

Bogotá D.C., 7 de diciembre de 2016

Doctor
JOSÉ LUIS SALAZAR LÓPEZ
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Ciudad

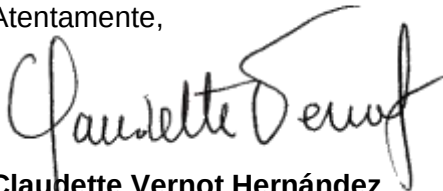
Expediente	14 - 155955
Patente	NUEVOS DERIVADOS DE PIRROL, SU PROCEDIMIENTO DE PREPARACIÓN Y LAS COMPOSICIONES FARMACÉUTICAS QUE LOS CONTIENEN
Solicitante	LES LABORATORIES SERVIER VERNALIS (R&D) LTD
Asunto	COMPLEMENTO DE INFORMACIÓN

CLAUDETTE VERNOT HERNÁNDEZ, mayor de edad, identificada con la cédula de ciudadanía No. 51.722.517 expedida en Bogotá, portadora de la tarjeta profesional No. 57.111 del Consejo Superior de la Judicatura, actuando en calidad de apoderada de **LES LABORATORIES SERVIER** y **VERNALIS (R&D) LTD**, conforme a los poderes que obran en el expediente, por medio del presente y encontrándome dentro del término concedido en virtud de la prórroga solicitada con fundamento en lo establecido en el artículo 45 de la Decisión 486 de 2000, me permito allegar al expediente la respuesta a los requerimientos efectuados mediante Oficio No. 8876 del 31 de agosto de 2016, en la cual se incluye la traducción al español de nuevo capítulo de reivindicaciones.

ANEXOS:

1. Respuesta al Oficio No. 8876 del 31 de agosto de 2016.
2. Comprobante de pago de solicitud de prórroga.

Atentamente,



Claudette Vernot Hernández
C.C. No. 51.722.517 de Bogotá.
T.P. No. 57.111 del C.S de la J.

Bogotá D.C., 28 de noviembre de 2016

Doctor
JOSÉ LUIS SALAZAR LÓPEZ
Dirección de Nuevas Creaciones
Superintendencia de Industria y Comercio
Ciudad

Expediente	14 - 155955
Patente	NUEVOS DERIVADOS DE PIRROL, SU PROCEDIMIENTO DE PREPARACIÓN Y LAS COMPOSICIONES FARMACÉUTICAS QUE LOS CONTIENEN
Solicitante	LES LABORATORIES SERVIER VERNALIS (R&D) LTD
Asunto	RESPUESTA AL OFICIO 8876 DEL 31 DE AGOSTO DE 2016

CLAUDETTE VERNOT HERNÁNDEZ, mayor de edad, identificada con la cédula de ciudadanía No. 51.722.517 expedida en Bogotá, portadora de la tarjeta profesional No. 57.111 del Consejo Superior de la Judicatura, actuando en calidad de apoderada de **LES LABORATORIES SERVIER** y **VERNALIS (R&D) LTD**, conforme a los poderes que obran en el expediente, por medio del presente escrito y encontrándome dentro del término concedido, me dirijo a usted para dar respuesta al requerimiento efectuado mediante Oficio 8876 del 31 de agosto de 2016.

I. RESPUESTA A LOS REQUERIMIENTOS

• **EXCEPCIÓN DE PATENTABILIDAD**

Manifiesta el examinador que el objeto de las reivindicaciones 19 a 26 y 29 a 31 no es patentable de acuerdo con el literal d) del artículo 20 de la Decisión 486 de 2000.

Por lo anterior, se ha decidido eliminar las reivindicaciones 19 a 26 y 29 a 31 las cuales se refieren a usos terapéuticos específicos de los compuestos de la invención.

• **DE LA SOLICITUD DE LA PATENTE**

Título

Manifiesta el examinador que el título no refleja completamente el alcance de la solicitud ya que la expresión “nuevos derivados del pirrol” es ambigua y amplia, razón por la cual sugiere dar un título más concreto a la solicitud.

Por lo anterior se propone modificar el título de la siguiente forma:

“Nuevos derivados de 5- [2- (3,4-dihidroisoquinolina-2 (1H) -ilcarbonil) fenil] -1H-pirrol-3-carboxamida, método de preparación de los mismos y composiciones farmacéuticas que los contienen”.

Reivindicaciones

• Con respecto a la reivindicación 1

El examinador es de la opinión que la reivindicación 1 no es clara y que su alcance no es conciso debido a las definiciones de los sustituyentes $A_1 - A_2$, $R_3 - R_4 - R_5$, $R_a - R_d$ las cuales se consideran como demasiado amplias. Por lo tanto, se requiere restringir el alcance de la reivindicación 1 sobre la base de la estructura de los ejemplos que han sido sintetizados, caracterizados (es decir, datos físico químicos disponibles) y probados.

Por favor encuentre adjunto un conjunto de reivindicaciones modificado en las que el alcance de la reivindicación 1 ha sido limitado.

- Con respecto a los grupos A_1 y A_2 :

La mayoría de los grupos descritos en la definición de A_1 y A_2 se han ilustrado a través de los ejemplos divulgados en la especificación. A_1 representa un átomo de hidrógeno en los ejemplos 2-9, A_2 representa un cicloalquilo en el ejemplo 7. Varios grupos alquilo no sustituidos han sido ejemplificados (etilo en el ejemplo 6, propan-2-ilo en el ejemplo 8). Además, se describen y caracterizan varios ejemplos en los que A_1 / A_2 representan un alquilo sustituido (véanse por ejemplo los ejemplos 11, 26, 27, 75, 81 ...). Además, A_1 y A_2 representan un grupo polihaloalquilo en los ejemplos 75 y 94-95, respectivamente.

Por favor tenga en cuenta que el grupo cicloalquilo se eliminó de la definición de A_1 . Las definiciones resultantes de A_1 y A_2 corresponden a una generalización razonable de los ejemplos que han sido caracterizados y probados en la descripción del presente caso.

- Con respecto al grupo T :

Todos los posibles grupos descritos en la definición de T han sido ilustrados a través de los ejemplos divulgados en la especificación; T representa (i) un átomo de hidrógeno en el ejemplo 467; (ii) un grupo alquilo en los ejemplos 1, 23, etc.; (iii) un grupo ($C_1 - C_4$) alquilo- NR_1R_2 en los ejemplos 2-19 ... (véase la discusión en el párrafo siguiente); (iv) un grupo ($C_1 - C_4$) alquilo- OR_6 en el ejemplo 29... Por tanto, la definición de T como fue inicialmente presentada es una generalización razonable de las estructuras de los ejemplos para los cuales se ha demostrado una actividad en la especificación.

- Con respecto a los grupos R_1 y R_2 :

La definición de estos grupos es clara y correspondiente con las estructuras de los compuestos divulgados en la descripción. En particular, se describen muchos ejemplos en los que R_1 y R_2 forman con el átomo de nitrógeno que los porta un heterocicloalquilo. Con respecto al heterocicloalquilo resultante, se han explorado diversos tamaños de anillo:

- (i) los ejemplos 115, 116 y 207 presentan anillo bicíclico;
- (ii) la mayoría de los ejemplos presentan seis miembros de anillo ya que R_1 y R_2 forman con el átomo de nitrógeno que los porta una morfolina o una piperazina.

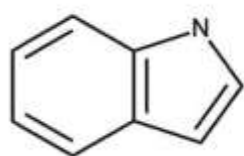
En el ejemplo 2, R_1 y R_2 representan ambos un átomo de hidrógeno.

En conclusión, la definición de R_1 y R_2 es una generalización razonable de las estructuras de los ejemplos para los cuales se ha demostrado una actividad en la especificación.

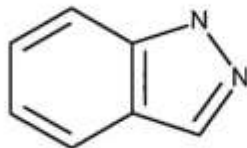
- Con respecto al grupo R_3 :

Aceptamos limitar significativamente la definición de R_3 con base en la estructura de los compuestos ejemplificados (véase el conjunto de reivindicaciones modificado). Todos los grupos posibles mantenidos en la definición de R_3 han sido ilustrados a través de los ejemplos divulgados en la especificación. Más precisamente:

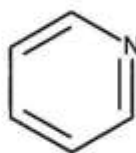
- (i) R_3 representa un alquilo en el ejemplo 64;
- (ii) R_3 representa un grupo arilo (opcionalmente sustituido) en los ejemplos 2, 10-11, 13, 16, 395, 401, etc.;
- (iii) en la mayoría de los casos, R_3 representa un grupo heteroarilo como se define en la reivindicación 1, es decir un grupo mono o bicíclico compuesto por de 5 a 10 miembros de anillo, que tiene al menos una fracción aromática y que contiene de 1 a 4 heteroátomos. Por ejemplo, R_3 puede representar (la siguiente lista no es exhaustiva):



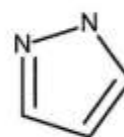
ejemplos 3, 5 etc.



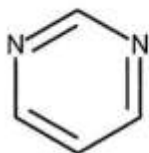
ejemplos 12, 14



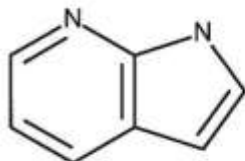
ejemplo 20



ejemplos 21,23-27, etc.



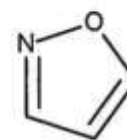
ejemplo 50



ejemplos 63-65



ejemplo 442



ejemplo 462

Así, se han probado varios tipos de anillos heteroarilo (monocíclicos o bicíclicos, incluyendo heteroátomos N, O ó S ...).

En conclusión, la definición modificada de R_3 es una generalización razonable de las estructuras de los ejemplos para los cuales se ha demostrado una actividad en la especificación.

- Con respecto al grupo R_4

Aceptamos limitar significativamente la definición de R_4 con base en la estructura de los compuestos ejemplificados (véase el conjunto de reivindicaciones modificado). En la mayoría de los casos, R_4 representa un fenilo opcionalmente sustituido. También se divulgan ejemplos en los que R_4 representa un heteroarilo (véanse los ejemplos 405, 464).

- Con respecto a las definiciones de los grupos R_a , R_b , R_c y R_d :

También restringimos el alcance de las definiciones de R_{a-d} inicialmente descritas en la reivindicación 1 con base en el contenido de las reivindicaciones 7 y 8 (véase el conjunto de reivindicaciones modificado). Todos los posibles grupos mantenidos en la definición de R_{a-d} se han ilustrado a través de los ejemplos divulgados en la especificación. Por ejemplo:

- (i) R_b y/o R_c representan un átomo de hidrógeno en los ejemplos 1, 2, etc.;
- (ii) uno de los grupos R_b o R_c representan un átomo de halógeno en los ejemplos 1 y 101;
- (iii) uno de los grupos R_b o R_c representa un alcoxi en los ejemplos 24 y 100;
- (iv) en la mayoría de los casos, R_b y R_c representan un alquilo opcionalmente sustituido;
- (v) R_c representa un hidroxilo en el ejemplo 68;
- (vi) por último, en muchos ejemplos (R_b , R_c) forman junto con los átomos de carbono que los portan un anillo, es decir un grupo 1,3-dioxolano en los ejemplos 4, 9, 13-14 o un grupo 1,4-dioxano en el ejemplo 21.

En conclusión, las definiciones modificadas de R_{a-d} son una generalización razonable de las estructuras de los ejemplos para los cuales se ha demostrado una actividad en la especificación. Compuestos tales como R_b o R_c representan R_7 -CO-NH-(C_0 - C_6) alquilo-, R_7 -SO₂-NH- (C_0 - C_6) alquilo-, R_7 -NH-CO-NH- (C_0 - C_6) alquil-, R_7 -O-CO- NH- (C_0 - C_6) - alquilo, etc. han sido excluidos.

Las reivindicaciones iniciales 7 y 8 fueron eliminadas.

- Con respecto a las definiciones de los grupos R_7 y R_7' :

Además de la restricción a las definiciones de R_{a-d} estas definiciones han sido eliminadas.

- Con respecto a la deuteración:

Contrariamente a la afirmación del Examinador, varios compuestos han sido deuterados (véanse en particular las estructuras de los ejemplos 416, 420, 445, 448 - 449). Por lo tanto, queremos mantener las referencias a la deuteración en la definición de la Markush definida en la reivindicación 1.

- Con respecto al término "opcionalmente sustituido":

El examinador es de la opinión que la expresión "opcionalmente sustituido" mencionada en la reivindicación 1 (así como en las reivindicaciones iniciales 3 y 13) no es clara. No estamos de acuerdo. Por ejemplo, T puede representar un grupo alquilo (C_1 - C_6) lineal o ramificado que está sin sustituir o sustituido por de uno a tres átomos de halógeno de acuerdo con la definición de la reivindicación 1 (véase el ejemplo 454). Si es aceptable, sugerimos sustituir la expresión "opcionalmente sustituido" por

"no sustituido o sustituido por" donde sea apropiado, y particularmente en la definición de T (así como en las reivindicaciones iniciales 3 y 13).

Por razones de claridad, la definición general de los sustituyentes dirigidos al arilo, heteroarilo, cicloalquilo, heterocicloalquilo, alquilo y alcoxi han sido restringidas en el conjunto de reivindicaciones modificado. Más exactamente, el término "*opcionalmente sustituido*" ha sido eliminado o reemplazado por "*no sustituido o sustituido por*". Además, se han especificado los tipos de posibles sustituyentes de acuerdo con la estructura de los ejemplos. De hecho, el término "*opcionalmente sustituido*" se cita 4 veces en las definiciones generales detalladas en la reivindicación 1. Más precisamente, este se dirige a los siguientes sustituyentes: alquilo ($C_1 - C_6$) lineal o ramificado; alcoxi ($C_1 - C_6$) lineal o ramificado; arilo; R' y R" los cuales pueden representar en una alternativa específica un grupo alquilo ($C_1 - C_6$) lineal o ramificado. Por favor tenga en cuenta que los posibles sustituyentes de los grupos anteriores han sido restringidos con base en la estructura de los ejemplos divulgados y caracterizados en la descripción (véase el conjunto de reivindicaciones modificado). Más precisamente:

- (i) el grupo alquilo ($C_1 - C_6$) lineal o ramificado está opcionalmente sustituido por una morfolina (*Ejemplo 455*);
- (ii) el grupo alcoxi ($C_1 - C_6$) lineal o ramificado está opcionalmente sustituido con una morfolina (*Ejemplo 456*);
- (iii) el grupo arilo está opcionalmente sustituido por uno o más átomos de halógeno (*Ejemplos 55 y 59*);
- (iv) R' y R", cada uno independientemente del otro, representan un átomo de hidrógeno o un grupo alquilo ($C_1 - C_6$) lineal o ramificado el cual es opcionalmente sustituido por un metoxi (*Ejemplos 99*).

Estas modificaciones están bien soportadas por la descripción (véanse las definiciones de los grupos de la Markush detalladas en las reivindicaciones 3 y 12, así como la estructura específica de los ejemplos listados anteriormente). Los posibles sustituyentes detallados en esta lista reflejan el trabajo de diversificación realizado comúnmente por el Químico Médico una vez que se identifica un armazón general (es decir, la fórmula general (I) en el presente caso) la cual retiene la actividad farmacológica sobre el objetivo (es decir, Bcl-2 en el presente caso).

En conclusión, la definición de la Markush como está propuesta en el conjunto de reivindicaciones modificado es una generalización razonable de las estructuras de los ejemplos que se han caracterizado completamente en la especificación y para los cuales se ha demostrado una actividad (ver las tablas farmacológicas 1-2 en la descripción en donde se han probado aproximadamente 200 compuestos). Además de estas modificaciones y explicaciones, el alcance de la reivindicación 1 para la cual se busca una protección es inequívocamente claro para la persona experta en la técnica.

- **Con respecto a la reivindicación 27**

El Examinador es de la opinión que la reivindicación 27 dirigida a terapias de combinación que incluyen compuestos de fórmula (I) con otros agentes anticancerígenos no es clara y carece de soporte con base en lo divulgado en la descripción. No estamos de acuerdo con tal afirmación. Las terapias de combinación en oncología son probadas actualmente con el fin de mejorar la eficacia de los tratamientos, así como la calidad de vida de los pacientes (véase Komarova y otros Nature, 2013 291; Ann, N.Y. Acad. Sci. 2005 1059: 61-69). Tales estrategias terapéuticas son operaciones de rutina para los médicos clínicos en oncología.

Por lo tanto, la combinación en la reivindicación 27 es una modalidad específica de la invención. Como estas combinaciones genéricas y la correspondiente Markush de fórmula (I) se reivindican en la misma solicitud de patente, no hay necesidad de probar ningún efecto sinérgico en el presente caso. La patentabilidad de las combinaciones se evalúa a partir de la patentabilidad de los compuestos de fórmula (I); estos deben ser considerados como novedosos e inventivos con base en el hecho que los compuestos de fórmula (I) son nuevos e inventivos.

Por razones de claridad, se sugiere reemplazar el término "asociación" por el término "combinación farmacéutica" en la reivindicación 27 (y la reivindicación dependiente 28).

También proponemos reemplazar el término "asociación" por el término "combinación farmacéutica" donde sea apropiado en la descripción.

- **EXAMEN DE PATENTABILIDAD:**

Los siguientes documentos son citados en el reporte de búsqueda:

- D1: Porter y otros, Bioorganic Et Medicinal Chemistry Letters - Cartas de Química Bioorgánica y Medicinal 2009 19 230-233
- D2: W02012162365 A1

El examinador considera que D1 es la técnica anterior más cercana a la presente invención. Además, el Examinador considera que la estructura de los compuestos de la invención es anticipada por la divulgación de D1 + D2. Por lo tanto, el Examinador concluye que la presente invención carece de nivel inventivo, con lo cual no estamos de acuerdo.

Con respecto a D1

Este documento divulga derivados de 1- (2- [1,2,3,4-tetraisoquinolinilcarbonil] fenil) -1H-pirazol, así como su actividad farmacológica como inhibidores selectivos de la proteína Bcl-2. En este documento, R3 representa un grupo seleccionado de -NH₂, -NHCOPh, -NHCOCH₂Ph, -NHCOCH₂OPh, -NHSO₂CH₂Ph, -OCH₂COPh, -OCH₂CO₂H, -NHCOCH₂SPh, -NHCOCH₂Oph.

Las diferencias principales con la fórmula general descrita en la reivindicación 1 de la presente invención son:

- 1) La naturaleza del núcleo central, es decir, un pirazol en D1 frente a un pirrol (en el cual la fracción pirrol, la posición del átomo de nitrógeno con respecto al resto de la molécula ha sido definida con precisión) en nuestra invención,
- 2) La naturaleza de los sustituyentes de la fracción fenilo: R3 como se define en D1 es claramente diferente de Rb y Rc, tal como se define en el conjunto de reivindicaciones modificado.

Con respecto a D2

D2 divulga las siguientes estructuras químicas, así como su actividad anticancerígena (inhibidores de Bcl-2):

En donde la definición de G incluye la fracción 1,2,3,4-tetrahidroisoquinolina.

Sin embargo, los compuestos de D2 presentan las siguientes características:

- 1) la presencia sistemática de un grupo sulfonilcarbamoílo (-CO-NH-SO₂-Q) injertado sobre la fracción fenilo,
- 2) la naturaleza específica del grupo W el cual está situado sobre la fracción fenilo en para posición con respecto al grupo sulfonilcarbamoílo anterior, más precisamente W Representa un grupo seleccionado de pirazol, imidazol, piridina y pirimidina.

Teniendo en cuenta el conocimiento técnico de D2, la persona experta en la técnica llega a la conclusión de que los dos fragmentos antes mencionados son cruciales para la actividad farmacológica de los compuestos sobre el objetivo Bcl-2.

Contrariamente a la afirmación del Examinador, la divulgación combinada de D1 + D2 no permite diseñar las estructuras de los compuestos de nuestra invención. Partiendo de los compuestos divulgados en D1, la persona experta en la materia es incitada a reemplazar R3 con un grupo sulfonilcarbamoílo (-CO-NH-SO₂-Q) el cual se presenta inequívocamente como una característica esencial para la actividad farmacológica de los compuestos en D2. Además, la definición de W en D2 es estrictamente limitada a algunos heterociclos monocíclicos aromáticos los cuales son pirazol, imidazol, piridina o pirimidina. No está sugerido de ninguna manera que W pueda ser reemplazado por otro fragmento heterocíclico, y mucho menos por un grupo de tipo pirrol.

Por lo tanto, la persona experta en la técnica no puede derivar la Markush de la invención combinando fragmentos de D1 y D2 citados por el Examinador. Así, la estructura de los compuestos del presente caso es original con respecto a D1 + D2. Los compuestos de la invención son el resultado de un programa intensivo de investigación con el fin de concebir inhibidores de Bcl-2 potentes y selectivos como se describe en la presente solicitud de patente. Por lo tanto, estos cumplen inequívocamente el requisito de nivel inventivo.

Tenga en cuenta que el caso correspondiente se ha concedido sin modificaciones en los Estados Unidos de América (véase el documento US 9,108,983 B2). El caso correspondiente ha sido permitido en Europa con reivindicaciones modificadas (patente que se concederá en un futuro próximo).

Consideramos que los argumentos y modificaciones expuestas a lo largo del presente escrito permitirán superar las objeciones presentadas por el examinador.

II. ANEXOS

1. Nuevo capítulo de Reivindicaciones.
2. Artículo titulado: Preclinical Modeling of Combination Treatments: Fantasy or Requirement?
3. Artículo titulado: Calculated treatment
4. Documento Patente US 9,108,983 B2

Atentamente,



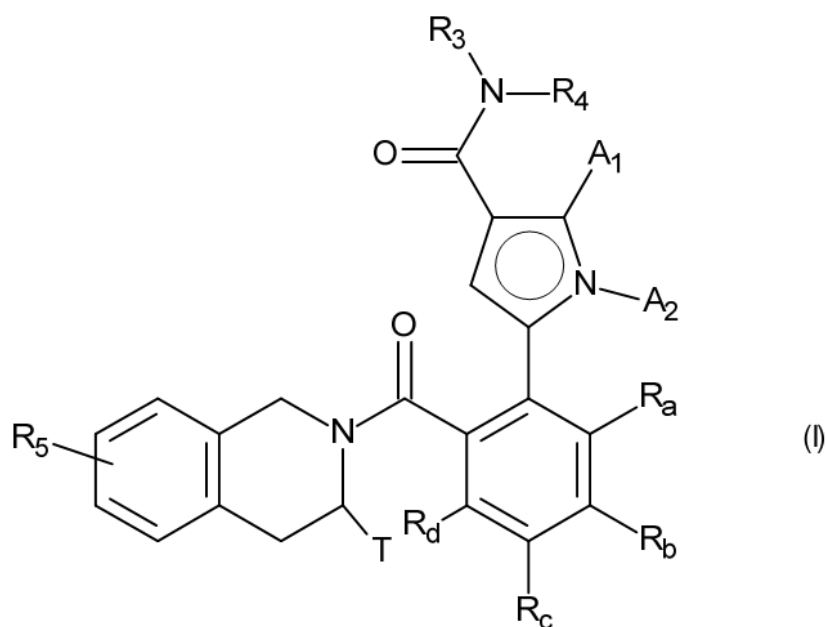
Claudette Vernot Hernández
C.C. No. 51.722.517 de Bogotá.
T.P. No. 57.111 del C.S de la J.

ANEXO 1

REIVINDICACIONES

(modificadas)

1. Compuesto de fórmula (I):



en la que:

- ♦ A₁ representa hidrógeno, un grupo polihalogenoalquilo (C₁-C₆) lineal o ramificado o un grupo alquilo (C₁-C₆) lineal o ramificado,
- ♦ A₂ representa hidrógeno, un grupo polihalogenoalquilo (C₁-C₆) lineal o ramificado, un grupo alquilo (C₁-C₆) lineal o ramificado o un grupo cicloalquilo,
- ♦ T representa un átomo de hidrógeno, un grupo alquilo (C₁-C₆) lineal o ramificado, el cual es no sustituido o sustituido por uno a tres átomos de halógeno, un grupo alquilo-NR₁R₂ (C₁-C₄) o un grupo alquilo-OR₆ (C₁-C₄),
- ♦ R₁ y R₂ representan, independientemente el uno del otro, un átomo de hidrógeno o un grupo alquilo (C₁-C₆) lineal o ramificado, o bien R₁ y R₂ forman con el átomo de nitrógeno al que están unidos un heterocicloalquilo,

- ♦ R₃ representa un grupo alquilo (C₁-C₆) lineal o ramificado, un grupo arilo, o un grupo heteroarilo, en donde uno o más de los átomos de carbono de los grupos precedentes, o los de sus posibles sustituyentes, pueden estar deuterados,
- ♦ R₄ representa un grupo arilo o un grupo heteroarilo, en donde uno o más de los átomos de carbono de los grupos precedentes, o los de sus posibles sustituyentes, pueden estar deuterados,
- ♦ R₅ representa un átomo de hidrógeno o de halógeno,
- ♦ R₆ representa un átomo de hidrógeno o un grupo alquilo (C₁-C₆) lineal o ramificado,
- ♦ R_a y R_d representan cada uno un átomo de hidrógeno y (R_b, R_c), juntos con los átomos de carbono a los que están unidos, forman un grupo 1,3-dioxolano o un grupo 1,4-dioxano; o R_a, R_c y R_d representan cada uno un átomo de hidrógeno y R_b representa átomo de hidrógeno o de halógeno o un grupo metoxi, o:

R_a y R_d representan cada uno un átomo de hidrógeno, R_b representa un átomo de hidrógeno o de halógeno y R_c representa un grupo hidroxil o metoxil, o:

R_a y R_d representan cada uno un átomo de hidrógeno, R_b representa un grupo hidroxil o metoxil y R_c representa un átomo de halógeno,

entendiéndose que:

- por "arilo", se entiende un grupo fenilo, naftilo, bifenilo o indenilo,
- por "heteroarilo", se entiende cualquier grupo mono o bicíclico constituido por 5 a 10 miembros, que posee al menos una parte aromática y que contiene de 1 a 4 heteroátomos elegidos entre oxígeno, azufre y nitrógeno (incluyendo los nitrógenos cuaternarios),
- por "cicloalquilo", se entiende cualquier grupo carbocíclico no aromático, mono o bicíclico, que contiene de 3 a 10 anillos,
- por "heterocicloalquilo", se entiende cualquier grupo fusionado o espiro, no aromático, mono o bicíclico, constituido por desde 3 a 10 anillos y que contiene de 1 a 3 heteroátomos elegidos entre oxígeno, azufre, SO, SO₂ o nitrógeno,

en donde los grupos arilo, heteroarilo, cicloalquilo y heterocicloalquilo así definidos y los grupos alquilo, alquenilo, alquinilo y alcoxi a ser sustituidos con desde 1 a 3 grupos elegidos entre: alquilo (C₁-C₆) lineal o ramificado, el cual es no sustituido o sustituido por morfolina; espiro (C₃-C₆), alcoxi (C₁-C₆) lineal o ramificado, el cual es no sustituido o sustituido por morfolina; alquilo-S-(C₁-C₆); hidroxilo; oxo (o N-óxido llegado el caso); nitro; ciano; -COOR'; -OCOR'; NR'R''; polihaloalquilo (C₁-C₆) lineal o ramificado; trifluorometoxi; alquilsulfonilo (C₁-C₆); halógeno; arilo, el cual es no sustituido o sustituido por uno o más átomos de halógeno; heteroarilo; ariloxi; ariltio; cicloalquilo; heterocicloalquilo, el cual es no sustituido o sustituido por uno o más átomos de halógeno o grupos alquilo, en donde R' y R'' representan, independientemente el uno del otro, un átomo de hidrógeno o un grupo alquilo (C₁-C₆) lineal o ramificado, el cual es no sustituido o sustituido por un metoxi,

sus enantiómeros y diastereoisómeros, así como sus sales de adición con un ácido o base farmacéuticamente aceptable.

2. Compuesto de fórmula (I) según la reivindicación 1 en donde A₁ representa un átomo de hidrogeno o un grupo metilo.

3. Compuesto de fórmula (I) según la reivindicación 1 o 2 en donde A₂ representa un grupo alquilo (C₁-C₆) lineal o ramificado, el cual es no sustituido o sustituido con un grupo elegido entre halógeno, hidroxilo, alcoxi (C₁-C₆) lineal o ramificado, NR'R'' y morfolina.

4. Compuesto de fórmula (I) según la reivindicación 1 o 2 en el que A₂ representa un polihaloalquilo (C₁-C₆) lineal o ramificado o un grupo ciclopropilo.

5. Compuesto de fórmula (I) según una de las reivindicaciones 1 a 3 en el que A₁ y A₂ representan los dos un grupo metilo.

6. Compuesto de fórmula (I) según una de las reivindicaciones 1 a 5, en donde T representa un metilo, aminometilo, (morfolin-4-il)metilo, (4-metilpiperazin-1-il)metilo, 2-(morfolin-4-il)etilo, [2-(morfolin-4-il)etoxi]metilo, hidroximetilo, [2-(dimetilamino)etoxi]metilo, hexahidropirazino[2,1-c][1,4] oxazin-8(1*H*)-ilmetilo, 1-oxa-6-azaespiro[3.3]hept-6-ilmetilo, 3-(morfolin-4-il)propilo, o un grupo trifluorometilo.

7. Compuesto de fórmula (I) según una de las reivindicaciones 1 a 6, en donde R₄ representa un grupo fenilo, 4-hidroxifenilo, 3-fluoro-4-hidroxifenilo, 2-hidroxipirimidina o 3-hidroxipiridina.

8. Compuesto de fórmula (I) según una de las reivindicaciones 1 a 7, en donde R₃ representa un grupo arilo o heteroarilo.

9. Compuesto de fórmula (I) según una de las reivindicaciones 1 a 7, en donde R₃ representa un grupo elegido entre metilo, fenilo, 1*H*-pirazol, 1*H*-indol, 1*H*-indazol, piridina, pirimidina, 1*H*-pirrolo[2,3-*b*]piridina, 2,3-dihidro-1*H*-pirrolo[2,3-*b*]piridina, 1*H*-bencimidazol, 1*H*-pirrol, 1*H*-pirrolo[2,3-*c*]piridina, 1*H*-pirrolo[3,2-*b*]piridina, 5*H*-pirrolo[3,2-*d*]pirimidina, tiofeno, pirazina, 1*H*-pirazolo[3,4-*b*]piridina, 1,2-oxazol, y 1*H*-pirazolo[1,5-*a*]pirimidina, conteniendo estos grupos opcionalmente uno o más sustituyentes elegidos entre halógeno, alquilo (C₁-C₆) lineal o ramificado, alcoxi (C₁-C₆) lineal o ramificado, ciano, ciclopropilo, oxetano, tetrahydrofurano, -CO-O-CH₃, trideuteriométilo, 2-(morfolin-4-il)etilo, y 2-(morfolin-4-il)etoxi.

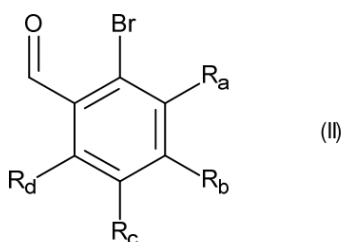
10. Compuesto de fórmula (1) según la reivindicación 1, elegido entre el grupo siguiente:

- 5-(5-cloro-2-[(3*S*)-3-(morfolin-4-ilmetil)-3,4-dihidroisoquinolin-2(1*H*)-il]carbonil}fenil)-*N*-(4-hidroxifenil)-1,2-dimetil-*N*-(1-metil-1*H*-pirazol-4-il)- 1*H*-pirrol-3-carboxamida,
- 5-(5-cloro-2-[(3*R*)-3-metil-3,4-dihidroisoquinolin-2(1*H*)-il]carbonil}fenil)-*N*-(4-hidroxifenil)-1,2-dimetil-*N*-(piridin-4-il)- 1*H*-pirrol-3-carboxamida,

- *N*-(4-hidroxifenil)-1,2-dimetil-*N*-(1-metil-1*H*-pirazol-4-il)-5-(6-[[*(3S)*-3-(morfolin-4-ilmetil)-3,4-dihidroisoquinolin-2(1*H*)-il]carbonil]-1,3-benzodioxol-5-il)- 1*H* pirrol-3-carboxamida,
- *N*-(4-hidroxifenil)-1,2-dimetil-5-(6-[[*(3R)*-3-metil-3,4-dihidroisoquinolin-2(1*H*)-il]carbonil]-1,3-benzodioxol-5-il)-*N*-(piridin-4-il)- 1*H* -pirrol-3-carboxamida,
- 5-(5-fluoro-2-[[*(3S)*-3-(morfolin-4-ilmetil)-3,4-dihidroisoquinolin-2(1*H*)-il]carbonil]fenil)-*N*-(4-hidroxifenil)-1,2-dimetil-*N* -(1-metil-1*H* -pirazol-4-il)- 1*H* pirrol-3-carboxamida,
- 5-(5-cloro-2-[[*(3S)*-3-(morfolin-4-ilmetil)-3,4-dihidroisoquinolin-2(1*H*)-il]carbonil]fenil)-*N*-(4-hidroxifenil)-1,2-dimetil-*N*-(1-metil-1*H* -pirrolo[2,3- *b*]piridin-5-il)- 1*H* -pirrol-3-carboxamida,
- 5-(5-cloro-2-[[*(3S)*-3-(morfolin-4-ilmetil)-3,4-dihidroisoquinolin-2(1*H*)-il]carbonil]fenil)-*N*-(4-hidroxifenil)-1,2-dimetil-*N*-(piridin-4-il)- 1*H* -pirrol-3- carboxamida,
- 5-(5-cloro-2-[[*(3S)*-3-(morfolin-4-ilmetil)-3,4-dihidroisoquinolin-2(1*H*)-il]carbonil]fenil)-*N*-(5-ciano-1-metil-1*H* -pirrol-3-il)-*N*-(4-hidroxifenil)-1,2-dimetil- 1*H* -pirrol-3-carboxamida,
- *N*-(5-ciano-1-metil-1*H* -pirrol-3-il)-5-(5-fluoro-2-[[*(3S)*-3-(morfolin-4-il-metil)-3,4-dihidroisoquinolin-2(1*H*)-il]carbonil]fenil)-*N*-(4-hidroxifenil)-1,2-dimetil-1*H* - pirrol-3-carboxamida,
- 5-(5-cloro-2-[[*(3S)*-3-(morfolin-4-ilmetil)-3,4-dihidroisoquinolin-2(1*H*)-il]carbonil]fenil)-*N*-(5-ciano-1,2-dimetil-1*H* -pirrol-3-il)-*N*-(4-hidroxifenil)-1,2- dimetil-1*H* -pirrol-3-carboxamida,
- 5-(5-cloro-2-[[*(3S)*-3-(morfolin-4-ilmetil)-3,4-dihidroisoquinolin-2(1*H*)-il]carbonil]fenil)-*N*-(4-hidroxifenil)-1,2-dimetil-*N*-(1-metil-2,3-dihidro-1*H*- pirrol[2,3-*b*]piridin-5-il)-]-pirrol-3-carboxamida,
- *N*-(5-ciano-1,2-dimetil-1*H* -pirrol-3-il)-5-(5-fluoro-2-[[*(3S)*-3-(morfolin-4-il-metil)-3,4-dihidroisoquinolin-2(1*H*)-il]carbonil]fenil)-*N*-(4-hidroxifenil)-1,2-dimetil-1*H* - pirrol-3-carboxamida,
- 5-(5-cloro-2-[[*(3S)*-3-(morfolin-4-ilmetil)-3,4-dihidroisoquinolin-2(1*H*)-il]carbonil]fenil)-*N*-[5-ciano-2-metil-1-(trideuteriometil)- 1*H* -pirrol-3-il]-*N*-(4- hidroxifenil)-1,2-dimetil-1*H* -pirrol-3-carboxamida,

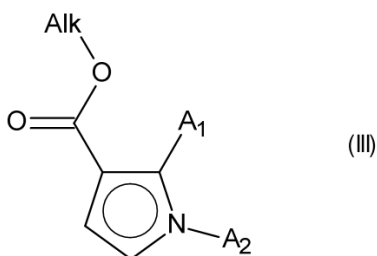
sus enantiómeros y diastereoisómeros, así como sus sales de adición con un ácido o base farmacéuticamente aceptable.

11. Procedimiento de preparación de los compuestos de fórmula (I) según la reivindicación 1, caracterizado porque se utiliza como producto de partida el compuesto de fórmula (II):



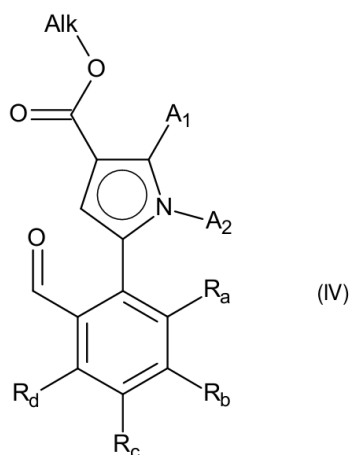
en donde R_a, R_b, R_c y R_d son tales como se han definido en la fórmula (I),

el compuesto de fórmula (II) se somete a una reacción de Heck, en medio acuoso u orgánico, en presencia de un catalizador de paladio, de una base, de una fosfina y del compuesto de fórmula (III):



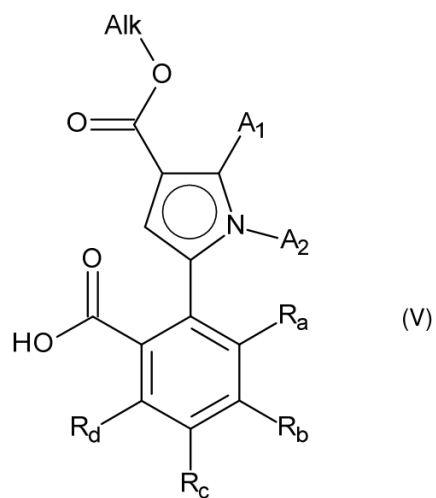
en donde los grupos A₁ y A₂ son tales como se han definido en la fórmula (I) y Alk representa un alquilo (C₁-C₆) lineal o ramificado,

para obtener el compuesto de fórmula (IV):



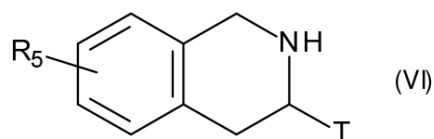
en donde A_1 , A_2 , R_a , R_b , R_c y R_d son tales como se han definido en la fórmula (I) y Alk es como se ha definido anteriormente,

el compuesto de fórmula (IV) cuya función aldehído se oxida en un ácido carboxílico para formar el compuesto de formula (V):



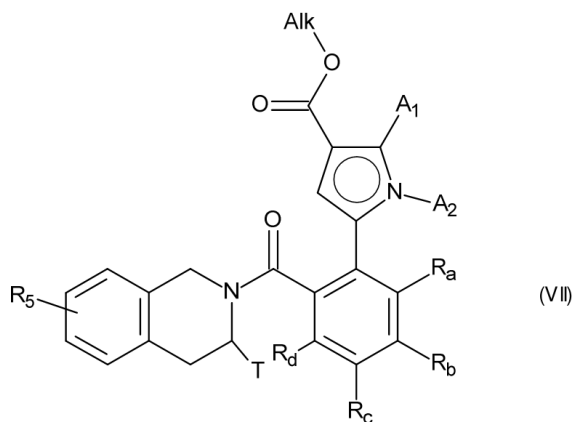
en donde A_1 , A_2 , R_a , R_b , R_c y R_d son tales como se han definido en la fórmula (I) y Alk es como se ha definido anteriormente,

el compuesto de fórmula (V) que se somete a un acoplamiento peptídico con un compuesto de fórmula (VI):



en donde T y R₅ son tales como se han definido en la fórmula (I),

para dar lugar al compuesto de fórmula (VII):

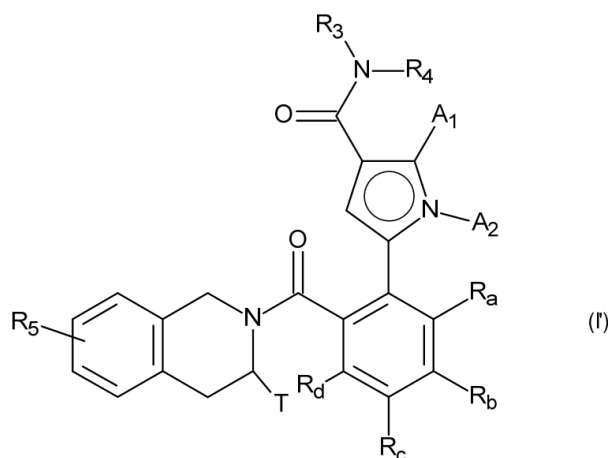


en donde A₁, A₂, R_a, R_b, R_c, R_d, T y R₅ son tales como se han definido en la fórmula (I) y Alk es como se ha definido anteriormente,

el compuesto de fórmula (VII) cuya función éster se hidroliza para dar lugar al ácido carboxílico o al carboxilato correspondiente, el cual puede convertirse en un derivado de ácido tal como el cloruro de acilo o el anhídrido correspondiente, antes de acoplarse con una amina NHR₃R₄, en la que R₃ y R₄ tienen el mismo significado que en la fórmula (I), para dar lugar al compuesto de fórmula (I),

el compuesto de fórmula (I) que puede purificarse según una técnica convencional de separación, que se transforma, si se desea, en sus sales de adición con un ácido o una base farmacéuticamente aceptable y del que se separan opcionalmente los isómeros según una técnica convencional de separación, en donde en cualquier momento que se considere oportuno en el curso del procedimiento descrito anteriormente, determinados grupos (hidroxi, amino...) de los reactivos o intermedios de síntesis pueden protegerse y después desprotegerse para las necesidades de la síntesis.

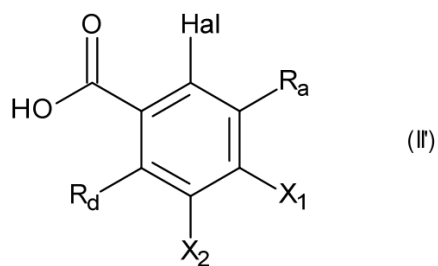
12. Procedimiento de preparación de los compuestos de fórmula (I'), casos particulares de los compuestos de fórmula (I) según la reivindicación 1, tal como se define a continuación:



en donde:

- A₁, A₂, R_a, R_d, R₃, R₄, T y R₅ son tales como se han definido en la fórmula (I),
- R_b y R_c son tales que uno representa un hidrógeno y el otro un grupo seleccionado de R₇-CO-NH-alquil(C₀-C₆)-, R₇-SO₂-NH-alquil(C₀-C₆)-, R₇-NH-CO-NH- alquil(C₀-C₆)- y R₇-O-CO-NH-alquil(C₀-C₆)-, R₇ siendo tal como se ha definido en la fórmula (I),

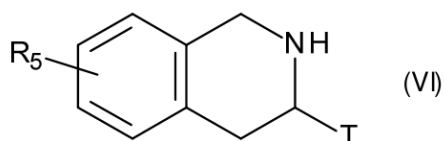
el procedimiento de preparación que utiliza como producto de partida un compuesto de formula (II'):



en donde:

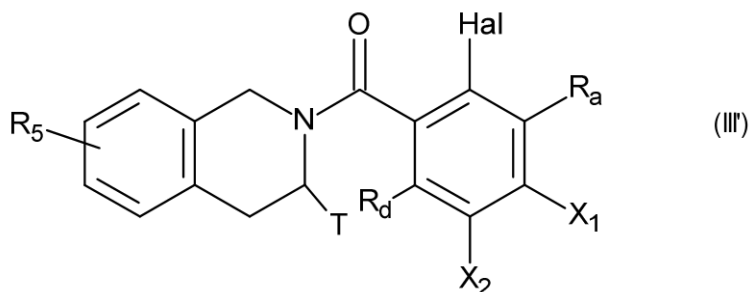
- R_a y R_d son como se define para la fórmula (I),
- Hal representa un átomo de halógeno,
- X_1 y X_2 son tales que uno representa un grupo alquil(C_0 - C_6)- NH_2 mientras que el otro representa un átomo de hidrógeno,

el compuesto de fórmula (II') se somete a un acoplamiento peptídico con un compuesto de fórmula (VI):



en donde T y R_5 son tales como se han definido en la fórmula (I),

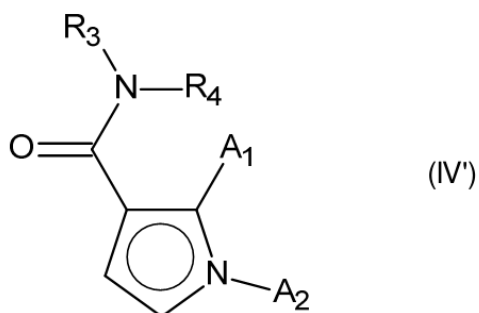
para dar lugar al compuesto de fórmula (III'):



en donde:

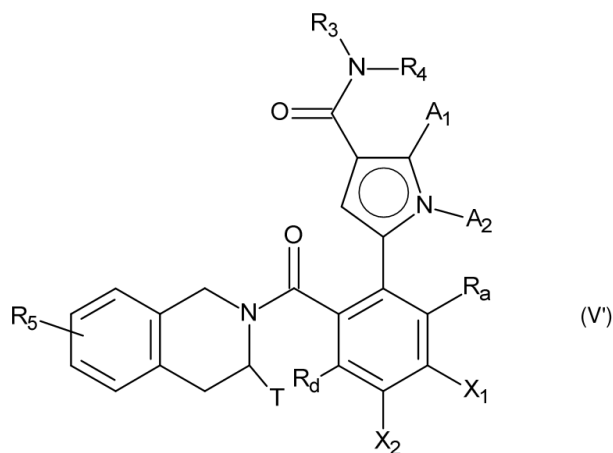
- R_a , R_d , T y R_5 son tales como se han definido en la fórmula (I),
- Hal representa un átomo de halógeno,
- X_1 y X_2 son tales que uno representa un grupo alquil(C_0 - C_6)- NH_2 mientras que el otro representa un átomo de hidrógeno,

el compuesto de fórmula (III') se somete a una reacción de Heck, en medio acuoso u orgánico, en presencia de un catalizador de paladio, de una base, de una fosfina y de un compuesto de fórmula (IV'):



en donde A_1 , A_2 , R_3 y R_4 son tales como se han definido en la fórmula (I),

para formar el compuesto de fórmula (V'):



en donde:

- $A_1, A_2, R_a, R_d, R_3, R_4, T$ y R_5 son tales como se han definido en la fórmula (I),
- X_1 y X_2 son tales que uno representa un grupo alquil(C_0 - C_6)- NH_2 mientras que el otro representa un átomo de hidrógeno,

el compuesto de fórmula (V') se somete a una reacción de acilación o de sulfonilación para dar lugar al compuesto de fórmula (I'),

el compuesto de fórmula (I') puede purificarse según una técnica convencional de separación, que se transforma, si se desea, en sus sales de adición con un ácido o base farmacéuticamente aceptable y del que se separan opcionalmente los isómeros según una técnica convencional de separación, I

en donde en cualquier momento que se considere oportuno en el curso del procedimiento descrito anteriormente, determinados grupos (hidroxi, amino...) de los reactivos o intermedios de síntesis pueden protegerse y después desprotegerse para las necesidades de la síntesis.

13. Procedimiento según la reivindicación 11 o 12 para la preparación de un compuesto de fórmula (I) en el que uno de los grupos R_3 o R_4 está sustituido con una función hidroxi, caracterizado porque la amina NHR_3R_4 se somete previamente a una reacción de protección de la función hidroxi antes de cualquier acoplamiento con el ácido carboxílico del compuesto de fórmula (VII), o con uno de los derivados de ácido correspondiente, el compuesto de fórmula (I) protegido resultante experimenta una reacción de desprotección y se convierte opcionalmente en sus sales de adición con un ácido o base farmacéuticamente aceptable.

14. Composición farmacéutica que contiene un compuesto de fórmula (I) según una cualquiera de las reivindicaciones 1 a 10 o una de sus sales de adición con un ácido o base farmacéuticamente aceptable en combinación con uno o más excipientes farmacéuticamente aceptables.

15. Combinación farmacéutica de un compuesto de fórmula (I) según una cualquiera de las reivindicaciones 1 a 10 con un agente anticancerígeno seleccionado de agentes genotoxicos, venenos mitoticos, anti-metabolitos, inhibidores del proteasoma, inhibidores de quinasas y anticuerpos.

16. Composición farmacéutica que contiene una combinación de acuerdo con la reivindicación 15 en combinación con uno o más excipientes farmacéuticamente aceptables.

ANEXO 2

Preclinical Modeling of Combination Treatments: Fantasy or Requirement?

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ABSTRACT: Combination chemotherapy is considered the “norm” in cancer chemotherapy. While the development of classical combination regimens took into account factors such as single-agent activity, different toxicity profiles, and advantageous pharmacology of the component drugs, in the era of targeted therapies there are additional considerations such as new mechanisms of resistance due to modulation of pathway dependence. Since it is not feasible to test all of the possible combinations clinically, some method for preclinically identifying and prioritizing promising combinations is necessary. While *in vivo* animal models can be used for safety testing and some pharmacokinetics, even they can quickly become prohibitively resource intensive for the purpose of efficacy determinations. Therefore, factors such as biologic rationale, reliable *in vitro* results in more than one tumor type, achievable *in vivo* pharmacology, and selectivity of primary tumor cell activity become important in the evaluation of potential combination regimens.

KEYWORDS: combination chemotherapy; cancer; synergy; preclinical models

COMBINATIONS ARE THE “NORM” IN CANCER CHEMOTHERAPY

In cancer treatment, combination chemotherapy has been found more effective than single-drug regimens and, in fact, is accepted as the “norm.” Combination therapies have been the basis of the major success stories in the treatment of various cancers. Initial treatment for acute lymphoblastic leukemia (ALL) usually consists of a regimen such as vincristine, prednisone, and anthracycline with or without asparaginase, resulting in complete remissions in a large majority of cases. More than 75% of all newly diagnosed patients with adult Hodgkin’s lymphoma can be cured with combination chemotherapy and/or radiation therapy. One of the most effective and least toxic chemotherapy regimens for this disease is known as ABVD and consists of a combination of adriamycin, bleomycin, vinblastine, and dacarbazine. In lung cancer, the combination of carboplatin and paclitaxel is clinically useful. Even in epithelial cancers, such as testis or adjuvant therapies for breast or colon cancers, combination therapies are standard.

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One empirical basis for understanding the success of certain combination therapies is that they represent pharmacologically tolerable combinations of drugs that affect the same target but that have often been selected due to different “large” organ toxicities.¹ Three of the four drugs in the ABVD regimen target DNA. While three of the four in the regimen cause decreases in white blood cells and platelets, the non-hematologic toxicities vary. Adriamycin produces cardiac toxicity, vinblastine causes neurotoxicity, and bleomycin has pulmonary side effects.

A different view of how to produce useful combination regimens suggests that in addition to having different spectra of toxicity, preferably with minimal cross resistance, other important criteria are that each of the drugs have proven efficacy as single agents, and they actually have different mechanisms of action in eliciting an anti-proliferative effect.² Ideally, the drugs should be administered at the maximum tolerated dose for the shortest time compatible with normal cell compartment recovery. In the lung cancer regimen mentioned above, both carboplatin and paclitaxel have some single-agent activity, with carboplatin targeting DNA and paclitaxel acting on tubulin. Both drugs lower white blood cell counts and platelets, with paclitaxel having neurotoxicity as an additional side effect.

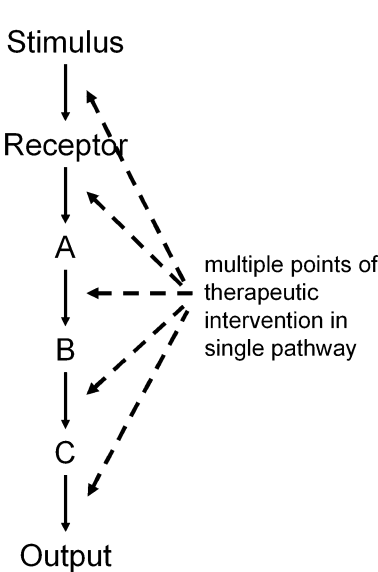
TARGETED THERAPY AND COMBINATION DESIGN

In addition to empirical approaches to combination design, the development of targeted therapies has created the possibility for a “rational” basis for constructing combinations where the drugs are selected to affect different targets and/or circumvent resistance. For example, the use of combinations of reverse transcriptase inhibitors and protease inhibitors is the standard of care in the treatment of AIDS and seems to prevent the facile development of mutant resistant strains of the HIV virus. In this case, two distinct targets—each crucial to creating a successful viral replication cycle—convey a profound antiviral effect when coincidentally inhibited. An analogous strategy is used in the treatment of tuberculosis, which rapidly becomes resistant to monotherapy.

This rational approach to combination design requires consideration of the targets and pathways involved. For instance, one can take into account whether a linear or concentric model of target action applies (FIG. 1). In the classic linear model with a single pathway affected, a series of drugs each acting on its own component of that linear pathway could be imagined as conveying benefit when used in combination. Alternatively and somewhat more likely, the tumor could exist in a “super state” where there are multiple pathways that all contribute to tumor survival and growth. One could then design a combination drug strategy that affects each of the targets contributing to the super state.

Another method for approaching targets and pathways in the context of combination design is to consider what has been described as the six essential alterations in cell physiology in malignancy: evasion of apoptosis; self-sufficiency in growth signals; insensitivity to anti-growth signals; sustained angiogenesis; limitless replicative potential; and capacity for tissue invasion and metastasis.³ The first three of these alterations can be thought of as the targets of more classical cancer chemotherapy agents, while the latter three are the focus of intense interest for the development of many new targeted therapies. Acting on the more “classical” targets, such as DNA

A. Linear



B. Concentric

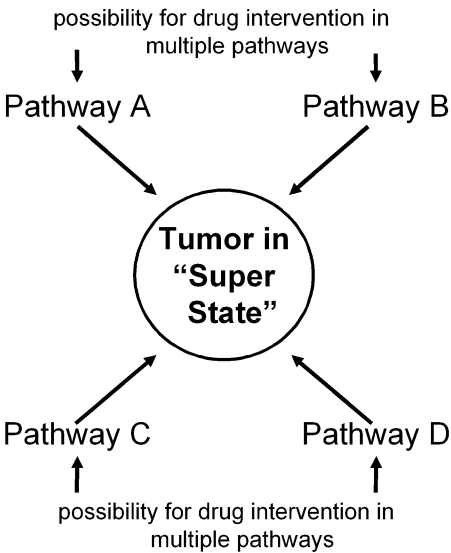


FIGURE 1. Models of target action. (A) In a classic linear model, a single pathway needs to be affected by candidate agents. (B) In a concentric model, multiple pathways contribute to tumor survival and growth.

or tubulin, is in essence a means of evoking a “stress response” leading to the induction of apoptosis. For DNA-interactive agents, this could mean affecting the p53 checkpoint response or p53-induced genes, while for a tubulin-targeted drug the stress evokes a mitotic checkpoint response. Useful targeted agents will also evoke a stress response depending on how important the drug’s target is in sustaining an anti-apoptotic influence.

While minimal cross resistance was a desired characteristic of a classical combination regimen, inclusion of targeted therapies in combination regimens offers potential additional avenues of resistance. In addition to the classical mechanisms of drug resistance related to the drug itself, such as efflux, metabolism, and target expression, another means of resistance that arises with targeted agents is through the modulation of pathway dependence. In the super state example in FIGURE 1, if a drug affecting only pathway A were used, the tumor could alter its growth and survival so as to exist without pathway A, rendering that drug alone ineffective. This was actually recently illustrated by the development of resistance to A431 squamous cell carcinoma xenografts to anti-epidermal growth factor receptor (EGFR) monoclonal antibodies for two cycles.⁴ A431 cell variants were developed from recurring resistant tumors which grew faster and were clearly less responsive to the anti-EGFR antibodies than the parental line. The investigators looked at the relative expression

levels of a number of different targets in these variants, including relative VEGF expression. In five of the six resistant cell variants, VEGF expression levels were elevated relative to the parent line. These results suggest that, at least in this example, acquired resistance can develop to a targeted therapy and can proceed, in part, by selecting advantageous tumor subpopulations which upregulate a different, parallel growth-modulating pathway, in this case modifying the tumor stroma. Resistance does not appear therefore to have arisen in relation to the drug-affected pathway, but with another pathway having been called into play.

Taking into account target, pathway, and resistance issues, one could imagine designing a combination of targeted agents for the treatment of bulk tumor that consisted of an anti-proliferative, a pro-apoptotic, and an anti-vascular therapy. A recent clinical trial of an anti-vascular agent with an anti-proliferative regimen demonstrated that this sort of combination could be beneficial in a patient population.⁵ The trial placed patients with previously untreated metastatic colorectal carcinoma into one of three groups: bolus IFL (5-fluorouracil, leucovorin, and irinotecan) + placebo; bolus IFL + the anti-vascular antibody bevacizumab; or 5-fluorouracil, leucovorin, and bevacizumab. The overall response rate for IFL + placebo was 34.7% with a duration of 7.1 months, while IFL + bevacizumab was 44.9% with a duration of 10.4 months ($P = 0.029$). Improvement was also seen in progression-free survival, 6.2 months for IFL + placebo versus 10.6 months for IFL + bevacizumab ($P < 0.00001$).

Other clinical results from the combination of classical regimens with targeted agents include those with the RAF-kinase and VEGFR inhibitor BAY43-9006. In a phase II randomized discontinuation trial in a variety of advanced solid tumors, there were no complete responses to the single agent, but partial responses in renal (35%), sarcoma (10%), thyroid (40%), and melanoma (2%).⁶ A phase II trial in melanoma of BAY-43-9006 with carboplatin and paclitaxel, however, achieved 40% PR and 43% stable disease.⁷ Taken together, these data raise the possibility of modulation of sensitivity *in vivo* to platinum by BAY43-9006. One potential mechanism is better delivery of the drug because of the effects of the anti-vascular compound on interstitial fluid pressure.⁸

In contrast to a classical combination regimen where each component of the regimen had some level of activity as a single agent, the possibility exists that the targeted agents may be relatively to completely inactive as single agents. Another design strategy therefore is to combine two or more anti-signaling molecules that alone may not be toxic, but in combination they affect two or more critical pathways or have an augmented effect on one pathway. For preventive therapy, a strategy that combines an anti-mutator, an anti-telomerase, and an anti-invasive could be envisioned.

PRECLINICAL TESTING OF COMBINATIONS

Clinical trials of combination regimens are extremely expensive and time-consuming. Furthermore, the number of potential combinations is virtually unlimited. So the question is whether it is possible to determine preclinically which combinations will be effective. In April 2003, the U.S. National Cancer Institute Developmental Therapeutics Program (NCI DTP) held a workshop on defining the

efficacy of combinations.⁹ Some of the goals of the workshop were to attempt to determine what preclinical data would represent convincing evidence that a combination should be tested clinically, and how best to prioritize the possibilities. The outcome of the workshop suggested that one should utilize the *in vitro* data to prioritize for those regimens clearly showing synergy as opposed to mere lack of antagonism. *In vitro* data should represent more than one tumor type. There should be a biologic rationale for the combination. Ideally, evidence should exist for greater activity against tumor cells as opposed to normal cells. *In vivo* tumor efficacy of the combination was not considered necessary, although obviously a plus if present. If possible, clear evidence of likely safety in the *in vivo* models should be demonstrated. Pharmacokinetics, however, should be utilized from early human studies, where available, to model regimens that approximate non-antagonistic interactions *in vitro*. The concentrations studied *in vitro* should clearly be those that are relevant clinically.

SYNERGY

Given the enormous number of possible combinations of drugs, the idea of prioritizing synergistic combinations and not selecting antagonistic ones is obviously desirable. Synergism in fact is almost critical to define in those situations where the single agents are relatively ineffective on their own. Defining synergy, however, is no simple matter, and a variety of techniques for doing so has been covered in great detail elsewhere.¹⁰

One of the more straightforward methods for determining synergy is known as fractional effect analysis, where the effect of the drugs alone is multiplied and compared with the effect of the combination at the same drug concentrations. Although simple, it has the significant limitation of assuming a linear concentration–effect relationship for each agent as well as the combination.

The isobologram representation is one of the most commonly used methods for calculating synergy. Concentration–effect curves are calculated for each drug alone and for the effect of a variable concentration of one drug in the presence of a fixed concentration of the other. The “apparent” IC_{50} (50% inhibitory concentration) of the combination is then plotted, representing expected additivity. If the observed effect of the combination falls to the left of the expected curve, there is synergy and to the right, antagonism. In addition to being a very labor-intensive method that does not allow quantitation of synergism, this method also occasionally produces sigmoidal observed curves that lie on both sides of the expected curve. Although there are complicated three-dimensional response surface approaches that overcome some of the limitations of isobolograms, their complexity often dictates against them.

The well-known Chou and Talalay median-drug effect analysis is a somewhat more accessible method to overcome the sigmoidicity problem found with isobolograms.¹¹ The drug mixture is at constant concentration ratios so that the relative effects of each drug in the mixture are identical. The growth inhibitory effect of each drug, the sigmoidicity of the curves, and an estimated IC_{50} are used to calculate a combination index (CI) that serves as a quantitative measure of synergism. This method has the advantage of allowing evaluation of drug combinations where the drugs interact in the same pathway or in completely separate pathways.

PROBLEMS IN DESIGNING SIGNALING COMBINATIONS

Definition of synergy is by no means the only issue that remains unresolved in the design of signaling combinations in cancer treatment. We do not know yet how to diagnose the “mixture” of pathways acting in a tumor, and what would be a basis for selecting certain combination regimen drug members. Also unknown is the best time in the natural history of the tumor for intervention with agents affecting combined pathways, whether “up front” or after a certain sequence of standard and investigational therapies. It would also be useful to know whether there are any qualitative differences in the results that are achievable between certain drug types, such as antibodies versus small molecules or between different types of small molecules. If so, why and how can they be exploited?

COMBINATIONS OF KINASE-DIRECTED AGENTS

A look at any of a number of schematic illustrations of the principal pathways involved for some of the new kinase-directed agents in development reveals the complexity of attempting to select the best possible combinations. Among the combinations of new agents that have been tried preclinically are the cyclin-dependent kinase (CDK) inhibitor flavopiridol with the erbB receptor-directed monoclonal antibody trastuzumab. Flavopiridol has been shown to inhibit CDK4 activity after cyclin D1 expression in MCF7 breast cancer cells.¹² On Western blots, cyclin D1 starts to diminish after 6 h of exposure to flavopiridol and is almost completely gone by 10 h. CDK4 activity follows slightly behind, beginning to diminish at 8 h. Effects on steady-state mRNA levels after treatment with 300 nM flavopiridol show a similar time course. Cyclin D1 is downstream of erbB2, and Nahta *et al.* demonstrated that cyclin D1 functions are essential and rate limiting for erbB2 transformation.¹³ These results suggested the combination of drugs active against erbB2 and cyclin D1 (trastuzumab and flavopiridol). They found that these two drugs were synergistically cytotoxic against erbB2-positive breast cancer cell lines and that adding flavopiridol to trastuzumab synergistically lowered erbB2 levels in these cells.

The PDK1-Akt survival pathway (FIG. 2) has also been the focus of numerous drug discovery efforts. The alkylphospholipid perifosine, which is currently in clinical trials, causes almost complete loss of Akt phosphorylation on at least two key sites.¹⁴ Perifosine was further shown to decrease plasma membrane localization of Akt at approximately 5 μ M. In patients, a loading dose followed by maintenance dosing produces approximately these levels.^{16,17} UCN-01 produced this effect by inhibiting the upstream kinase, PDK1. The combination of perifosine and UCN-01 was tested *in vitro* because these two drugs both produce loss of phosphorylation of Akt, but through different mechanisms.¹⁸ Using the Chou and Talalay method, this combination was shown to be moderately synergistic. Further, cell cycle analysis of the effect of the combination showed an increase in the percentage of cells arresting in G0/G1, 87% for the combination versus 51% for controls, 52% for perifosine-treated, and 69% for UCN-01-treated.

UCN-01 was also tested *in vitro* in combination with the geldanamycin analogue 17-AAG, an antagonist of the molecular chaperone hsp90. Synergistic induction of apoptosis and loss of mitochondrial membrane potential was observed in leukemia

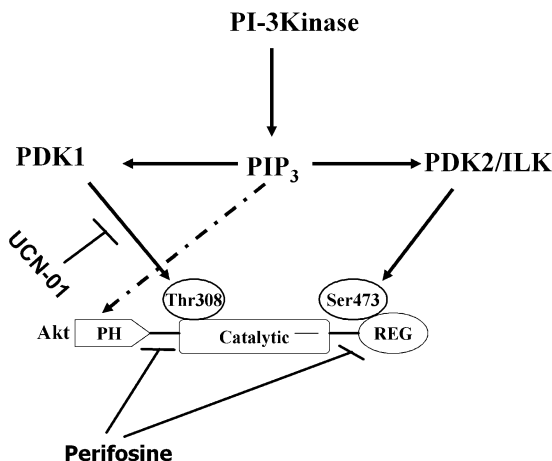


FIGURE 2. The PDK1-Akt survival pathway. Points of action of perifosine and UCN-01 are shown. Numerous drug discovery efforts not reviewed here have focused on various other targets in the pathway.

cells.¹⁹ Explication of the basis of this synergy indicated that 17-AAG potentiates UCN-01 cytotoxicity and that interference with both the Akt and Raf-1/MEK/MAP kinase cytoprotective signaling pathways contributes to this effect.

ANIMAL MODELS AND COMBINATIONS

While the above examples all demonstrate synergy *in vitro*, the question often arises whether *in vitro* combination data are sufficient to justify moving forward to human clinical trials. There are, however, a number of problems with using animal models for the assessment of combinations. An appropriately powered animal experiment with untreated controls, vehicle controls, a Drug A alone group, a Drug B alone group, and a combination group easily exceeds over 100 animals. Logistical and cost issues aside, the pharmacology in mice, or whatever species is desired, must approximate the pharmacology in humans, and even then it will be difficult to predict the pharmacokinetic interactions. One must either control for or actively design pharmacology into the study. Finally, the results can easily show not only additive or synergistic efficacy, but also additive or synergistic toxicity that may or may not be relevant to the human experience.

Animal models have both logistical and technical limitations; therefore, in attempting to define a “roadmap” to the clinic for new combination therapies, the guidelines emerging from the NCI DTP workshop on prioritizing on synergy, biologic rationale, selectivity, likely safety, and favorable pharmacokinetics can serve as an initial series of filters to weed out combinations that do not merit animal or clinical testing. Given that combination therapies have always been a major basis of success in the treatment of cancer and that the nature of the new generations of drugs

that is emerging makes it even less likely that a monotherapy will suffice, it is hoped that what will materialize after applying a series of appropriate *in vitro* filters will be a select and manageable number of combination designs for more advanced testing in a clinical setting.

[COMPETING INTERESTS: Dr. Edward A. Sausville is on the Scientific Advisory Board for Kosan Biosciences and is a consultant for Kosan Biosciences and Keryx Pharmaceuticals. The author declares a competing financial interest.]

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ANEXO 3

explored by comparing the rate of a process — such as the rate at which a particle will decay into other, lighter particles — with the rate of its CP-related process, in which all the initial and final particles are replaced with the corresponding antiparticles. If these rates are measured to be different, then a ‘CP asymmetry’ has been observed. Measurements of CP asymmetries are interesting for two reasons. First, they provide stringent tests of the standard model of particle physics. Second, they may provide hints that could point scientists in the direction of a solution to the mystery of the Universe’s matter–antimatter imbalance.

Among the four known forces of nature — the standard model’s weak, strong and electromagnetic forces, and the gravitational force — the weak force is the only one that distinguishes between matter and antimatter. But even the weak force would not do so if it were not that three quark particles exist for each of two charge types: the down, strange and bottom quarks, which have a charge that is minus one-third of the proton’s charge; and the up, charm and top quarks, which have a charge that is two-thirds of the proton’s charge. With three quarks of either charge, the weak force has a single coupling constant (a parameter that quantifies the force’s strength), which is different for particles and antiparticles^{2,3}. If, as the standard model predicts, all CP asymmetries are proportional to this single coupling constant, then the sizes of these asymmetries are correlated. By contrast, most theories that go beyond the standard model have many independent coupling constants that distinguish particles from antiparticles, and thus predict deviations from the standard-model correlations.

Mesons are bound states of one quark and one antiquark. Until the LHCb measurement was made, CP asymmetries had been observed in the decays of three types of meson: K^0 mesons, B^0 mesons, and $B^\pm$ mesons. The LHCb experiment is the first to measure CP asymmetry in the decay of a fourth type of meson, the B_s^0 meson. The fact that, within the standard model, the difference in the laws of physics followed by matter and antimatter is encoded in a single parameter provides a particularly strong correlation between this asymmetry and an asymmetry in B^0 decay that has been measured by several experiments with high accuracy. Although neither of these asymmetries, nor the corresponding decay rates, can be theoretically predicted with any accuracy, the product of the CP asymmetry with the decay rate should, according to the standard model, be equal (to a good approximation) between the B_s^0 decay and the B^0 decay^{4,5}. The LHCb measurement is consistent with the predicted equality at the level of a few per cent, implying yet another triumph of the standard model.

In many extensions of the standard model, new particles are predicted to interact more strongly with the heavier quarks (strange, bottom, charm and top) than with the lighter ones

(up and down). The K^0 mesons, the B^0 mesons and the $B^\pm$ mesons all have either a down (anti)quark or an up (anti)quark. But the B_s^0 mesons are different: they are made up of a strange quark and a bottom antiquark. Their antiparticles are composed of a bottom quark and a strange antiquark. Thus, scientists had hoped that although the effects of new physics were negligibly small in all previously measured CP asymmetries, they would be large enough to be observed in B_s^0 decays. Frustratingly, this seems not to be the case.

“The LHCb measurement reinforces the standard model’s explanation of how the weak force distinguishes matter from antimatter.”

The standard-model prediction² of how the weak force distinguishes between matter and antimatter therefore continues to successfully describe all measurements of CP asymmetries in meson decays. However, the standard model fails to explain the Universe’s matter–antimatter imbalance. All structures in the Universe, from clusters of galaxies to human cells, are made of matter: protons, neutrons and electrons. Their antiparticles — the antiprotons, antineutrons and positrons — are not found in the Universe at large. If the laws of nature were identical for matter and antimatter, then particles and antiparticles would have been created in equal amounts and would then have annihilated each other,

leaving only pure radiation and no matter structures in the Universe. Our very existence is possible only because of CP asymmetries. The standard model allows all antimatter to disappear from the Universe, but it predicts that the amount of surviving matter is many orders of magnitude smaller than observed.

Therefore, there must exist a force, as yet unknown to us, that distinguishes matter from antimatter in a way that is much stronger than that of the weak force. Theorists have made various suggestions as to what this new force might be. To disclose the nature of this force, further hints from experiments are needed. Searching for CP asymmetries in neutrino ‘oscillations’ of one type into another and for the electric-dipole moments of the neutron and the electron, in addition to measuring CP asymmetries in B_s^0 -meson decays, seem the most promising avenues through which to obtain such hints. The consistency of the LHCb measurement with the standard model provides further motivation to pursue the other searches even more vigorously. ■

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CANCER

Calculated treatment

Mathematical modelling linked with patient data suggests that combination therapy is more effective than sequential treatment at preventing drug resistance in cancer. This predictive approach may pave the way for personalized therapies.

NATALIA L. KOMAROVA
& C. RICHARD BOLAND

In a study published in *eLIFE*, Bozic *et al.*¹ use a mathematical approach to examine tumour evolution and response to chemotherapy. In one example, they describe a patient who had the skin cancer melanoma characterized by an estimated tumour burden of 9.8×10^{10} cells and 8 metastatic lesions. Their modelling predicts a 0% chance of disease control using a single drug, but that the likelihood of successful treatment could rise to 88% during combined therapy with two drugs. The approach offers a brave, quantitative look at designing targeted therapy for cancer.

The search for cancer treatments has traversed a long and thorny path, with more

failures and disappointments than glimpses of success. A major breakthrough was achieved with the development of a drug called imatinib in the 1990s. This inhibitor of tyrosine kinase enzymes showed breathtaking success for treating chronic myelogenous leukaemia (CML). Imatinib and other small-molecule inhibitors ‘recognize’ and attack cancer cells, but spare normal cells, thereby reducing side effects compared with conventional chemotherapy. Since the discovery of imatinib, dozens of other such inhibitors have been developed for treating different cancers. However, the initial excitement surrounding these drugs was tempered by the appearance of drug resistance — the phenomenon in which disease returns a few months after initial treatment success².

Cancer is a process of Darwinian evolution played out in a particular organ. Normal cells divide and die, and each division brings a small chance of genetic change. Most such mutations are deleterious, and the cells die without leaving offspring, but some confer new properties that promote growth or survival and can lead to cancer. The greatest challenge for drugs targeted at such cells is the further evolution of mutations that confer drug resistance. Combining multiple drugs that have distinct mechanisms of action might provide a solution to this problem. The concept of a 'drug cocktail' was introduced in 1996 in the context of treating AIDS. There, the emergence of viral strains resistant to single drug treatments rendered all previous attempts to control the disease unsuccessful. Viral evolution in a patient is conceptually similar to the evolution of cancer cells, so similar treatment strategies might work well for both diseases.

Current common practice for treating cancers with small-molecule inhibitors is to administer the agents sequentially, starting with a 'first-line' drug and switching to 'second-line' therapies if the tumour relapses. Bozic *et al.* assessed the effectiveness of this approach using sophisticated mathematical techniques and data from patients with melanoma or with pancreatic or colorectal cancers. They convincingly demonstrate that a sequential strategy "precludes any chance for cure", even in the best-case scenario in which no single mutants confer resistance to both drugs. However, they show that simultaneously combining two or more drugs can provide much-needed hope for patients.

As demonstrated last year³, drug-resistant mutants typically exist at low levels in tumours before the beginning of treatment. Treatment with a single drug gives a competitive advantage to mutants resistant to that drug, such that by the time of the switch to a second-line therapy, there is a high chance that a mutant that is also resistant to the second drug (a doubly resistant mutant) has already emerged (Fig. 1). But combination therapy eliminates cells that are singly resistant to either drug and therefore — because the likelihood of a doubly mutated cell emerging in such a population is low — greatly increases the chance of success.

The greatest obstacle for combination treatments is the phenomenon of cross-resistance, in which a single mutation confers resistance to more than one drug. But even if such mutants are generated, the authors estimate that combination treatment can be beneficial in some cases, whereas single-drug and sequential strategies offer no hope.

Previous mathematical analyses have also shown⁴ that cyclic treatments are ineffective compared with combination treatments, and have led to the proposal⁵ that a combination of three anticancer drugs would be needed to treat CML. It has also already been argued⁶ that, even in the presence of cross-resistant

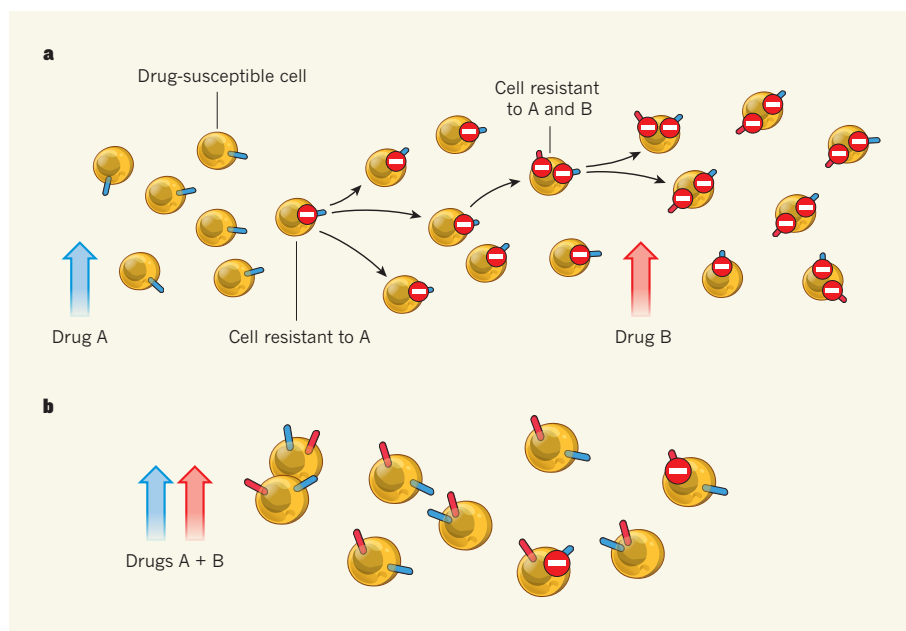


Figure 1 | Single-drug versus combination therapy. **a**, During therapy with one drug alone, a cell that acquires a mutation that confers resistance to the drug will be at a proliferative advantage. By the time this is recognized and treatment with a second drug is started, it is likely that a cell resistant to both drugs will already have emerged. **b**, Starting therapy with both drugs simultaneously means that cells acquiring single resistance will be immediately eliminated by the other drug. Bozic *et al.*¹ use mathematical modelling to show that this approach increases the chance of effective treatment.

mutations in CML, combination treatments give patients a better chance of cure than do single-drug treatments. And *in vitro* studies⁷ that compared CML cells treated with one small-molecule inhibitor with those treated with a combination of two or three demonstrated that the combined therapy suppressed cell proliferation more effectively. But with Bozic and colleagues' success in synthesizing theoretical and experimental methods and applying the analysis to solid tumours, these modelling studies have taken a leap forward.

Even more significantly, the authors' paper outlines a roadmap for future personalized therapies, by showing that specific parameters for a patient can be measured and used in a mathematical model to calculate the probability of treatment success and to design the best possible treatment strategy. The authors extracted tumour parameters — including its size at presentation, cell division and cell death rates, and changes in the associated kinetic parameters following treatment — from 20 patients with melanoma who were treated with the small-molecule inhibitor vemurafenib. With this information, they were able to predict the most likely outcome of single, dual and triple therapies for each patient.

There is a bright future for this approach. As new drugs and more information on the exact mechanisms of drug action become available, the model can be iteratively improved. For example, there is currently a strong research focus on cellular plasticity, the heterogeneity of cells within a tumour and the role of

cancer stem cells. But it is not known how the presence of cancer cells with differing properties affects a tumour's susceptibility to targeted treatments. Moreover, the evolutionary costs of resistance for a cell have not been quantified in most cases, nor have mutation rates for molecular changes of various kinds, although estimates have been made for the number of mutations conferring resistance to certain drugs in CML^{7,8}. The potential complications of drug cocktails — including toxicity and undesirable drug interactions — must also be taken into account. But the overall message is loud and clear: mathematics can help to calculate treatment strategies, and the best hope so far lies in combination therapies. ■

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ANEXO 4

The
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The Director of the United States
Patent and Trademark Office

Has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

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United States Patent

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US009108983B2

(12) **United States Patent**
Le Tiran et al.

(10) **Patent No.:** **US 9,108,983 B2**

(45) **Date of Patent:** **Aug. 18, 2015**

(54) **PYRROLE COMPOUNDS, A PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM**

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(58) **Field of Classification Search**

None

See application file for complete search history.

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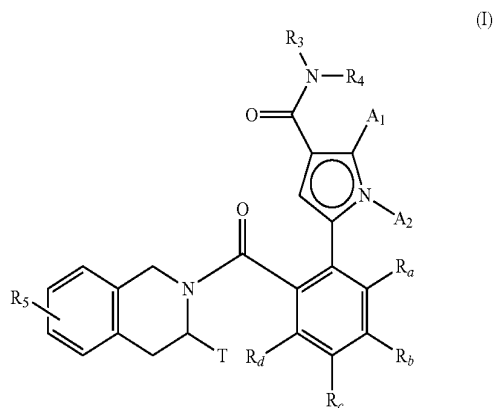
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(57) **ABSTRACT**

Compounds of formula (I):



wherein A₁, A₂, R_a, R_b, R_c, R_d, R₅, R₃, R₄, R₅ and T are as defined in the description.

Medicinal products containing the same which are useful in treating pathologies involving a deficit in apoptosis, such as cancer, auto-immune diseases, and diseases of the immune system.

18 Claims, No Drawings

**PYRROLE COMPOUNDS, A PROCESS FOR
THEIR PREPARATION AND
PHARMACEUTICAL COMPOSITIONS
CONTAINING THEM**

The present invention relates to new pyrrole compounds, to a process for their preparation and to pharmaceutical compositions containing them.

The compounds of the present invention are new and have very valuable pharmacological characteristics in the field of apoptosis and cancerology.

Apoptosis, or programmed cell death, is a physiological process that is crucial for embryonic development and maintenance of tissue homeostasis.

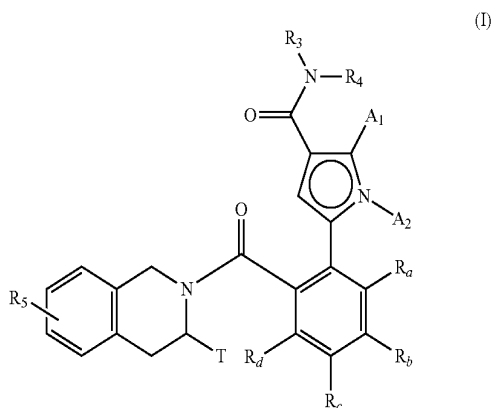
Apoptotic-type cell death involves morphological changes such as condensation of the nucleus, DNA fragmentation and also biochemical phenomena such as the activation of caspases which cause damage to key structural components of the cell, so inducing its disassembly and death. Regulation of the process of apoptosis is complex and involves the activation or repression of several intracellular signalling pathways (Cory S. et al., Nature Review Cancer, 2002, 2, 647-656).

Deregulation of apoptosis is involved in certain pathologies. Increased apoptosis is associated with neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease and ischaemia. Conversely, deficits in the implementation of apoptosis play a significant role in the development of cancers and their chemoresistance, in autoimmune diseases, inflammatory diseases and viral infections. Accordingly, absence of apoptosis is one of the phenotypic signatures of cancer (Hanahan D. et al., Cell 2000, 100, 57-70).

The anti-apoptotic proteins of the Bcl-2 family are associated with numerous pathologies. The involvement of proteins of the Bcl-2 family is described in numerous types of cancer, such as colorectal cancer, breast cancer, small-cell lung cancer, non-small-cell lung cancer, bladder cancer, ovarian cancer, prostate cancer, chronic lymphoid leukaemia, follicular lymphoma, myeloma, etc. Overexpression of the anti-apoptotic proteins of the Bcl-2 family is involved in tumorigenesis, in resistance to chemotherapy and in the clinical prognosis of patients affected by cancer. There is, therefore, a therapeutic need for compounds that inhibit the anti-apoptotic activity of the proteins of the Bcl-2 family.

In addition to being new, the compounds of the present invention have pro-apoptotic properties making it possible to use them in pathologies involving a defect in apoptosis, such as, for example, in the treatment of cancer, auto-immune diseases and diseases of the immune system.

The present invention relates more especially to compounds of formula (I):



wherein:

A₁ and A₂, each independently of the other, represent a hydrogen or halogen atom, a linear or branched (C₁-C₆) polyhaloalkyl group, a linear or branched (C₁-C₆)alkyl group or a cycloalkyl group,

T represents a hydrogen atom, a linear or branched (C₁-C₆)alkyl group optionally substituted by from one to three halogen atoms, a group (C₁-C₄)alkyl-NR₁R₂, or a group (C₁-C₄)alkyl-OR₆,

R₁ and R₂, each independently of the other, represent a hydrogen atom or a linear or branched (C₁-C₆)alkyl group,

or R₁ and R₂ form with the nitrogen atom carrying them a heterocycloalkyl,

R₃ represents a linear or branched (C₁-C₆)alkyl group, a linear or branched (C₂-C₆)alkenyl group, a linear or branched (C₂-C₆)alkynyl group, a cycloalkyl group, a (C₃-C₁₀)cycloalkyl-(C₁-C₆)alkyl group wherein the alkyl moiety is linear or branched, a heterocycloalkyl group, an aryl group or a heteroaryl group, it being understood that one or more of the carbon atoms of the preceding groups, or of their possible substituents, may be deuterated,

R₄ represents an aryl group, a heteroaryl group, a cycloalkyl group or a linear or branched (C₁-C₆)alkyl group, it being understood that one or more of the carbon atoms of the preceding groups, or of their possible substituents, may be deuterated,

R₅ represents a hydrogen or halogen atom, a linear or branched (C₁-C₆)alkyl group, or a linear or branched (C₁-C₆)alkoxy group,

R₆ represents a hydrogen atom or a linear or branched (C₁-C₆)alkyl group,

R_a, R_b, R_c and R_d, each independently of the others, represent R₇, a halogen atom, a linear or branched (C₁-C₆)alkoxy group, a hydroxy group, a linear or branched (C₁-C₆)polyhaloalkyl group, a trifluoromethoxy group, —NR₇R₇', nitro, R₇—CO—(C₀-C₆)alkyl-, R₇—CO—NH—(C₀-C₆)alkyl-, NR₇R₇'—CO—(C₀-C₆)alkyl-, NR₇R₇'—CO—(C₀-C₆)alkyl-O—, R₇—SO₂—NH—(C₀-C₆)alkyl-, R₇—NH—CO—NH—(C₀-C₆)alkyl-, R₇—O—CO—NH—(C₀-C₆)alkyl-, a heterocycloalkyl group, or the substituents of one of the pairs (R_a, R_b), (R_b, R_c) or (R_c, R_d) form together with the carbon atoms carrying them a ring composed of from 5 to 7 ring members, which may contain from one to 2 hetero atoms selected from oxygen and sulphur, it also being understood that one or more carbon atoms of the ring defined hereinbefore may be deuterated or substituted by from one to 3 groups selected from halogen and linear or branched (C₁-C₆)alkyl,

R₇ and R₇', each independently of the other, represent a hydrogen, a linear or branched (C₁-C₆)alkyl, a linear or branched (C₂-C₆)alkenyl, a linear or branched (C₂-C₆)alkynyl, an aryl or a heteroaryl, or R₇ and R₇', together with the nitrogen atom carrying them, form a heterocycle composed of from 5 to 7 ring members,

it being understood that:

"aryl" means a phenyl, naphthyl, biphenyl or indenyl group,

"heteroaryl" means any mono- or bi-cyclic group composed of from 5 to 10 ring members, having at least one aromatic moiety and containing from 1 to 4 hetero atoms selected from oxygen, sulphur and nitrogen (including quaternary nitrogens),

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"cycloalkyl" means any mono- or bi-cyclic, non-aromatic, carbocyclic group containing from 3 to 10 ring members,

"heterocycloalkyl" means any mono- or bi-cyclic, non-aromatic, condensed or spiro group composed of from 3 to 10 ring members and containing from 1 to 3 hetero atoms selected from oxygen, sulphur, SO, SO₂ and nitrogen,

it being possible for the aryl, heteroaryl, cycloalkyl and heterocycloalkyl groups so defined and the groups alkyl, alkenyl, alkynyl and alkoxy to be substituted by from 1 to 3 groups selected from optionally substituted, linear or branched (C₁-C₆)alkyl, (C₃-C₆)spiro, optionally substituted, linear or branched (C₁-C₆)alkoxy, (C₁-C₆)alkyl-S—, hydroxy, oxo (or N-oxide where appropriate), nitro, cyano, —COOR', —OCOR', NR'R'', linear or branched (C₁-C₆)polyhaloalkyl, trifluoromethoxy, (C₁-C₆)alkylsulphonyl, halogen, optionally substituted aryl, heteroaryl, aryloxy, arylthio, cycloalkyl, heterocycloalkyl optionally substituted by one or more halogen atoms or alkyl groups, it being understood that R' and R'', each independently of the other, represent a hydrogen atom or an optionally substituted, linear or branched (C₁-C₆)alkyl group,

to their enantiomers and diastereoisomers, and to addition salts thereof with a pharmaceutically acceptable acid or base.

Among the pharmaceutically acceptable acids there may be mentioned, without implying any limitation, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphonic acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, oxalic acid, methanesulphonic acid, camphoric acid etc.

Among the pharmaceutically acceptable bases there may be mentioned, without implying any limitation, sodium hydroxide, potassium hydroxide, triethylamine, tert-butylamine etc.

Advantageously, A₁ represents a hydrogen atom or a methyl group.

Furthermore, A₂ preferably represents a linear or branched (C₁-C₆)alkyl group optionally substituted by a group selected from halogen, hydroxy, linear or branched (C₁-C₆)alkoxy, NR'R'' and morpholine.

In another embodiment of the invention, A₂ represents a linear or branched (C₁-C₆)polyhaloalkyl group or a cyclopropyl group.

Even more preferably, A₁ and A₂ both represent a methyl group.

In a preferred embodiment of the invention, T represents a linear or branched (C₁-C₆)alkyl.

In another preferred embodiment, T represents a group alkyl(C₁-C₄)—NR₁R₂, and more particularly a group alkyl(C₁-C₄)—NR₁R₂ wherein R₁ and R₂ form with the nitrogen atom carrying them a heterocycloalkyl.

In preferred compounds of the invention, T represents a methyl, aminomethyl, (morpholin-4-yl)methyl, (4-methylpiperazin-1-yl)methyl, 2-(morpholin-4-yl)ethyl, [2-(morpholin-4-yl)ethoxy]methyl, hydroxymethyl, [2-(dimethylamino)ethoxy]methyl, hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl, 1-oxa-6-azaspiro[3.3]hept-6-ylmethyl, 3-(morpholin-4-yl)propyl or trifluoromethyl group. Even more preferably, T represents a (morpholin-4-yl)methyl, methyl or 3-(morpholin-4-yl)propyl group.

Preferably, R_a and R_d each represent a hydrogen atom and (R_b,R_c), together with the carbon atoms carrying them, form a 1,3-dioxolane group or a 1,4-dioxane group; or R_a, R_c and R_d each represent a hydrogen atom and R_b represents a hydrogen or halogen atom or a methoxy group. Even more prefer-

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ably, R_a and R_d each represent a hydrogen atom and (R_b,R_c), together with the carbon atoms carrying them, form a 1,3-dioxolane group; or R_a, R_c and R_d each represent a hydrogen atom and R_b represents a halogen, preferably a chlorine or fluorine atom.

In another embodiment of the invention, R_a and R_d each represent a hydrogen atom, R_b represents a hydrogen or halogen atom and R_c a hydroxy or methoxy group, or: R_a and R_d each represent a hydrogen atom, R_b represents a hydroxy or methoxy group and R_c a halogen atom.

Alternatively, R_a, R_b and R_d advantageously each represent a hydrogen atom and R_c represents a group selected from R₇—CO—NH—(C₀-C₆)alkyl-, R₇—SO₂—NH—(C₀-C₆)alkyl-, R₇—NH—CO—NH—(C₀-C₆)alkyl- and R₇—O—CO—NH—(C₀-C₆)alkyl-. For those specific compounds, R₃ preferably represents a linear or branched (C₁-C₆)alkyl or a heteroaryl optionally substituted by a linear or branched (C₁-C₆)alkyl, and R₄ represents a 4-hydroxyphenyl group. Even more preferably, R₃ represents a methyl.

Preferred R₄ groups are as follows: phenyl; 4-hydroxyphenyl; 3-fluoro-4-hydroxyphenyl; 2-hydroxypyrimidine; 3-hydroxypyridine. Even more preferably, R₄ represents a 4-hydroxyphenyl group.

In preferred compounds of the invention, R₃ represents a linear or branched (C₁-C₆)alkyl group (preferably methyl), aryl or heteroaryl, all being optionally substituted. The groups aryl and heteroaryl are more especially preferred. Finally, R₃ preferably represents a group selected from phenyl, 1H-pyrazole, 1H-indole, 1H-indazole, pyridine, pyrimidine, 1H-pyrrolo[2,3-b]pyridine, 2,3-dihydro-1H-pyrrolo[2,3-b]pyridine, 1H-benzimidazole, 1H-pyrrole, 1H-pyrrolo[2,3-c]pyridine, 1H-pyrrolo[3,2-b]pyridine, 5H-pyrrolo[3,2-d]pyrimidine, thiophene, pyrazine, 1H-pyrazolo[3,4-b]pyridine, 1,2-oxazole, and 1H-pyrazolo[1,5-a]pyrimidine, those groups optionally having one or more substituents selected from halogen, linear or branched (C₁-C₆)alkyl, linear or branched (C₁-C₆)alkoxy, cyano, cyclopropyl, oxetane, tetrahydrofuran, —CO—O—CH₃, trideuteriomethyl, 2-(morpholin-4-yl)ethyl and 2-(morpholin-4-yl)ethoxy. More preferably, R₃ represents a group 1-methyl-1H-pyrazol-4-yl, pyridin-4-yl, 1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl, 5-cyano-1-methyl-1H-pyrrol-3-yl, 5-cyano-1,2-dimethyl-1H-pyrrol-3-yl, 1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl, 5-cyano-2-methyl-1-(trideuteriomethyl)-1H-pyrrol-3-yl.

Preferred compounds according to the invention are included in the following group:

5-(5-chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide,

5-(5-chloro-2-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(pyridin-4-yl)-1H-pyrrole-3-carboxamide, N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-5-(6-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-1H-pyrrole-3-carboxamide,

N-(4-hydroxyphenyl)-1,2-dimethyl-5-(6-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-N-(pyridin-4-yl)-1H-pyrrole-3-carboxamide,

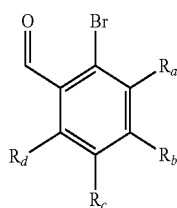
5-(5-fluoro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide,

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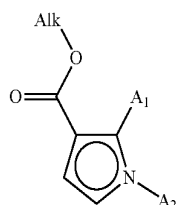
5-(5-chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide,
 5-(5-chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(pyridin-4-yl)-1H-pyrrole-3-carboxamide,
 5-(5-chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(5-cyano-1-methyl-1H-pyrrol-3-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide,
 N-(5-cyano-1-methyl-1H-pyrrol-3-yl)-5-(5-fluoro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide,
 5-(5-chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(5-cyano-1,2-dimethyl-1H-pyrrol-3-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide,
 5-(5-chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide,
 N-(5-cyano-1,2-dimethyl-1H-pyrrol-3-yl)-5-(5-fluoro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide,
 5-(5-chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-[5-cyano-2-methyl-1-(trideuteriomethyl)-1H-pyrrol-3-yl]-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide,

their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

The invention relates also to a process for the preparation of compounds of formula (I), which process is characterised in that there is used as starting material the compound of formula (II):



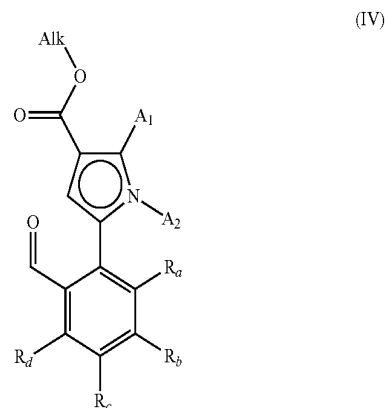
wherein R_a , R_b , R_c and R_d are as defined for formula (I), which compound of formula (II) is subjected to a Heck reaction, in an aqueous or organic medium, in the presence of a palladium catalyst, of a base, of a phosphine and of the compound of formula (III):



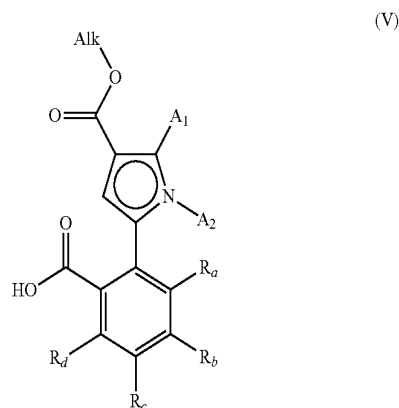
wherein the groups A_1 and A_2 are as defined for formula (I) and Alk represents a linear or branched (C_1 - C_6) alkyl,

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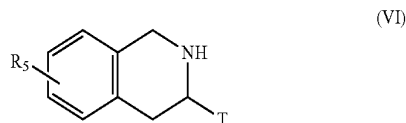
to obtain the compound of formula (IV):



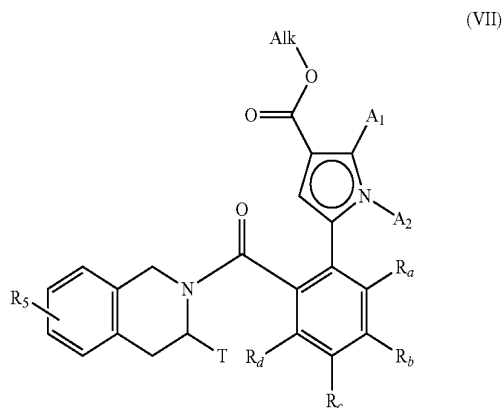
wherein A_1 , A_2 , R_a , R_b , R_c and R_d are as defined for formula (I) and Alk is as defined hereinbefore, the aldehyde function of which compound of formula (IV) is oxidised to a carboxylic acid to form the compound of formula (V):



wherein A_1 , A_2 , R_a , R_b , R_c and R_d are as defined for formula (I) and Alk is as defined hereinbefore, which compound of formula (V) is then subjected to peptide coupling with a compound of formula (VI):



wherein T and R_5 are as defined for formula (I), to yield the compound of formula (VII):



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wherein A_1 , A_2 , R_a , R_b , R_c , R_d , T and R_5 are as defined for formula (I) and Alk is as defined hereinbefore,

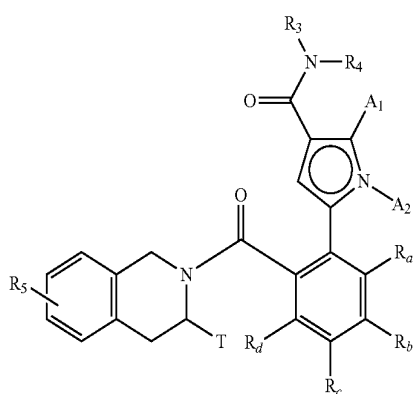
the ester function of which compound of formula (VII) is hydrolysed to yield the corresponding carboxylic acid or carboxylate, which may be converted into an acid derivative such as the corresponding acyl chloride or anhydride before being coupled with an amine NHR_3R_4 wherein R_3 and R_4 have the same meanings as for formula (I), to yield the compound of formula (I),

which compound of formula (I) may be purified according to a conventional separation technique, which is converted, if desired, into its addition salts with a pharmaceutically acceptable acid or base and which is optionally separated into its isomers according to a conventional separation technique,

it being understood that, at any time considered appropriate in the course of the above-described process, certain groups (hydroxy, amino . . .) of the reagents or intermediates of synthesis may be protected and then deprotected according to the requirements of synthesis.

More particularly, when one of the groups R_3 or R_4 of the amine NHR_3R_4 is substituted by a hydroxy function, the latter may be subjected beforehand to a protection reaction prior to any coupling with the carboxylic acid formed from the compound of formula (VII), or with a corresponding acid derivative thereof, the resulting protected compound of formula (I) subsequently undergoes a deprotection reaction and is then optionally converted into one of its addition salts with a pharmaceutically acceptable acid or base.

The present invention relates also to an alternative process for the preparation of compounds of formula (I'), which are particular cases of the compounds of formula (I) as defined hereinbefore:



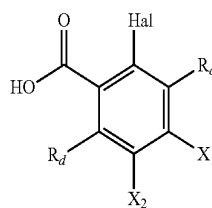
wherein:

A_1 , A_2 , R_a , R_b , R_3 , R_4 , T and R_5 are as defined for formula (I),

R_b and R_c are such that one represents a hydrogen and the other a group selected from $R_7-CO-NH-(C_0-C_6)$ alkyl-, $R_7-SO_2-NH-(C_0-C_6)$ alkyl-, $R_7-NH-CO-NH-(C_0-C_6)$ alkyl- and $R_7-O-CO-NH-(C_0-C_6)$ alkyl-,

which preparation process uses as starting material a compound of formula (II'):

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(II')

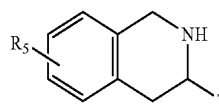
wherein:

R_a and R_d are as defined for formula (I),

Hal represents a halogen atom,

X_1 and X_2 are such that one represents a (C_0-C_6) alkyl-NH₂ group while the other represents a hydrogen atom,

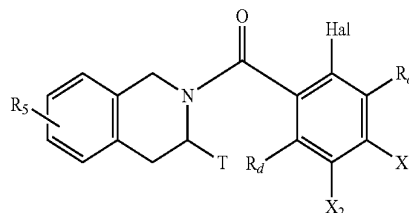
which compound of formula (II') is then subjected to peptide coupling with a compound of formula (VI):



(VI)

wherein T and R_5 are as defined for formula (I),

to yield the compound of formula (III'):



(III')

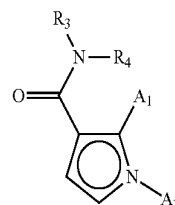
wherein:

R_a , R_d , T and R_5 are as defined for formula (I),

Hal represents a halogen atom,

X_1 and X_2 are such that one represents a (C_0-C_6) alkyl-NH₂ group while the other represents a hydrogen atom,

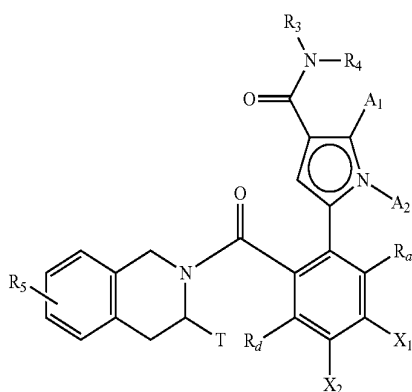
which compound of formula (III') is subjected to a Heck reaction, in an aqueous or organic medium, in the presence of a palladium catalyst, of a base, of a phosphine and of a compound of formula (IV'):



(IV')

wherein A_1 , A_2 , R_3 and R_4 are as defined for formula (I), to form the compound of formula (V'):

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wherein:

$A_1, A_2, R_a, R_d, R_3, R_4, T$ and R_5 are as defined for formula (I),

X_1 and X_2 are such that one represents a (C_0-C_6) alkyl-NH $_2$ group while the other represents a hydrogen atom, which compound of formula (V') is then subjected to an acylation or sulphonylation reaction to yield the compound of formula (I'),

which compound of formula (I') may be purified according to a conventional separation technique, which is converted, if desired, into its addition salts with a pharmaceutically acceptable acid or base and which is optionally separated into its isomers according to a conventional separation technique, it being understood that, at any time considered appropriate in the course of the above-described process, certain groups (hydroxy, amino . . .) of the reagents or intermediates of synthesis may be protected and then deprotected according to the requirements of synthesis.

The compounds of formulae (II), (III), (II'), (IV'), (VI) and the amine NHR_3R_4 are either commercially available or can be obtained by the person skilled in the art using conventional chemical reactions described in the literature.

Pharmacological study of the compounds of the invention has shown that they have pro-apoptotic properties. The ability to reactivate the apoptotic process in cancerous cells is of major therapeutic interest in the treatment of cancers, autoimmune diseases and diseases of the immune system.

More especially, the compounds according to the invention will be useful in the treatment of chemo- or radio-resistant cancers, and in malignant haemopathies and small-cell lung cancer.

Among the cancer treatments envisaged there may be mentioned, without implying any limitation, cancers of the bladder, brain, breast and uterus, chronic lymphoid leukaemias, colorectal cancer, cancers of the oesophagus and liver, lymphoblastic leukaemias, non-Hodgkin lymphomas, melanomas, malignant haemopathies, myelomas, ovarian cancer, non-small-cell lung cancer, prostate cancer and small-cell lung cancer. Among non-Hodgkin lymphomas, there may be mentioned more preferably follicular lymphomas, mantle cell lymphomas, diffuse large B-cell lymphomas, small lymphocytic lymphomas and marginal zone B-cell lymphomas.

The present invention relates also to pharmaceutical compositions comprising at least one compound of formula (I) in combination with one or more pharmaceutically acceptable excipients.

Among the pharmaceutical compositions according to the invention there may be mentioned more especially those that are suitable for oral, parenteral, nasal, per- or trans-cutaneous,

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rectal, perlingual, ocular or respiratory administration, especially tablets or dragées, sublingual tablets, sachets, paquets, capsules, glossettes, lozenges, suppositories, creams, ointments, dermal gels, and drinkable or injectable ampoules.

The dosage varies according to the sex, age and weight of the patient, the administration route, the nature of the therapeutic indication, or of any associated treatments, and ranges from 0.01 mg to 1 g per 24 hours in one or more administrations.

Furthermore, the present invention relates also to the association of a compound of formula (I) with an anticancer agent selected from genotoxic agents, mitotic poisons, anti-metabolites, proteasome inhibitors, kinase inhibitors and antibodies, and also to pharmaceutical compositions comprising that type of association and their use in the manufacture of medicaments for use in the treatment of cancer.

The compounds of the invention may also be used in association with radiotherapy in the treatment of cancer.

Finally, the compounds of the invention may be linked to monoclonal antibodies or fragments thereof or linked to scaffold proteins that can be related or not to monoclonal antibodies.

Antibody fragments must be understood as fragments of Fv, scFv, Fab, F(ab') $_2$, F(ab'), scFv-Fc type or diabodies, which generally have the same specificity of binding as the antibody from which they are descended. According to the present invention, antibody fragments of the invention can be obtained starting from antibodies by methods such as digestion by enzymes, such as pepsin or papain, and/or by cleavage of the disulfide bridges by chemical reduction. In another manner, the antibody fragments comprised in the present invention can be obtained by techniques of genetic recombination likewise well known to the person skilled in the art or else by peptide synthesis by means of, for example, automatic peptide synthesizers such as those supplied by the company Applied Biosystems, etc.

Scaffold proteins that can be related or not to monoclonal antibodies are understood to mean a protein that contains or not an immunoglobulin fold and that yields a binding capacity similar to a monoclonal antibody. The man skilled in the art knows how to select the protein scaffold. More particularly, it is known that, to be selected, such a scaffold should display several features as follow (Skerra A., J. Mol. Recogn., 13, 2000, 167-187): phylogenetically good conservation, robust architecture with a well-known three-dimensional molecular organization (such as, for example, crystallography or NMR), small size, no or only a low degree of post-translational modifications, easy to produce, express and purify. Such a protein scaffold can be, but without limitation, a structure selected from the group consisting in fibronectin and preferentially the tenth fibronectin type III domain (FNfn10), lipocalin, anticain (Skerra A., J. Biotechnol., 2001, 74(4):257-75), the protein Z derivative from the domain B of staphylococcal protein A, thioredoxin A or any protein with a repeated domain such as an "ankyrin repeat" (Kohl et al., PNAS, 2003, vol. 100, No. 4, 1700-1705), "armadillo repeat", "leucine-rich repeat" or "tetratricopeptide repeat". There could also be mentioned a scaffold derivative from toxins (such as, for example, scorpion, insect, plant or mollusc toxins) or protein inhibitors of neuronal nitric oxide synthase (PIN).

The following Preparations and Examples illustrate the invention without limiting it in any way.

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PREPARATION 1

4-Chloro-2-[4-(ethoxycarbonyl)-1,5-dimethyl-1H-pyrrol-2-yl]benzoic acid

Step A: Ethyl 1,2-dimethyl-1H-pyrrole-3-carboxylate

To a solution of 10 g of ethyl 2-methyl-1H-pyrrole-3-carboxylate (65.3 mmol) and 8.95 mL (130.6 mmol) of methyl iodide in 70 mL of dimethylformamide placed at 0° C. there are added, in three portions, 2.61 g (65.3 mmol) of sodium hydride (NaH) 60%. The batch is then stirred at 0° C. for 1 hour. Then, the reaction mixture is hydrolysed by the addition of 420 mL of ice-cold water. The reaction mixture is then diluted with ethyl acetate, successively washed with 0.1M aqueous hydrochloric acid (HCl) solution, saturated aqueous LiCl solution and then brine. The organic phase is then dried over MgSO₄, filtered, concentrated to dryness and purified by chromatography over silica gel (petroleum ether/AcOEt gradient).

¹H NMR: δ (400 MHz; dmsd-d₆; 300K): 6.65 (d, 1H pyrrole); 6.3 (1d, 1H pyrrole); 4.1 (1q, 2H, OCH₂CH₃); 3.5 (s, 3H N-pyrrole); 2.4 (s, 3H pyrrole); 1.5 (it, 3H OCH₂CH₃)

IR: v: >C=O: 1688 cm⁻¹; v: C—O—C: 1172 cm⁻¹

Step B: Ethyl 5-(5-chloro-2-formylphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxylate

To a solution of 10.5 g of the compound obtained in Step A (62.8 mmol) in 65 mL of N,N-dimethylacetamide there are successively added 15.2 g of 2-bromo-4-chlorobenzaldehyde (69 mmol), 12.3 g of potassium acetate (125.6 mmol) and then the batch is stirred under argon for 20 minutes. There are then added 2.2 g of palladium catalyst PdCl₂(PPh₃)₂ (3.14 mmol). The reaction mixture is then heated at 130° C. overnight. The mixture is allowed to return to ambient temperature and it is then diluted with dichloromethane. Animal charcoal is added (2 g per g of product) and the batch is stirred at ambient temperature for 1 hour and then filtered. The organic phase is then washed with water, dried over MgSO₄ and concentrated to dryness. The crude product thereby obtained is purified by chromatography over silica gel (petroleum ether/AcOEt gradient). The title product is obtained in the form of a solid.

¹H NMR: δ (400 MHz; dmsd-d₆; 300K): 9.8 (s, 1H, formyl); 7.91-7.69-7.61 (d, 3H, aromatic Hs); 6.5 (s, 1H pyrrole); 4.2 (q, 2H, OCH₂CH₃); 3.4 (s, 3H, CH₃—N-pyrrole); 2.55 (s, 3H pyrrole); 1.28 (t, 3H, OCH₂CH₃)

Step C: 4-Chloro-2-[4-(ethoxycarbonyl)-1,5-dimethyl-1H-pyrrol-2-yl]benzoic acid

A solution is prepared containing 12.85 g of the compound obtained in Step B (42 mmol) and 35.7 mL (336 mmol) of 2-methyl-2-butene in a mixture containing 20 mL of acetone and 20 mL of tetrahydrofuran. There are added, dropwise, 200 mL of an aqueous solution containing a mixture of 13.3 g of sodium chlorite (NaClO₂) (147 mmol) and 14.5 g of sodium hydrogen phosphate (NaHPO₄) (105 mmol). The batch is then vigorously stirred at ambient temperature for 7 hours. The reaction mixture is then concentrated to remove the acetone. Ethyl acetate is added, and the organic phase is washed with water, dried over MgSO₄ and then concentrated to dryness. The residue is then taken up in a minimum of ethyl ether. The solid then obtained is filtered off, washed with ether and then dried in vacuo at 40° C. overnight. The title product is obtained in the form of a solid, which is subsequently used without being otherwise purified.

¹H NMR: δ (400 MHz; dmsd-d₆; 300K): 13 (m, 1H COOH); 7.85-7.6-7.41 (d,dd, wd, 3H, aromatic Hs); 6.3 (s, 1H, H pyrrole); 4.15 (q, 2H, OCH₂CH₃); 3.25 (s, 3H, CH₃—N-pyrrole); 2.5 (s, 3H, CH₃-pyrrole); 1.25 (t, 3H, OCH₂CH₃)

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IR: v: —OH: 3100-2500 cm⁻¹ acid; v: >C=O: 1681 cm⁻¹ ester+acid

PREPARATION 2

2-[4-(Ethoxycarbonyl)-1-methyl-1H-pyrrol-2-yl]benzoic acid

The procedure is in accordance with the process of Preparation 1, replacing, on the one hand, the ethyl 2-methyl-1H-pyrrole-3-carboxylate used in Step A by ethyl 1H-pyrrole-3-carboxylate and, on the other hand, the 2-bromo-4-chlorobenzaldehyde used in Step B by 2-bromobenzaldehyde.

PREPARATION 3

4-Chloro-2-[4-(ethoxycarbonyl)-1-methyl-1H-pyrrol-2-yl]benzoic acid

The procedure is in accordance with the process of Preparation 1, replacing the ethyl 2-methyl-1H-pyrrole-3-carboxylate used in Step A by ethyl 1H-pyrrole-3-carboxylate.

PREPARATION 4

6-[4-(Ethoxycarbonyl)-1-methyl-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid

The procedure is in accordance with the process of Preparation 1, replacing, on the one hand, the ethyl 2-methyl-1H-pyrrole-3-carboxylate used in Step A by ethyl 1H-pyrrole-3-carboxylate and, on the other hand, the 2-bromo-4-chlorobenzaldehyde used in Step B by 6-bromo-1,3-benzodioxole-5-carbaldehyde.

IR: v: —OH: 3500-2300 cm⁻¹ acid; v: >C=O: 1688-1670 cm⁻¹ ester+acid

PREPARATION 5

4-Chloro-2-[4-(ethoxycarbonyl)-1-ethyl-1H-pyrrol-2-yl]benzoic acid

The procedure is in accordance with the process of Preparation 1, replacing in Step A, on the one hand, the ethyl 2-methyl-1H-pyrrole-3-carboxylate by ethyl 1H-pyrrole-3-carboxylate and, on the other hand, the methyl iodide by ethyl iodide (see the protocol described in U.S. Pat. No. 6,258,805 B1).

PREPARATION 6

4-Chloro-2-[1-cyclopropyl-4-(ethoxycarbonyl)-1H-pyrrol-2-yl]benzoic acid

The procedure is in accordance with the process of Preparation 1, replacing in Step A, on the one hand, the ethyl 2-methyl-1H-pyrrole-3-carboxylate by ethyl 1H-pyrrole-3-carboxylate and, on the other hand, the methyl iodide by cyclopropylboronic acid (see the protocol described in Bénard S. et al, Journal of Organic Chemistry 73(16), 6441-6444, 2008).

PREPARATION 7

4-Chloro-2-[4-(ethoxycarbonyl)-1-(propan-2-yl)-1H-pyrrol-2-yl]benzoic acid

The procedure is in accordance with the process of Preparation 1, replacing in Step A, on the one hand, the ethyl

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2-methyl-1H-pyrrole-3-carboxylate by ethyl 1H-pyrrole-3-carboxylate and, on the other hand, the methyl iodide by isopropyl iodide (see the protocol described in Okada E. et al, Heterocycles 34(7), 1435-1441, 1992).

PREPARATION 8

4-Fluoro-2-[4-(methoxycarbonyl)-1,5-dimethyl-1H-pyrrol-2-yl]benzoic acid

The procedure is in accordance with the process of Preparation 1, replacing, in Step A, the ethyl 2-methyl-1H-pyrrole-3-carboxylate by methyl 2-methyl-1H-pyrrole-3-carboxylate and also the 2-bromo-4-chlorobenzaldehyde used in Step B by 2-bromo-4-fluorobenzaldehyde.

IR: ν : —OH: 2727-2379 cm^{-1} acid; ν : >C=O : 1687 cm^{-1}

PREPARATION 9

6-{1-[2-(Benzyloxy)ethyl]-4-(ethoxycarbonyl)-5-methyl-1H-pyrrol-2-yl}-1,3-benzodioxole-5-carboxylic acid

Step A: Ethyl 1-[2-(benzyloxy)ethyl]-2-methyl-1H-pyrrole-3-carboxylate

The procedure is in accordance with the process of Step A of Preparation 1, replacing the methyl iodide used as alkylating agent by benzyl 2-bromoethyl ether.

^1H NMR: δ (400 MHz; dmsO-d_6 ; 300K): 7.32 (t, 2H, aromatic Hs, H meta benzyl ether); 7.3 (t, 1H, aromatic H, H para benzyl ether); 7.23 (d, 2H, aromatic Hs, H ortho benzyl ether); 6.72 (d, 1H, H—pyrrole); 6.35 (d, 1H, H—pyrrole); 4.48 (s, 2H, aliphatic Hs, $\text{O—CH}_2\text{—Ph}$); 4.15 (q, 2H, aliphatic Hs, $\text{O—CH}_2\text{—CH}_3$); 4.1 (t, 2H, aliphatic Hs, $\text{CH}_2\text{—O—CH}_2\text{—Ph}$); 3.7 (t, 2H, aliphatic Hs, $\text{CH}_2\text{—CH}_2\text{—O—CH}_2\text{—Ph}$); 2.45 (s, 3H, CH_3 —pyrrole); 1.25 (t, 3H, aliphatic Hs, $\text{O—CH}_2\text{—CH}_3$)

IR: ν : >C=O : 1689 cm^{-1}

Step B: 6-{1-[2-(Benzyloxy)ethyl]-4-(ethoxycarbonyl)-5-methyl-1H-pyrrol-2-yl}-1,3-benzodioxole-5-carboxylic acid

The procedure is in accordance with the processes of Steps B and C of Preparation 1, replacing the 2-bromo-4-chlorobenzaldehyde by 6-bromo-1,3-benzodioxole-5-carbaldehyde.

^1H NMR: δ (400 MHz; dmsO-d_6 ; 300K): 7.35 (s, 1H, aromatic H, H benzodioxole); 7.30 (m, 3H, aromatic Hs, H benzyl ether); 7.25 (s, 1H, aromatic H, H benzodioxole); 7.10 (d, 2H, aromatic Hs, H ortho benzyl ether); 12.55 (broad s, 1H, COOH); 6.75 (s, 1H, H-pyrrole); 6.15 (broad s, 2H, aliphatic Hs, $\text{O—CH}_2\text{—O}$); 4.30 (s, 2H, aliphatic Hs, $\text{O—CH}_2\text{—Ph}$); 4.15 (q, 2H, aliphatic Hs, $\text{O—CH}_2\text{—CH}_3$); 3.9 (m, 2H, aliphatic Hs, $\text{CH}_2\text{—CH}_2\text{—O—CH}_2\text{—Ph}$); 3.40 (t, 2H, aliphatic Hs, $\text{CH}_2\text{—CH}_2\text{—O—CH}_2\text{—Ph}$); 2.50 (s, 3H, CH_3 —pyrrole); 1.25 (t, 3H, aliphatic Hs, $\text{O—CH}_2\text{—CH}_3$)

IR: ν : —OH: 3200-2300 cm^{-1} acid; ν : >C=O : 1687 cm^{-1} acid

PREPARATION 10

2-{1-[3-(Benzyloxy)propyl]-4-(ethoxycarbonyl)-5-methyl-1H-pyrrol-2-yl}-4-fluorobenzoic acid

The procedure is in accordance with the process of Preparation 9, replacing the benzyl 2-bromoethyl ether used in Step

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A by benzyl 3-bromopropyl ether and also the 6-bromo-1,3-benzodioxole-5-carbaldehyde used in Step B by 2-bromo-4-fluorobenzaldehyde.

IR: ν : —OH: 3200-2305 cm^{-1} acid; ν : >C=O : 1690 cm^{-1} acid

PREPARATION 11

6-[4-(Ethoxycarbonyl)-1,5-dimethyl-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid

The procedure is in accordance with the process of Preparation 1, replacing the 2-bromo-4-chlorobenzaldehyde used in Step B by 6-bromo-1,3-benzodioxole-5-carbaldehyde.

PREPARATION 12

4-Methoxy-2-[4-(methoxycarbonyl)-1,5-dimethyl-1H-pyrrol-2-yl]-benzoic acid

The procedure is in accordance with the process of Preparation 1, replacing the ethyl 2-methyl-1H-pyrrole-3-carboxylate used in Step A by methyl 2-methyl-1H-pyrrole-3-carboxylate and also the 2-bromo-4-chlorobenzaldehyde used in Step B by 2-bromo-4-methoxybenzaldehyde.

IR: ν : —OH: 3000-2500 cm^{-1} acid; ν : >C=O : 1693+1670 cm^{-1} acid+ester

PREPARATION 13

7-[4-(Methoxycarbonyl)-1,5-dimethyl-1H-pyrrol-2-yl]-2,3-dihydro-1,4-benzodioxin-6-carboxylic acid

The procedure is in accordance with the process of Preparation 1, replacing in Step A the ethyl 2-methyl-1H-pyrrole-3-carboxylate by methyl 2-methyl-1H-pyrrole-3-carboxylate and also the 2-bromo-4-chlorobenzaldehyde used in Step B by 7-bromo-2,3-dihydro-1,4-benzodioxin-6-carbaldehyde.

IR: ν : —OH: 3100-2500 cm^{-1} acid; ν : >C=O : 1690+1674 cm^{-1} acid+ester

PREPARATION 14

4-Fluoro-5-methoxy-2-[4-(methoxycarbonyl)-1,5-dimethyl-1H-pyrrol-2-yl]benzoic acid

The procedure is in accordance with the process of Preparation 1, replacing in Step A the ethyl 2-methyl-1H-pyrrole-3-carboxylate by methyl 2-methyl-1H-pyrrole-3-carboxylate and also the 2-bromo-4-chlorobenzaldehyde used in Step B by 2-bromo-4-fluoro-5-methoxybenzaldehyde.

PREPARATION 15

4-Fluoro-5-hydroxy-2-[4-(methoxycarbonyl)-1,5-dimethyl-1H-pyrrol-2-yl]benzoic acid

The procedure is in accordance with the process of Preparation 1, replacing in Step A the ethyl 2-methyl-1H-pyrrole-3-carboxylate by methyl 2-methyl-1H-pyrrole-3-carboxylate and also the 2-bromo-4-chlorobenzaldehyde used in Step B by 2-bromo-4-fluoro-5-hydroxy-benzaldehyde.

PREPARATION 16

6-[4-(Ethoxycarbonyl)-1-methyl-5-trifluoromethyl-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid

The procedure is in accordance with the process of Preparation 1, replacing in Step A the ethyl 2-methyl-1H-pyrrole-

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3-carboxylate by ethyl 2-(trifluoromethyl)-1H-pyrrole-3-carboxylate and also the 2-bromo-4-chlorobenzaldehyde used in Step B by 6-bromo-1,3-benzodioxole-5-carbaldehyde.

PREPARATION 17

6-[4-(Ethoxycarbonyl)-1-ethyl-5-methyl-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid

The procedure is in accordance with the process of Preparation 11, replacing the methyl iodide by ethyl iodide (see the protocol described in U.S. Pat. No. 6,258,805 B1).

PREPARATION 18

6-[4-(Ethoxycarbonyl)-1-methyl-5-(trifluoromethyl)-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid

Step A: Ethyl 1-methyl-2-(trifluoromethyl)pyrrole-3-carboxylate

Ethyl 4,4,4-trifluoro-3-oxo-butanoate (29 ml, 0.219 mmol) is added to methylamine (40% solution in water) (50 ml, 0.580 mmol) cooled to 10° C.; a white precipitate forms. 1,2-Dibromoethyl acetate (prepared according to Molecules, 16, 9368-9385; 2011) is added dropwise. The reactor is then sealed and heated at 70° C. for 45 minutes. The reaction mixture is cooled, then extracted with ethyl acetate, dried over sodium sulphate (Na₂SO₄) and evaporated to dryness. The crude reaction product obtained is purified by chromatography over silica gel using heptane and ethyl acetate as eluants. The expected compound is obtained in the form of crystals.

¹H NMR (400 MHz, dmsO-d₆) δ ppm: 7.11 (d, 1 H), 6.52 (d, 1 H), 4.21 (quad, 2 H), 3.8 (s, 3 H), 1.27 (t, 3 H)

¹⁹F NMR (400 MHz, dmsO-d₆) δ ppm: -53.9

IR (ATR) cm⁻¹: 3145+3128 ν —CH, 1711 ν >C=O, 1183+1117+1078 ν —CF₃

Step B: 6-[4-(Ethoxycarbonyl)-1-methyl-5-(trifluoromethyl)-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid

The procedure is in accordance with the protocol described in Steps B and C of Preparation 1, replacing the 2-bromo-4-chlorobenzaldehyde used in Step B by 6-bromo-1,3-benzodioxole-5-carbaldehyde.

PREPARATION 19

6-[1-(2-Benzyloxyethyl)-4-ethoxycarbonyl-5-methyl-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid

Step A: Ethyl 1-(2-benzyloxyethyl)-2-methyl-pyrrole-3-carboxylate

Ethyl 2-methyl-1H-pyrrole-3-carboxylate (10 g, 65.3 mmol) is dissolved in 100 mL of dimethylformamide under argon cooled to 0° C., and then 2-bromoethoxymethylbenzene (28.1 g, 130.6 mmol) is added all at once. The reaction mixture is placed under stirring. There is then added thereto, at 0° C., in three portions, NaH (1.72 g, 71.83 mmol) over a period of 15 minutes. The reaction mixture is stirred for 15 minutes at 0° C., and then for 15 hours at ambient temperature. It is then poured into an ice bath and then extracted 3 times with ethyl acetate. The organic phase is washed 3 times with saturated aqueous lithium chloride solution, dried over MgSO₄, filtered and then evaporated to dryness. The residue thereby obtained is purified by chromatography over silica

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gel using petroleum ether and ethyl acetate as eluants. The expected compound is obtained in the form of an oil.

¹H NMR (400 MHz, dmsO-d₆) δ ppm: 7.32 (t, 2 H), 7.3 (t, 1 H), 7.23 (d, 2 H), 6.72 (d, 1 H), 6.35 (d, 1 H), 4.48 (s, 2 H), 4.15 (quad., 2 H), 4.1 (t, 2 H), 3.7 (t, 2 H), 2.45 (s, 3 H), 1.25 (t, 3 H)

IR (ATR) cm⁻¹: 1689 ν —C=O

Step B: Ethyl 1-(2-benzyloxyethyl)-5-(6-formyl-1,3-benzodioxol-5-yl)-2-methyl-pyrrole-3-carboxylate

The procedure is in accordance with the process of Step B of Preparation 1, replacing the 2-bromo-4-chlorobenzaldehyde by 6-bromo-1,3-benzodioxole-5-carbaldehyde.

¹H NMR (400 MHz, dmsO-d₆) δ ppm: 9.5 (s, 1 H), 7.3 (s, 1 H), 7.25 (m, 3 H), 7.05 (m, 2 H), 7 (s, 1 H), 6.4 (s, 1 H), 6.2 (bs, 2 H), 4.25 (s, 2 H), 4.2 (quad., 2 H), 4.05 (m, 2 H), 3.4 (m, 2 H), 2.55 (s, 3 H), 1.25 (t, 3 H)

Step C: 6-[1-(2-Benzyloxyethyl)-4-ethoxycarbonyl-5-methyl-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid

The procedure is in accordance with the process of Step C of Preparation 1.

¹H NMR (400 MHz, dmsO-d₆) δ ppm: 12.55 (bs, 1 H), 7.35 (s, 1 H), 7.3 (m, 3 H), 7.2 (m, 3 H), 6.75 (s, 1 H), 6.15 (s, 2 H), 4.3 (s, 2 H), 4.15 (quad., 2 H), 3.9 (m, 2 H), 3.4 (t, 2 H), 2.5 (s, 3 H), 1.25 (t, 3 H)

IR (ATR) cm⁻¹: 3200-2300 ν —OH, 1687 (+shoulder) ν C=O carboxylic acid+conjugated ester

PREPARATION 20

6-[4-(Ethoxycarbonyl)-1-ethyl-5-methyl-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid

The procedure is in accordance with the protocol described in Preparation 11, replacing the methyl iodide by ethyl iodide.

¹H NMR (400 MHz, dmsO-d₆) δ ppm: 12.49 (bs, 1 H), 7.33 (s, 1 H), 6.89 (s, 1 H), 6.17 (s, 2 H), 6.13 (s, 1 H), 4.15 (quad, 2 H), 3.69 (quad, 2 H), 2.51 (s, 3 H), 1.24 (t, 3 H), 1.01 (t, 3 H)

PREPARATION 21

6-[4-(Ethoxycarbonyl)-1-(2-fluoroethyl)-5-methyl-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid

The procedure is in accordance with the process of Preparation 11, replacing the methyl iodide by 1-bromo-2-fluoroethane.

¹H NMR (400 MHz, dmsO-d₆, 300K) δ ppm: 12.53 (bs, 1 H), 7.34 (s, 1 H), 6.9 (s, 1 H), 6.16 (s, 1 H), 6.16 (s, 2 H), 4.4 (dt, 2 H), 4.15 (quad, 2 H), 4.01 (m, 2 H), 2.51 (s, 3 H), 1.24 (t, 3 H)

¹⁹F NMR (400 MHz, dmsO-d₆, 300 K) δ ppm: -222
IR: ν: —OH: 3700-2400 cm⁻¹ acid; ν: >C=O: 1689 cm⁻¹ acid; ν: >CF: 1213 cm⁻¹

PREPARATION 22

6-{4-(Ethoxycarbonyl)-1-methyl-5-[2-(morpholin-4-yl)ethyl]-1H-pyrrol-2-yl}-1,3-benzodioxole-5-carboxylic acid

Step A: 3,3-Diethoxypropanoic acid

To a solution of 25 g of ethyl 3,3-diethoxypropionate (131 mmol) in 79 mL of methanol there are added 13.1 mL of aqueous 35% sodium hydroxide solution (452 mmol). The reaction mixture is stirred at ambient temperature for 3 hours. The reaction mixture is then concentrated to remove the methanol. After dissolving the undissolved material by add-

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ing water, aqueous 5N HCl solution is added to obtain a pH of 5. Dichloromethane is added and then the organic phase is washed with brine. After drying over MgSO_4 and concentrating to dryness, the title product is obtained in the form of an oil which is used in the next Step without being otherwise purified.

^1H NMR (400 MHz, dmsO-d_6) δ ppm: 12.2 (s, 1 H), 4.8 (t, 1 H), 3.58/3.47 (2m, 4 H), 2.5 (d, 2 H), 1.09 (t, 6 H)

Step B: Ethyl 5,5-diethoxy-3-oxo-pentanoate

To a solution of 16 mL of 3-ethoxy-3-oxomalonic acid (135 mmol) in 40 mL of tetrahydrofuran there are added, under argon, 21.9 g of powdered magnesium (90.4 mmol). The mixture obtained is then heated at 80°C . for 7 hours. After returning to ambient temperature, this mixture is transferred by cannula to a solution of 10 g of the compound obtained in Step A (61.7 mmol) in 64 mL of tetrahydrofuran to which there has previously been added, in portions, 11 g of carbonyldiimidazole (66 mmol). The reaction mixture is stirred for 3 days at ambient temperature. After concentration, the residue is taken up in a mixture of ethyl acetate and aqueous sodium hydrogen sulphate (NaHSO_4) solution. The mixture is stirred vigorously until no more gas is evolved. After separation of the phases, the organic phase is washed successively with water, saturated aqueous NaHCO_3 solution and finally brine. After drying over MgSO_4 and concentrating to dryness, the title product is obtained in the form of an oil which is used in the next Step without being otherwise purified.

^1H NMR (400 MHz, dmsO-d_6) δ ppm: 4.84 (t, 1 H), 4.08 (q, 2 H), 3.59 (s, 2 H), 3.56/3.46 (2m, 4 H), 2.8 (d, 2 H), 1.18 (t, 3 H), 1.09 (t, 6 H)

Step C: Ethyl 2-(2,2-diethoxyethyl)-1-methyl-pyrrole-3-carboxylate

To a solution of 11.8 g of the compound obtained in Step B (50.8 mmol) in 76 mL of water there are added, dropwise at 0°C ., 6.6 mL of aqueous 40% methylamine solution (76.2 mmol). The reaction mixture is stirred and gently reheated to ambient temperature over 5 hours. After returning to 0°C ., 8.8 mL of aqueous 40% methylamine solution (102 mmol) and then 16.6 mL of aqueous 50% chloroacetaldehyde solution (127 mmol) are each added dropwise at a temperature of less than 10°C . The reaction mixture is stirred at ambient temperature for 16 hours and then diluted with ethyl acetate. The organic phase is washed with brine, dried over MgSO_4 and concentrated to dryness. The crude product thereby obtained is purified by chromatography over silica gel using petroleum ether and ethyl acetate as eluants. The title product is obtained in the form of an oil.

^1H NMR (400 MHz, dmsO-d_6) δ ppm: 6.7 (d, 1 H), 6.33 (d, 1 H), 4.55 (t, 1 H), 4.15 (q, 2 H), 3.6 (m, 2 H), 3.6 (s, 3 H), 3.3 (m, 2 H), 3.15 (d, 2 H), 1.25 (t, 3 H), 1.05 (t, 6 H)

Step D: Ethyl 1-methyl-2-(2-morpholinoethyl)pyrrole-3-carboxylate

To a solution of 3.8 g of the compound obtained in Step C (14.05 mmol) in 28 mL of tetrahydrofuran there are added 58 mL of aqueous 10% sulphuric acid solution. The reaction mixture is stirred at ambient temperature for 2 hours and then diluted with a mixture of ethyl acetate and water. After separation, the organic phase is washed with brine, dried over MgSO_4 and concentrated to dryness. To a solution of the residue thereby obtained in 70 mL of dichloroethane there are added a solution of 13.5 mL of morpholine (14.5 mmol) in a mixture composed of 30 mL of dichloroethane and 3.6 mL of 4N aqueous HCl solution in dioxane (14.5 mmol), and then 7.4 g of sodium triacetoxyborohydride ($\text{NaBH}(\text{OAc})_3$) (35.13 mmol). The reaction mixture is stirred at ambient temperature for 3 hours and then diluted with a mixture of

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dichloromethane and saturated aqueous NaHCO_3 solution. After separation of the phases and extraction of the aqueous phase with dichloromethane, the organic phases are dried over MgSO_4 and concentrated to dryness. The crude product thereby obtained is purified by chromatography over silica gel using dichloromethane and methanol as eluants. The title product is isolated in the form of an oil.

^1H NMR (400 MHz, dmsO-d_6) δ ppm: 6.66 (d, 1 H), 6.31 (d, 1 H), 4.14 (q, 2 H), 3.58 (s, 3 H), 3.57 (m, 4 H), 3.05 (m, 2 H), 2.45-2.38 (m, 6 H), 1.24 (t, 3 H)

Step E: 6-[4-(Ethoxycarbonyl)-1-methyl-5-[2-(morpholin-4-yl)ethyl]-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid

The procedure is in accordance with Steps B and C of Preparation, 1 replacing the 2-bromo-4-chlorobenzaldehyde used in Step B by 6-bromo-1,3-benzodioxole-5-carbaldehyde.

PREPARATION 23

6-[4-(Ethoxycarbonyl)-1-methyl-5-(morpholin-4-ylmethyl)-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid

Step A: Ethyl 4,4-diethoxy-3-oxo-butanoate

To a solution of 40 g of ethyl diethoxyacetate (227 mmol) in 67 mL of ethyl acetate there are added under argon, in portions, 6 g of sodium (261 mmol). The reaction mixture is then stirred at ambient temperature for 48 hours. There are added 10 mL of methanol, and then the mixture is hydrolysed with 65 mL of water. The pH of the reaction mixture is adjusted to pH 6 by adding 1N aqueous HCl solution. The mixture is separated and then extracted with ethyl acetate. The organic phases are combined, washed with brine, dried over MgSO_4 , filtered and concentrated to dryness. The title product is obtained in the form of an oil which is used in the next Step without being otherwise purified.

^1H NMR (400 MHz, CDCl_3) δ ppm: 3.6 (s, 2 H), 1.28 (t, 9H), 3.7-3.6 (2m, 4 H), 4.7 (s, 1 H), 4.2 (quad, 2 H)

Step B: Ethyl 2-(2,2-diethoxymethyl)-1-methyl-pyrrole-3-carboxylate

The title compound is obtained in accordance with the process described in Step C of Preparation 22, starting from the ethyl 4,4-diethoxy-3-oxo-butanoate obtained in the preceding Step.

^1H NMR (400 MHz, dmsO-d_6) δ ppm: 6.73 (d, 1 H), 6.32 (d, 1 H), 6.23 (s, 1 H), 4.17 (q, 2 H), 3.7 (s, 3 H), 3.68/3.43 (2m, 4 H), 1.26 (t, 3 H), 1.13 (t, 6 H)

Step C: Ethyl 1-methyl-2-(2-morpholinomethyl)pyrrole-3-carboxylate

The title compound is obtained in accordance with the process described in Step D of Preparation 22, starting from the ethyl 2-(2,2-diethoxymethyl)-1-methyl-pyrrole-3-carboxylate obtained in the preceding Step.

^1H NMR (400 MHz, dmsO-d_6) δ ppm: 6.74 (d, 1 H), 6.32 (d, 1 H), 4.15 (q, 2 H), 3.8 (s, 2H), 3.65 (s, 3 H), 3.5 (m, 4 H), 2.32 (m, 4 H), 1.22 (t, 3 H)

Step D: 6-[4-(Ethoxycarbonyl)-1-methyl-5-(morpholin-4-ylmethyl)-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid

The procedure is in accordance with the protocol described in Steps B and C of Preparation 1, replacing the 2-bromo-4-chlorobenzaldehyde used in Step B by 6-bromo-1,3-benzodioxole-5-carbaldehyde.

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PREPARATION 24

6-[4-(Methoxycarbonyl)-5-(2-methoxyethyl)-1-methyl-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid

Step A: Methyl 2-(2-methoxyethyl)-1-methyl-pyrrole-3-carboxylate

The title compound is obtained in accordance with the protocol of Step C of Preparation 22, using methyl 5-methoxy-3-oxovalerate.

¹H NMR (400 MHz, dms_o-d₆) δ ppm: 6.69 (wd, 1H), 6.31 (wd, 1H), 3.69 (s, 3 H), 3.59 (s, 3 H), 3.49 (t, 2 H), 3.2 (s, 3 H), 3.11 (t, 2 H)

Step B: 6-[4-(Methoxycarbonyl)-5-(2-methoxyethyl)-1-methyl-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid

The procedure is in accordance with the protocol described in Steps B and C of Preparation 1, replacing the 2-bromo-4-chlorobenzaldehyde used in Step B by 6-bromo-1,3-benzodioxole-5-carbaldehyde.

PREPARATION 25

2-[4-(Ethoxycarbonyl)-1,5-dimethyl-1H-pyrrol-2-yl]benzoic acid

The procedure is in accordance with the process of Preparation 1, replacing the 2-bromo-4-chlorobenzaldehyde used in Step B by 2-bromobenzaldehyde.

¹H NMR (400 MHz, dms_o-d₆) δ ppm: 12.81 (m, 1 H), 7.84 (m, 1 H), 7.59 (m, 1 H), 7.51 (m, 1 H), 7.35 (m, 1 H), 6.23 (s, 1 H), 4.16 (q, 2 H), 3.24 (s, 3 H), 2.5 (s, 3 H), 1.25 (t, 3 H)

PREPARATION 26

5-Fluoro-2-[4-(methoxycarbonyl)-1,5-dimethyl-1H-pyrrol-2-yl]-benzoic acid

The procedure is in accordance with the process of Preparation 1, replacing in Step A the ethyl 2-methyl-1H-pyrrole-3-carboxylate by methyl 2-methyl-1H-pyrrole-3-carboxylate and also the 2-bromo-4-chlorobenzaldehyde used in Step B by 2-bromo-5-fluorobenzaldehyde.

¹H NMR (400 MHz, dms_o-d₆) δ ppm: 7.6 (dd, 1 H), 7.42 (m, 2 H), 6.22 (s, 1 H), 4.15 (q, 2 H), 3.21 (s, 3 H), 2.5 (s, 3 H), 1.23 (t, 3 H)

¹⁹F NMR (400 MHz, dms_o-d₆) δ ppm: -113

PREPARATION 27

2-[4-(Ethoxycarbonyl)-1,5-dimethyl-1H-pyrrol-2-yl]-5-fluoro-4-methoxybenzoic acid

The procedure is in accordance with the process of Preparation 1, replacing in Step A the ethyl 2-methyl-1H-pyrrole-3-carboxylate by methyl 2-methyl-1H-pyrrole-3-carboxylate and also the 2-bromo-4-chlorobenzaldehyde used in Step B by 2-bromo-4-methoxy-5-fluorobenzaldehyde.

¹H NMR (400 MHz, dms_o-d₆) δ ppm: 9.65 (d, 1 H), 7.67 (d, 1 H), 7.24 (d, 1 H), 6.48 (s, 1 H), 4.19 (q, 2 H), 3.97 (s, 3 H), 3.38 (s, 3 H), 2.56 (s, 3 H), 1.26 (t, 3 H).

PREPARATION 28

2-(4-Ethoxycarbonyl-1,5-dimethyl-1H-pyrrol-2-yl)-4-fluoro-5-methoxybenzoic acid

The procedure is in accordance with Preparation 1, replacing the 2-bromo-4-chlorobenzaldehyde used in Step B by 4-fluoro-5-methoxybenzaldehyde.

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¹H NMR (400 MHz, dms_o-d₆) δ ppm: 12.9 (m, 1 H), 7.6 (d, 1 H), 7.22 (d, 1 H), 6.23 (s, 1 H), 4.2 (quad, 2 H), 3.95 (s, 3 H), 3.25 (s, 3 H), 2.5 (s, 3 H), 1.25 (t, 3 H)

PREPARATION 29

5-Chloro-2-[4-(ethoxycarbonyl)-1,5-dimethyl-1H-pyrrol-2-yl]benzoic acid

The procedure is in accordance with the process of Preparation 1, replacing the 2-bromo-4-chlorobenzaldehyde used in Step B by 2-bromo-5-chlorobenzaldehyde.

PREPARATION 30

2-{1-[2-(Benzyloxy)ethyl]-4-(ethoxycarbonyl)-5-methyl-1H-pyrrol-2-yl}-4-chlorobenzoic acid

The procedure is in accordance with the process of Preparation 19, replacing the 6-bromo-1,3-benzodioxole-5-carbaldehyde by 2-bromo-4-chlorobenzaldehyde.

PREPARATION 31

5-Methoxy-2-[4-(methoxycarbonyl)-1,5-dimethyl-1H-pyrrol-2-yl]-benzoic acid

The procedure is in accordance with the process of Preparation 1, replacing in Step A the ethyl 2-methyl-1H-pyrrole-3-carboxylate by methyl 2-methyl-1H-pyrrole-3-carboxylate and also the 2-bromo-4-chlorobenzaldehyde used in Step B by 2-bromo-5-methoxybenzaldehyde.

¹H NMR (400 MHz, dms_o-d₆) δ ppm: 12.8 (bs, 1 H), 7.34 (wd, 1 H), 7.26 (d, 1 H), 7.15 (dd, 1 H), 6.19 (s, 1 H), 3.84 (s, 3 H), 3.69 (s, 3 H), 3.22 (s, 3 H), 2.5 (s, 3 H)

PREPARATION 32

6-[1-(2,2-Difluoroethyl)-4-(ethoxycarbonyl)-5-methyl-1H-pyrrol-2-yl]-1,3-benzodioxole-5-carboxylic acid

The procedure is in accordance with the protocol of Preparation 19, replacing the 2-bromoethoxymethylbenzene used in Step A by 2-bromo-1,1-difluoro-ethane.

PREPARATION 1'

(3R)-3-Methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride

Step A: {(3S)-2-[(4-Methylphenyl)sulphonyl]-1,2,3,4-tetrahydroisoquinolin-3-yl}methyl 4-methylbenzenesulphonate

To a solution of 30.2 g of [(3S)-1,2,3,4-tetrahydroisoquinolin-3-yl]methanol (185 mmol) in 750 mL of dichloromethane there are successively added 91.71 g of tosyl chloride (481 mmol) and then, dropwise, 122.3 mL of N,N,N-triethylamine (740 mmol). The reaction mixture is then stirred at ambient temperature for 20 hours. It is then diluted with dichloromethane, washed successively with 1M HCl solution, saturated aqueous NaHCO₃ solution and then brine until neutral. The organic phase is then dried over MgSO₄, filtered and concentrated to dryness. The solid obtained is then dissolved in a minimum volume of dichloromethane and then cyclohexane is added until a precipitate is formed. This

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precipitate is then filtered off and washed with cyclohexane. After drying, the title product is obtained in the form of crystals.

¹H NMR: δ (400 MHz; dms_o-d₆; 300K): 7.75 (d, 2H, aromatic Hs, ortho O-tosyl); 7.6 (d, 2H, aromatic Hs, ortho N-tosyl); 7.5 (d, 2H, aromatic Hs, meta O-tosyl); 7.3 (d, 2H, aromatic Hs, meta N-tosyl); 7.15-6.9 (m, 4H, aromatic Hs, tetrahydroisoquinoline); 4.4-4.15 (dd, 2H, aliphatic Hs, tetrahydroisoquinoline); 4.25 (m, 1H, aliphatic H, tetrahydroisoquinoline); 4.0-3.8 (2dd, 2H, aliphatic Hs, CH₂-O-tosyl); 2.7 (2dd, 2H, aliphatic Hs, tetrahydroisoquinoline); 2.45 (s, 3H, O-SO₂-Ph-CH₃); 2.35 (s, 3H, N-SO₂-Ph-CH₃)

IR: ν : —SO₂: 1339-1165 cm⁻¹

Step B: (3R)-3-Methyl-2-[(4-methylphenyl)sulphonyl]-1,2,3,4-tetrahydroisoquinoline

To a suspension of 8.15 g (214.8 mmol) of lithium aluminium hydride (LiAlH₄) in 800 mL of methyl tert-butyl ether (MTBE) there are added 101.2 g of the ditosyl compound obtained in Step A (214.8 mmol) dissolved in 200 mL of MTBE. The batch is then heated at 50° C. for 2 hours. It is allowed to cool and placed at 0° C., and there are then added, dropwise, 12 mL of 5N NaOH solution. The batch is stirred at ambient temperature for 45 minutes. The solid thereby obtained is then filtered off and washed with MTBE and then with dichloromethane. The filtrate is then concentrated to dryness. The title product is then obtained in the form of a solid.

¹H NMR: δ (400 MHz; dms_o-d₆; 300K): 7.70 (d, 2H, aromatic Hs, ortho N-tosyl); 7.38 (d, 2H, aromatic Hs, meta N-tosyl); 7.2-7.0 (m, 4H, aromatic Hs, tetrahydroisoquinoline); 4.4 (m, 2H, aliphatic Hs, tetrahydroisoquinoline); 4.3 (m, 1H, aliphatic H, tetrahydroisoquinoline); 2.85-2.51 (2dd, 2H, aliphatic Hs, tetrahydroisoquinoline); 2.35 (s, 3H, N-SO₂-Ph-CH₃); 0.90 (d, 3H, tetrahydroisoquinoline-CH₃)

IR: ν : —SO₂: 1332-1154 cm⁻¹

Step C: (3R)-3-Methyl-1,2,3,4-tetrahydroisoquinoline

To a solution of 31.15 g (103.15 mmol) of the monotosyl compound obtained in Step B in 500 mL of anhydrous methanol there are added, in portions, 3.92 g (161 mmol) of magnesium turnings. The batch is stirred in the presence of ultrasound for 96 hours. The reaction mixture is then filtered and the solid is washed several times with methanol. The filtrate is then concentrated to dryness. After purification by chromatography over silica gel using dichloromethane and ammonia-in-ethanol as eluants, the title product is obtained in the form of an oil.

¹H NMR: δ (400 MHz; dms_o-d₆; 300K): 7.05 (m, 4H, aromatic Hs, tetrahydroisoquinoline); 3.90 (m, 2H, aliphatic Hs, tetrahydroisoquinoline); 2.85 (m, 1H, aliphatic H, tetrahydroisoquinoline); 2.68-2.4 (2dd, 2H, aliphatic Hs, tetrahydroisoquinoline); 1.12 (d, 3H, tetrahydroisoquinoline-CH₃); 2.9-2.3 (m, broad, 1H, HN (tetrahydroisoquinoline))

IR: ν : —NH: 3248 cm⁻¹

Step D: (3R)-3-Methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride

To a solution of 14.3 g (97.20 mmol) of the compound obtained in Step C in 20 mL of anhydrous ethanol there are added, dropwise, 100 mL of a 1M solution of HCl in ether. The batch is stirred at ambient temperature for 1 hour and then filtered. The crystals thereby obtained are washed with ethyl ether. After drying, the title product is obtained in the form of crystals.

¹H NMR: δ (400 MHz; dms_o-d₆; 300K): 9.57 (m, broad, 2H, NH₂+(tetrahydroisoquinoline); 7.22 (m, 4H, aromatic Hs, tetrahydroisoquinoline); 4.27 (s, 2H, aliphatic Hs, tetrahydroisoquinoline); 3.52 (m, 1H, aliphatic H, tetrahydroisoquinoline); 3.03-2.85 (2dd, 2H, aliphatic Hs, tetrahydroisoquinoline); 1.39 (d, 3H, tetrahydroisoquinoline-CH₃)

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droisoquinoline); 3.03-2.85 (2dd, 2H, aliphatic Hs, tetrahydroisoquinoline); 1.39 (d, 3H, tetrahydroisoquinoline-CH₃)

IR: ν : —NH₂+: 3000-2300 cm⁻¹; ν : aromatic —CH: 766 cm⁻¹

PREPARATION 2'

tert-Butyl [(3S)-1,2,3,4-tetrahydroisoquinolin-3-ylmethyl]-carbamate

Step A: Benzyl (3S)-3-(hydroxymethyl)-3,4-dihydro-1H-isoquinoline-2-carboxylate

This compound is obtained using a protocol from the literature (R. B. Kawthekar et al *South Africa Journal of Chemistry* 63, 195, 2009) starting from 15 g of (3S)-1,2,3,4-tetrahydroisoquinolin-3-ylmethanol (91.9 mmol) in the presence of benzyl chloroformate and triethylamine in solution in dichloromethane. After purification by chromatography over silica gel using petroleum ether and ethyl acetate as eluants, the title product is obtained in the form of an oil.

¹H NMR: δ (300 MHz; DMSO-d₆; 300K): 7.33 (m, 5H, aromatic Hs, O-benzyl); 7.15 (s, 4H, aromatic Hs, H tetrahydroisoquinoline); 5.13 (s, 2H, CH₂-Ph); 4.73 (d, 1H, H tetrahydroisoquinoline); 4.47 (m, H, CH₂OH); 4.36 (m, 1H, H tetrahydroisoquinoline); 4.28 (d, 1H, H tetrahydroisoquinoline); 3.39 (dd, 1H, CH₂OH); 3.23 (dd, 1H, CH₂OH); 2.93 (dd, 1H, H tetrahydroisoquinoline); 2.86 (dd, 1H, H tetrahydroisoquinoline)

IR: ν : OH: 3416 cm⁻¹; ν : <C=O 1694 cm⁻¹; ν : aromatic >C—H: 754 cm⁻¹

Step B: Benzyl (3S)-3-(azidomethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

This compound is obtained using a protocol from the literature (D. Pagé et al *J. Med. Chem.* 44, 2387, 2001) starting from 23 g of the compound obtained in Step A (77.3 mmol) in the presence of diphenylphosphoryl azide and triphenylphosphine in solution in THF. After purification by chromatography over silica gel using petroleum ether and ethyl acetate as eluants, the title product is obtained in the form of an oil.

¹H NMR: δ (400 MHz; DMSO-d₆; 300K): 7.36 (m, 5H, aromatic Hs, O-benzyl); 7.19 (m, 4H, aromatic Hs, H tetrahydroisoquinoline); 5.16 (s, 2H, CH₂-Ph); 4.76 (d, 1H, H tetrahydroisoquinoline); 4.53 (m, 1H, H tetrahydroisoquinoline); 4.30 (m, 1H, H tetrahydroisoquinoline); 3.28 (m, 2H, CH₂N₃); 3.06 (dd, 1H, H tetrahydroisoquinoline); 2.78 (dd, 1H, H tetrahydroisoquinoline)

IR: ν : N₃: 2095 cm⁻¹; ν : <C=O: 1694 cm⁻¹; ν : aromatic >C—H: 754 cm⁻¹

Step C: Benzyl (3S)-3-(aminomethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

To a solution of 20.9 g (64.5 mmol) of the azido compound obtained in Step B in 650 mL of THF, there are successively added 25.5 g (97.2 mmol) of triphenylphosphine and 157 mL of water. The batch is refluxed for 2 hours 30 minutes. The reaction mixture is then concentrated to dryness and the residue oil is then taken up in isopropyl ether. A white precipitate appears; it is filtered off and washed with isopropyl ether. The filtrate is then concentrated to dryness and then purified by chromatography over silica gel using dichloromethane and methanol as eluants. The title product is obtained in the form of an oil.

¹H NMR: δ (400 MHz; DMSO-d₆; 300K): 7.40 (m, 5H, aromatic Hs, O-benzyl); 7.20 (m, 4H, aromatic Hs, H tetrahydroisoquinoline); 5.15 (s, 2H, CH₂-Ph); 4.75-4.3 (m, 2H, H tetrahydroisoquinoline); 4.30 (d, 1H, H tetrahydroisoquinoline); 2.90 (m, 2H, CH₂NH₂); 2.45 (m, 2H, H tetrahydroisoquinoline); 1.40 (m, 2H, NH₂)

IR: ν : NH₂: 3400-3300 cm⁻¹; ν : <C=O: 1688 cm⁻¹

Step D: Benzyl (3S)-3-[[[tert-butoxycarbonyl]amino]methyl]-3,4-dihydroisoquinoline-2(1H)-carboxylate

To a solution of 18.4 g (62.1 mmol) of the compound obtained in Step C in 630 mL of dichloromethane there are successively added 17.5 mL (124 mmol) of triethylamine and, in portions, 14.9 g (68.3 mmol) of di-tert-butyl dicarbonate. The batch is stirred at ambient temperature for 2 h. The reaction mixture is then concentrated and ethyl acetate is then added. The organic phase is successively washed with 1M HCl solution, brine, saturated aqueous NaHCO₃ solution and then brine. After drying, concentrating to dryness and purifying by chromatography over silica gel using petroleum ether and ethyl acetate as eluants, the title product is obtained in the form of an oil.

¹H NMR: δ (400 MHz; DMSO-d₆; 300K): 7.35 (m, 5H, aromatic Hs, O-benzyl); 7.15 (m, 4H, aromatic Hs, H tetrahydroisoquinoline); 6.51 (m, 1H, NHBoc); 5.12 (s, 2H, CH₂-Ph); 4.76 (d, 1H, H tetrahydroisoquinoline); 4.51 (m, 1H, H tetrahydroisoquinoline); 4.36 (d, 1H, H tetrahydroisoquinoline); 2.95 (m, 3H, H tetrahydroisoquinoline+CH₂NHBoc); 2.71 (d, 1H, H tetrahydroisoquinoline); 1.34 (s, 9H, NHBoc)

IR: ν: NH: 3351 cm⁻¹; ν: <C=O: 1686 cm⁻¹

Step E: tert-Butyl [(3S)-1,2,3,4-tetrahydroisoquinolin-3-ylmethyl]carbamate

To a solution of 21 g (53 mmol) of the compound obtained in Step D in 600 mL of ethyl acetate there are added 2.1 g of palladium-on-carbon 10%. The batch is stirred at ambient temperature under a pressure of 1.3 bars of dihydrogen for 5 hours. The reaction mixture is then filtered and then concentrated to dryness. The title product is obtained in the form of a solid.

¹H NMR: δ (400 MHz; DMSO-d₆; 300K): 7.15 (m, 4H, aromatic Hs, H tetrahydroisoquinoline); 6.85 (t, 1H, NHBoc); 3.90 (m, 2H, H tetrahydroisoquinoline); 3.00 (m, 2H, CH₂NHBoc); 2.80 (m, 1H, H tetrahydroisoquinoline); 2.65 (dd, 1H, H tetrahydroisoquinoline); 2.40 (dd, 1H, H tetrahydroisoquinoline); 1.40 (s, 9H, NHBoc)

IR: ν: NH: 3386-3205 cm⁻¹ (NH amide); ν: <C=O: 1688 cm⁻¹; ν: NH: 1526 cm⁻¹ (NH amine)

PREPARATION 3'

(3S)-3-(4-Morpholinylmethyl)-1,2,3,4-tetrahydroisoquinoline

Step A: Benzyl (3S)-3-(4-morpholinylcarbonyl)-3,4-dihydro-2(1H)-isoquinolinecarboxylate

To a solution of 5 g of (3S)-2-[(benzyloxy)carbonyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (16 mmol) in 160 mL of dichloromethane there are added 1.5 mL of morpholine (17.6 mmol), then 9 mL of N,N,N-triethylamine (64 mmol), 3.3 g of 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide (EDC) (19.2 mmol) and 2.6 g of hydroxybenzotriazole (HOBt) (19.2 mmol). The reaction mixture is stirred at ambient temperature overnight; it is then poured into ammonium chloride solution and extracted with ethyl acetate. The organic phase is then dried over MgSO₄, and then filtered and evaporated to dryness. The crude product thereby obtained is then purified by chromatography over silica gel using dichloromethane and methanol as eluants. The product is obtained in the form of a foam.

¹H NMR: δ (400 MHz; dmsd-d₆; 353K): 7.30 (m, 5H benzyl); 7.15 (m, 4H, aromatic Hs); 5.2-5.0 (m, 3H, 2H benzyl, 1H dihydroisoquinoline); 4.75-4.5 (2d, 2H dihydroisoquinoline); 3.55-3.3 (m, 8H morpholine); 3.15-2.9 (2dd, 2H dihydroisoquinoline)

IR: ν: >C=O: 1694; 1650 cm⁻¹

Step B: Benzyl (3S)-3-(4-morpholinylmethyl)-3,4-dihydro-2(1H)-isoquinolinecarboxylate

To a solution of 5.3 g of the product obtained in Step A (13.9 mmol) in 278 mL of tetrahydrofuran there are added 14 mL of borane-dimethylsulphide complex (BH₃Me₂S) (27.8 mmol) at ambient temperature. The batch is heated for 4 hours at 80° C. It is allowed to return to ambient temperature and there are then added 7 mL (14 mmol) of BH₃Me₂S. The reaction mixture is again heated at 80° C. for 2 hours. The tetrahydrofuran is then evaporated off and then there is slowly added methanol and then 5.6 mL of 5N aqueous HCl solution (27.8 mmol). The mixture is stirred at ambient temperature overnight, and then at 80° C. for 1 hour. Saturated aqueous NaHCO₃ solution is then added to the reaction mixture placed at 0° C. until a pH of 8 is obtained, and extraction with ethyl acetate is then carried out. The organic phase is then dried over MgSO₄, and then filtered and evaporated to dryness. The title product is obtained in the form of an oil.

¹H NMR: δ (400 MHz; dmsd-d₆; 353K): 7.43-7.30 (unresolved peak, 5H benzyl); 7.19 (m, 4H, aromatic Hs); 5.16 (m, 2H, 2H benzyl); 4.79-4.29 (d, 2H dihydroisoquinoline); 4.58 (m, 1H dihydroisoquinoline); 3.50 (m, 4H morpholine); 3.02-2.80 (dd, 2H dihydroisoquinoline); 2.42-2.28 (unresolved peak, 5H, 4H morpholine, 1H morpholine); 2.15 (dd, 1H morpholine)

IR: ν: >CH: 2810 cm⁻¹; ν: >C=O: 1694 cm⁻¹; ν: >C—O—C<: 1114 cm⁻¹; ν: >CH—Ar: 751; 697 cm⁻¹

Step C: (3S)-3-(4-Morpholinylmethyl)-1,2,3,4-tetrahydroisoquinoline

To a solution of 4.9 g of the compound of Step B (13.4 mmol) in 67 mL of ethanol there is added 0.980 g of palladium dihydroxide (20% by weight) at ambient temperature. The reaction mixture is placed under 1.2 bars of hydrogen at ambient temperature for 4 hours. It is then passed through a Whatman filter and the palladium is then rinsed several times with ethanol. The filtrate is evaporated to dryness. The title product is obtained in the form of an oil.

¹H NMR: δ (400 MHz; dmsd-d₆; 300K): 7.12-7.0 (unresolved peak, 4H, aromatic Hs); 3.92 (s, 2H tetrahydroisoquinoline); 3.60 (t, 4H morpholine); 2.98 (m, 1H tetrahydroisoquinoline); 2.68 (dd, 1H tetrahydroisoquinoline); 2.5-2.3 (unresolved peak, 8H, 1H tetrahydroisoquinoline, 6H morpholine, 1H NH)

IR: ν: >NH: 3322 cm⁻¹; ν: >C—O—C<: 1115 cm⁻¹; ν: >CH—Ar: 742 cm⁻¹

PREPARATION 4'

(3S)-3-[(4-Methyl-1-piperazinyl)methyl]-1,2,3,4-tetrahydroisoquinoline

The procedure is in accordance with the process of Preparation 3', replacing the morpholine used in Step A by 1-methyl-piperazine.

PREPARATION 5'

(3S)-3-[2-(Morpholin-4-yl)ethyl]-1,2,3,4-tetrahydroisoquinoline hydrochloride

Step A: tert-Butyl (3S)-3-(2-morpholino-2-oxo-ethyl)-3,4-dihydro-1H-isoquinoline-2-carboxylate

To a solution of 3 g (10.30 mmol) of [(3S)-2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-3-yl]acetic acid in 100 mL of dichloromethane, there are added dropwise 1.10 mL (11.32 mmol) of morpholine, still dropwise 4.3 mL (30.9 mmol) of triethylamine, 2.20 g (12.40 mmol) of EDC and

1.70 g (1.68 mmol) of HOBt (hydroxybenzotriazole). The batch is stirred at ambient temperature for 15 hours. The reaction mixture is then diluted with dichloromethane, successively washed with 1M HCl solution, saturated aqueous NaHCO₃ solution and then brine until neutral. The organic phase is then dried over MgSO₄, filtered and concentrated to dryness. After purification by chromatography over silica gel using dichloromethane and methanol as eluants, the title product is obtained in the form of an oil.

¹H NMR: δ (400 MHz; dms₂-d₆; 300K): 7.20-7.10 (m, 4H, aromatic Hs, tetrahydroisoquinoline); 4.70 (m, 1H, aliphatic Hs, CH tetrahydroisoquinoline); 4.75-4.20 (2m, 2H, aliphatic Hs, CH₂ alpha to N tetrahydroisoquinoline); 3.60 (m, 8H, aliphatic Hs, morpholine); 3.00 and 2.70 (2dd, 2H, aliphatic H, tetrahydroisoquinoline); 2.50-2.20 (2d, 2H, aliphatic Hs, CH₂CO); 1.40 (s, 9H, 'Bu)

IR: ν: C=O: 1687; 1625 cm⁻¹

Step B: 1-(Morpholin-4-yl)-2-[(3S)-1,2,3,4-tetrahydroisoquinolin-3-yl]ethanone hydrochloride

To a solution of 2.88 g (7.18 mmol) of the compound obtained in Step A in 16 mL of dichloromethane, there are added dropwise 80 mL (80 mmol) of 1M solution of HCl in ether. The batch is stirred at ambient temperature for 15 hours, and then the suspension is filtered and the precipitate washed with ether. After drying, the title product is obtained in the form of a solid.

¹H NMR: δ (400 MHz; dms₂-d₆; 300K): 9.80-9.50 (m, 2H, NH₂⁺); 7.30-7.10 (m, 4H, aromatic Hs, tetrahydroisoquinoline); 4.30 (m, 2H, aliphatic Hs, CH₂ alpha to N tetrahydroisoquinoline); 3.80 (m, 1H, aliphatic Hs, CH tetrahydroisoquinoline); 3.70-3.40 (2m, 8H, aliphatic Hs, morpholine); 3.15 and 2.8 (m, 4H, aliphatic H, CH₂ tetrahydroisoquinoline and CH₂CO)

IR: ν: —NH₂⁺: 2800-1900 cm⁻¹; ν: C=O: 1620 cm⁻¹

Step C: (3S)-3-[2-(Morpholin-4-yl)ethyl]-1,2,3,4-tetrahydroisoquinoline hydrochloride

A solution of 2.2 g (7.44 mmol) of the compound obtained in Step B in 22 mL of MTBE and 5 mL of dichloromethane is prepared. After cooling in an ice bath at 0° C., there are added thereto, dropwise, 15 mL (15 mmol) of 1M LiAlH₄ solution in tetrahydrofuran. The batch is then stirred at ambient temperature for 6 hours. It is placed at 0° C., and there is then added, dropwise, 1 mL of 5N NaOH solution. The batch is stirred at ambient temperature for 45 minutes. The solid is then filtered off and washed with MTBE and then with dichloromethane and the filtrate is concentrated to dryness. The oil thereby obtained is diluted with dichloromethane and there are added, dropwise, 6.3 mL of a 1M solution of HCl in ether. The batch is stirred at ambient temperature for 1 hour and then filtered. The crystals thereby obtained are washed with ethyl ether. After drying, the title product is obtained in the form of a solid.

¹H NMR: δ (400 MHz; dms₂-d₆; 300K): 11.35+9.80 (2m, 2H, NH₂⁺); 10.00 (m, H, NH⁺); 7.20 (m, 4H, aromatic Hs, tetrahydroisoquinoline); 4.30 (s, 2H, aliphatic Hs, CH₂ alpha to N tetrahydroisoquinoline); 4.00+3.85 (2m, 4H, aliphatic Hs, CH₂ alpha to N morpholine); 3.70 (m, 1H, aliphatic Hs, CH tetrahydroisoquinoline); 3.55-3.30 (m, 4H, aliphatic Hs, CH alpha to O morpholine and CH₂-morpholine); 3.15 (dd, 1H, aliphatic H, CH₂ tetrahydroisoquinoline); 3.10 (m, 2H, aliphatic H, CH alpha to O morpholine); 2.90 (dd, 1H, aliphatic H, CH₂ tetrahydroisoquinoline); 2.30+2.15 (2m, 2H, aliphatic H, CH₂-tetrahydroisoquinoline)

IR: ν: NH⁺—NH₂⁺: between 3500 and 2250 cm⁻¹; ν: C=C: weak 1593 cm⁻¹; ν: aromatic C—H: 765 cm⁻¹

PREPARATION 6'

(3R)-3-[3-(Morpholin-4-yl)propyl]-1,2,3,4-tetrahydroisoquinoline

Step A: {(3S)-2-[(4-Methylphenyl)sulphonyl]-1,2,3,4-tetrahydroisoquinolin-3-yl}methyl 4-methylbenzenesulphonate

The process is the same as that of Step A of Preparation 1'.

Step B: tert-Butyl 2-[(3R)-2-[(4-methylphenyl)sulphonyl]-1,2,3,4-tetrahydroisoquinolin-3-yl]methyl-3-(morpholin-4-yl)-3-oxopropanoate

To a suspension of 1 g of NaH (60%) (25.08 mmol) in 30 mL of MTBE there are added, dropwise, a solution of 5 g of tert-butyl 3-morpholino-3-oxopropanoate (21.81 mmol) in 20 mL of anhydrous MTBE. This suspension stirred at ambient temperature for 1 hour and then the compound obtained in Step A is added in the form of a powder. The batch is stirred at 60° C. for 30 hours. 100 mL of saturated aqueous ammonium chloride solution are added. The resulting solution is extracted with dichloromethane. The organic phase is then dried over MgSO₄, filtered and concentrated to dryness. After purification by chromatography over silica gel using dichloromethane and MeOH as eluants, the expected product is obtained in the form of an oil.

¹H NMR (500 MHz, dms₂-d₆) δ ppm: 7.63/7.59 (2d, 2 H), 7.3/7.26 (2d, 2 H), 7.13 (m, 2 H), 7.09/6.97 (2t, 2 H), 4.64/4.55/4.36/4.28 (2AB, 2 H), 4.25/4.11 (2m, 1H), 3.81 (m, 1 H), 3.73-3.48 (m, 4 H), 3.57-3.32 (m, 4 H), 2.51 (m, 2 H), 2.32/2.31 (2s, 3 H), 1.88/1.79 (2m, 2 H), 1.39/1.38 (2s, 9 H)

IR (ATR) cm⁻¹: ν: >C=O: 1731 (ester); ν: >C=O: 1644 (amide); ν: —SO₂: 1334-1156; ν: >C—O—C<: 1115; γ: >CH—Ar: 815-746-709

Step C: 2-[(3R)-2-[(4-Methylphenyl)sulphonyl]-1,2,3,4-tetrahydroisoquinolin-3-yl]methyl-3-(morpholin-4-yl)-3-oxopropanoic acid

To a solution of 9.5 g (17.97 mmol) of the compound obtained in Step B in 40 mL of dioxane there are added, dropwise, 20 mL of a 4M solution of HCl in dioxane. The batch is stirred at ambient temperature for 48 hours and then the solution is concentrated to dryness. After drying, the expected product is obtained in the form of an oil.

¹H NMR (400 MHz, dms₂-d₆) δ ppm: 12.75 (m, 1 H), 7.6 (2*d, 2 H), 7.3 (2*d, 2 H), 7.1/6.95 (2*m, 4 H), 4.7-4.2 (d, 2 H), 4.25/4.12 (2*m, 1 H), 3.9-3.3 (m, 9 H), 2.55 (d, 2 H), 2.3 (2*s, 3 H), 1.8 (t, 2 H)

IR (ATR) cm⁻¹: ν: —OH: 3500 to 2000; ν: >C=O: 1727 (acid); ν: >C=O: 1634 (amide); ν: —SO₂: 1330-1155

Step D: 3-[(3R)-2-[(4-Methylphenyl)sulphonyl]-1,2,3,4-tetrahydroisoquinolin-3-yl]-1-(morpholin-4-yl)propan-1-one

To a solution of 7.80 g (16.51 mmol) of the compound obtained in Step C in 100 mL of DMSO there are added 1.16 g (19.83 mmol) of solid sodium chloride (NaCl) and then, dropwise, 5 mL of water. The batch is stirred at 130° C. for 1 hour and then the solution is concentrated to 3/4. The reaction mixture is then diluted with dichloromethane and washed successively with saturated aqueous lithium chloride solution and then with brine. The organic phase is then dried over MgSO₄, filtered and concentrated to dryness. After purification by chromatography over silica gel using cyclohexane and ethyl acetate as eluants, the expected product is obtained in the form of an oil.

¹H NMR (400 MHz, dms₂-d₆) δ ppm: 7.65 (d, 2 H), 7.3 (d, 2 H), 7.15/7 (2 m, 4 H), 4.6 (d, 1 H), 4.25 (d, 1 H), 4.2 (m, 1 H), 3.5 (m, 4 H), 3.4 (2 m, 4 H), 2.6 (2 dd, 2 H), 2.35 (s, 3 H), 2.3 (m, 2 H), 1.5 (quad., 2 H)

IR (ATR) cm^{-1} : ν : >C=O : 1639; ν : —SO_2 : 1331-1156; γ : >CH—Ar : 815-675

Step E: (3R)-2-[(4-Methylphenyl)sulphonyl]-3-[3-(morpholin-4-yl)propyl]-1,2,3,4-tetrahydroisoquinoline

To a solution of 6.0 g (14.0 mmol) of the compound obtained in Step D in 60 mL of MTBE and 14 mL of dichloromethane there are added 1.06 g (28 mmol) of LAH in portions over 5 minutes. The batch is stirred at ambient temperature for 15 hours. There are added, dropwise, 1.5 mL of water and stirring is carried out for 15 minutes. There are then added, dropwise, 1.5 mL of 5M sodium hydroxide solution and stirring is carried out for 15 minutes. The reaction mixture is then diluted with MTBE and dichloromethane. The suspension is then filtered and the precipitate is washed with MTBE and dichloromethane. The organic phase is then dried over MgSO_4 , filtered and concentrated to dryness. After purification by chromatography over silica gel using dichloromethane and ammonia-in-ethanol as eluants, the expected product is obtained in the form of an oil.

^1H NMR (400 MHz, dmsO-d_6) δ ppm: 7.68 (d, 2 H), 7.32 (d, 2 H), 7.1 (unresolved peak, 4 H), 4.65/4.23 (AB, 2 H), 4.2 (m, 1 H), 3.55 (t, 4 H), 2.7/2.6 (ABX, 2 H), 2.35 (s, 3 H), 2.25 (t, 4 H), 2.2 (t, 2 H), 1.4/1.3 (2m, 4 H).

IR (ATR) cm^{-1} : ν : —SO_2 : 1333-1158

Step F: (3R)-3-[3-(Morpholin-4-yl)propyl]-1,2,3,4-tetrahydroisoquinoline

To a solution of 1.50 g (3.62 mmol) of the compound obtained in Step E in 20 mL of anhydrous methanol there are added 2.0 g (82.3 mmol), in portions, of magnesium turnings. The batch is stirred in the presence of ultrasound for 96 hours. The reaction mixture is then filtered, the solid is washed several times with methanol, and the filtrate is concentrated to dryness. After purification by chromatography over silica gel using dichloromethane and ammonia-in-ethanol as eluants, the expected product is obtained in the form of an oil.

^1H NMR (400 MHz, dmsO-d_6) δ ppm: 7.3 (d, 2 H), 7.1 (t, 2 H), 7.1 (d+t, 3 H), 7 (d, 2 H), 3.9 (s, 2 H), 3.55 (t, 4 H), 2.75 (m, 1 H), 2.72/2.45 (dd, 2 H), 2.35 (t, 4 H), 2.25 (t, 2 H), 1.6 (m, 2 H), 1.45 (m, 2 H)

IR (ATR) cm^{-1} : ν : $\text{>NH}_2/\text{NH}^+$: 3500-2300; ν : >C—O—C< : 1115

High-resolution mass spectrometry (ESI+/-/FIA/HR):

Empirical formula: $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}$

$[\text{M}+\text{H}]^+$ calculated: 261.1961

$[\text{M}+\text{H}]^+$ measured: 261.1959

PREPARATION 7'

(3S)-3-[(9aS)-Octahdropiperazino[2,1-c]morpholin-8-ylmethyl]-1,2,3,4-tetrahydroisoquinoline trihydrochloride

Step A: tert-Butyl (9aS)-4-oxo-octahdropiperazino[2,1-c]morpholine-8-carboxylate

The synthesis of this compound is known in the literature (J. Med. Chem. 2012, 55, 5887 for the opposite enantiomer).

Step B: (9aS)-Octahdropiperazino[2,1-c]morpholin-4-one hydrochloride

A 4M solution of HCl in dioxane (60 mL, 240 mmol) is added to the compound tert-butyl (9aS)-4-oxo-octahdropiperazino[2,1-c]morpholine-8-carboxylate (11.8 g, 46.0 mmol) cooled using an ice bath. The solution is then stirred at ambient temperature for 2 hours, and then at 50-60° C. for 1.5 hours. The solution is then evaporated to dryness. The residue is co-evaporated with dioxane (3×20 mL) and then dried in vacuo to obtain the expected compound in the form of a solid.

^1H NMR (400 MHz, dmsO-d_6) δ ppm: 2.80-2.94 (m, 2 H), 2.94-3.05 (m, 1 H), 3.23-3.37 (m, 2 H), 3.59-3.69 (m, 1 H), 3.83-3.93 (m, 1 H), 3.95-4.04 (m, 1 H), 4.02-4.13 (m, 2 H), 4.45-4.55 (m, 1 H), 9.58 (br s, 2 H)

Step C: tert-Butyl (3S)-3-[(9aS)-4-oxo-octahdropiperazino[2,1-c]morpholine-8-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate

EDC (3.90 g, 20.3 mmol) is added to a solution of the compound of Step B (3.02 g, 15.7 mmol), (3S)-2-[(tert-butoxy)carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (4.6 g, 16.6 mmol), triethylamine (8.0 mL, 57.4 mmol) and HOBt (2.72 g, 20.1 mmol) in dichloromethane (150 mL). The mixture is stirred at ambient temperature for 21 hours. 1N aqueous HCl solution (105 mL) is added and the precipitate formed is filtered off using a Buchner funnel. The phases of the filtrate are separated. The aqueous phase is extracted with dichloromethane (2×10 mL). The combined organic phases are washed with 3N aqueous HCl solution (35 mL), then with aqueous 5% potassium bicarbonate solution (2×35 mL) and finally with brine (35 mL). The organic phase is dried over Na_2SO_4 , filtered and then concentrated under reduced pressure. The product is purified by chromatography over silica gel using ethyl acetate and heptane as eluants to obtain the expected compound in the form of a solid.

^1H NMR (400 MHz, CDCl_3) δ ppm: 1.38-1.57 (m, 9 H), 2.39-2.89 (m, 2 H), 2.89-3.34 (m, 3 H), 3.34-3.70 (m, 2 H), 3.90-4.06 (m, 1 H), 4.09-4.27 (m, 2 H), 4.30-5.00 (m, 5 H), 5.20-5.37 (m, 1 H), 7.03-7.24 (m, 4 H)

Step D: (3S)-3-[(9aS)-Octahdropiperazino[2,1-c]morpholin-8-ylmethyl]-1,2,3,4-tetrahydroisoquinoline trihydrochloride

4M HCl solution in dioxane (45 mL, 180 mmol) is added to the compound of Step C (6.6 g, 46.0 mmol) cooled in an ice bath. The suspension is then stirred at ambient temperature for 24 hours and then it is evaporated to dryness. The residue is co-evaporated with MTBE and then dried in vacuo. The solid thereby obtained is suspended in tetrahydrofuran (160 mL), and then LiAlH_4 (3.0 g, 79.1 mmol) is added. The suspension is refluxed for 6.5 hours, and it is then cooled in an ice bath. Water (3 mL) is then added over a period of 7 minutes. After 0.5 hours, 2N aqueous sodium hydroxide solution (6 mL) is added. Water (6 mL) is again added 0.25 hours later. Finally, Celite (7 g) and Na_2SO_4 (25 g) are added 0.5 hours later. The suspension is filtered over Celite and rinsed with tetrahydrofuran (2×100 mL). The filtrate is concentrated to dryness. The oil thereby obtained is dissolved in MTBE (50 mL). The resulting solution is filtered and the filtrate concentrated. The residue is dissolved in methanol (60 mL), and then 4M HCl solution in dioxane (20 mL) is added. The solution is heated to 40° C. and treated with activated charcoal (0.66 g), with stirring, for 1 hour. The suspension is filtered over Celite and rinsed with warm methanol. The filtrate is concentrated until the product starts to crystallise out. Crystallisation is allowed to continue for 16 hours at ambient temperature. The solid obtained is filtered off and rinsed with a mixture of 2-propanol/MTBE (4/6) (2×20 mL), and then with MTBE (2×20 mL). After drying, the expected compound is obtained.

^1H NMR (400 MHz, D_2O) δ ppm: 2.28-2.44 (m, 1 H), 2.74-3.00 (m, 4 H), 3.08-3.27 (m, 3 H), 3.27-3.42 (m, 2 H), 3.43-3.56 (m, 2 H), 3.56-3.69 (m, 2 H), 3.76-3.95 (m, 2 H), 4.00-4.22 (m, 2 H), 4.35-4.50 (m, 2 H), 7.20-7.41 (m, 4 H)

^{13}C NMR (100 MHz, D_2O) δ ppm: 29.00, 44.58, 50.30, 51.08, 51.17, 52.75, 53.17, 58.08, 61.60, 64.61, 66.37, 127.14, 127.71, 128.00, 128.77, 129.55, 131.15

MS (ESI): $[\text{M}+\text{H}]^+$ +288.16

PREPARATION 8'

(3S)-3-(1-Oxa-6-azaspiro[3.3]hept-6-ylmethyl)-1,2,3,4-tetrahydroisoquinoline

Step A: (3S)-3-(Iodomethyl)-2-[(4-methylphenyl)sulphonyl]-1,2,3,4-tetrahydroisoquinoline

The compound of Step A of Preparation 6' (4.0 g; 8.48 mmol) in acetonitrile (10 mL) is placed in a 27-ml microwave tube and then sodium iodide (1.40 g; 9.33 mmol) is added. The reaction mixture is heated for 5 hours at 100° C. using microwaves (200 W). It is then filtered and the solid is washed with dichloromethane. The filtrate is evaporated to dryness and then the residue is purified by chromatography over silica gel using heptane and ethyl acetate as eluants. The title compound is obtained in the form of an oil.

¹H NMR (400 MHz, dmsO-d₆) δ ppm: 7.64 (d, 2 H), 7.28 (d, 2 H), 7.15-7 (m, 4 H), 4.5/4.3 (2d, 2 H), 4.14 (m, 1 H), 3.22 (m, 2 H), 2.82 (m, 2 H), 2.31 (s, 3 H)

IR (ATR) cm⁻¹: 1897 ν —Ar, 1333+1156 ν —SO₂

Step B: (3S)-2-[(4-Methylphenyl)sulphonyl]-3-(1-oxa-6-azaspiro[3.3]hept-6-ylmethyl)-1,2,3,4-tetrahydroisoquinoline

The iodinated compound (2.5 g; 5.85 mmol) obtained in the preceding Step is dissolved in acetonitrile (50 mL). 1-Oxa-6-azaspiro[3.3]heptane oxalate (1.21 g; 6.36 mmol) is added, followed by potassium carbonate (1.61 g; 11.7 mmol). The reaction mixture is heated for 15 hours at reflux. The reaction mixture is filtered and washed with acetonitrile, and then is evaporated to dryness.

The compound is purified by chromatography over silica gel using dichloromethane and ammonia-in-methanol as eluants. The title compound is obtained in the form of an oil.

¹H NMR (400 MHz, dmsO-d₆) δ ppm: 7.68 (d, 2 H), 7.32 (d, 2 H), 7.14-7 (m, 4 H), 4.53/4.2 (dd, 2 H), 4.34 (t, 2 H), 3.95 (m, 1 H), 3.5/3.4/2.98 (3m, 4 H), 2.7 (t, 2 H), 2.68-2.58 (m, 2 H), 2.34 (s, 3 H), 2.31-2.24 (m, 2 H)

IR (ATR) cm⁻¹: 1333+1156 ν —SO₂

Step C: (3S)-3-(1-Oxa-6-azaspiro[3.3]hept-6-ylmethyl)-1,2,3,4-tetrahydroisoquinoline

The tosylated compound of the above Step (1.3 g; 3.26 mmol) is dissolved in 10 mL of methanol. Powdered magnesium (633 mg; 26.08 mmol) is added in portions of 160 mg every 3 hours. The reaction mixture is stirred in an ultrasound bath 15 hours. It is then filtered over Celite, washed with copious amounts of methanol, and then evaporated to dryness. The compound is purified by chromatography over silica gel using dichloromethane and ammonia-in-methanol as eluants. The compound is obtained in the form of an oil.

¹H NMR (400 MHz, dmsO-d₆) δ ppm: 7.01 (m, 4 H), 4.46 (t, 2 H), 3.85 (s, 2 H), 3.51/3.05 (dd, 2 H), 2.73 (t, 2 H), 2.61/2.4 (m, 4 H), 2.4 (m, 1 H), 2.4 (m, 1 H)

IR (ATR) cm⁻¹: 3325 ν>NH

PREPARATION 9'

(3S)-3-[(9aR)-Octahydropiperazino[2,1-c]morpholin-8-ylmethyl]-1,2,3,4-tetrahydroisoquinoline trihydrochloride

Step A: tert-Butyl (9aR)-4-oxo-octahydropiperazino[2,1-c]morpholine-8-carboxylate

Synthesis of this compound is described in the literature (*J. Med. Chem.* 2012, 55, 5887).

Step B: (9aR)-Octahydropiperazino[2,1-c]morpholin-4-one hydrochloride

A 4M solution of HCl in dioxane (39 mL, 154 mmol) is added to the compound of Step A (11.3 g, 44.1 mmol). The solution is then stirred at ambient temperature for 5 hours, and then a 4M solution of HCl in dioxane (12 mL, 48 mmol) is added again. The mixture is stirred for 16 hours. The solution is then evaporated to dryness to yield the expected product in the form of a solid.

¹H NMR (400 MHz, dmsO-d₆) δ ppm: 2.79-2.93 (m, 2 H), 3.02 (td, J=13.1, 2.7 Hz, 1 H), 3.22-3.34 (m, 2 H), 3.59-3.67 (m, 1 H), 3.86-3.96 (m, 1 H), 3.96-4.01 (m, 1 H), 4.05 (AB q, J=13.3 Hz, 2 H), 4.48 (dd, J=14.1, 2.5 Hz, 1 H), 9.71 (br. s, 1 H), 9.91 (br. s, 1 H)

Step C: tert-Butyl (3S)-3-[(9aR)-4-oxo-octahydropiperazino[2,1-c]morpholine-8-carbonyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate

EDC (5.17 g, 27.0 mmol) is added to a solution of the compound of the above Step (4.0 g, 20.7 mmol), (3S)-2-[(tert-butoxy)carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (6.04 g, 21.8 mmol), triethylamine (11.6 mL, 83.1 mmol) and HOBt (3.65 g, 27.0 mmol) in dichloromethane (100 mL). The mixture is stirred at ambient temperature for 16 hours. 1N aqueous HCl solution (70 mL) is added and the precipitate formed is filtered off using a Buchner funnel. The phases of the filtrate are separated. The organic phase is washed with saturated aqueous potassium carbonate solution and is then concentrated under reduced pressure. The residue is pre-absorbed onto silica gel and is purified by chromatography over silica gel using ethyl acetate and heptane as eluants to yield the expected compound in the form of a solid.

¹H NMR (400 MHz, dmsO-d₆) δ ppm: 1.25-1.58 (m, 9 H), 2.50-2.76 (m, 2 H), 2.76-3.25 (m, 3 H), 3.37-3.76 (m, 2 H), 3.92-4.50 (m, 5 H), 4.06 (s, 2 H), 4.66 (d, J=15.6 Hz, 1 H), 4.76-5.28 (m, 1 H), 7.05-7.31 (m, 4 H)

Step D: (3S)-3-[(9aR)-Octahydropiperazino[2,1-c]morpholin-8-ylmethyl]-1,2,3,4-tetrahydroisoquinoline trihydrochloride

A 4M solution of HCl in dioxane (24.0 mL, 96.2 mmol) is added to a solution of the compound of Step C (8.00 g, 12.25 mmol) in dichloromethane (25 mL). The mixture is stirred at ambient temperature for 16 hours and is then concentrated to dryness. The crude product obtained is added to a suspension of LiAlH₄ (1.97 g, 51.91 mmol) in tetrahydrofuran (140 mL). The mixture is refluxed until the reaction (monitored by LC-MS) is complete and it is then cooled to 0° C. Water (2.5 mL) is added dropwise. After stirring for 10 minutes, aqueous 2M sodium hydroxide solution (5 mL) is added dropwise. Water (5 mL) is again added after stirring for 10 minutes. There are finally added Celite (4 g) and Na₂SO₄ (12 g) after stirring for an additional 10 minutes. The suspension is filtered over Celite and the filtrate is concentrated to dryness. The crude residue thereby obtained is dissolved in methanol (80 mL), and then a 4M solution of HCl in dioxane (16.75 mL, 67.0 mmol) is added. The mixture is stirred at ambient temperature for 3 hours, and then concentrated to dryness. The residue is dissolved in a minimum of warm methanol (70 mL), and then MTBE (3-5 mL) is added. The solution is cooled at 0° C. for 1 hour in an ice-cold water bath, and the product precipitates out. A little MTBE (2-3 mL) is again added and the mixture is allowed to stand for a further 1 hour at 0° C. The solid obtained is filtered over a Buchner funnel and dried in vacuo to yield the expected compound in the form of a solid.

¹H NMR (400 MHz, CD₃OD) δ ppm: 2.65 (t, J=11.1 Hz, 1 H), 2.74-2.97 (m, 4 H), 3.10 (d, J=12.5 Hz, 1 H), 3.19 (dd,

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J=17.6, 4.8 Hz, 1 H), 3.25-3.55 (m, 5 H), 3.59-3.74 (m, 2 H), 3.82-4.15 (m, 4 H), 4.45 (AB q, J=15.9 Hz, 2 H), 7.21-7.35 (m, 4 H).

¹³C NMR (100 MHz, CD₃OD) δ ppm: 30.21, 45.67, 50.22, 51.99, 52.90, 53.58, 53.71, 59.25, 62.58, 65.30, 67.07, 127.76, 128.40, 129.08, 129.36, 130.16, 131.95

MS (ESI): [M+H]⁺ 288.2

PREPARATION 1"

N-[4-[tert-Butyl(dimethyl)silyl]oxyphenyl]-1-methyl-pyrazol-4-amine

Step A: 4-[[tert-Butyl(dimethyl)silyl]oxy]aniline

The title compound is obtained starting from 4-aminophenol in THF in the presence of imidazole and tert-butyl(dimethyl)silyl chloride in accordance with the protocol described in the literature (S. Knaggs et al, *Organic & Biomolecular Chemistry*, 3(21), 4002-4010; 2005).

¹H NMR: δ (400 MHz; dms_o-d₆; 300K): 6.45-6.55 (dd, 4H, aromatic Hs); 4.60 (m, 2H, NH₂-Ph); 0.90 (s, 9H, Si (CH₂)₂CH(CH₃)₂); 0.10 (s, 6H, Si (CH₂)₂CH(CH₃)₂)

IR: ν: —NH₂⁺: 3300-3400 cm⁻¹

Step B: N-[4-[tert-Butyl(dimethyl)silyl]oxyphenyl]-1-methyl-pyrazol-4-amine

To a solution of 30.8 g (0.137 mol) of the compound of Step A in 525 mL of anhydrous toluene there are successively added 29.8 g of sodium tert-butyrate (0.310 mol), 4.55 g of Pd₂(dba)₃ (also referred to as tris(dibenzylideneacetone)dipalladium(0)) (4.96 mmol), 4.81 g of 2-di-tert-butylphosphino-2',4',6'-tri-isopropyl-1,1'-biphenyl (9.91 mmol) and 12.8 mL of 4-bromo-1-methyl-1H-pyrazole (0.124 mol). The batch is degassed under argon for 30 minutes and then refluxed for 3 hours. It is allowed to cool. The reaction mixture is concentrated to dryness and then taken up in dichloromethane, filtered over Celite and then concentrated to dryness again. The residue is then purified by chromatography over silica gel using dichloromethane and ethyl acetate as eluants to provide the expected product in the form of a solid.

¹H NMR: δ (400 MHz; dms_o-d₆; 300K): 7.55 (s, 1H, pyrazole); 7.23 (s, 1H, pyrazole); 7.18 (broad s, 1H, NH₂-Ph); 6.64 (m, 4H, aromatic Hs); 3.77 (s, 3H, CH₃-pyrazole); 0.90 (s, 9H, Si (CH₂)₂CH(CH₃)₂); 0.12 (s, 6H, Si (CH₂)₂CH(CH₃)₂)

IR: ν —NH⁺: 3275 cm⁻¹; ν Ar and C=N: 1577 and 1502 cm⁻¹; ν —Si—C—: 1236 cm⁻¹; ν —Si—O—: 898 cm⁻¹; ν —Si—C—: 828, 774 cm⁻¹

PREPARATION 2"

4-[[tert-Butyl(dimethyl)silyl]oxy]-N-phenylaniline

To a solution of 12 g of 4-anilinophenol (64.7 mmol) in 200 mL of acetonitrile there are added, at ambient temperature, 6.7 g of imidazole (97.05 mmol) and 11.7 g of tert-butyl(dimethyl)silyl chloride (77.64 mmol). The batch is stirred at 70° C. for 4 hours. The reaction mixture is then poured into water and extracted with ether. The organic phase is then dried over MgSO₄, then filtered and evaporated to dryness. The crude product thereby obtained is then purified by chromatography over silica gel using petroleum ether and dichloromethane as eluants. The title product is obtained in the form of a powder.

¹H NMR: δ (400 MHz; dms_o-d₆; 300K): 7.84 (s, 1H NH); 7.17 (t, 2H aniline); 6.98 (d, 2H phenoxy); 6.94 (d, 2H

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aniline); 6.76 (d, 2H phenoxy); 6.72 (t, 1H aniline); 0.95 (s, 9H tert-butyl); 0.15 (s, 6H dimethyl)

IR: ν: >NH: 3403 cm⁻¹; ν:>Ar: 1597 cm⁻¹

PREPARATION 3"

tert-Butyl 5-[(4-[[tert-butyl(dimethyl)silyl]oxy]phenyl)amino]-1H-indole-1-carboxylate

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1H-pyrazole used in Step B by tert-butyl 5-bromo-1H-indole-1-carboxylate.

¹H NMR: δ (400 MHz; dms_o-d₆; 300K): 7.85 (d, 1H); 7.78 (s, 1H); 7.55 (d, 1H); 7.15 (d, 1H); 6.95 (m, 3H); 6.75 (d, 2H); 6.58 (d, 1H); 1.65 (s, 9H); 1.00 (s, 9H); 0.2 (s, 6H)

PREPARATION 4"

N-(4-[[tert-Butyl(dimethyl)silyl]oxy]phenyl)-1-methyl-1H-indol-5-amine

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1H-pyrazole used in Step B by 5-bromo-1-methyl-1H-indole.

PREPARATION 5"

N-(4-[[tert-Butyl(dimethyl)silyl]oxy]phenyl)-1-methyl-1H-indazol-5-amine

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1H-pyrazole used in Step B by 5-bromo-1-methyl-1H-indazole.

PREPARATION 6"

N-(4-[[tert-Butyl(dimethyl)silyl]oxy]phenyl)-3-fluoro-4-methylaniline

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1H-pyrazole used in Step B by 4-bromo-2-fluoro-1-methylbenzene.

PREPARATION 7"

N-(4-[[tert-Butyl(dimethyl)silyl]oxy]phenyl)-3-fluoroaniline

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1H-pyrazole used in Step B by 1-bromo-3-fluorobenzene.

PREPARATION 8"

4-Benzyloxy-N-phenyl-aniline

To a solution of 4-hydroxy-N-phenyl-aniline (30 g; 162 mmol) in acetonitrile (400 mL) there are added 58 g of Cs₂CO₃ (178 mmol) and stirring is carried out for 15 minutes at ambient temperature. Benzyl bromide (22.5 mL; 178 mmol) is then added dropwise and then the reaction mixture is refluxed for 4 hours. After filtering and rinsing with acetonitrile, the filtrate is concentrated and purified by chromatography over silica gel using petroleum ether and ethyl acetate as eluants. The title product is then obtained in the form of a colourless solid.

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¹H NMR: δ (400 MHz; dms_o-d₆; 300K): 7.80 (m, 1H, NH); 7.45 (m, 2H, aryl); 7.40 (m, 2H, aryl); 7.30 (m, 1H, aryl); 7.15 (s, 2H, aryl); 7.05 (d, 2H, aryl); 6.9-7.0 (m, 4H, aryl); 6.70 (t, 1H, aryl); 5.05 (s, 2H, benzyl).

IR: ν: >NH: 3408 cm⁻¹

PREPARATION 9"

N-(4-{[tert-Butyl(dimethyl)silyl]oxy}phenyl)pyridin-4-amine

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1H-pyrazole used in Step B by 4-bromopyridine.

IR: ν —NH—: 3200 and 2500 cm⁻¹; ν:—Si—O—: 902 cm⁻¹; ν:—Si—C—: 820 cm⁻¹

PREPARATION 10"

N-(4-{[tert-Butyl(dimethyl)silyl]oxy}phenyl)-4-fluoroaniline

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1H-pyrazole used in Step B by 1-bromo-4-fluorobenzene.

PREPARATION 11"

N-(4-{[tert-Butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-1H-pyrrolo[2,3-b]pyridin-5-amine

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1H-pyrazole used in Step B by 5-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridine (obtained in accordance with a protocol from the literature: *Heterocycles*, 60(4), 865, 2003).

IR: ν: —NH—: 3278 cm⁻¹; ν: aromatic —C=C— moieties: 1605 cm⁻¹

PREPARATION 12"

N-(4-{[tert-Butyl(dimethyl)silyl]oxy}phenyl)-2-methoxypyrimidin-5-amine

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1H-pyrazole used in Step B by 5-bromo-2-methoxypyrimidine.

PREPARATION 13"

N-(4-{[tert-Butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-amine

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1H-pyrazole used in Step B by 5-bromo-1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine.

PREPARATION 14"

N-(4-{[tert-Butyl(dimethyl)silyl]oxy}phenyl)-1-methyl-1H-benzimidazol-5-amine

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1H-pyrazole used in Step B by 5-bromo-1-methyl-1H-benzimidazole.

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PREPARATION 15"

N⁴-(4-{[tert-Butyl(dimethyl)silyl]oxy}phenyl)-N², N²-dimethyl-pyridine-2,4-diamine

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1H-pyrazole used in Step B by 4-bromo-N,N-dimethylpyridin-2-amine.

PREPARATION 16"

N-(4-{[tert-Butyl(dimethyl)silyl]oxy}phenyl)pyrazolo[1,5-a]pyrimidin-6-amine

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1H-pyrazole used in Step B by 6-bromopyrazolo[1,5-a]pyrimidine.

IR: ν —NH—: 3272 cm⁻¹; ν —C=N—: 1634 cm⁻¹; ν —C=C—: 1616 cm⁻¹

PREPARATION 17"

N-[4-{[tert-Butyl(dimethyl)silyl]oxy}phenyl]-1-methyl-pyrazolo-[3,4-b]pyridin-5-amine

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1H-pyrazole used in Step B by 5-bromo-1-methyl-pyrazolo[3,4-b]pyridine (obtained in accordance with a protocol from the literature: WO 2006/052568 starting from 2-methyl-pyrazol-3-amine and 2-bromopropanedial).

PREPARATION 18"

4-(4-{[tert-Butyl(dimethyl)silyl]oxy}phenyl)amino)-1,5-dimethyl-1H-pyrrole-2-carbonitrile

Step A: 4-Bromo-1,5-dimethyl-1H-pyrrole-2-carbonitrile

A solution of bromine (6.58 mL, 0.13 mol) in acetic acid (60 mL) is added dropwise, with the aid of a dropping funnel, to a solution of 1,5-dimethyl-1H-pyrrole-2-carbonitrile (15.0 g, 0.12 mol) in acetic acid (300 mL). The batch is stirred at ambient temperature for 24 hours. The reaction mixture is then poured into a beaker containing 300 mL of water. The solid formed is filtered off and rinsed with water. It is then dissolved in dichloromethane (300 mL) and the organic phase is washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo to yield the expected product in the form of a solid.

¹H NMR (CDCl₃) δ ppm: 2.25 (s, 3 H), 3.67 (s, 3 H), 6.74 (s, 1 H)

Step B: 4-(4-{[tert-Butyl(dimethyl)silyl]oxy}phenyl)amino)-1,5-dimethyl-1H-pyrrole-2-carbonitrile

A solution of the compound of the above Step (1.5 g, 7.53 mmol), 4-{[tert-butyl(dimethyl)silyl]oxy}aniline (2.02 g, 9.04 mmol), sodium tert-butyrate (1.45 g, 15.06 mmol) and 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl (0.13 g, 0.30 mmol) in toluene (20 mL) is purged with nitrogen. Tris(dibenzylideneacetone)-dipalladium(0) (0.28 g, 0.30 mmol) is added, and then the reaction mixture is heated at 90° C. until the reaction is complete (monitored by TLC). Heating is stopped and the mixture is allowed to return to ambient temperature. Water (75 mL) is added and the mixture is extracted with ethyl acetate (3×75 mL). The combined organic phases are washed with brine and then concentrated. The crude product is absorbed onto silica gel and purified by chromatography over silica gel using ethyl acetate and heptane.

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tane as eluants. The product thereby obtained is dissolved in heptane in the warm state and is allowed to precipitate, with stirring, at ambient temperature, and then at 0° C. The solid is filtered off and the operation is repeated on the filtrate to yield the expected compound in the form of a solid.

¹H NMR (400 MHz, CDC₃) δ ppm: 0.15 (s, 6 H), 0.97 (s, 9 H), 2.13 (s, 3 H), 3.66 (s, 3 H), 4.68 (br. s, 1 H), 6.49 (d, J=8.5 Hz, 2 H), 6.64 (s, 1 H), 6.66 (d, J=8.7 Hz, 2 H)

¹³C NMR (100 MHz, CDC₃) δ ppm: 4.34, 9.72, 18.30, 25.88, 32.94, 101.27, 114.37, 114.70, 116.41, 120.73, 124.52, 131.23, 141.54, 148.27

MS (ESI+): [M+H]⁺ measured: 342.3

PREPARATION 19"

4-[(4-{[tert-Butyl(dimethyl)silyl]oxy}phenyl)amino]-1-methyl-1H-pyrrole-2-carbonitrile

Step A: 1-Methyl-1H-pyrrole-2-carbonitrile

N,N-Dimethylformamide (3 mL) and 1,4-diazabicyclo [2.2.2]octane (0.49 g, 4.3 mmol) are added to a solution of pyrrole-2-carbonitrile (4 g, 43.4 mmol) in dimethyl carbonate (56 mL). The solution is stirred at 90° C. for 15 hours, and is then heated at 110° C. for 8 hours. The mixture is cooled to ambient temperature, and then ethyl acetate (80 mL) is added. The phases are separated and the organic phase is washed with water (2×80 mL) and 1N aqueous HCl solution (1×80 mL). The combined aqueous phases are extracted again with ethyl acetate (1×80 mL). The combined organic phases are washed with brine (1×80 mL), dried over MgSO₄, filtered and concentrated in vacuo to obtain the expected product in the form of a liquid.

¹H NMR (400 MHz, CDC₃) δ ppm: 3.78 (m, 2 H), 6.12-6.18 (m, 1 H), 6.74-6.82 (m, 1 H)

Step B: 4-Bromo-1-methyl-1H-pyrrole-2-carbonitrile

N-Bromosuccinimide (6.2 g, 34.9 mmol) is added to a solution of 1-methyl-1H-pyrrole-2-carbonitrile (3.7 g, 34.9 mmol) in N,N-dimethylformamide (150 mL). The solution is stirred for 15 hours at ambient temperature. Another amount of N-bromosuccinimide (2.0 g, 11 mmol) is added and the mixture is stirred for 3 hours. Silica (7 g) is then added and the suspension is then evaporated to dryness. The material pre-absorbed onto the silica is placed on a silica gel column and the product is purified by chromatography over silica gel using ethyl acetate and heptane as eluants to obtain the expected product in the form of a solid.

¹H NMR (400 MHz, CDC₃) δ ppm: 3.77 (s, 3 H), 6.75 (d, J=1.7 Hz, 1 H), 6.80 (d, J=1.7 Hz, 1 H)

Step C: 4-[(tert-Butyl(dimethyl)silyl)oxy]phenyl]amino)-1-methyl-1H-pyrrole-2-carbonitrile

Nitrogen is bubbled through a solution of 4-bromo-1-methyl-1H-pyrrole-2-carbonitrile (2.82 g, 15.2 mmol) and 4-[(tert-butyl(dimethyl)silyl)oxy]aniline (4.08 g, 18.3 mmol) in toluene (55 mL) for 5 minutes. Sodium tert-butyrate (2.92 g, 30.4 mmol), tris(dibenzylideneacetone)dipalladium(0) (556 mg, 0.6 mmol) and 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl (255 mg, 0.6 mmol) are then added to the reaction mixture. The mixture is stirred for 1 hour at 80° C. under nitrogen. The suspension is then cooled to ambient temperature and filtered over Celite. The Celite cake is then rinsed with ethyl acetate. The filtrate is washed with water and then with brine. The organic phase is dried over MgSO₄, filtered and concentrated in vacuo. The product is purified twice by chromatography over silica gel using ethyl acetate and heptane as eluants, and then by trituration in heptane to obtain the expected product in the form of a solid.

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¹H NMR (400 MHz, CDC₃) δ ppm: 0.16 (s, 6 H), 0.97 (s, 9 H), 3.73 (s, 3 H), 6.57 (d, J=1.9 Hz, 1 H), 6.64-6.66 (m, 1 H), 6.70 (s, 4 H); NMR

¹³C NMR (100 MHz, CDC₃) δ ppm: -4.48, 18.17, 25.72, 35.46, 103.01, 113.56, 113.69, 115.92, 119.55, 120.67, 129.04, 139.94, 148.85

MS (ESI+): [M+H]⁺ 328.25

PREPARATION 20"

N-[4-[tert-Butyl(dimethyl)silyl]oxy-3-fluoro-phenyl]-1-methyl-1H-pyrazol-4-amine

The procedure is in accordance with the protocol of Preparation 1", replacing the 4-aminophenol used in Step A by 2-fluoro-4-aminophenol.

¹H NMR (400 MHz, dmsd-d₆) δ ppm: 7.59 (bs, 1 H), 7.39 (m, 1 H), 7.24 (d, 1 H), 6.74 (dd, 1 H), 6.52 (dd, 1 H), 6.42 (ddd, 1 H), 3.76 (s, 3 H), 0.92 (s, 9 H), 0.1 (d, 6 H)

PREPARATION 21"

2-({4-[(tert-Butyl(dimethyl)silyl)oxy]phenyl}amino)pyridine-4-carbonitrile

A solution composed of 2-bromo-4-pyridinecarbonitrile (5.00 g, 36.1 mmol), 4-[(tert-butyl(dimethyl)silyl)oxy]aniline (8.06 g, 36.1 mmol), sodium tert-butyrate (4.50 g, 46.9 mmol) and 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl (0.458 g, 1.08 mmol) in toluene (50 mL) is purged with nitrogen. Tris(dibenzylideneacetone)dipalladium(0) (0.99 g, 1.08 mmol) is then added to the reaction mixture, and then the batch is heated at 50° C. for 1.5 hours. The mixture is then allowed to cool to ambient temperature. Water is added and the reaction mixture is extracted with ethyl acetate (3×20 mL). The combined organic phases are washed with brine, and then concentrated under reduced pressure. The crude product is absorbed onto silica gel and purified by chromatography over silica gel using ethyl acetate and heptane as eluants. The product obtained is dissolved in the warm state in heptane and precipitates, with stirring, at ambient temperature, and then at 0° C. After filtration, the expected compound is obtained in the form of a solid.

¹H NMR (400 MHz, CDC₃) δ ppm: 0.22 (s, 6 H), 1.00 (s, 9 H), 6.61 (br. s, 1 H), 6.81-6.84 (m, 2 H), 6.84-6.89 (m, 2 H), 7.12-7.17 (m, 2 H), 8.26 (dd, J=5.1, 0.9 Hz, 1 H)

¹³C NMR (100 MHz, CDC₃) δ ppm: -4.29, 18.31, 25.78, 109.11, 114.73, 117.23, 121.17, 121.74, 124.93, 132.12, 149.79, 153.45, 158.00

MS (ESI+): [M+H]⁺ 326.19

PREPARATION 22"

N-[4-[tert-Butyl(dimethyl)silyl]oxyphenyl]-1-tetrahydrofuran-3-yl-pyrazol-4-amine

4-[tert-Butyl(dimethyl)silyl]oxyaniline (0.92 g, 3.48 mmol) and 4-iodo-1-tetrahydrofuran-3-yl-pyrazole (0.78 g, 3.48 mmol) dissolved in anhydrous tetrahydrofuran (20 mL) are stirred for one hour at ambient temperature in the presence of sodium tert-butyrate (1.7 mL, 2M solution in THF) and chloro(2-di-tert-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) (84 mg, 0.122 mmol). The reaction mixture is filtered over Celite and then evaporated to dryness. The residue is crystallised from a mixture of heptane/ethyl acetate, filtered and washed with

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heptane and then purified by chromatography over silica gel using dichloromethane and methanol as eluants to yield the expected product.

¹H NMR (500 MHz, dms_o-d₆, 300 K) δ ppm: 7.62 (d, 1H, pyrazole-H₅), 7.29 (d, 1H, pyrazole-H₃), 7.26 (s, 1H, NH), 6.68 (d, 2H, Ar—H), 6.64 (d, 2H, Ar—H), 4.93 (m, 1H, THF-3'H), 3.95 (m, 1H, THF-5'H), 3.94 (m, 1H, THF-2'H), 3.87 (m, 1H, THF-2'H), 3.80 (m, 1H, THF-5'H), 2.33 (m, 1H, THF-4'H), 2.27 (m, 1H, THF-4'H), 0.93 (s, 9H, ^tBu), 0.12 (s, 6H, Me)

IR: ν C—H: 2857 cm⁻¹; ν aromatic: 1505 cm⁻¹; ν Si—C: 1249 cm⁻¹

PREPARATION 23"

6-({4-[(tert-Butyldimethylsilyl)oxy]phenyl}amino)
pyridine-2-carbonitrile

4-Aminophenol (3.3 g, 30.2 mmol) is added to a solution of 6-chloropyridine-2-carbonitrile (3.5 g, 25.3 mmol) in 1-methyl-2-pyrrolidinone (70 mL). The reaction mixture is heated at 140-150° C. for 16 hours in a sealed flask. The batch is then cooled to ambient temperature. Imidazole (3.4 g, 49.9 mmol) and tert-butyl(dimethyl)silyl chloride (7.6 g, 50.4 mmol) are subsequently added and the mixture is stirred for 16 hours at ambient temperature. The mixture is diluted with water (140 mL) and the product is extracted with AcOEt (4×50 mL). The organic phases are combined and washed with water (3×50 mL), and then brine (1×50 mL). The organic phase is then dried over MgSO₄, filtered and concentrated in vacuo. The crude product is purified by chromatography over silica gel using ethyl acetate and heptane as eluants to obtain the title product.

¹H NMR (400 MHz, CDC₃) δ ppm: 0.20 (s, 6 H), 0.99 (s, 9 H), 6.74 (dd, J=7.6, 4.9 Hz, 1 H), 6.81-6.88 (m, 3 H), 7.36-7.42 (m, 2 H), 7.74 (dd, J=7.6, 1.9 Hz, 1 H), 8.34 (dd, J=4.9, 1.9 Hz, 1 H)

¹³C NMR (100 MHz, CDC₃) δ ppm: -4.38, 18.21, 25.73, 92.58, 113.50, 116.53, 120.30, 123.20, 131.97, 141.67, 152.42, 152.45, 156.51

MS (ESI): [M+H]⁺ 326.24

PREPARATION 24"

4-({4-[(tert-Butyldimethylsilyl)oxy]phenyl}amino)
pyrimidine-2-carbonitrile

Step A: N-{4-[(tert-Butyldimethylsilyl)oxy]phenyl}-2-chloropyrimidin-4-amine

4-Aminophenol (8.8 g, 80.6 mmol) and triethylamine (18.6 mL, 133.4 mmol) are added to a solution of 2,4-dichloropyrimidine (10.0 g, 67.1 mmol) in ethanol (150 mL). The reaction mixture is heated at 150° C. for 14 hours in a sealed flask. The batch is then cooled to ambient temperature and the solvent is evaporated off in vacuo. Dichloromethane (200 mL) is added to the residue, and then imidazole (9.1 g, 133.7 mmol) and tert-butyl(dimethyl)silyl chloride (12.1 g, 80.3 mmol) are added. The mixture is stirred for 15 hours at ambient temperature. The reaction mixture is diluted with water (200 mL). The phases are separated and the organic phase is washed with brine (1×100 mL). It is then dried over MgSO₄, filtered and concentrated in vacuo. The residue is purified by chromatography over silica gel using ethyl acetate and heptane as eluants to obtain a solid. The latter is triturated in heptane, filtered off and rinsed with heptane to yield the expected compound in the form of a solid.

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¹H NMR (400 MHz, dms_o-d₆) δ ppm: 0.22 (s, 6 H), 0.99 (s, 9 H), 6.42 (d, J=5.9 Hz, 1 H), 6.81 (br. s, 1 H), 6.85-6.90 (m, 1 H), 7.13 (d, J=8.7 Hz, 2 H), 8.07 (d, J=5.9 Hz, 2 H)

Step B: 4-({4-[(tert-Butyldimethylsilyl)oxy]phenyl}amino)pyrimidine-2-carbonitrile

Anhydrous N,N-dimethylformamide (10 mL) is placed under nitrogen in a flask and then the compound of Step A (670 mg, 2.0 mmol) is added. Zinc cyanide (468 mg, 4.0 mmol) and tetrakis(triphenylphosphine)palladium(0) (404 mg, 0.3 mmol) are subsequently added. Nitrogen is bubbled through the solution for 5 minutes and then the reaction mixture is stirred at 120° C. for 2 hours under a nitrogen atmosphere. The reaction, monitored by LC-MS, is complete. The mixture is cooled to ambient temperature, and then water (15 mL) is added thereto. The product is extracted with AcOEt (3×25 mL). The organic phases are combined and washed with water (4×25 mL), and then with brine (1×25 mL). The organic phase is dried over MgSO₄, filtered and concentrated in vacuo. The residue is purified by chromatography over silica gel using ethyl acetate and heptane as eluants to obtain the expected compound in the form of a solid.

¹H NMR (400 MHz, CDC₃) δ ppm: 0.22 (s, 6 H), 0.99 (s, 9 H), 6.63 (d, J=6.1 Hz, 1 H), 6.86-6.92 (m, 2 H), 7.03 (br. s, 1 H), 7.17 (d, J=8.5 Hz, 2 H), 8.22 (d, J=6.1 Hz, 1 H)

¹³C NMR (100 MHz, CDC₃) δ ppm: -4.51, 18.10, 25.55, 106.32, 115.92, 121.00, 125.22, 129.73, 144.55, 154.16, 156.07, 161.56

PREPARATION 25"

N-{4-[(tert-Butyldimethylsilyl)oxy]phenyl}-1-tri-deuteriomethyl-1H-pyrazol-4-amine

Step A: 4-Bromo-1-trideuteriomethyl-1H-pyrazole

4-Bromo-1H-pyrazole (9.05 g, 61.6 mmol) is added in portions to a suspension of NaH (60% in oil) (2.83 g, 70.8 mmol) in tetrahydrofuran (90 mL) cooled in an ice bath. After having taken away the ice bath, the solution is stirred at ambient temperature for 0.5 hours. It is again cooled in an ice bath and iodomethane-d₃ (5.0 mL, 80.3 mmol) is added. The solution is stirred at ambient temperature for 19 hours. The suspension is then concentrated. The evaporation residue is triturated with MTBE (90 mL) and filtered. The filtrate is concentrated in vacuo to obtain the expected compound in the form of an oil.

¹H NMR (400 MHz, CDC₃) δ ppm: 7.37 (s, 1 H), 7.43 (s, 1 H)

Step B: N-{4-[(tert-Butyldimethylsilyl)oxy]phenyl}-1-tri-deuteriomethyl-1H-pyrazol-4-amine

4-Bromo-1-trideuteriomethyl-1H-pyrazole (9.6 g, 58.5 mmol), 4-[(tert-butyl(dimethyl)silyl)oxy]aniline (14.4 g, 64.6 mmol) and toluene (150 mL) are added to a 500-ml three-necked flask. The solution is degassed with nitrogen for 15 minutes, and then sodium tert-butyrate (11.4 g, 0.12 mol), 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl (0.77 g, 1.81 mmol) and tris(dibenzylideneacetone)dipalladium(0) (1.64 g, 1.79 mmol) are successively added. The suspension is heated at 85° C. for 1.5 hours. The reaction mixture is then cooled to ambient temperature and water (270 mL) is added. The mixture is stirred for 30 minutes. Celite (30 g) is then added and the suspension is filtered on a bed of Celite. The phases of the filtrate are separated and the aqueous phase is extracted with ethyl acetate (3×200 mL). The combined organic phases are dried over Na₂SO₄ and filtered. Silica (36 g) is added to the filtrate and the batch is evaporated to dryness. The product is purified by chromatography over silica gel using ethyl acetate and heptane as eluants. The

product obtained is recrystallised from heptane (80 mL) to obtain the expected compound.

^1H NMR (400 MHz, CDCl_3) δ ppm: 0.16 (s, 6 H), 0.97 (s, 9 H), 4.92 (s, 1 H), 6.61-6.73 (m, 4 H), 7.25 (s, 1 H), 7.36 (s, 1 H)

^{13}C NMR (100 MHz, CDCl_3) δ ppm: -4.37, 18.28, 25.86, 38.67 (sept., $^1J_{\text{C-D}}=21.0\text{ Hz}$), 115.12, 120.73, 123.76, 126.52, 134.74, 141.07, 148.43

MS (ESI): $[\text{M}+\text{H}]^+$ 307.08

PREPARATION 26"

N-[4-[tert-Butyl(dimethyl)silyl]oxyphenyl]-1-(oxetan-3-yl)-1H-pyrazol-4-amine

Step A: 4-Bromo-1-(oxetan-3-yl)-1H-pyrazole

4-Bromo-1H-pyrazole (1.53 g, 10.7 mmol) is dissolved in anhydrous dimethylformamide (15 mL). 3-Bromooxetane (2.0 g, 14.6 mmol) and caesium carbonate (4.7 g, 14 mmol) are successively added thereto. The reaction mixture is heated for 8 hours at 130°C . in a sealed flask. At the end of the reaction, the solvent is evaporated off in vacuo and the residue is purified by chromatography over silica gel using dichloromethane containing diethylamine and methanol as eluants to yield the expected compound.

Step B: N-[4-[tert-Butyl(dimethyl)silyl]oxyphenyl]-1-(oxetan-3-yl)-1H-pyrazol-4-amine

4-[tert-Butyl(dimethyl)silyl]oxyaniline (1.5 g, 7.2 mmol) and 4-bromo-1-(oxetan-3-yl)-pyrazole (1.6 g, 7.2 mmol) dissolved in anhydrous tetrahydrofuran (25 mL) are stirred for 3 hours at ambient temperature in the presence of sodium tert-butyrate (3.7 mL, 2M solution in THF) and chloro(2-di-tert-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) (101 mg, 0.145 mmol). The reaction mixture is filtered over Celite and then evaporated to dryness. The residue is purified by chromatography over silica gel using dichloromethane containing diethylamine and ethyl acetate as eluants to yield the expected product.

^1H NMR (500 MHz, dmsO-d_6 , 300 K) δ ppm: 7.76 (s, 1H, pyrazole-5'H), 7.40 (s, 1H, pyrazole-3'H), 7.34 (br s, 1H, NH), 6.70 (d, 2H, Ar—H), 6.65 (d, 2H, Ar—H), 5.49 (m, 1H, oxetane), 4.89 (d, 4H, oxetane), 0.93 (s, 9H, ^tBu), 0.13 (s, 6H, Me)

IR: ν : C—H: 2955 cm^{-1} ; aromatic: 1505 cm^{-1} ; Si—C: 1237 cm^{-1}

PREPARATION 27"

Mixture of N-(4-{[tert-butyl(dimethyl)silyl]oxy}phenyl)-1,5-dimethyl-1H-pyrazol-4-amine and N-(4-{[tert-butyl(dimethyl)silyl]oxy}phenyl)-1,3-dimethyl-1H-pyrazol-4-amine

Step A: Mixture of 4-bromo-1,5-dimethyl-1H-pyrazole and 4-bromo-1,3-dimethyl-1H-pyrazole

To a suspension of NaH 60% in oil (0.3 g; 7.45 mmol) in tetrahydrofuran (150 mL) there is added, at 10°C ., 4-bromo-3-methyl-1H-pyrazole dissolved in 15 mL of tetrahydrofuran dropwise, over 15 minutes. After stirring for 40 minutes at ambient temperature, iodomethane (0.45 mL; 7.45 mmol) is added dropwise, and then the reaction mixture is stirred overnight. After adding water, the reaction mixture is evaporated and taken up in dichloromethane. The organic phase is separated off and dried over MgSO_4 , filtered and concentrated to dryness. The residue is purified by chromatography over

silica gel to yield a mixture of the title compounds (4-bromo-1,3-dimethyl-pyrazole and 4-bromo-1,5-dimethyl-pyrazole respectively in a ratio of 4:6).

4-bromo-1,5-dimethyl-1H-pyrazole

^1H NMR (500 MHz, dmsO-d_6) δ ppm: 7.41 (s, 1 H), 3.76 (s, 3 H), 2.22 (s, 3 H)

4-bromo-1,3-dimethyl-1H-pyrazole

^1H NMR (500 MHz, dmsO-d_6) δ ppm: 7.81 (s, 1 H), 3.74 (s, 3 H), 2.09 (s, 3 H)

Step B: Mixture of N-(4-{[tert-butyl(dimethyl)silyl]oxy}phenyl)-1,5-dimethyl-1H-pyrazol-4-amine and N-(4-{[tert-butyl(dimethyl)silyl]oxy}phenyl)-1,3-dimethyl-1H-pyrazol-4-amine

The procedure is in accordance with Step B of Preparation 1", replacing the 4-bromo-1-methyl-1H-pyrazole by the mixture of isomers from Step A. A mixture of isomers in a ratio of 4:6 is obtained (respectively N-(4-{[tert-butyl(dimethyl)silyl]oxy}phenyl)-1,5-dimethyl-1H-pyrazol-4-amine and N-(4-{[tert-butyl(dimethyl)silyl]oxy}phenyl)-1,3-dimethyl-1H-pyrazol-4-amine).

PREPARATION 28"

N-[4-[tert-Butyl(dimethyl)silyl]oxyphenyl]-1-cyclopropyl-1H-pyrazol-4-amine

Step A: 4-Bromo-1-cyclopropyl-1H-pyrazole

4-Bromo-1H-pyrazole (1.76 g, 12 mmol) is dissolved in anhydrous dimethylformamide (15 mL). Cyclopropyl bromide (2.9 mL, 36 mmol) and caesium carbonate (7.8 g, 24 mmol) are successively added thereto. The reaction mixture is heated for 15 hours at 160°C . in a sealed flask. At the end of the reaction, the solvent is evaporated off in vacuo and the residue is purified by chromatography over silica gel using heptane and dichloromethane as eluants to yield the expected compound.

Step B: N-[4-[tert-Butyl(dimethyl)silyl]oxyphenyl]-1-cyclopropyl-1H-pyrazol-4-amine

4-[tert-Butyl(dimethyl)silyl]oxyaniline (1.64 g, 7.3 mmol) and 4-bromo-1-cyclopropyl-1H-pyrazole (1.4 g, 7.3 mmol) dissolved in anhydrous tetrahydrofuran (30 mL) are stirred for 3 hours at ambient temperature in the presence of sodium tert-butyrate (3.7 mL, 2M solution in THF) and chloro(2-di-tert-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) (101 mg, 0.146 mmol). The reaction mixture is filtered over Celite and then evaporated to dryness. The residue is purified by chromatography over silica gel using heptane and ethyl acetate as eluants to yield the expected product.

^1H NMR (500 MHz, dmsO-d_6 , 300 K) δ ppm: 7.61 (s, 1H, pyrazole-5'H), 7.23 (s, 1H, pyrazole-3'H), 7.22 (br s, 1H, NH), 6.65 (d, 2H, Ar—H), 6.63 (d, 2H, Ar—H), 3.64 (m, 1H, cyclopropyl-H), 1.00-0.91 (m, 4H, cyclopropyl), 0.93 (s, 9H, ^tBu), 0.12 (s, 6H, Me)

IR: ν : C—H: 2930 cm^{-1} ; aromatic: 1504 cm^{-1} ; Si—C: 1237 cm^{-1}

High-resolution mass spectrometry (ESI+):

Empirical formula: $\text{C}_{18}\text{H}_{27}\text{N}_3\text{OSi}$

$[\text{M}+\text{H}]^+$ calculated: 330.2003

$[\text{M}+\text{H}]^+$ measured: 330.1989

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PREPARATION 29"

1,5-Dimethyl-4-(phenylamino)-1H-pyrrole-2-carbonitrile

The procedure is in accordance with the protocol of Preparation 1", replacing the 4-[(tert-butyl(dimethyl)silyl)oxy]aniline used in Step B by aniline.

¹H NMR (400 MHz, dms_o-d₆) δ ppm: 7.19 (s, 1 H), 7.05 (t, 2 H), 6.79 (s, 1 H), 6.6 (m, 3 H), 3.61 (s, 3 H), 2.1 (s, 3 H)

PREPARATION 30"

1-Methyl-N-phenyl-1H-pyrrolo[2,3-b]pyridin-6-amine

The procedure is in accordance with the protocol of Step B of Preparation 1" using aniline and 5-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridine (obtained in accordance with a protocol from the literature: Heterocycles, 60(4), 865, 2003).

¹H NMR (400 MHz, dms_o-d₆) δ ppm: 8.1 (d, 1 H), 7.9 (s, 1 H), 7.7 (d, 1 H), 7.45 (d, 1 H), 7.17 (t, 2 H), 6.9 (d, 2 H), 6.7 (t, 1 H), 6.38 (d, 1 H), 3.8 (s, 3 H)

PREPARATION 31"

N-(4-[(tert-Butyl(dimethyl)silyl)oxy]phenyl)-1-trideuteriomethyl-1H-pyrrolo[2,3-b]pyridin-5-amine

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1H-pyrazole used in Step B by 5-bromo-1-(trideuteriomethyl)-1H-pyrrolo[2,3-b]pyridine (obtained in accordance with a protocol from the literature Heterocycles, 60(4), 865, 2003, replacing the methyl iodide by trideuterated methyl iodide).

¹H NMR (400 MHz, dms_o-d₆) δ ppm: 8.05 (d, 1 H), 7.6 (m+d, 2 H), 7.4 (d, 1 H), 6.85/6.7 (2d, 4 H), 6.3 (d, 1 H), 0.95 (s, 9 H), 0.15 (s, 6 H)

PREPARATION 32"

4-({4-[(tert-Butyl(dimethyl)silyl)oxy]phenyl}amino)-1-trideuteriomethyl-1H-pyrrole-2-carbonitrile

Step A: 1-Trideuteriomethyl-1H-pyrrole-2-carbonitrile

NaH (60% in oil) (2.61 g, 65.2 mmol) is suspended in tetrahydrofuran (110 mL) at 0° C. 1H-Pyrrole-2-carbonitrile (5 g, 54.3 mmol) is added dropwise over 10 minutes. The reaction mixture is then warmed up to ambient temperature over 30 minutes. It is again cooled to 0° C., and then iodomethane-d₃ (10.23 g, 70.6 mmol) is added. The reaction mixture is stirred for 16 hours under nitrogen at ambient temperature. The reaction mixture is then evaporated under reduced pressure, and then ethyl acetate (200 mL) and water (200 mL) are added. The phases are separated, and the aqueous phase is extracted with ethyl acetate (2×200 mL). The combined organic phases are washed with brine (1×80 mL), dried over MgSO₄, filtered and concentrated in vacuo. The residue is purified by chromatography over silica gel using ethyl acetate and heptane as eluants. The fractions are combined and evaporated in vacuo to obtain the expected compound.

¹H NMR (400 MHz, CDC₃) δ ppm: 6.13 (dd, J=2.7, 3.9 Hz, 1 H), 6.75 (dd, J=1.5, 4.1 Hz, 1 H), 6.79 (dd, J=1.7, 2.6 Hz, 1 H)

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Step B: 4-Bromo-1-trideuteriomethyl-1H-pyrrole-2-carbonitrile

N-Bromosuccinimide (6.68 g, 37.5 mmol) is added to a solution of the compound of the above Step (4.09 g, 37.5 mmol) in N,N-dimethylformamide (188 mL). The solution is stirred for 16 hours at ambient temperature. The residue is purified by chromatography using ethyl acetate and heptane as eluants to obtain the expected compound in the form of a solid.

¹H NMR (400 MHz, CDC₃) δ ppm: 6.75 (d, J=1.7 Hz, 1 H), 6.80 (d, J=1.7 Hz, 1 H)

Step C: 4-({4-[(tert-Butyl(dimethyl)silyl)oxy]phenyl}amino)-1-trideuteriomethyl-1H-pyrrole-2-carbonitrile

Nitrogen is bubbled through a solution composed of the compound obtained in the above Step (5.85 g, 31.1 mmol), 4-[(tert-butyl(dimethyl)silyl)oxy]aniline (8 g, 35.8 mmol), sodium tert-butyrate (3.88 g, 40.4 mmol) and 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl (662 mg, 1.56 mmol) in toluene (260 mL) for 5 minutes. Tris(dibenzylideneacetone)-dipalladium(0) (1.43 g, 1.56 mmol) is then added. The mixture is stirred for 1 hour at 70° C. under nitrogen. The suspension is then cooled to ambient temperature, diluted with ethyl acetate and filtered over Celite. The Celite cake is then rinsed with ethyl acetate. The filtrate is washed with water (3 times), and then brine (once). The organic phase is dried over Na₂SO₄, filtered and concentrated in vacuo. The product is purified twice by chromatography over silica gel using ethyl acetate and heptane as eluants, and then by reverse-phase chromatography using methanol and water as eluants to obtain the expected compound in the form of a powder.

¹H NMR (400 MHz, CDC₃) δ ppm: 0.17 (s, 6 H), 0.98 (s, 9 H), 4.96 (br. s, 1 H), 6.57 (d, J=1.9 Hz, 1 H), 6.64 (d, J=1.8 Hz, 1 H), 6.70 (br. s, 4 H)

¹³C NMR (100 MHz, CDC₃) δ ppm: -4.38, 18.26, 25.83, 34.83, 102.96, 113.69, 113.71, 115.95, 119.58, 120.75, 129.14, 140.10, 148.84

MS (ESI): [M+H]⁺ 331.09

PREPARATION 33"

4-({4-[(tert-Butyl(dimethyl)silyl)oxy]phenyl}amino)-1-trideuteriomethyl-5-methyl-1H-pyrrole-2-carbonitrile

Step A: 5-Methyl-1H-pyrrole-2-carbonitrile

The compound is prepared in accordance with the protocol described in Heterocycles 2011, 82, 1503.

Step B: 1-Trideuteriomethyl-5-methyl-1H-pyrrole-2-carbonitrile

A solution of 5-methyl-1H-pyrrole-2-carbonitrile (0.30 g, 2.82 mmol) in N,N-dimethylformamide (5 mL) is cooled to 0° C. NaH (60% in oil) (0.118 g, 2.96 mmol) is added in portions, and the reaction mixture is stirred at 0° C. for 30 minutes. Iodomethane-d₃ (4.15 mL, 67.2 mmol) is added in a single portion, and the reaction mixture is stirred at ambient temperature until the reaction is complete. It is then diluted with water (30 mL) and ethyl acetate (15 mL). The phases are separated and the aqueous phase is extracted a second time with ethyl acetate (15 mL). The combined organic phases are washed with water (1×50 mL), and then brine, and dried over Na₂SO₄. After filtration and concentration under reduced pressure, the residue is purified by chromatography over silica gel using ethyl acetate and heptane as eluants to yield the expected compound in the form of a solid.

¹H NMR (400 MHz, CDC₃) δ ppm: 2.25 (s, 3 H), 5.91 (dd, J=3.9, 0.6 Hz, 1 H), 6.69 (d, J=3.9 Hz, 1 H)

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Step C: 4-Bromo-1-trideuteriomethyl-5-methyl-1H-pyrrole-2-carbonitrile

A solution of bromine (0.133 mL, 2.60 mmol) in acetic acid (1.5 mL) is added dropwise to a solution of the compound obtained in the above Step (0.305 g, 2.48 mmol) in acetic acid (5.5 mL) previously cooled to 0° C. The reaction mixture is stirred and gradually warmed up to ambient temperature over a period of 20 hours. The reaction mixture is poured into water (50 mL) and the mixture is extracted with dichloromethane (2×50 mL). The organic phase is dried over Na₂SO₄, filtered and concentrated under reduced pressure to yield the expected compound in the form of a solid.

¹H NMR (400 MHz, CDCl₃) δ ppm: 2.24 (s, 3 H), 6.73 (s, 1 H)

Step D: 4-({4-[(tert-Butyldimethylsilyl)oxy]phenyl}amino)-1-trideuteriomethyl-5-methyl-1H-pyrrole-2-carbonitrile

A solution composed of the compound obtained in the above Step (7.00 g, 34.6 mmol), 4-[(tert-butyldimethylsilyl)oxy]aniline (8.90 g, 39.8 mmol), sodium tert-butyrate (4.33 g, 45.0 mmol) and 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl (0.441 g, 1.04 mmol) in toluene (70 mL) is purged with nitrogen. Tris(dibenzylideneacetone)-dipalladium(0) (0.951 g, 1.04 mmol) is added, and then the reaction mixture is heated at 65° C. until the reaction, monitored by TLC, is complete. Heating is stopped and the mixture is cooled to ambient temperature. Water (200 mL) is added and the mixture is extracted with ethyl acetate (3 times). The combined organic phases are washed with brine, and then concentrated. The crude product is purified by chromatography over silica gel using ethyl acetate and heptane as eluents. The product obtained is dissolved in heptane in the warm state; it is allowed to precipitate out at ambient temperature and then at 0° C. to yield the expected product in the form of crystals.

¹H NMR (400 MHz, CDCl₃) δ ppm: 0.15 (s, 6 H), 0.96 (s, 9 H), 2.12 (s, 3 H), 4.66 (br. s, 1 H), 6.46-6.51 (m, 2 H), 6.64 (s, 1 H), 6.64-6.69 (m, 2 H)

¹³C NMR (100 MHz, CDCl₃) δ ppm: -4.37, 9.64, 18.26, 25.84, 31.62-32.87 (m), 101.14, 114.35, 114.66, 116.33, 120.68, 124.51, 131.17, 141.53, 148.18

MS (ESI): [M+H]⁺ 345.13

PREPARATION 34"

5-[(4-{{tert-Butyl(dimethyl)silyl}oxy}phenyl)amino]-1-methyl-1H-pyrazole-3-carbonitrile

Step A: 5-Amino-1-methyl-1H-pyrazole-3-carbonitrile

To a suspension of 1-methyl-5-nitro-1H-pyrazole-3-carbonitrile (2 g; 13.1 mmol) in a mixture of water (14 mL) and ethanol (120 mL) there are added HCl 37% (170 L) and iron filings (5.1 g; 91 mmol). The reaction mixture is heated for 5 hours at 50° C. After cooling to ambient temperature, the reaction mixture is filtered. The filtrate is concentrated to dryness and then purified by chromatography over silica gel using dichloromethane and ethyl acetate as eluents to yield the expected compound in the form of a solid.

¹H NMR (400 MHz, dmsd-d₆) δ ppm: 5.8 (s, 1 H), 5.7 (m, 2 H), 3.6 (s, 3 H)

Step B: 5-[(4-{{tert-Butyl(dimethyl)silyl}oxy}phenyl)amino]-1-methyl-1H-pyrazole-3-carbonitrile

The procedure is in accordance with the protocol of Step B of Preparation 1", replacing the 4-bromo-1-methyl-1H-pyrazole by (4-bromophenoxy)-(tert-butyl)dimethyl-silane and the 4-{{tert-butyl(dimethyl)silyl}oxy}aniline by the compound from Step A.

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¹H NMR (400 MHz, dmsd-d₆) δ ppm: 8.15 (s, 1 H), 6.9 (d, 2 H), 6.75 (d, 2 H), 6.45 (s, 1 H), 3.75 (s, 3 H), 0.95 (s, 9 H), 0.15 (s, 6 H)

PREPARATION 35"

4-[(4-{{tert-Butyl(dimethyl)silyl}oxy}phenyl)amino]-5-methyl-1-[2-(morpholin-4-yl)ethyl]-1H-pyrrole-2-carbonitrile

The procedure is in accordance with the process of Preparation 33", replacing the iodomethane-d₃ in Step B by 2-(chloroethyl)morpholine hydrochloride.

¹H NMR (400 MHz, dmsd-d₆) δ ppm: 6.85 (s, 1 H), 6.75 (s, 1 H), 6.6 (d, 2 H), 6.5 (d, 2 H), 4.1 (t, 2 H), 3.55 (t, 4 H), 2.6 (t, 2 H), 2.4 (t, 4 H), 2.1 (s, 3 H), 0.9 (s, 9 H), 0.1 (s, 6 H)

PREPARATION 36"

N-(4-{{tert-Butyl(dimethyl)silyl}oxy}phenyl)-2-[2-(morpholin-4-yl)ethoxy]pyrimidin-5-amine

Step A: 4-[2-(5-Bromopyrimidin-2-yl)oxyethyl]morpholine

NaH (1.0 g, 25.0 mmol, 60% in oil) suspended in anhydrous tetrahydrofuran is cooled at 0° C. in an ice bath under argon, and then 2-morpholinoethanol (2.7 g, 20.7 mmol) is added dropwise. The ice bath is withdrawn and the suspension is stirred for 1 hour at ambient temperature. 5-Bromo-2-chloro-pyrimidine (4.0 g, 20.7 mmol) is then added at ambient temperature and the reaction mixture is stirred for 16 hours at ambient temperature. Saturated aqueous ammonium chloride solution (10 mL) and water (10 mL) are added to the reaction mixture; the pH is adjusted to 9 by adding saturated aqueous NaHCO₃ solution. The resulting solution is extracted 3 times with ethyl acetate, the organic phase is then washed with brine, dried over MgSO₄, and then evaporated to dryness. The expected compound precipitates out by means of the addition of petroleum ether.

¹H NMR (400 MHz, dmsd-d₆) δ ppm: 8.75 (s, 2 H), 4.4 (t, 2 H), 3.55 (t, 4 H), 2.7 (t, 2 H), 2.45 (t, 4 H)

IR (ATR) cm⁻¹: 1562 ν>C=C< and C=N, 787 ν—C—H Ar

Step B: N-(4-{{tert-Butyl(dimethyl)silyl}oxy}phenyl)-2-[2-(morpholin-4-yl)ethoxy]-pyrimidin-5-amine

The procedure is in accordance with the protocol of Step B of Preparation 1", replacing the 4-bromo-1-methyl-1H-pyrazole by the compound from Step A.

¹H NMR (400 MHz, dmsd-d₆) δ ppm: 8.3 (s, 2 H), 7.8 (s, 1 H), 6.9/6.75 (2d, 4 H), 4.35 (t, 2 H), 3.55 (t, 4 H), 2.7 (t, 2 H), 2.45 (t, 4 H), 0.95 (s, 9 H), 0.15 (s, 6 H)

IR (ATR) cm⁻¹: 3300 ν—NH, 1506 ν—NH, 837 ν—Si—Me, 837 and 778 ν—CH Ar

PREPARATION 37"

4-({4-[(tert-Butyldimethylsilyl)oxy]phenyl}amino)-1,3-dimethyl-1H-pyrrole-2-carbonitrile

Step A: 4-Methyl-N-(prop-2-en-1-yl)benzene-1-sulphonamide

Allylamine (10.6 mL, 0.14 mol) is added over a period of 4 minutes to a solution of tosyl chloride (25.1 g, 0.13 mol) in dichloromethane (250 mL) cooled in an ice bath. Triethylamine (24 mL, 0.18 mol) is added and then the solution is stirred at ambient temperature for 1.25 hours. Aqueous 3N HCl solution (60 mL) is added and the phases are then separated. The organic phase is washed with another amount of

aqueous 3N HCl solution (60 mL) and then with 5% aqueous sodium bicarbonate solution (60 mL). The organic phase is dried over Na₂SO₄, filtered and concentrated to obtain the expected compound in the form of a solid.

¹H NMR (400 MHz, CDCl₃) δ ppm: 2.43 (s, 3 H), 3.54-3.63 (m, 2 H), 4.50 (1s, 1 H), 5.05-5.22 (m, 2 H), 5.66-5.79 (m, 1 H), 7.31 (d, J=8.1 Hz, 2 H), 7.76 (d, J=8.1 Hz, 2 H)

Step B: 4-Methyl-N-(2-methylprop-2-en-1-yl)-N-(prop-2-en-1-yl)benzene-1-sulphonamide

3-Chloro-2-methylpropene (20 mL, 0.20 mol) is added over a period of 5 minutes to a suspension of 4-methyl-N-(prop-2-en-1-yl)benzene-1-sulphonamide (27.9 g, 0.13 mol) and potassium carbonate (28.1 g, 0.20 mol) in N,N-dimethylformamide (200 mL) cooled in an ice bath. After 20 minutes, the suspension is stirred at ambient temperature for 18 hours. The suspension is concentrated to dryness. The residue is taken up in ethyl acetate (250 mL) and water (110 mL). The aqueous phase is extracted with ethyl acetate (2×50 mL). The combined organic phases are washed successively with aqueous 3N HCl solution (50 mL), water (3×50 mL), aqueous 5% potassium bicarbonate solution (50 mL), and finally brine (50 mL). The organic phase is dried over Na₂SO₄, filtered and concentrated to obtain the expected compound in the form of an oil.

¹H NMR (400 MHz, CDCl₃) δ ppm: 1.69 (s, 3 H), 2.43 (s, 3 H), 3.70 (s, 2 H), 3.75-3.79 (m, 2 H), 4.87 (d, J=25.1 Hz, 1 H), 5.04-5.09 (m, 1 H), 5.09-5.12 (m, 1 H), 5.45-5.59 (m, 1 H), 7.29 (d, J=8.1 Hz, 2 H), 7.71 (d, J=8.1 Hz, 2 H)

Step C: 3-Methyl-1-(4-methylbenzenesulphonyl)-1H-pyrrole

A solution of the compound obtained in Step B (15.2 g, 57.3 mmol) in toluene (550 mL) is heated at 80° C. in the presence of (1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium (Grubbs' catalyst, 2nd generation) (150 mg, 0.18 mmol) for 1 hour. 2,3-Dichloro-5,6-dicyano-p-benzoquinone (16.1 g, 70.9 mmol) is then added in one portion, and the solution is heated at 80° C. for 24 hours. The solution is filtered over Celite, and the filtrate is concentrated in vacuo. The product is purified by chromatography over silica gel using ethyl acetate and heptane as eluants to obtain the expected compound in the form of a solid.

¹H NMR (400 MHz, CDCl₃) δ ppm: 2.02 (d, J=1.0 Hz, 3 H), 2.39 (s, 3 H), 6.09-6.13 (m, 1 H), 6.85-6.90 (m, 1 H), 7.03-7.07 (m, 1 H), 7.27 (d, J=8.4 Hz, 2 H), 7.72 (d, J=8.4 Hz, 2 H)

Step D: 3-Methyl-1-(4-methylbenzenesulphonyl)-1H-pyrrole-2-carbonitrile

Aluminium chloride (19.4 g, 0.15 mol) is added all at once to a solution of 3-methyl-1-(4-methylbenzenesulphonyl)-1H-pyrrole (13.0 g, 55.3 mmol) in 1,2-dichloroethane (230 mL) at ambient temperature. After stirring for 20 minutes, cyanogen bromide (11.11 g, 0.10 mol) is added in portions over a period of 20 minutes. After 4.5 hours, an additional amount of cyanogen bromide (1.94 g, 18.3 mmol) is added. After stirring for 17 hours at ambient temperature, the reaction mixture is poured slowly into a mixture of dichloromethane (300 mL) and water (600 mL) cooled to 0° C. The resulting mixture is stirred for 1 hour. Subsequently the phases are separated and the aqueous phase is extracted with dichloromethane (3×150 mL). The combined organic phases are washed with water (2×150 mL) and brine (150 mL). The organic phase is dried over Na₂SO₄, filtered and concentrated in vacuo to obtain the expected compound in the form of a solid.

¹H NMR (400 MHz, CDCl₃) δ ppm: 2.18 (s, 3 H), 2.43 (s, 3 H), 6.17 (d, J=3.2 Hz, 1 H), 7.33-7.39 (m, 3 H), 7.90 (d, J=8.5 Hz, 2 H)

Step E: 4-Bromo-3-methyl-1-(4-methylbenzenesulphonyl)-1H-pyrrole-2-carbonitrile

N-Bromosuccinimide (12.0 g, 67.4 mmol) is added all at once to a suspension of 3-methyl-1-(4-methylbenzenesulphonyl)-1H-pyrrole-2-carbonitrile (14.45 g, 55.6 mmol) in N,N-dimethylformamide (60 mL) at ambient temperature. The mixture is stirred at ambient temperature for 29 hours and is then cooled in an ice bath. Saturated aqueous sodium bisulphite solution (90 mL), water (90 mL) and ethyl acetate (250 mL) are then added. The phases are separated, and then the aqueous phase is extracted with ethyl acetate (2×70 mL). The combined organic phases are washed with 5% aqueous potassium bicarbonate solution (90 mL), water (3×90 mL), and then brine (3×90 mL). The organic phase is dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product is purified by chromatography over silica gel using toluene and heptane as eluants to obtain the expected compound in the form of a solid.

¹H NMR (400 MHz, CDCl₃) δ ppm: 2.13 (s, 3 H), 2.45 (s, 3 H), 7.38 (d, J=8.4 Hz, 2H), 7.43 (s, 1 H), 7.92 (d, J=8.4 Hz, 2H)

Step F: 4-Bromo-1,3-dimethyl-1H-pyrrole-2-carbonitrile

Potassium hydroxide (3.65 g, 65.1 mmol) is added all at once to a suspension of 4-bromo-3-methyl-1-(4-methylbenzenesulphonyl)-1H-pyrrole-2-carbonitrile (4.66 g, 13.7 mmol) in methanol (95 mL) cooled using an ice bath. After 15 minutes, the suspension is stirred at ambient temperature for 17 hours. The methanol is evaporated to dryness. The evaporation residue is taken up in MTBE (25 mL) and washed with water (25 mL). The aqueous phase is extracted with MTBE (2×25 mL). The combined organic phases are dried over Na₂SO₄, filtered and concentrated in vacuo. The residue obtained is dissolved in tetrahydrofuran (50 mL) and the solution is cooled using an ice bath. NaH (60% in oil) (1.02 g, 25.5 mmol) is added. After 10 minutes, iodomethane (2.4 mL, 38.6 mmol) is also added. The mixture is stirred at ambient temperature for 1.5 hours. The tetrahydrofuran is evaporated to dryness. The residue is taken up in dichloromethane and washed with water. The aqueous phase is extracted with dichloromethane. The combined organic phases are dried over Na₂SO₄, filtered and concentrated in vacuo to obtain the expected compound in the form of a solid.

¹H NMR (400 MHz, CDCl₃) δ ppm: 2.16 (s, 3 H), 3.71 (s, 3 H), 6.74 (s, 1 H)

Step G: 4-({4-[(tert-Butyldimethylsilyl)oxy]phenyl}amino)-1,3-dimethyl-1H-pyrrole-2-carbonitrile

4-Bromo-1,3-dimethyl-1H-pyrrole-2-carbonitrile (2.03 g, 10.2 mmol) and 4-[(tert-butyldimethylsilyl)oxy]aniline (3.41 g, 15.3 mmol) are dissolved in toluene (40 mL). The solution is degassed with nitrogen for 10 minutes. Sodium tert-butyrate (1.18 g, 12.2 mmol), 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl (0.17 g, 0.41 mmol) and tris(dibenzylideneacetone)dipalladium(0) (0.187 g, 0.2 mmol) are then added. The mixture is heated at 100° C. for 30 minutes and then cooled to ambient temperature. Water (50 mL) and Celite (6 g) are added. The suspension is filtered over Celite, and the filtrate is diluted with MTBE. The phases are separated and the aqueous phase is extracted with MTBE (2×50 mL). The combined organic phases are dried over Na₂SO₄ and filtered. The residue is purified by chromatography over silica gel using ethyl acetate and heptane as eluants followed by reverse-phase chromatography using methanol and water as eluants. The product obtained is lyophilised to provide the expected compound in the form of a solid.

¹H NMR (400 MHz, CDCl₃) δ ppm: 0.15 (s, 6 H), 0.98 (s, 9 H), 2.05 (s, 3 H), 3.70 (s, 3 H), 4.69 (br. s, 1 H), 6.55-6.57 (m, 2 H), 6.64-6.69 (m, 3 H)

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^{13}C NMR (100 MHz, CDCl_3) δ ppm: -4.37, 9.42, 18.27, 25.84, 35.50, 102.59, 113.77, 115.13, 120.72, 121.91, 126.77, 126.94, 140.98, 148.39

PREPARATION 38"

4-[(4-{[tert-Butyl(dimethyl)silyl]oxy}phenyl)amino]-1-ethyl-5-methyl-1H-pyrrole-2-carbonitrile

The procedure is in accordance with the process of Preparation 33", replacing the iodomethane- d_3 in Step B by iodoethane.

^1H NMR (400 MHz, $\text{dms}\text{-d}_6$) δ ppm: 6.85 (s, 1 H), 6.75 (s, 1 H), 6.6/6.5 (2d, 4 H), 4 (quad, 2 H), 2.1 (s, 3 H), 1.3 (s, 3 H), 0.9 (s, 9 H), 0.1 (s, 6 H)

PREPARATION 39"

N-[4-[tert-Butyl(dimethyl)silyl]oxyphenyl]-2-ethoxy-pyrimidin-5-amine

Step A: 5-Bromo-2-ethoxy-pyrimidine

5-Bromo-2-chloro-pyrimidine (5.0 g, 25 mmol) is dissolved in ethanol (55 mL) and sodium ethylate (1.81 g, 26.6 mmol) is added in portions. The reaction mixture is stirred for 15 hours at ambient temperature. When the reaction is complete, the solvent is evaporated off, water (200 mL) is added, and then the reaction mixture is extracted with dichloromethane (2x100 mL). The organic phase is dried over Na_2SO_4 , and then evaporated to dryness to yield 5-bromo-2-ethoxy-pyrimidine.

Step B: N-[4-[tert-Butyl(dimethyl)silyl]oxyphenyl]-2-ethoxy-pyrimidin-5-amine

4-[tert-Butyl(dimethyl)silyl]oxyaniline (1.8 g, 8 mmol) and 5-bromo-2-ethoxy-pyrimidine (1.6 g, 8 mmol) dissolved in anhydrous tetrahydrofuran (30 mL) are stirred for 1 hour at ambient temperature in the presence of sodium tert-butyrate (4 mL, 2M solution in THF) and chloro(2-di-tert-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)-phenyl]palladium(II) (111 mg, 0.16 mmol). The reaction mixture is filtered over Celite and then evaporated to dryness. The residue is triturated in heptane to obtain the expected compound after filtration.

^1H NMR (500 MHz, $\text{dms}\text{-d}_6$, 300 K) δ ppm: 8.31 (s, 2H, pyrimidine-H), 7.80 (s, 1H, NH), 6.73 (d, 2H, Ar—H), 6.68 (d, 2H, Ar—H), 4.26 (q, 2H, CH_2CH_3), 1.31 (t, 3H, CH_2CH_3), 0.94 (s, 9H, 'Bu), 0.15 (s, 6H, Me)

IR: v: aromatic: 1504 cm^{-1} ; Si—C: 1247 cm^{-1} ; C—O—C: 1057 cm^{-1}

PREPARATION 40"

tert-Butyl 6-[(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)amino]-pyridin-3-yl carbonate

Step A: 6-Bromopyridin-3-yl tert-butyl carbonate

To a solution of 5 g of 6-bromopyridin-3-ol (28.7 mmol) and 7.53 g of di-tert-butyl dicarbonate (34.5 mmol) in 50 mL of tetrahydrofuran there is added 0.18 g of 4-dimethylaminopyridine (1.4 mmol). The mixture is stirred at ambient temperature for 6 hours and then concentrated. The residue obtained is dissolved in a mixture of ethyl ether and water. After separation of the phases, the separated-off organic phase is dried over MgSO_4 and concentrated to dryness. The title product is obtained in the form of a solid which is used in the next Step without being otherwise purified.

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^1H NMR (400 MHz, $\text{dms}\text{-d}_6$) δ ppm: 8.4 (s, 1 H), 7.71 (s, 2 H), 1.5 (s, 9 H)

Step B: tert-Butyl 6-[(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)amino]pyridin-3-yl carbonate

To a solution of 2.79 g of the compound obtained in Step A (10.2 mmol) in 15 mL of toluene and 15 mL of tetrahydrofuran there are added 1.18 g of sodium tert-butyrate (12.2 mmol), and then the batch is stirred under argon for 15 minutes. There is then added 0.35 g of palladium catalyst (0.5 mmol). The reaction mixture is then stirred at ambient temperature for 16 hours and then filtered. The filtrate is concentrated and taken up in a mixture of dichloromethane and water. The organic phase is separated off and then washed with water, dried over MgSO_4 , filtered and concentrated to dryness. The crude product thereby obtained is purified by chromatography over silica gel using dichloromethane and ethyl acetate as eluants. The residue is then taken up in a minimum of isopropyl ether. The solid then obtained is filtered off, washed with ether and then dried. The title product is obtained in the form of a solid, which is subsequently used without being otherwise purified.

^1H NMR (400 MHz, $\text{dms}\text{-d}_6$) δ ppm: 9 (s, 1 H), 8.35 (wd, 1 H), 8.3 (wd, 1 H), 8 (wd, 1H), 7.45 (dd, 1 H), 7.45 (wd, 1 H), 6.8 (d, 1 H), 6.4 (wd, 1 H), 3.8 (s, 3 H), 1.5 (s, 9 H)

PREPARATION 41"

3-[4-[tert-Butyl(dimethyl)silyl]oxyanilino]benzonitrile

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1H-pyrazole used in Step B by 3-bromobenzonitrile.

^1H NMR (400 MHz, $\text{dms}\text{-d}_6$) δ ppm: 8.3 (s, 1 H), 7.3 (t, 1 H), 7.2/7.1 (2 dd, 2 H), 7.15 (t, 1 H), 7.05 (d, 2 H), 6.8 (d, 2 H), 0.95 (s, 9 H), 0.2 (s, 6 H)

PREPARATION 42"

4-[4-[tert-Butyl(dimethyl)silyl]oxyanilino]thiophene-2-carbonitrile

The procedure is in accordance with the process of Preparation 1", replacing the 4-bromo-1-methyl-1H-pyrazole used in Step B by 4-bromothiophene-2-carbonitrile.

^1H NMR (400 MHz, $\text{dms}\text{-d}_6$) δ ppm: 8.35 (s, 1 H), 7.59 (wd, 1 H), 7.08 (wd, 1 H), 6.95 (d, 2 H), 6.75 (d, 2 H), 0.94 (s, 9 H), 0.16 (s, 6 H)

The amines NHR_3R_4 wherein R_3 and R_4 , each independently of the other, represent an aryl or heteroaryl group are obtained in accordance with processes described in the literature (Surry D. S. et al., *Chemical Science*, 2011, 2, 27-50, Charles M. D. et al., *Organic Letters*, 2005, 7, 3965-3968). The reaction protecting the hydroxy function of the 4-anilino-phenol described in Preparation 2" can be applied to various secondary amines NHR_3R_4 (as defined hereinbefore) having one or more hydroxy functions, when they are available commercially. Alternatively, the secondary amines having at least one hydroxy substituent may be synthesised directly in a protected form, i.e. starting from reagents whose hydroxy function has been protected beforehand. Among the protecting groups, tert-butyl(dimethyl)silyloxy and benzyloxy are especially preferred.

Among the amines NHR_3R_4 having a hydroxy substituent that are used for synthesising the compounds of the invention there may be mentioned: 4-(4-toluidino)phenol, 4-(4-chloroanilino)phenol, 4-(3-fluoro-4-methylanilino)phenol, 4-[4-

(trifluoromethoxy)anilino]-phenol, 4-[4-hydroxyanilino]phenol, 4-[(1-methyl-1H-indol-6-yl)amino]phenyl]-methanol, 4-(2,3-dihydro-1H-indol-6-ylamino)phenol, 4-[(1-methyl-2,3-dihydro-1H-indol-6-yl)amino]phenol, 4-[(1-methyl-1H-indol-6-yl)amino]phenol, 4-[(1-methyl-1H-indol-6-yl)amino]cyclohexanol, 4-[(1-methyl-1,2,3,4-tetrahydro-6-quinolyl)amino]phenol, 4-[(4-methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl)amino]phenol, 4-[4-(diethylamino)anilino]-phenol, 4-(2,3-dihydro-1H-inden-5-ylamino)phenol, 4-[(1-methyl-1H-indazol-5-yl)amino]phenol, 4-[(1'-methyl-1',2'-dihydrospiro[cyclopropane-1,3'-indol]-5'-yl)amino]phenol, 4-[(1,3,3-trimethyl-2,3-dihydro-1H-indol-5-yl)amino]phenol, 4-[4-methoxy-3-(trifluoromethyl)anilino]phenol, 4-[4-(methylsulphonyl)-3-(trifluoromethyl)anilino]phenol, 2-fluoro-4-[(1-methyl-1H-indol-5-yl)amino]phenol, 4-[(1-ethyl-1H-indol-5-yl)amino]phenol, 4-[(1-ethyl-2,3-dihydro-1H-indol-5-yl)amino]phenol, 4-[(1-isopropyl-2,3-dihydro-1H-indol-5-yl)amino]phenol, 4-(butylamino)phenol, 3-[(1-methyl-1H-indol-5-yl)amino]-1-propanol, 4-[(1-methyl-1H-indol-5-yl)amino]-1-butanol, 4-[(3-fluoro-4-methylphenyl)-amino]phenol, 4-[(3-chloro-4-methylphenyl)amino]phenol, 4-[(4-fluorophenyl)amino]-phenol, 4-[(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)amino]phenol, 4-[(4-fluorophenyl)-amino]phenol, 4-[(2-fluorophenyl)amino]phenol, 4-[(3-fluorophenyl)amino]phenol, 4-[(2,4-difluorophenyl)amino]phenol, 4-[(3,4-difluorophenyl)amino]phenol, 3-[(4-hydroxyphenyl)amino]benzonitrile, 4-[(3-methoxyphenyl)amino]phenol, 4-[(3,5-difluorophenyl)-amino]phenol, 4-[(3-methylphenyl)amino]phenol, 4-[(4-hydroxyphenyl)amino]benzonitrile, 4-[(3-chlorophenyl)amino]phenol, 4-(pyrimidin-2-ylamino)phenol, 4-[(cyclobutyl-methyl)amino]phenol, 2-[(4-hydroxyphenyl)amino]benzonitrile, 4-[[[(1-methyl-1H-pyrazol-4-yl)methyl]amino]phenol, 4-[(cyclopropylmethyl)amino]phenol, 4-[[[(1-methyl-1H-pyrazol-3-yl)methyl]amino]phenol, 4-(but-2-yn-1-ylamino)phenol, 4-(pyrazin-2-yl-amino)phenol, 4-(pyridin-2-ylamino)phenol, 4-(pyridazin-3-ylamino)phenol, 4-(pyrimidin-5-ylamino)phenol, 4-(pyridin-3-ylamino)phenol, 4-[(3,5-difluoro-4-methoxyphenyl)-amino]phenol, 4-(pyridin-4-ylamino)phenol, 4-[(3-fluoro-4-methoxyphenyl)amino]phenol, 2-(phenylamino)pyrimidin-5-ol, 5-[(4-hydroxyphenyl)amino]-2-methoxybenzonitrile, 4-[[3-(trifluoromethyl)phenyl]amino]phenol and 4-(methylamino)phenol.

The hydroxy function(s) of the secondary amines listed above is (are) protected beforehand by a suitable protecting group prior to any coupling to an acid derivative of the compound of formula (VII) as defined in the preceding general process.

PREPARATION I

tert-Butyl[2-(3-iodo-4-[[[(3R)-3-methyl-3,4-dihydroisquinolin-2(1H)-yl]carbonyl]phenyl]ethyl]carbamate

Step A: 4-[2-(tert-Butoxycarbonylamino)ethyl]benzoic acid tert-Butyl dicarbonate (1.64 g; 7.5 mmol) is dissolved in 1,4-dioxane (5 mL) and the solution is added to a well-stirred solution of 4-(2-aminoethyl)benzoic acid (1.0 g; 5 mmol) in 1M aqueous sodium hydroxide solution (25 mL) and 1,4-dioxane (10 mL), and the mixture is then stirred at ambient temperature for 3 hours. The 1,4-dioxane is removed by evaporation in vacuo, and then ethyl acetate (200 mL) is added to the residue. The pH of the aqueous phase is adjusted to 1.5 with 2M aqueous HCl solution. The organic phase is separated off and the aqueous phase is then extracted with

ethyl acetate (100 mL). The combined organic extracts are washed with water, dried over Na₂SO₄ and evaporated to a volume of 10 mL. Heptane is added to the residue and then the solid precipitate is filtered off to yield the title compound.

¹H NMR (500 MHz, dmsO-d₆, 300K): 12.81 (br s, 1H, COOH), 7.85 (m, 2H, Ar-2' and 6'H), 7.31 (m, 2H, Ar-3' and 5'H), 6.91 and 6.51 (2×br s, 1H, NH), 3.16 (m, 2H, CH₂), 2.75 (t, 2H, CH₂), 1.35 and 1.31 (2×br s, 9H, Bu^t); ¹³C NMR (125 MHz, dmsO-d₆, 300 K): 167.8 (q), 156.0 (CH), 145.3 (q), 129.8 (2×CH), 129.3 (2×CH), 129.1 (q), 78.0 (q), 41.5 (CH₂), 35.9 (CH₂), 28.7 (CH₃)

Step B: 4-[2-(tert-Butoxycarbonylamino)ethyl]-2-iodo-benzoic acid

The compound of the above Step (0.88 g; 3.31 mmol), iodobenzene diacetate (1.07 g; 3.31 mmol), tetrabutylammonium iodide (1.22 g; 3.31 mmol), iodine (0.84 g; 3.31 mmol) and diacetoxypalladium (0.04 g; 0.165 mmol) are dissolved in 1,2-dichloroethane (8 mL), and the mixture is then heated in a microwave reactor at 80° C. for 90 minutes. The cooled mixture is partitioned between saturated aqueous Na₂CO₃ solution (30 mL) and the original solvent. The organic phase is separated off and the aqueous residue is extracted with diethyl ether (2×15 mL). The pH of the resulting aqueous solution is adjusted to 2 with 2M aqueous HCl solution and the product is then extracted with ethyl acetate (2×75 mL). The organic phase is dried over Na₂SO₄ and evaporated. The crude product is purified by chromatography over silica gel to yield the mixture of regioisomers, which are separated by preparative HPLC using water-TFA and acetonitrile as eluants. The pH of the appropriate combined fractions is adjusted to 5 with NaHCO₃, and then the acetonitrile is evaporated off under reduced pressure. The precipitate is recovered by filtration and then dried to yield the title compound.

¹H NMR (500 MHz, dmsO-d₆, 300K): 13.16 (broad s, 1H, COOH), 7.81 (s, 1H, Ar-3'H), 7.66 (d, 1H, Ar-6'H), 7.29 (d, 1H, Ar-5'H), 6.89 (t, 1H, NH), 3.14 (t, 1H, CH₂), 2.69 (t, 1H, CH₂), 1.35 (s, 9H, Boc)

Step C: tert-Butyl[2-(3-iodo-4-[[[(3R)-3-methyl-3,4-dihydroisquinolin-2(1H)-yl]carbonyl]phenyl]ethyl]carbamate

The compound of the above Step (0.714 g; 1.82 mmol), TBTU (0.73 g; 2.28 mmol), N-ethyl-N-isopropyl-propan-2-amine (0.94 mL; 5.46 mmol) and N,N-dimethylpyridin-4-amine (22 mg) are stirred in dichloromethane (20 mL) for 5 minutes, and then (3R)-3-methyl-1,2,3,4-tetrahydroisquinoline (0.282 g; 1.92 mmol) (cf Preparation I') is added. The mixture is stirred for three more hours. The reaction mixture is diluted with dichloromethane (150 mL) and then washed with water (25 mL), dried over Na₂SO₄ and evaporated. The crude product is purified by chromatography over silica gel using dichloromethane and methanol as eluants to yield the title compound.

High-resolution mass spectrometry (ESI+):

Empirical formula: C₂₄H₂₉IN₂O₃

[M+H]⁺ calculated: 521.1303

[M+H]⁺ measured: 521.1282

IR: ν: C—H: 2931 cm⁻¹; >C=O: 1706, 1627 cm⁻¹; amide: 1505 cm⁻¹; C—O—C: 1248, 1166 cm⁻¹

PREPARATION II

tert-Butyl (4-Iodo-3-[[[(3R)-3-methyl-3,4-dihydroisquinolin-2(1H)-yl]carbonyl]benzyl]carbamate

Step A: 2-Iodo-5-methyl-benzoic acid

3-Methylbenzoic acid (6.12 g; 45 mmol), iodobenzene diacetate (14.49 g; 45 mmol), tetrabutylammonium iodide (16.62 g; 45 mmol), iodine (11.43 g; 45 mmol) and diacetoxypalladium (0.5 g; 2.2 mmol) are dissolved in 1,2-dichloroethane, and then the mixture is heated in a sealed tube at 85° C.

for 1 hour and 45 minutes. The cooled solution is purified by chromatography over silica gel using dichloromethane and methanol as eluants to yield the title compound.

Step B: Methyl 2-iodo-5-methyl-benzoate

The compound of the above Step (6.25 g, 23.9 mmol) is dissolved in anhydrous methanol (100 mL), and then SOCl_2 (3.6 mL, 49 mmol) is added dropwise to the well-stirred solution. The solution is refluxed for 18 hours and then evaporated to a volume of 25 mL and then poured into crushed ice (100 g). The resulting mixture is extracted with diethyl ether (2x75 mL). The organic phase is washed with saturated aqueous NaHCO_3 solution and then brine, dried over Na_2SO_4 and evaporated to dryness to yield the title compound.

Step C: Methyl 5-(bromomethyl)-2-iodo-benzoate

The compound of the above Step (5.7 g, 20.7 mmol), N-bromo-succinimide (3.67 g, 20.7 mmol) and dibenzoyl peroxide (0.24 g, 1 mmol) are dissolved in carbon tetrachloride (40 mL) and then refluxed for 5 hours. New portions of N-bromosuccinimide (1.0 g, 5.6 mmol) and dibenzoyl peroxide (0.05 g, 0.2 mmol) are then added and heating is continued for 4 more hours. The reaction mixture is cooled to ambient temperature. The insoluble parts are removed by filtration, and the concentrated filtrate is then purified by chromatography over silica gel using heptane and ethyl acetate as eluants to yield the title compound.

Step D: Methyl 5-(aminomethyl)-2-iodo-benzoate

The compound of the above Step (0.53 g, 1.5 mmol) is dissolved in 7M methanolic ammonia (20 mL) and then stirred at ambient temperature for 1 hour. The solution is evaporated to dryness to yield the title compound, which was used in the next Step without purification.

Step E: 5-[(tert-Butoxycarbonylamino)methyl]-2-iodo-benzoic acid

Methyl 5-(aminomethyl)-2-iodo-benzoate hydrobromide (0.56 g, 1.5 mmol) was dissolved in pyridine (10 mL), then di-tert-butyl dicarbonate (0.80 g, 3.6 mmol) is added and the mixture is stirred at ambient temperature for 30 minutes and then evaporated to dryness. The residue is redissolved in methanol (10 mL), and then 2M aqueous NaOH solution (3 mL) and 2 mL of water are added. The resulting solution is stirred for 2 hours at 50° C., then diluted with water (20 mL), and the methanol is evaporated off under reduced pressure. The pH of the resulting aqueous solution is adjusted to 3 with 2M aqueous HCl solution; the product is then extracted with ethyl acetate. The organic phase is washed with brine, and then dried over Na_2SO_4 and evaporated to dryness. The crude product is triturated with DCM. The solid formed is recovered by filtration to yield the title compound.

^1H NMR (500 MHz, dmsO-d_6 , 300 K): 13.24 (broad s, 1H, COOH), 7.91 (d, 1H, Ar-3'H), 7.58 (d, 1H, Ar-6'H), 7.47 (t, 1H, NH), 7.09 (d, 1H, (Ar-5'H), 4.09 (d, 2H, CH_2), 1.38 (s, 9H, Boc); ^{13}C NMR (125 MHz, dmsO-d_6 , 300K): 168.6 (q), 156.3 (q), 141.1 (q), 140.9 (CH), 137.1 (q), 131.6 (CH), 129.1 (CH), 92.2 (q), 78.5 (q), 28.7 (CH_3)

Step F: tert-Butyl (4-iodo-3-[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl)-benzyl)carbamate

The compound of the above Step (1.62 g, 4.3 mmol), TBTU (2.76 g, 8.59 mmol), N-ethyl-N-isopropyl-propan-2-amine (1.48 mL, 8.59 mmol) and N,N-dimethylpyridin-4-amine (10 mg) are stirred in DCM (50 mL) for 5 minutes; (3R)-3-methyl-1,2,3,4-tetrahydroisoquinoline (0.76 g, 5.15 mmol) (cf Preparation 1') is then added and the mixture is stirred for 15 minutes more. The insoluble parts are removed by filtration, and then the concentrated filtrate is purified by chromatography over silica gel using dichloromethane and methanol as eluants to yield the title compound.

PREPARATION III

tert-Butyl (3-bromo-4-[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl)benzyl)carbamate

Step A: Methyl 4-(aminomethyl)-2-bromo-benzoate

A solution of methyl 2-bromo-4-(bromomethyl)benzoate (4.57 g, 14.84 mmol) in 50 mL of methanol is added dropwise to a well-stirred solution of ammonia in methanol (7M; 315 mL) at ambient temperature, and the solution is then stirred for 3 hours. All the solvents are evaporated off and the residue is purified by chromatography over silica gel using dichloromethane-methanol as eluants to yield the title compound.

Step B: 2-Bromo-4-[(tert-butoxycarbonylamino)methyl]benzoic acid

The compound of the above Step (4.04 g, 16.6 mmol) is dissolved in pyridine (55 mL) and then di-tert-butyl dicarbonate (5.43 g, 24.9 mmol) is added and the mixture is stirred at ambient temperature for 16 hours; it is then evaporated to dryness. The residue is redissolved in methanol (100 mL), and then 1M aqueous NaOH solution (54 mL) is added. The resulting solution is stirred for 1.5 hours at 50° C. and is then allowed to cool to ambient temperature. The pH of the solution is adjusted to 7 using 2M aqueous HCl solution; the methanol is then evaporated off under reduced pressure. The resulting aqueous solution is diluted with water (50 mL), and then the pH is adjusted to 3 using 2M aqueous HCl solution. The product is extracted with dichloromethane (2x100 mL). The organic phase is washed with brine, then dried over Na_2SO_4 and evaporated to dryness to yield the title compound which is used in the next Step without purification.

IR: ν : N—H: 3359 cm^{-1} ; C—H: 2983 cm^{-1} ; >C=O: 1685, 1603 cm^{-1} ; amide: 1519 cm^{-1} ; C—O—C: 1248, 1162, 1057 cm^{-1}

Step C: tert-Butyl (3-bromo-4-[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl)benzyl)carbamate

The compound of the above Step (3.7 g, 11.2 mmol), TBTU (7.19 g, 22.4 mmol), N-ethyl-N-isopropyl-propan-2-amine (3.86 mL, 22.4 mmol) and N,N-dimethylpyridin-4-amine (48 mg) are stirred in dichloromethane (100 mL) for 5 minutes, and then (3R)-3-methyl-1,2,3,4-tetrahydroisoquinoline (1.98 g, 13.44 mmol) (cf. Preparation 1') is added, and the mixture is stirred for 1 hour more. The insoluble parts are removed by filtration, and then the concentrated filtrate is purified by chromatography over silica gel using dichloromethane and methanol as eluants to yield the title compound.

High-resolution mass spectrometry (ESI+):

Empirical formula: $\text{C}_{23}\text{H}_{27}\text{BrN}_2\text{O}_3$

[M+H]⁺ calculated: 459.1285

[M+H]⁺ measured: 459.1282

^1H NMR (500 MHz, dmsO-d_6 , 300K, presence of amide rotamers): 7.66-6.87 (m, 7H, aromatic), 5.34 and 4.12 (d, 2H, CH_2 -isoquinoline), 5.02 and 4.97 and 3.87 and 3.83 (m, 1H, CH_2 -isoquinoline), 4.17 (d, 2H, CH_2 -benzyl), 3.18-2.48 (m, 1H, CH_2 -isoquinoline), 1.16 and 1.14 and 1.10 and 0.98 (d, 3H, isoquinoline CH_3), 1.31 and 1.41 (s, 9H, Boc).

EXAMPLE 1

5-(5-Chloro-2-[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl)phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

Step A: Ethyl 5-(5-chloro-2-[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl)phenyl)-1,2-dimethyl-1H-pyrrole-3-carboxylate

To a solution of 1.4 g of the compound obtained in Preparation 1 (4.35 mmol) in 50 mL of dichloromethane there are

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successively added 0.7 g of the compound obtained in Preparation 1' (4.79 mmol), 0.7 g of HOBt (5.22 mmol), 0.81 g of EDC (5.22 mmol) and 1.6 mL of triethylamine (21.7 mmol). The batch is then stirred overnight at ambient temperature. The reaction mixture is then diluted with dichloromethane and washed 3 times with saturated aqueous NaHCO₃ solution. The organic phase is then dried over MgSO₄, filtered, concentrated to dryness, and then purified by chromatography over silica gel using dichloromethane and methanol as eluants.

¹H NMR: δ (500 MHz; dmsd-d₆; 300K): 7.6-7.3 (m, 3H, aromatic Hs, 4-chlorophenyl); 7.2-6.85 (m, 4H, aromatic Hs, tetrahydroisoquinoline); 6.45-6.3 (m, 1H, H pyrrole); 5.0-4.8-3.8 (m, 1H, aliphatic H, tetrahydroisoquinoline); 5.3-3.75 (dd, 2H, aliphatic Hs tetrahydroisoquinoline); 4.2-4.0 (m, 2H, OCH₂CH₃); 3.25 (s, 3H, CH₃-N-pyrrole); 3.0-2.2 (m, 2H, aliphatic Hs, tetrahydroisoquinoline); 2.5 (s, 3H, CH₃-pyrrole); 1.25 (t, 3H, OCH₂CH₃); 1.05 (d, 3H, tetrahydroisoquinoline-CH₃)

IR: ν: >C=O: 1693 cm⁻¹ ester; ν: >C=O: 1625 cm⁻¹ amide

Step B: 5-(5-Chloro-2-[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-phenyl)-1,2-dimethyl-1H-pyrrole-3-carboxylic acid

To a solution of 1.7 g of the compound obtained in Step A (3.77 mmol) in 5 mL of dioxane there is added 0.317 g of LiOH (7.5 mmol) dissolved in 5 mL of water. The batch is heated in a microwave apparatus for 4 hours at 100° C. (power 140 W). The reaction mixture is then filtered and concentrated to dryness. The residue thereby obtained is taken up in dichloromethane (50 mL) and then saturated aqueous NH₄Cl solution is added thereto. The organic phase is washed with water and then with brine, dried over MgSO₄, filtered and concentrated to dryness. The title product is obtained in the form of a solid and is used directly in the next Step.

¹H NMR: δ (500 MHz; dmsd-d₆; 300K): 11.05 (broad s, 1H, COOH), 7.5-7.2 (m, 3H, aromatic Hs, 4-chlorophenyl); 7.2-6.9 (m, 4H, aromatic Hs, tetrahydroisoquinoline); 6.45-6.2 (m, 1H, aliphatic H, H pyrrole); 5.3-3.75 (dd, 2H, aliphatic Hs, tetrahydroisoquinoline); 5.0-4.8-3.8 (m, 1H, aliphatic H, tetrahydroisoquinoline); 3.5-3.2 (s, 3H, CH₃-N-pyrrole); 3.0-2.1 (aliphatic Hs, CH₃-tetraisoquinoline); 2.5-2.4-1.98 (m, 3H, CH₃-pyrrole); 1.05-0.52 (m, 3H, aliphatic Hs, CH₃-tetraisoquinoline)

IR: ν: —OH: 3500-2000 cm⁻¹ carboxylic acid; ν: >C=O: 1699+1658 cm⁻¹ carboxylic acid; ν: >C=N—: 1625 cm⁻¹ amide

Step C: N-(4-[[tert-Butyl(dimethyl)silyl]oxy]phenyl)-5-(5-chloro-2-[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

To a solution of 0.65 g of the compound obtained in Step B (1.54 mmol) in 15 mL of dichloroethane there is added, dropwise, 0.244 mL of 1-chloro-N,N,2-trimethyl-prop-1-en-1-amine. The reaction mixture is stirred at ambient temperature for 1 hour, and there are then added 0.56 g of the compound of Preparation 1" (1.84 mmol), 10 mL of dichloroethane and 0.376 g of 4-dimethylaminopyridine (DMAP) (3.07 mmol). The batch is stirred at 110° C. overnight. The reaction mixture is concentrated, dissolved in dichloromethane and washed with saturated aqueous NaHCO₃ solution. The title product is obtained in the form of an oil and is used directly in the next Step.

Step D: 5-(5-Chloro-2-[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

To a solution of 0.8 g of the compound obtained in Step C (1.03 mmol) in 2 mL of methanol, there are added 1.55 mL of

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a 1M solution of potassium hydroxide in methanol (1.55 mmol). The batch is stirred at ambient temperature for 30 minutes. The reaction mixture is then diluted with dichloromethane and successively washed with 1M aqueous HCl solution, saturated aqueous NaHCO₃ solution and then brine until neutral. The organic phase is then dried over MgSO₄, filtered and evaporated. The crude product thereby obtained is purified by chromatography over silica gel using dichloromethane and methanol as eluants. The solid thereby obtained is dissolved in a mixture of water/acetonitrile until dissolution is complete, filtered and then lyophilised.

Elemental microanalysis: (% theoretical:measured)

% C=68.74:68.25; % H=5.43:5.69; % N=11.79:11.66; % Cl=5.97:5.95

High-resolution mass spectrometry (ESI+):

Empirical formula: C₃₄H₃₂ClN₅O₃

[M+H]⁺ calculated: 594.2266

[M+H]⁺ measured: 594.2289

EXAMPLE 2

5-(2-[(3S)-3-(Aminomethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-1-methyl-N,N-diphenyl-1H-pyrrole-3-carboxamide

Step A: tert-Butyl [(3S)-2-{2-[4-(diphenylcarbamoyl)-1-methyl-1H-pyrrol-2-yl]benzoyl}-1,2,3,4-tetrahydroisoquinolin-3-yl]methyl]carbamate

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 2 and tert-butyl [(3S)-1,2,3,4-tetrahydroisoquinolin-3-ylmethyl]carbamate (see Preparation 2') in Step A, and N-phenylaniline in Step C.

Step B: 5-(2-[(3S)-3-(Aminomethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-1-methyl-N,N-diphenyl-1H-pyrrole-3-carboxamide

A solution of the NH-Boc compound of Step A in dichloromethane is placed at 0° C. 10 molar equivalents of trifluoroacetic acid are added thereto dropwise. The batch is stirred at ambient temperature for 4 hours until the starting material has disappeared completely. The reaction mixture is then concentrated to dryness, taken up again and co-evaporated twice with toluene, then taken up in a mixture of acetonitrile/H₂O and finally lyophilised. The title product is then obtained after a neutralisation step.

Elemental microanalysis: (% theoretical:measured)

% C=77.75:77.27; % H=5.97:5.73; % N=10.36:10.44

EXAMPLE 3

5-(5-Chloro-2-[(3S)-3-[(4-methylpiperazin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(4-hydroxyphenyl)-N-(1H-indol-5-yl)-1-methyl-1H-pyrrole-3-carboxamide

Step A: tert-Butyl 5-[(4-[[tert-butyl(dimethyl)silyl]oxy]phenyl){5-(5-chloro-2-[(3S)-3-[(4-methylpiperazin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-1-methyl-1H-pyrrol-3-yl]carbonyl]amino]-1H-indole-1-carboxylate

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 3 and (3S)-3-[(4-methyl-1-piperazinyl)methyl]-1,2,3,4-tetrahydroisoquinoline (see Preparation 4') in Step A, and the compound of Preparation 3" in Step C.

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Step B: 5-(5-Chloro-2-[[[(3S)-3-[(4-methylpiperazin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl]-N-(4-hydroxyphenyl)-N-(1H-indol-5-yl)-1-methyl-1H-pyrrole-3-carboxamide

To a solution of 455 mg (0.49 mmol) of the product obtained in Step A in 5 mL of methanol there are added 135 mg (2.5 mmol) of KOH. After stirring for 3 hours at ambient temperature, the reaction mixture is concentrated, treated with saturated aqueous NaHCO₃ solution and extracted with methylene chloride. The organic phase is then dried over MgSO₄, filtered and evaporated to dryness. The crude product thereby obtained is then purified by chromatography over silica gel using dichloromethane and methanol as eluants to yield the expected product in the form of a foam.

Elemental microanalysis: (% theoretical:measured)

% C=70.72:68.54; % H=5.79:5.37; % N=11.78:11.41; % Cl=4.97:4.79

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₂H₄₁ClN₆O₃

[M+H]⁺ calculated: 713.3007

[M+H]⁺ measured: 713.2973

EXAMPLE 4

N-(4-Hydroxyphenyl)-N-(1H-indol-5-yl)-1-methyl-5-(6-[[[(3S)-3-[(4-methylpiperazin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 3 using the compound of Preparation 4 in Step A.

Elemental microanalysis: (% theoretical:measured)

% C=71.45:69.32; % H=5.86:5.22; % N=11.63:11.08

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₃H₄₂N₆O₅

[M+H]⁺ calculated: 723.3295

[M+H]⁺ measured: 723.3262

Unless otherwise mentioned, the compounds of the following Examples are synthesised in accordance with the process of Example 1 using, in Step A: (i) the appropriate acid obtained according to one of Preparations 1 to 32 and (ii) the appropriate tetrahydroisoquinoline compound obtained according to one of Preparations 1' to 9' and, in Step C: (iii) the suitable NHR₃R₄ amine (a non-exhaustive list is proposed in Preparations 1" to 42"). The compounds thereby obtained are optionally subjected to a step of conversion into salt form in the presence of HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the hydrochloride of the expected compound is obtained.

EXAMPLE 5

5-(5-Chloro-2-[[[(3S)-3-[(4-methylpiperazin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl]-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-indol-5-yl)-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% theoretical:measured)

% C=64.54:64.9; % H=5.67:5.49; % N=10.5:10.4; % Cl=13.29:12.52; % Cl—=8.86:7.39

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EXAMPLE 6

5-(5-Chloro-2-[[[(3S)-3-[(4-methylpiperazin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl]-1-ethyl-N-(4-hydroxyphenyl)-N-(1-methyl-1H-indol-5-yl)-1H-pyrrole-3-carboxamide

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₄H₄₅ClN₆O₃

[M+H]⁺ calculated: 741.3320

[M+H]⁺ measured: 741.3326

EXAMPLE 7

5-(5-Chloro-2-[[[(3S)-3-[(4-methylpiperazin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl]-1-cyclopropyl-N-(4-hydroxyphenyl)-N-(1-methyl-1H-indol-5-yl)-1H-pyrrole-3-carboxamide

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₅H₄₅ClN₆O₃

[M+H]⁺ calculated: 753.3320

[M+H]⁺ measured: 753.3306

EXAMPLE 8

5-(5-Chloro-2-[[[(3S)-3-[(4-methylpiperazin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl]-N-(4-hydroxyphenyl)-N-((1-methyl-1H-indol-5-yl)-1-(propan-2-yl)-1H-pyrrole-3-carboxamide

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₅H₄₇ClN₆O₃

[M+H]⁺ calculated: 755.3476

[M+H]⁺ measured: 755.3466

EXAMPLE 9

N-(4-Hydroxyphenyl)-1-methyl-N-(1-methyl-1H-indol-5-yl)-5-(6-[[[(3S)-3-[(4-methylpiperazin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% theoretical:measured)

% C=65.26:65.8; % H=5.73:5.47; % N=10.38:10.48; % Cl=8.76:8.46; % Cl—=8.76:8.02

EXAMPLE 10

5-(5-Fluoro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl]-N-(4-hydroxyphenyl)-1,2-dimethyl-N-phenyl-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% theoretical:measured)

% C=69.11:68.56; % H=5.8:5.31; % N=8.06:8.13; % Cl—=5.1:4.68

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EXAMPLE 11

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-(3-hydroxypropyl)-2-methyl-N-phenyl-1H-pyrrole-3-carboxamide hydrochloride

Step A: 1-[3-(Benzyloxy)propyl]-5-(5-fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-phenyl-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 10 and the compound of Preparation 3' in Step A, and the compound of Preparation 2" in Step C.

Step B: 5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-(3-hydroxypropyl)-2-methyl-N-phenyl-1H-pyrrole-3-carboxamide hydrochloride

The compound of Step A is subjected to a deprotection reaction in accordance with a protocol analogous to that described in Step B of Example 23.

Elemental microanalysis: (% , theoretical:measured)

% C=68.24:67.96; % H=6.5:7.9; % N=7.58:7.61; % Cl=4.8:4.75

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₂H₄₃FN₄O₅

[M+H]⁺ calculated: 703.3296

[M+H]⁺ measured: 703.33294

EXAMPLE 12

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-indazol-5-yl)-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% , theoretical:measured)

% C=67.33:67.39; % H=5.65:5.18; % N=11.22:11.52; % Cl=4.73:3.82

EXAMPLE 13

N-(3-Fluoro-4-methylphenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-5-(6-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% , theoretical:measured)

% C=66.97:66.72; % H=5.62:5.21; % N=7.44:7.59; % Cl=4.71:4.54

EXAMPLE 14

N-(4-Hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-indazol-5-yl)-5-(6-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% , theoretical:measured)

% C=66.62:66.59; % H=5.59:4.67; % N=10.84:10.85; % Cl=4.57:4.24

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EXAMPLE 15

N-(4-Hydroxyphenyl)-1,2-dimethyl-5-(6-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-phenyl-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% , theoretical:measured)

% C=68.28:67.07; % H=5.73:5.09; % N=7.77:7.75; %

Cl=4.92:5.71

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₁H₄₀N₄O₆

[M+H]⁺ calculated: 685.3026

[M+H]⁺ measured: 685.3033

EXAMPLE 16

N-(3-Fluorophenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-5-(6-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% , theoretical:measured)

% C=66.62:66.11; % H=5.45:5.2; % N=7.58:7.89; % Cl=4.8:5.59

EXAMPLE 17

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-phenyl-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% , theoretical:measured)

% C=67.51:66.91; % H=5.66:5.05; % N=7.87:7.88; % Cl=4.98:5.75

EXAMPLE 18

1-(2-Hydroxyethyl)-N-(4-hydroxyphenyl)-2-methyl-5-(6-{[(3S)-3-[2-(morpholin-4-yl)ethyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-phenyl-1H-pyrrole-3-carboxamide hydrochloride

Step A: 1-[2-(Benzyloxy)ethyl]-N-[4-(benzyloxy)phenyl]-2-methyl-5-(6-{[(3S)-3-[2-(morpholin-4-yl)ethyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-phenyl-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 9 and (3S)-3-[2-(morpholin-4-yl)ethyl]-1,2,3,4-tetrahydroisoquinoline (see Preparation 5') in Step A, and 4-(benzyloxy)-N-phenylaniline (see Preparation 8") in Step C.

Step B: 1-(2-Hydroxyethyl)-N-(4-hydroxyphenyl)-2-methyl-5-(6-{[(3S)-3-[2-(morpholin-4-yl)ethyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-phenyl-1H-pyrrole-3-carboxamide hydrochloride

The compound of Step A is subjected to a deprotection reaction in accordance with a protocol analogous to that described in Step B of Example 23.

High-resolution mass spectrometry (ESI+):

Empirical formula: C₃₈H₄₀N₆O₅

[M+H]⁺ calculated: 729.3283

[M+H]⁺ measured: 729.3282

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EXAMPLE 19

N-(4-Hydroxyphenyl)-5-(5-methoxy-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-1,2-dimethyl-N-phenyl-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% , theoretical:measured)
% C=69.63:69.45; % H=6.13:5.94; % N=7.92:7.79; % Cl=5.01:4.58

EXAMPLE 20

N-(4-Hydroxyphenyl)-5-(5-methoxy-2-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-1,2-dimethyl-N-(pyridin-4-yl)-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% , theoretical:measured)
% C=69.39:69.66; % H=5.66:5.46; % N=8.99:8.92; % Cl=5.69:5.29

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{36}H_{35}N_4O_4$

[M+H]⁺ calculated: 587.2653

[M+H]⁺ measured: 587.2649

EXAMPLE 21

N-(4-Hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-5-(7-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-2,3-dihydro-1,4-benzodioxin-6-yl]-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% , theoretical:measured)
% C=64.99:64.67; % H=5.86:5.67; % N=11.37:11.27; % Cl=4.8:4.71

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{40}H_{43}N_6O_6$

[M+H]⁺ calculated: 703.3236

[M+H]⁺ measured: 703.3239

EXAMPLE 22

N-(4-Hydroxyphenyl)-1,2-dimethyl-5-(7-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-2,3-dihydro-1,4-benzodioxin-6-yl]-N-phenyl-1H-pyrrole-3-carboxamide hydrochloride

% C=68.61:67.97; % H=5.89:5.59; % N=7.62:7.55; % Cl=4.82:4.27

EXAMPLE 23

1-(2-Hydroxyethyl)-N-(4-hydroxyphenyl)-2-methyl-5-(6-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

Step A: 1-[2-(Benzyloxy)ethyl]-N-(4-[[tert-butyl(dimethyl)silyl]oxy]phenyl)-2-methyl-5-(6-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 9 and the compound of Preparation 1" in Step C.

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Step B: N-(4-[[tert-Butyl(dimethyl)silyl]oxy]phenyl)-1-(2-hydroxyethyl)-2-methyl-5-(6-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

To a solution of 6.86 g (8.19 mmol) of the compound of Step A in 70 mL of anhydrous methanol there are added 1.37 g of Pd/C 10%. The batch is degassed for 0.5 hours and then stirred at ambient temperature under dihydrogen pressure (1.5 bar) for 12 hours. The reaction mixture is then filtered and then concentrated to dryness. The expected product is obtained in the form of a solid.

¹H NMR: δ (500 MHz; dmsd-d₆; 300K): 7.7-7.4 (s, 1H, H pyrazole); 7.1-6.8 (s, 1H, H pyrazole); 7.3-6.9 (m, 4H, aromatic Hs, H tetrahydroisoquinoline); 7.0-6.7 (m, 2H, aromatic Hs); 6.9-6.4 (m, 2H, aromatic Hs); 6.8-6.4 (m, 2H, aromatic Hs); 6.1 (m, 2H, OCH₂O); 5.2, 5.0, 4.7 (4s, H, H-pyrrole (presence of conformational isomers); 5.15 (d, 1H, aliphatic H, H tetrahydroisoquinoline); 4.9 (m, 1H, aliphatic H, H tetrahydroisoquinoline); 4.9-4.8 (m, 1H, CH₂OH); 4.7 (m, 1H, aliphatic H, H tetrahydroisoquinoline); 3.9 (d, 1H, aliphatic H, H tetrahydroisoquinoline); 3.85 (m, 1H, aliphatic H, H tetrahydroisoquinoline); 3.7 (m, 2H, aliphatic Hs, CH₂CH₂OH); 3.75 (2s, 3H); 3.5-3.2 (m, 2H, aliphatic Hs, CH₂CH₂OH); 3.0-2.4 (m, 2H, aliphatic H, H tetrahydroisoquinoline); 2.4-2.3 (4s, 3H, CH₃-pyrrole); 1.5, 0.95, 0.75 (4 d, 3H, CH₃-THIQ); 0.85 (broad s, 9H, Si(CH₃)₂(CH(CH₃)₂); 0.15 (m, 6H, Si(CH₃)₂(CH(CH₃)₂))

IR: ν: —OH: 3346 cm⁻¹ carboxylic acid; ν: >C=O: 1621 cm⁻¹

Step C: 1-(2-Hydroxyethyl)-N-(4-hydroxyphenyl)-2-methyl-5-(6-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

The phenol function of the compound of Step B is deprotected following the process of Step D of Example 1.

Elemental microanalysis: (% , theoretical:measured)
% C=68.23:68.12; % H=5.57:5.29; % N=11.05:10.79

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{36}H_{36}N_5O_6$

[M+H]⁺ calculated: 634.2662

[M+H]⁺ measured: 634.2660

EXAMPLE 24

N-(4-Hydroxyphenyl)-5-(5-methoxy-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% , theoretical:measured)
% C=65.86:64.47; % H=6.09:5.88; % N=11.82:11.45; % Cl=4.98:6.7

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{39}H_{42}N_6O_5$

[M+H]⁺ calculated: 675.3289

[M+H]⁺ measured: 675.3287

EXAMPLE 25

5-(5-Chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide hydrochloride

% C=63.77:62.83; % H=5.63:5.83; % N=11.74:11.29; % Cl=4.95:5.42

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EXAMPLE 26

N-(4-Hydroxyphenyl)-2-methyl-1-[2-(methylamino)ethyl]-5-(6-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide hydrochloride

The procedure is in accordance with Steps A, B and C of the process of Example 30 replacing the sodium azide used in Step B by methylamine. After purification over silica gel (CH₂Cl₂/MeOH/NH₃ gradient), the compound obtained, 0.3 g (0.46 mmol), is dissolved in 5 mL of anhydrous methanol and there is added, dropwise, 0.464 mL (0.47 mmol) of 1M HCl solution in ether. The batch is stirred for 0.5 hours at ambient temperature. The precipitate thereby obtained is filtered off and dried and then dissolved in a mixture of CH₃CN/H₂O before being lyophilised at low temperature. The expected product is obtained in the form of a solid.

Elemental microanalysis: (%), theoretical:measured)

% C=65.05:64.64; % H=5.75:5.43; % N=12.3:12.3; % Cl=5.19:5.39

High-resolution mass spectrometry (ESI+):

Empirical formula: C₃₇H₃₈N₆O₅

[M+H]⁺ calculated: 647.2903

[M+H]⁺ measured: 647.2922

EXAMPLE 27

1-[2-(Dimethylamino)ethyl]-N-(4-hydroxyphenyl)-2-methyl-5-(6-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide hydrochloride

The procedure is in accordance with the process of Example 26, replacing the methylamine in Step B by dimethylamine.

Elemental microanalysis: (%), theoretical:measured)

% C=65.46:65.07; % H=5.93:5.87; % N=12.05:12.06; % Cl=5.08:5.55

High-resolution mass spectrometry (ESI+):

Empirical formula: C₃₈H₄₀N₆O₅

[M+H]⁺ calculated: 661.3060

[M+H]⁺ measured: 661.3045

EXAMPLE 28

5-(5-Chloro-2-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(pyridin-4-yl)-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (%), theoretical:measured)

% C=66.99:66.88; % H=5.14:5.28; % N=8.93:8.87; % Cl=5.65:4.98

High-resolution mass spectrometry (ESI+):

Empirical formula: C₃₅H₃₂ClN₄O₃

[M+H]⁺ calculated: 591.2157

[M+H]⁺ measured: 591.2178

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EXAMPLE 29

5-(5-Chloro-2-[[[(3S)-3-[[2-(morpholin-4-yl)ethoxy]methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-1,2-dimethyl-N-phenyl-4H-pyrrole-3-carboxamide hydrochloride

Step A: Methyl 5-(5-chloro-2-[[[(3S)-3-(hydroxymethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-1,2-dimethyl-1H-pyrrole-3-carboxylate

To a solution of 4.9 g of the compound of Preparation 1 in a mixture of 40 mL of dimethylformamide and 40 mL of tetrahydrofuran there are added 2.73 g (1.1 equivalents) of (3S)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline, 7.95 mL of diisopropylethylamine and 9.84 g (1.7 equivalents) of HATU. After stirring for 2 hours at ambient temperature, the reaction mixture is dried, taken up in ethyl acetate and then washed with 10% aqueous citric acid solution and water. The combined aqueous phases are extracted with ethyl acetate. The organic phases thereby obtained are combined, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product obtained is purified by chromatography over silica gel using dichloromethane and ethanol as eluants to yield the title compound.

¹H NMR: δ (500 MHz; dmsd-d₆; 300K): 7.6-7.4 (m, 3H, Cl-Ph); 7.2-6.9 (m, 4H, Ar(THIQ)); 6.5-6.15 (broad 4s, 1H, pyrrole); 4.9-3.8 (6 d, 2H, NCH₂ THIQ); 4.85-3.6 (m, 1H, NCH THIQ); 4.2-4.0 (m, 2H, OCH₂ ester), 3.45-3.2 (3s, 3H, N—CH₃); 3.35-3.0 (3m, 2H, HOCH₂); 3.0-2.0 (m, 2H, THIQ); 2.5-2.1 (m, 3H, CH₃ pyrrole); 1.25-1.1 (m, 3H, CH₃ ester)

IR: ν—OH: 3388 cm⁻¹, ν>C=O: 1693 cm⁻¹ (conjugated ester), ν>C=O: 1620 cm⁻¹ (amide)

Step B: Methyl 5-(5-chloro-2-[[[(3S)-3-[[2-(morpholin-4-yl)ethoxy]methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-1,2-dimethyl-1H-pyrrole-3-carboxylate

A solution of 1.7 g (3.2 mmol) of the compound obtained in the above Step in 20 mL of dimethylformamide is added, dropwise at 0° C., to a suspension of 0.280 g of NaH 60% in oil (2.2 equivalents) in 10 mL of dimethylformamide. After stirring for 5 minutes at ambient temperature, a suspension of 0.68 g of 4-(2-bromoethyl)morpholine hydrobromide (1.1 equivalents) is added dropwise. The reaction mixture is stirred at ambient temperature for 45 minutes. There are then added, in two steps over 20 hours, 2.2 equivalents of 4-(2-bromoethyl)morpholine hydrobromide, and then 3 equivalents of NaH 60% in oil. The reaction mixture is then poured into a mixture of 10% aqueous ammonium chloride and ethyl acetate. The resulting organic phase is successively washed with water, and then with saturated aqueous LiCl solution and brine. It is then dried over Na₂SO₄, filtered and concentrated under reduced pressure. The oil obtained is purified by chromatography over silica gel using dichloromethane and ethanol as eluants to provide the expected product.

¹H NMR: δ (500 MHz; dmsd-d₆; 300K): 7.6-7.3 (m, 3H, Cl-Ph); 7.2-6.85 (m, 4H, Ar(THIQ)); 6.5-6.15 (broad s, 1H, pyrrole); 5.25-3.8 (m, 2H, NCH₂ THIQ); 5.05-3.75 (m, 1H, NCH THIQ); 4.2-4.0 (m, 2H, OCH₂ ester), 3.5-3.25 (m, 3H, N—CH₃); 3.6-2.75 (m, 8H, OCH₂ morpholinoethoxymethyl); 2.95-2.05 (m, 2H, THIQ); 2.55-2.15 (m, 6H, NCH₂ morpholinoethoxymethyl); 2.55-2.05 (m, 3H, CH₃ pyrrole), 1.25-1.1 (m, 3H, CH₃ ester)

IR: ν>C=O: 1694 cm⁻¹ (conjugated ester), ν>C=O: 1629 cm⁻¹ (amide)

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Step C: 5-(5-Chloro-2-[[[(3S)-3-[[2-(morpholin-4-yl)ethoxy]methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-1,2-dimethyl-1H-pyrrole-3-carboxylic acid

To a solution of 1.46 g of the compound of the above Step in 5 mL of dioxane there are added 5 mL of 1M aqueous LiOH solution. The batch is heated in a microwave apparatus (100 W) at 100° C. for 2 hours. The reaction mixture is poured into water and then extracted with ethyl ether. The ethereal phase is extracted again with 10 mL of water. The aqueous phases are acidified to pH 5-6 by adding saturated aqueous ammonium chloride solution and then extracted twice with dichloromethane. The dichloromethane phase is dried over Na₂SO₄, filtered and concentrated to dryness. The title product is obtained in the form of a meringue.

¹H NMR: δ (500 MHz; dmsd-d₆; 300K): 11.4 (broad s, 1H, CO₂H), 7.6-7.3 (m, 3H, Cl-Ph); 7.2-6.8 (m, 4H, Ar(THIQ); 6.5-6.2 (broad 4s, 1H, pyrrole); 5.25-3.75 (m, 2H, NCH₂ THIQ); 5.05-3.7 (3m, 1H, NCH THIQ); 3.5-3.2 (3s, 3H, N—CH₃); 3.6-2.7 (m, 8H, OCH₂ morpholinoethoxymethyl); 2.5-2.2 (m, 6H, NCH₂ morpholinoethoxymethyl); 3.0-2.0 (m, 2H, THIQ), 2.5-2.0 (3s, 3H, CH₃ pyrrole)

IR: ν —OH: 3300-2200 cm⁻¹, ν >C=O: 1697-1662 cm⁻¹ (double band, carboxylic acid), ν >C=O: 1628 cm⁻¹ (amide) Step D: N-(4-[[[tert-Butyl(dimethyl)silyl]oxy]phenyl]-5-(5-chloro-2-[[[(3S)-3-[[2-(morpholin-4-yl)ethoxy]methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-1,2-dimethyl-1H-pyrrle-3-carboxamide

The acid obtained in Step C (1.48 g) is suspended in 15 mL of 1,2-dichloroethane. 1.1 equivalents of 1-chloro-N,N,2-trimethylpropenylamine are added thereto. After stirring for 1 hour at ambient temperature, there are added 15 mL of toluene and 1.05 equivalents of the compound of Preparation 2". The reaction mixture is heated for 14 hours at 110° C. and then dried. The crude product thereby obtained is purified by chromatography over silica gel using dichloromethane and ethanol as eluents to yield the expected product.

¹H NMR: δ (500 MHz; dmsd-d₆; 300K): 7.55-7.25 (m, 3H, Cl-Ph); 7.25-6.6 (m, 9H, Ar(THIQ)+phenyl); 6.8-6.5 (m, 2H, phenoxy); 7.0-6.6 (m, 2H, phenoxy); 5.7-5.05 (broad 4s, 1H, pyrrole); 5.2-3.6 (8d, 2H, THIQ); 5.05-3.6 (4m, 1H, NCH THIQ), 3.6-2.9 (m, 8H, aliphatic morpholinoethoxymethyl); 3.4-3.2 (broad 3s, 3H, N—CH₃); 3.0-2.1 (m, 2H, THIQ), 2.35 (m, 2H, NCH₂ morpholinoethoxymethyl); 2.4-2.2 (m, 4H, NCH₂ morpholine); 2.4-2.15 (broad 3s, 3H, CH₃ pyrrole); 0.8 (broad 2s, 9H, Si(CH₃)₃); 0.1 (4s, 6H, SiCH₃)

IR: ν >C=O: 1635-1595 cm⁻¹ (double band), ν Si—O: 1117 cm⁻¹, ν Si—C: 837 cm⁻¹

Step E: 5-(5-Chloro-2-[[[(3S)-3-[[2-(morpholin-4-yl)ethoxy]methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-phenyl-1H-pyrrole-3-carboxamide hydrochloride

To a solution of 0.7 g of the compound of Step D in 5 mL of methanol there is added 0.92 mL of a 1M solution of potassium hydroxide in methanol. After stirring for 1 hour 10 minutes at ambient temperature, saturated aqueous sodium bicarbonate solution is added. The product which precipitates is extracted with ethyl acetate and then washed with water and brine. The resulting aqueous phases are extracted again with ethyl acetate. The organic phases thereby obtained are dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product obtained is purified by chromatography over silica gel using dichloromethane and ammonia-in-ethanol as eluents to provide 0.536 g of the title product, in the form of the base. The latter is dissolved in acetonitrile and

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converted into salt form using 1M aqueous HCl solution. After a lyophilisation step, the expected product is obtained in the form of a solid.

Elemental microanalysis: (% , measured(theoretical))

% C=66.4 (66.75); % H=5.98 (5.87); % N=7.38 (7.41); % Cl=9.42 (9.38); % Cl⁻=4.57 (4.69)

EXAMPLE 30

1-(2-Aminoethyl)-N-(4-hydroxyphenyl)-2-methyl-5-(6-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide hydrochloride

Step A: 2-{3-[[4-[[[tert-Butyl(dimethyl)silyl]oxy]phenyl](1-methyl-1H-pyrazol-4-yl)carbamoyl]-2-methyl-5-(6-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl)-1H-pyrrol-1-yl]ethyl methanesulphonate

A solution of 4.65 g of the compound obtained in Step B of Example 23 (6.22 mmol) in 100 mL of anhydrous THF is placed at 0° C. There are successively added thereto 3.5 mL (12.44 mmol) of triethylamine and then, dropwise, 0.722 mL of methanesulphonic chloride (9.33 mmol) dissolved in 20 mL of THF. The batch is then stirred at ambient temperature for 2 hours. The reaction mixture is hydrolysed by addition of saturated aqueous NaHCO₃ solution and then extracted twice with ethyl acetate. The organic phases are combined, dried over MgSO₄ and concentrated to dryness. The expected compound is obtained in the form of a glassy solid.

¹H NMR: δ (500 MHz; dmsd-d₆; 300K): 7.7-7.45 (s, 1H, H pyrazole); 7.1-6.9 (s, 1H, H pyrazole); 7.2-6.4 (m, 8H, aromatic Hs); 6.95-6.65 (m, 2H, aromatic Hs); 6.1 (m, 2H, OCH₂O); 5.2, 4.6 (4s, H, H-pyrrole (presence of conformational isomers); 4.9, 4.6, 3.9, 3.8 (m, 1H), 5.05-3.75 (m, 1H, aliphatic H, H tetrahydroisoquinoline); 4.3-4.05 (m, 2H, aliphatic Hs, CH₂CH₂OSO₂CH₃); 4.2-3.95 (m, 2H, aliphatic Hs, CH₂CH₂OSO₂CH₃); 3.75-2.7 (2s, 3H, CH₃-pyrazole); 3.0 (several s, 3H, CH₂OSO₂CH₃); 3.05-2.5 (several m, 2H, aliphatic Hs, H tetrahydroisoquinoline); 2.45-2.3 (several s, 3H, CH₃-pyrrole); 1.05, 0.75 (several d, 3H, CH₃-tetraisoquinoline); 0.9 (several s, 9H, Si(CH₃)₂(CH(CH₃)₂); 0.1 (m, 6H, Si(CH₃)₂(CH(CH₃)₂))

IR: ν: >C=O: 1626 cm⁻¹, ν: —SO₂: 1349 and 1172 cm⁻¹

Step B: 1-(2-Azidoethyl)-N-(4-[[[tert-butyl(dimethyl)silyl]oxy]phenyl]-2-methyl-5-(6-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

To a solution of 2 g (2.42 mmol) of compound of Step A in 20 mL of anhydrous DMF there is added 0.472 g (7.26 mmol) of sodium azide. The batch is stirred at 65° C. for 4 hours 30 minutes. The reaction mixture is poured into saturated aqueous NaHCO₃ solution and then extracted twice with ethyl acetate. The organic phases are combined and washed with saturated aqueous LiCl solution, dried over MgSO₄ and concentrated to dryness. After purification over silica gel using dichloromethane and ammonia-in-methanol as eluents, the expected product is obtained in the form of a foam.

¹H NMR: δ (500 MHz; dmsd-d₆; 300K): 7.65-7.45 (several s, 1H, H pyrazole); 7.1-6.9 (several s, 1H, H pyrazole); 7.3-6.4 (several m, 6H, aromatic Hs); 7.1-6.9 (several s, 1H, aromatic Hs); 6.8, 6.5 (2m, 2H, aromatic Hs); 6.1 (several s, 2H, OCH₂O); 5.25-4.65 (several s, 1H, H-pyrrole (presence of conformational isomers); 4.9, 4.6, 3.8 (several m, 1H); 5.05-3.7 (several m, 4H, aliphatic Hs, H-THIQ+CH₂CH₂N₃); 3.7 (several s, 3H, H CH₃-pyrazole); 3.5-3.25 (m, 2H, CH₂CH₂N₃); 3.1-2.4 (several m, 3H, CH₃-pyrrole); 2.45-2.3

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(several s, 3H, CH₃-pyrrole); 1.0-0.75 (several d, 3H, CH₃-THIQ); 0.9 (several s, 9H, Si(CH₃)₂(CH(CH₃)₂); 0.1 (several s, 6H, Si(CH₃)₂(CH(CH₃)₂))

IR: v: —N=N=N: 2100 cm⁻¹, v: >C=O: 1630 cm⁻¹, v: —Si—O—: 1035 cm⁻¹

Step C: 1-(2-Azidoethyl)-N-(4-hydroxyphenyl)-2-methyl-5-(6-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

To a solution of 1.12 g of the compound obtained in Step B (14.49 mmol) in 5 mL of methanol there are added, dropwise, 7.24 mL of 1M methanolic potassium hydroxide solution (72.45 mmol). The batch is stirred at ambient temperature for 3 hours. The reaction mixture is then concentrated to dryness, taken up in dichloromethane, hydrolysed with saturated aqueous NaHCO₃ solution and then extracted twice with dichloromethane. The organic phases are then combined, washed with water, dried over MgSO₄ and concentrated to dryness. The expected product is obtained in the form of a foam and used directly in the next Step.

¹H NMR: δ (500 MHz; dmsd-d₆; 300K): 9.60 ((s, 1H, CH₂CH₂zOH); 7.65-7.45 (several s, 1H, H pyrazole); 7.1-6.9 (several s, 1H, H pyrazole); 7.3-6.4 (several m, 6H, aromatic Hs); 7.1-6.9 (several s, 1H, aromatic Hs); 6.8, 6.5 (2m, 2H, aromatic Hs); 6.15 (several s, 2H, OCH₂O); 5.35-4.8 (several s, 1H, H-pyrrole (presence of conformational isomers); 4.9, 4.6, 3.8 (several m, 1H, aliphatic H, H tetrahydroisoquinoline); 3.7 (several s, 3H, H CH₃-pyrazole); 3.5-3.25 (m, 2H, CH₂CH₂N₃); 3.1-2.4 (several m, 3H, CH₃-pyrrole); 2.45-2.3 (several s, 3H, H THIQ); 2.45-2.3 (several s, 3H, CH₃-pyrrole); 1.0-0.75 (several d, 3H, CH₃-THIQ)

IR: v: —OH: 3171 cm⁻¹, v: —N=N=N: 2100 cm⁻¹, v: >C=O: 1617 cm⁻¹

Step D: 1-(2-Aminoethyl)-N-(4-hydroxyphenyl)-2-methyl-5-(6-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide hydrochloride

To a solution of 1.27 g of the compound obtained in the above Step (1.93 mmol) in 15 mL of anhydrous ethanol there is added 0.154 g of Pd/C 10%. The batch is degassed for 0.5 hours. It is then stirred for 12 hours at ambient temperature under hydrogen pressure (1.5 bar). The reaction mixture is then filtered and then concentrated to dryness. After purification by chromatography over silica gel (CH₂Cl₂/MeOH/NH₃ gradient), an oily residue is obtained. The residue is dissolved in 10 mL of anhydrous ethanol and then converted into salt form by adding two molar equivalents of a 1N solution of HCl in ethanol. The product is then dried before being dissolved in a minimum of a mixture of water and acetonitrile. After a lyophilisation step at low temperature, the expected product is obtained in the form of a solid.

Elemental microanalysis: (% , theoretical:measured)

% C=64.62:63.84; % H=5.57:5.55; % N=12.56:12.36; % Cl=5.3:5.56

High-resolution mass spectrometry (ESI+):

Empirical formula: C₃₆H₃₆N₆O₅

[M+H]⁺ calculated: 633.2820

[M+H]⁺ measured: 633.2808

EXAMPLE 31

N-(4-Hydroxyphenyl)-5-(5-methoxy-2-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

Elemental microanalysis: (% , theoretical:measured)

% C=71.29:70.17; % H=5.98:5.98; % N=11.88:11.49

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High-resolution mass spectrometry (ESI+):

Empirical formula: C₃₅H₃₆N₅O₄

[M+H]⁺ calculated: 590.2762

[M+H]⁺ measured: 590.2778

EXAMPLE 32

Phenyl (4-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1H-pyrrol-2-yl}-3-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]benzyl]-carbamate

Step A: N-(4-Benzyloxyphenyl)-N,1,2-trimethyl-pyrrole-3-carboxamide

The process is analogous to that described in Step A of Example 45.

Step B: tert-Butyl[4-(4-{[4-(benzyloxy)phenyl](methyl)carbamoyl]-1,5-dimethyl-1H-pyrrol-2-yl}-3-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]benzyl]-carbamate

The compound of Preparation II (1.5 g; 2.96 mmol) and the compound of Step A (1.16 g; 3.44 mmol) are dissolved in dimethylacetamide (25 mL) and then nitrogen is bubbled through the solution for 5 minutes. Potassium acetate (0.586 g; 5.92 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.2 g; 0.295 mmol) are added to the mixture which is then heated to 100° C. and, after stirring for 20 minutes, water (10 μL) is added. Stirring at 100° C. under a nitrogen atmosphere is continued for 2 hours more. The reaction mixture is allowed to cool to ambient temperature and is then evaporated to a volume of 15 mL. The resulting mixture is filtered over a short Celite column and then purified by preparative HPLC using water-TFA and acetonitrile as eluants. The pH of the appropriate fractions is adjusted to 7 with NaHCO₃, and then the acetonitrile is evaporated off under reduced pressure. The aqueous residue is extracted with DCM. The organic phase is washed with brine, dried over Na₂SO₄ and evaporated to dryness to yield the title compound.

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₀H₄₁N₅O₄

[M+H]⁺ calculated: 713.3705

[M+H]⁺ measured: 713.3709

Step C: 5-[4-(Aminomethyl)-2-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl]phenyl]-N-[4-(benzyloxy)phenyl]-N,1,2-trimethyl-1H-pyrrole-3-carboxamide hydrochloride

The compound of the above Step (1.18 g, 1.66 mmol) is dissolved/suspended in 4M HCl in dioxane (20 mL). The heterogeneous mixture is stirred for 30 minutes at ambient temperature and then evaporated to dryness to yield 1.19 g of the title compound which is used in the next Step without purification.

Step D: Phenyl (4-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1H-pyrrol-2-yl}-3-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]benzyl]carbamate

The title compound is obtained starting from the compound of the above Step in accordance with the protocol of Step D of Example 45.

Elemental microanalysis: (% , measured(theoretical))

% C=72.83 (72.88); % H=6.01 (5.96); % N=8.02 (8.72)

High-resolution mass spectrometry (ESI+):

Empirical formula: C₃₉H₃₈N₄O₅

[M+H]⁺ calculated: 643.2922

[M+H]⁺ measured: 643.2916

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EXAMPLE 33

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-fluorophenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% , measured(theoretical))
% C=65.75 (65.84); % H=5.38 (5.39); % N=7.62 (7.68); % Cl=9.77 (9.72); % Cl—4.84 (4.86)

EXAMPLE 34

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(3-fluorophenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% , measured(theoretical))
% C=65.61 (65.84); % H=5.09 (5.39); % N=7.76 (7.68); % Cl=4.83 (4.86)

EXAMPLE 35

N-(4-Hydroxyphenyl)-N,1,2-trimethyl-5-(2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-4-[(phenoxyacetyl)amino]methyl}phenyl)-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 32 using 2-phenoxyacetyl chloride as acylating agent in Step D.

Elemental microanalysis: (% , measured(theoretical))
% C=72.53 (73.15); % H=5.76 (6.14); % N=8.31 (8.53)
High-resolution mass spectrometry (ESI+):
Empirical formula: C₄₀H₄₀N₄O₅
[M+H]⁺ calculated: 657.3079
[M+H]⁺ measured: 657.3061

EXAMPLE 36

5-(4-{[(Ethylcarbamoyl)amino]methyl}-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-N,1,2-trimethyl-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 32 using ethyl isocyanate as acylating agent in Step D.

Elemental microanalysis: (% , measured(theoretical))
% C=70.88 (70.8); % H=6.02 (6.62); % N=11.17 (11.8)
High-resolution mass spectrometry (ESI+):
Empirical formula: C₃₅H₃₅N₅O₄
[M+H]⁺ calculated: 594.3100
[M+H]⁺ measured: 594.3083

EXAMPLE 37

5-(4-{[(Benzylcarbamoyl)amino]methyl}-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-N,1,2-trimethyl-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 32 using benzyl isocyanate as acylating agent in Step D.

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Elemental microanalysis: (% , measured(theoretical))
% C=73.21 (73.26); % H=5.98 (6.3); % N=10.23 (10.68)
High-resolution mass spectrometry (ESI+):
Empirical formula: C₄₀H₄₁N₅O₄
[M+H]⁺ calculated: 656.3239
[M+H]⁺ measured: 656.3256

EXAMPLE 38

5-(5-Chloro-2-{[(3S)-3-(hydroxymethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-phenyl-1H-pyrrole-3-carboxamide

Elemental microanalysis: (% , measured(theoretical))
% C=70.97 (71.34); % H=5.2 (5.32); % N=6.96 (6.93)

EXAMPLE 39

N-(4-Hydroxyphenyl)-1,2-dimethyl-5-(6-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

Elemental microanalysis: (% , measured(theoretical))
% C=69.81 (69.64); % H=5.6 (5.51); % N=11.55 (11.6)
High-resolution mass spectrometry (ESI+):
Empirical formula: C₃₅H₃₄N₅O₅
[M+H]⁺ calculated: 604.2554
[M+H]⁺ measured: 604.2565

EXAMPLE 40

Phenyl (3-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1H-pyrrol-2-yl}-4-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}benzyl)-carbamate

Step A: N-(4-Benzoyloxyphenyl)-N,1,2-trimethyl-pyrrole-3-carboxamide

The process is analogous to that described in Step A of Example 45.

Step B: 5-[5-(Aminomethyl)-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl}phenyl]-N-[4-(benzyloxy)phenyl]-N,1,2-trimethyl-1H-pyrrole-3-carboxamide hydrochloride

The compound of Preparation III (1.84 g; 3.99 mmol) and the compound of Step A (1.60 g; 4.48 mmol) are dissolved in dimethylacetamide (20 mL) and then nitrogen is bubbled through the solution for 5 minutes. Potassium acetate (0.78 g; 7.48 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.28 g; 0.4 mmol) are added to the mixture which is then heated to 105° C. and, after stirring for 10 minutes, water (11 μL) is added. Stirring at 105° C. under a nitrogen atmosphere is continued for 6 hours more. The reaction mixture is allowed to cool to ambient temperature, the resulting mixture is filtered over a short Celite column and is then purified by preparative HPLC using water-TFA and acetonitrile as eluants. The pH of the appropriate fractions is adjusted to 7 with NaHCO₃ and then the acetonitrile is evaporated off under reduced pressure. The solid precipitate is removed by filtration and then dried (5 mbar, 45° C., 16 hours) to form tert-butyl[3-(4-{[4-(benzyloxy)phenyl](methyl)carbamoyl]-1,5-dimethyl-1H-pyrrol-2-yl}-4-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}benzyl)carbamate which is dissolved/suspended in 4M HCl in dioxane (35 mL). The heterogeneous mixture is stirred for 30 minutes at ambi-

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ent temperature and then evaporated to dryness to yield the title compound which is used in the next Step without purification.

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{39}H_{40}N_4O_3$

$[M+H]^+$ calculated: 613.3180

$[M+H]^+$ measured: 613.3194

IR: ν : N—H+: 2854 cm^{-1} ; $>C=O$: 1621 cm^{-1} ; C—O—C: $1234, 1120, 1011\text{ cm}^{-1}$

Step C: Phenyl (3-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1H-pyrrol-2-yl}-4-[[{(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}benzyl]carbamate

The title compound is obtained starting from the compound of the above Step in accordance with the process of Step D of Example 45.

Elemental microanalysis: (% , measured(theoretical))

% C=73.2 (72.88); % H=5.83 (5.96); % N=8.13 (8.72)

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{39}H_{38}N_4O_5$

$[M+H]^+$ calculated: 643.2922

$[M+H]^+$ measured: 643.2902

EXAMPLE 41

N-(3-Fluorophenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-5-(6-[[{(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl]-1H-pyrrole-3-carboxamide

Elemental microanalysis: (% , measured(theoretical))

% C=71.44 (71.95); % H=4.95 (5.22); % N=6.8 (6.8)

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{37}H_{33}FN_3O_5$

$[M+H]^+$ calculated: 618.2399

$[M+H]^+$ measured: 618.2392

EXAMPLE 42

N-(4-Hydroxyphenyl)-1,2-dimethyl-5-(6-[[{(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

Elemental microanalysis: (% , measured(theoretical))

% C=71.32 (71.65); % H=5.17 (5.4); % N=10.67 (10.71)

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{39}H_{36}N_5O_5$

$[M+H]^+$ calculated: 654.2711

$[M+H]^+$ measured: 654.2710

EXAMPLE 43

N-(4-Hydroxyphenyl)-1,2-dimethyl-5-(6-[[{(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl]-N-phenyl-1H-pyrrole-3-carboxamide

Elemental microanalysis: (% , measured(theoretical))

% C=73.9 (74.11); % H=5.16 (5.55); % N=6.81 (7.01)

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{37}H_{34}N_3O_5$

$[M+H]^+$ calculated: 600.2493

$[M+H]^+$ measured: 600.2495

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EXAMPLE 44

N-(4-Hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-[[{(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl]-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% , measured(theoretical))

% C=66.41 (66.62); % H=5.08 (5.59); % N=10.85 (10.84); % Cl=4.68 (4.57)

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{43}H_{42}N_6O_6$

$[M+H]^+$ calculated: 739.3239

$[M+H]^+$ measured: 739.3246

EXAMPLE 45

Phenyl[2-(3-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1H-pyrrol-2-yl}-4-[[{(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-phenyl]ethyl]carbamate

Step A: N-(4-Benzyloxyphenyl)-N,1,2-trimethyl-pyrrole-3-carboxamide

To a suspension of 1,2-dimethylpyrrole-3-carboxylic acid (2.085 g; 15 mmol) in 1,2-dichloroethane (40 mL) there is added 1-chloro-N,N,2-trimethyl-prop-1-en-1-amine (2.37 mL; 17.9 mmol), and the solution formed is stirred for 1 hour. To the resulting solution there is added, dropwise, an ice-cold solution of 4-benzyloxy-N-methyl-aniline (3.73 g; 15 mmol) and N-ethyl-N-isopropyl-propan-2-amine (7.75 mL; 45 mmol) in 1,2-dichloroethane (40 mL). The reaction mixture is stirred at ambient temperature for 1 hour; it is then diluted with dichloromethane (250 mL) and washed with water (2×30 mL), dried over Na_2SO_4 and evaporated. The crude product is triturated with diethyl ether and the solid formed is filtered off to yield the title compound.

IR: ν : $>C=O$: 1616 cm^{-1} ; amide: 1508 cm^{-1} ; C—O—C: $1230, 1172, 1009\text{ cm}^{-1}$

Step B: tert-Butyl {2-[3-(4-[[4-(benzyloxy)phenyl](methyl)carbamoyl]-1,5-dimethyl-1H-pyrrol-2-yl]-4-[[{(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl]ethyl]-carbamate

The compound of Preparation I (0.869 g; 1.67 mmol) and the compound of Step A (0.558 g; 1.67 mmol) are dissolved in dimethylacetamide (8 mL) and then nitrogen is bubbled through the solution for 5 minutes. Potassium acetate (0.33 g; 3.34 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.117 g; 0.167 mmol) are added to the mixture which is then heated to 140°C . and, after stirring for 10 minutes, water (80 L) is added. Stirring at 140°C . under a nitrogen atmosphere is continued for 16 hours more. The reaction mixture is allowed to cool to ambient temperature and then evaporated. The residue is partitioned between dichloromethane (100 mL) and water (20 mL). The organic phase is washed with water (20 mL), dried over Na_2SO_4 and evaporated. The residue was purified by preparative HPLC using water-TFA and acetonitrile as eluants. The pH of the appropriate fractions is adjusted to 12 using aqueous NaOH solution and then the acetonitrile is evaporated off under reduced pressure. The aqueous residue is extracted with dichloromethane (2×100 mL). The organic phase is dried over Na_2SO_4 and evaporated to dryness to yield the title compound.

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High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{45}H_{50}N_4O_5$

$[M+H]^+$ calculated: 727.3861

$[M+H]^+$ measured: 727.3852

IR: ν : $>C=O$: 1705, 1618 cm^{-1} ; amide: 1509 cm^{-1} ; $C-O-C$: 1242, 1166, 1012 cm^{-1}

Step C: 5-[5-(2-Aminoethyl)-2-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl]phenyl]-N-[4-(benzyloxy)phenyl]-N,1,2-trimethyl-1H-pyrrole-3-carboxamide hydrochloride

The compound of Step B (0.35 g; 0.48 mmol) was dissolved/suspended in 4M HCl in dioxane (3 mL). The heterogeneous mixture is stirred for 30 minutes at ambient temperature and then evaporated to dryness to yield the title compound which is used in next Step without being otherwise purified.

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{40}H_{42}N_4O_3$

$[M+H]^+$ calculated: 627.3337

$[M+H]^+$ measured: 627.3309

IR: ν : $C-H$: 2931 cm^{-1} ; $>C=O$: 1608 cm^{-1} ; amide: 1508 cm^{-1} ; $C-O-C$: 1233, 1012 cm^{-1}

Step D: Phenyl 2-(3-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1H-pyrrol-2-yl}-4-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]ethyl)-carbamate

The compound of Step C (0.10 g; 0.15 mmol) is dissolved in dichloromethane. Phenyl chloroformate (0.027 g; 0.17 mmol) and diisopropylethylamine (0.097 g, 0.75 mmol) are added thereto. The reaction mixture is stirred at ambient temperature for 30 minutes. After dilution with dichloromethane (100 mL), the organic phase is washed with water (20 mL), evaporated and concentrated. The residue is then dissolved in ethanol and a Pd/C catalyst is added (10 mg). The reaction mixture is hydrogenated at atmospheric pressure at ambient temperature. When the reaction is complete, the catalyst is removed by filtration, the filtrate is concentrated and the crude product is purified by chromatography over silica gel using dichloromethane and methanol as eluants, to yield the title product.

Elemental microanalysis: (% , measured(theoretical))

% C=72.36 (73.15); % H=6.15 (6.14); % N=8.14 (8.53)

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{40}H_{40}N_4O_5$

$[M+H]^+$ calculated: 657.3077

$[M+H]^+$ measured: 657.3062

EXAMPLE 46

N-(4-Hydroxyphenyl)-N,1,2-trimethyl-5-(2-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-5-{2-[(phenoxyacetyl)amino]ethyl}phenyl]-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 45 using 2-phenoxyacetyl chloride as acylating agent in Step D.

Elemental microanalysis: (% , measured(theoretical))

% C=72.74 (73.41); % H=6.38 (6.31); % N=7.65 (8.35)

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{41}H_{42}N_4O_5$

$[M+H]^+$ calculated: 671.3235

$[M+H]^+$ measured: 671.3226

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EXAMPLE 47

N-(4-Hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-5-(6-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% , measured(theoretical))

% C=64.25 (64.59); % H=5.4 (5.7); % N=11.41 (11.59); % Cl=4.93 (4.89)

EXAMPLE 48

N-(4-Hydroxyphenyl)-N-(2-methoxypyrimidin-5-yl)-1,2-dimethyl-5-(6-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-1H-pyrrole-3-carboxamide

Elemental microanalysis: (% , measured(theoretical))

% C=68.07 (68.45); % H=5(5.27); % N=10.74 (11.09)

EXAMPLE 49

N-(4-Hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-1H-pyrrole-3-carboxamide dihydrochloride

Step A: N-(4-{[tert-Butyl(dimethyl)silyl]oxy}phenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 11 and (3S)-3-(4-morpholinylmethyl)-1,2,3,4-tetrahydroisoquinoline (see Preparation 3') in Step A, and the compound of Preparation 11" in Step C.

Step B: N-(4-Hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-1H-pyrrole-3-carboxamide dihydrochloride

To a solution of 0.21 g (0.2 mmol) of the compound of Step A in 3 mL of acetic acid there are added 85 mg of sodium cyanoborohydride (5 equivalents). The reaction mixture is stirred for 3 hours at ambient temperature and then overnight at 50° C. There are then added 2.6 equivalents of sodium cyanoborohydride and the reaction mixture is heated at 50° C. for 3 hours. The operation is repeated for a second time (addition of 2.6 equivalents of sodium cyanoborohydride and then heating at 50° C. for 3 hours). After coevaporation of the acetic acid in the presence of toluene, the residue is taken up in 3 mL of methanol. The pH of the solution is adjusted to 12 using 1M methanolic potassium hydroxide solution. After stirring overnight at ambient temperature, the reaction mixture is poured into saturated aqueous sodium bicarbonate solution and extracted with dichloromethane. The resulting organic phase is washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The product obtained is purified by chromatography over silica gel (dichloromethane/ethanol/ammonia 94/6/0.6) and then over a Lichroprep RP18 column (water/acetonitrile/trifluoroacetic

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acid). After evaporation of the acetonitrile, the product is neutralised with sodium bicarbonate. It is then extracted with ethyl acetate. The organic phase is dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue obtained is dissolved in acetonitrile and converted into salt form with 1M aqueous HCl solution. After lyophilisation, the title product is obtained in the form of a solid.

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₃H₄₄N₆O₆

[M+H]⁺ calculated: 741.3395

[M+H]⁺ measured: 741.3400

EXAMPLE 50

N-(4-Hydroxyphenyl)-N-(2-methoxypyrimidin-5-yl)-1,2-dimethyl-5-(6-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-1H-pyrrole-3-carboxamide hydrochloride

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₀H₄₀N₆O₇

[M+H]⁺ calculated: 717.3031

[M+H]⁺ measured: 717.3031

EXAMPLE 51

5-(5-[[[(Benzylcarbamoyl)amino]methyl]-2-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-N,1,2-trimethyl-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 40 using benzyl isocyanate as acylating agent in Step C.

Elemental microanalysis: (% , measured(theoretical))

% C=73.39 (73.26); % H=6.16 (6.3); % N=10.08 (10.68)

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₀H₄₁N₅O₄

[M+H]⁺ calculated: 656.3239

[M+H]⁺ measured: 656.3226

EXAMPLE 52

5-(5-[[[(Ethylcarbamoyl)amino]methyl]-2-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-N,1,2-trimethyl-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 40 using ethyl isocyanate as acylating agent in Step C.

Elemental microanalysis: (% , measured(theoretical))

% C=71.4 (70.8); % H=6.41 (6.62); % N=11.24 (11.8)

High-resolution mass spectrometry (ESI+):

Empirical formula: C₃₅H₃₅N₅O₄

[M+H]⁺ calculated: 594.3082

[M+H]⁺ measured: 594.3069

EXAMPLE 53

N-(4-Hydroxyphenyl)-N,1,2-trimethyl-5-(2-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-5-[[[(phenoxyacetyl)amino]methyl]phenyl]-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 40 using 2-phenoxyacetyl chloride as acylating agent in Step C.

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Elemental microanalysis: (% , measured(theoretical))

% C=72.32 (73.15); % H=6.21 (6.14); % N=7.84 (8.53)

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₀H₄₀N₄O₅

[M+H]⁺ calculated: 657.3079

[M+H]⁺ measured: 657.3105

EXAMPLE 54

N-(4-Hydroxyphenyl)-1,2-dimethyl-5-(2-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-5-[[[(phenoxyacetyl)amino]methyl]phenyl]-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

Elemental microanalysis: (% , measured(theoretical))

% C=73.87 (73.04); % H=5.47 (5.74); % N=10.26 (10.87)

EXAMPLE 55

5-(5-[2-[[[2-(4-Fluorophenyl)ethyl]sulphonyl]amino]ethyl]-2-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-N,1,2-trimethyl-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 45 using 2-(4-fluorophenyl)ethanesulphonyl chloride as acylating agent in Step D.

Elemental microanalysis: (% , measured(theoretical))

% C=67.42 (68.12); % H=5.76 (6); % N=7.27 (7.75); S=3.68 (4.44)

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₁H₄₃FN₄O₅S

[M+H]⁺ calculated: 723.3018

[M+H]⁺ measured: 723.3011

EXAMPLE 56

5-(5-[2-[[[(Benzylcarbamoyl)amino]ethyl]-2-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-N,1,2-trimethyl-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 45 using benzyl isocyanate as acylating agent in Step D.

Elemental microanalysis: (% , measured(theoretical))

% C=71.14 (73.52); % H=6.47 (6.47); % N=9.42 (10.46)

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₁H₄₃N₅O₄

[M+H]⁺ calculated: 670.3395

[M+H]⁺ measured: 670.3390

EXAMPLE 57

N-(4-Hydroxyphenyl)-N,1,2-trimethyl-5-(2-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-5-[[2-[[[(phenylacetyl)amino]ethyl]phenyl]-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 45 using phenylacetyl chloride as acylating agent in Step D.

Elemental microanalysis: (% , measured(theoretical))

% C=75.46 (75.21); % H=6.11 (6.46); % N=8.31 (8.56)

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High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{41}H_{42}N_4O_4$

$[M+H]^+$ calculated: 655.3286

$[M+H]^+$ measured: 655.3285

EXAMPLE 58

N-(4-Hydroxyphenyl)-N,1,2-trimethyl-5-(2-((3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl)carbonyl)-5-{2-[(phenylcarbamoyl)amino]ethyl}phenyl)-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 45 using phenyl isocyanate as acylating agent in Step D.

Elemental microanalysis: (% , measured(theoretical))

% C=71.25 (73.26); % H=6.12 (6.3); % N=9.61 (10.68)

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{40}H_{41}N_5O_4$

$[M+H]^+$ calculated: 656.3239

$[M+H]^+$ measured: 656.3226

EXAMPLE 59

5-(4-((2-(4-Fluorophenyl)ethyl)sulphonyl)amino)methyl)-2-((3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl)carbonyl}phenyl)-N-(4-hydroxyphenyl)-N,1,2-trimethyl-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 32 using 2-(4-fluorophenyl)ethanesulphonyl chloride as sulphonylation agent in Step D.

Elemental microanalysis: (% , measured(theoretical))

% H=5.19 (5.83); % N=7.28 (7.9); S=4.45 (4.52); % C=66.17 (67.78)

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{40}H_{41}FN_4O_5S$

$[M+H]^+$ calculated: 709.2866

$[M+H]^+$ measured: 709.2866

EXAMPLE 60

5-(5-Chloro-2-((3S)-3-([2-(dimethylamino)ethoxy]methyl)-3,4-dihydroisoquinolin-2(1H)-yl)carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-phenyl-1H-pyrrole-3-carboxamide hydrochloride

The process of Example 29 is used, on the one hand replacing the 4-(2-bromoethyl)morpholine hydrobromide used in Step B by 2-chloroethyldimethylamine hydrochloride and on the other hand adding a catalytic amount of tetrabutylammonium iodide.

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{40}H_{41}ClN_4O_4$

$[M+H]^+$ calculated: 677.2890

$[M+H]^+$ measured: 677.2887

EXAMPLE 61

N-(4-Hydroxyphenyl)-1,2-dimethyl-5-(6-((3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl)carbonyl)-1,3-benzodioxol-5-yl)-N-(pyridin-4-yl)-1H-pyrrole-3-carboxamide hydrochloride

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{36}H_{32}N_4O_5$

$[M+H]^+$ calculated: 601.2445

$[M+H]^+$ measured: 601.2424

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EXAMPLE 62

5-(5-Fluoro-4-methoxy-2-((3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl)carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrol-4-yl)-1H-pyrrole-3-carboxamide

Elemental microanalysis: (% , measured(theoretical))

% C=68.99 (69.18); % H=5.89 (5.64); % N=11.35 (11.52)

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{35}H_{34}FN_5O_4$

$[M+H]^+$ calculated: 608.2668

$[M+H]^+$ measured: 608.2640

EXAMPLE 63

5-(5-Chloro-2-((3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl)carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

Elemental microanalysis: (% , measured(theoretical))

% C=70.48 (70.85); % H=5.67 (5.32); % N=11.2 (10.87)

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{38}H_{34}ClN_5O_3$

$[M+H]^+$ calculated: 666.2242

$[M+H]^+$ measured: 666.2235

EXAMPLE 64

N,1,2-Trimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-((3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl)carbonyl)-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide hydrochloride

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{38}H_{40}N_6O_5$

$[M+H]^+$ calculated: 661.3133

$[M+H]^+$ measured: 661.3125

EXAMPLE 65

1,2-Dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-((3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl)carbonyl)-1,3-benzodioxol-5-yl)-N-phenyl-1H-pyrrole-3-carboxamide hydrochloride

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{43}H_{42}N_6O_5$

$[M+H]^+$ calculated: 723.3289

$[M+H]^+$ measured: 723.3287

EXAMPLE 66

4-Methylphenyl (4-{4-[(4-hydroxyphenyl)(methyl)carbamoyl]-1,5-dimethyl-1H-pyrrol-2-yl}-3-((3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl)carbonyl}benzyl)carbamate

The title compound is obtained in accordance with the process of Example 32 using 4-methylphenyl chloroformate as acylating agent in Step D.

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{40}H_{40}N_4O_5$

$[M+H]^+$ calculated: 657.3079

$[M+H]^+$ measured: 657.3076

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EXAMPLE 67

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% , measured(theoretical))
 % C=65.69 (65.28); % H=5.38 (5.77); % N=11.18 (12.02); % Cl=5.61 (5.07)

EXAMPLE 68

5-(5-Fluoro-4-hydroxy-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

A 1N solution of tribromoborane (1.3 equivalents) in dichloromethane is poured rapidly, at ambient temperature, into a solution of the compound of Example 62 in dichloromethane.

This operation is repeated twice in order to complete the reaction in 5 hours. The reaction mixture is poured into anhydrous ethanol at 5° C. After stirring for 10 minutes, saturated aqueous NaHCO₃ solution is added. The mixture is extracted with dichloromethane, dried over Na₂SO₄ and concentrated to dryness. The crude product obtained is purified by preparative HPLC using water, TFA and acetonitrile as eluants. The pH of the appropriate fractions is adjusted to 12 with saturated aqueous NaHCO₃ solution, and then the acetonitrile is evaporated off under reduced pressure. The aqueous residue is extracted with dichloromethane. The organic phase is dried over Na₂SO₄ and evaporated to dryness to yield the title compound.

High-resolution mass spectrometry (ESI+):

Empirical formula: C₃₄H₃₂FN₅O₄

[M+H]⁺ calculated: 594.2511

[M+H]⁺ measured: 594.2517

EXAMPLE 69

N-(4-Hydroxyphenyl)-1,2-dimethyl-5-(6-{[(3S)-3-[(4-methylpiperazin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide hydrochloride

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₄H₄₅N₇O₅

[M+H]⁺ calculated: 752.3555

[M+H]⁺ measured: 752.3552

EXAMPLE 70

N-(4-Hydroxyphenyl)-1,2-dimethyl-5-(6-{[(3S)-3-[(4-methylpiperazin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-4,3-benzodioxol-5-yl)-N-(pyridin-4-yl)-1H-pyrrole-3-carboxamide hydrochloride

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₁H₄₂N₆O₅

[M+H]⁺ calculated: 699.3289

[M+H]⁺ measured: 699.3293

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EXAMPLE 71

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide hydrochloride

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₂H₄₁ClN₆O₄

[M+H]⁺ calculated: 723.3289

[M+H]⁺ measured: 723.3287

EXAMPLE 72

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-benzimidazol-5-yl)-1H-pyrrole-3-carboxamide

Elemental microanalysis: (% , measured (theoretical))

% C=68.90 (69.17); % H=5.32 (5.67); % N=11.40 (11.52)

EXAMPLE 73

N-(4-Hydroxyphenyl)-1,2-dimethyl-5-(6-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(pyridin-4-yl)-1H-pyrrole-3-carboxamide dihydrochloride

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₀H₃₉N₅O₆

[M+H]⁺ calculated: 686.2973

[M+H]⁺ measured: 686.2971

EXAMPLE 74

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(pyridin-4-yl)-1H-pyrrole-3-carboxamide hydrochloride

High-resolution mass spectrometry (ESI+):

Empirical formula: C₃₉H₃₈ClN₅O₄

[M+H]⁺ calculated: 676.2685

[M+H]⁺ measured: 676.2684

EXAMPLE 75

N-(4-Hydroxyphenyl)-1-methyl-N-(1-methyl-4H-pyrazol-4-yl)-5-(6-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-2-(trifluoromethyl)-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% , theoretical:measured)

% C=60.12:59.77; % H=4.92:4.76; % N=10.79: 10.39%
 Cl=4.55:5.17

High-resolution mass spectrometry (ESI+):

Empirical formula: C₃₉H₃₇F₃N₆O₆

[M+H]⁺ calculated: 743.2799

[M+H]⁺ measured: 742.2802

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EXAMPLE 76

2-(Difluoromethyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrazol-4-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 77

N-(4-Hydroxyphenyl)-2-(methoxymethyl)-1-methyl-N-(1-methyl-1H-pyrazol-4-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 78

2-(2,2-Difluoroethyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrazol-4-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 79

N-(4-Hydroxyphenyl)-1-methyl-N-(1-methyl-4H-pyrazol-4-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-2-(2,2,2-trifluoroethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 80

N-(4-Hydroxyphenyl)-2-(2-methoxyethyl)-1-methyl-N-(1-methyl-1H-pyrazol-4-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 81

N-(4-Hydroxyphenyl)-1-methyl-5-(6-{{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-N-(1-methyl-1H-pyrazol-4-yl)-2-[2-(morpholin-4-yl)ethyl]-1H-pyrrole-3-carboxamide hydrochloride

The procedure is in accordance with the general protocol of Example 1 using the compound of Preparation 22 in Step A. The product obtained is finally dissolved in acetonitrile and converted into salt form using 0.1M aqueous HCl solution. After a lyophilisation step, the expected compound is obtained in the form of a solid.

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{40}H_{42}N_6O_6$

$[M+H]^+$ calculated: 703.3239

$[M+H]^+$ measured: 703.3236

EXAMPLE 82

N-(4-Hydroxyphenyl)-1-methyl-5-(6-{{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-N-(1-methyl-1H-pyrazol-4-yl)-2-(morpholin-4-ylmethyl)-1H-pyrrole-3-carboxamide

The procedure is in accordance with the general protocol of Example 1 using the compound of Preparation 23 in Step A.

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High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{39}H_{40}N_6O_6$

$[M+H]^+$ calculated: 689.3082

$[M+H]^+$ measured: 689.3085

EXAMPLE 83

N-(4-Hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-2-(trifluoromethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 84

2-(Difluoromethyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 85

N-(4-Hydroxyphenyl)-2-(methoxymethyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 86

2-(2,2-Difluoroethyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-4,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 87

N-(4-Hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-2-(2,2,2-trifluoroethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 88

N-(4-Hydroxyphenyl)-2-(2-methoxyethyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-4,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide hydrochloride

The procedure is in accordance with the general protocol of Example 1 using the appropriate Preparations. The product obtained is finally dissolved in acetonitrile and converted into salt form using 0.1M aqueous HCl solution. After a lyophilisation step, the expected compound is obtained in the form of a solid.

% C=65.97:66.15; % H=5.78:5.46; % N=10.26:10.24; % Cl=4.33:4.76

High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):

Empirical formula: $C_{45}H_{46}N_6O_7$

$[M+H]^+$ calculated: 783.3501

$[M+H]^+$ measured: 783.3502

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EXAMPLE 89

N-(4-Hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-[2-(morpholin-4-yl)ethyl]-5-(6-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-1H-pyrrole-3-carboxamide

EXAMPLE 90

N-(4-Hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-(morpholin-4-ylmethyl)-5-(6-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-1H-pyrrole-3-carboxamide

EXAMPLE 91

N-(4-Hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-5-(6-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-1H-pyrrole-3-carboxamide

EXAMPLE 92

1-Ethyl-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-5-(6-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-1H-pyrrole-3-carboxamide hydrochloride

The procedure is in accordance with the protocol described in Example 1, using the compounds from Preparations 20 and 3' in Step A and the compound from Preparation 1" in Step C. The product obtained is finally dissolved in acetonitrile and converted into salt form using 0.1M aqueous HCl solution. After a lyophilisation step, the expected compound is obtained in the form of a solid.

Elemental microanalysis: (% , theoretical:measured)

% C=64.99:65.61; % H=5.86:5.39; % N=11.37:11.43; % Cl=4.80:4.42

[M+H]⁺ measured: 703.3236

EXAMPLE 93

N-(4-Hydroxyphenyl)-1-(2-methoxyethyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-5-(6-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% , theoretical:measured)

% C=64.01:64.10; % H=5.90:5.63; % N=10.92:10.88; % Cl=4.61:4.70.

High-resolution mass spectrometry (ESI⁺):

Empirical formula: C₄₁H₄₄N₆O₇

[M+H]⁺ calculated: 733.3344

[M+H]⁺ measured: 733.3345

EXAMPLE 94

1-(2-Fluoroethyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-5-(6-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-1H-pyrrole-3-carboxamide hydrochloride

The procedure is in accordance with the protocol described in Steps A-D of Example 1, using the compounds from Prepa-

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rations 21 and 3' in Step A and the compound from Preparation 1" in Step C. The product obtained is finally dissolved in acetonitrile and converted into salt form using 0.1M aqueous HCl solution. After a lyophilisation step, the expected compound is obtained in the form of a solid.

Elemental microanalysis: (% , theoretical:measured)

% C=63.44:63.25; % H=5.59:5.09; % N=11.10:11.02; % Cl=4.68:4.74

High-resolution mass spectrometry (ESI⁺):

Empirical formula: C₄₀H₄₁N₆O₆

[M+H]⁺ calculated: 721.3144

[M+H]⁺ measured: 721.3147

EXAMPLE 95

1-(2,2-Difluoroethyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-5-(6-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 32 and the compound of Preparation 3' in Step A, and the compound of Preparation 1" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)

% C=61.97:61.89; % H=5.33:5.04; % N=10.84:10.85; % Cl=4.57:4.55

High-resolution mass spectrometry (ESI⁺/HR, ESI⁻/LR):

Empirical formula: C₄₀H₄₀F₂N₆O₆

[M+H]⁺ calculated: 739.3050

[M+H]⁺ measured: 739.3052

EXAMPLE 96

N-(4-Hydroxyphenyl)-2-methyl-5-(6-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-pyrrole-3-carboxamide hydrochloride

Step A: N-[4-[tert-Butyl(dimethyl)silyl]oxyphenyl]-2-methyl-5-[6-[[[(3R)-3-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl]-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrazol-4-yl)-1-(2-morpholinoethyl)pyrrole-3-carboxamide

The compound obtained in Step E of Example 99 is dissolved in 6 mL of tetrahydrofuran. Sodium iodide (100 mg, 0.67 mmol) is added, followed by morpholine (0.21 mL, 2.53 mmol) dropwise. The reaction mixture is heated in a sealed flask at 90° C. for 72 hours.

After cooling, the solution is evaporated to dryness and the residue is purified by chromatography over silica gel using dichloromethane and methanol as eluants. The expected product is obtained in the form of a foam.

¹H NMR (500 MHz, dmsO-d₆) δ ppm: 7.7-7.45 (4 bs, 1 H), 7.2-6.9 (m, 4 H), 7.1-6.4 (m, 2 H), 7.1-6.9 (4 bs, 1 H), 7-6.8 (4 m, 2 H), 6.75/6.48 (d+bs, 2 H), 6.1 (4 bs, 2 H), 5.25-4.7 (4 bs, 1 H), 5.2-3.8 (m, 2 H), 4.9/4.65/3.8 (3 m, 1 H), 3.75 (4 s, 3 H), 3.5 (bs, 4 H), 3-2 (m, 10 H), 2.41/2.3 (2 bs, 3 H), 1.02/0.95/0.78 (3 bd, 3 H), 0.88 (m, 9 H), 0.1 (m, 6 H)

IR (ATR) cm⁻¹: 1626 δ>C=O amides

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Step B: N-(4-Hydroxyphenyl)-2-methyl-5-(6-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-pyrrole-3-carboxamide hydrochloride

The procedure is in accordance with the protocol described in Step D of Example 1. The product obtained is finally subjected to a step of conversion into salt form in the presence of HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the expected compound is obtained.

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{40}H_{42}N_6O_6$

$[M+H]^+$ calculated: 703.3239

$[M+H]^+$ measured: 703.3238

EXAMPLE 97

N-(4-Hydroxyphenyl)-2-methyl-5-(6-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-1-[2-(morpholin-4-yl)ethyl]-N-phenyl-1H-pyrrole-3-carboxamide hydrochloride

The procedure is in accordance with the protocol described in Example 96 replacing the compound of Preparation 1" by that of Preparation 2".

Elemental microanalysis: (% theoretical:measured)

% C=68.61:68.12; % H=5.89:5.23; % N=7.62:7.54; % Cl=4.82:4.66

High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):

Empirical formula: $C_{42}H_{42}N_4O_6$

$[M+H]^+$ calculated: 699.3177

$[M+H]^+$ measured: 699.3173

EXAMPLE 98

1-[2-(Dimethylamino)ethyl]-N-(4-hydroxyphenyl)-2-methyl-5-(6-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-N-phenyl-1H-pyrrole-3-carboxamide hydrochloride

The procedure is in accordance with the protocol described in Example 27 replacing the compound of Preparation 1" by that of Preparation 2. The product obtained is finally subjected to a step of conversion into salt form in the presence of 1M HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the expected compound is obtained.

Elemental microanalysis: (% theoretical:measured)

% C=69.30:69.20; % H=5.96:5.48; % N=8.08:8.08; % Cl=5.11:5.03

High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):

Empirical formula: $C_{40}H_{40}N_4O_5$

$[M+H]^+$ calculated: 657.3071

$[M+H]^+$ measured: 657.3066

EXAMPLE 99

N-(4-Hydroxyphenyl)-1-[2-[(2-methoxyethyl)(methylamino)ethyl]-2-methyl-5-(6-[[[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide hydrochloride

Step A: Ethyl 1-(2-benzyloxyethyl)-2-methyl-5-[6-[(3R)-3-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl]-1,3-benzodioxol-5-yl]pyrrole-3-carboxylate

The procedure is in accordance with the protocol described in Step A of Example 1 replacing the compound of Preparation 1 by that of Preparation 19.

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^1H NMR (500 MHz, dmsd-d6) δ ppm: 7.35-6.95 (m, 9 H), 7-6.8 (several s, 2 H), 6.35-5.85 (several s, 1 H), 6.15 (several s, 2 H), 5.15-3.5 (several m, 4 H), 4.9/4.7/3.95 (several m, 1 H), 4.4 (m, 2 H), 4.2-3.95 (m, 2 H), 3.55 (m, 2 H), 3.1-2.35 (several m, 2 H), 2.5-2.2 (several s, 3 H), 1.25-1.1 (several m, 3 H), 1.05-0.7 (several d, 3 H)

Step B: 1-(2-Benzyloxyethyl)-2-methyl-5-[6-[(3R)-3-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl]-1,3-benzodioxol-5-yl]pyrrole-3-carboxylic acid

The procedure is in accordance with the protocol described in Step B of Example 1.

IR (ATR) cm^{-1} : 3000-2500 ν —OH, 1675-1625 ν —C=O carboxylic acid+amide

Step C: 1-(2-Benzyloxyethyl)-N-[4-[tert-butyl(dimethyl)silyl]oxyphenyl]-2-methyl-5-[6-[(3R)-3-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl]-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrazol-4-yl)pyrrole-3-carboxamide

The procedure is in accordance with the protocol described in Step C of Example 1.

^1H NMR (500 MHz, dmsd-d6) δ ppm: 7.7-7.5 (several s, 1 H), 7.35-6.5 (several m, 11 H), 7.1-6.9 (several s, 1 H), 6.95-6.5 (several s, 2 H), 6.8/6.5 (m, 2 H), 6.05 (several s, 2 H), 5.25-4.7 (several s, 1 H), 5.1-3.6 (several m, 4 H), 4.85/4.6/3.75 (several m, 1 H), 4.3 (m, 2 H), 3.7 (2xs, 3 H), 3.4 (m, 2 H), 3.05-2.4 (several m, 2 H), 2.4-2.25 (several s, 3 H), 1-0.75 (several d, 3 H), 0.9 (several s, 9 H), 0.1 (several s, 6 H)

IR (ATR) cm^{-1} : 1629 ν >C=O amides

Step D: N-[4-[tert-Butyl(dimethyl)silyl]oxyphenyl]-1-(2-hydroxyethyl)-2-methyl-5-[6-[(3R)-3-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl]-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrazol-4-yl)pyrrole-3-carboxamide

In a hydrogenating reactor, the compound of the above Step is dissolved in 30 mL of methanol. The solution is degassed by bubbling argon in, and palladium-on-carbon 10% (550 mg) is added. The resulting suspension is stirred under a pressure of 1 bar of hydrogen for 15 hours, and then passed through a Whatman® filter. The catalyst is rinsed with methanol and the filtrate is evaporated in vacuo. The residue thereby obtained is purified by chromatography over silica gel using dichloromethane and methanol as eluants. The expected product is obtained in the form of an oil.

^1H NMR (500 MHz, pyridine-d5) δ ppm: 7.7-7.4 (4 s, 1 H), 7.3-6.9 (m, 4 H), 7.1-6.8 (4 s, 1 H), 7-6.7 (m, 2 H), 6.9-6.4 (m, 2 H), 6.8-6.4 (4 m, 2 H), 6.1 (m, 2 H), 5.2/5/4.7 (4 s, 1 H), 5.15-3.9 (8 d, 2 H), 4.9-4.8 (m, 1 H), 4.9/4.7/3.85 (3 m, 1 H), 3.9-3.7 (m, 2 H), 3.75 (2 s, 3 H), 3.5-3.2 (m, 2 H), 3-2.4 (m, 2 H), 2.4-2.3 (4 s, 3 H), 1.05/0.95/0.75 (4 d, 3 H), 0.85 (bs, 9 H), 0.15-0 (m, 6 H)

IR (ATR) cm^{-1} : 3346 ν —OH primary alcohol, 1621 ν —C=O amides

Step E: 2-[3-[[4-[tert-Butyl(dimethyl)silyl]oxyphenyl]-(1-methyl-1H-pyrazol-4-yl)-carbonyl]-2-methyl-5-[6-[(3R)-3-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl]-1,3-benzodioxol-5-yl]pyrrol-1-yl]ethyl methanesulphonate

The compound of the above Step (2.37 g, 3.17 mmol) is dissolved in 30 mL of tetrahydrofuran. The reaction mixture is cooled to 0° C. and there are successively added triethylamine (1.8 mL, 13.9 mmol) and, dropwise, methanesulphonyl chloride (0.40 mL, 5.17 mmol). The reaction mixture is stirred for 2 hours at 0° C. The reaction mixture is then poured into saturated aqueous sodium hydrogen carbonate solution and extracted 3 times with ethyl acetate. The organic phase is washed 3 times with brine, dried over $MgSO_4$, filtered and then evaporated to dryness. The evaporation residue is used without purification in the next Step.

^1H NMR (500 MHz, dmsd-d6) δ ppm: 7.7-7.45 (several s, 1 H), 7.25-6.4 (m, 8 H), 7.1-6.9 (several s, 1 H), 6.95-6.65

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(several s, 2 H), 6.1 (several s, 2 H), 5.2-4.6 (several s, 1 H), 5.05-3.75 (several d, 2 H), 4.9/4.6/3.9/3.8 (several m, 1 H), 4.3-4.05 (m, 2 H), 4.2-3.95 (m, 2 H), 3.75/3.7 (2 s, 3 H), 3.05-2.5 (several m, 2 H), 3 (several s, 3 H), 2.45-2.3 (several s, 3 H), 1.05-0.75 (several d, 3 H), 0.9 (several s, 9 H), 0.1 (several s, 6 H)

IR (ATR) cm^{-1} : 1626 ν —C=O, 1349 ν —SO₂, 1249 δ —CH₃, 1172 ν —SO₂

Step F: N-[4-[tert-Butyl(dimethyl)silyloxyphenyl]-1-[2-[2-methoxyethyl(methylamino)ethyl]-2-methyl-5-[6-[(3R)-3-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl]-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrazol-4-yl)pyrrole-3-carboxamide

The compound of the above Step (1.33 mg, 1.61 mmol) is dissolved in 6 mL of tetrahydrofuran. Sodium iodide (100 mg, 0.67 mmol) is added, followed by dimethylamine (0.172 g, 1.932 mmol) dropwise. The reaction mixture is heated in a sealed flask at 60° C. for 36 hours. After cooling, it is evaporated to dryness and purified by chromatography over silica gel using dichloromethane and ammonia-in-methanol as eluants. The expected product is obtained in the form of a foam.

¹H NMR (500 MHz, dmso-d₆) δ ppm 7.7-7.45 (4 bs, 1 H), 7.2-6.9 (m, 4 H), 7.1-6.9 (4 bs, 1 H), 7-6.7 (4 m, 2 H), 7/6.45 (2 m, 2 H), 6.8/6.45 (2 m, 2 H), 6.1 (m, 2 H), 5.22/5.05/4.7 (4 bs, 1 H), 5.2-3.8 (m, 2 H), 4.91/4.65/3.9 (3 m, 1 H), 3.75 (2 bs, 3 H), 3.7 (m, 2 H), 3.2 (bs, 3 H), 3-2 (m, 2 H), 2.7-2 (ml, 6 H), 2.7-2 (m, 3 H), 2.45/2.35 (2 bs, 3 H), 1.05/0.95/0.8 (3 bd, 3 H), 0.9 (m, 9 H), 0.1 (m, 6 H)

IR (ATR) cm^{-1} : 1628 (shoulder) δ —C=O amides

Step G: N-(4-hydroxyphenyl)-1-[2-[2-methoxyethyl(methylamino)ethyl]-2-methyl-5-[6-[(3R)-3-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl]-1,3-benzodioxol-5-yl]-N-(1-methyl-1H-pyrazol-4-yl)pyrrole-3-carboxamide hydrochloride

The procedure is in accordance with the protocol described in Step D of Example 1. The product obtained is finally subjected to a step of conversion into salt form in the presence of 1M HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the expected compound is obtained.

IR (ATR) cm^{-1} : 2000 to 3500 ν —NH⁺/OH, 1615 ν >C=O amides, 1237-1161 δ >C—O—C<, 745 ν >CH—Ar

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₀H₄₄N₆O₆

[M+H]⁺ calculated: 705.3395

[M+H]⁺ measured: 705.3391

EXAMPLE 100

5-(5-Fluoro-4-methoxy-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-4,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide hydrochloride

The procedure is in accordance with the general protocol of Example 1 using the appropriate Preparations. The product obtained is finally dissolved in acetonitrile and converted into salt form using 0.1M aqueous HCl solution. After a lyophilisation step, the expected compound is obtained in the form of a solid.

Elemental microanalysis: (% theoretical:measured)

% C=64.23:64.31; % H=5.80:5.43; % N=11.52:11.46; % Cl=4.86:4.95

High-resolution mass spectrometry (ESI+):

Empirical formula: C₃₉H₄₄FN₅O₅

[M+H]⁺ calculated: 693.3195

[M+H]⁺ measured: 693.3194

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EXAMPLE 101

5-(4-Fluoro-5-methoxy-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 27 and the compound of Preparation 3' in Step A, and the compound of Preparation 1" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% theoretical:measured)

% C=64.23:63.12; % H=5.80:5.20; % N=11.52:11.38. % Cl=4.86:5.03

High-resolution mass spectrometry (ESI+HR, ESI-/LR):

Empirical formula: C₃₉H₄₄FN₅O₅

[M+H]⁺ calculated: 693.3195

[M+H]⁺ measured: 693.3195

EXAMPLE 102

5-(5-Chloro-2-[[[(3S)-3-[(4-methylpiperazin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide trihydrochloride

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₃H₄₄ClN₇O₃

[M+H]⁺ calculated: 742.3267

[M+H]⁺ measured: 742.3268

EXAMPLE 103

5-(5-Chloro-2-[[[(3S)-3-[(4-methylpiperazin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-phenyl-1H-pyrrole-3-carboxamide

EXAMPLE 104

N-(4-Hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-5-(6-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-1H-pyrrole-3-carboxamide

EXAMPLE 105

5-(5-Chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 106

5-(5-Chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-phenyl-1H-pyrrole-3-carboxamide

The procedure is in accordance with the general protocol of Example 1 using the appropriate Preparations, it being understood that Step D is not carried out. The expected product is obtained in free base form.

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Elemental microanalysis: (% , theoretical:measured)
 % C=70.72:69.77; % H=5.79:5.96; % N=11.78:11.43
 High-resolution mass spectrometry (ESI+):
 Empirical formula: C₄₂H₄ClN₆O₃
 [M+H]⁺ calculated: 713.3001
 [M+H]⁺ measured: 713.2998

EXAMPLE 107

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-fluorophenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 108

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(5-cyano-1-methyl-1H-pyrrol-3-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and (3S)-3-(4-morpholinylmethyl)-1,2,3,4-tetrahydroisoquinoline (see Preparation 3') in Step A, and the compound of Preparation 19" in Step C. The product obtained is finally subjected to a step of conversion into salt form in the presence of HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the expected compound is obtained.

Elemental microanalysis: (% , theoretical:measured)
 % C=64.95:65.09; % H=5.45:5.20; % N=11.36:11.26; % Cl=4.79:4.62

High-resolution mass spectrometry (ESI/+):

Empirical formula: C₄₀H₃₉ClN₆O₄

[M+H]⁺ calculated: 703.2794

[M+H]⁺ measured: 703.2789

EXAMPLE 109

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(6-cyanopyridin-2-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 23" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

High-resolution mass spectrometry (ESI+/-/FIA/HR, ESI-/FIA):

Empirical formula: C₄₀H₃₇ClN₆O₄

[M+H]⁺ calculated: 701.2638

[M+H]⁺ measured: 701.2639

EXAMPLE 110

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-cyanopyridin-2-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% , theoretical:measured)
 % C=65.13:65.72; % H=5.19:4.76; % N=11.39:12.04; % Cl=4.81:4.45

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High-resolution mass spectrometry (ESI+/-/FIA/HR, ESI-/FIA):

Empirical formula: C₄₀H₃₇ClN₆O₄

[M+H]⁺ calculated: 701.2638

[M+H]⁺ measured: 701.2643

EXAMPLE 111

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(2-cyanopyrimidine-2-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide

EXAMPLE 112

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-[2-(dimethylamino)pyridin-4-yl]-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide

EXAMPLE 113

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-benzimidazol-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 114

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(pyrazolo[1,5-a]pyrimidin-6-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 115

5-(5-Chloro-2-{[(3S)-3-[(9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide dihydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 7' in Step A, and the compound of Preparation 1" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)

% C=61.01:60.17; % H=5.74:5.09; % N=12.15:12.02; % Cl=8.78:9.81

High-resolution mass spectrometry (ESI+/-/FIA/HR, ESI-/FIA):

Empirical formula: C₄₁H₄₄ClN₇O₄

[M+H]⁺ calculated: 734.3216

[M+H]⁺ measured: 734.3220

EXAMPLE 116

5-(5-Chloro-2-{[(3S)-3-[(9aR)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide dihydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the

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compound of Preparation 9' in Step A, and the compound of Preparation 1" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)

% C=61.01:61.90; % H=5.74:5.65; % N=12.15:12.14; % Cl=13.15:11.51

High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):

Empirical formula: C₄₁H₄₄ClN₇O₄

[M+H]⁺ calculated: 734.3216

[M+H]⁺ measured: 734.3218

EXAMPLE 117

5-(5-Chloro-2-{[(3S)-3-(fluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 118

5-(5-Chloro-2-{[(3S)-3-(difluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 119

5-(5-Chloro-2-{[(3S)-3-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 120

5-(5-Chloro-2-{[(3S)-3-[(3-cyanoazetidin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 121

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(1-ethyl-1H-pyrazol-4-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide

EXAMPLE 122

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(1-cyclopropyl-1H-pyrazol-4-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 28" in Step C.

Elemental microanalysis: (% , theoretical:measured)

% C=68.12:67.94; % H=5.86:5.77; % N=11.92:11.65

High-resolution mass spectrometry (ESI+/HR, ESI-/LR):

Empirical formula: C₄₀H₄₁ClN₆O₄

[M+H]⁺ calculated: 705.2951

[M+H]⁺ measured: 705.2952

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EXAMPLE 123

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-[1-(trifluoromethyl)-1H-pyrazol-4-yl]-1H-pyrrole-3-carboxamide

EXAMPLE 124

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-[1-(difluoromethyl)-1H-pyrazol-4-yl]-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide

EXAMPLE 125

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-N-[1-(2-methoxyethyl)-1H-pyrazol-4-yl]-1,2-dimethyl-4H-pyrrole-3-carboxamide

EXAMPLE 126

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-[1-(oxetan-3-yl)-1H-pyrazol-4-yl]-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 26" in Step C.

High-resolution mass spectrometry (ESI+/HR, ESI-/LR):

Empirical formula: C₄₀H₄₁ClN₆O₅

[M+H]⁺ calculated: 721.2900

[M+H]⁺ measured: 721.2902

EXAMPLE 127

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-[1-(tetrahydrofuran-3-yl)-1H-pyrazol-4-yl]-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 22" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)

% C=63.81:63.63; % H=5.75:5.74; % N=10.89:10.71; % Cl=4.59:4.52

High-resolution mass spectrometry (ESI+/HR, ESI-/LR):

Empirical formula: C₄₁H₄₃ClN₆O₅

[M+H]⁺ calculated: 735.3056

[M+H]⁺ measured: 735.3061

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EXAMPLE 128

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-[1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl]-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide

EXAMPLE 129

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-phenyl-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process described in Step B of Example 49 using Example 106 as starting material, it being understood that the product is not subjected to the step of conversion into salt form.

Elemental microanalysis: (% , theoretical:measured)

% C=70.53:70.51; % H=6.06:5.81; % N=11.75:11.71

High-resolution mass spectrometry (ESI+/-/FIA):

Empirical formula: C₄₂H₄₃ClN₆O₃

[M+H]⁺ calculated: 715.3158

[M+H]⁺ measured: 715.3159

EXAMPLE 130

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-fluorophenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 131

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-N,1,2-trimethyl-1H-pyrrole-3-carboxamide

EXAMPLE 132

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(2-hydroxypyrimidin-5-yl)-1,2-dimethyl-N-phenyl-1H-pyrrole-3-carboxamide

EXAMPLE 133

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(2-hydroxypyrimidin-5-yl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

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EXAMPLE 134

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(2-hydroxypyrimidin-5-yl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 135

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(2-hydroxypyrimidin-5-yl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 136

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 137

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 138

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 139

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 140

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 141

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

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EXAMPLE 142

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-1-ethyl-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 143

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-1-ethyl-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 144

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-1-ethyl-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 145

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-(2-methoxyethyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 146

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-(2-methoxyethyl)-2-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 147

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-(2-methoxyethyl)-2-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 148

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-1-(2-fluoroethyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 149

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-1-(2-fluoroethyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 150

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-1-(2-fluoroethyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

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EXAMPLE 151

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-1-(2,2-difluoroethyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 152

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-1-(2,2-difluoroethyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 153

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-1-(2,2-difluoroethyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 154

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1-(2,2,2-trifluoroethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 155

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1-(2,2,2-trifluoroethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 156

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1-(2,2,2-trifluoroethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 157

5-(5-Chloro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-pyrrole-3-carboxamide

EXAMPLE 158

5-(5-Chloro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-pyrrole-3-carboxamide

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EXAMPLE 159

5-(5-Chloro-2-{{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl}-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-pyrrole-3-carboxamide

EXAMPLE 160

5-(5-Chloro-2-{{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl}-N-(4-hydroxyphenyl)-2-methyl-1-[2-(morpholin-4-yl)ethyl]-N-phenyl-1H-pyrrole-3-carboxamide

EXAMPLE 161

5-(5-Chloro-2-{{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl}-1-[2-(dimethylamino)ethyl]-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 162

5-(5-Chloro-2-{{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl}-1-[2-(dimethylamino)ethyl]-N-(4-hydroxyphenyl)-2-methyl-N-phenyl-1H-pyrrole-3-carboxamide

EXAMPLE 163

5-(5-Chloro-2-{{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl}-1-[2-(dimethylamino)ethyl]-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 164

5-(5-Chloro-2-{{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl}-1-[2-(dimethylamino)ethyl]-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 165

5-(5-Chloro-2-{{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl}phenyl}-N-(4-hydroxyphenyl)-1-{2-[(2-methoxyethyl)(methyl)amino]ethyl}-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 166

5-(5-Chloro-2-{{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl}phenyl}-N-(4-hydroxyphenyl)-1-{2-[(2-methoxyethyl)(methyl)amino]ethyl}-2-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 167

5-(5-Chloro-2-{{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl}phenyl}-N-(4-hydroxyphenyl)-1-{2-[(2-methoxyethyl)(methyl)amino]ethyl}-2-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

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EXAMPLE 168

5-(5-Chloro-2-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl}-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrazol-4-yl)-2-(trifluoromethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 169

5-(5-Chloro-2-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl}-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-(trifluoromethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 170

5-(5-Chloro-2-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl}-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-(trifluoromethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 171

5-(5-Chloro-2-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl}-2-(difluoromethyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 172

5-(5-Chloro-2-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl}-2-(difluoromethyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 173

5-(5-Chloro-2-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl}-2-(difluoromethyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 174

5-(5-Chloro-2-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl}-N-(4-hydroxyphenyl)-2-(methoxymethyl)-1-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 175

5-(5-Chloro-2-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl}-N-(4-hydroxyphenyl)-2-(methoxymethyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

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EXAMPLE 176

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-(methoxymethyl)-1-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 177

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 178

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-(2,2,2-trifluoroethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 179

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-(2,2,2-trifluoroethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 180

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-2-(2,2-difluoroethyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 181

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-2-(2,2-difluoroethyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 182

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-2-(2,2-difluoroethyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 183

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-(2-methoxyethyl)-1-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

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EXAMPLE 184

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-(2-methoxyethyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 185

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-(2-methoxyethyl)-1-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 186

5-(5-Chloro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrazol-4-yl)-2-(morpholin-4-ylmethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 187

5-(5-Chloro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-(morpholin-4-ylmethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 188

5-(5-Chloro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-(morpholin-4-ylmethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 189

5-(5-Chloro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrazol-4-yl)-2-[2-(morpholin-4-yl)ethyl]-1H-pyrrole-3-carboxamide

EXAMPLE 190

5-(5-Chloro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-[2-(morpholin-4-yl)ethyl]-1H-pyrrole-3-carboxamide

EXAMPLE 191

5-(5-Chloro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-[2-(morpholin-4-yl)ethyl]-1H-pyrrole-3-carboxamide

EXAMPLE 192

5-(5-Chloro-2-{[(3S)-3-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

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EXAMPLE 193

5-(5-Chloro-2-{[(3S)-3-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 194

5-(5-Chloro-2-{[(3S)-3-(difluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 195

5-(5-Chloro-2-{[(3S)-3-(difluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 196

5-(5-Chloro-2-{[(3S)-3-(fluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 197

5-(5-Chloro-2-{[(3S)-3-(fluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 198

5-(5-Chloro-2-{[(3S)-3-[(9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 199

5-(5-Chloro-2-{[(3S)-3-[(9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 200

5-(5-Chloro-2-{[(3S)-3-[(9aR)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

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EXAMPLE 201

5-(5-Chloro-2-{[(3S)-3-[(9aR)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 202

5-(2-{[(3S)-3-(Aminomethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-5-chlorophenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 203

5-(2-{[(3S)-3-(Aminomethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-5-chlorophenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 204

5-(2-{[(3S)-3-(Aminomethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-5-chlorophenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 205

5-(5-Chloro-2-{[(3S)-3-[(3-cyanoazetidin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 206

5-(5-Chloro-2-{[(3S)-3-[(3-cyanoazetidin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 207

5-(5-Chloro-2-{[(3S)-3-(1-oxa-6-azaspiro[3.3]hept-6-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 8' in Step A, and the compound of Preparation 1" in Step C.

High-resolution mass spectrometry (ESI+/FIA/HR, ESI-/FIA):

Empirical formula: C₃₉H₃₉ClN₆O₄

[M+H]⁺ calculated: 691.2794

[M+H]⁺ measured: 691.2796

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EXAMPLE 208

5-(5-Chloro-2-[[[(3S)-3-(1-oxa-6-azaspiro[3.3]hept-6-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 209

5-(5-Fluoro-4-methoxy-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide hydrochloride

The procedure is in accordance with the general protocol of Example 1 using the appropriate Preparations. The product obtained is finally dissolved in acetonitrile and converted into salt form using 0.1M aqueous HCl solution. After a lyophilisation step, the expected compound is obtained in the form of a solid.

Elemental microanalysis: (% , theoretical:measured)

% C=66.27:66.84; % H=5.69:5.15; % N=10.78:10.71; %

Cl=4.55:4.46

High-resolution mass spectrometry (ESI+/FIA):

Empirical formula: C₄₃H₄₃FN₆O₅

[M+H]⁺ calculated: 743.3352

[M+H]⁺ measured: 743.3353

EXAMPLE 210

5-(5-Fluoro-4-methoxy-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide hydrochloride

Step A: 5-(5-Fluoro-4-methoxy-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 1 using the compound of Preparation 14 and (3S)-3-(4-morpholinylmethyl)-1,2,3,4-tetrahydroisoquinoline (see Preparation 3') in Step A, and the compound of Preparation 11" in Step C.

Step B: 5-(5-Chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-phenyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process described in Step B of Example 49 starting from compound of the above Step, it being understood that the product is finally subjected to a step of conversion into salt form in the presence of 1M HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the expected product is obtained.

Elemental microanalysis: (% , theoretical:measured)

% C=60.12:59.77; % H=4.92:4.76; % N=10.79:10.39; %

Cl=4.55:5.17

High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):

Empirical formula: C₄₀H₄₀N₄O₅

[M+H]⁺ calculated: 657.3071

[M+H]⁺ measured: 657.3066

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EXAMPLE 211

5-(4-Fluoro-5-methoxy-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 212

5-(4-Fluoro-5-methoxy-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 213

N-(1-Ethyl-1H-pyrazol-4-yl)-5-(5-fluoro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide

EXAMPLE 214

N-(1-Cyclopropyl-1H-pyrazol-4-yl)-5-(5-fluoro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 8 and the compound of Preparation 3' in Step A, and the compound of Preparation 28" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)

% C=66.24:66.53; % H=5.84:5.39; % N=10.59:10.92%

Cl=4.89:5.68

EXAMPLE 215

5-(5-Fluoro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-[1-(trifluoromethyl)-1H-pyrazol-4-yl]-1H-pyrrole-3-carboxamide

EXAMPLE 216

N-[1-(Difluoromethyl)-1H-pyrazol-4-yl]-5-(5-fluoro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide

EXAMPLE 217

5-(5-Fluoro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(4-hydroxyphenyl)-N-[1-(2-methoxyethyl)-1H-pyrazol-4-yl]-1,2-dimethyl-1H-pyrrole-3-carboxamide

EXAMPLE 218

5-(5-Fluoro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-[1-(oxetan-3-yl)-1H-pyrazol-4-yl]-1H-pyrrole-3-carboxamide

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EXAMPLE 219

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-[1-(tetrahydrofuran-3-yl)-1H-pyrazol-4-yl]-1H-pyrrole-3-carboxamide

EXAMPLE 220

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-[1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl]-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide

EXAMPLE 221

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-phenyl-1H-pyrrole-3-carboxamide

EXAMPLE 222

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-phenyl-1H-pyrrole-3-carboxamide

EXAMPLE 223

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-fluorophenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 224

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-fluorophenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 225

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-N,1,2-trimethyl-1H-pyrrole-3-carboxamide

EXAMPLE 226

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(2-hydroxypyrimidin-5-yl)-1,2-dimethyl-N-phenyl-1H-pyrrole-3-carboxamide

EXAMPLE 227

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(2-hydroxypyrimidin-5-yl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

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EXAMPLE 228

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(2-hydroxypyrimidin-5-yl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 229

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(2-hydroxypyrimidin-5-yl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 230

N-(5-Cyano-1-methyl-1H-pyrrol-3-yl)-5-(5-fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 8 and the compound of Preparation 3' in Step A, and the compound of Preparation 19" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)
% C=66.43:67.09; % H=5.57:5.21; % N=11.62:11.48%
Cl⁻=4.90:4.75

High-resolution mass spectrometry (ESI⁺):

Empirical formula: C₄₀H₃₉FN₆O₄

[M+H]⁺ calculated: 687.3097

[M+H]⁺ measured: 687.3073

EXAMPLE 231

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 232

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 233

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 234

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

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EXAMPLE 235

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 236

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 237

1-Ethyl-5-(5-fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 238

1-Ethyl-5-(5-fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 239

1-Ethyl-5-(5-fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 240

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-(2-methoxyethyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 241

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-(2-methoxyethyl)-2-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 242

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-(2-methoxyethyl)-2-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 243

1-(2-Fluoroethyl)-5-(5-fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

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EXAMPLE 244

1-(2-Fluoroethyl)-5-(5-fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 245

1-(2-Fluoroethyl)-5-(5-fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 246

1-(2,2-Difluoroethyl)-5-(5-fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 247

1-(2,2-Difluoroethyl)-5-(5-fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 248

1-(2,2-Difluoroethyl)-5-(5-fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 249

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1-(2,2,2-trifluoroethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 250

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1-(2,2,2-trifluoroethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 251

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1-(2,2,2-trifluoroethyl)-1H-pyrrole-3-carboxamide

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EXAMPLE 252

5-(5-Fluoro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-pyrrole-3-carboxamide

EXAMPLE 253

5-(5-Fluoro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-pyrrole-3-carboxamide

EXAMPLE 254

5-(5-Fluoro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-pyrrole-3-carboxamide

EXAMPLE 255

5-(5-Fluoro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-1-[2-(morpholin-4-yl)ethyl]-N-phenyl-1H-pyrrole-3-carboxamide

EXAMPLE 256

1-[2-(Dimethylamino)ethyl]-5-(5-fluoro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 257

1-[2-(Dimethylamino)ethyl]-5-(5-fluoro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-phenyl-1H-pyrrole-3-carboxamide

EXAMPLE 258

1-[2-(Dimethylamino)ethyl]-5-(5-fluoro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 259

1-[2-(Dimethylamino)ethyl]-5-(5-fluoro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 260

5-(5-Fluoro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-{2-[(2-methoxyethyl)(methyl)amino]ethyl}-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

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EXAMPLE 261

5-(5-Fluoro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-{2-[(2-methoxyethyl)(methyl)amino]ethyl}-2-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 262

5-(5-Fluoro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-{2-[(2-methoxyethyl)(methyl)amino]ethyl}-2-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 263

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrazol-4-yl)-2-(trifluoromethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 264

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-(trifluoromethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 265

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-(trifluoromethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 266

2-(Difluoromethyl)-5-(5-fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 267

2-(Difluoromethyl)-5-(5-fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 268

2-(Difluoromethyl)-5-(5-fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

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EXAMPLE 269

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-(methoxymethyl)-1-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 270

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-(methoxymethyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 271

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-(methoxymethyl)-1-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 272

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 273

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-(2,2,2-trifluoroethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 274

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-(2,2,2-trifluoroethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 275

2-(2,2-Difluoroethyl)-5-(5-fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 276

2-(2,2-Difluoroethyl)-5-(5-fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 277

2-(2,2-Difluoroethyl)-5-(5-fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

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EXAMPLE 278

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-(2-methoxyethyl)-1-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 279

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-(2-methoxyethyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 280

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-2-(2-methoxyethyl)-1-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 281

5-(5-Fluoro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrazol-4-yl)-2-(morpholin-4-ylmethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 282

5-(5-Fluoro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-(morpholin-4-ylmethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 283

5-(5-Fluoro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-(morpholin-4-ylmethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 284

5-(5-Fluoro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrazol-4-yl)-2-[2-(morpholin-4-yl)ethyl]-1H-pyrrole-3-carboxamide

EXAMPLE 285

5-(5-Fluoro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-[2-(morpholin-4-yl)ethyl]-1H-pyrrole-3-carboxamide

EXAMPLE 286

5-(5-Fluoro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-[2-(morpholin-4-yl)ethyl]-1H-pyrrole-3-carboxamide

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EXAMPLE 287

5-(5-Fluoro-2-{[(3S)-3-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 288

5-(5-Fluoro-2-{[(3S)-3-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 289

5-(5-Fluoro-2-{[(3S)-3-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 290

5-(2-{[(3S)-3-(Difluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-5-fluorophenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 291

5-(2-{[(3S)-3-(Difluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-5-fluorophenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 292

5-(2-{[(3S)-3-(Difluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-5-fluorophenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 293

5-(5-Fluoro-2-{[(3S)-3-(fluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 294

5-(5-Fluoro-2-{[(3S)-3-(fluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 295

5-(5-Fluoro-2-{[(3S)-3-(fluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

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EXAMPLE 296

5-(5-Fluoro-2-{[(3S)-3-(fluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 297

5-(5-Fluoro-2-{[(3S)-3-[(9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 298

5-(5-Fluoro-2-{[(3S)-3-[(9aS)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 299

5-(5-Fluoro-2-{[(3S)-3-4(9aR)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 300

5-(5-Fluoro-2-{[(3S)-3-[(9aR)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 301

5-(5-Fluoro-2-{[(3S)-3-[(9aR)-hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 302

5-(2-{[(3S)-3-(Aminomethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-5-fluorophenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 303

5-(2-{[(3S)-3-(Aminomethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-5-fluorophenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

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EXAMPLE 304

5-(2-{{[(3S)-3-(Aminomethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-5-fluorophenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 305

5-(2-{{[(3S)-3-[(3-Cyanoazetidin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-5-fluorophenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 306

5-(2-{{[(3S)-3-[(3-Cyanoazetidin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-5-fluorophenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 307

5-(2-{{[(3S)-3-[(3-Cyanoazetidin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-5-fluorophenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 308

5-(5-fluoro-2-{{[(3S)-3-(1-oxa-6-azaspiro[3.3]hept-6-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 309

5-(5-Fluoro-2-{{[(3S)-3-(t-oxa-6-azaspiro[3.3]hept-6-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 310

N-(1-Ethyl-1H-pyrazol-4-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 311

N-(1-Cyclopropyl-1H-pyrazol-4-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 312

N-(4-Hydroxyphenyl)-1,2-dimethyl-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-[1-(trifluoromethyl)-1H-pyrazol-4-yl]-1H-pyrrole-3-carboxamide

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EXAMPLE 313

N-[1-(Difluoromethyl)-1H-pyrazol-4-yl]-N-(4-hydroxyphenyl)-1,2-dimethyl-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 314

N-(4-Hydroxyphenyl)-N-[1-(2-methoxyethyl)-1H-pyrazol-4-yl]-1,2-dimethyl-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 315

N-(4-Hydroxyphenyl)-1,2-dimethyl-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-[1-(oxetan-3-yl)-1H-pyrazol-4-yl]-1H-pyrrole-3-carboxamide

EXAMPLE 316

N-(4-Hydroxyphenyl)-1,2-dimethyl-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-[1-(tetrahydrofuran-3-yl)-1H-pyrazol-4-yl]-1H-pyrrole-3-carboxamide

EXAMPLE 317

N-[1-(2-Hydroxy-2-methylpropyl)-1H-pyrazol-4-yl]-N-(4-hydroxyphenyl)-1,2-dimethyl-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 318

1,2-Dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-phenyl-1H-pyrrole-3-carboxamide

EXAMPLE 319

1,2-Dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-phenyl-1H-pyrrole-3-carboxamide

EXAMPLE 320

N-(4-Fluorophenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide

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EXAMPLE 321

N-(4-Fluorophenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl})-1H-pyrrole-3-carboxamide

EXAMPLE 322

N-(4-Hydroxyphenyl)-N,1,2-trimethyl-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl})-1H-pyrrole-3-carboxamide

EXAMPLE 323

N-(2-Hydroxypyrimidin-5-yl)-1,2-dimethyl-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl})-N-phenyl-1H-pyrrole-3-carboxamide

EXAMPLE 324

N-(2-Hydroxypyrimidin-5-yl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl})-1H-pyrrole-3-carboxamide

EXAMPLE 325

N-(2-Hydroxypyrimidin-5-yl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl})-1H-pyrrole-3-carboxamide

EXAMPLE 326

N-(2-Hydroxypyrimidin-5-yl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl})-1H-pyrrole-3-carboxamide

EXAMPLE 327

N-(5-Cyano-1-methyl-1H-pyrrol-3-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl})-1H-pyrrole-3-carboxamide

EXAMPLE 328

N-(4-Hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl})-1H-pyrrole-3-carboxamide

EXAMPLE 329

N-(4-Hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl})-1H-pyrrole-3-carboxamide

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EXAMPLE 330

N-(4-Hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrazol-4-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl})-1H-pyrrole-3-carboxamide

EXAMPLE 331

N-(4-Hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl})-1H-pyrrole-3-carboxamide

EXAMPLE 332

N-(4-Hydroxyphenyl)-1-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo-[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl})-1H-pyrrole-3-carboxamide

EXAMPLE 333

1-Ethyl-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl})-1H-pyrrole-3-carboxamide

EXAMPLE 334

1-Ethyl-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl})-1H-pyrrole-3-carboxamide

EXAMPLE 335

N-(4-Hydroxyphenyl)-1-(2-methoxyethyl)-2-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl})-1H-pyrrole-3-carboxamide

EXAMPLE 336

N-(4-Hydroxyphenyl)-1-(2-methoxyethyl)-2-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl})-1H-pyrrole-3-carboxamide

EXAMPLE 337

1-(2-Fluoroethyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl})-1H-pyrrole-3-carboxamide

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EXAMPLE 338

1-(2-Fluoroethyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 339

1-(2,2-Difluoroethyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 341

1-(2,2-Difluoroethyl)-N-(4-hydroxyphenyl)-2-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 341

N-(4-Hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-4,3-benzodioxol-5-yl)-1-(2,2,2-trifluoroethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 342

N-(4-Hydroxyphenyl)-2-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-1-(2,2,2-trifluoroethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 343

N-(4-Hydroxyphenyl)-2-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo-[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-1-(2,2,2-trifluoroethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 344

N-(4-Hydroxyphenyl)-2-methyl-5-(6-{{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-pyrrole-3-carboxamide

EXAMPLE 345

N-(4-Hydroxyphenyl)-2-methyl-5-(6-{{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1-[2-(morpholin-4-yl)ethyl]-1H-pyrrole-3-carboxamide

EXAMPLE 346

1-[2-(Dimethylamino)ethyl]-N-(4-hydroxyphenyl)-2-methyl-5-(6-{{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

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EXAMPLE 347

1-[2-(Dimethylamino)ethyl]-N-(4-hydroxyphenyl)-2-methyl-5-(6-{{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 348

1-[2-(Dimethylamino)ethyl]-N-(4-hydroxyphenyl)-2-methyl-5-(6-{{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 349

N-(4-Hydroxyphenyl)-1-[2-[(2-methoxyethyl)(methylamino)ethyl]-2-methyl-5-(6-{{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 350

N-(4-Hydroxyphenyl)-1-[2-[(2-methoxyethyl)(methylamino)ethyl]-2-methyl-5-(6-{{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-N-(1-methyl-2,3-dihydro-4H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 351

N-(4-Hydroxyphenyl)-1-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo-[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-2-(trifluoromethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 352

2-(Difluoromethyl)-N-(4-hydroxyphenyl)-1-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 353

N-(4-Hydroxyphenyl)-2-(methoxymethyl)-t-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 354

N-(4-Hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrazol-4-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-2-(2,2,2-trifluoroethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 355

N-(4-Hydroxyphenyl)-1-methyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}}-1,3-benzodioxol-5-yl)-2-(2,2,2-trifluoroethyl)-1H-pyrrole-3-carboxamide

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EXAMPLE 356

N-(4-Hydroxyphenyl)-1-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-2-(2,2,2-trifluoroethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 357

2-(2,2-Difluoroethyl)-N-(4-hydroxyphenyl)-t-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 358

N-(4-Hydroxyphenyl)-2-(2-methoxyethyl)-1-methyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process described in Step B of Example 49 using Example 88 as starting material, it being understood that the product is finally dissolved in acetonitrile and converted into salt form in 0.1M aqueous HCl solution. After a lyophilisation step, the expected product is obtained in the form of a solid.

Elemental microanalysis: (%), theoretical:measured)

% C=65.80:64.71; % H=6.01:5.74; % N=10.23:10.03; % Cl=4.32:6.47

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₅H₄₈N₆O₇

[M+H]⁺ calculated: 785.3657

[M+H]⁺ measured: 785.3658

EXAMPLE 359

N-(4-Hydroxyphenyl)-1-methyl-5-(6-{{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-(morpholin-4-ylmethyl)-1H-pyrrole-3-carboxamide

EXAMPLE 360

N-(4-Hydroxyphenyl)-1-methyl-5-(6-{{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-2-[2-(morpholin-4-yl)ethyl]-1H-pyrrole-3-carboxamide

EXAMPLE 361

N-(4-Hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-5-(6-{{[(3S)-3-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 362

N-(4-Hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide

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EXAMPLE 363

N-(4-Hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{{[(3S)-3-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 364

5-(6-{{[(3S)-3-(Difluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 365

5-(6-{{[(3S)-3-(Difluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 366

5-(6-{{[(3S)-3-(Difluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 367

5-(6-{{[(3S)-3-(Fluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 368

5-(6-{{[(3S)-3-(Fluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 369

5-(6-{{[(3S)-3-(Fluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 370

5-(6-{{[(3S)-3-[(9aS)-Hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 371

5-(6-{{[(3S)-3-[(9aS)-Hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

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EXAMPLE 372

5-(6-{[(3S)-3-[(9aS)-Hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 373

5-(6-{[(3S)-3-[(9aR)-Hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 374

5-(6-{[(3S)-3-[(9aR)-Hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 375

5-(6-{[(3S)-3-[(9aR)-Hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 376

5-(6-{[(3S)-3-(Aminomethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 377

5-(6-{[(3S)-3-(Aminomethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 378

5-(6-{[(3S)-3-(Aminomethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 379

5-(6-{[(3S)-3-[(3-Cyanoazetidin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 380

5-(6-{[(3S)-3-[1(3-Cyanoazetidin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

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EXAMPLE 381

5-(6-{[(3S)-3-[(3-Cyanoazetidin-1-yl)methyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 382

10 N-(4-Hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-5-(6-{[(3S)-3-(1-oxa-6-azaspiro[3.3]hept-6-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 383

20 N-(4-Hydroxyphenyl)-1,2-dimethyl-N-(t-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(6-{[(3S)-3-(1-oxa-6-azaspiro[3.3]hept-6-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide

EXAMPLE 384

30 5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(pyridin-4-yl)-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% , theoretical:measured)
35 % C=67.28:67.73; % H=5.65:5.30; % N=10.06:9.41%
Cl=5.09:5.79

EXAMPLE 385

40 5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide hydrochloride

45 High-resolution mass spectrometry (ESI+):
Empirical formula: C₄₁H₄₁ClN₆O₄
[M+H]⁺ calculated: 713.3253
[M+H]⁺ measured: 713.3272

EXAMPLE 386

55 5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(5-cyano-1,2-dimethyl-1H-pyrrol-3-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

Step A: N-[4-[tert-Butyl(dimethyl)silyl]oxyphenyl]-5-[5-chloro-2-[(3S)-3-(morpholinomethyl)-3,4-dihydro-1H-isoquinoline-2-carbonyl]phenyl]-N-(5-cyano-1,2-dimethylpyrrol-3-yl)-1,2-dimethyl-pyrrole-3-carboxamide

60 The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 18" in Step C.

IR: ν—CN—: 2210 cm⁻¹; ν—C=O—: 1631 cm⁻¹

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Step B: 5-(5-Chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(5-cyano-1,2-dimethyl-1H-pyrrol-3-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The compound of Step A is deprotected in accordance with the protocol described in Step D of Example 1. The product thereby obtained is finally subjected to a step of conversion into salt form in the presence of HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the expected product is obtained.

¹H NMR (500 MHz, dms_o-d₆) δ ppm: 11.2 (bs, 1H), 9.39 (bs, 1H), 7.83 (d, 1H), 7.54 (d, 1H), 7.33 (s, 1H), 7.14 (m, 2H), 7 (m, 2H), 6.8 (d, 2H), 6.62 (d, 2H), 6.57 (bs, 1H), 5.26 (s, 1H), 5.26 (m, 1H), 4.64/4.03 (AB, 2H), 4.01/3.92 (2 m, 4H), 3.75/3.43/3.15/3.02 (4m, 4H), 3.59 (s, 3H), 3.3/3.15 (2m, 2H), 2.97 (s, 3H), 2.69/2.52 (dd+d, 2H), 2.06 (s, 3H), 1.91 (s, 3H)

Elemental microanalysis: (% theoretical:measured)

% C=65.34:65.50; % H=5.62:5.15; % N=11.15:10.84%
Cl=4.70:4.44

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₁H₄₁ClN₆O₄

[M+H]⁺ calculated: 717.2952

[M+H]⁺ measured: 717.2951

EXAMPLE 387

N-(4-Hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-c]pyridin-5-yl)-5-(6-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]-1,3-benzodioxol-5-yl]-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% theoretical:measured)

% C=66.62:66.36; % H=5.59:5.62; % N=10.84:10.72%
Cl=4.57:4.55

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₃H₄₂N₆O₆

[M+H]⁺ calculated: 739.3239

[M+H]⁺ measured: 739.3241

EXAMPLE 388

5-(5-Chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide dihydrochloride

The title compound is obtained in accordance with the process described in Step B of Example 49 using Example 71 as starting material, it being understood that the product is finally subjected to a step of conversion into salt form in the presence of 1M HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the expected compound is obtained.

Elemental microanalysis: (% theoretical:measured)

% C=62.73:62.96; % H=5.64:4.95; % N=10.45:10.32; %
Cl=13.23:12.91

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₂H₄₃ClN₆O₄

[M+H]⁺ calculated: 731.3107

[M+H]⁺ measured: 731.3111

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EXAMPLE 389

5-(5-Chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-c]pyridin-5-yl)-1H-pyrrole-3-carboxamide hydrochloride

The procedure is in accordance with the general protocol of Example 1 using the appropriate Preparations. The product obtained is finally dissolved in acetonitrile and converted into salt form using 0.1M aqueous HCl solution. After a lyophilisation step, the expected compound is obtained in the form of a solid.

Elemental microanalysis: (% theoretical:measured)

% C=65.88:66.28; % H=5.53:5.15; % N=10.98:10.95; %
Cl=4.63:4.47

High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):

Empirical formula: C₄₂H₄₁ClN₆O₄

[M+H]⁺ calculated: 729.2951

[M+H]⁺ measured: 729.2954

EXAMPLE 390

5-(5-Chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-phenyl-1H-pyrrole-3-carboxamide

The procedure is in accordance with the general protocol of Example 1 using the appropriate Preparations, it being understood that Step D is not carried out. The expected product is obtained in free base form.

Elemental microanalysis: (% theoretical:measured)

% C=70.72:69.77; % H=5.79:5.96; % N=11.78:11.43

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₂H₄₄ClN₆O₃

[M+H]⁺ calculated: 713.3001

[M+H]⁺ measured: 713.2998

EXAMPLE 391

5-(5-Chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[3,2-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% theoretical:measured)

% C=65.88:65.69; % H=5.33:4.87; % N=10.98:10.86; %
Cl=4.63:4.51

High-resolution mass spectrometry (ESI+/FIA):

Empirical formula: C₄₂H₄₁ClN₆O₄

[M+H]⁺ calculated: 729.2951

[M+H]⁺ measured: 729.2953

EXAMPLE 392

5-(5-Chloro-2-[[[(3R)-3-[3-(morpholin-4-yl)propyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-1,2-dimethyl-N-phenyl-1H-pyrrole-3-carboxamide hydrochloride

% C=68.19:68.33; % H=6.00:5.49; % N=10.78:10.71; %

Cl=4.55:4.46; % Cl=9.58:9.78

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High-resolution mass spectrometry (ESI+/-FIA):

Empirical formula: $C_{42}H_{43}ClN_4O_4$

$[M+H]^+$ calculated: 703.3046

$[M+H]^+$ measured: 703.3042

EXAMPLE 393

5-(5-Chloro-2-{[(3R)-3-[3-(morpholin-4-yl)propyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide hydrochloride

High-resolution mass spectrometry (ESI+/-FIA):

Empirical formula: $C_{44}H_{45}ClN_6O_4$

$[M+H]^+$ calculated: 757.3264

$[M+H]^+$ measured: 757.3263

EXAMPLE 394

5-(5-Chloro-2-{[(3R)-3-[3-(morpholin-4-yl)propyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process described in Step B of Example 49 using Example 393 as starting material, it being understood that the product is not subjected to the step of conversion into salt form.

Elemental microanalysis: (% theoretical:measured)

% C=69.60:69.56; % H=6.21:6.24; % N=11.07:11.08

High-resolution mass spectrometry (ESI+/-FIA):

Empirical formula: $C_{44}H_{47}ClN_6O_4$

$[M+H]^+$ calculated: 759.3420

$[M+H]^+$ measured: 759.3422

EXAMPLE 395

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(3-cyano-4-methoxyphenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The procedure is in accordance with the general protocol of Example 1 using the appropriate Preparations. The product obtained is finally dissolved in acetonitrile and converted into salt form using 0.1M aqueous HCl solution. After a lyophilisation step, the expected compound is obtained in the form of a solid.

High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):

Empirical formula: $C_{42}H_{40}ClN_5O_5$

$[M+H]^+$ calculated: 730.2791

$[M+H]^+$ measured: 730.2790

EXAMPLE 396

N-(3-Fluoro-4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-5-(6-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 11 and (3S)-3-(4-morpholinylmethyl)-1,2,3,4-tetrahydroisoquino-

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line (see Preparation 3') in Step A, and the compound of Preparation 20" in Step C. The product obtained is finally subjected to a step of conversion into salt form in the presence of 1M HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the expected compound is obtained.

Elemental microanalysis: (% theoretical:measured)

% C=65.79:65.43; % H=5.39:5.19; % N=11.31:11.21; % Cl=4.77:4.34

High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):

Empirical formula: $C_{39}H_{39}FN_6O_6$

$[M+H]^+$ calculated: 707.2988

$[M+H]^+$ measured: 707.2988

EXAMPLE 397

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-N-(2-methoxypyrimidin-5-yl)-1,2-dimethyl-1H-pyrrole-3-carboxamide

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{39}H_{39}ClN_6O_5$

$[M+H]^+$ calculated: 707.2743

$[M+H]^+$ measured: 707.2746

EXAMPLE 398

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(3-cyanophenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% theoretical:measured)

% C=66.85:66.75; % H=5.34:5.42; % N=9.51:9.73; % Cl=9.62:9.67; % Cl⁻=4.81:4.71

High-resolution mass spectrometry (ESI+/-FIA/HR, ESI-/FIA):

Empirical formula: $C_{41}H_{38}ClN_5O_4$

$[M+H]^+$ calculated: 700.2685

$[M+H]^+$ measured: 700.2686

EXAMPLE 399

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(3-fluoro-4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and (3S)-3-(4-morpholinylmethyl)-1,2,3,4-tetrahydroisoquinoline (see Preparation 3') in Step A, and the compound of Preparation 20" in Step C. The product obtained is finally subjected to a step of conversion into salt form in the presence of 1M HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the expected compound is obtained.

Elemental microanalysis: (% theoretical:measured)

% C=62.21:61.32; % H=5.36:5.18; % N=11.46:11.14; % Cl=9.66:10.16; % Cl⁻=4.83:5.23

High-resolution mass spectrometry (ESI+/-FIA/HR, ESI-/FIA):

Empirical formula: $C_{38}H_{38}ClFN_6O_4$

$[M+H]^+$ calculated: 697.2700

$[M+H]^+$ measured: 697.2704

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EXAMPLE 400

Methyl 2-[[[5-(5-chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-1,2-dimethyl-1H-pyrrol-3-yl]carbonyl](4-hydroxyphenyl)amino]pyridine-4-carboxylate hydrochloride

The title compound is a secondary product which forms in the course of synthesis of Example 110 (in the final Step before the step of conversion into salt form) owing to hydrolysis of the nitrile function into a methyl ester function. The compound is separated from that of Example 110 by chromatography over silica gel in a mixture of methanol and dichloromethane.

Elemental microanalysis: (% , theoretical:measured)

% C=63.90:64.43; % H=5.36:5.01; % N=9.09:9.34; %

Cl=4.60:4.46

High-resolution mass spectrometry (ESI+/HR and ESI-/LR):

Empirical formula: C₄₁H₄₀ClN₅O₆

[M+H]⁺ calculated: 734.2740

[M+H]⁺ measured: 734.2743

EXAMPLE 401

5-(5-Chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(3-cyano-4-fluorophenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% , theoretical:measured)

% C=65.25:64.23; % H=5.07:4.71; % N=9.28:9.36; % Cl=9.40:9.59; % Cl⁻=4.70:4.50

High-resolution mass spectrometry (ESI+-FIA/HR, ESI-/FIA):

Empirical formula: C₄₁H₃₇ClFN₅O₄

[M+H]⁺ calculated: 718.2591

[M+H]⁺ measured: 718.2593

EXAMPLE 402

5-(5-Fluoro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-{1-[(3S or R)-tetrahydrofuran-3-yl]-1H-pyrazol-4-yl}-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% , theoretical:measured)

% C=65.20:65.92; % H=5.87:5.78; % N=11.13:10.36% Cl⁻=4.69:4.79)

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₁H₄₃FN₆O₅

[M+H]⁺ calculated: 719.3359

[M+H]⁺ measured: 719.3362 and

EXAMPLE 403

5-(5-Fluoro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-{1-[(3R or S)-tetrahydrofuran-3-yl]-1H-pyrazol-4-yl}-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% , theoretical:measured)

% C=65.20:66.04; % H=5.87:5.87; % N=11.13:10.62; % Cl⁻=4.69:4.76

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High-resolution mass spectrometry (ESI/+):

Empirical formula: C₄₁H₄₃FN₆O₅

[M+H]⁺ calculated: 719.3359

[M+H]⁺ measured: 719.3350

The compounds of Examples 402 and 403 are obtained in accordance with the process of Example 1 using the acid of Preparation 8 and the compound of Preparation 3' in Step A, and the compound of Preparation 22" in Step C. The diastereoisomers obtained are separated by chiral chromatography and then converted into salt form and lyophilised as described in the general process to yield the title compounds.

EXAMPLE 404

5-(5-Chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(2-cyanopyrimidin-4-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

EXAMPLE 405

5-(5-Chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-(pyridazin-4-yl)-1H-pyrrole-3-carboxamide dihydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the appropriate amine in Step C, it being understood that Step D is not carried out. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

High-resolution mass spectrometry (ESI+-FIA/HR, ESI-/FIA):

Empirical formula: C₄₀H₃₉ClN₈O₃

[M+H]⁺ calculated: 715.2906

[M+H]⁺ measured: 715.2909

EXAMPLE 406

N-(5-Cyano-1,2-dimethyl-1H-pyrrol-3-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-5-(2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 25 and the compound of Preparation 3' in Step A, and the compound of Preparation 18" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)

% C=68.46:68.27; % H=6.03:5.12; % N=11.68:11.75; % Cl⁻=4.93:4.73

High-resolution mass spectrometry (ESI/FIA/HR and MS/MS, ESI-/FIA):

Empirical formula: C₄₁H₄₂N₆O₄

[M+H]⁺ calculated: 683.3340

[M+H]⁺ measured: 683.3334

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EXAMPLE 407

N-(3-Fluoro-4-hydroxyphenyl)-5-(5-methoxy-2-
 {[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroiso-
 quinolin-2(1H)-yl]carbonyl}phenyl)-1,2-dimethyl-
 N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-car-
 boxamide hydrochloride

The title compound is obtained in accordance with the
 process of Example 1 using the acid of Preparation 12 and the
 compound of Preparation 3' in Step A, and the compound of
 Preparation 20" in Step C. The compound obtained is con-
 verted into salt form and lyophilised as described in the gen-
 eral process to obtain the title compound.

Elemental microanalysis: (% theoretical:measured)
 % C=64.23:63.94; % H=5.80:5.00; % N=11.52:11.56; %
 Cl=4.86:4.99

High-resolution mass spectrometry (ESI+/FIA/HR and
 MS/MS, ESI-/FIA):

Empirical formula: C₃₉H₄₁FN₆O₅

[M+H]⁺ calculated: 693.3195

[M+H]⁺ measured: 693.3191

EXAMPLE 408

N-(5-Cyano-1,2-dimethyl-1H-pyrrol-3-yl)-N-(4-
 hydroxyphenyl)-5-(5-methoxy-2-
 {[(3S)-3-(morpho-
 lin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]
 carbonyl}phenyl)-1,2-dimethyl-1H-pyrrole-3-
 carboxamide hydrochloride

The title compound is obtained in accordance with the
 process of Example 1 using the acid of Preparation 12 and the
 compound of Preparation 3' in Step A, and the compound of
 Preparation 18" in Step C. The compound obtained is con-
 verted into salt form and lyophilised as described in the gen-
 eral process to obtain the title compound.

Elemental microanalysis: (% theoretical:measured)
 % C=67.32:67.30; % H=6.05:5.28; % N=11.22:11.15; %
 Cl=4.73:4.59

High-resolution mass spectrometry (ESI+/FIA/HR and
 ESI-/FIA):

Empirical formula: C₄₂H₄₄N₆O₅

[M+H]⁺ calculated: 713.3446

[M+H]⁺ measured: 713.3443

EXAMPLE 409

N-(4-Hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-
 1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(2-
 {[(3S)-3-(morpho-
 lin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-
 yl]carbonyl}phenyl)-1H-pyrrole-3-carboxamide
 hydrochloride

The title compound is obtained in accordance with the
 process of Example 1 using the acid of Preparation 25 and the
 compound of Preparation 3' in Step A, and the compound of
 Preparation 11" in Step C. The compound obtained is con-
 verted into salt form and lyophilised as described in the gen-
 eral process to obtain the title compound.

Elemental microanalysis: (% theoretical:measured)
 % C=68.98:68.95; % H=5.93:4.76; % N=11.49:11.43
 High-resolution mass spectrometry (ESI/FIA/HR and
 MS/MS):

Empirical formula: C₄₂H₄₂N₆O₄

[M+H]⁺ calculated: 695.3340

[M+H]⁺ measured: 695.3341

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EXAMPLE 410

N-(4-Hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,
 3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-5-(2-
 {[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroiso-
 quinolin-2(1H)-yl]carbonyl}phenyl)-1H-pyrrole-3-
 carboxamide hydrochloride

The title compound is obtained in accordance with the
 process described in Step B of Example 49 using Example
 409 as starting material. The compound obtained is converted
 into salt form and lyophilised as described in the general
 process to obtain the title compound.

High-resolution mass spectrometry (ESI/FIA/HR and
 ESI-/FIA):

Empirical formula: C₄₂H₄₄N₆O₄

[M+H]⁺ calculated: 697.3497

[M+H]⁺ measured: 697.3497

EXAMPLE 411

5-(5-Chloro-2-
 {[(3R)-3-methyl-3,4-dihydroisoquino-
 lin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphe-
 nyl)-2-methyl-N-(1-methyl-1H-pyrazol-4-yl)-1-[2-
 (morpholin-4-yl)ethyl]-1H-pyrrole-3-carboxamide
 hydrochloride

The title compound is obtained in accordance with the
 process of Example 96 using the acid of Preparation 30, the
 compound of Preparation 1', and the compound of Prepara-
 tion 1". The compound obtained is converted into salt form
 and lyophilised as described in the general process to obtain
 the title compound.

High-resolution mass spectrometry (ESI/FIA/HR and
 MS/MS):

Empirical formula: C₃₉H₄₁ClN₆O₄

[M+H]⁺ calculated: 693.2951

[M+H]⁺ measured: 693.2947

EXAMPLE 412

5-(5-Chloro-2-
 {[(3R)-3-[3-(morpholin-4-yl)propyl]-
 3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-
 N-(5-cyano-1,2-dimethyl-1H-pyrrol-3-yl)-N-(4-hy-
 droxyphenyl)-1,2-dimethyl-1H-pyrrole-3-
 carboxamide hydrochloride

The title compound is obtained in accordance with the
 process of Example 1 using the acid of Preparation 1 and the
 compound of Preparation 6' in Step A, and the compound of
 Preparation 18" in Step C. The compound obtained is con-
 verted into salt form and lyophilised as described in the gen-
 eral process to obtain the title compound.

Elemental microanalysis: (% theoretical:measured)

% C=66.06:65.61; % H=5.93:5.22; % N=10.75:10.69; %
 Cl=4.53:4.68

High-resolution mass spectrometry (ESI/FIA/HR and
 MS/MS, ESI-/FIA):

Empirical formula: C₄₃H₄₅ClN₆O₄

[M+H]⁺ calculated: 745.3264

[M+H]⁺ measured: 745.3260

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EXAMPLE 413

N-(5-Cyano-1,2-dimethyl-1H-pyrrol-3-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-5-(7-[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl)-2,3-dihydro-1,4-benzodioxin-6-yl)-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 13 and the compound of Preparation 3' in Step A, and the compound of Preparation 18" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% theoretical:measured)
% C=66.44:66.40; % H=5.83:4.84; % N=10.81:10.79; % Cl=4.56:4.22

High-resolution mass spectrometry (ESI/FIA/HR and MS/MS, ESI-/FIA):

Empirical formula: $C_{43}H_{44}N_6O_6$

[M+H]⁺ calculated: 741.3395

[M+H]⁺ measured: 741.3397

EXAMPLE 414

5-(5-Chloro-2-[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(5-methyl-5H-pyrrolo[3,2-d]pyrimidin-2-yl)-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the appropriate amine in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% theoretical:measured)
% C=64.23:64.38; % H=5.39:5.25; % N=12.79:12.62; % Cl=4.62:4.39

High-resolution mass spectrometry (ESI/FIA/HR and MS/MS, ESI-/FIA):

Empirical formula: $C_{41}H_{40}ClN_7O_4$

[M+H]⁺ calculated: 730.2903

[M+H]⁺ measured: 730.2904

EXAMPLE 415

5-(5-Chloro-2-[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(5-cyano-1,2-dimethyl-1H-pyrrol-3-yl)-N-(4-hydroxyphenyl)-1-methyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 3 and the compound of Preparation 3' in Step A, and the compound of Preparation 18" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% theoretical:measured)
% C=64.95:65.14; % H=5.45:5.34; % N=11.36:11.36; % Cl=4.79:4.67

High-resolution mass spectrometry (ESI+/FIA/HR, ESI-/FIA):

Empirical formula: $C_{40}H_{39}ClN_6O_4$

[M+H]⁺ calculated: 703.2794

[M+H]⁺ measured: 703.2795

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EXAMPLE 416

5-(5-Chloro-2-[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-[1-(trideuteriomethyl)-1H-pyrazol-4-yl]-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 25" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% theoretical:measured)
% C=63.51:63.41; % H=5.63:5.42; % N=11.69:11.61; % Cl=4.93:4.85

High-resolution mass spectrometry (ESI+/FIA/HR, ESI-/FIA):

Empirical formula: $C_{38}H_{36}ClD_3N_6O_4$

[M+H]⁺ calculated: 682.2982

[M+H]⁺ measured: 682.2986

EXAMPLE 417

N-(5-Cyano-1,2-dimethyl-1H-pyrrol-3-yl)-N-(4-hydroxyphenyl)-5-(4-methoxy-2-[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 31 and the compound of Preparation 3' in Step A, and the compound of Preparation 18" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% theoretical:measured)
% C=67.32:67.56; % H=6.05:5.84; % N=11.22:11.21; % Cl=4.73:4.71

High-resolution mass spectrometry (ESI/FIA/HR and MS/MS, ESI-/FIA):

Empirical formula: $C_{42}H_{44}N_6O_5$

[M+H]⁺ calculated: 713.3446

[M+H]⁺ measured: 713.3446

EXAMPLE 418

N-(4-Hydroxyphenyl)-5-(4-methoxy-2-[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 31 and the compound of Preparation 3' in Step A, and the compound of Preparation 1" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% theoretical:measured)
% C=65.86:65.51; % H=6.09:6.09; % N=11.82:11.73; % Cl=4.98:5.14

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High-resolution mass spectrometry (ESI/FIA/HR, ESI-/FIA):

Empirical formula: $C_{39}H_{42}N_6O_5$

$[M+H]^+$ calculated: 675.3289

$[M+H]^+$ measured: 675.3286

EXAMPLE 419

N-(3-Cyanophenyl)-5-(5-fluoro-2-[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 8 and the compound of Preparation 3' in Step A, and the compound of Preparation 41" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

High-resolution mass spectrometry (ESI+):

Empirical formula: $C_{41}H_{38}FN_5O_4$

$[M+H]^+$ calculated: 684.2988

$[M+H]^+$ measured: 684.2975

EXAMPLE 420

5-(5-Fluoro-2-[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-[1-(trideuteriomethyl)-1H-pyrazol-4-yl]-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 8 and the compound of Preparation 3' in Step A, and the compound of Preparation 25" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

High-resolution mass spectrometry (ESI/+):

Empirical formula: $C_{38}D_3H_3FN_6O_4$

$[M+H]^+$ calculated: 666.3285

$[M+H]^+$ measured: 666.3265

EXAMPLE 421

N-(5-Cyano-1,2-dimethyl-1H-pyrrol-3-yl)-5-(5-fluoro-2-[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 8 and the compound of Preparation 3' in Step A, and the compound of Preparation 18" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):

Empirical formula: $C_{41}H_{41}FN_6O_4$

$[M+H]^+$ calculated: 701.3246

$[M+H]^+$ measured: 701.3282

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EXAMPLE 422

N-(4-Hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-5-(2-[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 25 and the compound of Preparation 3' in Step A, and the compound of Preparation 1" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% theoretical:measured)

% C=67.00:67.47; % H=6.07:5.54; % N=12.34:12.46; % Cl=5.20:4.58

High-resolution mass spectrometry (ESI+/FIA/HR, ESI-/FIA):

Empirical formula: $C_{38}H_{40}N_6O_4$

$[M+H]^+$ calculated: 645.3184

$[M+H]^+$ measured: 645.3182

EXAMPLE 423

5-(5-Fluoro-2-[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-[1-(oxetan-3-yl)-1H-pyrazol-4-yl]-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 8 and the compound of Preparation 3' in Step A, and the compound of Preparation 26" in Step C.

Elemental microanalysis: (% theoretical:measured)

% C=68.17:67.82; % H=5.86:5.97; % N=11.92:11.48

High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):

Empirical formula: $C_{40}H_{41}FN_6O_5$

$[M+H]^+$ calculated: 705.3202

$[M+H]^+$ measured: 705.3207

EXAMPLE 424

N-(4-Hydroxyphenyl)-N-(2-methoxypyrimidin-5-yl)-1,2-dimethyl-5-(2-[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 25 and the compound of Preparation 3' in Step A, and the compound of Preparation 12" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% theoretical:measured)

% C=66.05:65.63; % H=5.83:5.45; % N=11.85:11.93; % Cl=5.00:4.91

High-resolution mass spectrometry (ESI+/FIA/HR, ESI-/FIA):

Empirical formula: $C_{39}H_{40}N_6O_5$

$[M+H]^+$ calculated: 673.3133

$[M+H]^+$ measured: 673.3129

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EXAMPLE 425

N-(3-Cyano-5-methoxyphenyl)-5-(5-fluoro-2-
{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroiso-
quinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydrox-
yphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide
hydrochloride

The title compound is obtained in accordance with the
process of Example 1 using the acid of Preparation 8 and the
compound of Preparation 3' in Step A, and the appropriate
amine in Step C. The compound obtained is converted into
salt form and lyophilised as described in the general process
to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)
% C=67.25:66.55; % H=5.51:5.28; % N=9.33:8.55%
Cl⁻=4.73:4.67

EXAMPLE 426

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-
dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-
hydroxyphenyl)-N-(2-methoxypyrimidin-5-yl)-1,2-
dimethyl-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the
process of Example 1 using the acid of Preparation 8 and the
compound of Preparation 3' in Step A, and the compound of
Preparation 12" in Step C.

High-resolution mass spectrometry (ESI/FIA/HR and
MS/MS):

Empirical formula: C₃₉H₃₉FN₆O₅
[M+H]⁺ calculated: 691.3038
[M+H]⁺ measured: 691.3060

EXAMPLE 427

N-(3-Cyano-4-methoxyphenyl)-5-(5-fluoro-2-
{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroiso-
quinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydrox-
yphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide
hydrochloride

The title compound is obtained in accordance with the
process of Example 1 using the acid of Preparation 8 and the
compound of Preparation 3' in Step A, and the appropriate
amine in Step C. The compound obtained is converted into
salt form and lyophilised as described in the general process
to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)
% C=67.24:66.41; % H=5.51:5.35; % N=9.33:8.97%
Cl⁻=4.73:4.81

EXAMPLE 428

N-(5-Cyano-1,2-dimethyl-1H-pyrrol-3-yl)-5-(4-
fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihy-
droisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-
hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-
carboxamide hydrochloride

The title compound is obtained in accordance with the
process of Example 1 using the acid of Preparation 26 and the
compound of Preparation 3' in Step A, and the compound of
Preparation 18" in Step C. The compound obtained is con-
verted into salt form and lyophilised as described in the gen-
eral process to obtain the title compound.

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Elemental microanalysis: (% , theoretical:measured)

% C=66.79:66.97; % H=5.74:5.36; % N=11.40:11.45; %
Cl⁻=4.81:4.53

High-resolution mass spectrometry (ESI+/-/FIA/HR,
ESI-/FIA):

Empirical formula: C₄₁H₄₁FN₆O₄
[M+H]⁺ calculated: 701.3246
[M+H]⁺ measured: 701.3245

EXAMPLE 429

N-(5-Cyano-1,2-dimethyl-1H-pyrrol-3-yl)-5-(4-
fluoro-5-methoxy-2-{[(3S)-3-(morpholin-4-ylm-
ethyl)-3,4-dihydroisoquinolin-2(1H)-yl]
carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-
dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the
process of Example 1 using the acid of Preparation 27 and the
compound of Preparation 3' in Step A, and the compound of
Preparation 18" in Step C. The compound obtained is con-
verted into salt form and lyophilised as described in the gen-
eral process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)
% C=65.75:65.43; % H=5.78:5.57; % N=10.95:10.81; %
Cl⁻=4.62:4.54

High-resolution mass spectrometry (ESI/FIA/HR and
MS/MS, ESI-/FIA):

Empirical formula: C₄₂H₄₃FN₆O₅
[M+H]⁺ calculated: 731.3352
[M+H]⁺ measured: 731.3351

EXAMPLE 430

5-(5-Chloro-2-{[3-(trifluoromethyl)-3,4-dihydroiso-
quinolin-2(1H)-yl]-carbonyl}phenyl)-N-(4-hydrox-
yphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-
b]-pyridin-5-yl)-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the
process of Example 1 using the acid of Preparation 1 and
racemic 3-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline
in Step A, and the compound of Preparation 11" in Step C.

High-resolution mass spectrometry (ESI+/-/FIA/HR and
MS/MS, ESI-/FIA):

Empirical formula: C₃₈H₃₁ClF₃N₅O₃
[M+H]⁺ calculated: 698.2140
[M+H]⁺ measured: 698.2144

EXAMPLE 431

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-
dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(1,
3-dimethyl-1H-pyrazol-4-yl)-N-(4-hydroxyphenyl)-
1,2-dimethyl-1H-pyrrole-3-carboxamide
hydrochloride

Elemental microanalysis: (% , theoretical:measured)
% C=64.19:64.37; % H=5.80:5.18; % N=11.52:11.55; %
Cl⁻=4.86:4.68

High-resolution mass spectrometry (ESI+/-/FIA/HR,
ESI-/FIA):

Empirical formula: C₃₉H₄₁ClN₆O₄
[M+H]⁺ calculated: 693.2951
[M+H]⁺ measured: 693.2952

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EXAMPLE 432

5-(5-Chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(1,5-dimethyl-1H-pyrazol-4-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% , theoretical:measured)
% C=64.19:64.43; % H=5.80:5.22; % N=11.52:11.60; % Cl=4.86:4.66

High-resolution mass spectrometry (ESI+/-/FIA/HR, ESI-/FIA):

Empirical formula: C₃₉H₄₁ClN₆O₄

[M+H]⁺ calculated: 693.2951

[M+H]⁺ measured: 693.2953

The compounds of Examples 431 and 432 are obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the mixture of Preparation 27" in Step C. At the end of Step D, the isomers are separated by preparative HPLC using acetonitrile and water-TFA as eluants. After evaporating off the solvent and neutralising with sodium bicarbonate, the products are subjected to a step of conversion into salt form in the presence of 1M HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the title products are obtained.

EXAMPLE 433

N-(5-Cyano-1-methyl-1H-pyrrol-3-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-5-(2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 25 and the compound of Preparation 3' in Step A, and the compound of Preparation 19" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)

% C=68.12:68.29; % H=5.86:5.40; % N=11.92:12.05; % Cl=5.03:4.92

High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):

Empirical formula: C₄₀H₄₀N₆O₄

[M+H]⁺ calculated: 669.3184

[M+H]⁺ measured: 669.3184

EXAMPLE 434

5-(5-Fluoro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process described in Step B of Example 49 using Example 385 as starting material. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

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Elemental microanalysis: (% , theoretical:measured)

% C=67.15:68.03; % H=5.90:5.50; % N=11.19:10.59% Cl=4.72:5.55

EXAMPLE 435

N-(4-Cyanopyridin-2-yl)-5-(5-fluoro-4-methoxy-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 14 and the compound of Preparation 3' in Step A, and the appropriate amine in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

High-resolution mass spectrometry (ESI+/-/FIA/HR, ESI-/FIA):

Empirical formula: C₄₁H₃₉FN₆O₅

[M+H]⁺ calculated: 715.3039

[M+H]⁺ measured: 715.3040

EXAMPLE 436

5-(5-Chloro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(5-cyanothiophen-2-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the appropriate amine in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)

% C=63.07:63.09; % H=5.02:4.78; % N=9.43:9.35; % S=4.32:4.09; % Cl=4.77:4.59

High-resolution mass spectrometry (ESI/FIA/HR and MS/MS, ESI+/-/FIA):

Empirical formula: C₃₉H₃₆ClN₅O₄S

[M+H]⁺ calculated: 706.2249;

[M+H]⁺ measured: 706.2250

EXAMPLE 437

N-(3-Cyano-4-fluorophenyl)-5-(5-fluoro-2-[[[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl]phenyl]-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 8 and the compound of Preparation 3' in Step A, and the appropriate amine in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

High-resolution mass spectrometry (ES+):

Empirical formula: C₄₁H₃₇F₂N₅O₄

[M+H]⁺ calculated: 702.2894

[M+H]⁺ measured: 702.2886

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EXAMPLE 438

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(pyrazin-2-yl)-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the appropriate amine in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)

% C=63.95:63.96; % H=5.37:5.17; % N=11.78:11.61; % Cl⁻=4.97:4.57

High-resolution mass spectrometry (ESI+/HR, ESI-/LR):

Empirical formula: C₃₈H₃₇ClN₆O₄

[M+H]⁺ calculated: 677.2638

[M+H]⁺ measured: 677.2639

EXAMPLE 439

5-(5-Fluoro-4-methoxy-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-N-(2-methoxy-pyrimidin-5-yl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 14 and the compound of Preparation 3' in Step A, and the compound of Preparation 12" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

High-resolution mass spectrometry (ESI/FIA/HR and MS/MS, ESI-/FIA):

Empirical formula: C₄₀H₄₁FN₆O₆

[M+H]⁺ calculated: 721.3144

[M+H]⁺ measured: 721.3144

EXAMPLE 440

N-(5-Cyano-1,2-dimethyl-1H-pyrrol-3-yl)-5-(5-fluoro-4-methoxy-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 14 and the compound of Preparation 3' in Step A, and the compound of Preparation 18" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)

% C=65.75:65.98; % H=5.78:5.50; % N=10.95:10.87; % Cl⁻=4.62:4.42

High-resolution mass spectrometry (ESI+/HR, ESI-/LR):

Empirical formula: C₄₂H₄₃FN₆O₅

[M+H]⁺ calculated: 731.3352

[M+H]⁺ measured: 731.3353

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EXAMPLE 441

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(5-cyano-1,2-dimethyl-1H-pyrrol-3-yl)-1,2-dimethyl-N-phenyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 29" in Step C, it being understood that Step D is not carried out. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)

% C=66.75:66.44; % H=5.74:5.59; % N=11.39:11.45; % Cl⁻=4.81:4.43

High-resolution mass spectrometry (ESI+/HR, ESI-/LR):

Empirical formula: C₄₁H₄₁ClN₆O₃

[M+H]⁺ calculated: 701.3001

[M+H]⁺ measured: 701.2998

EXAMPLE 442

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(5-cyanothiophen-3-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 42" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)

% C=63.07:63.14; % H=5.02:4.87; % N=9.43:9.41; % S=4.32:4.24; % Cl⁻=4.77:4.57

High-resolution mass spectrometry (ESI+/HR, ESI-/LR):

Empirical formula: C₃₉H₃₆ClN₅O₄S

[M+H]⁺ calculated: 706.2249

[M+H]⁺ measured: 706.2252

EXAMPLE 443

5-(5-Fluoro-4-hydroxy-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-phenyl-1H-pyrrole-3-carboxamide

Step A: 5-(5-Fluoro-4-methoxy-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-phenyl-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 1 (Steps A to C) using the acid of Preparation 28 and the compound from Preparation 3' in Step A, and the compound of Preparation 30" in Step C.

Step B: 5-(5-Fluoro-4-hydroxy-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-N-phenyl-1H-pyrrole-3-carboxamide

To a solution of the compound of Step A (1 g; 1.37 mmol) in anhydrous dichloromethane (10 mL) there is added, drop-

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wise at 0° C., a 1M solution of boron tribromide in dichloromethane (1.8 mL; 1.8 mmol). After stirring for 15 hours at ambient temperature, the reaction mixture is poured dropwise into a solution of ethanol (15 mL) at -10° C. After stirring for one hour, saturated aqueous sodium bicarbonate solution is added, and the reaction mixture is extracted with dichloromethane. After drying over MgSO₄, the residue is purified on a silica gel column using a mixture of dichloromethane and methanol as eluant to yield the expected product.

High-resolution mass spectrometry (ESI+/HR, ESI-/LR):
Empirical formula: C₄₂H₄₁FN₆O₄
[M+H]⁺ calculated: 713.3246
[M+H]⁺ measured: 713.3244

EXAMPLE 444

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-N-(5-methoxy-pyrazin-2-yl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the appropriate amine in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)
% C=62.99:62.72; % H=5.42:5.24; % N=11.30:11.19; % Cl=4.77:4.67

High-resolution mass spectrometry (ESI+/HR, ESI-/LR):
Empirical formula: C₃₉H₃₉ClN₆O₅
[M+H]⁺ calculated: 707.2743
[M+H]⁺ measured: 707.2747

EXAMPLE 445

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-[1-(trideuteriomethyl)-2,3-dihydro-H-pyrrolo[2,3-b]pyridin-5-yl]-1H-pyrrole-3-carboxamide hydrochloride

Step A: 5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-[1-(trideuteriomethyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-1H-pyrrole-3-carboxamide

The intermediate is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 31" in Step C.

Step B: 5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-[1-(trideuteriomethyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-5-yl]-1H-pyrrole-3-carboxamide hydrochloride

The procedure is in accordance with the protocol described in Step B of Example 49, it being understood that the product is then subjected to a step of conversion into salt form in the presence of 1M HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the title product is obtained.

Elemental microanalysis: (% , theoretical:measured)
% C=65.45:65.33; % H=5.78:5.59; % N=10.90:10.82; % Cl=4.60:4.28

High-resolution mass spectrometry (ESI+/HR, ESI-/LR):
Empirical formula: C₄₂H₄₀ClD₃N₆O₄

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[M+H]⁺ calculated: 734.3295
[M+H]⁺ measured: 734.3300

EXAMPLE 446

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(5-fluoropyrazin-2-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the appropriate amine in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)
% C=62.28:62.16; % H=5.10:4.97; % N=11.04:11.35; % Cl=4.85:4.48

High-resolution mass spectrometry (ESI+/HR, ESI-/LR):
Empirical formula: C₃₈H₃₆ClF N₆O₄
[M+H]⁺ calculated: 695.2543
[M+H]⁺ measured: 695.2545

EXAMPLE 447

5-(4-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 26 and the compound of Preparation 3' in Step A, and the compound of Preparation 1" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)
% C=65.28:65.27; % H=5.77:5.51; % N=12.02:1.90; % Cl=5.07:4.74

High-resolution mass spectrometry (ESI+/HR, ESI-/LR):
Empirical formula: C₃₈H₃₉FN₆O₄
[M+H]⁺ calculated: 663.3090
[M+H]⁺ measured: 663.3084

EXAMPLE 448

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-[5-cyano-1-(trideuteriomethyl)-1H-pyrrol-3-yl]-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 32" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)
% C=64.69:64.23; % H=5.45:5.47; % N=11.32:11.16; % Cl=4.77:4.56

High-resolution mass spectrometry (ESI+/HR, ESI-/LR):
Empirical formula: C₄₀H₃₆ClD₃N₆O₄
[M+H]⁺ calculated: 706.2982
[M+H]⁺ measured: 706.2985

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EXAMPLE 449

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-[5-cyano-2-methyl-1-(trideuteriomethyl)-1H-pyrrol-3-yl]-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 33" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)

% C=65.07:64.55; % H=5.62:5.51; % N=11.11:10.98; % Cl⁻=4.68:4.58

High-resolution mass spectrometry (ESI+/HR, ESI-/LR):

Empirical formula: C₄₁H₃₈ClD₃N₆O₄

[M+H]⁺ calculated: 720.3139

[M+H]⁺ measured: 720.3143

EXAMPLE 450

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(3-cyano-1-methyl-1H-pyrazol-5-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 34" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)

% C=63.24:62.62; % H=5.31:5.09; % N=13.24:13.04; % Cl⁻=4.79:4.37

High-resolution mass spectrometry (ESI+/HR, ESI-/LR):

Empirical formula: C₃₉H₃₈ClN₇O₄

[M+H]⁺ calculated: 704.2747

[M+H]⁺ measured: 704.2747

EXAMPLE 451

5-(5-Fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 8 and the compound of Preparation 3' in Step A, and the compound of Preparation 17" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)

% C=65.64:66.28; % H=5.51:5.45; % N=13.07:12.17% Cl⁻=4.73:5.51

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EXAMPLE 452

N-(1,3-Dimethyl-1H-pyrazol-4-yl)-5-(5-fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% , theoretical:measured)

% C=65.68:64.77; % H=5.94:5.55; % N=11.78:10.69% Cl⁻=4.97:6.48

and

EXAMPLE 453

N-(1,5-Dimethyl-1H-pyrazol-4-yl)-5-(5-fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

Elemental microanalysis: (% , theoretical:measured)

% C=65.68:65.43; % H=5.94:5.62; % N=11.78:10.95%

Cl⁻=4.97:5.60

The compounds of Examples 452 and 453 are obtained in accordance with the process of Example 1 using the acid of Preparation 8 and the compound of Preparation 3' in Step A, and the mixture of Preparation 27" in Step C. At the end of Step D, the isomers are separated by preparative HPLC using acetonitrile and water-TFA as eluants. After evaporating off the solvent and neutralising with sodium bicarbonate, the products are subjected to a step of conversion into salt form in the presence of 1M HCl in ether. After filtration and lyophilisation in a mixture of acetonitrile/water, the title products are obtained.

EXAMPLE 454

5-(5-Chloro-2-{[3-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(5-cyano-1,2-dimethyl-1H-pyrrol-3-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 1 using the acid from Preparation 1 and racemic 3-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline in Step A, and the compound of Preparation 18" in Step C.

Elemental microanalysis: (% , theoretical:measured)

% C=64.77:64.81; % H=4.55:4.52; % N=10.21:10.33

High-resolution mass spectrometry (ESI+/HR):

Empirical formula: C₃₇H₃₁ClF₃N₅O₃

[M+H]⁺ calculated: 686.2140

[M+H]⁺ measured: 686.2145

EXAMPLE 455

5-(5-Chloro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl}phenyl)-N-{5-cyano-2-methyl-1-[2-(morpholin-4-yl)ethyl]-1H-pyrrol-3-yl]-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 1' in Step A, and the compound of Preparation 35" in Step C. The compound obtained is con-

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verted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)

% C=65.71:66.07; % H=5.78:5.82; % N=10.95:10.66; % Cl=4.62:4.45

High-resolution mass spectrometry (ESI+/HR, ESI-/LR):

Empirical formula: C₄₂H₄₃ClN₆O₄

[M+H]⁺ calculated: 731.3107

[M+H]⁺ measured: 731.3109

EXAMPLE 456

5-(5-Chloro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-{2-[2-(morpholin-4-yl)-ethoxy]pyrimidin-5-yl}-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 1' in Step A, and the compound of Preparation 36" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)

% C=63.41:63.51; % H=5.59:5.26; % N=11.09:11.10; % Cl=4.68:4.46

High-resolution mass spectrometry (ESI+/HR, ESI-/LR):

Empirical formula: C₄₀H₄₁ClN₆O₅

[M+H]⁺ calculated: 721.2900

[M+H]⁺ measured: 721.2907

EXAMPLE 457

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(6-cyano-5-methoxypyridin-2-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the appropriate amine in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)

% C=64.15:63.95; % H=5.25:4.79; % N=10.95:10.97; % Cl=4.62:4.22

High-resolution mass spectrometry (ESI+/HR):

Empirical formula: C₄₁H₃₉ClN₆O₅

[M+H]⁺ calculated: 731.2743

[M+H]⁺ measured: 731.2746

EXAMPLE 458

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(5-cyano-1,4-dimethyl-1H-pyrrol-3-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 37" in Step C. The compound obtained is con-

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verted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)

% C=65.34:65.68; % H=5.62:5.31; % N=11.15:11.15; % Cl=4.70:4.33

High-resolution mass spectrometry (ESI+/HR, ESI-/LR):

Empirical formula: C₄₁H₄₁ClN₆O₄

[M+H]⁺ calculated: 717.2951

[M+H]⁺ measured: 717.2954

EXAMPLE 459

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(5-cyano-1-ethyl-2-methyl-1H-pyrrol-3-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 38" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)

% C=65.71; 65.29; % H=5.78:5.51; % N=10.95:10.95; % Cl=4.62:4.39

High-resolution mass spectrometry (ESI+/HR, ESI-/LR):

Empirical formula: C₄₂H₄₃ClN₆O₄

[M+H]⁺ calculated: 731.3107

[M+H]⁺ measured: 731.3109

EXAMPLE 460

5-(5-Chloro-2-{[(3R)-3-[3-(morpholin-4-yl)propyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-[1-(tetrahydrofuran-3-yl)-1H-pyrazol-4-yl]-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 6' in Step A, and the compound of Preparation 22" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)

% C=64.58:64.24; % H=6.05:5.88; % N=10.51:10.53; % Cl=4.43:4.39

High-resolution mass spectrometry (ESI+/HR, ESI-/LR):

Empirical formula: C₄₃H₄₇ClN₆O₅

[M+H]⁺ calculated: 763.3369

[M+H]⁺ measured: 763.3371

EXAMPLE 461

5-(5-Chloro-2-{[(3R)-3-[3-(morpholin-4-yl)propyl]-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(5-cyano-1,2-dimethyl-1H-pyrrol-3-yl)-1,2-dimethyl-N-phenyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 6' in Step A, and the compound of Preparation 29" in Step C, it being understood that Step D is

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not carried out. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)

% C=67.44:66.68; % H=6.05:5.80; % N=10.97:10.95; % Cl⁻=4.63:4.57

High-resolution mass spectrometry (ESI+/HR):

Empirical formula: C₄₃H₄₅ClN₆O₃

[M+H]⁺ calculated: 729.3314

[M+H]⁺ measured: 729.3316

EXAMPLE 462

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(5-methyl-1,2-oxazol-3-yl)-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the appropriate amine in Step C.

Elemental microanalysis: (% , theoretical:measured)

% C=67.10:66.64; % H=5.63:5.40; % N=10.30:10.24

High-resolution mass spectrometry (ESI+/HR, ESI-/LR):

Empirical formula: C₃₈H₃₈ClN₅O₅

[M+H]⁺ calculated: 680.2634

[M+H]⁺ measured: 680.2637

EXAMPLE 463

N-(2-Ethoxypyrimidin-5-yl)-5-(5-fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 8 and the compound of Preparation 3' in Step A, and the compound of Preparation 39" in Step C.

Elemental microanalysis: (% , theoretical:measured)

% C=68.17:67.52; % H=5.86:5.60; % N=11.92:11.43

EXAMPLE 464

5-(5-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(5-hydroxypyridin-2-yl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide dihydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and the compound of Preparation 3' in Step A, and the compound of Preparation 40" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

High-resolution mass spectrometry (ESI+/HR, ESI-/LR):

Empirical formula: C₄₁H₄₀ClN₇O₄

[M+H]⁺ calculated: 730.2903

[M+H]⁺ measured: 730.2907

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EXAMPLE 465

5-(4-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(5-cyano-1,2-dimethyl-1H-pyrrol-3-yl)-N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 29 and the compound of Preparation 3' in Step A, and the compound of Preparation 18" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)

% C=65.34:64.81; % H=5.62:5.27; % N=11.15:10.95% Cl⁻=4.70:5.09

High-resolution mass spectrometry (ESI+):

Empirical formula: C₄₁H₄₁ClN₆O₄

[M+H]⁺ calculated: 717.2951

[M+H]⁺ measured: 717.2952

EXAMPLE 466

5-(4-Chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide hydrochloride

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 29 and the compound of Preparation 3' in Step A, and the compound of Preparation 1" in Step C. The compound obtained is converted into salt form and lyophilised as described in the general process to obtain the title compound.

Elemental microanalysis: (% , theoretical:measured)

% C=66.77:62.82; % H=5.63:5.29; % N=11.74:11.75; % Cl⁻=5.01:5.23

High-resolution mass spectrometry (ESI+/HR, ESI-/LR):

Empirical formula: C₃₈H₃₉ClN₆O₄

[M+H]⁺ calculated: 679.2794

[M+H]⁺ measured: 679.2796

EXAMPLE 467

5-(5-Chloro-2-{[3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-phenyl-1H-pyrrole-3-carboxamide

The title compound is obtained in accordance with the process of Example 1 using the acid of Preparation 1 and 1,2,3,4-tetrahydroisoquinoline in Step A, and the compound of Preparation 2" in Step C.

Elemental microanalysis: (% , theoretical:measured)

% C=72.97:72.93; % H=5.25:5.08; % N=7.29:7.34

High-resolution mass spectrometry (ESI/FIA/HR and MS/MS):

Empirical formula: C₃₅H₃₀ClN₃O₃

[M+H]⁺ calculated: 576.2048

[M+H]⁺ measured: 576.2067

Example A

Inhibition of Bcl-2 by the Fluorescence Polarisation Technique

The fluorescence polarisation tests were carried out on microplates (384 wells). The Bcl-2 protein, labelled (histag-Bcl-2 such that Bcl-2 corresponds to the UniProtKB® primary accession number: P10415), at a final concentration of 2.50×10^{-8} M, is mixed with a fluorescent peptide (Fluorescein-REIGAQLRRMADDLNAQY), at a final concentration of 1.00×10^{-8} M in a buffer solution (Hepes 10 mM, NaCl 150 mM, Tween20 0.05%, pH 7.4), in the presence or absence of increasing concentrations of test compounds. After incubation for 2 hours, the fluorescence polarisation is measured.

The results are expressed in IC_{50} (the concentration of compound that inhibits fluorescence polarisation by 50%) and are presented in Table 1 below.

The results show that the compounds of the invention inhibit interaction between the Bcl-2 protein and the fluorescent peptide described hereinbefore.

Example B

In vitro Cytotoxicity

The cytotoxicity studies were carried out on the RS4;11 leukaemia tumour line.

The cells are distributed onto microplates and exposed to the test compounds for 48 hours.

The cell viability is then quantified by a colorimetric assay, the Microculture Tetrazolium Assay (Cancer Res., 1987, 47, 939-942).

The results are expressed in IC_{50} (the concentration of compound that inhibits cell viability by 50%) and are presented in Table 1 below.

The results show that the compounds of the invention are cytotoxic.

TABLE 1

IC ₅₀ of Bcl-2 inhibition (fluorescence polarisation test) and of cytotoxicity for RS4;11 cells		
	IC ₅₀ (nM) Bcl-2 FP	IC ₅₀ (nM) MTT RS4;11
Example 1	5.0	33.6
Example 2	ND	1660
Example 3	24.6	94.9
Example 4	ND	231
Example 5	21.2	44.8
Example 6	25.2	69
Example 7	25.6	90.6
Example 8	ND	255
Example 9	22.4	87.5
Example 10	16.2	205
Example 11	14.2	202
Example 12	5.5	39.6
Example 13	4.4	19.8
Example 14	3.7	8.23
Example 15	11.1	69.4
Example 16	12.6	22.7
Example 17	8.0	75.2
Example 18	3.9	27.6
Example 19	6.0	65.5
Example 20	4.9	164
Example 21	4.7	79.9
Example 22	6.6	45.7
Example 23	3.6	25.4
Example 24	6.2	79.1

TABLE 1-continued

IC ₅₀ of Bcl-2 inhibition (fluorescence polarisation test) and of cytotoxicity for RS4;11 cells		
	IC ₅₀ (nM) Bcl-2 FP	IC ₅₀ (nM) MTT RS4;11
Example 25	4.0	33.3
Example 26	4.1	541
Example 27	5.2	93.4
Example 28	7.5	95.3
Example 29	6.6	47.5
Example 30	4.7	771
Example 31	7.2	89.3
Example 32	13.3	240
Example 33	10.9	57.8
Example 34	8.2	47
Example 35	50.0	560
Example 36	71.4	>600
Example 37	60.4	>600
Example 38	7.5	134
Example 39	7.2	19.7
Example 40	64.4	431
Example 41	10.0	22.6
Example 42	5.2	4.36
Example 43	5.1	28.9
Example 44	3.0	5.41
Example 45	38.9	403
Example 46	76.6	>600
Example 47	5.9	44.5
Example 48	4.4	14.9
Example 49	4.0	14.1
Example 50	5.9	33.1
Example 51	26.7	354
Example 52	28.9	433
Example 53	43.5	293
Example 54	18.0	30.5
Example 55	209.6	>600
Example 56	75.0	>600
Example 57	80.0	>600
Example 58	133.3	>600
Example 59	134.0	>600
Example 60	ND	18.3
Example 61	4.5	37.8
Example 62	14.3	127
Example 63	5.1	11.2
Example 65	21.9	113
Example 66	16.9	241
Example 67	12.5	98.6
Example 68	2.1	20.7
Example 69	5.3	3.68
Example 70	8.5	63.5
Example 71	6.1	12.9
Example 72	7.7	43.6
Example 73	8	42.6
Example 74	4	45.4
Example 75	52.9	367
Example 81	ND	249
Example 82	19.5	427
Example 88	15.9	69.6
Example 92	8.4	37.8
Example 93	19.7	368
Example 94	8.6	104
Example 95	7	174
Example 96	13.5	161
Example 97	19	98
Example 98	7.6	68.3
Example 99	6.4	108
Example 100	22.9	193
Example 101	21.1	743
Example 102	2	6.51
Example 108	3.9	15.4
Example 109	91.5	930
Example 110	8.5	39.5
Example 115	3.6	18.3
Example 116	3.4	47.8
Example 122	3.4	82.4
Example 126	4.2	49.2
Example 127	5.3	111
Example 129	18.1	275
Example 207	4.6	32.2
Example 209	7.4	25.4

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TABLE 1-continued

IC ₅₀ of Bcl-2 inhibition (fluorescence polarisation test) and of cytotoxicity for RS4;11 cells		
	IC ₅₀ (nM) Bcl-2 FP	IC ₅₀ (nM) MTT RS4;11
Example 210	8.8	47.2
Example 214	6.3	236
Example 230	5.1	18.3
Example 358	14.8	165
Example 384	9.7	216
Example 385	5.7	28.7
Example 386	2.6	9.23
Example 387	20.6	243
Example 388	3.6	16.5
Example 389	14.7	208
Example 390	21.2	173
Example 391	30.3	255
Example 392	3.8	11.4
Example 393	2.1	1.95
Example 394	2.5	2.76
Example 395	3.5	7.57
Example 396	15.7	116
Example 397	4.5	37.1
Example 398	3.9	13.4
Example 399	9.9	155
Example 400	49	469
Example 401	8	24.3
Example 402	26.1	241
Example 403	24.2	289
Example 404	24.4	85.5
Example 406	4.2	10.6
Example 407	20.6	150
Example 408	5.4	4.46
Example 409	12.2	41.9
Example 410	9.9	61.6
Example 411	5.5	32.8
Example 412	3.1	0.398
Example 413	3.1	9.43
Example 415	3.8	29.9
Example 416	2.9	42.5
Example 417	3	11
Example 418	10.1	159
Example 419	2.8	15.8
Example 420	6.1	51.8
Example 421	2.5	3.73
Example 422	9.2	101
Example 423	11.7	344
Example 424	13.6	102
Example 425	4.2	62
Example 426	5.2	139
Example 427	2.2	23.3
Example 428	3.5	59.2
Example 429	3.1	109
Example 430	19.9	328
Example 431	3	89
Example 432	3.4	76.6
Example 433	2.6	48.2
Example 434	3.5	45.7
Example 435	14.9	441
Example 436	49.1	338
Example 437	4.4	70.5
Example 438	11.3	379
Example 439	6.1	329
Example 440	2.6	13.6
Example 441	3.5	132
Example 442	3	42.8
Example 443	ND	57.9
Example 444	5.5	181
Example 445	2	19
Example 446	7.8	249
Example 447	20	>600
Example 448	2.4	12.1
Example 449	1.7	11.9
Example 450	2.7	53.2
Example 451	2.9	102
Example 452	8.3	112
Example 453	6.9	99.9
Example 454	6.5	158
Example 455	1.9	11.8
Example 456	2.7	80.6

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TABLE 1-continued

IC ₅₀ of Bcl-2 inhibition (fluorescence polarisation test) and of cytotoxicity for RS4;11 cells		
	IC ₅₀ (nM) Bcl-2 FP	IC ₅₀ (nM) MTT RS4;11
Example 457	ND	80.4
Example 458	10.5	197
Example 459	2.5	5.93
Example 460	2.8	22.9
Example 461	3.1	18.6
Example 462	13.3	368
Example 463	ND	40.8
Example 464	36.6	723
Example 465	ND	50.6
Example 466	ND	493
Example 467	19.2	188

ND: not determined

Example C

Induction of Caspase Activity in vivo

25 The ability of the compounds of the invention to activate caspase 3 is evaluated in a xenograft model of RS4;11 leukaemia cells.

30 1×10⁷ RS4;11 cells are grafted sub-cutaneously into immunosuppressed mice (SCID strain). 25 to 30 days after the graft, the animals are treated orally with the various compounds. Sixteen hours after treatment, the tumour masses are recovered and lysed, and the caspase 3 activity is measured in the tumour lysates.

35 This enzymatic measurement is carried out by assaying the appearance of a fluorogenic cleavage product (DEVDase activity, Promega). It is expressed in the form of an activation factor corresponding to the ratio between the two caspase activities: the activity for the treated mice divided by the activity for the control mice.

40 The results obtained show that the compounds of the invention are capable of inducing apoptosis in RS4;11 tumour cells in vivo.

Example D

Quantification of the Cleaved Form of Caspase 3 in vivo

50 The ability of the compounds of the invention to activate caspase 3 is evaluated in a xenograft model of RS4;11 leukaemia cells.

55 1×10⁷ RS4;11 cells are grafted sub-cutaneously into immunosuppressed mice (SCID strain). 25 to 30 days after the graft, the animals are treated orally with the various compounds. After treatment, the tumour masses are recovered and lysed, and the cleaved (activated) form of caspase 3 is quantified in the tumour lysates.

60 The quantification is carried out using the "Meso Scale Discovery (MSD) ELISA platform" test, which specifically assays the cleaved form of caspase 3. It is expressed in the form of an activation factor corresponding to the ratio between the quantity of cleaved caspase 3 in the treated mice divided by the quantity of cleaved caspase 3 in the control mice.

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The results show that the compounds of the invention are capable of inducing apoptosis in RS4;11 tumour cells in vivo.

TABLE 2

Caspase activation factors (cleaved caspase 3 MSD test in the tumours of treated mice versus control mice) in vivo, after treatment by the oral route (exact doses in brackets)		
Compound tested	Time period after which the tumour is removed (T)	Activation factor $\pm$ SEM (versus control)
Example 25	2 hours	45.7 $\pm$ 2.0 (25 mg/kg)
Example 28	2 hours	72.3 $\pm$ 5.4 (12.5 mg/kg)
Example 47	2 hours	12.3 $\pm$ 2.4 (25 mg/kg)
Example 61	2 hours	76.0 $\pm$ 5.2 (12.5 mg/kg)
Example 67	2 hours	29.8 $\pm$ 4.0 (25 mg/kg)
Example 71	2 hours	46.8 $\pm$ 16.1 (25 mg/kg)
Example 74	2 hours	24.5 $\pm$ 7.4 (12.5 mg/kg)
Example 108	2 hours	22.6 $\pm$ 2.4 (12.5 mg/kg)
Example 230	2 hours	42.2 $\pm$ 9.3 (25 mg/kg)
Example 386	2 hours	52.0 $\pm$ 8.6 (12.5 mg/kg)
Example 388	2 hours	85.7 $\pm$ 3.7 (25 mg/kg)
Example 421	2 hours	38.7 $\pm$ 10.7 (12.5 mg/kg)
Example 449	2 hours	50.5 $\pm$ 3.4 (12.5 mg/kg)

Example E

Anti-Tumour Activity in vivo

The anti-tumour activity of the compounds of the invention is evaluated in a xenograft model of RS4;11 leukaemia cells.

1 $\times$ 10⁷ RS4;11 cells are grafted sub-cutaneously into immunosuppressed mice (SCID strain). 25 to 30 days after the graft, when the tumour mass has reached about 150 mm³, the mice are treated orally with the various compounds in two different regimes (daily treatment for five days per week for two weeks, or two treatments weekly for two weeks). The tumour mass is measured twice weekly from the start of treatment.

The results obtained accordingly show that the compounds of the invention are capable of inducing significant tumour regression, which can be total, during the treatment period.

Example F

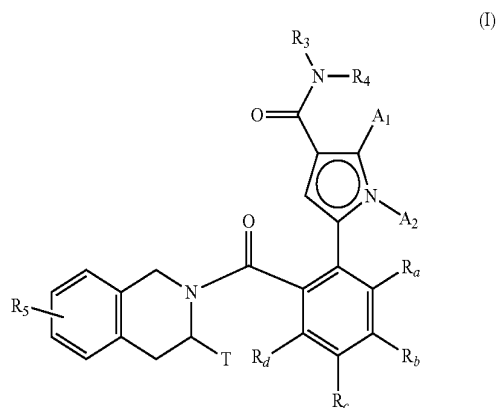
Pharmaceutical Composition: Tablets

1000 tablets containing a dose of 5 mg of a compound selected from Examples 1 to 467	5 g
Wheat starch	20 g
Maize starch	20 g
Lactose	30 g
Magnesium stearate	2 g
Silica	1 g
Hydroxypropylcellulose	2 g

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The invention claimed is:

1. A compound of formula (I):



wherein:

A₁ and A₂, each independently of the other, represent a hydrogen atom, a halogen atom, a linear or branched (C₁-C₆)polyhaloalkyl group, a linear or branched (C₁-C₆)alkyl group or a cycloalkyl group;

T represents a hydrogen atom, a linear or branched (C₁-C₆)alkyl group optionally substituted by from one to three halogen atoms, a (C₁-C₄)alkyl-NR₁R₂ group, or a (C₁-C₄)alkyl-OR₆ group;

R₁ and R₂, each independently of the other, represent a hydrogen atom or a linear or branched (C₁-C₆)alkyl group,

or R₁ and R₂ form with the nitrogen atom carrying them a heterocycloalkyl;

R₃ represents a linear or branched (C₁-C₆)alkyl group, a linear or branched C₂-C₆alkenyl group, a linear or branched (C₂-C₆)alkynyl group, a cycloalkyl group, a (C₃-C₁₀)cycloalkyl-(C₁-C₆)alkyl group wherein the alkyl moiety is linear or branched, a heterocycloalkyl group, an aryl group or a heteroaryl group, wherein one or more of the carbon atoms of the preceding groups, or of their possible substituents, may be deuterated;

R₄ represents an aryl group, a heteroaryl group, a cycloalkyl group or a linear or branched (C₁-C₆)alkyl group, wherein one or more of the carbon atoms of the preceding groups, or of their possible substituents, may be deuterated;

R₅ represents a hydrogen or halogen atom, a linear or branched (C₁-C₆)alkyl group, or a linear or branched (C₁-C₆)alkoxy group;

R₆ represents a hydrogen atom or a linear or branched (C₁-C₆)alkyl group;

R_a, R_b, R_c and R_d, each independently of the others, represent a hydrogen atom, a linear or branched (C₁-C₆)alkyl group, a linear or branched (C₂-C₆)alkenyl group, a linear or branched (C₂-C₆)alkynyl group, an aryl group, a heteroaryl group, a halogen atom, a linear or branched (C₁-C₆)alkoxy group, a hydroxy group, a linear or branched (C₁-C₆)polyhaloalkyl group, a trifluoromethoxy group, —NR₇R_{7'}, nitro, R₇—CO—(C₆-C₆)alkyl-, R₇—CO—NH—(C₆-C₆)alkyl-, NR₇R_{7'}—CO—(C₆-C₆)alkyl-, NR₇R_{7'}—CO—(C₆-C₆)alkyl-O-, R₇—SO₂—NH—(C₆-C₆)alkyl-, R₇—NH—CO—NH—(C₆-C₆)alkyl-, R₇—O—CO—NH—(C₆-C₆)alkyl-, a heterocycloalkyl group, or the substituents of one of the pairs (R_a, R_b), (R_b, R_c), or (R_c, R_d) form

together with the carbon atoms carrying them a ring composed of from 5 to 7 ring members, which ring may have from one to 2 hetero atoms selected from oxygen and sulphur, wherein one or more carbon atoms of the ring defined hereinbefore may be deuterated or substituted by from one to 3 groups selected from halogen and linear or branched (C₁-C₆)alkyl;

R₇ and R₇', each independently of the other, represent a hydrogen atom, a linear or branched (C₁-C₆)alkyl group, a linear or branched (C₂-C₆)alkenyl group, a linear or branched (C₂-C₆)alkynyl group, an aryl group or a heteroaryl group, or R₇ and R₇', together with the nitrogen atom carrying them, form a heterocycle composed of from 5 to 7 ring members;

it being understood that:

"aryl" means a phenyl, naphthyl, biphenyl or indenyl group,

"heteroaryl" means any mono- or bi-cyclic group composed of from 5 to 10 ring members, having at least one aromatic moiety and having from 1 to 4 hetero atoms selected from oxygen, sulphur and nitrogen (including quaternary nitrogens),

"cycloalkyl" means any mono- or bi-cyclic, non-aromatic, carbocyclic group having from 3 to 10 ring members,

"heterocycloalkyl" means any mono- or bi-cyclic, non-aromatic, condensed or spiro group composed of from 3 to 10 ring members and having from 1 to 3 hetero atoms selected from oxygen, sulphur, SO, SO₂ and nitrogen,

wherein the aryl, heteroaryl, cycloalkyl and heterocycloalkyl groups so defined and the alkyl, alkenyl, alkynyl and alkoxy groups may be optionally substituted by from 1 to 3 groups selected from optionally substituted, linear or branched (C₁-C₆)alkyl, (C₃-C₆)spiro, optionally substituted, linear or branched (C₁-C₆)alkoxy, (C₁-C₆)alkyl-S—, hydroxy, oxo (or N-oxide where appropriate), nitro, cyano, —COOR', —OCOR', NR'R'', linear or branched (C₁-C₆)polyhaloalkyl, trifluoromethoxy, (C₁-C₆)alkylsulphonyl, halogen, optionally substituted aryl, heteroaryl, aryloxy, arylthio, cycloalkyl, heterocycloalkyl optionally substituted by one or more halogen atoms or alkyl groups, wherein R' and R'', each independently of the other, represent a hydrogen atom or an optionally substituted, linear or branched (C₁-C₆)alkyl group, or an enantiomer, a diastereoisomer, or an addition salt thereof with a pharmaceutically acceptable acid or base.

2. The compound according to claim 1, wherein A₁ represents a hydrogen atom or a methyl group.

3. The compound according to claim 1, wherein A₂ represents a linear or branched (C₁-C₆)alkyl group optionally substituted by a group selected from halogen, hydroxy, linear or branched (C₁-C₆)alkoxy, NR'R'' and morpholine.

4. The compound according to claim 1, wherein A₂ represents a linear or branched (C₁-C₆)polyhaloalkyl group or a cyclopropyl group.

5. The compound according to claim 1, wherein A₁ and A₂ both represent a methyl group.

6. The compound according to claim 1, wherein T represents methyl, aminomethyl, (morpholin-4-yl)methyl, (4-methylpiperazin-1-yl)methyl, 2-(morpholin-4-yl)ethyl, [2-(morpholin-4-yl)ethoxy]methyl, hydroxymethyl, [2-(dimethylamino)ethoxy]methyl, hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-ylmethyl, 1-oxa-6-azaspiro[3.3]hept-6-ylmethyl, 3-(morpholin-4-yl)propyl or trifluoromethyl.

7. The compound according to claim 1, wherein R_a and R_d each represent a hydrogen atom and (R_b, R_c), together with the carbon atoms carrying them, form a 1,3-dioxolane group

or a 1,4-dioxane group; or R_a, R_c and R_d each represent a hydrogen atom and R_b represents a hydrogen atom, a halogen atom, or a methoxy group.

8. The compound according to claim 1, wherein R_a and R_d each represent a hydrogen atom, R_b represents a hydrogen or halogen atom and R_c represents a hydroxy or methoxy group; or R_a and R_d each represent a hydrogen atom, R_b represents a hydroxy or methoxy group and R_c represents a halogen atom.

9. The compound according to claim 1, wherein R_a, R_b and R_d each represent a hydrogen atom and R_c represents a group selected from R₇—CO—NH—(C₀-C₆)alkyl-, R₇—SO₂—NH—(C₀-C₆)alkyl-, R₇—NH—CO—NH—(C₀-C₆)alkyl- and R₇—O—CO—NH—(C₀-C₆)alkyl-.

10. The compound according to claim 1, wherein R₄ represents phenyl, 4-hydroxyphenyl, 3-fluoro-4-hydroxyphenyl, 2-hydroxypyrimidine or 3-hydroxypyridine.

11. The compound according to claim 1, wherein R₃ represents an aryl or heteroaryl group.

12. The compound according to claim 1, wherein R₃ represents a group selected from methyl, phenyl, 1H-pyrazole, 1H-indole, 1H-indazole, pyridine, pyrimidine, 1H-pyrrolo[2,3-b]pyridine, 2,3-dihydro-1H-pyrrolo[2,3-b]pyridine, 1H-benzimidazole, 1H-pyrrole, 1H-pyrrolo[2,3-c]pyridine, 1H-pyrrolo[3,2-b]pyridine, 5H-pyrrolo[3,2-d]pyrimidine, thiophene, pyrazine, 1H-pyrazolo[3,4-b]pyridine, 1,2-oxazole, and 1H-pyrazolo[1,5-a]pyrimidine, those groups optionally having one or more substituents selected from halogen, linear or branched (C₁-C₆)alkyl, linear or branched (C₁-C₆)alkoxy, cyano, cyclopropyl, oxetane, tetrahydrofuran, —CO—O—CH₃, trideuteriomethyl, 2-(morpholin-4-yl)ethyl and 2-(morpholin-4-yl)ethoxy.

13. The compound according to claim 10, wherein R₃ represents a linear or branched (C₁-C₆)alkyl or a heteroaryl optionally substituted by a linear or branched (C₁-C₆)alkyl, and R₄ represents a 4-hydroxyphenyl group.

14. The compound according to claim 1, which is selected from:

5-(5-chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide,

5-(5-chloro-2-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(pyridin-4-yl)-1H-pyrrole-3-carboxamide, N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-5-(6-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-1H-pyrrole-3-carboxamide,

N-(4-hydroxyphenyl)-1,2-dimethyl-5-(6-{[(3R)-3-methyl-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}-1,3-benzodioxol-5-yl)-N-(pyridin-4-yl)-1H-pyrrole-3-carboxamide,

5-(5-fluoro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrole-3-carboxamide,

5-(5-chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-carboxamide,

5-(5-chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl}phenyl)-N-(4-hydroxyphenyl)-1,2-dimethyl-N-(pyridin-4-yl)-1H-pyrrole-3-carboxamide,

5-(5-chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihydroisoquinolin-2(1H)-yl]-carbonyl}phenyl)-N-(5-cy-

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ano-1-methyl-1H-pyrrol-3-yl)-N-(4-hydroxyphenyl)-1,
 2-dimethyl-1H-pyrrole-3-carboxamide,
 N-(5-cyano-1-methyl-1H-pyrrol-3-yl)-5-(5-fluoro-2-
 {[(3S)-3-(morpholin-4-yl-methyl)-3,4-dihydroiso-
 quinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydrox-
 yphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide,
 5-(5-chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihy-
 droisoquinolin-2(1H)-yl]-carbonyl}phenyl)-N-(5-cy-
 ano-1,2-dimethyl-1H-pyrrol-3-yl)-N-(4-hydroxyph-
 enyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide,
 5-(5-chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihy-
 droisoquinolin-2(1H)-yl]-carbonyl}phenyl)-N-(4-hy-
 droxyphenyl)-1,2-dimethyl-N-(1-methyl-2,3-dihydro-
 1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrrole-3-
 carboxamide,
 N-(5-cyano-1,2-dimethyl-1H-pyrrol-3-yl)-5-(5-fluoro-2-
 {[(3S)-3-(morpholin-4-yl-methyl)-3,4-dihydroiso-
 quinolin-2(1H)-yl]carbonyl}phenyl)-N-(4-hydrox-
 yphenyl)-1,2-dimethyl-1H-pyrrole-3-carboxamide, and
 5-(5-chloro-2-{[(3S)-3-(morpholin-4-ylmethyl)-3,4-dihy-
 droisoquinolin-2(1H)-yl]-carbonyl}phenyl)-N-[5-cy-

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ano-2-methyl-1-(trideuteriomethyl)-1H-pyrrol-3-yl]-
 N-(4-hydroxyphenyl)-1,2-dimethyl-1H-pyrrole-3-
 carboxamide,

or an enantiomer, a diastereoisomer, or an addition salt
 thereof with a pharmaceutically acceptable acid or base.

15. A pharmaceutical composition comprising a com-
 pound according to claim 1 in combination with one or more
 pharmaceutically acceptable excipients.

16. A composition comprising a compound according
 claim 1 in combination with an anti-cancer agent selected
 from genotoxic agents, mitotic poisons, anti-metabolites,
 proteasome inhibitors, kinase inhibitors and antibodies.

17. The composition according to claim 16 further com-
 15 prising one or more pharmaceutically acceptable excipients.

18. A combination comprising the compound according to
 claim 1 and an anti-cancer agent selected from genotoxic
 agents, mitotic poisons, anti-metabolites, proteasome inhibi-
 tors, kinase inhibitors and antibodies.

* * * * *

Bogotá D.C., 28 de noviembre de 2016

Doctor
JOSÉ LUIS SALAZAR LÓPEZ
Dirección de Nuevas Creaciones
Superintendencia de Industria y Comercio
Ciudad

Expediente	15 - 155955
Patente	NUEVOS DERIVADOS DE PIRROL, SU PROCEDIMIENTO DE PREPARACIÓN Y LAS COMPOSICIONES FARMACÉUTICAS QUE LOS CONTIENEN
Solicitante	LES LABORATORIES SERVIER VERNALIS (R&D) LTD
Asunto	SOLICITUD DE PRORROGA

CLAUDETTE VERNOT HERNÁNDEZ, mayor de edad, identificada con la cédula de ciudadanía No. 51.722.517 expedida en Bogotá, portadora de la tarjeta profesional No. 57.111 del Consejo Superior de la Judicatura, actuando en calidad de apoderada de **LES LABORATORIES SERVIER y VERNALIS (R&D) LTD**, conforme a los poderes que obran en el expediente, por medio del presente y con fundamento en lo establecido en el artículo 45 de la Decisión 486 de 200. Respetuosamente solicito la prórroga del término concedido mediante Oficio No. 8876 del 31 de agosto de 2016, con el fin de presentar la traducción al español de nuevo capítulo de reivindicaciones.

Para tal efecto se adjunta al presente escrito el pago realizado el día de hoy por un valor de **CIENTO DIECISIETE MIL PESOS** (\$117.000) correspondientes a la tasa establecida para la solicitud de prórroga.

Atentamente,



Claudette Vernot Hernández
C.C. No. 51.722.517 de Bogotá.
T.P. No. 57.111 del C.S de la J.

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**
PAGO ELECTRÓNICO DE SERVICIOS EN LINEA**PAGO ENTIDADES PSE****Confirmación del Pago del Servicio**

Razón Social: Superintendencia de Industria y Comercio

NIT: 8001760892

Número de Factura: 32565

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Tipo de Documento: CC

Documento Solicitante: 51722517

Valor del Servicio \$117,000.00

IVA \$0.00

Total a Pagar \$117,000.00

Fecha 11/28/2016

Número de Transacción 228675145

Nombre Banco BANCO DAVIVIENDA

Mensaje Transacción Aprobada Si desea conocer el estado de su transacción comuníquese con Superintendencia de Industria y Comercio en el Tel: 3820840 ext 338 / 3822693

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