dissolved in DMSO to generate 10 mM stock solutions. These solutions were first 10-fold diluted by 100% DMSO to get 1 mM solutions in 100% DMSO, then 100-fold diluted by 50% DMSO to get 10 µM solutions in 50% DMSO.

For the assay, 0.5 µl of a 10 µM solution of the test compound in 50% DMSO was pipetted into a black, low-volume 384-well microtiter plate (Greiner Bio-One, Frickenhausen, Germany). 2 µl of a solution of the above mTOR fusion protein in aqueous assay buffer [50 mM HEPES/NaOH pH 7.5, 5 mM magnesium chloride, 1.0 mM dithiothreitol, 1 mM EGTA, 0.01% (v/v) Triton-X100, 0.01% (w/v) bovine serum albumin (BSA)] was added, and the mixture was incubated for 15 min at 22°C to allow pre-binding of the test compound to the enzyme. Then, the kinase reaction was started by the addition of 2.5 µl of a solution of adenosine triphosphate (ATP, 80 µM; final concentration in the 5 µl assay volume = 40 µM) and substrate (0.6 µM; final concentration in the 5 µl assay volume = 0.3 µM) in assay buffer, and the resulting mixture was incubated for a reaction time of 60 min at 22°C. The concentration of mTOR fusion protein was chosen appropriately to have the assay in the linear range (a typical final concentration in the 5 µl assay volume was 1.25 ng/µl). The reaction was stopped by the addition of 5 µl of 30 mM EDTA (final concentration in the 10 µl assay volume = 15 mM) and 2 nM Tb-chelate labelled anti-4E-BP1 [pT46] phosphospecific antibody [Invitrogen Cat.-No. PV4755] (final concentration in the 10 µl assay volume = 1 nM) in FRET buffer.

The resulting mixture was incubated for 1 h at 22°C to allow formation of the complex between the phosphorylated substrate and the Tb-chelate labelled antibody. Subsequently, the amount of phosphorylated substrate was evaluated by measurement of the resonance energy transfer from the Tb-chelate to the GFP. For this, the fluorescence emissions at 495 nm and 520 nm after excitation at 340 nm was measured in an Envision 2104 multilabel reader (Perkin-Elmer). The ratio of the emissions at 520 nm and at 495 nm was taken as the measure for the amount of phosphorylated substrate. Data were normalised (enzyme reaction without inhibitor = 0% inhibition, all other assay

components but no enzyme = 100% inhibition), and either mean values (if tested in replicates at a single concentration) or IC_{50} values (by a 4-parameter fit using an in-house software) were calculated.

Mean inhibition values at 1 µM for individual compounds of the present invention are listed in Table 3 below:

Table 3

Example No.	mTOR % inhibition @ 1 µM
1	8.7
2	7.2
3	8.2
5	9.7
6	0.3
7	3.1
8	7.8
9	*no inhib. effect detect.*
10	6.0
11	33.2
12	25.8
13	14.9
14	15.7
16	36.9
17	6.7
18	*no inhib. effect detect.*
19	17.6
20	31.3
21	5.0

Example No.	mTOR % inhibition @ 1 µM
22	17.6
23	11.6
24	6.3
25	3.5
26	6.8
27	5.9
28	*no inhib. effect detect.*
29	28.5
30	21.1
31	16.3
32	1.6
33	0.9
34	25.9
35	1.4
36	14.4
37	8.6
38	20.8
39	11.5
40	0.1

Example No.	mTOR % inhibition @ 1 µM
41	*no inhib. effect detect.*
42	*no inhib. effect detect.*
43	10.1
44	13.3
45	15.5
46	11.0
47	14.7
48	4.1
51	8.4
52	4.2
53	3.3
54	1.7
56	16.1
57	2.0
58	4.0
59	0.8
60	11.1
61	15.9
62	0.2
64	1.1
65	13.9
66	15.8
67	8.4
68	8.0

Example No.	mTOR % inhibition @ 1 µM
69	8.7
70	5.8
71	0.1
72	8.2
73	18.5
74	18.6
75	10.2
76	8.5
77	0.7
78	5.8
79	14.7
80	3.9
81	4.1
82	7.1
83	6.3
84	9.1
85	0.9
87	12.7
88	5.3
89	*no inhib. effect detect.*
93	12.5
98	*no inhib. effect detect.*
99	5.3
103	*no inhib. effect detect.*

Example No.	mTOR % inhibition @ 1 µM
107	*no inhib. effect detect.*
108	8.5

Example No.	mTOR % inhibition @ 1 µM
119	*no inhib. effect detect.*
121	*no inhib. effect detect.*

(*no inhib. effect detect.* = no inhibitory effect detectable at 1 µM).

The data in Table 3 show that the compounds of the present invention only have a weak, if any, inhibitory effect on mTOR kinase which is not considered to contribute to the pharmacological activity observed with these compounds.

B-5. Inhibition of growth factor-mediated cell proliferation

Human umbilical vein endothelial cells (HUVEC) were obtained from Cellsystems (FC-0003) and grown in Vasculife VEGF complete medium (Cellsystems, LL-1020) containing 2% fetal bovine serum (FBS) at 37°C and 5% CO_2. The cells were used for proliferation assays up to passage 7.

The HUVEC cells were harvested using accutase (PAA, L11-007) and seeded in columns 2 to 12 of 96-well plates (Falcon MICROTEST tissue culture plate 96-well flat bottom, BD 353075, or µCLEAR-PLATE, black, 96-well, Greiner Bio-One, No. 655090) at a cell density of 2500 cells/well in 100 µl Vasculife VEGF complete medium with column 1 remaining empty as blank. Cells were allowed to incubate at 37°C and 5% CO_2 for at least 6 h. Then, the cells were washed once with PBS and starved overnight in Vasculife basal medium (Cellsystems, LM-0002) containing heparin, ascorbate and L-glutamine (components of the Vasculife Life Factors Kit, Cellsystems, LL-1020) as well as 0.2% FBS.

After about 18 h, the starving medium was discarded, and the cells were exposed for 72 h to 9 consecutive log or half-log concentrations of test compound in the range of 10 pM to 30 µM and to 5, 10 or 20 ng/ml hFGF-2 (recombinant human FGF basic, R&D Systems, 233-FB) in 100 µl starving medium. 10 mM stock solutions of test compounds in DMSO were diluted to 200 x final concentration in DMSO resulting in a final DMSO concentration of 0.5% in all wells. Controls consisted of cells grown in starving medium only and of cells grown in hFGF-2 containing starving medium with 0.5% DMSO. To determine cell proliferation, 5 µl Alamar Blue solution (Biosource, DAL1100) was added to each well (1:20 dilution), and the cells were allowed to incubate for further 4 h at 37°C and 5% CO_2 before measuring fluorescence (ex. 535 nm, em. 595 nm) with a Spectrafluor Plus Tecan plate reader (XFLUOR4 version 4.20). In some experiments, an ATP Determination Kit (BIAFFIN GmbH, LBR-T100) was used according to the manufacturer's in-

structions. In each experiment, samples were assayed in triplicate, and the standard deviations were determined. GraphPad Prism 5 software was used to analyze the data and to obtain IC_{50} values. All test compounds were assayed 2 to 10 times in independent experiments and similar results were obtained.

The data listed in Table 4 below represent the IC_{50} values for representative compounds of the invention resulting from the corresponding averaged pIC_{50} values:

Table 4

Example No.	hFGF-2 mediated HUVEC proliferation, IC_{50} [nM]
1	16.4
4	17.5
5	5.3
8	9.7
10	16.0
11	150.0
13	17.0
14	25.0
16	117.3
18	10.4
21	3.7
26	56.7
34	37.3
38	213.3
39	365.0
45	171.0
46	84.5

Example No.	hFGF-2 mediated HUVEC proliferation, IC_{50} [nM]
48	360.0
51	1.2
52	4.0
53	3.3
54	2.2
56	18.1
57	3.2
59	51.1
60	250.0
64	4.5
67	12.1
68	14.4
71	5.4
72	1.6
73	5.5
74	0.2
75	1.5

Example No.	hFGF-2 mediated HUVEC proliferation, IC_{50} [nM]
76	1.5
77	3.2
79	3.5
80	1.6
81	1.6

Example No.	hFGF-2 mediated HUVEC proliferation, IC_{50} [nM]
84	46.6
85	126.0

Most compounds of the present invention displayed about ten- to hundred-fold reduced inhibitory activity in this proliferation assay when vascular endothelial growth factor (VEGF-A_{165} isoform) was used as mediating growth factor (instead of FGF-2), indicating a significant selectivity of these compounds for FGFR versus VEGFR kinases.

B-6. Human xenograft and syngeneic tumor models

Different tumor models have been conducted in order to profile compounds of the present invention *in vivo*. Human, rat or mouse tumor cells were cultivated *in vitro* and implanted into either immunodeficient or immunocompetent mice, or immunodeficient rats. Treatment started after tumor establishment, and tumor-bearing animals were treated with substances via different routes (per os, intravenously, intraperitoneally or subcutaneously). Substances were tested as mono-therapy or in combination therapy with other pharmacological substances. Treatment of the tumor-bearing animals was conducted until the tumors reached an average size of 120 mm^2. Tumors were measured in two dimensions using a caliper, and tumor volume was calculated according to the formula (length x $width^2$)/2. Substance efficacy was evaluated at the end of the experiment using the T/C ratio [T = final tumor weight in the treated group; C = final tumor weight in the control group]. Statistical significance of the efficacy between control and treated groups was determined using the ANOVA variance test. All animal studies were conducted according to the German regulatory guidelines.

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:

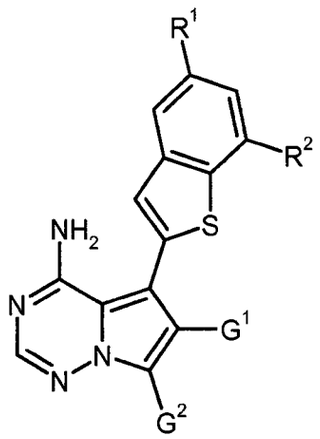
A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 mg of the desired compound of the invention, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8 mg of lactose. Appropriate aqueous 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

R^1 is hydrogen, chloro, methyl or methoxy,

R^2 is hydrogen or methoxy,

with the proviso that at least one of R^1 and R^2 is other than hydrogen,

G^1 represents chloro, $(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_4)$-alkoxycarbonyl, 5-membered aza-heteroaryl, or the group $-CH_2\text{-}OR^3$, $-CH_2\text{-}NR^4R^5$ or $-C(=O)\text{-}NR^4R^6$, wherein

R^3 is hydrogen, $(C_1\text{-}C_4)$-alkyl, $(C_3\text{-}C_6)$-cycloalkyl or phenyl,

(*i*) said $(C_1\text{-}C_4)$-alkyl is optionally substituted with hydroxy, $(C_1\text{-}C_4)$-alkoxy, hydroxycarbonyl, $(C_1\text{-}C_4)$-alkoxycarbonyl, amino, aminocarbonyl, mono-$(C_1\text{-}C_4)$-alkylaminocarbonyl, di-$(C_1\text{-}C_4)$-alkylaminocarbonyl, $(C_3\text{-}C_6)$-cycloalkyl or up to three fluoro atoms,

and

(*ii*) said $(C_3\text{-}C_6)$-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of $(C_1\text{-}C_4)$-alkyl, hydroxy and amino,

and

(*iii*) said phenyl is optionally substituted with one or two substituents independently selected from the group consisting of fluoro, chloro, bromo, cyano, trifluoromethyl, trifluoromethoxy, (C_1-C_4)-alkyl and (C_1-C_4)-alkoxy,

R^4 is hydrogen or (C_1-C_4)-alkyl,

R^5 is hydrogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkylcarbonyl, (C_3-C_6)-cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein

(*i*) said (C_1-C_4)-alkyl is optionally substituted with hydroxy, (C_1-C_4)-alkoxy, hydroxycarbonyl, (C_1-C_4)-alkoxycarbonyl, aminocarbonyl, mono-(C_1-C_4)-alkylaminocarbonyl, di-(C_1-C_4)-alkylaminocarbonyl or (C_3-C_6)-cycloalkyl,

and

(*ii*) said (C_3-C_6)-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy and amino,

and

(*iii*) said 4- to 6-membered heterocycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy, oxo and amino,

R^6 is hydrogen, (C_1-C_4)-alkyl, (C_3-C_6)-cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein

(*i*) said (C_1-C_4)-alkyl is optionally substituted with hydroxy, (C_1-C_4)-alkoxy, hydroxycarbonyl, (C_1-C_4)-alkoxycarbonyl, amino, aminocarbonyl, mono-(C_1-C_4)-alkylaminocarbonyl, di-(C_1-C_4)-alkylaminocarbonyl or (C_3-C_6)-cycloalkyl,

and

(*ii*) said (C_3-C_6)-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy and amino,

and

(*iii*) said 4- to 6-membered heterocycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy, oxo and amino,

or

R^4 and R^5, or R^4 and R^6, respectively, are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 4- to 7-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from $N(R^7)$ and O, and which may be substituted on ring carbon atoms with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, oxo, hydroxy, amino and aminocarbonyl, and wherein

R^7 is hydrogen, (C_1-C_4)-alkyl, formyl or (C_1-C_4)-alkylcarbonyl,

and

G^2 represents chloro, cyano, (C_1-C_4)-alkyl, or the group $-CR^{8A}R^{8B}$-OH, $-CH_2-NR^9R^{10}$, $-C(=O)-NR^{11}R^{12}$ or $-CH_2-OR^{15}$, wherein

R^{8A} and R^{8B} are independently selected from the group consisting of hydrogen, (C_1-C_4)-alkyl, cyclopropyl and cyclobutyl,

R^9 is hydrogen or (C_1-C_4)-alkyl,

R^{10} is hydrogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkylcarbonyl, (C_3-C_6)-cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein

(*i*) said (C_1-C_4)-alkyl is optionally substituted with hydroxy, amino, aminocarbonyl, mono-(C_1-C_4)-alkylaminocarbonyl or di-(C_1-C_4)-alkylaminocarbonyl,

and

(*ii*) said (C_3-C_6)-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy and amino,

and

(*iii*) said 4- to 6-membered heterocycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy, oxo and amino,

R^{11} is hydrogen or (C_1-C_4)-alkyl,

R^{12} is hydrogen, (C_1-C_4)-alkyl, (C_3-C_6)-cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein

(*i*) said (C_1-C_4)-alkyl is optionally substituted with hydroxy, amino, aminocarbonyl, mono-(C_1-C_4)-alkylaminocarbonyl or di-(C_1-C_4)-alkylaminocarbonyl,

and

(*ii*) said (C_3-C_6)-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy and amino,

and

(*iii*) said 4- to 6-membered heterocycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy, oxo and amino,

or

R^9 and R^{10}, or R^{11} and R^{12}, respectively, are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 4- to 7-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from $N(R^{13})$, O, S and $S(O)_2$, and which may be substituted on ring carbon atoms with up to three substituents independently selected from the group consisting of fluoro, (C_1-C_4)-alkyl, oxo, hydroxy, amino and aminocarbonyl, and wherein

R^{13} is hydrogen, (C_1-C_4)-alkyl, (C_3-C_6)-cycloalkyl, formyl or (C_1-C_4)-alkylcarbonyl,

and

R^{15} is $(C_1$-$C_4)$-alkyl,

with the proviso that G^1 is not chloro when G^2 is chloro or cyano,

or a pharmaceutically acceptable salt, hydrate and/or solvate thereof.

2. The compound of formula (I) according to Claim 1, wherein

R^1 is chloro, methyl or methoxy,

R^2 is hydrogen or methoxy,

G^1 represents chloro, $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkoxycarbonyl or 5-membered aza-heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl, or represents the group $-CH_2$-OR^3 or $-CH_2$-NR^4R^5, wherein

R^3 is hydrogen, $(C_1$-$C_4)$-alkyl or $(C_3$-$C_6)$-cycloalkyl,

wherein said $(C_1$-$C_4)$-alkyl is optionally substituted with hydroxy, $(C_1$-$C_4)$-alkoxy, hydroxycarbonyl, $(C_1$-$C_4)$-alkoxycarbonyl, amino, aminocarbonyl, $(C_3$-$C_6)$-cycloalkyl or up to three fluoro atoms,

R^4 is hydrogen or $(C_1$-$C_4)$-alkyl,

R^5 is hydrogen, $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkylcarbonyl, $(C_3$-$C_6)$-cycloalkyl or 5- or 6-membered heterocycloalkyl, wherein

(*i*) said $(C_1$-$C_4)$-alkyl is optionally substituted with hydroxy, hydroxycarbonyl or $(C_3$-$C_6)$-cycloalkyl,

and

(*ii*) said 5- or 6-membered heterocycloalkyl is optionally substituted with oxo,

or

R^4 and R^5 are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 4- to 6-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from $N(R^7)$ and

O, and which may be substituted on a ring carbon atom with oxo or hydroxy, and wherein

R^7 is hydrogen or $(C_1$-$C_4)$-alkyl,

and

G^2 represents chloro, cyano, $(C_1$-$C_4)$-alkyl, or the group $-CR^{8A}R^{8B}$-OH, $-CH_2$-NR^9R^{10}, $-C(=O)$-$NR^{11}R^{12}$ or $-CH_2$-OR^{15}, wherein

R^{8A} and R^{8B} are independently selected from the group consisting of hydrogen, $(C_1$-$C_4)$-alkyl and cyclopropyl,

R^9 is hydrogen or methyl,

R^{10} is hydrogen, $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkylcarbonyl, $(C_3$-$C_6)$-cycloalkyl or 5- or 6-membered heterocycloalkyl, wherein

(*i*) said $(C_1$-$C_4)$-alkyl is optionally substituted with hydroxy or amino-carbonyl,

and

(*ii*) said 5- or 6-membered heterocycloalkyl is optionally substituted with oxo,

R^{11} is hydrogen or methyl,

R^{12} is hydrogen, $(C_1$-$C_4)$-alkyl, $(C_3$-$C_6)$-cycloalkyl or 5- or 6-membered hetero-cycloalkyl, wherein

(*i*) said $(C_1$-$C_4)$-alkyl is optionally substituted with hydroxy,

and

(*ii*) said 5- or 6-membered heterocycloalkyl is optionally substituted with oxo,

or

R^9 and R^{10}, or R^{11} and R^{12}, respectively, are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 4- to

6-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from $N(R^{13})$, O, S and $S(O)_2$, and which may be substituted on ring carbon atoms with up to three substituents independently selected from the group consisting of fluoro, $(C_1$-$C_4)$-alkyl, oxo, hydroxy, amino and aminocarbonyl, and wherein

R^{13} is hydrogen, $(C_1$-$C_4)$-alkyl, cyclopropyl, cyclobutyl, formyl or $(C_1$-$C_4)$-alkylcarbonyl,

and

R^{15} is methyl or ethyl,

with the proviso that G^1 is not chloro when G^2 is chloro or cyano,

or a pharmaceutically acceptable salt, hydrate and/or solvate thereof.

3. The compound of formula (I) according to Claim 1 or 2, wherein

R^1 is methyl,

R^2 is methoxy,

G^1 represents methyl, oxazol-5-yl or the group $-CH_2-OR^3$ or $-CH_2-NR^4R^5$, wherein

R^3 is hydrogen, $(C_1$-$C_4)$-alkyl, cyclopropyl or cyclobutyl,

wherein said $(C_1$-$C_4)$-alkyl is optionally substituted with hydroxy, methoxy, ethoxy, hydroxycarbonyl, methoxycarbonyl, ethoxycarbonyl, amino, aminocarbonyl, cyclopropyl, cyclobutyl or up to three fluoro atoms,

R^4 is hydrogen, methyl or ethyl,

R^5 is hydrogen, $(C_1$-$C_4)$-alkyl, acetyl, cyclopropyl, cyclobutyl or 2-oxopyrrolidin-3-yl,

wherein said $(C_1$-$C_4)$-alkyl is optionally substituted with hydroxy, hydroxycarbonyl, cyclopropyl or cyclobutyl,

or

R^4 and R^5 are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 5- or 6-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from NH and O, and which may be substituted on a ring carbon atom with oxo or hydroxy,

and

G^2 represents methyl or the group $-CR^{8A}R^{8B}-OH$, $-CH_2-NR^9R^{10}$ or $-C(=O)-NR^{11}R^{12}$, wherein

R^{8A} and R^{8B} are independently hydrogen or methyl,

R^9 is hydrogen,

R^{10} is hydrogen, (C_1-C_4)-alkyl, acetyl, cyclopropyl, cyclobutyl or 2-oxopyrrolidin-3-yl,

wherein said (C_1-C_4)-alkyl is optionally substituted with hydroxy or aminocarbonyl,

R^{11} is hydrogen or methyl,

R^{12} is hydrogen, (C_1-C_4)-alkyl, cyclopropyl, cyclobutyl or 2-oxopyrrolidin-3-yl,

wherein said (C_1-C_4)-alkyl is optionally substituted with hydroxy,

or

R^9 and R^{10}, or R^{11} and R^{12}, respectively, are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 4- to 6-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from $N(R^{13})$, O and $S(O)_2$, and which may be substituted on ring carbon atoms with up to three substituents independently selected from the group consisting of fluoro, methyl, oxo, hydroxy, amino and aminocarbonyl, and wherein

R^{13} is hydrogen, formyl or acetyl,

or a pharmaceutically acceptable salt, hydrate and/or solvate thereof.

4. The compound of formula (I) according to Claim 1, 2 or 3, wherein

R^1 is methyl,

R^2 is methoxy,

G^1 represents the group $-CH_2-OR^3$, wherein

R^3 is (C_1-C_4)-alkyl optionally substituted with hydroxy, amino or aminocarbonyl,

and

G^2 represents the group $-CH_2-NR^9R^{10}$ or $-C(=O)-NR^{11}R^{12}$, wherein

R^9 is hydrogen,

R^{10} is 2-oxopyrrolidin-3-yl,

or

R^9 and R^{10} are joined and, taken together with the nitrogen atom to which they are attached, form a piperazin-1-yl, 3-oxopiperazin-1-yl or 4-acetylpiperazin-1-yl ring,

R^{11} is hydrogen,

R^{12} is 2-oxopyrrolidin-3-yl,

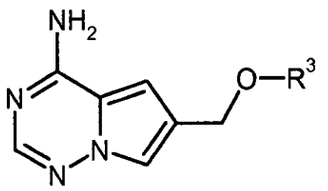
or

R^{11} and R^{12} are joined and, taken together with the nitrogen atom to which they are attached, form a 3-hydroxyazetidin-1-yl, 4-hydroxypiperidin-1-yl or 3-oxopiperazin-1-yl ring,

or a pharmaceutically acceptable salt, hydrate and/or solvate thereof.

5. Process for preparing a compound of formula (I) as defined in Claims 1 to 4, characterized in that

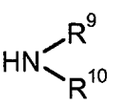
[A] a 6-substituted 4-aminopyrrolo[2,1-f][1,2,4]triazine of formula (II)



(II),

wherein R^3 has the meaning indicated in Claim 1 to 4,

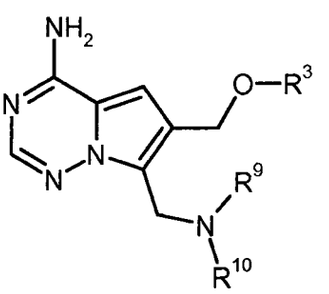
is at first reacted with formaldehyde and an amine of formula (III)



(III),

wherein R^9 and R^{10} have the meanings indicated in Claim 1 to 4,

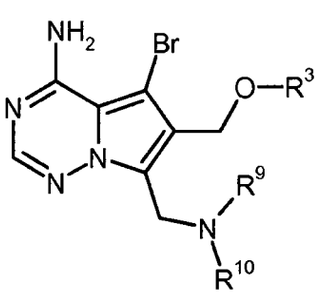
in the presence of an acid to give a compound of formula (IV)



(IV),

wherein R^3, R^9 and R^{10} have the meanings indicated in Claim 1 to 4,

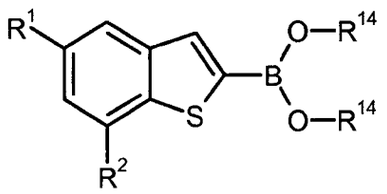
then brominated to a compound of formula (V)



(V),

wherein R^3, R^9 and R^{10} have the meanings indicated in Claim 1 to 4,

and subsequently coupled with a benzothiophen-2-yl boronate of formula (VI)



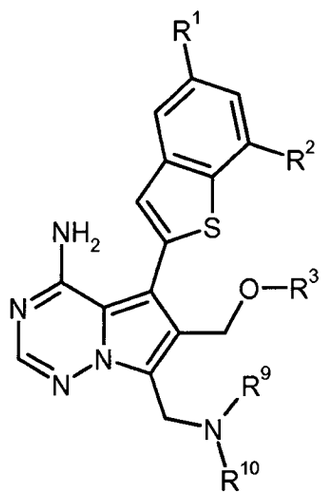
(VI),

wherein R^1 and R^2 have the meanings indicated in Claim 1 to 4,

and

R^{14} represents hydrogen or (C_1-C_4)-alkyl, or both R^{14} residues are linked together to form a $-(CH_2)_2-$, $-C(CH_3)_2-C(CH_3)_2-$, $-(CH_2)_3-$, $-CH_2-C(CH_3)_2-CH_2-$ or $-C(=O)-CH_2-N(CH_3)-CH_2-C(=O)-$ bridge,.

in the presence of a palladium catalyst and a base to yield the target compound of formula (I-A)

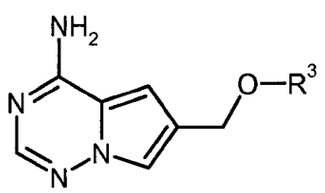


(I-A),

wherein R^1, R^2, R^3, R^9 and R^{10} have the meanings indicated in Claim 1 to 4,

or

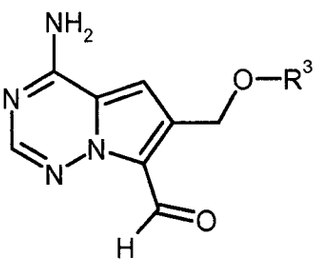
[B] a 6-substituted 4-aminopyrrolo[2,1-f][1,2,4]triazine of formula (II)



(II),

wherein R^3 has the meaning indicated in Claim 1 to 4,

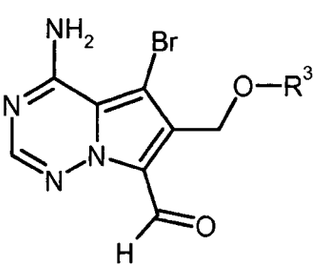
is at first formylated with *N,N*-dimethylformamide in the presence of phosphoryl chloride to an aldehyde of formula (VII)



(VII),

wherein R^3 has the meaning indicated in Claim 1 to 4,

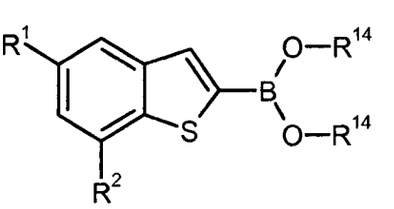
then brominated to a compound of formula (VIII)



(VIII),

wherein R^3 has the meaning indicated in Claim 1 to 4,

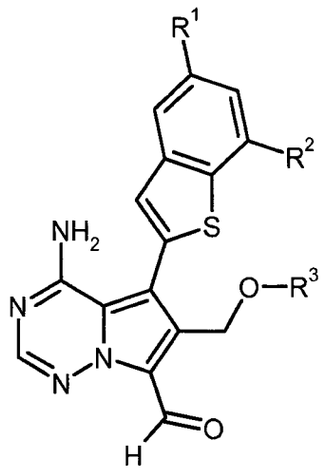
and subsequently coupled with a benzothiophen-2-yl boronate of formula (VI)



(VI),

wherein R^1, R^2 and R^{14} have the meanings indicated above,

in the presence of a palladium catalyst and a base to give a compound of formula (IX)

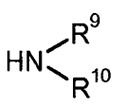


(IX),

wherein R^1, R^2 and R^3 have the meanings indicated in Claim 1 to 4,

which then is either

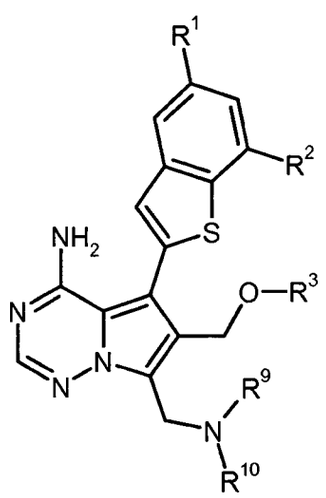
[B-1] reacted with an amine of formula (III)



(III),

wherein R^9 and R^{10} have the meanings indicated in Claim 1 to 4,

in the presence of an acid and a reducing agent to yield the target compound of formula (I-A)

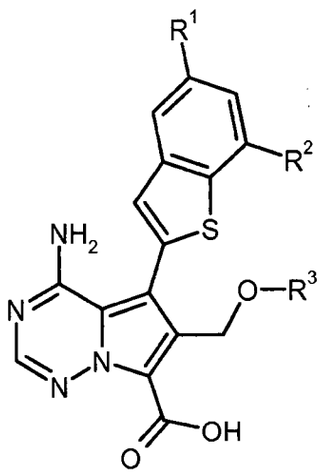


(I-A),

wherein R^1, R^2, R^3, R^9 and R^{10} have the meanings indicated in Claim 1 to 4,

or

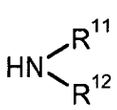
[B-2] oxidized to a carboxylic acid of formula (X)



(X),

wherein R^1, R^2 and R^3 have the meanings indicated in Claim 1 to 4,

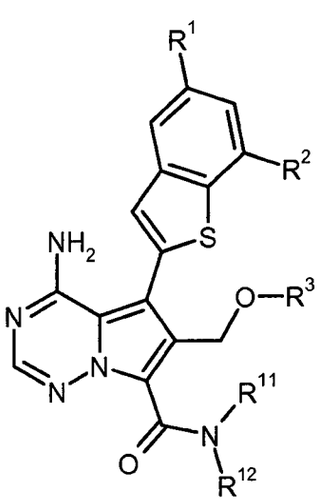
and finally coupled with an amine of formula (XI)



(XI),

wherein R^{11} and R^{12} have the meanings indicated in Claim 1 to 4,

in the presence of a condensing agent to yield the target compound of formula (I-B)

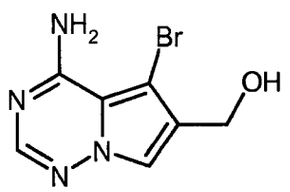


(I-B),

wherein R^1, R^2, R^3, R^{11} and R^{12} have the meanings indicated in Claim 1 to 4,

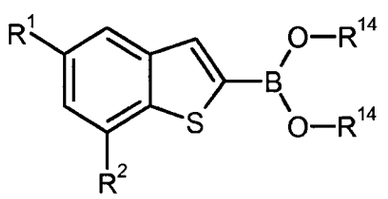
or

[C] a 6-substituted 4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazine of formula (XII)



(XII)

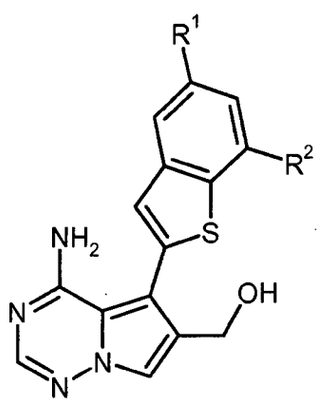
is at first coupled with a benzothiophen-2-yl boronate of formula (VI)



(VI),

wherein R^1, R^2 and R^{14} have the meanings indicated above,

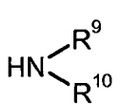
in the presence of a palladium catalyst and a base to give a compound of formula (XIII)



(XIII),

wherein R^1 and R^2 have the meanings indicated in Claim 1 to 4,

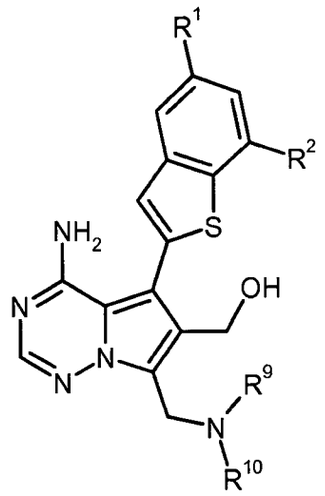
and then reacted with formaldehyde and an amine of formula (III)



(III),

wherein R^9 and R^{10} have the meanings indicated in Claim 1 to 4,

in the presence of an acid to yield the compound of formula (I-C)

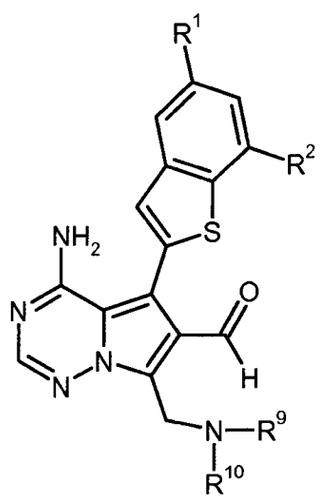


(I-C),

wherein R^1, R^2, R^9 and R^{10} have the meanings indicated in Claim 1 to 4,

which subsequently is either

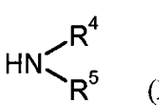
[C-1] oxidized to an aldehyde of formula (XIV)



(XIV),

wherein R^1, R^2, R^9 and R^{10} have the meanings indicated in Claim 1 to 4,

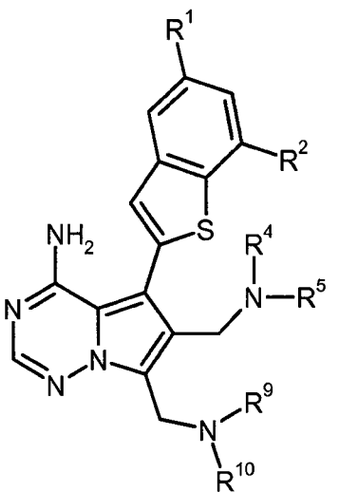
and treated with an amine of formula (XV)



(XV),

wherein R^4 and R^5 have the meanings indicated in Claim 1 to 4,

in the presence of an acid and a reducing agent to yield the target compound of formula (I-D)

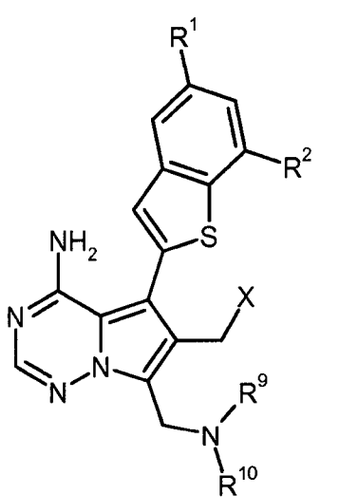


(I-D),

wherein R^1, R^2, R^4, R^5, R^9 and R^{10} have the meanings indicated in Claim 1 to 4,

or

[C-2] converted into the corresponding 6-(halomethyl) derivative of formula (XVI)



(XVI),

wherein R^1, R^2, R^9 and R^{10} have the meanings indicated in Claim 1 to 4,

and

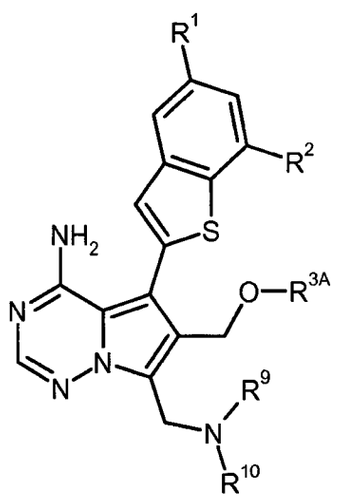
X is chloro, bromo or iodo,

and treated with an alcohol of formula (XVII)

R^{3A}—OH (XVII),

wherein R^{3A} has the meaning of R^3 as indicated in Claim 1 to 4, except for hydrogen,

in the presence of a base to yield the target compound of formula (I-E)



(I-E),

wherein R^1, R^2, R^{3A}, R^9 and R^{10} have the meanings indicated above,

optionally followed, where appropriate, by (*i*) separating the compounds of formula (I) thus obtained 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 or bases.

6. Compound as defined in any of Claims 1 to 4 for the treatment and/or prevention of diseases.

7. Compound as defined in any of Claims 1 to 4 for use in a method for the treatment and/or prevention of cancer and tumor diseases.

8. Use of a compound as defined in any of Claims 1 to 4 for the manufacture of a pharmaceutical composition for the treatment and/or prevention of cancer and tumor diseases.

9. Pharmaceutical composition comprising a compound as defined in any of Claims 1 to 4 and one or more pharmaceutically acceptable excipients.

10. The pharmaceutical composition of Claim 9 further comprising one or more additional therapeutic agents.

11. The pharmaceutical composition as defined in Claim 9 or 10 for the treatment and/or prevention of cancer and tumor diseases.

12. Method for the treatment and/or prevention of cancer and tumor diseases 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 4, or of a pharmaceutical composition as defined in any of Claims 9 to 11.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/074977

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/53 A61P35/00
ADD.

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

B. FIELDS SEARCHED

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

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, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/061737 A2 (OSI PHARM INC [US]; CHEN XIN [US]; COATE HEATHER [US]; CREW ANDREW-PHI) 31 May 2007 (2007-05-31) cited in the application the whole document	1-12
A	WO 00/71129 A1 (SQUIBB BRISTOL MYERS CO [US]) 30 November 2000 (2000-11-30) cited in the application the whole document	1-12
A	WO 2007/079164 A2 (ABBOTT LAB [US]; SHEPPARD GEORGE [US]; WANG GARY [US]; PALAZZO FABIO [] 12 July 2007 (2007-07-12) cited in the application the whole document	1-12

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

☒ See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
6 February 2013	13/02/2013

Name and mailing address of the ISA/	Authorized officer
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524

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2012/074977

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007061737 A2	31-05-2007	AR 056884 A1	31-10-2007
		AT 507227 T	15-05-2011
		AU 2006316605 A1	31-05-2007
		BR PI0618622 A2	06-09-2011
		CA 2630271 A1	31-05-2007
		CN 101316845 A	03-12-2008
		DK 1951724 T3	15-08-2011
		EA 200801341 A1	30-12-2008
		EP 1951724 A2	06-08-2008
		EP 2325186 A2	25-05-2011
		EP 2385053 A2	09-11-2011
		ES 2365869 T3	11-10-2011
		HK 1121158 A1	16-12-2011
		HR P20110553 T1	30-09-2011
		JP 4491510 B2	30-06-2010
		JP 2009519222 A	14-05-2009
		JP 2010065049 A	25-03-2010
		KR 20080078668 A	27-08-2008
		NZ 569050 A	26-11-2010
		PT 1951724 E	02-08-2011
		RS 51843 B	29-02-2012
		SI 1951724 T1	30-09-2011
		TW 200801006 A	01-01-2008
		US 2007112005 A1	17-05-2007
		US 2009163468 A1	25-06-2009
		US 2010099679 A1	22-04-2010
		US 2011190496 A1	04-08-2011
		US 2011218183 A1	08-09-2011
		WO 2007061737 A2	31-05-2007
		ZA 200804237 A	30-09-2009
WO 0071129 A1	30-11-2000	AR 043087 A1	20-07-2005
		AT 318603 T	15-03-2006
		AU 770377 B2	19-02-2004
		AU 4852400 A	12-12-2000
		BR 0010482 A	23-04-2002
		CA 2373990 A1	30-11-2000
		CN 1351498 A	29-05-2002
		CZ 20014169 A3	16-10-2002
		DE 60026297 T2	02-11-2006
		DK 1183033 T3	06-06-2006
		EG 24027 A	26-03-2008
		EP 1183033 A1	06-03-2002
		ES 2258459 T3	01-09-2006
		ES 2328269 T3	11-11-2009
		HK 1041599 A1	15-09-2006
		HU 0301005 A2	28-07-2003
		IL 144977 A	10-12-2006
		JP 4649046 B2	09-03-2011
		JP 2003500359 A	07-01-2003
		JP 2011037878 A	24-02-2011
		MX PA01011832 A	21-06-2002
		MY 128370 A	31-01-2007
		NO 20015650 A	20-11-2001
		NZ 516292 A	30-01-2004
		PE 01262001 A1	22-04-2001
		PL 351720 A1	02-06-2003
		RU 2331640 C2	20-08-2008

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2012/074977

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		TR 200103352 T2	21-03-2005
		TW I238163 B	21-08-2005
		UY 26150 A1	29-12-2000
		WO 0071129 A1	30-11-2000
WO 2007079164 A2	12-07-2007	CA 2635231 A1	12-07-2007
		CN 101389630 A	18-03-2009
		EP 1973917 A2	01-10-2008
		JP 2009522284 A	11-06-2009
		TW 200801008 A	01-01-2008
		US 2007203143 A1	30-08-2007
		WO 2007079164 A2	12-07-2007

5/26

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DOCUMENT MADE AVAILABLE UNDER THE PATENT COOPERATION TREATY (PCT)

International application number:		**PCT/EP2012/074977**
International filing date:		**10 December 2012 (10.12.2012)**
Document type:		**Certified copy of priority document**
Document details:	Country/Office:	**EP**
	Number:	**11193841.1**
	Filing date:	**15 December 2011 (15.12.2011)**
Date of receipt at the International Bureau:		**10 January 2013 (10.01.2013)**

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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527

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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°**

11193841.1 / EP11193841

The organization code and number of your priority application, to be used for filing abroad under the Paris Convention, is EP11193841.

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

528

Anmeldung Nr:
Application no.: 11193841.1
Demande no :

Anmeldetag:
Date of filing: 15.12.11
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.)

Disubstituted benzothienyl-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

Disubstituted benzothienyl-pyrrolotriazines and uses thereof

This invention relates to novel substituted 5-(1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine derivatives having protein tyrosine kinase inhibitory activities, 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 proliferative disorders, in particular cancer and tumor diseases.

Cancer is a leading cause of death worldwide and accounted for 7.6 million deaths (around 13% of all deaths) in 2008. Deaths from cancer are projected to continue to rise worldwide to over 11 million in 2030 (WHO source, Fact Sheet No. 297, February 2011).

There are many ways how cancers can arise which is one of the reasons why their therapy is difficult. One way that transformation of cells can occur is following a genetic alteration. The completion of the human genome project showed genomic instability and heterogeneity of human cancer genes. Recent strategies to identify these genetic alterations sped up the process of cancer-gene discovery. Gene abnormality can, for instance, lead to the overexpression of proteins, and hence to a non-physiological activation of these proteins. One family of proteins from which a number of oncoproteins derive are tyrosine kinases and in particular receptor tyrosine kinases (RTKs). In the past two decades, numerous avenues of research have demonstrated the importance of RTK-mediated signalling in adverse cell growth leading to cancer. In recent years, promising results have been achieved in the clinic with selective small-molecule inhibitors of tyrosine kinases as a new class of anti-tumorigenic agents [Swinney and Anthony, *Nature Rev. Drug Disc.* 10 (7), 507-519 (2011)].

Fibroblast growth factors (FGFs) and their receptors (FGFRs) form part of a unique and diverse signalling system which plays a key role in a variety of biological processes which encompass various aspects of embryonic development and adult pathophysiology [Itoh and Ornitz, *J. Biochem.* 149 (2), 121-130 (2011)]. In a spatio-temporal manner, FGFs stimulate through FGFR binding a wide range of cellular functions including migration, proliferation, differentiation, and survival.

The FGF family comprises 18 secreted polypeptidic growth factors that bind to four highly conserved receptor tyrosine kinases (FGFR-1 to -4) expressed at the cell surface. In addition, FGFR-5 can bind to FGFs but does not have a kinase domain, and therefore is devoid of intracellular signalling. The specificity of the ligand/receptor interaction is enhanced by a number of transcriptional and translational processes which give rise to multiple isoforms by alternative transcriptional initiation, alternative splicing, and C-terminal truncations. Various heparan sulfate proteo-

glycans (e.g. syndecans) can be part of the FGF/FGFR complex and strongly influence the ability of FGFs to induce signalling responses [Polanska *et al.*, *Developmental Dynamics* 238 (2), 277-293 (2009)]. FGFRs are cell surface receptors consisting of three extracellular immunoglobulin-like domains, a single-pass transmembrane domain, and an intracellular dimerized tyrosine kinase domain. Binding of FGF bring the intracellular kinases into close proximity, enabling them to transphosphorylate each other. Seven phosphorylation sites have been identified (e.g., in FGFR-1 Tyr463, Tyr583, Tyr585, Tyr653, Tyr654, Tyr730, and Tyr766).

Some of these phosphotyrosine groups act as docking sites for downstream signalling molecules which themselves may also be directly phosphorylated by FGFR, leading to the activation of multiple signal transduction pathways. Thus, the MAPK signalling cascade is implicated in cell growth and differentiation, the PI3K/Akt signalling cascade is involved in cell survival and cell fate determination, while the PI3K and PKC signalling cascades have a function in the control of cell polarity. Several feedback inhibitors of FGF signalling have now been identified and include members of the Spry (Sprouty) and Sef (similar expression to FGF) families. Additionally, in certain conditions, FGFR is released from pre-Golgi membranes into the cytosol. The receptor and its ligand, FGF-2, are co-transported into the nucleus by a mechanism that involves importin, and are engaged in the CREB-binding protein (CBP) complex, a common and essential transcriptional co-activator that acts as a gene activation gating factor. Multiple correlations between the immunohistochemical expression of FGF-2, FGFR-1 and FGFR-2 and their cytoplasmic and nuclear tumor cell localizations have been observed. For instance, in lung adenocarcinomas this association is also found at the nuclear level, emphasizing an active role of the complex at the nucleus [Korc and Friesel, *Curr. Cancer Drugs Targets* 5, 639-651 (2009)].

FGFs are widely expressed in both developing and adult tissues and play important roles in a variety of normal and pathological processes, including tissue development, tissue regeneration, angiogenesis, neoplastic transformation, cell migration, cellular differentiation, and cell survival. Additionally, FGFs as pro-angiogenic factors have also been implicated in the emerging phenomenon of resistance to vascular endothelial growth factor receptor-2 (VEGFR-2) inhibition [Bergers and Hanahan, *Nat. Rev. Cancer* 8, 592-603 (2008)].

Recent oncogenomic profiles of signalling networks demonstrated an important role for aberrant FGF signalling in the emergence of some common human cancers [Wesche *et al.*, *Biochem. J.* 437 (2), 199-213 (2011)]. Ligand-independent FGFR constitutive signalling has been described in many human cancers, such as brain cancer, head and neck cancer, gastric cancer and ovarian cancer. FGFR-mutated forms as well as FGFR-intragenic translocations have been identified in malignancies such as myeloproliferative diseases. Interestingly, the same mutations discovered to

be the cause of many developmental disorders are also found in tumor cells (e.g., the mutations found in achondroplasia and thanatophoric dysplasia, which cause dimerization and thus constitutive activation of FGFR-3, are also frequently found in bladder cancer). A mutation that promotes dimerization is just one mechanism that can increase ligand-independent signalling from FGFRs. Other mutations located inside or outside of the kinase domain of FGFRs can change the conformation of the domain giving rise to permanently active kinases.

Amplification of the chromosomal region 8p11-12, the genomic location of *FGFR-1*, is a common focal amplification in breast cancer and occurs in approximately 10% of breast cancers, predominantly in oestrogen receptor-positive cancers. *FGFR-1* amplifications have also been reported in non-small cell lung squamous carcinoma and are found at a low incidence in ovarian cancer, bladder cancer and rhabdomyosarcoma. Similarly, approximately 10% of gastric cancers show *FGFR-2* amplification, which is associated with poor prognosis, diffuse-type cancers. Moreover, multiple single nucleotide polymorphisms (SNPs) located in FGFR-1 to -4 were found to correlate with an increased risk of developing selective cancers, or were reported to be associated with poor prognosis (e.g., FGFR-4 G388R allele in breast cancer, colon cancer and lung adenocarcinoma). The direct role of these SNPs to promote cancer is still controversial.

In summary, a great number of *in vitro* and *in vivo* studies have been performed that validate FGFR-1 to -4 as important cancer targets, and comprehensive reviews have summarized these findings [see, for example, Heinzle *et al.*, *Expert Opin. Ther. Targets* 15 (7), 829-846 (2011); Wesche *et al.*, *Biochem. J.* 437 (2), 199-213 (2011); Greulich and Pollock, *Trends in Molecular Medicine* 17 (5), 283-292 (2011); Haugsten *et al.*, *Mol. Cancer Res.* 8 (11), 1439-1452 (2010)]. Several strategies have been followed to attenuate aberrant FGFR-1 to -4 signalling in human tumors including blocking antibodies and small-molecule inhibitors, amongst others. A number of selective small-molecule FGFR inhibitors are currently in clinical development, such as AZD-4547 (AstraZeneca) and BJG-398 (Novartis).

Notwithstanding the significant advancements that have generally been achieved in cancer therapy in recent years, there is a continuing need to identify new anti-cancer compounds with improved properties, such as higher potency, greater selectivity, reduced toxicity and/or better tolerability. Therefore, the technical problem to be solved according to the present invention may be seen in providing alternative compounds having inhibitory activity on the FGFR kinases, thus offering new therapeutic options for the treatment of FGFR-mediated diseases, in particular cancer and other proliferative disorders.

Fused hetero-5,6-bicyclic kinase inhibitors bearing a 9- or a 10-membered bicyclic heteroaryl substituent have been disclosed in WO 2007/061737-A2 and WO 2005/097800-A1, respectively.

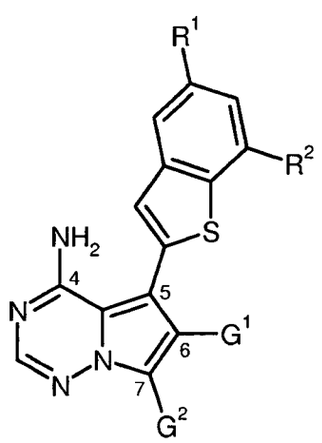
These compounds were stated to be useful for the treatment of cancer and other diseases owing to their inhibitory action on the mTOR (mammalian target of Rapamycin) and/or IGF-1R (type 1 insulin-like growth factor receptor) kinases. Further hetero-5,6-bicyclic template structures associated with the inhibition of kinases have been described in, *inter alia*, WO 01/19828-A2, WO 2007/079164-A2 and WO 2010/051043-A1.

4-Aminopyrrolo[2,1-f][1,2,4]triazine derivatives with differing inhibition profiles against a number of protein kinases have been disclosed in, *inter alia*, WO 00/71129-A1, WO 2007/056170-A2, WO 2007/061882-A2, WO 2007/064932-A2, WO 2009/136966-A1, and WO 2010/126960-A1.

In WO 2005/121147-A1, WO 2007/064883-A2 and WO 2007/064931-A2, 4-aminopyrrolo[2,1-f]-[1,2,4]triazine derivatives containing a substituted diarylurea group in 5-position were described as having FGFR-1 inhibiting activity. However, other receptor tyrosine kinases, notably the VEGFR, PDGFR and Tie-2 kinases, are also significantly inhibited by this particular class of compounds. As it was hypothesized that such multi-kinase activity might lead to an augmentation of potential side effects during treatment, it was the aim of the present invention to identify new agents having an improved selectivity for the FGFR kinases, thus providing new options for a more tolerable cancer therapy.

Surprisingly, it has now been found that certain 4-aminopyrrolo[2,1-f][1,2,4]triazine derivatives bearing a specifically substituted benzothiophen-2-yl residue in 5-position exhibit potent and selective inhibition of FGFR kinases, notably of the FGFR-1 and FGFR-3 kinases, which renders these compounds particularly useful for the treatment of proliferative disorders, such as cancer and tumor diseases.

Thus, in one aspect, the present invention relates to 6,7-disubstituted 5-(1-benzothiophen-2-yl)-pyrrolo[2,1-f][1,2,4]triazin-4-amine derivatives of the general formula (I)



(I),

wherein

R^1 is hydrogen, chloro, methyl or methoxy,

R^2 is hydrogen or methoxy,

with the proviso that at least one of R^1 and R^2 is other than hydrogen,

G^1 represents chloro, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxycarbonyl, 5-membered aza-heteroaryl, or the group $-CH_2-OR^3$, $-CH_2-NR^4R^5$ or $-C(=O)-NR^4R^6$, wherein

R^3 is hydrogen, (C_1-C_4)-alkyl, (C_3-C_6)-cycloalkyl or phenyl, wherein

(*i*) said (C_1-C_4)-alkyl is optionally substituted with hydroxy, (C_1-C_4)-alkoxy, hydroxycarbonyl, (C_1-C_4)-alkoxycarbonyl, amino, aminocarbonyl, mono-(C_1-C_4)-alkylaminocarbonyl, di-(C_1-C_4)-alkylaminocarbonyl, (C_3-C_6)-cycloalkyl or up to three fluoro atoms,

and

(*ii*) said (C_3-C_6)-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy and amino,

and

(*iii*) said phenyl is optionally substituted with one or two substituents independently selected from the group consisting of fluoro, chloro, bromo, cyano, trifluoromethyl, trifluoromethoxy, (C_1-C_4)-alkyl and (C_1-C_4)-alkoxy,

R^4 is hydrogen or (C_1-C_4)-alkyl,

R^5 is hydrogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkylcarbonyl, (C_3-C_6)-cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein

(*i*) said (C_1-C_4)-alkyl is optionally substituted with hydroxy, (C_1-C_4)-alkoxy, hydroxycarbonyl, (C_1-C_4)-alkoxycarbonyl, aminocarbonyl, mono-(C_1-C_4)-alkylaminocarbonyl, di-(C_1-C_4)-alkylaminocarbonyl or (C_3-C_6)-cycloalkyl,

and

(*ii*) said (C_3-C_6)-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy and amino,

and

(*iii*) said 4- to 6-membered heterocycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy, oxo and amino,

R^6 is hydrogen, (C_1-C_4)-alkyl, (C_3-C_6)-cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein

(*i*) said (C_1-C_4)-alkyl is optionally substituted with hydroxy, (C_1-C_4)-alkoxy, hydroxycarbonyl, (C_1-C_4)-alkoxycarbonyl, amino, aminocarbonyl, mono-(C_1-C_4)-alkylaminocarbonyl, di-(C_1-C_4)-alkylaminocarbonyl or (C_3-C_6)-cycloalkyl,

and

(*ii*) said (C_3-C_6)-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy and amino,

and

(*iii*) said 4- to 6-membered heterocycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy, oxo and amino,

or

R^4 and R^5, or R^4 and R^6, respectively, are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 4- to 7-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from $N(R^7)$ and O, and which may be substituted on ring carbon atoms with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, oxo, hydroxy, amino and aminocarbonyl, and wherein

R^7 is hydrogen, (C_1-C_4)-alkyl, formyl or (C_1-C_4)-alkylcarbonyl,

and

G^2 represents chloro, cyano, $(C_1$-$C_4)$-alkyl, or the group $-CR^{8A}R^{8B}$-OH, $-CH_2-NR^9R^{10}$ or $-C(=O)-NR^{11}R^{12}$, wherein

R^{8A} and R^{8B} are independently selected from the group consisting of hydrogen, $(C_1$-$C_4)$-alkyl, cyclopropyl and cyclobutyl,

R^9 is hydrogen or $(C_1$-$C_4)$-alkyl,

R^{10} is hydrogen, $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkylcarbonyl, $(C_3$-$C_6)$-cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein

(*i*) said $(C_1$-$C_4)$-alkyl is optionally substituted with hydroxy, amino, aminocarbonyl, mono-$(C_1$-$C_4)$-alkylaminocarbonyl or di-$(C_1$-$C_4)$-alkylaminocarbonyl,

and

(*ii*) said $(C_3$-$C_6)$-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of $(C_1$-$C_4)$-alkyl, hydroxy and amino,

and

(*iii*) said 4- to 6-membered heterocycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of $(C_1$-$C_4)$-alkyl, hydroxy, oxo and amino,

R^{11} is hydrogen or $(C_1$-$C_4)$-alkyl,

R^{12} is hydrogen, $(C_1$-$C_4)$-alkyl, $(C_3$-$C_6)$-cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein

(*i*) said $(C_1$-$C_4)$-alkyl is optionally substituted with hydroxy, amino, aminocarbonyl, mono-$(C_1$-$C_4)$-alkylaminocarbonyl or di-$(C_1$-$C_4)$-alkylaminocarbonyl,

and

(*ii*) said $(C_3$-$C_6)$-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of $(C_1$-$C_4)$-alkyl, hydroxy and amino,

and

(*iii*) said 4- to 6-membered heterocycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy, oxo and amino,

or

R^9 and R^{10}, or R^{11} and R^{12}, respectively, are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 4- to 7-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from $N(R^{13})$, O, S and $S(O)_2$, and which may be substituted on ring carbon atoms with up to three substituents independently selected from the group consisting of fluoro, (C_1-C_4)-alkyl, oxo, hydroxy, amino and aminocarbonyl, and wherein

R^{13} is hydrogen, (C_1-C_4)-alkyl, (C_3-C_6)-cycloalkyl, formyl or (C_1-C_4)-alkylcarbonyl,

with the proviso that G^1 is not chloro when G^2 is chloro or cyano.

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 (I-A), (I-B), (I-C), (I-D) and (I-E) 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 process products and/or 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, formic acid, acetic acid, trifluoroacetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid, and benzoic acid.

Pharmaceutically acceptable salts also include salts of customary bases, such as for example and preferably alkali metal salts (for example sodium and potassium salts), alkaline earth metal salts (for example calcium and magnesium salts), and ammonium salts derived from ammonia or organic amines, such as illustratively and preferably ethylamine, diethylamine, triethylamine, *N,N*-diisopropylethylamine, monoethanolamine, diethanolamine, triethanolamine, dimethylaminoethanol, diethylaminoethanol, procaine, dicyclohexylamine, dibenzylamine, *N*-methylmorpholine, *N*-methylpiperidine, arginine, lysine, and 1,2-ethylenediamine.

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.

The present invention also encompasses all suitable isotopic variants of the compounds according to the invention. An isotopic variant of a compound according to the invention is understood to mean a compound in which at least one atom within the compound according to the invention has been exchanged for another atom of the same atomic number, but with a different atomic mass than the atomic mass which usually or predominantly occurs in nature. Examples of isotopes which can be incorporated into a compound according to the invention are those of hydrogen, carbon, nitrogen, oxygen, fluorine, chlorine, bromine and iodine, such as ^{2}H (deuterium), ^{3}H (tritium), ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{18}F, ^{36}Cl, ^{82}Br, ^{123}I, ^{124}I, ^{129}I and ^{131}I. Particular isotopic variants of a compound according to the invention, especially those in which one or more radioactive isotopes have been incorporated, may be beneficial, for example, for the examination of the mechanism of action or of the active compound distribution in the body. Due to comparatively easy preparability and detectability, especially compounds labelled with ^{3}H or ^{14}C isotopes are suitable for this purpose. In addition, the incorporation of isotopes, for example of deuterium, can lead to particular therapeutic benefits as a consequence of greater metabolic stability of the compound, for example an extension of the half-life in the body or a reduction in the active dose required. Such modifications of the compounds according to the invention may therefore in some cases also constitute a preferred embodiment of the present invention. Isotopic variants of the compounds according to the invention can be prepared by processes known to those skilled in the art, for example by the methods described below and the methods described in the working examples, by using corresponding isotopic modifications of the particular reagents and/or starting compounds therein.

In the context of the present invention, the substituents and residues have the following meaning, unless specified otherwise:

$(C_1\text{-}C_4)$-Alkyl in the context of the invention represents a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. There may be mentioned by way of example and preferably: methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *iso*-butyl, *sec*-butyl, and *tert*-butyl.

$(C_1\text{-}C_4)$-Alkoxy in the context of the invention represents a straight-chain or branched alkoxy radical having 1 to 4 carbon atoms. There may be mentioned by way of example and preferably: methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *iso*-butoxy, *sec*-butoxy, and *tert*-butoxy.

Mono-$(C_1\text{-}C_4)$-alkylamino in the context of the invention represents an amino group with a straight-chain or branched alkyl substituent which contains 1 to 4 carbon atoms. There may be mentioned by way of example and preferably: methylamino, ethylamino, *n*-propylamino, isopropylamino, *n*-butylamino, and *tert*-butylamino.

Di-(C_1-C_4)-alkylamino in the context of the invention represents an amino group with two identical or different straight-chain or branched alkyl substituents which each contain 1 to 4 carbon atoms. There may be mentioned by way of example and preferably: *N,N*-dimethylamino, *N,N*-diethylamino, *N*-ethyl-*N*-methylamino, *N*-methyl-*N*-*n*-propylamino, *N*-isopropyl-*N*-methylamino, *N*-isopropyl-*N*-*n*-propylamino, *N,N*-diisopropylamino, *N*-*n*-butyl-*N*-methylamino, and *N*-*tert*-butyl-*N*-methylamino.

(C_1-C_4)-Alkylcarbonyl in the context of the invention represents a straight-chain or branched alkyl radical having 1 to 4 carbon atoms which is bonded to the rest of the molecule via a carbonyl group [-C(=O)-]. There may be mentioned by way of example and preferably: acetyl, propionyl, *n*-butyryl, *iso*-butyryl, *n*-pentanoyl, and pivaloyl.

(C_1-C_4)-Alkoxycarbonyl in the context of the invention represents a straight-chain or branched alkoxy radical having 1 to 4 carbon atoms which is bonded to the rest of the molecule via a carbonyl group [-C(=O)-]. There may be mentioned by way of example and preferably: methoxycarbonyl, ethoxycarbonyl, *n*-propoxycarbonyl, isopropoxycarbonyl, *n*-butoxycarbonyl, and *tert*-butoxycarbonyl.

Mono-(C_1-C_4)-alkylaminocarbonyl in the context of the invention represents an amino group which is bonded to the rest of the molecule via a carbonyl group [-C(=O)-] and which has a straight-chain or branched alkyl substituent having 1 to 4 carbon atoms. There may be mentioned by way of example and preferably: methylaminocarbonyl, ethylaminocarbonyl, *n*-propylaminocarbonyl, isopropylaminocarbonyl, *n*-butylaminocarbonyl, and *tert*-butylaminocarbonyl.

Di-(C_1-C_4)-alkylaminocarbonyl in the context of the invention represents an amino group which is bonded to the rest of the molecule via a carbonyl group [-C(=O)-] and which has two identical or different straight-chain or branched alkyl substituents having in each case 1 to 4 carbon atoms. There may be mentioned by way of example and preferably: *N,N*-dimethylaminocarbonyl, *N,N*-diethylaminocarbonyl, *N*-ethyl-*N*-methylaminocarbonyl, *N*-methyl-*N*-*n*-propylaminocarbonyl, *N*-isopropyl-*N*-methylaminocarbonyl, *N,N*-diisopropylaminocarbonyl, *N*-*n*-butyl-*N*-methylaminocarbonyl, and *N*-*tert*-butyl-*N*-methylaminocarbonyl.

(C_3-C_6)-Cycloalkyl in the context of the invention represents a monocyclic, saturated carbocycle having 3 to 6 ring carbon atoms. There may be mentioned by way of example: cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Preferred are cyclopropyl and cyclobutyl.

4- to 7-membered heterocycloalkyl and 4- to 6-membered heterocycloalkyl in the context of the invention represent a monocyclic, saturated heterocycle with 4 to 7 or, respectively, 4 to 6 ring

atoms in total, which contains one or two identical or different ring heteroatoms from the series N, O, S and $S(O)_2$, and which is bonded via a ring carbon atom or optionally via a ring nitrogen atom (when present). 4- to 6-membered heterocycloalkyl containing one ring nitrogen atom and optionally one further ring heteroatom from the series N, O or $S(O)_2$ is preferred. 5- or 6-membered heterocycloalkyl containing one ring nitrogen atom and optionally one further ring heteroatom from the series N or O is particularly preferred. There may be mentioned by way of example: azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, tetrahydrofuranyl, thiolanyl, 1,1-dioxidothiolanyl, 1,2-oxazolidinyl, 1,3-oxazolidinyl, 1,3-thiazolidinyl, piperidinyl, piperazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,2-oxazinanyl, morpholinyl, thiomorpholinyl, 1,1-dioxidothiomorpholinyl, azepanyl, 1,4-diazepanyl, and 1,4-oxazepanyl. Preferred are azetidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, 1,1-dioxidothiolanyl, 1,2-oxazolidinyl, 1,3-oxazolidinyl, piperidinyl, piperazinyl, 1,2-oxazinanyl, morpholinyl, and 1,1-dioxidothiomorpholinyl. Particularly preferred are pyrrolidinyl, piperidinyl, piperazinyl, and morpholinyl.

5-membered aza-heteroaryl in the context of the invention represents an aromatic heterocyclic radical (heteroaromatic) having 5 ring atoms in total, which contains at least one ring nitrogen atom and optionally one or two further ring heteroatoms from the series N, O and/or S, and which is bonded via a ring carbon atom or optionally via a ring nitrogen atom (when allowed by valency). 5-membered aza-heteroaryl containing one ring nitrogen atom and one or two further ring heteroatoms from the series N and/or O is preferred. There may be mentioned by way of example: pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, and thiadiazolyl. Preferred are pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, and oxadiazolyl.

An oxo substituent in the context of the invention represents an oxygen atom, which is bonded to a carbon atom via a double bond.

In the context of the present invention, for all the radicals which occur several times, the meaning thereof is independent of each other. If radicals in the compounds according to the invention are substituted, the radicals can be mono- or polysubstituted, unless specified otherwise. Substitution by one or by two or three identical or different substituents is preferred. Substitution by one or by two identical or different substituents is particularly preferred.

In a preferred embodiment, the present invention relates to compounds of general formula (I), wherein

R^1 is chloro, methyl or methoxy,

R^2 is hydrogen or methoxy,

G^1 represents chloro, $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkoxycarbonyl or 5-membered aza-heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl, or represents the group $-CH_2-OR^3$ or $-CH_2-NR^4R^5$, wherein

R^3 is hydrogen, $(C_1$-$C_4)$-alkyl or $(C_3$-$C_6)$-cycloalkyl,

wherein said $(C_1$-$C_4)$-alkyl is optionally substituted with hydroxy, $(C_1$-$C_4)$-alkoxy, hydroxycarbonyl, $(C_1$-$C_4)$-alkoxycarbonyl, amino, aminocarbonyl, $(C_3$-$C_6)$-cycloalkyl or up to three fluoro atoms,

R^4 is hydrogen or $(C_1$-$C_4)$-alkyl,

R^5 is hydrogen, $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkylcarbonyl, $(C_3$-$C_6)$-cycloalkyl or 5- or 6-membered heterocycloalkyl, wherein

(*i*) said $(C_1$-$C_4)$-alkyl is optionally substituted with hydroxy, hydroxycarbonyl or $(C_3$-$C_6)$-cycloalkyl,

and

(*ii*) said 5- or 6-membered heterocycloalkyl is optionally substituted with oxo,

or

R^4 and R^5 are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 4- to 6-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from $N(R^7)$ and O, and which may be substituted on a ring carbon atom with oxo or hydroxy, and wherein

R^7 is hydrogen or $(C_1$-$C_4)$-alkyl,

and

G^2 represents chloro, cyano, $(C_1$-$C_4)$-alkyl, or the group $-CR^{8A}R^{8B}-OH$, $-CH_2-NR^9R^{10}$ or $-C(=O)-NR^{11}R^{12}$, wherein

R^{8A} and R^{8B} are independently selected from the group consisting of hydrogen, $(C_1$-$C_4)$-alkyl and cyclopropyl,

R^9 is hydrogen or methyl,

R^{10} is hydrogen, $(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_4)$-alkylcarbonyl, $(C_3\text{-}C_6)$-cycloalkyl or 5- or 6-membered heterocycloalkyl, wherein

(*i*) said $(C_1\text{-}C_4)$-alkyl is optionally substituted with hydroxy or aminocarbonyl,

and

(*ii*) said 5- or 6-membered heterocycloalkyl is optionally substituted with oxo,

R^{11} is hydrogen or methyl,

R^{12} is hydrogen, $(C_1\text{-}C_4)$-alkyl, $(C_3\text{-}C_6)$-cycloalkyl or 5- or 6-membered heterocycloalkyl, wherein

(*i*) said $(C_1\text{-}C_4)$-alkyl is optionally substituted with hydroxy,

and

(*ii*) said 5- or 6-membered heterocycloalkyl is optionally substituted with oxo,

or

R^9 and R^{10}, or R^{11} and R^{12}, respectively, are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 4- to 6-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from $N(R^{13})$, O, S and $S(O)_2$, and which may be substituted on ring carbon atoms with up to three substituents independently selected from the group consisting of fluoro, $(C_1\text{-}C_4)$-alkyl, oxo, hydroxy, amino and aminocarbonyl, and wherein

R^{13} is hydrogen, $(C_1\text{-}C_4)$-alkyl, cyclopropyl, cyclobutyl, formyl or $(C_1\text{-}C_4)$-alkylcarbonyl,

with the proviso that G^1 is not chloro when G^2 is chloro or cyano.

In a particularly preferred embodiment, the present invention relates to compounds of general formula (I), wherein

R^1 is methyl,

R^2 is methoxy,

G^1 represents methyl, oxazol-5-yl or the group $-CH_2\text{-}OR^3$ or $-CH_2\text{-}NR^4R^5$, wherein

R^3 is hydrogen, (C_1-C_4)-alkyl, cyclopropyl or cyclobutyl,

wherein said (C_1-C_4)-alkyl is optionally substituted with hydroxy, methoxy, ethoxy, hydroxycarbonyl, methoxycarbonyl, ethoxycarbonyl, amino, aminocarbonyl, cyclopropyl, cyclobutyl or up to three fluoro atoms,

R^4 is hydrogen, methyl or ethyl,

R^5 is hydrogen, (C_1-C_4)-alkyl, acetyl, cyclopropyl, cyclobutyl or 2-oxopyrrolidin-3-yl,

wherein said (C_1-C_4)-alkyl is optionally substituted with hydroxy, hydroxycarbonyl, cyclopropyl or cyclobutyl,

or

R^4 and R^5 are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 5- or 6-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from NH and O, and which may be substituted on a ring carbon atom with oxo or hydroxy,

and

G^2 represents methyl or the group $-CR^{8A}R^{8B}-OH$, $-CH_2-NR^9R^{10}$ or $-C(=O)-NR^{11}R^{12}$, wherein

R^{8A} and R^{8B} are independently hydrogen or methyl,

R^9 is hydrogen,

R^{10} is hydrogen, (C_1-C_4)-alkyl, acetyl, cyclopropyl, cyclobutyl or 2-oxopyrrolidin-3-yl,

wherein said (C_1-C_4)-alkyl is optionally substituted with hydroxy or aminocarbonyl,

R^{11} is hydrogen or methyl,

R^{12} is hydrogen, (C_1-C_4)-alkyl, cyclopropyl, cyclobutyl or 2-oxopyrrolidin-3-yl,

wherein said (C_1-C_4)-alkyl is optionally substituted with hydroxy,

or

R^9 and R^{10}, or R^{11} and R^{12}, respectively, are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 4- to 6-membered

heterocycloalkyl ring which may contain a second ring heteroatom selected from $N(R^{13})$, O and $S(O)_2$, and which may be substituted on ring carbon atoms with up to three substituents independently selected from the group consisting of fluoro, methyl, oxo, hydroxy, amino and aminocarbonyl, and wherein

R^{13} is hydrogen, formyl or acetyl.

In a distinct embodiment, the present invention relates to compounds of general formula (I), wherein

R^1 is methyl,

and

R^2 is methoxy.

In a further distinct embodiment, the present invention relates to compounds of general formula (I), wherein

G^1 represents the group $-CH_2-OR^3$, wherein

R^3 is hydrogen or (C_1-C_4)-alkyl optionally substituted with hydroxy, methoxy, amino, aminocarbonyl or up to three fluoro atoms.

In another distinct embodiment, the present invention relates to compounds of general formula (I), wherein

G^1 represents the group $-CH_2-NR^4R^5$, wherein

R^4 is hydrogen or methyl,

R^5 is (C_1-C_4)-alkyl, acetyl, cyclopropyl, cyclobutyl or 2-oxopyrrolidin-3-yl,

wherein said (C_1-C_4)-alkyl is optionally substituted with hydroxy,

or

R^4 and R^5 are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 5- or 6-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from NH and O, and which may be substituted on a ring carbon atom with oxo or hydroxy.

In another distinct embodiment, the present invention relates to compounds of general formula (I), wherein

G^2 represents the group $-CH_2-NR^9R^{10}$, wherein

R^9 is hydrogen,

R^{10} is acetyl or 2-oxopyrrolidin-3-yl,

or

R^9 and R^{10} are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 5- or 6-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from $N(R^{13})$ and O, and which may be substituted on ring carbon atoms with up to two substituents independently selected from the group consisting of methyl, oxo, hydroxy and amino, and wherein

R^{13} is hydrogen, formyl or acetyl.

In yet another distinct embodiment, the present invention relates to compounds of general formula (I), wherein

G^2 represents the group $-C(=O)-NR^{11}R^{12}$, wherein

R^{11} is hydrogen,

R^{12} is (C_1-C_4)-alkyl or 2-oxopyrrolidin-3-yl,

wherein said (C_1-C_4)-alkyl is optionally substituted with hydroxy,

or

R^{11} and R^{12} are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 4- to 6-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from NH and O, and which may be substituted on a ring carbon atom with oxo or hydroxy.

In an especially preferred embodiment, the present invention relates to compounds of general formula (I), wherein

R^1 is methyl,

R^2 is methoxy,

G^1 represents the group $-CH_2-OR^3$, wherein

R^3 is (C_1-C_4)-alkyl optionally substituted with hydroxy, amino or aminocarbonyl,

and

G^2 represents the group $-CH_2-NR^9R^{10}$ or $-C(=O)-NR^{11}R^{12}$, wherein

R^9 is hydrogen,

R^{10} is 2-oxopyrrolidin-3-yl,

or

R^9 and R^{10} are joined and, taken together with the nitrogen atom to which they are attached, form a piperazin-1-yl, 3-oxopiperazin-1-yl or 4-acetylpiperazin-1-yl ring,

R^{11} is hydrogen,

R^{12} is 2-oxopyrrolidin-3-yl,

or

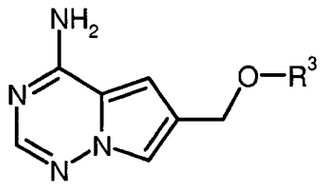
R^{11} and R^{12} are joined and, taken together with the nitrogen atom to which they are attached, form a 3-hydroxyazetidin-1-yl, 4-hydroxypiperidin-1-yl or 3-oxopiperazin-1-yl ring.

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.

The compounds of the general formula (I) can be prepared by various synthetic routes which are primarily governed by the nature of the particular G^1 and G^2 groups chosen (see definitions above).

Thus, in another embodiment, the present invention relates to a process for preparing the compounds of the general formula (I), characterized in that

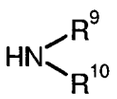
[A] a 6-substituted 4-aminopyrrolo[2,1-f][1,2,4]triazine of formula (II)



(II),

wherein R^3 has the meaning described above,

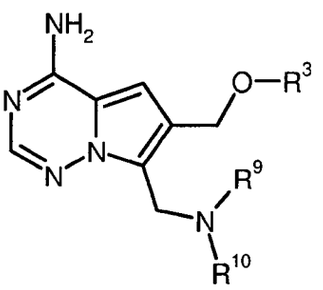
is at first reacted with formaldehyde and an amine of formula (III)



(III),

wherein R^9 and R^{10} have the meanings described above,

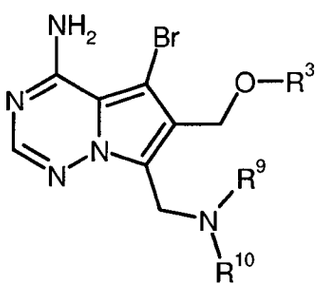
in the presence of an acid to give a compound of formula (IV)



(IV),

wherein R^3, R^9 and R^{10} have the meanings described above,

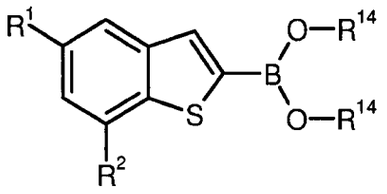
then brominated to a compound of formula (V)



(V),

wherein R^3, R^9 and R^{10} have the meanings described above,

and subsequently coupled with a benzothiophen-2-yl boronate of formula (VI)



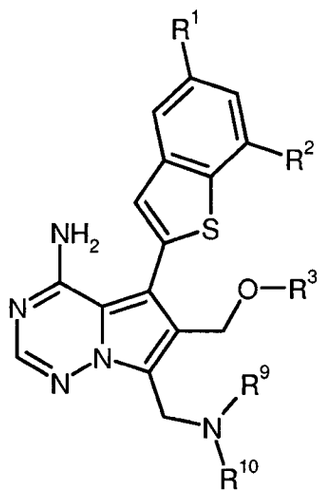
(VI),

wherein R^1 and R^2 have the meanings described above,

and

R^{14} represents hydrogen or $(C_1$-$C_4)$-alkyl, or both R^{14} residues are linked together to form a $-(CH_2)_2-$, $-C(CH_3)_2-C(CH_3)_2-$, $-(CH_2)_3-$, $-CH_2-C(CH_3)_2-CH_2-$ or $-C(=O)-CH_2-N(CH_3)-CH_2-C(=O)-$ bridge,

in the presence of a palladium catalyst and a base to yield the target compound of formula (I-A)

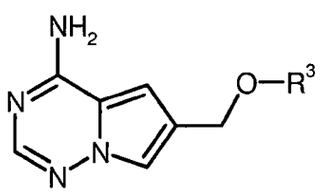


(I-A),

wherein R^1, R^2, R^3, R^9 and R^{10} have the meanings described above,

or

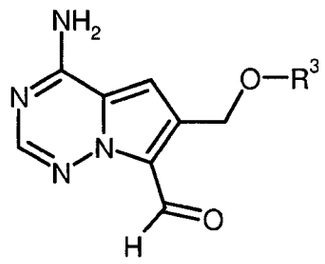
[B] a 6-substituted 4-aminopyrrolo[2,1-f][1,2,4]triazine of formula (II)



(II),

wherein R^3 has the meaning described above,

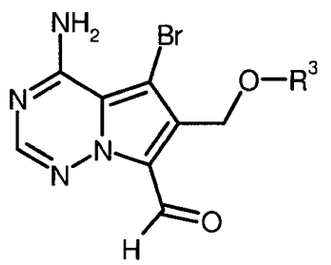
is at first formylated with *N,N*-dimethylformamide in the presence of phosphoryl chloride to an aldehyde of formula (VII)



(VII),

wherein R^3 has the meaning described above,

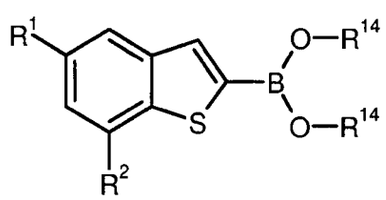
then brominated to a compound of formula (VIII)



(VIII),

wherein R^3 has the meaning described above,

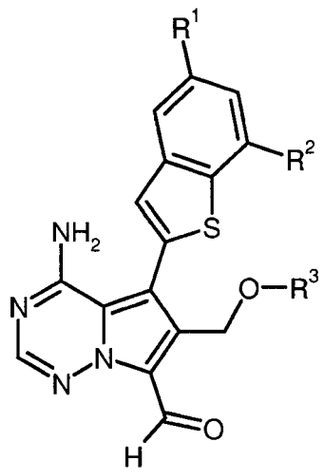
and subsequently coupled with a benzothiophen-2-yl boronate of formula (VI)



(VI),

wherein R^1, R^2 and R^{14} have the meanings described above,

in the presence of a palladium catalyst and a base to give a compound of formula (IX)

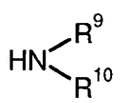


(IX),

wherein R^1, R^2 and R^3 have the meanings described above,

which then is either

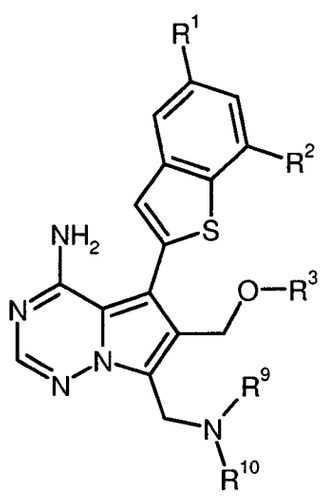
[B-1] reacted with an amine of formula (III)



(III),

wherein R^9 and R^{10} have the meanings described above,

in the presence of an acid and a reducing agent to yield the target compound of formula (I-A)

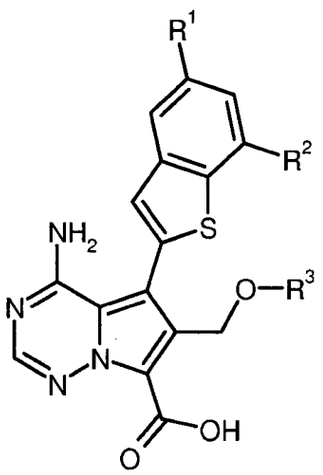


(I-A),

wherein R^1, R^2, R^3, R^9 and R^{10} have the meanings described above,

or

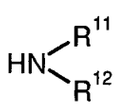
[B-2] oxidized to a carboxylic acid of formula (X)



(X),

wherein R^1, R^2 and R^3 have the meanings described above,

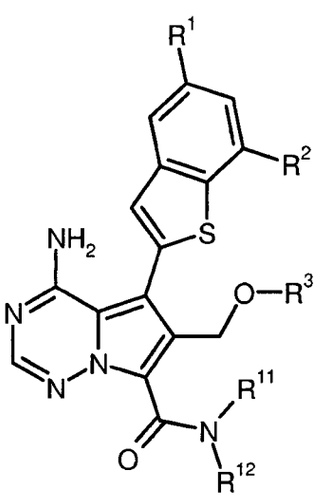
and finally coupled with an amine of formula (XI)



(XI),

wherein R^{11} and R^{12} have the meanings described above,

in the presence of a condensing agent to yield the target compound of formula (I-B)

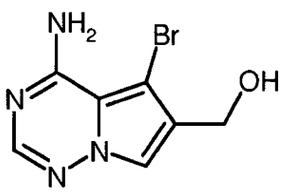


(I-B),

wherein R^1, R^2, R^3, R^{11} and R^{12} have the meanings described above,

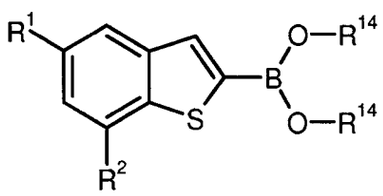
or

[C] a 6-substituted 4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazine of formula (XII)



(XII)

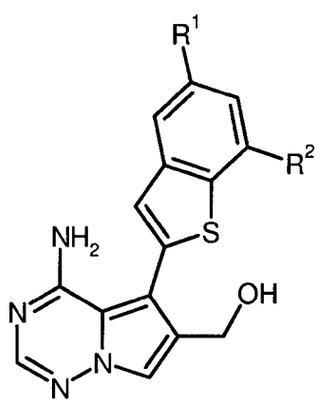
is at first coupled with a benzothiophen-2-yl boronate of formula (VI)



(VI),

wherein R^1, R^2 and R^{14} have the meanings described above,

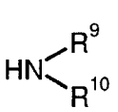
in the presence of a palladium catalyst and a base to give a compound of formula (XIII)



(XIII),

wherein R^1 and R^2 have the meanings described above,

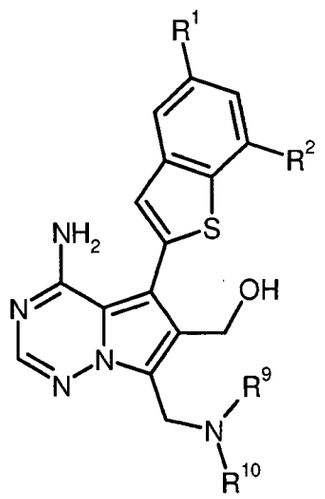
and then reacted with formaldehyde and an amine of formula (III)



(III),

wherein R^9 and R^{10} have the meanings described above,

in the presence of an acid to yield the compound of formula (I-C)

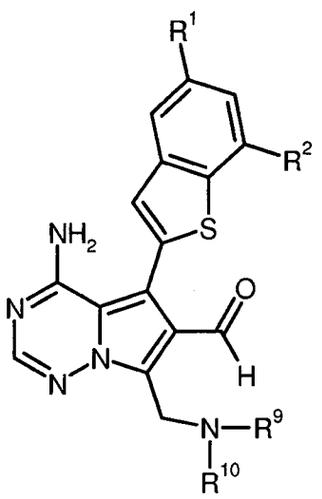


(I-C),

wherein R^1, R^2, R^9 and R^{10} have the meanings described above,

which subsequently is either

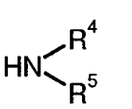
[C-1] oxidized to an aldehyde of formula (XIV)



(XIV),

wherein R^1, R^2, R^9 and R^{10} have the meanings described above,

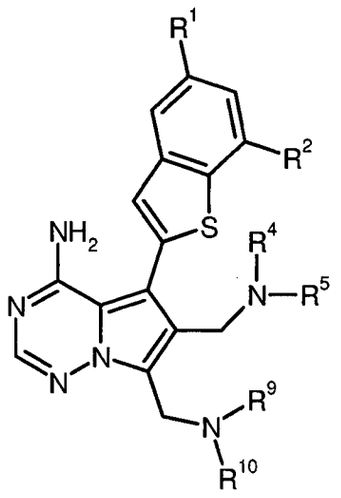
and treated with an amine of formula (XV)



(XV),

wherein R^4 and R^5 have the meanings described above,

in the presence of an acid and a reducing agent to yield the target compound of formula (I-D)

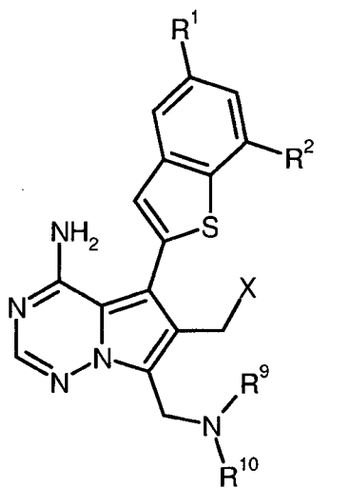


(I-D),

wherein R^1, R^2, R^4, R^5, R^9 and R^{10} have the meanings described above,

or

[C-2] converted into the corresponding 6-(halomethyl) derivative of formula (XVI)



(XVI),

wherein R^1, R^2, R^9 and R^{10} have the meanings described above,

and

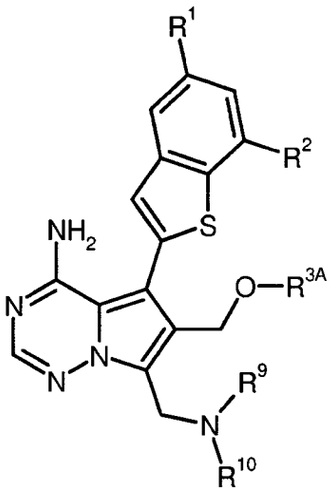
X is chloro, bromo or iodo,

and treated with an alcohol of formula (XVII)

R^{3A}—OH (XVII),

wherein R^{3A} has the meaning of R^3 as described above except for hydrogen,

in the presence of a base to yield the target compound of formula (I-E)



(I-E),

wherein R^1, R^2, R^{3A}, R^9 and R^{10} have the meanings described above,

optionally followed, where appropriate, by (*i*) separating the compounds of formula (I) thus obtained 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 or bases.

The compounds of the formulae (I-A), (I-B), (I-C), (I-D) and (I-E), which can be prepared by the processes described above, each represent a particular subset of the compounds of the general formula (I).

Process steps [A] (II) → (IV) and [C] (XIII) → (I-C), representing Mannich-type aminomethylation reactions, are carried out in the usual way by treating the respective starting compound with a mixture of aqueous formaldehyde and amine component (III) in the presence of an acid catalyst such as formic acid or acetic acid. Preferably, acetic acid is used both as catalyst and solvent. The reaction is usually performed at a temperature ranging from +20°C to +80°C.

As the brominating agent for process steps [A] (IV) → (V) and [B] (VII) → (VIII), preferably *N*-bromosuccinimide (NBS), 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) or elemental bromine is used. The reactions are generally carried out in an inert solvent, such as dichloromethane,

chloroform, tetrahydrofuran, acetonitrile or *N,N*-dimethylformamide (DMF), within a temperature range from -78°C to +20°C.

The coupling reactions [A] (V) + (VI) → (I-A), [B] (VIII) + (VI) → (IX) and [C] (XII) + (VI) → (XIII) ["Suzuki-Miyaura coupling"] are generally carried out in an inert solvent with the aid of a palladium catalyst and an aqueous base. Palladium catalysts suitable for this purpose include, for example, palladium(II) acetate, palladium(II) chloride, bis(triphenylphosphine)palladium(II) chloride, bis(acetonitrile)palladium(II) chloride, [1,1'-bis(diphenylphosphino)ferrocene]palladium-(II) chloride, tetrakis(triphenylphosphine)palladium(0), bis(dibenzylideneacetone)palladium(0), and tris(dibenzylideneacetone)dipalladium(0), optionally in combination with other phosphine ligands such as, for example, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-Phos), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (S-Phos), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos), or 4-(di-*tert*-butylphosphino)-*N,N*-dimethylaniline. Also, palladium pre-catalysts from which the catalytically active species is generated under the reaction conditions, such as (2'-aminobiphenyl-2-yl)(chloro)palladium-dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)-phosphine, can be used [see, for example, S. Kotha *et al.*, *Tetrahedron* 58, 9633-9695 (2002); T. E. Barder *et al.*, *J. Am. Chem. Soc.* 127 (13), 4685-4696 (2005); S. L. Buchwald *et al.*, *J. Am. Chem. Soc.* 132 (40), 14073-14075 (2010), and further references cited therein].

Suitable bases for these coupling reactions are in particular alkali carbonates, such as sodium, potassium or caesium carbonate, alkali phosphates, such as sodium or potassium phosphate, or alkali fluorides, such as potassium or caesium fluoride. Usually, these bases are employed as aqueous solutions. The reactions are carried out in organic solvents that are inert under the reaction conditions. Preferably, water-miscible organic solvents, such as 1,2-dimethoxyethane, tetrahydrofuran, 1,4-dioxane, acetonitrile, *N,N*-dimethylformamide (DMF) or dimethylsulfoxide (DMSO), are employed but other inert solvents, such as dichloromethane or toluene, may also be used.

Process step [B] (II) → (VII) ["Vilsmeier-Haack formylation"] is carried out in the usual manner by treating the pyrrolotriazine (II) in *N,N*-dimethylformamide (DMF) solvent with phosphoryl chloride. The reaction is usually performed at a temperature from 0°C to +80°C.

Reducing agents suitable for the reductive amination reactions [B-1] (IX) + (III) → (I-A) and [C-1] (XIV) + (XV) → (I-D) are customary alkali borohydrides, such as lithium borohydride, sodium borohydride, potassium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride. The transformations are generally carried out in the presence of an acid, preferably acetic acid, in an alcohol or ether solvent, such as methanol, ethanol, isopropanol, tetrahydrofuran or 1,4-dioxane,

within a temperature range from 0°C to +80°C, depending on the reactivity of the amine components (III) and (XV), respectively, and/or the particular borohydride used.

For the oxidation reaction in process step [B-2] (IX) → (X), oxidation with sodium chlorite in the presence of a hypochlorite scavenger such as 2-methyl-2-butene represents the method of choice [*cf.* H. W. Pinnick *et al.*, *Tetrahedron* 37, 2091-2096 (1981); A. Raach and O. Reiser, *J. Prakt. Chem.* 342 (6), 605-608 (2000), and references cited therein]. The reaction is usually carried out in a tetrahydrofuran/water mixture at a temperature between 0°C and ambient temperature.

Condensing agents suitable for process step [B-2] (X) + (XI) → (I-B) [amide formation] include, for example, carbodiimides such as *N,N'*-diethyl-, *N,N'*-dipropyl-, *N,N'*-diisopropyl-, *N,N'*-dicyclohexylcarbodiimide (DCC) or *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide (EDC), phosgene derivatives such as *N,N'*-carbonyldiimidazole (CDI) or isobutyl chloroformate, α-chloroenamines such as 1-chloro-2-methyl-1-dimethylamino-1-propene, phosphorus compounds such as propanephosphonic anhydride, diethyl cyanophosphonate, bis(2-oxo-3-oxazolidinyl)phosphoryl chloride, benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP) or benzotriazol-1-yloxy-tris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP), and uronium compounds such as *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU), *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU), 2-(2-oxo-1-(2*H*)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) or *O*-(1*H*-6-chlorobenzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TCTU), if appropriate in combination with further auxiliaries, such as 1-hydroxybenzotriazole (HOBt) or *N*-hydroxysuccinimide (HOSu), and/or bases such as alkali carbonates, for example sodium or potassium carbonate, or organic amine bases, such as triethylamine, *N*-methylpiperidine, *N*-methylmorpholine (NMM), *N,N*-diisopropylethylamine (DIPEA), pyridine or 4-*N,N*-dimethylaminopyridine (DMAP). Preference is given to using *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) or *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) in combination with *N,N*-diisopropylethylamine (DIPEA) and optionally 1-hydroxybenzotriazole (HOBt).

Inert solvents for process step [B-2] (X) + (XI) → (I-B) are, for example, ethers such as diethyl ether, *tert*-butyl methyl ether, tetrahydrofuran, 1,4-dioxane or 1,2-dimethoxyethane, hydrocarbons such as benzene, toluene, xylene, hexane or cyclohexane, halogenated hydrocarbons such as dichloromethane, trichloromethane, carbon tetrachloride, 1,2-dichloroethane, trichloroethylene or chlorobenzene, or other solvents such as acetone, acetonitrile, ethyl acetate, pyridine, dimethylsulfoxide (DMSO), *N,N*-dimethylformamide (DMF), *N,N'*-dimethylpropylene urea (DMPU) or *N*-methylpyrrolidinone (NMP). It is also possible to use mixtures of these solvents. Preference is

given to using dichloromethane, tetrahydrofuran, *N,N*-dimethylformamide or mixtures thereof. The reactions are generally carried out at a temperature ranging from 0°C to +60°C, preferably at +10°C to +40°C.

Oxidizing agents that are capable of converting the primary alcohol (I-C) into the aldehyde (XIV) (process [C-1]) under mild conditions include 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one ("Dess-Martin periodinane"), 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) in combination with secondary oxidants such as iodosobenzene-*I,I*-diacetate or sodium hypochlorite, and dimethylsulfoxide (DMSO)-based oxidation systems such as DMSO/trifluoroacetic anhydride or DMSO/*N,N'*-dicyclohexylcarbodiimide (DCC). Preference is given to 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one. The reaction is generally carried out in an inert solvent, preferably using dichloromethane.

For the hydroxy-to-halogen transformation in process step [C-2] (I-C) → (XVI), various standard methods and reagents that are well known in the art may be employed. Reagents of choice are thionyl chloride [for X = Cl], tetrabromomethane/triphenylphosphine [for X = Br], and iodine/triphenylphosphine [for X = I]. The preparation of 6-(chloromethyl) derivatives (XVI) [X = Cl] is preferred for reasons of convenience of work-up and compound stability.

Bases suitable for the process step [C-2] (XVI) + (XVII) → (I-E) [ether formation] are in particular alkali carbonates such as lithium, sodium, potassium or caesium carbonate, alkali acetates such as sodium or potassium acetate, or customary tertiary amine bases such as triethylamine, *N*-methylmorpholine, *N*-methylpiperidine, *N,N*-diisopropylethylamine or pyridine. Preference is given to *N,N*-diisopropylethylamine (DIPEA). The reaction (XVI) + (XVII) → (I-E) is performed in an inert solvent, such as tetrahydrofuran, or without solvent, using an excess of alcohol (XVII), at a temperature ranging from +20°C to +200°C, preferably at +50°C to +150°C. Advantageously, the conversion is carried out by means of a microwave reactor device.

The reaction sequence (I-C) → (XVI) → (I-E) may be carried out in two separate steps, i.e. with isolation and purification of the intermediate compound (XVI), or it may be performed using a one-pot procedure, i.e. employing the crude intermediate (XVI) as obtained in the preparation reaction.

The preparation of the compounds of the invention may be illustrated by means of the following reaction schemes:

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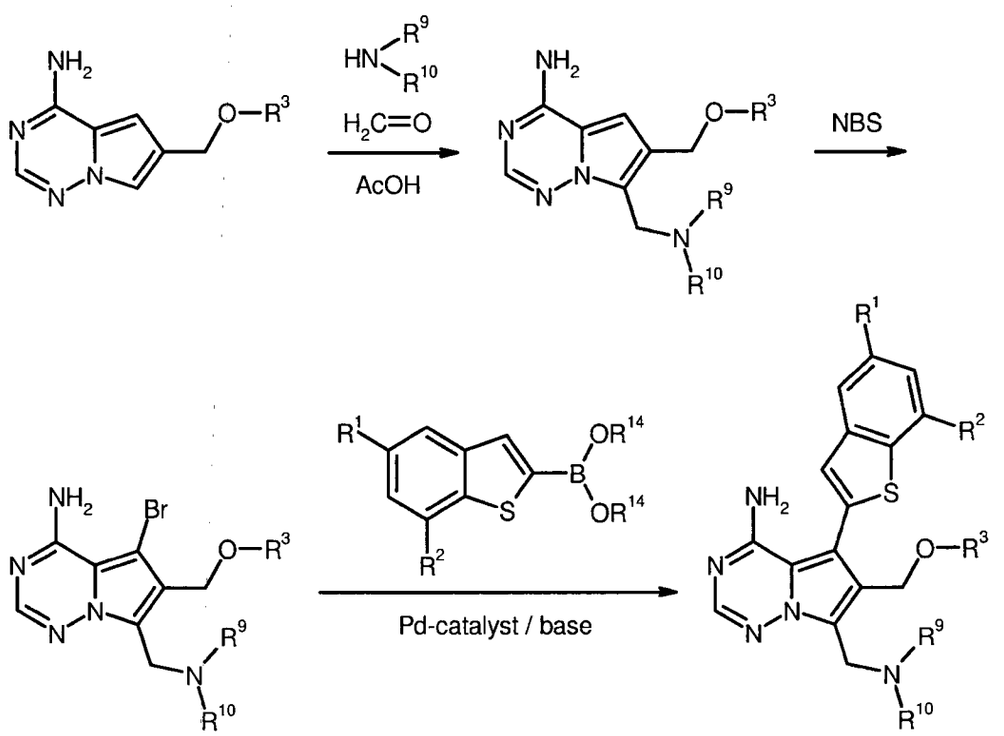
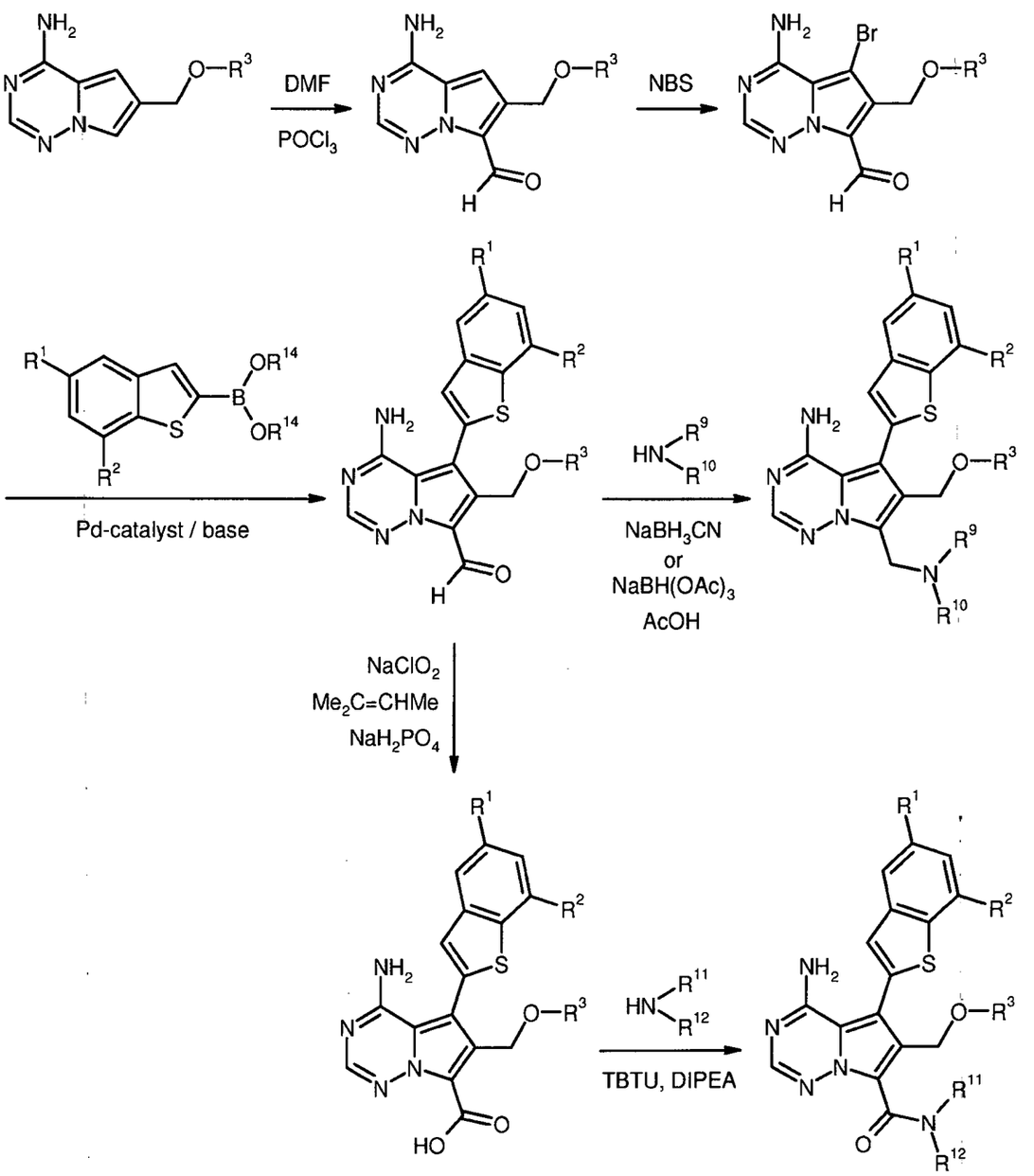
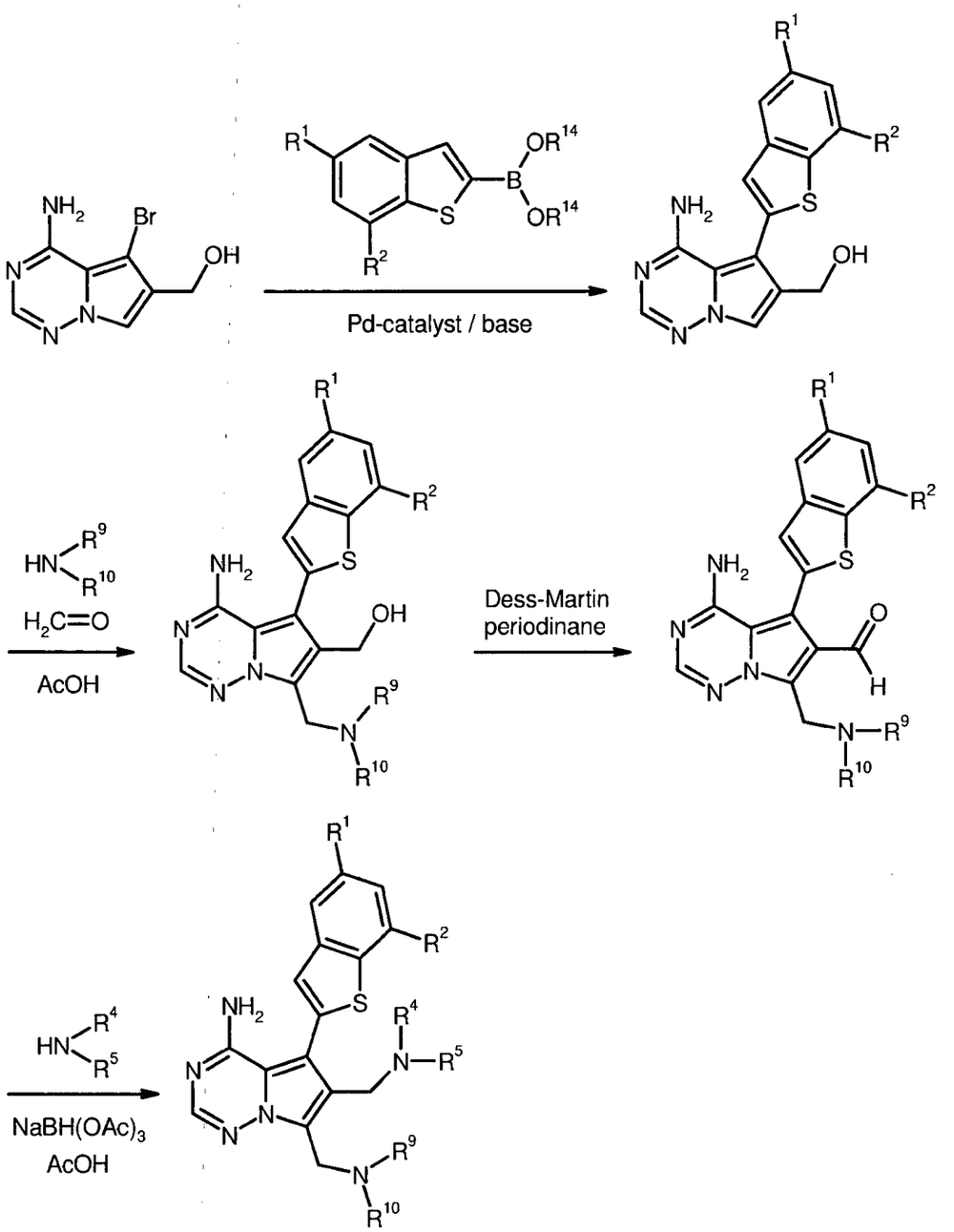
Scheme 1



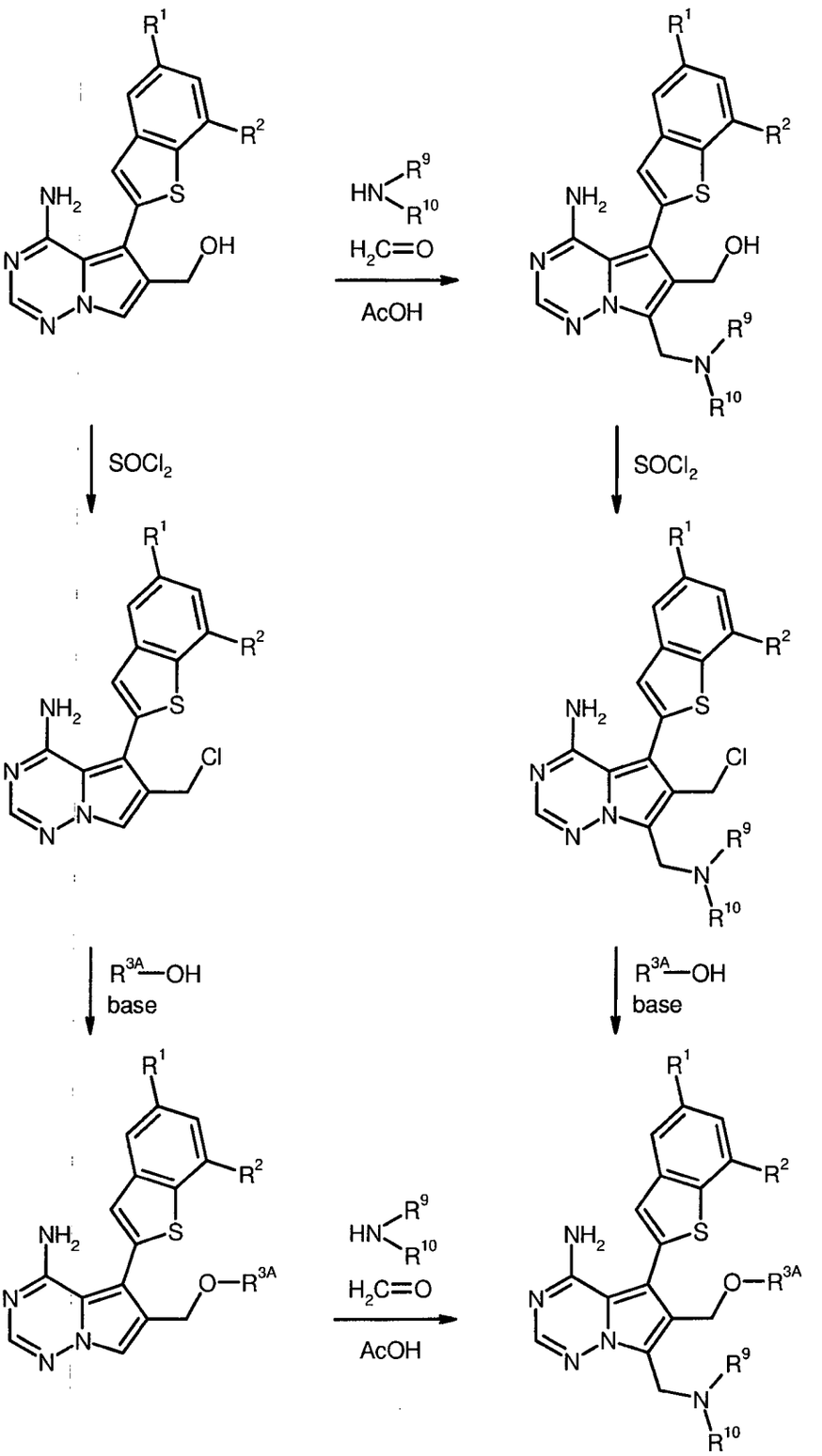
Scheme 2


NH2
O—R3
DMF
POCl3
NBS
Br
H
O
R1
R2
OR14
B
S
Pd-catalyst / base
HN
R9
R10
NaBH3CN
or
NaBH(OAc)3
AcOH
N
NaClO2
Me2C=CHMe
NaH2PO4
HO
TBTU, DIPEA
R11
R12

Scheme 3


NH2
Br
OH
N
N
N
R1
R2
OR14
B
OR14
S
Pd-catalyst / base
HN
R9
R10
H2C=O
AcOH
Dess-Martin
periodinane
O
H
NaBH(OAc)3
AcOH
R4
R5

Scheme 4

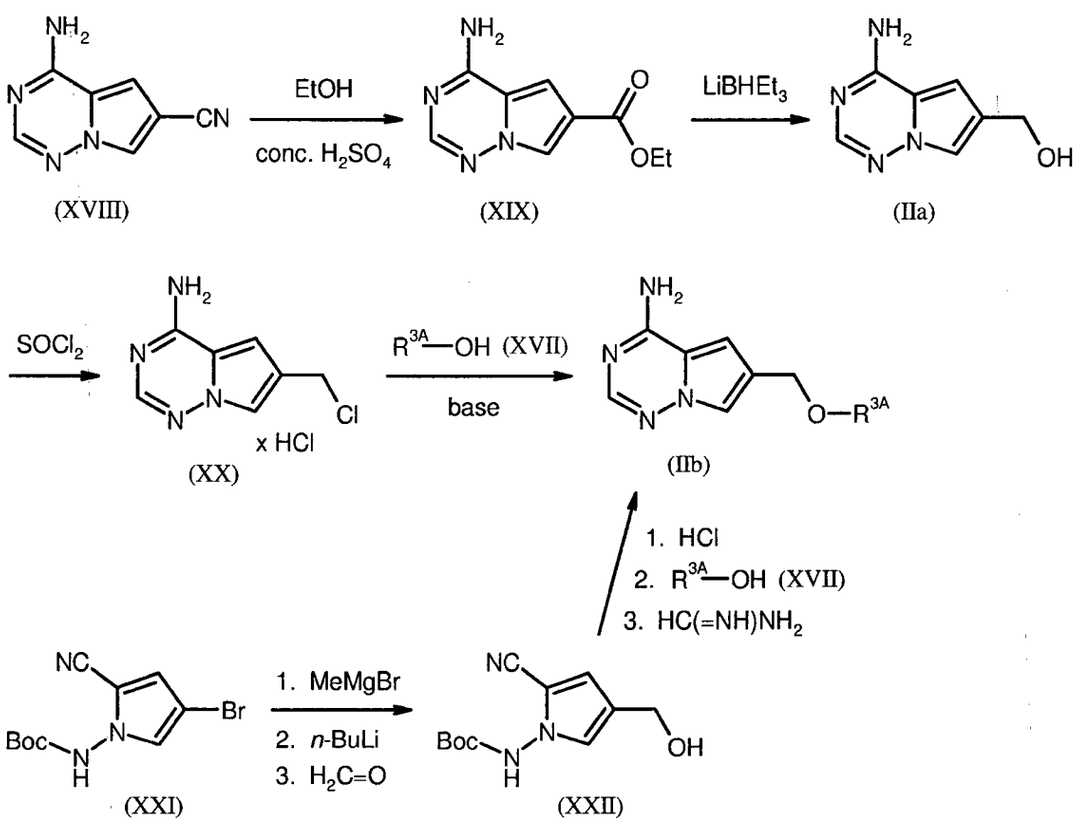


The 6-substituted 4-aminopyrrolo[2,1-f][1,2,4]triazines of formula (II) can, for example, be prepared by two different routes which are depicted in Scheme 5 below. In the first route, 4-amino-6-cyanopyrrolo[2,1-f][1,2,4]triazine (XVIII) is converted into the ester (XIX) by acid-mediated alco-

holysis and then reduced to the 6-(hydroxymethyl) compound (IIa) [R^3 in (II) = H] using lithium triethylborohydride. Standard transformation into the corresponding 6-(halomethyl)pyrrolotriazine, such as the chloro compound (XX), followed by treatment with an alcohol of formula (XVII) in the presence of a base readily provides the ether derivatives of formula (IIb) [R^3 in (II) ≠ H]. The preparation of the starting compound (XVIII) has been described previously [see Int. Pat. Appl. WO 2007/ 064883 (Intermediate AX / Step 3)].

The second route starts from the protected 1-amino-4-bromo-2-cyanopyrrole (XXI) [preparation given in Int. Pat. Appl. WO 2007/064883 (Intermediate AAE, Step 3)]. Deprotonation of the urethane nitrogen, subsequent metalation in 4-position and reaction with formaldehyde affords the 4-(hydroxymethyl) derivative (XXII). Treatment with hydrogen chloride followed by addition of alcohol (XVII) and condensation with formamidine using a one-pot procedure then provides the target compound of formula (IIb). This route is especially suited for the preparation of alkyl ether derivatives [R^{3A} in (IIb) = (C_1-C_4)-alkyl] in that the alcohol reactant (XVII) may also serve as the reaction solvent in these cases.

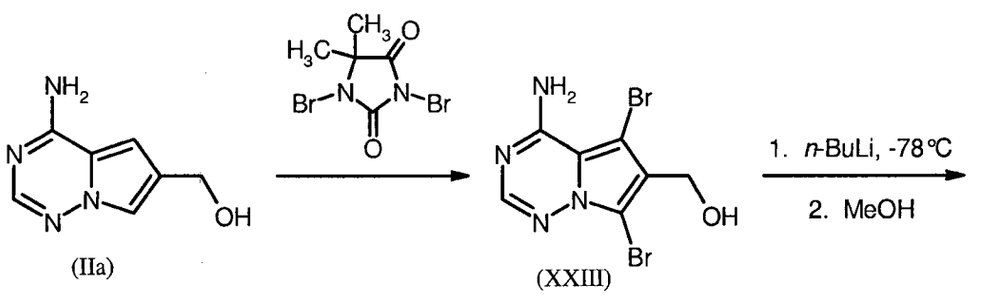
Scheme 5

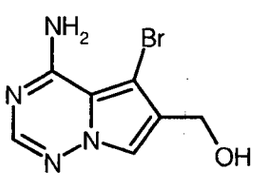


The 4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazine derivative of formula (XII) is readily available from 4-amino-6-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazine (IIa) (cf. Scheme 5) by initial 5,7-

dibromination using 1,3-dibromo-5,5-dimethylhydantoin and subsequent selective 7-debromination via a halogen-metal exchange with *n*-butyllithium followed by methanol quenching (see Scheme 6 below).

Scheme 6

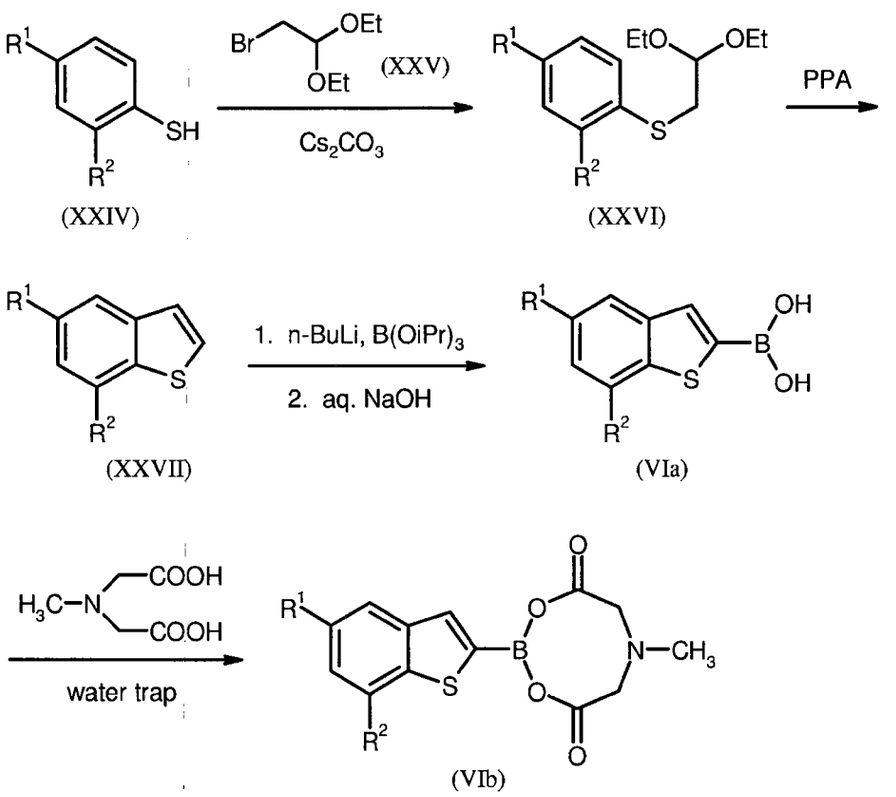




(XII)

The benzothiophen-2-yl boronates of formula (VI) can conveniently be prepared starting from the substituted thiophenol derivatives of formula (XXIV) (see Scheme 7 below). Alkylation with bromo-acetal (XXV) and subsequent polyphosphoric acid-mediated cyclization provides the benzothiophene intermediates of formula (XXVII) which are then metalated in 2-position and reacted with a trialkyl borate. Alkaline work-up affords the free (benzothiophen-2-yl)boronic acids of formula (VIa) which may be transformed, if desired, into cyclic boronates, *e.g.* so-called MIDA boronates of formula (VIb), by standard procedures known in the art [see, for example, D. M. Knapp *et al.*, *J. Am. Chem. Soc.* 131 (20), 6961-6963 (2009)].

Scheme 7



[*cf.* P. A. Plé and L. J. Marnett, *J. Heterocyclic Chem.* 25 (4), 1271-1272 (1988); A. Venturelli *et al.*, *J. Med. Chem.* 50 (23), 5644-5654 (2007)].

The compounds of the formulae (III), (XI), (XV), (XVII), (XXIV) and (XXV) 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. Detailed procedures and literature references for preparing the starting materials can also be found in the Experimental Part in the section on the preparation of the starting materials and intermediates.

The preparation of further subgroups of the compounds of general formula (I) is illustrated in the following reaction schemes 8–14. The required pyrrolotriazine precursors can be readily synthesized by customary methods well known in the art, and further synthetic transformations, in most instances, follow the preparation routes that have been outlined in the process section above, using similar types of reactions, such as, for example, bromination, boronate coupling, aminomethylation, reductive amination, oxidation and/or ether or amide forming reactions. Further details are provided in the Experimental Part on the preparation of the exemplary embodiments and their respective precursor compounds.

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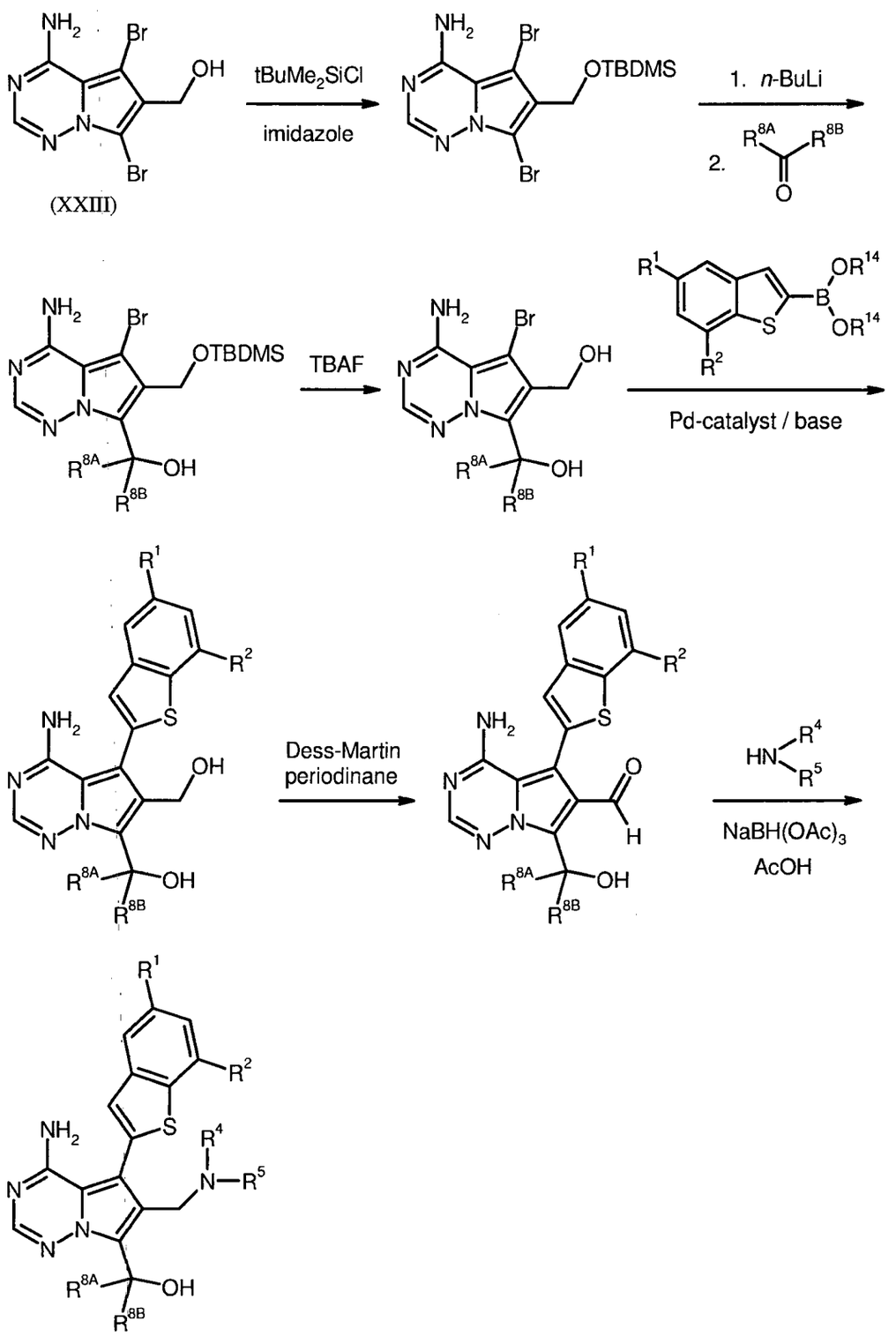
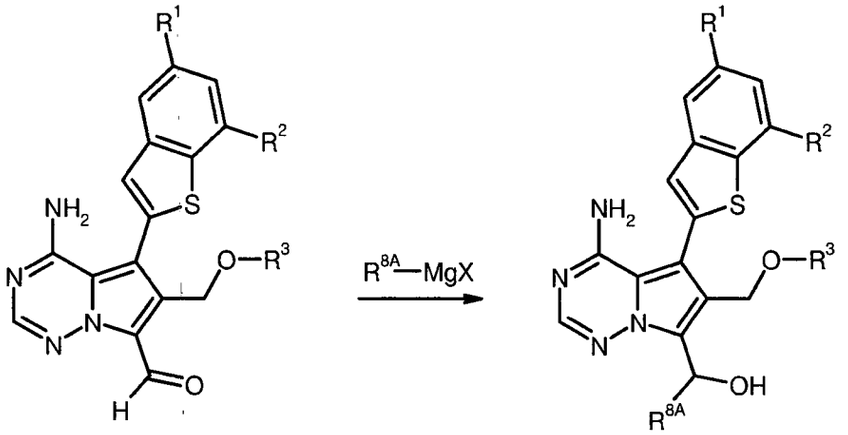
Scheme 8



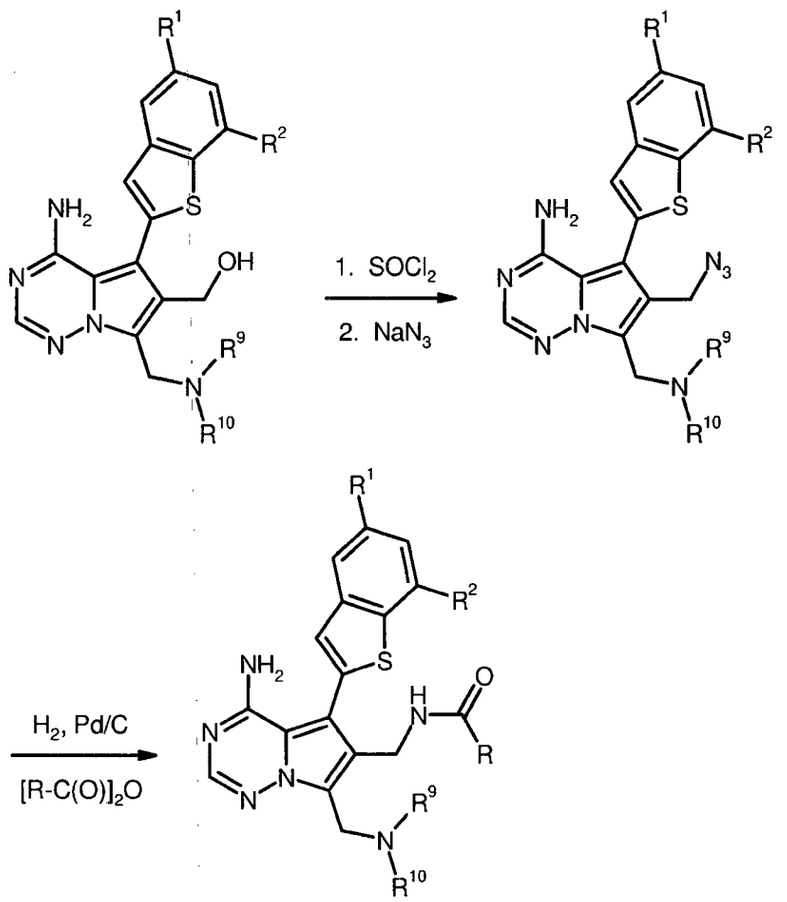
[R^{8A}, R^{8B} = (C_1-C_4)-alkyl, cyclopropyl or cyclobutyl].

Scheme 9



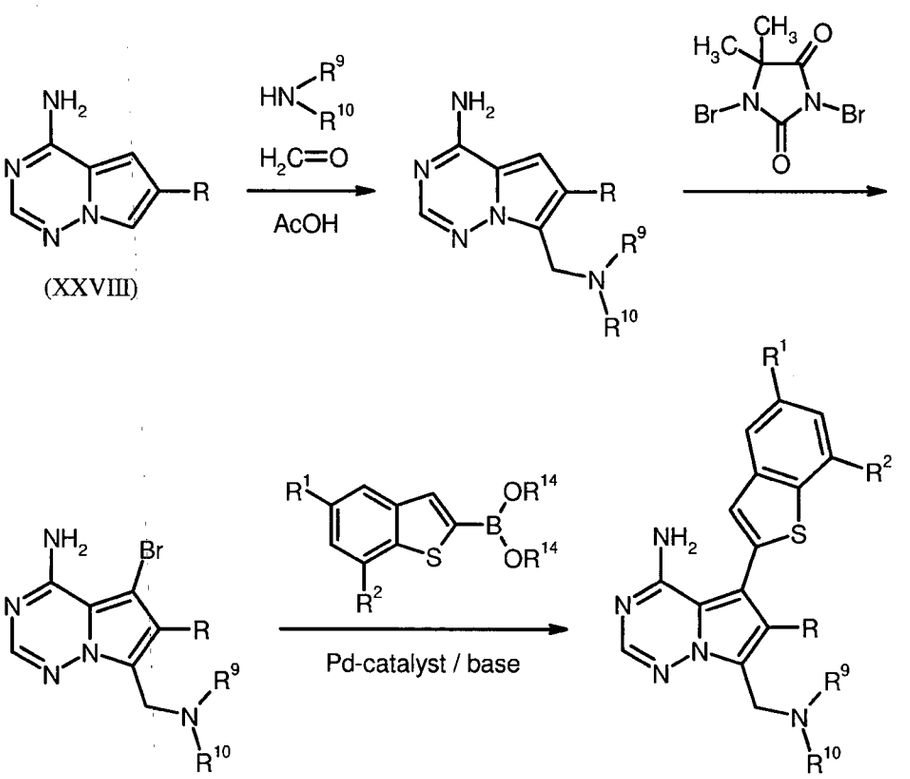
[R^{8A} = (C_1-C_4)-alkyl, cyclopropyl or cyclobutyl; X = Cl, Br or I].

Scheme 10



[R = (C_1-C_4)-alkyl].

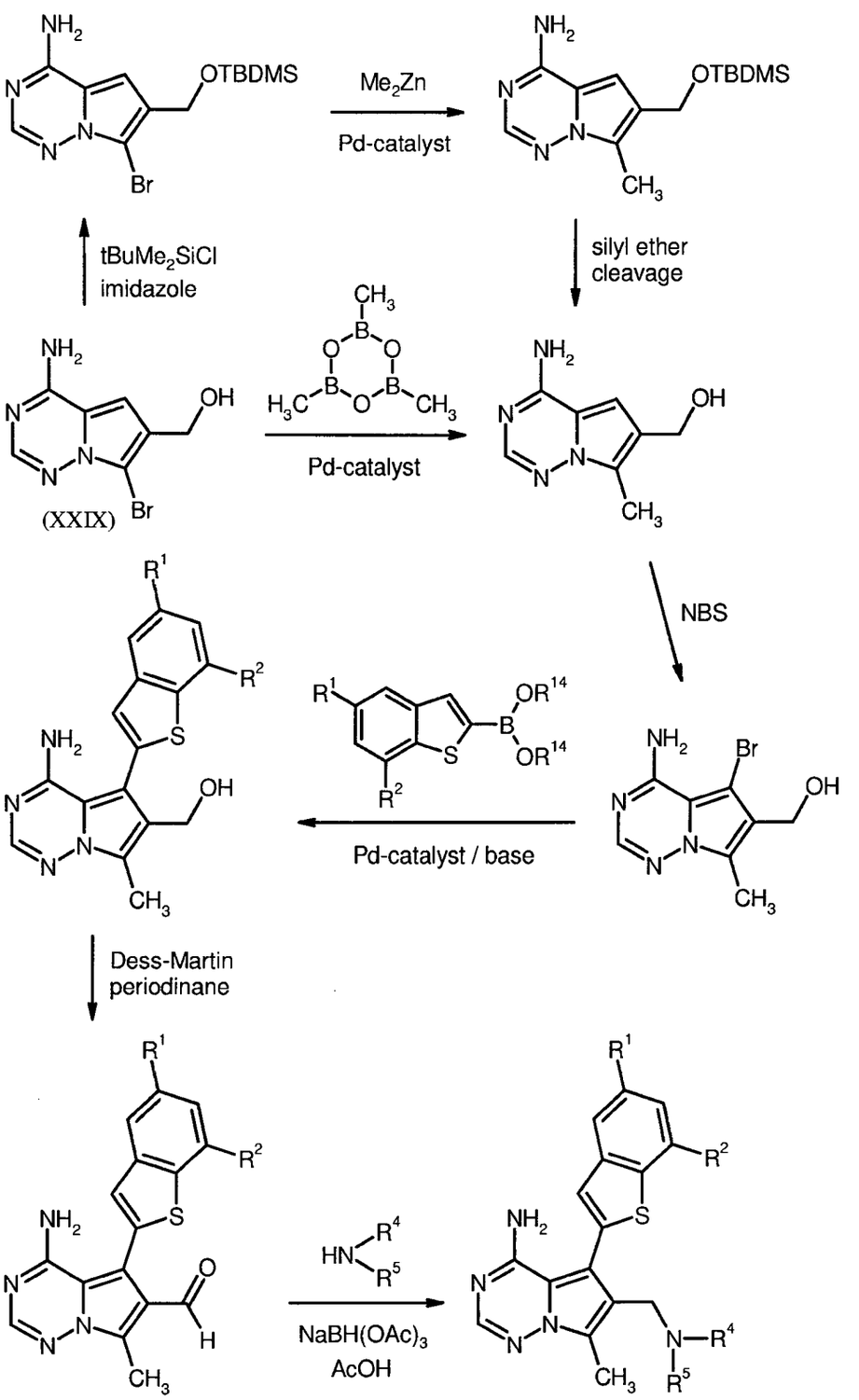
Scheme 11



[R = chloro or (C_1-C_4)-alkyl; for the preparation of the starting material (XXVIII), see Int. Pat. Appl. WO 2007/064883 and WO 2007/056170, respectively].

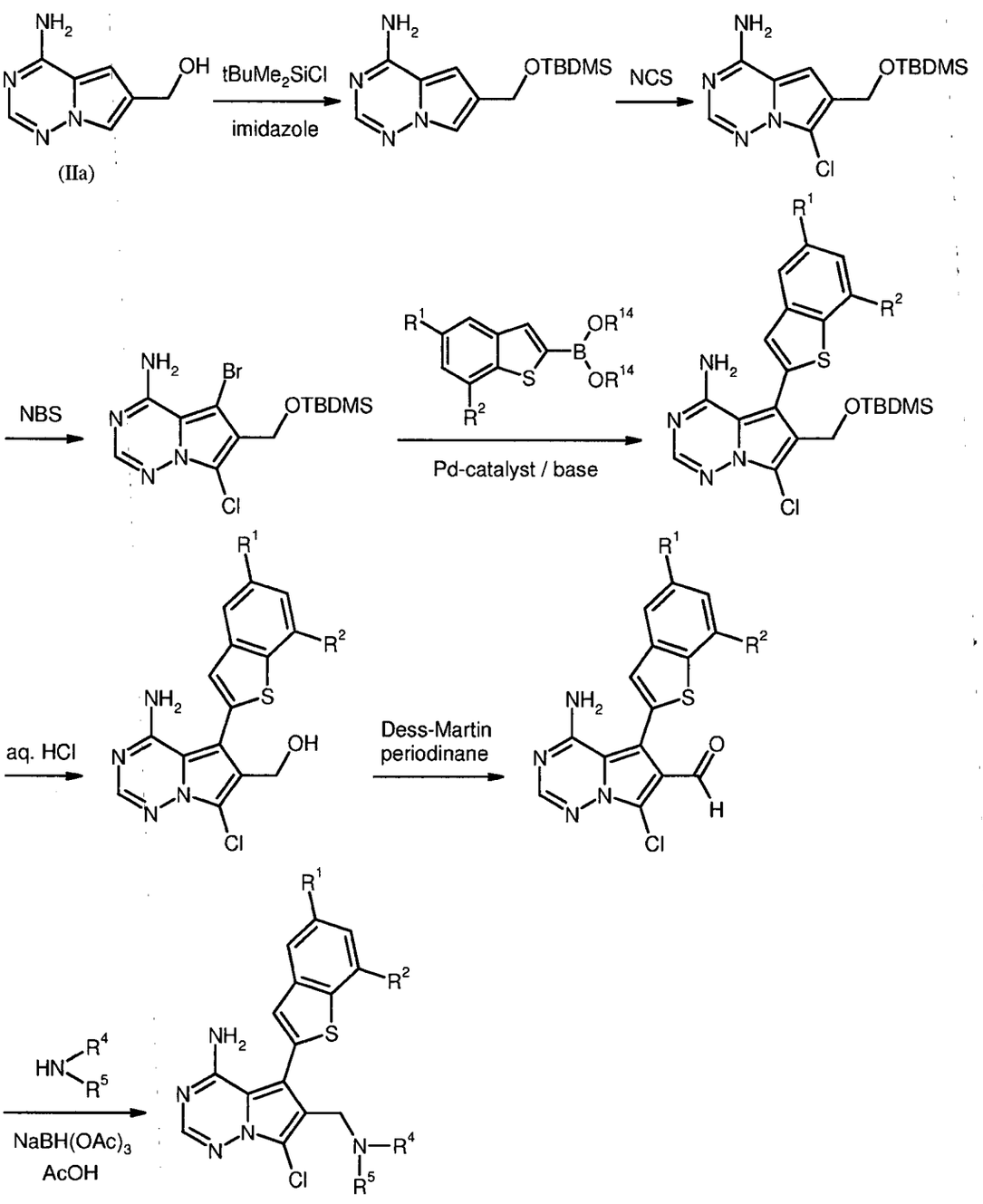
BHC 11 1 045

Scheme 12

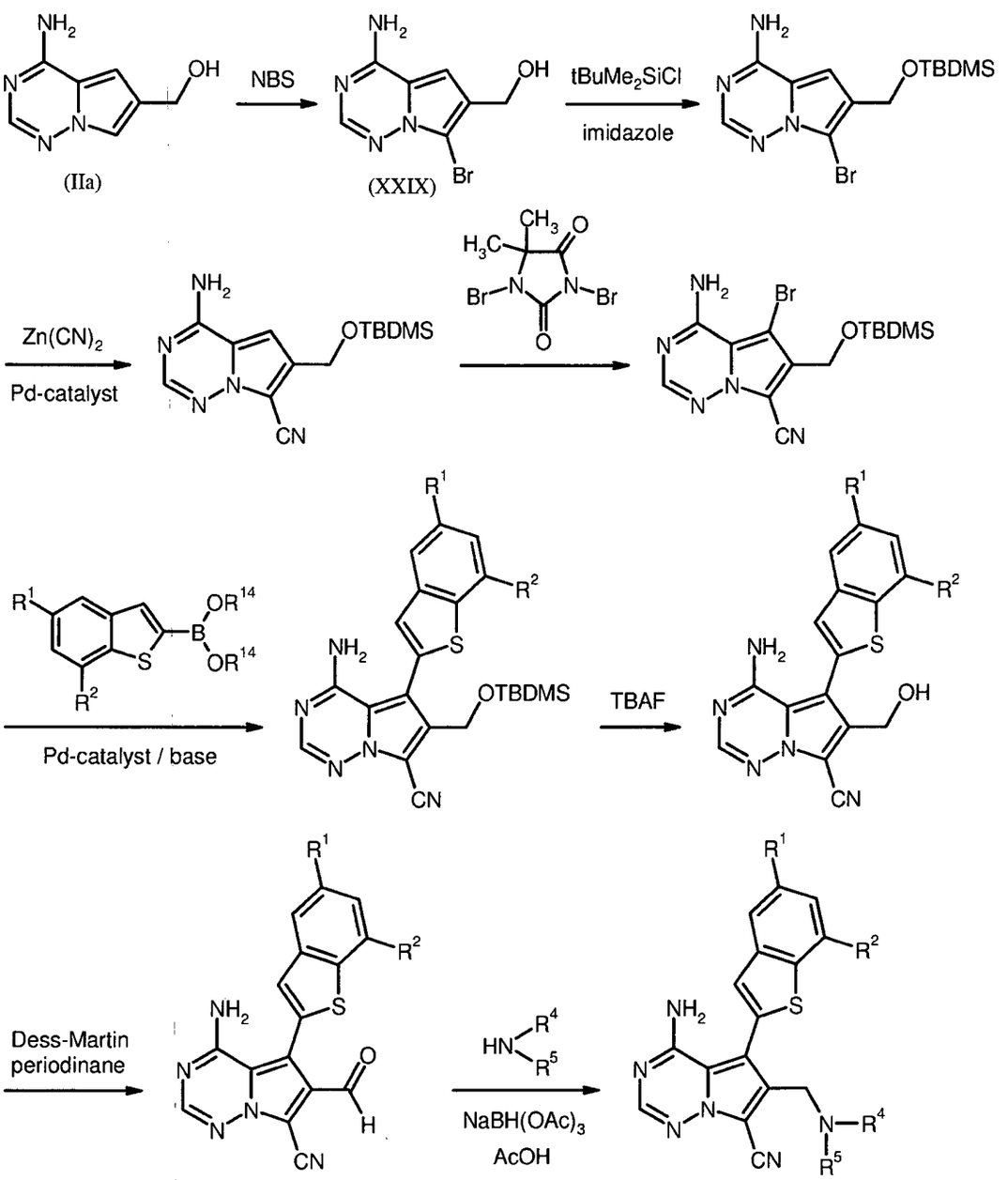


[for the preparation of the starting compound (XXIX), see Scheme 14 below].

Scheme 13


NH2
OH
tBuMe2SiCl
imidazole
OTBDMS
NCS
Cl
(IIa)
NBS
Br
R1
R2
OR14
B
S
Pd-catalyst / base
aq. HCl
Dess-Martin
periodinane
O
H
HN
R4
R5
NaBH(OAc)3
AcOH
N

Scheme 14



The compounds of the present invention have valuable pharmacological properties and can be used for the prevention and treatment of disorders in humans and other mammals.

The compounds of the present invention are potent inhibitors of the activity or expression of receptor tyrosine kinases, particularly of the FGFR kinases, and most notably of the FGFR-1 and FGFR-3 kinases. Accordingly, in another embodiment, the present invention provides a method of treating disorders relating to or mediated by the activity of FGFR kinases in a patient in need of such treatment, comprising administering to the patient an effective amount of a compound of

formula (I) as defined above. In certain embodiments, the disorders relating to the activity of FGFR kinases are proliferative disorders, in particular cancer and tumor diseases.

In the context of 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 disorder, disease, condition, or state may be partial or complete.

The term "proliferative disorder" includes disorders involving the undesired or uncontrolled proliferation of a cell. The compounds of the present invention can be utilized to prevent, inhibit, block, reduce, decrease, control, etc., cell proliferation and/or cell division, and/or produce apoptosis. This method comprises administering to a subject in need thereof, including a mammal, including a human, an amount of a compound of this invention, or a pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate or solvate thereof which is effective to treat or prevent the disorder.

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. For example, 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).

Proliferative disorders that can be treated and/or prevented with the compounds of the present invention particularly include, but are not limited to, the group of cancer and tumor diseases. These are understood as meaning, in particular, the following diseases, but without being limited to them: mammary carcinomas and mammary tumors (ductal and lobular forms, also *in situ*), tumors of the respiratory tract (small cell and non-small cell lung carcinoma, parvicellular and non-parvicellular carcinoma, bronchial carcinoma, bronchial adenoma, pleuropulmonary blastoma), cerebral tumors (e.g. of the brain stem and of the hypothalamus, astrocytoma, glioblastoma, medulloblastoma, ependymoma, and neuro-ectodermal and pineal tumors), tumors of the digestive organs (oesophagus, stomach, gall bladder, small intestine, large intestine, rectum, anus), liver tumors (inter alia hepatocellular carcinoma, cholangiocellular carcinoma and mixed hepatocellular and cholangiocellular carcinoma), tumors of the head and neck region (larynx, hypopharynx, nasopharynx, oropharynx, lips and oral cavity), skin tumors (squamous epithelial carcinoma, Kaposi

sarcoma, malignant melanoma, Merkel cell skin cancer and non-melanomatous skin cancer), tumors of soft tissue (inter alia soft tissue sarcomas, osteosarcomas, malignant fibrous histiocytomas, lymphosarcomas and rhabdomyosarcomas), tumors of the eyes (inter alia intraocular melanoma, uveal melanoma and retinoblastoma), tumors of the endocrine and exocrine glands (e.g. thyroid and parathyroid glands, pancreas and salivary gland), tumors of the urinary tract (tumors of the bladder, penis, kidney, renal pelvis and ureter), tumors of the reproductive organs (carcinomas of the endometrium, cervix, ovary, vagina, vulva and uterus in women, and carcinomas of the prostate and testicles in men), as well as distant metastases thereof. These disorders also include proliferative blood diseases in solid form and as circulating blood cells, such as lymphomas, leukaemias and myeloproliferative diseases, e.g. acute myeloid, acute lymphoblastic, chronic lymphocytic, chronic myelogenic and hairy cell leukaemia, and AIDS-related lymphomas, Hodgkin's lymphomas, non-Hodgkin's lymphomas, cutaneous T-cell lymphomas, Burkitt's lymphomas, and lymphomas in the central nervous system.

Due to their activity and selectivity profile, the compounds of the present invention are believed to be particularly suitable for the treatment of breast (mammary), lung, stomach (gastric), bladder and ovary cancer and tumor diseases. Furthermore, the compounds of the present invention may be especially suited for the prevention or suppression of tumor metastasis in general.

Other proliferative disorders that can be treated and/or prevented with the compounds and methods of the present invention include psoriasis, keloids and other hyperplasias affecting the skin, bullous disorders associated with subepidermal blister formation including bullous pemphigoid, erythema multiforme and dermatitis herpetiformis, fibrotic disorders such as lung fibrosis, atherosclerosis, restenosis and hepatic cirrhosis, renal diseases including mesangial cell proliferative disorders, glomerulopathies, glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis and polycystic kidney disease, benign prostate hyperplasia (BPH), angiogenic or blood vessel proliferative disorders, and thrombotic microangiopathy syndromes.

The compounds of the present invention are also useful for the treatment and/or prevention of ophthalmological diseases such as, for example, age-related macular degeneration (AMD), dry macular degeneration, ischemic retinal vein occlusion, diabetic macula edema, diabetic retinopathy, retinopathy of prematurity, and other retinopathies.

Other conditions that may be treated and/or prevented by administering a compound of the present invention include gynaecological diseases such as endometriosis, myoma and ovarian cysts, metabolic disorders related to adipogenesis, bile metabolism, phosphate metabolism, calcium metabolism and/or bone mineralization, skeletal disorders such as, for example, dwarfism, achondro-

dysplasia and Pfeiffer syndrome, cartilage diseases such as osteoarthritis and polyarthritis, rheumatoid arthritis, calvities, and transplant rejection.

The diseases mentioned above have been well characterized in humans, but also exist with a comparable aetiology in other mammals, and can be treated in those with the compounds and methods 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 as long as this combination does not lead to undesirable and/or unacceptable side effects. Such 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 (fixed) 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 other anti-cancer agents such as alkylating agents, anti-metabolites, plant-derived anti-tumor agents, hormonal therapy agents, topoisomerase inhibitors, tubulin inhibitors, kinase inhibitors,

targeted drugs, antibodies, antibody-drug conjugates (ADCs), immunologicals, biological response modifiers, anti-angiogenic compounds, and other anti-proliferative, cytostatic and/or cytotoxic substances. In this regard, the following is a non-limiting list of examples of secondary agents that may be used in combination with the compounds of the present invention:

Abarelix, abiraterone, aclarubicin, afatinib, aflibercept, aldesleukin, alemtuzumab, alitretinoin, alpharadin, altretamine, aminoglutethimide, amonafide, amrubicin, amsacrine, anastrozole, andromustine, arglabin, asparaginase, axitinib, 5-azacitidine, basiliximab, belotecan, bendamustine, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin, bortezomib, bosutinib, brivanib alaninate, buserelin, busulfan, cabazitaxel, CAL-101, calcium folinate, calcium levofolinate, camptothecin, capecitabine, carboplatin, carmofur, carmustine, catumaxomab, cediranib, celmoleukin, cetuximab, chlorambucil, chlormadinone, chlormethine, cidofovir, cisplatin, cladribine, clodronic acid, clofarabine, combretastatin, crisantaspase, crizotinib, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, darbepoetin alfa, darinaparsin, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftitox, denosumab, deslorelin, dibrospidium chloride, docetaxel, dovitinib, doxifluridine, doxorubicin, dutasteride, eculizumab, edrecolomab, eflornithine, elliptinium acetate, eltrombopag, endostatin, enocitabine, epimbicin, epirubicin, epitiostanol, epoetin alfa, epoetin beta, epothilone, eptaplatin, eribulin, erlotinib, estradiol, estramustine, etoposide, everolimus, exatecan, exemestane, exisulind, fadrozole, fenretinide, filgrastim, finasteride, flavopiridol, fludarabine, 5-fluorouracil, fluoxymesterone, flutamide, foretinib, formestane, fotemustine, fulvestrant, ganirelix, gefitinib, gemcitabine, gemtuzumab, gimatecan, gimeracil, glufosfamide, glutoxim, goserelin, histrelin, hydroxyurea, ibandronic acid, ibritumomab tiuxetan, idarubicin, ifosfamide, imatinib, imiquimod, improsulfan, intedanib, interferon alpha, interferon alpha-2a, interferon alpha-2b, interferon beta, interferon gamma, interleukin-2, ipilimumab, irinotecan, ixabepilone, lanreotide, lapatinib, lasofoxifene, lenalidomide, lenograstim, lentinan, lenvatinib, lestaurtinib, letrozole, leuprorelin, levamisole, linifanib, linsitinib, lisuride, lobaplatin, lomustine, lonidamine, lurtotecan, mafosfamide, mapatumumab, masitinib, masoprocol, medroxyprogesterone, megestrol, melarsoprol, melphalan, mepitiostane, mercaptopurine, methotrexate, methyl aminolevulinate, methyltestosterone, mifamurtide, mifepristone, miltefosine, miriplatin, mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane, mitoxantrone, molgramostim, motesanib, nandrolone, nedaplatin, nelarabine, neratinib, nilotinib, nilutamide, nimotuzumab, nimustine, nitracrine, nolatrexed, ofatumumab, oprelvekin, oxaliplatin, paclitaxel, palifermin, pamidronic acid, panitumumab, pazopanib, pegaspargase, peg-epoetin beta, pegfilgastrim, peg-interferon alpha-2b, pelitrexol, pemetrexed, pemtumomab, pentostatin, peplomycin, perfosfamide, perifosine, pertuzumab, picibanil, pirambicin, pirarubicin, plerixafor, plicamycin, poliglusam, polyestradiol phosphate, ponatinib, porfimer sodium, pralatrexate, prednimustine, procarbazine, procodazole, PX-866, quinagolide, raloxifene, raltitrexed, ranibizumab, ranimustine, razoxane,

regorafenib, risedronic acid, rituximab, romidepsin, romiplostim, rubitecan, saracatinib, sargramostim, satraplatin, selumetinib, sipuleucel-T, sirolimus, sizofiran, sobuzoxane, sorafenib, streptozocin, sunitinib, talaporfin, tamibarotene, tamoxifen, tandutinib, tasonermin, teceleukin, tegafur, telatinib, temoporfin, temozolomide, temsirolimus, teniposide, testolactone, testosterone, tetrofosmin, thalidomide, thiotepa, thymalfasin, tioguanine, tipifarnib, tivozanib, toceranib, tocilizumab, topotecan, toremifene, tositumomab, trabectedin, trastuzumab, treosulfan, tretinoin, triapine, trilostane, trimetrexate, triptorelin, trofosfamide, ubenimex, valrubicin, vandetanib, vapreotide, varlitinib, vatalanib, vemurafenib, vidarabine, vinblastine, vincristine, vindesine, vinflunine, vinorelbine, volociximab, vorinostat, zinostatin, zoledronic acid, and zorubicin.

Generally, the following aims may be pursued with the combination of compounds of the present invention with other anti-cancer agents:

- improved activity in slowing down the growth of a tumor, in reducing its size or even in its complete elimination compared with treatment with a single active compound;
- possibility of employing the chemotherapeutics used in a lower dosage than in monotherapy;
- possibility of a more tolerable therapy with few side effects compared with individual administration;
- possibility of treatment of a broader spectrum of cancer and tumor diseases;
- achievement of a higher rate of response to therapy;
- longer survival time of the patient compared with standard therapy.

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.

In cancer treatment, the compounds of the present invention may also be employed in conjunction with radiation therapy and/or surgical intervention.

Furthermore, the compounds of formula (I) may be utilized, as such or in compositions, in research and diagnostics, or as analytical reference standards, and the like, which are well known in the art.

When the compounds of the present invention are administered as pharmaceuticals, to humans and other mammals, they can be given *per se* or as a pharmaceutical composition containing, for

example, 0.1% to 99.5% (more preferably, 0.5% to 90%) of active ingredient in combination with one or more pharmaceutically acceptable excipients.

Thus, in another aspect, the present invention relates to pharmaceutical compositions comprising at least one of the compounds according to the invention, conventionally together with one or more inert, non-toxic, pharmaceutically suitable excipients, and to the use thereof for the treatment and/or prevention of disorders, especially of the aforementioned disorders.

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, otic or topical route, or as an implant or stent.

For these application routes, the compounds of the invention can be administered in suitable application forms.

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 application can be carried out with avoidance of an absorption step (intravenously, intraarterially, intracardially, intraspinally or intralumbarly) or with inclusion of an absorption (intramuscularly, subcutaneously, intracutaneously, percutaneously or intraperitoneally). Useful parenteral application forms include injection and infusion preparations in the form of solutions, suspensions, emulsions, lyophilisates and sterile powders.

Forms suitable for other application routes include, for example, inhalatory pharmaceutical forms (e.g. powder inhalers, nebulizers), nasal drops, solutions or sprays, tablets or capsules to be administered lingually, sublingually or buccally (e.g. troches, lozenges), suppositories, ear and eye preparations (e.g. drops, ointments), vaginal capsules, aqueous suspensions (lotions, shaking mixtures), lipophilic suspensions, ointments, creams, milks, pastes, foams, dusting powders, transdermal therapeutic systems (e.g. patches), implants and stents.

In a preferred embodiment, the pharmaceutical composition comprising a compound of formula (I) as defined above is provided in a form suitable for oral administration. In another preferred embodiment, the pharmaceutical composition comprising a compound of formula (I) as defined above is provided in a form suitable for intravenous administration.

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 alia, 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.

A preferred dose of the compound of the present invention is the maximum that a patient can tolerate and not develop serious side effects. Illustratively, the compound of the present invention may be administered parenterally at a dose of about 0.001 mg/kg to about 1 mg/kg, preferably of about 0.01 mg/kg to about 0.5 mg/kg of body weight. 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. Ranges intermediate to the above-recited values are also intended to be part of the invention.

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, the bioavailability and pharmacodynamic characteristics of the particular compound and its mode and route of administration, the time or interval over which administration takes place, the dose regimen selected, the response of the individual patient to the active ingredient, the specific disease involved, the degree of or the involvement or severity of the disease, the kind of concurrent treatment (i.e., the interaction of the compound of the invention with other co-administered therapeutics), and other relevant circumstances.

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. Treatment can be initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage may be increased by small increments until the optimum effect under the circumstances is

reached. For convenience, the total daily dosage may be divided and administered in individual portions spread over the day.

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
Ac_2O	acetic anhydride
AcOH	acetic acid
aq.	aqueous (solution)
Boc	*tert*-butoxycarbonyl
br.	broad (^{1}H-NMR signal)
Bu	butyl
cat.	catalytic
conc.	concentrated
d	doublet (^{1}H-NMR signal)
DBDMH	1,3-dibromo-5,5-dimethylhydantoin
DCI	direct chemical ionization (MS)
DCM	dichloromethane
Dess-Martin periodinane	1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one
DIPEA	*N,N*-diisopropylethylamine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
EI	electron impact ionization (MS)
eq.	equivalent(s)
ESI	electro-spray ionization (MS)
Et	ethyl
EtOAc	ethyl acetate
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
iPr	isopropyl
LC-MS	liquid chromatography-coupled mass spectroscopy
Me	methyl
MeOH	methanol
min	minute(s)
MS	mass spectroscopy

m/z	mass-to-charge ratio (MS)
NBS	*N*-bromosuccinimide
n-Bu	*n*-butyl
NCS	*N*-chlorosuccinimide
of th.	of theory (chemical yield)
Pd/C	palladium on charcoal
$PdCl_2$(dppf)	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
$Pd(dba)_2$	bis(dibenzylideneacetone)palladium
Ph	phenyl
PPA	polyphosphoric acid
q	quartet (^{1}H-NMR signal)
quant.	quantitative (yield)
rac	racemic
R_f	TLC retention factor
RP	reverse phase (HPLC)
rt	room temperature
R_t	retention time (HPLC)
s	singlet (^{1}H-NMR signal)
sat.	saturated (solution)
t	triplet (^{1}H-NMR signal)
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBTU	*N*-[(1*H*-benzotriazol-1-yloxy)(dimethylamino)methylene]-*N*-methyl-methanaminium tetrafluoroborate
tBu	*tert*-butyl
tert	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

LC-MS and GC-MS methods:

Method 1 (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% aq. formic acid, eluent B: 1 L

acetonitrile + 0.5 ml 50% aq. 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 2 (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; oven: 50°C; flow rate: 0.40 mL/min; UV detection: 210-400 nm.

Method 3 (LC-MS):

Instrument: Micromass Quattro Micro with HPLC Agilent 1100 Series; column: YMC-Triart C18 3µ, 50 mm x 3 mm; eluent A: 1 L water + 0.01 mol ammonium carbonate, eluent B: 1 L acetonitrile; gradient: 0.0 min 100% A → 2.75 min 5% A → 4.5 min 5% A; oven: 40°C; flow rate: 1.25 mL/min; UV detection: 210 nm.

Method 4 (LC-MS):

Instrument: Waters Acquity SQD UPLC System; column: Waters Acquity UPLC HSS T3 1.8µ, 30 mm x 2 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; oven: 50°C; flow rate: 0.60 mL/min; UV detection: 208-400 nm.

Method 5 (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% aq. formic acid, eluent B: 1 L acetonitrile + 0.5 ml 50% aq. formic acid; gradient: 0.0 min 97% A → 0.5 min 97% A → 3.2 min 5% A → 4.0 min 5% A; temperature: 50°C; flow rate: 0.3 mL/min; UV detection: 210 nm.

Method 6 (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 (maintain for 3 min).

General purification methods *(see Table I and II below)*:

Method P1:

Preparative RP-HPLC (Reprosil C18, gradient acetonitrile/0.2% aq. trifluoroacetic acid).

Method P2:

Preparative RP-HPLC (XBridge C18, gradient acetonitrile/water + 0.1% aq. ammonia).

Method P3:

Preparative RP-HPLC (Sunfire C18, gradient acetonitrile/water).

Method P4:

Preparative RP-HPLC (XBridge C18, gradient acetonitrile/water + 0.05% aq. ammonia).

Method P5:

The product obtained from the preceding RP-HPLC purification is dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge is eluted with methanol, and the filtrate is evaporated.

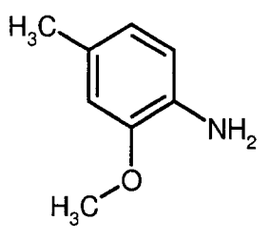
Method P6:

A solution of the product in ethyl acetate is washed with sat. aq. sodium hydrogencarbonate solution followed by sat. aq. sodium chloride solution, dried over magnesium sulfate, filtered and evaporated.

Starting Materials and Intermediates:

Intermediate 1A

2-Methoxy-4-methylaniline



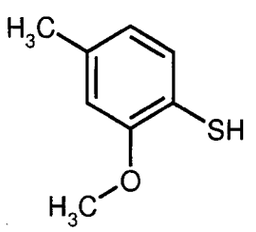
A mixture of 5-methyl-2-nitroanisol (265 g, 1.58 mol) and 10% Pd/C (39.75 g) in THF (1.32 L) was stirred overnight at rt under 1 atm of hydrogen. Filtration over kieselguhr and evaporation afforded 216.1 g of the crude product which was used in the next step without further purification.

LC-MS (method 3): R_t = 2.39 min; MS (ESIpos): m/z = 138 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 6.45-6.63 (m, 3H), 4.46 (s, 2H), 3.72 (s, 3H), 2.16 (s, 3H) ppm.

Intermediate 2A

2-Methoxy-4-methylbenzenethiol



Method 1:

A solution of sodium nitrite (7 g, 101.4 mmol) in water (25 ml) was added dropwise to a cooled (0°-5°C) solution of Intermediate 1A (13.7 g, 100 mmol) in concentrated hydrochloric acid (30 ml) and water (85 ml). After stirring at 0°C for 10 min, sodium acetate (15 g, 182.8 mmol) was added. The resulting mixture was added dropwise to a hot solution (70°-80°C) of potassium *O*-ethyl dithiocarbonate (30 g, 187.1 mmol) in water (140 ml), stirred between 70°C and 80°C for 1 h and then cooled to rt. The mixture was extracted twice with ethyl acetate, and the combined organic extracts were dried over sodium sulfate and evaporated. The residue was taken up in a 1.3 M solution of potassium hydroxide in ethanol (300 ml). Glucose (8 g) was added, and the resulting mix-

ture was refluxed for 3 h. Then, the ethanol solvent was evaporated, and the residue was diluted with water and acidified with 6 N aqueous sulfuric acid. Zinc powder (15 g) was added carefully, and the resulting mixture was heated to 50°C for 30 min. The mixture was then cooled to rt, diluted with dichloromethane and filtered. The filtrate was extracted twice with dichloromethane, and the combined organic extracts were dried over sodium sulfate and evaporated affording 14.3 g of the crude product which was used in the next step without further purification.

Method 2:

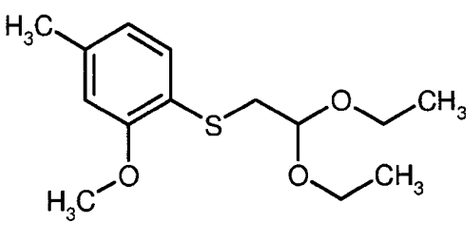
To 2.9 L of THF was added a warm solution of 355 ml (6.67 mol) concentrated sulfuric acid in 1.1 L of water. At 50°C, 293 g (1.33 mol) 2-methoxy-4-methylbenzenesulfonyl chloride were added under stirring. Then, 521 g (7.97 mol) of zinc powder were added carefully in portions (foaming), and the slightly exothermic reaction was cooled in a water bath to maintain a temperature of 50°-55°C. The mixture was subsequently stirred at 55°C for 3 h. The progress of the reaction was monitored by TLC (silica gel, petrolether/ethyl acetate 95:5). The reaction mixture was poured into 13.6 L of water, 6.8 L dichloromethane were added, and the mixture was stirred for 5 min. After decanting from remaining zinc and phase separation, the aqueous phase was extracted once more with 6.8 L dichloromethane. The combined organic phases were washed with 10% brine, dried and evaporated at 40°C under reduced pressure yielding 237 g of crude product. This material was used in the next step without further purification. An analytical sample was obtained by silica gel chromatography with petrolether/ethyl acetate (97:3) as eluent.

LC-MS (method 1): R_t = 1.21 min; MS (ESIneg): m/z = 153 $(M-H)^-$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.17 (d, 1H), 6.81 (s, 1H), 6.66 (d, 1H), 4.63 (br. s, 1H), 3.80 (s, 3H), 2.26 (s, 3H) ppm.

Intermediate 3A

1-[(2,2-Diethoxyethyl)sulfanyl]-2-methoxy-4-methylbenzene



237 g crude material from Intermediate 2A, 287 g (1.46 mol) bromoacetaldehyde-diethylacetal and 862 g (2.65 mol) caesium carbonate were suspended in 2 L DMF. The reaction temperature increased initially to 40°C, then stirring was continued overnight at ambient temperature. The reac-

tion mixture was partitioned between 10 L of water and 2.7 L of ethyl acetate. The aqueous phase was extracted with another portion of 2.7 L ethyl acetate. The combined organic phases were washed with 10% brine, dried and evaporated. The resulting oily residue was purified by silica gel chromatography with petrolether/ethyl acetate (95:5) as eluent.

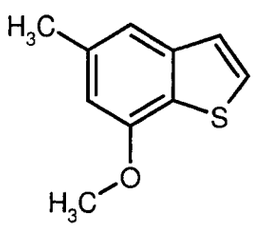
Yield: 236 g of an oil (66% of th.)

GC-MS (method 6): R_t = 6.03 min; MS (EIpos): m/z = 270 $(M)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.16 (d, 1H), 6.82 (s, 1H), 6.73 (d, 1H), 4.55 (t, 1H), 3.80 (s, 3H), 3.52-3.64 (m, 2H), 3.39-3.51 (m, 2H), 2.96 (d, 2H), 2.33 (s, 3H), 1.09 (t, 6H) ppm.

Intermediate 4A

7-Methoxy-5-methyl-1-benzothiophene



To a refluxing mixture of 13 g polyphosphoric acid and 150 ml chlorobenzene was added dropwise a solution of 5.2 g (19.2 mmol) of Intermediate 3A, and refluxing was continued overnight. After cooling, the organic layer was decanted, and the residue and flask were rinsed twice with DCM. The combined organic phases were evaporated at reduced pressure. The residue (3.76 g) was chromatographed on silica gel with isohexane/0-10% ethyl acetate as eluent.

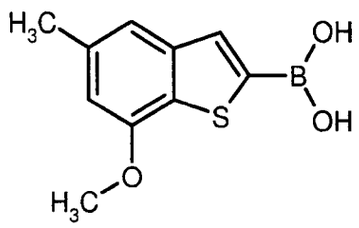
Yield: 1.69 g of an oil (49% of th.)

GC-MS (method 6): R_t = 5.20 min; MS (EIpos): m/z = 178 $(M)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.68 (d, 1H), 7.34 (d, 1H), 7.28 (s, 1H), 6.78 (s, 1H), 3.93 (s, 3H), 2.43 (s, 3H) ppm.

Intermediate 5A

(7-Methoxy-5-methyl-1-benzothiophen-2-yl)boronic acid



Under argon atmosphere, 26.7 g (150 mmol) of Intermediate 4A were dissolved in 270 ml of THF and cooled to -70°C. Between -70°C and -65°C, 66 ml (165 mmol) of a 2.5 N solution of *n*-butyllithium in hexane were added dropwise within 20 min, resulting in formation of a white precipitate. After stirring for 1 h at -70°C, 41.5 ml (180 mmol) triisopropyl borate were added at this temperature within 10 min (resulting in a thick suspension). Stirring was continued for 1 h at -70°C, before the reaction mixture was allowed to warm up to rt overnight. Then, 400 ml of saturated aq. ammonium chloride solution were added, the layers were separated, and the aqueous layer was extracted once more with THF. The combined organic phases were evaporated under reduced pressure. To the residue thus obtained, 200 ml of water and 86 ml of 2 N aq. sodium hydroxide solution were added. The solution was washed twice with DCM, then acidified with 35 ml of 3 M sulfuric acid, and the resulting suspension was stirred vigorously for 1 h. The precipitate was filtered off by suction and dried overnight at 45°C *in vacuo*.

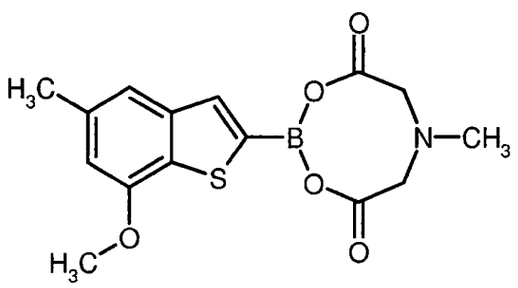
Yield: 28.25 g of a colorless solid (94% pure by LC-MS, 80% of th.)

LC-MS (method 2): R_t = 0.87 min; MS (ESIpos): m/z = 223 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.17 (d, 1H), 6.81 (s, 1H), 6.66 (d, 1H), 4.63 (br. s, 1H), 3.80 (s, 3H), 2.26 (s, 3H) ppm.

Intermediate 6A

2-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione



6.3 g (28.4 mmol) of Intermediate 5A and 4.2 g (28.4 mmol) 2,2'-(methylimino)diacetic acid were dissolved in a mixture of 45 ml DMSO and 400 ml toluene and refluxed for 16 h using a Dean-

Stark trap. After evaporation, the residue was taken up in ethyl acetate and washed three times with water and once with brine. The organic phase was dried over magnesium sulfate and evaporated to a volume of about 200 ml. A white solid precipitated which was filtered, washed with ethyl acetate and dried *in vacuo* to give a first crop (5.52 g) of the title compound. A second crop (3.32 g) was obtained after evaporation of the mother liquor and flash-chromatography over a layer of silica gel using cyclohexane/0-100% ethyl acetate as the eluent.

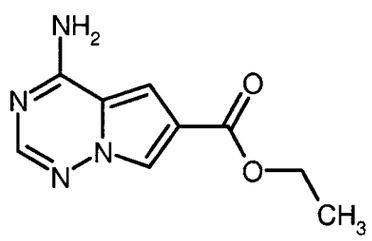
Yield: 8.84 g (overall purity 92.5% by LC-MS, 87% of th.)

LC-MS (method 2): R_t = 0.93 min; MS (ESIpos): m/z = 334 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.42 (s, 1H), 7.26 (s, 1H), 6.76 (s, 1H), 4.40 (d, 2H), 4.17 (d, 2H), 3.92 (s, 3H), 2.63 (s, 3H), 2.42 (s, 3H) ppm.

Intermediate 7A

Ethyl 4-aminopyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



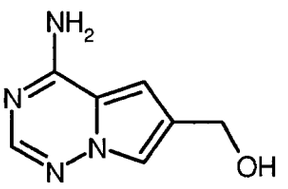
A solution of 4-aminopyrrolo[2,1-f][1,2,4]triazine-6-carbonitrile (3.9 g, 24.5 mmol; preparation described in PCT Int. Pat. Appl. WO 2007/064883) in ethanol (124.8 ml) was stirred with concentrated sulfuric acid (62.4 ml) at 80°C overnight. After cooling to rt, the reaction mixture was poured onto 800 g of ice and brought to pH 6-7 with concentrated aq. sodium hydroxide solution. Ethyl acetate (500 ml) and dichloromethane (500 ml) were added to the suspension, and the resulting mixture was filtered over kieselguhr. The organic layer was separated from the aqueous layer. The solid was dissolved in hot water (1 L), and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over sodium sulfate and evaporated. The residue was triturated with an isopropanol/diethylether mixture, and the solid was filtered off yielding 2.5 g (49% of th.) of the title compound.

LC-MS (method 2): R_t = 0.59 min; MS (ESIpos): m/z = 206 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.11-7.97 (m, 3H), 7.88 (s, 1H), 7.34 (br. s, 1H), 4.27 (q, 2H), 1.30 (t, 3H) ppm.

Intermediate 8A

(4-Aminopyrrolo[2,1-f][1,2,4]triazin-6-yl)methanol



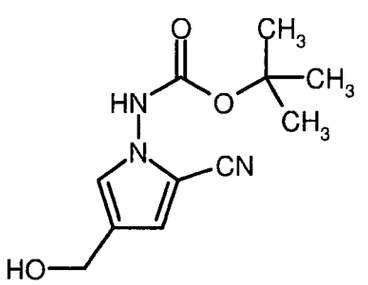
An ice-cooled solution of Intermediate 7A (3.0 g, 14.5 mmol) in THF (30 ml) was treated with a 1 M solution of lithium triethylborohydride in THF (58 ml) and stirred at rt for 45 min. The reaction mixture was then cooled to 0°C, quenched with methanol, warmed slowly to rt and adsorbed on kieselguhr. Purification by column chromatography over silica gel (dichloromethane/methanol 20:1 → 4:1 gradient) afforded 2.21 g (92.5% of th.) of the title compound.

LC-MS (method 3): R_t = 1.46 min; MS (ESIpos): m/z = 164 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.75 (s, 1H), 7.64 (br. s, 2H), 7.50 (br. d, 1H), 6.79 (br. d, 1H), 5.01 (t, 1H), 4.50 (d, 2H) ppm.

Intermediate 9A

tert-Butyl [2-cyano-4-(hydroxymethyl)-1*H*-pyrrol-1-yl]carbamate



Under argon, a 1 M solution of methylmagnesium bromide in THF (13.3 ml) was added over 15 min to a solution of *tert*-butyl (4-bromo-2-cyano-1*H*-pyrrol-1-yl)carbamate (3.7 g, 12.09 mmol; preparation described in PCT Int. Pat. Appl. WO 2007/064883, Intermediate AAE, Step 3) in THF (37 ml) cooled to -60°C. After 30 min, a 1.6 M solution of *n*-butyllithium in hexane (15.1 ml, 24.2 mmol) was added over 10 min to the reaction, and the resulting mixture was stirred between -60°C and -40°C for 1 h. Then, paraformaldehyde (1.09 g, 36.3 mmol) was added to the reaction, and the reaction mixture was slowly warmed to rt and stirred overnight. After quenching with sat. aq. ammonium chloride solution, the aqueous layer was extracted twice with ethyl acetate. The com-

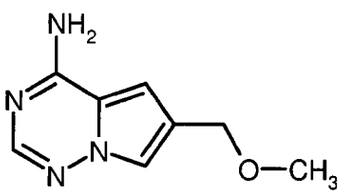
bined organic phases were washed with sat. aq. sodium chloride solution, dried over sodium sulfate and evaporated. Purification by column chromatography on silica gel (cyclohexane/ethyl acetate 2:1 → 1:1) afforded 2.04 g (69% of th.) of the title compound.

LC-MS (method 4): R_t = 0.70 min; MS (ESIpos): m/z = 238 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.79 (br. s, 1H), 7.09 (d, 1H), 6.86 (d, 1H), 4.97 (t, 1H), 4.28 (d, 2H), 1.45 (s, 9H) ppm.

Intermediate 10A

6-(Methoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



Method 1:

A solution of Intermediate 8A (1.3 g, 7.9 mmol) in THF (25 ml) was treated with thionyl chloride (1.15 ml, 15.8 mmol) and stirred at rt for 2 h. After evaporation, the residue was dissolved in methanol (25 ml) and treated with sodium acetate (1.3 g, 15.8 mmol). The mixture was stirred for 3 h at 65°C and then evaporated again. Purification by column chromatography on silica gel (dichloromethane/methanol 100:2) afforded 787 mg (55% of th.) of the title compound.

Method 2:

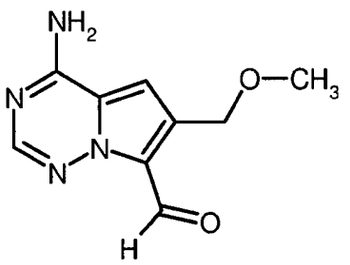
A solution of Intermediate 9A (6.14 g, 25.88 mmol) in a 4 M solution of hydrogen chloride in 1,4-dioxane (15 ml) was stirred at rt for 5 h. After dilution with methanol (73 ml), stirring at rt was continued overnight. Then, potassium phosphate (54.9 g, 258.65 mmol) and formamidinium acetate (13.46 g, 129.32 mmol) were added, and the resulting mixture was stirred at 65°C for 17 h. The reaction mixture was evaporated, sat. aq. sodium chloride solution was added, and the mixture was extracted with dichloromethane followed by ethyl acetate. The combined organic phases were dried over sodium sulfate and evaporated. Purification by column chromatography on silica gel (dichloromethane/methanol 40:1 → 20:1) afforded 2.36 g (49% of th.) of the title compound.

LC-MS (method 3): R_t = 1.72 min; MS (ESIpos): m/z = 179 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.77 (s, 1H), 7.69 (br. s, 2H), 7.57 (s, 1H), 6.81 (s, 1H), 4.42 (s, 2H), 3.25 (s, 3H) ppm.

Intermediate 11A

4-Amino-6-(methoxymethyl)pyrrolo[2,1-f][1,2,4]triazine-7-carbaldehyde



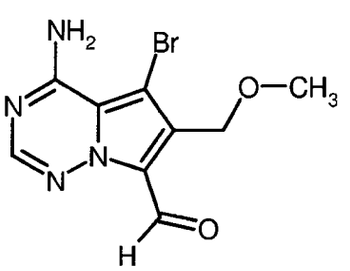
Phosphoryl chloride (13.7 ml, 147.18 mmol) was added to a solution of Intermediate 10A (5.24 g, 29.43 mmol) in DMF (80 ml) at 0°C. The resulting mixture was stirred at 60°C for 8 h, then carefully quenched with water and neutralized with 4 M aq. sodium hydroxide solution. The aqueous layer was extracted with ethyl acetate. The combined organic phases were washed with sat. aq. sodium chloride solution, dried over magnesium sulfate and evaporated. A solution of the residue in methanol (50 ml) was treated with sodium acetate (2.41 g, 29.43 mmol) and refluxed overnight. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic phases were washed with sat. aq. sodium chloride solution, dried over magnesium sulfate and evaporated, affording 2.66 g of the crude product which was used in the next step without further purification.

LC-MS (method 4): R_t = 0.50 min; MS (ESIpos): m/z = 207 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.35 (s, 1H), 8.20 (br. s, 2H), 8.07 (s, 1H), 7.06 (s, 1H), 4.72 (s, 2H), 3.39 (s, 3H) ppm.

Intermediate 12A

4-Amino-5-bromo-6-(methoxymethyl)pyrrolo[2,1-f][1,2,4]triazine-7-carbaldehyde



A solution of Intermediate 11A (crude, 2.66 g) in DMF (30 ml), cooled to -30°C, was treated with a solution of *N*-bromosuccinimide (NBS; 2.52 g, 14.19 mmol) in DMF (14 ml). The resulting mix-

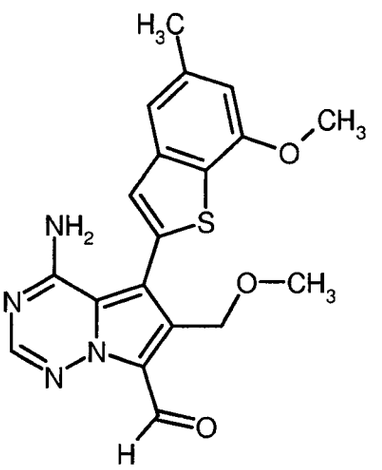
ture was slowly warmed to 0°C. After 1 hour, the mixture was warmed to rt, stirred for further 15 min and then quenched with 1 M aq. sodium thiosulfate solution. The precipitate was filtered off and washed with ethyl acetate, affording 1.1 g (100% purity, 30% of th.) as a first crop of the title compound. The remaining filtrate was extracted with ethyl acetate. The combined organic phases were washed with sat. aq. sodium chloride solution, dried over sodium sulfate and evaporated. Purification of the residue by column chromatography on silica gel (cyclohexane/ethyl acetate 1:1 → 1:3) afforded further 1.39 g (70% purity, 26% of th.) of the title compound.

LC-MS (method 2): R_t = 0.67 min; MS (ESIpos): m/z = 283/285 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.36 (s, 1H), 8.63 (br. s, 1H), 8.13 (s, 1H), 7.23 (br. s, 1H), 4.64 (s, 2H), 3.26 (s, 3H) ppm.

Intermediate 13A

4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazine-7-carbaldehyde



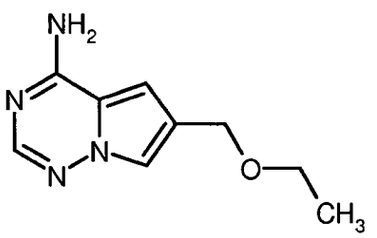
Under argon, a degassed 0.5 M aq. potassium phosphate solution (9.9 ml) was added to a solution of Intermediate 12A (710 mg, 2.49 mmol), Intermediate 5A (921 mg, 3.73 mmol) and (2'-amino-biphenyl-2-yl)(chloro)palladium-dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (1:1; 196 mg, 249 µmol; see S. L. Buchwald *et al.*, *J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)) in degassed THF (28.4 ml). The resulting mixture was stirred at 60°C for 2 h and then evaporated. Purification of the residue by column chromatography on silica gel (cyclohexane/ethyl actetate 5:1 → 1:1) afforded 550 mg (51% of th.) of the title compound.

LC-MS (method 2): R_t = 1.06 min; MS (ESIpos): m/z = 383 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.50 (s, 1H), 8.43 (br. s, 1H), 8.21 (s, 1H), 7.42 (s, 1H), 7.33 (s, 1H), 6.87 (s, 1H), 6.09 (br. s, 1H), 4.58 (s, 2H), 3.96 (s, 3H), 3.19 (s, 3H), 2.46 (s, 3H) ppm.

Intermediate 14A

6-(Ethoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



Method 1:

To a suspension of 2 g (12.2 mmol) of Intermediate 8A in 40 ml THF were added 1.78 ml (24.4 mmol) thionyl chloride at rt within 20 sec. The mixture was stirred for 1.5 h, then evaporated to dryness, and the residue was dissolved in 40 ml ethanol. 2 g (24.4 mmol) sodium acetate were added, and the mixture was stirred at 70°C for 1 h 45 min. The reaction mixture was evaporated again, and sat. aq. sodium hydrogencarbonate solution was added. The mixture was extracted five times with ethyl acetate. The combined organic phases were washed with sat. aq. sodium chloride solution, dried with magnesium sulfate and evaporated to dryness, giving 2.02 g of crude product which was purified by column chromatography on silica gel with dichloromethane/methanol (0-2%) as the eluent.

Yield: 1.37 g (58% of th.).

Method 2:

Step 1: A solution of Intermediate 9A (2.3 g, 9.69 mmol) in 1,4-dioxane (5 ml) was treated with a 4 M solution of hydrogen chloride in 1,4-dioxane (24 ml, 96.9 mmol) and stirred at rt for 130 min. Then, the suspension was filtered, and the precipitate was washed with 1,4-dioxane (5 ml) and dried *in vacuo* yielding 1.01 g (54% of th.) of the intermediate compound 1-amino-4-(chloromethyl)-1*H*-pyrrole-2-carbonitrile hydrochloride.

Step 2: Freshly prepared 1-amino-4-(chloromethyl)-1*H*-pyrrole-2-carbonitrile hydrochloride from Step 1 (0.3 g, 1.82 mmol) was dissolved in ethanol (10 ml) and stirred at rt for 5 min. The clear solution was treated with formamidine acetate (813 mg, 7.81 mmol) and potassium phosphate (1.66 g, 7.81 mmol) and stirred first at rt for 3 days, then at 80°C for 10.5 h. More formamidine acetate (488 mg, 4.69 mmol) was added, and the mixture was stirred for further 18 h at 80°C. The

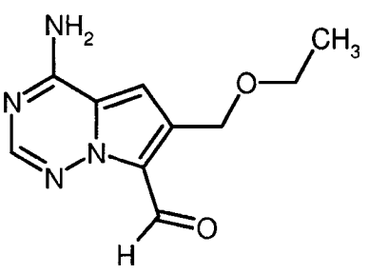
mixture was then cooled to rt, and water and ethyl acetate were added. The organic phase was separated, and the aqeous phase was extracted twice with ethyl acetate. The combined organic phases were washed with sat. aq. sodium chloride solution, dried with magnesium sulfate and evaporated. The residue was dissolved in a mixture of methanol and dichloromethane, adsorbed on diatomaceous earth, dried *in vacuo* and finally purified by chromatography on silica gel (gradient 0-10% methanol/dichloromethane) yielding 260 mg (78% of th.) of the title compound.

LC-MS (method 3): R_t = 2.02 min; MS (ESIpos): m/z = 193 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.77 (s, 1H), 7.59-7.74 (br. s, 2H), 7.56 (s, 1H), 6.82 (s, 1H), 5.76 (s, 1H), 4.46 (s, 2H), 3.46 (q, 2H), 1.13 (t, 3H) ppm.

Intermediate 15A

4-Amino-6-(ethoxymethyl)pyrrolo[2,1-f][1,2,4]triazine-7-carbaldehyde



To a solution of 2.1 g (10.9 mmol) of Intermediate 14A in 40 ml dry DMF, 5.1 ml (54.6 mmol) phosphoryl chloride were added dropwise at 0°C under an argon atmosphere. The mixture was stirred at 60°C for 10 h. Then, water was added carefully, and the mixture was stirred at ambient temperature until all reactive intermediates were destroyed (HPLC control). The acidic solution was neutralized with 1 M aq. sodium hydroxide solution and extracted three times with ethyl acetate. The combined organic phases were washed with sat. aq. sodium chloride solution, dried over magnesium sulfate and evaporated at reduced pressure.

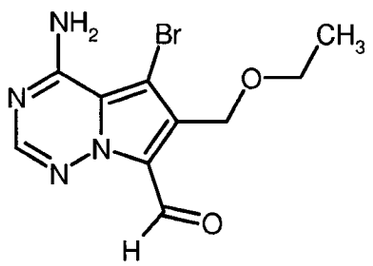
Yield: 1.94 g (purity 90%, 81% of th.)

LC-MS (method 5): R_t = 1.49 min; MS (ESIpos): m/z = 221 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.35 (s, 1H), 8.14-8.26 (m, 2H), 8.07 (s, 1H), 7.07 (s, 1H), 4.76 (s, 2H), 3.58 (q, 2H), 1.20 (t, 3H) ppm.

Intermediate 16A

4-Amino-5-bromo-6-(ethoxymethyl)pyrrolo[2,1-f][1,2,4]triazine-7-carbaldehyde



To a solution of 73 g (0.33 mol) of Intermediate 15A in 1.9 L DMF was added dropwise a solution of 65 g (0.37 mol) NBS in 200 ml DMF at -15°C. The mixture was allowed to warm to 0°C and stirred for 3 h at this temperature. The reaction mixture was poured into 2% aq. sodium thiosulfate solution under stirring, and the precipitate was filtered off, washed with water and dried over phosphorous pentoxide *in vacuo*.

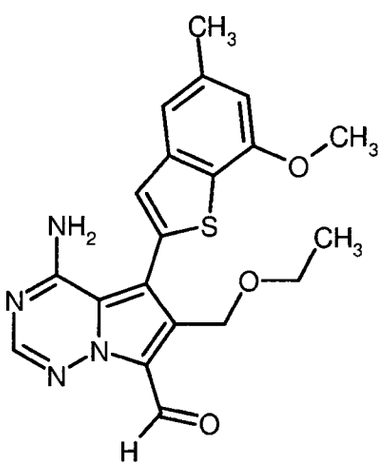
Yield: 85.6 g (86% of th.)

LC-MS (method 2): R_t = 0.76 min; MS (ESIpos): m/z = 299/301 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.36 (s, 1H), 8.62 (br. s, 1H), 8.13 (s, 1H), 7.22 (br. s, 1H), 4.68 (s, 2H), 3.49 (q, 2H), 1.10 (t, 3H) ppm.

Intermediate 17A

4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazine-7-carbaldehyde



Under an argon atmosphere, 714 mg (purity 85%, 2.03 mmol) of Intermediate 16A, 946 mg (2.84 mmol) of Intermediate 6A and 160 mg (0.2 mmol) (2'-aminobiphenyl-2-yl)(chloro)palladium-dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (1:1; see S.L. Buchwald *et al.*, *J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)) were suspended in 15.5 ml THF. Then, 15.5 ml of a

degassed 0.5 M aq. potassium phosphate solution were added, and the mixture was stirred at 50°C for 16 h. After addition of water, the mixture was extracted with ethyl acetate, and the combined organic phases were dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (100 g) with 10-50% ethyl acetate/ cyclohexane as the eluent.

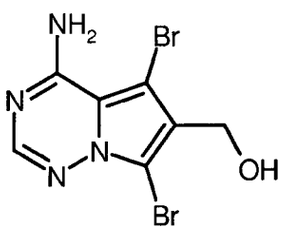
Yield: 452 mg (75% pure by HPLC, 42% of th.)

LC-MS (method 5): R_t = 2.38 min; MS (ESIpos): m/z = 397 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.50 (s, 1H), 8.42 (br. s, 1H), 8.21 (s, 1H), 7.43 (s, 1H), 7.33 (s, 1H), 6.87 (s, 1H), 6.07 (br. s, 1H), 4.63 (s, 2H), 3.96 (s, 3H), 3.40 (q, 2H), 2.46 (s, 3H), 1.02 (t, 3H) ppm.

Intermediate 18A

(4-Amino-5,7-dibromopyrrolo[2,1-f][1,2,4]triazin-6-yl)methanol



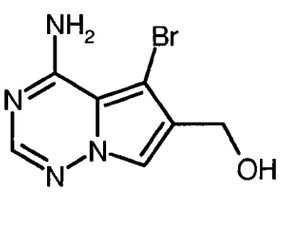
A solution of Intermediate 8A (5 g, 30.4 mmol) in THF (100 ml) was treated with 1,3-dibromo-5,5-dimethylhydantoin (9.58 g, 33.5 mmol) and stirred at rt for 2 h. The precipitate was filtered off and dried *in vacuo* to afford 6.60 g (64% of th.) of the title compound.

LC-MS (method 2): R_t = 0.56 min; MS (ESIpos): m/z = 321/323/325 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.23 (br. s, 1H), 7.96 (s, 1H), 6.94 (br. s, 1H), 5.09 (br. s, 1H), 4.43 (s, 2H) ppm.

Intermediate 19A

(4-Amino-5-bromopyrrolo[2,1-f][1,2,4]triazin-6-yl)methanol



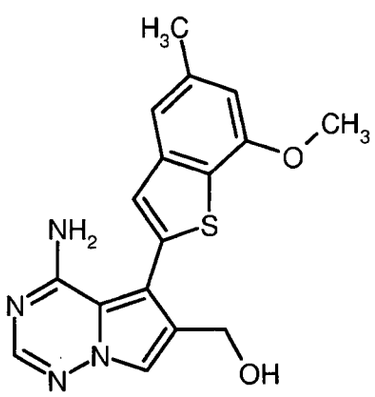
A suspension of Intermediate 18A (3.7 g, 11.5 mmol) in THF (800 ml) was heated under stirring until complete dissolution. The mixture was then cooled to -78°C, and a 1.6 M solution of *n*-butyllithium in hexanes (20 ml, 32.1 mmol) was added dropwise. After 5 min, a further portion of 1.6 M *n*-butyllithium solution (1.5 ml, 2.29 mmol) was added. The resulting mixture was stirred at -78°C for 5 min, then quenched with methanol (5 ml) and warmed to rt. The reaction mixture was diluted with sat. aq. ammonium chloride solution, sat. aq. sodium hydrogencarbonate solution, sat. aq. sodium chloride solution and ethyl acetate. After phase separation, the organic layer was washed with sat. aq. sodium chloride solution. The combined aqueous phases were re-extracted with ethyl acetate. The combined organic phases were washed again with sat. aq. sodium chloride solution, dried over magnesium sulfate and evaporated to afford 2.87 g of the crude product which was used in subsequent steps without further purification.

LC-MS (method 3): R_t = 1.73 min; MS (ESIpos): m/z = 243/245 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.41-7.89 (br. s, 1H), 7.82 (s, 1H), 7.66 (s, 1H), 7.13-6.48 (br. s, 1H), 5.11 (t, 1H), 4.45 (d, 2H) ppm.

Intermediate 20A

[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methanol



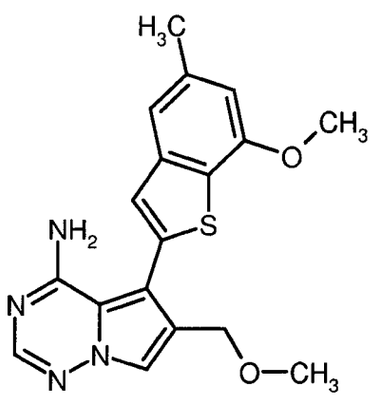
A suspension of Intermediate 19A (70% purity, 2.52 g, 7.26 mmol), Intermediate 6A (3.63 g, 10.9 mmol) and caesium fluoride (5.51 g, 36.3 mmol) in a THF/water mixture (10:1; 80 ml) was degassed under argon. 4-(Di-*tert*-butylphosphino)-*N,N*-dimethylaniline-dichloropalladium (2:1; 176 mg, 0.248 mmol) was added, and the resulting mixture was degassed again and stirred at 50°C for 16 h. The reaction mixture was then washed with sat. aq. sodium chloride solution, and the organic layer was separated, dried over magnesium sulfate, filtered and evaporated. The residue was suspended in methanol, and the resulting solid was filtered off and dried *in vacuo* to afford 1.97 g (90% purity, 72% of th.) of the title compound.

LC-MS (method 2): R_t = 0.85 min; MS (ESIpos): m/z = 340 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.91 (s, 1H), 7.5-8.1 (br. s, 1H), 7.72 (s, 1H), 7.35 (s, 1H), 7.30 (s, 1H), 6.84 (s, 1H), 5.5-6.0 (br. s, 1H), 5.06 (t, 1H), 4.49 (d, 2H), 3.95 (s, 3H), 2.45 (s, 3H) ppm.

Intermediate 21A

6-(Methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



A solution of Intermediate 20A (400 mg, 1.17 mmol) in dichloromethane (12 ml) was treated with thionyl chloride (128 µl, 1.76 mmol) and stirred at rt for 15 min. After evaporation, the residue was taken up in methanol (12 ml) and treated with DIPEA (409 µl, 2.35 mmol). The mixture was refluxed overnight and then evaporated again. Purification by column chromatography on silica gel (dichloromethane/methanol 98:2 → 95:5) afforded 388 mg (93% of th.) of the title compound.

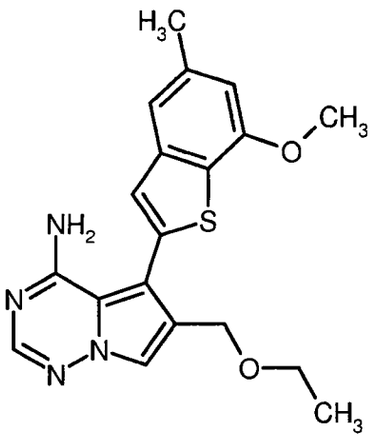
LC-MS (method 2): R_t = 1.00 min; MS (ESIpos): m/z = 355 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.93 (s, 1H), 7.82 (s, 1H), 7.35 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 4.38 (s, 2H), 3.95 (s, 3H), 3.22 (s, 3H), 2.45 (s, 3H) ppm.

Intermediate 22A

6-(Ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine

BHC 11 1 045



Intermediate 20A (200 mg, 587 µmol) in dichloromethane (5 ml) was treated with thionyl chloride (64 µl, 881 µmol) and stirred at rt for 15 min. After evaporation, the residue was refluxed in ethanol (5 ml) for 1 h, then treated with DIPEA (204 µl, 1.17 mmol) and refluxed again overnight. The reaction mixture was evaporated, and the crude product was purified by column chromatography on silica gel (dichloromethane/methanol 98:2 → 95:5) affording 202 mg (90% of th.) of the title compound.

LC-MS (method 5): R_t = 2.32 min; MS (ESIpos): m/z = 369 $(M+H)^+$

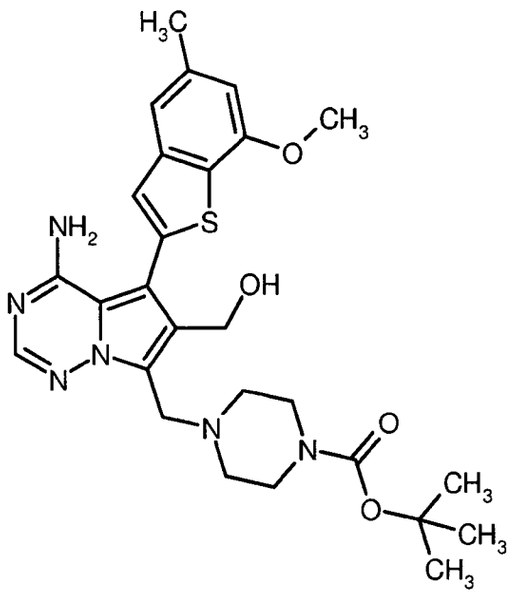
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.31-7.59 (br. s, 1H), 7.93 (s, 1H), 7.81 (s, 1H), 7.35 (s, 1H), 7.30 (s, 1H), 6.84 (s, 1H), 6.20-5.50 (br. s, 1H), 4.41 (s, 2H), 3.95 (s, 3H), 3.41 (q, 2H), 2.45 (s, 3H), 1.08 (t, 3H) ppm.

Intermediate 23A

tert-Butyl 4-{[4-amino-6-(hydroxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo-[2,1-f][1,2,4]triazin-7-yl]methyl}piperazine-1-carboxylate

600

BHC 11 1 045



A solution of Intermediate 20A (9.5 g, 27.9 mmol) in acetic acid (136.8 ml) was treated with *tert*-butyl piperazine-1-carboxylate (6.24 g, 33.49 mmol) and 37% aq. formaldehyde solution (2.5 ml, 33.49 mmol). The mixture was stirred at 60°C for 2.5 h. After evaporation, the residue was taken up in ethyl acetate, and the mixture was washed twice with sat. aq. sodium hydrogencarbonate solution, dried over sodium sulfate and evaporated. The residue was triturated in boiling ethanol (100 ml). The solid was filtered off and washed with ethanol and diethylether affording 9.70 g (58% of th.) of the title compound.

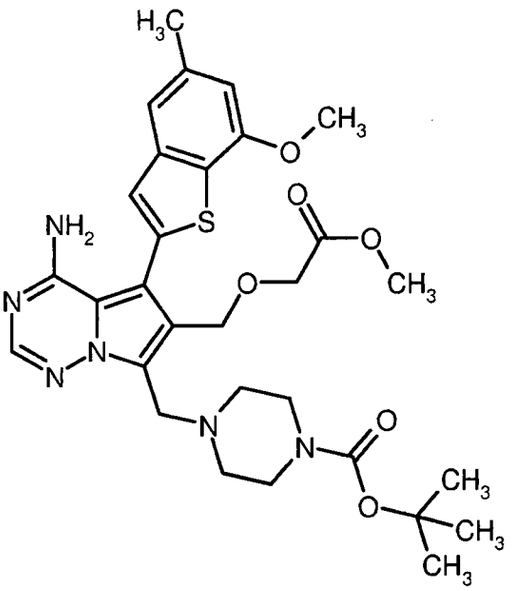
LC-MS (method 2): R_t = 0.88 min; MS (ESIpos): m/z = 539 $(M+H)^+$

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.94 (s, 1H), 7.13-7.35 (m, 2H, overlap with $CHCl_3$ peak), 6.67 (s, 1H), 5.86 (br. s, 1H), 5.54 (br. s, 2H), 4.68 (s, 2H), 4.08 (s, 2H), 4.00 (s, 3H), 3.45 (br. s, 4H), 2.59-2.48 (m, 7H), 1.45 (s, 9H) ppm.

Intermediate 24A

tert-Butyl 4-({4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-6-[(2-methoxy-2-oxo-ethoxy)methyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}methyl)piperazine-1-carboxylate

BHC 11 1 045



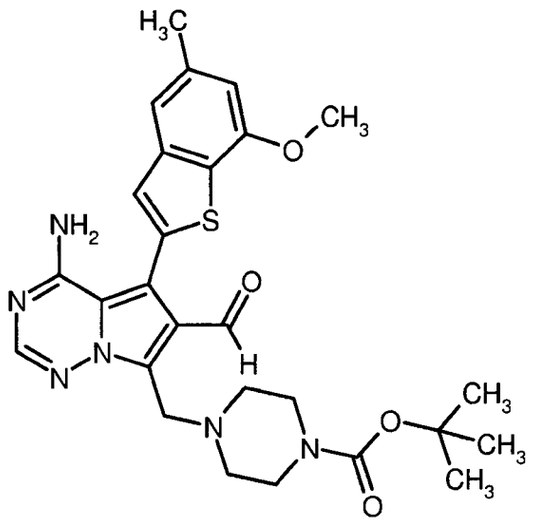
A solution of Intermediate 23A (300 mg, 556 µmol) in dichloromethane (12 ml) was treated with thionyl chloride (81 µl, 1.11 mmol) and stirred at rt for 15 min. After evaporation, the residue was dissolved in freshly distilled methylglycolate (2.5 ml) and treated with DIPEA (485 µl, 2.78 mmol). The mixture was stirred at 70°C for 2 h, then evaporated again, and excess methylglycolate was removed by distillation. Purification of the residue by column chromatography on silica gel (cyclohexane/ethyl acetate 1:5) afforded 136 mg (33% of th.) of the title compound.

LC-MS (method 2): R_t = 0.88 min; MS (ESIpos): m/z = 611 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.99 (s, 1H), 7.39 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 4.58 (s, 2H), 4.11 (s, 2H), 3.96 (s, 3H), 3.93 (s, 2H), 3.57 (s, 3H), 3.30-3.24 (m, 4H), 2.45-2.38 (m, 7H), 1.39 (s, 9H) ppm.

Intermediate 25A

tert-Butyl 4-{[4-amino-6-formyl-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}piperazine-1-carboxylate



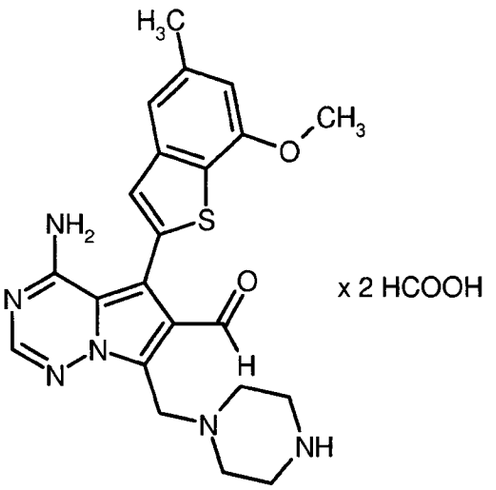
A solution of Intermediate 23A (300 mg, 556 µmol) in dichloromethane (4.2 ml) was treated with Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one; 307 mg, 724 µmol) and stirred at rt for 2 h. The reaction mixture was quenched with sat. aq. sodium hydrogencarbonate solution and sat. aq. sodium thiosulfate solution (1:1) and stirred at rt for 30 min. The aqueous layer was extracted three times with dichloromethane, and the combined organic layers were dried over magnesium sulfate and evaporated. Purification by column chromatography on silica gel (cyclohexane/ethyl acetate 1:1 → 100% ethyl acetate) afforded 273 mg (87% of th.) of the title compound.

LC-MS (method 2): R_t = 0.87 min; MS (ESIpos): m/z = 537 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.02 (s, 1H), 8.44-8.18 (br. s, 1H), 8.08 (s, 1H), 7.51 (s, 1H), 7.32 (s, 1H), 6.88 (s, 1H), 6.01-5.74 (br. s, 1H), 4.16 (s, 2H), 3.96 (s, 3H), 3.30-3.22 (m, 4H), 2.48-2.40 (m, 7H), 1.38 (s, 9H) ppm.

Intermediate 26A

4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f]-[1,2,4]triazine-6-carbaldehyde bis(formiate)



A solution of Intermediate 23A (80 mg, 148 µmol) in THF (3.9 ml) was treated with Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one; 94 mg, 222 µmol) and stirred at rt for 30 min. The reaction mixture was quenched with sat. aq. sodium hydrogencarbonate solution and sat. aq. sodium thiosulfate solution (1:1). The aqueous layer was extracted three times with ethyl acetate, and the combined organic layers were dried over magnesium sulfate and evaporated. The residue was dissolved in a 4 M solution of hydrogen chloride in 1,4-dioxane (4 ml) and stirred at rt for 1 h. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) affording 34 mg (52% of th.) of the title compound.

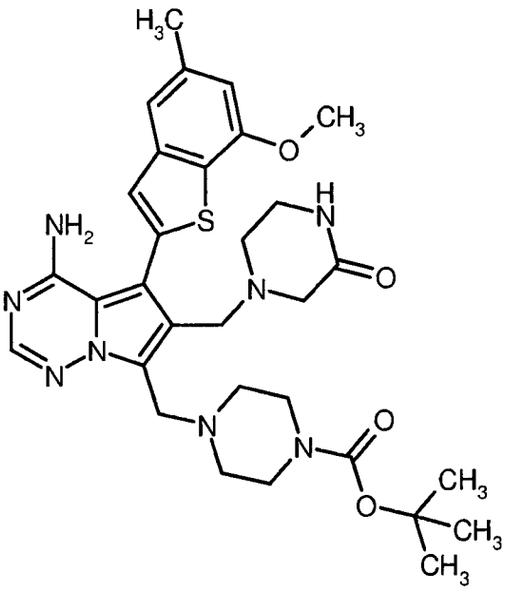
LC-MS (method 2): R_t = 0.78 min; MS (ESIpos): m/z = 437 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.02 (s, 1H), 8.29 (br. s, 2H), 8.09 (s, 1H), 7.50 (s, 1H), 7.33 (s, 1H), 6.88 (s, 1H), 4.17 (s, 2H), 3.96 (s, 3H), 2.90-2.81 (m, 4H), 2.63-2.56 (m, 4H), 2.46 (s, 3H) ppm.

Intermediate 27A

tert-Butyl 4-({4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-6-[(3-oxopiperazin-1-yl)-methyl]pyrrolo[2,1-f][1,2,4]triazin-7-yl}methyl)piperazine-1-carboxylate

BHC 11 1 045

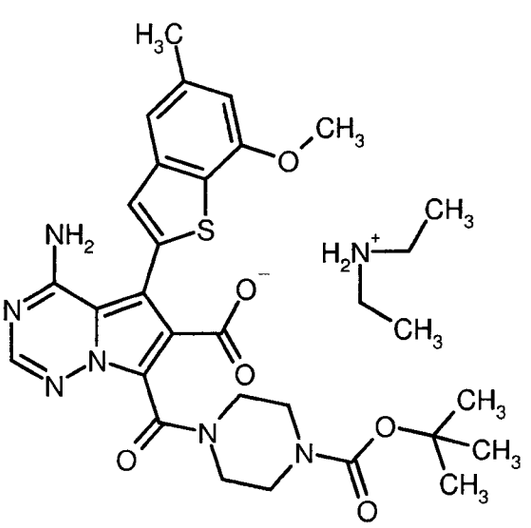


A solution of Intermediate 25A (185 mg, 344 µmol) in THF (4.6 ml) was treated with 2-oxo-piperazine (344 mg, 3.4 mmol), sodium triacetoxyborohydride (365 mg, 1.7 mmol) and acetic acid (39 µl, 689 µmol). The resulting mixture was stirred at rt for 2 h, then adsorbed on kieselguhr and purified by column chromatography on silica gel (dichloromethane → dichloromethane/methanol 100:8) affording 221 mg (quant.) of the title compound.

LC-MS (method 4): R_t = 0.77 min; MS (ESIpos): m/z = 621 $(M+H)^+$.

Intermediate 28A

N-Ethylethanaminium 4-amino-7-{[4-(*tert*-butoxycarbonyl)piperazin-1-yl]carbonyl}-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxylate



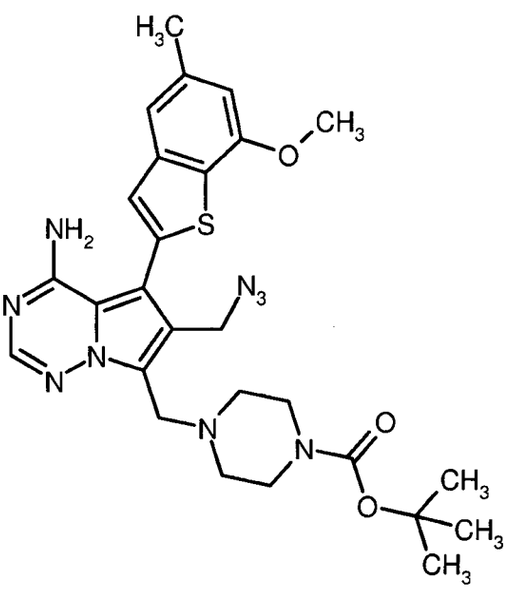
A solution of Intermediate 25A (70 mg, 130 µmol) in THF/water (10:1, 4.85 ml) was treated with a 2 M solution of 2-methyl-2-buten in THF (521 µl, 1.04 mmol) and sodium dihydrogenphosphate (107 mg, 783 µmol) and stirred at rt for 5 min. Sodium chlorite (70 mg, 783 µmol) was added, and the resulting mixture was stirred at rt overnight. After dilution with water, the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were dried over sodium sulfate and evaporated, and the residue was purified by preparative RP-HPLC (XBridge C18, gradient 5-50% acetonitrile/water + 0.05% diethylamine) affording 18 mg (21% of th.) of the title compound.

LC-MS (method 1): R_t = 1.14 min; MS (ESIpos): m/z = 567 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.26-7.89 (br. s, 1H), 7.94 (s, 1H), 7.33 (s, 1H), 7.28 (s, 1H), 6.83 (s, 1H), 5.64-5.33 (br. s, 1H), 3.95 (s, 3H), 2.80 (q, 4H), 2.45 (s, 3H), 1.40 (s, 9H), 1.09 (t, 6H) ppm.

Intermediate 29A

tert-Butyl 4-{[4-amino-6-(azidomethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo-[2,1-f][1,2,4]triazin-7-yl]methyl}piperazine-1-carboxylate



A solution of Intermediate 23A (150 mg, 0.278 mmol) in dichloromethane (7.5 ml) was treated with thionyl chloride (40 µl, 0.56 mmol) and stirred at rt for 15 min. After evaporation, the residue was dissolved in DMF (6 ml) and treated with sodium azide (362 mg, 5.57 mmol) and sodium iodide (208 mg, 1.39 mmol). The mixture was heated to 80°C for 1 h, then diluted with water and extracted three times with ethyl acetate. The combined organic layers were washed with water and

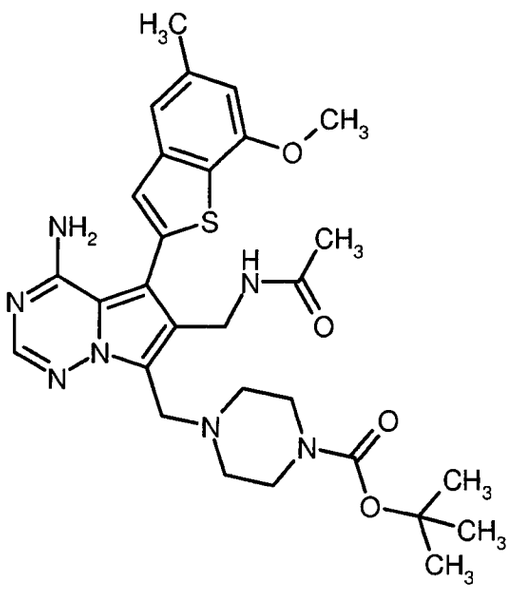
with sat. aq. sodium chloride solution, dried over magnesium sulfate and evaporated. Purification by column chromatography on silica gel (cyclohexane/ethyl acetate 98:2 → 100% ethyl acetate) afforded 95.8 mg (57% of th.) of the title compound.

LC-MS (method 4): R_t = 0.99 min; MS (ESIpos): m/z = 564 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.20-7.80 (br. s, 1H), 8.01 (s, 1H), 7.39 (s, 1H), 7.33 (s, 1H), 6.86 (s, 1H), 6.05-5.55 (br. s, 1H), 4.50 (s, 2H), 3.96 (s, 3H), 3.94 (s, 2H), 3.32-3.25 (m, 4H), 2.45 (s, 3H), 2.43-2.36 (m, 4H), 1.39 (s, 9H) ppm.

Intermediate 30A

tert-Butyl 4-{[6-(acetamidomethyl)-4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazine-1-carboxylate



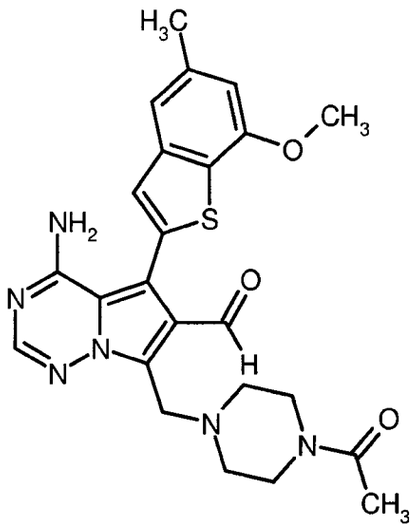
A mixture of Intermediate 29A (320 mg, 567 µmol), 10% Pd/C (320 mg) and acetic anhydride (106 µl, 1.13 mmol) in methanol (32 ml) was stirred for 90 min under 1 atm of hydrogen at rt. The mixture was then filtered through kieselguhr, and the filtrate was evaporated. Purification by column chromatography on silica gel (cyclohexane/ethyl acetate 1:1 → 100% ethyl acetate) afforded 440 mg (quant.) of the title compound.

LC-MS (method 2): R_t = 0.91 min; MS (ESIpos): m/z = 580 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.02-7.97 (m, 2H), 7.38 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 4.27 (br. d, 2H), 3.95 (s, 3H), 3.89 (s, 2H), 3.31-3.24 (m, 4H), 2.45 (s, 3H), 2.43-2.36 (m, 4H), 1.74 (s, 3H), 1.39 (s, 9H) ppm.

Intermediate 31A

7-[(4-Acetylpiperazin-1-yl)methyl]-4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-pyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde

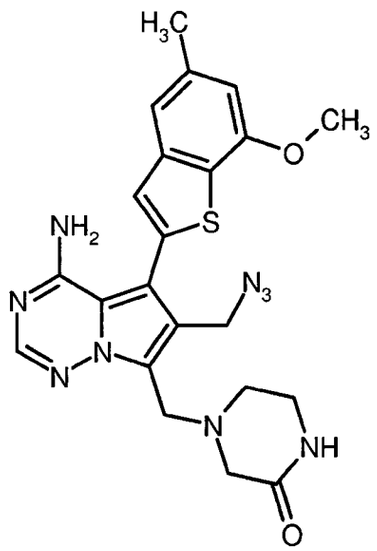


A solution of Example 55 (678 mg, purity 89%, 1.26 mmol) in dichloromethane (4 ml) containing molecular sieves (4Å) was treated with Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one; 623 mg, 1.47 mmol) and stirred at rt for 5 min. The reaction mixture was then adsorbed on diatomaceous earth and purified by column chromatography on silica gel (gradient of 30-100% ethyl acetate/cyclohexane, then 0-10% methanol/dichloromethane) yielding 449 mg (49% of th.) of the title compound.

LC-MS (method 4): R_t = 0.70 min; MS (ESIpos): m/z = 479 $(M+H)^+$.

Intermediate 32A

4-{[4-Amino-6-(azidomethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-7-yl]methyl}piperazin-2-one



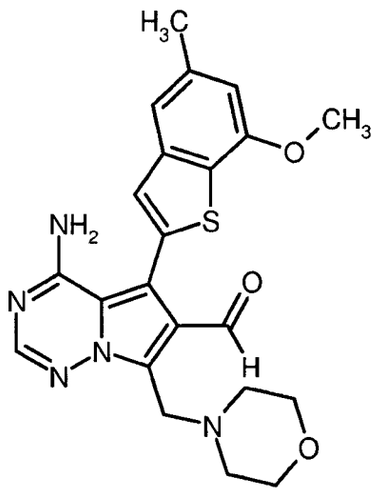
A solution of Example 13 (59 mg, 130 µmol) in dichloromethane (3.5 ml) was treated with thionyl chloride (19 µl, 261 µmol) and stirred at rt for 15 min. After evaporation, the residue was dissolved in DMF (2.8 ml) and treated with sodium iodide (97 mg, 652 µmol) and sodium azide (169 mg, 2.6 mmol). The mixture was stirred at 80°C for 1 h. After dilution with sat. aq. sodium chloride solution, the aqueous phase was extracted four times with ethyl acetate, and the combined organic layers were dried over magnesium sulfate and evaporated. Purification by column chromatography on silica gel (dichloromethane/methanol 98:2 → 90:10) afforded 35 mg (56% of th.) of the title compound.

LC-MS (method 5): R_t = 2.04 min; MS (ESIpos): m/z = 478 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.02 (s, 1H), 7.75 (br. s, 1H), 7.41 (s, 1H), 7.33 (s, 1H), 6.86 (s, 1H), 4.51 (s, 2H), 4.01 (s, 2H), 3.96 (s, 3H), 3.16-3.08 (m, 2H), 3.04-2.98 (m, 2H), 2.65-2.58 (m, 2H), 2.45 (s, 3H) ppm.

Intermediate 33A

4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)pyrrolo[2,1-f]-[1,2,4]triazine-6-carbaldehyde

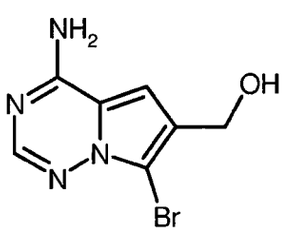


A solution of Example 50 (710 mg, purity 70%, 1.13 mmol) in dichloromethane (5 ml) containing molecular sieves (4Å) was treated with Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one; 623 mg, 1.47 mmol) and stirred at rt for 5 min. The reaction mixture was then adsorbed on diatomaceous earth and purified by column chromatography on silica gel (gradient of 30-100% ethyl acetate/cyclohexane) yielding 386 mg (72% of th.) of the title compound.

LC-MS (method 2): R_t = 0.76 min; MS (ESIpos): m/z = 438 $(M+H)^+$.

Intermediate 34A

(4-Amino-7-bromopyrrolo[2,1-f][1,2,4]triazin-6-yl)methanol



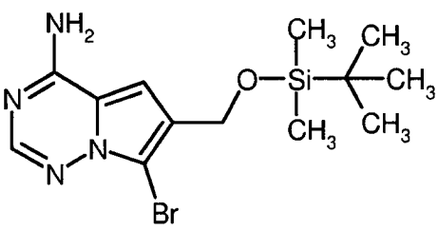
A solution of 1,3-dibromo-5,5-dimethylhydantoin (87 mg, 0.305 mmol) in THF (1 ml) was added dropwise to a solution of Intermediate 8A (100 mg, 0.609 mmol) in THF (4 ml) and methanol (2 ml) at -78°C. The mixture was stirred at -78°C for 16 h, then diluted with water and extracted with ethyl acetate. The combined organic layers were washed with sat. aq. sodium chloride solution, dried over magnesium sulfate and evaporated. Purification by column chromatography on silica gel (dichloromethane/methanol 20:1 → 10:1) afforded 55 mg (32% of th.) of the title compound.

LC-MS (method 3): R_t = 1.71 min; MS (ESIpos): m/z = 243/245 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.74-7.94 (m, 3H), 7.04 (s, 1H), 5.12 (t, 1H), 4.48 (d, 2H) ppm.

Intermediate 35A

7-Bromo-6-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



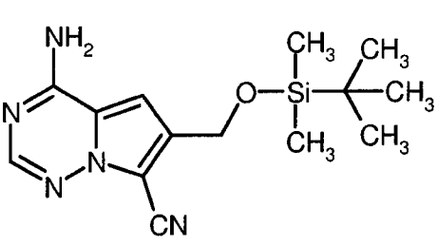
A solution of Intermediate 34A (885 mg, 3.64 mmol) in DMF (11 ml) was treated with *tert*-butyldimethylsilyl chloride (823 mg, 5.46 mmol) and imidazole (743 mg, 10.92 mmol) and stirred at rt for 2 h. The reaction mixture was combined with the reaction mixture of a 100 mg test run, diluted with water and extracted twice with ethyl acetate. The combined organic phases were washed with water and sat. aq. sodium chloride solution, dried over magnesium sulfate and evaporated. Purification by column chromatography on silica gel (cyclohexane/ethyl acetate 2:1 → 100% ethyl acetate) afforded 1.36 g (93% of th.) of the title compound.

LC-MS (method 2): R_t = 1.13 min; MS (ESIpos): m/z = 357/359 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.98-7.68 (m, 3H), 7.04 (s, 1H), 4.68 (s, 2H), 0.89 (s, 9H), 0.09 (s, 6H) ppm.

Intermediate 36A

4-Amino-6-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)pyrrolo[2,1-f][1,2,4]triazine-7-carbonitrile



Under argon, a mixture of Intermediate 35A (880 mg, 2.46 mmol), [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II)-dichloromethane complex [$PdCl_2$(dppf) x DCM] (120 mg, 0.148 mmol), bis(dibenzylideneacetone)palladium [$Pd(dba)_2$] (135 mg, 0.148 mmol), zinc cyanide (578 mg, 4.92 mmol), zinc powder (64 mg, 0.985 mmol) and zinc acetate (180 mg, 0.985 mmol) in

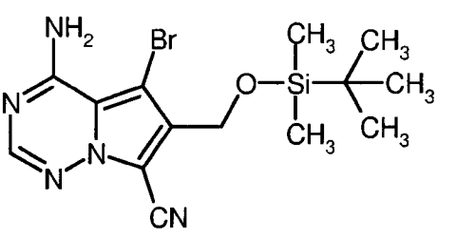
degassed DMF/water (100:1, 9.2 ml) was stirred at 160°C overnight. The reaction mixture was then combined with the reaction mixture of a 100 mg test run, and the combined mixtures were adsorbed on kieselguhr, filtered over another layer of kieselguhr and eluted with *tert*-butyl methyl ether. The filtrate was washed with sat. aq. sodium hydrogencarbonate solution, and the aqueous layer was re-extracted three times with *tert*-butyl methyl ether. The combined organic phases were dried over sodium sulfate and evaporated. Purification by column chromatography on silica gel (cyclohexane/ethyl acetate 1:1) afforded 453 mg (44% of th.) of the title compound.

LC-MS (method 2): R_t = 1.09 min; MS (ESIpos): m/z = 304 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.22-8.35 (m, 2H), 8.06 (s, 1H), 6.95 (s, 1H), 4.83 (s, 2H), 0.91 (s, 9H), 0.11 (s, 6H) ppm.

Intermediate 37A

4-Amino-5-bromo-6-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)pyrrolo[2,1-f][1,2,4]triazine-7-carbonitrile



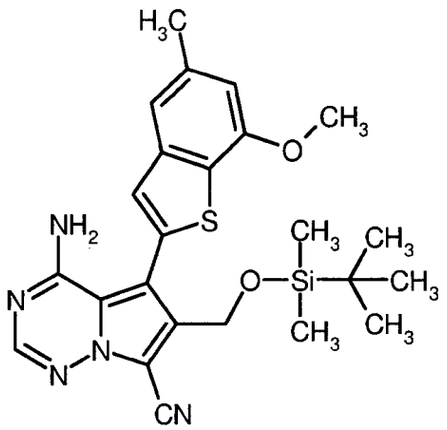
A solution of 1,3-dibromo-5,5-dimethylhydantoin (621 mg, 2.17 mmol) in THF (20 ml) was added dropwise to a solution of Intermediate 36A (1.1 g, 3.62 mmol) in THF (80 ml) at -50°C. The resulting mixture was slowly warmed to rt, stirred for 2 h and then quenched with 10% aq. sodium thiosulfate solution and sat. aq. sodium hydrogencarbonate solution. The aqueous phase was extracted three times with ethyl acetate. A solid precipitating from the ethyl acetate solution was filtered off and washed with ethyl acetate, affording 508 mg (100% purity, 36% of th.) as a first crop of the title compound. The remaining filtrate was dried over sodium sulfate and evaporated. The residue was precipitated from DMSO and washed with DMSO and ethyl acetate affording further 498 mg (85% purity, 26% of th.) of the title compound.

LC-MS (method 5): R_t = 2.70 min; MS (ESIpos): m/z = 382/384 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.10 (s, 1H), 4.76 (s, 2H), 0.90 (s, 9H), 0.12 (s, 6H) ppm.

Intermediate 38A

4-Amino-6-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazine-7-carbonitrile



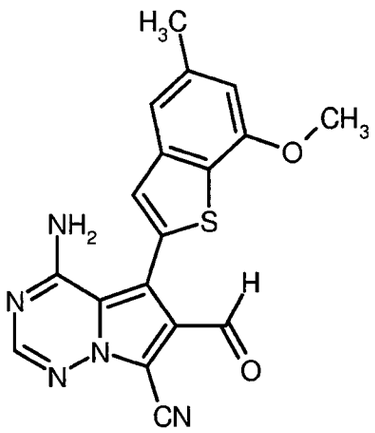
Under argon, a solution of Intermediate 37A (459 mg, 1.29 mmol) in degassed THF (14.8 ml) was added to (2'-aminobiphenyl-2-yl)(chloro)palladium-dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (1:1; 152 mg, 0.19 mmol; see S.L. Buchwald *et al., J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)) and Intermediate 6A (647 mg, 1.94 mmol). Degassed 0.5 M aq. potassium phosphate solution (5.1 ml) was added dropwise, and the resulting mixture was stirred at 60°C for 2 h. The reaction mixture was then combined with the reaction mixtures of previous 70 mg, 90 mg and 500 mg test runs and evaporated. Purification of the residue by column chromatography on silica gel (cyclohexane/ethyl acetate 3:1 → 100% ethyl acetate) afforded 1.0 g (58% of th.) of the title compound.

LC-MS (method 2): R_t = 1.49 min; MS (ESIpos): m/z = 480 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.57-8.35 (br. s, 1H), 8.18 (s, 1H), 7.41 (s, 1H), 7.30 (s, 1H), 6.86 (s, 1H), 6.28-6.03 (br. s, 1H), 4.74 (s, 2H), 3.95 (s, 3H), 2.44 (s, 3H), 0.83 (s, 9H), 0.00 (s, 6H) ppm.

Intermediate 39A

4-Amino-6-formyl-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazine-7-carbonitrile



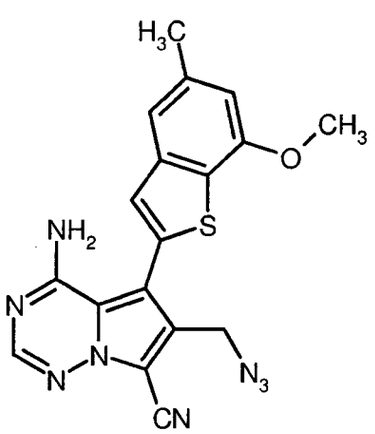
A solution of Example 68 (250 mg, 0.684 mmol) in dichloromethane (5 ml) was treated with Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one; 377 mg, 0.889 mmol) and stirred at rt for 1 h. The reaction mixture was combined with the reaction mixture from a 50 mg test run, quenched with sat. aq. sodium hydrogencarbonate solution and sat. aq. sodium thiosulfate solution (1:1) and stirred at rt for 30 min. The aqueous phase was extracted three times with ethyl acetate, and the combined organic phases were dried over sodium sulfate and evaporated. Purification by column chromatography on silica gel (cyclohexane/25% ethyl acetate → 100% ethyl acetate) afforded 102 mg (24% of th.) of the title compound.

LC-MS (method 2): R_t = 1.02 min; MS (ESIpos): m/z = 364 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 9.86 (s, 1H), 8.78 (br. s, 1H), 8.30 (s, 1H), 7.62 (s, 1H), 7.36 (s, 1H), 6.91 (s, 1H), 6.51 (br. s, 1H), 3.97 (s, 3H), 2.46 (s, 3H) ppm.

Intermediate 40A

4-Amino-6-(azidomethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazine-7-carbonitrile



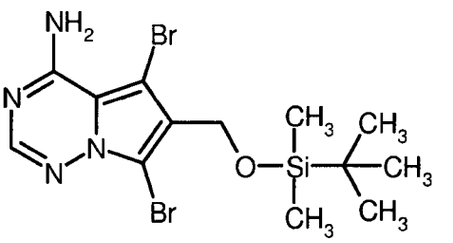
A solution of Example 68 (100 mg, 273 µmol) in dichloromethane (5 ml) was treated with thionyl chloride (39 µl, 547 µmol) and stirred at rt for 15 min. After evaporation, the residue was dissolved in DMF (6 ml) and treated with sodium iodide (205 mg, 1.36 mmol) and sodium azide (355 mg, 5.47 mmol). The mixture was stirred at 80°C overnight, then diluted with water and extracted three times with ethyl acetate. The combined organic layers were washed with water, followed by sat. aq. sodium chloride solution, dried over sodium sulfate and evaporated affording 91 mg of the crude product which was used in the next step without further purification.

LC-MS (method 2): R_t = 1.13 min; MS (ESIpos): m/z = 391 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): d = 8.65-8.45 (br. s, 1H), 8.23 (s, 1H), 7.46 (s, 1H), 7.34 (s, 1H), 6.88 (s, 1H), 6.41-6.10 (br. s, 1H), 4.57 (s, 2H), 3.96 (s, 3H), 2.46 (s, 3H) ppm.

Intermediate 41A

5,7-Dibromo-6-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



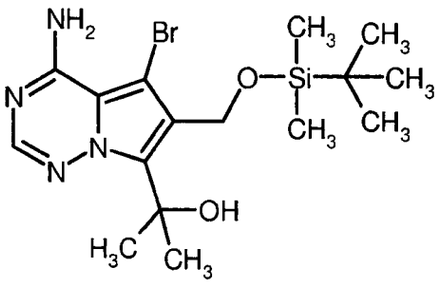
A solution of Intermediate 18A (2 g, 6.21 mmol) in DMF (20 ml) was treated with imidazole (846 mg, 12.4 mmol) and *tert*-butyldimethylsilyl chloride (1.12 g, 7.45 mmol) and stirred at rt for 20 h. The reaction mixture was then diluted with water (200 ml) and stirred at rt for further 2 h. Filtration of the solid afforded 2.46 g (88% of th.) of the title compound.

LC-MS (method 2): R_t = 1.37 min; MS (ESIpos): m/z = 437 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.49-8.05 (br. s, 1H), 7.96 (s, 1H), 7.15-6.76 (br. s, 1H), 4.64 (s, 2H), 0.87 (s, 9H), 0.09 (s, 6H) ppm.

Intermediate 42A

2-[4-Amino-5-bromo-6-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]-propan-2-ol



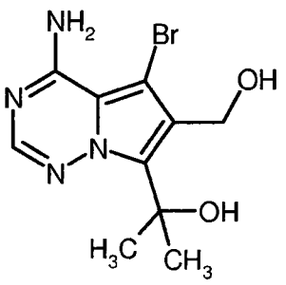
Under argon, a solution of Intermediate 41A (1 g, 2.29 mmol) in THF (40 ml) was cooled to -78°C and treated with a 1.6 M solution of methyllithium in diethylether (1.5 ml, 2.40 mmol). After stirring for 10 min at -78°C, a 1.6 M solution of *n*-butyllithium in hexanes (1.58 ml, 2.52 mmol) was added, and stirring was continued for 10 min. Acetone (1.68 ml, 22.92 mmol) was added, and the resulting mixture was slowly warmed to rt and stirred at rt for 18 h. The reaction was then quenched with water, and the aqueous phase was extracted twice with ethyl acetate. The combined organic phases were washed with sat. aq. sodium chloride solution, dried over magnesium sulfate and evaporated. Purification by flash chromatography on silica gel (cyclohexane/ethyl acetate 2:1) afforded 306 mg (30% of th.) of the title compound.

LC-MS (method 4): R_t = 1.39 min; MS (ESIpos): m/z = 415/417 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.23-7.85 (br. s, 1H), 7.89 (s, 1H), 7.05-6.82 (br. s, 1H), 5.49 (s, 1H), 4.88 (s, 2H), 1.66 (s, 6H), 0.87 (s, 9H), 0.08 (s, 6H) ppm.

Intermediate 43A

2-[4-Amino-5-bromo-6-(hydroxymethyl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]propan-2-ol



A solution of Intermediate 42A (304 mg, 0.732 mmol) in THF (15 ml) was treated with a 1 M solution of tetra-*n*-butylammonium fluoride in THF (768 µl, 768 µmol) and stirred at rt for 2 min. The reaction mixture was diluted with acetonitrile (20 ml), then evaporated, and the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-30% acetonitrile/0.2% aq. TFA). The product thus obtained was dissolved in methanol and filtered through an anion exchange cartridge

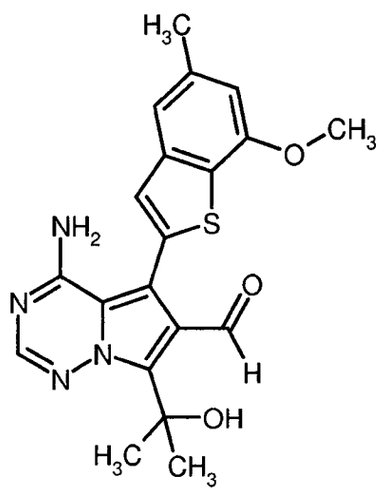
(Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated affording 180 mg (67% of th.) of the title compound.

LC-MS (method 2): R_t = 0.55 min; MS (ESIpos): m/z = 301/303 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.21-7.90 (m, 1H), 7.87 (s, 1H), 7.09-6.60 (br. s, 1H), 5.90 (br. s, 1H), 5.03 (br. s, 1H), 4.63 (s, 2H), 1.66 (s, 6H) ppm.

Intermediate 44A

4-Amino-7-(2-hydroxypropan-2-yl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazine-6-carbaldehyde

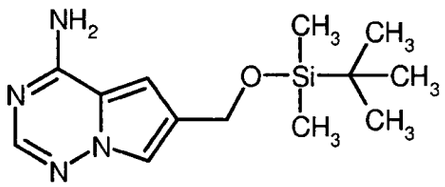


A solution of Example 73 (135 mg, purity 89%, 302 µmol) in dichloromethane (7 ml) was treated with Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one; 166 mg, 392 µmol) and stirred at rt for 70 min. The reaction mixture was combined with the reaction mixture of a 18 mg (45 µmol) test run and quenched with sat. aq. sodium hydrogencarbonate solution and sat. aq. sodium thiosulfate solution (1:1). The aqueous phase was extracted three times with dichloromethane. The combined organic phases were washed with sat. aq. sodium chloride solution, dried over magnesium sulfate and evaporated yielding 143 mg (purity 77%, 92% of th.) of the title compound.

LC-MS (method 2): R_t = 1.08 min; MS (ESIpos): m/z = 397 $(M+H)^+$.

Intermediate 45A

6-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine

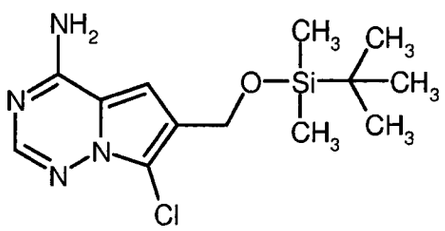


A solution of 1.5 g (9.14 mmol) of Intermediate 8A in 15 ml dry DMF was treated with 1.65 g (10.96 mmol) *tert*-butyldimethylsilyl chloride and 1.24 g (18.27 mmol) imidazole and stirred at rt overnight. The reaction mixture was poured into 250 ml water and stirred for 5 min. The resulting precipitate was filtered off and dried *in vacuo* at 45°C. Yield: 2.28 g (90% of th.).

LC-MS (method 5): R_t = 2.12 min; MS (ESIpos): m/z = 279 $(M+H)^+$.

Intermediate 46A

6-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-7-chloropyrrolo[2,1-f][1,2,4]triazin-4-amine



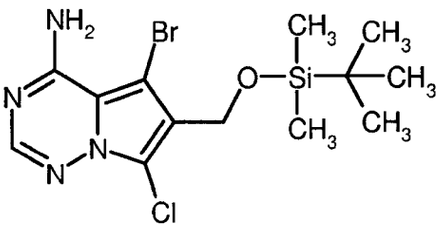
A solution of 2 g (7.18 mmol) of Intermediate 45A in 20 ml THF was treated with 893 mg (6.47 mmol) *N*-chlorosuccinimide in 6 portions over 60 min at -10°C. Stirring was continued for 15 min at -10°C, then the mixture was allowed to warm to rt. Another 192 mg (1.44 mmol) *N*-chlorosuccinimide were added at rt, and stirring was continued overnight. About one-tenth of the reaction mixture was evaporated to dryness, and the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) furnishing 94 mg (4% of th.) of the title compound. The major part of the reaction mixture was adsorbed on silica gel and subjected to chromatography on silica gel with isohexane/ethyl acetate 5-66% as eluent, yielding 899 mg (40% of th.) of the title compound. Total yield: 993 mg (44% of th.).

LC-MS (method 5): R_t = 2.45 min; MS (ESIpos): m/z = 313 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.69-8.04 (m, 3H), 7.0 (s, 1H), 4.70 (s, 2H), 0.88 (s, 9H), 0.08 (s, 6H) ppm.

Intermediate 47A

5-Bromo-6-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-7-chloropyrrolo[2,1-f][1,2,4]triazin-4-amine



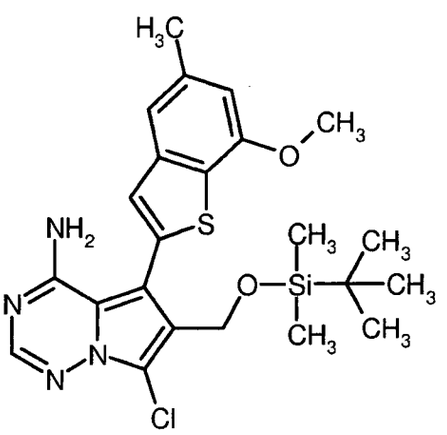
A solution of 890 mg (2.85 mmol) of Intermediate 46A in 20 ml DMF was treated with 506 mg (2.85 mmol) *N*-bromosuccinimide in portions over 1 h at -10°C. Stirring was continued for 3 h at -10°C and then overnight at rt. Water (200 ml) was added, and the mixture was stirred for 2 h. The precipitated solid was filtered off, washed with water and dried *in vacuo* at 45°C. Yield: 997 mg (89% of th.).

LC-MS (method 5): R_t = 2.82 min; MS (ESIpos): m/z = 391/393/395 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.32 (br. s, 1H), 7.97 (s, 1H), 6.97 (br. s, 1H), 4.66 (s, 2H), 0.87 (s, 9H), 0.09 (s, 6H) ppm.

Intermediate 48A

6-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-7-chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



Under an argon atmosphere, a flask was charged with 800 mg (2.04 mmol) of Intermediate 47A, 680 mg (2.04 mmol) of Intermediate 6A, 80 mg (0.1 mmol) (2'-aminobiphenyl-2-yl)(chloro)-palladium-dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (1:1; see S. L. Buchwald *et al.*, *J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)) and 1.3 g (6.13 mmol) potassium phosphate. Then, 30 ml of a degassed 1,4-dioxane/water mixture (5:1) were added, and the solution was stirred at 70°C for 1 h. Further 680 mg (2.04 mmol) of Intermediate 6A and 32 mg (0.04 mmol) (2'-aminobiphenyl-2-yl)(chloro)palladium-dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phos-

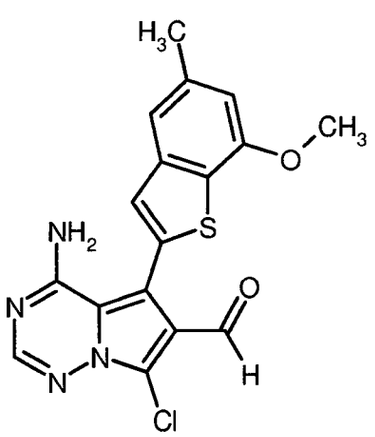
phine (1:1) were added, and stirring at 70°C was continued for another 1 h. This procedure was repeated three times until the starting material was consumed (control by LC-MS). With the last portion of reagents, also 1.6 ml of 5 M aq. sodium hydroxide solution were added to achieve a pH value of 8-9. At the end of the reaction period, 30 ml water and 5 M aq. formic acid were added (pH 3-4) whereupon an oil separated. A part of this oil was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid). Two fractions of the title compound were obtained: 103 mg of a solid (89% purity by LC-MS, 9% of th.), and 23 mg of a solid (100% purity by LC-MS, 2% of th.). The rest of the oil and the supernatant were diluted with water, adjusted to pH 8-9 with sat. aq. sodium hydrogencarbonate solution and extracted three times with dichloromethane. The combined organic phases were washed with water, dried and evaporated under reduced pressure, yielding 2.1 g of an oil. This material was purified by column chromatography on silica gel with dichloromethane/0-5% methanol as eluent to afford further 709 mg (43% purity by LC-MS, 31% of th.) of the title compound. Total yield: 42% of th.

LC-MS (method 2): R_t = 1.57 min; MS (ESIpos): m/z = 489 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.08 (s, 1H), 7.43 (s, 1H), 7.32 (s, 1H), 6.88 (s, 1H), 4.66 (s, 2H), 3.98 (s, 3H), 2.47 (s, 3H), 0.84 (s, 9H), –0.03 (s, 6H) ppm.

Intermediate 49A

4-Amino-7-chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde



To a suspension of 166 mg (0.44 mmol) of Example 79 and molecular sieves (3Å) in 3 ml dichloromethane were added 207 mg (0.49 mmol) Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one) at 0-5°C. The mixture was stirred for 10 min at this temperature, then further 56 mg (0.13 mmol) Dess-Martin periodinane were added, and stirring was con-

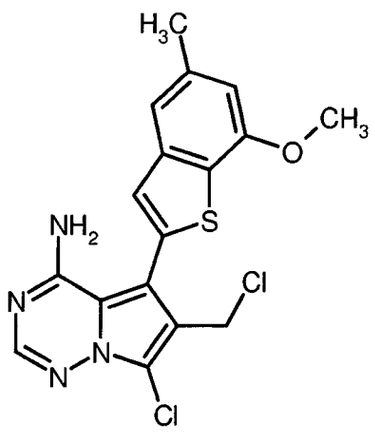
tinued for 15 min at 5°C and 10 min at ambient temperature. After this, the mixture was adsorbed on diatomaceous earth and purified by column chromatography on silica gel with dichloromethane/ 0-10% methanol as eluent. Yield: 100 mg of a solid (92.7% pure by LC-MS, 56% of th.).

LC-MS (method 2): R_t = 1.08 min; MS (ESIpos): m/z = 373 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 9.90 (s, 1H), 8.46 (br. s, 1H), 8.15 (s, 1H), 7.54 (s, 1H), 7.34 (s, 1H), 6.89 (s, 1H), 6.07 (br. s, 1H), 3.96 (s, 3H), 2.46 (s, 3H) ppm.

Intermediate 50A

7-Chloro-6-(chloromethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-4-amine

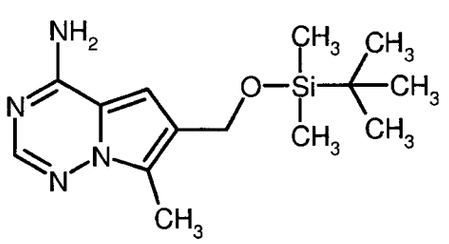


The title compound was isolated as a by-product in the preparation of Example 79 (see below). Yield: 9.2 mg (10% of th.).

LC-MS (method 3): R_t = 2.98 min; MS (ESIpos): m/z = 393/395 $(M+H)^+$.

Intermediate 51A

6-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-7-methylpyrrolo[2,1-f][1,2,4]triazin-4-amine



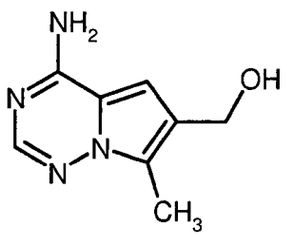
To a solution of 3 g (8.4 mmol) of Intermediate 35A in 60 ml 1,4-dioxane under an argon atmosphere were added 171 mg (0.21 mmol) of $PdCl_2$(dppf) x DCM and then dropwise over 10 min 16.8 ml of a 2 M solution of dimethylzinc in toluene (causing a rise in temperature from 22°C to 31°C). Stirring was continued first for 10 min at ambient temperature, then for 13 h at 90°C. After this, water (10 ml) was added to the reaction mixture at rt, and the suspension was stirred for 1 h. The mixture was evaporated under reduced pressure, and the residue was taken up in water and ethyl acetate and stirred for another 1 h. The precipitate was filtered off and discarded, the phases were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic phases were dried and evaporated affording 2.45 g (92% purity by LC-MS, 92% of th.) of the title compound.

LC-MS (method 5): R_t = 2.18 min; MS (ESIpos): m/z = 293 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.98-7.78 (m, 3H), 7.04 (s, 1H), 4.68 (s, 2H), 0.89 (s, 9H), 0.09 (s, 6H) ppm.

Intermediate 52A

(4-Amino-7-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl)methanol



Method 1:

To a solution of 100 mg (0.28 mmol) of Intermediate 35A in 2 ml 1,4-dioxane under an argon atmosphere were added 6 mg (0.01 mmol) $PdCl_2$(dppf) x DCM and then dropwise over 10 min 0.56 ml of a 2 M solution of dimethylzinc in toluene. The mixture was stirred at 90°C overnight, then evaporated, and the residue was treated with acetonitrile and 5 M aq. formic acid. The precipitate was filtered off, the filtrate was evaporated, and the residue was taken up in DMSO/acetonitrile and purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid). Yield: 33 mg (66% of th.).

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.79 (s, 1H), 7.47 (br. s, 2H), 6.80 (s, 1H), 4.84 (t, 1H), 4.49 (d, 2H), 2.36 (s, 3H) ppm.

Method 2:

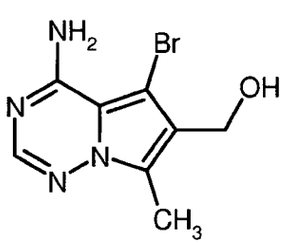
Under an argon atmosphere, a microwave reaction vessel was charged with 750 mg (3.1 mmol) of Intermediate 34A, 515 µl (3.7 mmol) trimethylboroxine, 786 mg (3.7 mmol) potassium phosphate and 73 mg (0.09 mmol) (2'-aminobiphenyl-2-yl)(chloro)palladium-dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (1:1; see S. L. Buchwald *et al.*, *J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)). Then, 13 ml of a degassed 1,4-dioxane/water mixture (5:1) were added, the vessel was sealed, and the mixture was heated to 140°C for 20 min in the microwave (4 bar, 50 watt). Further 50 mg (2'-aminobiphenyl-2-yl)(chloro)palladium-dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (1:1) were added, and the mixture was heated again to 140°C for 20 min in the microwave. Another portion of 515 µl trimethylboroxine was added, and the vessel was heated again to 140°C for 20 min. The latter procedure was repeated two more times with heating periods of 30 min each until LC-MS showed only minor amounts of starting material left. The mixture was filtered over kieselguhr, washed with 1,4-dioxane, and the combined filtrates were evaporated to dryness. This residue was combined with a previous 100 mg test run and purified by preparative RP-HPLC (XBridge C18, gradient 5-42% acetonitrile/0.05% aq. ammonium hydroxide solution). Yield: 238 mg (38% of th.).

LC-MS (method 5): R_t = 0.51 min; MS (ESIneg): m/z = 177 $(M-H)^-$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.79 (s, 1H), 7.48 (br. s, 2H), 6.80 (s, 1H), 4.84 (t, 1H), 4.49 (d, 2H), 2.36 (s, 3H) ppm.

Intermediate 53A

(4-Amino-5-bromo-7-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl)methanol



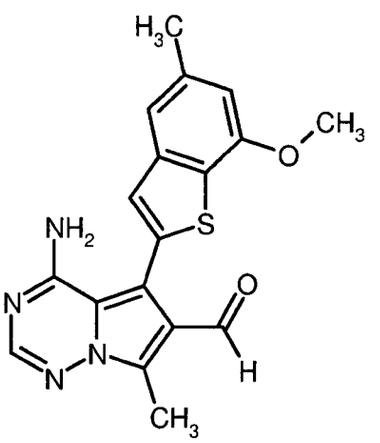
A solution of 245 mg (1.38 mmol) of Intermediate 52A in 8.8 ml DMF was treated with 288 mg (1.62 mmol) *N*-bromosuccinimide in portions over 2 h at -10°C. Stirring was continued at -10°C for 30 min and then for 2 h at ambient temperature. The mixture was poured into 50 ml water and extracted with ethyl acetate. The combined organic phases were dried and evaporated. The residue was flash-chromatographed on silica gel with dichloromethane/0-15% methanol as eluent. Yield: 148 mg (42% of th.).

LC-MS (method 4): R_t = 0.42 min; MS (ESIpos): m/z = 257/259 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.85 (s, 1H), 6.14-8.22 (broad, 2H), 4.88 (t, 1H), 4.45 (d, 2H), 2.43 (s, 3H) ppm.

Intermediate 54A

4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-methylpyrrolo[2,1-f][1,2,4]triazine-6-carbaldehyde



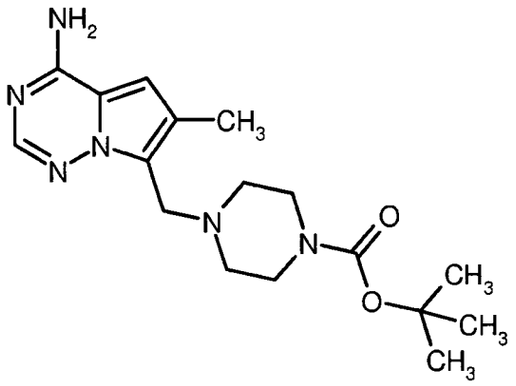
To a suspension of 175 mg (0.49 mmol) of Example 75 and molecular sieves (3Å) in 3.5 ml dichloromethane were added 230 mg (0.54 mmol) Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one) at 0-5°C. The mixture was stirred for 5 min at this temperature, followed by 30 min at rt. After this, the mixture was adsorbed on diatomaceous earth and purified by flash-chromatography on silica gel with isohexane/10-100% ethyl acetate as eluent. Yield: 139 mg of a solid (79% of th.).

LC-MS (method 5): R_t = 2.34 min; MS (ESIpos): m/z = 353 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 9.93 (s, 1H), 8.06 (s, 1H), 7.50 (s, 1H), 7.33 (s, 1H), 6.88 (s, 1H), 3.96 (s, 3H), 2.71 (s, 3H), 2.46 (s, 3H) ppm.

Intermediate 55A

tert-Butyl 4-[(4-amino-6-methylpyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]piperazine-1-carboxylate



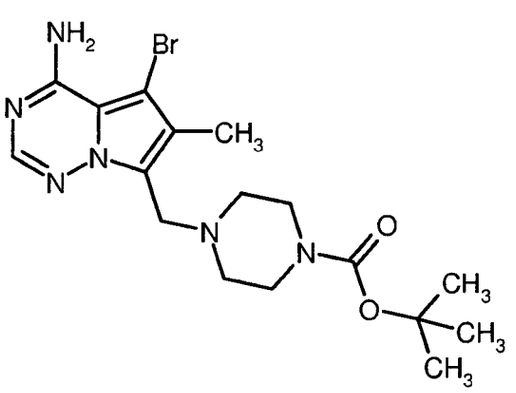
A solution of 6-methylpyrrolo[2,1-f][1,2,4]triazin-4-amine (500 mg, 3.3 mmol; preparation described in PCT Int. Pat. Appl. WO 2007/056170) in acetic acid (8 ml) was treated with 37% aq. formaldehyde solution (328 µl, 4.04 mmol) and *tert*-butyl piperazine-1-carboxylate (754 mg, 4.04 mmol). The mixture was stirred at 60°C overnight. After evaporation, the residue was taken up in ethyl acetate and washed with sat. aq. sodium hydrogencarbonate solution. The aqueous layer was extracted twice with ethyl acetate. The combined organic phases were dried over magnesium sulfate and evaporated affording 1.2 g of the crude product which was used in the next step without further purification.

LC-MS (method 2): R_t = 0.56 min; MS (ESIpos): m/z = 347 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.79 (s, 1H), 7.51 (br. s, 2H), 6.67 (s, 1H), 3.76 (br. s, 2H), 3.29-3.17 (m, 4H), 2.36-2.29 (m, 4H), 2.22 (s, 3H), 1.37 (s, 9H) ppm.

Intermediate 56A

tert-Butyl 4-[(4-amino-5-bromo-6-methylpyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]piperazine-1-carboxylate



A solution of Intermediate 55A (1.17 g, 3.37 mmol) in THF (20 ml) was cooled to -60°C and treated with 1,3-dibromo-5,5-dimethylhydantoin (5.78 mg, 2.02 mmol). The mixture was stirred

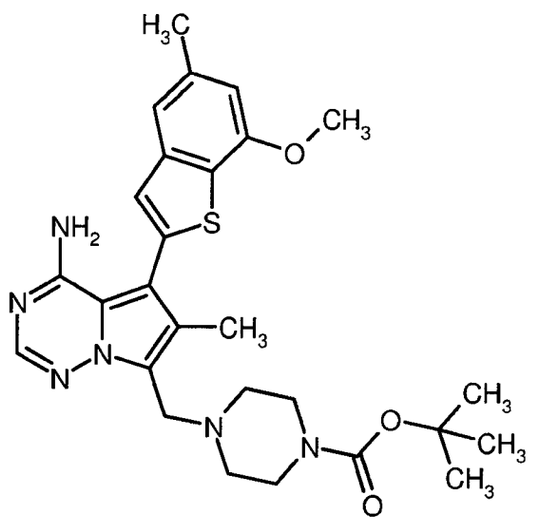
for 4 h at -60°C to -20°C. After this, the reaction mixture was quenched with 10% aq. sodium thiosulfate solution. Most of the THF solvent was evaporated whereupon a solid precipitated. Filtration and recrystallization from acetone afforded 862 mg (59% of th.) of the title compound.

LC-MS (method 2): R_t = 0.66 min; MS (ESIpos): m/z = 425/427 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.29-7.62 (br. s, 1H), 7.85 (s, 1H), 7.17-6.44 (br. s, 1H), 3.80 (s, 2H), 3.29-3.22 (m, 4H), 2.37-2.27 (m, 4H), 2.16 (s, 3H), 1.37 (s, 9H) ppm.

Intermediate 57A

tert-Butyl 4-{[4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-6-methylpyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}piperazine-1-carboxylate



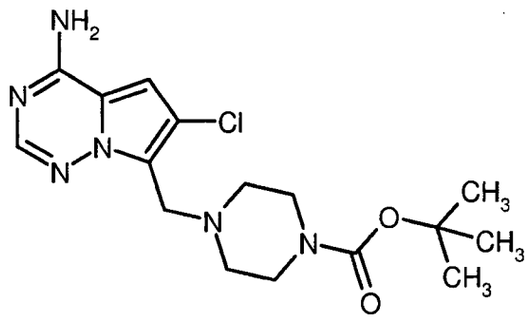
A solution of Intermediate 56A (100 mg, 235 µmol) in degassed 1,4-dioxane (3 ml) was treated with Intermediate 6A (93 mg, 282 µmol), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (S-Phos; 9.6 mg, 23 µmol) and palladium diacetate (2.6 mg, 11 µmol). Degassed 3 M aq. potassium phosphate solution (588 µl) was added, and the resulting mixture was stirred at 60°C for 1 h. A further portion of Intermediate 6A (78 mg, 235 µmol) was added, and stirring at 60°C was continued overnight. The reaction mixture was quenched with 2 M aq. sodium hydroxide solution, and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with sat. aq. sodium chloride solution, dried over magnesium sulfate and evaporated. Purification by column chromatography on silica gel (cyclohexane/ethyl acetate 3:2) afforded 82 mg (62% of th.) of the title compound.

LC-MS (method 2): R_t = 0.97 min; MS (ESIpos): m/z = 523 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.94 (s, 1H), 7.34 (s, 1H), 7.30 (s, 1H), 6.84 (s, 1H), 3.95 (s, 3H), 3.84 (s, 2H), 3.30-3.23 (m, 4H, overlap with water peak), 2.45 (s, 3H), 2.42-2.33 (m, 4H), 2.19 (s, 3H), 1.39 (s, 9H) ppm.

Intermediate 58A

tert-Butyl 4-[(4-amino-6-chloropyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]piperazine-1-carboxylate



Following the procedure of Intermediate 55A, 4 g (23.7 mmol) 6-chloropyrrolo[2,1-f][1,2,4]-triazin-4-amine (preparation described in PCT Int. Pat. Appl. WO 2007/064883) were reacted to give 11.2 g of the title compound as crude material which was used in the next step without further purification.

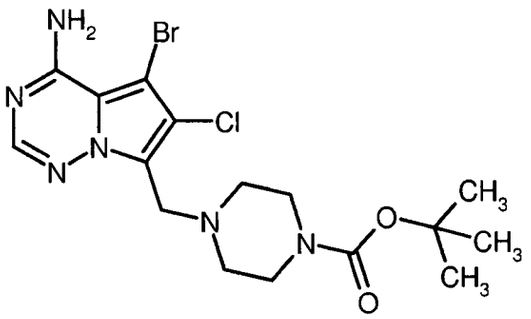
LC-MS (method 5): R_t = 0.74 min; MS (ESIpos): m/z = 367 $(M+H)^+$

A sample of 67 mg of the corresponding formiate salt, *tert*-butyl 4-[(4-amino-6-chloropyrrolo-[2,1-f][1,2,4]triazin-7-yl)methyl]piperazine-1-carboxylate formiate, was isolated after preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) of 100 mg of the crude material obtained above.

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.14 (s, 1H), 7.91 (s, 1H), 7.83 (br. s, 2H), 6.95 (s, 1H), 3.80 (s, 2H), 3.17 (s, 2H), 2.38 (br. s, 4H), 1.37 (s, 9H) ppm.

Intermediate 59A

tert-Butyl 4-[(4-amino-5-bromo-6-chloropyrrolo[2,1-f][1,2,4]triazin-7-yl)methyl]piperazine-1-carboxylate



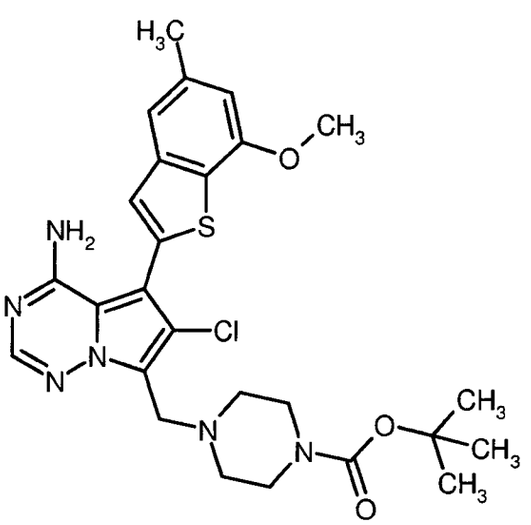
Following the procedure of Intermediate 56A, 11 g (30 mmol) of Intermediate 58A were reacted to give 1.17 g (9% of th.) of the title compound after flash-chromatography on silica gel (dichloromethane/methanol 10:1) and subsequent preparative RP-HPLC (Daiso C18, gradient 40-65% acetonitrile/water).

LC-MS (method 2): R_t = 0.74 min; MS (ESIpos): m/z = 445/447/449 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 7.96 (s, 1H), 3.84 (s, 2H), 2.37 (br. s, 4H), 1.37 (s, 9H) ppm.

Intermediate 60A

tert-Butyl 4-{[4-amino-6-chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}piperazine-1-carboxylate



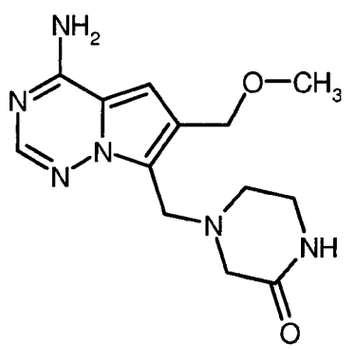
Under an argon atmosphere, a flask was charged with 140 mg (0.31 mmol) of Intermediate 59A, 102 mg (0.46 mmol) of Intermediate 5A, 16 mg (0.02 mmol) $PdCl_2$(dppf) x DCM and 122 mg (1.15 mmol) sodium carbonate. After addition of 3 ml degassed 1,2-dimethoxyethane/water (3:1), the suspension was stirred at 60°C for 2.5 h. Further portions of Intermediate 5A (50 mg, 0.23

mmol) and $PdCl_2$(dppf) x DCM (8 mg, 0.01 mmol) were added, and stirring was continued at 40°C for 2.5 h. The latter procedure was repeated once more until the starting material was consumed. Then, the reaction mixture was partially evaporated under reduced pressure, water was added, and the mixture was extracted with dichloromethane. The combined organic phases were washed with water and sat. aq. sodium chloride solution, dried and evaporated under reduced pressure. The residue (322 mg) was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) to give 49 mg of a mixture of the title compound and the Boc-deprotected derivative, 6-chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine. This mixture was used as such in the next reaction step (see Example 85).

LC-MS (method 2): R_t = 1.00 min; MS (ESIpos): m/z = 543 $(M+H)^+$, and R_t = 0.81 min; MS (ESIpos): m/z = 443 $(M+H)^+$.

Intermediate 61A

4-{[4-Amino-6-(methoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one

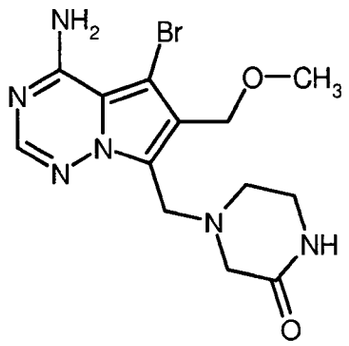


A solution of Intermediate 10A (5 g, 28.1 mmol) and piperazin-2-one (3.09 g, 30.9 mmol) in acetic acid (85 ml) was treated with 37% aq. formaldehyde solution (3.15 ml, 42.1 mmol) and stirred at 60°C for 16 h. The volatiles were evaporated under reduced pressure, and the residue was dissolved in methanol and adsorbed on diatomaceous earth. Purification by column chromatography on silica gel (5-10% methanol/dichloromethane) afforded 3.91 g (46% of th.) of the title compound.

LC-MS (method 3): R_t = 1.68 min; MS (ESIpos): m/z = 291 $(M+H)^+$.

Intermediate 62A

4-{[4-Amino-5-bromo-6-(methoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one



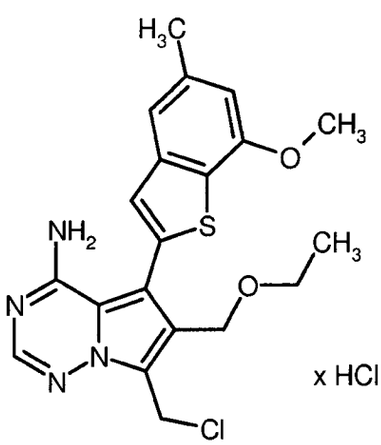
A solution of Intermediate 61A (3.9 g, 13.4 mmol) in DMF (50 ml) was cooled to 0°C and treated with a solution of *N*-bromosuccinimide (2.63 g, 14.8 mmol) in DMF (6 ml). The mixture was stirred at 0°C for 1 h. Then, the solvent was evaporated, and the residue was dissolved in methanol and adsorbed on diatomaceous earth. Purification by column chromatography on silica gel (5-10% methanol/dichloromethane) afforded 1.99 g (39% of th.) of the title compound.

LC-MS (method 3): R_t = 1.86 min; MS (ESIpos): m/z = 369/371 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.96-8.23 (br. s, 1H), 7.90 (s, 1H), 7.71 (s, 1H), 6.72-6.98 (br. s, 1H), 4.45 (s, 2H), 3.91 (s, 2H), 3.27 (s, 3H), 3.07 (br. s, 2H), 2.96 (s, 2H), 2.56 (br. s, 2H) ppm.

Intermediate 63A

7-(Chloromethyl)-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-4-amine hydrochloride

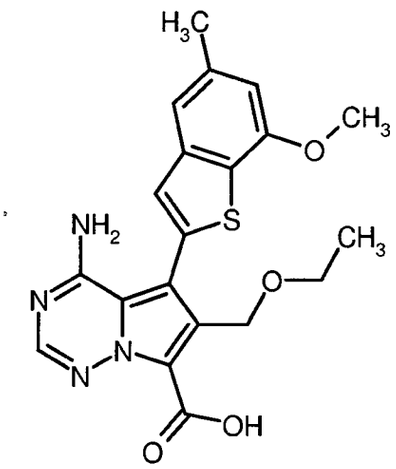


A suspension of Example 86 (1 g, 2.51 mmol) in toluene (60 ml) was treated dropwise with thionyl chloride (1.83 ml, 25.1 mmol), and the mixture was stirred at rt overnight. The volatiles were evaporated under reduced pressure. The residue was co-evaporated with toluene under reduced

pressure for three times affording 0.85 g (74% of th.) of the title compound which was immediately used for the next step without further purification.

Intermediate 64A

4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazine-7-carboxylic acid



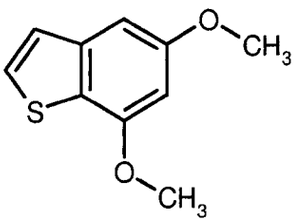
A suspension of Intermediate 17A (5 g, 12.6 mmol) in THF/water (10:1, 220 ml) was treated with a 2 M solution of 2-methyl-2-butene in THF (31.5 ml, 63.1 mmol) and with sodium dihydrogenphosphate (6.96 g, 50.4 mmol). The mixture was stirred at rt for 5 min. Then, sodium chlorite (4.56 g, 50.44 mmol) was added, and the resulting mixture was stirred at rt for 20 h. The suspension was filtered, and the resulting solid was washed with water affording 4.24 g (74% of th.) of the title compound which was used in the next step without further purification.

LC-MS (method 4): R_t = 1.06 min; MS (ESIpos): m/z = 413 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 13.22 (br. s, 1H), 8.53-8.00 (br. s, 1H), 8.14 (s, 1H), 7.41 (s, 1H), 7.33 (s, 1H), 6.86 (s, 1H), 6.28-5.65 (br. s, 1H), 4.61 (s, 2H), 3.96 (s, 3H), 3.36 (q, 2H), 2.46 (s, 3H), 1.01 (t, 3H) ppm.

Intermediate 65A

5,7-Dimethoxy-1-benzothiophene



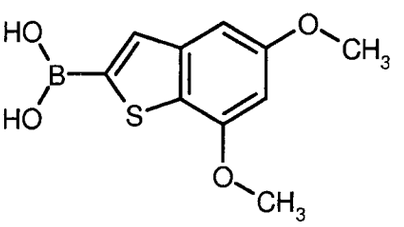
To a solution of 1-benzothiophene-5,7-diol (1.16 g, 6.98 mmol) in acetone (20 ml) under argon were added potassium carbonate (2.89 g, 20.9 mmol) and iodomethane (912 µl, 14.6 mmol). The resulting mixture was stirred under reflux for 18 h. After cooling to rt, the mixture was treated with a 7 M solution of ammonia in methanol (10 ml) for 30 min and then adsorbed on silica gel. Purification by column chromatography over silica gel (cyclohexane/ethyl acetate 40:1) afforded 0.52 g (32% of th.) of the title compound.

LC-MS (method 4): R_t = 1.02 min; MS (ESIpos): m/z = 195 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.69 (d, 1H), 7.35 (d, 1H), 7.02 (d, 1H), 6.57 (d, 1H), 3.92 (s, 3H), 3.81 (s, 3H) ppm.

Intermediate 66A

(5,7-dimethoxy-1-benzothiophen-2-yl)boronic acid



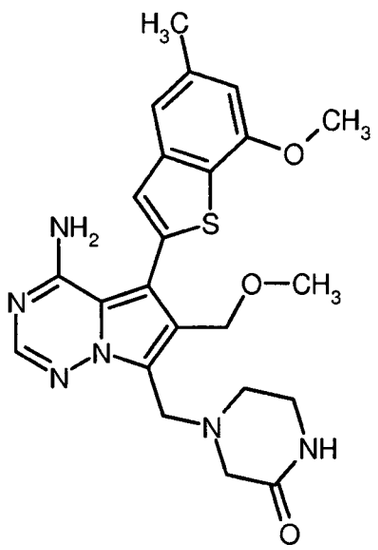
Under an argon atmosphere, a 1.6 M solution of *n*-butyllithium in hexane (1.84 ml, 2.95 mmol) was added dropwise to a solution of Intermediate 65A (520 mg, 2.68 mmol) in dry THF (5 ml) at -70°C. After 1 h at -70°C, triisopropyl borate (742 µl, 3.21 mmol) was added, and the mixture was stirred for 16 h while slowly warming up to rt. Dichloromethane and sat. aq. ammonium chloride solution were added, and the pH value was adjusted to 6 by addition of 1 M hydrochloric acid. The organic phase was separated, and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried with magnesium sulfate, filtered and evaporated. The resulting residue was purified by column chromatography over silica gel (at first eluting with dichloromethane/methanol 40:1, then methanol, finally methanol/4 M hydrogen chloride in 1,4-dioxane 10:1) yielding 631 mg (71% purity, 71% of th.) of the title compound.

LC-MS (method 4): R_t = 0.83 min; MS (ESIpos): m/z = 239 $(M+H)^+$.

Preparation Examples:

Example 1

4-{[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}piperazin-2-one



Method 1:

A solution of Intermediate 13A (3 g, 7.84 mmol) in methanol (87 ml) was treated with acetic acid (0.898 ml, 15.68 mmol), 2-oxopiperazine (1.17 g, 11.76 mmol) and sodium triacetoxyborohydride (4.98 g, 23.53 mmol). The mixture was stirred at rt for 4.5 h. Further portions of 2-oxopiperazine (392 mg, 3.9 mmol) and sodium triacetoxyborohydride (3.3 g, 15.68 mmol) were added, and the resulting mixture was stirred at 60°C overnight. After evaporation, the residue was taken up in sat. aq. sodium hydrogencarbonate solution and extracted with ethyl acetate. The combined organic phases were dried over sodium sulfate and evaporated, and the residue was purified by column chromatography on silica gel (dichloromethane/methanol 40:1 → 10:1). The product thus obtained was triturated in methanol and filtered off affording 540 mg (14% of th.) of the title compound. The methanolic mother liquor was evaporated and the residue purified by two-fold RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid). The fractions containing pure product were combined and neutralized with sat. aq. sodium hydrogencarbonate solution. The acetonitrile solvent was evaporated, and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried over sodium sulfate and evaporated affording 395 mg (13% of th.) as a second batch of the title compound.

Method 2:

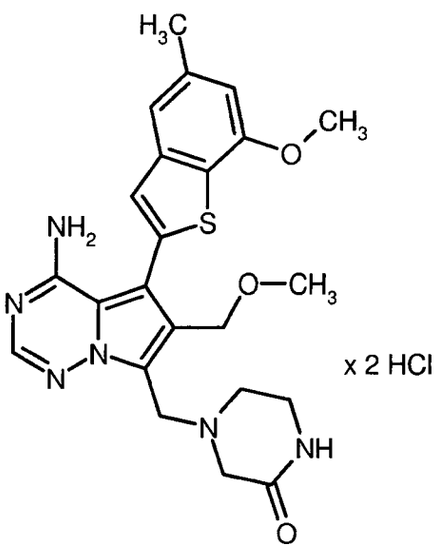
A solution of Intermediate 21A (291 mg, 0.82 mmol) in acetic acid (2.9 ml) was treated with 37% aq. formaldehyde solution (104 µl, 1.39 mmol) and 2-oxopiperazine (139 mg, 1.39 mmol). The mixture was stirred at 60°C for 3 h and then evaporated. Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 184 mg (44% of th.) of the title compound.

LC-MS (method 4): R_t = 0.77 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.00 (s, 1H), 7.73 (br. s, 1H), 7.37 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 4.41 (s, 2H), 3.97 (s, 2H), 3.96 (s, 3H), 3.20 (s, 3H), 3.15-3.08 (br. s, 2H), 3.01 (s, 2H), 2.64 (br. t, 2H), 2.45 (s, 3H) ppm.

Example 2

4-{[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}piperazin-2-one dihydrochloride



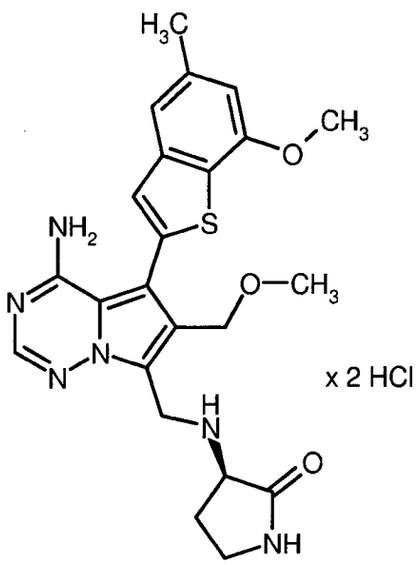
A solution of Example 1 (100 mg, 214 µmol) in 1,4-dioxane (2 ml) was treated with a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml, 8 mmol). The solvent was evaporated leaving 130 mg (quant.) of the title compound.

LC-MS (method 2): R_t = 0.79 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.39 (br. s, 1H), 8.31-8.53 (br. s, 1H), 8.17 (s, 1H), 7.38 (s, 1H), 7.34 (s, 1H), 6.87 (s, 1H), 6.21-6.42 (br. s, 1H), 4.81 (br. s, 2H), 4.52 (br. s, 2H), 3.96 (s, 3H), 3.57 (s, 2H), 3.32-3.72 (m, 4H), 3.26 (s, 3H), 2.46 (s, 3H) ppm.

Example 3

(*3R*)-3-({[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo-[2,1-f][1,2,4]triazin-7-yl]methyl}amino)pyrrolidin-2-one dihydrochloride



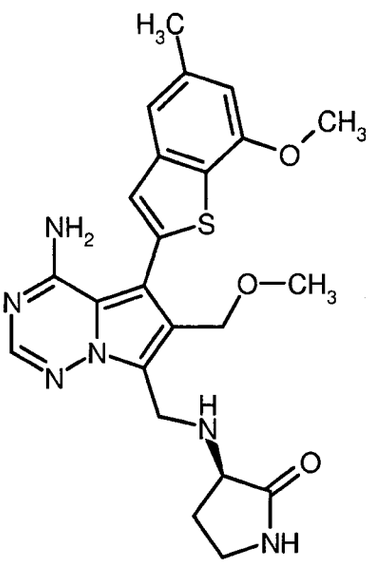
A solution of Intermediate 13A (520 mg, 1.36 mmol) in methanol (15 ml) and acetic acid (156 µl, 2.7 mmol) was treated with (*R*)-3-aminopyrrolidin-2-one (503 mg, 5.0 mmol) and triacetoxyborohydride (1.06 g, 5.0 mmol). The mixture was stirred at rt overnight and then evaporated. Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) and lyophilization of the product thus obtained from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 272 mg (36% of th.) of the title compound.

LC-MS (method 2): R_t = 0.70 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): d = 9.62 (br. s, 1H), 9.46 (br. s, 1H), 8.56-8.22 (br. s, 1H), 8.44 (s, 1H), 8.19 (s, 1H), 7.38 (s, 1H), 7.34 (s, 1H), 6.87 (s, 1H), 6.54-6.12 (br. s, 1H), 4.89-4.65 (m, 2H), 4.58-4.46 (m, 2H), 4.17-4.07 (br. s, 1H, overlap with water peak), 3.96 (s, 3H), 3.36-3.16 (m, 2H), 3.25 (s, 3H), 2.48-2.39 (m, 1H), 2.46 (s, 3H), 2.23-2.06 (m, 1H) ppm.

Example 4

(*3R*)-3-({[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo-[2,1-f][1,2,4]triazin-7-yl]methyl}amino)pyrrolidin-2-one



A solution of Intermediate 13A (2.0 g, 5.2 mmol) in methanol (58 ml) and acetic acid (0.6 ml) was treated with (*R*)-3-aminopyrrolidin-2-one (785 mg, 7.8 mmol) and triacetoxyborohydride (3.32 g, 15.6 mmol). The mixture was stirred at rt overnight. After this, the reaction mixture was diluted with sat. aq. sodium hydrogencarbonate solution and extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate and evaporated. The residue was purified by two-fold column chromatography on silica gel (dichloromethane/methanol 40:1 to 10:1) to afford 957 mg (37% of th.) of the title compound.

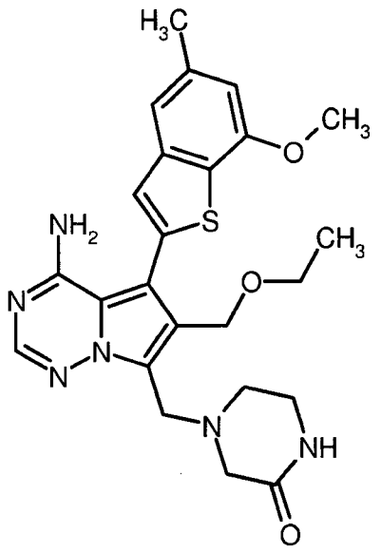
LC-MS (method 4): R_t = 0.72 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.01 (s, 1H), 7.75 (s, 1H), 7.35 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 4.46-4.34 (m, 2H), 4.24-4.02 (m, 2H), 3.96 (s, 3H), 3.24-3.04 (m, 3H), 3.21 (s, 3H), 2.45 (s, 3H), 2.40-2.27 (m, 1H), 1.80-1.65 (m, 1H) ppm.

Example 5

4-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}piperazin-2-one

BHC 11 1 045



Method 1:

A solution of Intermediate 17A (2 g, 5.05 mmol) in THF (100 ml) was treated at 0°C with 2-oxopiperazine (1.01 g, 10.1 mmol), sodium triacetoxyborohydride (1.07 g, 5.04 mmol) and acetic acid (0.29 ml, 5.04 mmol). The resulting mixture was stirred at 0°C for 30 min. Four additional portions of sodium triacetoxyborohydride (1.07 g, 5.04 mmol) and of acetic acid (0.29 ml, 5.04 mmol) were added every 30 minutes, and the resulting mixture was stirred for further 30 min at 0°C, then for 25 min at 35°C and finally at rt overnight. The reaction was quenched with 10% aq. sodium chloride solution and extracted twice with ethyl acetate. The combined organic layers were evaporated. The residue was purified by column chromatography over silica gel (dichloromethane/ methanol 95:5 → 90:10) affording 360 mg (17% of th.) of the compound described in Example 86 (see below) and 1.82 g of the title compound in separate fractions. The title product thus obtained was suspended in ethanol (20 ml), refluxed for 2 h and then cooled to 15°C. The solid was filtered off and washed with ethanol affording 1.63 g (67% of th.) of the pure title compound.

Method 2:

A solution of Example 13 (930 mg, 1.9 mmol) in dichloromethane (18 ml) was treated with thionyl chloride (210 µl, 2.8 mmol) and stirred at rt for 15 min. After evaporation, the residue was dissolved in ethanol (18 ml) and treated with DIPEA (670 µl, 3.8 mmol). The mixture was stirred at 70°C for 2 h and then evaporated. The residue was purified by column chromatography on silica gel (dichloromethane/methanol 98:2 → 90:10). The product thus obtained was triturated in an acetonitrile/diethylether mixture and filtered. The filtrate was evaporated, and the residue was repurified by column chromatography on silica gel (dichloromethane/methanol 98:2 → 90:10). Again, the product thus obtained was triturated in acetonitrile/diethylether and filtered. This procedure was repeated one more time. The three batches of solids obtained in this way were com-

bined, triturated in acetonitrile/diethylether once again and finally filtered off affording 600 mg (62% of th.) of the title compound.

Method 3:

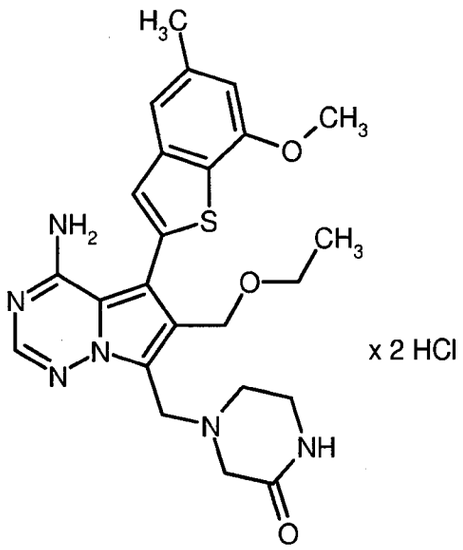
A solution of Intermediate 22A (720 mg, purity 89%, 1.74 mmol) in acetic acid (10 ml) was stirred with piperazin-2-one (261 mg, 2.61 mmol) at 60°C. To this, 37% aq. formaldehyde solution (260 µl, 3.48 mmol) was added in three portions after 0, 3 and 12 h, respectively, and the mixture was stirred at 60°C for a total of 24 h. Then, the volatiles were removed under reduced pressure, and the residue was partitioned between ethyl acetate and sat. aq. sodium hydrogencarbonate solution. The organic phase was washed with sat. aq. sodium chloride solution, dried with magnesium sulfate and evaporated. The residue was dissolved in a mixture of methanol and dichloromethane, adsorbed on diatomaceous earth, dried *in vacuo* and purified by flash-chromatography on silica gel (gradient 0-6% methanol/dichloromethane). The product fractions were combined, evaporated and re-purified by preparative RP-HPLC (Reprosil C18, gradient 30-50% acetonitrile/0.2% aq. TFA). The product fractions were combined again, diluted with sat. aq. sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic phase was washed with sat. aq. sodium chloride solution, dried with magnesium sulfate and evaporated yielding 281 mg (31% of th.) of the title compound.

LC-MS (method 2): R_t = 0.86 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.01 (s, 1H), 7.8-8.05 (br. s, 1H), 7.74 (br. s, 1H), 7.38 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 5.6-5.9 (br. s, 1H), 4.45 (s, 2H), 3.97 (s, 2H), 3.94 (s, 3H), 3.41 (q, 2H), 3.09-3.13 (m, 2H), 3.02 (s, 2H), 2.63-2.69 (br. s, 2H), 2.45 (s, 3H), 1.07 (t, 3H) ppm.

Example 6

4-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo-[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one dihydrochloride



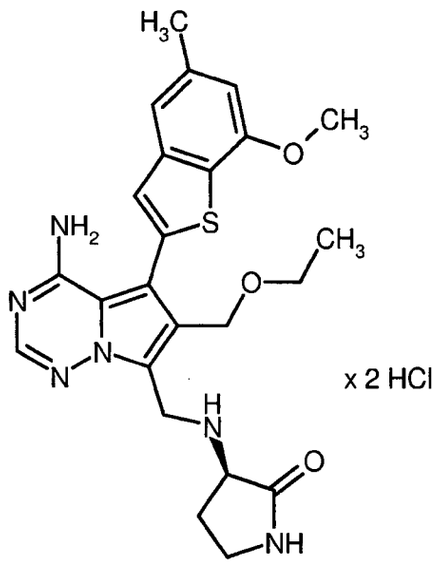
A solution of Intermediate 17A (60 mg, purity 69%, 104 µmol) in methanol (6 ml) was treated with 2-oxopiperazine (22 mg, 209 µmol), sodium cyanoborohydride (33 mg, 522 mmol) and acetic acid (12 µl, 209 µmol). The mixture was stirred at 60°C for 16 h and then filtered. The filtrate and the residue were purified separately by preparative RP-HPLC (Reprosil C18, gradient 40-60% acetonitrile/0.2% aq. TFA). The product fractions were combined, diluted with 1 M hydrochloric acid (3 ml) and evaporated to dryness yielding 46 mg (79% of th.) of the title compound.

LC-MS (method 2): R_t = 0.87 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.37 (br. s, 1H), 8.31 (br. s, 1H), 8.14 (s, 1H), 7.38 (s, 1H), 7.33 (s, 1H), 6.87 (s, 1H), 6.13 (br. s, 1H), 4.80 (br. s, 2H), 4.52 (s, 2H), 3.96 (s, 3H), 3.86 (br. s, 2H), 3.36-3.51 (m, 5H), 2.46 (s, 3H), 1.11 (t, 3H) ppm.

Example 7

(*3R*)-3-({[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}amino)pyrrolidin-2-one dihydrochloride



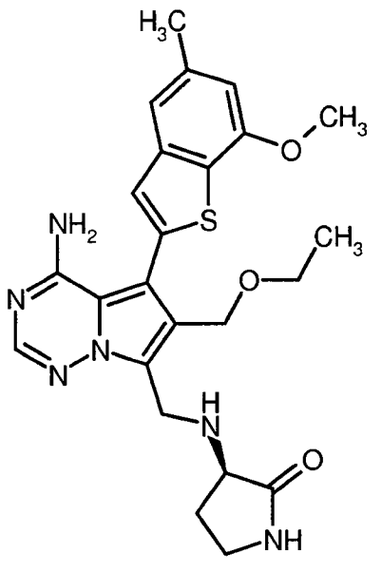
A solution of Intermediate 17A (60 mg, purity 69%, 104 µmol) in methanol (3 ml) was treated with (*R*)-3-aminopyrrolidin-2-one (22 mg, 209 µmol), sodium cyanoborohydride (33 mg, 522 µmol) and acetic acid (12 µl, 209 µmol). The mixture was stirred at 60°C for 4 h and then filtered. The filtrate was purified by preparative RP-HPLC (Reprosil C18, gradient 40-60% acetonitrile/ 0.2% aq. TFA). The product fractions were combined, diluted with 1 M hydrochloric acid and evaporated to dryness yielding 46 mg (79% of th.) of the title compound.

LC-MS (method 4): R_t = 0.74 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 9.58-9.75 (m, 1H), 9.33-9.54 (m, 1H), 8.44 (s, 1H), 8.27-8.71 (br. s, 1H), 8.19 (s, 1H), 7.38 (s, 1H), 7.34 (s, 1H), 6.87 (s, 1H), 6.18-6.48 (br. s, 1H), 4.68-4.87 (m, 2H), 4.49-4.62 (q, 2H), 3.96 (s, 3H), 3.45 (q, 2H), 3.18-3.35 (m, 2H), 2.46 (s, 4H), 2.08-2.22 (m, 1H), 1.10 (t, 3H) ppm.

Example 8

(*3R*)-3-({[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}amino)pyrrolidin-2-one



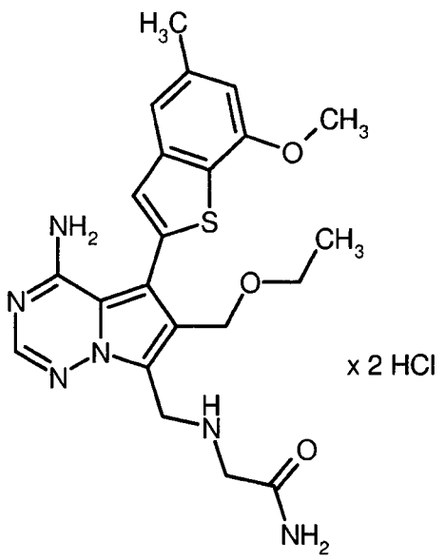
A solution of Intermediate 17A (226 mg, purity 75%, 428 µmol) in methanol (4 ml) was treated with (*R*)-3-aminopyrrolidin-2-one (85 mg, 855 µmol), sodium cyanoborohydride (134 mg, 2.14 mmol) and acetic acid (49 µl, 855 µmol). The mixture was stirred at rt for 1.5 h. After this, the mixture was directly separated by preparative RP-HPLC (Reprosil C18, gradient 40-60% acetonitrile/0.2% aq. TFA). The product fractions were combined, diluted with sat. aq. sodium hydrogencarbonate solution and extracted with ethyl acetate. The combined organic phases were washed with sat. aq. sodium chloride solution, dried over magnesium sulfate and evaporated to dryness yielding 180 mg (88% of th.) of the title compound.

LC-MS (method 4): R_t = 0.74 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.00 (s, 1H), 7.76 (s, 1H), 7.8-8.1 (br. s, 1H), 7.35 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 5.6-5.9 (br. s, 1H), 4.39-4.49 (m, 2H), 4.04-4.23 (m, 2H), 3.96 (s, 3H), 3.41 (q, 2H), 3.05-3.23 (m, 3H), 2.45 (s, 3H), 2.31-2.40 (m, 1H), 1.68-1.79 (m, 1H), 1.08 (t, 3H) ppm.

Example 9

N^2-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}glycinamide dihydrochloride



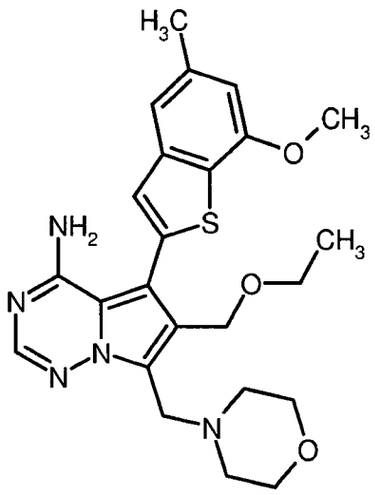
A solution of Intermediate 17A (60 mg, purity 69%, 104 µmol) in methanol (3 ml) was treated with glycinamide hydrochloride (23 mg, 209 µmol), sodium cyanoborohydride (32 mg, 522 mmol) and acetic acid (12 µl, 209 µmol). The mixture was stirred at 60°C for 16 h. After filtration, the filtrate was separated by preparative RP-HPLC (Reprosil C18, gradient 20-40% acetonitrile/0.2% aq. TFA). The product fractions were combined, diluted with 1 M hydrochloric acid, evaporated to dryness and combined with the residue from the filtration step. This material was re-purified by two-fold preparative RP-HPLC (Reprosil C18, gradient 20-40% acetonitrile/0.2% aq. TFA). The product fractions were combined again, diluted with 1 M hydrochloric acid and evaporated to dryness yielding 7.4 mg (13% of th.) of the title compound.

LC-MS (method 2): R_t = 0.80 min; MS (ESIpos): m/z = 455 $(M+H)^+$

^{1}H-NMR (500 MHz, DMSO-d_6): δ = 9.33 (br. s, 2H), 9.05 (br. s, 1H), 8.31 (s, 1H), 7.93 (br. s, 1H), 7.58 (br. s, 1H), 7.40 (s, 1H), 7.35 (s, 1H), 7.05 (br. s, 1H), 6.88 (s, 1H), 4.65 (br. m, 2H), 4.56 (s, 2H), 3.96 (s, 3H), 3.74 (br. m, 2H), 3.46 (q, 2H), 2.46 (s, 3H), 1.10 (t, 3H) ppm.

Example 10

6-(Ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-amine



A solution of Intermediate 17A (55 mg, purity 73%, 101 µmol) in methanol (3 ml) was treated with morpholine (18 mg, 202 µmol), sodium cyanoborohydride (19 mg, 303 mmol) and acetic acid (18 µl, 304 µmol). The mixture was stirred at 60°C for 18 h. Further amounts of morpholine (18 mg, 202 µmol), sodium cyanoborohydride (19 mg, 303 mmol) and acetic acid (18 µl, 304 µmol) were added, and stirring at 60°C was continued for another 3 h. The resulting mixture was diluted with THF to dissolve precipitates and separated by preparative RP-HPLC (Reprosil C18, gradient 20-40% acetonitrile/0.2% aq. TFA). The product fractions were combined and evaporated to dryness. The residue was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated yielding 32 mg (68% of th.) of the title compound.

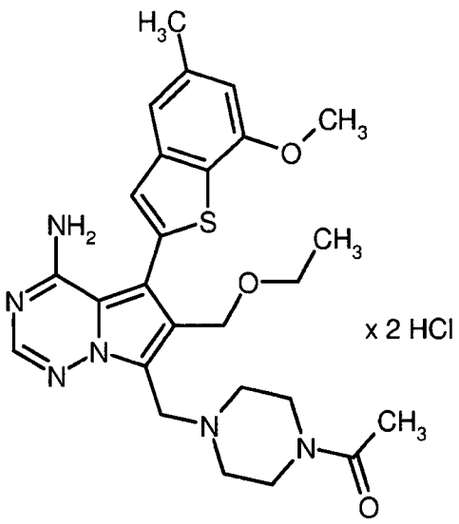
LC-MS (method 2): R_t = 0.78 min; MS (ESIpos): m/z = 468 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.98 (s, 1H), 7.9 (br. s, 1H), 7.37 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 5.75 (br. s, 1H), 4.45 (s, 2H), 3.95 (s, 3H), 3.88 (s, 2H), 3.51-3.56 (m, 4H), 3.40 (q, 2H), 2.4-2.5 (m, 4H), 2.45 (s, 3H), 1.06 (t, 3H) ppm.

Example 11

1-(4-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}piperazin-1-yl)ethanone dihydrochloride

BHC 11 1 045



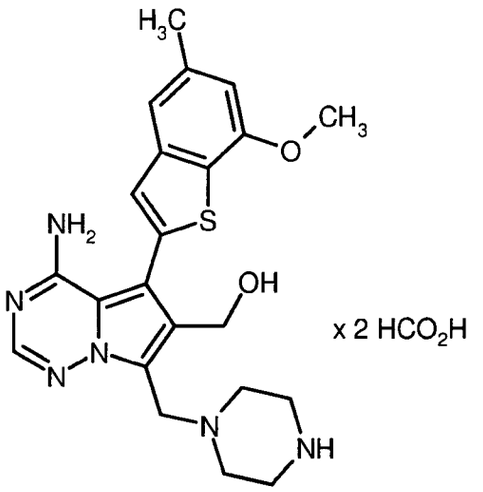
A solution of Intermediate 17A (130 mg, 0.328 mmol) in methanol (8 ml) was treated with *N*-acetylpiperazine (63 mg, 0.492 mmol), sodium cyanoborohydride (103 mg, 1.63 mmol) and acetic acid (37 µl, 0.655 mmol). The mixture was stirred at 60°C for 3 h. It was then combined with the reaction mixture of a 30 mg test run, evaporated and purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid). The product thus obtained was lyophilized from 1,4-dioxane, then dissolved in ethyl acetate and washed with sat. aq. sodium hydrogencarbonate solution. The organic layer was dried over magnesium sulfate, evaporated and lyophilized again from 1,4-dioxane. Re-purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid), followed by two-fold column chromatography on silica gel (dichloromethane/methanol 98:2 → 4:1) and lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 49 mg (18% of th.) of the title compound.

LC-MS (method 2): R_t = 0.82 min; MS (ESIpos): m/z = 509 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.65-8.26 (br. s, 1H), 8.17 (s, 1H), 7.38 (s, 1H), 7.34 (s, 1H), 6.87 (s, 1H), 6.53-6.05 (br. s, 1H), 4.75 (br. s, 2H), 4.56 (br. s, 2H), 3.96 (s, 3H), 3.45 (q, 2H, overlap with water peak), 2.46 (s, 3H), 2.03 (s, 3H), 1.09 (t, 3H) ppm.

Example 12

[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f]-[1,2,4]triazin-6-yl]methanol bis(formiate)



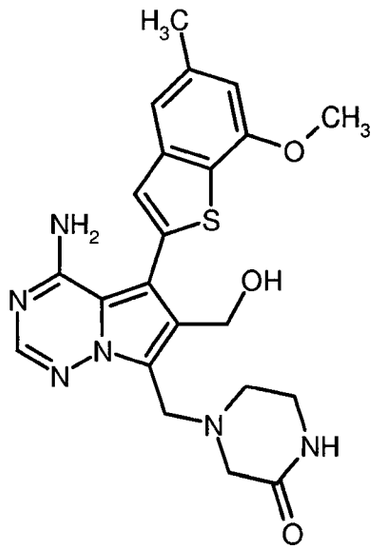
A solution of Intermediate 23A (95 mg, 152 µmol) in a 4 M solution of hydrogen chloride in 1,4-dioxane (3.7 ml) was stirred at rt for 2 h. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) affording 44 mg (62% of th.) of the title compound.

LC-MS (method 2): R_t = 0.63 min; MS (ESIpos): m/z = 439 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.28 (br. s, 2H), 7.98 (s, 1H), 7.37 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 4.50 (s, 2H, overlap with water peak), 3.98 (s, 2H, overlap with water peak), 3.95 (s, 3H, overlap with water peak), 2.95-2.84 (m, 4H), 2.61-2.55 (m, 4H, overlap with DMSO peak), 2.45 (s, 3H) ppm.

Example 13

4-{[4-Amino-6-(hydroxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}piperazin-2-one



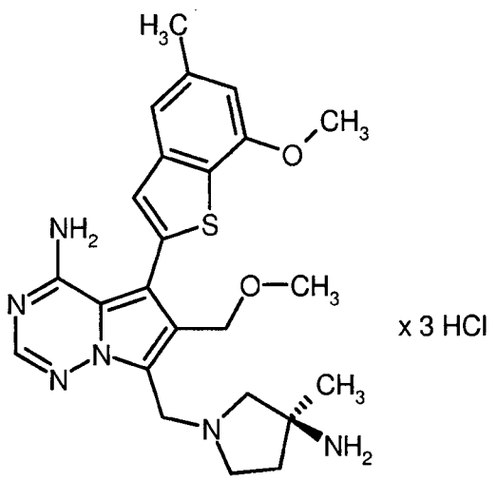
A solution of Intermediate 20A (1.34 g, 3.96 mmol) in acetic acid (13.9 ml) was treated with 37% aq. formaldehyde solution (501 µl, 6.6 mmol) and 2-oxopiperazine (670 mg, 6.6 mmol). The mixture was stirred at 50°C for 2 h and then evaporated. Purification by column chromatography on silica gel (dichloromethane/methanol 98:2 → 90:10) afforded 942 mg (49% of th.) of the title compound.

LC-MS (method 2): R_t = 0.67 min; MS (ESIpos): m/z = 453 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.99 (s, 1H), 7.76 (br. s, 1H), 7.39 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 4.51 (s, 2H), 4.03 (br. s, 2H), 3.95 (s, 3H), 3.18-3.13 (m, 2H), 3.07-2.98 (m, 2H), 2.72-2.60 (m, 2H), 2.45 (s, 3H) ppm.

Example 14

7-{[(*3S*)-3-Amino-3-methylpyrrolidin-1-yl]methyl}-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride



x 3 HCl

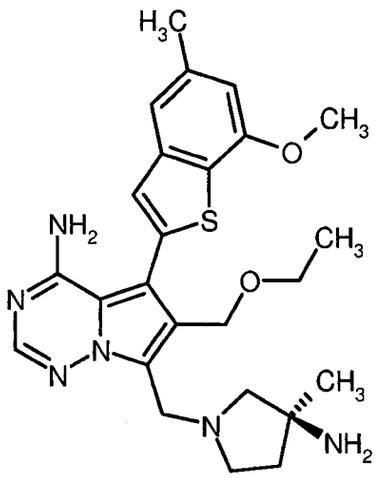
A solution of Intermediate 21A (100 mg, 0.28 mmol) in acetic acid (1 ml) was treated with 37% aq. formaldehyde solution (25 µl, 0.33 mmol) and *tert*-butyl [(*3S*)-3-methylpyrrolidin-3-yl]carbamate (Yoshida *et al.*, *Chem. Pharm. Bull.* 1996, 44 (7), 1376-1386; 67 mg, 0.33 mmol). The mixture was stirred at rt for 3 h and then evaporated. The residue was diluted with sat. aq. sodium hydrogencarbonate solution, and solid potassium carbonate was added until no more gas generation occurred. The aqueous phase was extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate and evaporated. The residue was dissolved in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) and stirred at rt for 2 h. After evaporation, the residue was purified by two-fold preparative RP-HPLC (first Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid; then Shield RP18, gradient 5-50% methanol + 0.1% aq. TFA/0.1% aq. TFA). The product thus obtained was lyophilized from a 4 M solution of hydrogen chloride in 1,4-dioxane affording 14 mg (8% of th.) of the title compound.

LC-MS (method 2): R_t = 0.67 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.50-8.22 (br. s, 1H), 8.14 (s, 1H), 7.36 (s, 1H), 7.34 (s, 1H), 6.87 (s, 1H), 6.36-6.01 (br. s, 1H), 4.88 (br. s, 2H), 4.56 (br. s, 2H), 3.96 (s, 3H, overlap with water peak), 3.26 (s, 3H), 2.46 (s, 3H), 1.52 (s, 3H) ppm.

Example 15

7-{[(*3S*)-3-Amino-3-methylpyrrolidin-1-yl]methyl}-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



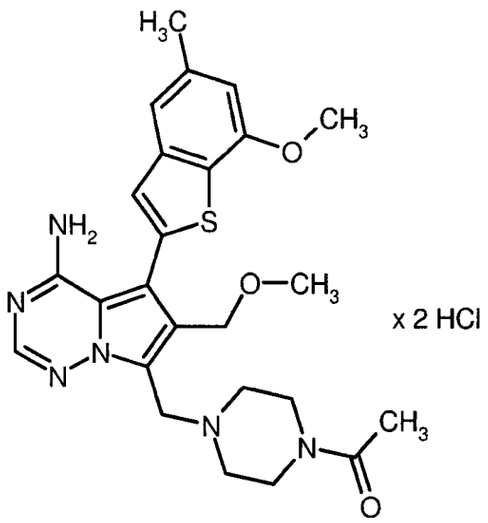
A solution of Intermediate 17A (100 mg, 271 µmol) in acetic acid (1 ml) was treated with 37% aq. formaldehyde solution (24 µl, 326 µmol) and *tert*-butyl [(*3S*)-3-methylpyrrolidin-3-yl]carbamate (Yoshida *et al.*, *Chem. Pharm. Bull.* 1996, 44 (7), 1376-1386; 65 mg, 326 µmol). The mixture was stirred at 60°C for 4 h. Then, further amounts of 37% aq. formaldehyde solution (10 µl, 136 µmol) and *tert*-butyl [(*3S*)-3-methylpyrrolidin-3-yl]carbamate (27 mg, 136 µmol) were added, and stirring at 60°C was continued overnight. After evaporation, the residue was partitioned between ethyl acetate and sat. aq. sodium hydrogencarbonate solution. Solid potassium carbonate was added until no more gas generation occurred. The aqueous phase was extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate, evaporated and purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid). The product thus obtained was dissolved in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) and stirred at rt for 1 h. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) affording 24 mg (18% of th.) of the title compound.

LC-MS (method 4): R_t = 0.70 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.19 (s, 1H), 7.38 (s, 1H), 7.34 (s, 1H), 6.87 (s, 1H), 4.90 (br. s, 2H), 3.96 (s, 3H), 3.46 (q, 3H), 2.46 (s, 3H), 1.54 (s, 3H), 1.14-1.05 (m, 3H) ppm.

Example 16

1-(4-{[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}piperazin-1-yl)ethanone dihydrochloride



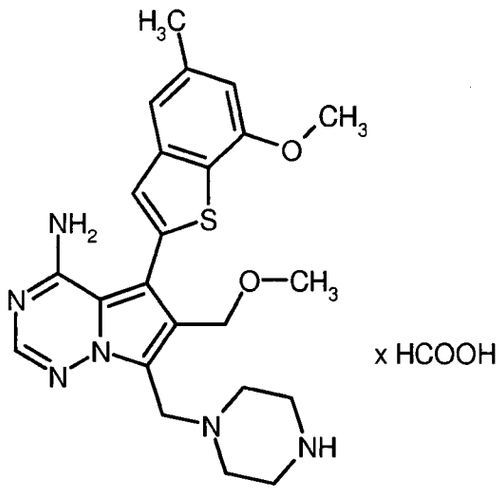
A solution of Intermediate 21A (50 mg, 141 µmol) in acetic acid (1 ml) was treated with 37% aq. formaldehyde solution (4.6 µl, 169 µmol) and *N*-acetylpiperazine (21.6 mg, 169 µmol). The mixture was stirred at 75°C for 3 h. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid). Lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 34 mg (39% of th.) of the title compound.

LC-MS (method 5): R_t = 1.78 min; MS (ESIpos): m/z = 495 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.70-8.35 (br. s, 1H), 8.18 (s, 1H), 7.37 (s, 1H), 7.34 (s, 1H), 6.86 (s, 1H), 6.61-6.19 (br. s, 1H), 4.74 (br. s, 2H), 4.54 (br. s, 2H), 3.96 (s, 3H), 3.25 (s, 3H), 2.46 (s, 3H), 2.03 (s, 3H) ppm.

Example 17

6-(Methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-amine formiate



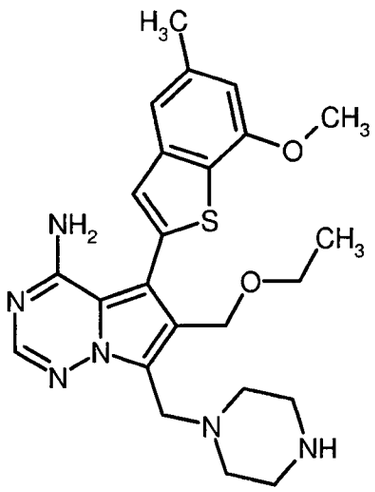
A solution of Intermediate 23A (110 mg, 204 µmol) in dichloromethane (2.2 ml) was treated with thionyl chloride (29 µl, 408 µmol) and stirred at rt for 15 min. After evaporation, the residue was dissolved in methanol (2.2 ml) and treated with DIPEA (39 µl, 224 µmol). The mixture was stirred at 70°C for 1 h and then evaporated. The residue was taken up in a 4 M solution of hydrogen chloride in 1,4-dioxane (2.2 ml) and stirred at rt for 2 h. Evaporation and purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 44.9 mg (46% of th.) of the title compound.

LC-MS (method 2): R_t = 0.73 min; MS (ESIpos): m/z = 453 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.28 (br. s, 1H), 8.00 (s, 1H), 7.35 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 4.41 (s, 2H), 4.00-3.90 (m, 5H), 3.00-2.90 (m, 4H), 2.65-2.56 (m, 4H), 2.45 (s, 3H) ppm.

Example 18

6-(Ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-4-amine



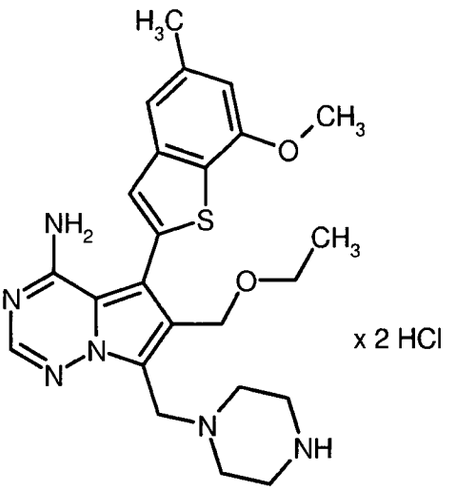
A solution of Intermediate 23A (80 mg, 317 µmol) in dichloromethane (2 ml) was treated with thionyl chloride (22 µl, 297 µmol) and stirred at rt for 15 min. After evaporation, the residue was dissolved in ethanol (2 ml) and treated with DIPEA (28 µl, 163 µmol). The mixture was stirred at 70°C for 1 h and then evaporated. The residue was taken up in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) and stirred at rt for 1 h. Evaporation and purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 35 mg (50% of th.) of the title compound.

LC-MS (method 2): R_t = 0.82 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.09 (br. s, 1H), 7.36 (s, 1H), 7.32 (s, 1H), 6.86 (s, 1H), 4.50 (br. s, 2H), 3.96 (s, 3H), 3.42 (q, 2H, overlap with water peak), 2.45 (s, 3H), 1.05 (t, 3H) ppm.

Example 19

6-(Ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-4-amine dihydrochloride



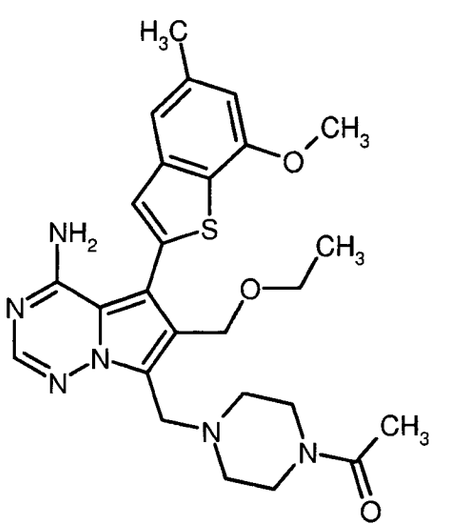
A solution of Example 18 (50 mg, 107 µmol) in a 4 M solution of hydrogen chloride in 1,4-dioxane (1 ml) was stirred at rt for 15 min. After evaporation 55 mg (93% of th.) of the title compound were obtained.

LC-MS (method 4): R_t = 0.74 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.18 (s, 1H), 7.37 (s, 1H), 7.34 (s, 1H), 6.87 (s, 1H), 4.76 (br. s, 2H), 4.60 (br. s, 2H), 3.96 (s, 3H), 3.45 (q, 2H), 2.46 (s, 3H), 1.09 (t, 3H) ppm.

Example 20

1-(4-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}piperazin-1-yl)ethanone



A solution of Example 18 (70 mg, 150 µmol) in dichloromethane (2 ml) and THF (0.8 ml) was treated with acetyl chloride (21 µl, 300 µmol) and sodium carbonate (127 mg, 1.2 mmol). The mix-

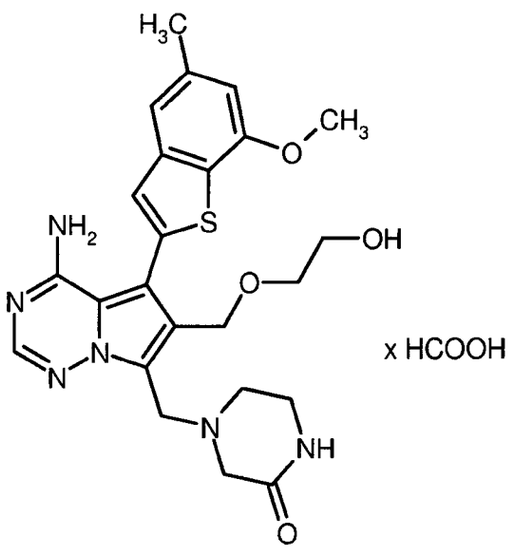
ture was stirred at rt overnight. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) affording 27 mg (31% of th.) of the title compound.

LC-MS (method 4): R_t = 0.77 min; MS (ESIpos): m/z = 509 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.98 (s, 1H), 7.37 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 4.45 (s, 2H), 3.95 (s, 3H), 3.92 (s, 2H), 3.45-3.36 (m, 6H), 2.48-2.38 (m, 7H, overlap with DMSO peak), 1.97 (s, 3H), 1.06 (t, 3H) ppm.

Example 21

4-({4-Amino-6-[(2-hydroxyethoxy)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo-[2,1-f][1,2,4]triazin-7-yl}methyl)piperazin-2-one formiate



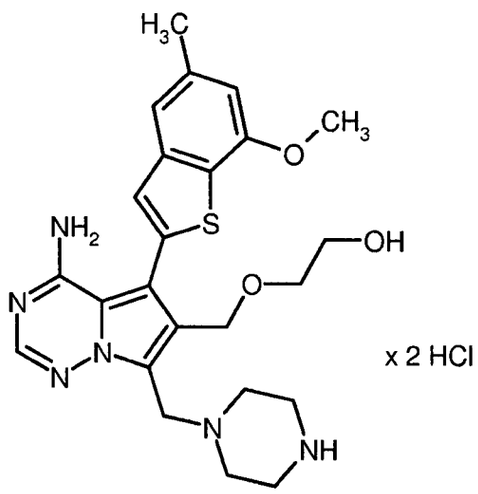
A solution of Example 13 (60 mg, 132 µmol) in dichloromethane (2 ml) was treated with thionyl chloride (14 µl, 198 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in ethylene glycol (500 µl) and stirred at 100°C for 90 min. Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 34 mg (47% of th.) of the title compound.

LC-MS (method 2): R_t = 0.69 min; MS (ESIpos): m/z = 497 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.14 (s, 1H), 8.00 (s, 1H), 7.74 (br. s, 1H), 7.42 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 4.49 (s, 2H), 3.99 (s, 2H), 3.96 (s, 3H), 3.50-3.43 (m, 2H), 3.42-3.36 (m, 2H, overlap with water peak), 3.15-3.07 (m, 2H), 3.03 (s, 2H), 2.69-2.61 (m, 2H), 2.45 (s, 3H) ppm.

Example 22

2-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methoxy}ethanol dihydrochloride



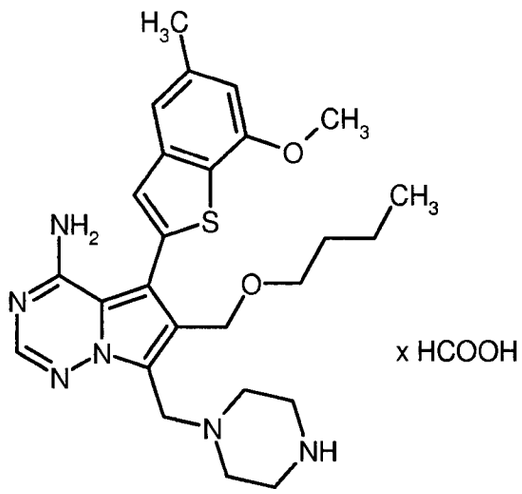
A solution of Intermediate 23A (100 mg, 185 µmol) in dichloromethane (4 ml) was treated with thionyl chloride (27 µl, 371 µmol). The mixture was stirred at rt for 20 min and then evaporated. The residue was dissolved in ethylene glycol/THF (2:1, 1.5 ml) and stirred at 100°C for 2 h. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid), followed by column chromatography on silica gel (dichloro-methane/methanol + 0.1% aq. ammonia 98:2 → 90:10). Lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 67 mg (64% of th.) of the title compound.

LC-MS (method 2): R_t = 0.66 min; MS (ESIpos): m/z = 483 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.16 (s, 1H), 7.49 (s, 1H), 7.43 (s, 1H), 6.98 (s, 1H), 4.86 (s, 2H), 4.69 (s, 2H), 4.03 (s, 3H), 3.81-3.49 (m, 12H), 2.50 (s, 3H) ppm.

Example 23

6-(Butoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-4-amine formiate



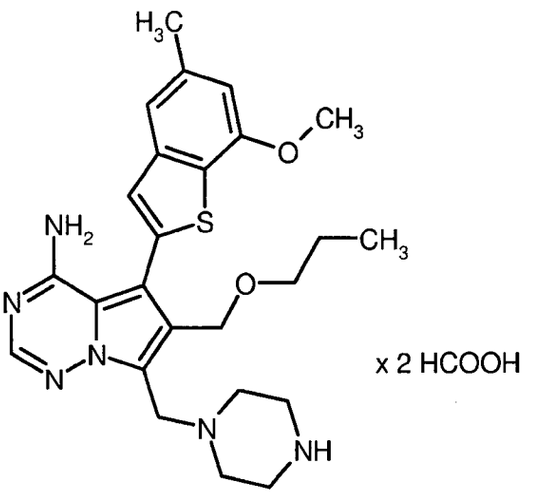
A solution of Intermediate 23A (100 mg, 185 µmol) in dichloromethane (2 ml) was treated with thionyl chloride (27 µl, 371 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in 1-butanol (2 ml) and heated to 70°C for 1 h. After evaporation, the residue was taken up in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) and stirred at rt for 2 h. Evaporation and purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 22 mg (24% of th.) of the title compound.

LC-MS (method 2): R_t = 0.82 min; MS (ESIpos): m/z = 495 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.29 (s, 1H), 7.99 (s, 1H), 7.35 (s, 1H), 7.29 (s, 1H), 6.84 (s, 1H), 4.43 (s, 2H), 3.95 (s, 3H), 3.92 (s, 2H), 3.35 (t, 2H), 2.90-2.79 (m, 4H), 2.45 (s, 3H), 1.47-1.37 (m, 2H), 1.31-1.18 (m, 2H), 0.80 (t, 3H) ppm.

Example 24

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)-6-(propoxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-amine bis(formiate)



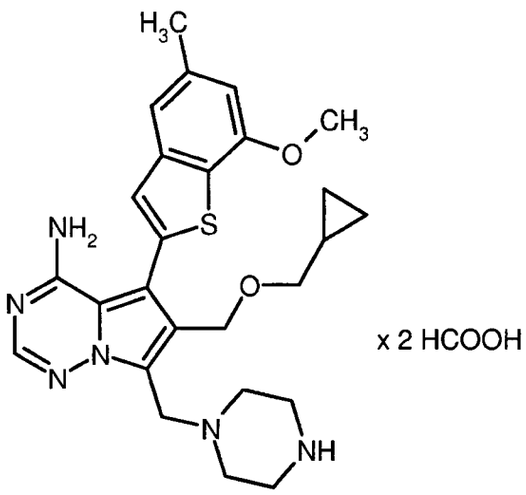
A solution of Intermediate 23A (100 mg, 185 µmol) in dichloromethane (2 ml) was treated with thionyl chloride (27 µl, 371 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in 1-propanol (2 ml), treated with DIPEA (48 µl, 278 µmol) and stirred at rt for 1 h. After evaporation, the residue was taken up in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) and stirred at rt for 2 h. Evaporation and purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 15 mg (16% of th.) of the title compound.

LC-MS (method 2): R_t = 0.78 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.26 (br. s, 2H), 7.98 (s, 1H), 7.36 (s, 1H), 7.30 (s, 1H), 6.84 (s, 1H), 4.44 (s, 2H), 3.95 (s, 3H), 3.92 (s, 2H), 3.32 (t, 2H), 2.87-2.79 (m, 4H), 1.52-1.39 (m, 2H), 0.81 (t, 3H) ppm.

Example 25

6-[(Cyclopropylmethoxy)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine bis(formiate)



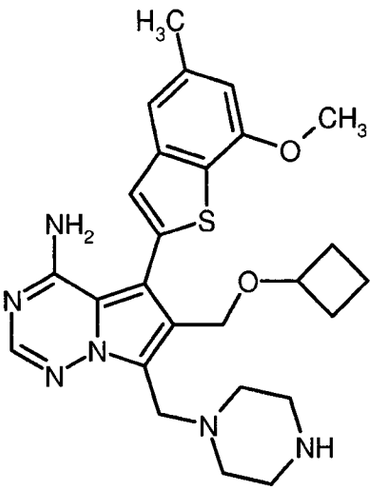
A solution of Intermediate 23A (100 mg, 185 µmol) in dichloromethane (2 ml) was treated with thionyl chloride (27 µl, 371 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in cyclopropylmethanol (2 ml), treated with DIPEA (48 µl, 278 µmol) and stirred at 70°C for 2 h. After evaporation, the residue was taken up in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) and stirred at rt for 2 h. Evaporation and purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 29 mg (30% of th.) of the title compound.

LC-MS (method 2): R_t = 0.78 min; MS (ESIpos): m/z = 493 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.28 (br. s, 2H), 7.99 (s, 1H), 7.37 (s, 1H), 7.30 (s, 1H), 6.84 (s, 1H), 4.45 (s, 2H), 3.95 (s, 3H), 3.93 (s, 2H), 3.21 (d, 2H), 2.95-2.83 (m, 4H), 2.61-2.56 (m, 4H), 2.45 (s, 3H), 1.01-0.91 (m, 1H), 0.46-0.37 (m, 2H), 0.15-0.08 (m, 2H) ppm.

Example 26

6-[(Cyclobutyloxy)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine



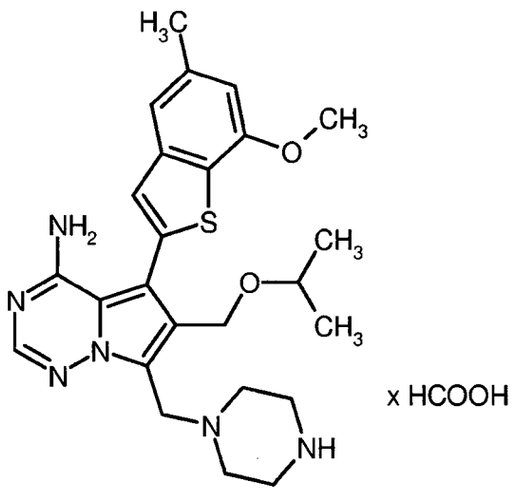
A solution of Intermediate 23A (85 mg, 157 µmol) in dichloromethane (1.7 ml) was treated with thionyl chloride (23 µl, 315 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in cyclobutanol (1.7 ml), treated with DIPEA (41 µl, 236 µmol) and stirred at 70°C for 2 h. After evaporation, the residue was taken up in a 4 M solution of hydrogen chloride in 1,4-dioxane (1.7 ml) and stirred at rt for 2 h. Evaporation and purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 23 mg (28% of th.) of the title compound.

LC-MS (method 2): R_t = 0.82 min; MS (ESIpos): m/z = 493 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.01 (s, 1H), 7.37 (s, 1H), 7.32 (s, 1H), 6.85 (s, 1H), 4.37 (s, 2H), 4.06-3.86 (m, 6H), 3.14-2.97 (m, 4H), 2.80-2.62 (m, 4H), 2.45 (s, 3H), 2.10-1.96 (m, 2H), 1.83-1.69 (m, 2H), 1.65-1.52 (m, 1H), 1.49-1.33 (m, 1H) ppm.

Example 27

6-(Isopropoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-amine formiate



A solution of Intermediate 23A (65 mg, 120 µmol) in dichloromethane (1.3 ml) was treated with thionyl chloride (17 µl, 241 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in 2-propanol (1.3 ml), treated with DIPEA (23 µl, 132 µmol) and stirred at 70°C for 1 h. Further DIPEA (23 µl, 132 µmol) was added, and the mixture was stirred again at 70°C for 1 h. Then, another portion of DIPEA (63 µl, 362 µmol) was added, and stirring was continued at 90°C for 3 h. After evaporation, the residue was taken up in a 4 M solution of hydrogen chloride in 1,4-dioxane (1.3 ml) and stirred at rt for 2 h. Evaporation and purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 23 mg (34% of th.) of the title compound.

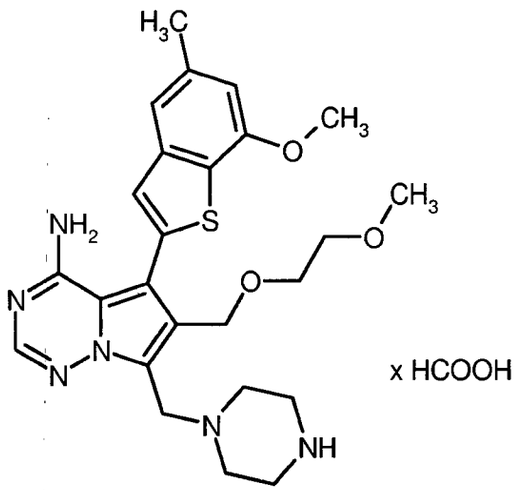
LC-MS (method 4): R_t = 0.74 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.30 (s, 1H), 7.98 (s, 1H), 7.37 (s, 1H), 7.30 (s, 1H), 6.84 (s, 1H), 4.43 (s, 2H), 3.95 (s, 3H), 3.90 (s, 2H), 3.57 (m, 1H, overlap with water peak), 2.88-2.78 (m, 4H), 2.45 (s, 3H), 1.04 (d, 6H) ppm.

Example 28

6-[(2-Methoxyethoxy)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine formiate

BHC 11 1 045



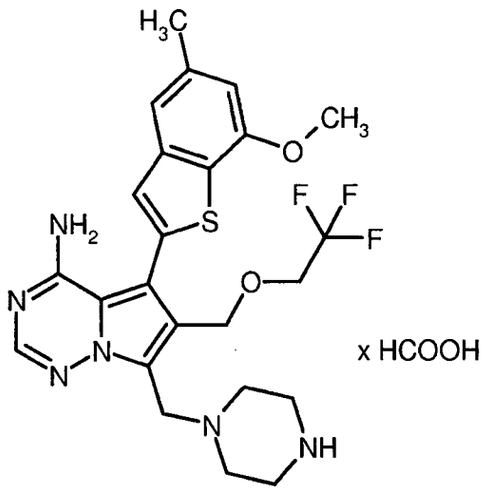
A solution of Intermediate 23A (100 mg, 185 µmol) in dichloromethane (2 ml) was treated with thionyl chloride (27 µl, 371 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in 2-methoxyethanol (2 ml), treated with DIPEA (35 µl, 204 µmol) and stirred at 70°C for 1 h. After evaporation, the residue was taken up in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) and stirred at rt for 2 h. Evaporation and purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 50 mg (50% of th.) of the title compound.

LC-MS (method 2): R_t = 0.75 min; MS (ESIpos): m/z = 497 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.26 (br. s, 1H), 7.99 (s, 1H), 7.39 (s, 1H), 7.30 (s, 1H), 6.84 (s, 1H), 4.48 (s, 2H), 3.95 (s, 3H), 3.94 (s, 2H), 3.52-3.46 (m, 2H, overlap with water peak), 3.44-3.37 (m, 2H, overlap with water peak), 3.20 (s, 3H), 2.94-2.84 (m, 4H), 2.61-2.54 (m, 4H, overlap with DMSO peak), 2.45 (s, 3H) ppm.

Example 29

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)-6-[(2,2,2-trifluoroethoxy)-methyl]pyrrolo[2,1-f][1,2,4]triazin-4-amine formiate



A solution of Intermediate 23A (100 mg, 185 µmol) in dichloromethane (2 ml) was treated with thionyl chloride (27 µl, 371 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in 2,2,2-trifluoroethanol (2 ml), treated with DIPEA (35 µl, 204 µmol) and stirred at 70°C for 1 h. Further DIPEA (35 µl, 204 µmol) was added, and stirring was continued at rt for 1 h. After evaporation, the residue was taken up in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) and stirred at rt for 2 h. Evaporation and purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 23 mg (23% of th.) of the title compound.

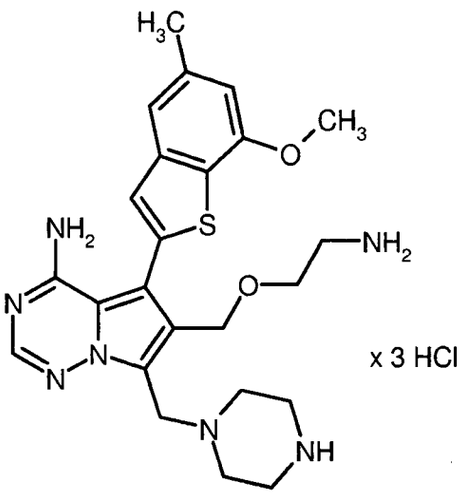
LC-MS (method 2): R_t = 0.79 min; MS (ESIpos): m/z = 521 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.28 (br. s, 1H), 8.00 (s, 1H), 7.37 (s, 1H), 7.30 (s, 1H), 6.85 (s, 1H), 4.66 (s, 2H), 4.08 (q, 2H), 3.95 (s, 3H), 3.92 (s, 2H), 2.85-2.75 (m, 4H), 2.45 (s, 3H) ppm.

Example 30

6-[(2-Aminoethoxy)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

BHC 11 1 045



A solution of Intermediate 23A (150 mg, 278 µmol) in dichloromethane (5 ml) was treated with thionyl chloride (40 µl, 556 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in THF (0.5 ml) and treated with *tert*-butyl (2-hydroxyethyl)carbamate (1 ml) and DIPEA (242 µl, 1.39 mmol). The mixture was stirred at 100°C overnight. After evaporation, the residue was taken up in 1,4-dioxane (10 ml), treated with a 4 M solution of hydrogen chloride in 1,4-dioxane (10 ml) and stirred at rt for 1 h. The volatiles were removed under reduced pressure, and the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid). Further purification by preparative RP-HPLC (Shield RP18, 25% acetonitrile/75% 0.01% aq. TFA) followed by lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 10 mg (6% of th.) of the title compound.

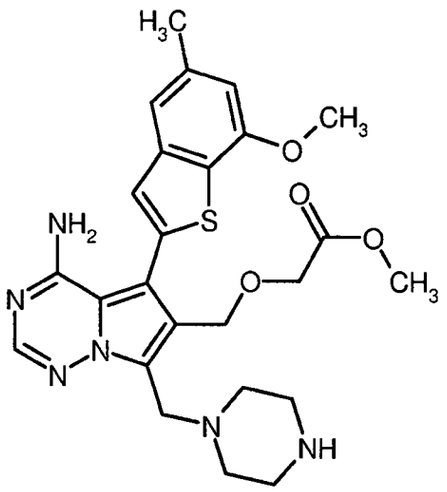
LC-MS (method 2): R_t = 0.58 min; MS (ESIpos): m/z = 482 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.12 (s, 1H), 7.50 (s, 1H), 7.44 (s, 1H), 6.99 (s, 1H), 4.61 (s, 2H), 4.04 (s, 3H), 3.88-3.80 (m, 1H), 3.70-3.60 (m, 3H), 3.52-3.46 (m, 4H), 3.40-3.34 (m, 4H), 3.07 (t, 2H), 2.51 (s, 3H) ppm.

Example 31

Methyl {[4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methoxy}acetate

BHC 11 1 045



A solution of Intermediate 23A (50 mg, 92 µmol) in dichloromethane (2 ml) was treated with thionyl chloride (13 µl, 186 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in methylglycolate (1 ml), treated with DIPEA (80 µl, 464 µmol) and stirred at 70°C for 2 h. After evaporation, the residue was taken up in dichloromethane (1.6 ml), treated with trifluoroacetic acid (400 µl, 5.19 mmol) and stirred at rt for 1 h. Then, the mixture was evaporated, and the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). Fractions containing the title compound were neutralized with sat. aq. sodium hydrogencarbonate solution and evaporated. The residue was taken up in water, and the mixture was extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and evaporated affording 21 mg (43% of th.) of the title compound.

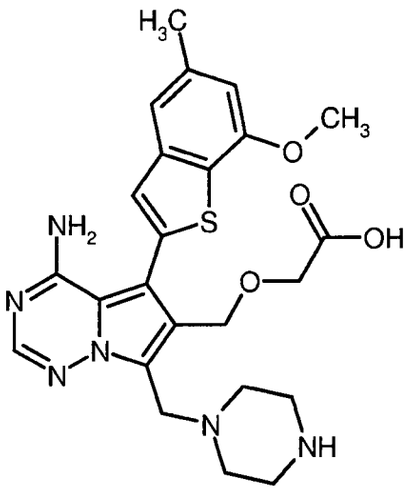
LC-MS (method 2): R_t = 0.72 min; MS (ESIpos): m/z = 511 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.99 (s, 1H), 7.39 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 4.59 (s, 2H), 4.11 (s, 2H), 3.95 (s, 3H), 3.90 (s, 2H), 3.57 (s, 3H), 2.81-2.69 (m, 4H), 2.48-2.39 (m, 7H) ppm.

Example 32

{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f]-[1,2,4]triazin-6-yl]methoxy}acetic acid

BHC 11 1 045



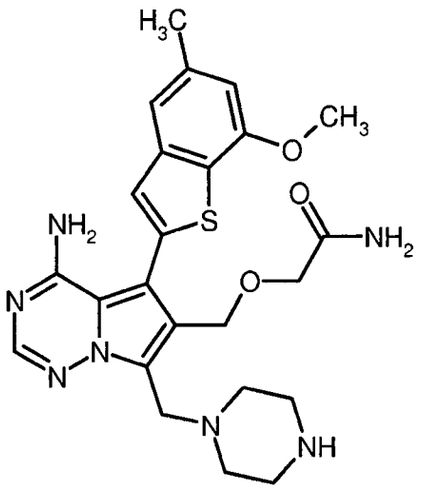
A solution of Intermediate 24A (200 mg, 327 µmol) in THF (14 ml) was treated with 2.5 M aq. lithium hydroxide solution (16 ml) and stirred at 80°C for 2 h. The mixture was then combined with the reaction mixture of a 27 mg test run. The aqueous phase was extracted twice with THF, and the combined organic phases were evaporated. The residue was dissolved in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) and stirred at rt for 3 h. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). Lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane and re-purification by preparative RP-HPLC (XBridge C18, gradient 5-95% acetonitrile/0.1% aq. ammonium hydroxide solution) afforded 13 mg (7% of th.) of the title compound.

LC-MS (method 2): R_t = 0.69 min; MS (ESIpos): m/z = 497 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.00 (s, 1H), 7.38 (s, 1H), 7.30 (s, 1H), 6.84 (s, 1H), 4.54 (s, 2H), 4.08 (s, 2H), 3.95 (s, 3H), 3.79 (s, 2H), 2.99-2.89 (m, 4H), 2.73-2.63 (m, 4H), 2.44 (s, 3H) ppm.

Example 33

2-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methoxy}acetamide



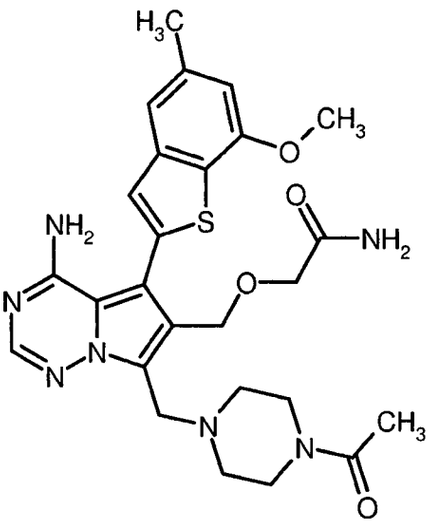
Intermediate 24A (200 mg, 327 µmol) was treated with a 7 M solution of ammonia in methanol (10 ml) and stirred at rt overnight. The mixture was then combined with the reaction mixture of a 20 mg test run, and the solvents were evaporated. The residue was treated with a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) and stirred at rt for 2 h. Evaporation and subsequent purifications by preparative RP-HPLC (first Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA; then XBridge C18, gradient 5-95% acetonitrile/0.1% aq. ammonium hydroxide solution) afforded 5.5 mg (3% of th.) of the title compound.

LC-MS (method 2): R_t = 0.69 min; MS (ESIpos): m/z = 496 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.14-7.59 (br. s, 1H), 7.99 (s, 1H), 7.39 (s, 1H), 7.35-7.22 (m, 3H), 6.85 (s, 1H), 4.54 (s, 2H), 3.95 (s, 3H), 3.90 (s, 2H), 3.79 (s, 2H), 2.73-2.66 (m, 4H), 2.45 (s, 3H), 2.43-2.35 (m, 4H) ppm.

Example 34

2-({7-[(4-Acetylpiperazin-1-yl)methyl]-4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-pyrrolo[2,1-f][1,2,4]triazin-6-yl}methoxy)acetamide



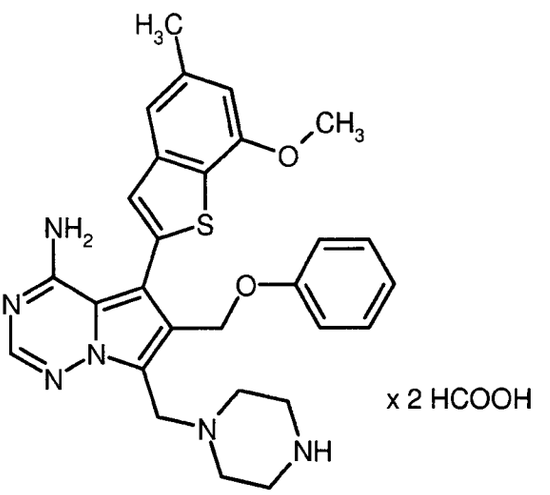
A solution of Example 33 (105 mg, 68% purity, 144 µmol) in THF/dichloromethane (1:2.5, 3.9 ml) was treated with sodium carbonate (179 mg, 1.6 mmol) and stirred at rt for 30 min. Acetyl chloride (30 µl, 424 µmol) was added, and the resulting mixture was stirred at rt for 30 min, then quenched with methanol (2 ml) and evaporated. Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 30 mg (85% purity, 34% of th.) of the title compound.

LC-MS (method 5): R_t = 1.67 min; MS (ESIpos): m/z = 538 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.99 (s, 1H), 7.40 (s, 1H), 7.33-7.19 (m, 3H), 6.85 (s, 1H), 4.55 (s, 2H), 3.96 (s, 5H), 3.80 (s, 2H), 3.43-3.36 (m, 4H), 2.47-2.38 (m, 7H), 1.97 (s, 3H) ppm.

Example 35

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-6-(phenoxymethyl)-7-(piperazin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-amine bis(formiate)



A solution of Intermediate 23A (100 mg, 185 µmol) in dichloromethane (2 ml) was treated with thionyl chloride (27 µl, 371 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in THF (2 ml), treated with phenol (174 mg, 1.85 mmol) and DIPEA (48 µl, 278 µmol) and stirred at 70°C for 2 h. Further amounts of phenol (174 mg, 1.85 mmol) and DIPEA (64 µl, 371 µmol) were added, and stirring was continued at 70°C overnight. After evaporation, the residue was taken up in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) and stirred at rt for 2 h. Evaporation and purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 8 mg (8% of th.) of the title compound.

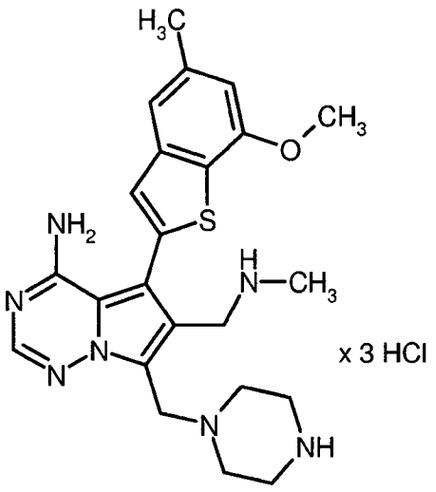
LC-MS (method 2): R_t = 0.84 min; MS (ESIpos): m/z = 515 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.26 (s, 2H), 8.02 (s, 1H), 7.36 (s, 1H), 7.30-7.22 (m, 3H), 6.99-6.89 (m, 3H), 6.81 (m, 1H), 5.04 (s, 2H), 3.93 (s, 5H), 2.78-2.71 (m, 4H), 2.42 (s, 3H) ppm.

Example 36

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-6-[(methylamino)methyl]-7-(piperazin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

BHC 11 1 045



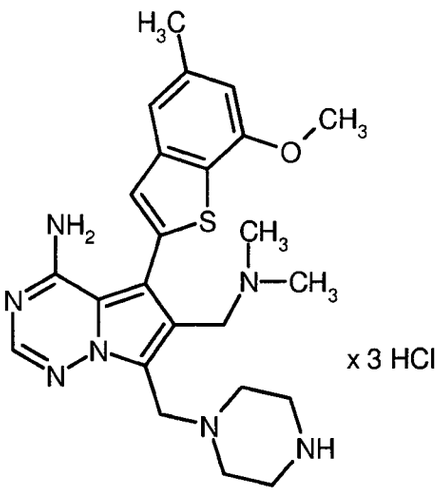
Intermediate 25A (150 mg, 279 µmol) in THF (3 ml) was treated with acetic acid (32 µl, 559 µmol), a 2 M solution of methylamine in THF (698 µl, 1.39 mmol) and sodium triacetoxyborohydride (296 mg, 1.39 mmol). The mixture was stirred at 60°C for 2 h and then evaporated. The residue was dissolved in a 4 M solution of hydrogen chloride in 1,4-dioxane (1.87 ml) and stirred at rt for 2 h. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). Lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 79 mg (49% of th.) of the title compound.

LC-MS (method 2): R_t = 0.56 min; MS (ESIpos): m/z = 452 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.17 (s, 1H), 7.57 (s, 1H), 7.46 (s, 1H), 7.01 (s, 1H), 4.52 (s, 2H), 4.46 (s, 2H), 4.04 (s, 3H), 3.48-3.39 (m, 4H), 3.25-3.15 (m, 4H), 2.59 (s, 3H), 2.51 (s, 3H) ppm.

Example 37

6-[(Dimethylamino)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride



A solution of Intermediate 25A (150 mg, 279 µmol) in THF (3 ml) was treated with acetic acid (32 µl, 559 µmol), a 2 M solution of dimethylamine in THF (698 µl, 1.39 mmol) and sodium triacetoxyborohydride (296 mg, 1.39 mmol). The mixture was stirred at 60°C for 2 h and then evaporated. The residue was dissolved in a 4 M solution of hydrogen chloride in 1,4-dioxane (1.88 ml) and stirred at rt for 2 h. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). Lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 83 mg (50% of th.) of the title compound.

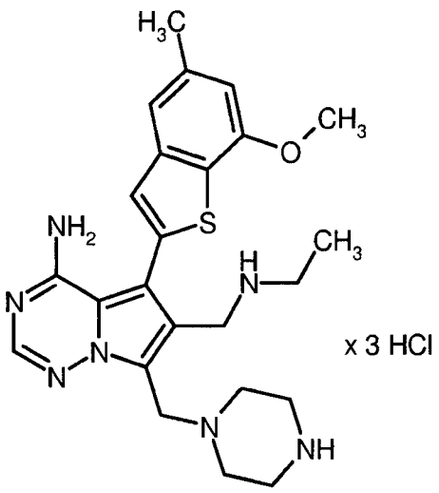
LC-MS (method 4): R_t = 0.50 min; MS (ESIpos): m/z = 466 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.17 (s, 1H), 7.57 (s, 1H), 7.45 (s, 1H), 7.01 (s, 1H), 4.57 (s, 2H), 4.50 (s, 2H), 4.04 (s, 3H), 3.47-3.36 (m, 4H), 3.21-3.12 (m, 4H), 2.80 (s, 6H), 2.51 (s, 3H) ppm.

Example 38

6-[(Ethylamino)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

BHC 11 1 045



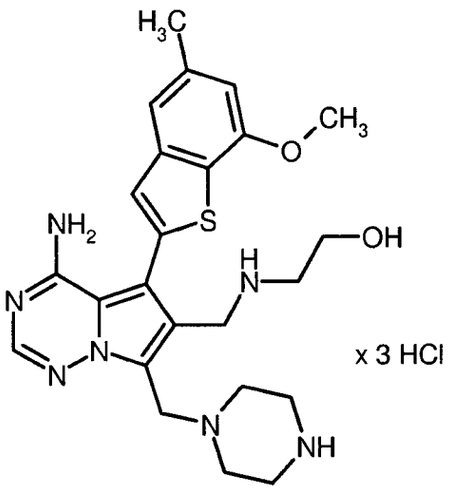
A solution of Intermediate 25A (60 mg, 111.8 µmol) in THF (1 ml) was treated with a 2 M solution of ethylamine in THF (83 µl, 167 µmol), sodium triacetoxyborohydride (118 mg, 559 µmol) and acetic acid (83 µl, 167 µmol). The mixture was stirred at 60°C for 90 min. Further amounts of 2 M ethylamine solution (83 µl, 167 µmol) and sodium triacetoxyborohydride (71 mg, 335 µmol) were added, and stirring at 60°C was continued for another 2 h. After evaporation, the residue was dissolved in a 4 M solution of hydrogen chloride in 1,4-dioxane (3 ml) and stirred at rt overnight. The mixture was evaporated, and the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) and lyophilized from a 4 M solution of hydrogen chloride in 1,4-dioxane. Re-purification by preparative RP-HPLC (Sunfire C18, 20% acetonitrile/80% 0.02% aq. TFA) and re-lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 19 mg (29% of th.) of the title compound.

LC-MS (method 2): R_t = 0.56 min; MS (ESIpos): m/z = 466 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.14 (s, 1H), 7.56 (s, 1H), 7.45 (s, 1H), 7.01 (s, 1H), 4.45 (s, 4H), 4.04 (s, 3H), 3.45-3.32 (m, 4H), 3.18-3.05 (m, 4H), 2.99 (q, 2H), 2.51 (s, 3H), 1.10 (t, 3H) ppm.

Example 39

2-({[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methyl}amino)ethanol trihydrochloride



A solution of Intermediate 25A (150 mg, 279 µmol) in THF (3 ml) was treated with 2-aminoethanol (84 µl, 1.39 mmol), sodium triacetoxyborohydride (296 mg, 1.39 mmol) and acetic acid (32 µl, 559 µmol). The mixture was stirred at 60°C for 2 h and then evaporated. The residue was dissolved in a 4 M solution of hydrogen chloride in 1,4-dioxane (1.87 ml) and stirred at rt for 2 h. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). Lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 140 mg (80% of th.) of the title compound.

LC-MS (method 2): R_t = 0.54 min; MS (ESIpos): m/z = 482 $(M+H)^+$

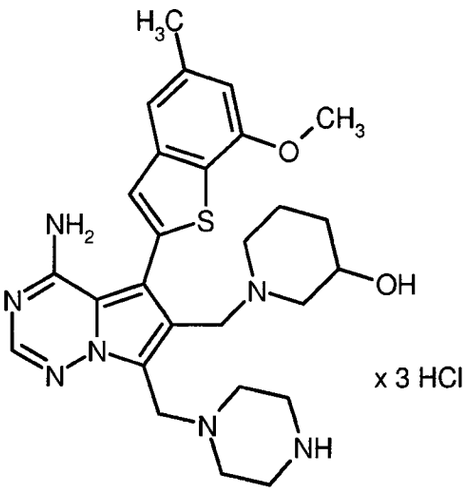
^{1}H-NMR (400 MHz, D_2O): δ = 8.15 (s, 1H), 7.56 (s, 1H), 7.45 (s, 1H), 7.00 (s, 1H), 4.47 (s, 2H), 4.37 (s, 2H), 4.04 (s, 3H), 3.79-3.71 (m, 2H), 3.42-3.34 (m, 4H), 3.19-3.12 (m, 2H), 3.06-2.97 (m, 4H), 2.51 (s, 3H) ppm.

General Procedure for reductive amination reactions with Intermediate 25A (GP1):

A 0.1 M solution of Intermediate 25A in THF was treated with 5 eq. of the respective amine component, 5 eq. of sodium triacetoxyborohydride and 2 eq. of acetic acid. The resulting mixture was stirred at 60°C for 2 h and then evaporated. A 0.15 M solution of the residue thus obtained in a 4 M solution of hydrogen chloride in 1,4-dioxane was stirred at rt for 1-2 h. After evaporation, the residue was purified as described below.

Example 40

rac-1-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methyl}piperidin-3-ol trihydrochloride



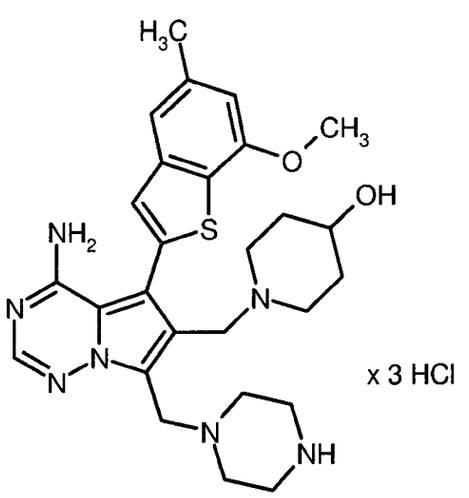
According to GP1, Intermediate 25A (150 mg, 279 µmol) was reacted with 3-hydroxypiperidine (141 mg, 1.39 mmol). Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA) and lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 178 mg (quant.) of the title compound.

LC-MS (method 2): R_t = 0.54 min; MS (ESIpos): m/z = 522 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.16 (s, 1H), 7.55 (s, 1H), 7.45 (s, 1H), 7.01 (s, 1H), 4.66-4.16 (m, 5H), 4.04 (s, 3H), 3.55-2.71 (m, 11H), 2.51 (s, 3H), 1.96-1.42 (m, 4H), 1.64-1.50 (m, 1H) ppm.

Example 41

1-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methyl}piperidin-4-ol trihydrochloride



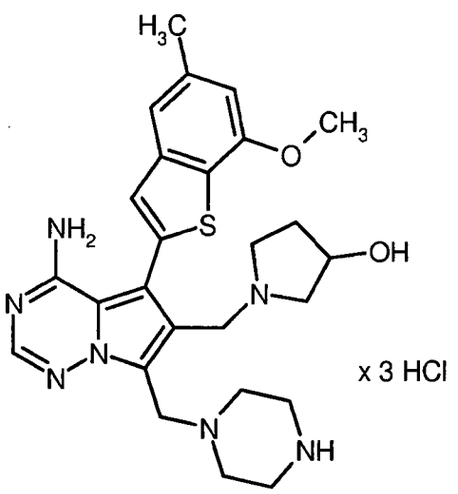
According to GP1, Intermediate 25A (150 mg, 279 µmol) was reacted with 4-hydroxypiperidine (141 mg, 1.39 mmol). Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA) and lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 162 mg (91% of th.) of the title compound.

LC-MS (method 4): R_t = 0.48 min; MS (ESIpos): m/z = 522 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.16 (s, 1H), 7.58 (br. s, 1H), 7.46 (s, 1H), 7.01 (s, 1H), 4.67-4.48 (m, 4H), 4.04 (s, 4H), 3.59-2.78 (m, 12H), 2.51 (s, 3H), 2.14-1.38 (m, 4H) ppm.

Example 42

rac-1-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methyl}pyrrolidin-3-ol trihydrochloride



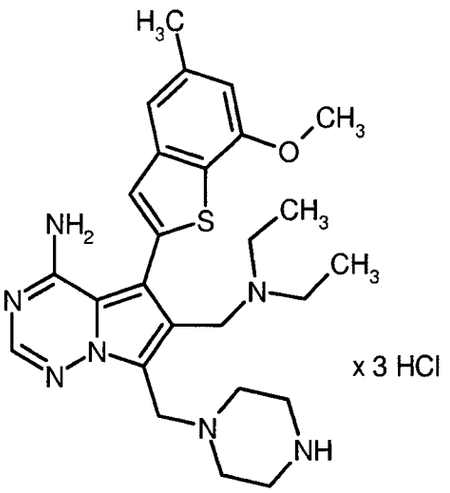
According to GP1, Intermediate 25A (150 mg, 279 µmol) was reacted with 3-hydroxypyrrolidine (113 µl, 1.39 mmol). Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA) and lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 148 mg (85% of th.) of the title compound.

LC-MS (method 4): R_t = 0.46 min; MS (ESIpos): m/z = 508 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.18 (s, 1H), 7.58 (s, 1H), 7.46 (s, 1H), 7.01 (s, 1H), 4.71-4.30 (m, 5H), 4.04 (s, 3H), 3.70-2.95 (m, 12H), 2.51 (s, 3H), 2.32-2.14 (m, 1H), 2.03-1.87 (m, 1H) ppm.

Example 43

6-[(Diethylamino)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride



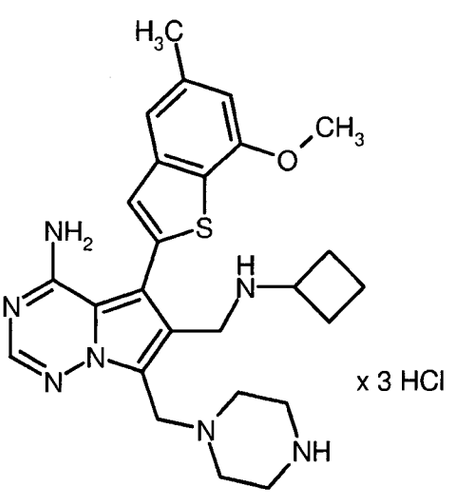
According to GP1, Intermediate 25A (150 mg, 279 µmol) was reacted with diethylamine (144 µl, 1.39 mmol). Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/ 0.1% aq. TFA) and lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 127 mg (69% of th.) of the title compound.

LC-MS (method 2): R_t = 0.55 min; MS (ESIpos): m/z = 494 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.19 (s, 1H), 7.61 (s, 1H), 7.47 (s, 1H), 7.01 (s, 1H), 4.59 (s, 2H), 4.51 (s, 2H), 4.04 (s, 3H), 3.47-3.35 (m, 4H), 3.29-3.00 (m, 8H), 2.51 (s, 3H), 1.07 (t, 6H) ppm.

Example 44

6-[(Cyclobutylamino)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride



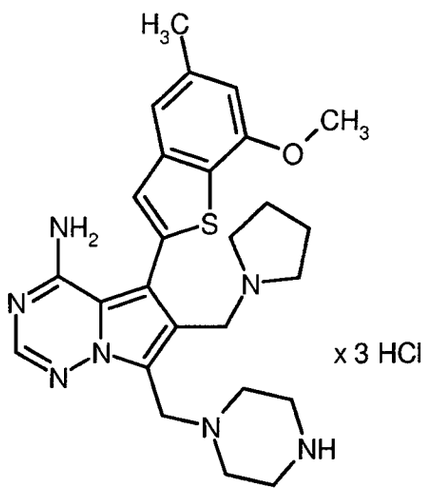
According to GP1, Intermediate 25A (150 mg, 279 µmol) was reacted with cyclobutylamine (119 µl, 1.39 mmol). Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA) and lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 127 mg (72% of th.) of the title compound.

LC-MS (method 2): R_t = 0.58 min; MS (ESIpos): m/z = 492 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.16 (s, 1H), 7.59 (s, 1H), 7.47 (s, 1H), 7.00 (s, 1H), 4.40 (s, 2H), 4.37 (s, 2H), 4.04 (s, 3H), 3.69-3.58 (m, 1H), 3.44-3.33 (m, 4H), 3.21-3.12 (m, 4H), 2.51 (s, 3H), 2.02-1.87 (m, 4H), 1.81-1.62 (m, 2H) ppm.

Example 45

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)-6-(pyrrolidin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride



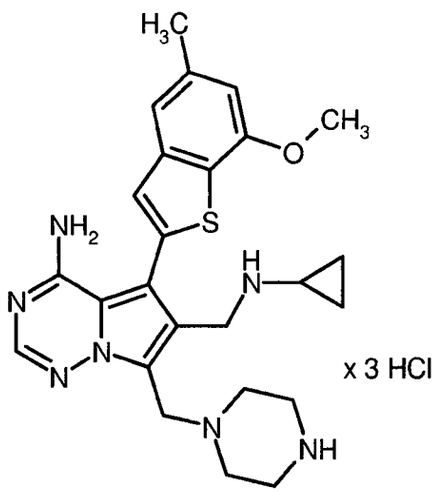
According to GP1, Intermediate 25A (150 mg, 279 µmol) was reacted with pyrrolidine (116 µl, 1.39 mmol). Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA) and lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 112 mg (64% of th.) of the title compound.

LC-MS (method 2): R_t = 0.54 min; MS (ESIpos): m/z = 492 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.19 (s, 1H), 7.60 (s, 1H), 7.46 (s, 1H), 7.01 (s, 1H), 4.70-4.61 (m, 4H), 4.04 (s, 3H), 3.55-3.40 (m, 6H), 3.35-3.26 (m, 4H), 3.02-2.87 (m, 2H), 2.51 (s, 3H), 1.97-1.83 (m, 4H) ppm.

Example 46

6-[(Cyclopropylamino)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride



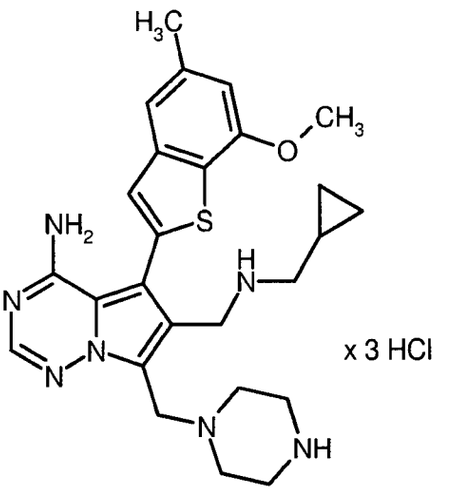
According to GP1, Intermediate 25A (200 mg, 372 µmol) was reacted with cyclopropylamine (129 µl, 1.86 mmol). Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA) and lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 140 mg (62% of th.) of the title compound.

LC-MS (method 5): R_t = 1.42 min; MS (ESIpos): m/z = 478 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.16 (s, 1H), 7.56 (s, 1H), 7.46 (s, 1H), 7.01 (s, 1H), 4.57 (s, 2H), 4.47 (s, 2H), 4.04 (s, 3H), 3.46-3.34 (m, 4H), 3.19-3.07 (m, 4H), 2.61-2.54 (m, 1H), 2.51 (s, 3H), 0.75-0.64 (m, 4H) ppm.

Example 47

6-{[(Cyclopropylmethyl)amino]methyl}-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride



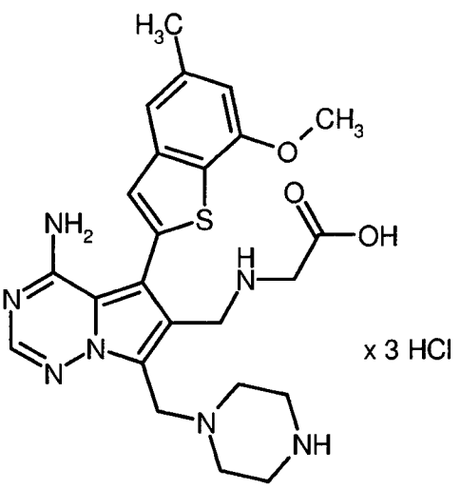
According to GP1, Intermediate 25A (200 mg, 372 µmol) was reacted with cyclopropylmethylamine (161 µl, 1.86 mmol). Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA) and lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 163 mg (69% of th.) of the title compound.

LC-MS (method 2): R_t = 0.60 min; MS (ESIpos): m/z = 492 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.14 (s, 1H), 7.57 (s, 1H), 7.45 (s, 1H), 7.00 (s, 1H), 4.50 (s, 2H), 4.44 (s, 2H), 4.04 (s, 3H), 3.42-3.34 (m, 4H), 3.16-3.07 (m, 4H), 2.86 (d, 2H), 2.50 (s, 3H), 0.89-0.76 (m, 1H), 0.55-0.45 (m, 2H), 0.23-0.14 (m, 2H) ppm.

Example 48

N-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methyl}glycine trihydrochloride



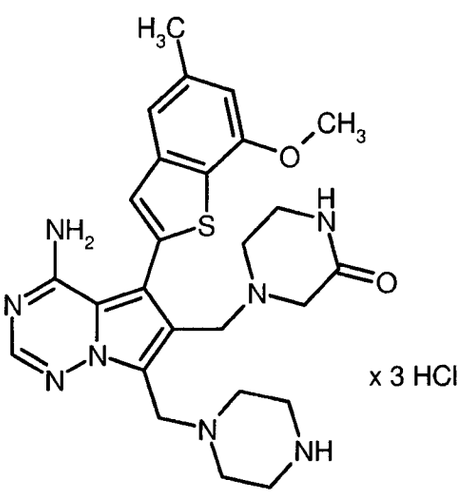
A solution of Intermediate 25A (161 mg, 300 µmol) in THF (3.2 ml) was treated with 2-amino-acetic acid (112 mg, 1.5 mmol), sodium triacetoxyborohydride (317 mg, 1.5 mmol) and acetic acid (34 µl, 600 µmol). The resulting mixture was stirred at 60°C for 2 h and then evaporated. The residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). The product thus obtained was dissolved in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) and stirred at rt for 1 h. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). Subsequent lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 18 mg (9% of th.) of the title compound.

LC-MS (method 2): R_t = 0.63 min; MS (ESIpos): m/z = 496 $(M+H)^+$

^{1}H-NMR (400 MHz, D_2O): δ = 8.14 (s, 1H), 7.54 (s, 1H), 7.45 (s, 1H), 6.99 (s, 1H), 4.42 (s, 2H), 4.36 (s, 2H), 4.03 (s, 3H), 3.64 (s, 2H), 3.42-3.33 (m, 4H), 3.07-2.96 (m, 4H), 2.50 (s, 3H) ppm.

Example 49

4-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one trihydrochloride

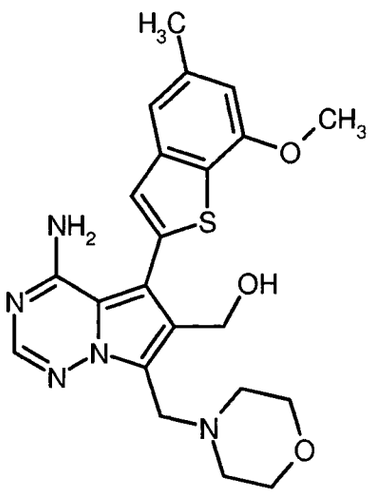


A solution of Intermediate 27A (220 mg, 354 µmol) in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) was stirred at rt for 2 h. Then, the mixture was evaporated leaving 235 mg of the crude product which was used in the next step without further purification.

LC-MS (method 4): R_t = 0.60 min; MS (ESIpos): m/z = 521 $(M+H)^+$.

Example 50

[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methanol



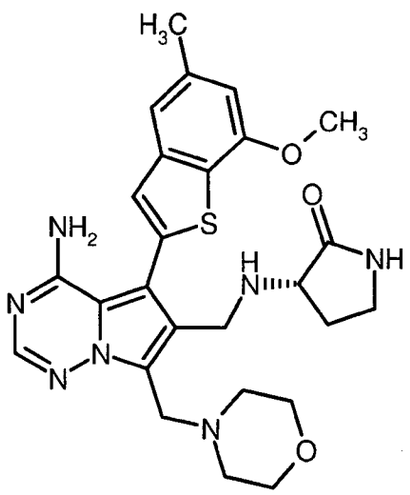
A solution of Intermediate 20A (500 mg, purity 87%, 1.28 mmol) and 4-methylenemorpholin-4-ium chloride (347 mg, 2.56 mmol) in DMF (28 ml) was stirred at 70°C for 1.5 h. The mixture was diluted with ethyl acetate and washed with sat. aq. sodium hydrogencarbonate solution and sat. aq. sodium chloride solution. The organic layer was dried with magnesium sulfate and evaporated under reduced pressure yielding 710 mg (purity 78%, 99% of th.) of the title compound.

LC-MS (method 2): R_t = 0.65 min; MS (ESIpos): m/z = 440 $(M+H)^+$.

Example 51

(*3S*)-3-({[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)pyrrolidin-2-one

BHC 11 1 045



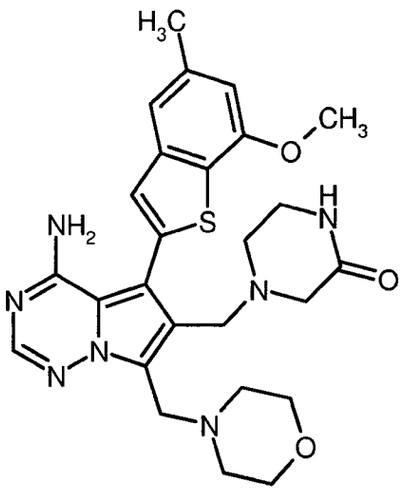
A solution of Intermediate 33A (65 mg, 149 µmol) in methanol (2 ml) was treated with (*3S*)-3-aminopyrrolidin-2-one (45 mg, 446 µmol), sodium cyanoborohydride (47 mg, 743 µmol) and acetic acid (26 µl, 446 µmol). After stirring at 60°C for 16 h, the resulting mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 20-40% acetonitrile/0.2% aq. TFA). The product thus obtained was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated yielding 49 mg (63% of th.) of the title compound.

LC-MS (method 2): R_t = 0.71 min; MS (ESIpos): m/z = 522 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.96 (s, 1H), 7.66 (s, 1H), 7.5-8.1 (br. s, 1H), 7.44 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 5.4-6.0 (br. s, 1H), 3.95 (s, 3H), 3.91 (s, 2H), 3.75 (d, 2H), 3.50-3.66 (m, 4H), 3.06-3.19 (m, 3H), 2.94-3.05 (m, 1H), 2.61 (t, 1H), 2.45 (t, 3H), 2.38-2.44 (m, 4H), 1.89-1.99 (m, 1H), 1.49-1.60 (m, 1H) ppm.

Example 52

4-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one



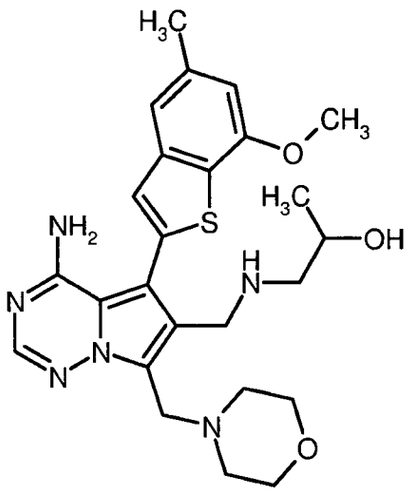
A solution of Intermediate 33A (65 mg, 149 µmol) in methanol (2 ml) was treated with 2-oxopiperazine (45 mg, 446 µmol), sodium cyanoborohydride (47 mg, 743 µmol) and acetic acid (26 µl, 446 µmol). After stirring at 60°C for 16 h, the resulting mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 20-40% acetonitrile/0.2% aq. TFA). The product thus obtained was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated yielding 41 mg (53% of th.) of the title compound.

LC-MS (method 2): R_t = 0.70 min; MS (ESIpos): m/z = 522 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.97 (s, 1H), 7.67 (br. s, 1H), 7.55-8.05 (br. s, 1H), 7.38 (s, 1H), 7.30 (s, 1H), 6.84 (s, 1H), 5.29-5.88 (br. s, 1H), 3.95 (s, 3H), 3.92 (s, 2H), 3.58 (s, 2H), 3.51-3.56 (m, 4H), 3.00-3.06 (m, 2H), 2.85 (s, 2H), 2.45 (s, 3H), 2.43-2.48 (m, 5H) ppm.

Example 53

rac-1-({[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)propan-2-ol



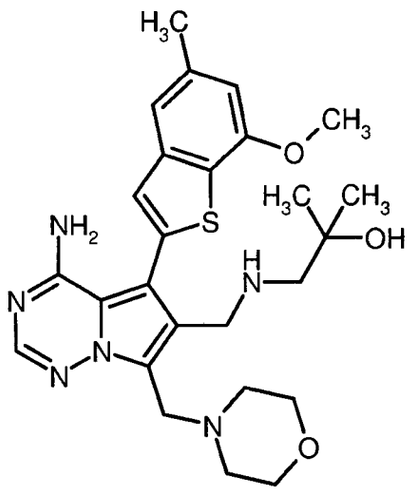
A solution of Intermediate 33A (64 mg, 146 µmol) in methanol (2 ml) was treated with *rac*-1-aminopropan-2-ol (33 mg, 439 µmol), sodium cyanoborohydride (46 mg, 731 µmol) and acetic acid (25 µl, 439 µmol). After stirring at 60°C for 16 h, the resulting mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 20-40% acetonitrile/0.2% aq. TFA). The product thus obtained was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated yielding 42 mg (57% of th.) of the title compound.

LC-MS (method 5): R_t = 1.63 min; MS (ESIpos): m/z = 497 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.96 (s, 1H), 7.47-7.92 (br. s, 1H), 7.39 (s, 1H), 7.30 (s, 1H), 6.84 (s, 1H), 5.36-5.92 (br. s, 1H), 4.36 (d, 1H), 3.95 (s, 3H), 3.90 (s, 2H), 3.64-3.75 (m, 2H), 3.49-3.61 (m, 5H), 2.45 (s, 3H), 2.39-2.47 (m, 4H), 2.31-2.38 (m, 2H), 0.97 (d, 3H) ppm.

Example 54

1-({[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(morpholin-4-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methyl}amino)-2-methylpropan-2-ol



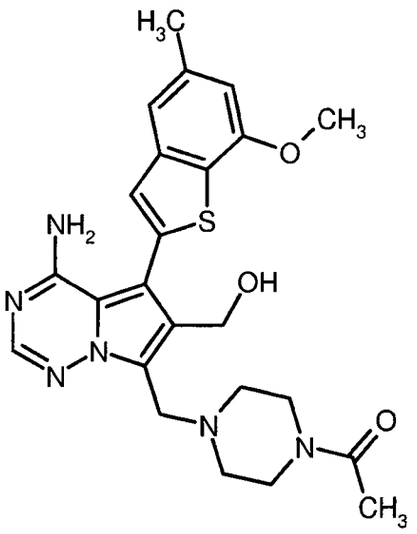
A solution of Intermediate 33A (80 mg, 183 µmol) in methanol (2 ml) was treated with 1-amino-2-methylpropan-2-ol (34 mg, 274 µmol), sodium cyanoborohydride (57 mg, 914 µmol) and acetic acid (21 µl, 366 µmol). After stirring at 60°C for 16 h, the resulting mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 20-40% acetonitrile/0.2% aq. TFA). The product thus obtained was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated yielding 29 mg (31% of th.) of the title compound.

LC-MS (method 2): R_t = 0.65 min; MS (ESIpos): m/z = 511 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.96 (s, 1H), 7.50-8.02 (br. s, 1H), 7.42 (s, 1H), 7.28 (s, 1H), 6.84 (s, 1H), 5.4-6.0 (br. s, 1H), 4.11 (s, 1H), 3.95 (s, 3H), 3.90 (s, 2H), 3.70 (d, 2H), 3.51-3.58 (m, 4H), 2.45 (s, 3H), 2.39-2.46 (m, 4H), 2.33 (d, 2H), 1.83-1.92 (m, 1H), 1.03 (s, 6H) ppm.

Example 55

1-(4-{[4-Amino-6-(hydroxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}piperazin-1-yl)ethanone

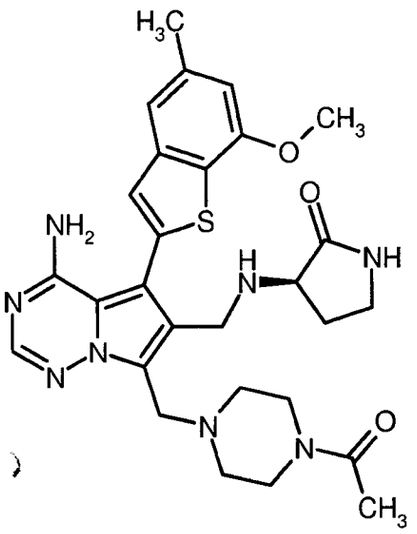


A solution of Intermediate 20A (345 mg, 1.01 mmol) in acetic acid (5 ml) was treated with 37% aq. formaldehyde solution (91 µl, 1.22 mmol) and 1-acetylpiperazine (160 mg, 1.22 mmol). The mixture was stirred at 60°C for 6 h and then evaporated. The residue was dissolved in a mixture of THF/1 M aq. lithium hydroxide solution (1:1, 10 ml) and stirred at rt for 2 h. The mixture was then combined with the reaction mixture of a 100 mg test run, and sat. aq. ammonium chloride solution was added. The mixture was extracted with ethyl acetate, and the organic phase was washed with sat. aq. sodium chloride solution, dried over magnesium sulfate and evaporated under reduced pressure yielding 678 mg (purity 87%, 94% of th.) of the title compound.

LC-MS (method 2): R_t = 0.71 min; MS (ESIpos): m/z = 481 $(M+H)^+$.

Example 56

(*3R*)-3-[({7-[(4-Acetylpiperazin-1-yl)methyl]-4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl}methyl)amino]pyrrolidin-2-one



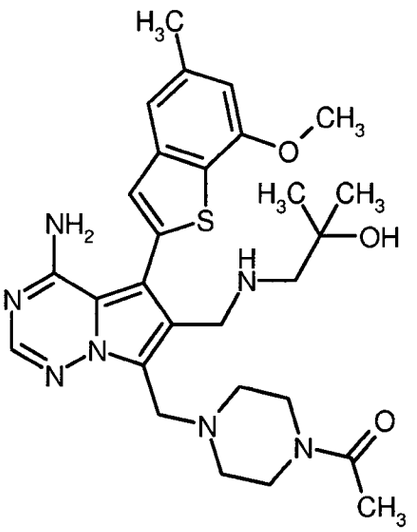
A solution of Intermediate 31A (80 mg, 167 µmol) in methanol (1.4 ml) was treated with (*3R*)-3-aminopyrrolidin-2-one (21 mg, 251 µmol), sodium cyanoborohydride (52 mg, 836 µmol) and acetic acid (19 µl, 334 µmol). After stirring at 60°C for 16 h, the resulting mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 20-40% acetonitrile/0.2% aq. TFA). The product thus obtained was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated yielding 46 mg (49% of th.) of the title compound.

LC-MS (method 2): R_t = 0.70 min; MS (ESIpos): m/z = 563 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.42 (s, 1H), 8.05 (s, 1H), 7.93-8.24 (br. s, 1H), 7.51 (s, 1H), 7.34 (s, 1H), 6.88 (s, 1H), 5.75-6.07 (br. s, 1H), 4.21-4.37 (m, 2H), 4.19 (s, 2H), 4.10 (t, 1H), 3.96 (s, 3H), 3.56-3.66 (m, 2H), 3.44-3.54 (m, 4H), 3.11-3.27 (m, 4H), 2.47 (s, 4H), 2.16-2.25 (m, 1H), 2.00 (s, 3H), 1.86-1.95 (m, 1H) ppm.

Example 57

1-(4-{[4-Amino-6-{[(2-hydroxy-2-methylpropyl)amino]methyl}-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-1-yl)ethanone



A solution of Intermediate 31A (80 mg, 183 µmol) in methanol (2 ml) was treated with 1-amino-2-methylpropan-2-ol (31 mg, 251 µmol), sodium cyanoborohydride (53 mg, 836 µmol) and acetic acid (19 µl, 334 µmol). After stirring at 60°C for 16 h, the resulting mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 20-40% acetonitrile/0.2% aq. TFA). The product thus obtained was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated yielding 29 mg (31% of th.) of the title compound.

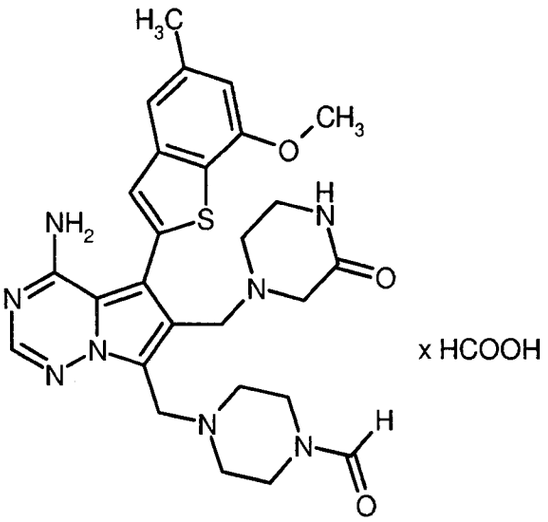
LC-MS (method 2): R_t = 0.71 min; MS (ESIpos): m/z = 552 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.96 (s, 1H), 7.59-8.02 (br. s, 1H), 7.42 (s, 1H), 7.28 (s, 1H), 6.84 (s, 1H), 5.45-5.93 (br. s, 1H), 4.13 (br. s, 1H), 3.95 (s, 3H), 3.93 (s, 2H), 3.71 (s, 2H), 3.37-3.44 (m, 4H), 2.45 (s, 3H), 2.32-2.43 (m, 6H), 1.97 (s, 3H), 1.03 (s, 6H) ppm.

Example 58

4-({4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-6-[(3-oxopiperazin-1-yl)methyl]-pyrrolo[2,1-f][1,2,4]triazin-7-yl}methyl)piperazine-1-carbaldehyde formiate

BHC 11 1 045



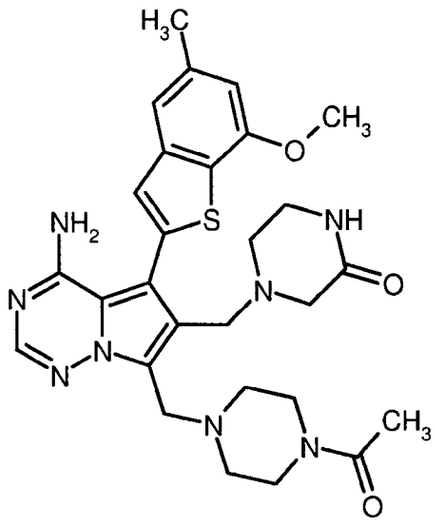
Acetic acid anhydride (498 µl, 5.17 mmol) and formic acid (237 µl, 6.28 mmol) were stirred first 2 h at 50°C and then overnight at rt. Subsequently, the mixture was diluted with dichloromethane (5.1 ml), and 1.16 ml of this solution were added to a solution of Example 49 (233 mg, 370 µmol) in pyridine (89 µl). After stirring at rt for 2 h, the mixture was diluted with methanol and then evaporated. The residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) affording 77 mg (35% of th.) of title compound.

LC-MS (method 4): R_t = 0.62 min; MS (ESIpos): m/z = 549 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.14 (s, 1H), 7.97 (s, 2H), 7.67 (s, 1H), 7.38 (s, 1H), 7.30 (s, 1H), 6.84 (s, 1H), 3.96 (s, 2H), 3.95 (s, 3H), 3.58 (s, 2H), 3.04 (br. t, 2H), 2.86 (s, 2H), 2.45 (s, 3H), 2.42 (br. t, 2H) ppm.

Example 59

4-({7-[(4-Acetylpiperazin-1-yl)methyl]-4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-pyrrolo[2,1-f][1,2,4]triazin-6-yl}methyl)piperazin-2-one



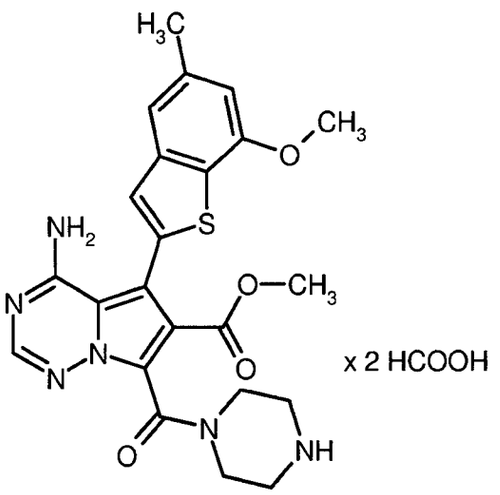
A suspension of Example 49 (310 mg, 522 µmol) in dichloromethane/THF (2.5:1, 9.64 ml) was treated with sodium carbonate (442 mg, 4.17 mmol) and stirred at rt for 30 min. Acetyl chloride (74 µl, 1.04 mmmol) was added, and the resulting mixture was stirred at rt for 2 h. After quenching with methanol, the mixture was evaporated, and the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) affording 133 mg (45% of th.) of the title compound.

LC-MS (method 2): R_t = 0.69 min; MS (ESIpos): m/z = 563 $(M+H)^+$

^{1}H-NMR (400 MHz, methanol-d_4): δ = 7.89 (s, 1H), 7.30 (s, 1H), 7.28 (s, 1H), 6.79 (s, 1H), 4.13 (s, 2H), 3.98 (s, 3H), 3.74 (s, 2H), 3.59 (t, 2H), 3.54 (t, 2H), 3.18 (t, 2H), 3.02 (s, 2H), 2.68-2.55 (m, 6H), 2.48 (s, 3H), 2.08 (s, 3H) ppm.

Example 60

Methyl 4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylcarbonyl)pyrrolo-[2,1-f][1,2,4]triazine-6-carboxylate bis(formiate)



To a solution of Intermediate 28A (15 mg, 26 µmol) in a THF/methanol mixture (5:1, 180 µl), cooled to 0°C, was added (trimethylsilyl)diazomethane (2 M solution in hexane, 15 µl, 32 µmol). The resulting mixture was slowly warmed to rt over 30 min and then evaporated. The residue was dissolved in a 4 M solution of hydrogen chloride in 1,4-dioxane (0.5 ml) and stirred at rt for 1 h. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) affording 4.8 mg (35% of th.) of the title compound.

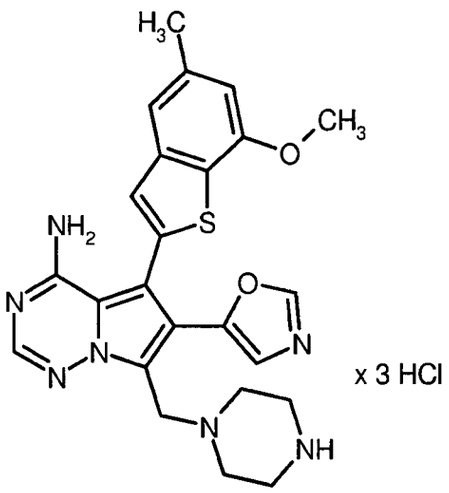
LC-MS (method 2): R_t = 0.66 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.17 (s, 2H), 8.38-8.23 (br. s, 1H), 8.04 (s, 1H), 7.43 (s, 1H), 7.31 (s, 1H), 6.86 (s, 1H), 5.71-5.58 (br. s, 1H), 3.96 (s, 3H), 3.60 (s, 3H, overlap with water peak), 2.46 (s, 3H) ppm.

Example 61

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-6-(1,3-oxazol-5-yl)-7-(piperazin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-amine trihydrochloride

BHC 11 1 045



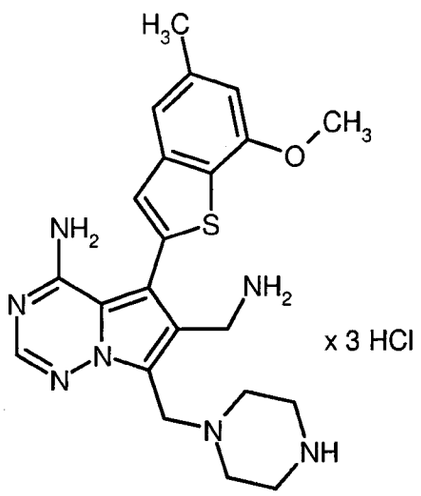
A solution of Intermediate 25A (100 mg, 0.19 mmol) in methanol (3.33 ml) was treated with (4-toluenesulfonyl)methylisocyanide (36 mg, 0.19 mmol) and potassium carbonate (25 mg, 186 µmol). The mixture was refluxed for 6 h. It was then combined with the reactions mixtures from three 30 mg test runs and evaporated. The residue was dissolved in a 4 M solution of hydrogen chloride in 1,4-dioxane (10 ml) and stirred at rt for 2 h. After evaporation, the residue was purified by two-fold preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). Further purification by column chromatography on silica gel (dichloromethane/methanol 5:1 with 0.5% aq. ammonia) and lyophilization from a 4 M solution of hydrogen chloride in 1,4-dioxane afforded 75 mg (34% of th.) of the title compound.

LC-MS (method 4): R_t = 0.69 min; MS (ESIpos): m/z = 476 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.40 (s, 1H), 8.20 (s, 1H), 7.46 (s, 1H), 7.35 (s, 1H), 6.96 (s, 1H), 6.89 (s, 1H), 3.95 (s, 3H), 2.46 (s, 3H) ppm.

Example 62

6-(Aminomethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-4-amine trihydrochloride



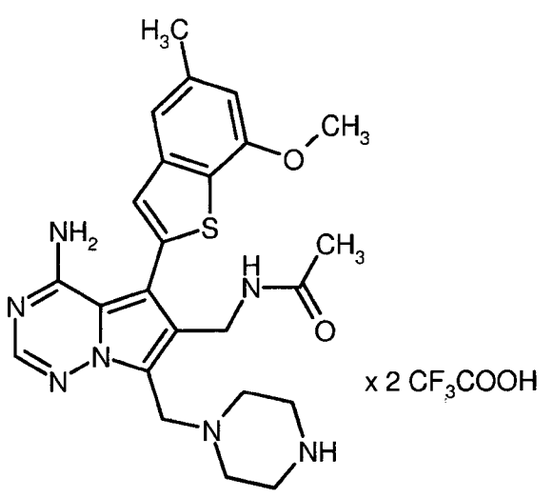
A suspension of Intermediate 29A (76 mg, 134 µmol) and 10% Pd/C (60 mg) in a 0.5 M solution of hydrogen chloride in methanol (20 ml) was stirred at rt for 3 h under 1 atm of hydrogen. The mixture was then filtered through kieselguhr, the filtrate was evaporated, and the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). The product thus obtained was lyophilized from a 4 M solution of hydrogen chloride in 1,4-dioxane affording 34 mg (46% of th.) of the title compound.

LC-MS (method 2): R_t = 0.55 min; MS (ESIpos): m/z = 438 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.24 (br. s, 3H), 8.12 (s, 1H), 7.52 (s, 1H), 7.34 (s, 1H), 6.89 (s, 1H), 3.96 (s, 3H), 3.76-3.63 (m, 1H), 3.52-3.42 (m, 1H), 2.47 (s, 3H) ppm.

Example 63

N-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methyl}acetamide bis(trifluoroacetate)



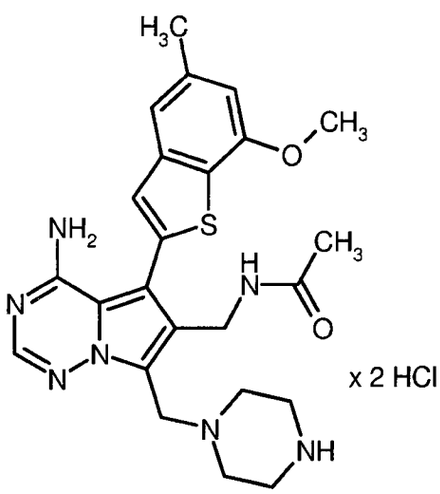
A solution of Intermediate 30A (210 mg, 362 µmol) in dichloromethane (26 ml) was treated with trifluoroacetic acid (5.2 ml) and stirred at rt for 1 h. After evaporation at rt, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA) affording 163 mg (63% of th.) of the title compound.

LC-MS (method 3): R_t = 2.42 min; MS (ESIpos): m/z = 480 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 9.00-8.75 (br. s, 1H), 8.30-8.16 (br. s, 1H), 8.08 (s, 1H), 7.38 (s, 1H), 7.33 (s, 1H), 6.87 (s, 1H), 4.32 (br. d, 2H), 3.96 (s, 3H), 3.40-2.98 (m, 8H), 2.46 (s, 3H), 1.77 (s, 3H) ppm.

Example 64

N-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methyl}acetamide dihydrochloride



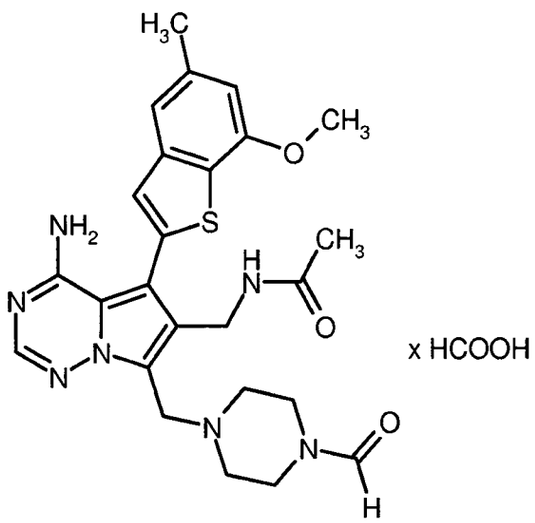
A solution of Intermediate 30A (80 mg, 0.14 mmol) in dichloromethane (10 ml) and trifluoroacetic acid (2 ml) was stirred at rt for 1 h and then evaporated. Purification by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) and lyophilization from a mixture of methanol and 4 M solution of hydrogen chloride in 1,4-dioxane afforded 39 mg (50% of th.) of the title compound.

LC-MS (method 5): R_t = 1.56 min; MS (ESIpos): m/z = 480 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 8.12 (s, 1H), 7.38 (s, 1H), 7.33 (s, 1H), 6.87 (s, 1H), 4.37 (br. d, 2H), 3.96 (s, 3H), 3.85-3.20 (m, 8H, overlap with water peak), 2.46 (s, 3H), 1.76 (s, 3H) ppm.

Example 65

N-({4-Amino-7-[(4-formylpiperazin-1-yl)methyl]-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-pyrrolo[2,1-f][1,2,4]triazin-6-yl}methyl)acetamide formiate



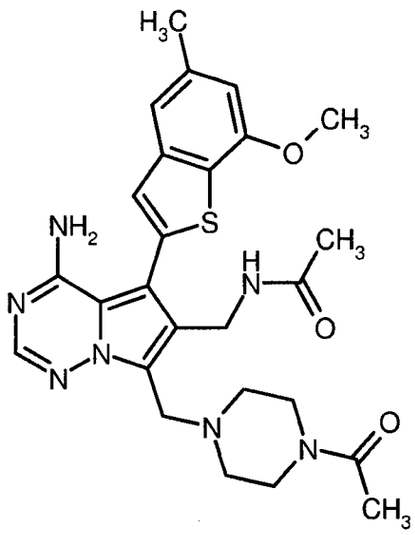
Acetic acid anhydride (304 µl, 3.16 mmol) and formic acid (145 µl, 3.16 mmol) were stirred first 2 h at 50°C and then overnight at rt. Subsequently, the mixture was diluted with dichloromethane (3.1 ml), and 663 µl of this solution were added to a solution of Example 63 (160 mg, 226 µmol) in pyridine (54 µl). The mixture was stirred at rt for 2 h, then diluted with methanol (1 ml), and stirring was continued at 40°C for another 2 h. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) affording 74 mg (61% of th.) of title compound.

LC-MS (method 4): R_t = 0.65 min; MS (ESIpos): m/z = 508 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.13 (s, 1H), 8.06-7.89 (m, 3H), 7.38 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 4.28 (d, 2H), 4.01-3.88 (m, 5H), 2.47-2.34 (m, 7H), 1.75 (s, 3H) ppm.

Example 66

N-({7-[(4-Acetylpiperazin-1-yl)methyl]-4-amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-pyrrolo[2,1-f][1,2,4]triazin-6-yl}methyl)acetamide



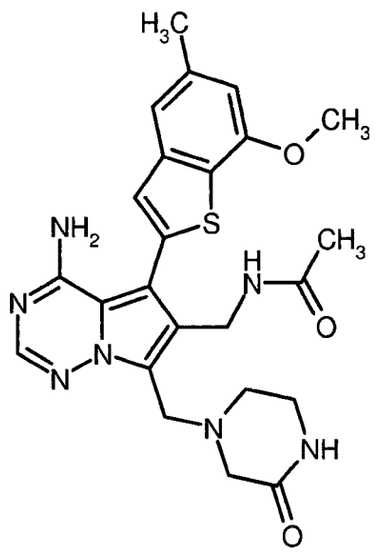
A solution of Example 63 (110 mg, 229 µmol) and acetyl chloride (32 µl, 458 µmol) in THF/dichloromethane (1:2, 3 ml) was treated with sodium carbonate (194 mg, 1.83 mmol) and stirred at rt overnight. Then, the mixture was diluted with methanol (2 ml) and water (1 ml) and stirred at rt for 1 h. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid). Lyophilization from 1,4-dioxane and re-purification by column chromatography on silica gel (dichloromethane/methanol 50:1 → 100% methanol) afforded 35 mg (28% of th.) of the title compound.

LC-MS (method 2): R_t = 0.70 min; MS (ESIpos): m/z = 522 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.04-7.98 (m, 2H), 7.38 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 4.27 (d, 2H), 3.95 (s, 3H), 3.91 (s, 2H), 3.44-3.36 (m, 4H), 2.48-2.35 (m, 7H), 1.98 (s, 3H), 1.75 (s, 3H) ppm.

Example 67

N-({4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-[(3-oxopiperazin-1-yl)methyl]-pyrrolo[2,1-f][1,2,4]triazin-6-yl}methyl)acetamide



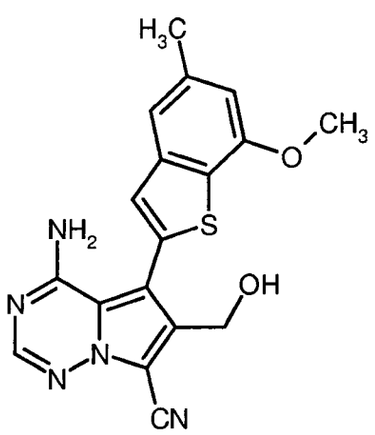
A suspension of Intermediate 32A (35 mg, 73 µmol) in methanol (4.1 ml) was treated with acetic anhydride (13 µl, 146 µmol) and 10% Pd/C (41 mg) and stirred at rt for 1 h under 1 atm of hydrogen. Filtration over kieselguhr and evaporation of the filtrate afforded 30 mg (79% of th.) of the title compound.

LC-MS (method 5): R_t = 1.65 min; MS (ESIpos): m/z = 494 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.99 (s, 2H), 7.75 (br. s, 1H), 7.39 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 4.27 (s, 1H), 4.26 (s, 1H), 3.95 (s, 5H), 3.19-3.08 (m, 2H), 3.05-2.96 (m, 2H), 2.66-2.57 (m, 2H), 2.45 (s, 3H), 1.72 (s, 3H) ppm.

Example 68

4-Amino-6-(hydroxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazine-7-carbonitrile



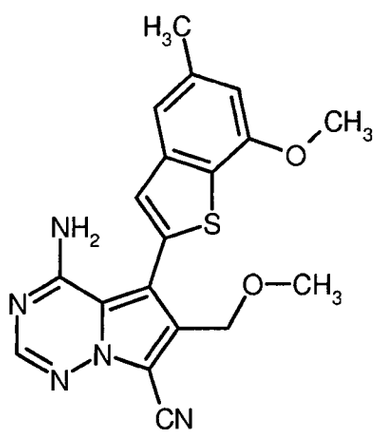
A solution of Intermediate 38A (1 g, 2.08 mmol) in THF (10 ml) was treated with a 1 M solution of tetra-*n*-butylammonium fluoride in THF (12 ml, 12 mmol). The mixture was stirred at rt overnight and then evaporated. The residue was taken up in water and extracted three times with ethyl acetate. The combined organic phases were dried over magnesium sulfate and evaporated. The residue was triturated in *tert*-butyl methyl ether, and the solid was filtered off affording 680 mg (78% of th.) of the title compound.

LC-MS (method 2): R_t = 0.95 min; MS (ESIpos): m/z = 366 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.61-8.29 (br. s, 1H), 8.18 (s, 1H), 7.43 (s, 1H), 7.32 (s, 1H), 6.87 (s, 1H), 6.32-6.03 (br. s, 1H), 5.46 (t, 1H), 4.55 (d, 2H), 3.96 (s, 3H), 2.45 (s, 3H) ppm.

Example 69

4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazine-7-carbonitrile



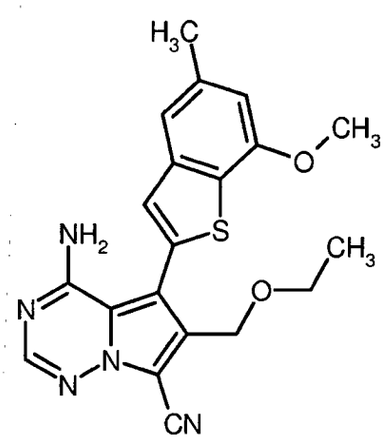
A solution of Example 68 (60 mg, 164 µmol) in dichloromethane (5 ml) was treated with thionyl chloride (18 µl, 246 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in methanol (2 ml) and treated with DIPEA (57 µl, 328 µmol). The mixture was stirred first 2 h at 60°C, then refluxed overnight and finally heated to 150°C for 30 min in a microwave device. After this, the mixture was evaporated, and the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). The product thus obtained was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated affording 18 mg (28% of th.) of the title compound.

LC-MS (method 4): R_t = 1.12 min; MS (ESIpos): m/z = 379 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.61-8.40 (br. s, 1H), 8.21 (s, 1H), 7.42 (s, 1H), 7.33 (s, 1H), 6.87 (s, 1H), 6.34-6.09 (br. s, 1H), 4.47 (s, 2H), 3.96 (s, 3H), 3.26 (s, 3H), 2.45 (s, 3H) ppm.

Example 70

4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazine-7-carbonitrile



A solution of Example 68 (60 mg, 164 µmol) in dichloromethane (5 ml) was treated with thionyl chloride (18 µl, 246 µmol). The mixture was stirred at rt for 15 min and then evaporated. The residue was dissolved in ethanol (2 ml) and treated with DIPEA (57 µl, 328 µmol). The mixture was stirred at 60°C overnight and then heated to 150°C for 30 min in a microwave device. After this, the mixture was evaporated, and the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). The product thus obtained was dissolved in ethanol (2 ml) and again heated to 150°C for 30 min in the microwave oven. DIPEA (57 µl, 328 µmol) was added, and heating to 150°C in the microwave oven was continued for further 30 min. After evaporation, the residue was purified by column chromatography on silica gel (dichloromethane/methanol 95:5) affording 16 mg (23% of th.) of the title compound.

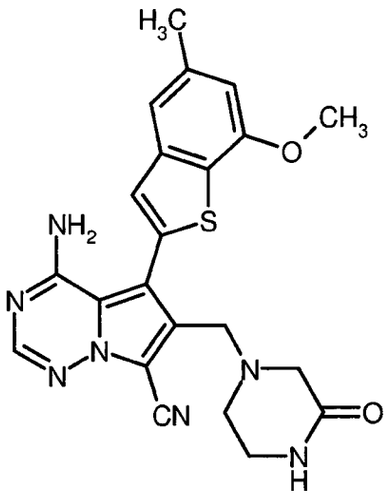
LC-MS (method 2): R_t = 1.18 min; MS (ESIpos): m/z = 393 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.61-8.38 (br. s, 1H), 8.20 (s, 1H), 7.42 (s, 1H), 7.33 (s, 1H), 6.87 (s, 1H), 6.33-6.08 (br. s, 1H), 4.51 (s, 2H), 3.96 (s, 3H), 3.45 (q, 2H), 2.45 (s, 3H), 1.10 (t, 3H) ppm.

Example 71

4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-6-[(3-oxopiperazin-1-yl)methyl]pyrrolo-[2,1-f][1,2,4]triazine-7-carbonitrile

BHC 11 1 045



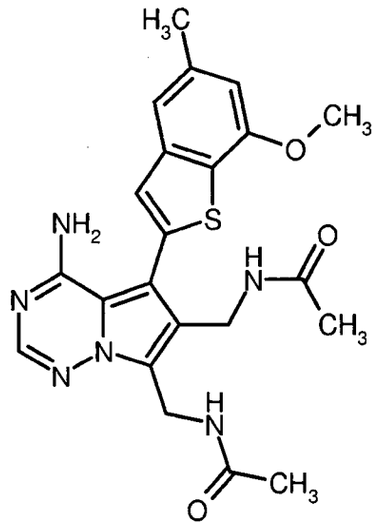
A solution of Intermediate 39A (20 mg, 55 µmol) in THF (0.73 ml) was treated with acetic acid (6 µl, 110 µmol), 2-oxopiperazine (27 mg, 275 µmol) and sodium triacetoxyborohydride (58 mg, 275 µmol). After stirring at rt for 3 h, further amounts of THF (1 ml), acetic acid (6 µl, 110 µmol), 2-oxopiperazine (27 mg, 275 µmol) and sodium triacetoxyborohydride (58 mg, 275 µmol) were added, and stirring at rt was continued overnight. After evaporation, the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). The product thus obtained was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated affording 13 mg (52% of th.) of the title compound.

LC-MS (method 2): R_t = 0.86 min; MS (ESIpos): m/z = 447 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.60-8.31 (br. s, 1H), 8.19 (s, 1H), 7.74 (s, 1H), 7.44 (s, 1H), 7.33 (s, 1H), 6.87 (s, 1H), 6.25-5.98 (br. s, 1H), 3.96 (s, 3H), 3.62 (s, 2H), 3.13-3.07 (m, 2H), 2.91 (s, 2H), 2.45 (s, 3H) ppm.

Example 72

N,N'-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazine-6,7-diyl]bis(methylene)}diacetamide



A suspension of Intermediate 40A (crude, 85 mg), 10% Pd/C (115 mg) and acetic anhydride (40 µl, 435 µmol) in methanol (12 ml) was stirred at rt under 1 atm of hydrogen. After 4 h, further amounts of 10% Pd/C (115 mg) and acetic anhydride (40 µl, 435 µmol) were added, and stirring at rt under 1 atm of hydrogen was continued for 2 h. The resulting mixture was filtered through kieselguhr, the filtrate was evaporated, and the residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. TFA). The product thus obtained was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated affording 18 mg (18% of th.) of the title compound.

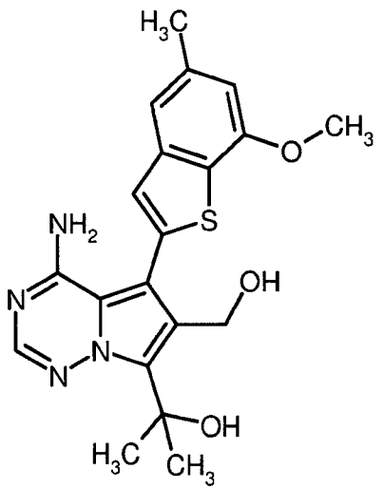
LC-MS (method 2): R_t = 0.73 min; MS (ESIpos): m/z = 452 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.29 (br. t, 1H), 8.04 (br. t, 1H), 8.00 (s, 1H), 7.34 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 4.58 (d, 2H), 4.26 (d, 2H), 3.95 (s, 3H), 2.45 (s, 3H), 1.81 (s, 3H), 1.74 (s, 3H) ppm.

Example 73

2-[4-Amino-6-(hydroxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]propan-2-ol

BHC 11 1 045



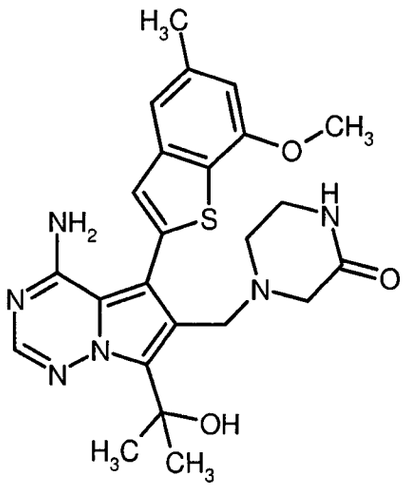
A flask containing a suspension of Intermediate 43A (180 mg, 598 µmol), Intermediate 6A (299 mg, 897 µmol) and caesium fluoride (454 mg, 2.99 mmol) in THF/water (10:1, 11 ml) was degassed under reduced pressure and then refilled with argon. 4-(Di-*tert*-butylphosphino)-*N,N*-dimethylaniline-dichloropalladium (2:1; 13 mg, 18 µmol) was added. The resulting mixture was degassed again and stirred under argon at 50°C for 16 h. After this, the reaction mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 30-50% acetonitrile/0.2% aq. TFA). The product fractions were diluted with a 7 M solution of ammonia in methanol and then concentrated under reduced pressure. The precipitate was filtered off, washed with water and dried *in vacuo* yielding 99 mg (42% of th.) of the title compound.

LC-MS (method 2): R_t = 0.89 min; MS (ESIpos): m/z = 399 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.96 (s, 1H), 7.51-8.02 (br. s, 1H), 7.37 (s, 1H), 7.31 (s, 1H), 6.86 (s, 1H), 5.99 (s, 1H), 5.23-5.82 (br. s, 1H), 5.04 (t, 1H), 4.53 (d, 2H), 3.96 (s, 3H), 2.45 (s, 3H), 1.73 (s, 6H) ppm.

Example 74

4-{[4-Amino-7-(2-hydroxypropan-2-yl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo-[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one



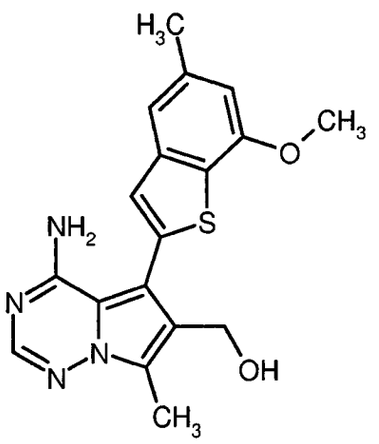
A solution of Intermediate 44A (50 mg, 73% purity, 92 µmol) in methanol (4 ml) was treated with 2-oxopiperazine (28 mg, 276 µmol), sodium cyanoborohydride (23 mg, 368 µmol) and acetic acid (21 µl, 368 µmol). The mixture was stirred first 18 h at 60°C and then 3 days at rt. After this, the mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 20-40% acetonitrile/0.2% aq. TFA). The product fractions were diluted with a 7 M solution of ammonia in methanol and evaporated under reduced pressure. The residue was dissolved in ethyl acetate and washed with water. The organic phase was dried with sodium sulfate and concentrated under reduced pressure. The residue was dissolved in 1,4-dioxane and lyophilized yielding 24 mg (52% of th.) of the title compound.

LC-MS (method 5): R_t = 1.85 min; MS (ESIpos): m/z = 481 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.99 (s, 1H), 7.73-8.01 (br. s, 1H), 7.41 (s, 1H), 7.33 (s, 1H), 6.87 (s, 1H), 5.2-5.7 (br. s, 1H), 3.95 (s, 3H), 3.57 (s, 2H), 3.14 (br. s, 2H), 2.60 (br. s, 4H), 2.46 (s, 3H), 1.70 (br. s, 6H) ppm.

Example 75

[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]methanol



Under an argon atmosphere, a flask was charged with 165 mg (0.64 mmol) of Intermediate 53A, 143 mg (0.64 mmol) of Intermediate 5A, 25 mg (0.03 mmol) (2'-aminobiphenyl-2-yl)(chloro)palladium-dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (1:1; see S.L. Buchwald *et al.*, *J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)) and 409 mg (1.93 mmol) potassium phosphate. Then, 7 ml of a degassed mixture of 1,4-dioxane and water (5:1) were added, and the solution was stirred at 70°C for 1 h. Another portion of Intermediate 5A (142 mg, 0.64 mmol) and of (2'-aminobiphenyl-2-yl)(chloro)palladium-dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (10 mg, 0.012 mmol) were added, and stirring was continued for 1 h. After this, the reaction mixture was partially evaporated under reduced pressure, water was added, and the mixture was extracted with ethyl acetate. The combined organic phases were evaporated under reduced pressure, and the residue was triturated with acetonitrile. The precipitate was filtered off and dried *in vacuo* yielding 180 mg (92% purity by LC-MS, 73% of th.) of the title compound. From the filtrate a second batch (41 mg, 18% of th.) was obtained by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid). Total yield: 91% of th.

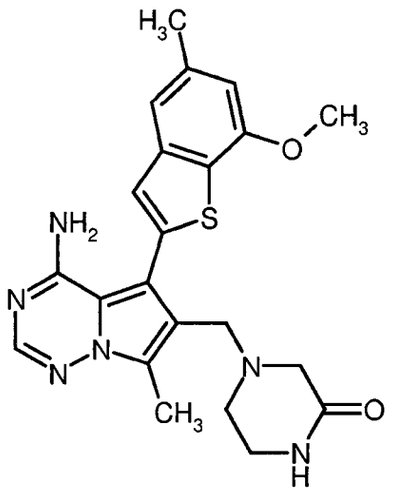
LC-MS (method 5): R_t = 1.92 min; MS (ESIpos): m/z = 355 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.95 (s, 1H), 7.35 (s, 1H), 7.30 (s, 1H), 6.83 (s, 1H), 4.82 (t, 1H), 4.44 (d, 2H), 3.95 (s, 3H), 2.45 (s, 3H) ppm.

Example 76

4-{[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one

BHC 11 1 045



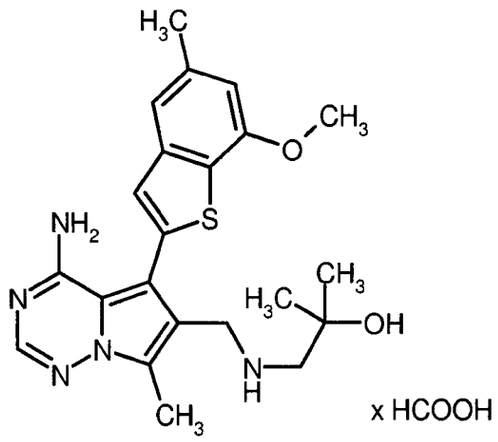
A suspension of 55 mg (0.16 mmol) of Intermediate 54A in THF (1.5 ml) was treated with 78 mg (0.78 mmol) piperazin-2-one, 18 µl (0.31 mmol) acetic acid and 166 mg (0.78 mmol) triacetoxyborohydride. The mixture was stirred at ambient temperature overnight. Then, 1.5 ml water were added, and most of the THF solvent was evaporated under reduced pressure. The remaining mixture was diluted with more water, and the precipitated solid was filtered off and dried (35 mg). This material was further purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid). The product fractions were adjusted to pH 9 with solid potassium carbonate and partially concentrated under reduced pressure. The precipitated solid was filtered off and dried at 45°C *in vacuo* to afford 16 mg (24% of th.) of the title compound.

LC-MS (method 5): R_t = 1.74 min; MS (ESIpos): m/z = 437 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.95 (s, 1H), 7.66 (br. s, 1H), 7.35 (s, 1H), 7.30 (s, 1H), 6.83 (s, 1H), 3.95 (s, 3H), 3.50 (s, 2H), 3.05 (m, 2H), 2.84 (s, 2H), 2.45 (m, 5H) ppm.

Example 77

1-({[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)-2-methylpropan-2-ol formiate



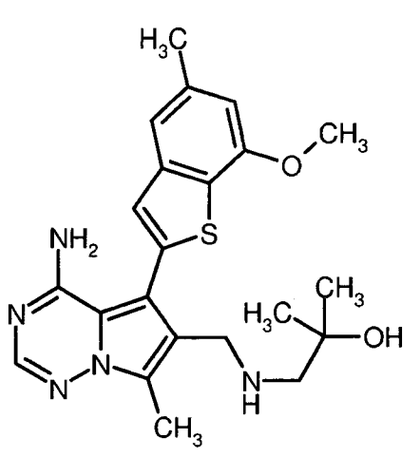
A suspension of 55 mg (0.16 mmol) of Intermediate 54A in THF (1.5 ml) was treated with 98 mg (0.78 mmol) 1-amino-2-methylpropan-2-ol hydrochloride, 39 mg (0.47 mmol) sodium acetate and 166 mg (0.78 mmol) sodium triacetoxyborohydride. The mixture was stirred at ambient temperature overnight. Then, 1.5 ml water were added, and the mixture was evaporated under reduced pressure. The residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) to afford 38 mg (52% of th.) of the title compound.

LC-MS (method 5): R_t = 1.68 min; MS (ESIpos): m/z = 426 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.19 (s, 1H), 7.94 (s, 1H), 7.38 (s, 1H), 7.29 (s, 1H), 6.84 (s, 1H), 3.95 (s, 3H), 2.45 (s, 3H), 2.34 (s, 2H), 1.02 (s, 6H) ppm.

Example 78

1-({[4-Amino-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)-2-methylpropan-2-ol



A solution of 29 mg (0.06 mmol) of Example 77 in 3 ml of methanol was run through a Stratospheres SPE PL-HCO_3 MP-resin cartridge, preconditioned with 2 ml of methanol. The cartridge

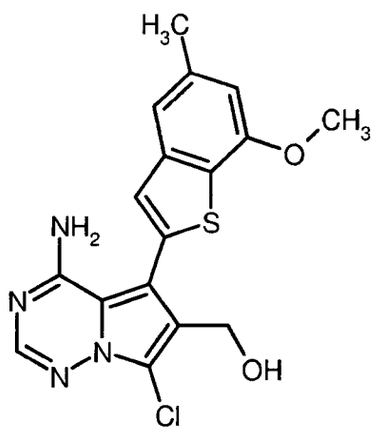
was washed with 4 ml of methanol, and the eluate was evaporated to afford 21.5 mg (82% of th.) of the title compound.

LC-MS (method 4): R_t = 0.68 min; MS (ESIpos): m/z = 426 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.94 (s, 1H), 7.37 (s, 1H), 7.28 (s, 1H), 6.83 (s, 1H), 4.07 (s, 1H), 3.95 (s, 3H), 3.63-3.75 (m, 2H), 2.45 (s, 3H), 2.32 (m, 3H), 1.42-1.56 (m, 1H), 1.02 (s, 6H) ppm.

Example 79

[4-Amino-7-chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methanol



A solution of Intermediate 48A (117 mg, 0.24 mmol) in 5 ml THF was treated with 5 ml conc. hydrochloric acid and stirred at ambient temperature overnight. Then, 12 ml of 5 M aq. sodium hydroxide solution as well as ethyl acetate were added, the layers were separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic phases were washed with sat. aq. sodium chloride solution, dried and evaporated. The residue was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) to afford 30 mg (34% of th.) of the title compound.

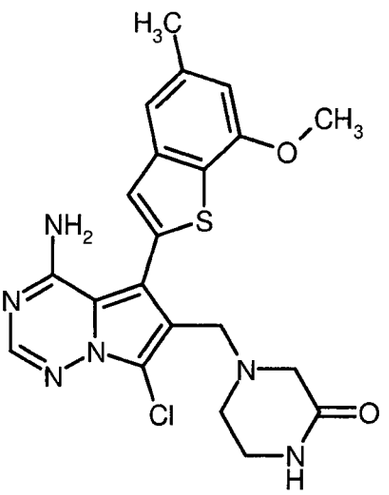
LC-MS (method 2): R_t = 0.90 min; MS (ESIpos): m/z = 375 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.04 (s, 1H), 7.43 (s, 1H), 7.32 (s, 1H), 6.85 (s, 1H), 5.02 (t, 1H), 4.43 (d, 2H), 3.96 (s, 3H), 2.45 (s, 3H) ppm.

9.2 mg (10% of th.) of 7-chloro-6-(chloromethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-pyrrolo[2,1-f][1,2,4]triazin-4-amine were isolated as a by-product (*cf.* Intermediate 50A).

Example 80

4-{[4-Amino-7-chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}piperazin-2-one



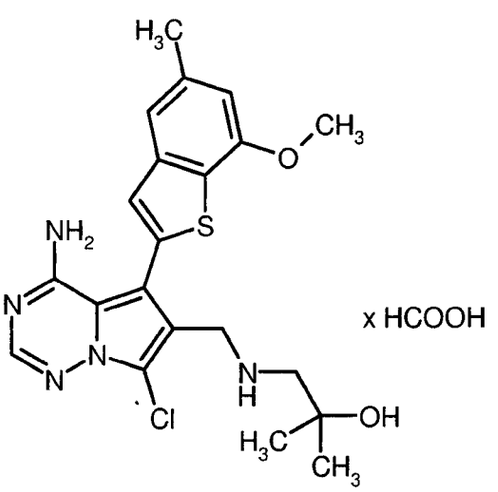
The title compound was prepared according to the procedure of Example 76 starting from 40 mg (0.11 mmol) of Intermediate 49A. Yield: 27 mg (55% of th.).

LC-MS (method 2): R_t = 0.86 min; MS (ESIpos): m/z = 457 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.05 (s, 1H), 7.68 (br. s, 1H), 7.44 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 3.96 (s, 3H), 3.52 (s, 2H), 3.05 (br. s, 2H), 2.86 (s, 2H), 2.45 (s, 3H) ppm.

Example 81

1-({[4-Amino-7-chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)-2-methylpropan-2-ol formiate



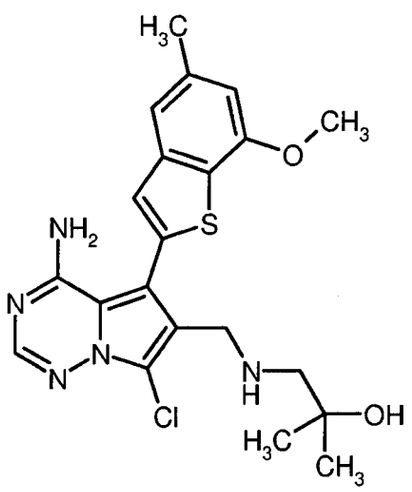
The title compound was prepared according to the procedure of Example 77 starting from 40 mg (0.11 mmol) of Intermediate 49A. Yield: 24 mg (45% of th.).

LC-MS (method 2): R_t = 0.73 min; MS (ESIpos): m/z = 446 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.15 (s, 1H), 8.04 (s, 1H), 7.45 (s, 1H), 7.30 (s, 1H), 6.85 (s, 1H), 3.96 (s, 3H), 3.73 (s, 2H), 2.45 (s, 3H), 2.32 (s, 2H), 1.00 (s, 6H) ppm.

Example 82

1-({[4-Amino-7-chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-6-yl]methyl}amino)-2-methylpropan-2-ol



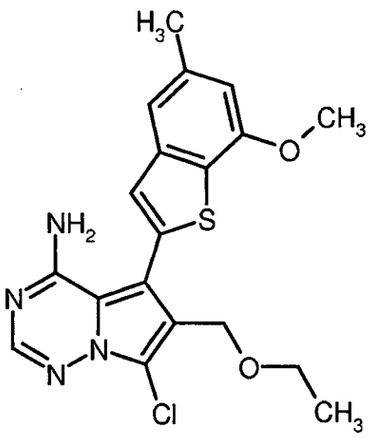
The title compound was prepared from Example 81 according to the procedure of Example 78.

LC-MS (method 2): R_t = 0.72 min; MS (ESIpos): m/z = 446 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.04 (s, 1H), 7.45 (s, 1H), 7.30 (s, 1H), 6.85 (s, 1H), 4.09 (br. s, 1H), 3.95 (s, 3H), 3.71 (s, 2H), 2.45 (s, 3H), 2.31 (s, 2H), 1.44-1.64 (m, 1H), 1.00 (s, 6H) ppm.

Example 83

7-Chloro-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-4-amine



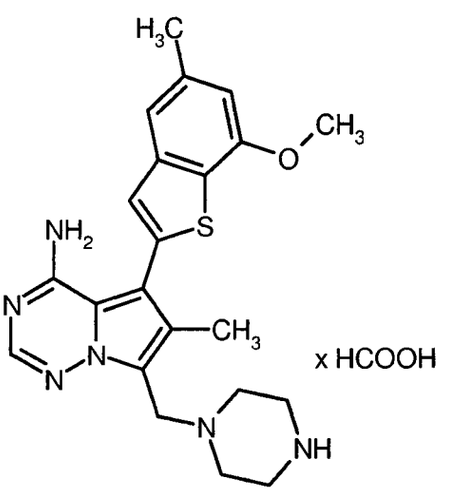
8.2 mg (0.02 mmol) of Intermediate 50A were suspended in 1 ml of ethanol, treated with 41 µl (0.11 mmol) of a 2.68 M solution of sodium ethanolate in ethanol and refluxed for 1 min. The clear solution was then evaporated, and the crude product was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) to afford 5 mg (56% of th.) of the title compound.

LC-MS (method 4): R_t = 1.25 min; MS (ESIpos): m/z = 402 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.06 (s, 1H), 7.40 (s, 1H), 7.32 (s, 1H), 6.86 (s, 1H), 4.40 (s, 2H), 3.96 (s, 3H), 3.40 (q, 2H), 2.45 (s, 3H), 1.06 (t, 3H) ppm.

Example 84

5-(7-Methoxy-5-methyl-1-benzothiophen-2-yl)-6-methyl-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f]-[1,2,4]triazin-4-amine formiate



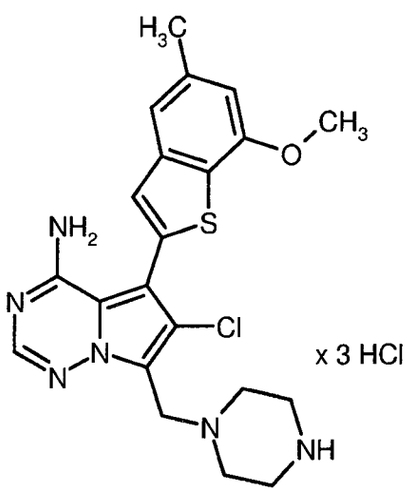
A solution of Intermediate 57A (100 mg, 191 µmol) in a 4 M solution of hydrogen chloride in 1,4-dioxane (2 ml) was stirred at rt for 3 h and then evaporated. Purification by two-fold preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. formic acid) afforded 71 mg (67% of th.) of the title compound.

LC-MS (method 2): R_t = 0.81 min; MS (ESIpos): m/z = 423 $(M+H)^+$

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.46 (br. s, 1H), 7.89 (s, 1H), 7.27 (s, 1H, overlap with $CHCl_3$ peak), 7.18 (s, 1H), 6.67 (s, 1H), 4.01 (s, 3H), 3.97 (s, 2H), 3.18-3.09 (m, 4H), 2.82-2.73 (m, 4H), 2.50 (s, 3H), 2.24 (s, 3H) ppm.

Example 85

6-Chloro-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-7-(piperazin-1-ylmethyl)pyrrolo[2,1-f]-[1,2,4]triazin-4-amine trihydrochloride



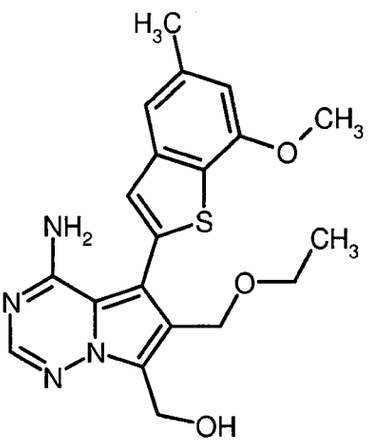
Intermediate 60A (65 mg, 0.12 mmol) was stirred in 1 ml of a 4 M solution of hydrogen chloride in 1,4-dioxane for 2 h at rt. The suspension was evaporated to dryness, and the crude product was purified by preparative RP-HPLC (Reprosil C18, gradient 10-95% acetonitrile/0.1% aq. hydrochloric acid) affording 49 mg (74% of th.) of the title compound.

LC-MS (method 2): R_t = 0.81 min; MS (ESIpos): m/z = 443 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): *inter al.* δ = 9.56 (br. s, 1H), 8.45 (br. s, 1H), 8.19 (s, 1H), 7.44 (s, 1H), 7.36 (s, 1H), 6.89 (s, 1H), 6.30 (br. s, 1H), 4.63 (br. s, 1H), 3.40 (br. s, 8H), 2.46 (s, 3H) ppm.

Example 86

[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-7-yl]methanol



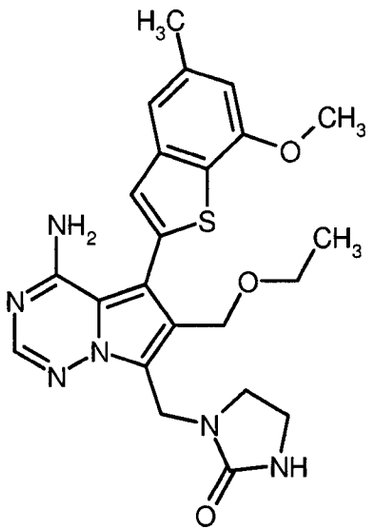
The title compound (360 mg) was obtained as a side product in the preparation of Example 5 by preparation method 1.

LC-MS (method 2): R_t = 0.99 min; MS (ESIpos): m/z = 399 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.09-7.72 (br. s, 1H), 7.99 (s, 1H), 7.35 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 6.05-5.48 (br. s, 1H), 5.04 (br. s, 1H), 4.81 (d, 2H), 4.47 (s, 2H), 3.96 (s, 3H), 3.39 (q, 3H), 2.45 (s, 3H), 1.05 (t, 3H) ppm.

Example 87

1-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}imidazolidin-2-one



A suspension of Intermediate 63A (100 mg, 0.221 mmol) in THF (5 ml) was treated with imidazolidin-2-one (57 mg, 0.662 mmol) and *N,N*-diisopropylethylamine (153 µl, 0.926 mmol), and the mixture was heated to 150°C for 90 min in a microwave oven. After this, the reaction mixture was purified by preparative RP-HPLC (Reprosil C18, gradient 40-60% acetonitrile/0.2% aq. trifluoroacetic acid). The product thus obtained was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated. The product was purified once again by preparative thin layer chromatography over silica gel (cyclohexane/ethyl acetate 3:1) affording 24 mg (22% of th.) of the title compound.

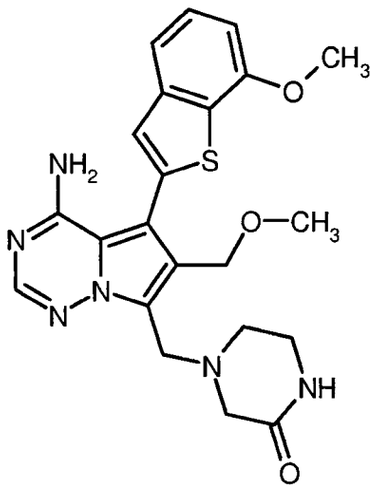
LC-MS (method 2): R_t = 0.99 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.21-7.65 (br. s, 1H), 7.99 (s, 1H), 7.36 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 6.38 (s, 1H), 6.04-5.56 (br. s, 1H), 4.65 (s, 2H), 4.46 (s, 2H), 3.95 (s, 3H), 3.38 (q, 2H), 3.31-3.10 (m, 4H), 2.45 (s, 3H), 1.06 (t, 3H) ppm.

Example 88

4-{[4-Amino-5-(7-methoxy-1-benzothiophen-2-yl)-6-(methoxymethyl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one

BHC 11 1 045



To a solution of Intermediate 62A (72.6 mg, 197 µmol), (7-methoxy-1-benzothiophen-2-yl)boronic acid (45 mg, 216 µmol) and caesium fluoride (149 mg, 983 µmol) in degassed THF/water (10:1, 2.2 ml) under argon was added (2'-aminobiphenyl-2-yl)(chloro)palladium-dicyclohexyl(2',4',6'-tri-isopropylbiphenyl-2-yl)phosphine (1:1; 7.7 mg, 9.8 µmol; see S. L. Buchwald *et al.*, *J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)). The resulting mixture was degassed again and stirred under argon at 60°C for 3 h. After this, the mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 20-40% acetonitrile/0.1% aq. TFA). The product fractions were combined and evaporated to dryness. The residue was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated affording 31 mg (35% of th.) of the title compound.

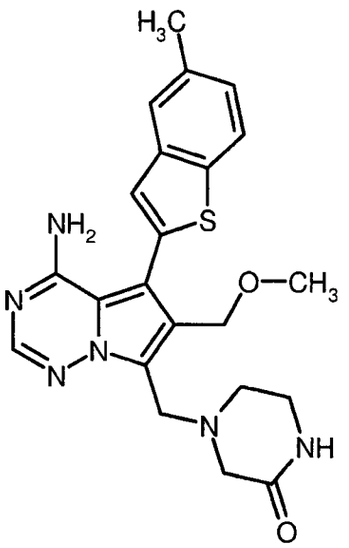
LC-MS (method 2): R_t = 0.71 min; MS (ESIpos): m/z = 453 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.00 (s, 1H), 7.72 (s, 1H), 7.61-8.23 (br. s, 1H), 7.51 (d, 1H), 7.46 (s, 1H), 7.40 (t, 1H), 6.99 (d, 1H), 5.57-6.11 (br. s, 1H), 4.42 (s, 2H), 3.98 (s, 5H), 3.20 (s, 3H), 3.11 (br. m, 2H), 3.01 (s, 2H), 2.62-2.67 (m, 2H) ppm.

Example 89

4-{[4-Amino-6-(methoxymethyl)-5-(5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl]methyl}piperazin-2-one

BHC 11 1 045



To a solution of Intermediate 62A (50 mg, 135 µmol), (5-methyl-1-benzothiophen-2-yl)boronic acid (28.6 mg, 149 µmol) and caesium fluoride (103 mg, 677 µmol) in degassed THF/water (10:1, 4.4 ml) under argon was added (2'-aminobiphenyl-2-yl)(chloro)palladium-dicyclohexyl(2',4',6'-tri-isopropylbiphenyl-2-yl)phosphine (1:1; 5.3 mg, 6.8 µmol; see S. L. Buchwald *et al.*, *J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)). The resulting mixture was degassed again and stirred under argon at 60°C for 16 h. After this, the mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 30-50% acetonitrile/0.1% aq. TFA). The product fractions were combined and evaporated to dryness. The residue was dissolved in methanol and filtered through an anion exchange cartridge (StratoSpheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated affording 27 mg (45% of th.) of the title compound.

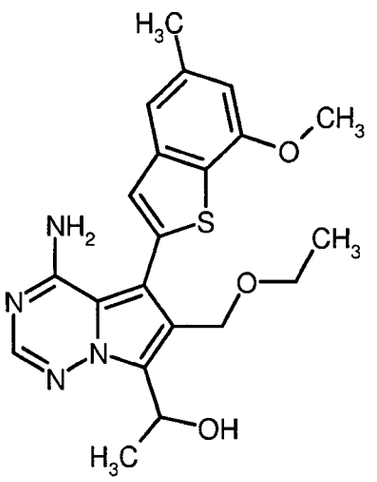
LC-MS (method 2): R_t = 0.79 min; MS (ESIpos): m/z = 437 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.00 (s, 1H), 7.89 (d, 1H), 7.73 (s, 1H), 7.71 (s, 1H), 7.58-8.18 (br. s, 1H), 7.40 (s, 1H), 7.24 (dd, 1H), 5.58-6.03 (m, 1H), 4.42 (s, 2H), 3.97 (s, 2H), 3.21 (s, 3H), 3.11 (br. t, 2H), 3.01 (s, 2H), 2.64 (t, 2H), 2.44 (s, 3H) ppm.

Example 90

1-[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-7-yl]ethanol

BHC 11 1 045



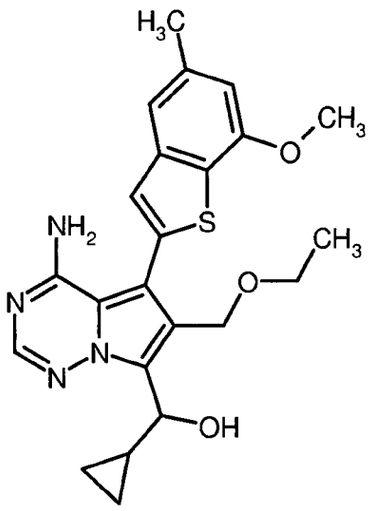
Under argon, a 1 M solution of methylmagnesium bromide in THF (630 µl, 630 µmol) was added dropwise at rt to a solution of Intermediate 17A (100 mg, 252 µmol) in THF (10 ml). The mixture was stirred at rt for 3 h and then treated with another portion of methylmagnesium bromide in THF (177 µl, 177 µmol). The reaction mixture was stirred for further 16 h, then quenched with sat. aq. ammonium chloride solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried with magnesium sulfate, filtered and evaporated. The residue was purified by preparative RP-HPLC (Reprosil C18, gradient 40-60% acetonitrile/0.1% aq. TFA). The product fractions were diluted with sat. aq. sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic phase was washed with sat. aq. sodium chloride solution, dried with magnesium sulfate, filtered and evaporated yielding 39 mg (36% of th.) of the title compound.

LC-MS (method 4): R_t = 1.07 min; MS (ESIpos): m/z = 413 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.95 (s, 1H), 7.56-8.07 (br. s, 1H), 7.35 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 5.46-5.54 (m, 1H), 5.37-5.95 (br. s, 1H), 5.26 (d, 1H), 4.67 (d, 1H), 4.38 (d, 1H), 3.95 (s, 3H), 3.38 (q, 2H), 2.45 (s, 3H), 1.52 (d, 3H), 1.05 (t, 3H) ppm.

Example 91

[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]-triazin-7-yl](cyclopropyl)methanol



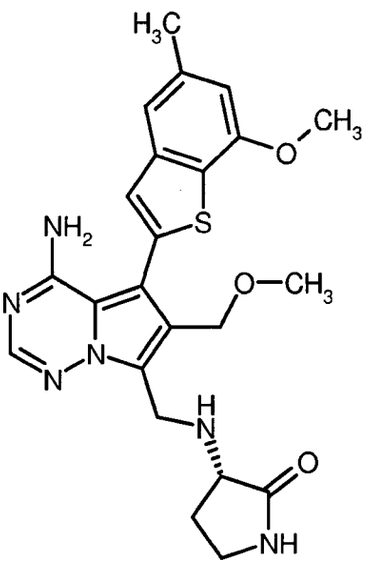
Under argon, a 0.5 M solution of cyclopropylmagnesium bromide in THF (1.26 ml, 630 µmol) was added dropwise at rt to a solution of Intermediate 17A (100 mg, 252 µmol) in THF (5 ml). The mixture was stirred at rt for 1 h, then quenched with sat. aq. ammonium chloride solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried with magnesium sulfate, filtered and evaporated. The residue was purified by preparative RP-HPLC (Reprosil C18, gradient 50-70% acetonitrile/0.1% aq. TFA). The product fractions were diluted with sat. aq. sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic phase was washed with sat. aq. sodium chloride solution, dried with magnesium sulfate, filtered and evaporated yielding 10 mg (10% of th.) of the title compound.

LC-MS (method 2): R_t = 1.13 min; MS (ESIpos): m/z = 439 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.94 (s, 1H), 7.68-8.04 (br. s, 1H), 7.36 (s, 1H), 7.31 (s, 1H), 6.84 (s, 1H), 5.47-5.89 (br. s, 1H), 5.30 (d, 1H), 4.64 (d, 1H), 4.59-4.67 (m, 1H), 4.39 (d, 1H), 3.96 (s, 3H), 3.38 (q, 2H), 2.45 (s, 3H), 1.54-1.64 (m, 1H), 1.04 (t, 3H), 0.51-0.59 (m, 1H), 0.40-0.47 (m, 1H), 0.28-0.38 (m, 2H) ppm.

Example 92

(*3S*)-3-({[4-Amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo-[2,1-f][1,2,4]triazin-7-yl]methyl}amino)pyrrolidin-2-one



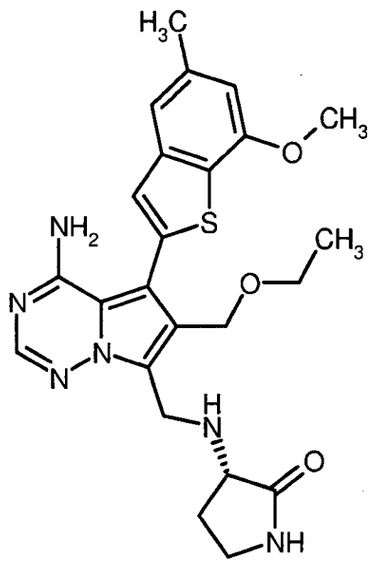
A suspension of Intermediate 13A (100 mg, 0.233 mmol) in THF (2 ml) was treated with (*S*)-3-aminopyrrolidin-2-one (35 mg, 0.349 mmol), sodium triacetoxyborohydride (148 mg, 0.698 mmol) and acetic acid (26.6 µl, 0.465 mmol). The resulting mixture was stirred at rt for 3 h and then directly purified by preparative RP-HPLC (Reprosil C18, gradient 40-60% acetonitrile/0.2% aq. trifluoroacetic acid). The product fractions were combined and evaporated to dryness. The residue was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated affording 56 mg (51% of th.) of the title compound.

LC-MS (method 4): R_t = 0.72 min; MS (ESIpos): m/z = 467 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.01 (s, 1H), 7.76 (s, 1H), 7.35 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 4.48 (d, 2H), 4.43 (d, 2H), 4.24-4.02 (m, 2H), 3.96 (s, 3H), 3.26-2.99 (m, 6H), 2.45 (s, 3H), 2.40-2.27 (m, 1H), 1.82-1.64 (m, 1H) ppm.

Example 93

(*3S*)-3-({[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]methyl}amino)pyrrolidin-2-one



A suspension of Intermediate 17A (100 mg, 0.252 mmol) in THF (2 ml) was treated with (*S*)-3-aminopyrrolidin-2-one (38 mg, 378 µmol), sodium triacetoxyborohydride (160 mg, 757 µmol) and acetic acid (30 µl, 504 µmol). The resulting mixture was stirred at rt for 3 h and then directly purified by preparative RP-HPLC (Reprosil C18, gradient 30-50% acetonitrile/0.2% aq. trifluoroacetic acid). The product fractions were combined and evaporated to dryness. The residue was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated affording 84 mg (69% of th.) of the title compound.

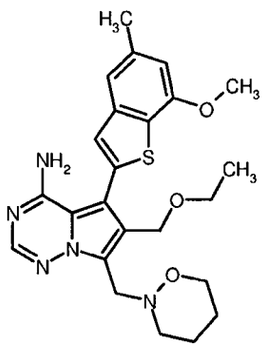
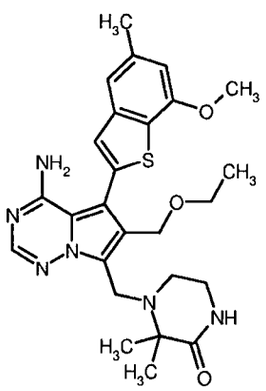
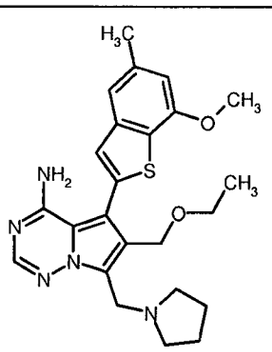
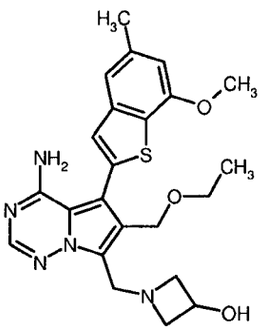
LC-MS (method 4): R_t = 0.75 min; MS (ESIpos): m/z = 481 $(M+H)^+$

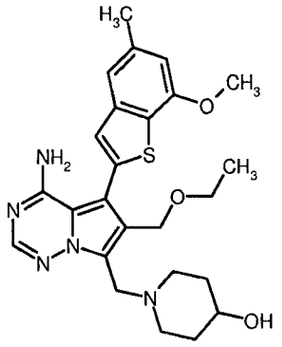
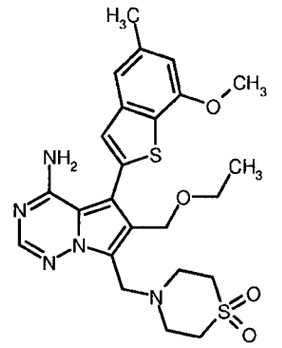
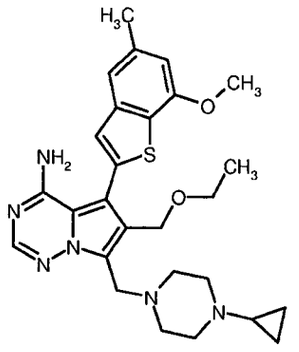
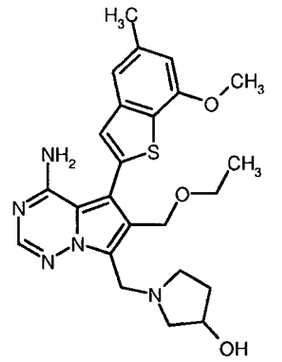
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.00 (s, 1H), 7.75 (s, 1H), 7.67-8.11 (br. s, 1H), 7.35 (s, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 5.5-6.0 (br. s, 1H), 4.44 (q, 2H), 4.14-4.21 (m, 1H), 4.02-4.11 (m, 1H), 3.38-3.45 (q, 2H), 3.16-3.24 (m, 1H), 3.05-3.16 (m, 2H), 2.45 (s, 3H), 2.31-2.40 (m, 1H), 1.67-1.79 (m, 1H), 1.08 (t, 3H) ppm.

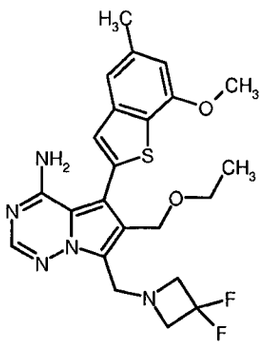
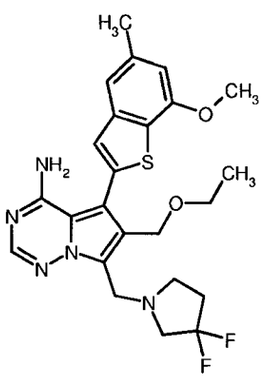
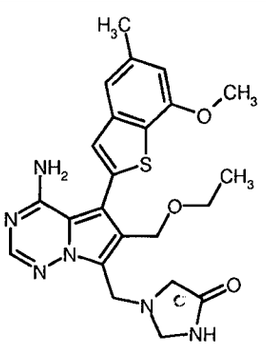
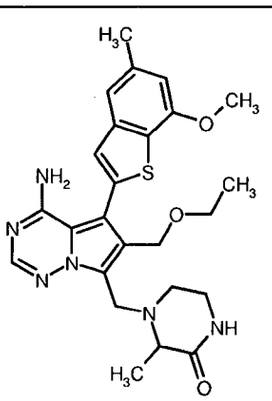
General procedure for the preparation of Examples 94–105 in Table I:

A 0.13 M suspension of Intermediate 17A in THF was treated with 1.5 eq. of the respective amine component, 3 eq. of sodium triacetoxyborohydride and 1.5 eq. of acetic acid. The resulting mixture was stirred at 60°C for 3–20 h. After this, purification was carried out according to the methods indicated.

Table I

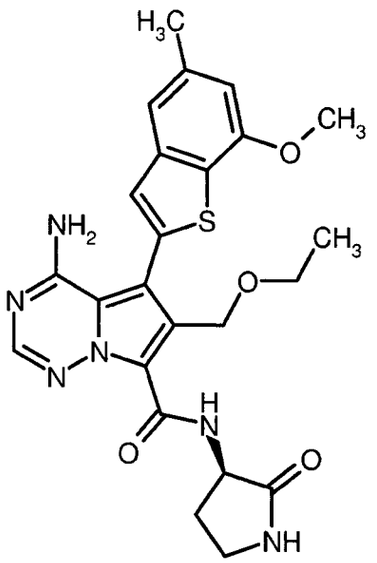
Example No.	Structure	Purification method(s)	LC-MS data
94		P1, P5	Method 4: R_t = 1.22 min; MS (ESIpos): m/z = 468 $(M+H)^+$
95		P6, P3	Method 2: R_t = 0.92 min; MS (ESIpos): m/z = 509 $(M+H)^+$
96		P1, P5	Method 4: R_t = 0.83 min; MS (ESIpos): m/z = 452 $(M+H)^+$
97		P1, P5	Method 5: R_t = 1.84 min; MS (ESIpos): m/z = 454 $(M+H)^+$

Example No.	Structure	Purification method(s)	LC-MS data
98		P1, P5	Method 5: R_t = 1.82 min; MS (ESIpos): m/z = 482 $(M+H)^+$
99		P1, P5	Method 5: R_t = 2.21 min; MS (ESIpos): m/z = 516 $(M+H)^+$
100		P1, P5	Method 2: R_t = 0.86 min; MS (ESIpos): m/z = 507 $(M+H)^+$
101		P1, P5	Method 2: R_t = 0.81 min; MS (ESIpos): m/z = 468 $(M+H)^+$

Example No.	Structure	Purification method(s)	LC-MS data
102		P1, P5, P4	Method 2: R_t = 1.03 min; MS (ESIpos): m/z = 474 $(M+H)^+$
103		P1, P5, P2	Method 2: R_t = 1.05 min; MS (ESIpos): m/z = 460 $(M+H)^+$
104		P1, P6	Method 2: R_t = 0.91 min; MS (ESIpos): m/z = 467 $(M+H)^+$
105		P1, P6	Method 2: R_t = 0.89 min; MS (ESIpos): m/z = 495 $(M+H)^+$

Example 106

4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)-*N*-[(*3R*)-2-oxo-pyrrolidin-3-yl]pyrrolo[2,1-f][1,2,4]triazine-7-carboxamide



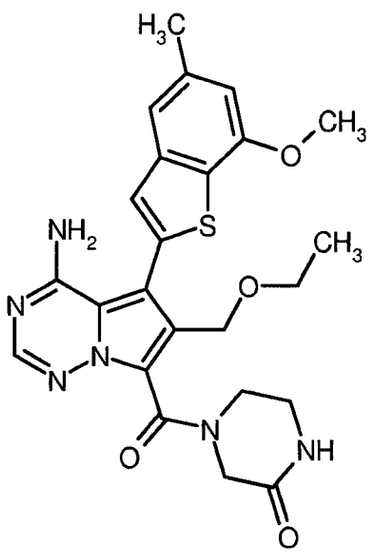
A stirred solution of Intermediate 64A (50 mg, 121 µmol) in DMF (2 ml) was treated at rt with *N*-[(1*H*-benzotriazol-1-yloxy)(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate (TBTU) (43 mg, 133 µmol) and DIPEA (53 µl, 303 µmol). After 15 min, (*3R*)-3-aminopyrrolidin-2-one (24 mg, 242 µmol) was added, and the resulting mixture was stirred at rt for further 2 h. After this, the mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 30-50% acetonitrile/0.2% aq. trifluoroacetic acid). The product fractions were combined and evaporated to dryness. The residue was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated affording 36 mg (60% of th.) of the title compound.

LC-MS (method 2): R_t = 0.91 min; MS (ESIpos): m/z = 495 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 9.50 (d, 1H), 8.21-8.45 (br. s, 1H), 8.17 (s, 1H), 7.97 (s, 1H), 7.41 (s, 1H), 7.33 (s, 1H), 6.86 (s, 1H), 5.84-6.09 (br. s, 1H), 4.74 (dd, 2H), 4.47-4.56 (m, 1H), 3.96 (s, 3H), 3.37 (q, 2H), 3.22-3.29 (m, 2H), 2.54-2.61 (m, 1H), 2.46 (s, 3H), 1.90-2.03 (m, 1H), 1.00 (t, 3H) ppm.

Example 107

4-{[4-Amino-6-(ethoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-f]-[1,2,4]triazin-7-yl]carbonyl}piperazin-2-one



A stirred solution of Intermediate 64A (50 mg, 121 µmol) in DMF (2 ml) was treated at rt with TBTU (43 mg, 133 µmol) and DIPEA (53 µl, 303 µmol). After 15 min, piperazin-2-one (24 mg, 242 µmol) was added, and the resulting mixture was stirred at rt for further 16 h. After this, the mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 40-60% acetonitrile/0.2% aq. trifluoroacetic acid). The product fractions were combined and evaporated to dryness. The residue was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated affording 45 mg (68% of th.) of the title compound.

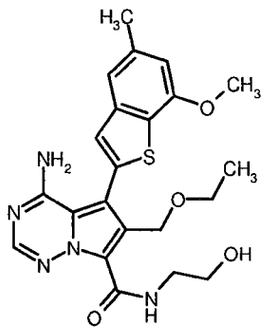
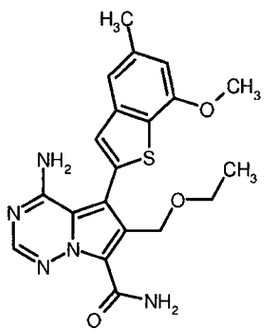
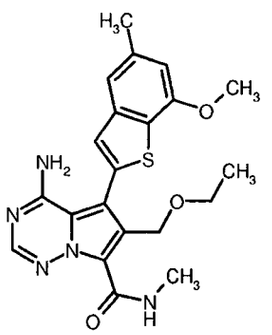
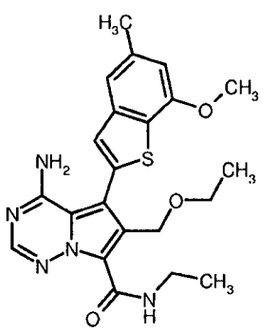
LC-MS (method 2): R_t = 0.92 min; MS (ESIpos): m/z = 495 $(M+H)^+$

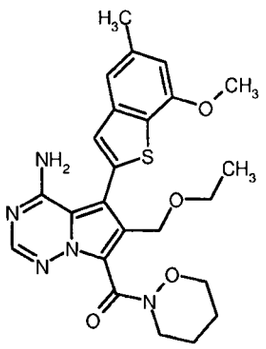
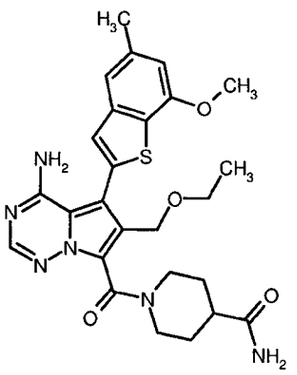
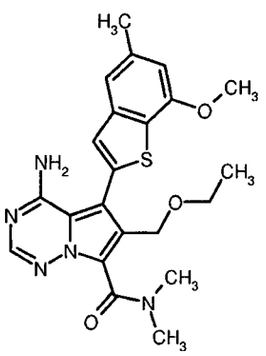
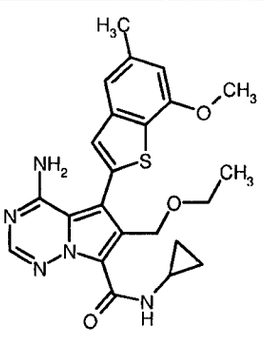
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.14 (br. s, 1H), 7.99-8.01 (m, 1H), 7.9-8.3 (br. s, 1H), 7.41 (d, 1H), 7.32 (s, 1H), 6.86 (s, 1H), 5.78-6.05 (br. s, 1H), 4.30-4.49 (m, 2H), 4.13-4.23 (m, 1H), 4.03-4.10 (m, 1H), 3.96 (s, 3H), 3.76-3.87 (m, 1H), 3.57-3.74 (m, 1H), 3.35-3.43 (m, 2H), 3.14-3.25 (m, 1H), 2.45 (s, 3H), 0.96-1.05 (m, 3H) ppm.

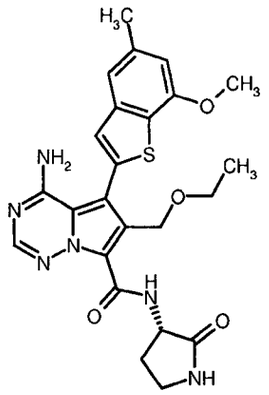
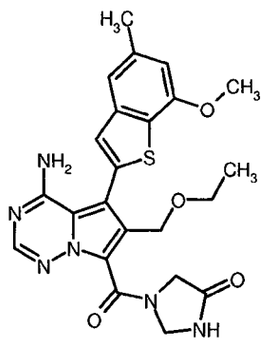
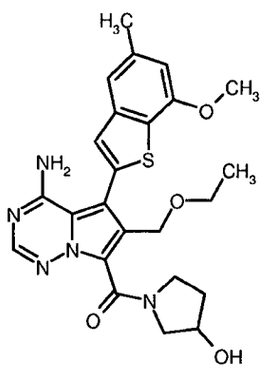
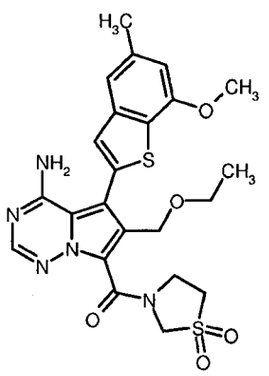
General procedure for the preparation of Examples 108–123 in Table II:

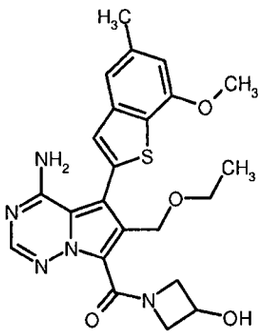
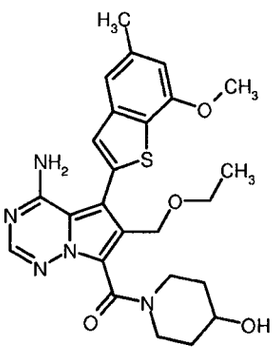
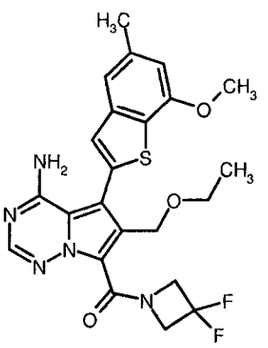
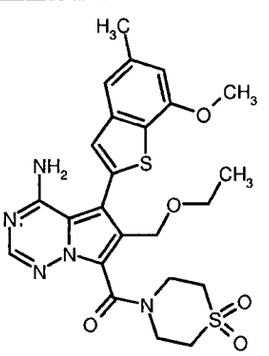
A 0.13 M solution of Intermediate 64A in DMF was treated with 1.1 eq. TBTU and 2.5 eq. DIPEA and stirred at rt for 15 min. 2 eq. of the respective amine were added, and the resulting mixture was stirred at rt for further 18 h. After this, purification was carried out according to the methods indicated.

Table II

Example No.	Structure	Purification method(s)	LC-MS data
108		P1	Method 2: R_t = 1.02 min; MS (ESIpos): m/z = 456 $(M+H)^+$
109		P1	Method 4: R_t = 0.97 min; MS (ESIpos): m/z = 412 $(M+H)^+$
110		P1, P5	Method 2: R_t = 1.01 min; MS (ESIpos): m/z = 426 $(M+H)^+$
111		P1, P5	Method 4: R_t = 1.11 min; MS (ESIpos): m/z = 440 $(M+H)^+$

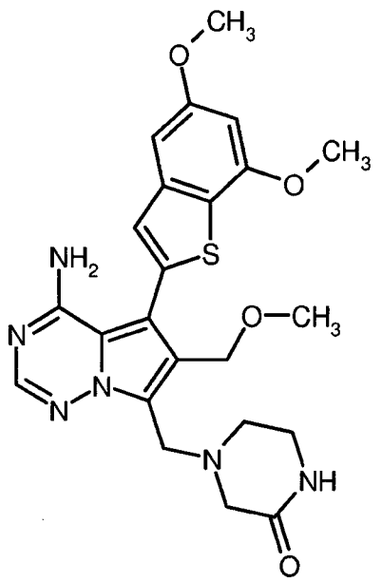
Example No.	Structure	Purification method(s)	LC-MS data
112		P1	Method 4: R_t = 1.07 min; MS (ESIpos): m/z = 482 $(M+H)^+$
113		P1, P5	Method 2: R_t = 0.84 min; MS (ESIpos): m/z = 523 $(M+H)^+$
114		P1, P5	Method 2: R_t = 0.96 min; MS (ESIpos): m/z = 440 $(M+H)^+$
115		P1, P5	Method 2: R_t = 1.09 min; MS (ESIpos): m/z = 452 $(M+H)^+$

Example No.	Structure	Purification method(s)	LC-MS data
116		P1, P5	Method 4: R_t = 0.95 min; MS (ESIpos): m/z = 495 $(M+H)^+$
117		P1, P5	Method 4: R_t = 0.93 min; MS (ESIpos): m/z = 481 $(M+H)^+$
118		P1, P5	Method 2: R_t = 0.93 min; MS (ESIpos): m/z = 482 $(M+H)^+$
119		P1, P5	Method 2: R_t = 1.04 min; MS (ESIpos): m/z = 516 $(M+H)^+$

Example No.	Structure	Purification method(s)	LC-MS data
120		P1, P5	Method 4: R_t = 0.88 min; MS (ESIpos): m/z = 468 $(M+H)^+$
121		P1, P5	Method 4: R_t = 0.91 min; MS (ESIpos): m/z = 496 $(M+H)^+$
122		P1, P5	Method 4: R_t = 1.09 min; MS (ESIpos): m/z = 488 $(M+H)^+$
123		P1, P5	Method 4: R_t = 0.98 min; MS (ESIpos): m/z = 530 $(M+H)^+$

Example 124

4-{[4-Amino-5-(5,7-dimethoxy-1-benzothiophen-2-yl)-6-(methoxymethyl)pyrrolo[2,1-f][1,2,4]-triazin-7-yl]methyl}piperazin-2-one



To a solution of Intermediate 62A (100 mg, 271 µmol), Intermediate 66A (77 mg, 325 µmol) and caesium fluoride (206 mg, 1.35 mmol) in degassed THF/water (10:1; 5 ml) under argon was added (2'-aminobiphenyl-2-yl)(chloro)palladium-dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (1:1; 42.6 mg, 54 µmol; see S. L. Buchwald *et al.*, *J. Am. Chem. Soc.* 132 (*40*), 14073-14075 (2010)). The resulting mixture was degassed again and stirred under argon at 60°C for 6 h. Then, another portion of Intermediate 66A (39 mg, 162 µmol) was added, and stirring at 60°C was continued for 10 h. After this, the reaction mixture was separated by preparative RP-HPLC (Reprosil C18, gradient 30-50% acetonitrile/0.1% aq. TFA). The product fractions were combined and evaporated to dryness. The residue was dissolved in methanol and filtered through an anion exchange cartridge (Stratospheres SPE, PL-HCO_3 MP-resin). The cartridge was eluted with methanol, and the filtrate was evaporated affording 40 mg (28% of th.) of the title compound.

LC-MS (method 2): R_t = 0.78 min; MS (ESIpos): m/z = 483 $(M+H)^+$

^{1}H-NMR (500 MHz, DMSO-d_6): δ = 7.99 (s, 1H), 7.68 (br. s, 1H), 7.49-8.17 (br. s, 1H), 7.37 (s, 1H), 7.05 (d, 1H), 6.63 (d, 1H), 5.5-6.0 (br. s, 1H), 4.42 (s, 2H), 3.97 (s, 2H), 3.94 (s, 3H), 3.84 (s, 3H), 3.20 (s, 3H), 3.09-3.14 (m, 2H), 3.01 (s, 2H), 2.62-2.67 (m, 2H) ppm.

B. Evaluation of Biological Activity

Abbreviations and Acronyms:

Ahx	6-aminohexanoic acid
ATP	adenosine triphosphate
BSA	bovine serum albumin
CREB	cAMP-response element-binding protein
DMSO	dimethylsulfoxide
EDTA	ethylenediaminetetraacetic acid
EGTA	ethyleneglycol-bis(2-aminoethylether)-*N,N,N',N'*-tetraacetic acid
FBS	fetal bovine serum
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
GFP	green fluorescent protein
GST	glutathione S-transferase
HEPES	4-(2-hydroxyethyl)piperazine-1-ethansulfonic acid
HRTF	homogeneous time-resolved fluorescence
MOPS	3-(*N*-morpholino)propanesulfonic acid
mTOR	mammalian target of Rapamycin
PBS	phosphate buffered saline
PI3K	phosphatidylinositol 3-kinase
RTK	receptor tyrosine kinase
SNP	single nucleotide polymorphism
TR-FRET	time-resolved fluorescence resonance energy transfer
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

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. FGFR-1 high ATP kinase assay

FGFR-1 inhibitory activity at high ATP concentration of the compounds of the present invention after their pre-incubation with FGFR-1 was quantified employing the TR-FRET based FGFR-1 high ATP assay as described in the following paragraphs:

A recombinant tagged FGFR-1 fusion protein [fusion of glutathione-*S*-transferase (GST) (N-terminally), His6-tag, thrombin cleavage site, and the intracellular part of human FGFR-1 from amino acids G400 to R800 as in GenBank entry NM_015850], expressed in SF9 insect cells using baculovirus expression system and purified via glutathione-agarose affinity chromatography, was purchased from Proqinase (product no. 0101-0000-1) and used as enzyme. As substrate for the kinase reaction, the biotinylated peptide biotin-Ahx-AAEEEYFFLFAKKK (C-terminus in amide form) was used which can be purchased, e.g., from Biosyntan (Berlin-Buch, Germany).

Usually, test compounds were tested on the same microtiter plate at 11 different concentrations in the range of 20 µM to 0.1 nM (e.g. 20 µM, 5.9 µM, 1.7 µM, 0.51 µM, 0.15 µM, 44 nM, 13 nM, 3.8 nM, 1.1 nM, 0.33 nM, and 0.1 nM) in duplicates for each concentration. The dilution series was prepared separately prior to the assay as 100-fold concentrated stock solutions in DMSO; exact concentrations could vary depending on the pipettor used. For the assay, 50 nl of each stock solution of the test compound in DMSO was pipetted into a black, low-volume 384-well microtiter plate (Greiner Bio-One, Frickenhausen, Germany). 2 µl of a solution of the above FGFR-1 fusion protein in aqueous assay buffer [8 mM MOPS pH 7.0, 10 mM magnesium acetate, 1.0 mM dithiothreitol, 0.05% (w/v) bovine serum albumin (BSA), 0.07% (v/v) Tween-20, 0.2 mM EDTA] was added, and the mixture was incubated for 15 min at 22°C to allow pre-binding of the test compound to the enzyme. Then, the kinase reaction was started by the addition of 3 µl of a solution of adenosine triphosphate (ATP, 3.3 mM; final concentration in the 5 µl assay volume = 2 mM) and substrate (0.16 µM; final concentration in the 5 µl assay volume = 0.1 µM) in assay buffer, and the resulting mixture was incubated for a reaction time of 15 min at 22°C. The concentration of FGFR-1 fusion protein was adjusted depending on the activity of the enzyme lot and was chosen appropriately to have the assay in the linear range (typical concentrations were in the range of 0.05 µg/ml). The reaction was stopped by the addition of 5 µl of a solution of HTRF detection reagents [25 nM streptavidin-XL665 (Cis Biointernational) and 1 nM PT66-Eu-chelate, an europium-chelate labelled anti-phosphotyrosine antibody (Perkin-Elmer; PT66-Tb-cryptate from Cis Biointernational may be used instead), in an aqueous EDTA solution (50 mM EDTA, 0.1% (w/v) BSA in 50 mM HEPES/NaOH pH 7.5)].

The resulting mixture was incubated for 1 h at 22°C to allow formation of the complex between the phosphorylated biotinylated peptide and the detection reagents. Subsequently, the amount of

phosphorylated substrate was evaluated by measurement of the resonance energy transfer from the Eu-chelate to the streptavidin-XL665. For this, the fluorescence emissions at 620 nm and 665 nm after excitation at 350 nm were measured in a TR-FRET reader [e.g. Rubystar (BMG Labtechnologies, Offenburg, Germany) or Viewlux (Perkin-Elmer)]. The ratio of the emissions at 665 nm and at 620 nm was taken as the measure for the amount of phosphorylated substrate. Data were normalised (enzyme reaction without inhibitor = 0% inhibition, all other assay components but no enzyme = 100% inhibition), and IC_{50} values were calculated by a 4-parameter fit using an in-house software.

IC_{50} values for individual compounds of the invention from this assay are listed in Table 1A below:

Table 1A

Example No.	FGFR-1 (high ATP) IC_{50} [nM]
1	12.2
2	7.2
3	6.6
4	13.7
5	4.6
6	9.0
7	4.2
8	9.4
9	31.0
10	12.7
11	6.5
12	3.3
13	2.5
14	1.4
15	1.0

Example No.	FGFR-1 (high ATP) IC_{50} [nM]
16	12.5
17	0.9
18	0.7
19	0.5
20	25.0
21	4.2
22	0.9
23	17.9
24	1.3
25	0.7
26	0.9
27	1.3
28	2.1
29	1.6
30	2.8

Example No.	FGFR-1 (high ATP) IC_{50} [nM]
31	1.5
32	5.2
33	1.0
34	6.0
35	61.3
36	3.0
37	22.1
38	6.9
39	1.1
40	2.1
41	2.8
42	5.1
43	8.6
44	2.1
45	3.4
46	3.2
47	1.7
48	12.8
51	4.4
52	9.7
53	3.9
54	11.2
56	2.4
57	3.2
58	6.8

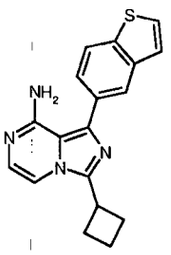
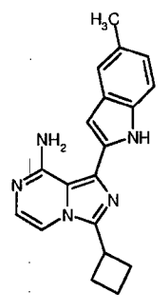
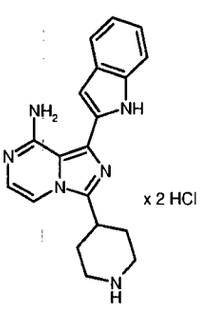
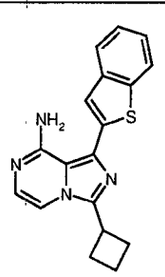
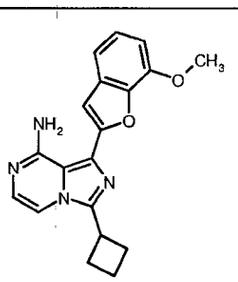
Example No.	FGFR-1 (high ATP) IC_{50} [nM]
59	3.8
60	16.2
61	0.5
62	3.1
64	1.0
65	5.6
66	1.6
67	5.0
68	27.0
69	55.3
70	39.1
71	2.7
72	1.4
73	4.4
74	4.0
75	4.1
76	2.8
77	1.4
78	1.7
79	12.6
80	1.3
81	1.9
82	3.4
83	14.5
84	3.7

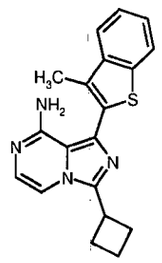
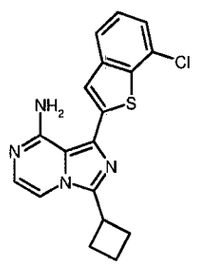
Example No.	FGFR-1 (high ATP) IC_{50} [nM]
85	26.4
86	3.9
87	14.1
88	79.6
89	82.9
90	9.9
91	52.9
92	8.2
93	5.5
94	81.9
95	17.0
96	54.5
97	16.4
98	17.0
99	24.8
100	54.5
101	30.8
102	39.2
103	50.3
104	5.6

Example No.	FGFR-1 (high ATP) IC_{50} [nM]
105	8.7
106	6.4
107	9.4
108	3.9
109	8.4
110	17.5
111	27.0
112	42.1
113	52.7
114	11.2
115	24.9
116	3.7
117	8.8
118	6.8
119	9.0
120	6.8
121	8.2
122	18.9
123	25.1
124	27.3

Selected 8-amino-1-(benzothiophen-2-yl)imidazo[1,5-a]pyrazine derivatives and related compounds which were regarded to be representative of closest prior art (see Int. Pat. Appl. WO 2007/061737-A2 and example compounds described therein) were synthesized following the published procedures and also tested in the FGFR-1 high ATP assay for comparative purposes. IC_{50} values that were obtained for these compounds are listed in Table 1B below:

Table 1B

Structure of comparative compound	Example No. in WO 2007/061737	FGFR-1 (high ATP) IC_{50} [nM]
	4	12000
	5	500
	25	880
	120	985
	205	20000

Structure of comparative compound	Example No. in WO 2007/061737	FGFR-1 (high ATP) IC_{50} [nM]
	210	456
	233	4600

The IC_{50} values specified in Table 1A and 1B demonstrate that the compounds of the present invention are about five to a thousand times more potent in inhibiting FGFR-1 kinase activity than the selected prior art compounds.

B-2. FGFR-3 kinase assay

FGFR-3 inhibitory activity of the compounds of the present invention after their pre-incubation with FGFR-3 was quantified employing the TR-FRET based FGFR-3 assay as described in the following paragraphs:

A recombinant tagged FGFR-3 fusion protein [fusion of glutathione-*S*-transferase (GST) (N-terminally), His6-tag, thrombin cleavage site, and the intracellular part of human FGFR-3 from amino acids R397 to T806 as in NCBI/Protein entry NP_000133.1], expressed in SF9 insect cells using baculovirus expression system and purified via glutathione-S-transferase affinity chromatography, was purchased from Proqinase (product no. 1068-0000-1) and used as enzyme. As substrate for the kinase reaction, the biotinylated peptide biotin-Ahx-AAEEEYFFLFAKKK (C-terminus in amide form) was used which can be purchased, e.g., from Biosyntan (Berlin-Buch, Germany).

Usually, test compounds were tested on the same microtiter plate at 11 different concentrations in the range of 20 µM to 0.1 nM (e.g. 20 µM, 5.9 µM, 1.7 µM, 0.51 µM, 0.15 µM, 44 nM, 13 nM, 3.8 nM, 1.1 nM, 0.33 nM, and 0.1 nM) in duplicates for each concentration. The dilution series was prepared separately prior to the assay as 100-fold concentrated stock solutions in DMSO;

exact concentrations could vary depending on the pipettor used. For the assay, 50 nl of each stock solution of the test compound in DMSO was pipetted into a black, low-volume 384-well microtiter plate (Greiner Bio-One, Frickenhausen, Germany). 2 µl of a solution of the above FGFR-3 fusion protein in aqueous assay buffer [8 mM MOPS pH 7.0, 10 mM magnesium acetate, 1.0 mM dithiothreitol, 0.05% (w/v) bovine serum albumin (BSA), 0.07% (v/v) Tween-20, 0.2 mM EDTA] was added, and the mixture was incubated for 15 min at 22°C to allow pre-binding of the test compound to the enzyme. Then, the kinase reaction was started by the addition of 3 µl of a solution of adenosine triphosphate (ATP, 16.7 µM; final concentration in the 5 µl assay volume = 10 µM) and substrate (0.8 µM; final concentration in the 5 µl assay volume = 0.5 µM) in assay buffer, and the resulting mixture was incubated for a reaction time of 60 min at 22°C. The concentration of FGFR-3 fusion protein was adjusted depending on the activity of the enzyme lot and was chosen appropriately to have the assay in the linear range (typical concentrations were in the range of 0.03 µg/ml). The reaction was stopped by the addition of 5 µl of a solution of HTRF detection reagents [100 nM streptavidin-XL665 (Cis Biointernational) and 1 nM PT66-Tb-cryptate, a terbium-cryptate labelled anti-phosphotyrosine antibody (Cis Biointernational; PT66-Eu-chelate from Perkin-Elmer may be used instead), in an aqueous EDTA solution (50 mM EDTA, 0.1% (w/v) BSA in 50 mM HEPES/NaOH pH 7.5)].

The resulting mixture was incubated for 1 h at 22°C to allow formation of the complex between the phosphorylated biotinylated peptide and the detection reagents. Subsequently, the amount of phosphorylated substrate was evaluated by measurement of the resonance energy transfer from the Tb-chelate to the streptavidin-XL665. For this, the fluorescence emissions at 620 nm and 665 nm after excitation at 350 nm were measured in a TR-FRET reader [e.g. Rubystar (BMG Labtechnologies, Offenburg, Germany) or Viewlux (Perkin-Elmer)]. The ratio of the emissions at 665 nm and at 620 nm was taken as the measure for the amount of phosphorylated substrate. Data were normalised (enzyme reaction without inhibitor = 0% inhibition, all other assay components but no enzyme = 100% inhibition), and IC_{50} values were calculated by a 4-parameter fit using an in-house software.

IC_{50} values for individual compounds of the invention from this assay are listed in Table 2A below:

Table 2A

Example No.	FGFR-3 IC_{50} [nM]
1	24.8

Example No.	FGFR-3 IC_{50} [nM]
2	29.4

Example No.	FGFR-3 IC_{50} [nM]
3	46.6
4	24.8
5	12.1
6	28.5
7	10.4
8	17.7
9	63.9
10	8.3
11	13.0
12	14.0
13	10.0
14	2.5
15	1.0
16	9.4
17	3.3
18	2.8
19	2.7
20	26.1
21	13.0
22	4.7
23	41.9
24	5.7
25	5.2
26	4.9
27	12.6
28	9.7

Example No.	FGFR-3 IC_{50} [nM]
29	2.5
30	6.4
31	13.3
32	52.3
33	7.2
34	10.5
35	65.4
36	9.8
37	34.6
38	18.8
39	4.9
40	7.9
41	7.2
42	18.4
43	32.4
44	6.1
45	9.7
46	8.1
47	3.4
48	45.4
51	3.9
52	7.0
53	2.5
54	6.8
56	2.0
57	1.8

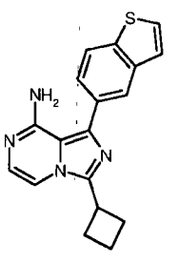
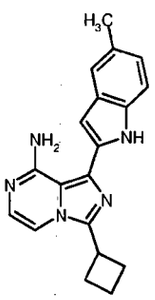
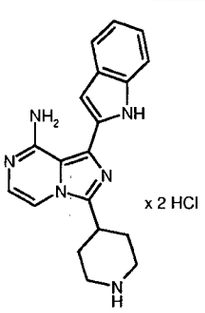
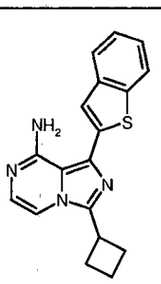
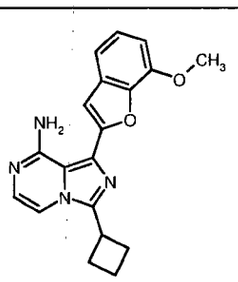
Example No.	FGFR-3 IC_{50} [nM]
58	9.8
59	6.8
60	77.9
61	0.9
62	11.0
64	2.9
65	3.1
66	3.7
67	9.4
68	42.7
69	58.1
71	5.4
72	0.7
73	12.2
74	1.4
75	19.8
76	1.4
77	3.8
78	2.0
79	17.9
80	0.2

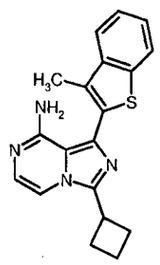
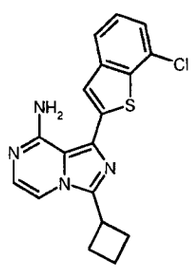
Example No.	FGFR-3 IC_{50} [nM]
81	0.5
82	16.0
83	2.1
84	16.5
85	26.0
86	6.8
87	28.1
90	11.0
91	31.1
93	8.7
95	28.7
98	26.5
99	36.9
102	39.8
106	7.1
107	17.4
108	7.7
114	9.6
117	5.3
119	4.5
121	24.6

Selected 8-amino-1-(benzothiophen-2-yl)imidazo[1,5-a]pyrazine derivatives and related compounds which were regarded to be representative of closest prior art (see Int. Pat. Appl. WO 2007/061737-A2 and example compounds described therein) were synthesized following the published procedures and also tested in the FGFR-3 assay for comparative purposes. IC_{50} values that were obtained for these compounds are listed in Table 2B below:

BHC 11 1 045

Table 2B

Structure of comparative compound	Example No. in WO 2007/061737	FGFR-3 IC_{50} [nM]
	4	2400
	5	250
	25	1200
	120	506
	205	20000

Structure of comparative compound	Example No. in WO 2007/061737	FGFR-3 IC_{50} [nM]
	210	554
	233	10000

The IC_{50} values specified in Table 2A and 2B demonstrate that the compounds of the present invention are about three to a thousand times more potent in inhibiting FGFR-3 kinase activity than the selected prior art compounds.

B-3. FGFR-4 high ATP kinase assay

FGFR-4 inhibitory activity at high ATP concentration of the compounds of the present invention after their pre-incubation with FGFR-4 was quantified employing the TR-FRET based FGFR-4 high ATP assay as described in the following paragraphs:

A recombinant tagged FGFR-4 fusion protein [fusion of glutathione-*S*-transferase (GST) (N-terminally), His6-tag, thrombin cleavage site, and the intracellular part of human FGFR-4 from amino acids R391 to T802 as in GenBank entry NM_002011], expressed in SF9 insect cells using baculovirus expression system and purified via glutathione-agarose affinity chromatography, was purchased from Proqinase (product no. 0127-0000-3) and used as enzyme. As substrate for the kinase reaction, the biotinylated peptide biotin-Ahx-AAEEEYFFLFAKKK (C-terminus in amide form) was used which can be purchased, e.g., from Biosyntan (Berlin-Buch, Germany).

Usually, test compounds were tested on the same microtiter plate at 11 different concentrations in the range of 20 µM to 0.1 nM (e.g. 20 µM, 5.9 µM, 1.7 µM, 0.51 µM, 0.15 µM, 44 nM, 13 nM, 3.8 nM, 1.1 nM, 0.33 nM, and 0.1 nM) in duplicates for each concentration. The dilution series was prepared separately prior to the assay as 100-fold concentrated stock solutions in DMSO;

exact concentrations could vary depending on the pipettor used. For the assay, 50 nl of each stock solution of the test compound in DMSO was pipetted into a black, low-volume 384-well microtiter plate (Greiner Bio-One, Frickenhausen, Germany). 2 µl of a solution of the above FGFR-4 fusion protein in aqueous assay buffer [8 mM MOPS pH 7.0, 10 mM magnesium acetate, 1.0 mM dithiothreitol, 0.05% (w/v) bovine serum albumin (BSA), 0.07% (v/v) Tween-20, 0.2 mM EDTA] was added, and the mixture was incubated for 15 min at 22°C to allow pre-binding of the test compound to the enzyme. Then, the kinase reaction was started by the addition of 3 µl of a solution of adenosine triphosphate (ATP, 3.3 mM; final concentration in the 5 µl assay volume = 2 mM) and substrate (0.8 µM; final concentration in the 5 µl assay volume = 0.5 µM) in assay buffer, and the resulting mixture was incubated for a reaction time of 60 min at 22°C. The concentration of FGFR-4 fusion protein was adjusted depending on the activity of the enzyme lot and was chosen appropriately to have the assay in the linear range (typical concentrations were in the range of 0.03 µg/ml). The reaction was stopped by the addition of 5 µl of a solution of HTRF detection reagents [100 nM streptavidin-XL665 (Cis Biointernational) and 1 nM PT66-Tb-cryptate, a terbium-cryptate labelled anti-phosphotyrosine antibody (Cis Biointernational; PT66-Eu-chelate from Perkin-Elmer may be used instead), in an aqueous EDTA solution (50 mM EDTA, 0.1% (w/v) BSA in 50 mM HEPES/NaOH pH 7.5)].

The resulting mixture was incubated for 1 h at 22°C to allow formation of the complex between the phosphorylated biotinylated peptide and the detection reagents. Subsequently, the amount of phosphorylated substrate was evaluated by measurement of the resonance energy transfer from the Tb-chelate to the streptavidin-XL665. For this, the fluorescence emissions at 620 nm and 665 nm after excitation at 350 nm were measured in a TR-FRET reader [e.g. Rubystar (BMG Labtechnologies, Offenburg, Germany) or Viewlux (Perkin-Elmer)]. The ratio of the emissions at 665 nm and at 620 nm was taken as the measure for the amount of phosphorylated substrate. Data were normalised (enzyme reaction without inhibitor = 0% inhibition, all other assay components but no enzyme = 100% inhibition), and IC_{50} values were calculated by a 4-parameter fit using an in-house software.

B-4. mTOR kinase assay (*for comparative purposes*)

mTOR inhibitory activity of the compounds of the present invention was quantified employing the TR-FRET based mTOR assay as described in the following paragraphs:

Recombinant fusion tagged mTOR protein [glutathione-*S*-transferase (GST) fused to human mTOR amino acids from 1360 to 2549], expressed in insect cells and purified by glutathione-sepharose affinity chromatography, was purchased from Invitrogen (Cat.-No. 4753) and used as

enzyme. As substrate for the kinase reaction, a recombinant fusion protein of GFP and 4E-BP1 (purchased from Invitrogen, Cat.-No. PV4759) was used.

Test compounds were dissolved in DMSO to generate 10 mM stock solutions. These solutions were first 10-fold diluted by 100% DMSO to get 1 mM solutions in 100% DMSO, then 100-fold diluted by 50% DMSO to get 10 µM solutions in 50% DMSO.

For the assay, 0.5 µl of a 10 µM solution of the test compound in 50% DMSO was pipetted into a black, low-volume 384-well microtiter plate (Greiner Bio-One, Frickenhausen, Germany). 2 µl of a solution of the above mTOR fusion protein in aqueous assay buffer [50 mM HEPES/NaOH pH 7.5, 5 mM magnesium chloride, 1.0 mM dithiothreitol, 1 mM EGTA, 0.01% (v/v) Triton-X100, 0.01% (w/v) bovine serum albumin (BSA)] was added, and the mixture was incubated for 15 min at 22°C to allow pre-binding of the test compound to the enzyme. Then, the kinase reaction was started by the addition of 2.5 µl of a solution of adenosine triphosphate (ATP, 80 µM; final concentration in the 5 µl assay volume = 40 µM) and substrate (0.6 µM; final concentration in the 5 µl assay volume = 0.3 µM) in assay buffer, and the resulting mixture was incubated for a reaction time of 60 min at 22°C. The concentration of mTOR fusion protein was chosen appropriately to have the assay in the linear range (a typical final concentration in the 5 µl assay volume was 1.25 ng/µl). The reaction was stopped by the addition of 5 µl of 30 mM EDTA (final concentration in the 10 µl assay volume = 15 mM) and 2 nM Tb-chelate labelled anti-4E-BP1 [pT46] phospho-specific antibody [Invitrogen Cat.-No. PV4755] (final concentration in the 10 µl assay volume = 1 nM) in FRET buffer.

The resulting mixture was incubated for 1 h at 22°C to allow formation of the complex between the phosphorylated substrate and the Tb-chelate labelled antibody. Subsequently, the amount of phosphorylated substrate was evaluated by measurement of the resonance energy transfer from the Tb-chelate to the GFP. For this, the fluorescence emissions at 495 nm and 520 nm after excitation at 340 nm was measured in an Envision 2104 multilabel reader (Perkin-Elmer). The ratio of the emissions at 520 nm and at 495 nm was taken as the measure for the amount of phosphorylated substrate. Data were normalised (enzyme reaction without inhibitor = 0% inhibition, all other assay components but no enzyme = 100% inhibition), and either mean values (if tested in replicates at a single concentration) or IC_{50} values (by a 4-parameter fit using an in-house software) were calculated.

Mean inhibition values at 1 µM for individual compounds of the present invention are listed in Table 3 below:

Table 3

Example No.	mTOR % inhibition @ 1 µM
1	8.7
2	7.2
3	8.2
5	9.7
6	0.3
7	3.1
8	7.8
9	*no inhib. effect detect.*
10	6.0
11	33.2
12	25.8
13	14.9
14	15.7
16	36.9
17	6.7
18	*no inhib. effect detect.*
19	17.6
20	31.3
21	5.0
22	17.6
23	11.6
24	6.3
25	3.5
26	6.8

Example No.	mTOR % inhibition @ 1 µM
27	5.9
28	*no inhib. effect detect.*
29	28.5
30	21.1
31	16.3
32	1.6
33	0.9
34	25.9
35	1.4
36	14.4
37	8.6
38	20.8
39	11.5
40	0.1
41	*no inhib. effect detect.*
42	*no inhib. effect detect.*
43	10.1
44	13.3
45	15.5
46	11.0
47	14.7
48	4.1
51	8.4
52	4.2

Example No.	mTOR % inhibition @ 1 µM
53	3.3
54	1.7
56	16.1
57	2.0
58	4.0
59	0.8
60	11.1
61	15.9
62	0.2
64	1.1
65	13.9
66	15.8
67	8.4
68	8.0
69	8.7
70	5.8
71	0.1
72	8.2
73	18.5
74	18.6
75	10.2

Example No.	mTOR % inhibition @ 1 µM
76	8.5
77	0.7
78	5.8
79	14.7
80	3.9
81	4.1
82	7.1
83	6.3
84	9.1
85	0.9
87	12.7
88	5.3
89	*no inhib. effect detect.*
93	12.5
98	*no inhib. effect detect.*
99	5.3
103	*no inhib. effect detect.*
107	*no inhib. effect detect.*
108	8.5
119	*no inhib. effect detect.*
121	*no inhib. effect detect.*

(*no inhib. effect detect.* = no inhibitory effect detectable at 1 µM).

The data in Table 3 show that the compounds of the present invention only have a weak, if any, inhibitory effect on mTOR kinase which is not considered to contribute to the pharmacological activity observed with these compounds.

B-5. Inhibition of growth factor-mediated cell proliferation

Human umbilical vein endothelial cells (HUVEC) were obtained from Cellsystems (FC-0003) and grown in Vasculife VEGF complete medium (Cellsystems, LL-1020) containing 2% fetal bovine serum (FBS) at 37°C and 5% CO_2. The cells were used for proliferation assays up to passage 7.

The HUVEC cells were harvested using accutase (PAA, L11-007) and seeded in columns 2 to 12 of 96-well plates (Falcon MICROTEST tissue culture plate 96-well flat bottom, BD 353075, or µCLEAR-PLATE, black, 96-well, Greiner Bio-One, No. 655090) at a cell density of 2500 cells/ well in 100 µl Vasculife VEGF complete medium with column 1 remaining empty as blank. Cells were allowed to incubate at 37°C and 5% CO_2 for at least 6 h. Then, the cells were washed once with PBS and starved overnight in Vasculife basal medium (Cellsystems, LM-0002) containing heparin, ascorbate and L-glutamine (components of the Vasculife Life Factors Kit, Cellsystems, LL-1020) as well as 0.2% FBS.

After about 18 h, the starving medium was discarded, and the cells were exposed for 72 h to 9 consecutive log or half-log concentrations of test compound in the range of 10 pM to 30 µM and to 5, 10 or 20 ng/ml hFGF-2 (recombinant human FGF basic, R&D Systems, 233-FB) in 100 µl starving medium. 10 mM stock solutions of test compounds in DMSO were diluted to 200 x final concentration in DMSO resulting in a final DMSO concentration of 0.5% in all wells. Controls consisted of cells grown in starving medium only and of cells grown in hFGF-2 containing starving medium with 0.5% DMSO. To determine cell proliferation, 5 µl Alamar Blue solution (Biosource, DAL1100) was added to each well (1:20 dilution), and the cells were allowed to incubate for further 4 h at 37°C and 5% CO_2 before measuring fluorescence (ex. 535 nm, em. 595 nm) with a Spectrafluor Plus Tecan plate reader (XFLUOR4 version 4.20). In some experiments, an ATP Determination Kit (BIAFFIN GmbH, LBR-T100) was used according to the manufacturer's instructions. In each experiment, samples were assayed in triplicate, and the standard deviations were determined. GraphPad Prism 5 software was used to analyze the data and to obtain IC_{50} values. All test compounds were assayed 2 to 10 times in independent experiments and similar results were obtained.

The data listed in Table 4 below represent the IC_{50} values for representative compounds of the invention resulting from the corresponding averaged pIC_{50} values:

Table 4

Example No.	hFGF-2 mediated HUVEC proliferation, IC_{50} [nM]
1	16.4
4	17.5
5	5.3
8	9.7
10	16.0
11	150.0
13	17.0
14	25.0
16	117.3
18	10.4
21	3.7
26	56.7
34	37.3
38	213.3
39	365.0
45	171.0
46	84.5
48	360.0
51	1.2
52	4.0

Example No.	hFGF-2 mediated HUVEC proliferation, IC_{50} [nM]
54	2.2
56	18.1
57	3.2
59	51.1
60	250.0
64	4.5
68	14.4
71	5.4
72	1.6
73	5.5
74	0.2
75	1.5
76	1.5
77	3.2
79	3.5
80	1.6
81	1.6
84	46.6
85	126.0

Most compounds of the present invention displayed about ten- to hundred-fold reduced inhibitory activity in this proliferation assay when vascular endothelial growth factor (VEGF-A_{165} isoform) was used as mediating growth factor (instead of FGF-2), indicating a significant selectivity of these compounds for FGFR versus VEGFR kinases.

B-6. Human xenograft and syngeneic tumor models

Different tumor models have been conducted in order to profile compounds of the present invention *in vivo*. Human, rat or mouse tumor cells were cultivated *in vitro* and implanted into either immunodeficient or immunocompetent mice, or immunodeficient rats. Treatment started after tumor establishment, and tumor-bearing animals were treated with substances via different routes (per os, intravenously, intraperitoneally or subcutaneously). Substances were tested as monotherapy or in combination therapy with other pharmacological substances. Treatment of the tumor-bearing animals was conducted until the tumors reached an average size of 120 mm^2. Tumors were measured in two dimensions using a caliper, and tumor volume was calculated according to the formula (length x $width^2$)/2. Substance efficacy was evaluated at the end of the experiment using the T/C ratio [T = final tumor weight in the treated group; C = final tumor weight in the control group]. Statistical significance of the efficacy between control and treated groups was determined using the ANOVA variance test. All animal studies were conducted according to the German regulatory guidelines.

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

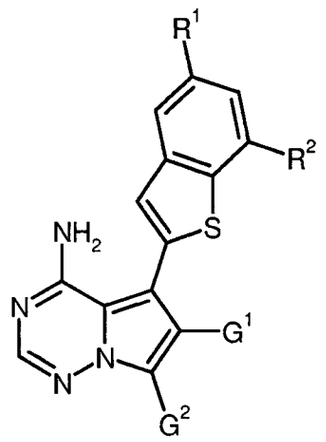
magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8 mg of lactose. Appropriate aqueous and non-aqueous coatings may be applied to increase palatability, improve elegance and stability, or delay absorption.

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

R^1 is hydrogen, chloro, methyl or methoxy,

R^2 is hydrogen or methoxy,

with the proviso that at least one of R^1 and R^2 is other than hydrogen,

G^1 represents chloro, $(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_4)$-alkoxycarbonyl, 5-membered aza-heteroaryl, or the group $-CH_2\text{-}OR^3$, $-CH_2\text{-}NR^4R^5$ or $-C(=O)\text{-}NR^4R^6$, wherein

R^3 is hydrogen, $(C_1\text{-}C_4)$-alkyl, $(C_3\text{-}C_6)$-cycloalkyl or phenyl,

(*i*) said $(C_1\text{-}C_4)$-alkyl is optionally substituted with hydroxy, $(C_1\text{-}C_4)$-alkoxy, hydroxycarbonyl, $(C_1\text{-}C_4)$-alkoxycarbonyl, amino, aminocarbonyl, mono-$(C_1\text{-}C_4)$-alkylaminocarbonyl, di-$(C_1\text{-}C_4)$-alkylaminocarbonyl, $(C_3\text{-}C_6)$-cycloalkyl or up to three fluoro atoms,

and

(*ii*) said $(C_3\text{-}C_6)$-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of $(C_1\text{-}C_4)$-alkyl, hydroxy and amino,

and

(*iii*) said phenyl is optionally substituted with one or two substituents independently selected from the group consisting of fluoro, chloro, bromo, cyano, trifluoromethyl, trifluoromethoxy, (C_1-C_4)-alkyl and (C_1-C_4)-alkoxy,

R^4 is hydrogen or (C_1-C_4)-alkyl,

R^5 is hydrogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkylcarbonyl, (C_3-C_6)-cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein

(*i*) said (C_1-C_4)-alkyl is optionally substituted with hydroxy, (C_1-C_4)-alkoxy, hydroxycarbonyl, (C_1-C_4)-alkoxycarbonyl, aminocarbonyl, mono-(C_1-C_4)-alkylaminocarbonyl, di-(C_1-C_4)-alkylaminocarbonyl or (C_3-C_6)-cycloalkyl,

and

(*ii*) said (C_3-C_6)-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy and amino,

and

(*iii*) said 4- to 6-membered heterocycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy, oxo and amino,

R^6 is hydrogen, (C_1-C_4)-alkyl, (C_3-C_6)-cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein

(*i*) said (C_1-C_4)-alkyl is optionally substituted with hydroxy, (C_1-C_4)-alkoxy, hydroxycarbonyl, (C_1-C_4)-alkoxycarbonyl, amino, aminocarbonyl, mono-(C_1-C_4)-alkylaminocarbonyl, di-(C_1-C_4)-alkylaminocarbonyl or (C_3-C_6)-cycloalkyl,

and

(*ii*) said (C_3-C_6)-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy and amino,

and

(*iii*) said 4- to 6-membered heterocycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy, oxo and amino,

or

R^4 and R^5, or R^4 and R^6, respectively, are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 4- to 7-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from $N(R^7)$ and O, and which may be substituted on ring carbon atoms with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, oxo, hydroxy, amino and aminocarbonyl, and wherein

R^7 is hydrogen, (C_1-C_4)-alkyl, formyl or (C_1-C_4)-alkylcarbonyl,

and

G^2 represents chloro, cyano, (C_1-C_4)-alkyl, or the group $-CR^{8A}R^{8B}$-OH, $-CH_2-NR^9R^{10}$ or $-C(=O)-NR^{11}R^{12}$, wherein

R^{8A} and R^{8B} are independently selected from the group consisting of hydrogen, (C_1-C_4)-alkyl, cyclopropyl and cyclobutyl,

R^9 is hydrogen or (C_1-C_4)-alkyl,

R^{10} is hydrogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkylcarbonyl, (C_3-C_6)-cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein

(*i*) said (C_1-C_4)-alkyl is optionally substituted with hydroxy, amino, aminocarbonyl, mono-(C_1-C_4)-alkylaminocarbonyl or di-(C_1-C_4)-alkylaminocarbonyl,

and

(*ii*) said (C_3-C_6)-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy and amino,

and

(*iii*) said 4- to 6-membered heterocycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy, oxo and amino,

R^{11} is hydrogen or (C_1-C_4)-alkyl,

R^{12} is hydrogen, (C_1-C_4)-alkyl, (C_3-C_6)-cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein

(*i*) said (C_1-C_4)-alkyl is optionally substituted with hydroxy, amino, aminocarbonyl, mono-(C_1-C_4)-alkylaminocarbonyl or di-(C_1-C_4)-alkylaminocarbonyl,

and

(*ii*) said (C_3-C_6)-cycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy and amino,

and

(*iii*) said 4- to 6-membered heterocycloalkyl is optionally substituted with one or two substituents independently selected from the group consisting of (C_1-C_4)-alkyl, hydroxy, oxo and amino,

or

R^9 and R^{10}, or R^{11} and R^{12}, respectively, are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 4- to 7-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from $N(R^{13})$, O, S and $S(O)_2$, and which may be substituted on ring carbon atoms with up to three substituents independently selected from the group consisting of fluoro, (C_1-C_4)-alkyl, oxo, hydroxy, amino and aminocarbonyl, and wherein

R^{13} is hydrogen, (C_1-C_4)-alkyl, (C_3-C_6)-cycloalkyl, formyl or (C_1-C_4)-alkylcarbonyl,

with the proviso that G^1 is not chloro when G^2 is chloro or cyano,

or a pharmaceutically acceptable salt, hydrate and/or solvate thereof.

2. The compound of formula (I) according to Claim 1, wherein

R^1 is chloro, methyl or methoxy,

R^2 is hydrogen or methoxy,

G^1 represents chloro, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxycarbonyl or 5-membered aza-heteroaryl selected from the group consisting of pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl, or represents the group $-CH_2-OR^3$ or $-CH_2-NR^4R^5$, wherein

R^3 is hydrogen, (C_1-C_4)-alkyl or (C_3-C_6)-cycloalkyl,

wherein said (C_1-C_4)-alkyl is optionally substituted with hydroxy, (C_1-C_4)-alkoxy, hydroxycarbonyl, (C_1-C_4)-alkoxycarbonyl, amino, aminocarbonyl, (C_3-C_6)-cycloalkyl or up to three fluoro atoms,

R^4 is hydrogen or (C_1-C_4)-alkyl,

R^5 is hydrogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkylcarbonyl, (C_3-C_6)-cycloalkyl or 5- or 6-membered heterocycloalkyl, wherein

(*i*) said (C_1-C_4)-alkyl is optionally substituted with hydroxy, hydroxy-carbonyl or (C_3-C_6)-cycloalkyl,

and

(*ii*) said 5- or 6-membered heterocycloalkyl is optionally substituted with oxo,

or

R^4 and R^5 are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 4- to 6-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from $N(R^7)$ and O, and which may be substituted on a ring carbon atom with oxo or hydroxy, and wherein

R^7 is hydrogen or (C_1-C_4)-alkyl,

and

G^2 represents chloro, cyano, (C_1-C_4)-alkyl, or the group $-CR^{8A}R^{8B}-OH$, $-CH_2-NR^9R^{10}$ or $-C(=O)-NR^{11}R^{12}$, wherein

R^{8A} and R^{8B} are independently selected from the group consisting of hydrogen, (C_1-C_4)-alkyl and cyclopropyl,

R^9 is hydrogen or methyl,

R^{10} is hydrogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkylcarbonyl, (C_3-C_6)-cycloalkyl or 5- or 6-membered heterocycloalkyl, wherein

(*i*) said (C_1-C_4)-alkyl is optionally substituted with hydroxy or aminocarbonyl,

and

(*ii*) said 5- or 6-membered heterocycloalkyl is optionally substituted with oxo,

R^{11} is hydrogen or methyl,

R^{12} is hydrogen, (C_1-C_4)-alkyl, (C_3-C_6)-cycloalkyl or 5- or 6-membered heterocycloalkyl, wherein

(*i*) said (C_1-C_4)-alkyl is optionally substituted with hydroxy,

and

(*ii*) said 5- or 6-membered heterocycloalkyl is optionally substituted with oxo,

or

R^9 and R^{10}, or R^{11} and R^{12}, respectively, are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 4- to 6-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from $N(R^{13})$, O, S and $S(O)_2$, and which may be substituted on ring carbon atoms with up to three substituents independently selected from the group consisting of fluoro, (C_1-C_4)-alkyl, oxo, hydroxy, amino and aminocarbonyl, and wherein

R^{13} is hydrogen, (C_1-C_4)-alkyl, cyclopropyl, cyclobutyl, formyl or (C_1-C_4)-alkylcarbonyl,

with the proviso that G^1 is not chloro when G^2 is chloro or cyano,

or a pharmaceutically acceptable salt, hydrate and/or solvate thereof.

3. The compound of formula (I) according to Claim 1 or 2, wherein

R^1 is methyl,

R^2 is methoxy,

G^1 represents methyl, oxazol-5-yl or the group $-CH_2-OR^3$ or $-CH_2-NR^4R^5$, wherein

R^3 is hydrogen, (C_1-C_4)-alkyl, cyclopropyl or cyclobutyl,

wherein said (C_1-C_4)-alkyl is optionally substituted with hydroxy, methoxy, ethoxy, hydroxycarbonyl, methoxycarbonyl, ethoxycarbonyl, amino, aminocarbonyl, cyclopropyl, cyclobutyl or up to three fluoro atoms;

R^4 is hydrogen, methyl or ethyl,

R^5 is hydrogen, (C_1-C_4)-alkyl, acetyl, cyclopropyl, cyclobutyl or 2-oxopyrrolidin-3-yl,

wherein said (C_1-C_4)-alkyl is optionally substituted with hydroxy, hydroxycarbonyl, cyclopropyl or cyclobutyl,

or

R^4 and R^5 are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 5- or 6-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from NH and O, and which may be substituted on a ring carbon atom with oxo or hydroxy,

and

G^2 represents methyl or the group $-CR^{8A}R^{8B}-OH$, $-CH_2-NR^9R^{10}$ or $-C(=O)-NR^{11}R^{12}$, wherein

R^{8A} and R^{8B} are independently hydrogen or methyl,

R^9 is hydrogen,

R^{10} is hydrogen, (C_1-C_4)-alkyl, acetyl, cyclopropyl, cyclobutyl or 2-oxopyrrolidin-3-yl,

wherein said (C_1-C_4)-alkyl is optionally substituted with hydroxy or aminocarbonyl,

R^{11} is hydrogen or methyl,

R^{12} is hydrogen, (C_1-C_4)-alkyl, cyclopropyl, cyclobutyl or 2-oxopyrrolidin-3-yl,

wherein said (C_1-C_4)-alkyl is optionally substituted with hydroxy,

or

R^9 and R^{10}, or R^{11} and R^{12}, respectively, are joined and, taken together with the nitrogen atom to which they are attached, form a monocyclic, saturated 4- to 6-membered heterocycloalkyl ring which may contain a second ring heteroatom selected from $N(R^{13})$, O and $S(O)_2$, and which may be substituted on ring carbon atoms with up to three substituents independently selected from the group consisting of fluoro, methyl, oxo, hydroxy, amino and aminocarbonyl, and wherein

R^{13} is hydrogen, formyl or acetyl,

or a pharmaceutically acceptable salt, hydrate and/or solvate thereof.

4. The compound of formula (I) according to Claim 1, 2 or 3, wherein

R^1 is methyl,

R^2 is methoxy,

G^1 represents the group $-CH_2-OR^3$, wherein

R^3 is (C_1-C_4)-alkyl optionally substituted with hydroxy, amino or aminocarbonyl,

and

G^2 represents the group $-CH_2-NR^9R^{10}$ or $-C(=O)-NR^{11}R^{12}$, wherein

R^9 is hydrogen,

R^{10} is 2-oxopyrrolidin-3-yl,

or

R^9 and R^{10} are joined and, taken together with the nitrogen atom to which they are attached, form a piperazin-1-yl, 3-oxopiperazin-1-yl or 4-acetylpiperazin-1-yl ring,

R^{11} is hydrogen,

R^{12} is 2-oxopyrrolidin-3-yl,

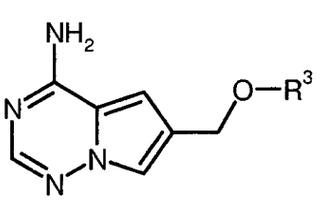
or

R^{11} and R^{12} are joined and, taken together with the nitrogen atom to which they are attached, form a 3-hydroxyazetidin-1-yl, 4-hydroxypiperidin-1-yl or 3-oxo-piperazin-1-yl ring,

or a pharmaceutically acceptable salt, hydrate and/or solvate thereof.

5. Process for preparing a compound of formula (I) as defined in Claims 1 to 4, characterized in that

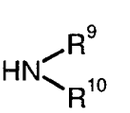
[A] a 6-substituted 4-aminopyrrolo[2,1-f][1,2,4]triazine of formula (II)



(II),

wherein R^3 has the meaning indicated in Claim 1 to 4,

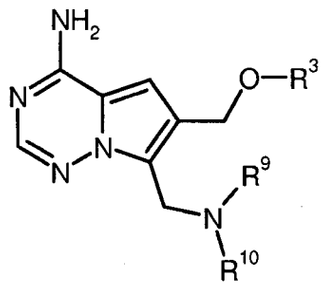
is at first reacted with formaldehyde and an amine of formula (III)



(III),

wherein R^9 and R^{10} have the meanings indicated in Claim 1 to 4,

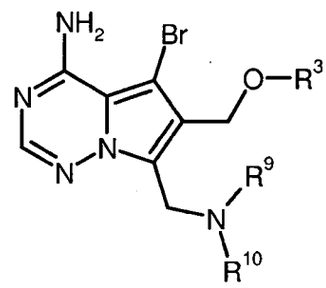
in the presence of an acid to give a compound of formula (IV)



(IV),

wherein R^3, R^9 and R^{10} have the meanings indicated in Claim 1 to 4,

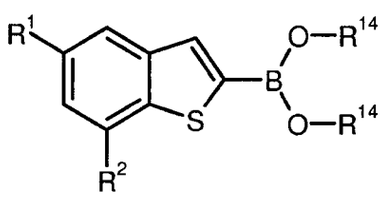
then brominated to a compound of formula (V)



(V),

wherein R^3, R^9 and R^{10} have the meanings indicated in Claim 1 to 4,

and subsequently coupled with a benzothiophen-2-yl boronate of formula (VI)



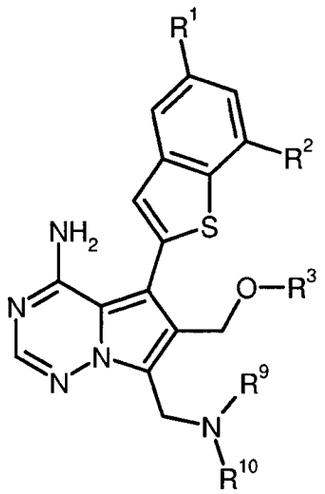
(VI),

wherein R^1 and R^2 have the meanings indicated in Claim 1 to 4,

and

R^{14} represents hydrogen or $(C_1$-$C_4)$-alkyl, or both R^{14} residues are linked together to form a $-(CH_2)_2-$, $-C(CH_3)_2-C(CH_3)_2-$, $-(CH_2)_3-$, $-CH_2-C(CH_3)_2-CH_2-$ or $-C(=O)-CH_2-N(CH_3)-CH_2-C(=O)-$ bridge,

in the presence of a palladium catalyst and a base to yield the target compound of formula (I-A)

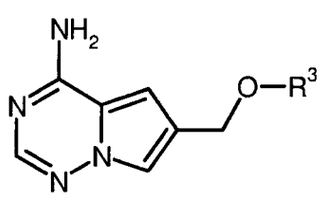


(I-A),

wherein R^1, R^2, R^3, R^9 and R^{10} have the meanings indicated in Claim 1 to 4,

or

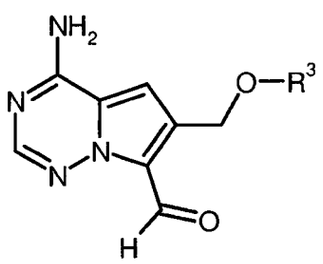
[B] a 6-substituted 4-aminopyrrolo[2,1-f][1,2,4]triazine of formula (II)



(II),

wherein R^3 has the meaning indicated in Claim 1 to 4,

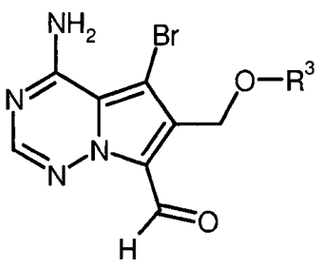
is at first formylated with *N,N*-dimethylformamide in the presence of phosphoryl chloride to an aldehyde of formula (VII)



(VII),

wherein R^3 has the meaning indicated in Claim 1 to 4,

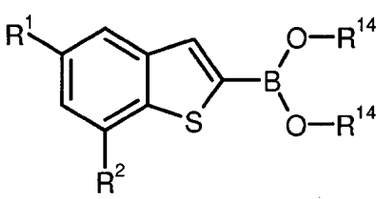
then brominated to a compound of formula (VIII)



(VIII),

wherein R^3 has the meaning indicated in Claim 1 to 4,

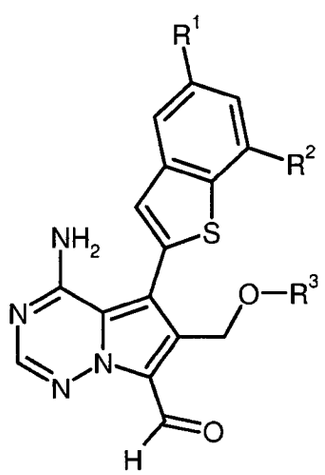
and subsequently coupled with a benzothiophen-2-yl boronate of formula (VI)



(VI),

wherein R^1, R^2 and R^{14} have the meanings indicated above,

in the presence of a palladium catalyst and a base to give a compound of formula (IX)

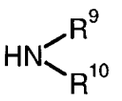


(IX),

wherein R^1, R^2 and R^3 have the meanings indicated in Claim 1 to 4,

which then is either

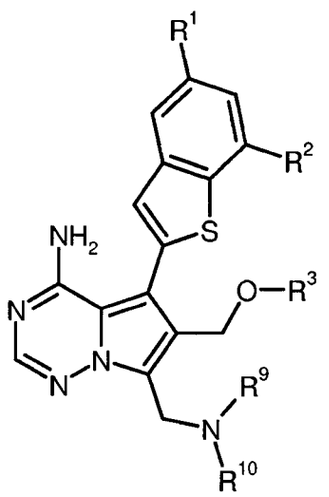
[B-1] reacted with an amine of formula (III)



(III),

wherein R^9 and R^{10} have the meanings indicated in Claim 1 to 4,

in the presence of an acid and a reducing agent to yield the target compound of formula (I-A)

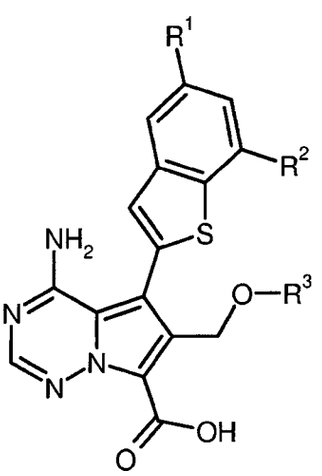


(I-A),

wherein R^1, R^2, R^3, R^9 and R^{10} have the meanings indicated in Claim 1 to 4,

or

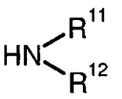
[B-2] oxidized to a carboxylic acid of formula (X)



(X),

wherein R^1, R^2 and R^3 have the meanings indicated in Claim 1 to 4,

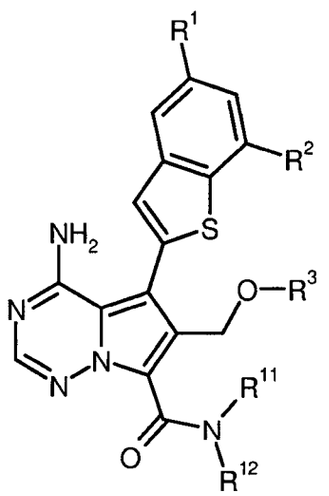
and finally coupled with an amine of formula (XI)



(XI),

wherein R^{11} and R^{12} have the meanings indicated in Claim 1 to 4,

in the presence of a condensing agent to yield the target compound of formula (I-B)

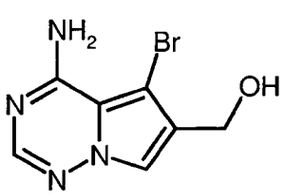


(I-B),

wherein R^1, R^2, R^3, R^{11} and R^{12} have the meanings indicated in Claim 1 to 4,

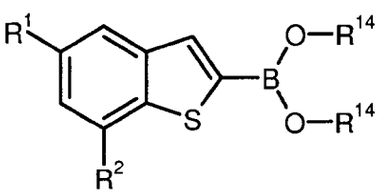
or

[C] a 6-substituted 4-amino-5-bromopyrrolo[2,1-f][1,2,4]triazine of formula (XII)



(XII)

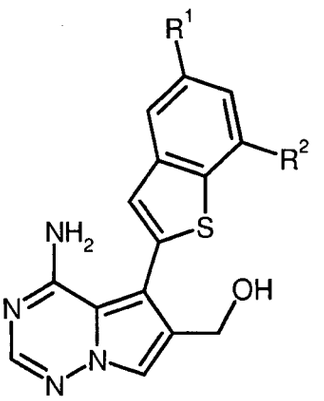
is at first coupled with a benzothiophen-2-yl boronate of formula (VI)



(VI),

wherein R^1, R^2 and R^{14} have the meanings indicated above,

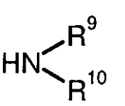
in the presence of a palladium catalyst and a base to give a compound of formula (XIII)



(XIII),

wherein R^1 and R^2 have the meanings indicated in Claim 1 to 4,

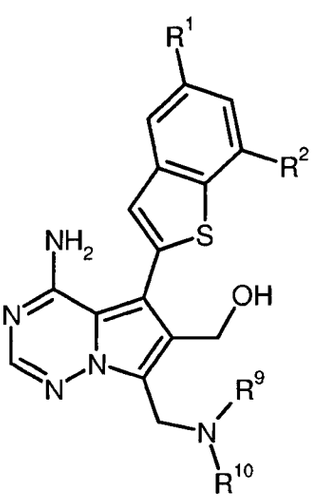
and then reacted with formaldehyde and an amine of formula (III)



(III),

wherein R^9 and R^{10} have the meanings indicated in Claim 1 to 4,

in the presence of an acid to yield the compound of formula (I-C)

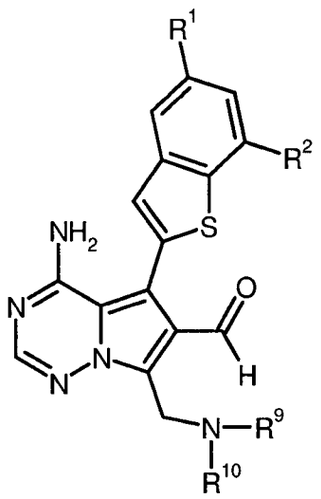


(I-C),

wherein R^1, R^2, R^9 and R^{10} have the meanings indicated in Claim 1 to 4,

which subsequently is either

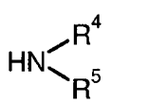
[C-1] oxidized to an aldehyde of formula (XIV)



(XIV),

wherein R^1, R^2, R^9 and R^{10} have the meanings indicated in Claim 1 to 4,

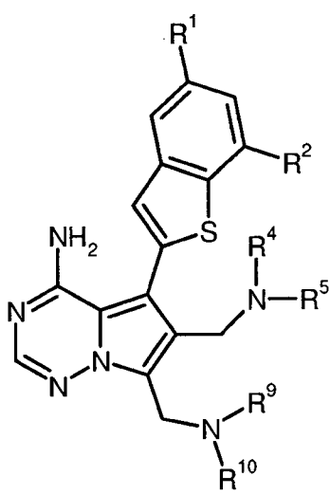
and treated with an amine of formula (XV)



(XV),

wherein R^4 and R^5 have the meanings indicated in Claim 1 to 4,

in the presence of an acid and a reducing agent to yield the target compound of formula (I-D)

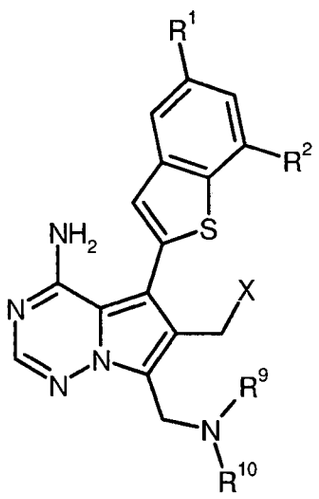


(I-D),

wherein R^1, R^2, R^4, R^5, R^9 and R^{10} have the meanings indicated in Claim 1 to 4,

or

[C-2] converted into the corresponding 6-(halomethyl) derivative of formula (XVI)



(XVI),

wherein R^1, R^2, R^9 and R^{10} have the meanings indicated in Claim 1 to 4,

and

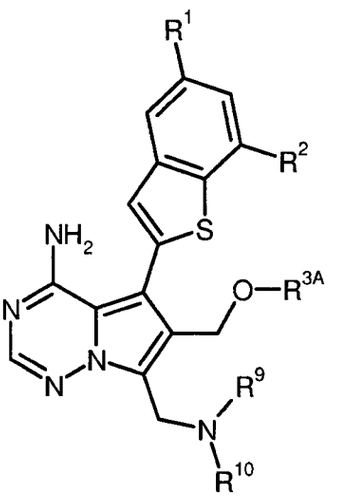
X is chloro, bromo or iodo,

and treated with an alcohol of formula (XVII)

$$R^{3A}—OH \quad (XVII),$$

wherein R^{3A} has the meaning of R^3 as indicated in Claim 1 to 4, except for hydrogen,

in the presence of a base to yield the target compound of formula (I-E)



(I-E),

wherein R^1, R^2, R^{3A}, R^9 and R^{10} have the meanings indicated above,

optionally followed, where appropriate, by (*i*) separating the compounds of formula (I) thus obtained 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 or bases.

6. Compound as defined in any of Claims 1 to 4 for the treatment and/or prevention of diseases.

7. Compound as defined in any of Claims 1 to 4 for use in a method for the treatment and/or prevention of cancer and tumor diseases.

8. Use of a compound as defined in any of Claims 1 to 4 for the manufacture of a pharmaceutical composition for the treatment and/or prevention of cancer and tumor diseases.

9. Pharmaceutical composition comprising a compound as defined in any of Claims 1 to 4 and one or more pharmaceutically acceptable excipients.

10. The pharmaceutical composition of Claim 9 further comprising one or more additional therapeutic agents.

11. The pharmaceutical composition as defined in Claim 9 or 10 for the treatment and/or prevention of cancer and tumor diseases.

12. Method for the treatment and/or prevention of cancer and tumor diseases 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 4, or of a pharmaceutical composition as defined in any of Claims 9 to 11.

BHC 11 1 045

Disubstituted benzothienyl-pyrrolotriazines and uses thereof

Abstract

This invention relates to novel substituted 5-(1-benzothiophen-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine derivatives having protein tyrosine kinase inhibitory activities, 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 proliferative disorders, in particular cancer and tumor diseases.

768

PATENT COOPERATION TREATY PCT/EP2012/074977

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION, OBTENTION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

BAYER INTELLECTUAL PROPERTY GMBH
Alfred-Nobel-Str. 10
40789 Monheim
ALLEMAGNE

Date of mailing *(day/month/year)* 17 January 2013 (17.01.2013)	
Applicant's or agent's file reference BHC111045-WO	**IMPORTANT NOTIFICATION**
International application No. PCT/EP2012/074977	International filing date *(day/month/year)* 10 December 2012 (10.12.2012)
International publication date *(day/month/year)* **Not yet published**	Priority date *(day/month/year)* 15 December 2011 (15.12.2011)
Applicant BAYER PHARMA AKTIENGESELLSCHAFT 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
15 December 2011 (15.12.2011)	11193841.1	EP	10 January 2013 (10.01.2013)

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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Authorized officer
Agnès Wittmann-Regis
e-mail pt06.pct@wipo.int
Telephone No. +41 22 338 74 06

769

PATENT COOPERATION TREATY PCT/EP2012/074977

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NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

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Alfred-Nobel-Str. 10
40789 Monheim
ALLEMAGNE

Date of mailing *(day/month/year)*
20 May 2014 (20.05.2014)

Applicant's or agent's file reference
BHC111045-WO

IMPORTANT NOTIFICATION

International application No.
PCT/EP2012/074977

International filing date *(day/month/year)*
10 December 2012 (10.12.2012)

1. The following indications appeared on record concerning:

☐ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
VOEHRINGER, Verena
Fischergasse 17
88364 Wolfegg
Germany

State of Nationality | State of Residence

Telephone No.

Facsimile No.

E-mail address

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address
VÖHRINGER, Verena
Fischergasse 17
88364 Wolfegg
Germany

State of Nationality | State of Residence

Telephone No.

Facsimile No.

E-mail address
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

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Authorized officer
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e-mail pt06.pct@wipo.int
Telephone No. +41 22 338 74 06

770

PATENT COOPERATION TREATY PCT/EP2012/074977

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

BAYER INTELLECTUAL PROPERTY GMBH
Alfred-Nobel-Str. 10
40789 Monheim
ALLEMAGNE

Date of mailing *(day/month/year)*
20 May 2014 (20.05.2014)

Applicant's or agent's file reference
BHC111045-WO

IMPORTANT NOTIFICATION

International application No.
PCT/EP2012/074977

International filing date *(day/month/year)*
10 December 2012 (10.12.2012)

1. The following indications appeared on record concerning:

☐ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
COLLIN, Marie-Pierre
Ottenbrucherstr. 38
42105 Wuppertal
Germany

State of Nationality | State of Residence

Telephone No.

Facsimile No.

E-mail address

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
COLLIN, Marie-Pierre
Katernberger Schulweg 52
42113 Wuppertal
Germany

State of Nationality | State of Residence

Telephone No.

Facsimile No.

E-mail address
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 89 70

Authorized officer
Rochaix Thomas
e-mail pt06.pct@wipo.int
Telephone No. +41 22 338 74 06

771

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Bogotá D.C., Junio 06 de 2014 - 14:06:02

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*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	589997240	05/06/2014	26.507.000.00

*** Conceptos Pagados ***

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

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

Responsable: _____
-*****-
Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 14-123802- -00000-0000
Fecha: 2014-06-09 14:44:51 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 772 773

772

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 14 - 0060992

Bogotá D.C., Junio 09 de 2014 - 14:30:38

RECIBIDO DE : POSSE HERRERA & RUIZ S.A. NI 830.022.196 RE

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
RECIBO DE CA	999999999	52480	19/05/2014		52.000.00
RECIBO DE CA	999999999	54395	23/05/2014		21.000.00
RECIBO DE CA	999999999	54396	23/05/2014		21.000.00
RECIBO DE CA	999999999	57281	30/05/2014		1.000.00
RECIBO DE CA	999999999	60396	06/06/2014		773.000.00
RECIBO DE CA	999999999	60397	06/06/2014		773.000.00
RECIBO DE CA	999999999	60398	06/06/2014		773.000.00
RECIBO DE CA	999999999	60399	06/06/2014		773.000.00
RECIBO DE CA	999999999	60400	06/06/2014		773.000.00
RECIBO DE CA	999999999	60401	06/06/2014		773.000.00
RECIBO DE CA	999999999	60402	06/06/2014		773.000.00
RECIBO DE CA	999999999	60403	06/06/2014		773.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
2	50005-01-01 SOLICITUDES	1607 REIVINDICACION PATENTE UNITARIA ADICIONAL A LAS 10 INIC	31.000.00	62.000.00
				$62.000.00

SON: **SESENTA Y DOS MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-******-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 14-123802- -00000-0000

Fecha: 2014-06-09 14:44:51 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
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Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 14-123802- -00000-0000

Fecha: 2014-06-09 14:44:51 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: ~~772~~ 773

773

PATENTE DE INVENCIÓN ☐ **MODELC**

- ☐ 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 ☐